TECHNISCHE UNIVERSITÄT WIEN
Vienna University of Technology

DISSERTATION

SYNTHETIC LIGNANS TARGETING CARDIOVASCULAR DISEASES

ausgeführt zum Zwecke der Erlangung des akademischen Grades
eines Doktors der technischen Wissenschaften

unter der Leitung von
Prof. Dr. Marko D. Mihovilovic
E163 - Institut für Angewandte Synthesechemie

eingereicht an der Technischen Universität Wien
Fakultät für Technische Chemie

von
DI Thomas Linder
Matrikel-Nr.: e0426636
Weingartshofstr. 33 / 2.34, 4020 Linz

Wien, am 04.04.2016

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SYNTHETIC LIGNANS TARGETING CARDIOVASCULAR DISEASES

conducted at the
Institute of Applied Synthetic Chemistry
Vienna University of Technology

under the supervision of
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performed by
DI Thomas Linder

Registration No. e0426636
Weingartshofstr. 33 / 2.34, 4020 Linz

We live in a very special time: the only time when we can observationally verify that we live at a very special time.

—LAWRENCE M. KRAUSS

Acknowledgements

Upon completion of this thesis, with its content put in place and the sentences actually made coherent, I increasingly found it to be an exercise in punctuation and getting the finer points of typography right. However, my biggest concern isn't about having overlooked some formatting error that might have slipped into print on the pages that follow (and if you find one, *you may as well keep it!*). Rather, I am somewhat worried about not including someone in my thanks who in fact deserves to be mentioned—for contributing to the project anywhere from its very beginning up to this point right now, or for helping me in any other way during that time. And while it appears to me that keeping notes in this regard would have been equally important as keeping lab records, I try my best to recall who I owe a debt of gratitude.

First, I would like to thank Prof. Marko Mihovilovic for the opportunity to work on this topic and for providing great support throughout. He always kept an open door and made sure that the project stayed in track when I managed to get bogged down too much in details. Many thanks go to Ass. Prof. Michael Schnürch, too, for his scientific insight and helpful suggestions to this text itself. Also, I'd like to thank Dr. Florian Rudroff for his contributions.

I would also like to express gratitude to Prof. Hermann Stuppner of the University of Innsbruck for initiating and coordinating the *Drugs from Nature Targeting Inflammation* National Research Network (NFN) of which this project was part. Financial support by the Austrian Science Fund (FWF S107) is also gratefully acknowledged.

This work would not have been possible without some members within the NFN: on the flip side of that coin called medicinal chemistry is the pharmacological assessment of the compounds which chemists produce. Therefore, I want to thank Prof. Verena Dirsch and Dr. Atanas Atanasov of the University of Vienna, as well as their co-workers, for their involvement and the successful collaboration that came from it.

Thanks also go to Dr. Laszlo Czollner and Prof. Erwin Rosenberg for conducting HRMS measurements, Prof. Christian Hametner for recording various non-routine NMR spectra, Prof. Peter Gärtner for assisting me with administrative matters, and Florian Untersteiner for helping solve computer-related issues.

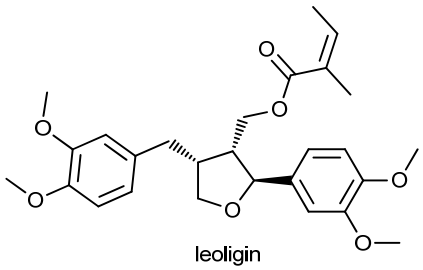
I'd like to mention Sophie Geyrhofer and Karin Harhammer who made important contributions with their own projects related to this one, and I want to say thank you for the nice time working together.

However, I could not possibly name all the people on and off campus I am grateful to (please bear with me for not starting to name people, for the reasons mentioned), so I try to get away by saying to all colleagues and friends that I really enjoyed the time I spent with you, both in and outside the lab.

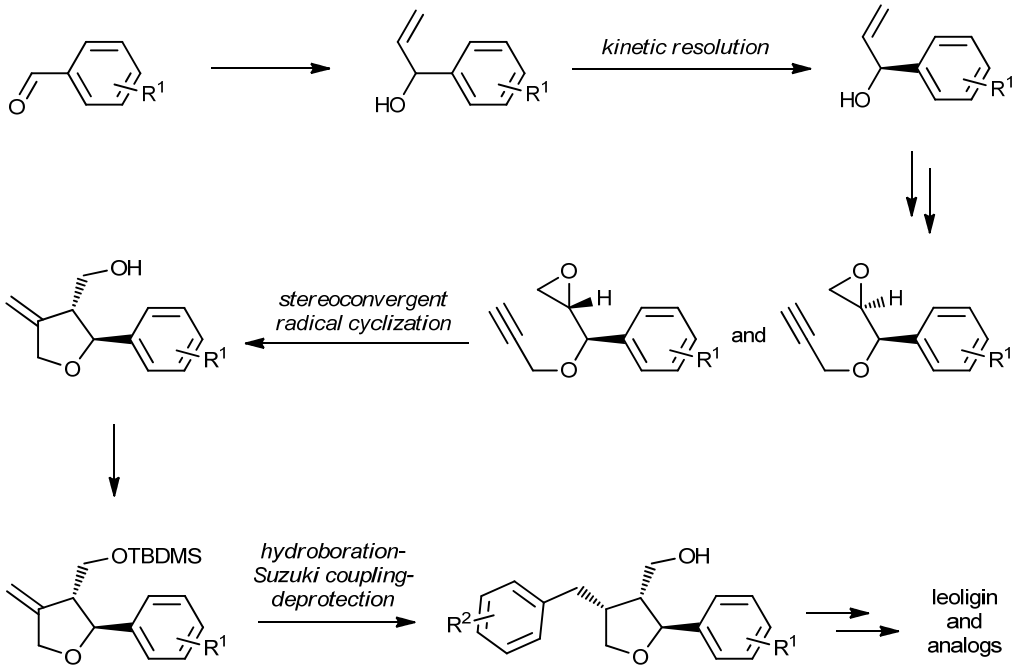
Finally, special thanks are in order for my parents, for their support in every regard along this journey.

Abstract

As a key feature of this work from the field of medicinal chemistry, the naturally occurring compound leoligin and structurally modified analogs thereof were synthesized. Leoligin, the major lignan from *Leontopodium nivale* ssp. *alpinum*, is capable of enhancing macrophage cholesterol efflux, suppression of the NF-κB pathway, and inhibition of intimal hyperplasia. For this reason, it is a molecular scaffold from which physiologically useful compounds may be developed for the prevention of atherosclerosis and treatment of restenosis in the wake of bypass grafting and angioplasty.

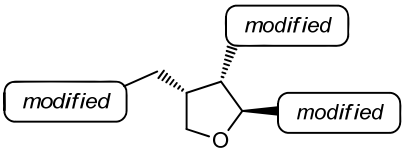


Particular emphasis has been put on modular synthesis in order to obtain a compound library which could be subjected to cell-based studies for structure-activity relationship elucidations. The synthetic strategy presented herein constitutes a general method for the stereoselective preparation of optically active furan-type lignans. Kinetic resolution was used as a convenient method for achieving high enantiomeric excess, and a stereoconvergent radical cyclization was employed to furnish intermediate compounds which were then elaborated to lignan scaffolds in a diastereoselective hydroboration-Suzuki coupling sequence, the latter hitherto not being used in this context.



This work therefore reflects on literature precedent for lignan synthesis and puts it into perspective with the newly developed approach herein, which permitted the synthesis of a sufficiently diverse

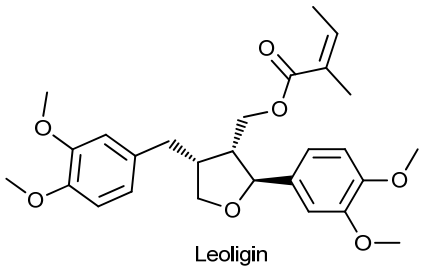
array of leoligin-like compounds to selectively improve on the biological activities of this plant-derived natural product. The pharmacological results of the synthetic compounds are discussed and conclusions are drawn on which molecular features are required for augmenting a particular physiological response.



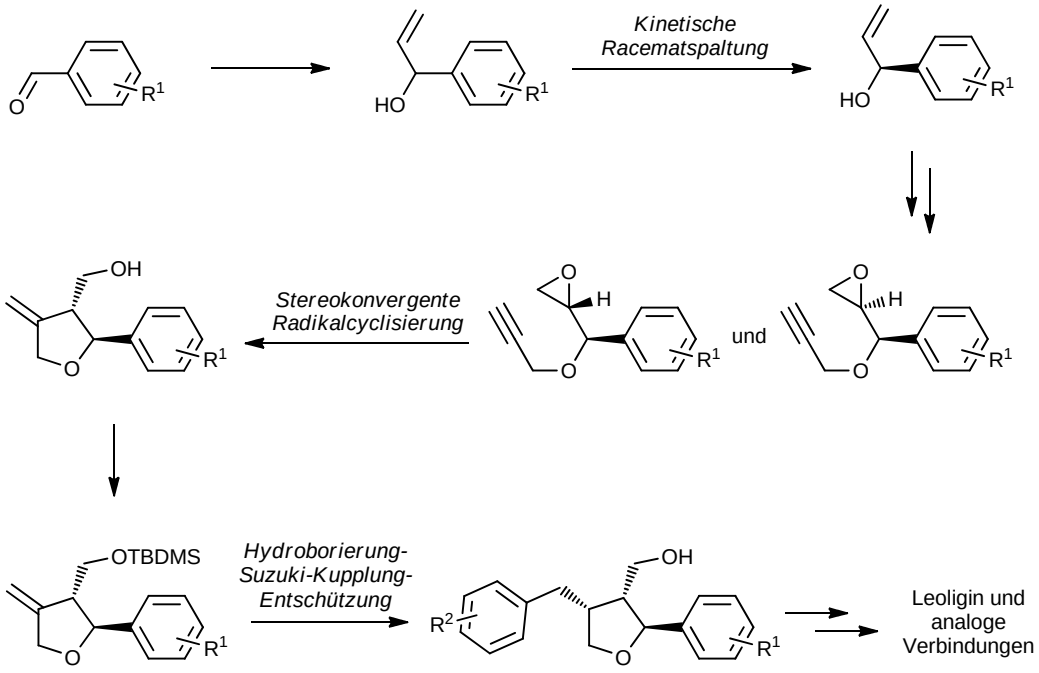
The promising pharmacological results also support the notion that Nature continues to hold a variety of useful substances in store, the medical potential of which can be tapped by chemically produced compounds based on their natural prototype.

Kurzfassung

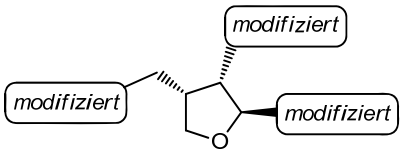
Zentraler Bestandteil für diese Arbeit aus dem Bereich der Medizinalchemie war die Darstellung des in der Natur vorkommenden Leoligins und strukturmodifizierter Analogverbindungen davon. Leoligin, das Hauptlignan aus dem Edelweiß (*Leontopodium nivale* ssp. *alpinum*), ist in der Lage den Ausstrom von Cholesterol aus Makrophagen zu verstärken, den NF-κB-Reaktionsweg zu unterdrücken und die Intimahyperplasie zu inhibieren, was es zu einem Ausgangsmolekül macht, von welchem physiologisch nützliche Stoffe zur Atherosklerosevorbeugung und Behandlung der Restenose nach Bypass- und Angioplastieeingriffen entwickelt werden könnten.



Besonderes Augenmerk wurde dabei auf die Modularität der Synthese gelegt um eine Verbindungsbibliothek zu erhalten, welche zellbasierten Untersuchungen zur Aufklärung von Struktur-Wirkungsbeziehungen zugeführt werden konnte. Die hier vorgestellte Synthesestrategie stellt eine allgemeine Methode zur stereoselektiven Herstellung optisch aktiver Lignane vom Furan-Typ dar. Eine kinetische Racematspaltung wurde als zweckdienliche Methode eingesetzt um hohen Enantiomerenüberschuss zu erreichen, und eine stereokonvergente Radikalcyclisierung wurde verwendet um Zwischenprodukte zu gewinnen, die danach in einer diastereoselektiven Hydroborierung-Suzuki-Kupplungssequenz zu Lignangerüsten umgesetzt wurden; dabei wurde letztere in diesem Zusammenhang bisher noch nicht angewendet.



Diese Arbeit stellt daher Lignan-Literatursynthesen dem neu entwickelten Zugang gegenüber, welcher die Darstellung einer hinreichend vielfältigen Sammlung leoliginartiger Verbindungen erlaubte um die biologische Aktivität dieses pflanzlichen Naturstoffes selektiv zu verbessern. Die pharmakologischen Ergebnisse der synthetischen Verbindungen werden besprochen und Schlussfolgerungen dazu erläutert, welche Merkmale am Molekül zur Steigerung einer bestimmten physiologischen Reaktion nötig sind.



Die vielversprechenden pharmakologischen Ergebnisse stützen ebenfalls die Ansicht, dass es in der Natur nach wie vor unterschiedlichste nützliche Substanzen gibt, deren medizinisches Potential durch chemische Herstellung von auf diesen natürlichen Mustern basierenden Verbindungen zur Geltung gebracht werden kann.

Key

Compounds prepared or used as starting materials, as well as unisolated intermediates, transition states and compounds presented as literature examples in this thesis are labeled with bold Arabic numbers. Isolated and characterized compounds unknown to the literature are additionally underlined in the body text.

Generic structures are labeled with bold Roman numerals.

Labels of structural fragments (synthons) are italicized.

Literature citations are indicated by superscript Arabic numbers. Footnotes are indicated by superscript lowercase letters.

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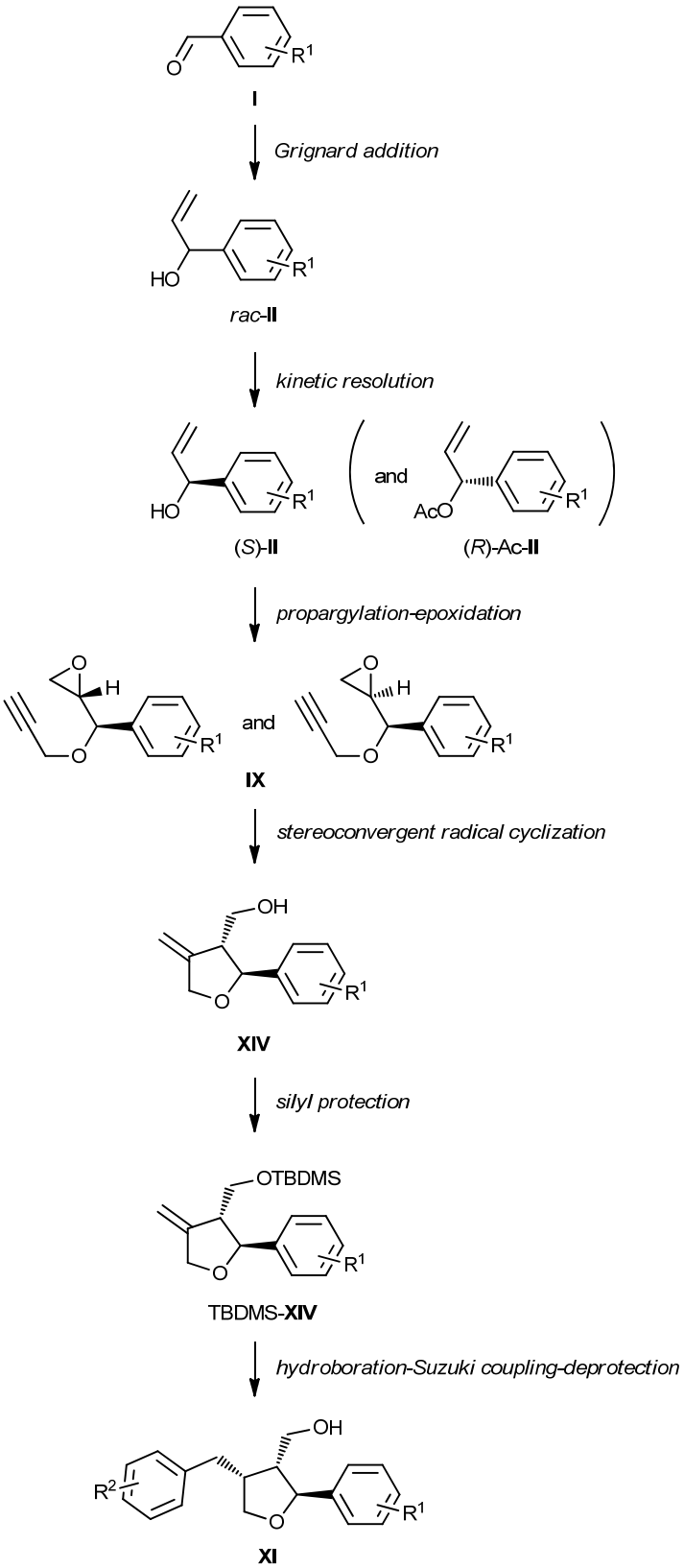
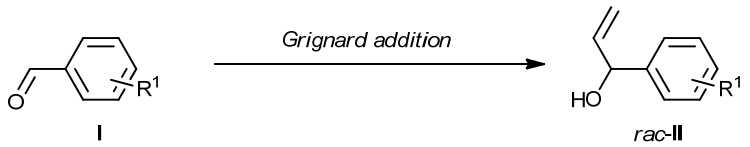
General Schemes

General Schemes

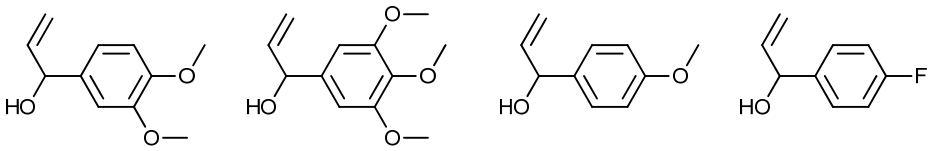
Overview of Synthetic Route: Canonical Steps to 3-(Hydroxymethyl) tetrahydrofuran-type Lignans



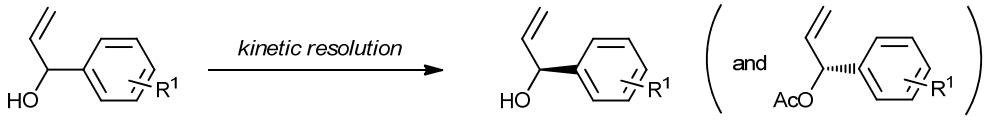
Synthesis of Intermediate Compounds



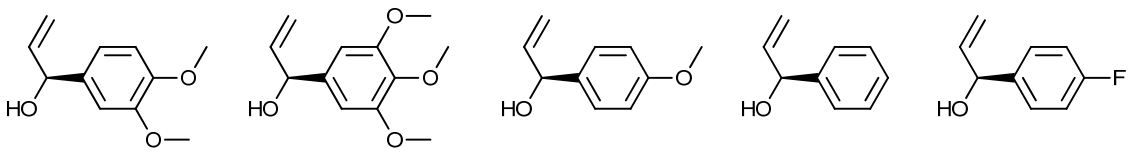
I *rac*-**II**



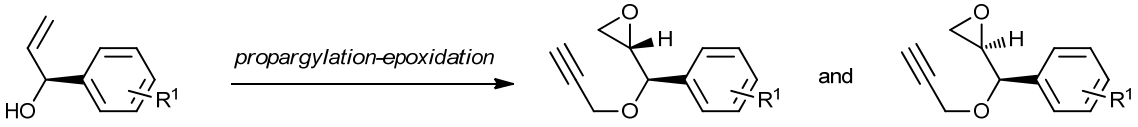
rac-**27**, 99 % *rac*-**69**, 98 % *rac*-**70**, 92 % *rac*-**72**, > 99 %



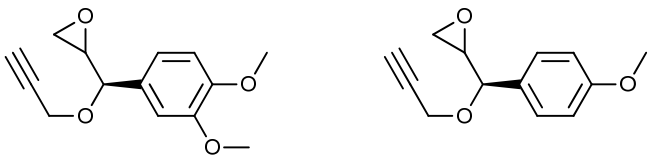
rac-**II** (*S*)-**II**, theor. max. yield is 50 % (*R*)-Ac-**II**



(*S*)-**27**, 40 % (*S*)-**69**, 39 % (*S*)-**70**, 32 % (*S*)-**71**, 46 % (*S*)-**72**, 40 %

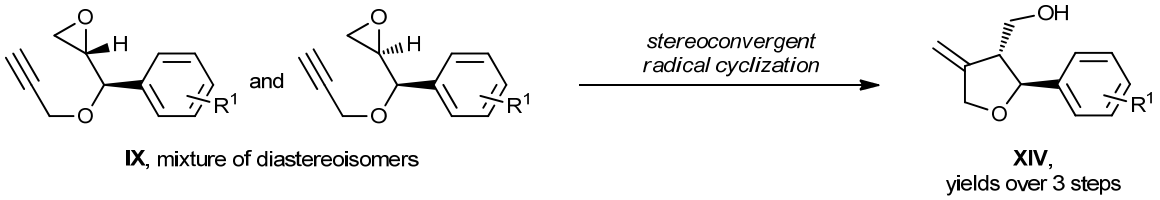


(*S*)-**II** **IX**, mixture of diastereoisomers, crude



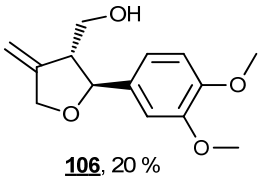
101 **110**

111 **112**

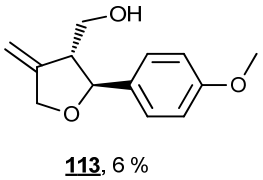


IX, mixture of diastereoisomers

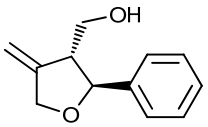
XIV,
yields over 3 steps



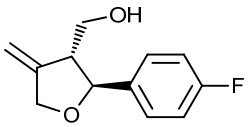
106, 20 %



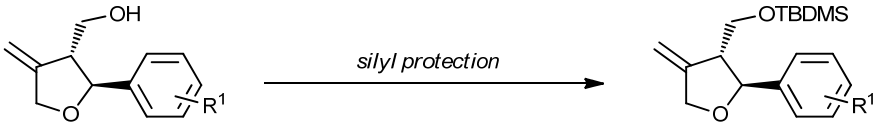
113, 6 %



114, 34 %

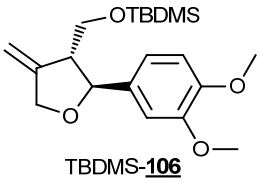


115, 26 %

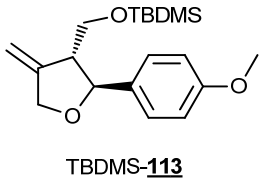


XIV

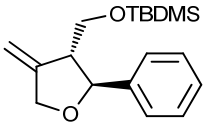
TBDMS-**XIV**, crude



TBDMS-**106**



TBDMS-**113**



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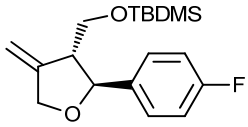
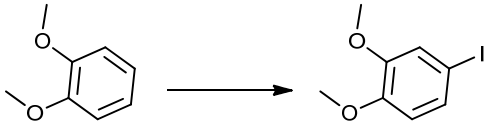
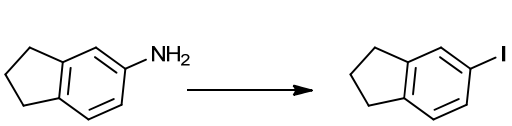


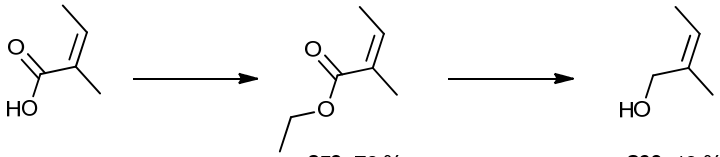
TBDMS-**115**



109, 86 %

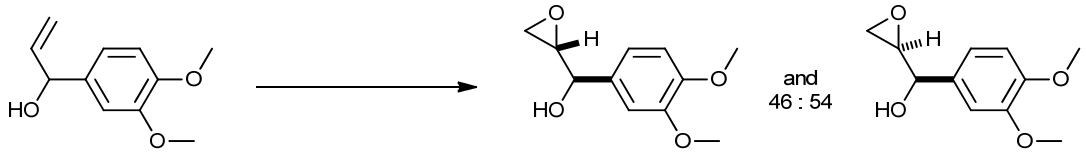


266, 19 %

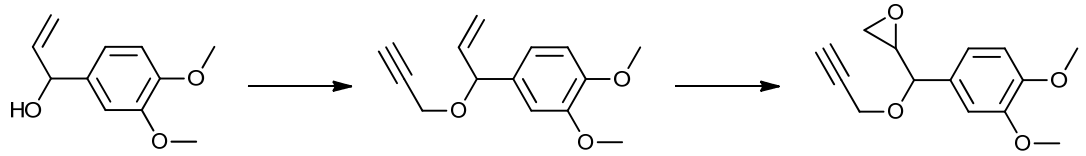


259, 70 %

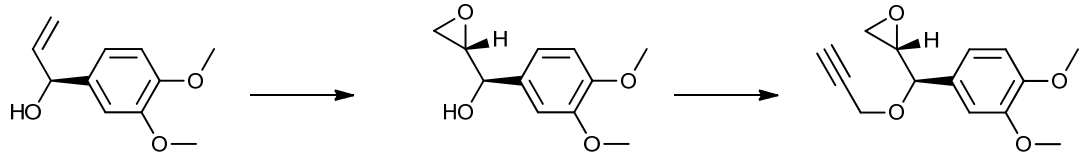
260, 19 %



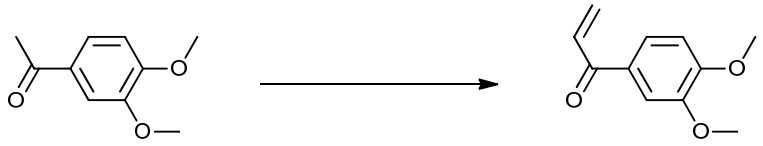
rac-**27** **73**, racemic mixture of diastereoisomers, 42 %



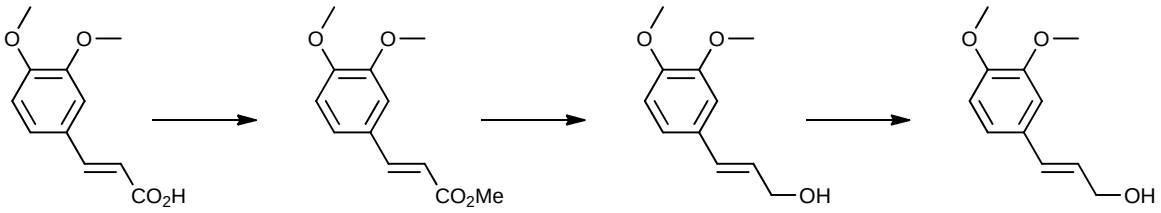
rac-**27** *rac*-**107**, 86 % **101**, racemic mixture of diastereoisomers, 41 %



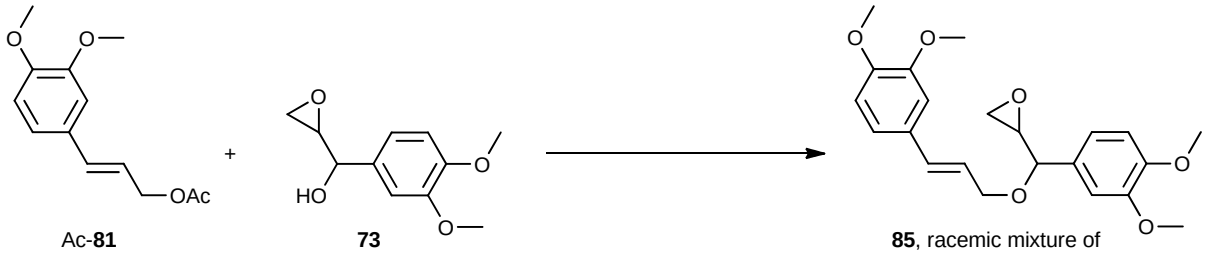
(*S*)-**27** (α*R*,β*S*)-**73**, 78 % (α*R*,β*S*)-**101**, 91 %



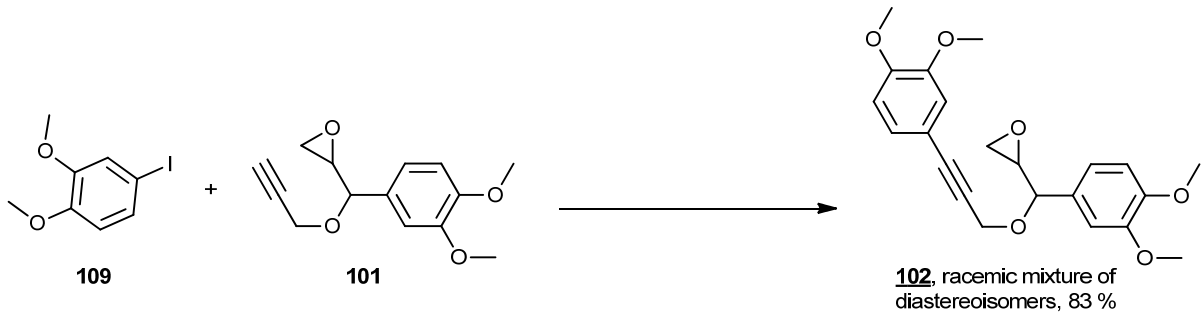
78, 69 %



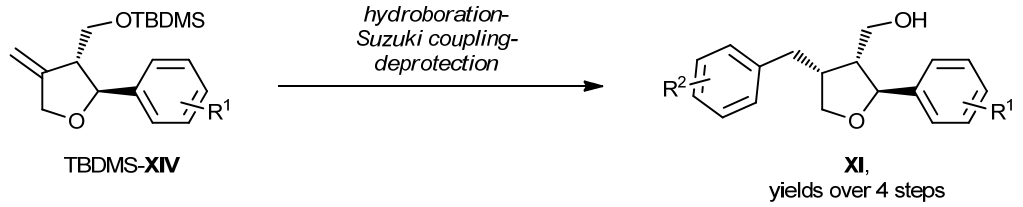
83, 99 % **81**, 98 % Ac-**81**, 96 %

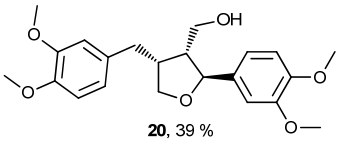


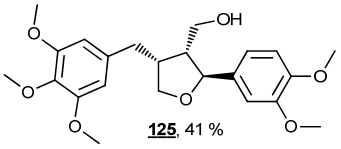
Ac-**81** **73** **85**, racemic mixture of diastereoisomers, 38 %

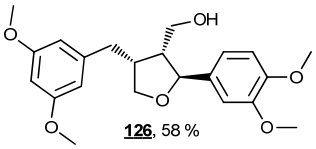


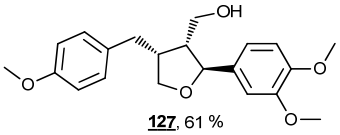
Sequence Reaction to 3-(Hydroxymethyl)tetrahydrofuran-type Lignans

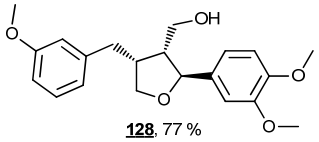


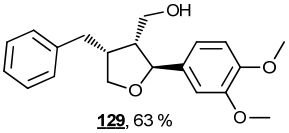


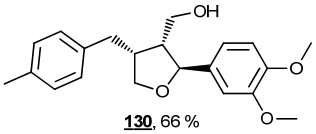


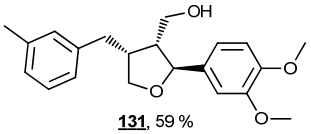


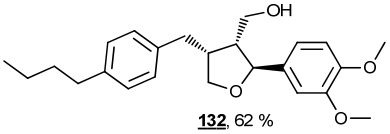


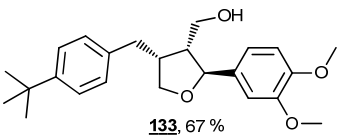


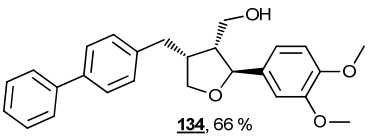


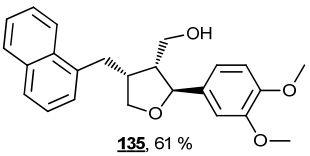


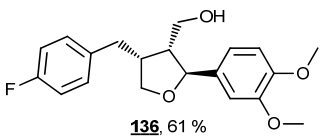


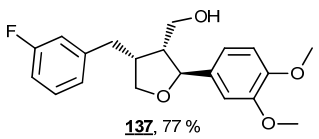


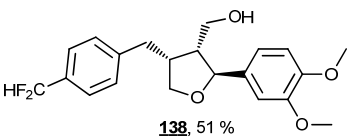


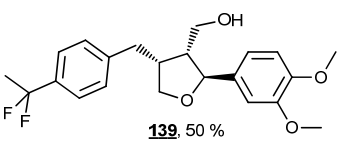


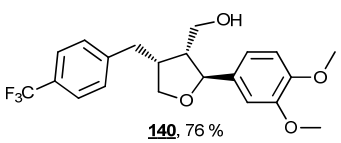


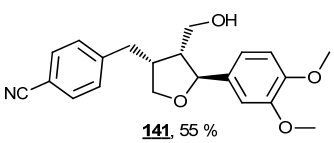


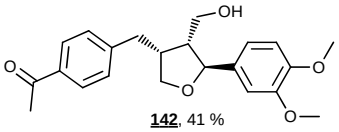




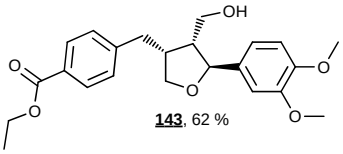








142, 41 %



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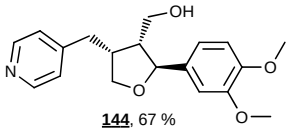
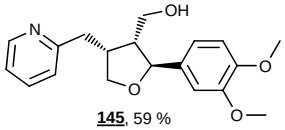


144, 67 %



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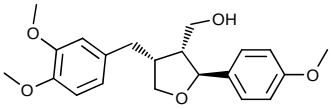

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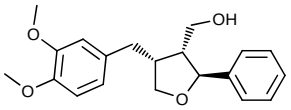
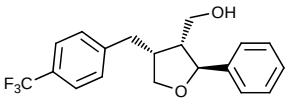


123, 51 %



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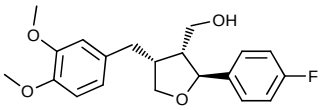
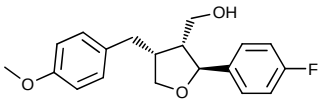
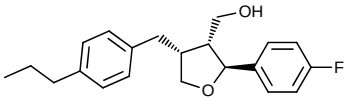


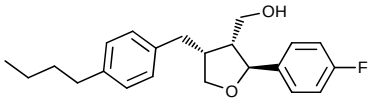
148, 58 %



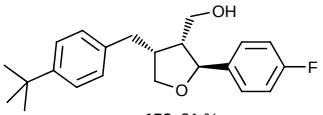
149, 58 %



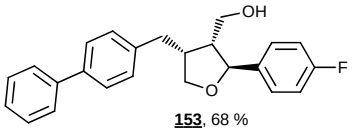
150, 69 %



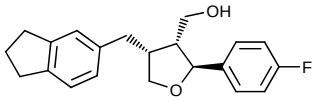
151, 64 %



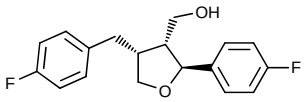
152, 31 %



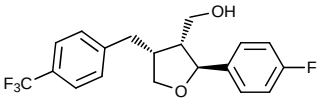
153, 68 %



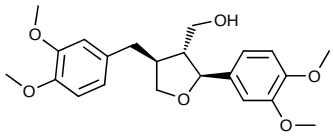
154, 66 %



155, 48 %



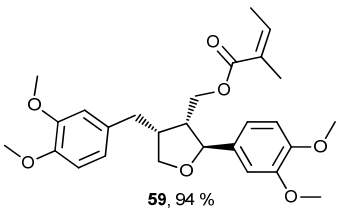
156, 41 %



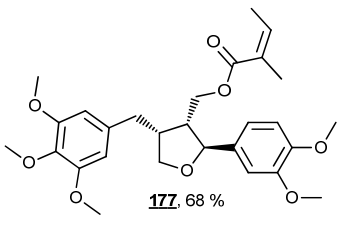
8'-*epi*-**20**

Modification of 3-(Hydroxymethyl)tetrahydrofuran-type Lignans

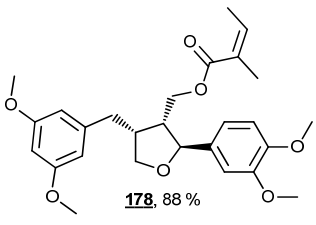
XI **XV**



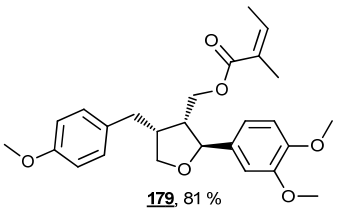
59, 94 %



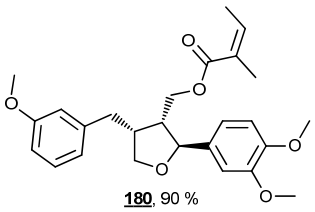
177, 68 %



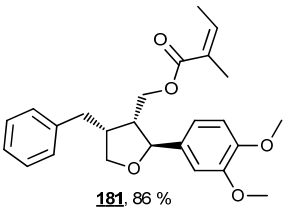
178, 88 %



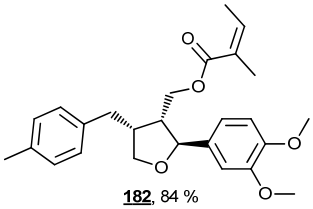
179, 81 %



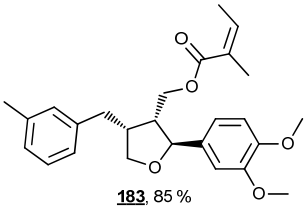
180, 90 %



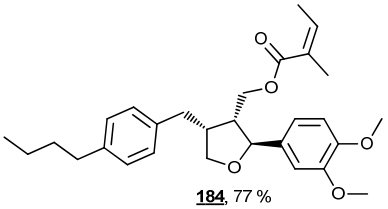
181, 86 %



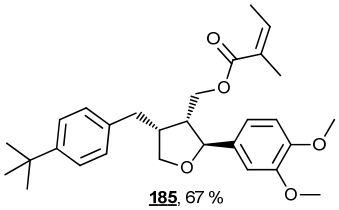
182, 84 %



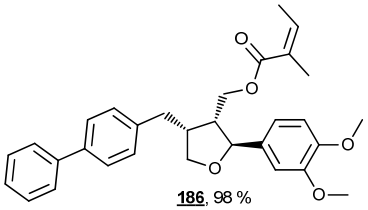
183, 85 %



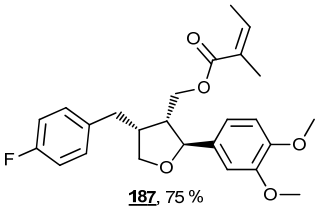
184, 77 %



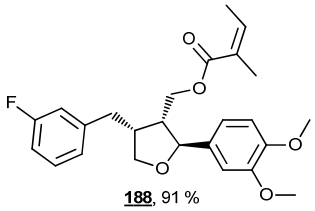
185, 67 %



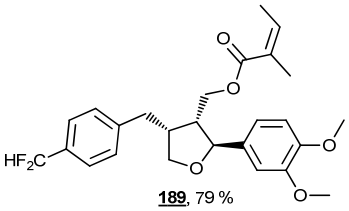
186, 98 %



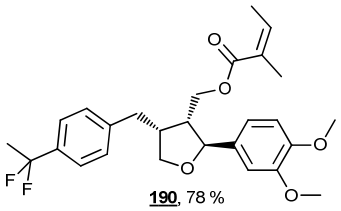
187, 75 %



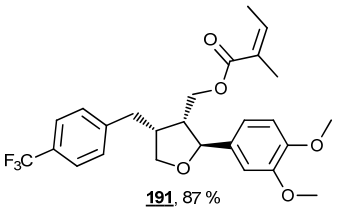
188, 91 %



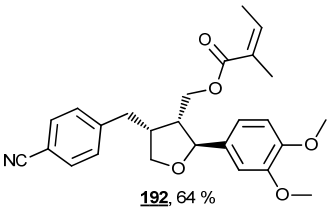
189, 79 %



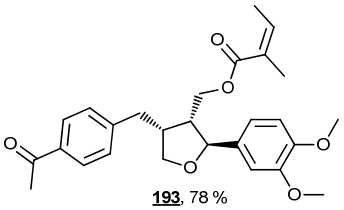
190, 78 %



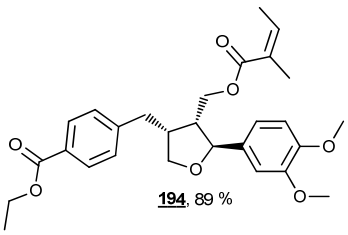
191, 87 %



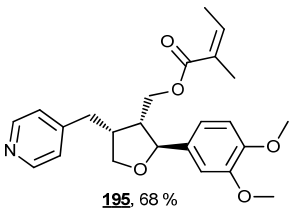
192, 64 %



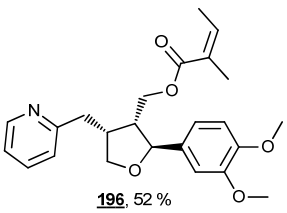
193, 78 %



194, 89 %



195, 68 %



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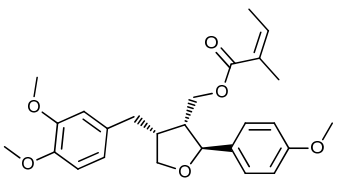
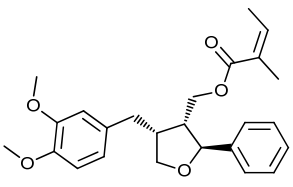
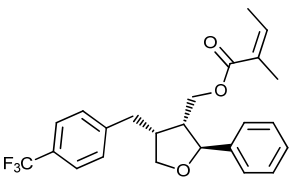


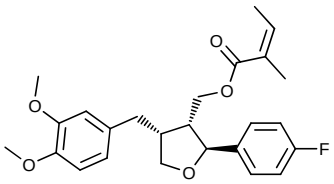
197, 89 %



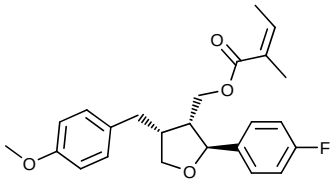
198, 48 %



199, 72 %



200, 55 %



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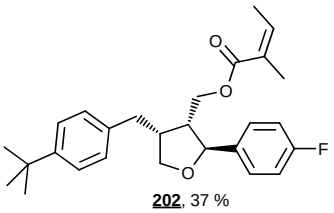
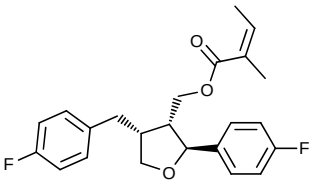
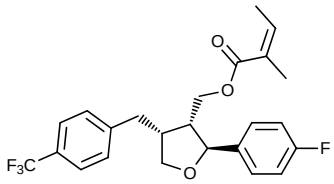


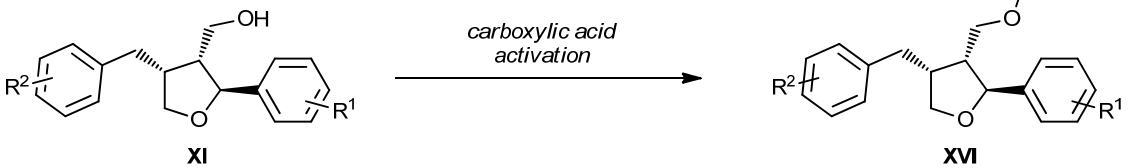
202, 37 %



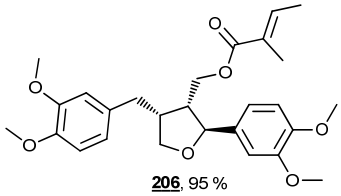
203, 64 %



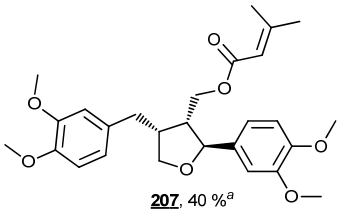
204, 61 %



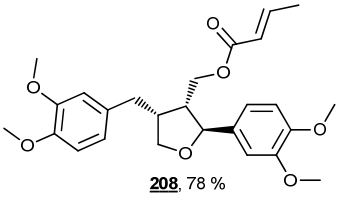
XI **XVI**



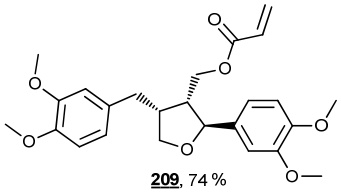
206, 95 %



207, 40 %[a]



208, 78 %



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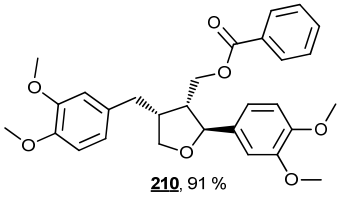
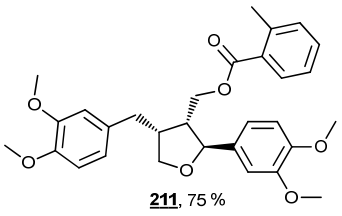
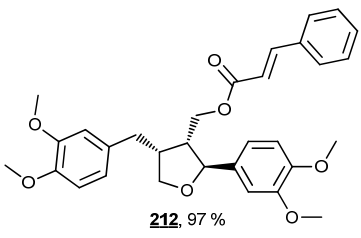


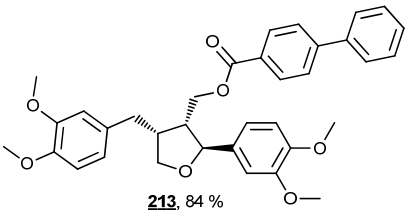
210, 91 %



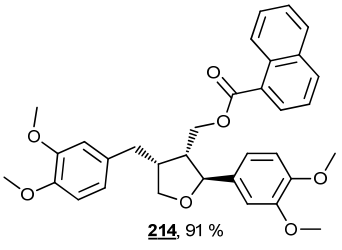
211, 75 %



212, 97 %



213, 84 %



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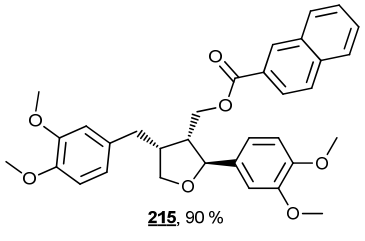

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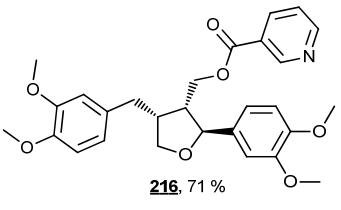

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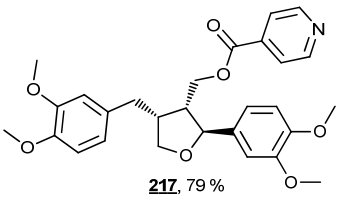
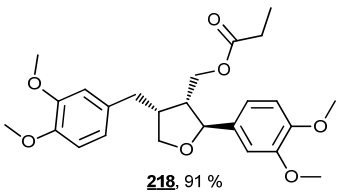
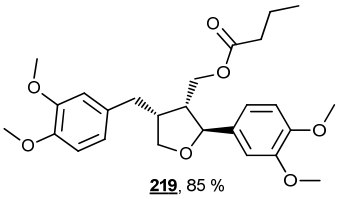


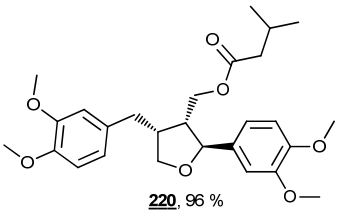
217, 79 %



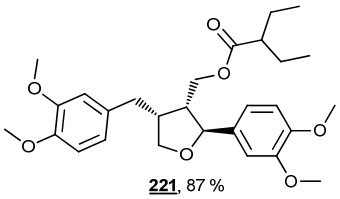
218, 91 %



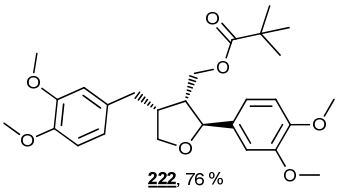
219, 85 %



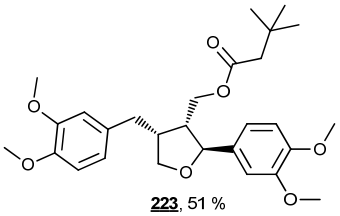
220, 96 %



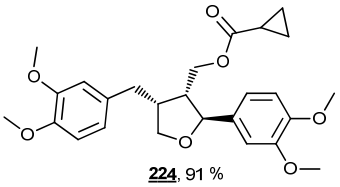
221, 87 %



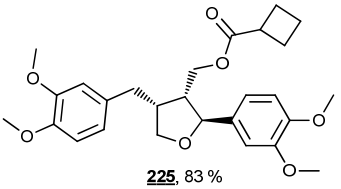
222, 76 %



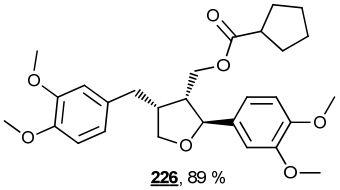
223, 51 %



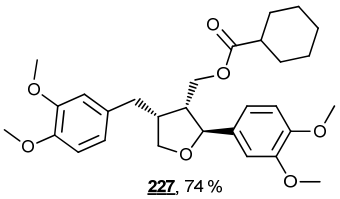
224, 91 %



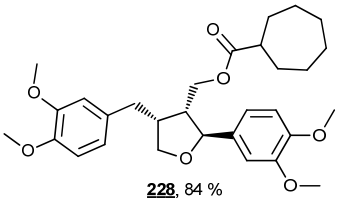
225, 83 %



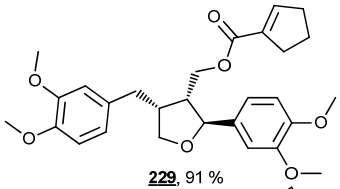
226, 89 %



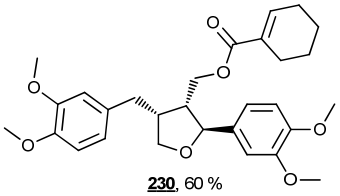
227, 74 %



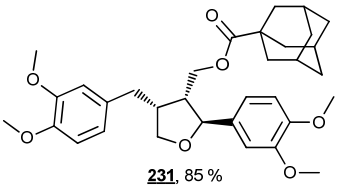
228, 84 %



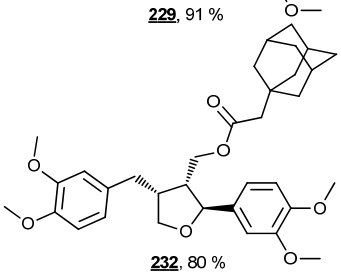
229, 91 %



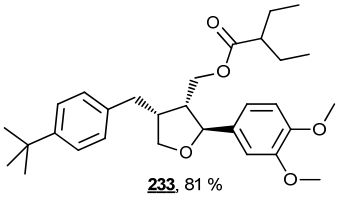
230, 60 %



231, 85 %



232, 80 %



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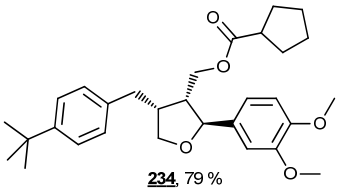
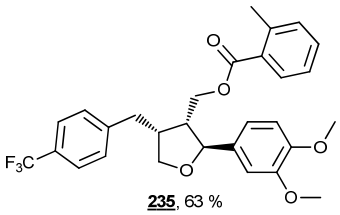
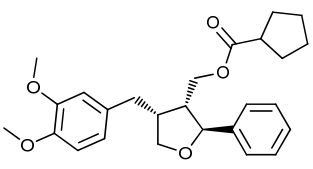


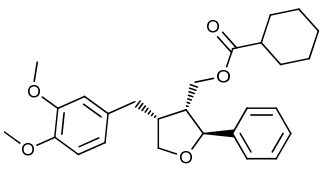
234, 79 %



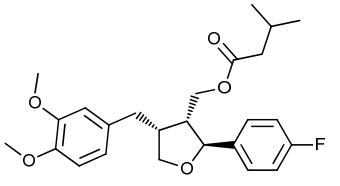
235, 63 %



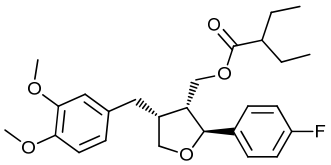
236, 86 %



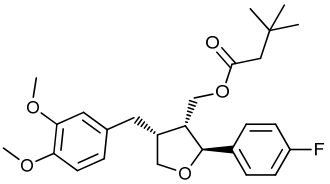
237, 84 %



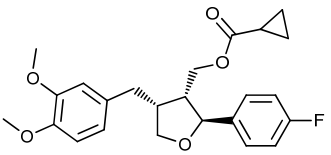
238, 63 %



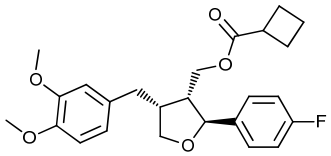
239, 83 %



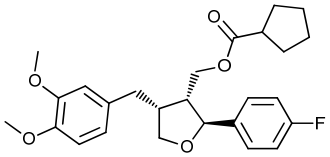
240, 92 %



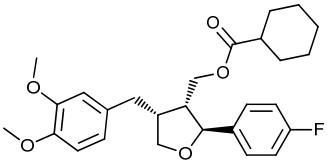
241, 75 %



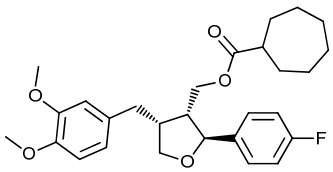
242, 75 %



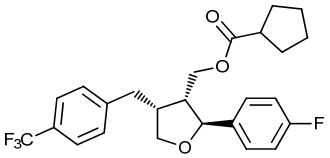
243, 96 %



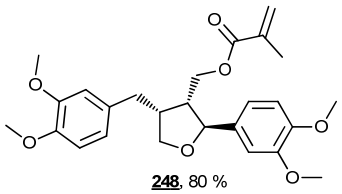
244, 91 %



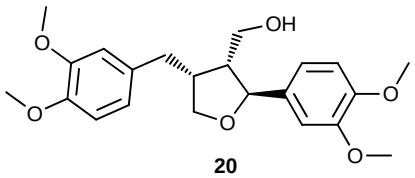
245, 88 %



246, 79 %



248, 80 %



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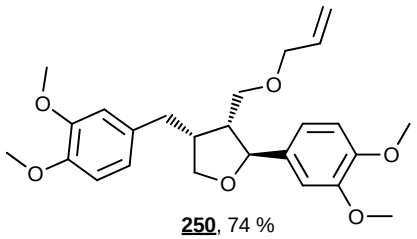

250, 74 %

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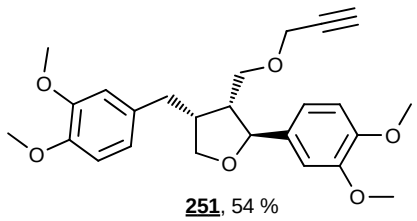

251, 54 %

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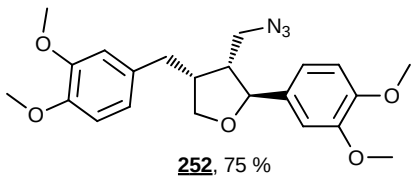
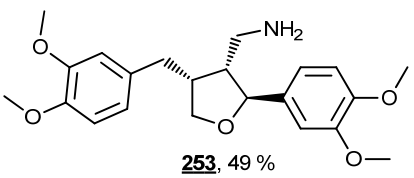
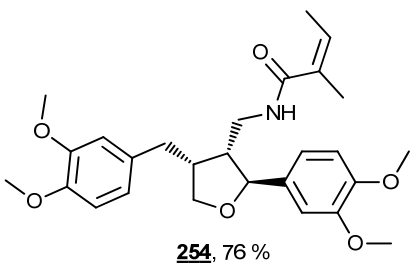


252, 75 %

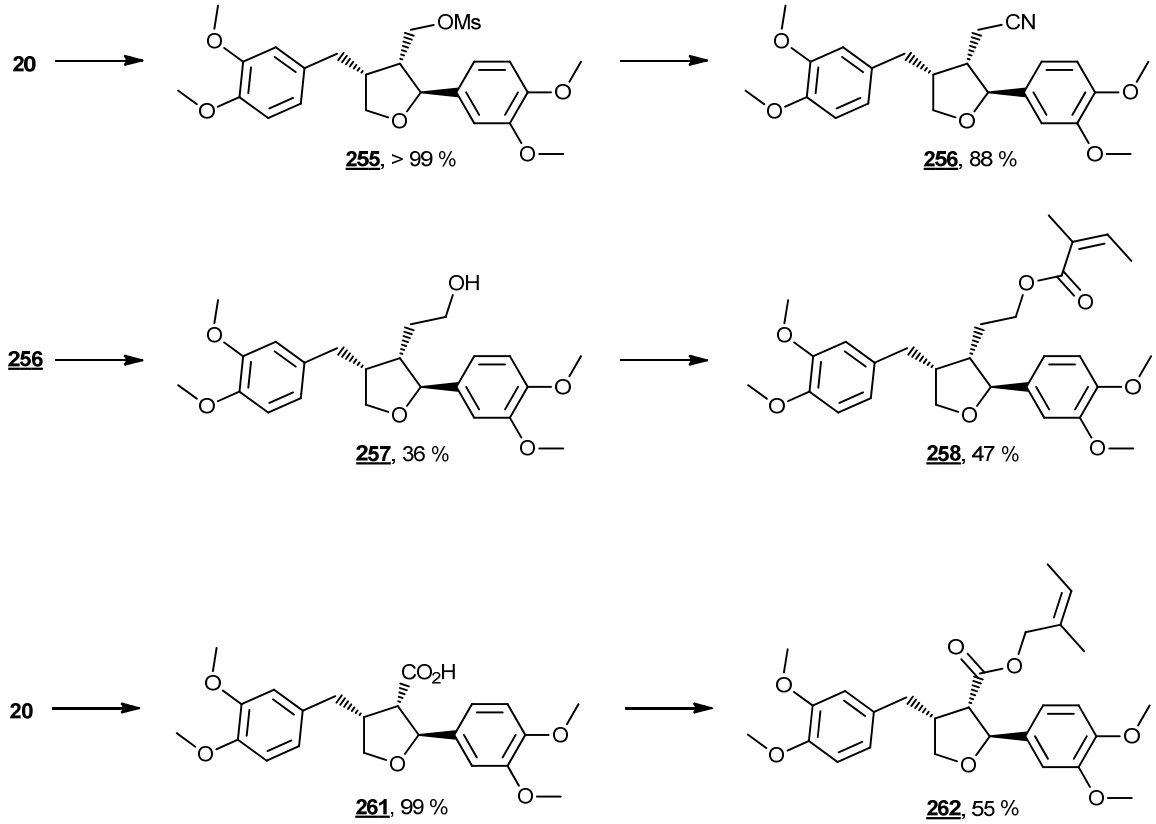
20



253, 49 %



254, 76 %


20
OMs
255, > 99 %
CN
256, 88 %
256
OH
257, 36 %
258, 47 %
20
CO2H
261, 99 %
262, 55 %

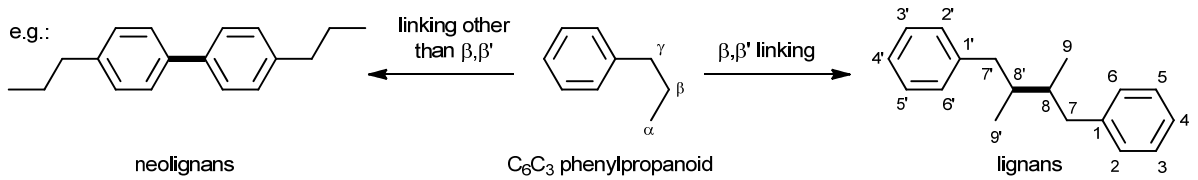
A Introduction

A.1 Lignans

This section introduces lignans as a class of natural products and highlights research surrounding their preparation in the laboratory, discussing aspects of concise and stereocontrolled synthesis.

A.1.1 Occurrence, Function and Bioactivity

Lignans form a wide range of natural compounds which occur in both herbaceous plants (herbs) and woody plants (trees, shrubs and vines). They are secondary metabolites[2] consisting of at least two phenylpropanoid units (C_6C_3 building blocks).[3] The definition is often restricted to *dimeric* phenylpropanoids[2] because it is the most prominent form in which they are known to appear in Nature.[4] The structural diversity of these compounds has led to various nomenclature proposals to number the skeletal atoms, resulting in IUPAC recommendations for rational and consistent naming[4] which will be used for description throughout sections A, B and C (but *cf.* NMR assignments in section D.1, page 120). Therein, a compound is considered a lignan if the two C_6C_3 units (in the dimeric case) are linked by a β-β' bond, subsequently termed the 8-8' bond, whereas if the units are combined in any other way (including linkages *via* the aryl moiety), the resulting structure is called a neolignan (**Scheme 1**).



Scheme 1: General coupling and atom numbering pattern of lignans. A bold bond is used to highlight the 8-8' linkage.

A classification approach for lignans based on their general structure has been used,[5] grouping them into eight different types: furan, furofuran, dibenzylbutane, dibenzylbutyrolactone, aryltetralin, arylnaphthalene, dibenzocyclooctadiene and dibenzylbutyrolactol lignans (**Figure 1** shows their skeletal structures). Moreover, these compounds also fall into one of three categories of oxygen appearance: lignans with oxygen at the 9(9')-carbon, lignans without oxygen at the 9(9')-carbon, and dicarboxylic acid lignans. Some lignan types appear in more than one category and/or there exist different cyclization patterns for a given type. For example, furan lignans occur with or without oxygen at the 9(9')-carbon, and the decoration of the tetrahydrofuran core can also vary.

Lignan biosynthesis in plants[5-6] starts with L-phenylalanine or, less frequently, L-tyrosine, from which ammonia is eliminated to give cinnamic acid or *p*-coumaric acid, respectively (**Scheme 2**). This deamination is accomplished by the enzyme phenylalanine ammonia lyase (PAL). There is some debate as to whether a separate tyrosine ammonia lyase (TAL) exists or if the PAL substrate selectivity in some plants is simply less stringent to accept tyrosine as well. However, *p*-coumaric acid is formed by hydroxylation of cinnamic acid by NADPH-dependent cytochrome P-450 (CYP) in most cases. The biosynthesis then continues through different steps of hydroxylation and methylation with *S*-adenosylmethionine (SAM), depending on the pathway which is operative in different plants, involving caffeic acid, ferulic acid, and sinapic acid. Caffeic acid is the cyclization precursor for

dicarboxylic acid lignans, while the others are reduced *via* esters of coenzyme A and the corresponding aldehydes to *p*-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol. The substitution pattern of the final lignan is not necessarily established completely at the acid stage, and which of the alcohols are used to generate lignans also depends on the plant, with coniferyl alcohol being the most prominent building block.

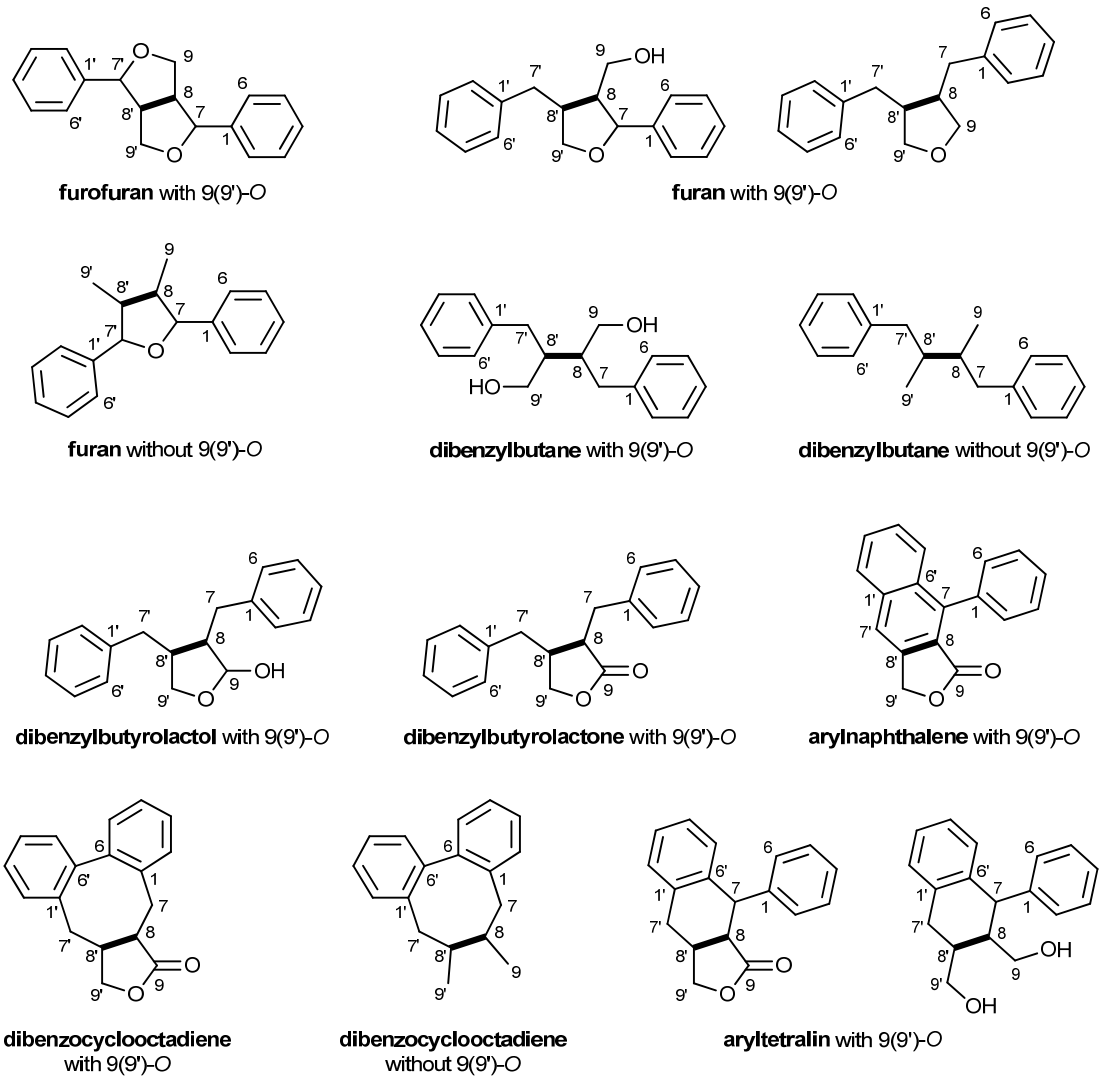
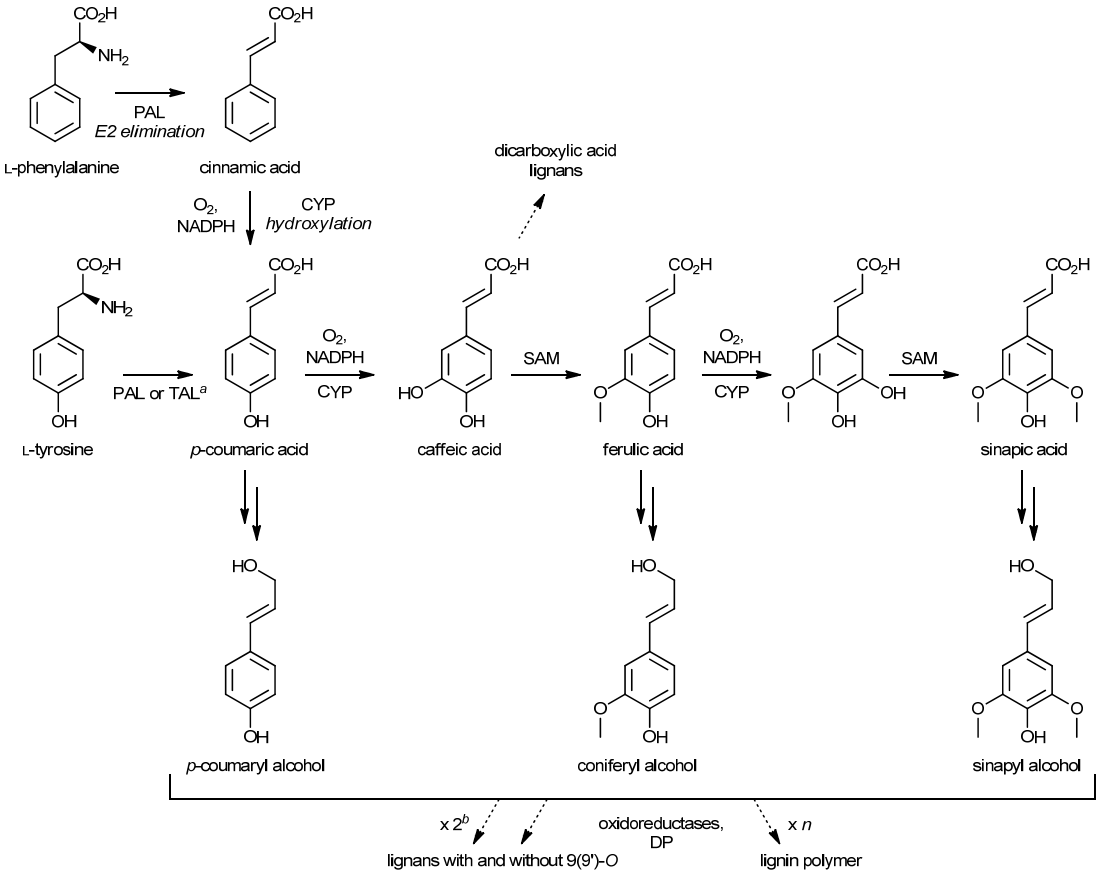


Figure 1: Generic lignan skeletons. A bold bond is used to highlight the 8-8' linkage.

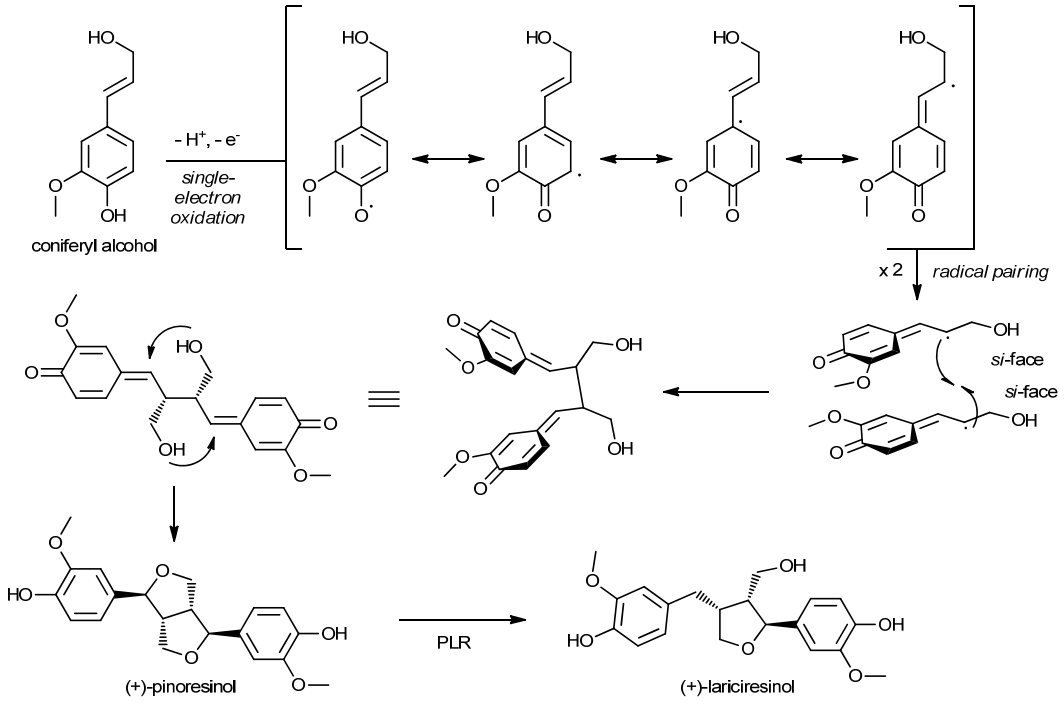
Certain oxidoreductase enzymes (including oxidases, peroxidases and laccases)[7-8] then abstract both a proton and an electron from the free phenolic hydroxy group in *para* position, which leads to resonance-stabilized quinone radicals. Pairing of these radicals gives different oxidative coupling products and thus different types of lignans (or neolignans), depending on the recombination sites. A dimeric protein of around 50 kD, called dirigent protein (DP or DIR), isolated from *Forsythia suspensa* (and later[9] *F. intermedia*) accounts for the diastereoselectivity of the reaction by *si-si* coupling and also ensures the optical purity of the resulting propanoid dimers. DP itself does not have oxidase activity, and it is thus suggested that coniferyl alcohol radical, rather than coniferyl alcohol itself, is the substrate which binds to the DP.[7-8]

The mechanism is shown for the formation of the furofuran lignan (+)-pinoresinol in **Scheme 3**. For this work, furan-type lignans are of central interest (section A.3, page 38). As an example, studies of *F. intermedia* revealed that (+)-lariciresinol is formed from (+)-pinoresinol by the action of

pinoresinol-lariciresinol reductase (PLR).[7] Additionally, insoluble polymeric lignin giving rise to both the rigidity and elasticity of woody plants is also an important product of this pathway.



Scheme 2: Formation of lignans and lignin. [a]*Cf.* text. [b]In the case of dimeric phenylpropanoids.



Scheme 3: Oxidative coupling to (+)-pinoresinol and reduction to (+)-lariciresinol.

Phenylpropanoids in general protect plants in stress conditions like infections, wounding, exposure to UV radiation and ozone, pollutants and herbivores.[10] As for lignans, various phytochemical roles have been demonstrated,[3] such as the protective function of those compounds that are formed by PLR against pests and pathogens.[11] An example of lignan activity is haedoxan A (**Figure 2**), isolated from *Phryma leptostachya*, which shows insecticidal activity.[12] The chemical structures and synergistic action of (+)-sesamin and (+)-asarinin (also called (+)-episesamin) with pyrethrum insecticides have been known for more than 70 years.[13-14] (+)-Epimagnolin A, which occurs in the flower buds of *Magnolia fargesii*, inhibits the growth of *Drosophila melanogaster* larvae,[15] and nordihydroguaiaretic acid from *Larrea tridentata* contributes to the negative allelopathy (the ability to hinder the growth of other plants nearby which are competing for resources) of this bush by suppressing the growth of the seedling roots of various grasses,[16] a biological property also explored on lariciresinol-like lignans.[17-18]

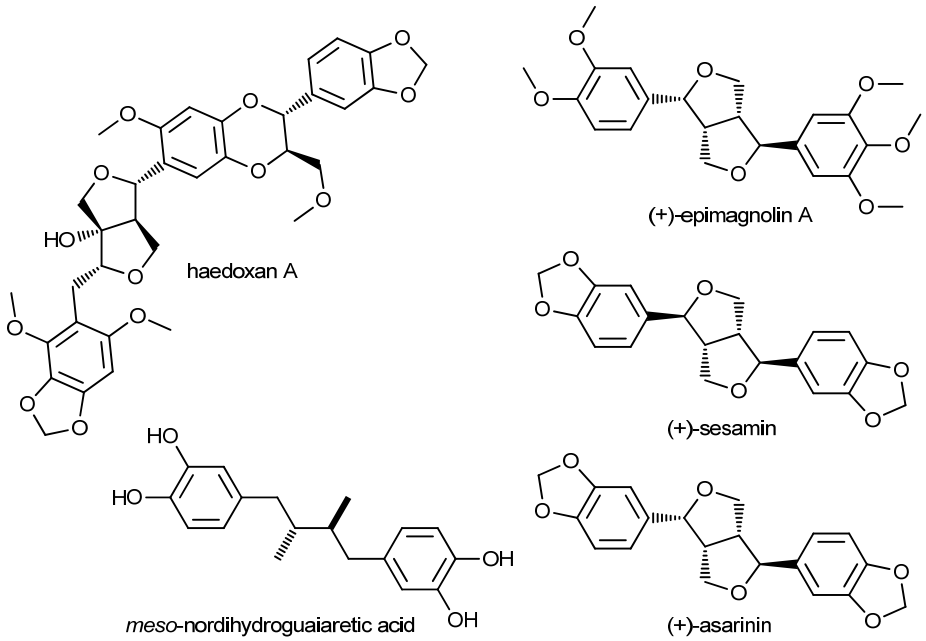


Figure 2: Lignans with known phytochemical roles.

Lignans are not exclusively plant-derived compounds. For instance, podophyllotoxin (*vide infra*) and a glycoside thereof were isolated from the fungal endophyte *Trametes hirsuta*, normally residing inside its host plant *Podophyllum hexandrum*.[19] It is conceivable that the capability of this fungus to produce the same compound as its host plant is a result of horizontal gene transfer during the course of evolution because producing and tolerating high levels of this secondary metabolite would allow symbiosis with the plant and therefore be advantageous for the endophytic organism.

The physiological properties of lignans have been made use of, one way or another, for centuries. For example, alcoholic extracts from *Podophyllum* species, containing high levels of the aforementioned podophyllotoxin (**Figure 3**), were employed by indigenous peoples in North America and the Himalayas as an effective poison.[20] Aside from such ethnopharmacological aspects, these compounds are the subject of current studies in pharmacognosy, pharmacology, and medicine because of their anti-viral, anti-cancer, anti-bacterial, anti-fungal, anti-oxidant, anti-inflammatory, parasiticidal, immunity-related, metabolic and cardiovascular effects (among others),[3, 21] a few of which are briefly outlined in the following paragraphs.

Topical application of podophyllotoxin is used clinically to treat genital warts caused by human papillomavirus (HPV). The mechanism of this activity is not entirely clear; it is thought that the compound is effective due to its cytotoxic properties, disrupting viral replication by killing the host cells, whereas direct influence on HPV is ambiguous.[22] The compound inhibits the polymerization of tubulin for microtubule assembly, halting the cell cycle during mitosis. Its application in oncology, however, is impeded by side effects. The semi-synthetic glycoconjugates of podophyllotoxin, etoposide and teniposide (**Figure 3**) are DNA topoisomerase II inhibitors. They do not possess the toxicity of podophyllotoxin and are applied as chemotherapeutics against certain forms of leukemia and other cancers.[23]

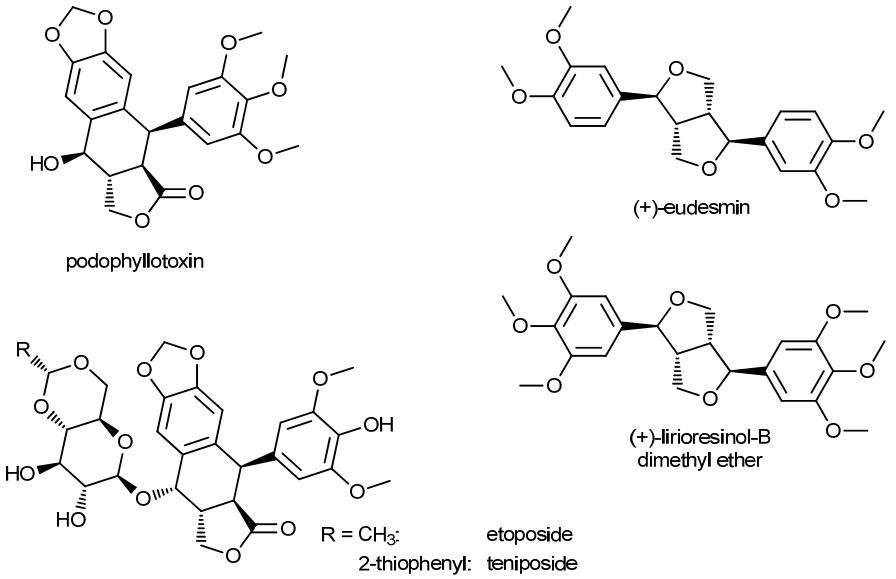
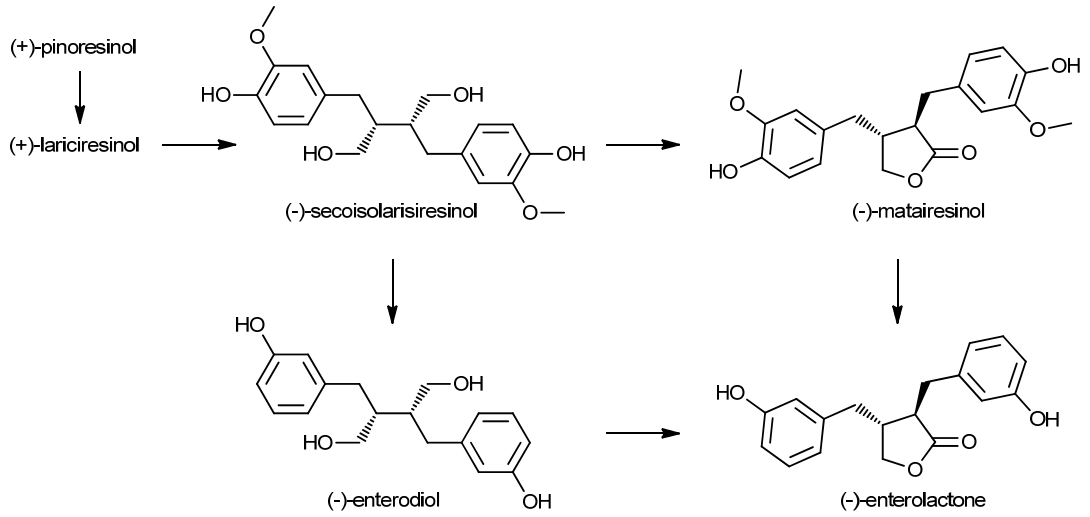


Figure 3: Pharmacologically relevant lignans.

Plant-derived lignans in food are metabolized by the mammalian intestinal microflora, with enterolactone (**Scheme 4**)[24] as the predominant end-product.[25]



Scheme 4: Proposed pathway for the metabolism from (+)-pinoresinol. In the source[24] for this scheme, the absolute stereoconfigurations of (-)-matairesinol, (-)-enterodiol and (-)-enterolactone (as well as the relative configuration of (+)-lariciresinol, **Scheme 3**) are in disagreement with literature consensus (registration with Chemical Abstracts Service (CAS)). Here, the structures of these compounds are depicted according to CAS.

High levels of lignans and their metabolites in humans have been shown to be inversely correlated with diseases such as cancer and cardiovascular disease (CVD),[24-26] in support of the common notion that vegetables and fruits constitute a healthy diet.
The suggested protective mechanism in the case of CVD is that these compounds have anti-atherogenic effects, that is, they reduce the formation of atheromas (accumulations of material at the inner lining of the arterial walls) by lowering plasma and liver cholesterol levels (e.g.: (+)-sesamin and (+)-asarinin) and behaving as platelet activating factor (PAF) antagonists (e.g.: (+)-eudesmin (also called (+)-pinoresinol dimethyl ether) and (+)-syringaresinol dimethyl ether (also called (+)-lirioresinol-B dimethyl ether), **Figure 3**).[27-28] As the effects of furan-type lignans on inflammation and the cardiovascular system are key to this work, a more detailed introduction to these disorders shall be presented further below (section A.2, page 28).

Research in this rather broad field of (phyto)chemistry is growing considerably. A simple SciFinder topic search using the term "lignan" reveals 1836 reference hits for the five-year period of 2000-2004, 2844 hits for 2005-2009, and 3952 hits for 2010-2014, i.e. the publication output related to the topic has roughly doubled within a decade.

A.1.2 **Synthetic Approaches to Lignans**

As a result of their physiological activity, lignans have been the subject of many studies to prepare them by chemical synthesis or biotechnological means. Following a discussion related to the biotechnology in the field, an overview of chemical approaches toward lignans of the furan-type (with a focus on concise preparation plans) is presented. This is followed by an outline for the furofuran- and dibenzylbutyrolactone-type as their closest structural relatives. Some of the strategies toward aryltetralin and dibenzylbutyrolactone,[29] as wells as dibenzocyclooctadiene[29-30] lignans have been reviewed in the literature, in addition to approaches to neolignans[31] and compounds termed (inconsistently with the IUPAC[4] recommendations) coumarinolignans, flavonolignans, and stilbenolignans.[32]

Lacking an active site, the dirigent protein (**Scheme 2**, in section A.1.1, page 14) is, as mentioned above, not capable of producing phenylpropanoid radicals on its own, requiring the presence of an enzyme with oxidoreductase activity (oxidases or laccases with molecular oxygen as the electron acceptor, or peroxidases with H_2O_2). These do not confer chiral information to the reaction; in fact, the radical-generating enzyme can also be replaced by other one-electron transferring reagents such as flavin mononucleotide or ammonium peroxydisulfate.[7-8] This separation of radical generation from the template-mediated enantioselective dimerization to lignan molecules consequently means that not only the rate of dimerization depends on the concentration of the DP: it also impacts the degree of regioselectivity and optical purity which can be achieved. This is because DP-catalyzed dimerization competes with unselective reaction of free radicals in solution.[33] In the original report[8] by Lewis and co-workers, conditions in *in vitro* experiments were established which avoided saturation of the DP (among other experiments, 770 nM DP was incubated with 4.1 nM laccase from *F. intermedia*, corresponding to a molar ratio of 188 : 1, together with 2 mM partially deuterated coniferyl alcohol in a total volume of 0.25 mL), resulting in enantiopure (> 99 % e.e.) (+)-pinoresinol, while less favorable ratios resulted in the appearance of the (-) enantiomer.[a] These observations were also confirmed by subsequent kinetic studies.[33] Although not explicitly stated as such, earlier reports of a stereoselective (+)-pinoresinol synthase[34-35] (by the same research group) were effectively revised in this paper, yet this putative enzyme re-surfaced in one later publication (as isolated from *Dysosma tsayuensis*, where it was characterized as having a molecular weight of 21.5 kDa,[36] coinciding with that of the DP monomers of 23 to 25 kDa[9] from *F. intermedia*).
With a biotechnological access to furofuran lignans, these compounds might then be transformed further to others types, including furan lignans by e.g. hydrogenation of one of the tetrahydrofuran rings with Perlman's catalyst[37] or simply by palladium on charcoal.[38] Accordingly, it has been suggested that the DP-methodology could be an alternative to chemical synthesis of this type of natural products.[39-40] However, there are some severe roadblocks in the way of general application. The substrate scope of the DP is very narrow; in fact, coniferyl alcohol has been cited as the only known substrate of DPs from different plants,[40] and even the closely related sinapyl alcohol was not a ligand to the DP from *F. suspensa*, although, if the general biosynthetic view is correct, there should be other naturally occurring DPs accepting different cinnamyl alcohols also. Enantiocomplementary DPs were identified and cloned into *Solanum peruvianum* (the genus which tomato plants belong to)

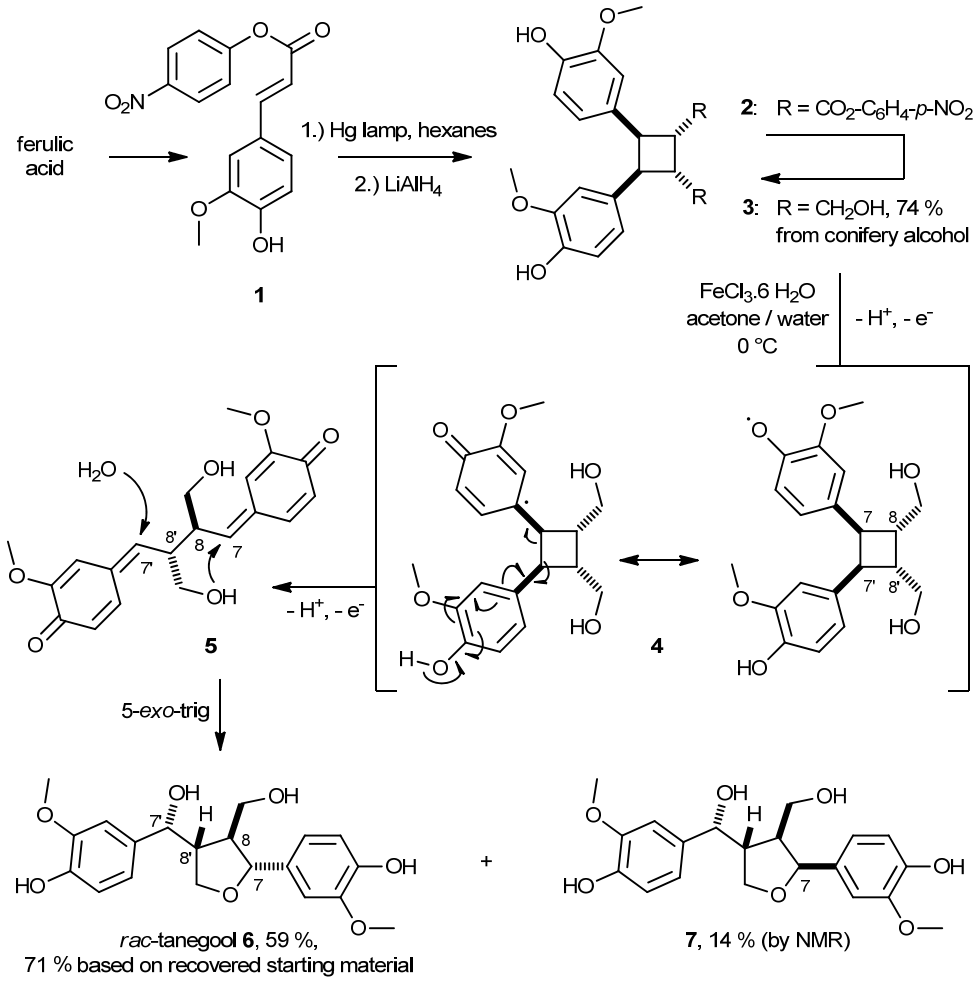
[a] A more precise statement of this is not possible because there appears to be a calculation consistency in the cited paper.

for cultivation in suspension cell culture,[41] and a certain understanding of the protein structure governing enantioselectivity is available as it was possible to reverse the coupling mode (i.e. the enantioselectivity for the product lignan) of a (+)-selective DP by exchanging an amino acid sequence with that from a (-)-selective DP.[42]

While much attention was given to the initial publication, this *in vitro* biotechnological approach has not yet turned into a practical method for synthesizing lignans during the intervening two decades (but for an example of a specific lignan potentially producible in hairy root culture, see section A.4, page 42). This is likely due to much more fundamental reasons related to their chemical structure: any oxidative phenol coupling requires a free hydroxy group in the *para* (or possibly also *ortho*) position for quinone formation if an 8-8' bond is to be formed, according to the resonance structures shown in **Scheme 3** (in section A.1.1, page 14), thus severely limiting of scope of compounds that could be synthesized. In the absence of such a hydroxy group, the radical could theoretically also be generated by homolytic cleavage directly at the β position of the phenylpropanoid precursor which might then be stable long enough to be a substrate for the DP because the resulting radical is still delocalized (as long as it is generated from some form of conjugated cinnamyl derivative). But even if this could be achieved under conditions compatible with the protein, there is a second problem: any versatile method needs to be capable of incorporating two non-identical aryl moieties into the new lignan molecule, and this would require distinguishing somehow between the two monomers as they line up for *si-si* coupling. This might be feasible, too, by choosing from a set of certain mutant DPs—or even a completely different form of template, in which case the method would be inspired from biology but have otherwise little in common with the natural precedent—which have varying ligand affinities. But in this methodology, radical formation and dimerization are spatially separated into two distinct processes, which is an intrinsic problem because non-selective coupling of free radicals needs to be avoided. There is no solid evidence of the existence of a pinoresinol synthase where these two processes might happen in close proximity, staying clear of unselective coupling in the solution phase. Getting these multiple issues of chemo-, regio-, and stereoselectivity under control seems a rather daunting task at present. Therefore, the need to procure new lignan compounds to explore their physiological properties still calls for a chemical way of preparing them, at least for the foreseeable future.

Biosynthesis can actually serve as a blueprint for chemical synthetic plans as well. Moreover, individual reaction steps and the order of events can be changed, which is the case in very recent work by Lumb and Albertson.[43] As mentioned above, regio- and stereochemistry is important in the attempt to dimerize two molecules of precursor to a lignan compound. It would be helpful if these precursor molecules could be brought together by a regio- and stereoselective process, even if the immediate reaction product is not a substituted tetrahydrofuran but some other cyclic structure. Therefore, a suspension of *p*-nitrocinnamyl ferulate **1** in hexanes (thereby avoiding issues with olefin isomerization which happens predominantly in the solution phase)[44] was cyclized in a [2+2] head-to-head-photodimerization to cyclobutane **2**, representing such a cyclic compound (**Scheme 5**). This was subsequently reduced to bishydroxymethyl compound **3**. The most efficient oxidant for ring expansion then appeared to be $FeCl_3$.6 H_2O in water / acetone, affording predominantly the furan-type *rac*-tanegool **6** (59 %, 71 % based on recovered starting material), separable from mixtures of starting material and 7-epimer **7**. The mechanism was proposed to proceed in a radical or radical cation fashion (the radical variant *via* **4** and then bis-*p*-quinone methide **5** is shown in the scheme), and the resulting diastereoselectivity was likely to arise from steric repulsion in the open-chain intermediate **5**. The link to lignan biosynthesis and the idea of changing the order of events here is

that the cyclization of **5** to **6** is akin to the one which occurs in plants as well, but the (relative) configurations at C8 and C8' are already set up during the orbital-controlled photochemical reaction. Consequently, the 8-8' bond remains untouched thereafter.

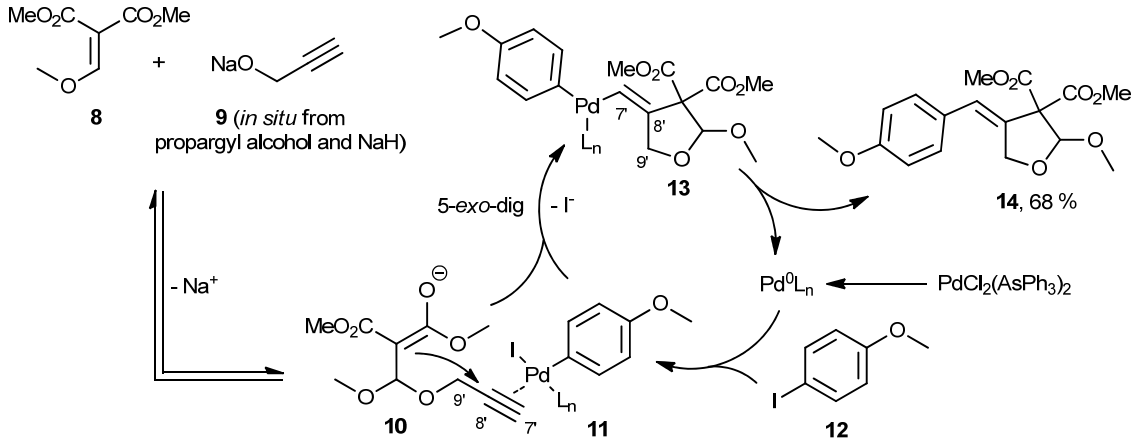


Scheme 5: Synthesis of *rac*-tanegool *via* photocyclization, $FeCl_3$-mediated oxidation and *in situ* 5-*exo*-trig cyclization.

Notably, when the hydroxymethyl substituents in intermediate **3** were switched into *trans* configuration (not shown), the 5-*exo*-trig cyclization occurred twice, with the second hydroxy group taking the role of a water molecule when compared to the above case, giving rise to *rac*-pinoresinol (48 %, 87 % based on recovered starting material). In the communication, the authors promised to explore asymmetric variants to this route; note that C_s-symmetric cyclobutane **3** is a *meso* compound and presumed intermediate **5** does not contain chiral information at C7 and C7' any more, opening the possibility to generate optically active tetrahydrofuran products from **3** if the 5-*exo*-trig reaction can be rendered enantioselective (bearing some resemblance to the natural, DP-mediated process).

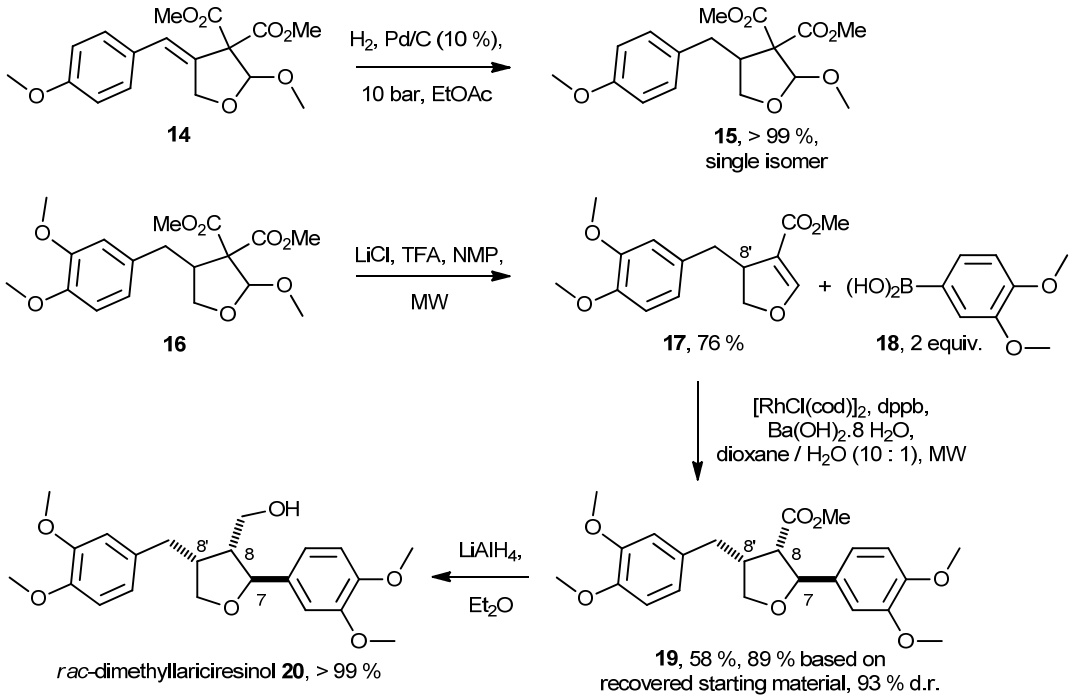
Bouyssi, Balme and co-workers developed a route[45-46] to trisubstituted furan lignans partly based on their previous work on multicomponent reactions.[47-48] The method makes extensive use of transition metal catalysis, beginning with a three-component cyclization which had been at work in a previous formal synthesis of a disubstituted furan lignan as well.[49] Therein, sodium propargyloxide **9** first adds to Michael acceptor **8** (**Scheme 6**). Next, intramolecular nucleophilic attack of the resulting enolate **10** to the triple bond, activated by organopalladium complex **11** (which originates from the oxidative

addition of aryl halide **12** to palladium(0)) takes place, according to the mechanistic rationale.[47-48] This 5-*exo*-dig cyclization results in intermediate **13**, and reductive elimination gives compound **14**.



Scheme 6: Palladium-catalyzed three-component reaction (shown as a particular example).

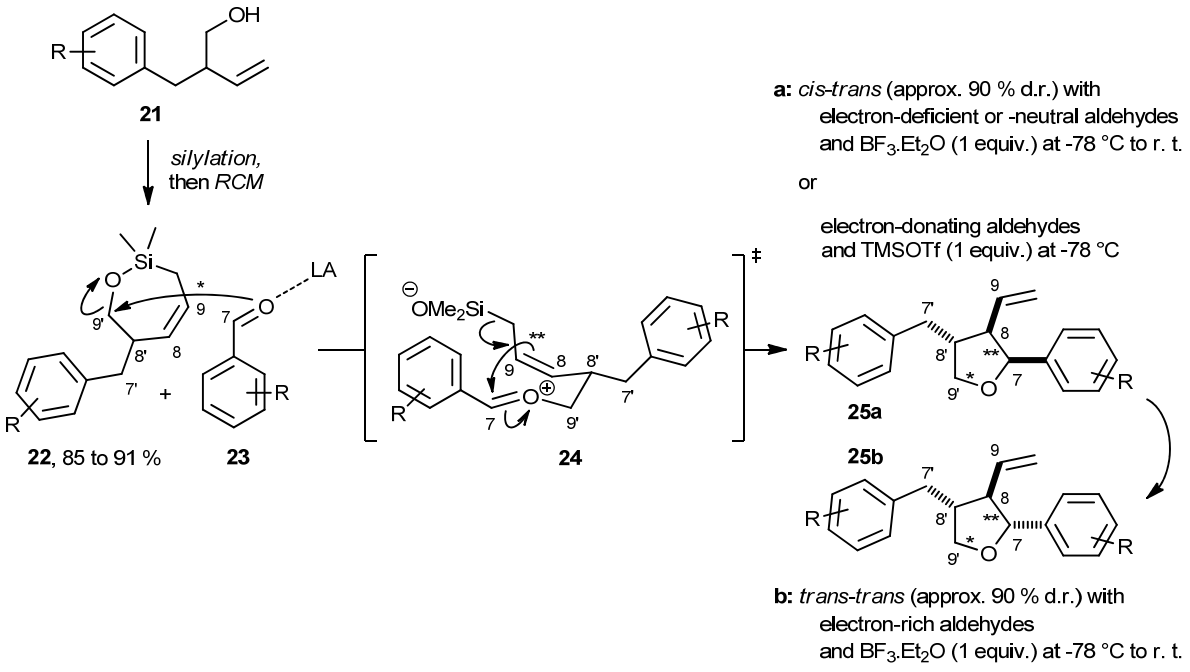
Catalytic hydrogenation then removes the double bond in **14** and gives **15** as a single, but unidentified, diastereoisomer (**Scheme 7**). Tandem decarboxylation-elimination of a similar diester **16** under microwave conditions affords dihydrofuran **17**. The authors then chose to employ a rhodium(I)-catalyzed Hayashi-Miyaura reaction[50] with aryl boronic acid **18** to incorporate the second aryl moiety in a 1,4-addition, occurring at the side of **17** which is less hindered by the 8' substituent. This yielded intermediate **19** in 58 % and predominantly *trans*-configured 7,8-relationship (93 % d.r.), and final reduction of the methyl ester gave *rac*-dimethyllariciresinol **20**.



Scheme 7: Synthesis of furan lignans. In the relevant literature, details for the steps to diester **16**[46] are not given, nor are those beyond **15**[45] (as far as the synthesis of lignans like **20** is concerned). Therefore, the scheme is discontinuous at **15** / **16**.

As this route is also divergent, it is possible to use intermediate **17** for swift variation of the substituent at C7. The furan-type lignans are racemic in this synthesis, but success at obtaining optically active final products would (only) hinge on efforts for asymmetric hydrogenation of **14**.

In the above example, dimethyllariciresinol (a compound which will play a pivotal role in this work, too) is *trans*-configured between C7 and C8, while it is *cis*-configured between C8 and C8'. Given its three chiral centers, there exist four pairs of enantiomers (all-*cis*, all-*trans*, *cis-trans*, *trans-cis*). The synthesis of all eight stereoisomers was indeed completed for the closely related lariciresinol (which has hydroxy in place of methoxy groups at both *para* positions)[18] by making use of Evans' oxazolidinone as a chiral auxiliary,[51] resulting in a somewhat lengthy overall route. It would be elegant if one could switch, at least to some extent, between different stereoconfigurations in a particular transformation, preferably by reagent control. An interesting approach in this direction was demonstrated by Marsden and co-workers.[52] Therein, oxasilacycloheptenes **22** were prepared in excellent yields by silylation of homoallylic alcohols **21**, followed by ring-closing metathesis with Grubbs' second-generation catalyst (**Scheme 8**). Intermediates **22** were then susceptible to Lewis acid-promoted ring cleavage, contracting to tetrahydrofurans **25** in the presence of aldehydes **23**. Following previous work by this[53] and the Cossy research group[54] in this area, the authors realized that the stereochemical result depended on the electronic properties of the aldehyde and the Lewis acid used. Electron-deficient benzaldehyde and -neutral hexanal, in the presence of BF_3, mainly gave *cis-trans*-configured products **25a** (yields around 70 %), while various electron-rich aldehydes mainly afforded *trans-trans* products **25b** (yields around 55 %) under otherwise identical conditions (approximately 90 % d.r. in both cases).

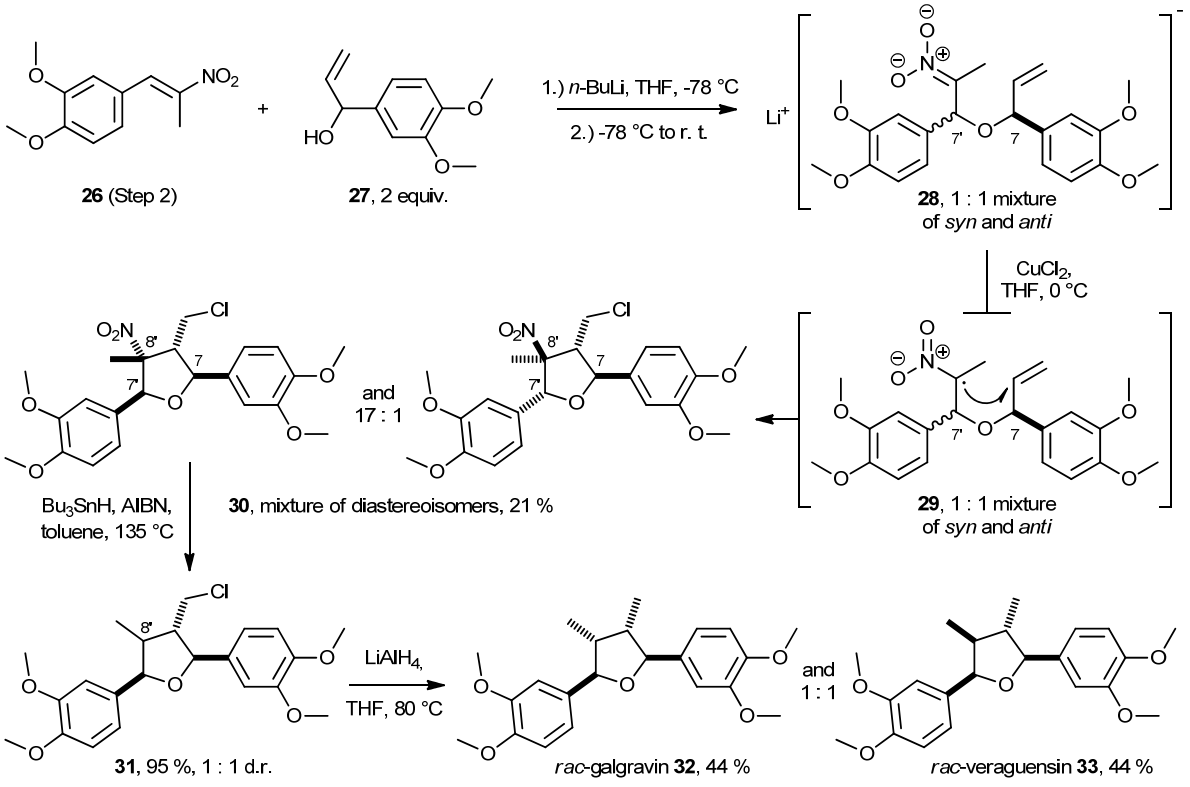


Scheme 8: Mechanistic rationale accounting for the stereoselectivity of tetrahydrofuran formation. Electron migrations and the corresponding bonds formed are marked as * and **, respectively.

In the cited work,[52] this was rationalized by assuming that the reaction, upon ring-opening, actually proceeds to the *cis-trans* product in both cases through a chair-like transition state **24** with the aryl and benzylic substituents equatorially disposed. While the reaction is then trapped in the 7,8-*cis*

arrangement of the five-membered ring with electron-deficient and -neutral aryl substituents at C7, subsequent Lewis acid-base interaction between BF_3 and the tetrahydrofuran oxygen results in C7-O bond cleavage in the case of electron-donating aryls, and re-formation of the bond gives the 7,8-*trans* product. That is to say, the initial *cis*-configuration is the kinetic product of the reaction, epimerizing to the thermodynamic *trans* product where the C7-C8 bond is allowed to rotate. When the Lewis acid was changed to TMSOTf, the temperature could be kept at -78 °C, such that epimerization did not take place (according to this model). Therefore, use of electron-donating piperonal also resulted in the formation of mainly *cis-trans* product (also around 90 % d.r. and approximately 75 % yield), thus switching the selectivity entirely with reagent control.
Compounds **25** were then subjected to OsO_4 / NMO dihydroxylation, cleavage with $NaIO_4$ and $NaBH_4$ reduction to afford furan-type lignans in exceptional (> 90 %) yield over these last three steps (not shown). This is also a case where asymmetry could be introduced by preparing homoallylic alcohols **21** enantioselectively, for instance by kinetic resolution. A somewhat similar strategy[55] to 7'-oxo furan lignans was developed later on by Rovis and Nasveschuk, based on the ring contraction of 1,3-dioxepins.

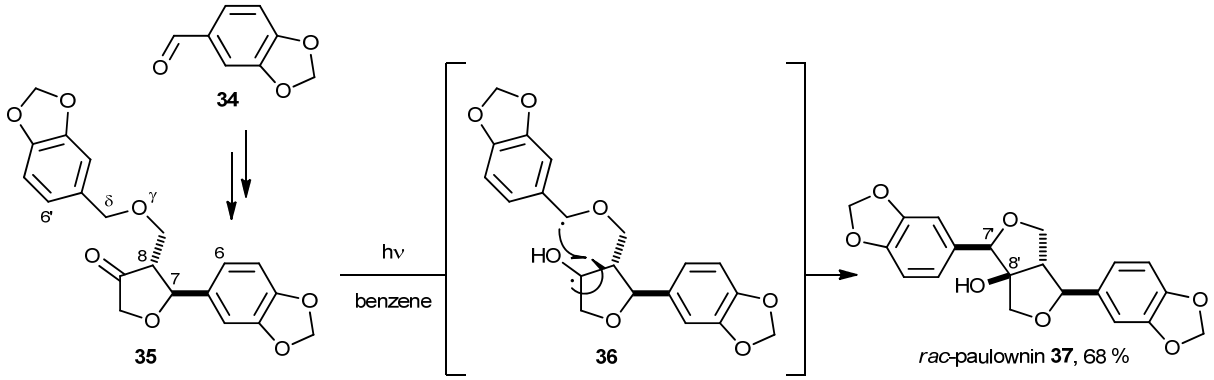
Creating a new short lignan synthesis is rather challenging because, as was pointed out, it is necessary to gain control over the stereochemistry of the reaction, and this difficulty is aggravated with highly substituted tetrahydrofurans. For example, all diastereoisomers of the tetrasubstituted furan-type lignan skeleton without 9(9')-oxygen (**Figure 1**, in section A.1.1, page 13) appear as known natural products,[56] and any methodology toward them is faced with the problem of establishing a target with four contiguous stereocenters, preferably as a single enantiomer. Jahn and Rudakov investigated the possibility of preparing such compounds *via* a tandem alkoxide conjugate addition-radical 5-*exo* cyclization procedure (**Scheme 9**).[57]



Scheme 9: Furolignans *rac*-galgravin and *rac*-veraguensin *via* tandem alkoxide conjugate addition-radical 5-*exo* cyclization.

This would be a very attractive approach because it is a very concise synthetic plan, and the starting nitroalkene **26**[58] and vinylbenzyl alcohol **27**[59] are readily accessible in good to excellent yields by Henry reaction and Grignard addition, respectively. Moreover, starting material **27** can be obtained in high optical purity by a number of methods[60-62] (this aspect will be discussed in more detail in section B.1.1, page 44), which would render the synthesis asymmetric if diastereocontrol over the remaining chiral centers could be established.
To this end, deprotonation with *n*-BuLi and conjugate addition of **27** to **26** furnished nitronate **28** which was shown to be a 1 : 1 mixture of *syn* and *anti* isomers with regard to the aryl substituents in positions 7 and 7' (relevant bonds emphasized in **Scheme 9**). However, subjecting this mixture immediately to an oxidant gave intermediate radicals **29**, where *syn*-**29** cyclized more efficiently to **30**, whereas *anti*-**29** was mainly trapped as an acyclic halonitroether (not shown) under certain conditions. In the case of $CuCl_2$ as the oxidant and THF as the solvent at 0 °C, the cyclization proceeded with low yield (21 % based on starting nitroalkene **26**) but high stereoselectivity (17 : 1 ratio in favor of the isomer as shown) to product **30**. Unfortunately, when removing the nitro group, the configuration at C8' could not be retained in **31** under radical reduction conditions, eventually furnishing a separable 1 : 1 mixture of *rac*-galgravin **32** and *rac*-veraguensin **33**.

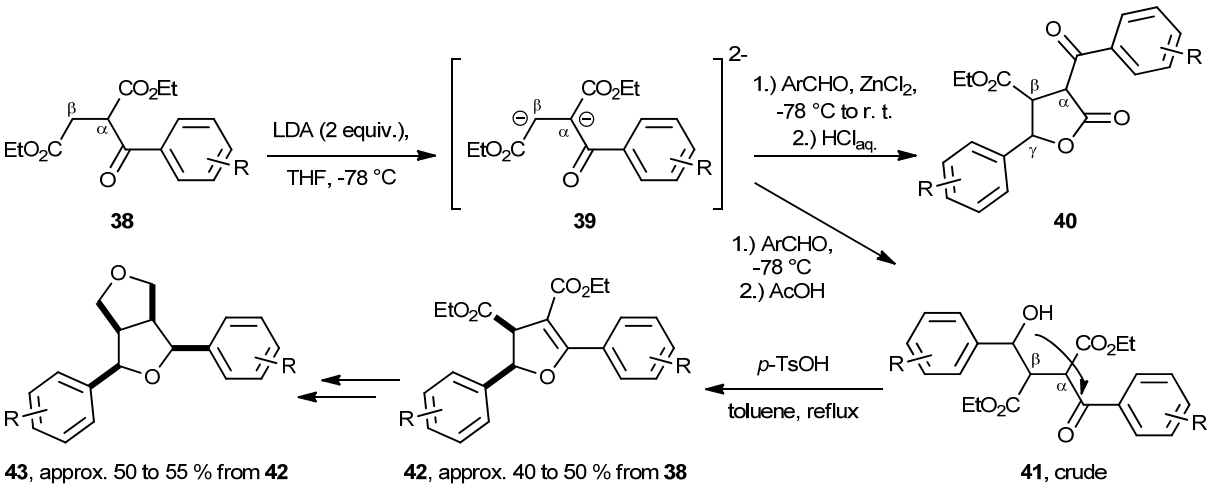
Kraus and Chen developed a strategy for the furofuran lignan *rac*-paulownin **37**,[63] in which piperonal **34** was elaborated to cyclic ketone **35** (**Scheme 10**) in which the aryl and piperonyloxmethyl substituents (C7 and C8) were in *trans* configuration.



Scheme 10: Synthesis of *rac*-paulownin using the photochemical Norrish-Yang cyclization.

The key step was then a Norrish-Yang cyclization to **37** in deoxygenated solvent with 68 % yield (based on recovered **35** and approximately 90 % completion of the reaction). The classic Norrish-Yang cyclization leads to 4-membered ring systems (cyclobutanes, oxetanes and azetidines) by γ-hydrogen abstraction of a photoexcited carbonyl group *via* a 1,4-diradical.[64] Where this is not possible, δ-hydrogen abstraction **36** can occur, forming the 5-membered product as shown. Although the authors reported complete kinetic stereoselectivity with the substituents in 7',8'-*cis* configuration as the sole product, later studies by Ishibashi and co-workers (conducted with optically active **35** and using rose bengal as a photosensitizer under modified illumination conditions) found that the 7'-epimer was also present in ratios of 9 : 1.[65] The diastereoselectivity of the cyclization also eroded drastically (down to about 3 : 2) when methoxy substituents were placed at the 6 or 6' position of the piperonyl moiety.

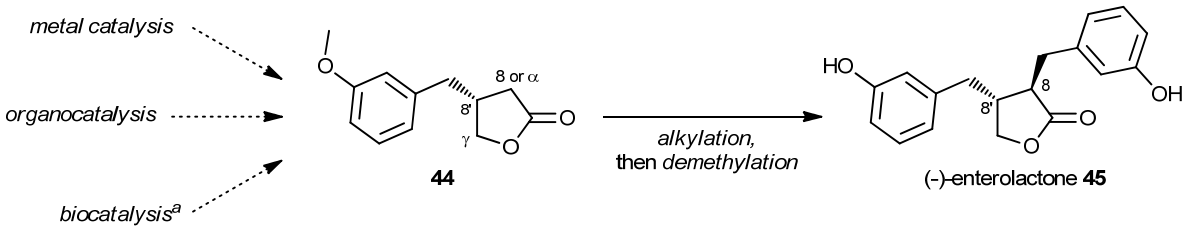
Pohmakotr and co-workers reported the synthesis of substituted α-aroyl-γ-butyrolactones **40** (**Scheme 11**) from α-aroylsuccinic esters **38**.[66]



Scheme 11: Furofuran-type lignans *via* vicinal dianions.

Based on this work, dihydrofurans **42** could be prepared under similar reaction conditions, involving the use of two equivalents of LDA for double proton abstraction to form vicinal dianions **39**, which then added to benzaldehydes at the otherwise less acidic but sterically more accessible β position, affording adducts **41**.[67] Without purification, these intermediates then underwent acid-catalyzed cyclization with sufficient diastereoselectivities (about 5 : 1) in favor of the *cis* products **42** and acceptable yields (around 40 to 50 % in most cases) after isolation and purification from *trans*- and other byproducts. Catalytic reduction with Pd/C was then completely *syn*-selective, which was followed by reduction of both esters with $LiAlH_4$ and treatment of the resulting diols with *p*-TsCl in pyridine to afford furofuran-type lignans **43**, typically between 50 and 55 % yield from **42**.

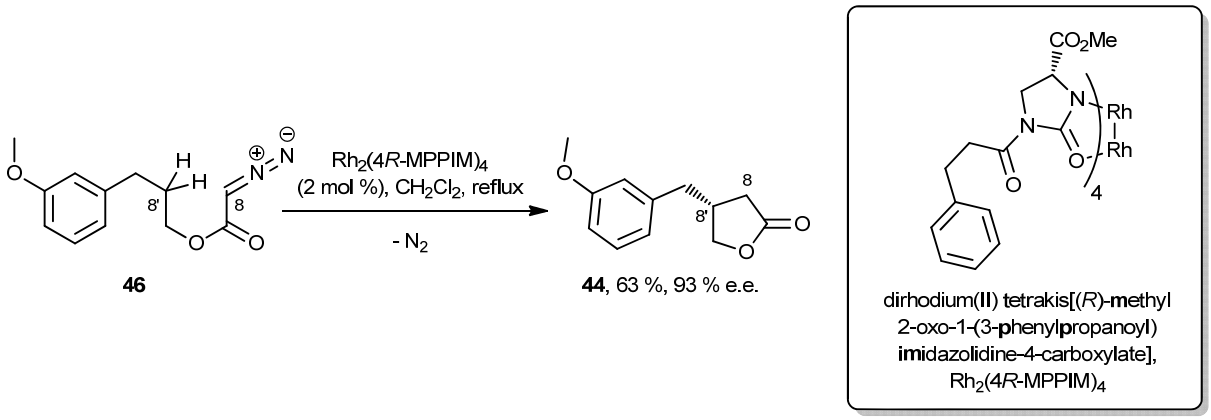
In the case of enterolactone **45**, an interesting comparison is possible between metal-, organo-, and biocatalytic methodologies. Valuable precursors for such 8,8'-*trans*-dibenzylbutyrolactone-type lignans in general are 8'-substituted γ-butyrolactones (intermediate **44** in the case of (-)-enterolactone), since base-mediated alkylation of the α-position proceeds diastereoselectively under good substrate control (> 95 : 5 *trans* selectivity, **Scheme 12**).[68-69]



Scheme 12: Different approaches to (-)-enterolactone *via* intermediate **44**. [a] *Cf.* text regarding the stereochemistry of the biocatalytic approach presented below.

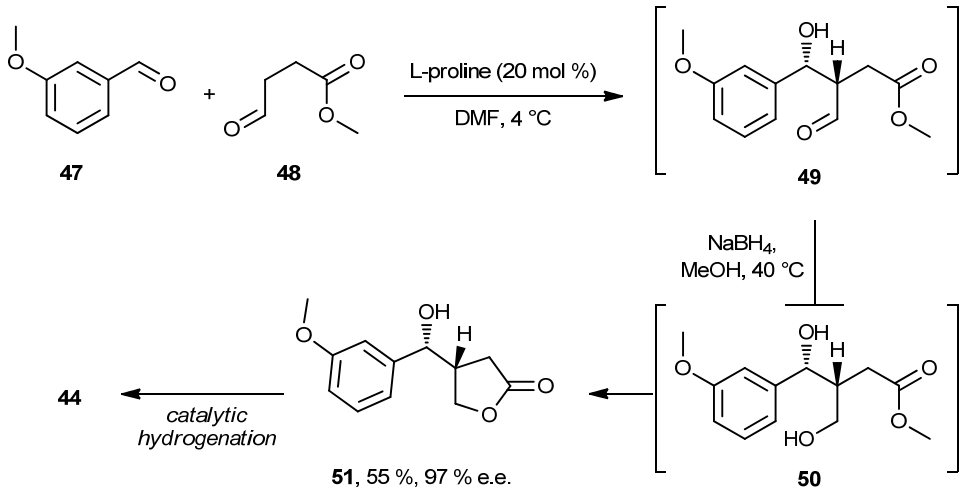
In a metal-catalyzed approach[68, 70] to **44**, Doyle and co-workers prepared diazoacetate **46** from the corresponding alcohol, diketene and mesyl azide. In a screening of dirhodium(II) catalysts, chiral complex Rh_2(4*R*-MPPIM)$_4$ proved to be the catalyst of choice for it afforded good yield (63 %) and high enantioselectivity (93 % e.e.) in a C-H activation-ring closure. In the model for this reaction,[71] the

dirhodium complex displaces dinitrogen from C8 to give a carbene complex, and with concomitant dirhodium dissociation, one hydrogen migrates from the 8' to the 8 position while the C8-C8' bond is formed and the catalyst is released (**Scheme 13**). The *N*-acylimidazolidinone ligand was synthesized from D-asparagine and then converted to $Rh_2(4R\text{-MPPIM})_4$ with $Rh_2(OAc)_4$, therefore the method makes both enantiomers of enterolactone-like lignans accessible with proper choice of ligand starting material.



Scheme 13: Enantio- and regioselective ring closure to chiral intermediate **44**.

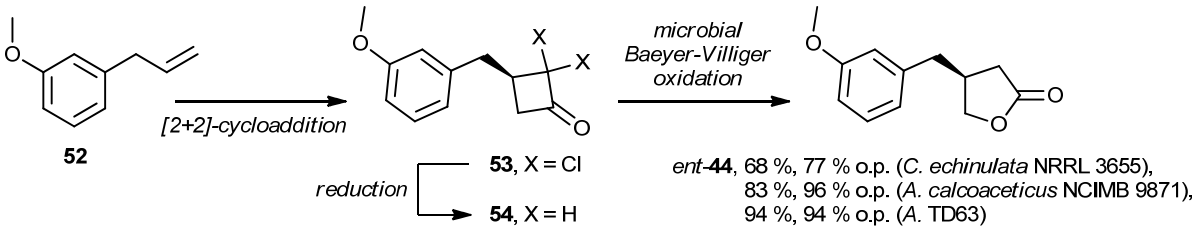
Amino acids and derivatives thereof can also perform enantioselective catalysis directly. L-Proline was used in the organocatalytic synthesis[69, 72] of **44** by Hajra and co-workers. Slow addition of oxobutyrate **48** to aldehyde **47** in the presence of 20 % organocatalyst gave aldol adduct **49**, which was reduced immediately thereafter to **50**, resulting in spontaneous lactonization to **51** in 55 % yield and 97 % e.e. (**Scheme 14**). Pd/C reduction of the benzylic hydroxy group then afforded intermediate **44**. Also this method allows both enantiomers of enterolactone-like lignans to be prepared.



Scheme 14: Enantioselective aldol addition to chiral intermediate **44**.

Baeyer-Villiger oxidation of cyclic prochiral ketones gives rapid access to optically active lactones for which, unlike with methods based on non-dynamic kinetic resolution of racemic substrates, the theoretical yield is 100 % (representing a desymmetrization process). The asymmetric insertion of oxygen into the ketone may be carried out with e.g. binol-derived phosphoric acids and H_2O_2[73] or Sc-

(*N*,*N*'-dioxide) complexes with *m*-CPBA[74] as the oxidant. Alternatively, enzymatic oxidations have been intensively studied.[75-77] Furstoss and co-workers described the use of whole-cell systems such as of the fungus *Cunninghamella echinulata* and Gram-negative *Acinetobacter* strains expressing flavin-dependent Baeyer-Villiger monooxygenases (BVMOs) for preparative biocatalytic transformation.[78-79] Cyclobutanone **53**, which can be obtained from allylbenzene **52** by [2+2]-cycloaddition with trichloroacetyl chloride, was followed by reduction to **54** with Cu-Zn couple.[74] This was then converted to *ent*-**44** in buffer at pH 7 (**Scheme 15**).



Scheme 15: Enantioselective Baeyer-Villiger oxidation to *ent*-**44**. O.p.: optical purity.

Both yields and enantioselectivities were high, yet this example points to a common issue in biocatalysis: the configuration of the reaction products (and the stereopreference for the reactants in the case of chiral substrates) is determined by the chiral environment in the active site of the enzyme, which is not readily mutated to equally active and selective catalysts to give the optical antipodes. Notably though, enantiocomplementary BVMOs were successfully identified for other arene substitution patterns,[80] and this area of biocatalysis experiences rapid development.

In summary, these approaches of lignan synthesis all have their virtues and issues. One important aspect of the work in this thesis was to develop a divergent (or modular) approach to furan-type lignans. The synthetic plans toward this aim and the literature relevant to it are presented in section A.4 (page 42), and the results discussed in section B (page 44).

A.2 **Cardiovascular Disease**

In its Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2020,[81] the World Health Organization (WHO) addressed the issue of cardiovascular disease (CVD), i.e. health issues associated with the heart and the circulatory system of the blood, as the number one cause of death globally. About 17.5 million people died from CVD in 2012, representing 31 % of all global deaths: of these, an estimated 7.4 million were due to coronary heart disease (CHD) and 6.7 million were due to stroke.[82] The WHO also points out that over three quarters of CVD deaths take place in low- and middle-income countries. Meanwhile, in the United States, the 2015 update of the Heart Disease and Stroke Statistics by the American Heart Association noted that coronary heart disease was the cause of about 14 %, and stroke of about 5 % of all deaths in 2011; total CVD accounted for 31 %.[83] The European Cardiovascular Disease Statistics 2012 by the European Heart Network and the European Society of Cardiology attributed 47 % of all deaths in Europe, and 40 % in the EU, to CVD.[84] It was estimated that the overall cost to the EU economy amounts almost €196 billion a year, roughly half of which are health care expenses and a quarter is due to productivity losses.

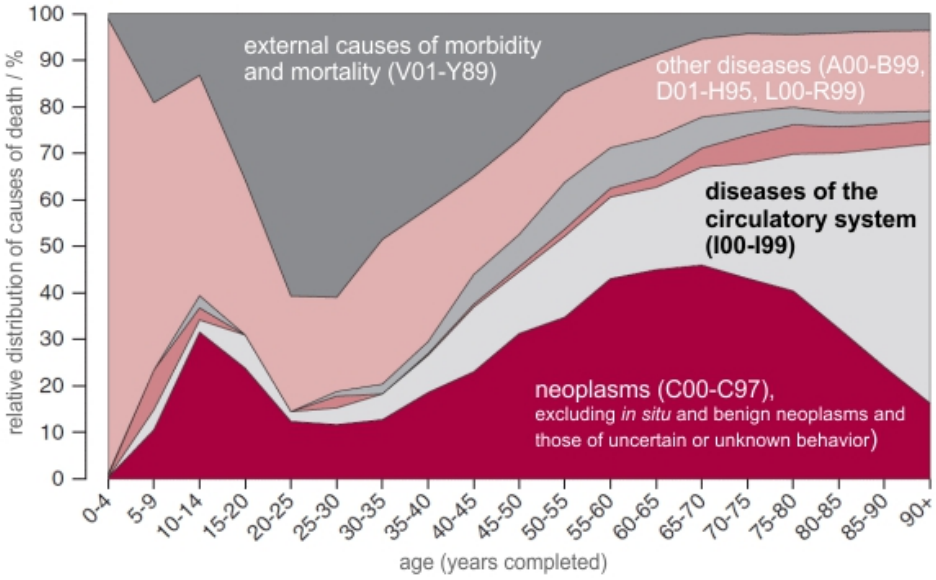


Figure 4: Distribution of causes of death in Austria in 2014, with ICD-10 codes. *Image adapted from Statistik Austria, 2015*.[85]

Although CVD-related mortality has generally declined since the beginning of the century in both of these regions, its impact on society evidently remains high. Moreover, data such as those compiled by Statistik Austia[85] show that the proportion of diseases of the circulatory system becomes more pronounced with age (**Figure 4**). In the elderly, CVD-related mortality outcompetes cancer as the leading cause of death. Arguably, this is additional reason for concern in light of the general demographic development.

In the following introduction to this topic, it will be viewed from two general vantage points: the causes and prevention of cardiovascular events (next section A.2.1, page 29), and the complications in and aftercare of convalescent patients following such an event (section A.2.2, page 35). The pharmacology-related results (section B.2, page 94) will then take the same perspective.

A.2.1 **Atherosclerosis and Hypercholesterolemia**

Atherosclerosis is by far the most frequent underlying cause of coronary artery/heart disease (when it affects the arteries supplying the heart muscle), carotid artery disease (when it affects those supplying the brain) and peripheral artery disease (when it affects the extremities).[86] Not to be confused with arteriosclerosis (which is the stiffening or hardening of the artery walls, a consequence of atherosclerosis), it is a focal disease process which is characterized by the formation of lesions at the blood vessel walls. Vessels have three distinct layers: the intima, the media, and the adventitia, separated by elastic lamina.[87] Lesions are slowly growing expansions (over decades) of the arterial intima, i.e. the normally narrow layer adjacent to the media and comprising the endothelial cell-monolayer on the lumen-side of the vessel. These expansions contain lipids, cells and extracellular matrix.[88] Atherosclerosis occurs predominantly at sites where the otherwise laminar blood flow is disturbed, and this process alone does not necessarily lead to major symptoms if the lumen remains (mainly) preserved. However, it can cause thrombus formation, precipitating clinical events such as angina pectoris (chest pain due to myocardial ischemia, the reduced blood supply of the heart muscle), myocardial infarction (heart attack) or stroke. The events at the histological level leading to thrombosis shall be briefly outlined.

At the earliest stages, apolipoprotein B-containing lipoproteins (apoB-LPs) accumulate below the endothelial layer (**Figure 5**).[89] They consist of cholesteryl fatty acyl esters and triglycerides, surrounded by phospholipids and proteins. Part of these apoB-LPs makes up low-density lipoprotein (LDL) which is therefore considered atherogenic, and hypercholesterolemia—excess levels of plasma cholesterol which is normally a vital component of cell membranes and a precursor of bile acids, steroid hormones and vitamin D[90]—is therefore a key risk factor, among others such as hypertension and diabetes. If cholesterol levels did not exceed 150 mg / dL (in adults), symptomatic disease would be rare.[86]

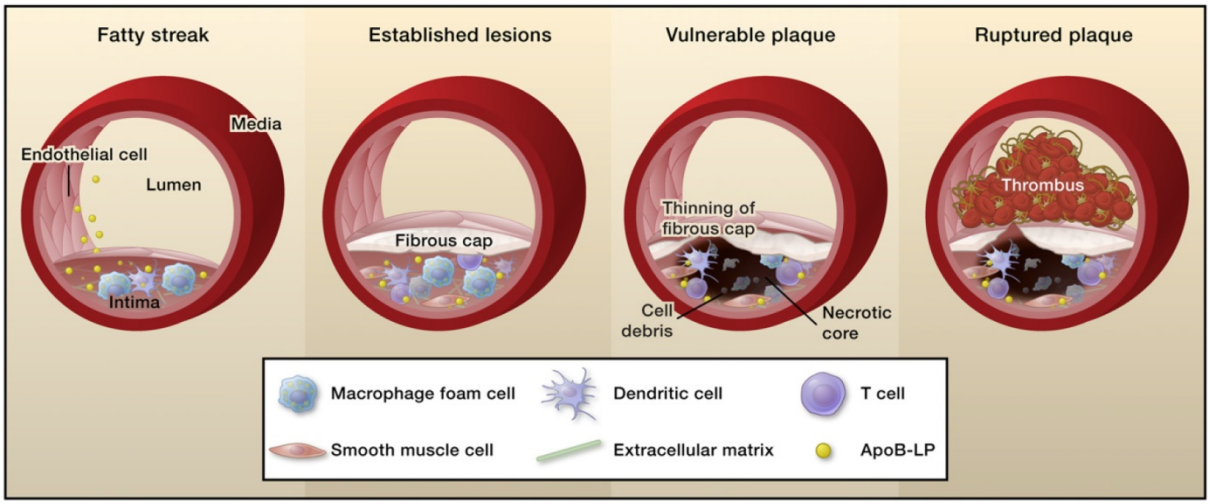
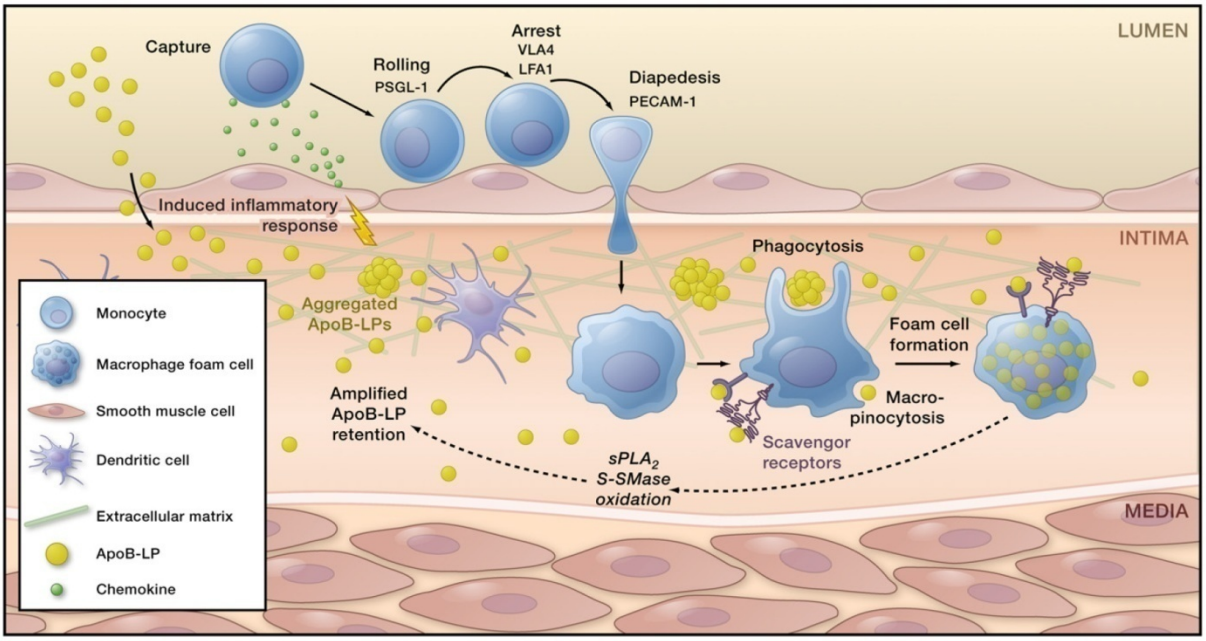


Figure 5: Successive stages of atherosclerosis. *Image taken from Tabas and Moore, 2011.*[88]

ApoB-LPs trigger the overlying endothelial cells to release chemokines to the lumen, which in turn bind to receptors on monocytes in the plasma (**Scheme 16**).[91-92] This is an inflammation response, which causes the monocytes to adhere to the endothelium above the lesion and then enter the intima below (diapedesis).[93] There, differentiation factors stimulate their differentiation into macrophages and dendritic cells.[94-95] Macrophages begin to ingest apoB-LPs, and hydrolyze and transesterify the cholesteryl esters, at which stage they are called foam cells.

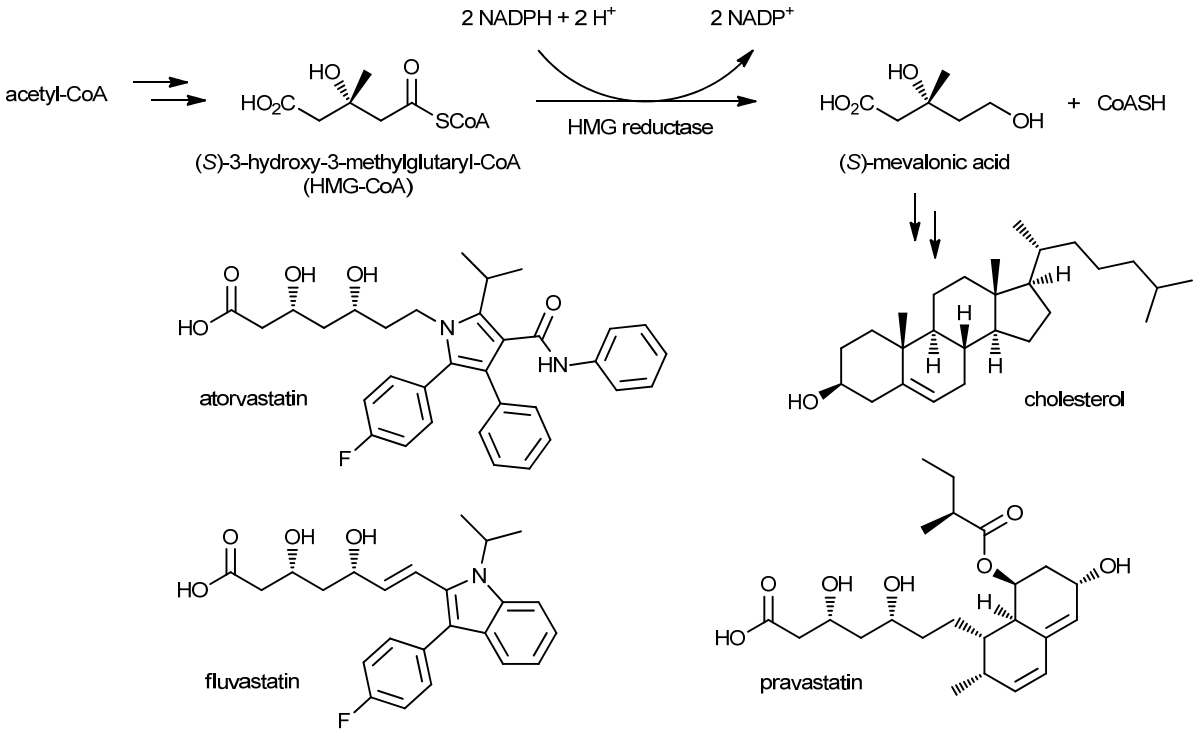


Scheme 16: Infiltration of the intima by monocytes. *Image taken from Tabas and Moore, 2011.*[88]

Atherosclerosis is a non-resolving inflammatory condition, which means that although the monocytes have been sent to the fatty streak on the arterial wall (from which the lesion developed) in order to remove apoB-LPs, it continues to accumulate material instead. While these foam cells are important to morphological changes of the developing atherosclerotic plaque,[88] they make up only about 8 % in volume of an average advanced plaque at more than 75 % stenosis. Approximately 16 % of such a plaque consists of a necrotic, lipid-rich core, 8 % is calcium, while the largest part, 68 %, consists of fibrous tissues.[86] This means that the simplistic picture that macrophage-derived foam cells contribute to the plaque just by their volume would be incorrect. Rather, they undergo apoptosis, and at early stages of atherosclerosis they are removed by other macrophages (phagocytosis). At advanced stages, they are not cleared any more (defective efferocytosis), disintegrate instead and contribute to the destabilizing necrotic core that is filled with cellular debris and crystalline cholesterol.[96] Failure of this disposal mechanism is a critical feature of plaque development, but the reasons for it are not fully understood. Other processes degrade the fibrous cap which lies on top of the atherosclerotic plaque, leaving it vulnerable to rupture. Once this happens, procoagulant and prothrombotic factors from the intima come into contact with coagulation factors and platelets in the lumen, resulting in thrombus formation.[88]

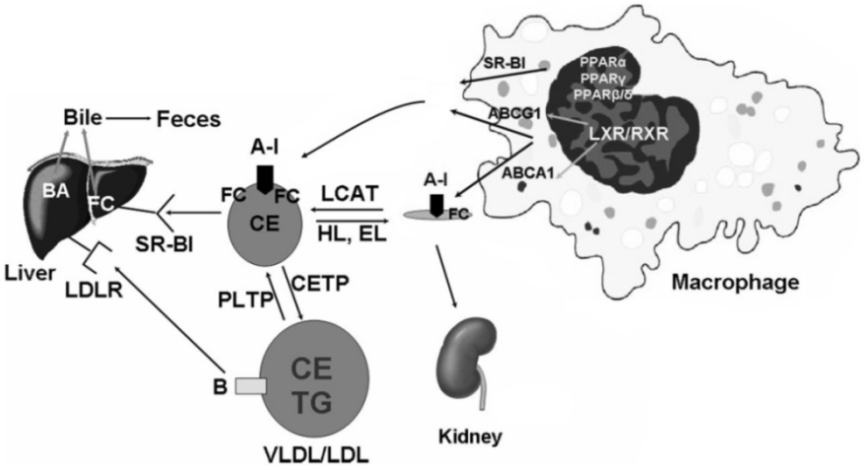
The most direct way to prevent atherosclerosis is to decrease apoB-LP retention in the intima by lowering apoB-LP levels in the plasma through changes in lifestyle.[97] Avoiding risk factors such as obesity, physical inactivity, insulin resistance and smoking would be effective at lowering the risk of lesion development and progression. Additionally, certain drugs (statins) are currently prescribed to reduce levels of endogenous cholesterol by inhibiting the hydroxymethylglutaryl reductase-mediated rate-determining step in its biosynthesis (**Scheme 17**),[98] because cholesterol from the diet does not influence plasma levels significantly and epidemiological data do not support a link between dietary cholesterol and CVD.[90] However, statins reduce cardiovascular events only by 20 to 40 %,[99-102] leaving a significant portion of untreated disease.[103] What is more, lesion initiation occurs in the early teens in Western societies,[88] and it has therefore been considered to direct therapeutic approaches to the

arterial wall, and the macrophages in particular, which could also have additive or synergistic effects when combined with realistic goals of lipid lowering.



Scheme 17: Statins inhibit cholesterol formation competitively by mimicking the natural substrate of HMG reductase.[104]

Aside from passive diffusion, macrophage cholesterol efflux occurs *via* different transporter proteins in the cell membrane, namely scavenger receptor class B type I (SR-BI), and two transporters of the adenosine triphosphate-binding cassette superfamiliy (ABCA1 and ABCG1, **Scheme 18**). When cholesterol leaves the cell through ABCA1, it can be taken up by lipid-poor apolipoprotein A-I (apoAI), or directly by mature high-density lipoprotein (HDL) *via* ABCG1 or SR-BI, and is then taken to the liver for metabolization and excretion.[105-106]



Scheme 18: Macrophage cholesterol efflux, reverse cholesterol transport and metabolism of cholesterol. FC: free cholesterol. CE: cholesteryl ester. TG: triglycerides. BA: bile acids. EL: endothelial lipase. HL: hepatic lipase. PLTP: phospholipid transfer protein. LCAT: lecithin-cholesterol acyltransferase. LDLR: LDL receptor. For the remaining abbreviations, *cf.* text. *Image adapted from Rader and Duffy, 2006.*[105]

It could therefore be beneficial to raise HDL or increase the rate of efflux from macrophages or their precursor cells, leading to lesion regression.[103] It is known that inhibition of the cholesterol ester transfer protein (CEPT) leads to an increase in HDL and a decrease in LDL. To this effect, CETP inhibitors were developed: anacetrapib[107] (by Merck) is currently in advanced clinical trials, while torcetrapib[108] (by Pfizer), dalcetrapib[109] (by Roche), and evacetrapib[110] (by Eli Lilly) had to be discontinued (**Figure 6**).

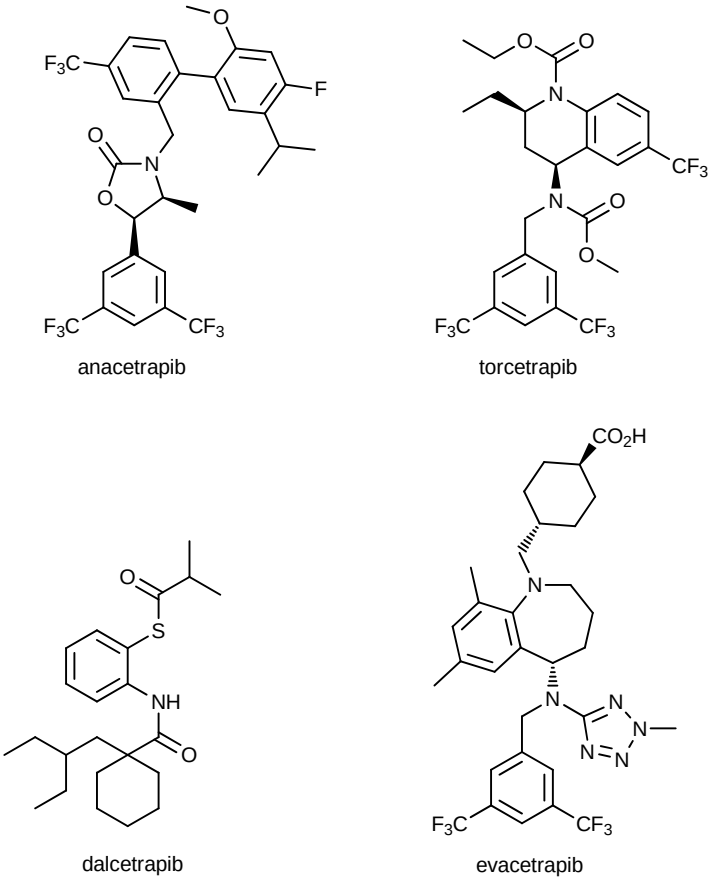


Figure 6: Inhibitors of the cholesterol ester transfer protein (CEPT).

Torcetrapib increased HDL but also raised systolic blood pressure as an off-target effect,[108] resulting in an excess of deaths and morbidity from cardiovascular endpoints in the group that received torcetrapib and atorvastatin, compared to atorvastatin alone. Dalcetrapib did not increase blood pressure, but the drug had no clinical efficiency either, despite its HDL-increasing effect.[109] Similarly, the insufficient efficacy of evacetrapib was made public very recently.[111] These disappointing results might cast some doubt on whether HDL and LDL levels should really be focused on, at least if they are to be influenced by CETP inhibition.

Increased removal of cholesterol from macrophages would be an alternative approach and is expected to have an overall anti-atherosclerotic effect.[112-113] In fact, the macrophage cholesterol efflux capacity in patients was shown to be inversely associated with carotid intima-media thickness and the likelihood of CHD, independent of HDL cholesterol levels.[114] In this study, macrophage cholesterol efflux was actually a better predictor for CHD than HDL cholesterol, lending further credit to the idea that its enhancement is a means of effectively treating atherosclerosis and preventing the otherwise ensuing cardiovascular events.

In the search for a new therapeutic of this kind, passive diffusion, which accounts for approximately 30 % of reverse cholesterol transport,[106] cannot be influenced by a drug, and SR-BI is not a good target because it mediates bidirectional flow of cholesterol and its overall contribution is only at 10 %.[106, 115] ABCA1 (with 25 %) and ABCG1 (35 %), thus accounting together for about 60 % of reverse cholesterol transport,[106] are driven by ATP[116] and promote unidirectional cholesterol flow to lipid-poor apoAI (ABCA1) and to HDL particles (ABCG1), respectively,[115] making them interesting targets. The beneficial effects of this likely include reduction of monocytosis-related inflammation, suppression of inflammatory signaling pathways in macrophages and the prevention of cholesterol- and oxysterol-induced efferocyte death,[103] thus being an effective treatment of atherosclerosis. It is known that agonists of the liver X receptors (LXRs) increase expression of apolipoprotein E, ABCA1 and ABCG1,[117] and cause redistribution of ABCG1 to the plasma membrane.[118] Furthermore, agonists of the peroxisome proliferator-activated receptors (PPARs), such as the antidiabetics pioglitazone,[119] rosiglitazone, and troglitazone (**Figure 7**),[120] increase ABC expression *via* the LXR/PPAR pathway. However, no drugs have been approved yet for atherosclerosis protection and prevention by specifically increasing macrophage cholesterol efflux as the mode of action. Therefore, compounds which display precisely this biological activity are interesting for further study, both as pharmacological probes and potential means for therapy that is complementary to lowering serum cholesterol levels.

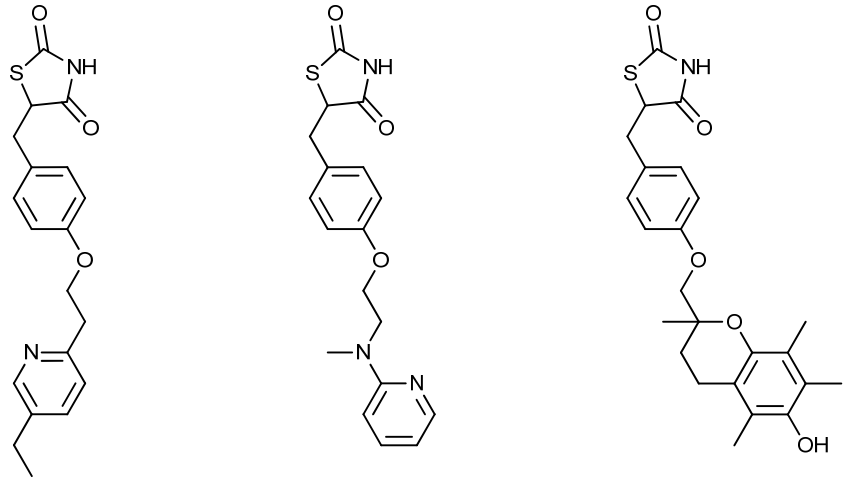


Figure 7: Antidiabetic drugs which are known to act as agonists of the peroxisome proliferator-activated receptors (PPARs).

A signaling pathway which has emerged as a potential target for the prevention and treatment of atherosclerosis is the activity of nuclear factor-kappa B (NF-κB). This is a family of structurally related proteins that are (dimeric) transcription factors.[121-122] NF-κB has a very complex biochemistry and is involved in a multitude of physiological and pathological conditions including immune response, carcinogenesis, angiogenesis and apoptosis.[123-125] Moreover, it participates in the expression of pro-inflammatory cytokines and has an important role in inflammatory responses. This transcription factor is a direct key activator of a range of mediators associated with atherosclerosis and restenosis. In fact, it is involved in all stages of atherosclerosis progression, from initiation to plaque rupture. For instance, the above mentioned recruitment of leucocytes (monocytes) to the vascular intima as an early stage of the disease depends on their chemotaxis (the stimulus-induced movement of cells) and their trans-endothelial migration mediated by chemokines and adhesion molecules.[126] Stimulation of

endothelial cells and expression of these proteins (e.g. vascular cell adhesion protein 1, VCAM-1) are in turn regulated by NF-κB signaling, and activation of this pathway occurs *via* stimuli such as tumor necrosis factor alpha (TNFα) and oxidized LDL.[125] As a result, specific NF-κB inhibitors may represent anti-atherosclerotic and anti-inflammatory treatments as well.

A.2.2 **Intimal Hyperplasia**

For patients who are running the risk of experiencing or have already suffered myocardial infarction, typically as a consequence of an atherosclerotic development, there exist two invasive procedures for treatment:[127] Coronary Artery Bypass Grafting (CABG) is the surgical procedure of reestablishing blood supply to the heart muscle by attaching a new conduit near the heart, thus bypassing the occluded vessel. Alternatively, Percutaneous Coronary Intervention (PCI) is an option, which involves the widening of a narrowed vessel by inserting and inflating a collapsed balloon (angioplasty), at which point a mechanical device (a stent) may also be placed to ensure that the vessel remains open. The preferred method of surgical intervention depends on the particular case. Both methods seem to have similar 10-year survival rates; CABG appears to be more effective in relieving angina and lead to fewer undesired repeated revascularizations, while PCI may have a lower risk of procedural stroke.[127] The U.S.-based National Center for Health Statistics states that 395 000 coronary artery bypass grafts and 454 000 coronary artery stents were placed in the U.S. in 2010.[128]
While these invasive methods have been used for decades and proved to be highly effective, a long-term complication in the wake of this sort of surgery may emerge which can ultimately lead to failure of vessel grafts and widened arteries. This is the pathological vascular remodeling known as intimal hyperplasia, which results in gradual narrowing of the vessel due to migration and proliferation of vascular smooth muscle cells (VSMCs) in the intimal region.[129] **Figure 8** shows the histological progression of neointima formation in a mouse model.

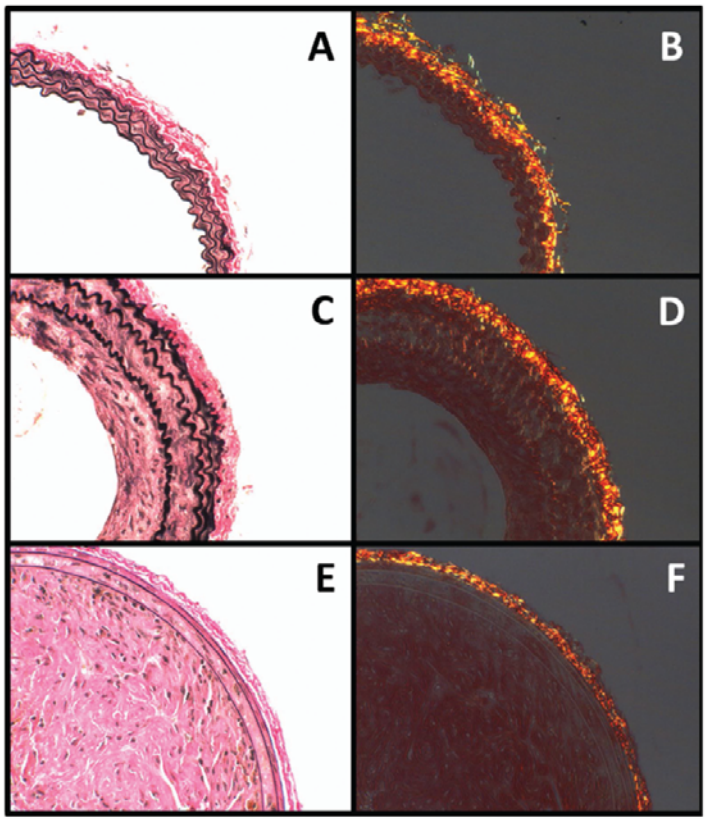


Figure 8: Sections of mouse carotid arteries using different staining methods. A, B: negative control. C, D: intimal hyperplasia on day 14. E, F: on day 28, with the lumen occluded completely. It should be noted that an optimized technique[130] was utilized to achieve rapid VSMC proliferation. *Image taken from Larson et al., 2012.*[129]

Intimal hyperplasia can occur as a consequence of mechanical trauma, immune injury, hypoxia and sheer stress.[129] Specifically, surgical handling appears to be a causative factor. In the case of CABG, the internal mammary arteries would be the best choice to serve as graft material; however, due to their limited availability, saphenous veins are frequently used instead in a typical medical institution.[131] Unfortunately, these veins are prone to hyperplasiate, in part because of the higher blood pressure and flow they are exposed to when used to replace arteries.[132] Likewise, mechanical injury due to ballooning with or without stenting, as in PCI, has a similar effect on the arteries themselves.[87, 133] In addition to diminished vessel lumen, the affected zone may develop atherosclerotic lesions and

result in thrombosis,[129] effectively eliminating the success originally achieved by the surgical intervention and raising new health risks for the patient.

The signaling pathways involved in this inflammatory response that eventually results in graft failure are rather complex. At the histological level, a key element is denudation damage to the endothelium[131] which lines the intima on the lumen side (**Figure 9**).

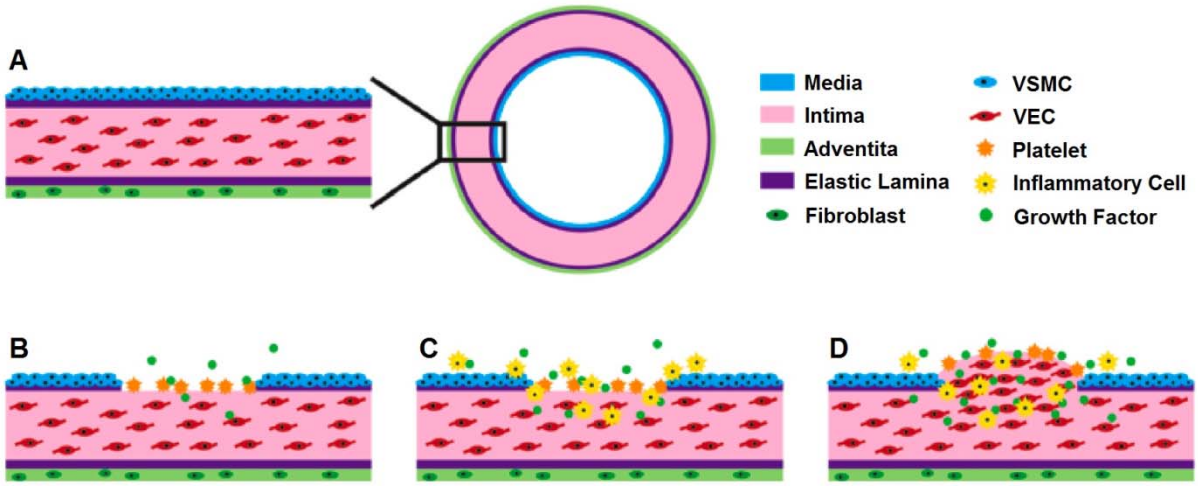


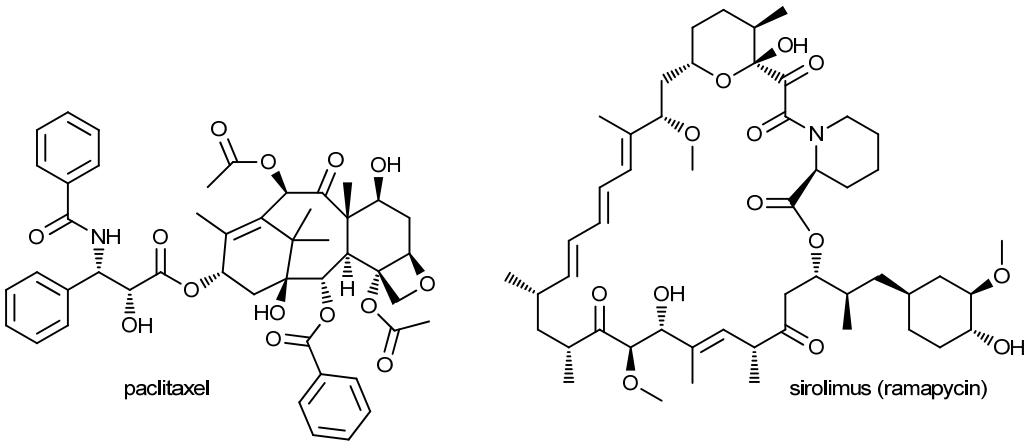
Figure 9: Healthy blood vessel (A) compared with successive stages of intimal hyperplasia (B, C, D), not to scale. *Image adapted from Panitch and Scott, 2014*.[87]

VSMCs normally reside in the collagen matrix of the media of the vessel[133] (which is the outward layer adjacent to the intima), but VSMC differentiation, proliferation and migration, mediated by vascular endothelial cells (VECs), can occur after CABG or PCI.[129] This is because endothelium denudation exposes the collagen matrix that lies underneath. Platelets can then bind, activate and secrete growth factors (including PDGF, platelet-derived growth factor). This process both recruits inflammatory cells to the site of injury and also stimulates VSMC proliferation and migration, as well as extracellular matrix synthesis.[87] The ultimate consequence is thus restenosis, i.e. a renewed occlusion of the blood vessel (note that initially, obstruction of blood flow had been due to an atherosclerotic thrombus following plaque rupture, the event which precipitated the clinical intervention in the first place—although the proliferation of phenotype-changing VSMCs in the plaque itself[134] has been implicated to play an important role in atherosclerotic progression, too).

In the case of PCI, a variety of methods exist to deal with the problem. Besides bare metal stents (BMS), drug-eluting (DES) and bioresorbable stents (BRS) have been developed, in addition to drug-eluting balloons (DEB), with their various virtues and disadvantanges.[87] A particularly interesting method is the placement of therapeutic devices on the *outside* of the vessel for drugs to diffuse from the adventitial side to the media and the intima. These perivascular approaches aim at suppressing intimal hyperplasia without causing the potential side effects that come from direct contact of the implant to blood and the endothelium.

For the more classic devices that elute drugs from the inside of the vessel for the purpose of proliferation inhibition, the anti-cancer compound paclitaxel[135-137] (found in the Pacific yew *Taxus brevifolia*, marketed by BMS) and the immunosuppressant sirolimus[138-139] (rapamycin, from *Streptomyces hygroscopicus*, by Pfizer) are in use **Scheme 19**. Compounds structurally related to rapamycin have also been introduced, such as 7-*O*-demethylsirolimus (by Elixir), everolimus (by Novartis), tacrolimus (by Astellas Pharma), umirolimus (by Biosensors International) and zotarolimus (J&J).[87] While paclitaxel is a cytotoxic compound which interferes with microtubule dynamics,[140]

rapamycin inhibits proliferation by its dedicated receptor, a protein kinase that regulates cell growth called mTOR (mammalian target of rapamycin).[141]



Scheme 19: Paclitaxel and sirolimus are used in drug-eluting stents.

Proliferation and migration inhibition by a chemical compound may not be cell-selective. Specifically, VECs can be affected in addition to VSMCs. This is a somewhat undesired effect because it would lead to reduced local healing of the graft.[131] The clinical significance of delayed endothelialization is subject to debate,[142-143] but concerns have been raised that DES which elute VEC proliferation inhibiting drugs like paclitaxel[144] or sirolimus[145] lead to an increased rate of stent thrombosis when compared to BMS,[146] although increased mortality as a consequence of this could not be established.[147] The incidence of such a complication following PCI is very low (around 1 %), making it difficult to ascertain this in a statistically significant manner. However, meta-analysis shows that—while DES are clearly superior to BMS because they prevent restenosis and therefore reduce the risk of another intervention becoming necessary—a small trade-off with respect to late stent thrombosis exists.[148-149] The current paradigm therefore is to apply antiplatelet therapy with a thienopyridine drug (clopidogrel or ticlopidine) and aspirin for a certain period after surgery (a year or longer), at least in patients who have no major risk for bleeding.[150] Moreover, the rapamycin analog tacrolimus shows a higher selectivity for VSMC *vs.* VEC inhibition, but the overall clinical performance of this drug is worse because it is less effective at preventing restenosis.[151]

As for CABG, not involving the placement of a stent, systemic application of the cytotoxic paclitaxel or an immunosuppressant rapamycin-like drug for the prevention of restenosis does not appear feasible at all. This warrants research into new agents which have a more selective activity profile for the treatment of intimal hyperplasia.

A.3 **Leontopodium and Leoligin**

The Alpine region in Europe, mainly stretching across Austria, Switzerland, northern Slovenia, southern Germany, north-west Italy and south-east France, is a habitat to a great diversity of plants that are native to the area.[152] Among those is the rather well-known edelweiss (*Alpen-Edelweiß*, or simply *Edelweiß* in standard German spelling, **Figure 10**), widely recognized as it features on coins, badges, emblems, coats of arms and the like. Prior to 2003, edelweiss had been referred to as a species of the genus *Leontopodium* (*L. alpinum* Cass.),[153] while the newer literature has adopted its reclassification as a subspecies of *L. nivale* (*L. nivale* ssp. *alpinum* (Cass.) Greuter).[154] Though its natural habitat is in the Alps at altitudes roughly above 1800 meters where it is a protected plant in many countries—it became the first protected plant by law in Austria in 1886[155]—it can be cultivated in large quantities and seeds can be readily purchased.[154] In folk medicine, the plant has a history of being used as a remedy for various aches and complaints,[153, 156] which made it interesting to study its contents.

Figure 10, top: details of *Leontopodium nivale ssp. alpinum*, contemporary drawings in *Flora von Deutschland Österreich und der Schweiz*, 1885, by Otto Wilhelm Thomé.
Bottom: *L. nivale ssp. alpinum* growing in its natural alpine environment.
Images adapted from Wikimedia Commons.[1]

A number of flavonoids and phenolic acids, in addition to isocomene-, modhephene-, caryophyllene- and bisabolane-type sesquiterpenes, as well as hexahydrofarnesylacetone and a chromane derivative have been known to occur in *L. nivale* spp. *alpinum*. In 2003, phytochemical investigations of root material by Stuppner and co-workers identified sesquiterpene **55**, glycosyl benzofuran **56** and coumarins **57** and **58** as constituents (**Figure 11**). Additionally, angelic acid dimethyllariciresinyl ester **59**, a furan-type lignan with 9(9')-oxygen was found,[153, 157] and appropriately called *leoligin* later on, as it is the major lignan in this *Leontopodium* species.[131] Subsequently, 5-methoxyleoligin **60** and 5,5'-dimethoxyleoligin **61** were also identified.[158]

First clues about the anti-inflammatory activity of leoligin were obtained when this compound, alongside others that originated from edelweiss, was found to significantly reduce croton oil-induced ear dermatitis in mice by topical application.[155] Furthermore, it turned out to be a potent inhibitor of the biosynthesis of leukotrines, substances which are

presumed to be mediators for allergic and anaphylactic reactions as well as inflammation.[158] Conversely, no inhibitory activity was found on inflammation-related prostaglandin-endoperoxide synthase, better known as cyclooxygenase (COX); significant effects were observed on neither COX-1 nor COX-2.

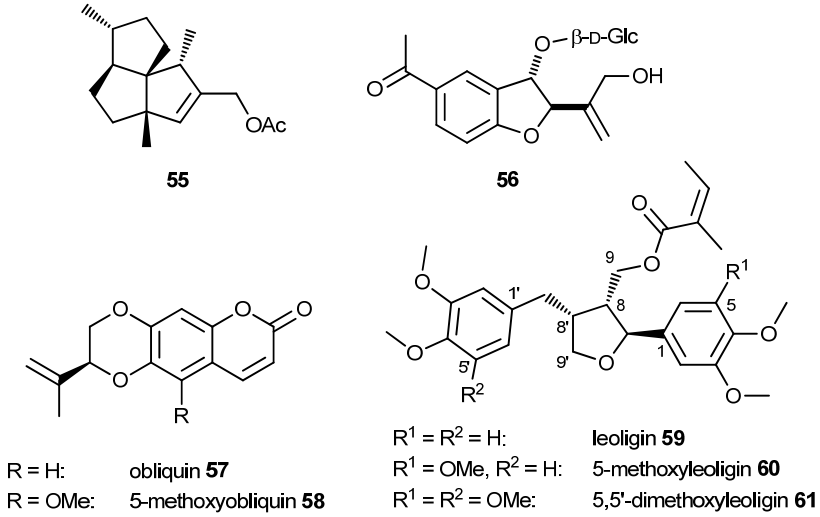


Figure 11: Some compounds from *L. nivale* spp. *alpinum*, with leoligin **59** as its major lignan.

In 2009, Stuppner, Bernhard and co-workers showed that leoligin inhibits intimal hyperplasia of venous bypass grafts.[131, 156] In the *in vitro* part of the study, surgical waste of human saphenous veins from CABG patients was collected and intimal hyperplasia was induced in these tissue pieces using an appropriate culture medium over an incubation period of two weeks. With different concentrations of leoligin added to the cultures during incubation, a dose-dependent effect of leoligin was observed when freshly added every second day. At a concentration of 5 µM, leoligin inhibited intimal hyperplasia completely, and 50 µM concentration actually reversed pre-existing hyperplasia of the veins (**Figure 12**).

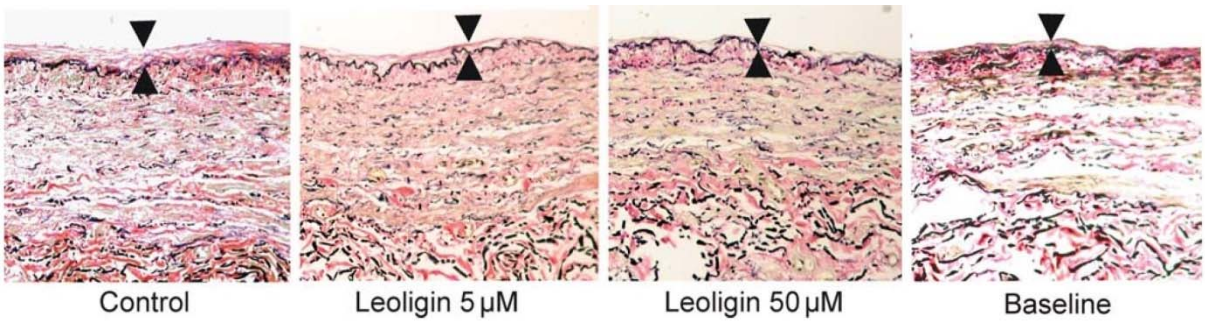


Figure 12: Intimal thickening of representative samples of human saphenous vein tissue *in vitro*. Control: incubated tissue without leoligin. Baseline: non-incubated sample. On average, 5 µM leoligin prevented intimal thickening with respect to baseline, and 50 µM leoligin had the effect of reversing mild pre-existing thickening. *Image adapted from Stuppner, Bernhard et al., 2009.*[131]

Similar results were obtained in *in vivo* investigations with mice. For these experiments, the vena cava of a donor mouse was interposed into the carotid artery of a recipient mouse. In the test group, a 0.1 mL depot of a NaCl solution containing a 100 µM concentration of leoligin was then placed around the vein graft, whereas the control group did not have leoligin in the NaCl solution. Four weeks thereafter, the mice were killed and the transplanted veins analyzed. While the control group

had developed neointima which was more than 40 µm thick on average, the leoligin group showed neointimal thickness of less than 20 µm.
Cell culture experiments with isolated primary human VSMCs (these originate from the human umbilical vein and are thus called HUVSMCs) showed that their proliferation is inhibited when leoligin was added to the incubation medium (for a detailed discussion of cell-based results on all biological activities, see section B.2, page 94), while there was no significant apoptosis or necrosis up to a concentration of 100 µM. This activity was traced to the inhibition of the cell cycle during G_1 phase, i.e. the first part of interphase which lies between cell divisions. It was noted that p27/KIP, a protein which regulates proliferation and motility of cells (and also apoptosis),[159] accumulated in the cells upon treatment with leoligin, being a first clue as to the underlying mechanism. Moreover, no thrombus formation activity or modulation of normal platelet function was observed. While these studies also showed no significant toxicity to human umbilical VECs (HUVECs) at concentrations up to 100 µM, and the endothelium remained intact in the *in vivo* experiments, leoligin also inhibited the proliferation of these cells to about the same extend as it did in the case of HUVSMCs. This effect is somewhat undesired for the reasons explained above (section A.2.2, page 35)

Incidentally, the close relative 5-methoxyleoligin **60** promoted migration of VSMCs and VECs in a wound scratch assay and induced angiogenesis in *in vitro* experiments. Arteriogenesis, but not angiogenesis, was also induced *in vivo* in the infarction area of rat hearts where artificial myocardial infarction had been triggered beforehand.[160-161] This suggested that the compound protects the myocardium and improves cardiac performance after heart attack. Varying the chemical structure of **60** to elucidate structure-activity relationships[162] has been the subject of separate work.[163]

The above mentioned characteristics of leoligin elicited interest in this compound for the use in after-care following coronary heart disease-related surgery, but it could also be interesting in prevention by lowering the risk for atherosclerosis. As was mentioned above, cholesterol ester transfer protein (CETP) has been considered a target in atherosclerosis because it takes part in the distribution of cholesterol across different binding states and places in the body. Later investigations on leoligin found that the compound modulated the activity of CETP in a dose-dependent manner. Low concentrations activated CETP in both human and rabbit plasma, while higher concentrations decreased it; significant modulation of CETP was also found *in vivo* in transgenic mice.[164]

The discovery that leoligin promotes cholesterol efflux from THP-1 macrophage cells is even more intriguing. This cell line had originally been derived more than three decades ago from the blood of a patient with acute monocytic leukemia and is extensively used to investigate the function and regulation of monocytes and macrophages in the cardiovascular system.[165] By *in vitro* experiments, Atanasov and co-workers discovered that leoligin enhanced cholesterol efflux in a macrophage cell model, as compared to negative control (solvent vehicle treatment), and also when compared to pioglitazone which was used as a positive control. Additionally, upregulated expression of the ABCA1 transporter protein upon exposure to leoligin suggested that this is the mode of action of the observed enhanced cholesterol efflux.[166]

Another important discovery during these on-going studies on leoligin was that the compound suppressed the activity of the TNFα-induced NF-κB pathway in Human Embryonic Kidney (HEK) 293 cells in a dose-dependent manner, a cell model that is very suitable to find NF-κB inhibitors.[166] In fact, the original study which had identified leoligin as an inhibitor of intimal hyperplasia had also

uncovered that THFα-mediated expression of the above mentioned VCAM-1 (but not that of intercellular adhesion molecule 1, ICAM-1) at 10 μM concentration is also inhibited by leoligin in HUVECs,[131] suggesting that this compound might suppress the NF-κB pathway in endothelial cells, too. As was discussed above, this represents a second possibility for tackling atherosclerosis by directing therapy toward the inflammatory development in the vasculature.

A.4 **Objectives and Synthetic Plan**

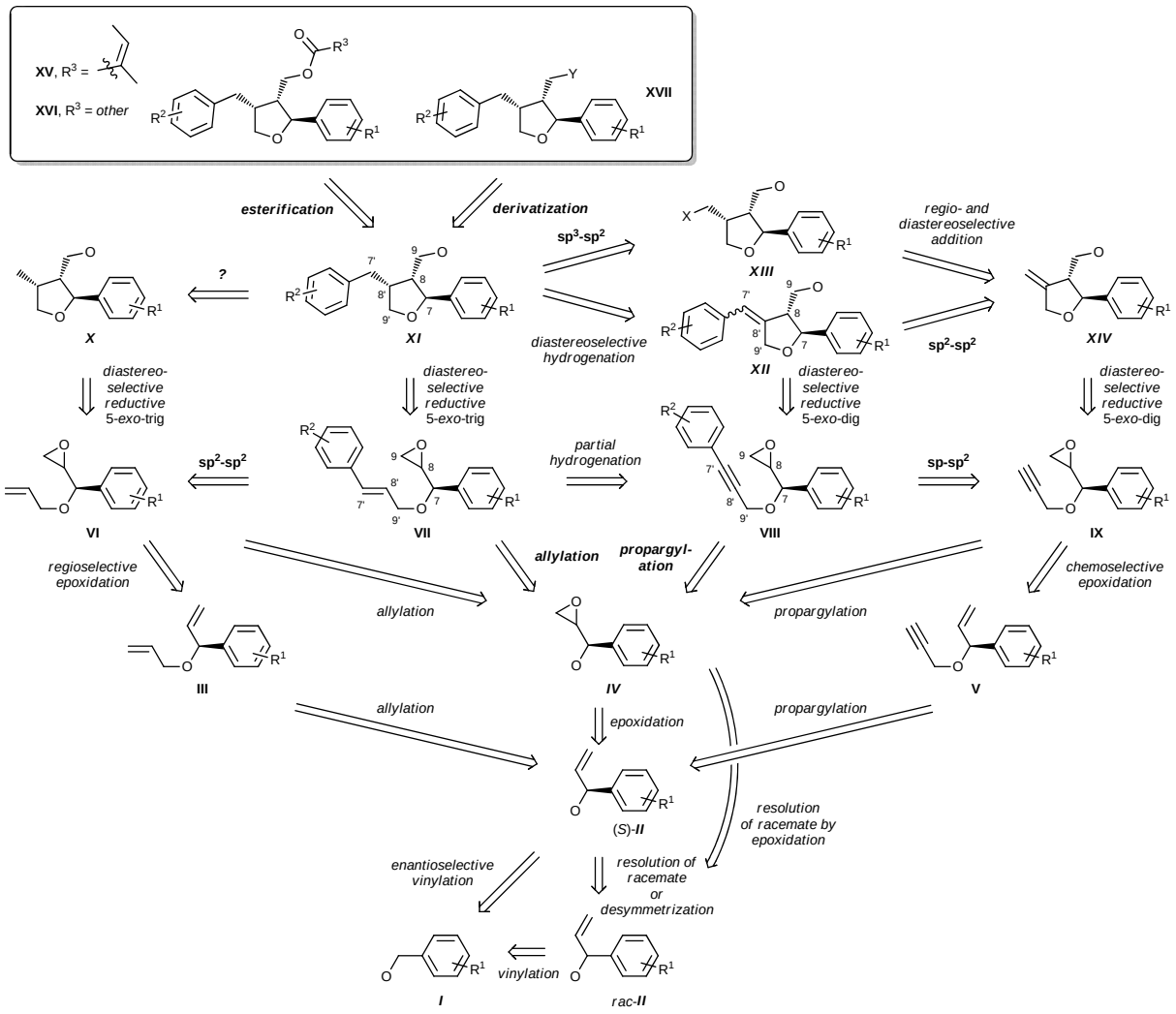
In the past, natural products proved to be an excellent pool for the identification of new drug lead compounds.[167] However, obtaining leoligin from its natural source is a rather tedious procedure.[168] For example, the initial isolation and purification afforded 38 mg of the compound from 804 g of dried root material,[153] which would amount to more than 20 kg of dried roots necessary for 1 g of leoligin. In fact, efforts were undertaken to improve this by transforming edelweiss shoots into a hairy root cell line using an *Agrobacterium rhizogenes* strain.[154] In these studies, varying conditions resulted in up to 0.06 to 0.07 w/w % of leoligin with respect to plant mass. With a final dry biomass of about 0.6 g in 50 mL nutrient medium after 4 weeks of culture, this would translate to approximately 125 L of culture medium necessary for 1 g leoligin (this calculation assumes that the process is scalable in a linear fashion and that the published analytical results of leoligin content in hairy roots reflect amounts of would-be isolated and purified compound in a tentative preparative process). Although this biotechnological approach is promising, it does not allow for variations of the chemical structure. This, however, is precisely what is required because the potency and selectivity of the various biological activities of leoligin itself would have to be improved by creating structural analogs in order to obtain tool compounds for further pharmacological investigations or possibly even a high-impact hit or lead molecule for translational research. For instance, decoupling VSMC proliferation inhibition from VEC inhibition would be advantageous (as explained above), as would be the separation of the macrophage cholesterol efflux-enhancing and the NF-κB-suppression capability inherent to the lead structure. Leoligin possesses all these biological activities, and ideally, structural analogs can be found which have only one particular activity, but with higher potency. Additionally, it is necessary to make sure the new analog compounds are not toxic when applied in the effective concentration range.

The objectives set out for this work are thus as follows:

- Synthetic plans for accessing furan-type lignans with 9(9')-oxygen should be assessed, taking account of the chiral nature of the molecule.
- A seizable amount of leoligin should then be prepared, required for on-going biological studies and as a proof of concept for scalable synthesis.
- The synthetic route should be divergent (or modular) in order to allow the creation of a compound library with reasonable effort and time investments.
- Cell-based biological screenings of the library should be performed and the results obtained should be fed back into the decision-making process for the preparation of new structural analog molecules.
- If attainable, one or more compounds should be selected to be assessed in *in vitro* experiments with human vein tissue, or *in vivo* animal (mouse) models, as outlined above.
- Conclusions on structure-activity relationships (SAR) should be reached in order to suggest further steps in synthesis and biological evaluation.

Scheme 20 explores how leoligin-like compounds **XV**, **XVI** and **XVII** may be prepared. The general synthetic methodology chosen focuses on a diastereoselective reductive 5-*exo* cyclization to afford tetrahydrofurans ***XI*** with the substituents at positions 7, 8 and 8' in proper relative configuration, relying on the beforehand-established chiral center in (*S*) configuration at position 7 for optical activity. This approach was selected because of existing literature precedents for particular routes

within **Scheme 20** which promised swift access to leoligin and analogs and avoid many issues of the synthetic plans that were outlined above (section A.1.2 page 18), such as lengthy syntheses, poor diastereocontrol, racemic products and low yields.



Scheme 20: Retrosynthetic overview over possible routes to leoligin-like molecules. Steps in which the synthesis is divergent are indicated in bold. Synthons which are not actual chemical entities are labeled in italic. A distinction was made between (*Z*)-2-methylbut-2-enoates **XV** (esters of angelic acid) and other esters **XVI** due to the prominence of the former in the present work. For clarity, positions are numbered only in four structures but the numbering applies throughout and is consistent with the IUPAC-recommended nomenclature for lignans as introduced in section A.1.1, page 12.

The above overview is key for orientation within the various routes explored and will therefore, in part, be a recurring scheme in subsequent sections. Because of the aim of modularity, points of divergence should occur late in the synthesis; this aspect is also discussed, as are the methods of introducing chirality into the synthetic route.

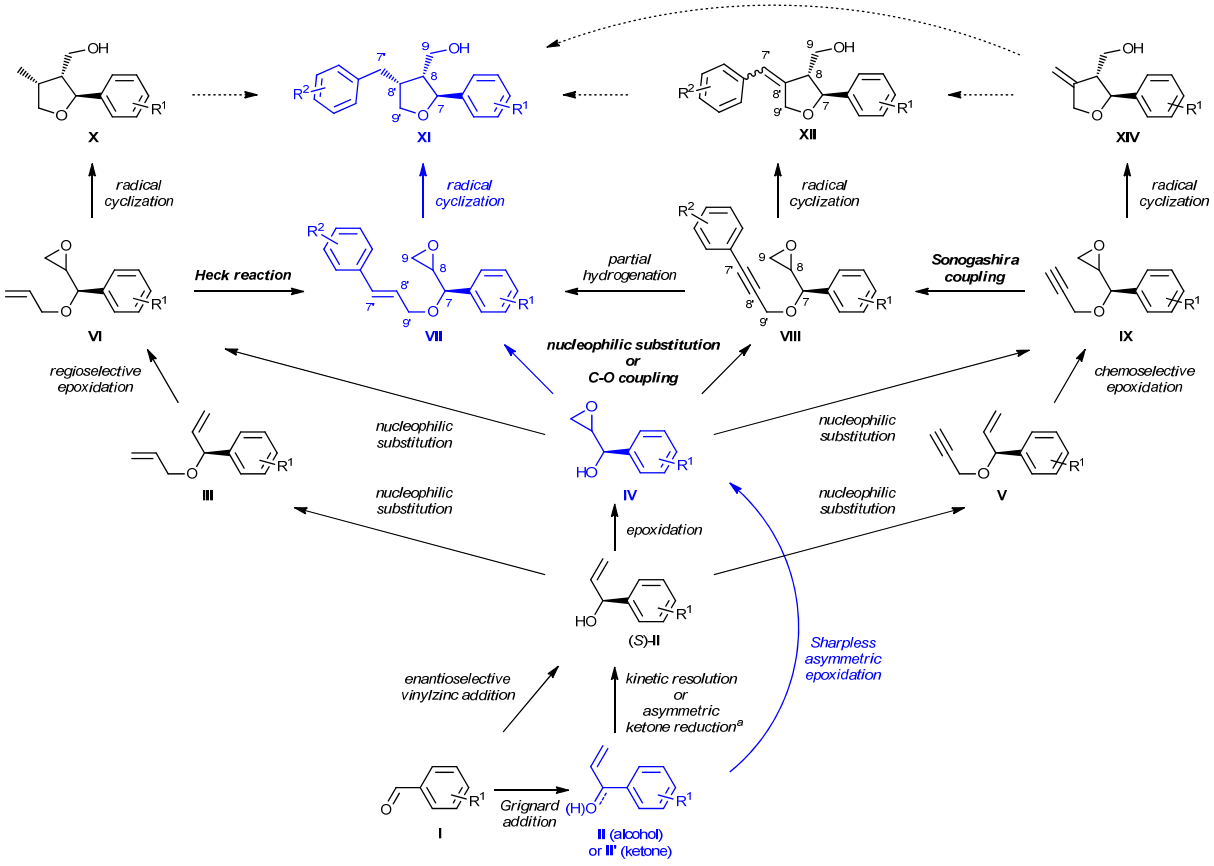
B Results and Discussion

B.1 Chemistry

For practical reasons, the discussion of the chemical aspects is divided into efforts toward the synthesis of cyclization precursors and their subsequent cyclization to substituted tetrahydrofurans (next section B.1.1), elaboration of these substituted tetrahydrofurans to furan-type lignans and leoligin in particular (section B.1.2, page 72), and further modifications of these lignans to particular compounds (section B.1.3, page 88). Mechanisms of known reactions are explained where relevant.

B.1.1 Synthesis of precursors and their cyclization to substituted tetrahydrofurans

Inspection of the literature available for the formation of furan-type lignans **XI** revealed that in 2005, Roy and Banerjee[169] had used the Sharpless asymmetric epoxidation to prepare intermediates **IV**, which were then subjected to a nucleophilic substitution reaction with appropriately substituted cinnamyl bromides to give intermediates **VII**, and then cyclized to **XI** in a titanium(III)-mediated radical reaction (highlighted in blue in **Scheme 21**).

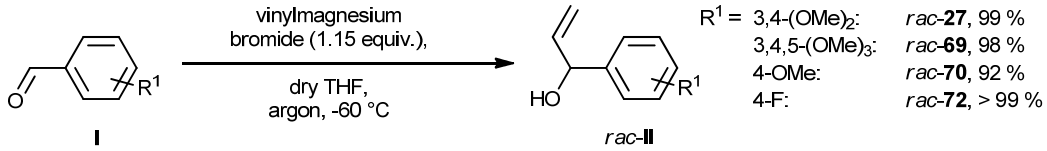


Scheme 21: Possible ways to obtain substituted tetrahydrofurans, relying on a radical cyclization as the key step. Intermediates **XI** would already be furan-type lignans of the sort required for leoligin and analogs. The asymmetric route by Roy and Banerjee[169] is highlighted in blue, and is discussed in more detail further below in relation to the other possibilities shown in this scheme. [a]Kinetic resolution if racemic allylic alcohol **II** is used, and asymmetric reduction if prochiral enone **II'** is used.

In earlier work by the same research group, the racemic synthesis of various **XI**-like lignans had been completed in essentially the same way, except for using simple *m*-CPBA in place of a chiral catalyst

for the epoxidation of **II**, thus affording **IV** and, eventually, **XI** in optically inactive form.[170] The highlighted route and its racemic variant therefore served as the entry point to this work because it would quickly lead to **XI** as the immediate precursor to leoligin. Once this would be in hand, variations to the synthetic plan would be made in order to render the synthesis more modular: a disadvantage of this plan is that if R^2 is to be changed, derivatives of cinnamic acid bearing the desired R^2 substituent(s) need to be prepared (unless commercially available), then reacted with epoxy alcohols **IV** and the resulting epoxy ethers **VII** cyclized, separately in each case.

Since allylic alcohols[b] *rac*-**II** are not generally available from commercial sources, the synthesis started with the Grignard addition of vinylmagnesium bromide to aldehydes **I** (**Scheme 22**).[59-60]

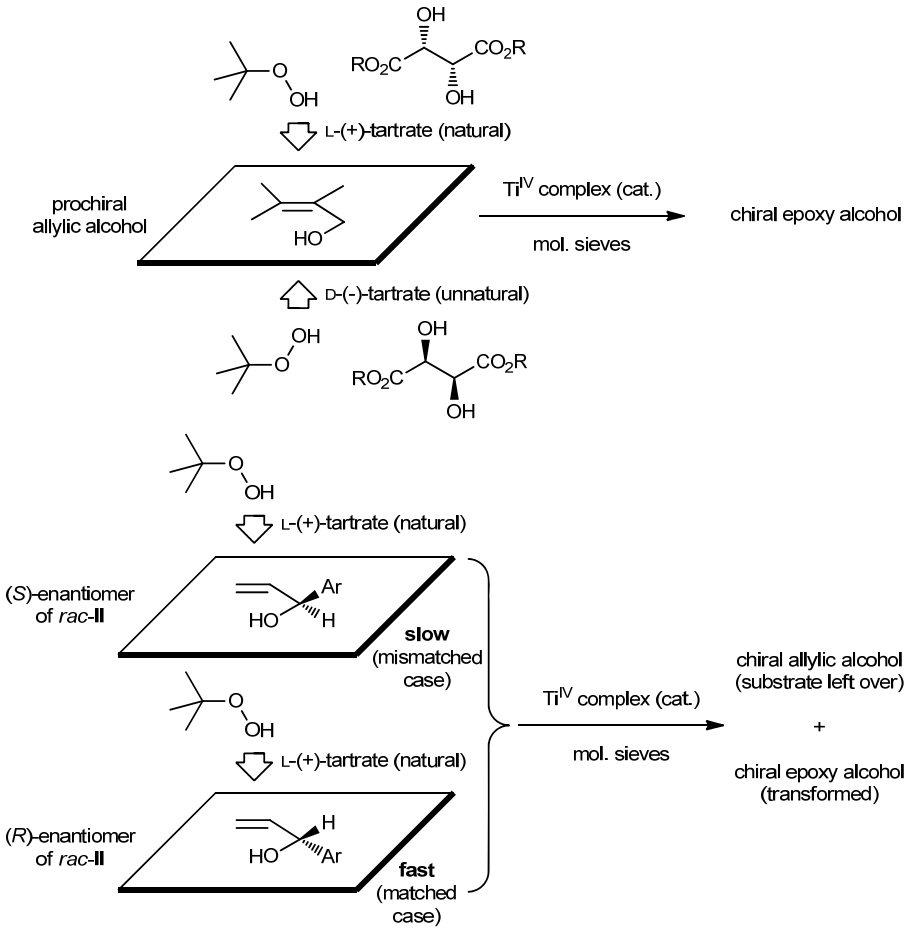


Scheme 22: Grignard addition to benzaldehydes.

Conducted at low temperature in THF with some excess of Grignard reagent, this afforded compounds *rac*-**II** in essentially quantitative yields and pure form after work-up. The reaction was also scalable; for example, 85 g of *rac*-**27** (99 % yield) could be prepared in this way.

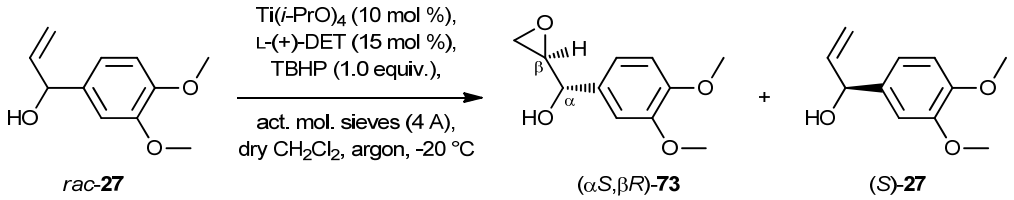
Next, the Sharpless asymmetric epoxidation was attempted in order to obtain optically active epoxy alcohols **IV**. First published in 1980[171] and then rendered a catalytic process several years later,[172] this reaction which chemo- and enantioselectively transforms prochiral allylic (or homoallylic)[173] alcohols into the corresponding epoxides under complete reagent control had a profound impact on organic chemistry as a whole. It can also be used as a kinetic resolution of chiral substrates because the reaction rates of the enantiomers are usually sufficiently different,[174-176] but the theoretically possible yield is limited to 50 % because it is not a dynamic process. These two modes in which it can be employed are depicted in **Scheme 23**.
$Ti(O\textit{i}\text{-}Pr)_4$ or, less frequently, $Ti(O\textit{tert}\text{-}Bu)_4$ for sensitive products prone to ring-opening, is used as the precatalytic species, and the chiral information is conferred by diethyl tartrate (DET; alternatively, dimethyl and diisopropyl tartrate can also be used). The alkoxide ligands of the titanium(IV) species are rapidly exchanged for the tartrate upon combination, and the resulting complex undergoes further exchange with the oxidant *tert*-butylhydroperoxide (TBHP) and the substrate allylic alcohol. The exact nature of the catalytically active complex is difficult to determine due to ligand exchange dynamics, but the enantiofacial selectivity of the reaction is highly predictable according to the mnemonics in **Scheme 23**. The role of the activated molecular sieves in making the reaction catalytic in titanium is also not well understood; in part, it removes adventitious water from the reaction mixture and thus protects the complex from hydrolysis. Running the reaction at -20 °C in dry CH_2Cl_2 and allowing the titanium(IV)-tartrate-TBHP to age for about 30 min prior to substrate addition is also part of the standard reaction protocol.[177]

[b] Compounds of this type will interchangably be called allylic alcohols or vinylbenzylic alcohols, depending on which aspect needs to the emphasized.



Scheme 23, top: General depiction of the Sharpless asymmetric epoxidation of prochiral allylic alcohols.[178] **Bottom**: Using this reaction for kinetic resolution as relevant for substrates *rac*-**II**. Because oxygen is delivered from the same side of the double bond where the tartrate complex is positioned, contact of the larger one of the allylic substituents (the aryl group) with the catalyst allows to predict the more slowly reacting enantiomer.

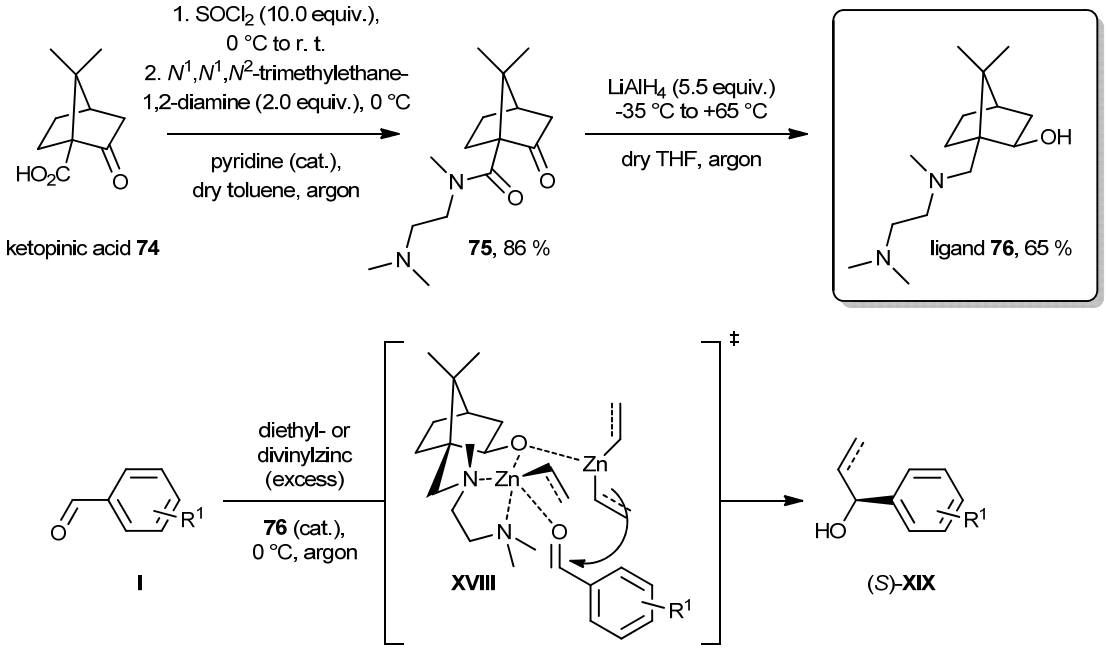
Compound *rac*-**27** was the most important substrate because was planned to lead to leoligin. However, when running the reaction under the reported standard conditions (to the point that also L-(+)-DET was used which would give the optical antipode of the required epoxy alcohol), difficulties were encountered at reproducing the stated[169] yield of 45 % (with respect to a theoretical maximum of 50 %) and enantiomeric excess of 96 %. Moreover, reproducibility among different runs was also poor: while no conversion was detected in one reaction batch after 4 h, a 58 % yield of epoxy alcohol (α*S*,β*R*)-**73** (together with 13 % left-over allylic alcohol (*S*)-**27**) was isolated after the same time in another batch (**Scheme 24**), meaning that the reaction had significantly overshot the resolution point at 50 % conversion.



Scheme 24: Using the Sharpless epoxidation for the kinetic resolution of *rac*-**27**. The (*R*) enantiomer of **27** represents the matched case with L-(+)-DET and is therefore converted at a higher rate than the mismatched (*S*) enantiomer.

A possible reason for this might have been that drying the molecular sieves by heating them to 200 °C for approximately 6 h in high vacuum prior to use did not result in uniformly desiccated material from batch to batch (DET, the starting material and the solvent were also dried using these sieves before the reaction). The cryogenic reaction conditions required throughout the procedure precluded the use of a glove box with standard cooling equipment; thus, insufficient exclusion of moisture using standard Schlenk technique is another likely cause for these variances observed. These issues and the possibility of finding an alternative route which would not be limited to 50 % maximum yield led to abandoning the Sharpless epoxidation for the time being.

Among the methods for enantioselective catalytic synthesis of allylic alcohols,[61-62] and addition reactions of organozinc reagents to carbonyl compounds in particular,[179-180] early work by Oppolzer and Radinov[181-182] appeared particularly interesting because it applied specifically to the asymmetric addition of unsubstituted divinylzinc and diethylzinc to benzaldehyde in the presence of chiral tridentate ligand **76** (**Scheme 25**). According to the mechanistic rationale, *si*-face addition of the organozinc species proceeds *via* complex **XVIII**, furnishing (*S*)-configured alcohols **XIX**.



Scheme 25, top: Synthesis of ligand **76**. **Bottom:** Proposed mechanism of **76**-catalyzed asymmetric addition of organozinc compounds to benzaldehydes.

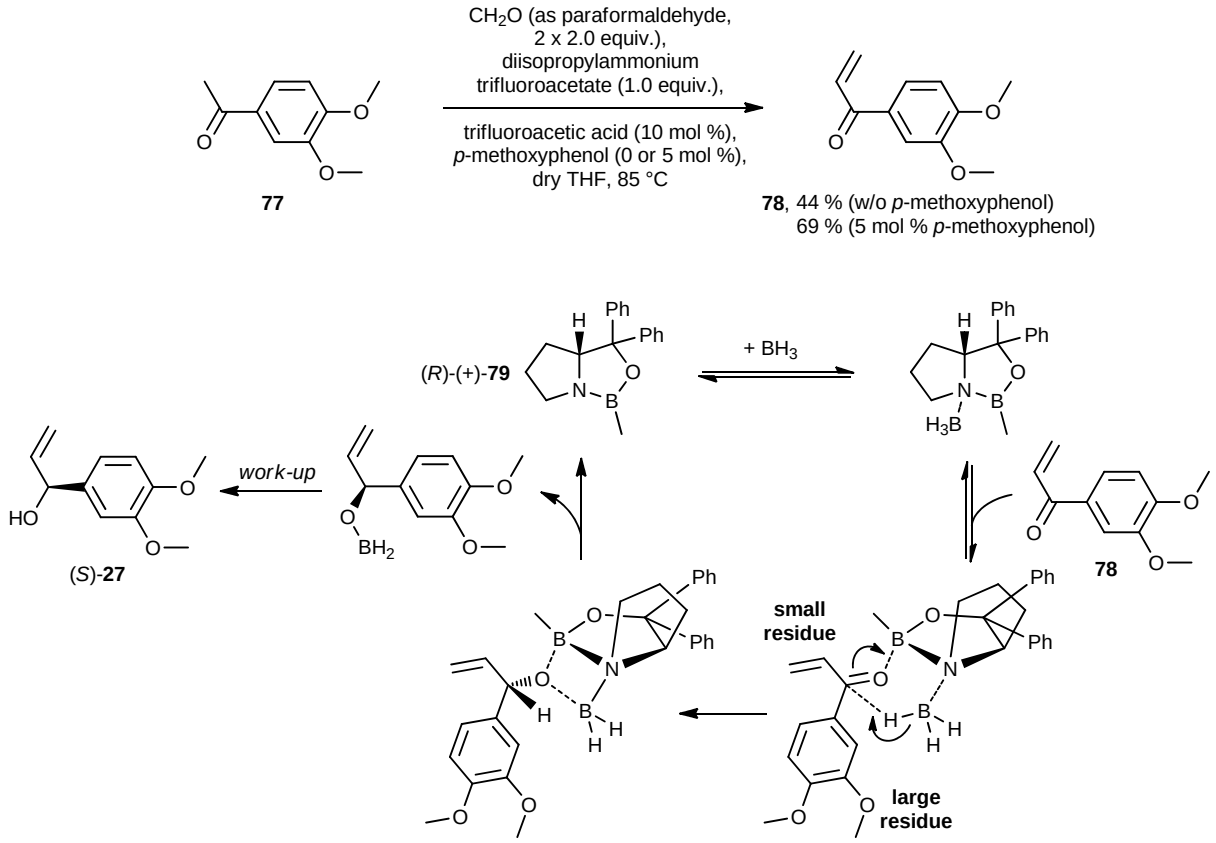
For this reason, ligand **76** was prepared as described[181] from commercially available ketopinic acid **74** *via* ketoamide **75**, and experiments were carried out with benzaldehyde (for reference to the literature) and 3,4-dimethoxybenzaldehyde **65** as the starting material of interest.
However, results were not encouraging (**Table 1**). In the absence of the chiral ligand, but with the reaction conditions otherwise identical to the literature protocol, only traces of racemic product alcohol **XIX** were formed when diethylzinc and benzaldehyde were used (blank experiment, entry 1), as should be because uncatalyzed addition of the organozinc species should not occur. In fact, the literature experiment itself with 5 mol % of ligand (entry 2) produced product alcohol, but in entirely racemic form.

entry	aldehyde (1 equiv.)	organozinc (2 equiv.)	ligand **76**	e.e. of **XIX**
1	benzaldehyde	diethylzinc	0 mol %	0 % (traces of product)
2	benzaldehyde	diethylzinc	5 mol %	0 %
3	benzaldehyde	divinylzinc (from solid $ZnCl_2$ + vinyl-MgBr)	3 mol %	0 %
4	3,4-diMeO-benzaldehyde **65**	divinylzinc (from solid $ZnCl_2$ + vinyl-MgBr)	3 mol %	0 %
5	3,4-diMeO-benzaldehyde **65**	divinylzinc ($ZnCl_2$ solution + vinyl-MgBr)	0 mol %	0 %
6	3,4-diMeO-benzaldehyde **65**	divinylzinc ($ZnCl_2$ solution + vinyl-MgBr)	6 mol %	0 %
7	3,4-diMeO-benzaldehyde **65**	divinylzinc ($ZnCl_2$ solution + vinyl-MgBr)	12 mol %	0 %

Table 1: Attempted asymmetric addition of organozinc species using chiral ligand **76**. Enantiomeric excess was determined by chiral HPLC after quenching the reaction with water.

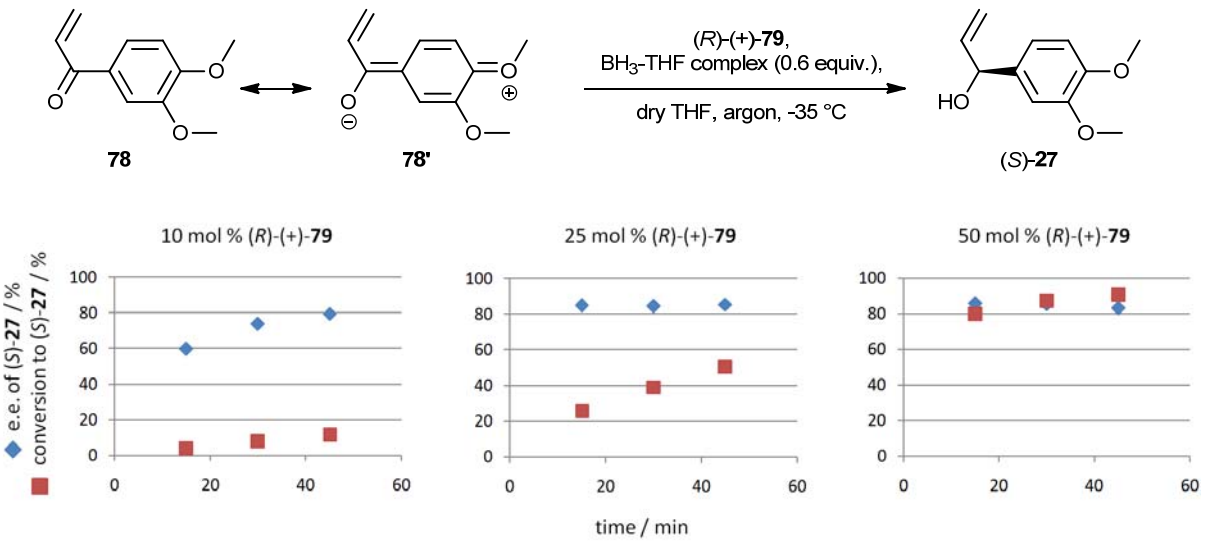
In the case of diethylzinc, a commercial solution thereof in hexanes could be used, the same solvent as in the literature protocol for the asymmetric addition. However, the suggested procedure[183] for the preparation and isolation of divinylzinc is rather unpractical and low yielding (10 %) due to the instability of the compound when concentrated. Therefore, it was prepared as a solution by exchange of vinylmagnesium bromide with zinc(II) chloride,[184] either by directly adding an available THF solution of vinylmagnesium bromide to solid and pre-dried $ZnCl_2$ under argon, or by combining with an etheral solution of $ZnCl_2$, followed by the removal of precipitated salts. This meant that THF (entries 3 and 4), or THF and diethyl ether (entries 5, 6, 7) were also present in the addition experiment, which might have changed the rate of complex formation with the ligand **76** and/or the reaction rate of uncatalyzed addition of divinylzinc to the aldehydes, because only racemic addition products were obtained in all cases. Notably, conversion occurred also in the absence of **76** (entry 5), which had not been observed in the case of diethylzinc. On the other hand, the result of entry 2 would suggest that the cause is related to the ligand itself.

At this point, the problem was not studied further because a different approach developed in parallel appeared more promising. Therein, enone **78** was prepared from the corresponding acetophenone **77** and paraformaldehyde in an aldol condensation (**Scheme 26**).[185] Compound **78** is a substrate for the Corey-Bakshi-Shibata (CBS) reduction[186-188] which utilizes catalytic amounts of a chiral oxazaborolidine to reduce a ketone enantioselectively to a secondary alcohol with diborane or another reducing agent. Both enantiomers of the commonly employed 2-methyl-CBS-oxazaborolidine **79** are available from commercial sources, making this approach very attractive.
During the isolation of **78**, however, it was noticed that this enone (although it had been reported previously)[189-190] is very prone to polymerization, giving only 44 % yield after chromatography, and the purified compound turned into a gum-like material upon standing, showing the characteristically broad signals of a polymer in ^{1}H NMR (i.e. this problem was related to the compound itself rather than the reaction by which it was prepared). The situation improved moderately by adding 5 mol % of *p*-methoxyphenol (an inhibitor of acrylic acid polymerization)[191] during the condensation reaction, and another 4 w/w % after chromatography but before evaporation of the eluent. This resulted in a 69 % yield of **78** as an oil which was used immediately for a screening of asymmetric reduction. Still, storing **78** with mixed-in *p*-methoxyphenol in the dark at -20 °C only slowed the appearance of the gummy polymer over time.



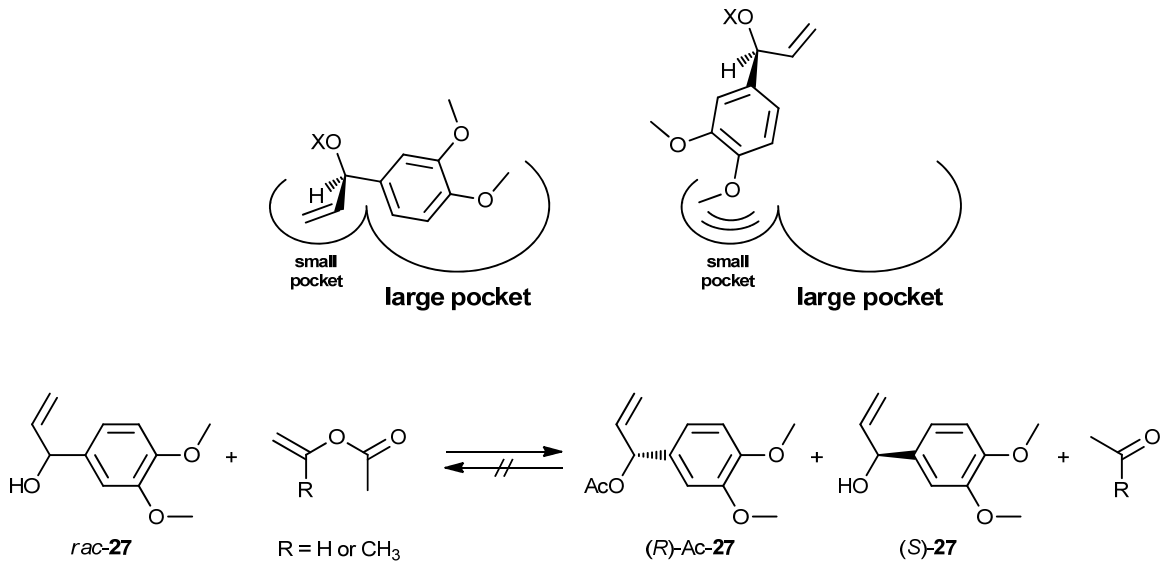
Scheme 26, top: Synthesis of enone **78** *via* aldol condensation. **Bottom:** Simplified catalytic cycle of the CBS reduction of **78**.

Typical CBS reaction conditions involve the use of excess borane (BH_3 complex with THF or Me_2S), 5 to 10 mol % of catalyst loading and reaction temperatures at or below room temperature. In a preliminary attempt, such conditions (0.6 equiv. BH_3-THF, 10 % (*R*)-(+)-**79** at 0 °C) gave (*S*)-**27** in only 53 % e.e. Therefore, the temperature was lowered and different catalyst loadings were evaluated (**Scheme 27**). The resulting enantioselectivities improved indeed, but unfortunately, ketone **78** is not a particularly reactive substrate, which may be due to the electron-rich nature of the arene moiety that is deactivating the carbonyl group. Reductions with 10 mol % of this catalyst are usually complete within 2 min,[187] but in this case, conversion rates were extremely low with 10 mol % (left panel of **Scheme 27**). Even 50 mol % and 45 min of reaction time left 9 % of the starting material unconverted (right panel). Moreover, e.e.s did not exceed 87 %, which would likely be insufficient for the synthesis of compounds of biological interest. Another reaction step dealing with the undesired enantiomer would be required. This and the modest yield of the aldol reaction due to the problem of product polymerization make this approach feasible, but very impractical.



Scheme 27: Evaluation of the CBS reduction for the asymmetric preparation of (*S*)-**27**. The slow conversion is likely because of attenuated carbonyl reactivity as visualized by resonance structure **78'**. Enantiomeric excess were determined by chiral HPLC.

Finally, a simple kinetic resolution *via* lipase-catalyzed enantioselective esterification was used as a general method to prepare compounds (*S*)-**II** from racemic **II**. Lipases are triacylglycerol acyl hydrolases (EC 3.1.1.3), i.e. their natural substrates are lipophilic triglycerides, which makes them versatile reagents for organic synthesis in non-aqueous media.[192] They do not change the oxidation state of their substrates and therefore do not require co-factors, and many of them are commercially available, particularly in immobilized form. Given the oftentimes high enantioselectivity of enzymes, very high e.e.s can be achieved by this method, especially if the desired product is the one left behind unchanged. Lipases generally obey Kazlauskas' rule which had originally been established by studying the enantiopreferences of lipases from *Pseudomonas cepacia* and *Candida rugosa* (cyclic substrates for the latter organism only).[193]



Scheme 28, top: This (simplistic) cartoon illustrates that only one enantiomer of a secondary alcohol (X = OH) or esters (X = O_2CR) will fit properly into the chiral environment of the active site of the lipase if the orientation of the C-O bond is kept the same. **Bottom**: Kinetic resolution by transesterification, made irreversible by tautomerization of the enol released.

While this rule cannot be used to explain the *degree* of enantioselectivity (the performance of the resolution), it translates well into a model where the active site of the enzyme consists of two pockets, a large and a small one (**Scheme 28, top**). If the difference in steric demand between the two residues of a secondary alcohol is sufficiently large, conversion rates will also differ, allowing to predict *which* one of the two enantiomers is converted faster. In the case of allylic alcohols **II**, the lipase will be (*R*)-selective.[c]

Kazlauskas and Weber had pointed out early on the importance of improving the activity, selectivity and stability of these enzymes,[194] and indeed, lipase enantioselectivity has also been inverted by engineering the host expression systems through e.g. directed evolution[195] and combinatorial mutation.[196] By contrast, serine proteases (such as subtilisin) are generally (*S*)-selective because their active site approximates the mirror image of that of lipases with respect to how the chiral substrate can be accomodatated.[197-199]

Racemic esters of secondary alcohols can therefore be selectively hydrolyzed. Alternatively, if the reaction is run in a non-aqueous medium, enantioselective transesterification can also be carried out by transferring the acyl group of an achiral donor component to one enantiomer of the racemic chiral alcohol faster than to the other (**Scheme 28, bottom**). This esterification activity of lipases is related to their enzymatic mechanism, during which a covalent enzyme-acyl-intermediate is formed. Since the undesired reverse reaction would also occur, the achiral alcohol that is formed from the donor component needs to be removed from equilibrium for the process to reach completion. This is usually achieved by employing donors such as vinyl or isopropenyl acetate; these release enols which do not participate in the reaction any longer upon tautomerization to the corresponding carbonyls. Given the (*R*)-selectivity of the lipases, this means that enantioselective transesterification would leave behind the (*S*) enantiomer which is also the one needed for the synthesis of leoligin and analogs of the same absolute configuration, while the transformed (*R*) antipode could be removed as its ester after the reaction by e.g. chromatography.

Literature precedent on this type of substrate exists, using enzymes such as *C. antarctica* lipase B[60] (a.k.a. CAL-B or Novozyme 435)[200] or *Burkholderia cepacia* lipase[201] (a.k.a. lipase PS-30)[202] in toluene at room temperature or 40 °C. A screening for the conversion rate of *rac*-**27** quickly revealed that, among the enzymes available, Amano lipase PS (which presumably[d] originates from *P. cepacia*[203] and is immobilized on diatomite) was the catalyst of choice (**Table 2**).

Both vinyl acetate and isopropenyl acetate showed comparable reaction rates with *rac*-**27**, while increasing the amount of donor to 8 equivalents did not speed up conversion (data not shown). However, switching from toluene to *tert*-butyl methyl ether (MTBE) had a noticeable effect, affording essentially enantiopure (*S*)-**27** (e.e. > 98 %) after 43 h (**Scheme 29**). This is somewhat longer than was expected from in-house experience with this lipase (17 to 23 h) with MTBE as the solvent.[204] Molecular sieves and inert conditions for the exclusion of water (as in the literature) were not required.

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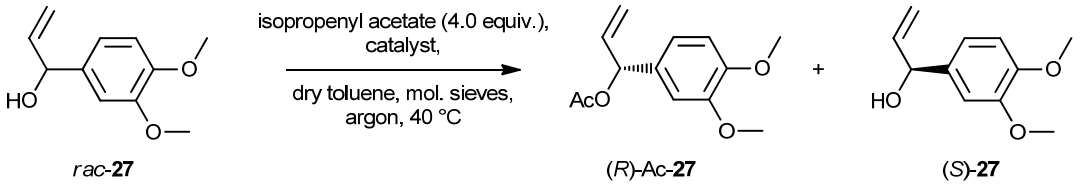
[c] '(*R*)-selectivity' may be a legitimate term to use because in all examples of alcohols **II** that follow, the sterically larger aryl residue is also higher in priority with respect to the vinyl residue, but lower in priority with respect to the hydroxy group, according to the CIP[329] rules.

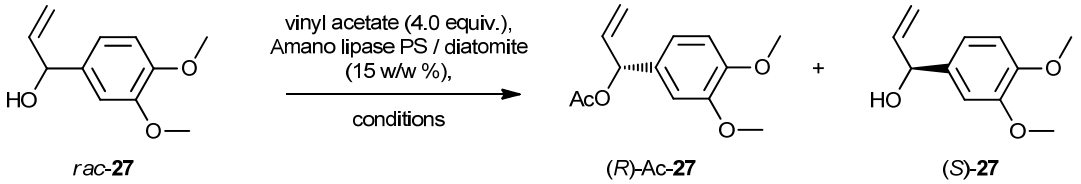
[d] Literature research on this branded enzyme did not turn up unambiguous confirmation that *Pseudomonas cepacia* is the organism of origin.



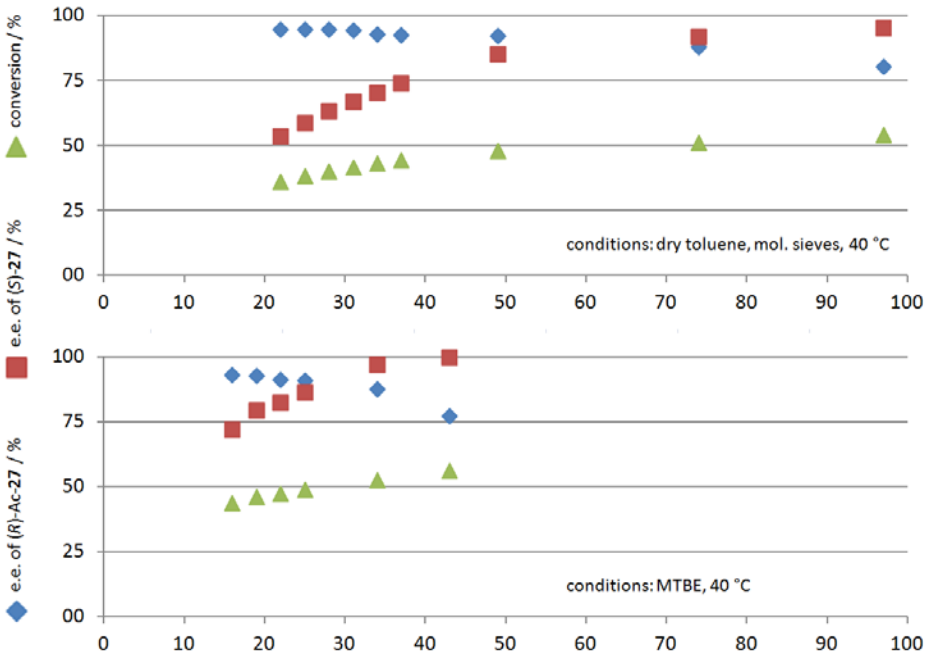
rac-**27** (*R*)-Ac-**27** (*S*)-**27**

entry	catalyst	conversion to Ac-**27** after 12 h	44 h
1	*C. antarctica* lipase B	< 5 %	< 5 %
2	*C. rugosa* lipase	< 5 %	< 5 %
3	*P. fluorescens* lipase	< 5 %	< 5 %
4	porcine pancreas lipase	< 5 %	< 5 %
5	Amano lipase PS	27 %	53 %
6	lipase AY "Amano" 30	< 5 %	< 5 %

Table 2: Activity screening of available lipases for the conversion of *rac*-**27** to its acetate, determined by GC.



rac-**27** (*R*)-Ac-**27** (*S*)-**27**



Scheme 29: Time course of the kinetic resolution of *rac*-**27** with Amano lipase PS. Enantiomeric excess was determined by chiral HPLC and conversion was calculated from the measured e.e. values according to Eq. (2).

Depletion of (*R*)-**27**, however, leads to a significant erosion of e.e. in the product as the reaction progresses and therefore also some loss of (*S*)-**27** yield. The E value is a quantitative measure for the

stereoselectivity of such a process and therefore the performance of the resolution.[205-206] It can be calculated as

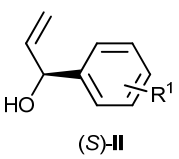
$$E = \frac{\ln[1 - c(1+K)(1+ee_P)]}{\ln[1 - c(1+K)(1-ee_P)]} \quad (1)$$

where ee_S and ee_P are the e.e.s of the substrate and the product, respectively, K is the equilibrium constant and c the conversion, with

$$c = \frac{ee_S}{ee_S + ee_P} \quad (2)$$

For an irreversible reaction, $K = 0$. In a non-selective process, $E = 1$, whereas a minimum $E \geq 20$ is considered necessary for an acceptable resolution.[192] Evaluating the data points according to eq. (1) gives an $E = 61$ for the resolution using 15 w/w % lipase and 4 equivalents of vinyl acetate at 40 °C in MTBE.

These optimized conditions were then applied to all substrates *rac*-**II** for preparative resolution (**Figure 13**). Reactions were monitored on-the-fly by chiral HPLC and terminated when less than 1 % of (*R*)-**II** enantiomer remained in the reaction mixture. Therefore, e.e. values for all isolated compounds (*S*)-**II** were in excess of 98 %. Required reaction times apparently increase with steric bulk and/or polarity of the substrate.



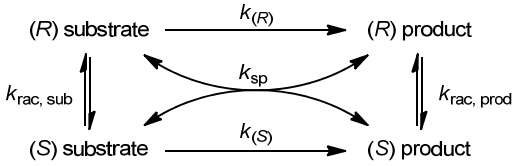
(*S*)-**II**

R^1 =	3,4-$(OMe)_2$:	(*S*)-**27**, 40 %; 45 h
	3,4,5-$(OMe)_3$:	(*S*)-**69**, 39 %; 95 h
	4-OMe:	(*S*)-**70**, 32 %; 48 h
	H:	(*S*)-**71**, 46 %; 23 h
	4-F:	(*S*)-**72**, 40 %; 26 h

Figure 13: Preparative kinetic resolution of *rac*-**II** with optimized conditions. Yields are expressed such that the theoretical maximum of enantiopure compound would be 50 %, and all e.e.s were > 98 % (by chiral HPLC).

This is a scalable method, too, even though chromatography is required to separate the (*R*)-acetates from the (*S*)-alcohols. For example, the polarity difference of (*S*)-**27** and (*R*)-Ac-**27** is large enough to separate 53 g of acetate / alcohol mixture on 180 g of silica (a ratio of roughly 1 : 3).

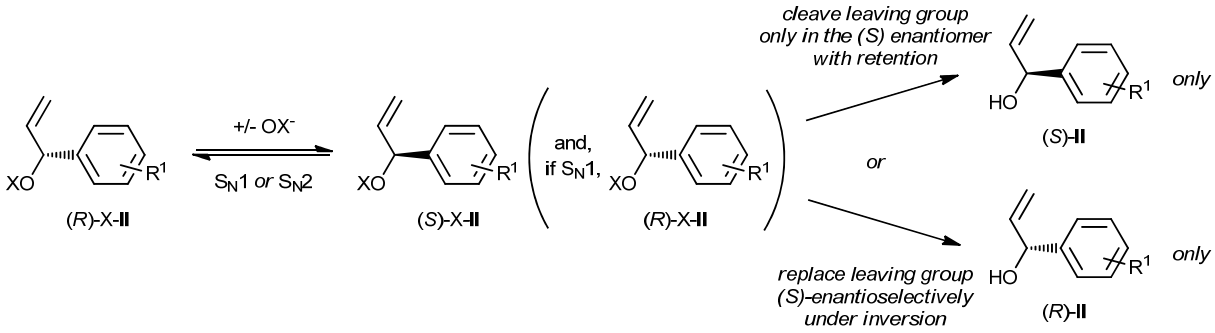
Attempts to translate this method into a dynamic kinetic resolution were unfortunately not successful. In such a reaction, two processes are coupled: the substrate is racemized continually while only one enantiomer is converted to a product (**Scheme 30**).



Scheme 30: Principle of dynamic kinetic resolution. $k_{rac,\ sub}$ and $k_{rac,\ prod}$: racemization rate constants for substrate and product, respectively. $k_{(R)}$ and $k_{(S)}$: rate constants for product formation from the (*R*) and (*S*) enantiomer, respectively. k_{sp}: spontaneous (non-catalyzed) interconversion.

As a prerequisite for this to work, the rate of the process which racemizes the substrate, expressed by $k_{\text{rac, sub}}$, needs to be much higher than the rate of product isomerization $k_{\text{rac, prod}}$, otherwise the optical purity would suffer. Moreover, spontaneous (non-catalyzed) substrate-product interconversion k_{sp} has to be minimal and, like in the non-dynamic process, catalyzed product formation needs to be enantioselective ($k_{(R)} > k_{(S)}$ or $k_{(R)} < k_{(S)}$).

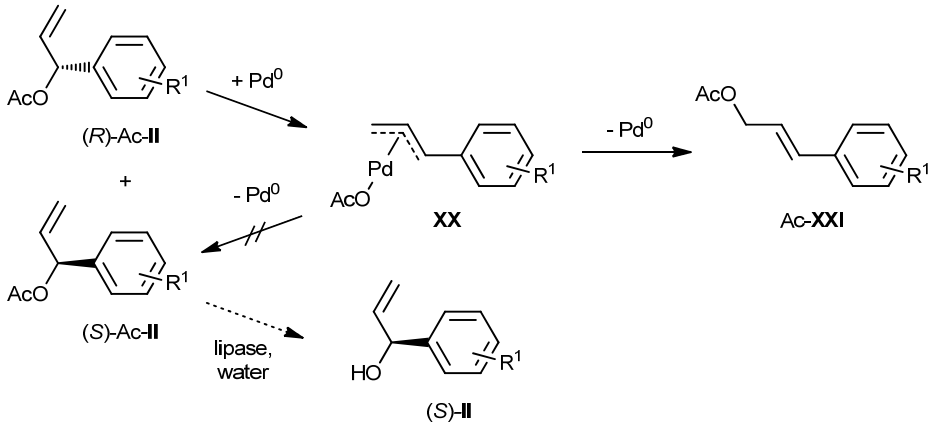
In the case of compounds of structure **II**, at least three methods for substrate racemization can be envisioned: nucleophilic substitution (both S_N1 and S_N2) at the chiral secondary carbon could, in principle, serve this role if the incoming (oxygen) nucleophile is identical to the leaving group and if an enantioselective reaction can be found which replaces the leaving group by a stable (oxygen) substituent, either under retention or inversion of configuration (**Scheme 31**). Certain other results with nucleophilic substitution indicate that such a rather hypothetical consideration does not appear feasible, though, for reasons explained further below.



Scheme 31: Hypothetical process in which a derivative of **II** is isomerized by nucleophilic substitution. If a concurrent process (here assumed to be (*S*)-selective) exists which converts only one enantiomer of X-**II** into a non-isomerizable product (specifically, the alcohol **II** as shown here), either under retention or inversion of configuration, all of X-**II** would eventually be transformed into only one enantiomer of **II**.

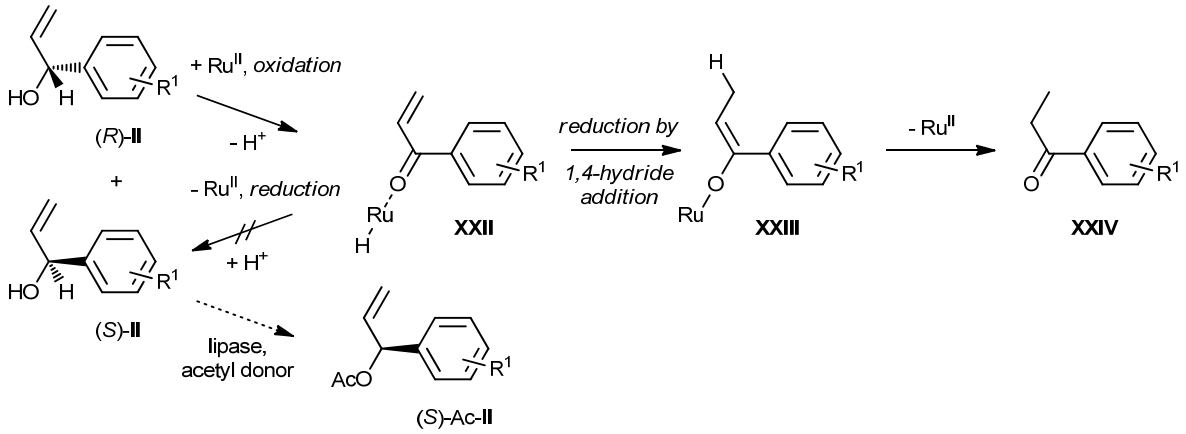
Combinations of enzymes for enantioselective, irreversible conversion to product with transition metal catalysts for substrate racemization have widely been used for dynamic kinetic resolution.[207] Aside from some aluminum-[208] and vanadium-based[209] isomerization catalysts, palladium is used for this purpose in the case of allylic substrates since it is well known to coordinate to olefins as in e.g. the Heck[210] reaction. Thus, reversible η^3-π-allyl complex formation of allylic acetates to palladium catalysts has been used to delete the chiral information from the adjacent stereogenic center, with a lipase selectively hydrolyzing one enantiomer of the acetate, whereas the resulting allylic alcohol cannot undergo racemization in this way.[211-212]

In the particular case of compounds Ac-**II**, this second possible approach is hampered by the thermodynamic properties of the species that can be involved in such a complexation-decomplexation process (**Scheme 32**): upon dissociation of the allylic cation-palladium complex **XX**, the double bond does not revert to the distal position, but rather moves into conjugation with the arene moiety, affording the linear isomer Ac-**XXI**. In fact, compounds Ac-**II** (and Ac-**27** specifically) rearrange rather easily into this thermodynamically more stable linear isomer, such as by treatment with acid, and it was observed that even silica during chromatography effects this rearrangement. Therefore, formation of allyl complexes cannot be used to racemize the substrate for the dynamic kinetic resolution of compounds **II**.



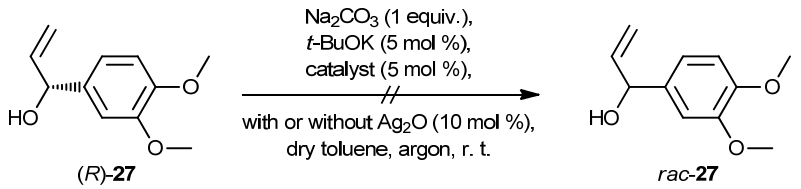
Scheme 32: Palladium-catalyzed isomerization of Ac-**II** based on π-complexation.

The third and most general option relies on redox isomerization by reversible hydrogen transfer reactions between the chiral secondary carbon atom and a metal complex *via* coordinated ketone **XXII** (**Scheme 33**).



Scheme 33: Ruthenium-catalyzed isomerization of **II**.

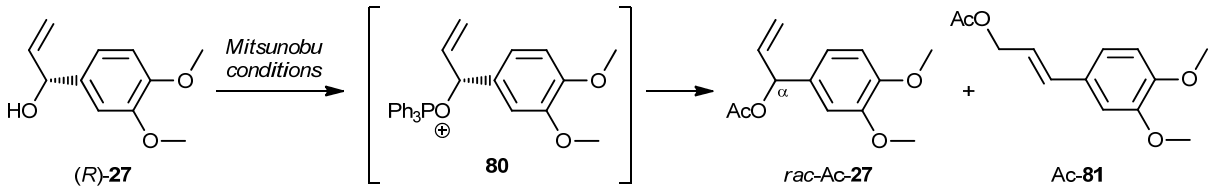
In particular, ruthenium catalysis coupled with enzymatic transformation developed by Bäckvall and co-workers,[213-223] as well was othes,[224-227] has become a widely applied methodology in the dynamic kinetic resolution of alcohols, and also in that of diols.[228-230] Certain allylic alcohols were also used as substrates, but in these cases the chiral center had not been between an aryl residue and the double bond as it is the case for compounds **II**.[219-220, 224] Conversely, it could be shown that such compounds, including α-vinylbenzyl alcohol, are redox-isomerized very efficiently to the corresponding enol form **XXIII**, (R^1 = H if the compound originates from α-vinylbenzyl alcohol), and consequently to the saturated ketone **XXIV**, under the conditions and with the ruthenium-cyclopentadienyl complexes which are usually employed for racemization.[231] Similarly, **XXIV** is the observed reaction product in unsuccessful (asymmetric) transfer hydrogenation (with e.g. dichloro(*p*-cymene)ruthenium(II) dimer),[232] suggesting that compounds **II** would be rather tricky substrates. Nevertheless, a limited screening with different ruthenium complexes was conducted to see if any of them would convert (*R*)-**27** into a mixture of enantiomers as desired (**Table 3**). However, under typical conditions (Na_2CO_3 and *tert*-BuOK in toluene),[216] this racemization could not be achieved, while the formation of the saturated ketone was reproduced using the cyclopentadienyl complex available (entry 12) and the reported conditions.[231] Silver oxide is also known to be effective as a base in these reactions[225] and was therefore used as an additive in these experiments, but no change in the results was observed.



entry	catalyst	no additive	Ag_2O additive
1	tris(triphenylphosphine)ruthenium(II) dichloride	no racemization	no racemization
2	ruthenium(III) acetylacetonate	no racemization	no racemization
3	tricarbonyldichlororuthenium(II) dimer	decomposition	decomposition
4	dichloro(1,5-cyclooctadiene)ruthenium(II) polymer	no racemization	no racemization
5	benzeneruthenium(II) chloride dimer	no racemization	no racemization
6	bis(triphenylphosphine)ruthenium(II) dicarbonyl chloride	no racemization	no racemization
7	triruthenium(0) dodecacarbonyl	no racemization	no racemization
8	dichlorodi-μ-chlorobis[(2,7-dimethyl-2,6-octadiene-1,8-diyl] diruthenium(IV)	no racemization	no racemization
9	dichloro(*p*-cymene)ruthenium(II) dimer	no racemization	no racemization
10	dihydridotetrakis(triphenylphosphine)ruthenium(II)	no racemization	no racemization
11	ruthenium(III) chloride hydrate	partial decomposition	partial decomposition
12[a]	chlorodicarbonyl(pentaphenylcyclopentadienyl) ruthenium(II)	formation of corresponding **XXIV**	n/d

Table 3: Attempted racemization of (*R*)-**27** (obtained by hydrolysis of (*R*)-Ac-**27**, not shown) with complexes of ruthenium in different oxidation states. Racemization was determined by chiral HPLC. [a]No Na_2CO_3 used.

Lastly, an attempt was made to invert isolated, undesired enantiomer (*R*)-**27** by an S_N2 process, specifically by Mitsunobu reaction. Therein, alkoxy phosphonium intermediate **80** is formed as an activated form of the secondary alcohol which is to be inverted, and this intermediate can then be attacked by a weak nucleophile such as a carboxylate (**Scheme 34**). However, using standard Mitsunobu conditions[233] for (*R*)-**27** (DEAD, triphenylphosphine and anhydrous acetic acid in dry THF at 0 °C) led to a complex mixture which contained Ac-**27** in racemic form, linear product Ac-**81** and other unidentified side products. As was mentioned earlier, also Ac-**27** itself shows the same isomerization behavior to Ac-**81** upon exposure to acid, albeit to a lower degree. The better the leaving group on the secondary Cα in the branched form ($OPPh_3$ *vs.* AcO^-), the more pronounced is the linear product which presumably arises from a [1,3]-sigmatropic rearrangement *via* a transition state that involves a partially cationic allyl moiety. This would mean that S_N2-type inversion with control over the stereocenter cannot occur. Accordingly, efforts to invert this chiral center in experiments where (*R*)-**27** was subjected to standard mesylation or tosylation conditions (*vide infra*) did not give the corresponding branched sulfonates either, for just the same reasons.



Scheme 34: Attempted Mitsunobu inversion of (*R*)-**27**. The Mitsunobu reaction was then made use of to a greater extend later on, *cf.* **Scheme 56** (in section B.1.2, page 81).

Having enantiopure compounds (*S*)-**II**—although not by *dynamic* kinetic resolution—in hand, the next step (*cf.* overview **Scheme 21**, page 44) was the oxidation of the double bond to prepare epoxides **IV**. In their account on the racemic synthesis of polysubstituted tetrahydrofurans,[234] Roy and co-workers had reported high yields in the standard Prilezhaev epoxidation[177] with *meta*-chloroperbenzoic acid (*m*-CPBA). Specifically, *rac*-**27** afforded a 91 % yield of epoxy alcohol **73** as an equimolar mixture of two pairs of enantiomers (i.e. 4 isomers in total, each accounting for 25 % of the mixture)[e] when using 1.3 equivalents of *m*-CPBA, added slowly in portions to the starting material in chloroform at 0 °C. Reproducing these conditions several times (for testing purposes, racemic **27** was actually used as the starting material, as in the literature precedent), left the conversion incomplete. This made the addition of more epoxidation agent and an increase in temperature necessary. Stepwise addition in the fashion 1.0 + 0.5 + 0.5 + 0.5 equivalents, each added at 0 °C with subsequent warming to room temperature, gave the highest yield (42 %) of isolated **73** among the various equivalents and addition regimes as well as other epoxidation methods that were tried (**Table 4**, entry 1).

rac-**27** **73**, mixture of 4 isomers

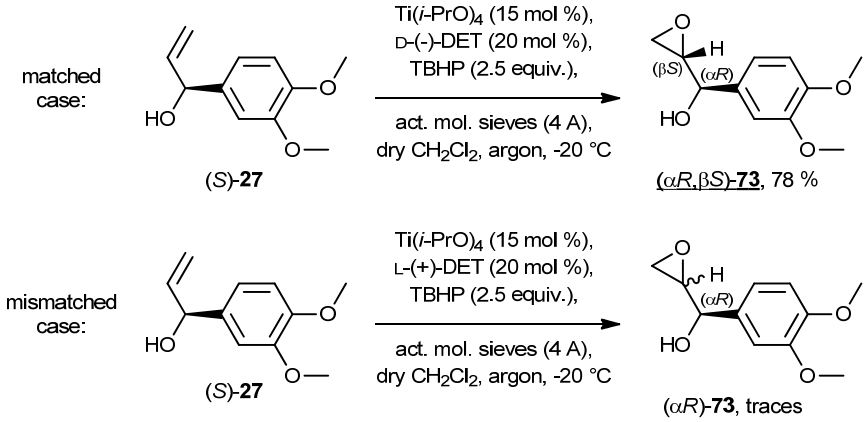
entry	conditions	yield
1	*m*-CPBA (2.5 equiv., stepwise addition), $CHCl_3$, 0 °C to r. t., 3.5 d	42 %
2	*m*-CPBA (2.5 equiv., stepwise addition), $NaHCO_3$ (3.5 equiv.), $CHCl_3$, 0 °C to r. t., 3.7 d	34 %
3	TBHP (1.5 equiv.), $VO(acac)_2$ (2 mol %), benzene, 0 °C to r. t., ovn.	29 %
4	$H_2O_2.CO(NH_2)_2$ (15.0 equiv.), $(CF_3CO)_2O$ (4.0 equiv.), Na_2HPO_4 (10 equiv.), dry CH_2Cl_2, argon, 0 °C, approx. 8 h	0 %
5	$H_2O_2.CO(NH_2)_2$ (15.0 equiv.), $(CF_3CO)_2O$ (4.0 equiv.), Na_2HPO_4 (10 equiv.), dry DMF, argon, 0 °C, approx. 8 h	0 %
6	H_2O_2 (30 % aq. solution, 15 equiv.), CF_3CO_2H / DCM (1 : 1), 0 °C, approx. 8 h	0 %
7	H_2O_2 (30 % aq. solution, 15 equiv.), CF_3CO_2H / DCM (1 : 1), Na_2HPO_4 (5 equiv.), 0 °C, approx. 8 h	0 %
8	1.) Et_2Zn (2.2 equiv.); 2.) O_2 (balloon); 3.) $Ti(i\text{-}PrO)_4$ (20 mol %); dry toluene, argon, 0 °C to r. t., ovn.	0 %
9	1.) Et_2Zn (2.2 equiv.); 2.) TBHP (5.0 equiv.); 3.) $Ti(i\text{-}PrO)_4$ (20 mol %); dry toluene, argon, 0 °C to r. t., ovn.	0 %

Table 4: Epoxidation of compound *rac*-**27** under various conditions. In those cases were product could be isolated, the use of racemic staring material with the non-chiral epoxidation systems resulted in mixtures of two pairs of enantiomers (a second chiral center is introduced at Cβ). Ovn.: overnight.

Still, the Prilezhaev reaction took more than three days for completion. Sodium bicarbonate addition (3.5 equiv.) to neutralize the moderately strong 3-chlorobenzoic acid byproduct did not improve the situation either (34 %, entry 2), nor did switching to other epoxidation methods such as *tert*-butylhydroperoxide (TBHP) and vanadium catalysis (29 %, entry 3), a system which had been shown to give good yields on allylic alcohols where the olefin was *not* terminal.[235] Trifluoroperacetic acid

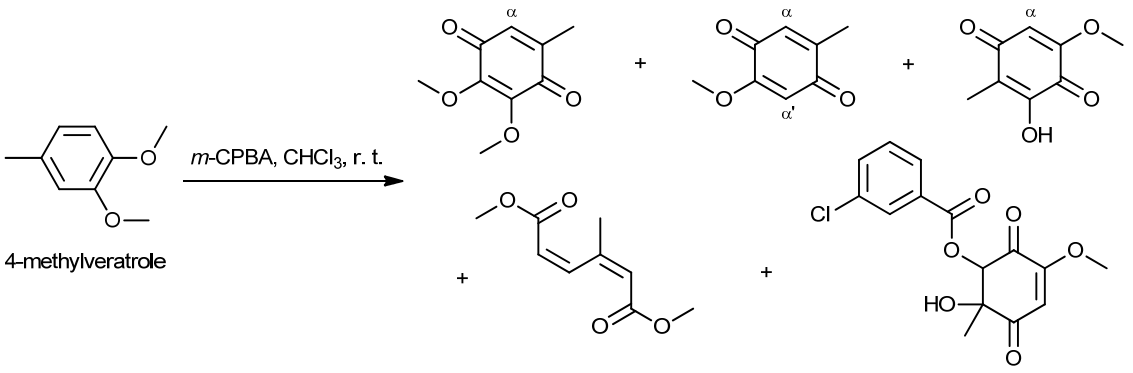
[e] If not specified otherwise, compounds like **73** are generally meant to be mixtures of all 4 possible isomers, but not necessarily always in equimolar distribution.

(generated *in situ* from trifluoroacetic anhydride and hydrogen peroxide-urea adduct)[236] gave only decomposition products, together with unconverted starting material (entries 4 and 5). Likewise, simple combination of aqueous hydrogen peroxide solution and trifluoroacetic acid merely decomposed the starting material (entries 6 and 7). Attempts were also made to adapt a literature procedure based on titanium catalysis in which an allylic alkoxide is formed by combining the allylic alcohol with diethyl zinc and where molecular oxygen or TBHP then acts as the oxidant (entries 8 and 9).[237-238] The latter conditions are somewhat close to those in the Sharpless asymmetric epoxidation. Later investigations indeed showed that when enantiopure (*S*)-**27** (rather than racemic starting material) was used, the matched case epoxidation with D-(-)-DET resulted in a 78 % yield of the corresponding epoxide (αR,βS)-**73**, while the mismatched L-(+)-DET did not give appreciable amounts of product (**Scheme 35**). This means that the reaction was also selective with respect to the configuration at Cβ, yet whether or not the epoxidation process delivers the oxygen selectively to one side of the double bond is irrelevant for the synthesis of enantiopure lignans because the chiral information at Cβ is not retained in a subsequent step, as shall be explained further below.



Scheme 35: Results of the Sharpless epoxidation when using enantiopure (*S*)-**27**. The finding that the top reaction ((*S*)-**27** and D-(-)-DET) represents the matched case is in agreement with **Scheme 23** (page 46, see there for the literature source). The configuration at Cβ in the matched case was also deduced from **Scheme 23**. In the bottom, mismatched case ((*S*)-**27** and L-(+)-DET), only traces of epoxy alcohol were found by TLC, and attempts to deduce or determine the configuration at Cβ were not undertaken.

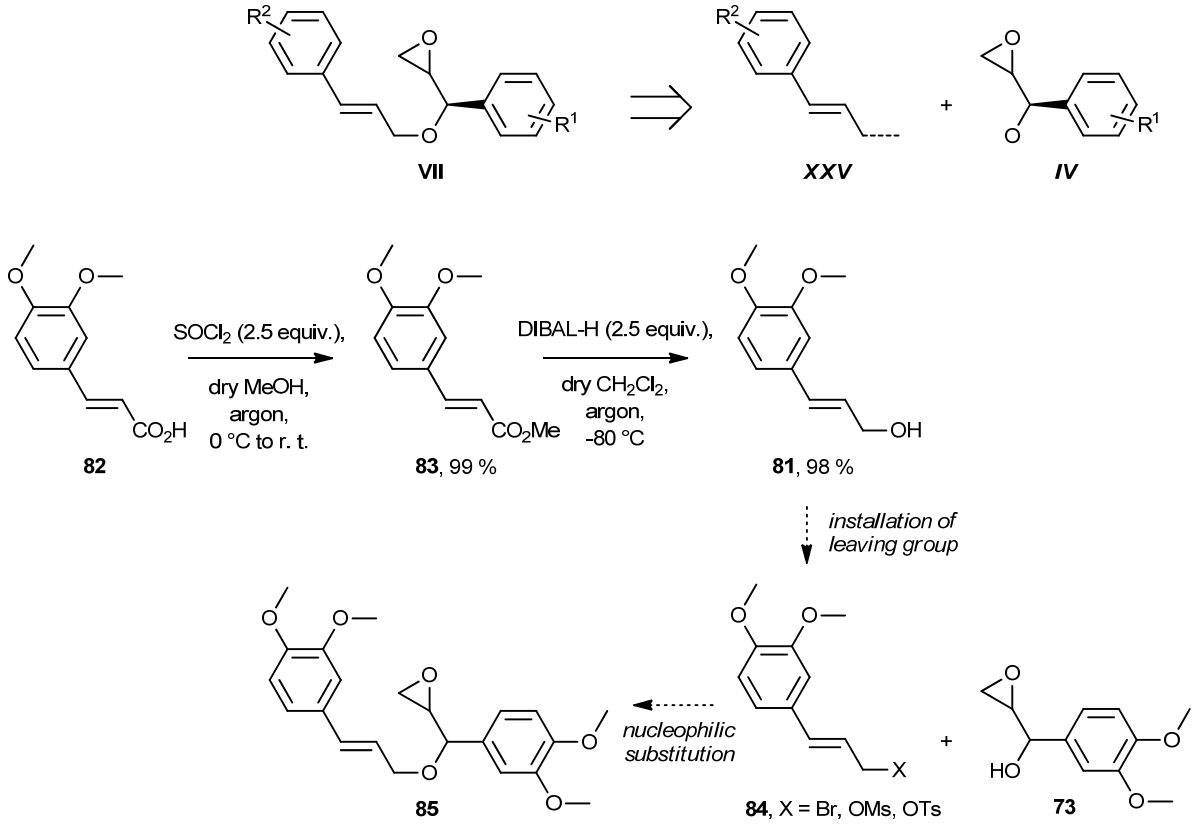
A possible explanation for the difficulty encountered when using electrophilic epoxidation reagents such as *m*-CPBA relies on two factors: the reaction rate of this process increases with electron-donating substituents at the olefin (including alkyl groups).[177] Conversely, unsubstituted olefins are therefore the slowest ones to react. Moreover, when the molecule contains an electron-rich arene, competing side reactions occur which not only decrease the yield by decomposing starting material and product, but also deplete the amount of epoxidation reagent. For example, combining 4-methylveratrole with *m*-CPBA in chloroform at room temperature is known to lead to a range of oxidation products (**Scheme 36**).[239-240] This literature result suggests that similar degradation processes are operational in the case of allylic alcohol **27** as well. ^{1}H NMR spectra of crude epoxidation products also hint at the presence of quinones by the typical chemical shifts of their α protons adjacent to the carbonyl groups.



Scheme 36: Electron-rich 4-methylveratrole gives a mixture of products with *m*-CPBA under conditions normally used for epoxidation; these could be the side reactions which account for the low yields when trying to oxidize the double bond in allylic alcohol **27**.

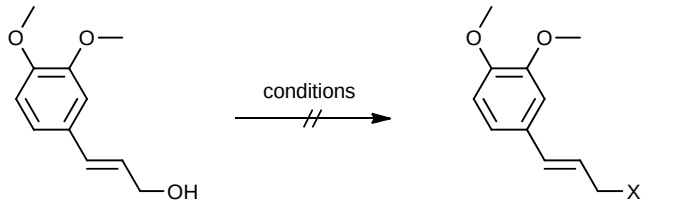
In order to conserve enantiopure material and evaluate the preparative options ahead, the synthesis was continued with the mixture of isomers of epoxy alcohol **73**.

According to the highlighted synthetic route of overview **Scheme 21** (page 44), an ether linkage (compound **VII**) needed to be established in order to incorporate the second half to the lignan molecule (**Scheme 37**). The cinnamyl fragment ***XXV*** is not chiral and would be derived from commercially available dimethylcaffeic acid **82** in the case of the synthesis towards—for now, racemic—leoligin.



Scheme 37: Route requiring cinnamyl synthon ***XXV***, which translates to allyl bromide, mesylate or tosylate **84**. Nucleophilic substitution with epoxy alcohol **73** would then furnish ether **85**.

As indicated, the preparation of alcohol **81** *via* methyl ester **83**[241] proceeded uneventfully. However, problems were encountered when replacing the hydroxy group in **81** with a leaving group, required for nucleophilic substitution to give ether **85**. Roy and co-workers has used allyl bromide **84** (where X = Br), but had never described how this compound (which is not commercial, unlike the parent cinnamyl bromide) was prepared. Attempts to synthesize compound **84** (with X = Br) or the corresponding sulfonates (with X = OMs or OTs) were, in short, unsuccessful (**Table 5**).
Standard procedures employing PBr_3[242-244] (entry 1) or *N*-bromosuccinimide (NBS) with PPh_3 [245] (entry 2) did not give any product as judged from TLC analysis or crude ^1H NMR after quench with aqueous $NaHCO_3$ solution, extraction wit Et_2O and drying with Na_2SO_4. Specifically, these spectra were devoid of signals that could be attributed to the aryl moiety, the methoxy groups or the double bond that would belong to either starting material or product. Similarly, a method using *p*-toluenesulfonic acid monohydrate and cobalt catalysis[246] (entry 3), as well as the more conventional tosylation with tosyl chloride and sterically hindered diisopropylethyl amine (DIPEA)[247] (entry 4) did not give product or left-over starting material after work-up, and the crude NMR spectra thereof showed no sign of these aromatic or olefinic signals.

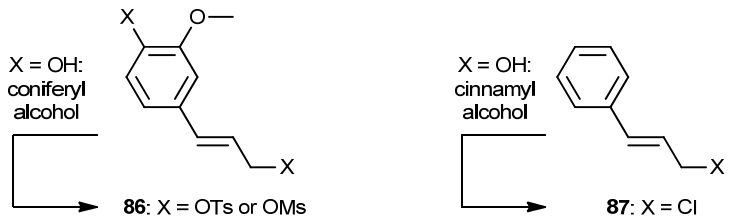


81 **84**, X = Br, OMs, OTs

entry	conditions	X in desired **84**
1	PBr_3 (0.4 equiv.), dry Et_2O, argon, -10 to 0 °C, then r. t.	Br
2	NBS (1.2 equiv.), PPh_3 (1.25 equiv.), dry CH_2CH_2, argon, -30 to +5 °C	Br
3	$TsOH.H_2O$ (1.3 equiv.), $CoCl_2.6\ H_2O$ (8 mol %), CH_2Cl_2, MW (80 °C)	OTs
4	TsCl (3.0 equiv.), DIPEA (4.0 equiv.), dry CH_2Cl_2, argon, r. t.	OTs
5	TsCl (3.0 equiv.), dry pyridine, argon, 0°C to r. t.	OTs
6	TsCl (2.0 equiv.), Et_3N (4.0 equiv.), dry CH_2Cl_2, argon, 0 °C to r. t.	OTs
7	TsCl (2.0 equiv.), Et_3N (4.0 equiv.), dry THF, argon, 0 °C to r. t.	OTs
8	MsCl (2.0 equiv.), Et_3N (4.0 equiv.), dry CH_2Cl_2, argon, 0 °C to r. t.	OMs
9	MsCl (2.0 equiv.), Et_3N (4.0 equiv.), dry THF, argon, 0 °C to r. t.	OMs

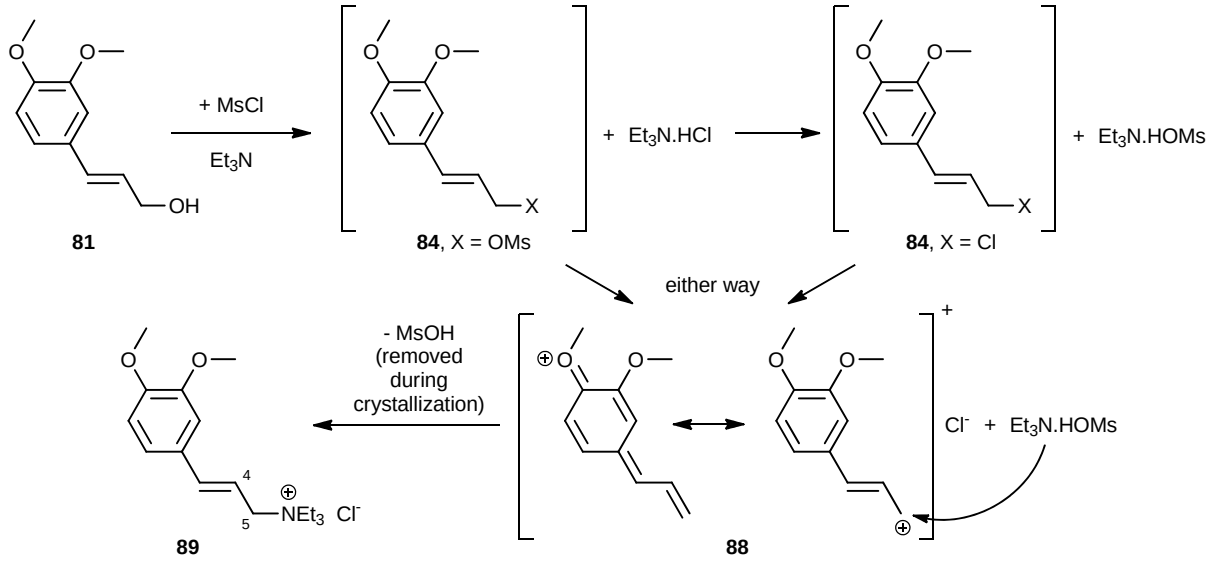
Table 5: Attempted installation of a leaving group on allylic alcohol **81**. The desired product **84** was obtained under none of the listed reaction conditions; additionally, remaining starting material was observed after 20 h when THF was used as the solvent (entries 7 and 9).

Switching to pyridine (entry 5) as both base and solvent, which would also change the mechanism of the reaction (activating the sulfonyl component by reacting with pyridine directly),[248] did not change the result. Entries 6 and 8, with triethylamine as the base, represent literature conditions[247] for the preparation of the ditosylate and dimesylate **86**, respectively, of coniferyl alcohol. When reproducing these reference experiments, compounds **86** were indeed formed (**Scheme 38**). By contrast, the parent cinnamyl alcohol gave the corresponding chloride **87** under these conditions.



Scheme 38: Using conditions of entries 6 (TsCl and Et_3N) and 8 (MsCl and Et_3N) in **Table 5**, the ditosylate and dimesylate **86** were obtained from coniferyl alcohol. Using the same two conditions on cinnamyl alcohol, cinnamyl chloride **87** was obtained in both cases.

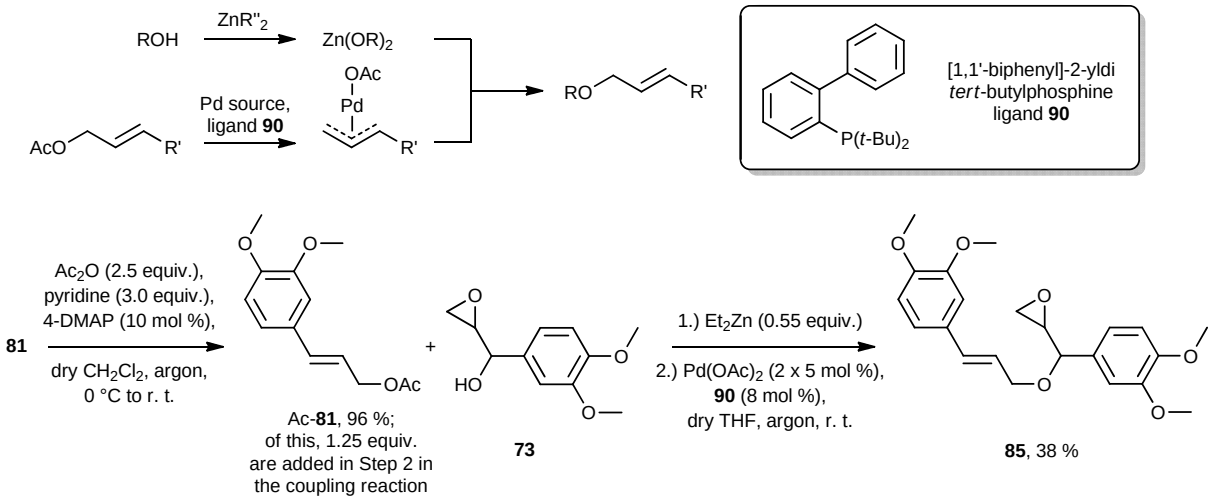
As stated above, no product material **84** was extracted into the organic phase upon work-up. However, a colorless compound could be crystallized from the aqueous phase of the experiment in entry 8 (which had used MsCl and Et_3N) after the excess base had been removed. NMR analysis strongly indicated that this crystalline, highly polar material consisted of quaternary ammonium compound **89**. **Scheme 39** shows a plausible mechanism which accounts for this observation.



Scheme 39: Mechanistic rationale for the negative results on leaving group installation on allylic alcohol **81**, producing compound **89** instead. Identification is based on the ethyl group in ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (t, ^3J = 7.1 Hz, 9H, $CH_2C\underline{H}_3$), 3.48 (q, ^3J = 7.2 Hz, 6H, $C\underline{H}_2CH_3$), 3.89 (s, 3H, Ar''-OCH_3), 3.95 (s, 3H, Ar''-OCH_3), 4.26 (d, ^3J = 7.4 Hz, 2H, H5), 6.14 (dt, $^3J_{trans}$ = 15.6 Hz, $^3J_{vic}$ = 7.5 Hz, 1H, H4), 6.79 – 7.13 (m, 4H, C4=CH-Ar'', Ar''-H).

The phenolic hydroxy group of coniferyl alcohol may react faster with the sulfonyl reagent than the allylic hydroxy group, giving first a monosulfonate intermediate which is then converted further into the resulting disulfonate **86** (with X = OTs or OMs). The sulfonyl group on the phenolic oxygen in *para* position would withdraw electron density from the system, balancing it such that disulfonate **86** results as a stable compound. When cinnamyl alcohol undergoes this reaction, sulfonate is expelled and replaced by chloride ion left over from the sulfonyl reagent as the weaker nucleofuge.[249] In the case of allylic alcohol **81** though, the system could either be too electron-rich even for the allylic chloride **84** (X = Cl) to be stable (and, by extension, also the corresponding bromide as seen in the bromination attempts), or the allylic halide stage is not even reached, giving intermediate cation **88** directly. In either case, **88** would be resonance-stabilized, and reaction with the base would then give compound **89** which was eventually found.

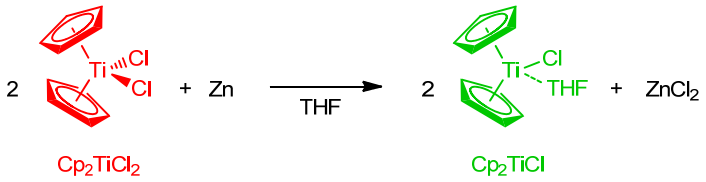
A decision was made not to attempt swapping the roles of nucleophilic and electrophilic component for ether synthesis (*cf.* **Scheme 37**) or to pursue a strategy that would hinge on trapping putative intermediate **88** to give ether **85** directly; the latter approach would not be a robust method because it could then be applied to electron-rich alcohols like **81** only. Moreover, an alternative had meanwhile been found for the synthesis of ether **85** by palladium-catalyzed allylic etherification, as developed by Lee and co-workers.[250-251] This C-O coupling method relies on the addition of a zinc(II) alkoxide nucleophile to a η^3-π-allylpalladium (as was discussed in the context of dynamic kinetic resolution) complex, derived from the corresponding allylic acetate, at room temperature (**Scheme 40, top**). In the literature source, $Pd(PPh_3)_4$ was used for intermolecular coupling of primary allylic acetates and primary zinc alkoxides, as well as for intramolecular reaction of secondary alkoxides, while Buchwald ligand **90** with $Pd(OAc)_2$ precatalyst was employed for intermolecular coupling of secondary alkoxides (to secondary acetates). For this experiment it was reasoned that the stereochemistry in epoxy alcohol **73** would not be affected, and the zinc reagent should not be nucleophilic enough to interfere with the epoxide. This assumption turned out to be correct; as shall be seen later, epoxy alcohols **IV** (like **73**) withstand fairly nucleophilic and basic conditions in other reactions as well.



Scheme 40: Synthesis of **85** based on C-O bond formation by palladium-catalyzed allylic etherification. Stoichiometry is ignored in the top scheme.

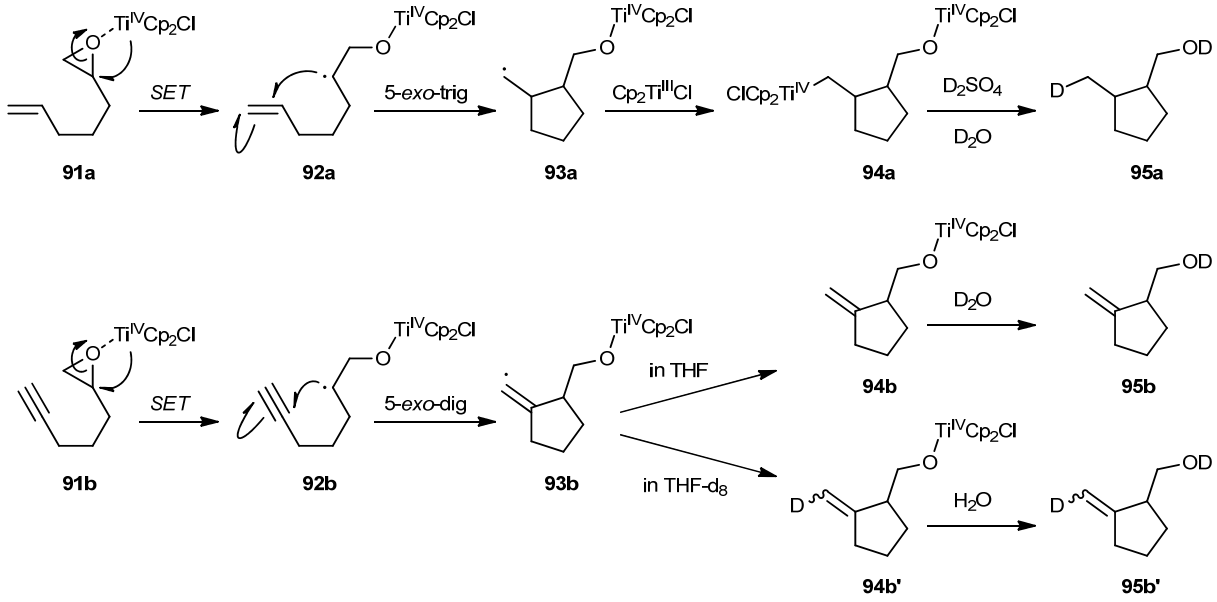
Linear Ac-**81** was readily accessible, either by isomerization of the branched acetate Ac-**27** with silica[252-253] (as explained), or by a dedicated reaction from the corresponding linear alcohol under 4-(dimethylamino)pyridine (4-DMAP) catalysis.[254] $Pd(OAc)_2$, in a first attempt, proved indeed ineffective at C-O coupling (not shown). Conversely, the $Pd(OAc)_2$ / **90** system furnished ether **85** under otherwise identical conditions, but palladium pre-catalyst had to be added twice to achieve completion of the reaction. Although rather moderate, the exact same yield (38 %) was obtained twice, suggesting that this method would be reproducible enough to allow optimization. Reported yields ranged between 51 and 76 % for intermolecular coupling,[250] unless the amount of alkoxide was used in large excess (2.2 equiv.), and with a tendency to lower yields when secondary alkoxides and/or secondary acetates were used. At this point, the availability of ether **85** meant that the next and crucial step—the cyclization to dimethyllariciresinol *rac*-**20**—could at last be attempted, with efforts to improve the synthesis of **85** depending on the success of the cyclization.

In 1994, Nugent and RajanBabu showed that bis(cyclopentadienyl)titanium(III), Cp_2TiCl, reacts with epoxides in a homolytic C-O cleavage.[255] This compound, first reported in 1972,[256] exists as a chloride-bridged dimer in the solid state, but dissociates in the presence of electron donor solvents such as THF, in which it is readily soluble, to give a lime-green solution caused by titanium(III). Cp_2TiCl was initially obtained from titanium(III) chloride and freshly sublimed cyclopentadienylthallium,[257] but the above mentioned authors found that it can be prepared in a much less noxious way by quantitatively reducing commercially available bis(cyclopentadienyl)titanium(IV), Cp_2TiCl_2, with metallic zinc at room temperature (**Scheme 41**). The reagent can be used as a solution in THF, and co-produced, THF-soluble $ZnCl_2$ (a Lewis acid) does not seem to affect the reactions. The shift in the oxidation state is patently visible as (solutions of) the titanium(IV) complex are red. For the discussion that follows, Cp_2TiCl shall be treated as a monomer.



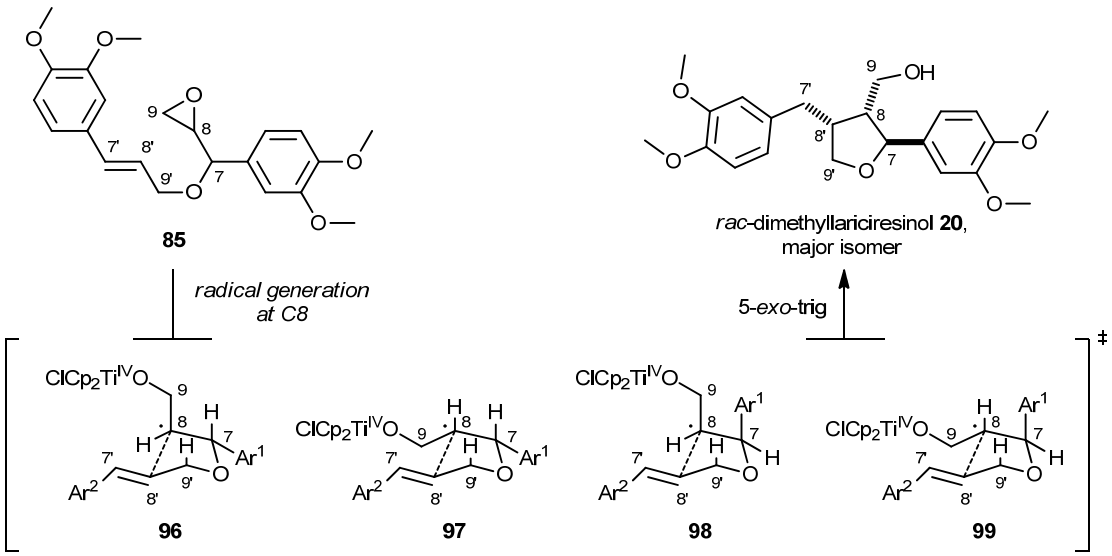
Scheme 41: Preparation of Cp_2TiCl for *in situ* use.

Radicals generated from exposing epoxides to Cp_2TiCl results in their deoxygenation to olefins or, in the presence of hydrogen donors such as 1,4-cyclohexadiene, reduction to alcohols. These radicals can also add intermolecularly to electron-deficient olefins, e.g. methacrylates. Most relevant to this work is that intramolecular radical addition to unactivated double and triple bonds can take place as well. In the first step, the titanium(III) reagent probably needs to coordinate to the oxygen of epoxide **91a** or **91b**, respectively (**Scheme 42**). Single electron transfer (SET) from titanium(III) then results in the regioselective homolysis of the C-O bond of the epoxide at the carbon which affords the more highly substituted, and therefore more stable, radical **92**. In the investigated substrates, the multiple bond was spaced by three atoms from the radical position, and rapid 5-*exo* attack led to ring-closed intermediates **93**. Notably, the reaction mechanism then takes two different paths depending on the type of the initial π system: in the case of a double bond, a methyl radical **93a** is formed which is stable enough to be eventually intercepted by a second molecule of Cp_2TiCl. This gives intermediate **94a** that can be isolated, and the Ti-C bond is only cleaved upon hydrolysis as was demonstrated by quenching the reaction mixture with 10 % D_2SO_4 in D_2O (**95a**). By contrast, deuterolysis of the experiment with triple bond-containing compound **91b** as the starting material produced **95b** which did not contain any deuterium at the methylene group, suggesting that the highly reactive vinyl radical **93b** abstracts hydrogen from the THF solvent before it can encounter another titanium(III) species. In fact, using THF-d_8 as the solvent and quenching the reaction with H_2O, deuterium is incorporated into the final product (**95b'**). This finding shall turn out to be important in explaining the reaction outcomes observed herein in attempts to synthesize substituted tetrahydrofurans *via* this methodology. A 70 % yield of **95a**, and 37 % of **95b**, respectively, had been obtained in these mechanistic studies by Nugent and RajanBabu.



Scheme 42: Mechanism of titanium(III)-promoted radical and reductive cyclization.

An important consequence of the formation of a trigonal-planar radical center is that no chiral information at this carbon is retained (i.e. the reaction is stereoconvergent). When Roy and co-workers (as a follow-up on similar radical chemistry for lignans synthesis)[258-262] used this process in 2002 for the synthesis of racemic furan-type lignans from ethers such as **85** (which also was a mixture of four isomers because the unselective epoxidation with a 1 : 1 distribution with *m*-CPBA had been used), the cyclization gave a mixture of dimethyllariciresinol *rac*-**20** and a minor isomer thereof in a ratio of 5 : 1, from which the major isomer (dimethyllariciresinol) was isolated *via* preparative TLC in 63 % yield (**Scheme 43**).[170] That is, the 7,8 configuration in the major isomer was obtained *trans*, while the configuration of 8,8' was *cis*. As the minor isomer could not be isolated in pure form, its stereochemistry could not be assigned. This result was rationalized by invoking four possible conformers of the transition state during radical attack at the double bond, i.e. by assuming that the stereochemistry is governed entirely by steric interaction.



Scheme 43: The radical cyclization of **85** is presumed to proceed mainly *via* transition state **96**, affording racemic dimethyllariciresinol (and similar lignans of the same relative configuration) as the major product.

This model essentially predicts that transition states **98** and **99**, where the aryl substituent at C7 is pseudo-axial, will be higher in free energy than in **96** and **97** due to 1,2-torsional and 1,3-diaxial[f] strain. Selecting **96** or **97** as the higher-energy state focuses on the *cis*-relation between the C7 and the C8 substituent in conformation **97**, and additional repulsion between the arylvinyl group and the C8 substituent in this conformation might be inferred because the arrangement in **97** is not a chair and these two residues are therefore not really diequatorially *trans*. This would make transition state **96** the lowest one in energy, corresponding to the configuration found in the major isomer.

While this is the proposed reasoning, one can arrive at the same conclusion in a slightly different way. It is reasonable to assume that the arylvinyl group will be oriented as shown in all four cases because rotating the C8'-C9' bond by 180 degrees would create additional torsional strain. Stating this is important because the configuration in the final product at C8' is determined (according to this model) by the orientation of the arylvinyl group as shown in the scheme. First, conformation **98** is eliminated from consideration for it is likely the most unfavorable alignment of all four (C7 and C8 are pseudoaxial and *cis*). Then, assuming that the pseudoequatorial *cis* arrangement of C7 and C8 (**97**) is the next-repulsive one leaves conformations **96** and **99**, with the C7 substituent pseudoequatorial and the C8 substituent pseudoaxial (**96**) or *vice versa* (**99**). Since the aryl group at C7 should exert more steric demand (more 1,2-torsional and 1,3-diaxial strain) than the titanyloxymethyl group at C8 (where the attached titanium complex is large but also two bonds further away, allowing it to be rotated out of the way more easily), one would again obtain transition state **96** as the lowest one in energy.

As mentioned above, the minor isomer had not been purified from the major isomer by preparative TLC in the cited report. For this work, it was assumed, though, that other separation techniques (such as preparative HPLC) should have sufficient resolution power to allow both isomers to be obtained in pure form. This would be advantageous with respect to the medicinal chemistry motivation of the project, while the stated yield of the major isomer (which would be the direct precursor of 7,8 *trans*- and 8,8' *cis*-configured leoligin as the prime target at this stage) would be highly appreciable. Moreover, the relative configuration of the chiral centers at C8 and C8' develops during the cyclization in relation to the configuration of C7. By using starting materials where C7 has defined absolute configuration,[169] the resulting products would also be optically active with known absolute configuration, and the degree of enantiopurity of these products could be inferred to be identical to that of the starting materials (ignoring the irrelevant configuration at C8 in the epoxy ether) because no chemical transformation happens that would cleave or create a bond at C7.

Zinc dust was activated with dilute hydrochloric acid, then thoroughly washed and dried (as described). Using the zinc in excess (7.0 equiv.), the titanium(III) reagent was also readily generated. The literature procedure called for conducting the reaction under inert conditions, and the 2.3 equivalents of green Cp_2TiCl solution were added to a stirred solution of the starting epoxy ether **85**, making sure that residual zinc would not be transferred with it. The reaction was then quenched with 10 % H_2SO_4. Initial difficulties with this transformation where the starting material was largely left unchanged were soon traced to the presence of molecular oxygen and/or peroxides—a general issue in radical chemistry—in the solvent which had been obtained dry by passing commercial THF over a cartridge of activated alumina (**Table 6**, entry 1).

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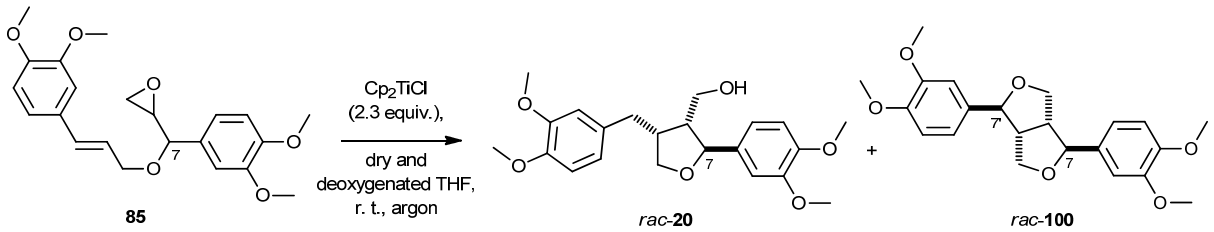
[f] Using a somewhat relaxed nomeclature because this interaction is not strictly diaxial in an arrangement where the cyclic structure under consideration is not a cyclohexane derivative.



entry	*rac*-**20** / *rac*-**100** ratio	comment
1	n/a	solvent not O_2- and peroxide-free: no conversion
2a	4 : 6	isolated *rac*-**20** could not be purified
2b	2 : 8	isolated *rac*-**20** (5 %, contaminated with isomer) and *rac*-**100** (12 %)
3	5 : 5	inverse addition
4	5 : 5	reaction quench with HCl in place of H_2SO_4
5	4 : 6	addition of $SnCl_2.2\ H_2O$ (1.0 equiv.)
6	2 : 8	addition of benzoic acid (2.0 equiv.)

Table 6: Attempts to synthesize dimethyllariciresinol *rac*-**20** from ether **85**. The approximate ratios of *rac*-**20** and *rac*-**100** were determined by ^{1}H NMR. Under the standard conditions (entry 2a and 2b), dry and deoxygenated THF was used and a Cp_2TiCl solution was added to a stirred solution of starting material **85** at room temperature; after 1 h, the reaction was quenched with 10 % H_2SO_4.

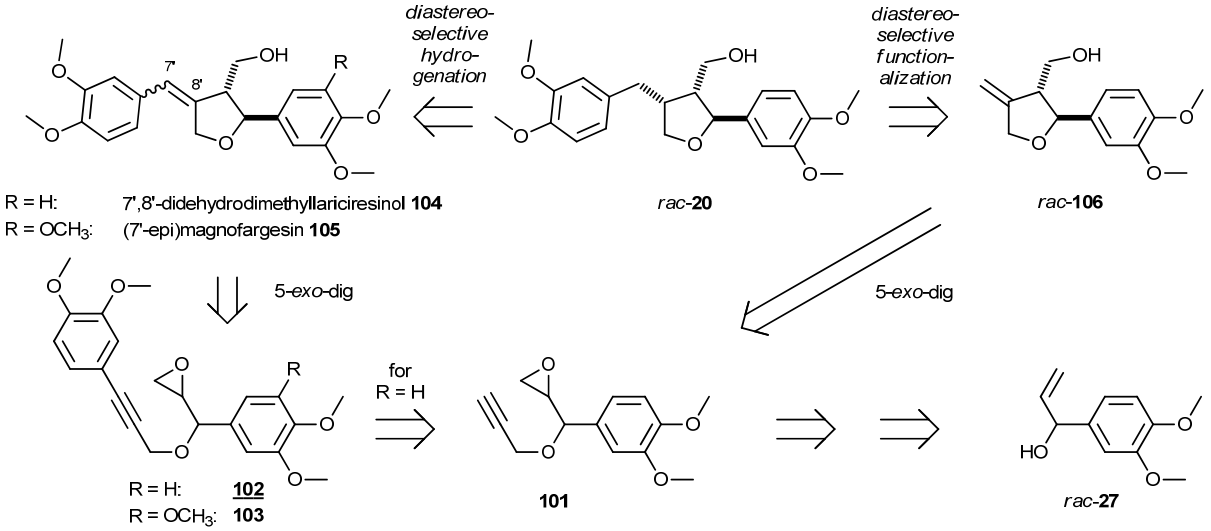
Thus, the dry solvent was additionally freshly distilled from sodium benzophenone ketyl prior to reaction as an effective method for removing oxygen and peroxides.[263] Although a related publication using this transformation specifically stated that the solvent had *not* been deoxygenated,[264] this treatment seemed to eliminate the problem because the starting material was indeed fully consumed. However, the reaction also gave furofuran compound *rac*-eudesmin (pinoresinol dimethyl ether) **100** in addition to dimethyllariciresinol, along with other products. The ratio of these two compounds, as judged from crude ^{1}H NMR by using the prominent H7 doublet (taking into account the H7 and H7' are identical in the C_2-symmetrical *rac*-**100**) varied rather erratically between experiments without apparent difference in the experimental setting (entries 2a and 2b). From the experiment in entry 2a, *rac*-**20** was isolated but could not be purified from unidentified byproducts to allow a meaningful yield determination. From the experiment in entry 2b, yields of 5 % *rac*-**20** and 12 % *rac*-**100** were isolated, but even this *rac*-**20** was heavily contaminated with another byproduct (presumably the aforementioned minor isomer of dimethyllariciresinol) by about 25 %. Inverse addition (adding the starting material to the titanium(III) reagent solution) or quenching the reaction with 10 % HCl instead of dilute H_2SO_4 did not have any significant impact on product distribution (entries 3 and 4). Addition of a reducing agent (entry 5) or a proton source (entry 6) to the reaction mixture did not alter the course of the reaction towards dimethyllariciresinol either.[g] **Table 6** is not an exhaustive list in that the experiment was repeated several more times under the standard conditions (corresponding to entries 2a and 2b), with continued variations in

[g] Incidentally, these two findings where starting material consumption took place despite water or acid being part of the reaction mixture means that radical formation does not require the exclusion of protic substances. Yet, when the solvent is made oxygen-free by the stated method, water is also largely eliminiated.

product distribution, high byproduct formation and problems when trying to isolate seizable quantities of pure product. The reason for these inconsistent results, or why the furofuran compound was formed at all, remained obscure, and this approach, disappointingly, turned out rather unrewarding.

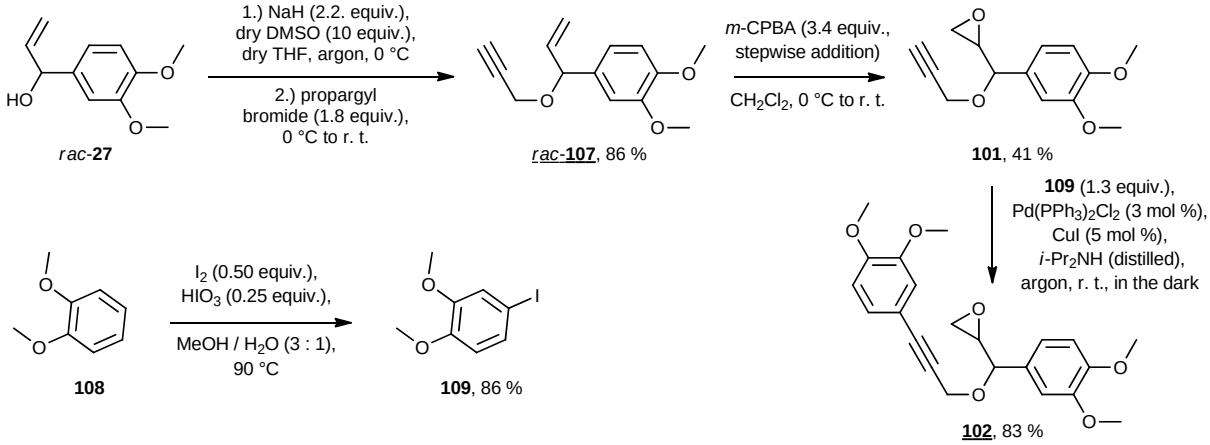
The main difference between the Nugent and Roy reports is that in the former case, the olefin had always been terminal, i.e. no arylvinyl compounds had been used; rather, starting materials like **91a** in **Scheme 42** (page 64) were employed. Such compounds, however, could not be used for lignan synthesis because position C7' would then be a simple methyl group in the cyclization product. Instead, there was a possibility that switching from double bond-containing starting materials to triple bonds may lead to more reproducible reaction results because of the difference in the reaction mechanism.

Retrosynthetically, two routes could be envisioned (**Scheme 44**). Compound *rac*-**20** could come from the diastereoselective hydrogenation of 7',8'-didehydrodimethyllariciresinol **104**, cyclization to which would require ether **102** (i.e. the triple bond analog of **85**). In fact, one report by Roy and co-workers states both the racemic and asymmetric preparation of a 1 : 1 mixture of magnofargesin and 7'-epimagnofargesin **105** (which could not be separated) from the corresponding acyclic precursor **103**.[264] The resulting configuration of the exocyclic double bond in **104** might not be important for the eventual synthesis of furan-lignans **XI** (such as **20**) as long as hydrogen could be delivered selectively to the top face of **104** by a heterogeneous catalyst (or alternatively also to the bottom face when using e.g. Crabtree's catalyst[265] which might afford 8'-*epi*-**20**). As for preparing **102** from **101**, this would have the advantage that **101** itself could be immediately subjected to radical cyclization to *rac*-**106**, too. Like in the case of olefins, Nugent had only used terminal acetylene **91b**, and **101** would come close to this cyclization precursor. Additionally, Roy had actually used compound **101** (and others of this type) in this radical cyclization.[234, 266] A method could possibly be devised that functionalizes the exocyclic double bond of *rac*-**106** stereoselectively, which would bear the advantage that this step occurs late in the synthesis and therefore opens up for divergence in the preparation of lignans.



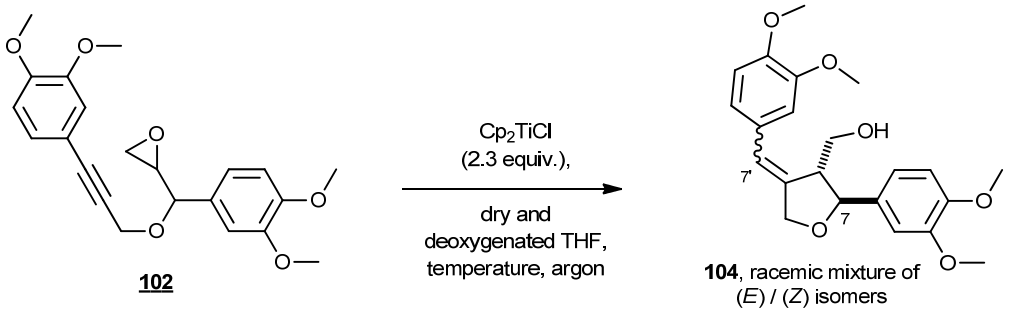
Scheme 44: Modification of the synthetic plan. In the lignan magnofargesin **105** (which had been obtained[264] as a mixture with its 7'-epimer *via* this cyclization), the double bond is (*Z*)-configured (i.e. the arene is pointing away from the hydroxymethyl group). Concerning the use or omission of the descriptor *rac*, *cf.* footnote e.

Preparing ether **101** *via* *rac*-**107** by nucleophilic substitution with *rac*-**27** and using propargyl bromide by the reported method[234] was, this time, smooth and reproducible (**Scheme 45**). In this reaction, DMSO was required as a co-solvent for reasonable reaction rates for the formation of *rac*-**107**. Epoxidation of the double bond—which can be accomplished selectively in the presence of triple bonds due to a rate difference with a factor of approximately 10^3,[177] meaning that the substitution and epoxidation steps can be reversed in this case—produced about the same yield as had been observed in the epoxidation of alcohol **27**. 4-Iodoveratrole **109** was prepared[267] from veratrole **108** with complete regioselectivity of iodine entry, and Sonogashira cross-coupling of these two compounds using a standard Pd/Cu protocol[267] gave cyclization precursor **102** in reproducibly good yield (two runs, 83 and 84 %, respectively).



Scheme 45: Synthesis of cyclization precursors **101** and **102**.

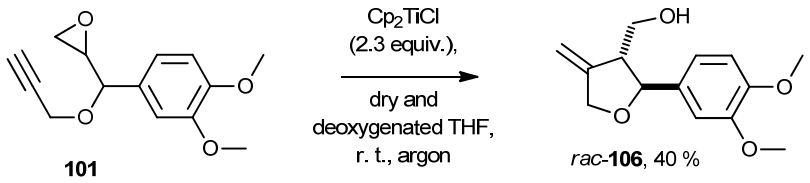
With epoxy ethers **101** and **102** in hand, the titanium(III)-mediated cyclization could be tried. First, compound **102** was subjected to the usual conditions because it would be a more direct way to dimethyllariciresinol, and because of the (7'-epi)magnofargesin literature precedent.



entry	(*E*) / (*Z*) ratio	temperature	combined yield
1	7 : 3	r. t.	27 %
2	7 : 3	-30 °C	30 %
3	7 : 3	+60 °C	n/d

Table 7: Synthesis of 7',8'-didehydrodimethyllariciresinol. (*E*) / (*Z*) ratios were determined by crude ^{1}H NMR. The structure that is shown would be (*E*)-configured (i.e. if the wavy bond is replaced by a normal single bond).

Compared with the cyclization of **85**, this reaction was found to be somewhat less intractable, although the yields obtained were still not nearly as high as those reported for the magnofargesin / 7'-epimagnofargesin mixture (84 and 73 % for racemic and optically active product, respectively; **Table 7**). Curiously, the (*E*) / (*Z*) isomeric ratio in the crude mixture was not 1 : 1 as reported, but 7 : 3 in favor of the (*E*)-configured product when compared with spectral data (especially the chemical shifts and coupling constants of H7 and H7') of natural, (*Z*)-configured magnofargesin (where NOE experiments had been used to establish the double bond geometry).[268-269] The temperature (with room temperature being the literature condition) did not seem to affect this ratio in any way, and the overall aspect of the crude product from these reactions in ^{1}H NMR was very similar as well, also in contrast to the results of **Table 6**.
When this was compared with the cyclization result on the terminal triple bond-containing **101**, a somewhat higher yield of 40 % *rac*-**106** was obtained (**Scheme 46**). This is comparable with the 37 % yield which had been reported by Nugent on compound **91b** (**Scheme 42**, page 64).

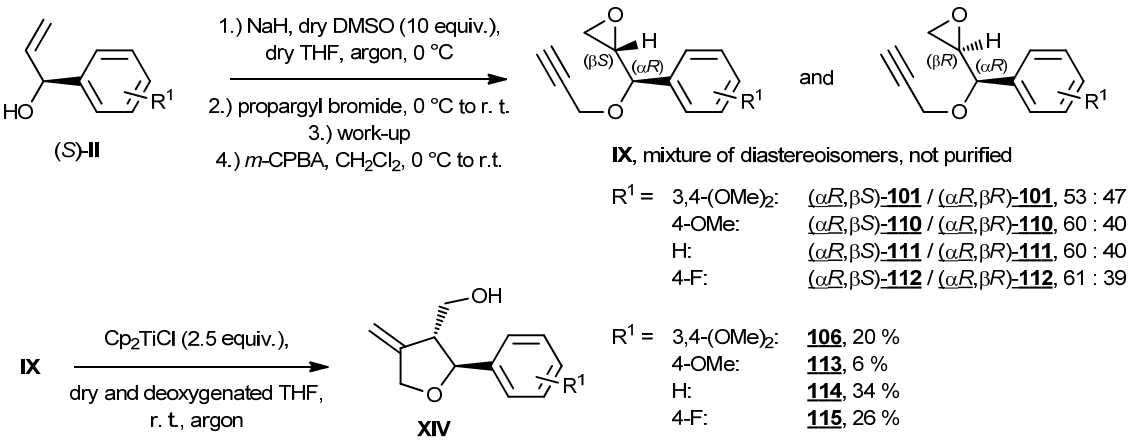


Scheme 46: Synthesis of intermediate *rac*-**106**.

Since this had been the best outcome on this crucial step so-far, and because of the opportunity to deviate from existing literature by finding ways to modularize the preparation of lignans at this point in the synthetic route (reliant on the appropriate functionalization of the exocyclic double bond in compounds like **106**), efforts were concentrated on this strategy.

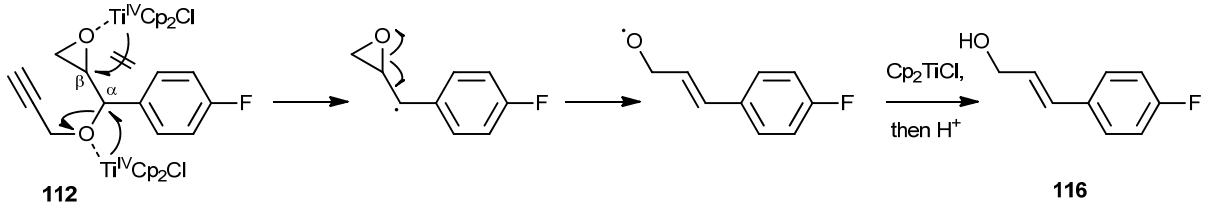
But before moving to the chemistry that finally elaborates *rac*-**106** to a lignan, the asymmetric preparation of **106**,[h] and that of the remaining compounds, shall be described. It was found convenient to combine the propargylation and epoxidation steps into one telescoped procedure, and use crude epoxy ether **IX** for the radical cyclization (**Scheme 47**). The only requirement for this to work was to remove the DMSO co-solvent prior to epoxidation (as it would otherwise consume the peracid and be converted to the sulfone), which was possible due to the miscibility gap of DMSO and Et_2O (used as the extraction solvent) that arises in the presence of water.

[h] Compounds like **106** (i.e. those of generic structure **XIV**) and all those which are derived from them in subsequent steps are meant to be optically active with the absolute configuration as shown, unless explicitly marked as *rac*.



Scheme 47: Preparation of enantiopure intermediates **XIV**. Yields are calculated from (*S*)-**II**. For the determination of the diastereomeric ratios of intermediates **IX**, *cf.* text.

The low overall yield in the case of **113** was mainly due to purification issues of the cyclized intermediate. In the case of the electron-deficient *para*-fluorine compound **115**, byproduct **116** was also isolated after cyclization which was possibly formed by the mechanism shown in **Scheme 48**. In general, the epoxide oxygen's lone pairs are likely more exposed for complexation with the radical-donating reagent and the adjacent Cβ-O bond is more easily cleaved than the other C-O bonds in the molecule. However, the titanium(III) complex would also be able to coordinate to the oxygen atom at the α position. Assuming that this is the correct mechanism, Cα-O bond cleavage apparently occurs when this benzylic position is slightly electron deficient (epoxy ether **112**), while it does not happen in the electron-rich or neutral cases (**101**, **110** and **111**).

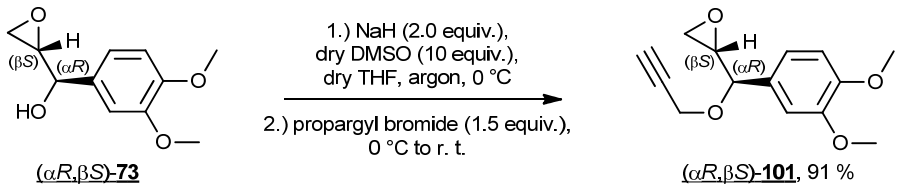


Scheme 48: Mechanistic rationale to explain how epoxy ether **112** forms byproduct **116**.

If true, this would imply a limitation of the method: the more electron deficient the arene (and hence the benzylic position), the more pronounced this side reaction might become as a consequence of increasingly competing Cα-O bond cleavage.

The best yield over these three steps was achieved for the electron-neutral **114** because the phenyl scaffold in it is most insensitive to both the *m*-CPBA epoxidation and the radical cyclization.

As mentioned above, the Sharpless asymmetric epoxidation had delivered (α*R*,β*S*)-**73** with defined stereochemistry also at C8. When this compound was subjected to propargylation (**Scheme 49**), which leaves both stereocenters untouched, then the resulting epoxy ether could be compared with the mixture of (α*R*,β*S*)-**101** / (α*R*,β*R*)-**101** of **Scheme 47**, and hence, the ^{1}H and ^{13}C NMR signals of the individual diastereoisomers could be unambiguously assigned.



(αR,βS)-**73** (αR,βS)-**101**, 91 %

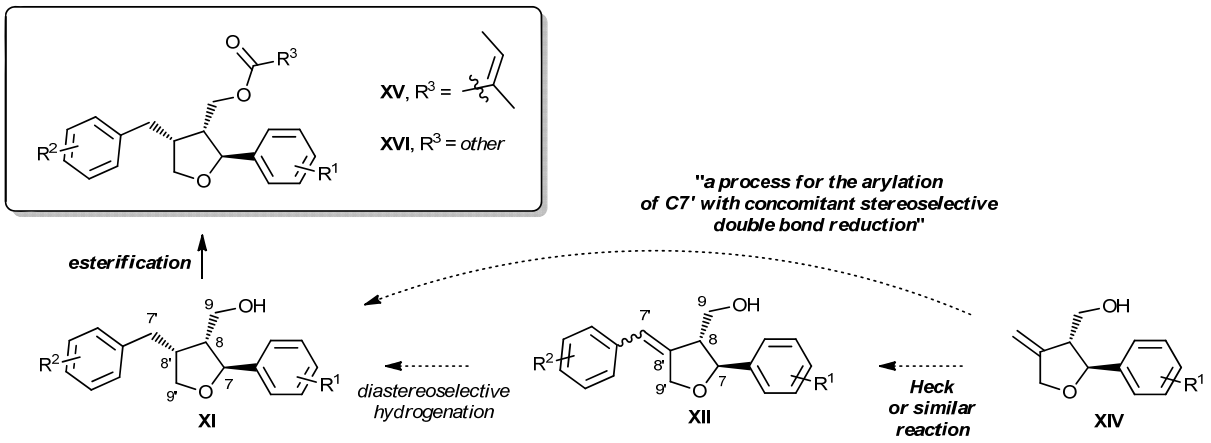
Scheme 49: Compound (αR,βS)-**101** with known configuration at Cβ was the basis of assigning the diastereomeric distributions of epoxy ethers **IX** in **Scheme 47**.

This also allowed the determination of which diastereoisomer was formed in slight excess during epoxidation in each case of **IX** by extending the NMR comparison. Although these ratios (shown in **Scheme 47**) are not quite 1 : 1 (as was reported previously),[234] *m*-CPBA epoxidation is by and large unselective in this case, with no significant bias of the intermediate propargyl allyl ether to facilitate peracid attack from either side. As was explained above, this non-selectivity in forming the *threo* or *erythro* epoxide is inconsequential for the remaining synthesis due to the stereoconvergence of the radical cyclization.

Finally, the elaboration of compound (*S*)-**69** (i.e. (*S*)-**II** with R^1 = 3,4,5-$(OMe)_3$, *cf.* **Figure 13**, page 53) could not be pursued further due to time constraints and was the subject of separate work dealing with the synthesis of 5-methoxyleoligin **60** and analogs therof.[163] Incidentally, this trimethoxy-substituted allylic alcohol **69** represented the most electron-rich variant of all substitution patterns and, consequently, was also found to be completely incompatible with the *m*-CPBA-mediated epoxidation.

B.1.2 **Elaboration of substituted tetrahydrofurans to lignans**

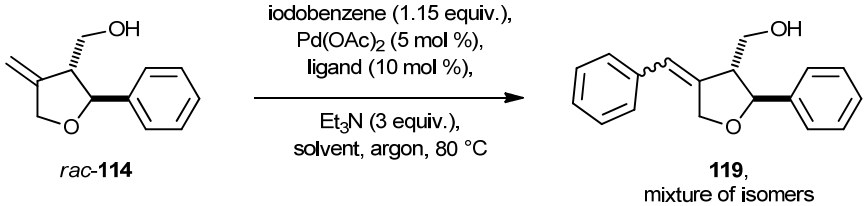
When consulting the top part of retrosynthetic **Scheme 20** (section A.4, page 43), is becomes apparent that a method needed to be found which accomplished two things: a second arene at C7' had to be installed, and a stereocenter at C8' which is adjacent and *cis* to the existing C8 needed to be created (**Scheme 50**).



Scheme 50: Cut-out of retrosynthetic **Scheme 20**, showing the elaboration of intermediates **XIV** to furan-type lignans **XI**, **XV** and **XVI**.

The exocyclic double bond in question is not activated, precluding conjugate addition methodology, but the Heck reaction could be considered for this purpose. As this is an addition-elimination process[210, 270-271] that would retain the double bond, an additional step is required to convert **XII** diastereoselectively into lignan compounds **XI**.

Closer examination of the literature revealed though that this would not be so straight-forward because examples are rare where unactivated, 1,1-disubstituted olefins have been functionalized in this way by intermolecular reaction. Therefore, a screening was conducted to find a catalytic system which would arylate *rac*-**114** as the test compound with iodobenzene in the presence of palladium acetate, different standard ligands and Et_3N as the base in different solvents (**Table 8**).

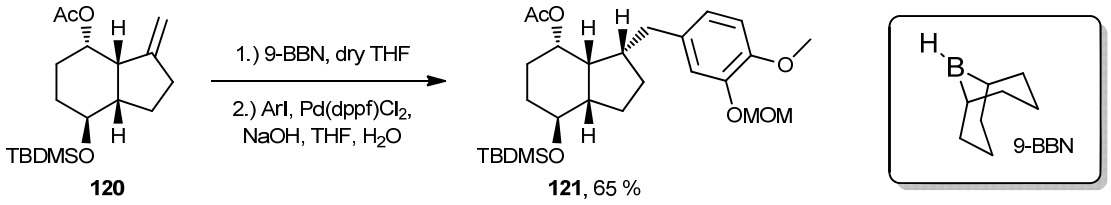


conversion after 22 h, ligand / solvent	DMF	MeCN	toluene
$P(Ph)_3$	< 1 %	< 1 %	1 %
$P(2\text{-Tol})_3$	< 1 %	3 %	2 %
$P(4\text{-Tol})_3$	< 1 %	< 1 %	< 1 %
none	< 1 %	1 %	< 1 %

Table 8: Attempted Heck reaction on *rac*-**114**, using racemic material for screening purposes. Conversion was determined by GC-MS.

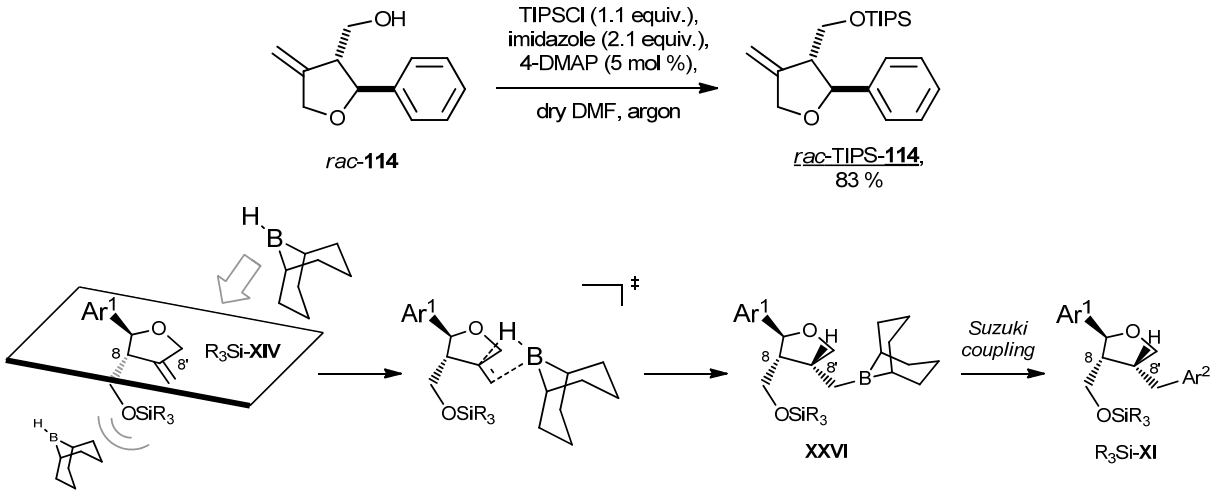
Not quite unexpectedly, conversion to **119** was negligible and only homocoupling product was found in significant amounts. An experiment where the $P(2\text{-Tol})_3$ / MeCN combination (i.e. the 3 % conversion entry in **Table 8**) was used but with the temperature increased to 125 °C (in a pressure vial), only produced biphenyl at a higher rate. Literature conditions that were used to arylate a 1,1-disubstituted olefin were also tried: a combination of Ag_2CO_3 (2 equiv.), $Pd(OAc)_2$ (6 mol %) and PPh_3 (12 mol %) in DMF at 80 °C[272] only led to starting material decomposition, while a mixture of $Pd(OAc)_2$ (10 mol %), P(*n*-Bu)$_3$ (20 mol %) and K_2CO_3 (1.3 equiv.) in DMF at 100 °C[273] only gave homocoupling product.

As the above screening provided no clues for how to optimize the Heck reaction for this problem, a different strategy was attempted. If the exocyclic double bond could not be used directly to couple it to an arene, it should be possible to use its reactivity in a different way. As **Scheme 50** implies, a "process for the arylation of C7' with concomitant stereoselective double bond reduction" might be devised. So far, the reduction step has been considered to proceed subsequently to the arylation, but reversing the order of events could actually lead to the desired **XI**. In a hydrometallation reaction, the metal-alkyl adduct can be used for a subsequent carbon-carbon bond-forming process.[274] Specifically, it is well established that hydroboration of olefins produces borylated intermediates which undergo Suzuki cross-coupling.[275-276] For steric reasons, a hydroboration reagent would regioselectively add to the double bond of **XIV** such that the boron atom forms a bond to the distal carbon. In addition, it would be important to control the stereochemistry of the reaction, and this is determined by the side from which the hydride is delivered. For instance, in their synthesis of the natural compounds otteliones A and B, Sha and co-workers[277] used the sterically demanding 9-borabicyclo[3.3.1]nonane (9-BBN) to hydroborate compound **120** which, upon completion of the addition reaction, was immediately subjected to Suzuki conditions, affording product **121** in good yield (**Scheme 51**) and as a single diastereoisomer as shown. Only the **120**-derived moiety of the corresponding borane intermediate is transferable during coupling because of the bicyclic nature of 9-BBN, making this a valuable reagent for tandem reactions of this kind. Compound **120** is rather rigid and also somewhat book-shaped, and one should expect good stereoselectivity for the addition there. The question was whether intermediates **XIV** would just do the same with reasonable selectivity.



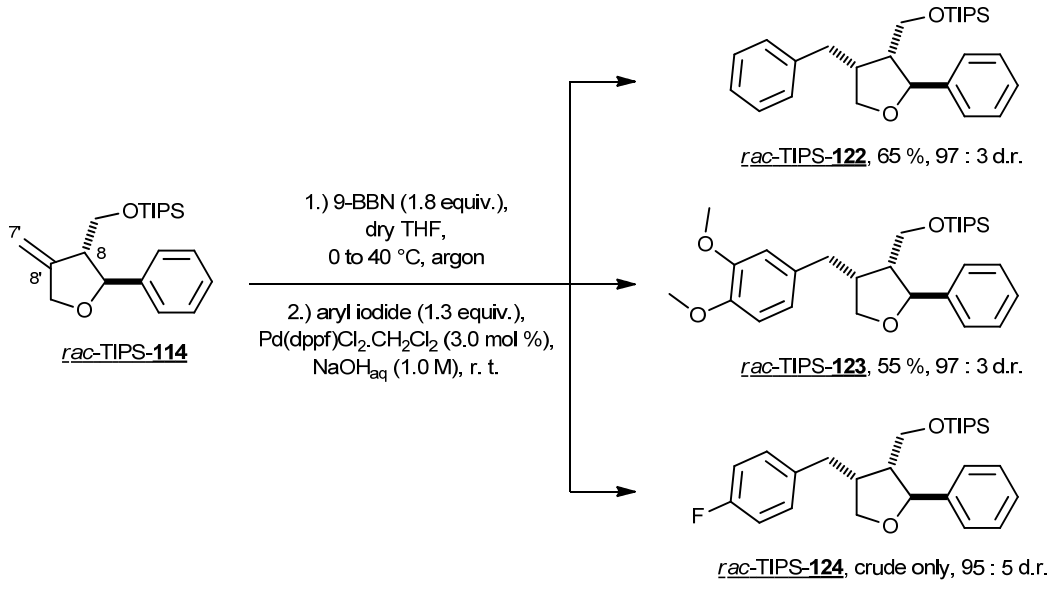
Scheme 51: Use of stereoselective hydroboration and Suzuki coupling during the synthesis of otteliones.[277]

Having the hydroxymethyl group silylated not only protects it from the hydroboration reagent, but also adds steric demand on the bottom face of the molecule as a directing effect (**Scheme 52**), making it less favorable than the approach to the top face of R_3Si-**XIV**. The aryl substituent might additionally help to create selectivity by pushing the protected hydroxymethyl group downward. Borylated intermediate **XXVI**, although stable to aqueous conditions, does not have to be worked-up and isolated for subsequent coupling.



Scheme 52, top: TIPS-protection of *rac*-**114**. **Bottom:** steric reasoning for the diastereoselectivity of this reaction in the case of the generic R_3Si-**XIV**, shown for the optically active compounds that would eventually be used for lignan synthesis. The addition occurs *trans* with respect to the directing side chain (on the opposite side of the ring system), but the resulting substitution pattern is 8,8'-*cis*.

For the Suzuki reaction, 1,1'-bis(diphenylphosphino)ferrocene (dppf) appears to be a popular ligand for transformations with 9-BBN-derived coupling partners.[277-278] The coupling part of the reaction can be conducted in THF, which is convenient because 9-BBN is commercially available as a solution in this solvent. When the reaction was conducted as shown in **Scheme 53**, the diastereoselectivity was around 95 : 5 in favor of the desired 8,8'-*cis* isomer as confirmed by comparing the coupling constants and chemical shifts in NMR spectroscopy of e.g. rac-TIPS-**123** with those of natural dimethyllariciresinol[279] and lariciresinol (in the latter case, all stereoisomers are known).[18] Initially, the temperature was raised gradually during hydroboration, but a constant 40 °C was eventually found to ensure a reasonable reaction rate without compromising the kinetic preference for the *cis* configuration.



Scheme 53: First racemic examples of the hydroboration-Suzuki coupling sequence. Diastereomeric ratios were determined by ^{1}H NMR.

Another matter concerned the size of the protecting (or directing) group: using TBDMS or TBDPS made no significant difference from 95 : 5, while an acetylated intermediate gave a worse ratio of 82 : 18 (see **Scheme 54** further below) and mesylate was incompatible. Therefore, the TBDMS group was eventually chosen as the most economical option; TBDMS ethers resist aqueous work-up very well but are readily cleaved under acidic conditions or with fluoride ion.[280] Eventually, it was found that crude TBDMS-**XIV** could be used for this hydroboration-Suzuki coupling sequence, and that the silyl group could be removed *in situ* by simply adding TBAF solution after coupling.

Later it was also found that $CsCO_3$ in place of aqueous NaOH gave slightly improved results, that the catalyst loading could be reduced to 2.5 mol % and that 1.5 equivalents of 9-BBN were sufficient. From the three examples above, it could already be anticipated that the reaction is also fairly robust with respect to the electron demand of the halide coupling partners. Moreover, aryl bromides and aryl iodides could be used interchangeably without noticeable differences in yield. Although removing molecular oxygen (and peroxides) from the THF solvent, e.g. by freshly distilling from sodium benzophenone ketyl, is not as imperative as it is in the radical reactions (*vide supra*), it was nonetheless found highly advisable in order to avoid inconsistencies in the results if the quality of the (stored) solvent varies with time.[i] In part, this is likely because dissolved oxygen can lead to more homocoupling product.[177] For the same reason, the coupling step should also be conducted under inert gas.

Enantiopure cyclization intermediates **XIV** were then used for the preparation of some unknown (and probably naturally not occurring) lignans. An important aspect of the final protocol (**Table 9**) is that it allows the swift synthesis of substance libraries with respect to altering the aryl scaffold at C7' by preparing a larger amount of borylated intermediate **XXVI** and then simply distributing aliquots of this completely homogeneous solution to mixtures of catalyst, base and different aryl halides, many of which are commercially available.

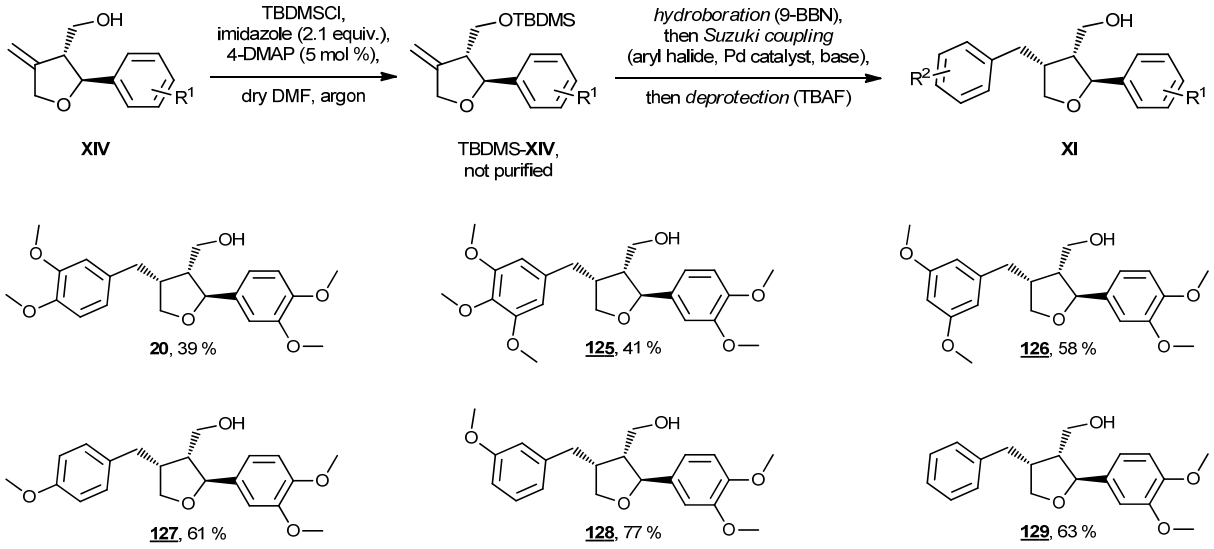


Table 9

[i] In one case, a series of reactions where aliquots of borylated intermediate had been used to prepare a range of new, unnatural lignans yielded no product at all. This was traced to a batch of aluminia-dried THF which had been used to transfer the aliquot solutions. Treating this THF by the sodium-benzophenone method and repeating the procedure gave satisfactory results again on all reactions.

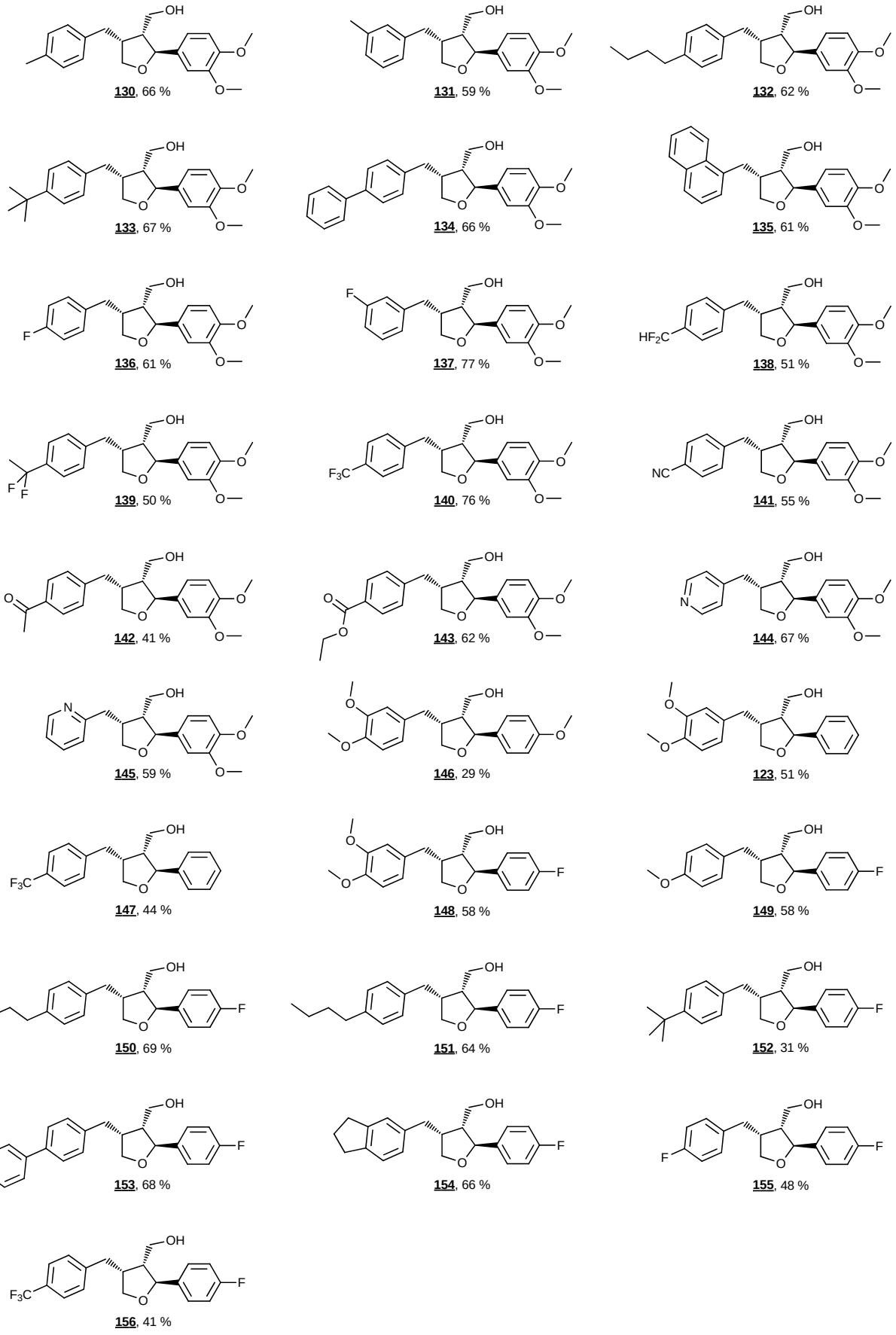
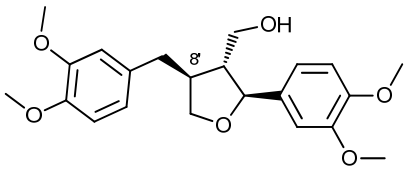


Table 9, continued: Synthesis of 3-(hydroxymethyl)tetrahydrofuran-type lignans *via* the hydroboration-Suzuki coupling sequence. Yields are calculated from unprotected **XIV**; d.r.s vary between 94 : 6 and 97 : 3 in all cases.

The reaction is also fairly scalable; for example, 1 g of (+)-dimethyllariciresinol **20** which had not been prepared asymmetrically before could be synthesized in a single batch. Like in the racemic test cases, the diastereoselectivity was generally between 94 : 6 and 97 : 3 in all cases, and yields (as calculated from unprotected alcohol **XIV**) were typically around 60 % for the telescoped method as shown above. The low yields in some cases were mainly due to issues with isolation. Generally, standard flash chromatography on silica gel was sufficient for purification, but preparative HPLC on reversed phase was necessary in some cases. Tracking the consumption of the borylated species **XXVI** by GC-MS, HPLC or TLC (baseline spot) during the coupling process was not successful, therefore the change in TBDMS-**XI** needs to monitored in order to know when to terminate the reaction. If the halide coupling partner contains a functional group which can be reduced by 9-BBN (such as a ketone), an equivalent of water needs to be added to **XXVI** after hydroboration is complete to ensure that excess 9-BBN is destroyed. In the case of heterocycles, 2- and 4-bromopyridine could be coupled, while the synthesis was not successful with 2-bromothiophene and 5-iodo-2-phenyloxazole; in the latter case, only β-eliminated **106** was isolated. The choice of the aryl halides was based on medicinal chemistry considerations, such as electronic and steric properties, as well as biological test results that had been obtained in the meantime (for details, *cf.* section B.2, page 94).

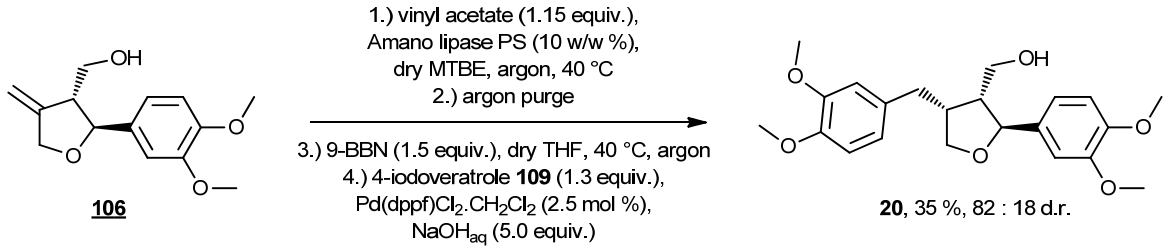
In the case of the dimethyllariciresinol synthesis, the scale of the reaction permitted the isolation and characterization of its 8'-epimer (**Figure 14**), but this required repeated preparative HPLC purification to remove the major isomer dimethyllariciresinol **20**. Surprisingly, 8'-*epi*-**20** has not been reported in the literature so-far. In fact, none of the compounds of **Table 9** are literature-known (that is, except for **20**). Accordingly, arylmethoxy compounds like **125** through **128**, which might be thought of as naturally occurring lignans, have not been reported to occur in plants either. It may be suggested that the continued elucidation of the lignan biosynthetic pathways could be assisted by screening plant extracts and indentifying the lignans contained therein with the help of a synthetic library by e.g. comparing HPLC-MS data of such extracts with those of pure synthetic compounds. An NMR spectroscopic comparison of **20** and 8'-*epi*-**20** is provided in section B.1.4 (page 92).



8'-*epi*-**20**

Figure 14: 8'-*epi*-Dimethyllariciresinol was isolated and purified in minute amount.

It would be nice if the protected **XIV** did not have to be worked-up prior to hydroboration. Adding 9-BBN directly to the solution of the protection step did not give borylated intermediate **XXVI**, presumably due to the incompatibility of 9-BBN with imidazole (Lewis acid-base interactions). While different reaction conditions for silylations might work, an alternative and perhaps more elegant way would be **Scheme 54**. Transient lipase-catalyzed acetylation could be conducted under anhydrous conditions (enzymes may lose their activity under such conditions due to the loss of structural water, which is especially pronounced in *polar* organic solvents,[281] but this does not appear to be the case with these lipases in non-polar, yet anhydrous solvents) and co-generated acetaldehyde was removed by purging the solution with argon (boiling point 20 °C). Then, the usual sequence was conducted in the same reaction vessel by simply adding the reagents in proper succession, and the acetate was cleaved concomitantly during the coupling step by the Suzuki base (aqueous NaOH solution).



Scheme 54: One-pot protection-hydroboration-Suzuki coupling-deprotection. Diastereoselective ratio was determined by ^{1}H NMR. The low yield in this case was likely related to problems with the solvent during the coupling step (*vide supra*).

Unfortunately, the acetyl group appears too small to give useful diastereoselectivity. Other, larger carboxylic acids (of which the vinyl or isopropenyl esters can be readily prepared and which are accepted by the enzyme) might give improved results, yet the relatively undemanding, trigonally planar sterics of all carboxylates—as opposed to the tetrahedral silicon atom—might preclude just that. More detailed investigations were not carried out (but *cf.* **Scheme 60**, page 87).

A limited study on the substrate scope of hydroboration selectivity with 9-BBN indicated that the 5-membered system is a rather fortunate case of stereoselectivity if there is only one pre-existing, adjacent bond to stereodirect the hydroboration. For these investigations, a tandem Wittig olefination-hydroboration-Suzuki coupling was devised[j] to convert cyclic ketones **XXVII** into arylmethylated products **XXVIII** in one pot (**Table 10**). However, *cis*-tetrahydrojasmone **157** was the only example to give diastereoselectivities comparable to that found in the case of R_3Si-**XIV**. Neither the benzyl group in **158** nor the isopropyl group in (-)-menthone **159** directed hydroboration to the effect of useful selectivity. The relative configurational assignments of the isomers found as a result of these reactions were merely based on the assumption that hydroboration *trans* to the vicinal substituent would be preferred (i.e. according to the rationale of **Scheme 52, bottom**, and the finding of the experiments in **Scheme 53** where the relative configuration was confirmed using literature NMR data). As it happens, the diastereomeric ratios in the case of **163a**-**e** are close to 1 : 1 and do not even permit to state with reasonable certainty that it was the *cis*-product which had been formed in (slight) excess. Similarly, products **164a**-**e**, derived from racemic camphor **160**, showed only poor diastereomeric ratios, and the relative stereochemical assignments (*cf.* the hydride delivery to ketopinic acid amide **75** in **Scheme 25, top**, section B.1.1, page 47) are somewhat ambiguous.
It should be noted that the selectivities are very similar for a given ketone, independently of the aryl bromide coupling partner. This is also to be expected because the reaction which determines d.r., the hydroboration, takes place prior to coupling, and the borylated intermediate was prepared as one batch and then distributed to the five aryl bromides by the aliquot method as described above. However, varying selectivities among aryl bromides for one and the same borylated intermediate could still arise if the coupling reaction is more sensitive to the steric environment in the case of one aryl bromide than in the case of another, i.e. if the reaction rate ratio to give *syn*- and *anti*- coupled product varies among aryl bromides. This appears not to be the case to any degree of significance; the small deviations that were found in some cases are likely due to measurement uncertainties of these single experiments.

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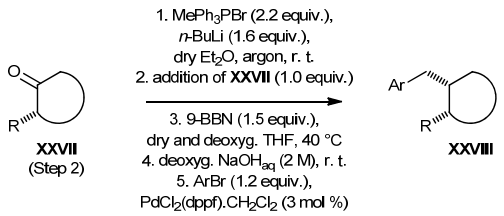
[j] The author would like to acknowledge S. Geyrhofer for performing the experiments on this idea.



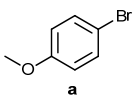
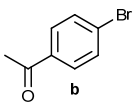
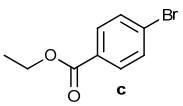
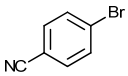
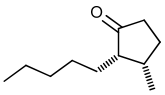
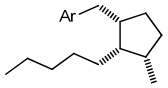
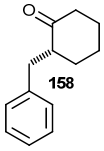
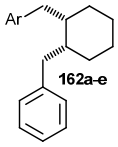
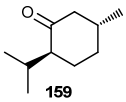
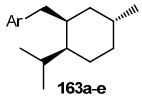
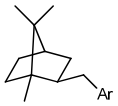
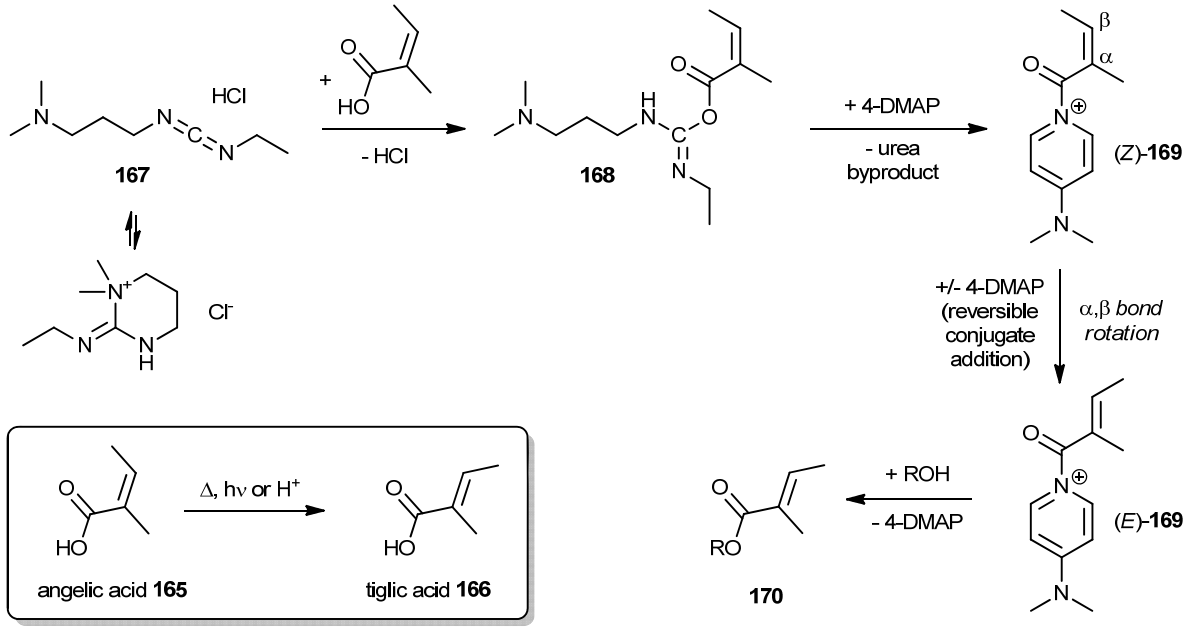
coupling partners ArBr / ketones **XXVII**	 **a**	 **b**	 **c**	 **d**	 **e**	arylmethylated products **XXVIII;** (presumed) major isomer is shown
 **157**	94 : 6	97 : 3	94 : 6	93 : 7	89 : 11	 **161a-e**
 **158**	71 : 29	74 : 26	73 : 27[a]	73 : 27	74 : 26	 **162a-e**
 **159**	57 : 43	59 : 41	58 : 42	56 : 44	56 : 44	 **163a-e**
 **160**, racemic	72 : 28	68 : 32	67 : 33	66 : 34	65 : 35	 **164a-e**, racemic

Table 10: One-pot reaction for the conversion of ketones **XXVII** to **XXVIII**. Products were identified and reaction completion was confirmed by GC-MS, and diastereomeric rations were determined by GC. [a]In this case, GC data is not available and the GC-MS ratio is stated instead. *Cf.* text for the relative stereochemical assignments on the major isomers of products **XXVIII** as shown.

While this data indicates that the method is limited in scope as far as the cyclic components are concerned (at least with regard to its developmental status as presented herein), it also shows that the diastereoselectivity of this method is robust against changes in aryl halide coupling partner—an important aspect when conducting the synthesis of compound libraries.

The last step in the synthesis of leoligin and analogs thereof is the acylation of the primary hydroxy group at C9. As for leoligin itself, esterification involving angelic acid **165** needed to be carried out. This acid is a somewhat sensitive compound because it is the thermodynamically less stable (*Z*) isomer of tiglic acid **166** to which it isomerizes upon exposure to heat, light or (strong) acid. Brute force methods for esterification (e.g. refluxing the reactants with mineral acid catalyst) were therefore not considered; rather, using a peptide coupling method seemed more appropriate. A widely used reaction is the 4-DMAP-catalyzed Steglich method[282] in which a carbodiimide **167** is reacted with the carboxylic acid to give an *O*-acylisourea intermediate **168** (**Scheme 55**). These react only slowly with alcohols and 4-DMAP is therefore added in catalytic amounts to accelerate formation of ester **170** *via* adduct **169**. The carbodiimide is classically *N*,*N*'-diyclohexylcarbodiimide (DCC) or *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDCI.HCl, as shown in the

scheme), the latter having the advantage of giving a highly polar urea byproduct which is removed from the desired ester more easily that the corresponding dicyclohexylurea from DCC.

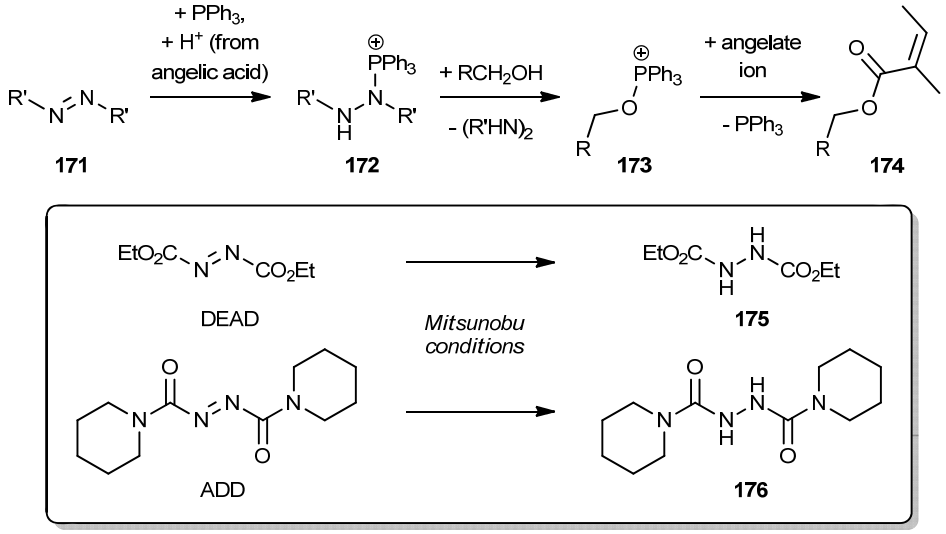


Scheme 55: The Steglich method afforded also tiglate isomerization product **170** when employing angelic acid **165**. The carbodiimide **167** shown here is EDCI.HCl (as was used), and the isomerization problem was noted when testing this reaction with benzyl alcohol (R = Bn).

The method had indeed been used successfully under mild conditions for the esterification of sensitive, α,β-unsaturated carboxylic acids[283] (including in-house precedent)[204] but in this case, GC-MS and ^{1}H NMR data from preliminary experiments (using benzyl alcohol as the test alcohol component, not shown) indicated that an 8 : 2 isomeric mixture was formed as the ester product. This was likely due to the reversible Michael addition of the catalyst to intermediate **168** or pyridinium adduct (*Z*)-**169** (as shown),[284-285] with ensuing bond rotation to the thermodynamically more stable (*E*) configuration.

This isomerization is actually a well-known issue; one published method for the synthesis of angelic acid esters (used in the industrial semi-synthesis of the natural compound derivative ingenol angelate from parent ingenol)[286] uses angelic anhydride and LiHMDS or $CsCO_3$, in the absence of pyridine bases. This approach would presumably be applicable here, but commercial angelic anhydride is very expensive and contains a few percent of angelic-tiglic mixed anhydride. Thus, instead of preparing this anhydride fresh or finding another way of activating the carboxylic acid, the activation of primary alcohol **XI** was considered.

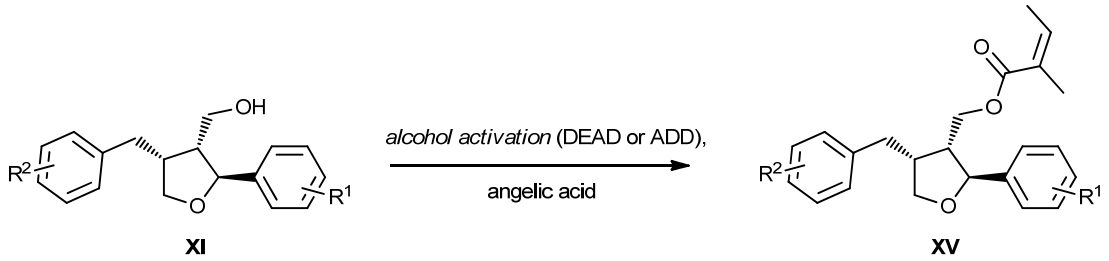
As a result, leoligin and all other angelic acid-containing esters of **XI** were prepared by Mitsunobu reaction.[233, 287] There, the carboxylic acid, as its anion, merely reacts as a nucleophile with phosphonium alkoxide **173** and displaces a phosphine oxide (**Scheme 56**). Accordingly, no tiglate isomer was found when testing the reaction with *n*-octanol. The phosphonium alkoxide is generated from a phosphine (mostly triphenylphosphine) and a diazo compound **171**. Originally, the most commonly employed diethyl azodicarboxylate (DEAD) was used in this transformation as well, but was replaced by 1,1'-(azodicarbonyl)dipiperidine (ADD) later on because the corresponding reduction product **176** of ADD is more polar than **175** and therefore more easily separated from the target ester during column chromatography.



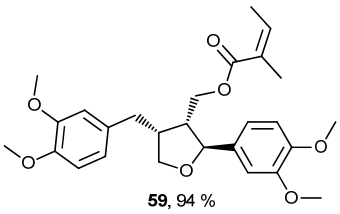
Scheme 56: Mitsunobu reaction used for the generation of angelic acid-bearing lignans because no isomerization problems were seen in a test reaction (with R = *n*-heptyl). Initially, DEAD (R' = CO_2Et) was used, but then replaced by ADD (R' = 1-piperidyl-CO).

Primary alcohols (on which the S_N2 inversion by the incoming carboxylate cannot be observed) represent good substrates for this reaction, and reasonable yields were usually obtained (**Table 11**). Leoligin **59** was prepare before switching from DEAD to ADD, which required carefully adjusted work-up conditions (light petroleum with a minimum amount of chloroform added as the extraction solvent in order to extract as little **175** byproduct as possible, which otherwise would cause problems in the subsequent chromatographic purification because it was roughly co-eluting). This represents the first synthesis of leoligin since its discovery[153] in 2003 to furnish approximately 1 g of this natural compound, and also the first time it could be (serendipitously) crystallized. The overall yield from 3,4-dimethoxybenzaldehyde is 2.9 %. This includes the non-dynamic kinetic resolution (where a 50 % maximum yield applies), the *m*-CPBA-mediated epoxidation (which is lower-yielding compared with the Sharpless epoxidation using enantiopure starting material, but the Sharpless epoxidation had not been conducted on a scale large enough to give sufficient amounts of epoxide intermediate that would be required to eventually afford 1 g of leoligin) and the—as was later determined—non-optimal conditions of the Suzuki coupling (using NaOH base, which is less yielding than $CsCO_3$). It may be estimated that if the synthesis were repeated on this scale and also incorporated the aforementioned synthetic improvements (the individual yield of which is known, albeit not on large scale), an overall yield of 7.5 % should be achievable.

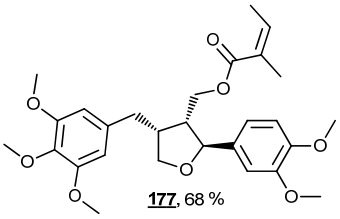
The other 3-(hydroxymethyl)tetrahydrofuran-type lignans **XI** followed suit, delivering the corresponding, leoligin-like angelic esters **XV**.



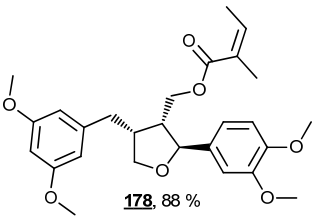
XI **XV**



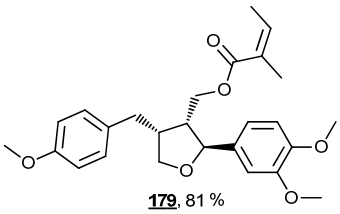
59, 94 %



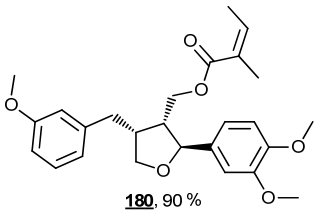
177, 68 %



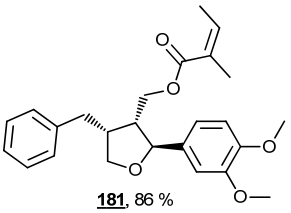
178, 88 %



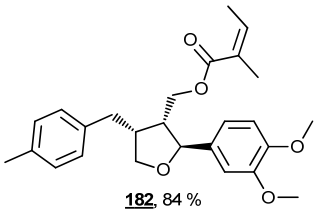
179, 81 %



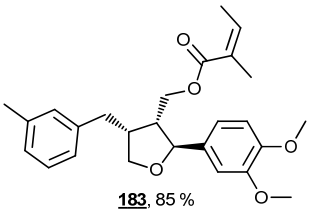
180, 90 %



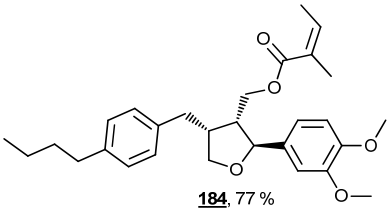
181, 86 %



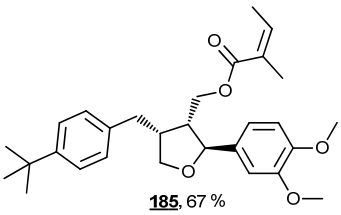
182, 84 %



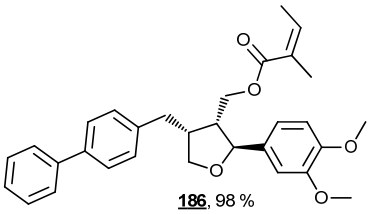
183, 85 %



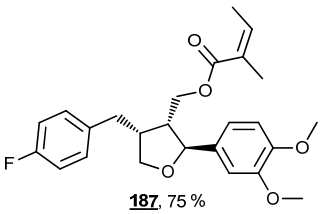
184, 77 %



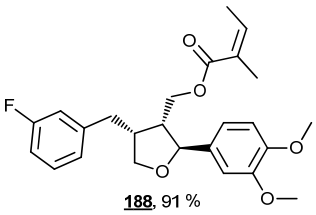
185, 67 %



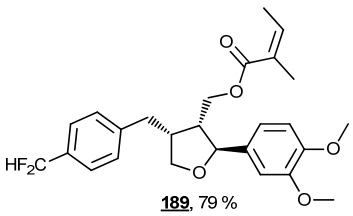
186, 98 %



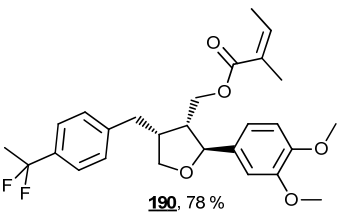
187, 75 %



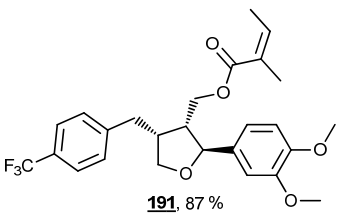
188, 91 %



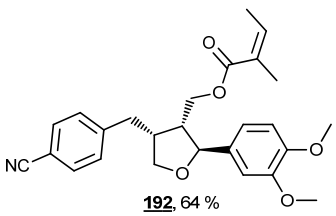
189, 79 %



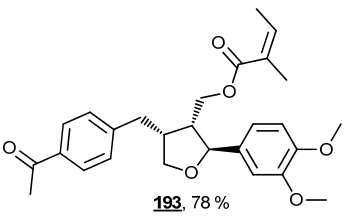
190, 78 %



191, 87 %



192, 64 %



193, 78 %

Table 11

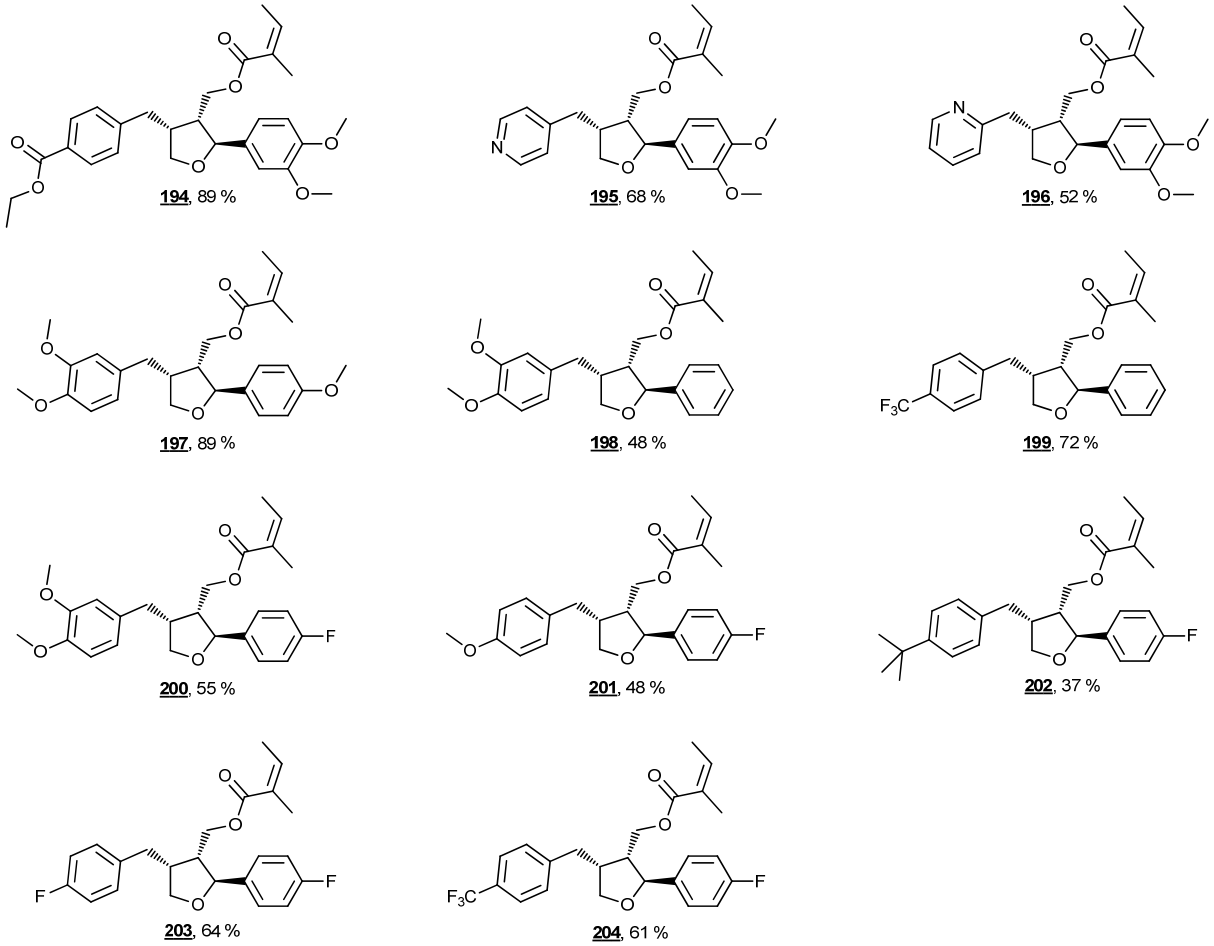
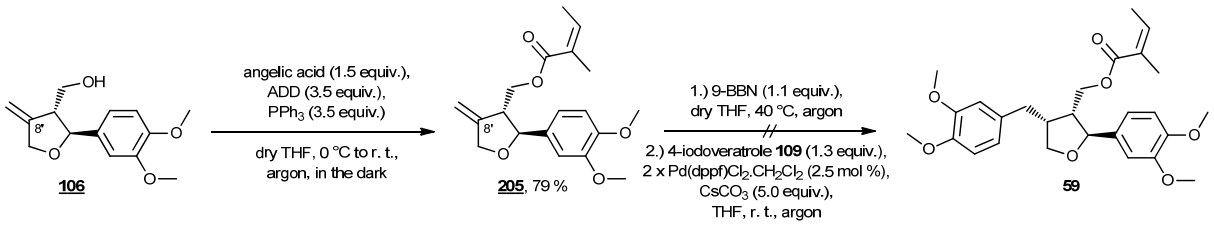


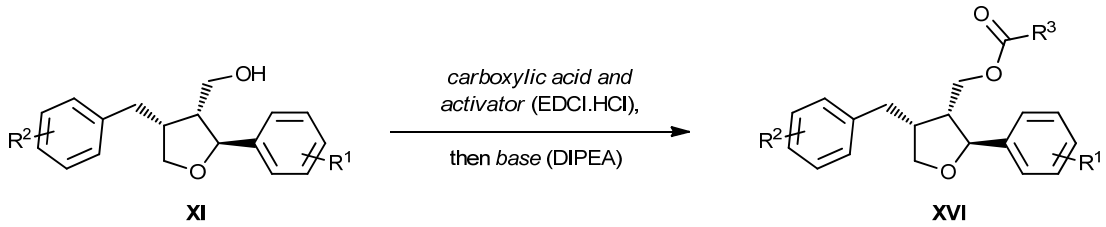
Table 11, continued: Synthesis of leoligin-like lignans pertaining an angelic acid moiety *via* Mitsunobu reaction.

Since alcohols **XI** were generally converted into these esters of angelic acid, it would seem practical to prepare a larger amount of compound **205** first (**Scheme 57**) and then couple it to the various aryl moieties individually. Yet, compounds **XI** were also starting materials for differently esterified lignans and were interesting themselves with respect to biological testing. As for the chemistry, compound **205** should be compatible with the hydroboration conditions because the double bond of the ester is electron-poorer and less accessible than the exocyclic double bond in position 8'. On the other hand, the experiment of **Scheme 54** (page 78) had already shown that the diastereoselectivity would probably be not as good with an acylated hydroxy group (acetyl in the above case) as when it is covered by a silyl group as in TBDMS-**XIV**. This hydroboration-Suzuki coupling experiment was attempted with the standard conditions still, but no coupling product (leoligin) could be isolated, even after addition of more catalyst-ligand complex. Instead, only starting material was found, together with unidentified side products.

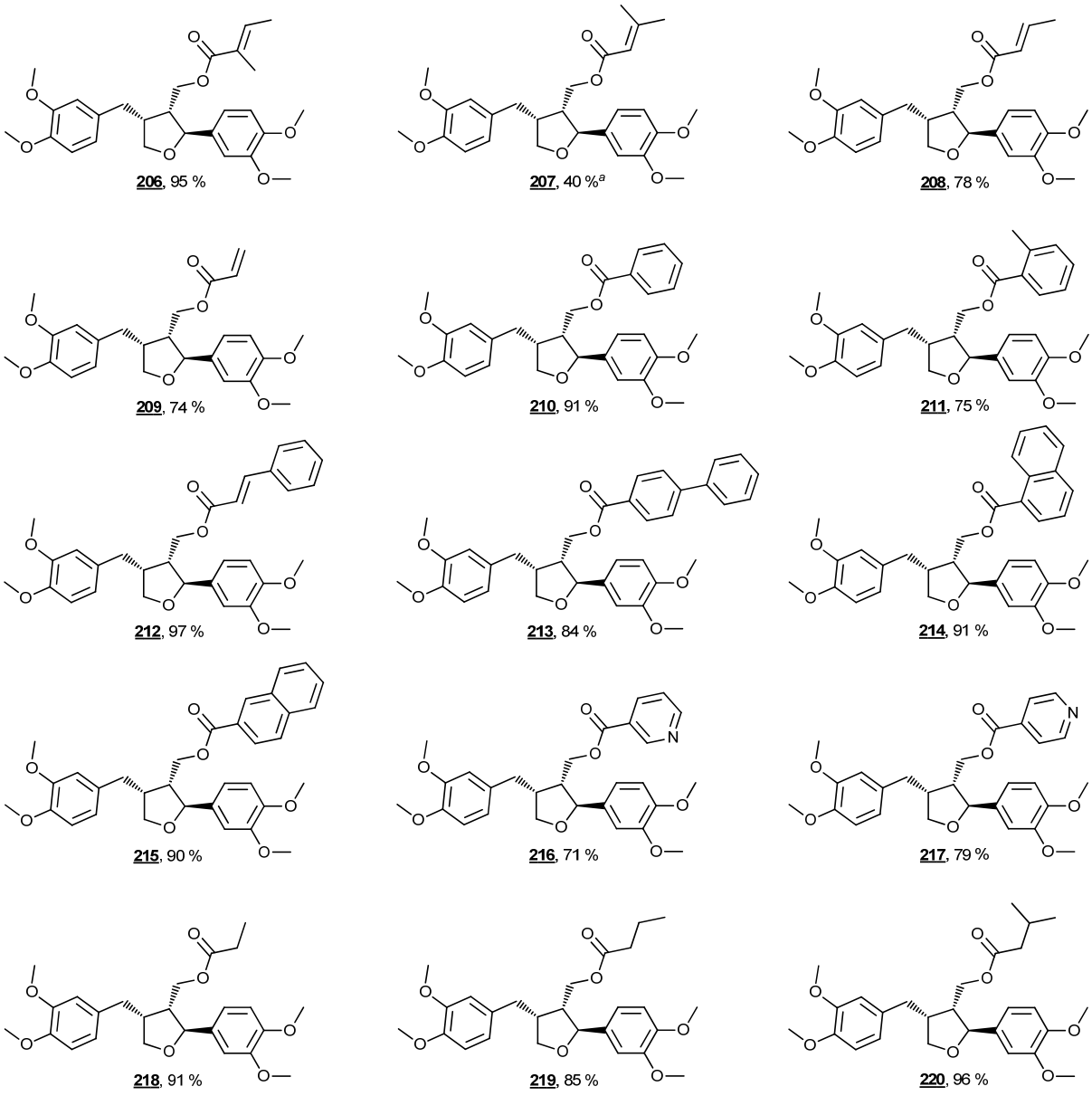


Scheme 57: Attempted synthesis of leoligin *via* intermediate **205**.

A potential explanation for this is that the catalyst might engage in a competing Heck reaction with the α,β-unsaturated ester. However, under these conditions, no Heck product could be found in the crude reaction mixture either, leaving the possibility that this competing catalytic cycle is interrupted and the catalyst is trapped because **205** is, although activated, still a highly substituted olefin.
Aside from these angelates, several other esters **XVI** of dimethyllariciresinol **20** and other 3-(hydroxymethyl)tetrahydrofuran-type lignans **XI** were prepared. The Steglich protocol gave satisfactory results in most of these cases (**Table 12**). Again, the choice of converting particular compounds **XI** into specified esters followed certain hypotheses based on preliminarily obtained biological test results.



XI **XVI**



206, 95 % **207**, 40 %[a] **208**, 78 %

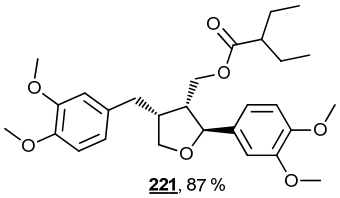
209, 74 % **210**, 91 % **211**, 75 %

212, 97 % **213**, 84 % **214**, 91 %

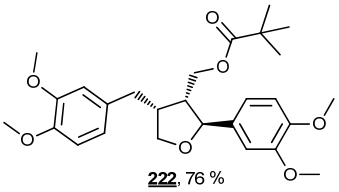
215, 90 % **216**, 71 % **217**, 79 %

218, 91 % **219**, 85 % **220**, 96 %

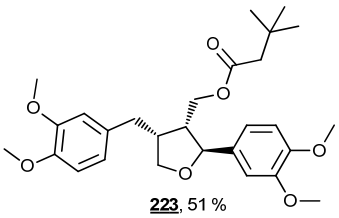
Table 12



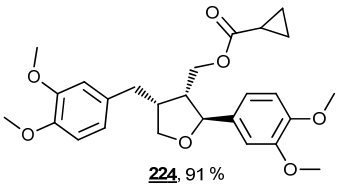
221, 87 %



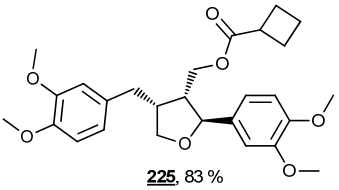
222, 76 %



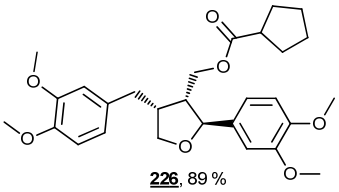
223, 51 %



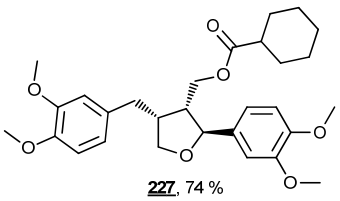
224, 91 %



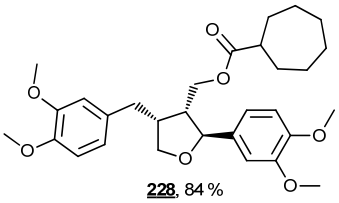
225, 83 %



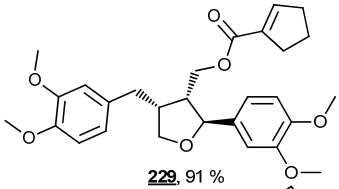
226, 89 %



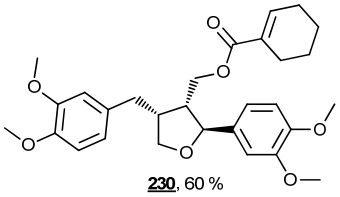
227, 74 %



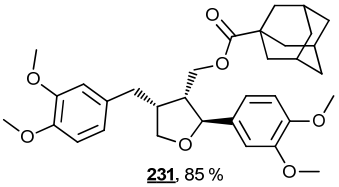
228, 84 %



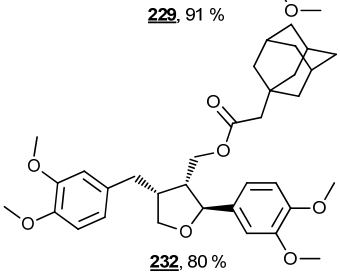
229, 91 %



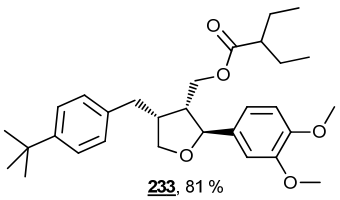
230, 60 %



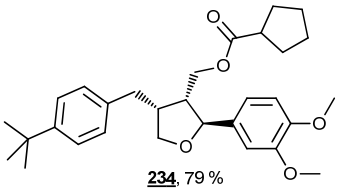
231, 85 %



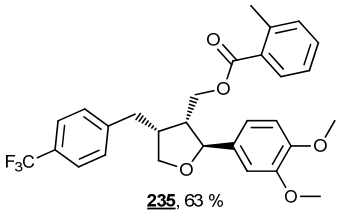
232, 80 %



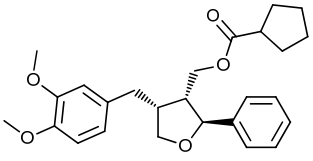
233, 81 %



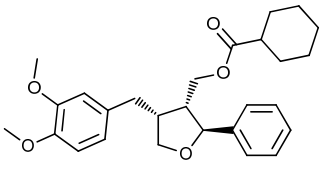
234, 79 %



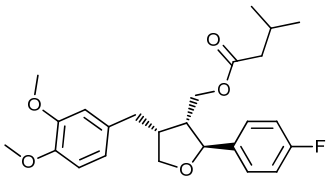
235, 63 %



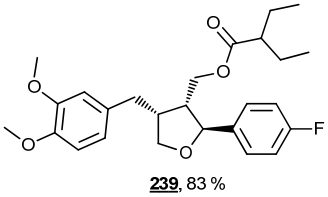
236, 86 %



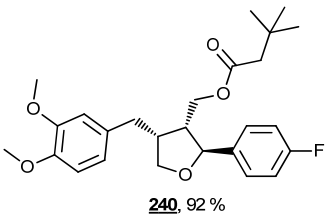
237, 84 %



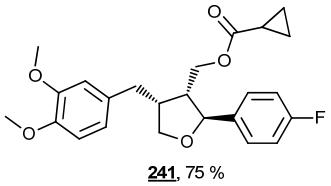
238, 63 %



239, 83 %



240, 92 %



241, 75 %

Table 12, continued

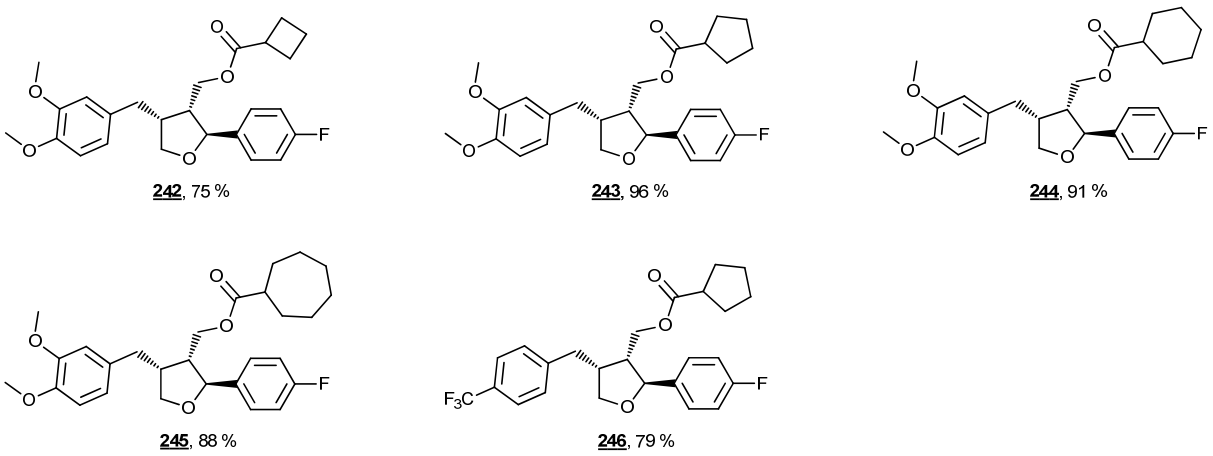
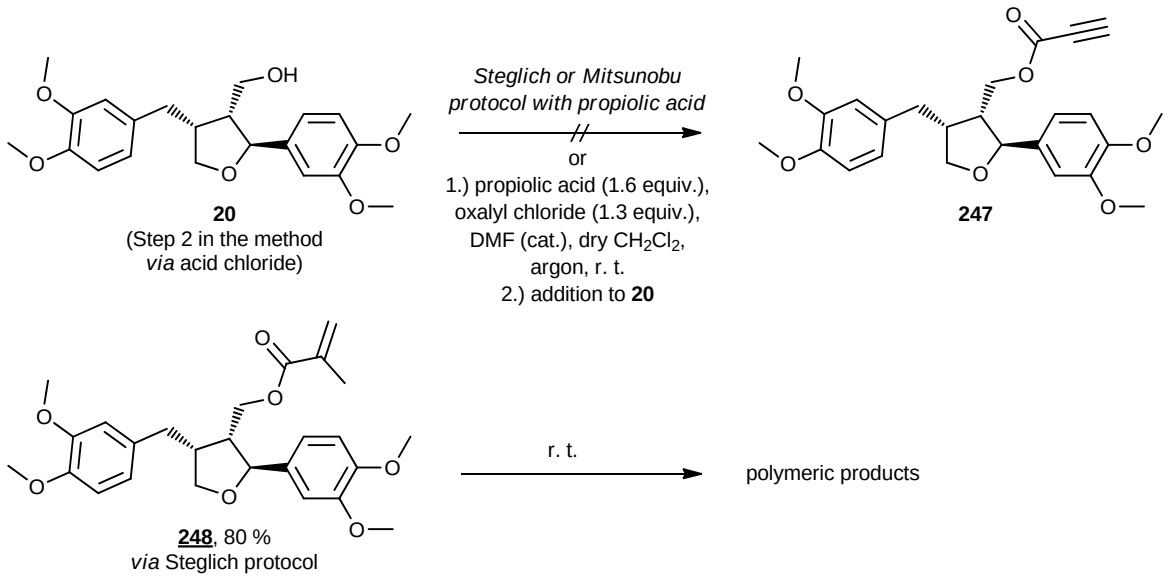


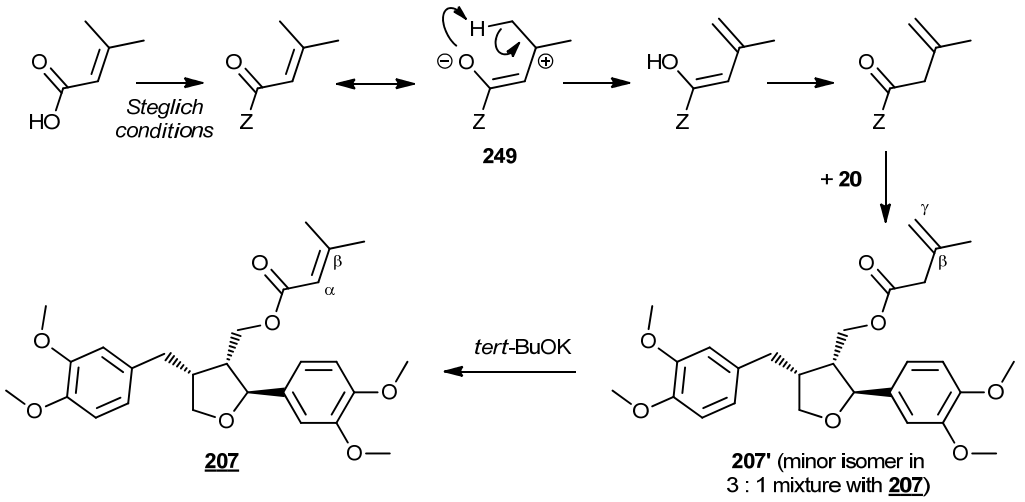
Table 12, continued: Synthesis of leoligin-like lignans with acyl moieties other than angelic acid *via* Steglich reaction. [a]Yield refers to product obtained with respect to amount of dimethyllariciresinol **20** used for the reaction; however, an intermediate de-isomerization step had to be carried out (*cf.* **Scheme 59**). The yield of this compound is 56 % with respect to intermediate material used for de-isomerization.

Several attempts to prepare the propiolic ester **247** of dimethyllariciresinol failed, though. Neither of the above protocols, nor a method *via* the *in situ* preparation of its acid chloride with oxalyl chloride and catalytic amounts of DMF[288] gave the desired product (**Scheme 58**). It seemed that such a propiolate could not be synthesized without protection of the terminal acetylene and a decision was made to scrub this rather unstable compound from the agenda. Methacrylate **248** polymerized after purification and was also removed from consideration for biological evaluation.



Scheme 58: Unsuccessful preparations. The acid chloride method with oxalyl chloride in the top reaction gave dimethyllariciresinyl formate instead.

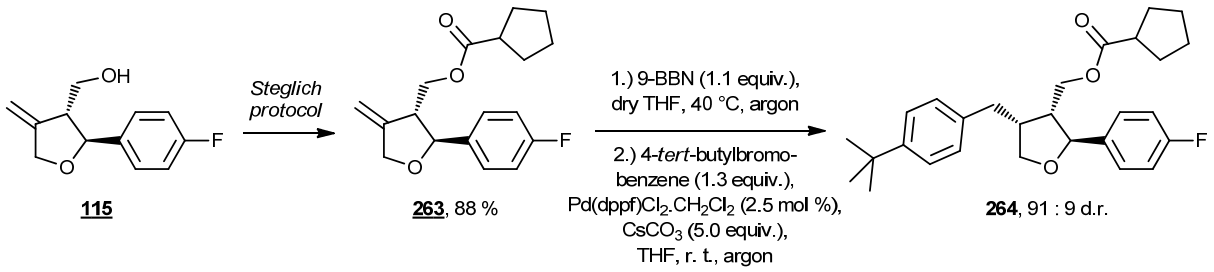
A case of double bond isomerization was observed with 3,3-dimethylacrylic acid. Under the standard conditions, an inseparable mixture of target compound **207** and β,γ-unsaturated isomer **207'** was obtained in a 3 : 1 ratio. This was likely due to the pronounced resonance form **249** in the activated acid derivative, leading to a 1,5-shift of the a proton (**Scheme 59**). Exposing the mixture to strong base[289] reversed this isomerization, whereas the Mitsunobu protocol avoids the problem completely.[163, 290]



Scheme 59: Compound **207'** was partly obtained, probably as a result of the 1,5-shift in **249**. Z represents the isourea- or pyridinium moiety in the activated intermediates.

Pivalate **222** and adamantyl carboxylate **231** were formed only slowly, obviously for reasons of steric hindrance (albeit still in good yields), whereas the reaction failed completely to give the 2,6-dimethylbenzoate of dimethyllariciresinol (not shown). Also in this case, the remedy is the Mitsunobu reaction as shown in related work.[290]

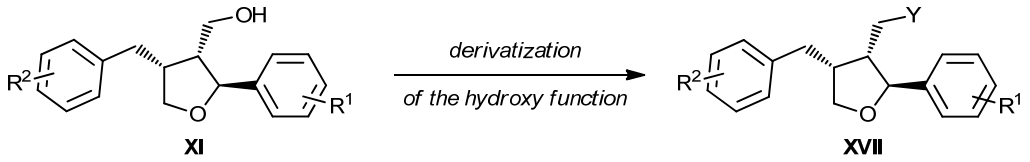
Another attempt was made to reverse the order of the events which elaborate compounds **XIV** to lignans molecules. Concurrently, preliminary results from the pharmacological evaluation suggested that the installment of a cyclopentanecarboxylic moiety (replacing the angelic acid motif) would be the ester cap of choice for a particular aspect of biological activity (*cf*. section B.2, page 94), and that *p*-fluoro and *p*-*tert*-butyl decoration (as shown in **Scheme 60**) should also contribute beneficially. Therefore, compound **264** was prepared *via* **263** as shown. Apparently the sterically more demanding cyclopentyl residue afforded better diastereoselectivity (ratio 91 : 9) when compared with intermediate Ac-**106** in **Scheme 54** (page 78, ratio 82 : 18), but producing compounds with isomeric mixtures possessing this sort of ratio (in view of that the existing method *via* TBDMS-**XIV** was better) did not seem very appealing. The compound was then not re-synthesized using the standard method because of further developments in the biological testing which made **264** less interesting.



Scheme 60: Decreased diastereoselectivity compared to the standard method. Diastereomeric ratio was determined by GC-MS.

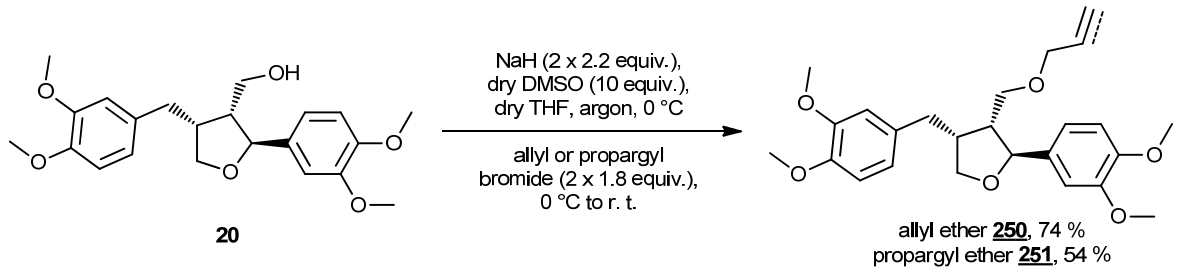
B.1.3 **Further modification of lignans**

The free hydroxy group in lignans **XI** allowed for some additional modifications in order to explore their biological properties, and these non-ester derivatives are collectively termed compounds **XVII** (**Scheme 61**). Specifically, dimethyllariciresinol **20** was used to prepare *O*- and *N*-analogs, as well as C_1-homologs.



Scheme 61: Further modification of lignans **XI**.

Allyl ether **250** and propargyl ether **251** were synthesized in reasonable yield *via* the nucleophilic substitution method that had already been used for epoxy ethers **IX** (**Scheme 62**).

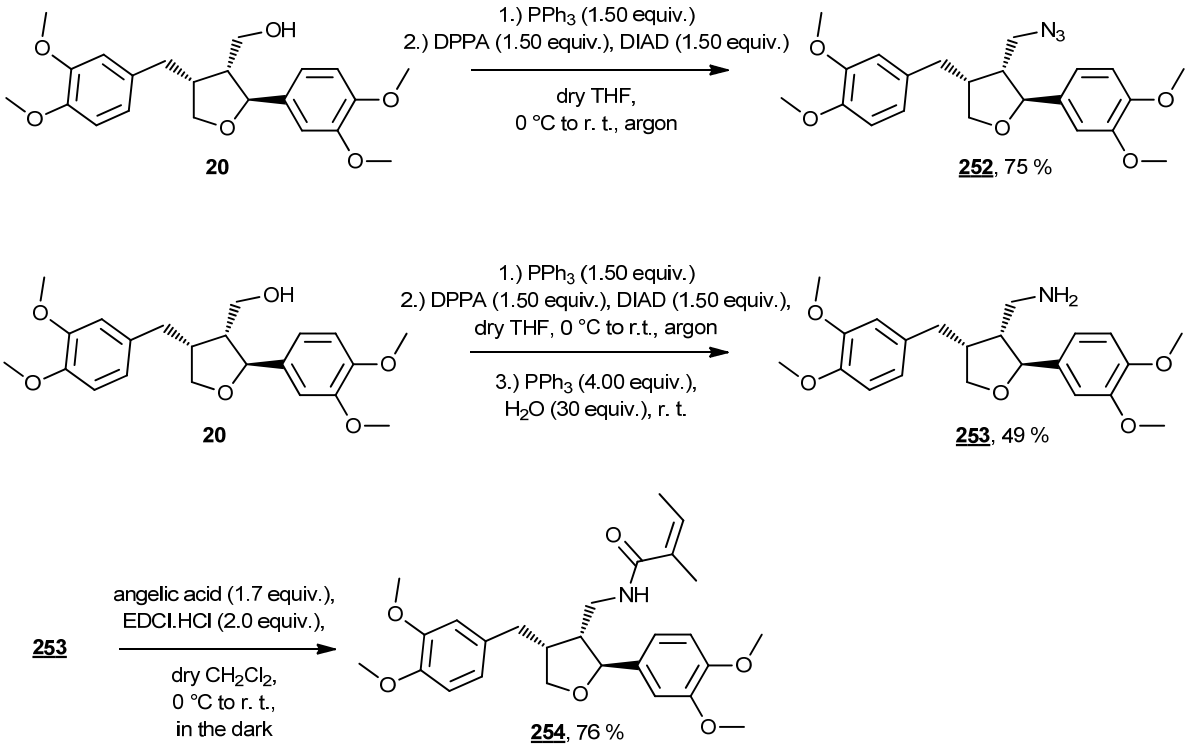


Scheme 62: Synthesis of dimethyllariciresinyl allyl and propargyl ether.

In order to obtain the *N*-analog of leoligin—that is, having an amide of angelic acid in place of an ester, **20** was first converted into the corresponding azide **252** in a variant[287] of the Mitsunobu reaction with diphenyl phosphoryl azide (DPPA), diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in 75 % isolated yield. This would be reducible by e.g. $LiAlH_4$ to the corresponding amine **253**, but the Staudinger reaction[291-292] was a more convenient way for this purpose because isolation of **252** was actually not necessary. Instead, all that had to be done was to add more PPh_3 and excess water to the reaction containing the azide (**Scheme 63**).

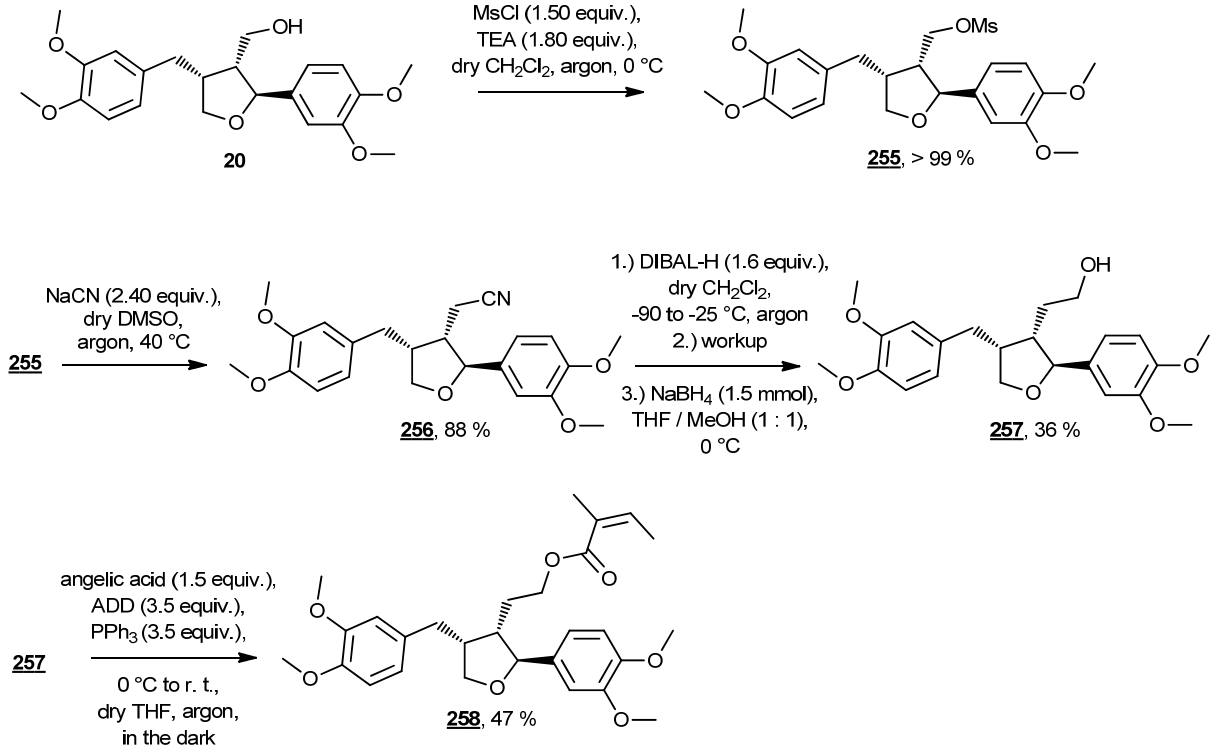
As was mentioned above, the Steglich reaction was not applicable for the preparation of esters of angelic acid because of its isomerization to tiglic acid, induced by a reversible Michael addition of the 4-DMAP catalyst. If amines are to be reacted with *O*-acylisoureas (the intermediate, reactive adducts), no 4-DMAP has to be added, and therefore, this isomerization cannot occur. Consequently, angelic amide **254** was obtained under standard Steglich conditions for peptide coupling.

Incidentally, azide **252** is in itself a very useful compound for it may e.g. also be clicked[293] to alkynes to yield triazoles (being complementary to propargyl ether **251** in this regard). Moreover, a compound of this sort could potentially be used in the bioorthogonal Staudinger ligation[294] to gain more insight into the actual mode of action of furan-type lignans (and leoligin in particular) with respect to their physiologically relevant activities.



Scheme 63: Synthesis of the *N*-analog **254** of leoligin.

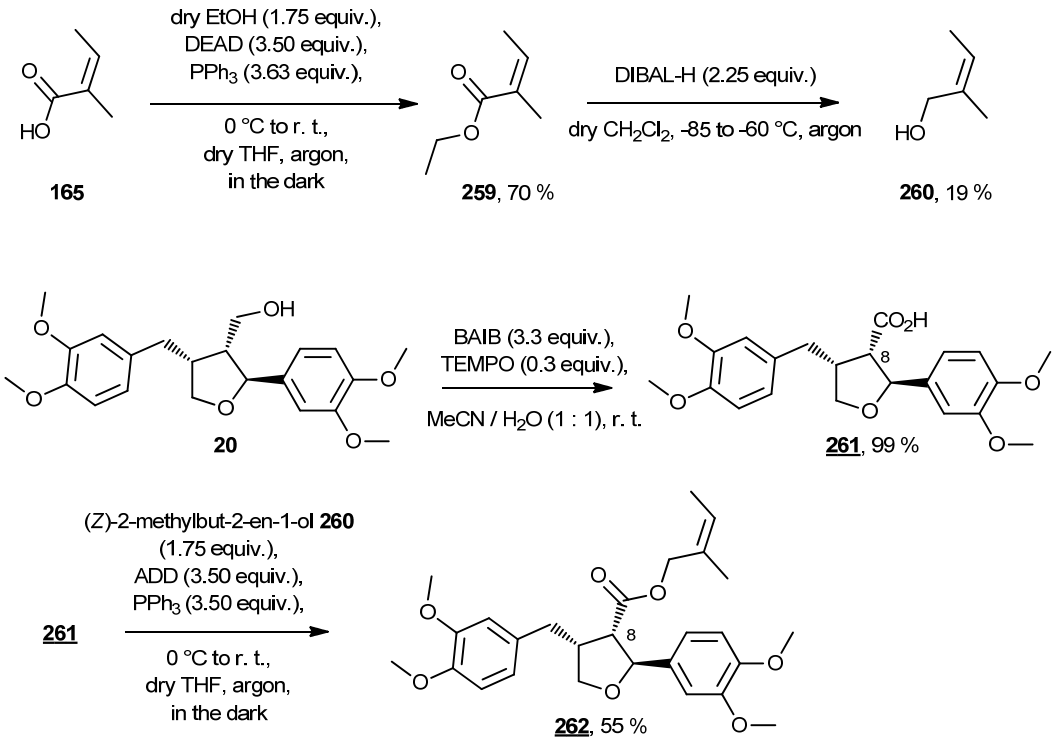
Another modification concerned the placement and orientation of the carboxyl group of leoligin. First, the C8 side chain was elongated by one CH_2 unit (C_1-homologisation). In a rather conventional approach, dimethyllariciresinol was *O*-mesylated quantitatively (**Scheme 64**), affording reaction product **255** which readily and reproducibly crystallized upon solvent removal.



Scheme 64: Synthesis of the C_1-elongated analog **258** of leoligin.

This is a noteworthy observation because most of the furan-type lignans prepared herein were only obtained as oils. Although (limited) efforts to grow crystals that are large enough and suitable for single-crystal X-ray crystallography were not successful, *O*-mesylates (and by inference, tosylates) of **XI** are probably the prime candidates for obtaining X-ray-suited crystalline material (aside from some other analog compounds that were also obtained in solid form) in case X-ray structure elucidation should be sought for additional structural confirmation.
Compound **255** was then converted into nitrile **256** by nucleophilic substitution with NaCN in DMSO, which was followed by two-step reduction, first with DIBAL-H to the intermediate aldehyde and then with $NaBH_4$ to the corresponding C_1-elongated analog of dimethyllariciresinol, compound **257**. The rather low yield of **257** (36 %) is not readily explained as both reductions were essentially spot-to-spot reactions. Nevertheless, the usual Mitsunobu procedure finally afforded the C_1 homolog of leoligin **258** which (surprisingly) required purification by preparative HPLC. The route to **258** also represents the longest linear sequence in this project.

In addition, flipping the oxo group in leoligin to the other side seemed interesting to gain more information on the importance of this group for biological activity. This essentially meant to produce an ester where the roles of the parent lignan scaffold (i.e. dimethyllariciresinol as the alcohol) and the structurally simpler modification moiety (which had been a carboxylic acid so-far) needed to be reversed.
First, alcohol **260** had to be prepared. An initial attempt by direct reduction of angelic acid **165** with $LiAlH_4$ gave a mixture of (*Z*) and (*E*) isomers; therefore, a milder route was chosen by first transforming **165** into its ethyl ester **259** *via* the Mitsunobu reaction, and then reducing this to **260** with DIBAL-H (**Scheme 65**).



Scheme 65: Synthesis of the ester-inverted analog **262** of leoligin.

The reduction went cleanly and the allylic alcohol was extracted from the reaction mixture with *n*-pentane, most of which was then carefully evaporated in an effort to avoid product loss by

evaporation because the scale of the experiment did not allow distillation to be conducted. This was only moderately successful, but nonetheless the required **260** was obtained as a solution in *n*-pentane with a defined molarity (by adding naphthalene as an internal standard and subsequent ^{1}H NMR analysis), to be used directly for esterification.

On the other side of the molecule to be prepared, dimethyllariciresinol had to be oxidized to the corresponding carboxylic acid **261**. This was achieved with a rather nice and very mild method published by Widlanski and Epp,[295] based on previous work of oxidation of alcohols to ketones and aldehydes.[296] Therein, 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO) is used catalytically in conjunction with [bis(acetoxy)iodo]benzene (BAIB) as the terminal oxidant. Finally, Mitsunobu esterification furnished the desired inverted ester **262**. Importantly, no isomerization of the stereocenter at C8, which had presumably become somewhat labile due to the installment of an adjacent carbonyl group, was observed. Compound **262** was also obtained crystalline after preparative HPLC purification.

B.1.4 **Spectroscopic characteristics of lignan epimers**

As was mentioned in the context of elaborating the synthetic intermediates to lignans (section B.1.2, page 77), the 8' epimer (**Figure 14)** of dimethyllariciresinol **20** could also be isolated and characterized. 8'-*epi*-**20** has been unknown to the literature in absolute as well as relative configuration. Therefore, the ^{1}H and ^{13}C NMR spectra of these epimers, and how they can be distinguished spectroscopically for the prospective identification of new natural and synthetic lignans, are briefly discussed.

Figure 15 shows that, among others, the chemical shifts of the protons at the three stereocenters at positions 7, 8, 8' and 9 are smaller in the 8' epimer. The exocyclic hydroxymethylene group at position 9 is clearly separated from (one of the) the protons of the endocyclic hydroxymethylene group of the tetrahydrofuran core and the large signals of the methoxy groups (in the region around δ 3.8 ppm as recorded in $CDCl_3$). Unlike in the situation of compound **20**—and the lignans synthesized herein in general—this signal appears as a doublet which amounts to two protons, i.e. geminal coupling of this methylene group is not observed. This is well explained by invoking the steric constraint that is set up by the 8-8'-*cis* configuration in compounds like **20**, forcing the position 9 protons to experience different chemical environments on time-average, and hence different chemical shifts with ensuing geminal coupling. Conversely, the 8-8'-*trans* configuration of 8'-*epi*-**20** allows rotation about the 8-9 bond more easily, thereby eliminating both shift difference and coupling.

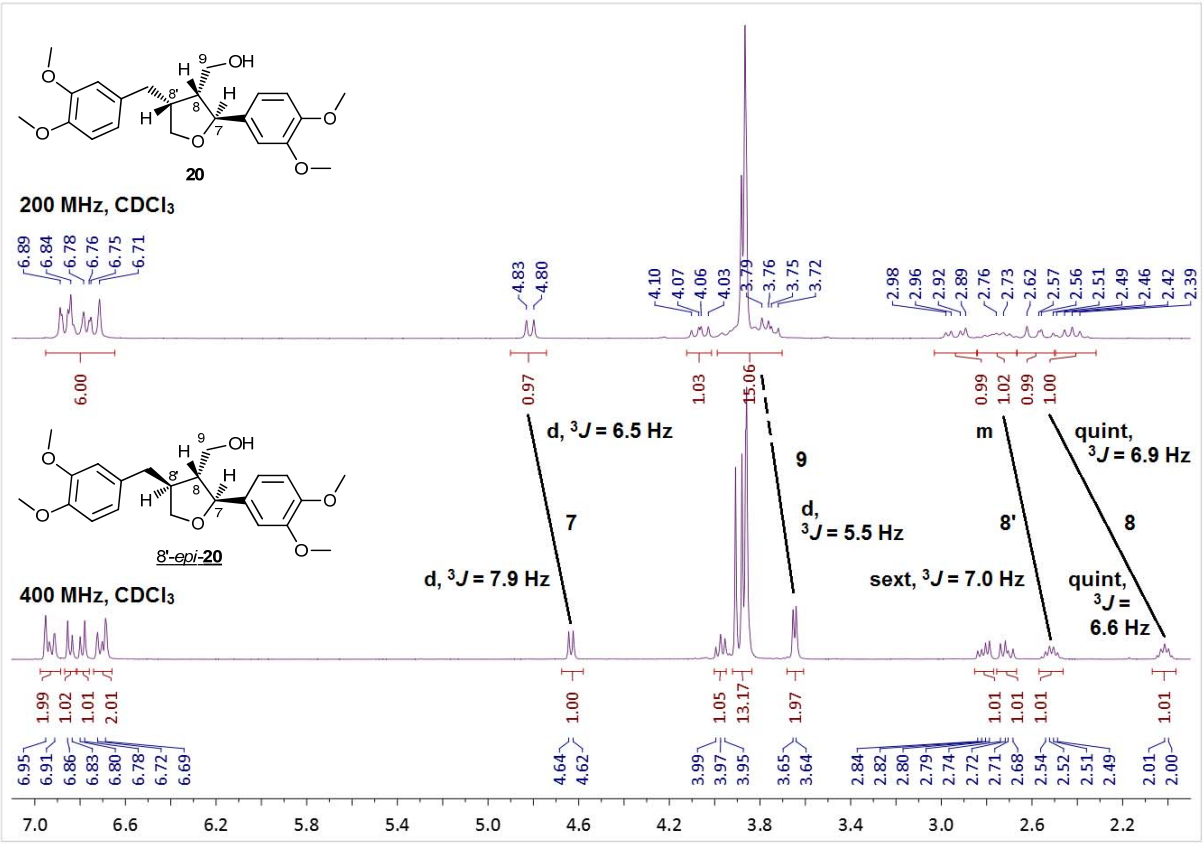


Figure 15: ^{1}H NMR spectra of **20** and 8'-*epi*-**20**. Note that the positions are assigned in accordance with existing literature nomenclature for lignans (section A.1.1, **Figure 1**, page 13). When comparing this with the NMR codes from the Experimental Section, the General Notes (section D.1, page 117) on the rules and reasons for a deviating assignment scheme should be consulted.

Another important characteristic of the 8'-*epi*-**20** is that the vicinal coupling constant of the position 7 proton is notably decreased by 1.4 Hz with regard to **20**. This doublet is generally well recognizable as it does not overlap with other signals when the substitution pattern is changed (as far as the compounds that were prepared are concerned), which makes it a useful marker to distinguish between the *cis-trans* and the *trans-trans* configurations of other lignans, too.

By contrast, the most pronounced carbon shift difference occurs at position 7', which is affected more strongly than the inverted stereocenter 8' itself (**Figure 16**). In the epimerized compound, this signal appears nearly 6 ppm further downfield. From the synthesized benzylic substitution pattern variants it can be concluded that this shift is fairly stable for *cis-trans*-configurated lignans and is not strongly influenced by the electron demand of the arene scaffold as the signal typically lies in a range between δ 32 and 34 ppm (in $CDCl_3$). The only exceptions found are the 2-pyridinyl analog **145** and its angelate **196**, with a δ 35.9 and 36.0 ppm, respectively. This suggests that C7' can be used to corroborate *cis-trans* and *trans-trans* assignments of new lignan compounds as well.

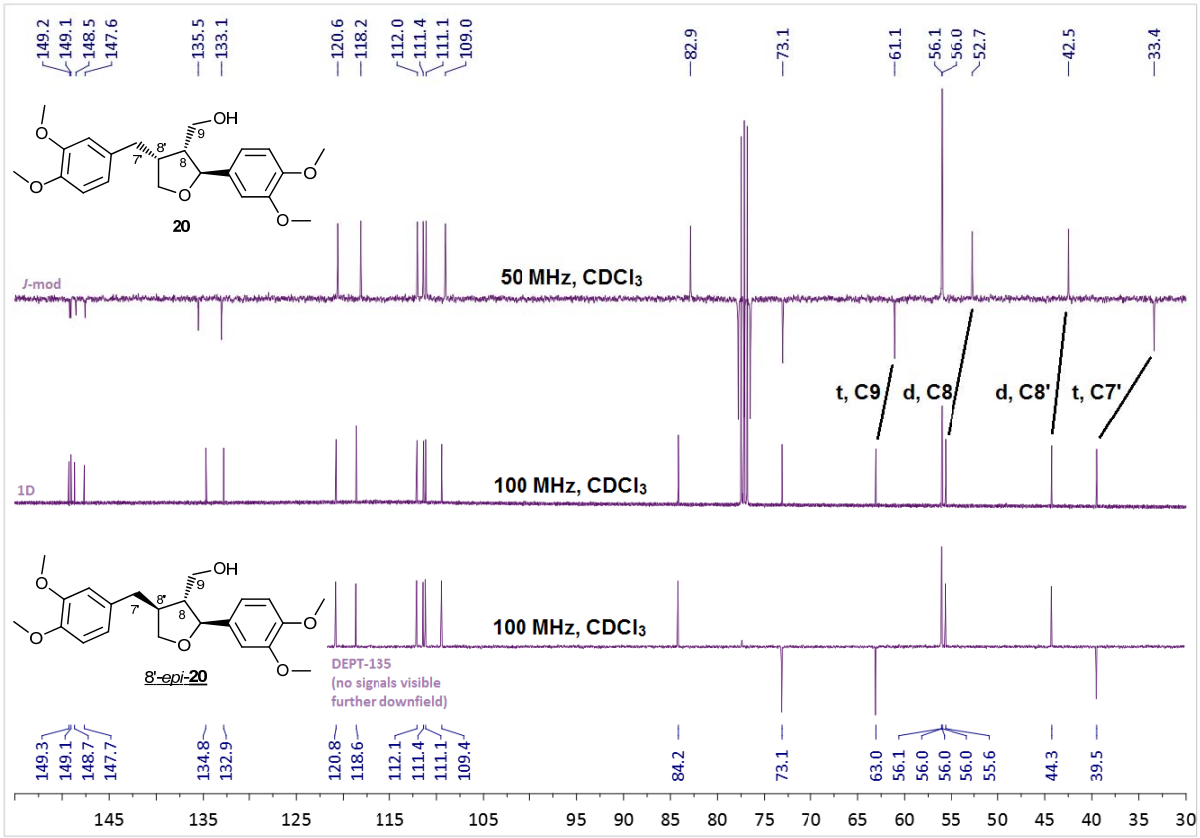


Figure 16: ^{13}C NMR spectra of **20** (topmost *J*-mod spectrum) and 8'-*epi*-**20** (middle 1D and bottom DEPT-135 spectra). Regarding the position numbering, *cf.* the remarks of **Figure 15**.

The above is also in agreement with the NMR characteristics of the literature-known stereoisomers of lariciresinol.[18]

B.2 Pharmacology

The synthesized compounds were subjected to cell-based assays reflecting approaches related to the prevention (macrophage cholesterol efflux enhancement and NF-κB inhibition) and aftercare (cell proliferation inhibition) of cardiovascular disease. The results are discussed in order to suggest possible patterns of molecular requirements for a particular activity, and the pharmacological tests are briefly explained.

The assays were conducted by Dr. Atanas G. Atanasov and co-workers of the Molecular Targets Group (headed by Prof. Verena M. Dirsch) at the Department of Pharmacognosy, Faculty of Life Sciences, at the University of Vienna. The assay procedures are detailed in the Experimental Section (D.5, page 283).

B.2.1 Macrophage Cholesterol Efflux Enhancement

In this assay, the apoAI-mediated cholesterol efflux was measured by determining the amount of radiolabeled cholesterol which was exported from THP-1 macrophage cells to the media when treated with a particular compound. The synthetic analogs were tested at 10 µM concentration and the data are displayed in terms of the *n*-fold increase of efflux relative to negative control. Leoligin **59**, 5-methoxyleoligin **60** and 5,5'-dimethoxyleoligin **61** were also assayed at 1 and 3 µM concentrations, and the known PPARγ agonist and cholesterol efflux enhancing compound pioglitazone[119] **267** served as a positive control at 10 µM (**Figure 17**).

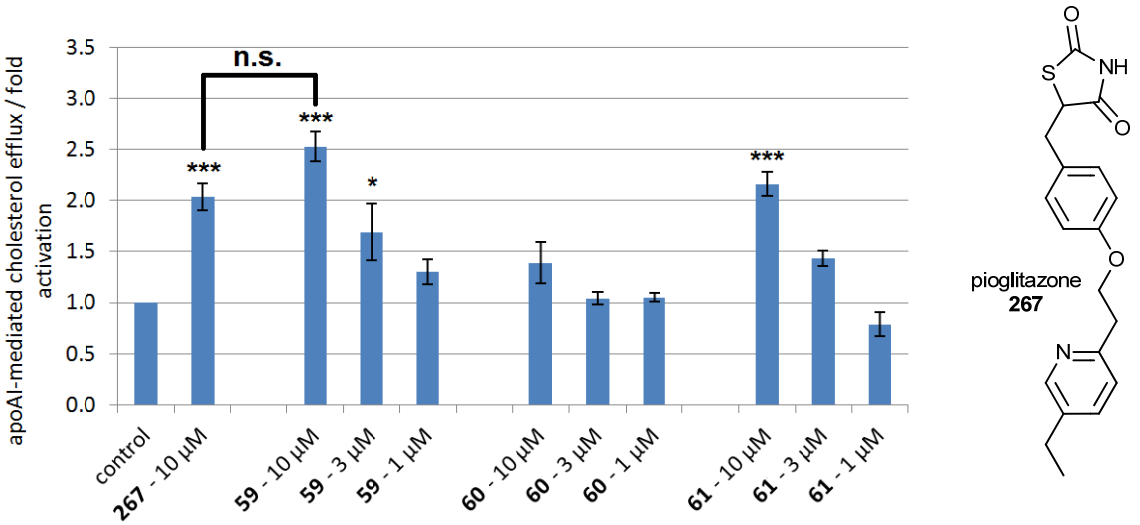


Figure 17a: ApoAI-mediated cholesterol efflux ± standard error of the mean. Analysis of variances (ANOVA) / Bonferroni was used to estimate significance (***: $p < 0.001$; **: $p < 0.01$; *: $p < 0.05$; n.s.: not significant). Differences from negative control are not significant unless marked by asterisk(s) (said remarks apply to the next two figures as well). Shown here is the activity of the naturally occurring compounds leoligin **59**, 5-methoxyleoligin **60** and 5,5'-dimethoxyleoligin **61** relative to that of pioglitazone **267**, with its chemical structure shown to the right. The data of this one and **Figure 17b** belong to the same assay round (round 1), whilst **Figure 19** shows efflux data from a second round.

Practical constraints (handling of radioactive material) limited the number of samples that could be tested; therefore, data is available only for the 18 synthetic compounds shown in **Figure 18**. There is also some deviation of the response between rounds of testing, as seen in the varying activity of pioglitazone and leoligin in **Figure 17ab** *vs.* **Figure 19** which represent two different rounds.

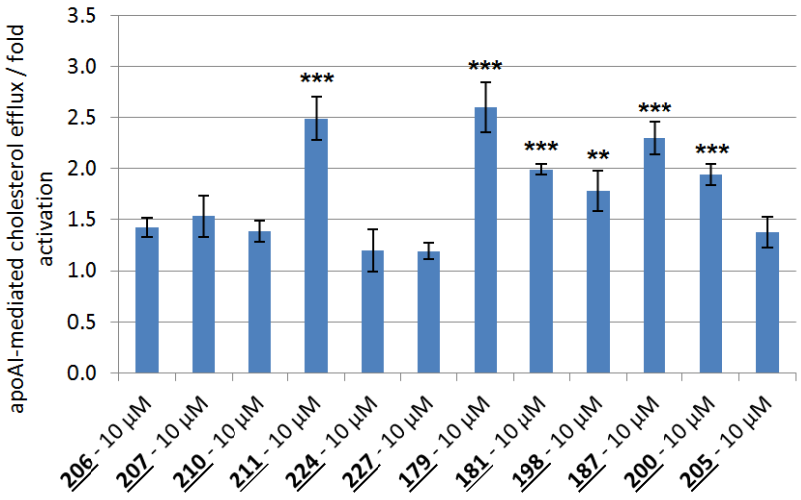


Figure 17b: Activity of 12 synthetic analog compounds of leoligin from round 1. Compounds are arranged in the order in which they are mentioned in the text.

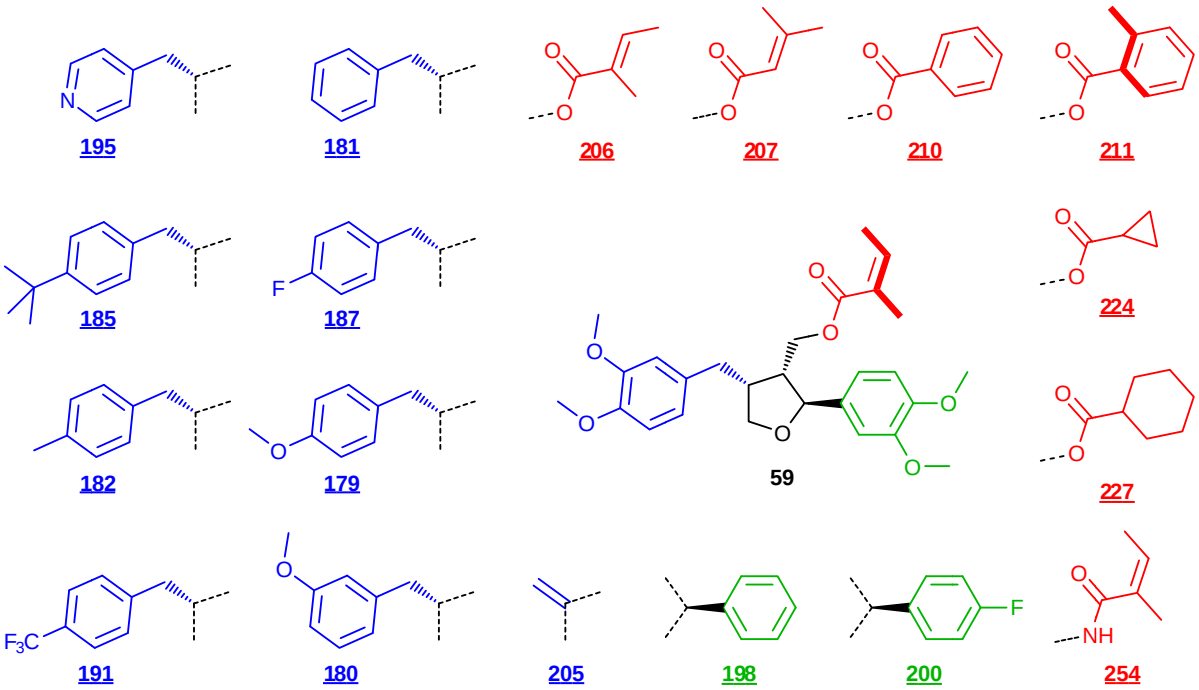


Figure 18: Structures of leoligin **59** and all 18 analog compounds which were tested in this assay. This shorthand depiction is to be understood such that the moieties shown were those which were varied in each particular compound, while the rest of the molecule was identical to that of leoligin (as indicated by the colors).

The first 6 synthetic compounds of **Figure 17b** are different esters of dimethyllariciresinol. Of these, **206**, **207**, **210** and **211** are very closely related to leoligin in that the angelic acid moiety is replaced by similar π systems. Yet only the 2-methybenzoic analog showed efflux activity comparable to that of leoligin, suggesting that the arrangement of the atoms depicted with bold bonds in the figure above might be of importance. The cyclopropylcarboxylic (with π-like bonding according to the Walsh model of cyclopropane and ethylene oxide)[297-298] and cyclohexylcarboxylic analogs (**224** and **227**, respectively) showed almost no activity. Removing the substituents on the arenes (**181** and **198**) or placing fluorine in *para* position instead (**187** and **200**) also lowered, to a varying degree, the activity (**187** is essentially equally active). Compound **179** (differing from leoligin merely by the absence of

one *meta*-methoxy group) had essentially the same activity as leoligin, while the truncated **205** was rather inactive. This, together with the data on the natural **60** and **61**, might have indicated that finding a more active leoligin-like compound would be rather difficult, given that not a single analog displayed higher values compared to leoligin itself.

In a second round of testing (**Figure 19**, which might show depressed values throughout compared to those before), amide analog **254** was active just below significance. Similarly, *p*-*tert*-butyl and *p*-pyridyl modifications **185** and **195**, rather different compounds, were not promising. On the other hand, deleting the *p*-methoxy group (**180**) brought some improvement, as did—surprisingly—*p*-methyl modification **182**. Most active was *p*-trifluoromethyl compound **191**, which enhanced cholesterol efflux by a factor of about three (for leoligin, a factor of two applies in this particular assay). The difference to leoligin is highly significant ($p < 0.01$), making **191** an interesting new tool compound for this activity. However, this dataset is still too limited to draw solid conclusions on what makes a compound more active. What can be said though is that small modifications in structure (such as switching from (*Z*)-configured angelic acid to (*E*)-configured tiglic acid) can have a large impact, making systematic charting of the structure-activity relationships a quite elaborate task.

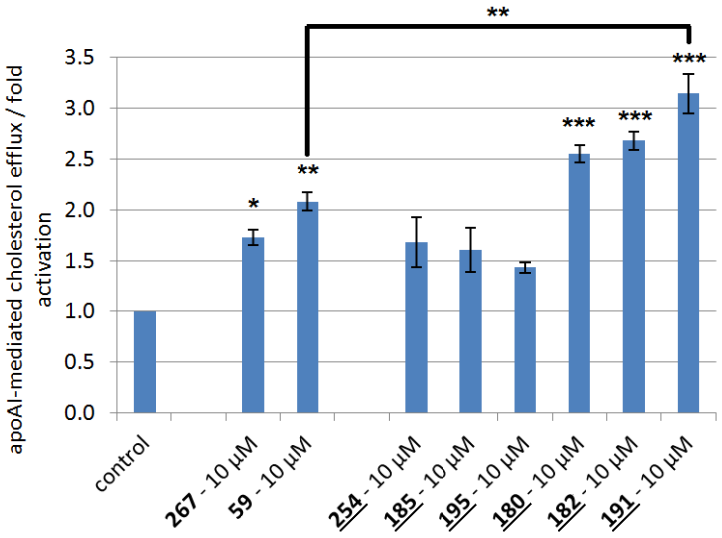


Figure 19: Activity of 6 more analogs (round 2). Compound **191** was the most active one found in this screening.

Additionally to cholesterol measurements, levels of ABCA1 (the transporter protein whose transcription may be suspected to be upregulated in response to treatment with a particular compound—which is known to be the case for pioglitazone—and therefore increase the efflux of cholesterol) were determined by gel electrophoresis, blotting and visualization techniques.

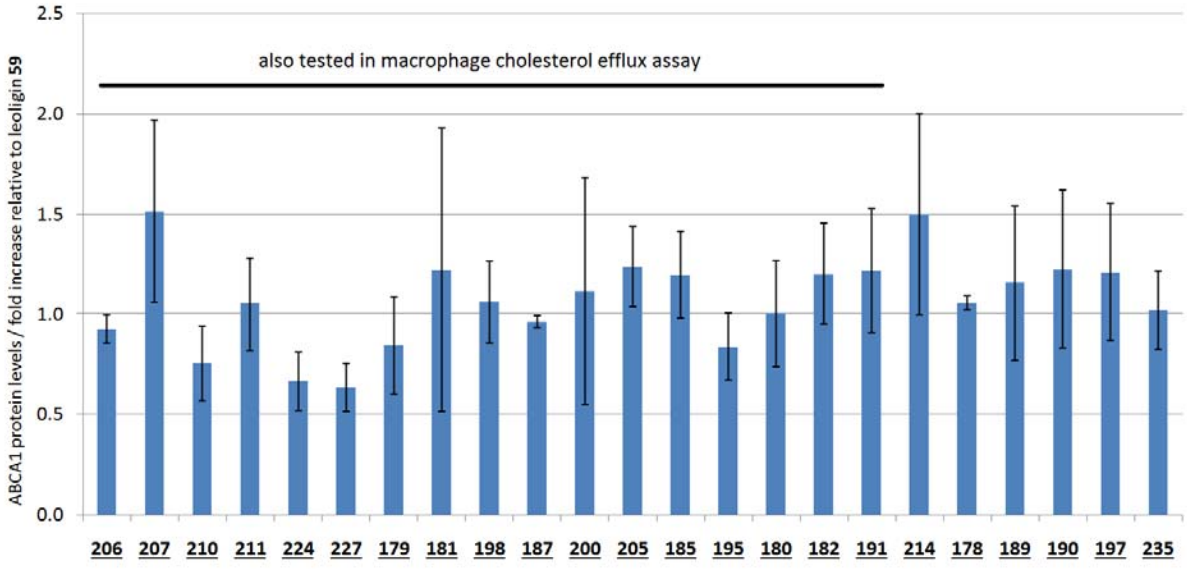
In addition to the compounds above which had already been efflux-tested (except for amide analog **254**), 1-naphthoate **214**, arene modifications **178**, **189**, **190** and **197** were subjected to this assay, as well as compound **235** in which the *p*-CF_3 group (as in the so-far most active derivate **191**) was present, plus being modified at the ester portion (the active 2-methylbenzoic scaffold, as in compound **211**, was installed, in place of having an ester of angelic acid). The reasoning behind compound **235** was that this compound might have similar activity as **191** (given that compound **211** was just as active as leoligin), but the rather undesired Michael acceptor (potential interaction with mercapto and amino residues in living systems)[299-300] would be replaced by an innocuous aromatic structure while preserving the π system. On the other hand, 1-naphthoate **214** was chosen because it

represented a bulkier version of **211**, while **178**, **189** and **190**, as well as **197**, are modifications to the rather active, methoxy or trifluoromethyl group-bearing analogs of the cholesterol efflux screening. In particular, the 1,1-difluoroethyl group of compound **190** would be a bioisoster to the methoxy group.[301]

The purpose of screening for ABCA1 upregulation activity with this selection of molecules was two-fold: if ABCA1 increase is the general mode of action of the synthetic compounds by which they enhance cholesterol efflux (as it is the case for leoligin), a correlation should exist between the results of both assays. In this case, the ABCA1 expression assay could be used as a predictor of cholesterol efflux enhancement activity without the need for dealing with radioactivity. Conversely, those of the new compounds (**Figure 21**)—being selected on the basis of structural rationales—that would be active in the ABCA1 assay could then be subjected to the actual cholesterol efflux assay individually for activity confirmation if said correlation should turn out real. The latter would be an important finding *per se* because it has thus far by no means been certain that efflux up-regulation (by the synthetic analogs) is caused by increased levels of ABCA1; in fact, different mechanisms and pathways could be operative among different compounds.

Figure 20 shows this data; the resulting values for ABCA1 expression are normalized to that of leoligin, for which the ABCA1 mechanism had been established.[166] This analysis was conducted in groups of four compounds each, and the protein bands of one such experiment are shown for illustration purposes.

Evidently, the differences in activation are not as pronounced as may be desired. Only compounds **207** and **214** showed activity which could reasonably be considered higher than that of leoligin **59**.



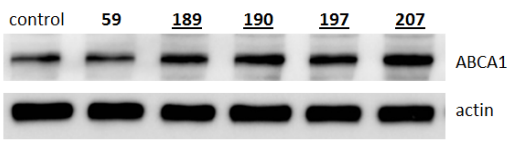


Figure 20: ABCA1 protein levels ± standard deviation, normalized to leoligin **59**. All compounds were tested at 5 µM concentration. Compounds that already appeared in the previous figures are arranged in the same order here as well. Right: example of the gel electrophoresis experiments that were used to quantify ABCA1 and actin protein expression.

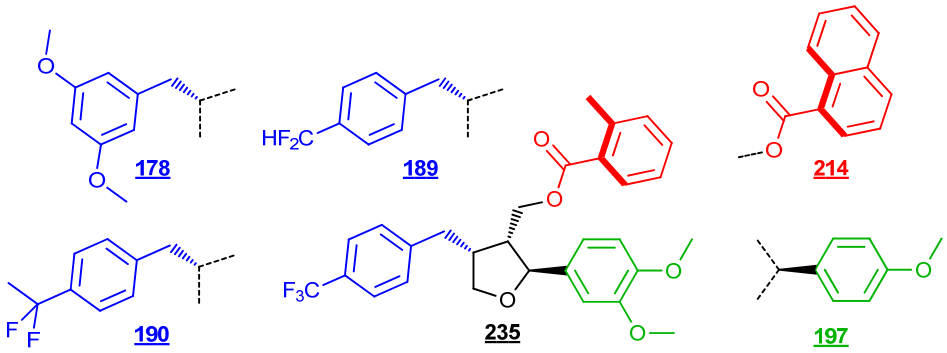


Figure 21: Structures of the additional compounds for the ABCA1 assay. For the meaning of the shorthand depiction (based on leoligin, *not* **235**), *cf.* **Figure 18**. Note the angelic acid-like arrangement of carbon atoms as emphasized in structures **214** and **235**.

Moreover, measurement uncertainty (in terms of the standard deviation) is higher than in the radiolabeling experiments of cholesterol efflux,[k] complicating the interpretation of the results.
In order to establish whether or not the aforementioned correlation exists, the cholesterol efflux and ABCA1 results may be plotted against each other (**Figure 22**).

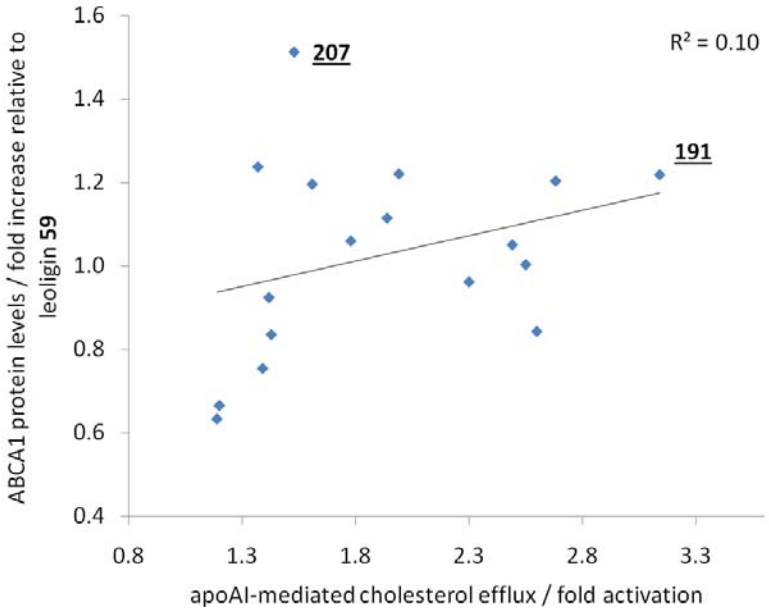
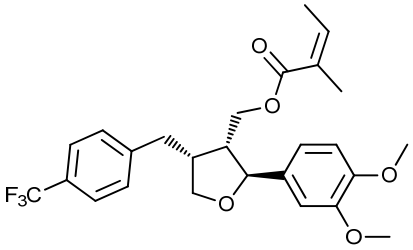


Figure 22: Attempted correlation of macrophage cholesterol efflux and ABCA1 protein expression (note that the R^2 in the graph mere indicates pool *linear* correlation, while there is no reason to assume that the data would necessarily be described best by such linear model, which was chosen merely for simplicity in view of the wide spread of the data points).

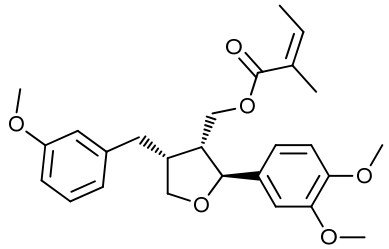
Although perhaps not a completely random distribution, ABCA1 activation does not appear to be a reliable predictor of cholesterol efflux for leoligin-like compounds (under these conditions of measuring). For example, compounds **191** and **207** (the most active ones in their respective domain) lie rather far apart in the above plot. This may hint at the possibility of other mechanisms than

[k] In the cholersterol efflux experiments, a standard error of the mean is given, which is inherently smaller than standard deviation itself.

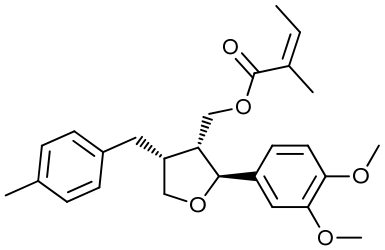
increased levels of the ABCA1 protein being at work (e.g. ABCG1, the expression of which is known to be augmented by pioglitazone, too).[119] Moreover, the rather high uncertainties in determining these levels certainly plays a role as well, which might explain why compound **207** was found to be up-regulating this protein 1.5-fold while it is not particularly effective at removing cholesterol from the cells (even if other mechanisms are also at play, such an up-regulation should result in enhanced efflux regardless). In any case, potential confirmation or refuting of the hypothesis that the particular mechanism in question is operative throughout all analogs of leoligin will likely benefit from improved precision when determining these protein levels in macrophages. Furthermore, it should be kept in mind that systematic deviations may also exist between subsequent assay rounds in the cholesterol efflux determination, as explained above.



191, 3.14 ± 0.20 fold increase



180, 2.55 ± 0.08 fold increase



182, 2.68 ± 0.09 fold increase

Figure 23: The three most active leoligin-like compounds identified at macrophage cholesterol efflux.

In summary, compound **191** and, to a lesser degree, **180** and **182** (**Figure 23**) were identified as significantly more active than both pioglitazone and leoligin in macrophage cholesterol efflux. Yet, the biochemical pathway by which this happens could not be confirmed within this study. Testing additional compounds (e.g. those that were already used in the ABCA1 quantification) might shed some more light on how structure and activity are related in this case.
The numerical values of the data presented can be found in the Appendix (page 296).

B.2.2 **NF-κB Inhibition**

Being a target in both cancer and inflammation, the nuclear factor-kappa B pathway has emerged as an intensively studied target. Leoligin itself is a weak inhibitor of this pathway, and it was therefore interesting to see how this activity would vary with modifications to the leoligin motif. For this purpose, HEK293/NF-κB-luc cells (containing a luciferase reporter gene downstream the relevant promoter) were labeled with a fluorescent probe, treated with the compounds at different concentrations and tumor necrosis factor alpha (TNFα) as an activator of the NF-κB pathway. The luminescence of the reporter protein was normalized to the fluorescence of the cells in order to quantify NF-κB inhibition, thereby accounting for differences in cell number. In this case, the assay was rather high-throughput, which allowed to determine IC_{50} values and compare the synthetic library with the naturally occurring parthenolide (a sesquiterpene lactone from feverfew, *Tanacetum parthenium* and similar plants, **Figure 25**) as a positive control, a compound which has been under study in, amongst others, atherosclerosis[302] and as an apoptosis inducer in leukemia.[303] In addition, synthetic analogs of 5-methoxyleoligin **60** from related work[163] were also screened; these compounds are marked with the label **SOGE**. Because of the rather large dataset comprising more than 150 compounds, only an indicative selection is discussed here. The numerical NF-κB and the concomitantly determined viability data of all compounds on HEK293/NF-κB-luc cells can thus be found in the Appendix (page 296).

There are many compounds known to inhibit NF-κB, such that any interesting molecule (that could potentially be used as a tool compound for further study) should rather possess inhibitory potency comparable to that of parthenolide, the IC_{50} of which was determined to be 1.7 µM under the conditions of the assay. To begin with, the leoligin IC_{50} is around 20 µM (**Figure 24** shows that natural and synthetic leoligin are bioequivalent), and the screening was conducted such that compounds which did not have appreciable activity (no more than 50 % inhibition at a single-dose concentration of 20 µM) were not considered for more detailed investigation. Accordingly, these compounds are taken to be inactive and their IC_{50} values are stated as ≥ 20 µM in the discussion that follows.

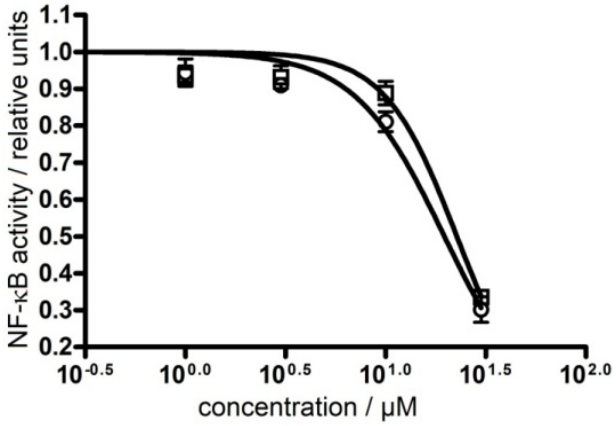


Figure 24: Dose-response curve of leoligin. IC_{50} = (22.7 ± 2.0) µM (natural leoligin, boxes), IC_{50} = (19.7 ± 2.1) µM (synthetic leoligin, circles); determined at 95 % confidence level. Error bars at the data points represent the standard error of the mean.

Of the dimethyllariciresinol analogs **XI**, none of those investigated were active at NF-κB inhibition, except for compounds **132** (IC_{50} determined twice: 9.4 and 12.5 µM) and **SOGE-35** (also determined

twice: 9.1 and 9.2 µM; **Figure 25**).[l] This suggests that lipophilicity plays a role because alcohols **XI** are in general considerably more polar than their corresponding esters. However, their corresponding esters of angelic acid **184** and **SOGE-47** were found to be inactive. On the other hand, the presence of the carboxyl function (as in leoligin) appears to be important as well, as corroborated by the activity of acrylate **209** (6.2 µM; this is a potentially toxic compound, but viability was not reduced at 20 µM concentration in HEK cells) and the inactivity of the—except for the oxo group identical—allylic ether **250**, or when the carbonyl strength was attenuated (inactive amide **254**; although in this case, inactivity might also be attributed to its property as a proton donor). A π system is not required; many aliphatic esters were also (moderately or highly) potent,[m] such as the saturated analog **218** (10.7 µM).

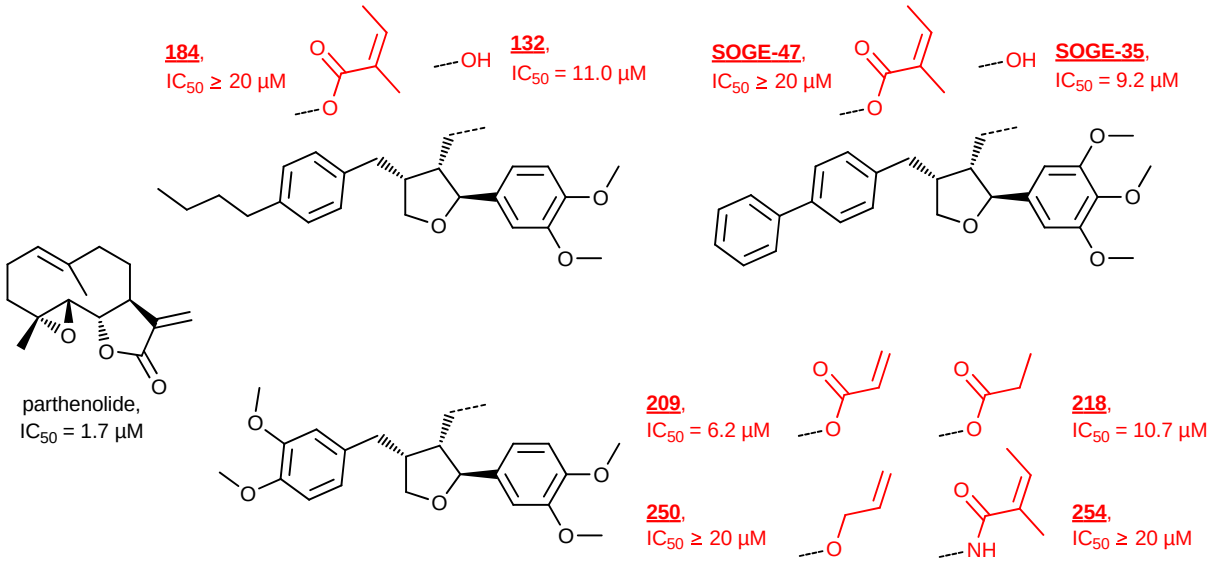


Figure 25: Chemical structures of parthenolide, the positive control and some of the tested library compounds.

As for variations of leoligin where the benzylic moiety (arenes at position 7') was modified, a tendency of decreased activity with Lewis basic / proton acceptor substituents was observed (**195**: ≥ 20 µM; **196**: ≈ 20 µM;[n] **193**: 14.0 µM, **Figure 26**) when compared with non-basic (and by and large less polar) substituents, such as methyl, fluoro or one (in place of two) methoxy groups, affording compounds with IC_{50} values mostly at or below 10 µM. Yet this is not a simple matter of polarity: compound **178** is essentially as polar as and also very similar to leoligin, but inhibits the NF-κB pathway much more strongly, as confirmed in two determinations of IC_{50} (5.7 and 4.7 µM, respectively). Notably also, the *p*-trifluoromethyl group appeared to shut down NF-κB activity as none of compounds **191**, **199**, **204**, **235**, **SOGE-39** (and their corresponding alcohols) showed potency

[l] In cases were the IC_{50} was determined more than once, the arithmetic mean is shown in the corresponding schemes or graphs. In the Appendix, all values are given individually.

[m] Potency: the amount (concentration) of a compound required to achieve a defined effect, in this case half of complete inhibition (IC_{50})

[n] Due to the screening regime, the following scenario occured in a few cases: in a first assessment, a compound showed slightly more than 50 % inhibition at 20 µM concentration and was therefore listed for IC_{50} determination. At this second stage of testing, however, the compound produced approximately yet *less* than 50 % inhibition (due to measurement uncertainty) at the highest concentration of the dose-response curve (i.e. 20 µM). In such an instance, the activity of the compound is stated as ≈ 20 µM.

stronger than 20 µM. This is relevant because this substituent is important in both macrophage cholesterol efflux (section B.2.1, page 94) and proliferation inhibition (section B.2.3, page 106) and is therefore a handle to tune selectivity. Likewise, a *tert*-butyl group in this position yielded rather inactive derivatives.

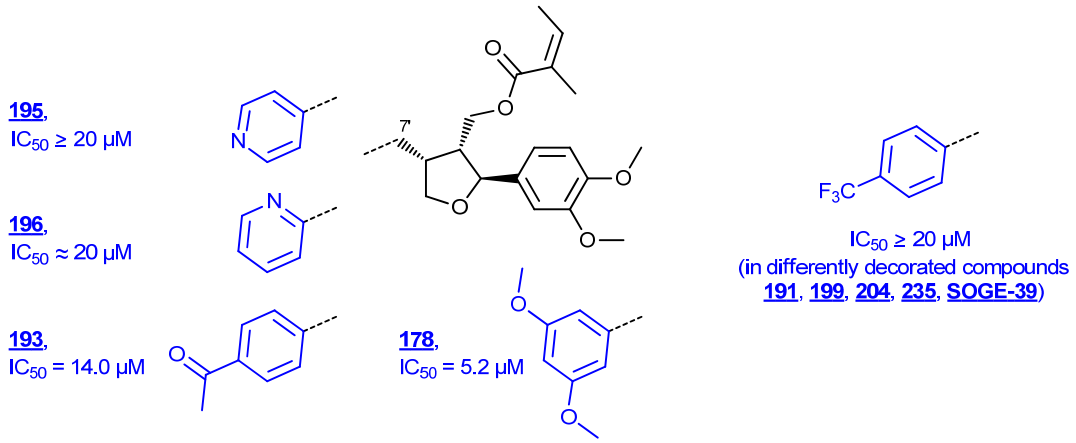
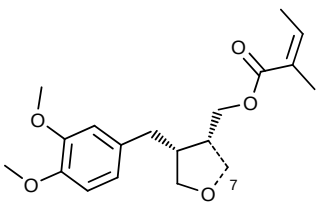


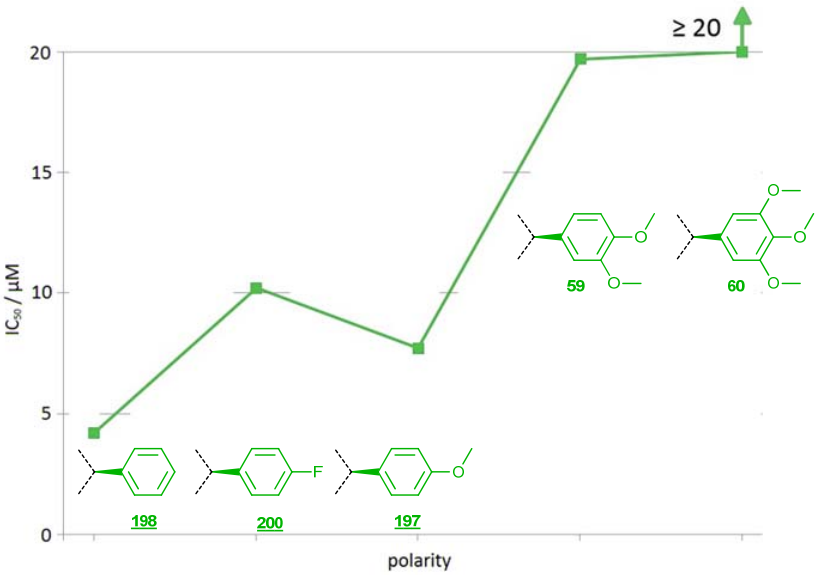
Figure 26: Potency subject to modifications of the benzylic moiety of leoligin. For the explicit structures of inactive **191**, **199**, **204**, **235** and **SOGE-39**, *cf.* Appendix (page 296).

In the series which compares modifications of leoligin at the opposite side (position 7), potency also seems to increase with lowered polarity. At the top end, 5-methoxyleoligin **60** is not readily assigned its NF-κB activity from the available data because two largely different results (10.6 µM and ≥ 20 µM) for natural and synthetic **60**, respectively, had been obtained. Given that ester variations of 5-methoxyleoligin were also less active in most cases (such as the tiglic, crotonic and 3,3-dimethylacrylic variations, which all had IC_{50}s higher than 20 µM) when compared to the corresponding less polar dimethyllariciresinyl esters (that is, ester variations of leoligin), it may be assumed that the value of 10.6 µM is spurious and **60** in fact *inactive*, too. This may also apply to compound **200** (10.2 µM and ≥ 20 µM, two measurements, same compound), but in this case it is more likely that this compound is really *active* (with the ≥ 20 µM determination being erroneous) because derivatives similar to **200** (varied at the acyl part of the molecule, *vide infra*) possess notable activity. With this sort of reasoning,

Figure 27 is obtained, suggesting said polarity-activity relationship.

Figure 27: Potency *vs.* polarity (as the most general difference of the compounds in this series) when modifying the moiety in position 7. Regarding the IC_{50} values in this diagram, *cf.* text.





Importantly, esters with flexible and open aliphatic chains adjacent to the oxo group and larger than *n*-propyl (*iso*- and *tert*-butyl, 3-pentyl, *neo*-pentyl) had IC_{50} values around or below 5 µM in the case of dimethyllariciresinyl esters and the *p*-fluorophenyl analogs (the latter are compounds such as **200**, but having the acyl part modified with the aliphatic residues as mentioned). Bulky and large-rigid ester moieties, both aliphatic and aromatic (such as those of 1- and 2-naphthoic, *p*-biphenyl-carboxylic, cinnamyl and adamantylacetic acid), showed low activity. For cyclic aliphatic esters of dimethyllariciresinol, activity increased roughly with ring size and thus also with reduced rigidity of the ring **(Figure 28**). Conversely, steric demand beyond that which is taken up by a simple monocyclic ring system was detrimental (adamantanecarboxylic ester **231**, shown to the top right of the figure), in agreement with the general finding that flexibility performs better than rigid bulk. The most important exception to this general trend is rather inactive fluoro compound **245** (≈ 20 µM, measured twice) that might have been expected to exhibit strong NF-κB inhibition, given that cycloheptanecarboxylic ester **228** was the most potent compound (1.6 µM) in this screening and thus comparable to parthenolide.

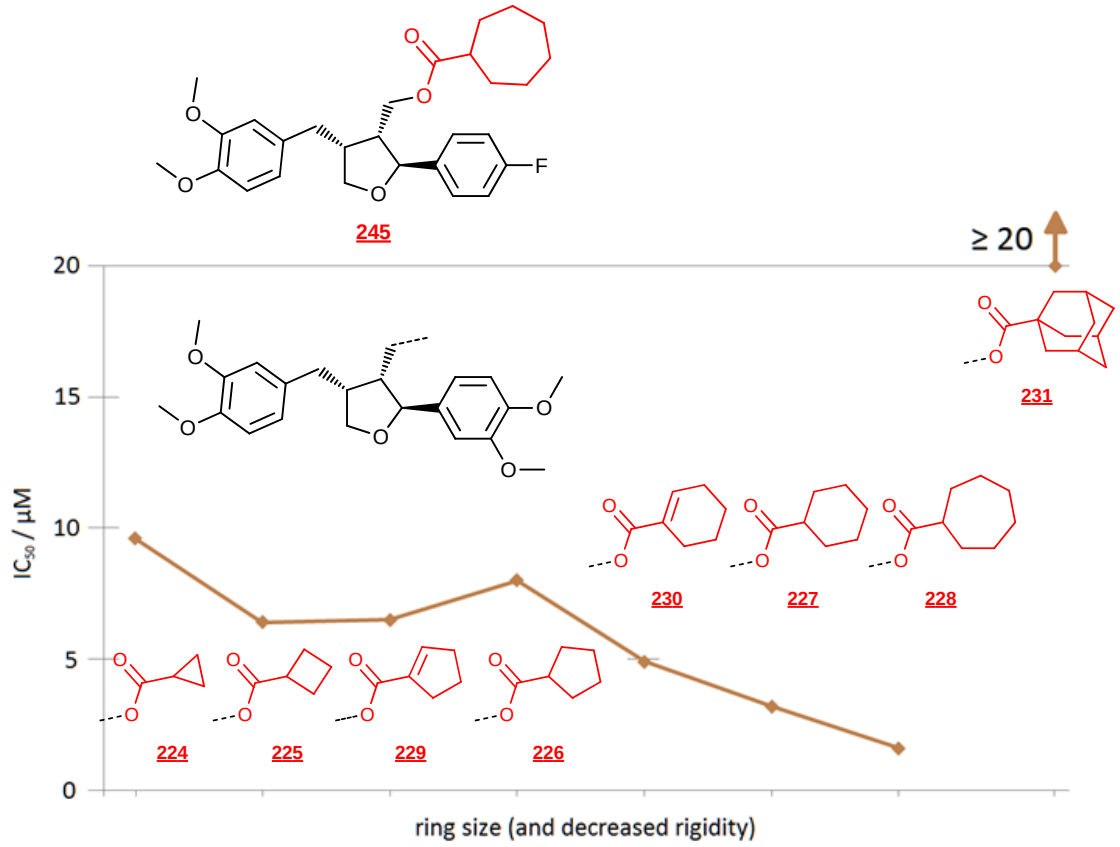


Figure 28: Potency *vs.* increasing ring size and (consequently) decreasing rigidity for cyclic aliphatic esters of dimethyllariciresinol. The unsaturated systems are taken to be more rigid than the corresponding saturated rings and are placed accordingly.

Generalized considerations of structure-activity relationships of leoligin-like lignans regarding NF-κB are to be stated with some caution, given the multiple factors which can influence it, in addition to the uncertainties associated with measuring biological systems in high throughput. That being said, it is likely that activity is increased by lowering polarity (removing or replacing methoxy groups) and/or switching to flexible aliphatic esters which may have cyclic or open-chain acyl moieties. These conclusions are reflected in the ten most potent compounds identified (**Figure 29**).

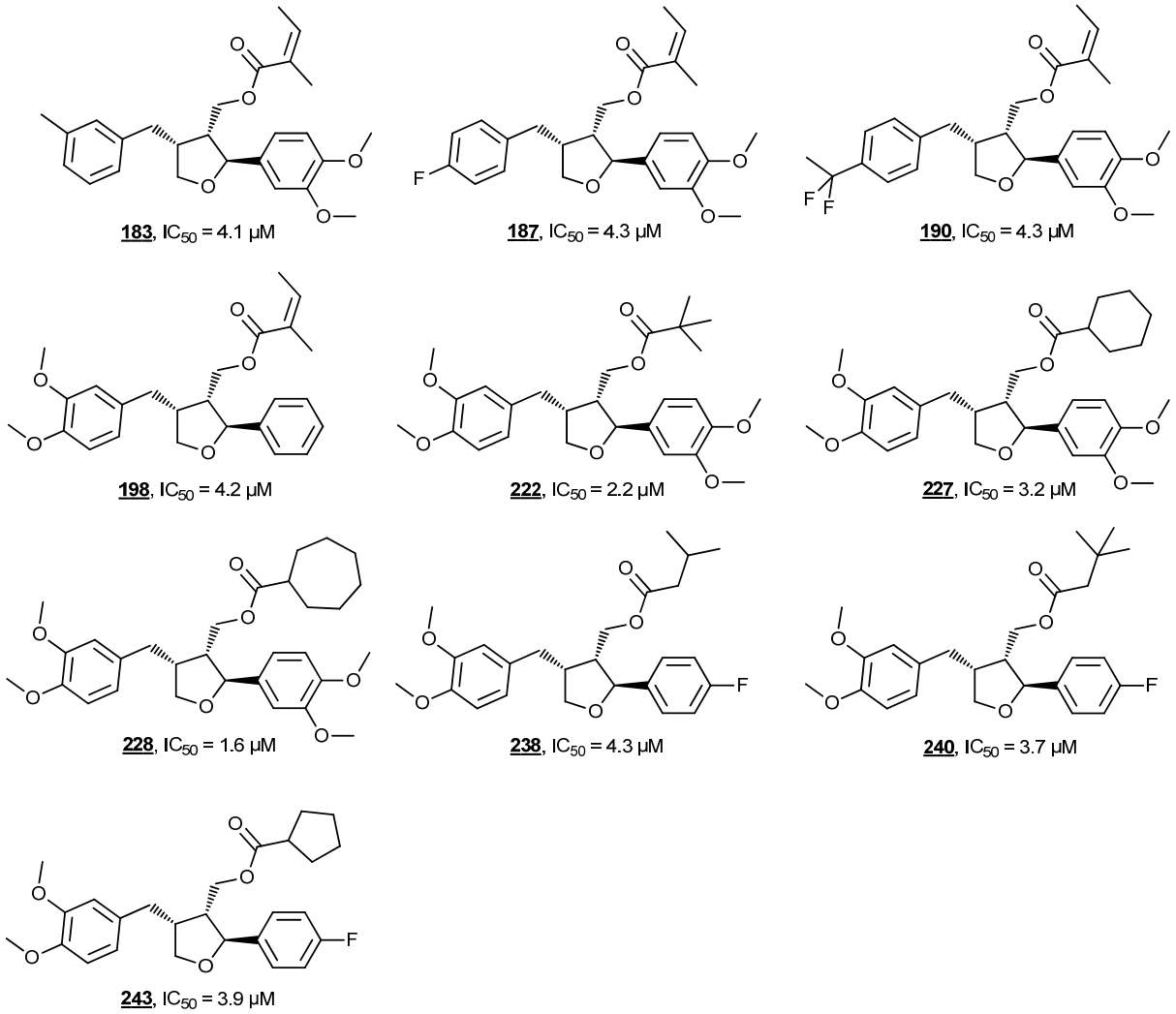


Figure 29: The ten most potent compounds which inhibited the NF-κB pathway are in agreement with the conclusions drawn in this section.

However, the above list showing compounds with IC_{50} values at or below 4 µM (roughly 5 to 10-fold more potent than leoligin) also reveals a very differentiated role of fluorine in this context. As was explained above, a trifluoromethyl group in *para* position on the benzylic scaffold inactivated a compound for NF-κB inhibition as seen in multiple examples and whatever the rest of the molecule. But compounds **187** and **190**, having fluorine placed in a similar fashion, are highly active. Since it is not clear how these compounds actually interfere with the NF-κB pathway, and with no information on their target(s) in the cells, attempts were not made to assign specific roles to the different substituents (such as donor or acceptor function, van der Waals-interactions, effects on electron distribution, etc.). Still, it may be hypothesized that the difluoroethyl group of compound **190** fulfills the role of a less polar methoxy bioisoster (as already pointed out in the last section). The corresponding compound **179** which actually has such a methoxy group in its place was active as well, albeit to a weaker extend (IC_{50} of 7.9 µM).

An important statistical aspect deserves mention: unlike in the case of the macrophage cholesterol efflux assays where only a small number of compounds—based on certain rationales and moving slowly away from leoligin—was selected for testing, the better part of the library was screened for NF-κB. This in turn might create the impression that if a particular substitution pattern appears very often in highly active compounds, then this pattern must be a preferred one (because no deliberate

pre-selection was done). In fact, the distribution of substitution patterns in the compounds that were submitted to testing was not even; instead, it was strongly biased toward the dimethoxy pattern because this is what appears in leoligin, and many more compounds pertaining it were synthesized than others without it. Thus, the appearance of dimethoxy substitution in all of the active derivatives of **Figure 29** is largely an artifact rather than a hint that placing methoxy groups on these structures tends to produce more actively inhibiting compounds.

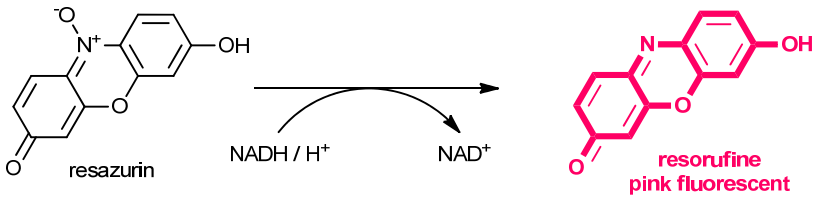
Lastly, there were no striking cases of reduced cell viability (no drop below 60 % viability at 20 µM, the highest concentration in the assay) or persisting cases (below 80 % viability in repeated measurements).[o] This viability data is also contained in the Appendix (page 296).

[o] A reduction of viable cells to 80 or even 60 % in a single experiment is not sufficient to indicate cytotoxicity due to the limited precision of the experimental setting. In some cases, the viability of cells treated with the positive control (5 µM parthenolide) dropped to as low as 40 %, although this compound does not exhibit a toxic effect on HEK293 cells at this concentration.

B.2.3 **Cell Proliferation Inhibition and Cytotoxicity**

So far, the pharmacological activities of leoligin analogs that were discussed were related to potential means of atherosclerosis prevention and hence that of myocardial events. Originally, though, leoligin elicited interest as a compound which reduced intimal hyperplasia in the vasculature as a consequence of CABG or PCI. For this potential after-care application, three histological criteria were therefore being focused on: a promising compound should inhibit the proliferation of vascular smooth muscle cells, it should *not* inhibit the proliferation (and migration) of vascular endothelial cells, and it should not be toxic to either of them.

The assay procedures for testing proliferation inhibition were similar for both cell types: cells were stimulated to proliferate and the extent of cell growth was then quantified by metabolic conversion of the *N*-oxide resazurin, added subsequently to the incubation period (**Scheme 66**). This reduction, mediated by cellular processes at the expense of one equivalent of NADH, is irreversible, and the resulting product resorufine is fluorescent, allowing photometric measurement.



Scheme 66: Metabolic conversion of resazurin.

In order to model intimal hyperplasia, rat aortic vascular SMCs were stimulated by platelet-derived growth factor (PDGF), which is also involved in the disease.[87] The number of cells in the presence of both PDGF and the synthetic compounds to be tested was then quantified with respect to negative control (PDGF and solvent vehicle only). Basal levels of cell growth (untreated cells, i.e. which occurs in the absence of PDGF and test compounds) were also measured. Conducting this experiment at different compound concentrations allowed to establish dose-response curves and determine the IC_{50} values of PDGF-induced SMC proliferation inhibition for the library compounds.

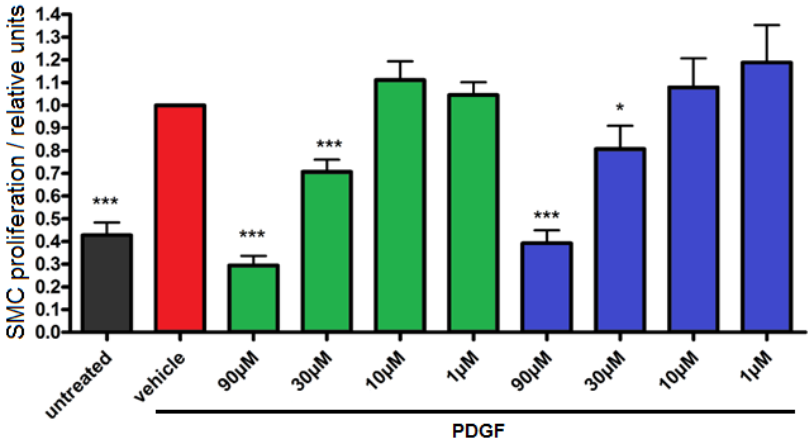


Figure 30: Dose-response curve of leoligin. IC_{50} = (27.7 ± 8.8) µM (natural leoligin, green bars), IC_{50} = (32.1 ± 10.8) µM (synthetic leoligin, blue bars); determined at 95 % confidence level. Untreated: Number of cells in the absence of both PDGF and leoligin. Vehicle (i.e. DMSO): Number of cells in the presence of PDGF but absence of leoligin. Analysis of variances (ANOVA) / Bonferroni was used to estimate significance (***: $p < 0.001$; **: $p < 0.01$; *: $p < 0.05$); error bars represent standard deviation.

Since the SMC inhibition-IC_{50} value of leoligin is about 30 µM (**Figure 30**), proliferation inhibition of human umbilical vein ECs cells as a relevant model was determined at this dose for promising, SMC-inhibiting candidates. The cells were stimulated by serum and incubated with the compounds to be tested, and the results were compared with negative control. At 30 µM, leoligin reduces the number of ECs by about half (*vide infra*). That is, rather than measuring dose-response curves of EC inhibition for the entire library, the aim was to find compounds which would not interfere with them at all at the 30 µM concentration, whereas they should potently inhibit SMCs (as expressed in terms of their IC_{50}s).

Metabolic conversion of resazurin measures the number of viable cells and does therefore not distinguish between reduced proliferation and cellular toxicity upon treatment with a particular compound.[304] This is not a problem in the case of EC determination by this assay because, as stated above, interesting compounds from the library should not show any interference with these cells whatever the cause. By contrast, a distinction between inhibition and potential toxicity needed to be made when testing the effect on SMCs. For this reason, the most promising candidates were also subjected to an assay which measured the amount of extracellular lactate dehydrogenase (LDH). This ubiquitous enzyme is contained within the membrane of healthy, viable cells. Upon cell death, the membrane becomes porous and leaks the enzyme into the media, where it can be quantified by the conversion of added NAD^+.[305-306] The experimental setting of this assay primarily measured necrosis, but also late apoptosis of SMCs induced by a particular compound. PDGF was also added in these experiments to obtain the conditions of the proliferation assay, and the detergent digitonin[p] (a glycoside from *Digitalis purpurea*) was used as a positive control.

Compounds which showed no more than 50 % inhibition at a single-dose concentration of 30 µM (the leoligin IC_{50}) with respect to basal proliferation were considered inactive, they were therefore not subjected to further study, and their IC_{50} values are stated as ≥ 30 µM. Synthetic compounds from related work were also investigated and are labeled as **SOGE**[163] or **KH**.[290] Due to the extent of the study, an indicative selection is discussed while the entire dataset can be found in the Appendix (page 296).

In the diagrams that follow, SMC- and EC-inhibition data is displayed as the number of cells in % normalized to negative control (which is always 100 %), as is the proportion of extracellular LDH in % released from SMCs (release is ≤ 5 % for negative control where cells are intact). All bar graph data relates to measurements at 30 µM concentration. Additionally, a horizontal line at the SMC bar indicates the number of these cells when left unstimulated and untreated, i.e. this is the basal level of proliferation. This threshold varies somewhat between assay rounds, which is why this line is at different heights in the graphs. The mode of action is currently not known in detail for leoligin, and proliferation inhibition may actually shift to different mechanisms in different library compounds as well. Moreover, the extent of basal proliferation is not known. In the absence of LDH release data, this makes interpretations difficult in those cases where the number of compound-treated SMCs drops below that of untreated SMCs because the compound could inhibit both PDGF-induced and basal proliferation, or it could be toxic to the cells (or both). What can be said though is that SMC levels ≤ 5 % do in fact indicate a toxic effect, as corroborated in those instances where this is the case and where LDH data is available (*vide infra*). Moreover, the IC_{50} values of SMC proliferation inhibition (as calculated with respect to the basal level) are also given in the diagrams, and the mean value is

[p] Not to be confused with the cardiac glycosides digoxin and digitoxin.

shown for compounds where this quantity was determined more than once. An ideal compound in this regard should therefore have a low SMC IC_{50}, should not inhibit ECs (bar near 100 %) and should not lead to the release of LDH (bar near 5 %).

5-Methoxyleoligin **60** possesses a better inhibition profile than leoligin **59**. However, no analogs of **60** (that is, compounds with modified acyl or benzylic moieties, but pertaining the 3,4,5-trimethoxyphenyl system) were found to bring the SMC-IC_{50} below 10 µM, with **SOGE-20** being the best compound in this regard (11.7 µM). Other ring sizes (esters of cyclopentane-, 1-cyclopentene-, cyclohexane- and 1-cyclohexenecarboxylic acid, as well as benzoic acid) afforded values between that and 20 µM, and other open-chain derivatives were less potent (**Figure 31**).

Dimethyllariciresinol **20**, its C_1 homolog **257** and other free alcohols of this sort were generally inactive, except for a few which possessed some form of extension of carbon atoms (**132**, **133**, **150**, **151**, **152**, **154**, **KH-85**, **SOGE-26** and **SOGE-35**). For **132** and **SOGE-35**, good compatibility with ECs was also determined. Conversely, toxic effects on SMCs were likely associated with **133**, **150**, **151**, **152**, **KH-85** and possibly also **SOGE-35** due to the extremely strong (apparent) reduction of basal proliferation at 30 µM concentration.

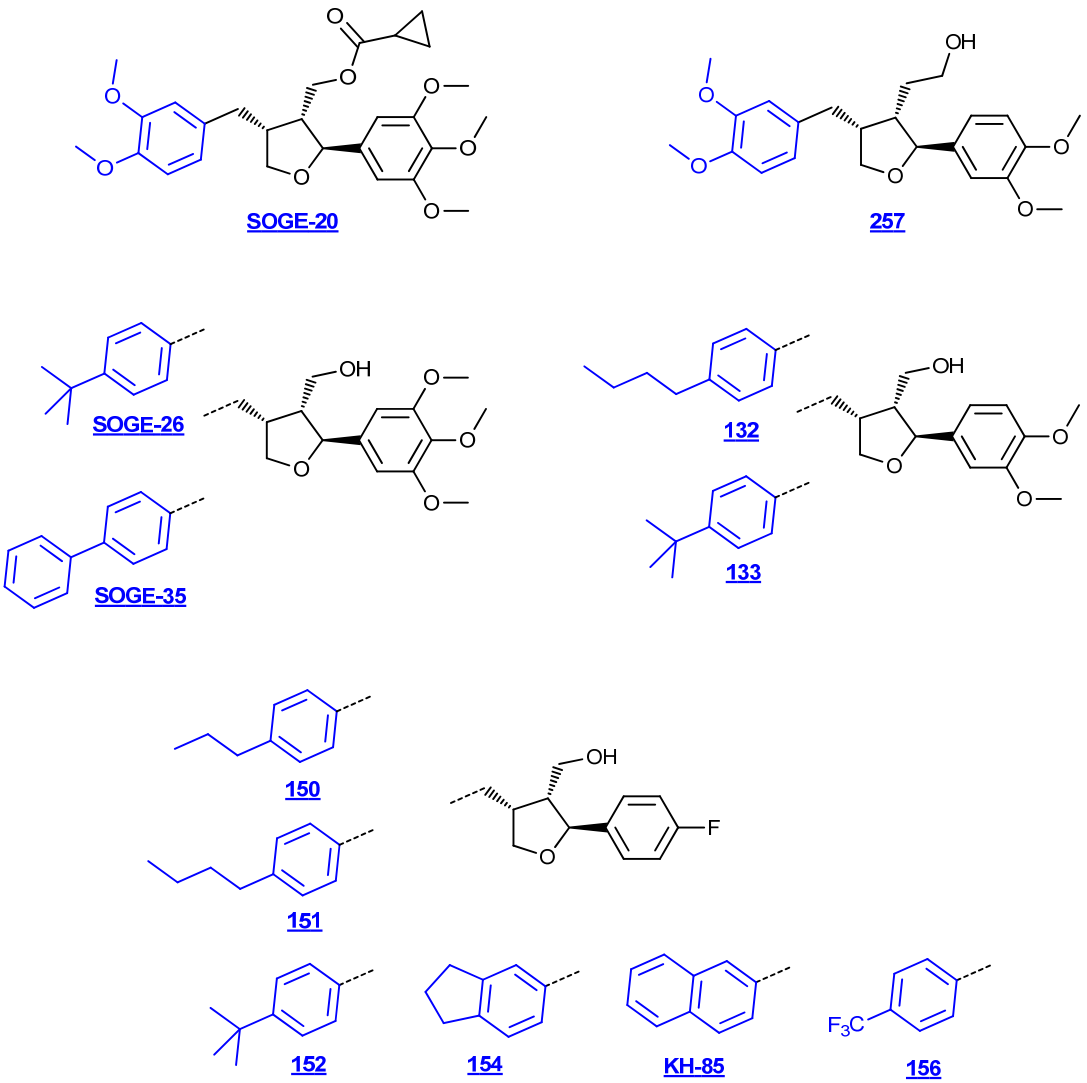


Figure 31

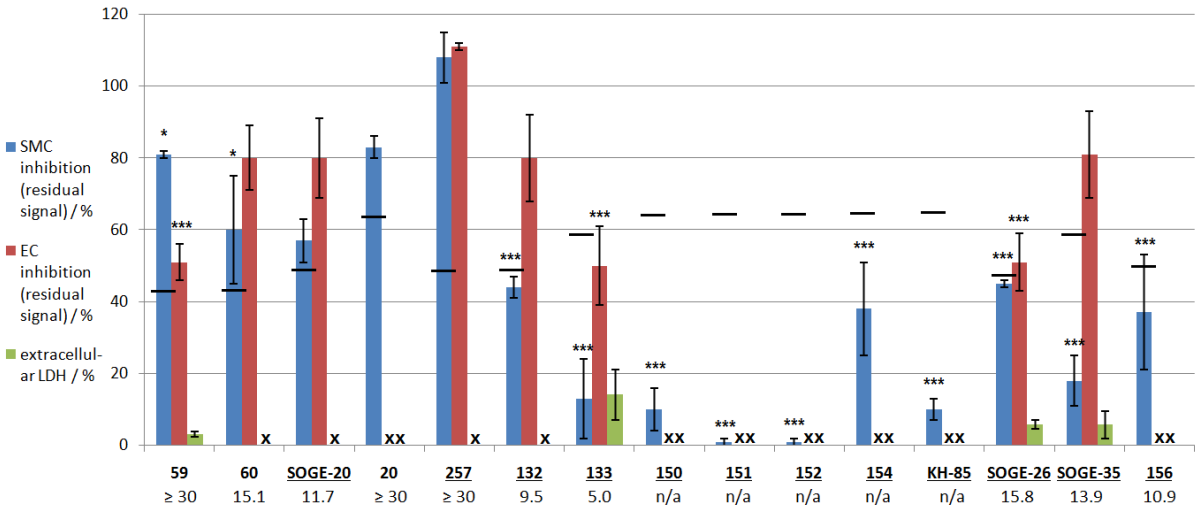


Figure 31, continued: Cell proliferation and toxicity data with the corresponding compound structures. SMC inhibition data is given ± standard deviation at 30 µM concentration (blue bars; no inhibition would be 100 % as the data is normalized to negative control where cells were stimulated to proliferate but not treated with compound). A horizontal black line indicates the readout for unstimulated and untreated cells (which is around 50 % in all cases, fluctuations of this value are due to experimental variations). The IC_{50} values for SMC inhibition are given in µM concentration below the compound labels, and mean values are shown where more than one determination was available. EC inhibition data is given ± standard error of the mean at 30 µM concentration (red bars; no inhibition would be 100 %, which is negative control). In those cases where more than one value for this readout was available due to multiple determinations, the one with the lowest standard error is shown. Extracellular LDH is given ± standard deviation at 30 µM concentration (green bars; negative control, i.e. intact cells, produce ≤ 5 % extracellular LDH). An **x** indicates that the corresponding data is not available. Analysis of variances (ANOVA) / Bonferroni was used to estimate significance (***: $p < 0.001$; **: $p < 0.01$; *: $p < 0.05$). Compounds are arranged in the order in which they are mentioned in the text. Aforementioned remarks also apply to the following diagrams. In the cases of leoligin **59** and 5-methoxyleoligin **60** herein, the data of the synthetic compounds are shown.

Although not significant statistically, SMC death seemed indeed to be somewhat increased with compound **133**,[q] while this was not the case with **SOGE-35**. Further investigations might have resolved these conflicting interpretations of the data on **SOGE-35**, but were not performed because of its rather moderate SMC-IC_{50} of 13.9 µM (mean of two determinations) and the steep dose-response curve it showed, making its effect on proliferation very sensitive to dosage (compared to other compounds in this study). Fluorinated alcohol **156** also had appreciable SMC inhibition activity (IC_{50} of 10.9 µM), an observation which will become important in subsequent parts of this discussion. Of alcohols **132**, **SOGE-26** and also **SOGE-35**, the corresponding angelates **184**, **SOGE-38** and **SOGE-47** (**Figure 32**) did not show improved IC_{50} values. Only **185** (from **133**) performed better, but the borderline toxicity seemed to persist and ECs were also greatly affected by this compound.

[q] Not significant at the usual $\alpha = 0.05$ (ANOVA / Bonferroni). In order to avoid discussing *statistically insignificant* results, it shall be noted that, when compared to negative control, $p < \alpha = 0.06$ in a one-tailed *t*-test (one-tailed because the relevant question is only whether the proportion of extracellular LDH in the case of **133** is *higher* than in the negative control), which warrents a cautious interpretation towards potential toxicity. Yet this is not to be understood as an attempt to set the significance level after the fact; rather, the intention here is to avoid undue over-use of hypothesis testing with uncritically accepting the calculated statistics.[331] This remark applies analogously to all similar cases of borderline toxicity.

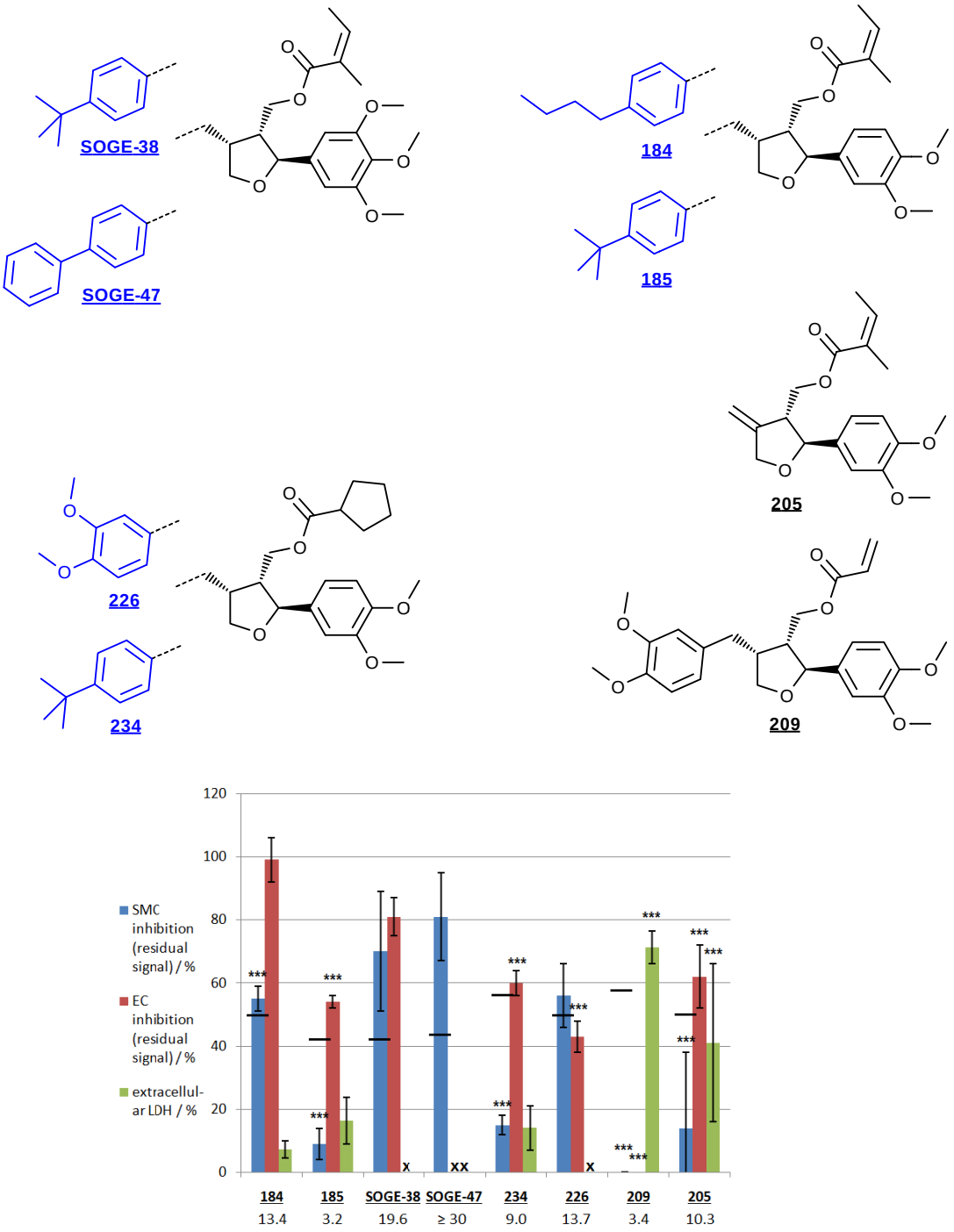


Figure 32: Cell proliferation and toxicity data with the corresponding compound structures. *Cf.* **Figure 31** for explanatory information.

Cyclopentanecarboxylate **234** was synthesized and tested for probing possible synergism regarding the desired properties (high SMC / EC selectivity) because the corresponding ester of dimethyllariciresinol, **226**, also had moderately improved performance on SMCs (IC_{50} of 13.7 µM, mean of two determinations), while its inhibitory effect on ECs was not significantly enhanced with respect to leoligin. It was hoped that this chimera (of **185** and **226**) would show improved overall behavior, but this turned out not to be the case (SMC-IC_{50} of 9.0 µM (mean of two determinations), but no improvement to selectivity). Most importantly, the subliminal toxicity continued to be an issue here as well. As for other esters of dimethyllariciresinol, 5- to 7-membered aliphatic cyclic carboxylates had activity profiles comparable to **226**, while smaller and acyclic ones generally lost

SMC activity and SMC / EC selectivity. Aromatic and heteroaromatic (nicotinic and isonicotinic) esters also proved to be largely SMC-inactive, and of the olefinic esters, acrylate **209**—a strong Michael acceptor—deserves mention because it was a rather striking case of cellular toxicity, apparently for both SMCs and ECs (at 30 µM concentration). Incidentally, truncated compound **205** also seemed to be rather toxic to SMCs.

The presence and position of the oxo group is likely to be of importance, as is the type of functional group it belongs to (leoligin, an ester of angelic acid, *vs.* amide **254**). Potency increases when this group is placed closer to the tetrahydrofuran ring (**262**), and decreases when it is further away (**258**, **Figure 33**).

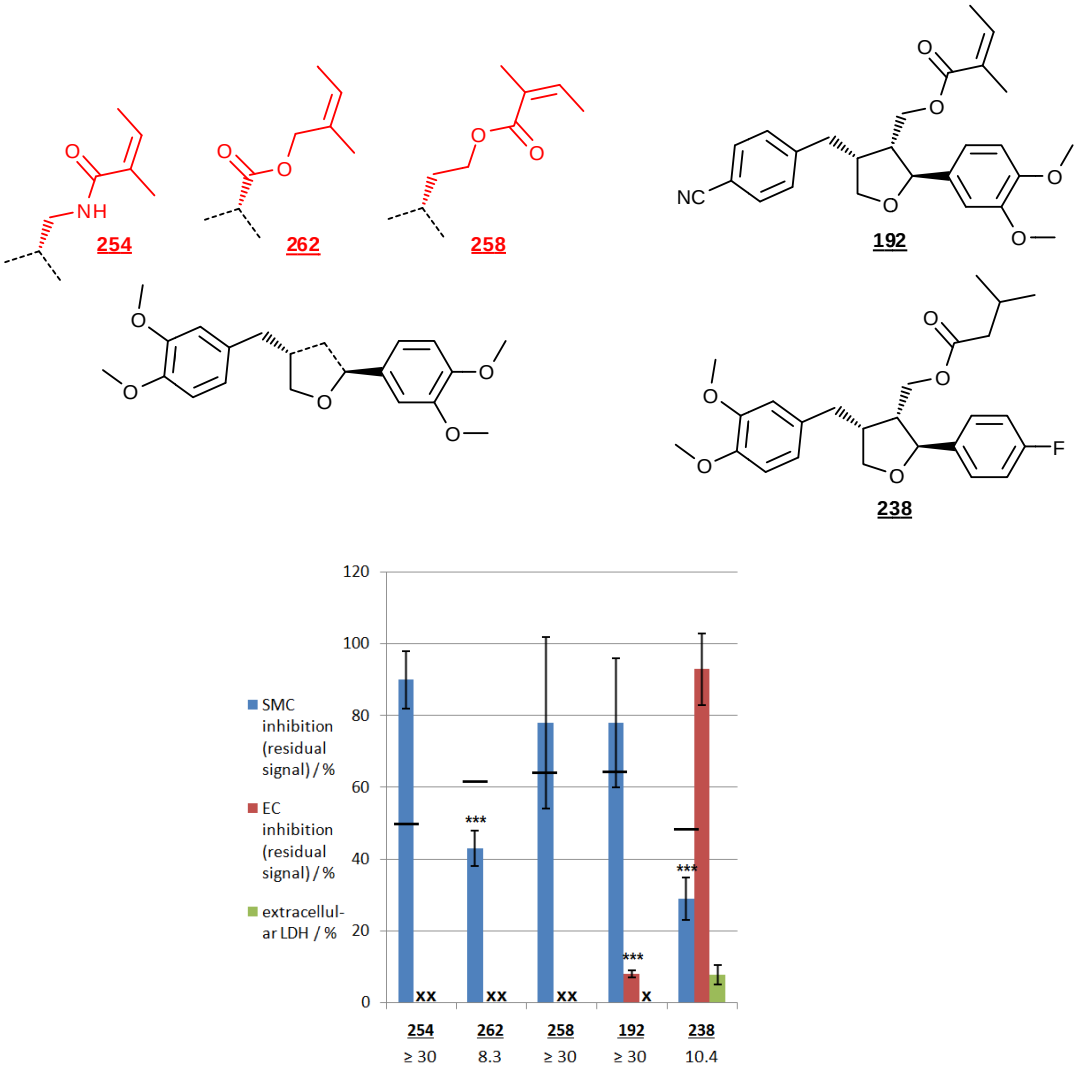


Figure 33: Cell proliferation and toxicity data with the corresponding compound structures. *Cf.* **Figure 31** for explanatory information.

Regarding modifications of the benzylic moiety, cyanoester **192** was a special case because it possessed a most pronounced inverse selectivity by inhibiting ECs much more strongly than SMCs. But achieving high SMC and low EC activity instead remained a challenge. Certain combinations of structural modifications, such as most-likely non-toxic compound **238**, turned out to be promising in this regard, but apart from that one, low SMC-IC_{50}s were always accompanied by pronounced EC inhibition, contrary to the stated objective. Eventually, compound **156** (from **Figure 31** further above) proved to be key to this aim. Given that most free alcohols were inactive, its IC_{50} (10.9 µM) was noteworthy. Although the extend of its EC proliferation inhibition had not been determined, it

appeared conceivable that equipping this compound with an acyl moiety might actually furnish a compound with the desired activity profile, but without potential toxicity as observed in **185**. In fact, its angelic acid ester **204** was highly active at inhibiting SMCs (the IC_{50} was determined twice, with values of 1.9 µM and 4.0, respectively, and the mean value is shown in **Figure 34**) and also cell-selective and non-toxic. Similar values obtained on compound **199** suggested that it is the *p*-trifluoromethyl group which might be pivotal, although it seems that a favorable result can only be achieved when the remaining dimethoxy substitution pattern of leoligin is also removed or replaced, considering compound **191** for comparison. The situation appears to be more complicated with simple fluorine substitution: replacing the methoxy groups on both arenes by fluorine affords **203,** which has essentially the same activity profile as **204** and **199**. Conversely, selectivity is reduced (**200**) or even inverted (**187** and **188**) when two of them are left in place, depending on which part of the molecule this is done. The gradual transition from **203** to **187**/**188** *via* **190** and **189** (i.e. from a compound primarily active on SMCs to one which acts on ECs) actually underlines the susceptibility (and the possibility for fine-tuning the activity) with regard to fluorine substitution in general.

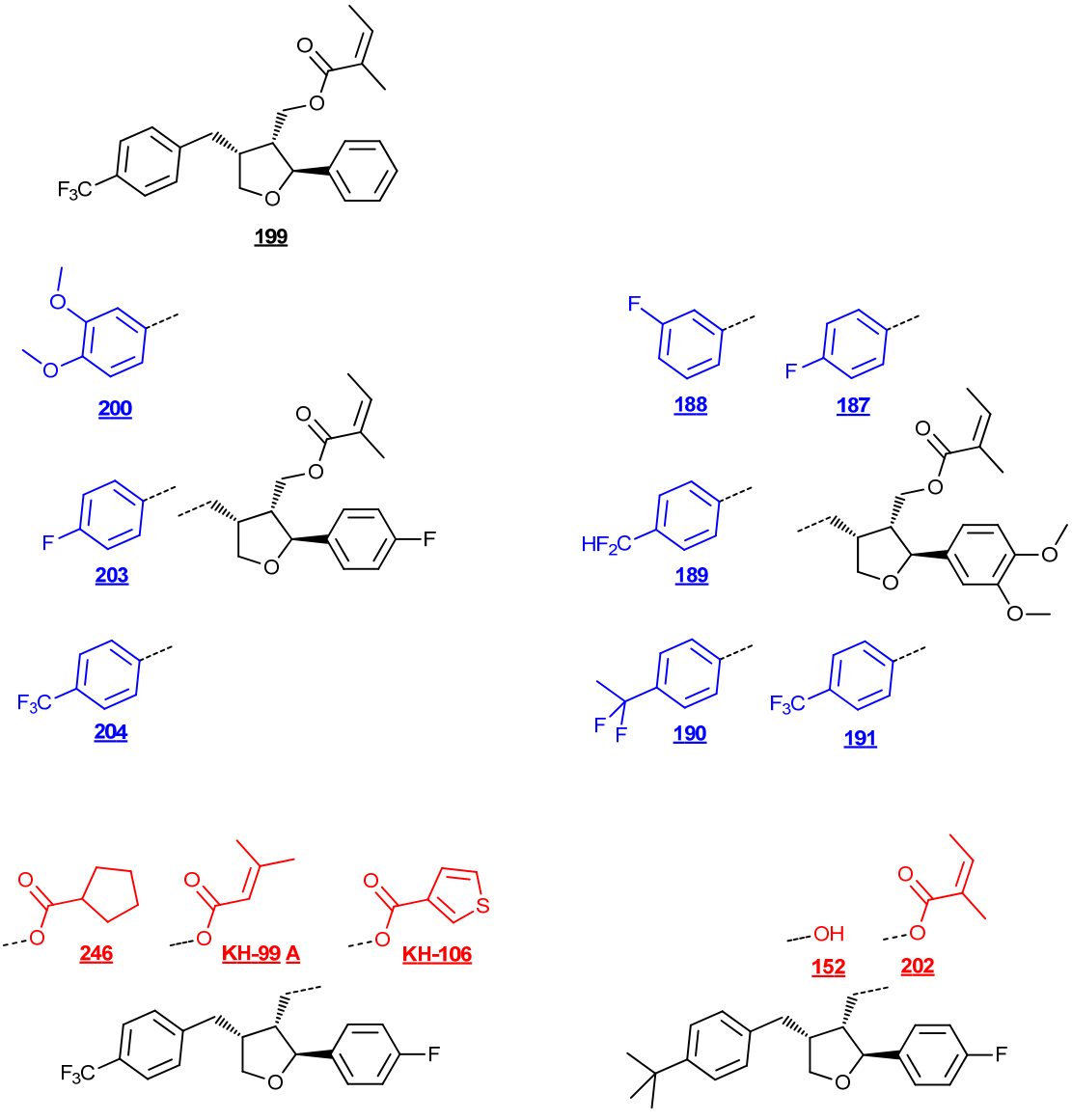


Figure 34

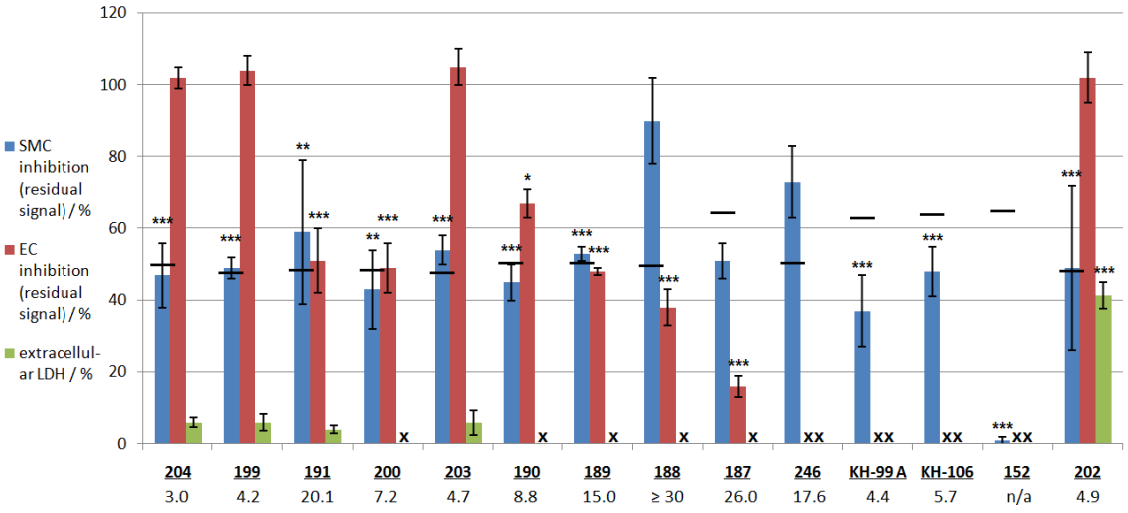


Figure 34, continued: Cell proliferation and toxicity data with the corresponding compound structures. *Cf.* **Figure 31** for explanatory information.

In addition to that, a marked decrease of SMC activity was measured in the case of compound **246**, where it was hoped that this one would be equally potent as **204** because the cyclopentanecarboxylic scaffold had afforded improved IC_{50}s in other examples before (when compared with those that retained the angelic moiety of leoligin). This was an attempt to remove or attenuate the Michael acceptor; therefore, a more conservative approach was chosen instead: preliminary results suggest that other π systems, such as those in compounds **KH-99 A** or **KH-106**, restore the SMC activity, although the rest of the biological profile (EC activity and LDH release) has not been assessed at the time of writing (for more detailed discussion of compounds labeled **KH**, including their synthesis, *cf.* related[290] work). Finally, compounds **152** and **202** support the view that the *p-tert*-butyl group was responsible for the potential cytotoxicity observed in previous compounds **133**, **185**, and **234**.

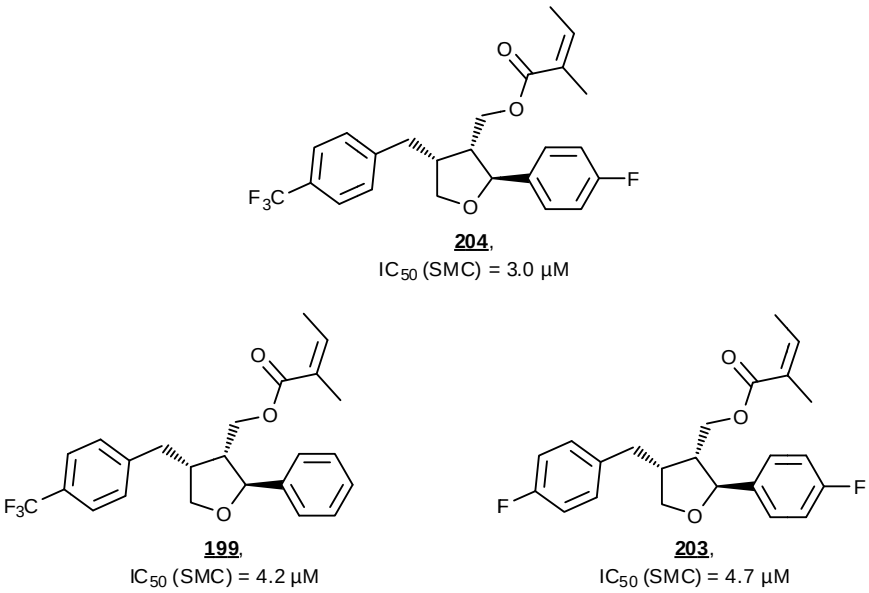


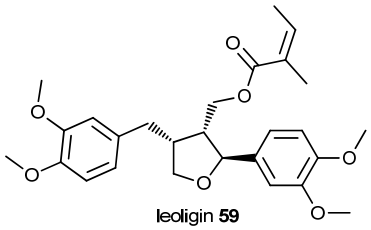
Figure 35: Three compounds with the most favorable inhibitory profile.

In summary, it was possible to increase the SMC proliferation inhibition activity by a factor of up to ten and concurrently remove EC inhibition, apparently without causing toxic effects even at concentrations far higher than the corresponding SMC-IC_{50} (**Figure 35**).

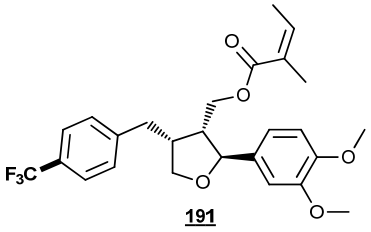
C Final Conclusions

Central to the tasks of this thesis were the development of a divergent strategy for the synthesis of furan-type lignans, the synthesis of seizable amounts of leoligin, the preparation of a library of analog compounds, and the biological evaluation of their physiological properties with regard to macrophage cholesterol efflux enhancement, NF-κB inhibition, and selective suppression of vascular smooth muscle cell proliferation in cooperation with project partners.

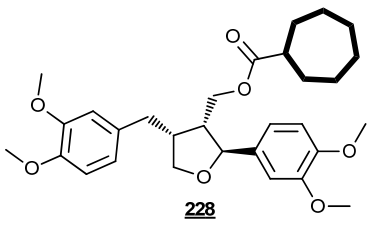
Following some detours and dead ends, a strategy was devised for lignan preparation and proven to be capable of delivering both the natural compound as well as a variety of novel and (probably) naturally not occurring lignans. Key to this new synthetic protocol is a diastereoselective hydroboration-Suzuki coupling sequence that furnished lignan compounds in typically 60 % yield. The five-membered cyclic scaffold pertinent to these structures turned out to be a fortunate case for achieving high diastereoselectivity (about 95 : 5) with relatively weak substrate control, as indicated in experiments with other ring types. The method could be used to generate molecules diverse enough to gain insight into the structural requirements for improving the above mentioned biological activities of leoligin individually, and this was accomplished by making synthetic decisions based on continually returning screening results. It shall be emphasized that the scientifically most valuable[307] findings herein—the conclusions on how to design a molecule in order to make it pharmacologically more active—originated from working at the interface of chemistry and biology.[308]



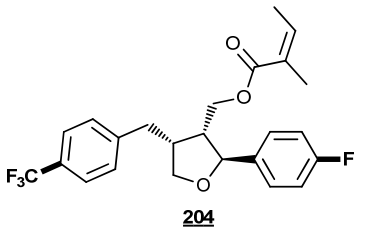
macrophage cholesterol efflux: 2.1-fold enhancement (at 10 μM)[a]
NF-κB: IC_{50} = 19.7 μM
SMCs: IC_{50} = 32.1 μM
SMC toxicity: not observed (at 30 μM)
ECs: reduction to 51 % (at 30 μM)



macrophage cholesterol efflux: 3.1-fold enhancement (at 10 μM)
NF-κB: IC_{50} ≥ 20 μM
SMCs: IC_{50} = 20.1 μM
SMC toxicity: not observed (at 30 μM)
ECs: reduction to 51 % (at 30 μM)



macrophage cholesterol efflux *not tested*
NF-κB: IC_{50} = 1.6 μM
SMCs: IC_{50} = 10.3 μM
SMC toxicity *not tested*
ECs: reduction to 35 % (at 30 μM)



macrophage cholesterol efflux *not tested*
NF-κB: IC_{50} ≥ 20 μM
SMCs: IC_{50} = 3.0 μM
SMC toxicity: not observed (at 30 μM)
ECs: reduction not observed (at 30 μM)

Figure 36: Comparative overview. [a]For reasons of comparability, the value from the assay round in which **191** was tested is shown here (rather than the average over all rounds, as given in the Appendix (page 296)).

The three analog compounds that performed best with regard to their respective class of biological activity are compared with leoligin in **Figure 36**, with the modifications emphasized. They are not completely orthogonal in their profile, but besides being more active, all three of them are mutually more selective than leoligin (as far as the data are available) toward either macrophage cholesterol efflux enhancement (compound **191**), NF-κB inhibition (**228**), or SMC inhibition (**204**). This is also true in the case of the SMC inhibition by **228** (i.e. its off-target activity in this context), because this activity is increased only three-fold, whereas the NF-κB activity is increased twelve-fold. Dimethyllariciresinyl pivalate **222** (**Figure 29**, section B.2.2, page 104) was the second most potent analog in this screening (NF-κB-IC_{50} of 2.2 μM) and even more selective with regard to its low activity at SMC inhibition (24.3 μM). Cholesterol efflux is doubled by **191** (at the measured concentration) and SMC proliferation inhibition activity is increased ten-fold by **204**. Yet the EC inhibition activity of **191** and **228** remains as a probably undesired effect.

Apart from structure-activity information obtained through this work, these results also suggest that some useful tool compounds were obtained for further study of the physiological pathways associated with the phenological observations made *in vitro*. Combined with the modular synthesis as presented herein, it is possible to prepare molecular probes of this sort as demanded for continued investigations in efforts to target cardiovascular diseases.

D Experimental Section

D.1 General Notes

Chemicals

Unless noted otherwise, reactants and reagents were purchased from commercial sources and used without further purification.

Dry toluene, CH_2Cl_2, Et_2O, THF and MeOH were obtained from a dispensing system by passing commercial material through a cartridge containing activated alumina (PURESOLV, Innovative Technology), stored under dry nitrogen and then used as such without further drying unless specified.

Dry EtOH and **DMF** were purchased from a commercial source and used without further drying.

DMSO was **dried** by treating commercial material with CaH_2 mesh at 150 °C under argon, followed by distillation under reduced pressure.[309]

Deoxygenated and dry THF was obtained by refluxing and distilling pre-dried material (as described above) from sodium and benzophenone under argon.[263]

Zinc dust was **activated** by treating commercially available zinc dust with aqueous HCl (2 M), followed by thorough washing with water, subsequently with MeOH and dry Et_2O. After drying *in vacuo* at 60 °C the material was stored under argon.[234]

Molecular sieves were activated by heating them to 200 °C for approximately 6 h in high vacuum and were then stored under argon.[175]

DIBAL-H in hydrocarbon solutions were reaction-titrated according to a literature procedure, and the content of active DIBAL-H was determined by standard ^{1}H NMR spectroscopy.[310]

An **iodine test** was used to check for the presence of oxidant in certain reactions. Therein, KI and starch (1 spatula tip each) was heated in water (approximately 10 mL) until completely dissolved and allowed to cool to room temperature before aliquots (approximately 1 mL) were then combined with a few drops of the solution to be tested.

Melting ranges were determined using a Kofler-type Leica Galen III micro hot stage microscope or an SRS OptiMelt Automated Melting Point System, and are uncorrected. Temperatures are reported in intervals of 0.5 °C.

Aluminum-backed Merck silica gel 60 with fluorescence indicator F_{254} was used for **Thin Layer Chromatography** (TLC). Spots were visualized under UV light (254 nm) and by staining with cerium ammonium molybdate (CAM) solution (20 g of ammonium pentamolybdate, 0.8 g of cerium(IV) ammonium sulfate, 400 mL of 10 v/v % sulfuric acid) as a general purpose reagent. Alcohols were

also visualized with *p*-anisaldehyde solution (3.5 g *p*-anisaldehyde, 1.5 mL acetic acid, 5 mL sulfuric acid, 120 mL ethanol), and compounds pertaining double bonds were visualized with potassium permangante solution (1.5 g potassium permanganate, 10 g potassium carbonate, 1 mL 10 w/w % NaOH, 200 mL water).

Specific rotation was measured using an Anton Parr MCP500 polarimeter and HPLC grade solvents under conditions as specified individually. Values are reported in the form *+ or - specific rotation* (*concentration in terms of g / 100 mL*, *solvent*).

Analytical Chromatography-Spectroscopy

Gas Chromatography-Mass Spectroscopy (GC-MS) was used to analyze samples of reaction products with sufficient volatility. The following instruments and columns were used:

Instrument 1 Thermo Scientific Finnigan Focus GC / Quadrupole DSQ II device using a helium flow of 2.0 mL / min, analyzing an *m/z* range from 50 to 650

Instrument 2 Thermo Scientific Trace 1300 / ISQ LT Single Quadrupole Mass Spectrometer device using a helium flow of 1.5 mL / min, analyzing an *m/z* range from 50 to 550

Column 1 BGB 5 (0.25 µm film; 30 m x 0.25 mm ID)

Column 2 Rxi-5Sil MS (0.25 µm film; 30 m x 0.25 mm ID)

Column 3 TR-5 MS (0.50 µm film; 30 m x 0.25 mm ID)

Temperature gradients are as follows:

Method A Instrument 1, Column 1:
100 °C (2 min), to 280 °C (15 °C / min)

Method B Instrument 1, Column 1:
40 °C (2 min), to 60 °C (1 °C / min), to 280 °C (70 °C / min), 280 °C (1 min)

Method C Instrument 1, Column 1:
100 °C (2 min), to 280 °C (18 °C / min), 280 °C (3 min)

Method D Instrument 1, Column 1:
100 °C (2 min), to 280 °C (40 °C / min), 280 °C (23 min)

Method E Instrument 1, Column 1:
100 °C (2 min), to 280 °C (40 °C / min), 280 °C (38 min)

Method F Instrument 1, Column 1:
100 °C (2 min), to 280 °C (40 °C / min), 280 °C (48 min)

Method G Instrument 2, Column 2:
100 °C (2 min), to 300 °C (35 °C / min), 300 °C (2 min)

Method H Instrument 2, Column 3:
40 °C (2 min), to 280 °C (32 °C / min), 280 °C (2 min)

Method I Instrument 2, Column 3:
100 °C (2 min), to 280 °C (40 °C / min), 280 °C (38 min)

Method J Instrument 2, Column 3:
100 °C (2 min), to 280 °C (40 °C / min), 280 °C (58 min)

Data is reported in the form *retention time*; m/z_1 (*relative intensity in %*), m/z_2 (*relative intensity in %*), … Only signals with $m/z \geq 90$ and relative intensity ≥ 15 % are given, except for the signal at 100 % relative intensity which is always given. Also, the molecular ion signal M^+ is given regardless of its intensity or *m/z*; in cases where M^+ was not visible due to excessive fragmentation, a characteristic fragment signal is identified instead.

High Pressure Liquid Chromatography (HPLC) was used to determine enantiomeric excess of reaction products, using a Dionex UltiMate 3000 device (RS Diode Array Detector). Chiral separation columns and analysis conditions are specified individually. In all cases, retention times include appropriate guard cartridges containing the same stationary phase as the separation column.

Liquid Chromatography-High Resolution Mass Spectroscopy (LC-HRMS) was used to confirm exact molecular mass of reaction products by their quasi-molecular ions ($M+H^+$ or $M+Na^+$). The following two instruments were used:

Instrument 1: Shimadzu Prominence HPLC device (DGU-20 A3 degassing unit, 2 x LC-20AD binary gradient pump, SIL-20 A auto injector, CTO-20AC column oven, CBM-20A control module, and SPD-M20A diode array detector). Samples were eluted through a Phenomenex Kinetex precolumn (5 µm core shell ODS(3) phase; 4 mm x 2 mm ID) at 40 °C under conditions comprising gradients of H_2O / MeOH containing formic acid (0.1 v/v %), and then detected using a Shimadzu IT-TOF-MS by Electrospray Ionization (ESI) or Atmospheric Pressure Chemical Ionization (APCI), as indicated individually. Analyses were performed by E. Rosenberg (CTA, VUT) and L. Czollner (IAS, VUT).

Instrument 2: Agilent 1100/1200 HPLC device (degassing unit, 1200SL binary gradient pump, column thermostat, and CTC Analytics HTC PAL autosampler). Samples were eluted through a silica-based Phenomenex C-18 Security guard cartridge (1.7 µm PD; 2.1 mm ID) at 40 °C under isocratic conditions comprising H_2O containing formic acid (0.1 v/v %) / MeOH containing formic acid (0.1 v/v %) in a ratio of 30 : 70 at a flow rate of 0.5 mL / min, and then detected using an Agilent 6230 LC-TOF-MS equipped with an Agilent Dual AJS ESI source by Electrospray Ionization (ESI). Analyses were performed by L. Czollner (IAS, VUT).

Preparative chromatography

Flash column chromatography was carried out on Merck silica gel 60 (40-63 µm), and separations were performed using a Büchi Sepacore system (dual Pump Module C-605, Pump Manager C-615, Fraction Collector C-660, and UV Monitor C-630 or UV Photometer C-635).

Preparative High Pressure Liquid Chromatography (preparative HPLC) was carried out on a Phenomenex Luna reversed-phase column (10 µm C18(2) phase, 100 A; 250 mm x 21.20 mm ID), and separations were performed using a Shimadzu LC-8A device (SIL-10AP autosampler, SPD-20 detector, and FRC-10A fraction collector).

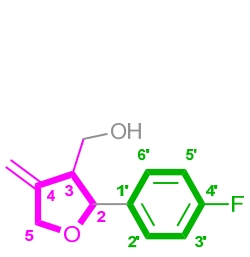
Reaction temperatures were measured externally (electronic thermometer connected to heater-stirrer or low temperature thermometer in case of cryogenic reactions) unless otherwise noted.

Partition coefficients (**log *P*** values) were calculated for compounds of sections **D.3** and **D.4**, using ACD/Labs 12 with LogP Accuracy Extender.

Nuclear Magnetic Resonance (NMR) spectroscopy

NMR spectra were recorded from $CDCl_3$ or DMSO-d_6 solutions on a Bruker AC 200 (200 MHz proton resonance frequency) or a Bruker Advanced UltraShield (400 MHz) spectrometer (as indicated individually), and chemical shifts are reported in ascending order in ppm relative to the nominal residual solvent signals, i.e. ^{1}H: δ = 2.50 ppm (DMSO-d_6); ^{13}C: δ = 77.16 ppm ($CDCl_3$), δ = 39.52 ppm (DMSO-d_6).[311-312] For all ^{1}H spectra in $CDCl_3$, however, shifts are reported relative to TMS as internal standard (δ = 0 ppm) due to the interference of aromatic signals of many samples with the residual solvent signal of $CDCl_3$. For ^{13}C spectra, *J*-modulated (APT) or DEPT-135 pulse sequences were used to aid in the assignment.

In the introduction, a published system for numbering the atoms in lignan compounds was used to achieve consistency with existing literature (section A.1.1, **Figure 1**, page 13). However, for the NMR assignments that follow, a different system is used which keeps the ring systems together. This is because in most examples that follow, certain structure motifs are prevalent, such as these depicted below:



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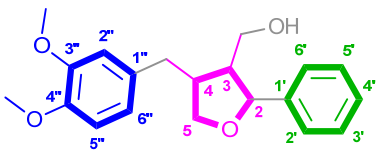
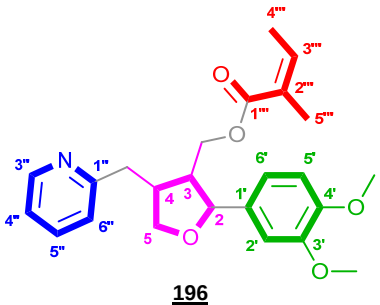


123



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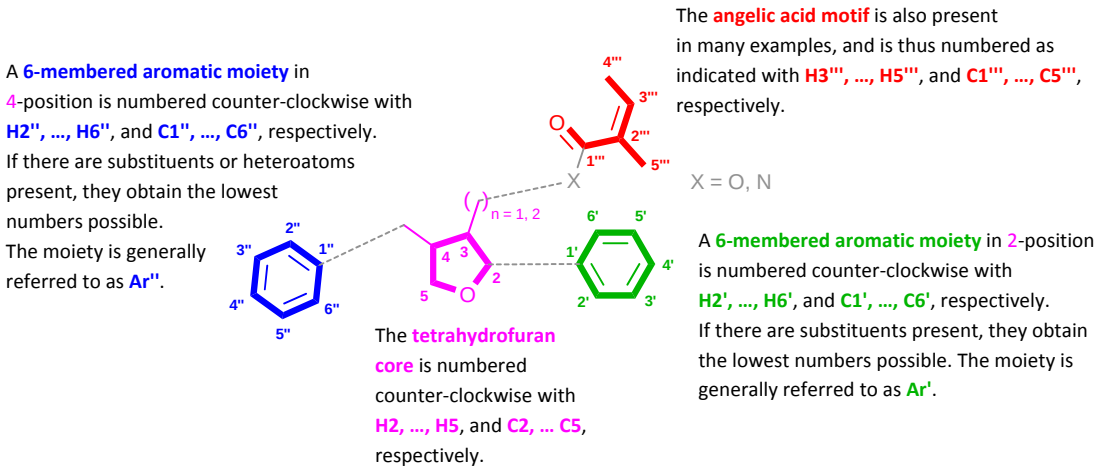
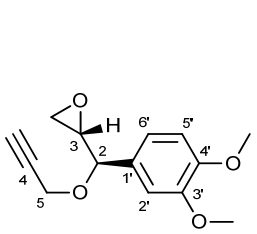
These compounds are always drawn in the above manner, such that signal assignment for H and C can be reported in accordance to these rules:

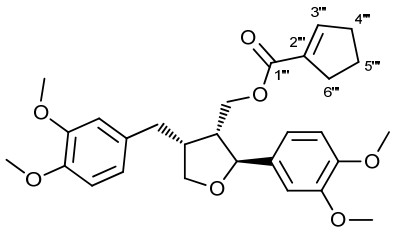


These numbering labels in structures of this type are therefore not depicted in the individual examples, and the reader is referred to the assignment rules as shown above. However, for compounds which cannot (completely) be accommodated in this way, or for the sake of clarity in some cases, individual numbering labels are added, such as:



(αR,βS)-**101**

here, the tetrahydrofuran core is not completed yet, but the numbering labels already correspond



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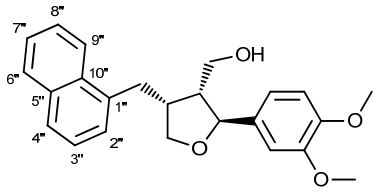
in these cases, the numbering is added because the above assignment rules cannot be used to identify all positions in the molecule



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Generally, signals were assigned by comparison with literature values, comparing newly synthesized compounds with one another, and by increment calculation or software prediction (ChemBioDraw Ultra 12). Identified signals were marked with an asterisk (*) when assignment was equivocal. Where it was not possible to identify which ring system and position an aromatic signal belongs to, it is denoted only with Ar (e.g.: Ar-H, Ar-OCH_3). Coupling constants *J* and signal multiplicities are denoted as: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), or unspecified multiplet (m). Combinations are also used, e.g.: dt: (doublet of triplets), and bond separations are indicated by superscripts of *J*. In ^{1}H spectra, *J*-s are arranged in ascending order (increasing number of intervening bonds through which the coupling is operative: ^{1}J, ^{2}J, ^{3}J, ...), and the order of *J*-s is the same as in the multiplet label. If appropriate and necessary, *J* is also specified more precisely by subscript, e.g.: dt, $^{3}J_{benzyl}$ = 3.5 Hz, $^{3}J_{oxirane}$ = 3.1 Hz (meaning a doublet of 3.5 Hz and a triplet of 3.1 Hz, with the coupling nuclei separated by 3 bonds in both cases). In ^{13}C spectra, only J_{C-X} (X any nucleus other than H) is given, e.g.: dd, $^{2}J_{C-F}$ = 21.4 Hz (meaning a doublet with an unspecified $^{1}J_{C-H}$ and a doublet with $^{2}J_{C-F}$ of 21.4 Hz); this is because $^{13}C\{^{1}H\}$ spectra were recorded exclusively whereby actual J_{C-H}-s cannot be measured. Accordingly, the signal multiplicities themselves were also inferred from peak orientation (by *J*-modulation or DEPT-135). All discernible signals are given.

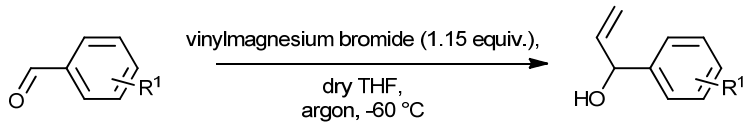
Abbreviations

ADD	1,1'-(azodicarbonyl)dipiperidine
ANOVA	analysis of variance
apoAI	apolipoprotein A1
BAIB	[bis(acetoxy)iodo]benzene ((diacetoxyiodo)benzene)
9-BBN	9-borabicyclo[3.3.1]nonane
BSA	bovine serum albumin
m-CPBA	*meta*-chloroperbenzoic acid
DEAD	diethyl azodicarboxylate
D-(-)-DET	(unnatural) (-)-diethyl D-tartrate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine (Hünig's base)
4-DMAP	4-(dimethylamino)pyridine
DMEM(/F12)	Dulbecco's Modified Eagle Medium (Nutrient Mixture F-12)
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenyl phosphoryl azide (diphenyl phosphorazidate)
dppf	1,1'-bis(diphenylphosphino)ferrocene
ECL	enhanced chemiluminescence
EDCI	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide
FBS	fetal bovine serum
HEPES	4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid
INT	2-(4-iodophenyl)-3-(4-nitrophenyl)-5-phenyl-2*H*-tetrazolium chloride
LDH	lactate dehydrogenase
LP	light petroleum (boiling range approximately 40 to 60 °C)
Ms	mesyl (methanesulfonyl)
MTBE	methyl *tert*-butyl ether (*tert*-butyl methyl ether)
NAD^+	nicotinamide adenine dinucleotide
PDGF(-BB)	platelet-derived growth factor (B homodimer)
PMA	phorbol 12-myristate 13-acetate
PMSF	phenylmethylsulfonyl fluoride
RPMI	Roswell Park Memorial Institute
SDS-PAGE	sodium dodecyl sulfate-polyacrylamide gel electrophoresis
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydroperoxide
TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
THF	tetrahydrofuran
TNFα	tumor necrosis factor alpha
(V)EC	(vascular) endothelial cell (specified *vascular* where appropriate)
(V)SMC	(vascular) smooth muscle cell (specified *vascular* where appropriate)

D.2 Synthesis of Intermediate Compounds

D.2.1 Grignard Addition

D.2.1.1 *General Procedure* for Grignard Addition

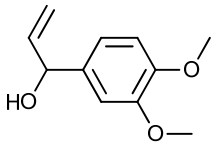


I *rac*-**II**

***Preparation**:* a reaction vessel was charged with a stirring bar, aldehyde **I** (1.00 equiv.) and was then evacuated and back-filled with argon using standard Schlenk technique. Dry THF was then added *via* syringe or canula and the stirred mixture was cooled to -60 °C in a MeOH / liquid N_2 bath, followed by the slow addition of vinylmagnesium bromide solution (1 M in THF, 1.15 equiv.) *via* syringe or by using an addition funnel while keeping the reaction at this temperature. Reaction progress was monitored by TLC and the reaction was terminated when complete.

***Work-up**:* the mixture was treated as detailed individually below to afford the title compound *rac*-**II**.

D.2.1.2 1-(3,4-Dimethoxyphenyl)prop-2-en-1-ol (*rac*-**27**)



rac-**27**, $C_{11}H_{14}O_3$
194.23 g mol^{-1}

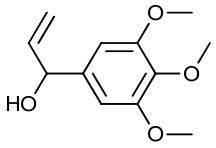
***Preparation**:* according to the *General Procedure* (section D.2.1.1, page 123), 3,4-dimethoxybenzaldehyde (73.1 g, 440.0 mmol, 1.00 equiv.) and THF (600 mL) were used, and vinylmagnesium bromide solution (506.0 mL, 506.0 mmol, 1.15 equiv.) was added over a period of 110 min, after which the mixture was allowed to warm to 10 °C over 2 h.

***Work-up**:* a saturated aqueous NH_4Cl solution (100 mL) was added slowly over 5 min while providing additional cooling to prevent the temperature from rising over +10 °C during the exothermic hydrolysis. To dissolve the magnesium salts, water (450 mL) was added and the mixture was extracted with Et_2O (1 x 500 mL, 5 x 250 mL). The combined organic phases were treated with saturated aqueous $NaHCO_3$ solution (150 mL) and brine (100 mL), followed by drying with Na_2SO_4. The solution was filtered through a plug of silica (15 g, pre-conditioned with Et_2O) and the solvents were evaporated to afford the title compound *rac*-**27**.

This compound is literature-known.[60]

Yield: 85.4 g, 99 %
Appearance: pale yellow oil
(for additional characterization, *cf.* section D.2.2.2, page 126)

D.2.1.3 1-(3,4,5-Trimethoxyphenyl)prop-2-en-1-ol (*rac*-**69**)



rac-**69**, $C_{12}H_{16}O_4$
224.25 g mol^{-1}

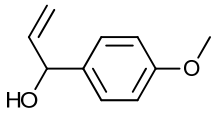
***Preparation**:* according to the *General Procedure* (section D.2.1.1, page 123), 3,4,5-trimethoxybenzaldehyde (18.64 g, 95.0 mmol 1.00 equiv.) and THF (110 mL) were used, and vinylmagnesium bromide solution (109.3 mL, 109.3 mmol, 1.15 equiv.) was added over a period of 30 min, after which the mixture was allowed to warm to -20 °C over 2.5 h.

***Work-up**:* a saturated aqueous NH_4Cl solution (20 mL) was added slowly while providing additional cooling with an ice bath during the exothermic hydrolysis, followed by additional water (160 mL) to deagglomerate salt precipitates, and the mixture was extracted with Et_2O (4 x 100). The combined organic phases were treated with saturated aqueous $NaHCO_3$ solution (50 mL) and brine (70 mL), followed by drying with Na_2SO_4. The solution was filtered and the solvents were evaporated to afford the title compound *rac*-**69**.

This compound is literature-known.[313]

Yield: 20.9 g, 98 %
Appearance: pale yellow oil
(for additional characterization, *cf.* section D.2.2.3, page 127)

D.2.1.4 1-(4-Methoxyphenyl)prop-2-en-1-ol (*rac*-**70**)



rac-**70**, $C_{10}H_{12}O_2$
164.20 g mol^{-1}

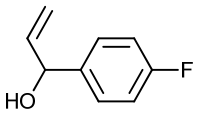
***Preparation**:* according to the *General Procedure* (section D.2.1.1, page 123), 4-anisaldehyde (8.27 g, 60.7 mmol, 1.00 equiv.) and THF (100 mL) were used, and vinylmagnesium bromide solution (70.0 mL, 70.0 mmol, 1.15 equiv.) was added, after which the mixture was stirred at the same temperature for 3 h.

***Work-up**:* a saturated aqueous NH_4Cl solution (30 mL) was added slowly while providing additional cooling with an ice bath during the exothermic hydrolysis. After another 10 min of stirring, water (100 mL) was added to dissolve the magnesium salts, and the mixture was extracted with Et_2O (4 x 100). The combined organic phases were treated with saturated aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL), followed by drying with Na_2SO_4. The solution was filtered and the solvents were evaporated to afford the title compound *rac*-**70**.

This compound is literature-known.[314]

Yield: 9.22 g, 92 %
Appearance: pale yellow oil
(for additional characterization, *cf.* section D.2.2.4, page 128)

D.2.1.5 1-(4-Fluorophenyl)prop-2-en-1-ol (*rac*-**72**)



rac-**72**, C_9H_9FO
152.17 g mol^{-1}

***Preparation**:* according to the *General Procedure* (section D.2.1.1, page 123), 4-fluorobenzaldehyde (6.82 g, 55.0 mmol, 1.00 equiv.) and THF (100 mL) were used, and vinylmagnesium bromide solution (63.3 mL, 63.3 mmol, 1.15 equiv.) was added over a period of 30 min, after which the mixture was allowed to warm to -30 °C over 2 h.

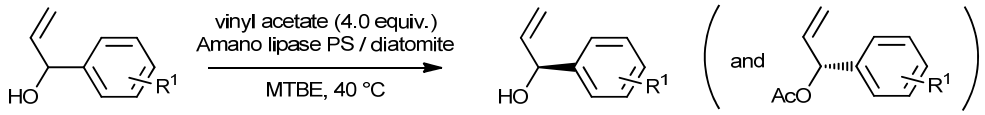
***Work-up**:* a saturated aqueous NH_4Cl solution (13 mL) was added slowly while providing additional cooling to prevent the temperature from rising over -20 °C during the exothermic hydrolysis. To dissolve the magnesium salts, water (160 mL) was added and the mixture was extracted with Et_2O (1 x 70 mL, 5 x 40 mL). The combined organic phases were treated with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (13 mL), followed by drying with Na_2SO_4. The solution was filtered through a plug of silica (10 g, pre-conditioned with Et_2O) and the solvents were evaporated at a minimum pressure of 100 mbar to afford the title compound *rac*-**72**.

This compound is literature-known.[314]

Yield: 8.36 g, > 99 %
Appearance: pale yellow oil
(for additional characterization, *cf.* section D.2.2.6, page 130)

D.2.2 **Kinetic Resolution**

D.2.2.1 *General Procedure* for Kinetic Resolution

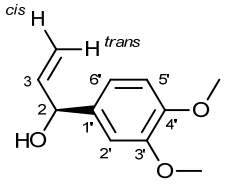


rac-**II** (*S*)-**II** (*R*)-Ac-**II**

***Preparation**:* a reaction vessel was charged with racemic alcohol *rac*-**II** (1.00 equiv.) and vinyl acetate (4.00 equiv.), followed by the addition of MTBE and Amano lipase PS (immobilized on diatomite). The suspension was stirred at 40 °C until conversion of the undesired enantiomer (*R*)-**II** to its acetate (*R*)-Ac-**II** was complete, as monitored by chiral HPLC.

***Work-up and purification**:* the mixture was treated as detailed individually below to afford the title compound (*S*)-**II**.

D.2.2.2 (*S*)-1-(3,4-Dimethoxyphenyl)prop-2-en-1-ol ((*S*)-**27**)



(*S*)-**27**, $C_{11}H_{14}O_3$
194.23 g mol^{-1}

***Preparation**:* according to the *General Procedure* (section D.2.2.1, page 126), starting material *rac*-**27** (85.4 g, 439.7 mmol, 1.0 equiv.), vinyl acetate (151.5 g, 162 mL, 1.76 mol, 4.0 equiv.) and Amano lipase PS (12.82 g, 15 w/w %) were used, and the suspension was stirred mechanically in MTBE (2.4 L) for 45 h.

***Work-up and purification**:* the mixture was filtered through a pad of celite 545, rinsed with Et_2O (100 mL) and the solvent were evaporated. Flash column chromatography was then performed (flow rate 50 mL / min, EtOAc / LP), splitting the crude material (in total 98.9 g) into batches for separate chromatographic runs as follows:

10.4 g crude: 90 g silica with 9 g precolumn, 15 : 85 isocratically for 30 min, then to 40 : 60 in 80 min.
15.0 g crude: 90 g silica with 9 g precolumn, 15 : 85 isocratically for 55 min, then to 40 : 60 in 40 min.
20.5 g crude: 130 g silica, 15 : 85 isocratically for 40 min, then to 25 : 75 in 5 min, then to 55 : 45 in 40 min.
53.0 g crude: 180 g silica 11 : 89 isocratically for 35 min, then 15 : 85 isocratically for 35 min, then to 25 : 75 in 5 min, then to 65 : 35 in 40 min.

This resulted in a pale yellow oil which crystallized upon standing to afford the title compound (*S*)-**27**.

This compound is literature-known.[60]

Yield:	34.4 g, 40 % (theoretical maximum yield is 50 %)
Appearance:	off-white crystals
Melting range:	51.0 – 53.5 °C; lit.[60] **melting range:** n/a (compound obtained as a liquid)
R_f (silica):	0.59 (EtOAc / LP, 2 : 1)
$[\alpha]_D^{20}$:	-13.4 (c 2.00, benzene); lit.[60] **$[\alpha]_D$**: -10.8 (c 2.78, benzene)
e.e.:	> 98 % (HPLC)

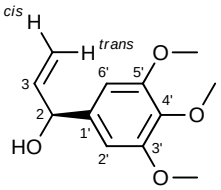
HPLC: 12.1 min ((*S*)-**27**, title compound), 13.5 min ((*R*)-**27**); Diacel CHIRALPAK AS-H, flow rate 1.0 mL / min, *i*-PrOH / heptane, 10.0 : 90.0, 25 °C, detection at 235 nm.

GC-MS (EI, 70 eV, Method A): 7.24 min; 194.1 (M^+, 100), 167.1 (17), 165.1 (25), 163.1 (59), 151.1 (29), 139.1 (92), 138.1 (22), 124.0 (18), 91.1 (16).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.08 (d, ^3J = 3.1 Hz, 1H, OH), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 5.10 – 5.18 (m, 1H, H2), 5.19 (ddd, ^2J = 1.3 Hz, ^3J = 10.2 Hz, ^4J = 1.3 Hz, 1H, C3=CH^{cis}), 5.34 (ddd, ^2J = 1.4 Hz, ^3J = 17.1 Hz, ^4J = 1.4 Hz, 1H, C3=CH^{trans}), 6.05 (ddd, $^3J_{cis}$ = 10.2 Hz, $^3J_{trans}$ = 17.0 Hz, $^3J_{vic}$ = 5.9 Hz, 1H, H3), 6.79 – 6.96 (m, 3H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 55.9 (q, Ar'-OCH_3), 56.0 (q, Ar'-OCH_3), 75.2 (d, C2), 109.6 (d, C2'), 111.1 (d, C5'), 115.0 (t, C3=C), 118.7 (d, C6'), 135.4 (s, C1'), 140.4 (d, C3), 148.7 (s, C4'), 149.2 (s, C3').

D.2.2.3 (*S*)-1-(3,4,5-Trimethoxyphenyl)prop-2-en-1-ol ((*S*)-**69**)



(*S*)-**69**, $C_{12}H_{16}O_4$
224.25 g mol^{-1}

***Preparation**:* according to the *General Procedure* (section D.2.2.1, page 126), starting material *rac*-**69** (20.83 g, 92.92 mmol, 1.0 equiv.), vinyl acetate (32.0 g, 34.3 mL, 372 mmol, 4.0 equiv.) and Amano lipase PS (2.7 g, 13 w/w %) were used, and the suspension was stirred magnetically in MTBE (500 mL) for 95 h.

***Work-up and purification**:* the mixture was filtered through a pad of celite 545, rinsed with Et_2O (60 mL) and the solvents were evaporated. Flash column chromatography (180 g silica, flow rate 50 mL / min, EtOAc / LP, 15 : 85 for 15 min, then to 25 : 75 in 5 min, then to 65 : 35 in 40 min) afforded the title compound (*S*)-**69**.

This compound is literature-known.[313]

Yield:	8.19 g, 39 % (theoretical maximum yield is 50 %)
Appearance:	nearly colorless oil
***R*$_f$ (silica)**:	0.25 (EtOAc)
[α]$_D^{20}$:	-8.6 (c 1.00, MeOH); lit.[313] **[α]$_D^{22}$**: -8.7 (c 1.0, $CHCl_3$)
e.e.:	> 98 % (HPLC)

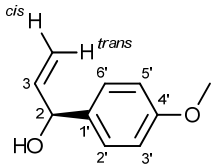
HPLC: 14.0 min ((*S*)-**69**, title compound), 15.9 min ((*R*)-**69**); Diacel CHIRALPAK IB, flow rate 1.0 mL / min, *i*-PrOH / heptane, 10.0 : 90.0, 25 °C, detection at 220 nm.

GC-MS (EI, 70 eV, Method C): 8.42 min; 224.0 (M^+, 77), 193.1 (22), 169.1 (62), 138.1 (23), 55.0 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.13 (bs, 1H, OH), 3.83 (s, 3H, C4'-OCH_3), 3.86 (s, 6H, C3'-OCH_3, C5'-OCH_3), 5.13 (d, ^3J = 5.9 Hz, 1H, H2), 5.21 (d, ^3J = 10.2 Hz, 1H, C3=CH^{cis}), 5.37 (d, ^3J = 17.1 Hz, 1H, C3=CH^{trans}), 6.04 (ddd, $^3J_{cis}$ = 10.3 Hz, $^3J_{trans}$ = 16.5 Hz, $^3J_{vic}$ = 6.0 Hz, 1H, H3), 6.60 (s, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 56.2 (q, C3'-OCH_3, C5'-OCH_3), 60.9 (q, C4'-OCH_3), 75.5 (d, C2), 103.3 (d, C2', C6'), 115.4 (t, C3=C), 137.4 (s, C4'*), 138.5 (s, C1'*), 140.1 (d, C3), 153.4 (s, C3', C5').

D.2.2.4 (*S*)-1-(4-Methoxyphenyl)prop-2-en-1-ol ((*S*)-**70**)



(*S*)-**70**, $C_{10}H_{12}O_2$
164.20 g mol^{-1}

***Preparation**:* according to the *General Procedure* (section D.2.2.1, page 126), starting material *rac*-**70** (8.50 g, 53.0 mmol, 1.0 equiv.), vinyl acetate (18.1 g, 19.4 mL, 212 mmol, 4.0 equiv.) and Amano lipase PS (850 mg, 10 w/w %) were used, and the suspension was stirred magnetically in MTBE (300 mL) for 48 h.

***Work-up and purification**:* the mixture was filtered through a pad of celite 545, rinsed with Et_2O (50 mL) and the solvents were evaporated. Flash column chromatography (180 g silica, flow rate 40 mL / min, EtOAc / LP, 5 : 95 to 10 : 90 in 15 min, then to 40 : 60 in 60 min) afforded the title compound (*S*)-**70**.

This compound is literature-known.[314-315]

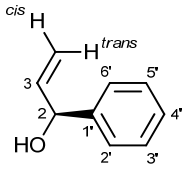
Yield:	2.71 g, 32 % (theoretical maximum yield is 50 %)
Appearance:	nearly colorless oil
***R*$_f$ (silica)**:	0.60 (EtOAc / LP, 1 : 2)
[α]$_D^{20}$:	-5.8 (c 1.41, $CHCl_3$); lit.[314] **[α]$_D^{20}$**: -3.9 (c 0.4, $CHCl_3$); lit.[315] **[α]$_D^{26}$**: -6.04 (c 1.0, $CHCl_3$)
e.e.:	> 98 % (HPLC)

HPLC: 17.7 min ((*R*)-**70**), 19.3 min ((*S*)-**70**, title compound); Diacel CHIRALPAK IB, flow rate 1.0 mL / min, *i*-PrOH / heptane, 2.0 : 98.0, 25 °C, detection at 235 nm.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.86 (d, ^3J = 3.7 Hz, 1H, OH), 3.81 (s, 3H, C4'-OCH_3), 5.13 – 5.23 (m, 2H, H2, C3=CH^{cis}), 5.36 (ddd, ^2J = 1.4 Hz, ^3J = 17.1 Hz, ^4J = 1.4 Hz, 1H, C3=CH^{trans}), 6.05 (ddd, $^3J_{cis}$ = 10.2 Hz, $^3J_{trans}$ = 17.1 Hz, $^3J_{vic}$ = 5.9 Hz, 1H, H3), 6.84 – 6.94 (m, 2H, H3', H5'), 7.24 – 7.35 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 55.5 (q, C4'-OCH3), 75.0 (d, C2), 114.1 (d, C3', C5'), 114.9 (t, C3=C), 127.8 (d, C2', C6'), 135.0 (s, C1'), 140.5 (d, C3), 159.5 (s, C4').

D.2.2.5 (*S*)-1-Phenylprop-2-en-1-ol ((*S*)-**71**)



(*S*)-**71**, $C_9H_{10}O$
134.18 g mol^{-1}

***Preparation**:* according to the *General Procedure* (section D.2.2.1, page 126), commercially available *rac*-1-phenylprop-2-en-1-ol (9.08 g, 67.7 mmol, 1.0 equiv.), vinyl acetate (23.3 g, 24.9 mL, 271 mmol, 4.0 equiv.) and Amano lipase PS (1.977 g, 22 w/w %) were used, and the suspension was stirred magnetically in MTBE (500 mL) for 23 h.

***Work-up and purification**:* the mixture was filtered through a pad of celite 545, rinsed with Et_2O (50 mL) and the solvents were evaporated. Flash column chromatography (180 g silica, flow rate 50 mL / min, Et_2O / LP, 10 : 90 for 23 min, then to 23 : 77 in 13 min, then to 48 : 52 in 14 min) and prolonged evaporation at a minimum pressure of 190 mbar afforded the title compound (*S*)-**71**.

This compound is literature-known.[60, 314-315]

Yield:	4.20 g, 46 % (theoretical maximum yield is 50 %)
Appearance:	nearly colorless oil
***R*$_f$ (silica)**:	0.36 (Et_2O / LP, 1 : 3)
[α]$_D^{20}$:	-4.2 (c 1.0, $CHCl_3$); lit.[314] **[α]$_D^{20}$**: -2.5 (c 1.0, $CHCl_3$); lit.[315] **[α]$_D^{25}$**: -5.9 (c 1.73, benzene)
e.e.:	> 98 % (HPLC)

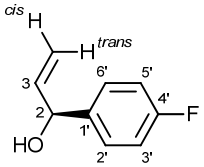
HPLC: 49.0 min ((*R*)-**71**), 52.0 min ((*S*)-**71**, title compound); Diacel CHIRALPAK IA, flow rate 1.0 mL / min, *i*-PrOH / heptane, 7.0 : 93.0, 25 °C, detection at 220 nm.

GC-MS (EI, 70 eV, Method G): 3.61 min; 134.2 (M^+, 54), 133.2 (98), 115.1 (36), 107.1 (18), 105.1 (80), 92.1 (69), 91.1 (39).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.11 (bs, 1H, OH), 5.16 – 5.26 (m, 2H, H2, C3=C*H*^{cis}), 5.36 (d, ^3J = 17.1 Hz, 1H, C3=C*H*^{trans}), 5.96 – 6.17 (m, 1H, H3), 7.25 – 7.41 (m, 5H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 75.5 (d, C2), 115.2 (t, C3=C), 126.5 (d, C2'*, C6'*), 127.9 (d, C4'), 128.7 (d, C3'*, C5'*), 140.4 (d, C3), 142.7 (s, C1').

D.2.2.6 (*S*)-1-(4-Fluorophenyl)prop-2-en-1-ol ((*S*)-**72**)



(*S*)-**72**, C_9H_9FO
152.17 g mol^{-1}

***Preparation**:* according to the *General Procedure* (section D.2.2.1, page 126), starting material *rac*-**72** (8.36 g, 55.0 mmol, 1.0 equiv.), vinyl acetate (18.9 g, 20.4 mL, 220 mmol, 4.0 equiv.) and Amano lipase PS (1.25 g, 15 w/w %) were used, and the suspension was stirred magnetically in MTBE (300 mL) for 26 h.

***Work-up and purification**:* the mixture was filtered through a pad of celite 545, rinsed with Et_2O (50 mL) and the solvents were evaporated. Flash column chromatography (90 g silica, flow rate 50 mL / min, EtOAc / LP, 1 : 99 to 5 : 95 in 40 min, then to 20 : 80 in 40 min) and prolonged evaporation at a minimum pressure of 170 mbar at 50 °C afforded the title compound (*S*)-**72**.

This compound is literature-known.[314]

Yield:	3.34 g, 40 % (theoretical maximum yield is 50 %)
Appearance:	nearly colorless oil
R_f **(silica)**:	0.40 (EtOAc / LP, 1 : 2)
$[\alpha]_D^{20}$:	+5.4 (c 2.74, MeOH); lit.[314] $[\alpha]_D^{20}$: +11.3 (c 0.81, $CHCl_3$), deviation likely due to different solvent used
e.e.:	> 98 % (HPLC)

HPLC: 27.5 min ((*R*)-**72**), 30.1 min ((*S*)-**72**, title compound); Diacel CHIRALPAK AS-H, flow rate 0.9 mL / min, *i*-PrOH / heptane, 1.5 : 98.5, 25 °C, detection at 254 nm.

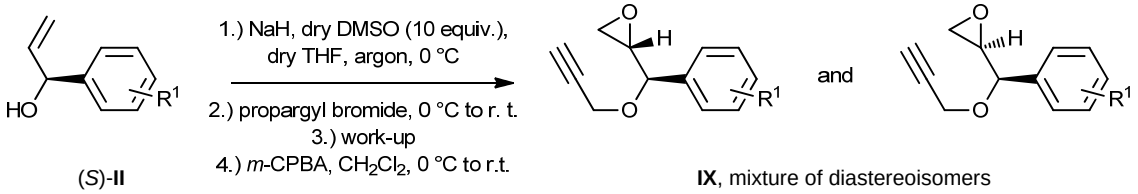
GC-MS (EI, 70 eV, Method G): 3.66 min; 152.1 (M^+, 58), 151.1 (90), 133.1 (47), 125.1 (36), 123.1 (90), 110.1 (56), 109.1 (61), 103.1 (23), 97.1 (100), 96.1 (51), 95.1 (60).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.00 (bs, 1H, OH), 5.14 – 5.25 (m, 2H, H2, C3=CH^{cis}), 5.34 (d, ^3J = 17.1 Hz, 1H, C3=CH^{trans}), 6.02 (ddd, $^3J_{cis}$ = 10.2 Hz, $^3J_{trans}$ = 16.5 Hz, $^3J_{vic}$ = 5.9 Hz, 1H, H3), 6.97 – 7.11 (m, 2H, H3', H5'), 7.28 – 7.40 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 74.8 (d, C2), 115.5 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 115.5 (t, C3=C), 128.2 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 138.4 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 140.2 (d, C3), 162.4 (d, C4', $^1J_{C\text{-}F}$ = 245.8 Hz).

D.2.3 **Propargylation-Epoxidation Sequence**

D.2.3.1 *General Procedure* for Propargylation-Epoxidation



(*S*)-**II** **IX**, mixture of diastereoisomers

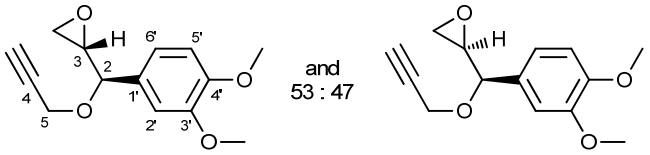
***Preparation**:* a reaction vessel was charged with a stirring bar, NaH (approximately 60 % dispersion in mineral oil) and then evacuated and back-filled with argon using standard Schlenk technique. Dry THF and dry DMSO (10.00 equiv.) were then added in this order *via* syringe or canula and the resulting suspension was cooled to 0 °C in an ice bath. Starting material (*S*)-**II** (1.0 equiv.), as a beforehand-prepared solution in dry THF under argon, was then slowly transferred to the stirred mixture for deprotonation, which after another 15 min of stirring was followed by a solution of propargyl bromide (80 % in toluene), both *via* syringe or canula. The ice bath was then removed and the reaction continued at room temperature.

Progress of this substitution reaction was monitored by TLC, and once complete, the mixture was cooled in an ice bath again and hydrolyzed, while still under argon, by careful addition of aqueous HCl (1 M). For intermediate work-up, most of the THF was then evaporated, followed by the addition of water and extraction with Et_2O (4 x). The combined organic phases were treated with brine, dried with Na_2SO_4, filtered and the solvents were evaporated in a new reaction vessel to give a residue of propargylated intermediate.

This residue was then dissolved in CH_2Cl_2 and cooled to 0 °C in an ice bath. *m*-CPBA (wet, approximately 77 %) was added to the stirred solution in small portions and the reaction was allowed to warm to room temperature. Progress of this epoxidation reaction was monitored by TLC and terminated when complete.

***Work-up**:* the mixture was treated as detailed individually below to afford crude compound **IX** as a mixture of diastereoisomers to be used directly in the next reaction step.

D.2.3.2 2-((*R*)-(3,4-Dimethoxyphenyl)(prop-2-yn-1-yloxy)methyl)oxirane ((αR)-**101**)



(αR)-**101**, mixture of diastereoisomers, $C_{14}H_{16}O_4$
248.27 g mol^{-1}

***Preparation**:* according to the *General Procedure* (section D.2.3.1, page 132), a suspension of NaH (15.55 g, 388.7 mmol, 2.20 equiv.) with DMSO (125 mL, 1.76 mol, 10.0 equiv.) in THF (300 mL) was used for deprotonation of starting material (*S*)-**27** (34.32 g, 176.7 mmol, 1.00 equiv.), itself transferred as a solution in THF (300 mL). This was then followed by the addition of propargyl bromide (35.4 mL, 318.1 mmol, 1.8 equiv.). In deviation from the *General Procedure*, additional dry THF (300 mL) was added *via* syringe immediately thereafter in order to facilitate stirring of the resulting slurry upon propargyl bromide addition. The mixture was then stirred for 13 h.

After work-up of the propargylated intermediate (***R*f (silica)**: 0.74 (EtOAc / LP, 1 : 1)), *m*-CPBA (178.2 g, 795.2 mmol, 4.5 equiv.) in CH_2Cl_2 (500 mL) was used for epoxidation, and the mixture was stirred for 17 h.

***Work-up**:* sufficient aqueous Na_2SO_3 solution was added to destroy residual peroxy acid (iodine test), which required cooling using an ice bath. This was followed by K_3PO_4 (185 g) as an aqueous solution in water (750 mL) to bring the pH to 8. After extraction with Et_2O (1 x 750 mL, 5 x 250 mL), the combined organic phases were treated with brine (250 mL), dried with Na_2SO_4, filtered and the solvents were evaporated to afford crude compound (αR)-**101** as a mixture of diastereoisomers (approximate ratio: major / minor, 53 : 47, by NMR) to be used directly in the next reaction step.

This mixture of isomers is literature-known in racemic form.[234]

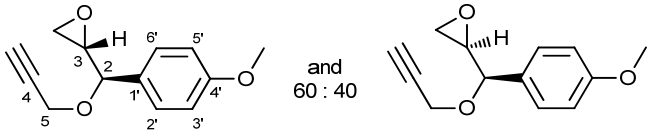
Yield: 50.09 g, crude
Appearance: yellow oil
***R*f (silica)**: 0.45 (EtOAc / LP, 1 : 1)

GC-MS (EI, 70 eV, Method C) major isomer: 9.26 min; 248.1 (M^+, 23), 205.1 (100), 166.1 (45), 165.1 (59), 151.1 (16), 146.1 (15). minor isomer: 9.31 min; 248.1 (M^+, 20), 205.1 (100), 179.1 (19), 166.1 (53), 165.1 (67), 151.1 (27), 146.1 (19), 138.1 (15), 91.1 (15).

^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ 2.43 (t, ^4J = 2.4 Hz, 1H, C4≡CH), 2.70 (dd, ^2J = 5.3 Hz, ^3J = 2.6 Hz, 1H, C3-CH), 2.80 (dd, ^2J = 5.2 Hz, ^3J = 3.9 Hz, 1H, C3-CH), 3.19 (ddd, $^3J_{oxirane}$ = 3.9 Hz, $^3J_{oxirane}$ = 2.6 Hz, $^3J_{benzyl}$ = 4.4 Hz, 1H, H3), 3.87 (s, 3H, Ar'-OCH_3), 3.89 (s, 3H, Ar'-OCH_3*), 3.95 (dd, ^2J = 15.8 Hz, ^4J = 2.3 Hz, 1H, H5), 4.18 (dd, ^2J = 15.7 Hz, ^4J = 2.4 Hz, 1H, H5), 4.48 (d, ^3J = 4.4 Hz, 1H, H2), 6.81 – 6.94 (m, 3H, Ar'-H). minor isomer: δ 2.42 (t, ^4J = 2.3 Hz, 1H, C4≡CH), 2.63 (dd, ^2J = 4.9 Hz, ^3J = 2.7 Hz, 1H, C3-CH), 2.75 (dd, ^2J = 4.8 Hz, ^3J = 4.3 Hz, 1H, C3-CH), 3.23 (ddd, $^3J_{oxirane}$ = 4.2 Hz, $^3J_{oxirane}$ = 2.7 Hz, $^3J_{benzyl}$ = 6.0 Hz, 1H, H3), 3.87 (s, 3H, Ar'-OCH_3), 3.89 (s, 3H, Ar'-OCH_3*), 4.04 (dd, ^2J = 15.7 Hz, ^4J = 2.4 Hz, 1H, H5), 4.23 (d, ^3J = 6.0 Hz, 1H, H2), 4.25 (dd, ^2J = 15.7 Hz, ^4J = 2.4 Hz, 1H, H5), 6.81 – 6.94 (m, 3H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$) major isomer: δ 45.4 (t, C3-C), 54.1 (d, C3), 56.0 (t, C5; overlap with corresponding signal of minor isomer), 56.0 (q, 2 x Ar'-OCH_3; overlap with corresponding signal of minor isomer), 74.9 (d, C4≡C; *J*-mod spectrum shows antipodal signal due to a large $^1J_{C\text{-}H}$ of approximately 250 Hz), 79.3 (d, C2), 79.5 (s, C4*), 110.4 (d, C2'), 111.0 (d, C5'), 120.5 (d, C6'), 129.4 (s, C1'), 149.3 (s, C4'*), 149.4 (s, C3'*; signal overlap with C4' of minor isomer). minor isomer: δ 44.4 (t, C3-C), 55.0 (d, C3), 56.0 (t, C5; overlap with corresponding signal of major isomer), 56.0 (q, Ar'-OCH_3; overlap with corresponding signal of major isomer), 56.1 (q, Ar'-OCH_3), 74.8 (d, C4≡C; *J*-mod spectrum shows antipodal signal due to a large $^1J_{C\text{-}H}$ of approximately 250 Hz), 79.5 (s, C4*), 81.4 (d, C2), 110.0 (d, C2'), 111.1 (d, C5'), 120.1 (d, C6'), 129.6 (s, C1'), 149.4 (s, C4'*; signal overlap with C3' of major isomer), 149.4 (s, C3'*).

D.2.3.3 2-((*R*)-(4-Methoxyphenyl)(prop-2-yn-1-yloxy)methyl)oxirane ((α*R*)-**110**)



(α*R*)-**110**, mixture of diastereoisomers, $C_{13}H_{14}O_3$
218.25 g mol^{-1}

***Preparation**:* according to the *General Procedure* (section D.2.3.1, page 132), a suspension of NaH (1.45 g, 36.2 mmol, 2.20 equiv.) with DMSO (11.6 mL, 164 mmol, 10.0 equiv.) in THF (40 mL) was used for deprotonation of starting material (*S*)-**70** (2.70 g, 16.44 mmol, 1.00 equiv.), itself transferred as a solution in THF (20 mL). This was then followed by the addition of propargyl bromide (3.5 mL, 31.4 mmol, 1.9 equiv.). In deviation from the *General Procedure*, after 18 h of stirring at room temperature, additional NaH (330 mg, 8.22 mmol, 0.5 equiv.) was added, and then again after another 24 h (330 mg, 8.22 mmol, 0.5 equiv.). The mixture was then finally stirred for another 4 h.

After work-up of the propargylated intermediate (***R*$_f$ (silica)**: 0.79 (EtOAc / LP, 1 : 2)), *m*-CPBA (8.25 g, 36.9 mmol, 2.25 equiv.) in CH_2Cl_2 (50 mL) was used for epoxidation, and the mixture was stirred for 25 h. In deviation from the *General Procedure*, more *m*-CPBA (2.42 g, 16.4 mmol, 1.0 equiv.) was added and stirring was continued for another 10 h.

***Work-up**:* sufficient aqueous Na_2SO_3 solution was added to destroy residual peroxy acid (iodine test), which required cooling using an ice bath. This was followed by K_3PO_4 (19 g) as an aqueous solution in water (80 mL) to bring the pH to 8. After extraction with Et_2O (4 x 40 mL), the combined organic phases were treated with brine (40 mL), dried with Na_2SO_4, filtered and the solvents were evaporated. In order to remove residual 3-chlorobenzoic acid, the residue was then taken up in Et_2O (30 mL), kept at -30 °C overnight and then filtered through celite 545, followed by treatment of the filtrate with a saturated aqueous solution of K_3PO_4 (20 mL). Drying with Na_2SO_4, filtration and evaporation of the solvent afforded crude compound (α*R*)-**110** as a mixture of diastereoisomers (approximate ratio: major / minor, 60 : 40, by NMR) to be used directly in the next reaction step.

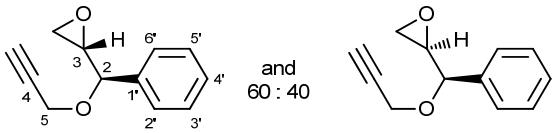
The optical antipode of the major isomer is literature-known.[264]

Yield: 5.1 g, crude
Appearance: yellow oil
***R*$_f$ (silica)**: 0.58 (EtOAc / LP, 1 : 2)

GC-MS (EI, 70 eV, Method C) major isomer: 7.88 min; 218.0 (M^+, 7), 175.0 (100), 135.0 (65), 121.1 (15). minor isomer: 7.92 min; 218.0 (M^+, 6), 175.0 (100), 135.0 (64), 121.1 (15).

^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ 2.42 (t, ^4J = 2.4 Hz, 1H, C4≡CH), 2.68 – 2.84 (m, 2H, C3-CH_2), 3.16 – 3.29 (m, 1H, H3), 3.82 (s, 3H, C4'-OCH_3), 3.94 (dd, ^2J = 15.8 Hz, ^4J = 2.3 Hz, 1H, H5), 4.14 – 4.31 (m, 1H, H5), 4.53 (d, ^3J = 4.1 Hz, 1H, H2), 6.87 – 6.96 (m, 2H, H3', H5'), 7.26 – 7.33 (m, 2H, H2', H6'). minor isomer: δ 2.42 (t, ^4J = 2.4 Hz, 1H, C4≡CH), 2.60 – 2.64 (m, 1H, C3-CH), 2.68 – 2.84 (m, 2H, C3-CH), 3.16 – 3.29 (m, 1H, H3), 3.82 (s, 3H, C4'-OCH_3), 4.05 (dd, ^2J = 15.7 Hz, ^4J = 2.4 Hz, 1H, H5), 4.31 (m, 2H, H2, H5), 6.87 – 6.96 (m, 2H, H3', H5'), 7.26 – 7.33 (m, 2H, H2', H2').

D.2.3.4 2-((*R*)-Phenyl(prop-2-yn-1-yloxy)methyl)oxirane (<u>(α*R*)-**111**</u>)



<u>(α*R*)-**111**</u>, mixture of diastereoisomers, $C_{12}H_{12}O_2$
188.22 g mol^{-1}

***Preparation**:* according to the *General Procedure* (section D.2.3.1, page 132), a suspension of NaH (2.75 g, 68.7 mmol, 2.20 equiv.) with DMSO (22.2 mL, 312 mmol, 10.0 equiv.) in THF (40 mL) was used for deprotonation of starting material (*S*)-**71** (4.19 g, 31.2 mmol, 1.00 equiv.), itself transferred as a solution in THF (120 mL). This was then followed by the addition of propargyl bromide (6.25 mL, 56.2 mmol, 1.8 equiv.). The mixture was then stirred for 14 h.

After work-up of the propargylated intermediate (***R*$_f$ (silica)**: 0.75 (Et_2O / LP, 1 : 10)), *m*-CPBA (31.47 g, 140.4 mmol, 4.5 equiv.) in CH_2Cl_2 (57 mL) was used for epoxidation, and the mixture was stirred for 22 h.

***Work-up**:* sufficient aqueous Na_2SO_3 solution was added to destroy residual peroxy acid (iodine test), which required cooling using an ice bath. This was followed by Na_3PO_4 as an aqueous solution in water (250 mL) to bring the pH to 9. After extraction with Et_2O (5 x 100 mL, 1 x 170 mL), the combined organic phases were treated with brine (100 mL), dried with Na_2SO_4, filtered and the solvents were evaporated. In order to remove residual 3-chlorobenzoic acid, the residue was then taken up in Et_2O, filtered, the filtrate diluted with Et_2O (total volume 200 mL) and treated with a saturated aqueous solution of Na_3PO_4 (2 x 50 mL). After evaporation of the organic phase, however, this process had to be repeated, this time by taking the residue up in a mixture of Et_2O / LP (3 : 5), keeping at -30 °C overnight, followed by filtration. Evaporation of the solvent then afforded crude compound <u>(α*R*)-**111**</u> as a mixture of diastereoisomers (approximate ratio: major / minor, 60 : 40, by NMR) to be used directly in the next reaction step.

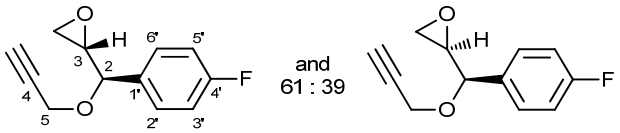
This mixture of isomers is literature-known in racemic form.[234]

Yield: 7.0 g, crude
Appearance: yellow oil
***R*$_f$ (silica)**: 0.53 (Et_2O / LP, 1 : 3)

GC-MS (EI, 70 eV, Method C) major isomer: 6.46 min; 145.1 (M-oxiranyl$^+$, 100), 117.1 (15), 115.1 (53), 105.1 (80), 91.1 (60), 77.1 (71), 65.1 (17), 51.1 (45). M^+ not visible. minor isomer: 6.52 min; 145.1 (M-oxiranyl$^+$, 100), 105.1 (67), 77.1 (55), 115.1 (51), 91.1 (45). M^+ not visible.

^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ 2.43 (t, ^4J = 2.4 Hz, 1H, C4≡CH), 2.72 – 2.78 (m, 1H, C3-CH), 2.81 (dd, ^2J = 5.2 Hz, ^3J = 4.0 Hz, 1H, C3-CH), 3.16 – 3.29 (m, 1H, H3), 3.98 (dd, ^2J = 15.8 Hz, ^4J = 2.3 Hz, 1H, H5), 4.23 (dd, ^2J = 15.7 Hz, ^4J = 2.4 Hz, 1H, H5), 4.57 (d, ^3J = 4.3 Hz, 1H, H2), 7.33 – 7.41 (m, 5H, Ar'-H). minor isomer: δ 2.43 (t, ^4J = 2.4 Hz, 1H, C4≡CH), 2.64 (dd, ^2J = 4.8 Hz, ^3J = 2.8 Hz, 1H, C3-CH), 2.72 – 2.78 (m, 1H, C3-CH), 3.16 – 3.29 (m, 1H, H3), 4.09 (dd, ^2J = 15.7 Hz, ^4J = 2.4 Hz, 1H, H5), 4.29 (d, ^3J = 6.5 Hz, 1H, H2), 4.29 (dd, ^2J = 15.7 Hz, ^4J = 2.4 Hz, 1H, H5), 7.33 – 7.41 (m, 5H, Ar'-H).

D.2.3.5 2-((*R*)-(4-Fluorophenyl)(prop-2-yn-1-yloxy)methyl)oxirane ((α*R*)-**112**)



(α*R*)-**112**, mixture of diastereoisomers, $C_{12}H_{11}FO_2$
206.21 g mol^{-1}

***Preparation**:* according to the *General Procedure* (section D.2.3.1, page 132), a suspension of NaH (1.79 g, 44.9 mmol, 2.20 equiv.) with DMSO (14.5 mL, 204 mmol, 10.0 equiv.) in THF (35 mL) was used for deprotonation of starting material (*S*)-**72** (3.10 g, 20.4 mmol, 1.00 equiv.), itself transferred as a solution in THF (15 mL). This was then followed by the addition of propargyl bromide (4.09 mL, 36.7 mmol, 1.8 equiv.). In deviation from the *General Procedure*, additional dry THF (10 mL) was added *via* syringe immediately thereafter in order to facilitate stirring of the resulting slurry upon propargyl bromide addition. The mixture was then stirred for 15 h.

After work-up of the propargylated intermediate (***R*$_f$ (silica)**: 0.66 (EtOAc / LP, 1 : 2)), *m*-CPBA (20.5 g, 91.8 mmol, 4.5 equiv.) in CH_2Cl_2 (500 mL) was used for epoxidation, and the mixture was stirred for 31 h. In deviation from the *General Procedure*, more *m*-CPBA (4.50 g, 20.4 mmol, 1.0 equiv.) was added and stirring was continued for another 14 h.

***Work-up**:* sufficient aqueous Na_2SO_3 solution was added to destroy residual peroxy acid (iodine test), which required cooling using an ice bath. This was followed by Na_3PO_4 (30 g) as an aqueous solution in water (90 mL) to bring the pH to 8. After extraction with Et_2O (1 x 120 mL, 6 x 80 mL), the combined organic phases were treated with brine (30 mL), dried with Na_2SO_4, filtered and the solvents were evaporated. In order to remove residual 3-chlorobenzoic acid, the residue was then taken up in a mixture of Et_2O / LP (1 : 2, 300 mL), kept at -30 °C overnight and filtered. After

evaporation of the solvents, however, this process had to be repeated, this time by taking the residue up in a mixture of Et_2O / LP (1 : 3, 100 mL), keeping at -30 °C overnight, followed by filtration. Evaporation of the solvent then afforded crude compound (α*R*)-**112** as a mixture of diastereoisomers (approximate ratio: major / minor, 61 : 39, by NMR) to be used directly in the next reaction step.

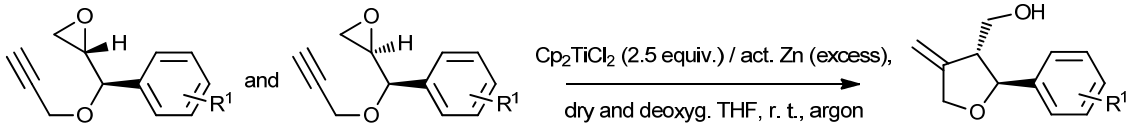
Yield: 4.2 g, crude
Appearance: yellow oil
***R*$_f$ (silica)**: 0.48 (EtOAc / LP, 1 : 2)

GC-MS (EI, 70 eV, Method C) major isomer: 6.44 min; 206.0 (M^+, < 1), 163.0 (87), 133.1 (28), 123.0 (100), 115.1 (44), 109.1 (52), 101.1 (18), 95.1 (33). minor isomer: 6.48 min; 163.0 (M-oxiranyl$^+$, 84), 133.1 (29), 123.0 (100), 115.1 (41), 109.1 (42), 101.1 (18), 95.1 (27), 75.1 (18). M^+ not visible.

^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ 2.44 (t, ^4J = 2.2 Hz, 1H, C4≡CH), 2.70 (dd, ^2J = 5.2 Hz, ^3J = 2.6 Hz, 1H, C3-CH), 2.81 (dd, ^2J = 5.1 Hz, ^3J = 4.0 Hz, 1H, C3-CH), 3.14 – 3.26 (m, 1H, H3), 3.97 (dd, ^2J = 15.9 Hz, ^4J = 2.4 Hz, 1H, H5), 4.23 (dd, ^2J = 15.9 Hz, ^4J = 2.4 Hz, 1H, H5), 4.55 (d, ^3J = 4.4 Hz, 1H, H2), 7.01 – 7.14 (m, 2H, H3', H5'), 7.30 – 7.41 (m, 2H, H2', H6'). minor isomer: δ 2.44 (t, ^4J = 2.2 Hz, 1H, C4≡CH), 2.62 (dd, ^2J = 4.8 Hz, ^3J = 2.7 Hz, 1H, C3-CH), 2.76 (dd, ^2J = 4.8 Hz, ^3J = 4.3 Hz, 1H, C3-CH), 3.14 – 3.26 (m, 1H, H3), 4.08 (dd, ^2J = 15.8 Hz, ^4J = 2.4 Hz, 1H, H5), 4.29 (dd, ^2J = 15.7 Hz, ^4J = 2.3 Hz, 1H, H5), 4.31 (d, ^3J = 6.3 Hz, 1H, H2), 7.01 – 7.14 (m, 2H, H3', H5'), 7.30 – 7.41 (m, 2H, H2', H6').

D.2.4 **Stereoconvergent Radical Cyclization**

D.2.4.1 *General Procedure* for Stereoconvergent Radical Cyclization



IX, mixture of diastereoisomers

XIV

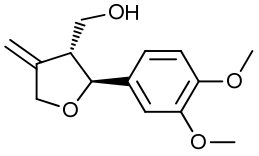
In this section, a crude mixture of diastereoisomers **IX** from the previous propargylation-epoxidation sequence (section D.2.3, page 132) was used. Molar amounts of **IX** are thus based on complete-conversion calculations in the propargylation-epoxidation step. However, masses of **IX** correspond to the actual gross weight of starting material as used. Yields are calculated over all three steps (propargylation, epoxidation and cyclization). Activated zinc and dry and deoxygenated THF were prepared as described in the General Notes (section D.1, page 117).

***Preparation**:* a reaction vessel was charged with a stirring bar, activated zinc dust (7.0 equiv.) and bis(cyclopentadienyl)titanium(IV) dichloride (2.5 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry and deoxygenated THF was added to this *via* syringe or canula, and the resulting suspension was stirred vigorously at room temperature for 1 h to give a green solution of bis(cyclopentadienyl)titanium(III) chloride, before unconverted residual zinc was allowed to settle for 5 to 10 min.

Meanwhile, a second reaction vessel was charged with a stirring bar, crude starting material **IX** (1.0 equiv.) and then evacuated and back-filled with argon, followed by the addition of dry and deoxygenated THF *via* syringe or canula. Using the canula, the bis(cyclopentadienyl)titanium(III) chloride solution, as prepared above, was then added slowly while stirring the starting material solution at a high rate at room temperature. Reaction progress was monitored by TLC and the reaction terminated when complete.

***Work-up and purification**:* the mixture was treated as detailed individually below to afford the title compound **XIV**.

D.2.4.2 ((2*S*,3*R*)-2-(3,4-Dimethoxyphenyl)-4-methylenetetrahydrofuran-3-yl)methanol (**106**)



106, $C_{14}H_{18}O_4$
250.29 g mol^{-1}

***Preparation**:* according to the *General Procedure* (section D.2.4.1, page 138), activated zinc dust (79.8 g, 1.22 mol, 7.0 equiv.), bis(cyclopentadienyl)titanium(IV) dichloride (108.6 g, 436.1 mmol, 2.5 equiv.), and THF (2.5 L) were used for the preparation of bis(cyclopentadienyl)titanium(III) chloride,

which was added to crude starting material (αR)-**101** (49.42 g, 174.3 mmol, 1.0 equiv.) in THF (1.2 L) over a period of 3 h, followed by stirring at room temperature for another 75 min.

***Work-up and purification**:* H_2SO_4 (10 %, 1 L) was added carefully and most of the THF was evaporated at a minimum pressure of 150 mbar at 40 °C. Following repeated extraction with Et_2O, the combined organic phases were treated with saturated aqueous $NaHCO_3$ solution (500 mL), brine (250 mL), dried with Na_2SO_4, filtered and the solvents were evaporated. Flash column chromatography of the entire crude material in two sequential runs (first run: 180 g silica, flow rate 40 mL / min, EtOAc / LP, 25 : 75 to 50 : 50 in 45 min, then to 100 : 0 in 3 h; second run: 90 g silica, flow rate 40 mL / min, EtOAc / LP, 15 : 85 to 50 : 50 in 45 min, then to 100 : 0 in 3 h) afforded the title compound **106**.

This compound is literature-known in racemic form.[234]

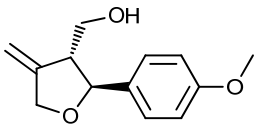
Yield:	8.62 g, 20 % (over 3 steps from (*S*)-**27**)
Appearance:	brown oil
R_f **(silica)**:	0.19 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{20}$:	+21.4 (c 2.07, MeOH)

GC-MS (EI, 70 eV, Method C): 10.37 min; 250.1 (M^+, 71), 219.1 (21), 167.1 (62), 166.1 (26), 165.1 (40), 152.1 (20), 151.1 (65), 139.1 (100), 124.1 (21).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.63 (bs, 1H, OH), 2.70 – 2.86 (m, 1H, H3), 3.62 – 3.86 (m, 2H, C3-CH_2), 3.88 (s, 3H, Ar'-OCH_3), 3.89 (s, 3H, Ar'-OCH_3), 4.42 (ddd, ^2J = 13.3 Hz, $^4J_{cis\text{-allyl}}$ = 2.2 Hz*, $^4J_{trans\text{-allyl}}$ = 4.3 Hz*, 1H, H5), 4.56 – 4.69 (m, 1H, H5), 4.79 (d, ^3J = 7.5 Hz, H2), 5.02 – 5.16 (m, 2H, C4=CH_2), 6.79 – 6.98 (m, 3H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 54.0 (d, C3), 55.98 (q, Ar'-OCH_3), 56.00 (q, Ar'-OCH_3), 62.0 (t, C3-C), 71.5 (t, C5), 83.5 (d, C2), 105.1 (t, C4=C), 109.4 (d, C2'), 111.0 (d, C5'), 119.0 (d, C6'), 133.6 (s, C1'), 148.9 (s, C4*), 149.0 (s, C4'*), 149.3 (s, C3').

D.2.4.3 ((2*S*,3*R*)-2-(4-Methoxyphenyl)-4-methylenetetrahydrofuran-3-yl)methanol (**113**)



113, $C_{13}H_{16}O_3$
220.26 g mol^{-1}

***Preparation**:* according to the *General Procedure* (section D.2.4.1, page 138), activated zinc dust (7.0 g, 107 mmol, 7.0 equiv.), bis(cyclopentadienyl)titanium(IV) dichloride (10.3 g, 41.1 mmol, 2.5 equiv.), and THF (250 mL) were used for the preparation of bis(cyclopentadienyl)titanium(III) chloride, which was added to crude starting material (αR)-**110** (5.10 g, 16.44 mmol, 1.0 equiv.) in THF (120 mL) over a period of 30 min, followed by stirring at room temperature for another 18 h.

Work-up and purification: H_2SO_4 (10 %, 100 mL) was added carefully and most of the THF was evaporated. Following extraction with Et_2O (2 x 100 mL, 3 x 50 mL), the combined organic phases were treated with saturated aqueous $NaHCO_3$ solution (2 x 50 mL), brine (50 mL), dried with Na_2SO_4, filtered and the solvents were evaporated. Flash column chromatography (180 g silica, flow rate 40 mL / min, EtOAc / LP, 15 : 85 to 30 : 70 in 45 min, to 100 : 0 in 2 h) afforded the title compound **113**.

This compound is literature-known as its optical antipode.[264]

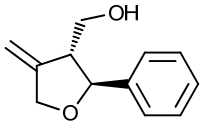
Yield:	210 mg, 6 % (over 3 steps from (*S*)-**70**)
Appearance:	brown oil
***R*$_f$ (silica)**:	0.30 (EtOAc / heptane, 1 : 1)
[α]$_D^{20}$:	+15.2 (c 0.36, MeOH); lit.[264] **[α]$_D$** of optical antipode: n/a (not stated)

GC-MS (EI, 70 eV, Method G): 6.79 min; 220.2 (M^+, 19), 137.1 (100), 135.1 (36), 121.1 (16), 109.1 (34), 94.1 (15).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.73 (bs, 1H), 2.69 – 2.84 (m, 1H, H3), 3.71 (dd, ^2J = 11.3 Hz, ^3J = 4.8 Hz, 1H, C3-CH), 3.80 (s, 3H, C4'-OCH_3), 3.85 (dd, ^2J = 11.3 Hz, ^3J = 5.6 Hz, 1H, C3-CH), 4.40 (ddd, ^2J = 13.3 Hz, $^4J_{cis\text{-allyl}}$ = 2.2 Hz*, $^4J_{trans\text{-allyl}}$ = 4.5 Hz*, 1H, H5), 4.54 – 4.65 (m, 1H, H5), 4.79 (d, ^3J = 7.4 Hz, 1H, H2), 5.03 – 5.12 (m, 2H, C4=CH_2), 6.83 – 6.94 (m, 2H, H3', H5'), 7.26 – 7.36 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 54.0 (d, C3), 55.4 (q, C4'-O<u>C</u>H_3), 62.1 (t, C3-<u>C</u>), 71.4 (t, C5), 83.3 (d, C2), 105.0 (t, C4=<u>C</u>), 114.1 (d, C3', C5'), 127.9 (d, C2', C6'), 133.2 (s, C1'), 149.1 (s, C4), 159.5 (s, C4').

D.2.4.4 ((2*S*,3*R*)-4-Methylene-2-phenyltetrahydrofuran-3-yl)methanol (**114**)



114, $C_{12}H_{14}O_2$
190.24 g mol^{-1}

Preparation: according to the *General Procedure* (section D.2.4.1, page 138), activated zinc dust (14.4 g, 218 mmol, 7.0 equiv.), bis(cyclopentadienyl)titanium(IV) dichloride (19.4 g, 78.0 mmol, 2.5 equiv.), and THF (600 mL) were used for the preparation of bis(cyclopentadienyl)titanium(III) chloride, which was added to crude starting material (α*R*)-**111** (6.96 g, 31.2 mmol, 1.0 equiv.) in THF (200 mL) over a period of 2 h, followed by stirring at room temperature for another 90 min.

Work-up and purification: H_2SO_4 (10 %, 400 mL) was added carefully and most of the THF was evaporated at a minimum pressure of 140 mbar. Following repeated extraction with Et_2O, the combined organic phases were treated with saturated aqueous $NaHCO_3$ solution (80 mL), brine (50 mL), dried with Na_2SO_4, filtered and the solvents were evaporated. Flash column chromatography (90 g silica, flow rate 40 mL / min, EtOAc / LP, 10 : 90 to 30 : 70 in 60 min), which was re-applied to impure fractions obtained in the first chromatographic run, afforded the title compound **114**.

This compound is literature-known in racemic form.[234]

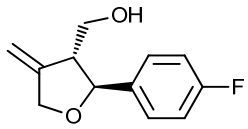
Yield:	2.02 g, 34 % (over 3 steps from (*S*)-**71**)
Appearance:	brown oil
***R*$_f$ (silica)**:	0.38 (EtOAc / heptane, 1 : 1)
[α]$_D^{25}$:	+6.3 (c 0.60, MeOH)

GC-MS (EI, 70 eV, Method C): 7.60 min; 190.1 (M^+, 23), 172.1 (20), 129.1 (18), 128.1 (21), 115.1 (18), 107.1 (100), 105.1 (33), 104.1 (26), 91.1 (34).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.63 (bs, 1H, OH), 2.72 – 2.86 (m, 1H, H3), 3.74 (dd, ^2J = 11.2 Hz, ^3J = 4.8 Hz, 1H, C3-CH), 3.88 (dd, ^2J = 11.3 Hz, ^3J = 5.6 Hz, 1H, C3-CH), 4.44 (ddd, ^2J = 13.4 Hz, $^4J_{cis\text{-allyl}}$ = 2.2 Hz*, $^4J_{trans\text{-allyl}}$ = 4.5 Hz*, 1H, H5), 4.57 – 4.69 (m, 1H, H5), 4.87 (d, ^3J = 7.1 Hz, 1H, H2), 5.04 – 5.09 (m, 1H, C4=CH), 5.09 – 5.13 (m, 1H, C4=CH), 7.25 – 7.43 (m, 5H, Ar'-H).

^{13}C NMR (50 MHz): δ 54.2 (d, C3), 62.1 (t, C3-C), 71.5 (t, C5), 83.5 (d, C2), 105.2 (t, C4=C), 126.4 (d, C2'*, C6'*), 127.9 (d, C4'), 128.6 (d, C3'*, C5'*), 141.3 (s, C1'), 148.8 (s, C4).

D.2.4.5 ((2*S*,3*R*)-2-(4-Fluorophenyl)-4-methylenetetrahydrofuran-3-yl)methanol (**115**)



115, $C_{12}H_{13}FO_2$
208.23 g mol^{-1}

***Preparation**:* according to the *General Procedure* (section D.2.4.1, page 138), activated zinc dust (9.3 g, 143 mmol, 7.0 equiv.), bis(cyclopentadienyl)titanium(IV) dichloride (12.7 g, 51.0 mmol, 2.5 equiv.), and THF (275 mL) were used for the preparation of bis(cyclopentadienyl)titanium(III) chloride, which was added to crude starting material (α*R*)-**112** (4.20 g, 20.4 mmol, 1.0 equiv.) in THF (150 mL) over a period of 30 min, followed by stirring at room temperature for another 2 h.

***Work-up and purification**:* H_2SO_4 (10 %, 115 mL) was added carefully while the mixture was cooled in an ice bath, and most of the THF was evaporated at a minimum pressure of 160 mbar at 50 °C. Following repeated extraction with Et_2O, the combined organic phases were treated with saturated aqueous $NaHCO_3$ solution (120 mL), brine (120 mL), dried with Na_2SO_4, filtered and the solvents were evaporated. Flash column chromatography in two sequential runs (first run: 90 g silica, flow rate 40 mL / min, EtOAc / LP, 0 : 100 to 30 : 70 in 2 h; second run: 90 g silica, flow rate 40 mL / min, CH_2Cl_2 / LP, 60 : 40 to 100 : 0 in 40 min, then MeOH / CH_2Cl_2, 10 : 90) afforded the title compound **115**.

Yield:	1.10 g, 26 % (over 3 steps from (*S*)-**72**)
Appearance:	off-white crystals
Melting range:	73.0 – 76.0 °C
R_f **(silica)**:	0.36 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{25}$:	+7.7 (c 0.96, MeOH)

GC-MS (EI, 70 eV, Method C): 7.68 min; 208.1 (M^+, 7), 190.1 (16), 146.1 (20), 133.1 (16), 125.0 (100), 123.1 (33), 122.1 (24), 109.1 (36), 97.1 (45), 95.1 (28).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65 (bs, 1H), 2.67 – 2.83 (m, 1H, H3), 3.72 (dd, ^2J = 11.3 Hz, ^3J = 4.8 Hz, 1H, C3-CH), 3.87 (dd, ^2J = 11.3 Hz, ^3J = 5.6 Hz, 1H, C3-CH), 4.42 (ddd, ^2J = 13.4 Hz, $^4J_{cis\text{-allyl}}$ = 2.3 Hz*, $^4J_{trans\text{-allyl}}$ = 4.5*, 1H, H5), 4.55 – 4.67 (m, 1H, H5), 4.85 (d, ^3J = 7.2 Hz, 1H, H2), 5.04 – 5.16 (m, 2H, C4=CH_2), 6.97 – 7.11 (m, 2H, H3', H5'), 7.30 – 7.43 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 54.2 (d, C3), 62.0 (t, C3-C), 71.5 (t, C5), 82.9 (d, C2), 105.4 (t, C4=C), 115.5 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 128.1 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 137.1 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 148.6 (s, C4), 162.5 (d, C4', $^1J_{C\text{-}F}$ = 245.9 Hz).

D.2.5 **Silyl Protection**

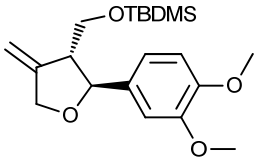
D.2.5.1 *General Procedure* for Silyl Protection

XIV TBDMS-**XIV**

***Preparation**:* a reaction vessel was charged with a stirring bar, starting material **XIV** (1.00 equiv.), imidazole (2.10 equiv.) and 4-DMAP (5 mol %); it was then evacuated and back-filled with argon using standard Schlenk technique. After adding dry DMF *via* syringe, a solution of TBDMSCl (3 M in THF) was added dropwise to the stirred mixture, also *via* syringe, and reaction progress was monitored by TLC and terminated when complete.

***Work-up and purification**:* the mixture was treated as detailed individually below to afford crude compound TBDMS-**XIV** to be used directly in the next reaction step.

D.2.5.2 *tert*-Butyl(((2*S*,3*R*)-2-(3,4-dimethoxyphenyl)-4-methylenetetrahydrofuran-3-yl)methoxy)dimethylsilane (TBDMS-**106**)



TBDMS-**106**, $C_{20}H_{32}O_4Si$
364.55 g mol^{-1}

***Preparation**:* According to the *General Procedure* (section D.2.5.1, page 143), starting material **106** (1.723 g, 6.885 mmol, 1.00 equiv.), imidazole (984 mg, 14.459 mmol, 2.10 equiv.), 4-DMAP (42 mg, 0.344 mmol, 5 mol %), TBDMSCl solution (3.14 mL, 9.42 mmol, 1.37 equiv.) and DMF (40 mL) were used, and the mixture was stirred at room temperature for 12.5 h.

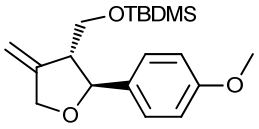
***Work-up and purification**:* Et_2O (100 mL) was added, followed by a saturated aqueous solution of NH_4Cl (40 mL). The layers were separated, the aqueous phase was extracted with Et_2O (3 x 50 mL), the combined organic phases were treated with a saturated aqueous solution of $NaHCO_3$ (25 mL), brine (25 mL), dried with Na_2SO_4, filtered and the solvents were evaporated to afford crude compound TBDMS-**106** to be used directly in the next reaction step.

Yield: 2.63 g, crude
Appearance: pale brown oil
***R*$_f$ (silica)**: 0.69 (EtOAc / LP, 2 : 5)

GC-MS (EI, 70 eV, Method C): 11.49 min; 364.2 (M^+, 5), 232.1 (36), 215.1 (41), 165.0 (42), 151.1 (36), 141.1 (22), 73.0 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H, $OSi(CH_3)_2$), 0.88 (s, 9H, $OSiC(CH_3)_3$), 2.71 – 2.85 (m, 1H, H3), 3.66 – 3.77 (m, 2H, C3-CH_2), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.34 – 4.46 (m, 1H, H5), 4.50 – 4.62 (m, 1H, H5), 4.86 (d, ^3J = 6.3 Hz, H2), 4.99 – 5.06 (m, 2H, C4=CH_2), 6.78 – 6.94 (m, 3H, Ar'-H).

D.2.5.3 *tert*-Butyl(((2*S*,3*R*)-2-(4-methoxyphenyl)-4-methylenetetrahydrofuran-3-yl)methoxy)dimethylsilane (TBDMS-**113**)



TBDMS-**113**, $C_{19}H_{30}O_3Si$
334.53 g mol^{-1}

***Preparation**:* According to the *General Procedure* (section D.2.5.1, page 143), starting material **113** (90 mg, 0.41 mmol, 1.00 equiv.), imidazole (58 mg, 0.86 mmol, 2.10 equiv.), 4-DMAP (2.5 mg, 0.02 mmol, 5 mol %), TBDMSCl solution (0.19 mL, 0.56 mmol, 1.37 equiv.) and DMF (2.0 mL) were used, and the mixture was stirred at room temperature for 24 h.

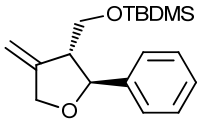
***Work-up and purification**:* Et_2O (30 mL) was added, followed by a saturated aqueous solution of NH_4Cl (15 mL) and water (5 mL). The layers were separated, the aqueous phase was extracted with Et_2O (2 x 10 mL), the combined organic phases treated with an aqueous solution of Na_2CO_3 (550 mg), brine (10 mL), dried with Na_2SO_4, filtered and the solvents were evaporated to afford crude compound TBDMS-**113** to be used directly in the next reaction step.

Yield: 190 mg, crude
Appearance: pale brown oil
***R*$_f$ (silica)**: 0.79 (EtOAc / LP, 1 : 1)

GC-MS (EI, 70 eV, Method G): 7.51 min; 334.4 (M^+, < 1), 202.2 (67), 185.2 (48), 173.2 (21), 141.1 (27), 135.1 (66), 121.1 (58), 101.1 (15), 73.1 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.02 (s, 6H, $OSi(CH_3)_2$), 0.86 (s, 9H, $OSiC(CH_3)_3$), 2.69 – 2.83 (m, 1H, H3), 3.65 – 3.77 (m, 2H, C3-CH_2), 3.79 (s, 3H, C4'-OCH_3), 4.31 – 4.45 (m, 1H, H5), 4.47 – 4.60 (m, 1H, H5), 4.84 (d, ^3J = 6.3 Hz, 1H, H2), 4.96 – 5.05 (m, 2H, C4=CH_2), 6.81 – 6.92 (m, 2H, H3', H5'), 7.22 – 7.34 (m, 2H, H2', H6').

D.2.5.4 *tert*-Butyldimethyl(((2*S*,3*R*)-4-methylene-2-phenyltetrahydrofuran-3-yl)methoxy)silane (TBDMS-**114**)



TBDMS-**114**, $C_{18}H_{28}O_2Si$
304.50 g mol^{-1}

***Preparation**:* According to the *General Procedure* (section D.2.5.1, page 143), starting material **114** (979 mg, 5.10 mmol, 1.00 equiv.), imidazole (730 mg, 10.66 mmol, 2.10 equiv.), 4-DMAP (33 mg, 0.25 mmol, 5 mol %), TBDMSCl solution (3.2 mL, 9.6 mmol, 1.9 equiv.) and DMF (35 mL) were used, and the mixture was stirred at room temperature for 14 h.

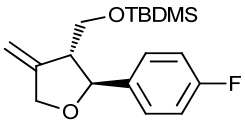
***Work-up and purification**:* Et_2O (70 mL) was added, followed by a saturated aqueous solution of NH_4Cl (30 mL). The layers were separated, the aqueous phase was extracted with Et_2O (3 x 50 mL), the combined organic phases treated with a saturated aqueous solution of Na_2CO_3 (15 mL), brine (15 mL), dried with Na_2SO_4, filtered and the solvents were evaporated to afford crude compound TBDMS-**114** to be used directly in the next reaction step.

Yield: 1.92 g, crude
Appearance: pale brown oil
***R*$_f$ (silica)**: 0.40 (EtOAc / LP, 1 : 20)

GC-MS (EI, 70 eV, Method C): 9.29 min; 304.0 (M^+, < 1), 247.1 (25), 199.1 (32), 172.1 (33), 155.1 (100), 143.1 (60), 141.1 (26), 129.1 (17), 128.1 (28), 115.1 (17), 105.1 (40), 91.1 (23).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H, $OSi(CH_3)_2$), 0.88 (s, 9H, $OSiC(CH_3)_3$), 2.74 – 2.87 (m, 1H, H3), 3.70 – 3.77 (m, 2H, C3-CH_2), 4.43 (ddd, ^2J = 13.1 Hz, $^4J_{cis\text{-allyl}}$ = 2.3 Hz*, $^4J_{trans\text{-allyl}}$ = 4.4 Hz*, 1H, H5), 4.52 – 4.63 (m, 1H, H5), 4.93 (d, ^3J = 6.0 Hz, 1H, H2), 4.99 – 5.05 (m, 2H, C4=CH_2), 7.24 – 7.41 (m, 5H, Ar'-H).

D.2.5.5 *tert*-Butyl(((2*S*,3*R*)-2-(4-fluorophenyl)-4-methylenetetrahydrofuran-3-yl)methoxy)dimethylsilane (TBDMS-**115**)



TBDMS-**115**, $C_{18}H_{27}FO_2Si$
322.49 g mol^{-1}

***Preparation**:* According to the *General Procedure* (section D.2.5.1, page 143), starting material **115** (1.10 g, 5.28 mmol, 1.00 equiv.), imidazole (755 mg, 11.09 mmol, 2.10 equiv.), 4-DMAP (32.3 mg, 0.26 mmol, 5 mol %), TBDMSCl solution (2.41 mL, 7.24 mmol, 1.37 equiv.) and DMF (33.0 mL) were used, and the mixture was stirred at room temperature for 16 h.

***Work-up and purification**:* Et_2O (80 mL) was added, followed by a saturated aqueous solution of NH_4Cl (40 mL). The layers were separated, the organic phase was treated with a saturated aqueous solution of $NaHCO_3$ (40 mL), brine (40 mL), dried with Na_2SO_4, filtered and the solvents were evaporated to afford crude compound TBDMS-**115** to be used directly in the next reaction step.

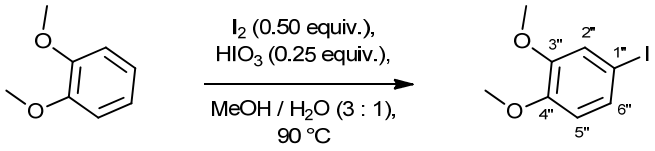
Yield: 1.91 g, crude
Appearance: pale brown oil
***R*$_f$ (silica)**: 0.74 (EtOAc / heptane, 1 : 3)

GC-MS (EI, 70 eV, Method C): 9.27 min; 190.1 (elimination of TBDMSO and H from M^+, 5), 161.1 (24), 146.1 (15), 123.0 (36), 109.0 (37), 101.0 (15), 73.0 (100). M^+ not visible.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H, $OSi(CH_3)_2$), 0.88 (s, 9H, $OSiC(CH_3)_3$), 2.68 – 2.84 (m, 1H, H3), 3.69 – 3.78 (m, 2H, C3-CH_2), 4.35 – 4.47 (m, 1H, H5), 4.49 – 4.62 (m, 1H, H5), 4.89 (d, ^3J = 6.2 Hz, 1H, H2), 4.98 – 5.07 (m, 2H, C4=CH_2), 6.95 – 7.10 (m, 2H, H3', H5'), 7.26 – 7.41 (m, 2H, H2', H6').

D.2.6 **Other Intermediate Compounds**

D.2.6.1 4-Iodo-1,2-dimethoxybenzene (4-iodoveratrole, **109**)



108 **109**, $C_8H_9IO_2$
264.06 g mol^{-1}

Procedure: A reaction vessel was charged with a stirring bar, veratrole **108** (4.18 g, 30.3 mmol, 1.00 equiv.), iodine (3.87 g, 15.1 mmol, 0.50 equiv.) and iodic acid (1.33 g, 7.36 mmol, 0.25 equiv.), followed by the addition of a mixture of MeOH / water (3 : 1, 300 mL). The reaction was then heated to 90 °C for 42 h. After cooling to room temperature, the mixture was discolored with a solution of Na_2SO_3 (5 % w/w, 20 mL). More water (100 mL) was added and then the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were treated with brine (50 mL), dried with Na_2SO_4, filtered through a short plug of silica and the solvents were evaporated. High vacuum distillation at 0.056 mbar then afforded the title compound **109**.

This compound is literature-known.[267, 316]

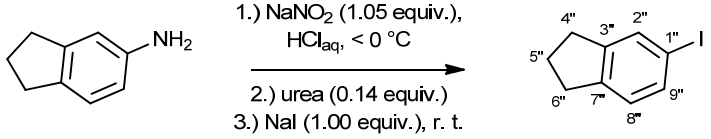
Yield:	6.88 g, 86 %
Appearance:	yellow oil which solidifies when stored refrigerated
Boiling point:	56 °C at 0.056 mbar; lit.[316] **boiling range**: 83 – 88 °C at 0.05 mmHg (0.067 mbar)
***R*$_f$ (silica)**:	0.18 (MTBE / heptane, 1 : 10)

GC-MS (EI, 70 eV, Method C): 6.89 min; 264.0 (M^+, 100), 249.0 (28), 94.1 (46).

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.83 (s, 3H, Ar''-OCH_3), 3.84 (s, 3H, Ar''-OCH_3), 6.60 (d, ^3J = 8.4 Hz, 1H, H5''), 7.10 (d, ^4J = 2.0 Hz, 1H, H2''), 7.21 (dd, ^3J = 8.4 Hz, ^4J = 2.0 Hz, 1H, H6'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 55.9 (q, Ar''-OCH_3), 56.1 (q, Ar''-OCH_3), 82.4 (s, C1''), 113.2 (d, C5''), 120.3 (d, C2''), 129.7 (d, C6''), 149.1 (s, C4''*), 149.8 (s, C3''*).

D.2.6.2 5-Iodo-2,3-dihydro-1*H*-indene (**266**)



265 **266**, C_9H_9I
244.07 g mol^{-1}

Procedure: A reaction vessel was charged with a stirring bar and 2,3-dihydro-1*H*-inden-5-amine **265** (1.00 g, 7.51 mmol, 1.00 equiv.), followed by the addition of aqueous HCl (6 M, 5.0 mL). The stirred mixture was cooled in an ice/salt bath, and after 15 min a solution of $NaNO_2$ (544 mg, 7.88 mmol,

1.05 equiv.) in water (3.0 mL) was added dropwise. After another 15 min, urea (65 mg, 1.08 mmol, 0.14 equiv.) was added followed by, after another 15 min, NaI (1.15 g, 7.51 mmol, 1.00 equiv.). The cooling bath was removed and stirring was continued at room temperature for 23 h. After extraction with CH_2Cl_2 (4 x 20 mL), the combined organic phases were treated with aqueous NaOH (2 M, 20 mL), aqueous HCl (2 M, 20 mL), saturated aqueous Na_2SO_3 (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). After drying with Na_2SO_4, filtration and evaporation of the solvent, the residue was dissolved in EtOAc / LP (1 : 3, 15 mL) and then filtered through a short plug of silica (3 x). The solvents were evaporated again, the residue was re-dissolved in LP (50 mL), treated with aqueous NaOH (2 M, 2 x 10 mL), dried with Na_2SO_4 and filtered. Finally, flash column chromatography (silica, EtOAc in LP, 3 : 97) afforded the title compound **266**.

This compound is literature-known.[317]

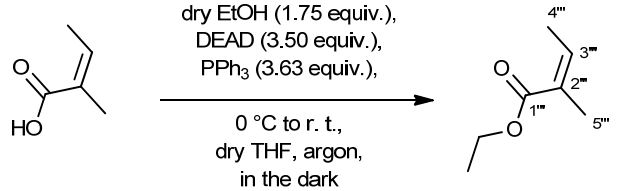
Yield: 350 mg, 19 % (literature yield[317] not stated)
Appearance: yellow oil
***R*$_f$ (silica)**: 0.62 (MTBE / heptane, 1 : 10)

GC-MS (EI, 70 eV, Method B): 9.53 min; 243.8 (M^+, 97), 126.8 (19), 117.1 (100), 116.1 (34), 115.0 (93), 91.0 (26).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.06 (quint, ^3J = 7.4 Hz, 2H, H5''), 2.86 (t, ^3J = 6.9 Hz, 2H, H4''*), 2.90 (t, ^3J = 6.9 Hz, 2H, H6''*), 6.99 (d, ^3J = 7.9 Hz, 1H, H8''), 7.45 (d, ^3J = 7.9 Hz, 1H, H9''), 7.57 (s, 1H, H2'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.5 (t, C5''), 32.6 (t, C4''*), 32.8 (t, C6''*), 91.1 (s, C1''), 126.4 (d, C8''*), 133.6 (d, C9''*), 135.0 (d, C2''*), 144.0 (s, C7''*), 147.2 (s, C3''*).

D.2.6.3 (*Z*)-Ethyl 2-methylbut-2-enoate (ethyl angelate, **259**)



165 **259**, $C_7H_{12}O_2$, 128.17 g mol^{-1}

***Procedure**:* a reaction vessel was charged with a stirring bar, commercially available angelic acid **165** (3.00 g, 30.0 mmol, 1.00 equiv.), and PPh_3 (28.56 g, 108.9 mmol, 3.63 equiv.); it was then evacuated and back-filled with argon using standard Schlenk technique. Dry THF (50 mL) was added and the solution was cooled to 0 °C in an ice bath. Dry EtOH (3.06 mL, 52.5 mmol, 1.75 equiv.) and DEAD (16.5 mL, 105.0 mmol, 3.50 equiv.) were then added dropwise to the stirred mixture *via* syringe, and the reaction was stirred for 5 h while being kept away from light and allowed to warm slowly to room temperature. The solution was then poured into water (60 mL), followed by the addition of pentane (90 mL), which resulted in a three-phase mixture. The top pentane layer was separated, and the other two phases were re-extracted with pentane (2 x 25 mL) and Et_2O (25 mL). The combined pentane / Et_2O phases were allowed to concentrate slowly by standing in a fume hood to

approximately 50 ml, then treated with brine (2 x 15 mL), dried with Na_2SO_4, filtered and the solvents were evaporated to a 10 g residue at a minimum pressure of 300 mbar at 45 °C. Vacuum distillation at 35 mbar from an oil bath at 100 °C then afforded the title compound **259**.

This compound is literature-known.[318-319]

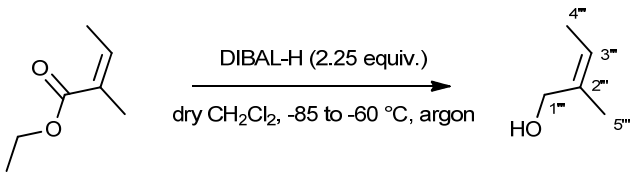
Yield:	2.69 g, 70 %
Appearance:	colorless liquid
Boiling range:	54 – 56 °C at 35 mbar; lit.[319] **boiling range**: 140 – 144 °C at ambient pressure
***R*$_f$ (silica)**:	0.39 (MTBE / heptane, 1 : 10)

GC-MS (EI, 70 eV, Method H): 4.49 min; 128.1 (M^+, 92), 100.1 (86), 83.1 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (t, ^3J = 7.1 Hz, 1H, $OCH_2C\underline{H}_3$), 1.86 – 1.91 (m, 1H, H5'''), 1.98 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 1H, H4'''), 4.20 (q, ^3J = 7.1 Hz, 1H, $OC\underline{H}_2CH_3$), 6.04 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3''').

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3 (q, $OCH_2\underline{C}H_3$), 15.7 (q, C4'''), 20.6 (q, C5'''), 60.0 (t, $O\underline{C}H_2CH_3$), 128.2 (s, C2'''), 137.3 (d, C3'''), 168.2 (s, C1''').

D.2.6.4 (*Z*)-2-Methylbut-2-en-1-ol (**260**)



259 **260**, $C_5H_{10}O$, 86.13 g mol^{-1}

***Procedure**:* a reaction vessel was charged with a stirring bar and evacuated and back-filled with argon using standard Schlenk technique. Ethyl angelate **259** (196.1 mg, 1.530 mmol, 1.00 equiv.) and dry CH_2Cl_2 (1.0 mL) were then added *via* syringe and the mixture was cooled to -85 °C in a MeOH / liquid N_2 bath. This was followed by the dropwise addition of a solution of DIBAL-H (1 M in heptane, 3.44 ml, 3.44 mmol, 2.25 equiv.) *via* syringe over approximately 3 min, and the mixture was allowed to warm to -60 °C over 2 h. Following the dropwise addition of aqueous HCl (0.5 M, 3 mL), the solution was warmed to room temperature and then poured into a mixture of more hydrochloric acid (0.5 M, 3 mL) and *n*-pentane (12 mL). The layers were separated, the organic phase was treated with brine (30 mL), dried with Na_2SO_4, filtered and concentrated at a minimum pressure of 500 mbar at 50 °C. Following this, naphthalene (15.7 mg, 0.122 mmol) was added as an inert standard to determine the concentration of the resulting solution by ^{1}H NMR spectroscopy, affording the title compound **260** as a solution in pentane to be used as such in a subsequent reaction.

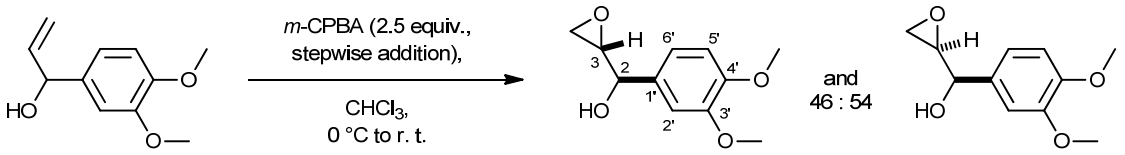
This compound is literature-known.[320]

Yield: 1.85 mL solution (0.154 M), 19 %
Appearance: colorless liquid
***R*$_f$ (silica)**: 0.54 (MTBE / heptane, 1 : 10)

GC-MS (EI, 70 eV, Method B): 3.43 min; 86.1 (M^+, 42), 71.0 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60 – 1.68 (m, 3H, H4'''), 1.76 – 1.81 (m, 3H, H5'''), 4.15 (s, 2H, H1'''), 5.38 (q, ^3J = 7.0 Hz, 1H, H3'''). OH not visible.

D.2.6.5 (3,4-Dimethoxyphenyl)(oxiran-2-yl)methanol (**73**)



rac-**27** **73**, racemic mixture of diastereoisomers, $C_{11}H_{14}O_4$ 210.23 g mol^{-1}

Procedure: A reaction vessel was charged with a stirring bar, starting material *rac*-**27** (19.4 mg, 0.10 mmol, 1.0 equiv.) and $CHCl_3$ (0.3 mL), and the mixture was cooled in an ice bath (insulated Dewar vessel). This was followed by the dropwise addition of a solution of *m*-CPBA (wet, approximately 77 %, 31.4 mg, 0.10 mmol, 1.0 equiv.) in $CHCl_3$ (0.3 mL, pre-cooled to 0 °C) over approximately 1 min and the reaction was stirred for 20 h, during which it was allowed to warm slowly to room temperature.
The above cooling-reagent addition-warming procedure (over 20 to 24 h each) was then repeated three times as described, using a solution of *m*-CPBA (wet, approximately 77 %, 15.7 mg, 0.05 mmol, 0.5 equiv.) in $CHCl_3$ (0.2 mL, pre-cooled to 0 °C) each time (totaling 2.5 equiv. of *m*-CPBA).
Then a saturated aqueous solution of Na_2CO_3 (10 mL) was added carefully, followed by extracting with Et_2O (2 x 10 mL), treating the combined organic phases with brine (10 mL), drying with Na_2SO_4, filtering and evaporating the solvents. Flash column chromatography (9 g silica, flow rate 10 mL / min, EtOAc / LP, 50 : 50) then afforded the title compound **73** as a racemic mixture of diastereoisomers (approximate ratio: major / minor, 54 : 46, by NMR).

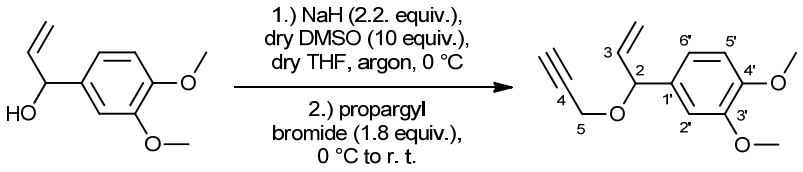
This mixture of isomers is literature-known.[234]

Yield: 8.9 mg, 42 %
Appearance: nearly colorless oil
***R*$_f$ (silica)**: 0.22 (EtOAc / LP, 1 : 1)

^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ 2.52 (bs, 1H, OH), 2.70 – 2.89 (m, 2H, C3-CH_2), 3.17 – 3.26 (m, 1H, H3), 3.88 (s, 3H, Ar'-OCH_3*), 3.90 (s, 3H, Ar'-OCH_3*), 4.41 (d, ^3J = 5.4 Hz, 1H, H2), 6.81 – 7.02 (m, 3H, Ar'-H). minor isomer: δ 2.52 (bs, 1H, OH), 2.70 – 2.89 (m, 1H, C3-CH), 2.94 (dd, ^2J = 5.0 Hz, ^3J = 2.8 Hz, 1H, C3-CH), 3.17 – 3.26 (m, 1H, H3), 3.88 (s, 3H, Ar'-OCH_3*), 3.89 (s, 3H, Ar'-OCH_3*), 4.84 (d, ^3J = 3.0 Hz, 1H, H2), 6.81 – 7.02 (m, 3H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$) major isomer: δ 45.4 (t, C3-C), 56.0 (q, Ar'-OCH_3; signal overlap with Ar'-OCH_3 of minor isomer), 56.0 (q, Ar'-OCH_3; signal overlap with Ar'-OCH_3 of minor isomer), 56.1 (d, C3*), 74.3 (d, C2), 109.5 (d, C2'), 111.2 (d, C5'; signal overlap with C5' of minor isomer), 118.7 (d, C6'), 132.9 (s, C1'), 149.0 (s, C4'*), 149.2 (s, C3'*). minor isomer: δ 43.8 (t, C3-C), 55.2 (d, C3), 56.0 (q, Ar'-OCH_3; signal overlap with Ar'-OCH_3 of major isomer), 56.0 (q, Ar'-OCH_3; signal overlap with Ar'-OCH_3 of major isomer), 70.9 (d, C2), 109.6 (d, C2'), 111.2 (d, C5'; signal overlap with C5' of major isomer), 118.8 (d, C6'), 132.1 (s, C1'), 149.0 (s, C4'*), 149.3 (s, C3'*).

D.2.6.6 1,2-Dimethoxy-4-(1-(prop-2-yn-1-yloxy)allyl)benzene (*rac*-**107**)



rac-**27**

rac-**107**, $C_{14}H_{16}O_3$
232.28 g mol^{-1}

Procedure: a reaction vessel was charged with a stirring bar and NaH (approximately 60 % dispersion in mineral oil, 659 mg, 16.48 mmol, 2.2 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry THF (13.0 mL) and dry DMSO (5.3 mL, 74.9 mmol, 10.0 equiv.) were then added in this order *via* syringe and the resulting suspension was cooled to 0 °C in an ice bath. Starting material *rac*-**27** (1.45 g, 7.49 mmol, 1.0 equiv.), as a beforehand-prepared solution in dry THF (25.0 mL) under argon, was then slowly transferred to the stirred mixture, which after another 20 min of stirring was followed by a solution of propargyl bromide (80 % in toluene, 1.50 mL, 13.48 mmol, 1.8 equiv.), both *via* syringe. The ice bath was then removed after 20 min of stirring and the reaction continued at room temperature for 8 h. The mixture was hydrolyzed, while still under argon, by careful addition of a saturated aqueous solution of NH_4Cl (480 mg in 30 mL), followed by the addition of Et_2O (80 mL). The layers were separated, the aqueous phase was re-extracted with Et_2O (2 x 80 mL), the combined organic phases were treated with brine (30 m), dried with Na_2SO_4, filtered and the solvents were evaporated. Flash column chromatography (90 g silica, flow rate 40 mL / min, EtOAc / LP, 18 : 82) afforded the title compound *rac*-**107**.

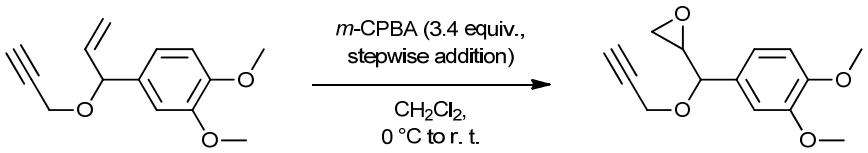
Yield: 1.50 g, 86 %
Appearance: pale yellow oil
***R*$_f$ (silica)**: 0.74 (EtOAc / LP, 1 : 1)

GC-MS (EI, 70 eV, Method C): 8.11 min; 232.2 (M^+, 52), 193.1 (17), 178.1 (27), 177.1 (100), 176.1 (34), 173.2 (23), 171.1 (20), 166.1 (29), 165.1 (94), 161.1 (21), 147.1 (24), 146.1 (73), 131.1 (29), 119.1 (18), 115.1 (21), 103.1 (23), 91.1 (30).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.43 (t, ^4J = 2.4 Hz, 1H, C4≡CH), 3.88 (s, 3H, Ar'-OCH_3), 3.89 (s, 3H, Ar'-OCH_3), 4.06 (dd, ^2J = 15.7 Hz, ^4J = 2.4 Hz, 1H, H5), 4.17 (dd, ^2J = 15.8 Hz, ^4J = 2.4 Hz, 1H, H5), 4.97 (d, ^3J = 6.5 Hz, 1H, H2), 5.20 – 5.37 (m, 2H, C3=CH_2), 5.96 (ddd, $^3J_{cis}$ = 10.3 Hz, $^3J_{trans}$ = 16.9 Hz, $^3J_{vis}$ = 6.5 Hz, 1H, H3), 6.80 – 6.93 (m, 3H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 55.3 (t, C5), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 74.5 (d, C4≡C; *J*-mod spectrum shows antipodal signal due to a large $^1J_{C\text{-}H}$ of approximately 250 Hz), 80.0 (s, C4), 81.1 (d, C2), 110.1 (d, C2'), 111.0 (d, C5'), 117.2 (t, C3=C), 119.9 (d, C6'), 132.6 (s, C1'), 138.1 (d, C3), 148.9 (s, C4'), 149.3 (s, C3').

D.2.6.7 2-((3,4-Dimethoxyphenyl)(prop-2-yn-1-yloxy)methyl)oxirane (**101**)



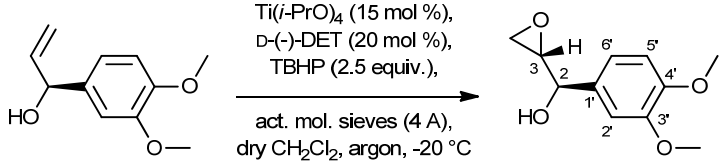
rac-**107** → **101**, $C_{14}H_{16}O_4$, racemic mixture of diastereoisomers, 248.27 g mol^{-1}

Procedure: A reaction vessel was charged with a stirring bar, starting material *rac*-**107** (1.49 g, 6.43 mmol, 1.0 equiv.) and CH_2Cl_2 (10 mL), and the mixture was cooled in an ice bath. This was followed by the dropwise addition of a solution of *m*-CPBA (wet, approximately 77 %, 2.45 g, 10.94 mmol, 1.70 equiv.) in CH_2Cl_2 (25 mL) over approximately 10 min and the reaction was stirred for 10 h, during which it was allowed to warm slowly to room temperature.
The above cooling-reagent addition-warming procedure (over 19 and 25 h, respectively) was then repeated two times as described, using a solution of *m*-CPBA (wet, approximately 77 %, 1.23 g, 5.47 mmol, 0.85 equiv.) in CH_2Cl_2 (15 mL) each time (totaling 3.4 equiv. of *m*-CPBA).
Then a saturated aqueous solution of Na_2CO_3 (25 mL) was added carefully, followed by extracting with Et_2O (4 x 50 mL), treating the combined organic phases with brine (25 mL), drying with Na_2SO_4, filtering and evaporating the solvents. Flash column chromatography (90 g silica, flow rate 40 mL / min, EtOAc / LP, 20 : 80 to 35 : 65 in 1 h) then afforded the title compound **101** as a racemic mixture of diastereoisomers.

This mixture of isomers is literature-known.[234]

Yield: 658 mg, 41 %
Appearance: nearly colorless oil
(for additional characterization, *cf.* section D.2.3.2, page 133)

D.2.6.8 (*R*)-(3,4-Dimethoxyphenyl)((*S*)-oxiran-2-yl)methanol ((α*R*,β*S*)-**73**)



(*S*)-**27** → (α*R*,β*S*)-**73**, $C_{11}H_{14}O_4$, 210.23 g mol^{-1}

For this reaction, molecular sieves (4 A) were activated as described in the General Notes (section D.1, page 117), and dry CH_2Cl_2 was treated with them overnight under argon before use.

***Procedure**:* a reaction vessel was charged with a stirring bar, D-(-)-DET (18.0 mg, 0.088 mmol, 20 mol %) and molecular sieves (crushed, 30 mg), and then evacuated and back-filled with argon using standard Schlenk technique. The vessel was cooled to -20 °C using a cryostat, and a beforehand-prepared solution of Ti(*i*-OPr)$_4$ (20 µL, 0.066 mmol, 15 mol %) in dry CH_2Cl_2 (1.0 mL) under argon was then added *via* syringe. The mixture was stirred for 5 min, which was followed by the slow addition of a solution of TBHP (5.5 M in decane, 0.20 mL, 1.09 mmol, 2.50 equiv.) *via* syringe. While this was stirred for another 30 min, a second vessel was charged with starting material (*S*)-**27** (85.0 mg, 0.438 mmol, 1.00 equiv.) and molecular sieves (30 mg), evacuated and back-filled with argon, followed by the addition of dry CH_2Cl_2 (1.0 mL) *via* syringe. This solution was then transferred to the reaction mixture, and using additional CH_2Cl_2 (0.5 mL), residual starting material was flushed into the reaction, both *via* syringe. Stirring was then continued at -20 °C for 22 h. Na_2SO_3 (200 mg) in water (2 mL), CH_2Cl_2 (25 mL) and additional water (10 mL) were then added, the layers were separated and the aqueous phase was re-extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried with Na_2SO_4, filtered and the solvent was evaporated. Flash column chromatography (18 g silica, flow rate 15 mL / min, EtOAc / LP, 40 : 60 to 60 : 40 in 30 min) afforded the title compound (α*R*,β*S*)-**73**.

This compound is literature-known as its optical antipode.[169]

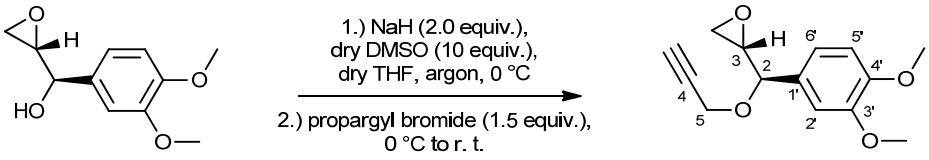
Yield:	71.6 mg, 78 %
Appearance:	off-white crystals
Melting range:	82 – 84.5 °C; lit.[169] **melting range** of optical antipode: n/a (physical state and melting range of compound not stated)
R_f **(silica)**:	0.19 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{31}$:	-71.2 (c 1.00, $CHCl_3$); lit.[169] $[\alpha]_D^{31}$ of optical antipode: +75.8 (c 1.0, $CHCl_3$)

GC-MS (EI, 70 eV, Method G): 6.43 min; 210.2 (M^+, 32), 167.2 (100), 139.2 (71), 124.1 (23), 108.1 (17).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.39 (bs, 1H, OH), 2.71 – 2.84 (m, 1H, C3-CH), 2.93 (dd, ^2J = 4.9 Hz, ^3J = 2.9 Hz, 1H, C3-CH), 3.20 (dt, $^3J_{benzyl}$ = 3.5 Hz, $^3J_{oxirane}$ = 3.1 Hz, 1H, H3), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.83 (d, ^3J = 2.6 Hz, 1H, H2), 6.77 – 7.03 (m, 3H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 43.8 (t, C3-C), 55.2 (d, C3), 56.00 (q, Ar'-OCH_3), 56.02 (q, Ar'-OCH_3), 70.9 (d, C2), 109.7 (d, C2'), 111.2 (d, C5'), 118.9 (d, C6'), 132.1 (s, C1'), 149.1 (s, C4'*), 149.3 (s, C3'*).

D.2.6.9 (*S*)-2-((*R*)-(3,4-Dimethoxyphenyl)(prop-2-yn-1-yloxy)methyl)oxirane (<u>(α*R*,β*S*)-**101**</u>)



<u>(α*R*,β*S*)-**73**</u>

<u>(α*R*,β*S*)-**101**</u>, $C_{14}H_{16}O_4$
248.27 g mol^{-1}

***Procedure**:* a reaction vessel was charged with a stirring bar and NaH (approximately 60 % dispersion in mineral oil, 421.2 mg, 10.53 mmol, 2.0 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry THF (20 mL) and dry DMSO (3.7 mL, 52.7 mmol, 10.0 equiv.) were then added in this order *via* syringe and the resulting suspension was cooled to 0 °C in an ice bath. Starting material <u>(α*R*,β*S*)-**73**</u> (1.107 g, 5.27 mmol, 1.0 equiv.), as a beforehand-prepared solution in dry THF (20 mL) under argon, was then slowly transferred to the stirred mixture, which after another 5 min of stirring was followed by a solution of propargyl bromide (80 % in toluene, 0.88 mL, 7.90 mmol, 1.5 equiv.), both *via* syringe. The ice bath was then removed after 1 h of stirring and the reaction continued at room temperature for 14 h. The mixture was hydrolyzed, while still under argon, by careful addition of a saturated aqueous solution of NH_4Cl (5 mL), followed by the addition of Et_2O (50 mL), brine (20 mL) and more water (10 mL) to dissolve precipitates. The layers were separated, the aqueous phase was re-extracted with Et_2O (2 x 50 mL), the combined organic phases were dried with Na_2SO_4, filtered and the solvents were evaporated. Flash column chromatography (70 g silica, flow rate 40 mL / min, EtOAc / heptane, 15 : 85 to 25 : 75 in 5 min, then to 50 : 50 in 45 min) afforded the title compound <u>(α*R*,β*S*)-**101**</u>.

This compound is literature-known in racemic form.[234]

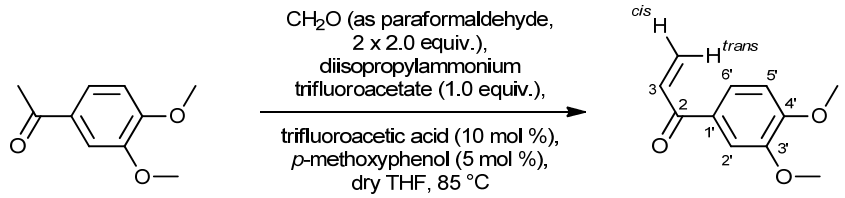
Yield: 1.187 g, 91 %
Appearance: pale yellow oil
***R*$_f$ (silica)**: 0.43 (EtOAc / LP, 1 : 1)

GC-MS (EI, 70 eV, Method G): 6.71 min; 248.2 (M^+, 26), 205.2 (100), 166.1 (49), 165.1 (62), 151.1 (19), 146.1 (15).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.45 (t, ^4J = 2.5 Hz, 1H, C4≡CH), 2.71 (dd, ^2J = 5.2 Hz, ^3J = 2.6 Hz, 1H, C3-CH), 2.81 (dd, ^2J = 5.2 Hz, ^3J = 3.9 Hz, 1H, C3-CH), 3.21 (ddd, $^3J_{oxirane}$ = 3.9 Hz, $^3J_{oxirane}$ = 2.6 Hz, $^3J_{benzyl}$ = 4.4 Hz, 1H, H3), 3.88 (s, 3H, Ar'-OCH_3), 3.90 (s, 3H, Ar'-OCH_3), 3.97 (dd, ^2J = 15.7 Hz, ^4J = 2.4 Hz, 1H, H5), 4.21 (dd, ^2J = 15.8 Hz, ^4J = 2.4 Hz, 1H, H5), 4.50 (d, ^3J = 4.5 Hz, 1H, H2), 6.82 – 6.95 (m, 3H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 45.3 (t, C3-<u>C</u>), 54.1 (d, C3), 55.9 (t, C5), 56.0 (q, 2 x Ar'-OCH_3), 74.8 (d, C4≡<u>C</u>; *J*-mod spectrum shows antipodal signal due to a large $^1J_{C\text{-}H}$ of approximately 250 Hz), 79.3 (d, C2), 79.5 (s, C4), 110.4 (d, C2'), 111.0 (d, C5'), 120.4 (d, C6'), 129.4 (s, C1'), 149.2 (s, C4'*), 149.3 (s, C3'*).

D.2.6.10 1-(3,4-Dimethoxyphenyl)prop-2-en-1-one (**78**)



77

78, $C_{11}H_{12}O_3$
192.21 g mol^{-1}

Procedure: For the preparation of diisopropylammonium trifluoroacetate, trifluoroacetic acid (2.3 mL) was added dropwise to a stirred solution of diisopropylamine (3.1 g) in dry Et_2O (30 mL) at 0 °C. The reaction vessel was capped and stirring was continued for 10 min, then the solution was filtered and the solid was washed with dry Et_2O (approx. 30 mL) before it was dried *in vacuo* at 40 °C.

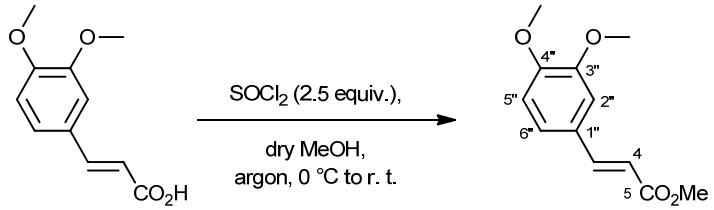
A reaction vessel was charged with a stirring bar, ketone **77** (541 mg, 3.0 mmol, 1.0 equiv.), paraformaldehyde (180.2 mg, 6.0 mmol, 2.0 equiv.), diisopropylammonium trifluoroacetate (646 mg, 3.0 mmol, 1.0 equiv.), *p*-methoxyphenol (18.6 mg, 0.15 mmol, 5 mol %) and dry THF (3.0 mL). This was followed by trifluoroacetic acid (23 µL, 0.3 mmol, 10 mol %) before the reaction vessel was closed and the stirred mixture was heated to 85 °C for 2 h. Then more paraformaldehyde (180.2 mg, 6.0 mmol, 2.0 equiv.) was added and stirring was continued at 85 °C for 24 h.
After cooling to room temperature, Et_2O (25 mL) and aqueous HCl (1 M, 10 mL) were added, the layers were separated, the organic phase was treated with aqueous NaOH solution (1 M, 10 mL) and brine (10 mL), then dried with Na_2SO_4, filtered and the solvents were evaporated. Flash column chromatography (90 g silica, flow rate 40 mL / min, EtOAc / LP, 5 : 95 to 55 : 45 in 80 min) was performed and *p*-methoxyphenol (16.5 mg, 4 w/w %) was added to the eluate before evaporation of the solvents as a polymerization inhibitor, to afford the title compound **78**.

This compound is literature-known[189] but polymerized before characterization (**GC-MS**, **^{13}C NMR**) could be completed.

Yield: 414 mg (incl. *p*-methoxyphenol), 69 %
Appearance: light-brown oil

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.96 (s, 6H, Ar'-OCH_3), 5.88 (dd, ^2J = 1.8 Hz, ^3J = 10.5 Hz, 1H, C3=CH^{cis}), 6.44 (dd, ^2J = 1.8 Hz, ^3J = 17.0 Hz, 1H, C3=CH^{trans}), 6.91 (d, ^3J = 8.2 Hz, 1H, H5'), 7.20 (dd, $^3J_{cis}$ = 10.5 Hz, $^3J_{trans}$ = 17.1 Hz, 1H, H3), 7.53 – 7.65 (m, 2H, H2', H6').

D.2.6.11 (*E*)-Methyl 3-(3,4-dimethoxyphenyl)acrylate (dimethylcaffeic acid methyl ester, **83**)



82 **83**, $C_{12}H_{14}O_4$, 222.24 g mol^{-1}

***Procedure**:* A reaction vessel was charged with a stirring bar and then evacuated and back-filled with argon using standard Schlenk technique. Dry MeOH (6 mL) was then added *via* syringe and the stirred reaction was cooled in an ice bath. This was followed by the dropwise addition of $SOCl_2$ (0.91 mL, 1.49 g, 12.5 mmol, 2.5 equiv.) *via* syringe over approximately 3 min. After 15 min, dimethylcaffeic acid **82** (1.041 g, 5.00 mmol, 1.0 equiv.) was quickly added in one go and stirring was continued for another 5 min. The ice bath was removed, more dry MeOH (20 mL) was added *via* syringe 10 min later and the reaction mixture was stirred for another 6.5 h. During this time, the initial suspension had given way to a clear solution, indicating the consumption of starting material **82**.

The reaction mixture was quickly transferred to a rotary evaporator that had been fitted with a cooling trap (immersed in liquid N_2) between the condenser and the pump, and the liquids were then evaporated at 40 °C. This was followed by concentrating the residue twice from toluene (25 mL each) and once from Et_2O (40 mL). Drying in high vacuum finally afforded the title compound **83**.

This compound is literature-known.[321]

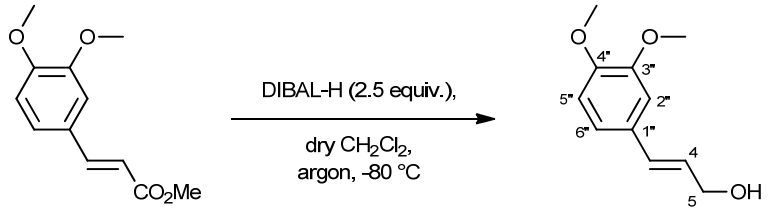
Yield:	1.104 g, 99 %
Appearance:	nearly colorless crystals
Melting range:	66.0 – 68.0 °C; lit.[321] **melting range**: 68 – 69 °C
***R*$_f$ (silica)**:	0.67 (EtOAc / LP, 2 : 1)

GC-MS (EI, 70 eV, Method A): 8.97 min; 222.0 (M^+, 100), 207.0 (16), 191.0 (48).

^{1}H NMR (200 MHz, $CDCl_3$): δ 3.80 (s, 3H, $C5O_2CH_3$), 3.91 (s, 6H, Ar''-OCH_3), 6.32 (d, ^3J = 15.9 Hz, 1H, H4), 6.87 (d, ^3J = 8.2 Hz, 1H, H5''), 7.01 – 7.16 (m, 2H, H2'', H6''), 7.64 (d, ^3J = 15.9 Hz, 1H, C4=CH-Ar'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 51.7 (q, $C5O_2\underline{C}H_3$), 56.0 (q, Ar''-OCH_3), 56.1 (q, Ar''-OCH_3), 109.7 (d, C2''*), 111.1 (d, C5''*), 115.6 (d, C4), 122.7 (d, C6''), 127.5 (s, C1''), 144.9 (d, C4=$\underline{C}$H-Ar''), 149.3 (s, C4''*), 151.2 (s, C3''*), 167.8 (s, C5).

D.2.6.12 (*E*)-3-(3,4-Dimethoxyphenyl)prop-2-en-1-ol (**81**)



83 **81**, $C_{11}H_{14}O_3$, 194.23 g mol^{-1}

***Procedure**:* A reaction vessel was charged with a stirring bar and starting material **83** (833 mg, 3.75 mmol, 1.0 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry CH_2Cl_2 (20 mL) was added *via* syringe and the stirred solution was cooled to -80 °C in a MeOH / liquid N_2 bath. This was followed by the dropwise addition of DIBAL-H solution (0.72 M in hexanes, 13.0 ml, 9.38 mmol, 2.5 equiv.) *via* syringe over 10 min. After stirring at -80 °C for 1 h, aqueous HCl (1 M, 10 mL) was added dropwise and the mixture was then allowed to warm to room temperature. More aqueous HCl (1 M, 40 mL) was added to delump the aluminum precipitates. After extracting with CH_2Cl_2 (2 x 30 mL), and treating the combined organic phases with brine (2 x 25 mL), they were dried with Na_2SO_4, filtered and the solvents were evaporated. Et_2O (25 mL) was added to the residue, and the solution was concentrated once more to afford crystalline title compound **81**.

This compound is literature-known.[322]

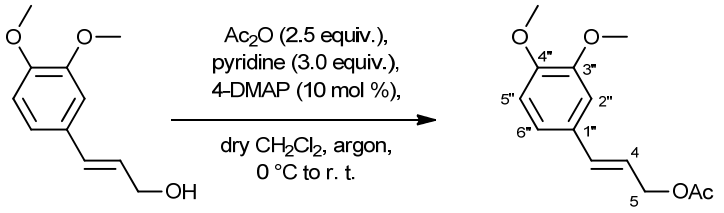
Yield: 718 mg, 98 %
Appearance: off-white crystals
Melting range: 74.5 – 77.5 °C; lit.[322] **melting range**: 76 – 79 °C
***R*$_f$ (silica)**: 0.48 (EtOAc / LP, 2 : 1)

GC-MS (EI, 70 eV, Method A): 8.38 min; 194.0 (M^+, 84), 166.1 (18), 151.1 (100), 138.1 (50), 91.1 (27).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.63 (bs, 1H, OH), 3.88 (s, 3H, Ar''-OCH_3), 3.89 (s, 3H, Ar''-OCH_3), 4.29 (dd, ^3J = 5.8 Hz, ^4J = 1.2 Hz, 2H, H5), 6.24 (dt, $^3J_{trans}$ = 15.8 Hz, $^3J_{vic}$ = 5.8 Hz, 1H, H4), 6.55 (d, ^3J = 15.9 Hz, 1H, C4=CH-Ar''), 6.77 – 6. 98 (m, 3H, Ar''-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 55.9 (q, Ar''-OCH_3), 56.0 (q, Ar''-OCH_3), 63.9 (t, C5), 109.0 (d, C2''*), 111.2 (d, C5''*), 119.8 (d, C6''), 126.7 (d, C4), 129.9 (s, C1''), 131.2 (d, C4=CH-Ar''), 149.0 (s, C4''*), 149.1 (s, C3''*).

D.2.6.13 (*E*)-3-(3,4-Dimethoxyphenyl)allyl acetate (Ac-**81**)



81 Ac-**81**, $C_{13}H_{16}O_4$, 236.26 g mol^{-1}

Procedure: A reaction vessel was charged with a stirring bar and starting material **81** (3.867 g, 19.91 mmol, 1.00 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry CH_2Cl_2 (25 mL) was added for dissolution, followed by a solution of pyridine (4.72 g, 59.7 mmol, 3.0 equiv.) and 4-DMAP (243 mg, 1.99 mmol, 10 mol %) in dry CH_2Cl_2 (25 mL), both *via* syringe. The stirred mixture was cooled in an ice bath, and a solution of Ac_2O (5.08 g, 49.8 mmol, 2.5 equiv.) in dry CH_2Cl_2 (10 mL) was added slowly *via* syringe over 3 min. After 2 min, the ice bath was removed and stirring was continued for 1.75 h. The solvent was then evaporated and flash column chromatography (90 g silica, flow rate 40 mL / min, EtOAc / LP, 20 : 80) afforded the title compound Ac-**81**.

This compound is literature-known.[323]

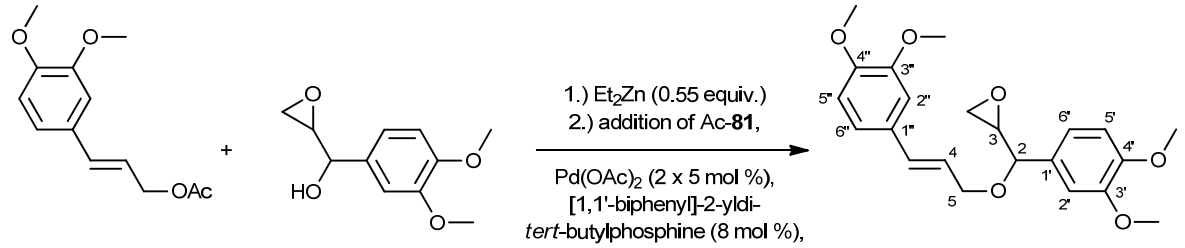
Yield: 4.50 g, 96 %
Appearance: nearly colorless oil
***R*$_f$ (silica)**: 0.68 (EtOAc / LP, 1 : 1)

GC-MS (EI, 70 eV, Method C): 9.33 min; 236.1 (M^+, 100), 194.1 (24), 193.1 (48), 177.1 (89), 165.1 (53), 163.1 (16), 161.1 (21), 151.1 (23), 147.1 (19), 146.1 (63), 138.1 (31), 133.1 (21), 131.1 (25), 119.1 (21), 115.1 (20), 105.1 (18), 103.1 (21), 91.1 (31).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.10 (s, 3H, $OCOCH_3$), 3.88 (s, 3H, Ar''-OCH_3), 3.90 (s, 3H, Ar''-OCH_3), 4.71 (dd, ^3J = 6.6 Hz, ^4J = 1.0 Hz, 2H, H5), 6.16 (dt, $^3J_{trans}$ = 15.8 Hz, $^3J_{vic}$ = 6.6 Hz, 1H, H4), 6.60 (d, ^3J = 15.9 Hz, 1H, C4=CH-Ar''), 6.78 – 6.85 (m, 1H, H5''), 6.88 – 6.98 (m, 2H, H2'', H6'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.1 (q, $OCOCH_3$), 55.9 (q, Ar''-OCH_3), 56.0 (q, Ar''-OCH_3), 65.3 (t, C5), 108.9 (d, C2''*), 111.1 (d, C5''*), 120.2 (d, C6''), 121.2 (d, C4), 129.3 (s, C1''), 134.3 (d, C4=CH-Ar''), 149.2 (s, C4''*), 149.2 (s, C3''*), 171.0 (s, OCO).

D.2.6.14 (*E*)-2-((3,4-Dimethoxyphenyl)((3-(3,4-dimethoxyphenyl)allyl)oxy)methyl)oxirane (**85**)



Ac-**81**
(1.25 equiv., Step 2)

73

85, racemic mixture of diastereoisomers, $C_{22}H_{26}O_6$
386.44 g mol^{-1}

A reaction vessel was charged with a stirring bar, epoxy alcohol **73** (racemic mixture of diastereoisomers, 60.8 mg, 0.289 mmol, 1.00 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry THF (0.2 mL) was added *via* syringe, followed by the dropwise addition of Et_2Zn (1 M solution in hexanes, 0.16 mL, 0.16 mmol, 0.55 equiv.) under stirring at room temperature, and stirring was continued for 55 min.
Meanwhile, a second vessel was charged with $Pd(OAc)_2$ (3.2 mg, 0.014 mmol, 5 mol %), [1,1'-biphenyl]-2-yldi-*tert*-butylphosphine (6.5 mg, 0.022 mmol, 8 mol %) and Ac-**81** (85.4 mg, 0.361 mmol, 1.25 equiv.), and then evacuated and back-filled with argon. This material was dissolved in dry THF (0.4 mL), and the so-obtained catalyst-ligand-allylic acetate solution was added dropwise to the first reaction vessel *via* syringe. Stirring was continued for 23 h at room temperature before more $Pd(OAc)_2$ (3.2 mg, 0.014 mmol, 5 mol %) was added as a solution in dry THF (0.2 mL) *via* syringe.
After another 21 h, $CHCl_3$ (15 mL) was added, the solution was concentrated and flash column chromatography was performed (40 g silica, flow rate 40 mL / min, EtOAc / LP, 20 : 80 to 60 : 40 in 45 min) to afford the title compound **85** as a racemic mixture of diastereoisomers.

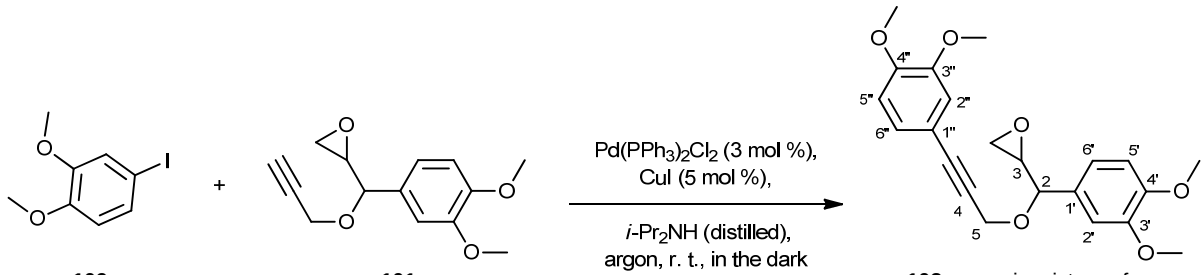
This compound is literature-known.[170]

Yield: 42.7 mg, 38 %
Appearance: light-brown oil
***R*$_f$ (silica)**: 0.42 (EtOAc / LP, 1 : 1)

^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ 2.64 – 2.78 (m, 2H, C3-CH_2), 3.08 – 3.22 (m, 1H, H3), 3.80 (s, 3H, Ar-OCH_3), 3.82 (s, 9H, Ar-OCH_3), 3.83 – 4.19 (m, 2H, H5), 4.29 (d, ^3J = 4.2 Hz, 1H, H2), 5.97 – 6.19 (m, 1H, H4), 6.41 (dd, ^3J = 15.9 Hz, 1H, C4=CH-Ar''), 6.69 – 6.91 (m, 6H, Ar-H). minor isomer: δ 2.54 (dd, ^2J = 4.8 Hz, ^3J = 2.7 Hz, 1H, C3-CH), 2.64 – 2.78 (m, 1H, C3-CH), 3.08 – 3.22 (m, 1H, H3), 3.80 (s, 3H, Ar-OCH_3), 3.82 (s, 9H, Ar-OCH_3), 3.83 – 4.19 (m, 3H, H2, 2 x H5), 5.97 – 6.19 (m, 1H, H4), 6.43 (dd, ^3J = 15.9 Hz, 1H, C4=CH-Ar''), 6.69 – 6.91 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$) major isomer: δ 45.3 (t, C3-C), 54.6 (d, C3*), 56.0 (q, 4 x Ar-OCH_3), 69.7 (t, C5*), 79.7 (d, C2*), 108.8 (d, C2''*), 110.3 (d, C2'*), 111.0 (d, C5'*), 111.1 (d, C5''*), 119.9 (d, C6''*), 120.1 (d, C6'*), 123.9 (d, C4), 129.8 (s, C1''), 130.8 (s, C1'), 132.7 (d, C4=C). minor isomer: δ 44.6 (t, C3-C), 55.5 (d, C3*), 56.0 (q, 4 x Ar-OCH_3), 69.6 (t, C5*), 82.4 (d, C2*), 108.8 (d, C2''*), 110.0 (d, C2'*), 111.0 (d, C5'*), 111.1 (d, C5''*), 119.8 (d, C6''*), 119.9 (d, C6'*), 123.9 (d, C4), 129.8 (s, C1'), 129.8 (s, C1''), 132.7 (d, C4=C). both isomers: 149.0 – 149.4 (s, C3'; s, C3''; s, C4'; s, C4''; multiple signals due to diastereoisomerism).

D.2.6.15 2-((3,4-Dimethoxyphenyl)((3-(3,4-dimethoxyphenyl)prop-2-yn-1-yl)oxy)methyl)oxirane (**102**)



109 (1.3 equiv.) + **101** → **102**, racemic mixture of diastereoisomers, $C_{22}H_{24}O_6$ 384.42 g mol^{-1}

A reaction vial was charged with a stirring bar, $Pd(PPh_3)_2Cl_2$ (32.3 mg, 0.046 mmol, 3 mol %) and CuI (17.5 mg, 0.092 mmol, 5 mol %), and then evacuated and back-filled with argon using standard Schlenk technique. A solution of iodoveratrole **109** (631.6 mg, 2.392 mmol, 1.3 equiv.) in freshly distilled *i*-Pr_2NH (2.5 mL) under argon was added *via* syringe and the mixture was stirred for 20 min at room temperature. This was followed by the dropwise addition of epoxy ether **101** (racemic mixture of diastereoisomers, 456.8 mg, 1.84 mmol, 1.00 equiv.) as a solution in *i*-Pr_2NH (4.0 mL) *via* syringe, and stirring was continued for 10 h while being kept away from light.
Then, $CHCl_3$ (approx. 30 mL) was added, the solution was concentrated and flash column chromatography was performed (50 g silica, flow rate 40 mL / min, EtOAc / LP, 30 : 70 to 50 : 50 in 60 min) to afford the title compound **102** as a racemic mixture of diastereoisomers.

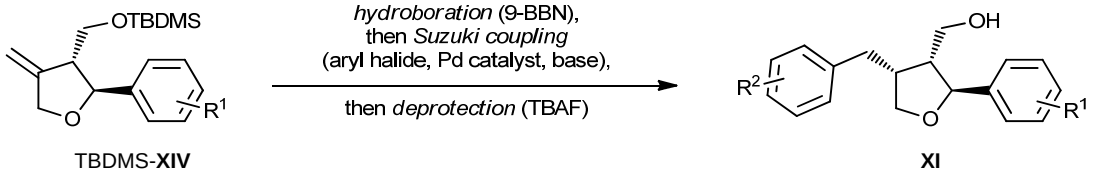
Yield: 587.5 mg, 83 %
Appearance: light-brown oil
***R*$_f$ (silica)**: 0.41 (EtOAc / LP, 1 : 1)

^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ 2.70 – 2.84 (m, 2H, C3-CH_2), 3.18 – 3.30 (m, 1H, H3), 3.84 (s, 3H, Ar-OCH_3), 3.86 (s, 6H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.13 – 4.61 (m, 3H, 2 x H5, H2), 6.73 – 7.06 (m, 6H, Ar-H). minor isomer: δ 2.63 (dd, ^2J = 4.9 Hz, ^3J = 2.7 Hz, 1H, C3-CH), 2.70 – 2.84 (m, 1H, C3-CH), 3.18 – 3.30 (m, 1H, H3), 3.67 (d, ^3J = 4.7 Hz, 1H, H2), 3.84 (s, 3H, Ar-OCH_3), 3.86 (s, 6H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.13 – 4.61 (m, 2H, H5), 6.73 – 7.06 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$) major isomer: δ 45.4 (t, C3-C), 54.2 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 56.9 (t, C5), 79.4 (d, C2), 83.3 (s, C4≡C*), 86.6 (s, C4*), 110.4 (d, C2'), 110.9 (d, C2''*), 111.0 (d, C5'*), 114.5 (d, C5''*), 114.8 (s, C1''), 120.4 (d, C6'), 125.2 (d, C6''), 129.7 (s, C1'), 148.6 (s, C3''*), 149.2 (s, C4'*), 149.3 (s, C3'*), 149.6 (s, C4''*). minor isomer: δ 44.4 (t, C3-C), 55.1 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 57.0 (t, C5), 81.6 (d, C2), 83.4 (s, C4≡C*), 86.5 (s, C4*), 110.1 (d, C2'), 110.9 (d, C2''*), 111.1 (d, C5'), 114.6 (d, C5''*), 114.7 (s, C1''), 120.0 (d, C6'), 125.2 (d, C6''), 129.9 (s, C1'), 148.6 (s, C3''*), 149.3 (s, C4'*), 149.3 (s, C3'*), 149.7 (s, C4''*).

D.3 **Sequence Reaction to 3-(Hydroxymethyl)tetrahydrofuran-type Lignans**

D.3.1 *General Outline* for 3-(Hydroxymethyl)tetrahydrofuran-type Lignans



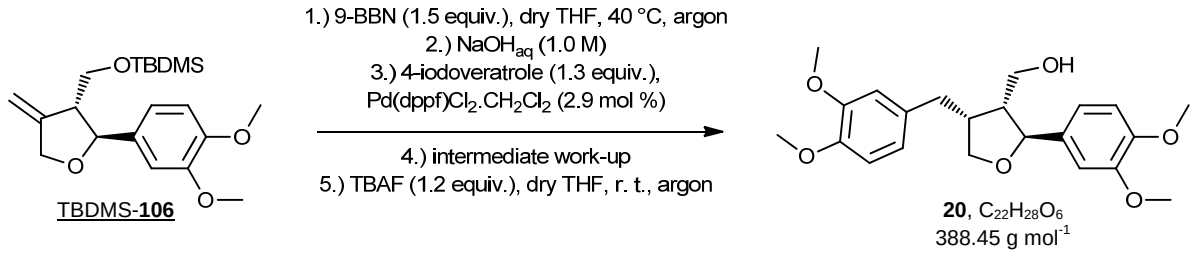
TBDMS-**XIV** **XI**

In this section, crude starting material TBDMS-**XIV** from the previous silyl protection (section D.2.5, page 143) was used. Molar amounts of TBDMS-**XIV** are thus based on complete-conversion calculations in the protection step. However, masses of TBDMS-**XIV** correspond to the actual gross weight of starting material as used. Yields are calculated over all four steps (protection, hydroboration, coupling and deprotection).

All compounds of generic structure **XI** in this section were prepared according to the *General Outline* above, and are arranged such that compounds with the same R^1 are grouped together. However, certain variations exist with respect to the experimental details, and a single general procedure is therefore not readily stated in more detail. Thus, for the ***Preparation*** of any particular compound, the experimental details are either given in full, or the reader is referred to an analogous procedure already described for a compound in this section. Generally, reaction progress was monitored by TLC and the reaction was terminated when complete or when no further conversion was observed.

Details for ***Work-up and purification*** are given for each case individually to afford compounds of structure **XI**.

D.3.2 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methanol (dimethyllariciresinol, leoligin alcohol, **20**)



TBDMS-**106** **20**, $C_{22}H_{28}O_6$, 388.45 g mol^{-1}

Preparation: a reaction vessel was charged with a stirring bar and crude starting material TBDMS-**106** (2.51 g, 6.88 mmol, 1.0 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. A solution of 9-BBN (0.5 M in THF, 20.7 mL, 10.3 mmol, 1.5 equiv.) was added *via* syringe, the reaction was stirred for 16.5 h at 40 °C and then allowed to cool to room temperature. Following this, a degassed aqueous solution of NaOH (2M, 20 mL) was added cautiously and stirring was continued for another 15 min. 4-Iodoveratrole **109** (2.36 g, 8.95 mmol, 1.30 equiv.) and $Pd(dppf)Cl_2.CH_2Cl_2$ (161 mg, 0.198 mmol, 2.9 mol %) were then added, and the resulting biphasic mixture was stirred vigorously at room temperature for 25 h. Et_2O (200 mL) and brine (50 mL) were

then added, the layers were separated, the aqueous phase was extracted with Et_2O (4 x 50 mL), the combined organic phases were dried with Na_2SO_4 and filtered into a new reaction vessel. From there, the solvent was evaporated, a stirring bar was added to the residue and the vessel was evacuated and back-filled with argon. For deprotection, a solution of TBAF (1.0 M in THF, 8.25 mL, 8.25 mmol, 1.2 equiv.) was added *via* syringe and the mixture was finally stirred for 18 h at room temperature.

***Work-up and purification**:* Et_2O (200 mL) and brine (50 mL) was added, the layers were separated and the aqueous phase was extracted with Et_2O (4 x 50 mL) and EtOAc (2 x 50 mL). The combined organic phases were dried with Na_2SO_4, filtered and the solvents were evaporated. Flash column chromatography of the entire crude material in two sequential runs (first run: 90 g silica with 9 g pre-column, flow rate 40 mL / min, EtOAc / LP, 30 : 70 for 3 min, then to 100 : 0 in 60 min; second run: 90 g silica, flow rate 40 mL / min, EtOAc / LP, 45 : 55 to 85 : 15 in 60 min) afforded the title compound **20.**

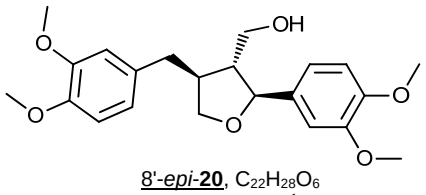
Dimethyllariciresinol is a literature-known natural compound.[279, 324]

Yield:	1.04 g, 39 % (over 4 steps from unprotected alcohol **106**)
Appearance:	slightly colored oil
R_f **(silica)**:	0.43 (EtOAc)
$[\alpha]_D^{20}$:	+19.2 (c 1.45, MeOH); lit.[279] $[\alpha]_D^{25}$: +19.4 (c 0.6, $CHCl_3$)
LC-HRMS (ESI):	calculated for $M+Na^+$: 411.1778, found: 411.1783, Δ: 1.22 ppm
$(\log P)_{calc}$:	3.18 ± 0.56

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52 (bs, 1H, OH), 2.42 (quint, ^3J = 6.9 Hz, 1H, H3), 2.56 (dd, ^2J = 12.7 Hz, ^3J = 10.4 Hz, 1H, C4-CH), 2.66 – 2.85 (m, 1H, H4), 2.94 (dd, ^2J = 12.8 Hz, ^3J = 4.7 Hz, 1H, C4-CH), 3.73 – 3.98 (m, 2H, C3-CH_2), 3.76 (dd, ^2J = 8.5 Hz, ^3J = 5.9 Hz, 1H, H5), 3.87 (s, 9H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.07 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 4.81 (d, ^3J = 6.5 Hz, 1H, H2), 6.70 – 6.81 (m, 3H, Ar-H), 6.81 – 6.91 (m, 3H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.4 (t, C4-C), 42.5 (d, C4), 52.7 (d, C3), 56.1 (q, 4 x Ar-OCH_3), 61.1 (t, C3-C), 73.1 (t, C5), 82.9 (d, C2), 109.1 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.6 (d, C6''), 133.1 (s, C1''), 135.5 (s, C1'), 147.6 (s, C4''), 148.5 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3').

D.3.3 ((2*S*,3*R*,4*S*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methanol (8'-*epi*-dimethyllariciresinol, 8'-*epi*-**20**)[r]



8'-*epi*-**20**, $C_{22}H_{28}O_6$
388.45 g mol^{-1}

Preparation: this compound was a byproduct following the ***Preparation*** of **20** (section D.3.2, page 161), which contained approximately 4 % of 8'-*epi*-**20**.

Purification: for isolation of this minor isomer from **20** (277 mg), three-fold preparative HPLC (flow rate 20.0 mL / min, MeOH / water, 42 : 58 to 48 : 52 in 70 min) was applied, collecting a minor fraction (enriched with 8'-*epi*-**20**) in each HPLC run, and resubmitting the major fraction (containing mainly **20**) to the next. Lastly, the three 8'-*epi*-**20**-enriched fractions were combined and finally purified again by preparative HPLC (flow rate 21.2 mL / min, MeCN / water, 25 : 75 to 35 : 65 in 60 min) to afford the title compound 8'-*epi*-**20**.

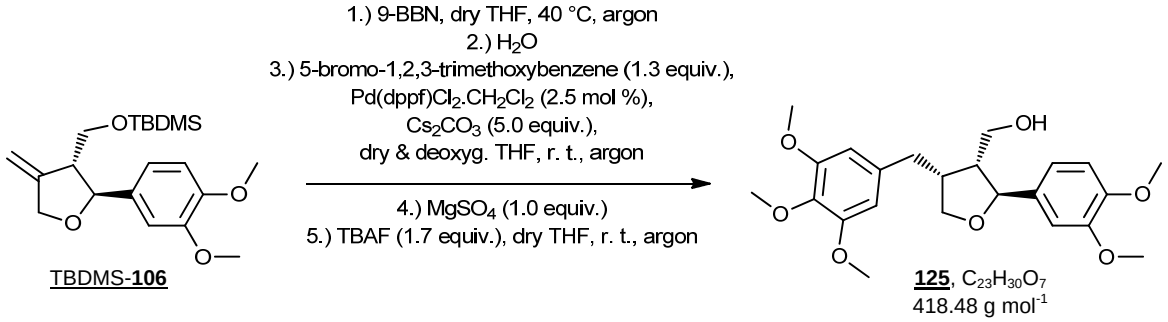
Yield:	4.6 mg, 1.7 % (with respect to the amount of material used for this isolation procedure)
Appearance:	colorless oil
R_f (silica):	0.45 (EtOAc)
$[\alpha]_D^{25}$:	-12.7 (c 0.32, MeOH)
LC-HRMS (ESI):	calculated for $M+Na^+$: 411.1784, found: 411.1812, Δ: 6.91 ppm
(log *P*)$_{calc}$:	3.18 ± 0.56

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (bs, 1H, OH), 2.01 (quint, ^3J = 6.6 Hz, 1H, H3), 2.51 (sext, ^3J = 7.0 Hz, 1H, H4), 2.71 (dd, ^2J = 13.6 Hz, ^3J = 8.6 Hz, 1H, C4-CH), 2.81 (dd, ^2J = 13.8 Hz, ^3J = 6.9 Hz, 1H, C4-CH), 3.65 (d, ^3J = 5.5 Hz, 2H, C3-CH_2), 3.84 – 3.89 (m, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.86 (s, 3H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 3.91 (s, 3H, Ar-OCH_3), 3.94 – 4.00 (m, 1H, H5), 4.63 (d, ^3J = 7.9 Hz, 1H, H2), 6.67 – 6.74 (m, 2H, H2'', H6''), 6.79 (d, ^3J = 8.1 Hz, 1H, H5''), 6.84 (d, ^3J = 8.1 Hz, 1H, H5'), 6.89 – 6.97 (m, 2H, H2', H6').

^{13}C NMR (100 MHz, $CDCl_3$): δ 39.5 (t, C4-C), 44.3 (d, C4), 55.6 (d, C3), 55.99 (q, Ar'-OCH_3), 56.01 (q, Ar'-OCH_3), 56.08 (q, Ar'-OCH_3), 56.11 (q, Ar'-OCH_3), 63.1 (t, C3-C), 73.1 (t, C5), 84.2 (d, C2), 109.4 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.1 (d, C2''*), 118.6 (d, C6'), 120.8 (d, C6''), 132.9 (s, C1''), 134.8 (s, C1'), 147.7 (s, C4''), 148.7 (s, C4'), 149.1 (s, C3''), 149.3 (s, C3').

[r] Labeling as 8'-epimer in agreement with lignan nomenclature as described in **Figure 1**, section A.1.1, page 3.

D.3.4 ((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(3,4,5-trimethoxybenzyl)tetrahydrofuran-3-yl)methanol (**125**)



TBDMS-**106** — **125**, $C_{23}H_{30}O_7$, 418.48 g mol^{-1}

***Preparation**:* a reaction vessel was charged with a stirring bar and crude starting material TBDMS-**106** (658.7 mg, 1.807 mmol), and then evacuated and back-filled with argon using standard Schlenk technique. A solution of 9-BBN (0.5 M in THF, 5.42 mL, 2.71 mmol) was added *via* syringe, the reaction stirred for 35 h at 40 °C and then allowed to cool to room temperature. Water (33 µL, 1.8 mmol) was subsequently added and stirring was continued for 1 h to decompose excess 9-BBN.

This mixture was then purged by bubbling argon into the solution through a needle, and dry and deoxygenated THF was added to produce a total volume of 7.0 mL, i.e. a 0.258 M solution of borylated intermediate, thus allowing the use of aliquots for subsequent coupling.

An aliquot (0.60 mL, 0.16 mmol, 1.0 equiv.) of this solution was transferred *via* syringe to a separate vessel which had been charged with a stirring bar, 5-bromo-1,2,3-trimethoxybenzene (49.8 mg, 0.202 mmol, 1.3 equiv.), Pd(dppf)Cl_2.CH_2Cl_2 (3.2 mg, 3.9 µmol, 2.5 mol %) and Cs_2CO_3 (253 mg, 0.775 mmol, 5.0 equiv.) under argon and was stirred for 37 h at room temperature. Following this, $MgSO_4$ (19 mg, 0.16 mmol, 1.0 equiv.) was added and stirring was continued for 2 h to remove residual water. For deprotection, a solution of TBAF (1.0 M in THF, 0.26 mL, 0.26 mmol, 1.7 equiv.) was added *via* syringe and the mixture was finally stirred for 12 h at room temperature.

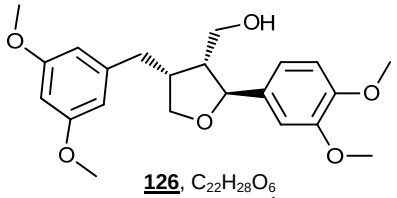
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 30 : 70 to 100 : 0 in 50 min), followed by preparative HPLC (flow rate 20.0 mL / min, MeOH / water, 45 : 55 to 55 : 45 in 60 min) afforded the title compound **125**.

Yield:	26.7 mg, 41 % (over 4 steps from unprotected alcohol **106**)
Appearance:	colorless oil
R_f (silica):	0.41 (EtOAc)
$[\alpha]_D^{23}$:	+15.1 (c 1.31, *i*-PrOH)
LC-HRMS (APCI):	calculated for M+Na^+: 441.1884, found: 441.1893, Δ: 2.04 ppm
(log *P*)$_{calc}$:	2.88 ± 0.58

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60 (bs, 1H, OH), 2.36 – 2.63 (m, 2H, H3, C4-CH), 2.66 – 2.85 (m, 1H, H4), 2.95 (dd, ^2J = 12.8 Hz, ^3J = 4.5 Hz, 1H, C4-CH), 3.72 – 3.99 (m, 3H, C3-CH_2, H5), 3.83 (s, 3H, C4''-OCH_3), 3.84 (s, 6H, C3''-OCH_3, C5''-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 3.89 (s, 3H, Ar'-OCH_3), 4.07 (dd, ^2J = 8.5 Hz, ^3J = 6.3 Hz, 1H, H5), 4.81 (d, ^3J = 6.7 Hz, 1H, H2), 6.41 (s, 2H, H2'', H6''), 6.79 – 6.92 (m, 3H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 34.1 (t, C4-C), 42.4 (d, C4), 52.7 (d, C3), 56.0 (q, 3 x Ar'-OCH_3), 56.2 (q, C3''-OCH_3, C5''-OCH_3), 61.0 (t, C3-C), 61.0 (q, C4''-OCH_3), 72.9 (t, C5), 82.8 (d, C2), 105.7 (d, C2'', C6''), 109.1 (d, C2'), 111.1 (d, C5'), 118.1 (d, C6'), 135.5 (s, C1'), 136.3 (s, C1''), 136.5 (s, C4''), 148.6 (s, C4'), 149.2 (s, C3'), 153.3 (s, C3'', C5'').

D.3.5 ((2*S*,3*R*,4*R*)-4-(3,5-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methanol (**126**)



126, $C_{22}H_{28}O_6$
388.45 g mol^{-1}

***Preparation**:* analogous to **125** (section D.3.4, page 164), using 1-bromo-3,5-dimethoxybenzene (43.7 mg, 0.202 mmol, 1.3 equiv.) as aryl halide coupling partner.

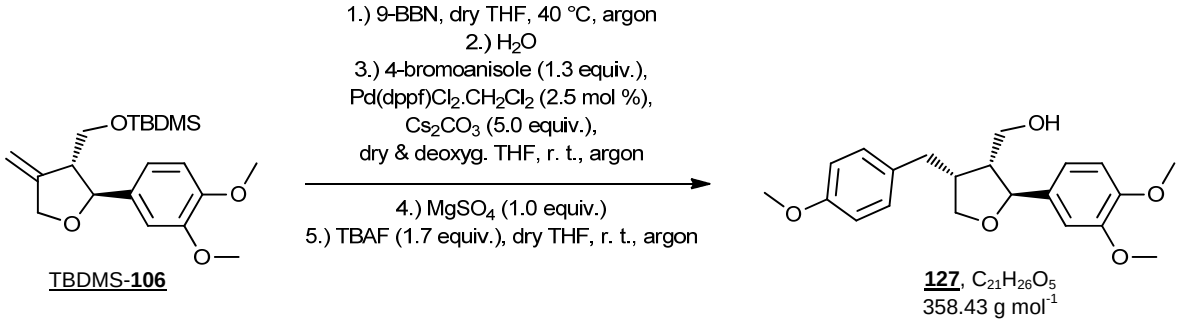
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 25 : 75 to 75 : 25 in 40 min) afforded the title compound **126**.

Yield:	35.1 mg, 58 % (over 4 steps from unprotected alcohol **106**)
Appearance:	brown oil
R_f (silica):	0.53 (EtOAc)
$[\alpha]_D^{23}$:	+13.6 (c 1.69, *i*-PrOH)
LC-HRMS (APCI):	calculated for M+Na^+: 411.1778, found: 411.1756, Δ: -5.35 ppm
(log *P*)$_{calc}$:	3.15 ± 0.56

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.67 (bs, 1H, OH), 2.41 (quint, ^3J = 6.8 Hz, 1H, H3), 2.55 (dd, ^2J = 12.7 Hz, ^3J = 10.1 Hz, 1H), 2.67 – 2.86 (m, 1H, H4), 2.92 (dd, ^2J = 12.7 Hz, ^3J = 4.8 Hz, 1H, C4-CH), 3.64 – 3.99 (m, 3H, C3-CH_2, H5), 3.77 (s, 6H, C3''-OCH_3, C5''-OCH_3), 3.86 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.07 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 4.81 (d, ^3J = 6.4 Hz, 1H, H2), 6.29 – 6.39 (m, 3H, Ar''-H), 6.78 – 6.95 (m, 3H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 34.0 (t, C4-C), 42.1 (d, C4), 52.6 (d, C3), 55.4 (q, C3''-OCH_3, C5''-OCH_3), 56.00 (q, Ar'-OCH_3), 56.04 (q, Ar'-OCH_3), 61.0 (t, C3-C), 73.1 (t, C5), 82.9 (d, C2), 98.1 (d, C4''), 106.9 (d, C2'', C6''), 109.0 (d, C2'), 111.1 (d, C5'), 118.1 (d, C6'), 135.5 (s, C1'), 143.0 (s, C1''), 148.5 (s, C4'), 149.2 (s, C3'), 161.0 (s, C3'', C5'').

D.3.6 ((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(4-methoxybenzyl)tetrahydrofuran-3-yl)methanol (**127**)



***Preparation**:* a reaction vessel was charged with a stirring bar and crude starting material TBDMS-**106** (715.9 mg, 1.964 mmol), and then evacuated and back-filled with argon using standard Schlenk technique. A solution of 9-BBN (0.5 M in THF, 5.89 mL, 2.95 mmol) was added *via* syringe, the reaction was stirred for 21 h at 40 °C and then allowed to cool to room temperature. Water (35 µL, 2.0 mmol) was subsequently added and stirring was continued for 2 h to decompose excess 9-BBN.

This mixture was then purged by bubbling argon into the solution through a needle, and dry and deoxygenated THF was added to produce a total volume of 10.0 mL, i.e. a 0.196 M solution of borylated intermediate, thus allowing the use of aliquots for subsequent coupling.

An aliquot (0.97 mL, 0.19 mmol, 1.0 equiv.) of this solution was transferred *via* syringe to a separate vessel which had been charged with a stirring bar, 4-bromoanisole (46.2 mg, 0.247 mmol, 1.3 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (3.9 mg, 4.8 µmol, 2.5 mol %) and Cs_2CO_3 (310 mg, 0.950 mmol, 5.0 equiv.) under argon and was stirred for 36 h at room temperature. Following this, $MgSO_4$ (23 mg, 0.19 mmol, 1.0 equiv.) was added and stirring was continued for 1.5 h to remove residual water. For deprotection, a solution of TBAF (1.0 M in THF, 0.32 mL, 0.32 mmol, 1.7 equiv.) was added *via* syringe and the mixture was finally stirred for 32 h at room temperature.

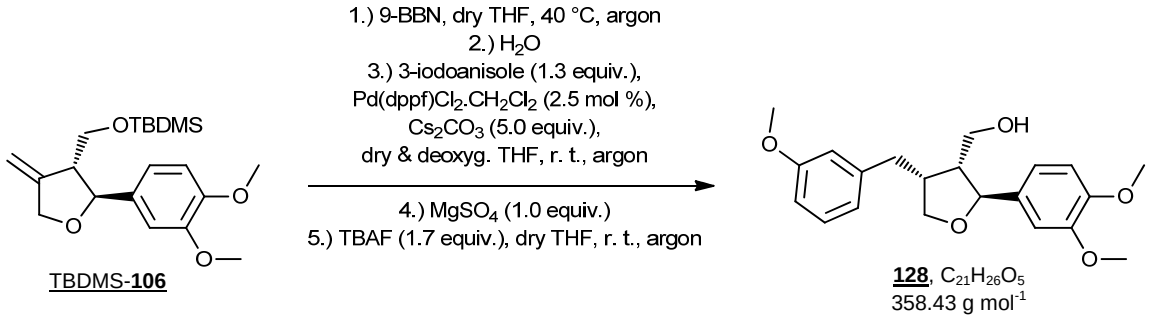
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with EtOAc (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 30 : 70 to 80 : 20 in 30 min) afforded the title compound **127**.

Yield:	41.7 mg, 61 % (over 4 steps from unprotected alcohol **106**)
Appearance:	light-brown oil
R_f (silica):	0.66 (EtOAc)
$[\alpha]_D^{25}$:	+13.0 (c 4.17, MeOH)
LC-HRMS (ESI):	calculated for $M+Na^+$: 381.1678, found: 381.1689, Δ: 2.89 ppm
$(\log P)_{calc}$:	3.36 ± 0.55

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.69 (t, ^3J = 4.8 Hz, 1H, OH), 2.39 (quint, ^3J = 6.7 Hz, 1H, H3), 2.55 (dd, ^2J = 12.6 Hz, ^3J = 10.1 Hz, 1H, C4-CH), 2.63 – 2.83 (m, 1H, H4), 2.90 (dd, ^2J = 12.7 Hz, ^3J = 4.7 Hz, 1H, C4-CH), 3.67 – 3.96 (m, 3H, C3-CH_2, H5), 3.78 (s, 3H, C4''-OCH_3), 3.86 (s, 3H, Ar'-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 4.05 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 4.82 (d, ^3J = 6.3 Hz, 1H, H2), 6.77 – 6.93 (m, 5H, 3 x Ar'-H, H3'', H5''), 7.11 (d, ^3J = 8.6 Hz, 2H, H2'', H6'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 32.8 (t, C4-C), 42.4 (d, C4), 52.5 (d, C3), 55.3 (q, C4''-OCH_3), 55.97 (q, Ar'-OCH_3), 56.02 (q, Ar'-OCH_3), 61.0 (t, C3-C), 73.0 (t, C5), 82.9 (d, C2), 109.0 (d, C2'), 111.0 (d, C5'), 114.1 (d, C3'', C5''), 118.1 (d, C6'), 129.6 (d, C2'', C6''), 132.5 (s, C1''), 135.6 (s, C1'), 148.4 (s, C4'), 149.1 (s, C3'), 158.1 (s, C4'').

D.3.7 ((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(3-methoxybenzyl)tetrahydrofuran-3-yl)methanol (**128**)



TBDMS-**106** → **128**, $C_{21}H_{26}O_5$, 358.43 g mol^{-1}

***Preparation**:* a reaction vessel was charged with a stirring bar and crude starting material TBDMS-**106** (843.2 mg, 2.313 mmol), and then evacuated and back-filled with argon using standard Schlenk technique. A solution of 9-BBN (0.5 M in THF, 6.94 mL, 3.47 mmol) was added *via* syringe, the reaction was stirred for 35 h at 40 °C and then allowed to cool to room temperature. Water (42 µL, 2.3 mmol) was subsequently added and stirring was continued for 2 h to decompose excess 9-BBN.

This mixture was then purged by bubbling argon into the solution through a needle, and dry and deoxygenated THF was added to produce a total volume of 13.0 mL, i.e. a 0.178 M solution of borylated intermediate, thus allowing the use of aliquots for subsequent coupling.

An aliquot (1.07 mL, 0.19 mmol, 1.0 equiv.) of this solution was transferred *via* syringe to a separate vessel which had been charged with a stirring bar, 3-iodoanisole (57.8 mg, 0.247 mmol, 1.3 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (3.9 mg, 4.8 µmol, 2.5 mol %) and Cs_2CO_3 (310 mg, 0.950 mmol, 5.0 equiv.) under argon and was stirred for 50 h at room temperature. Following this, $MgSO_4$ (23 mg, 0.19 mmol, 1.0 equiv.) was added and stirring was continued for 1.5 h to remove residual water. For deprotection, a solution of TBAF (1.0 M in THF, 0.32 mL, 0.32 mmol, 1.7 equiv.) was added *via* syringe and the mixture was finally stirred for 24 h at room temperature.

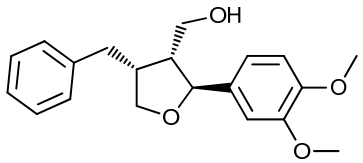
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 15 : 85 to 85 : 15 in 40 min) afforded the title compound **128**.

Yield: 52.6 mg, 77 % (over 4 steps from unprotected alcohol **106**)
Appearance: pale brown oil
R_f (silica): 0.58 (EtOAc)
$[\alpha]_D^{25}$: +19.4 (c 3.69, MeOH)
LC-HRMS (ESI): calculated for M+Na^+: 381.1672, found: 381.1681, Δ: 2.36 ppm
(log *P*)$_{calc}$: 3.36 ± 0.55

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.87 (bs, 1H, OH), 2.40 (quint, ^3J = 6.8 Hz, 1H, H3), 2.58 (dd, ^2J = 12.6 Hz, ^3J = 10.3 Hz, 1H, C4-CH), 2.66 – 2.86 (m, 1H, H4), 2.94 (dd, ^2J = 12.7 Hz, ^3J = 4.7 Hz, 1H, C4-CH), 3.68 – 3.94 (m, 3H, C3-CH_2, H5), 3.78 (s, 3H, C3''-OCH_3), 3.85 (s, 3H, Ar'-OCH_3), 3.86 (s, 3H, Ar'-OCH_3), 4.06 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 4.82 (d, ^3J = 6.3 Hz, 1H, H2), 6.70 – 6.91 (m, 6H, 3 x Ar'-H, 3 x Ar''-H), 7.15 – 7.25 (m, 1H, H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.6 (t, C4-C), 42.1 (d, C4), 52.5 (d, C3), 55.2 (q, C3''-OCH_3), 55.9 (q, Ar'-OCH_3), 56.0 (q, Ar'-OCH_3), 60.8 (t, C3-C), 73.0 (t, C5), 82.8 (d, C2), 108.9 (d, C2'), 111.0 (d, C5'*), 111.4 (d, C4''*), 114.6 (d, C2''), 118.1 (d, C6'), 121.1 (d, C6''), 129.6 (d, C5''), 135.5 (s, C1'), 142.2 (s, C1''), 148.4 (s, C4'), 149.1 (s, C3'), 159.8 (s, C3'').

D.3.8 ((2*S*,3*R*,4*R*)-4-Benzyl-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methanol (**129**)



129, $C_{20}H_{24}O_4$
328.40 g mol^{-1}

***Preparation**:* analogous to **127** (section D.3.6, page 166), using bromobenzene (38.8 mg, 0.247 mmol, 1.3 equiv.) as aryl halide coupling partner.

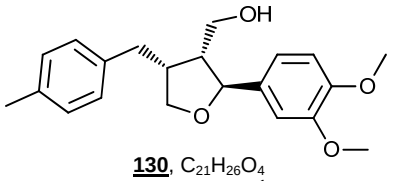
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc in LP, 20 : 80 to 70 : 30 in 30 min) afforded the title compound **129**.

Yield: 39.3 mg, 63 % (over 4 steps from unprotected alcohol **106**)
Appearance: light-brown oil
R_f (silica): 0.45 (EtOAc / LP, 2 : 1)
$[\alpha]_D^{23}$: +18.3 (c 3.80, MeOH)
LC-HRMS (ESI): calculated for M+Na^+: 351.1567, found: 351.1577, Δ: 2.85 ppm
(log *P*)$_{calc}$: 3.44 ± 0.54

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.70 (bs, 1H, OH), 2.40 (quint, ^3J = 6.8 Hz, 1H, H3), 2.61 (dd, ^2J = 12.5 Hz, ^3J = 10.2 Hz, 1H, C4-CH), 2.67 – 2.87 (m, 1H, H4), 2.96 (dd, ^2J = 12.6 Hz, ^3J = 4.6 Hz, 1H, C4-CH), 3.69 – 3.98 (m, 3H, C3-CH_2, H5), 3.85 (s, 3H, Ar'-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 4.05 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 4.83 (d, ^3J = 6.3 Hz, 1H, H2), 6.77 – 6.94 (m, 3H, Ar'-H), 7.14 – 7.35 (m, 5H, Ar''-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.7 (t, C4-C), 42.2 (d, C4), 52.5 (d, C3), 55.98 (q, Ar'-OCH_3), 56.02 (q, Ar'-OCH_3), 61.0 (t, C3-C), 73.0 (t, C5), 82.9 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 118.1 (d, C6'), 126.3 (d, C4''), 128.7 (d, C2''*, C6''*), 128.7 (d, C3''*, C5''*), 135.6 (s, C1'), 140.5 (s, C1''), 148.4 (s, C4'), 149.1 (s, C3').

D.3.9 ((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(4-methylbenzyl)tetrahydrofuran-3-yl)methanol (**130**)



130, $C_{21}H_{26}O_4$
342.43 g mol^{-1}

***Preparation**:* analogous to **127** (section D.3.6, page 166), using 4-bromotoluene (42.2 mg, 0.247 mmol, 1.3 equiv.) as aryl halide coupling partner.

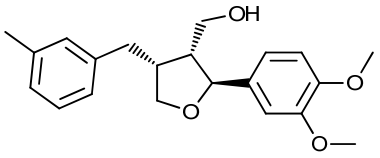
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc in LP, 20 : 80 to 70 : 30 in 30 min) afforded the title compound **130**.

Yield:	43.2 mg, 66 % (over 4 steps from unprotected alcohol **106**)
Appearance:	light-brown oil
R_f (silica):	0.47 (EtOAc / LP, 2 : 1)
$[\alpha]_D^{23}$:	+15.0 (c 4.34, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 365.1723, found: 365.1727, Δ: 1.10 ppm
$(\log P)_{calc}$:	3.90 ± 0.54

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72 (t, ^3J = 5.0 Hz, 1H, OH), 2.31 (s, 3H, C4''-CH_3), 2.39 (quint, ^3J = 6.7 Hz, 1H, H3), 2.57 (dd, ^2J = 12.6 Hz, ^3J = 10.0 Hz, 1H, C4-CH), 2.65 – 2.85 (m, 1H, H4), 2.91 (dd, ^2J = 12.6 Hz, ^3J = 4.8 Hz, 1H, C4-CH), 3.66 – 3.98 (m, 3H, C3-CH_2, H5), 3.85 (s, 3H, Ar'-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 4.05 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 4.82 (d, ^3J = 6.3 Hz, 1H, H2), 6.77 – 6.90 (m, 3H, Ar'-H), 7.02 – 7.13 (m, 4H, Ar''-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.1 (q, C4''-CH_3), 33.2 (t, C4-C), 42.3 (d, C4), 52.5 (d, C3), 55.9 (q, Ar'-OCH_3), 56.0 (q, Ar'-OCH_3), 60.9 (t, C3-C), 73.1 (t, C5), 82.9 (d, C2), 109.0 (d, C2'), 111.0 (d, C5'), 118.1 (d, C6'), 128.6 (d, C2'', C6''), 129.3 (d, C3'', C5''), 135.6 (s, C1'), 135.8 (s, C4''), 137.4 (s, C1''), 148.4 (s, C4'), 149.1 (s, C3').

D.3.10 ((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(3-methylbenzyl)tetrahydrofuran-3-yl)methanol (**131**)



131, $C_{21}H_{26}O_4$
342.43 g mol^{-1}

***Preparation**:* analogous to **125** (section D.3.4, page 164), using 3-bromotoluene (34.5 mg, 0.202 mmol, 1.3 equiv.) as aryl halide coupling partner.

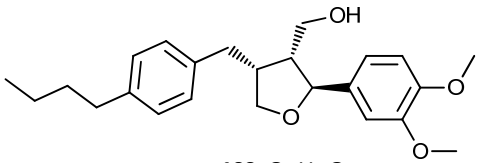
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc in LP, 20 : 80 to 70 : 30 in 45 min) afforded the title compound **131**.

Yield:	31.2 mg, 59 % (over 4 steps from unprotected alcohol **106**)
Appearance:	slightly colored oil
R_f (silica):	0.59 (EtOAc)
$[\alpha]_D^{23}$:	+19.2 (c 1.55, MeOH)
LC-HRMS (APCI):	calculated for M+Na$^+$: 365.1729, found: 365.1755, Δ: 7.12 ppm
(log *P*)$_{calc}$:	3.90 ± 0.54

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.57 (bs, 1H, OH), 2.33 (s, 3H, C3''-CH_3), 2.41 (quint, ^3J = 6.8 Hz, 1H, H3), 2.58 (dd, ^2J = 12.6 Hz, ^3J = 10.1 Hz, 1H, C4-CH), 2.67 – 2.86 (m, 1H, H4), 2.93 (dd, ^2J = 12.6 Hz, ^3J = 4.8 Hz, 1H, C4-CH), 3.68 – 3.99 (m, 3H, C3-CH_2, H5), 3.86 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.06 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 4.83 (d, ^3J = 6.4 Hz, 1H, H2), 6.77 – 6.92 (m, 3H, Ar'-H), 6.93 – 7.08 (m, 3H, H2'', H4'', H6''), 7.11 – 7.24 (m, 1H, H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.5 (q, C3''-$\underline{C}H_3$), 33.6 (t, C4-$\underline{C}$), 42.3 (d, C4), 52.6 (d, C3), 56.00 (q, Ar'-OCH_3), 56.02 (q, Ar'-OCH_3), 61.1 (t, C3-$\underline{C}$), 73.1 (t, C5), 82.9 (d, C2), 109.1 (d, C2'), 111.1 (d, C5'), 118.1 (d, C6'), 125.7 (d, C6''), 127.1 (d, C4''), 128.6 (d, C5''), 129.6 (d, C2''), 135.6 (s, C1'), 138.3 (s, C3''), 140.5 (s, C1''), 148.5 (s, C4'), 149.2 (s, C3').

D.3.11 ((2*S*,3*R*,4*R*)-4-(4-Butylbenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methanol (**132**)



132, $C_{24}H_{32}O_4$
384.51 g mol^{-1}

***Preparation**:* analogous to **125** (section D.3.4, page 164), using 1-bromo-4-butylbenzene (42.9 mg, 0.202 mmol, 1.3 equiv.) as aryl halide coupling partner.

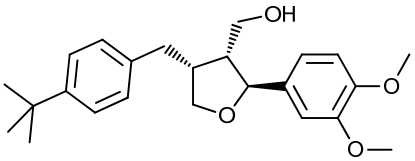
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc in LP, 20 : 80 to 70 : 30 in 40 min) afforded the title compound **132**.

Yield:	37.0 mg, 62 % (over 4 steps from unprotected alcohol **106**)
Appearance:	nearly colorless oil
R_f (silica):	0.62 (EtOAc)
$[\alpha]_D^{23}$:	+4.7 (c 1.88, *i*-PrOH)
LC-HRMS (APCI):	calculated for $M+Na^+$: 407.2193, found: 407.2194, Δ: 0.25 ppm
$(\log P)_{calc}$:	5.50 ± 0.54

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.92 (t, ^3J = 7.2 Hz, 3H, C4''-$CH_2CH_2CH_2CH_3$), 1.35 (sext, ^3J = 7.2 Hz, 2H, C4''-$CH_2CH_2CH_2CH_3$), 1.48 – 1.69 (m, 3H, C4''-$CH_2CH_2CH_2CH_3$), 2.40 (quint, ^3J = 6.7 Hz, 1H, H3), 2.50 – 2.65 (m, 3H, C4''-$CH_2CH_2CH_2CH_3$, C4-CH), 2.66 – 2.85 (m, 1H, H4), 2.92 (dd, ^2J = 12.6 Hz, ^3J = 4.8 Hz, 1H, C4-CH), 3.68 – 3.98 (m, 3H, C3-CH_2, H5), 3.86 (s, 3H, Ar'-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 4.06 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 4.83 (d, ^3J = 6.3 Hz, 1H, H2), 6.78 – 6.90 (m, 3H, Ar'-H), 7.00 – 7.14 (m, 4H, Ar''-H). OH not visible.

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (q, C4''-$CH_2CH_2CH_2CH_3$), 22.5 (t, C4''-$CH_2CH_2CH_2CH_3$), 33.3 (t, C4-C), 33.8 (t, C4''-$CH_2CH_2CH_2CH_3$), 35.3 (t, C4''-$CH_2CH_2CH_2CH_3$), 42.3 (d, C4), 52.6 (d, C3), 55.99 (q, Ar'-OCH_3), 56.02 (q, Ar'-OCH_3), 61.0 (t, C3-C), 73.1 (t, C5), 82.9 (d, C2), 109.1 (d, C2'), 111.1 (d, C5'), 118.1 (d, C6'), 128.6 (d, C2''*, C6''*), 128.7 (d, C3''*, C5''*), 135.7 (s, C1'), 137.6 (s, C1''), 140.9 (s, C4''), 148.5 (s, C4'), 149.2 (s, C3').

D.3.12 ((2*S*,3*R*,4*R*)-4-(4-(*tert*-Butyl)benzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methanol (**133**)



133, $C_{24}H_{32}O_4$
384.51 g mol^{-1}

***Preparation**:* analogous to **127** (section D.3.6, page 166), using 1-bromo-4-(*tert*-butyl)benzene (52.6 mg, 0.247 mmol, 1.3 equiv.) as aryl halide coupling partner.

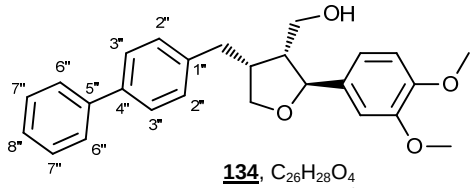
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc in LP, 20 : 80 to 70 : 30 in 30 min) afforded the title compound **133**.

Yield: 49.1 mg, 67 % (over 4 steps from unprotected alcohol **106**)
Appearance: light-brown oil
***R*$_f$ (silica)**: 0.76 (EtOAc)
[α]$_D^{25}$: +12.0 (c 4.91, MeOH)
LC-HRMS (ESI): calculated for M+Na$^+$: 407.2193, found: 407.2183, Δ: -2.46 ppm
(log *P*)$_{calc}$: 5.13 ± 0.55

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 9H, C4''-C(CH_3)$_3$), 1.68 (bs, 1H, OH), 2.40 (quint, ^3J = 6.7 Hz, 1H, H3), 2.59 (dd, ^2J = 12.5 Hz, ^3J = 9.8 Hz, 1H, C4-CH), 2.67 – 2.86 (m, 1H, H4), 2.92 (dd, ^2J = 12.6 Hz, ^3J = 4.8 Hz, 1H, C4-CH), 3.69 – 3.98 (m, 3H, C3-CH_2, H5), 3.86 (s, 3H, Ar'-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 4.08 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 4.83 (d, ^3J = 6.2 Hz, 1H, H2), 6.78 – 6.94 (m, 3H, Ar'-H), 7.12 (d, ^3J = 8.2 Hz, 2H, H2'', H6''), 7.31 (d, ^3J = 8.2 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 31.5 (q, C4''-C(<u>C</u>H_3)$_3$), 33.1 (t, C4-<u>C</u>), 34.5 (s, C4''-<u>C</u>(CH_3)$_3$), 42.2 (d, C4), 52.5 (d, C3), 56.00 (q, Ar'-OCH_3), 56.03 (q, Ar'-OCH_3), 61.0 (t, C3-<u>C</u>), 73.2 (t, C5), 82.9 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 118.1 (d, C6'), 125.5 (d, C3'', C5''), 128.4 (d, C2'', C6''), 135.7 (s, C1'), 137.4 (s, C1''), 148.4 (s, C4'), 149.1 (s, C3'; s, C4''; signal overlap).

D.3.13 ((2*S*,3*R*,4*R*)-4-([1,1'-Biphenyl]-4-ylmethyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methanol (**<u>134</u>**)



<u>134</u>, $C_{26}H_{28}O_4$
404.50 g mol^{-1}

***Preparation**:* analogous to **<u>127</u>** (section D.3.6, page 166), using 4-bromo-1,1'-biphenyl (57.6 mg, 0.247 mmol, 1.3 equiv.) as aryl halide coupling partner.

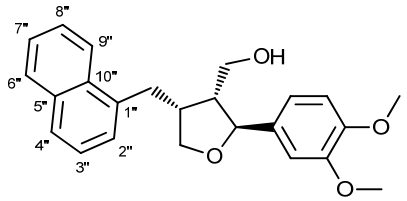
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc in LP, 20 : 80 to 95 : 5 in 45 min) afforded the title compound **<u>134</u>**.

Yield: 50.6 mg, 66 % (over 4 steps from unprotected alcohol **<u>106</u>**)
Appearance: colorless needles
Melting range: 155.0 – 160.5 °C
***R*$_f$ (silica)**: 0.18 (EtOAc / LP, 1 : 1)
[α]$_D^{23}$: -4.6 (c 3.62, $CHCl_3$)
LC-HRMS (ESI): calculated for M+Na$^+$: 427.1880, found: 427.1865, Δ: -3.51 ppm
(log *P*)$_{calc}$: 5.20 ± 0.57

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.68 (bs, 1H, OH), 2.43 (quint, ^3J = 6.8 Hz, 1H, H3), 2.66 (dd, ^2J = 12.4 Hz, ^3J = 10.3 Hz, 1H, C4-CH), 2.70 – 2.92 (m, 1H, H4), 3.00 (dd, ^2J = 12.5 Hz, ^3J = 4.3 Hz, 1H, C4-CH), 3.71 – 4.01 (m, 3H, C3-CH_2, H5), 3.86 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.10 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 4.85 (d, ^3J = 6.3 Hz, 1H, H2), 6.78 – 6.95 (m, 3H, Ar'-H), 7.22 – 7.62 (m, 9H, Ar''-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.3 (t, C4-C), 42.2 (d, C4), 52.5 (d, C3), 55.99 (q, Ar'-OCH_3), 56.04 (q, Ar'-OCH_3), 60.9 (t, C3-C), 73.0 (t, C5), 82.9 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 118.1 (d, C6'), 127.0 (d, C3''*), 127.2 (d, C8''), 127.3 (d, C6''*), 128.8 (d, C7''), 129.2 (d, C2''), 135.6 (s, C1'), 139.2 (s, C4''), 139.6 (s, C1''), 140.9 (s, C5''), 148.4 (s, C4'), 149.1 (s, C3').

D.3.14 ((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(naphthalen-1-ylmethyl)tetrahydrofuran-3-yl)methanol (**135**)



135, $C_{24}H_{26}O_4$
378.46 g mol^{-1}

***Preparation**:* analogous to **128** (section D.3.7, page 167), using 1-bromonaphthalene (51.1 mg, 0.247 mmol, 1.3 equiv.) as aryl halide coupling partner.

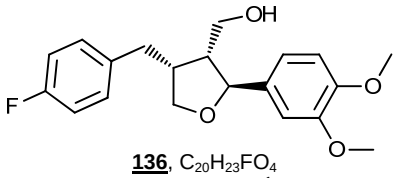
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography was performed (18 g silica, flow rate 20 mL / min, EtOAc in LP, 15 : 85 to 80 : 20 in 45 min), followed by re-crystallization from *i*-PrOH (11 mL). Therein, the hot solution was decanted from insoluble material, allowed to cool, and crystallization was then completed by storing at -25 °C. Removal of the mother liquor and rinsing with pentane (approximately 3 mL) afforded the title compound **135**.

Yield:	43.7 mg, 61 % (over 4 steps from unprotected alcohol **106**)
Appearance:	colorless hexagonal plates
Melting range:	163.5 – 166.5 °C
R_f (silica):	0.74 (EtOAc)
$[\alpha]_D^{20}$:	+39.5 (c 0.78, DMSO-d_6)
LC-HRMS (ESI):	calculated for M+Na^+: 401.1723, found: 401.1741, Δ: 4.49 ppm
(log *P*)$_{calc}$:	4.67 ± 0.54

^{1}H NMR (200 MHz, DMSO-d_6): δ 2.37 (quint, ^3J = 6.9 Hz, 1H, H3), 2.64 – 2.98 (m, 2H, H4, C4-CH), 3.48 – 3.90 (m, 4H, C3-CH, C3-CH*, C4-CH, H5), 3.73 (s, 6H, Ar'-OCH_3), 4.73 (d, ^3J = 7.4 Hz, 1H, H2), 4.89 (d, ^2J = 4.4 Hz, ^3J = 4.4 Hz, 1H, H5*), 6.76 – 6.98 (m, 3H, Ar'-H), 7.33 – 7.60 (m, 4H, H2'', H3'', H7'', H8''), 7.79 (d, ^3J = 7.3 Hz, 1H, H4''), 7.92 (m, 1H, H6''), 8.19 (m, 1H, H9''). OH not visible.

^{13}C NMR (50 MHz, DMSO-d_6): δ 29.6 (t, C4-C), 41.3 (d, C4), 53.0 (d, C3), 55.4 (q, Ar'-OCH_3), 55.5 (q, Ar'-OCH_3), 58.5 (t, C3-C), 71.7 (t, C5), 81.3 (d, C2), 109.5 (d, C2'), 111.5 (d, C5'), 117.9 (d, C6'), 123.8 (d, C9''*), 125.6 (d, C3''*), 125.7 (d, C7''*), 126.0 (d, C8''*), 126.6 (d, C4''*), 126.7 (d, C2''*), 128.7 (d, C6''*), 131.6 (s, C1''*), 133.6 (s, C5''*), 136.1 (s, C1'*), 137.0 (s, C10''*), 148.0 (s, C4'), 148.7 (s, C3').

D.3.15 ((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(4-fluorobenzyl)tetrahydrofuran-3-yl)methanol (**136**)



136, $C_{20}H_{23}FO_4$
346.39 g mol^{-1}

***Preparation**:* analogous to **127** (section D.3.6, page 166), using 1-bromo-4-fluorobenzene (43.2 mg, 0.247 mmol, 1.3 equiv.) as aryl halide coupling partner.

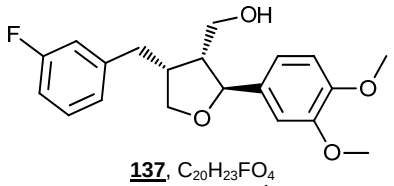
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 30 : 70 to 50 : 50 in 15 min, then to 85 : 15 in 5 min, then 85 : 15 isocratically) afforded the title compound **136**.

Yield:	40.2 mg, 61 % (over 4 steps from unprotected alcohol **106**)
Appearance:	light-brown oil
R_f (silica):	0.59 (EtOAc)
$[\alpha]_D^{25}$:	+18.5 (c 3.82, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 369.1473, found: 369.1475, Δ: 0.54 ppm
(log *P*)$_{calc}$:	3.49 ± 0.60

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.66 (bs, 1H, OH), 2.40 (quint, ^3J = 6.7 Hz, 1H, H3), 2.58 (dd, ^2J = 12.4 Hz, ^3J = 10.6 Hz, 1H, C4-CH), 2.62 – 2.82 (m, 1H, H4), 2.95 (dd, ^2J = 12.5 Hz, ^3J = 4.1 Hz, 1H, C4-CH), 3.71 (dd, ^2J = 8.5 Hz, ^3J = 6.1 Hz, 1H, H5), 3.75 – 3.96 (m, 2H, C3-CH_2), 3.86 (s, 3H, Ar'-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 4.04 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.82 (d, ^3J = 6.3 Hz, 1H, H2), 6.79 – 6.90 (m, 3H, Ar'-H), 6.91 – 7.04 (m, 2H, H3'', H5''), 7.08 – 7.20 (m, 2H, H2'', H6'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 32.8 (t, C4-C), 42.4 (d, C4), 52.5 (d, C3), 56.00 (q, Ar'-OCH_3), 56.04 (q, Ar'-OCH_3), 60.9 (t, C3-C), 72.8 (t, C5), 82.9 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 115.4 (dd, C3'', C5'', $^2J_{C\text{-}F}$ = 21.2 Hz), 118.1 (d, C6'), 130.1 (dd, C2'', C6'', $^3J_{C\text{-}F}$ = 7.8 Hz), 135.5 (s, C1'), 136.2 (d, C1'', $^4J_{C\text{-}F}$ = 3.2 Hz), 148.5 (s, C4'), 149.2 (s, C3'), 161.5 (d, C4'', $^1J_{C\text{-}F}$ = 244.2 Hz).

D.3.16 ((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(3-fluorobenzyl)tetrahydrofuran-3-yl)methanol (**137**)



137, $C_{20}H_{23}FO_4$
346.39 g mol^{-1}

***Preparation**:* analogous to **128** (section D.3.7, page 167), using 1-bromo-3-fluorobenzene (43.2 mg, 0.247 mmol, 1.3 equiv.) as aryl halide coupling partner.

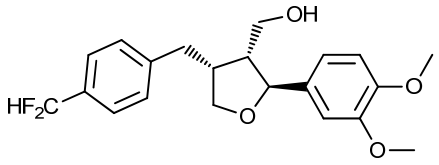
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 15 : 85 to 80 : 20 in 40 min) afforded the title compound **137**.

Yield:	50.9 mg, 77 % (over 4 steps from unprotected alcohol **106**)
Appearance:	colorless oil
R_f (silica):	0.61 (EtOAc)
$[\alpha]_D^{25}$:	+21.0 (c 2.22, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 369.1473, found: 369.1476, Δ: 0.81 ppm
(log *P*)$_{calc}$:	3.49 ± 0.60

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78 (bs, 1H, OH), 2.40 (quint, ^3J = 6.7 Hz, 1H, H3), 2.61 (dd, ^2J = 12.4 Hz, ^3J = 10.6 Hz, 1H, C4-CH), 2.64 – 2.85 (m, 1H, H4), 2.97 (dd, ^2J = 12.5 Hz, ^3J = 4.1 Hz, 1H, C4-CH), 3.71 (dd, ^2J = 8.5 Hz, ^3J = 6.2 Hz, 1H, H5), 3.76 – 3.90 (m, 2H, C3-CH_2), 3.86 (s, 3H, Ar'-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 4.05 (dd, ^2J = 8.5 Hz, ^3J = 6.3 Hz, 1H, H5), 4.81 (d, ^3J = 6.4 Hz, 1H, H2), 6.78 – 7.00 (m, 6H, 3 x Ar'-H, 3 x Ar''-H), 7.31 – 7.18 (m, 1H, H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.4 (td, C4-C, $^4J_{C\text{-}F}$ = 1.6 Hz), 42.1 (d, C4), 52.4 (d, C3), 55.98 (q, Ar'-OCH_3), 56.02 (q, Ar'-OCH_3), 60.8 (t, C3-C), 72.8 (t, C5), 82.8 (d, C2), 108.9 (d, C2'), 111.0 (d, C5'), 113.2 (dd, C4'', $^2J_{C\text{-}F}$ = 21.0 Hz), 115.6 (dd, C2'', $^2J_{C\text{-}F}$ = 21.0 Hz), 118.1 (d, C6'), 124.4 (dd, C6'', $^4J_{C\text{-}F}$ = 2.8 Hz), 130.1 (dd, C5'', $^3J_{C\text{-}F}$ = 8.4 Hz), 135.4 (s, C1'), 143.2 (d, C1'', $^3J_{C\text{-}F}$ = 7.2 Hz), 148.5 (s, C4'), 149.1 (s, C3'), 163.0 (d, C3'', $^1J_{C\text{-}F}$ = 245.9 Hz).

D.3.17 ((2*S*,3*R*,4*R*)-4-(4-(Difluoromethyl)benzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methanol (**138**)



138, $C_{21}H_{24}F_2O_4$
378.41 g mol^{-1}

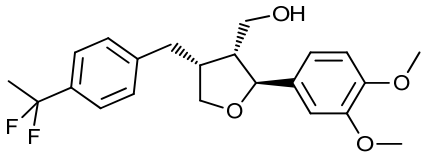
***Preparation**:* analogous to **125** (section D.3.4, page 164), using 1-bromo-4-(difluoromethyl)benzene (41.7 mg, 0.202 mmol, 1.3 equiv.) as aryl halide coupling partner.
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 20 : 80 to 70 : 30 in 40 min) afforded the title compound **138**.

Yield:	29.9 mg, 51 % (over 4 steps from unprotected alcohol **106**)
Appearance:	slightly colored oil
***R*$_f$ (silica)**:	0.57 (EtOAc)
[α]$_D^{23}$:	+12.5 (c 1.45, *i*-PrOH)
LC-HRMS (APCI):	calculated for M+H$^+$: 379.1715, found: 379.1717, Δ: 0.53 ppm
(log *P*)$_{calc}$:	3.81 ± 0.70

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.64 (bs, 1H, OH), 2.42 (quint, ^3J = 6.7 Hz, 1H, H3), 2.59 – 2.87 (m, 2H, H4, C4-CH), 2.96 – 3.09 (m, 1H, C4-CH), 3.71 (dd, ^2J = 8.6 Hz, ^3J = 6.0 Hz, 1H, H5), 3.74 – 3.96 (m, 2H, C3-CH_2), 3.86 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.04 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.83 (d, ^3J = 6.4 Hz, 1H, H2), 6.62 (t, $^2J_{H\text{-}F}$ = 56.5 Hz, 1H, C4''-CF_2H), 6.78 – 6.94 (m, 3H, Ar'-H), 7.28 (d, ^3J = 7.7 Hz, 2H, H2''*, H6''*), 7.44 (d, ^3J = 8.0 Hz, 2H, H3''*, H5''*).

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.5 (t, C4-C), 42.2 (d, C4), 52.5 (d, C3), 56.00 (q, Ar'-OCH_3), 56.03 (q, Ar'-OCH_3), 61.0 (t, C3-C), 72.8 (t, C5), 82.9 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 114.8 (dt, C4''-CF_2H, $^1J_{C\text{-}F}$ = 238.4 Hz), 118.1 (d, C6'), 125.9 (dt, C3'', C5'', $^3J_{C\text{-}F}$ = 6.0 Hz), 129.1 (d, C2'', C6''), 132.5 (t, C4'', $^2J_{C\text{-}F}$ = 22.4 Hz), 135.4 (s, C1'), 143.6 (t, C1'', $^5J_{C\text{-}F}$ = 2.0 Hz), 148.6 (s, C4'), 149.2 (s, C3').

D.3.18 ((2*S*,3*R*,4*R*)-4-(4-(1,1-Difluoroethyl)benzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methanol (**139**)



139, $C_{22}H_{26}F_2O_4$
392.44 g mol^{-1}

***Preparation**:* analogous to **125** (section D.3.4, page 164), using 1-bromo-4-(1,1-difluoroethyl)benzene (44.5 mg, 0.202 mmol, 1.3 equiv.) as aryl halide coupling partner.

***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 20 : 80 to 70 : 30 in 40 min) afforded the title compound **139**.

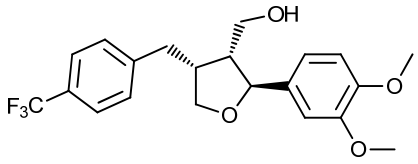
Yield:	30.5 mg, 50 % (over 4 steps from unprotected alcohol **106**)
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.58 (EtOAc)
[α]$_D^{23}$:	+10.4 (c 1.52, *i*-PrOH)
LC-HRMS (APCI):	calculated for M+Na$^+$: 415.1691, found: 415.1667, Δ: -5.78 ppm

(log *P*)$_{calc}$: 4.16 ± 0.70

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65 (bs, 1H, OH), 1.91 (t, $^3J_{H\text{-}F}$ = 18.1 Hz, 3H, C4''-CF_2CH_3), 2.41 (quint, ^3J = 6.7 Hz, 1H, H3), 2.56 – 2.90 (m, 2H, H4, C4-CH), 3.00 (dd, ^2J = 12.2 Hz, ^3J = 3.7 Hz, 1H, C4-CH), 3.63 – 3.99 (m, 3H, C3-CH_2, H5), 3.86 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.05 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.83 (d, ^3J = 6.3 Hz, 1H, H2), 6.78 – 6.94 (m, 3H, Ar'-H), 7.24 (d, ^3J = 7.9 Hz, 2H, H2''*, H6''*), 7.43 (d, ^3J = 8.2 Hz, 2H, H3''*, H5''*).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.0 (qt, C4''-$CF_2\underline{C}H_3$, $^2J_{C\text{-}F}$ = 30.1 Hz), 33.4 (t, C4-<u>C</u>), 42.2 (d, C4), 52.5 (d, C3), 55.97 (q, Ar'-OCH_3), 56.01 (q, Ar'-OCH_3), 61.0 (t, C3-<u>C</u>), 72.9 (t, C5), 82.9 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 118.1 (d, C6'), 122.0 (s, C4''-$\underline{C}F_2CH_3$), 125.0 (dt, C3'', C5'', $^3J_{C\text{-}F}$ = 6.0 Hz), 128.8 (s, C2'', C6''), 135.5 (s, C1'), 136.3 (t, C4'', $^2J_{C\text{-}F}$ = 26.8 Hz), 142.4 (t, C1'', $^5J_{C\text{-}F}$ = 1.7 Hz), 148.5 (s, C4'), 149.2 (s, C3').

D.3.19 ((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methanol (**<u>140</u>**)



<u>140</u>, $C_{21}H_{23}F_3O_4$
396.40 g mol^{-1}

***Preparation**:* analogous to **<u>128</u>** (section D.3.7, page 167), using 1-bromo-4-(trifluoromethyl)benzene (55.6 mg, 0.247 mmol, 1.3 equiv.) as aryl halide coupling partner.

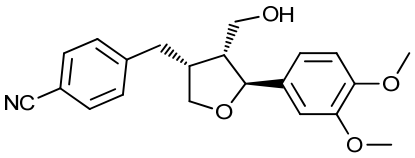
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 15 : 85 to 80 : 20 in 45 min) afforded the title compound **<u>140</u>.**

Yield: 57.2 mg, 76 % (over 4 steps from unprotected alcohol **<u>106</u>**)
Appearance: nearly colorless oil
R_f (silica): 0.59 (EtOAc)
$[\alpha]_D^{25}$: +18.7 (c 2.68, MeOH)
LC-HRMS (ESI): calculated for M+Na^+: 419.1441, found: 419.1437, Δ: -0.95 ppm
(log *P*)$_{calc}$: 4.01 ± 0.58

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.79 (bs, 1H, OH), 2.42 (quint, ^3J = 6.7 Hz, 1H, H3), 2.60 – 2.86 (m, 2H, H4, C4-CH), 3.04 (d, ^2J = 11.4 Hz, 1H, C4-CH), 3.71 (dd, ^2J = 8.6 Hz, ^3J = 5.9 Hz, 1H, H5), 3.76 – 3.97 (m, 2H, C3-CH_2), 3.86 (s, 3H, Ar'-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 4.03 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.82 (d, ^3J = 6.4 Hz, 1H, H2), 6.78 – 6.91 (m, 3H, Ar'-H), 7.31 (d, ^3J = 8.0 Hz, 2H, H2'', H6''), 7.55 (d, ^3J = 8.2 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.4 (t, C4-C), 42.1 (d, C4), 52.4 (d, C3), 55.99 (q, Ar'-OCH_3), 56.02 (q, Ar'-OCH_3), 60.8 (t, C3-C), 72.7 (t, C5), 82.8 (d, C2), 108.9 (d, C2'), 111.1 (d, C5'), 118.1 (d, C6'), 124.3 (q, C4''-CF_3, $^1J_{C\text{-}F}$ = 271.7 Hz), 125.6 (dq, C3'', C5'', $^3J_{C\text{-}F}$ = 3.8 Hz), 128.7 (q, C4'', $^2J_{C\text{-}F}$ = 32.3 Hz), 129.1 (d, C2'', C6''), 135.3 (s, C1'), 144.8 (q, C1'', $^5J_{C\text{-}F}$ = 1.3 Hz), 148.5 (s, C4'), 149.2 (s, C3').

D.3.20 4-(((3*R*,4*R*,5*S*)-5-(3,4-Dimethoxyphenyl)-4-(hydroxymethyl)tetrahydrofuran-3-yl)methyl)benzonitrile (**141**)



141, $C_{21}H_{23}NO_4$
353.41 g mol^{-1}

***Preparation**:* analogous to **127** (section D.3.6, page 166), using 4-bromobenzonitrile (45.0 mg, 0.247 mmol, 1.3 equiv.) as aryl halide coupling partner.

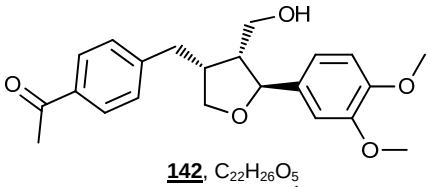
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography in two sequential runs (first run: 18 g silica, flow rate 20 mL / min, EtOAc / LP, 30 : 70 to 75 : 25 in 30 min, then 75 : 25 isocratically; second run: 18 g silica, flow rate 20 mL / min, EtOAc : LP, 30 : 70 to 80 : 20 in 40 min) afforded the title compound **141**.

Yield:	37.2 mg, 55 % (over 4 steps from unprotected alcohol **106**)
Appearance:	light-brown oil
R_f (silica):	0.57 (EtOAc)
$[\alpha]_D^{20}$:	+14.8 (c 1.16, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 376.1519, found: 376.1523, Δ: 1.06 ppm
(log *P*)$_{calc}$:	2.88 ± 0.57

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.75 (bs, 1H, OH), 2.43 (quint, ^3J = 6.7 Hz, 1H, H3), 2.62 – 2.85 (m, 2H, H4, C4-CH), 2.97 – 3.16 (m, 1H, C4-CH), 3.68 (dd, ^2J = 8.6 Hz, ^3J = 5.9 Hz, 1H, H5), 3.73 – 3.98 (m, 2H, C3-CH_2), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.03 (dd, ^2J = 8.6 Hz, ^3J = 6.1 Hz, 1H, H5), 4.81 (d, ^3J = 6.6 Hz, 1H, H2), 6.79 – 6.93 (m, 3H, Ar'-H), 7.31 (d, ^3J = 8.2 Hz, 2H, H2'', H6''), 7.59 (d, ^3J = 8.3 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.8 (t, C4-C), 42.0 (d, C4), 52.4 (d, C3), 56.00 (q, Ar'-OCH_3), 56.03 (q, Ar'-OCH_3), 60.8 (t, C3-C), 72.6 (t, C5), 82.7 (d, C2), 109.0 (d, C2'), 110.2 (s, C4''), 111.1 (d, C5'), 118.1 (d, C6'), 119.0 (s, C4''-CN), 129.6 (d, C2'', C6''), 132.5 (d, C3'', C5''), 135.2 (s, C1'), 146.4 (s, C1''), 148.6 (s, C4'), 149.2 (s, C3').

D.3.21 1-(4-(((3*R*,4*R*,5*S*)-5-(3,4-Dimethoxyphenyl)-4-(hydroxymethyl)tetrahydrofuran-3-yl)methyl)phenyl)ethanone (**142**)



142, $C_{22}H_{26}O_5$
370.44 g mol^{-1}

***Preparation**:* analogous to **127** (section D.3.6, page 166), using 1-(4-bromophenyl)ethanone (49.2 mg, 0.247 mmol, 1.3 equiv.) as aryl halide coupling partner.

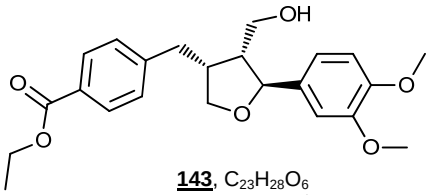
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography in two sequential runs (first run: 18 g silica, flow rate 20 mL / min, EtOAc / LP, 30 : 70 to 75 : 25 in 30 min, then 75 : 25 isocratically for 3 min, then 80 : 20 isocratically; second run: 18 g silica, flow rate 20 mL / min, EtOAc / LP, 30 : 70 to 85 : 15 in 40 min) afforded the title compound **142**.

Yield:	29.1 mg, 41 % (over 4 steps from unprotected alcohol **106**)
Appearance:	light-brown oil
***R*$_f$ (silica)**:	0.56 (EtOAc)
$[\alpha]_D^{20}$:	+14.0 (c 1.09, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 393.1673, found: 393.1689, Δ: 4.07 ppm
(log *P*)$_{calc}$:	2.89 ± 0.56

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.81 (bs, 1H, OH), 2.43 (quint, ^3J = 6.7 Hz, 1H, H3), 2.59 (s, 3H, C4''-$COCH_3$), 2.61 – 2.87 (m, 2H, H4, C4-CH), 3.06 (dd, ^2J = 11.7 Hz, ^3J = 3.3 Hz, 1H, C4-CH), 3.71 (dd, ^2J = 8.6 Hz, ^3J = 6.0 Hz, 1H, H5), 3.75 – 3.96 (m, 2H, C3-CH_2), 3.86 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.04 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.83 (d, ^3J = 6.4 Hz, 1H, H2), 6.81 – 6.90 (m, 3H, Ar'-H), 7.29 (d, ^3J = 9.0 Hz, 2H, H2'', H6''), 7.86 – 7.93 (m, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.7 (q, C4''-CO<u>C</u>H$_3$), 33.7 (t, C4-<u>C</u>), 42.1 (d, C4), 52.5 (d, C3), 55.98 (q, Ar'-OCH_3), 56.02 (q, Ar'-OCH_3), 60.9 (t, C3-<u>C</u>), 72.8 (t, C5), 82.8 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 118.1 (d, C6'), 128.8 (d, C2''*, C6''*), 129.0 (d, C3''*, C5''*), 135.4 (s, C1'*), 135.5 (s, C4''*), 146.5 (s, C1''), 148.5 (s, C4'), 149.2 (s, C3'), 198.0 (s, C4''-<u>C</u>OCH$_3$).

D.3.22 Ethyl 4-(((3*R*,4*R*,5*S*)-5-(3,4-dimethoxyphenyl)-4-(hydroxymethyl)tetrahydrofuran-3-yl)methyl)benzoate (**143**)



143, $C_{23}H_{28}O_6$
400.46 g mol^{-1}

***Preparation**:* analogous to **127** (section D.3.6, page 166), using ethyl 4-bromobenzoate (56.6 mg, 0.247 mmol, 1.3 equiv.) as aryl halide coupling partner.

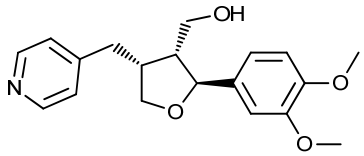
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 30 : 70 to 52 : 48 in 17 min, then to 74 : 26 in 9 min, then 74 : 26 isocratically) afforded the title compound **143**.

Yield:	47.3 mg, 62 % (over 4 steps from unprotected alcohol **106**)
Appearance:	light-brown oil
R_f (silica):	0.38 (EtOAc / LP, 2 : 1)
$[\alpha]_D^{23}$:	+11.8 (c 4.64, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 423.1778, found: 423.1795, Δ: 4.02 ppm
(log *P*)$_{calc}$:	3.95 ± 0.55

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (t, ^3J = 7.1 Hz, 3H, C4''-$CO_2CH_2C\underline{H}_3$), 1.86 (t, ^3J = 4.6 Hz, 1H, OH), 2.42 (quint, ^3J = 6.7 Hz, 1H, H3), 2.59 – 2.88 (m, 2H, H4, C4-CH), 3.04 (dd, ^2J = 11.9 Hz, ^3J = 3.3 Hz, 1H, C4-CH), 3.71 (dd, ^2J = 8.6 Hz, ^3J = 6.0 Hz, 1H, H5), 3.74 – 3.99 (m, 2H, C3-CH_2), 3.86 (s, 3H, Ar'-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 4.03 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.36 (q, ^3J = 7.1 Hz, 2H, C4''-$CO_2C\underline{H}_2CH_3$), 4.82 (d, ^3J = 6.4 Hz, 1H, H2), 6.78 – 6.94 (m, 3H, Ar'-H), 7.27 (d, ^3J = 8.2 Hz, 2H, H2'', H6''), 7.97 (d, ^3J = 8.2 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4 (q, C4''-$CO_2CH_2\underline{C}H_3$), 33.7 (t, C4-$\underline{C}$), 42.1 (d, C4), 52.5 (d, C3), 55.99 (q, Ar'-OCH_3), 56.03 (q, Ar'-OCH_3), 60.8 (t, C3-$\underline{C}$*), 61.0 (t, C4''-$CO_2\underline{C}H_2CH_3$*), 72.8 (t, C5), 82.8 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 118.1 (d, C6'), 128.6 (s, C4''), 128.8 (d, C2''*, C6''*), 129.9 (d, C3''*, C5''*), 135.4 (s, C1'), 146.0 (s, C1''), 148.5 (s, C4'), 149.1 (s, C3'), 166.6 (s, C4''-$\underline{C}O_2CH_2CH_3$).

D.3.23 ((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(pyridin-4-ylmethyl)tetrahydrofuran-3-yl)methanol (**144**)



144, $C_{19}H_{23}NO_4$
329.39 g mol^{-1}

***Preparation**:* analogous to **128** (section D.3.7, page 167), using 4-bromopyridine hydrochloride (48.0 mg, 0.247 mmol, 1.3 equiv.) as aryl halide coupling partner, and repeating the $MgSO_4$ addition and TBAF addition steps due to initially incomplete deprotection.

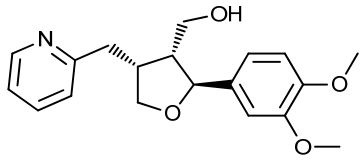
***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content and the mixture was extracted with aqueous HCl (1 M, 3 x 5 mL). CH_2Cl_2 (10 mL) was then added to the combined aqueous phases followed by the careful addition of solid Na_2CO_3 (1.5 g). The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL), the combined organic phases were dried with Na_2SO_4, filtered and the solvents were evaporated. Flash column chromatography was performed (18 g silica, flow rate 20 mL / min, MeOH / EtOAc, 0 : 100 to 30 : 70 in 35 min), followed by re-crystallization from a mixture of toluene (9 mL) and cyclohexane (5 mL). Therein, the hot solution was decanted from insoluble material, allowed to cool, and crystallization was then completed by storing at -25 °C. Removal of the mother liquor afforded the title compound **144**.

Yield:	42.0 mg, 67 % (over 4 steps from unprotected alcohol **106**)
Appearance:	colorless crystals
Melting range:	115.0 – 118.0 °C
***R*$_f$ (silica)**:	0.51 (MeOH / EtOAc, 1 : 2)
$[\alpha]_D^{25}$:	+25.2 (c 0.90, MeOH)
LC-HRMS (ESI):	calculated for $M+H^+$: 330.1700, found: 330.1697, Δ: -0.91 ppm
(log *P*)$_{calc}$:	1.95 ± 0.54

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.43 (quint, ^3J = 6.7 Hz, 1H, H3), 2.52 – 2.89 (m, 3H, H4, C4-CH, OH), 3.02 (dd, ^2J = 12.6 Hz, ^3J = 4.1 Hz, 1H, C4-CH), 3.69 (dd, ^2J = 8.5 Hz, ^3J = 6.1 Hz, 1H, H5), 3.73 – 3.94 (m, 2H, C3-CH_2), 3.87 (s, 3H, Ar'-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 4.06 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.83 (d, ^3J = 6.4 Hz, 1H, H2), 6.80 – 6.90 (m, 3H, Ar'-H), 7.14 (d, ^3J = 5.1 Hz, 2H, H2'', H6''), 8.47 (bs, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.0 (t, C4-C), 41.4 (d, C4), 52.4 (d, C3), 56.00 (q, Ar'-OCH_3), 56.03 (q, Ar'-OCH_3), 60.5 (t, C3-C), 72.6 (t, C5), 82.7 (d, C2), 108.9 (d, C2'), 111.1 (d, C5'), 118.0 (d, C6'), 124.3 (d, C2'', C6''), 135.3 (s, C1'), 148.5 (s, C4'), 149.1 (s, C3'), 149.8 (d, C3'', C5''), 150.1 (s, C1'').

D.3.24 ((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(pyridin-2-ylmethyl)tetrahydrofuran-3-yl)methanol (**145**)



145, $C_{19}H_{23}NO_4$
329.39 g mol^{-1}

***Preparation**:* analogous to **128** (section D.3.7, page 167), using 2-bromopyridine (39.0 mg, 0.247 mmol, 1.3 equiv.) as aryl halide coupling partner, and repeating the $MgSO_4$ addition and TBAF addition steps due to initially incomplete deprotection.

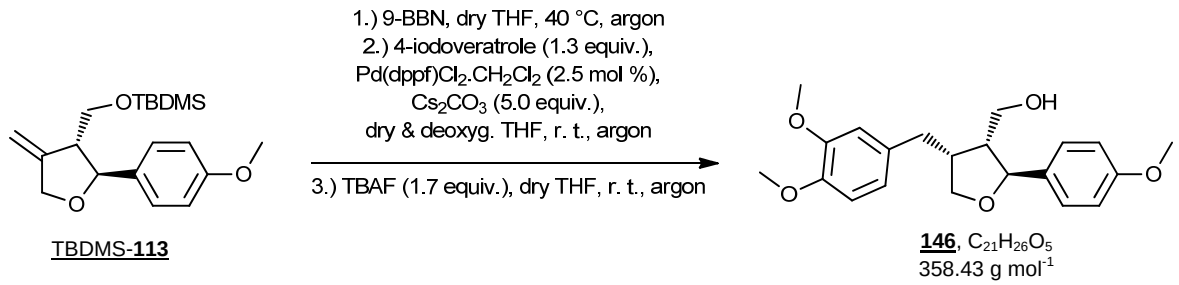
***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content and the mixture was extracted with aqueous HCl (1 M, 2 x 5 mL). CH_2Cl_2 (10 mL) was then added to the combined aqueous phases followed by the careful addition of solid Na_2CO_3 (1.5 g). The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (10 mL), the combined organic phases were dried with Na_2SO_4, filtered and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc) followed by preparative HPLC (flow rate 20.0 mL / min, MeOH / water, 38 : 62) afforded the title compound **145**.

Yield:	36.7 mg, 59 % (over 4 steps from unprotected alcohol **106**)
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.57 (MeOH / EtOAc, 1 : 2)
[α]$_D^{25}$:	+22.1 (c 1.91, MeOH)
LC-HRMS (ESI):	calculated for $M+H^+$: 330.1700, found: 330.1698, Δ: -0.61 ppm
(log *P*)$_{calc}$:	1.95 ± 0.54

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.41 – 2.57 (m, 1H, H4), 2.72 – 2.89 (m, 2H, H3, C4-CH), 3.24 (dd, ^2J = 15.5 Hz, ^3J = 9.9 Hz, 1H, C4-CH), 3.69 (dd, ^2J = 11.6 Hz, ^3J = 4.1 Hz, 1H, C3-CH), 3.79 (dd, ^2J = 8.4 Hz, ^3J = 6.5 Hz, 1H, H5), 3.86 (s, 3H, Ar'-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 3.91 – 4.01 (m, 1H, C3-CH), 4.25 (dd, ^2J = 8.5 Hz, ^3J = 6.3 Hz, 1H, H5), 4.66 (d, ^3J = 6.4 Hz, 1H, H2), 6.77 – 6.90 (m, 3H, Ar'-H), 7.11 – 7.24 (m, 2H, H4'', H6''), 7.64 (td, ^3J = 7.7 Hz, ^4J = 1.8 Hz, 1H, H5''), 8.47 (d, ^3J = 4.9 Hz, 1H, H3''). OH not visible.

^{13}C NMR (50 MHz, $CDCl_3$): δ 35.9 (t, C4-C), 41.4 (d, C4), 52.9 (d, C3), 55.9 (q, Ar'-OCH_3), 56.0 (q, Ar'-OCH_3), 60.6 (t, C3-C), 74.1 (t, C5), 83.3 (d, C2), 108.9 (d, C2'), 111.0 (d, C5'), 118.1 (d, C6'), 121.7 (d, C4''), 123.7 (d, C6''), 135.4 (s, C1'), 137.3 (d, C5''), 148.4 (s, C4'), 148.7 (d, C3''), 149.1 (s, C3'), 160.5 (s, C1'').

D.3.25 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(4-methoxyphenyl)tetrahydrofuran-3-yl)methanol (**146**)



TBDMS-**113**

146, $C_{21}H_{26}O_5$
358.43 g mol^{-1}

***Preparation**:* a reaction vessel was charged with a stirring bar and crude starting material TBDMS-**113** (190 mg, 0.41 mmol), and then evacuated and back-filled with argon using standard Schlenk technique. A solution of 9-BBN (0.5 M in THF, 1.25 mL, 0.61 mmol) was added *via* syringe, the reaction was stirred for 18 h at 40 °C and then allowed to cool to room temperature.

This mixture was then purged by bubbling argon into the solution through a needle, and dry and deoxygenated THF was added to produce a total volume of 3.0 mL, i.e. a 0.137 M solution of borylated intermediate, thus allowing the use of aliquots for subsequent coupling.

An aliquot (1.50 mL, 0.21 mmol, 1.0 equiv.) of this solution was transferred *via* syringe to a separate vessel which had been charged with a stirring bar, 4-iodoveratrole **109** (70.4 mg, 0.267 mmol, 1.3 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (4.2 mg, 5.1 µmol, 2.5 mol %) and Cs_2CO_3 (334 mg, 1.025 mmol, 5.0 equiv.) under argon and was stirred for 77 h at room temperature. For deprotection, a solution of TBAF (1.0 M in THF, 0.35 mL, 0.35 mmol, 1.7 equiv.) was added *via* syringe and the mixture was finally stirred for 14 h at room temperature.

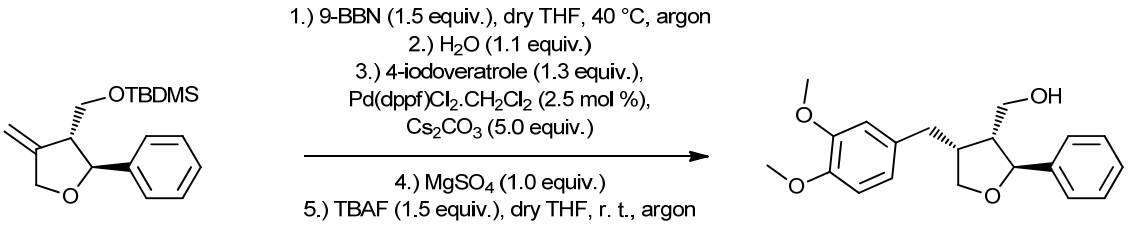
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography in two sequential runs (18 g silica, flow rate 20 mL / min, EtOAc / LP, 30 : 70 to 80 : 20 in 40 min) afforded the title compound **146**.

Yield:	21.4 mg, 29 % (over 4 steps from unprotected alcohol **113**)
Appearance:	nearly colorless oil
R_f (silica):	0.41 (EtOAc)
$[\alpha]_D^{25}$:	+11.8 (c 1.14, *i*-PrOH)
LC-HRMS (APCI):	calculated for $M+Na^+$: 381.1672, found: 381.1661, Δ: -2.89 ppm
$(\log P)_{calc}$:	3.36 ± 0.55

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.55 (bs, 1H, OH), 2.40 (quint, ^3J = 6.8 Hz, 1H, H3), 2.55 (dd, ^2J = 12.6 Hz, ^3J = 10.5 Hz, 1H, C4-CH), 2.65 – 2.84 (m, 1H, H4), 2.93 (dd, ^2J = 12.8 Hz, ^3J = 4.6 Hz, 1H, C4-CH), 3.68 – 3.98 (m, 3H, C3-CH_2, H5), 3.79 (s, 3H, C4'-OCH_3), 3.86 (s, 6H, Ar''-OCH_3), 4.05 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 4.80 (d, ^3J = 6.6 Hz, 1H, H2), 6.68 – 6.83 (m, 3H, 3 x Ar''-H), 6.87 (d, ^3J = 8.6 Hz, 2H, H3', H5'), 7.25 (d, ^3J = 8.7 Hz, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.3 (t, C4-C), 42.5 (d, C4), 52.8 (d, C3), 55.4 (q, C4'-OCH_3), 55.99 (q, Ar''-OCH_3), 56.03 (q, Ar''-OCH_3), 61.0 (t, C3-C), 73.0 (t, C5), 82.7 (d, C2), 111.4 (d, C5''*), 112.0 (d, C2''*), 114.0 (d, C3', C5'), 120.6 (d, C6''), 127.2 (d, C2', C6'), 133.1 (s, C1''), 135.1 (s, C1'), 147.6 (s, C4''), 149.1 (s, C3''), 159.1 (s, C4').

D.3.26 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-phenyltetrahydrofuran-3-yl)methanol (**123**)



TBDMS-**114** **123**, $C_{20}H_{24}O_4$, 328.40 g mol^{-1}

***Preparation**:* a reaction vessel was charged with a stirring bar and crude starting material TBDMS-**114** (54.8 mg, 0.146 mmol, 1.0 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. A solution of 9-BBN (0.5 M in THF, 0.44 mL, 0.22 mmol, 1.5 equiv.) was added *via* syringe, the reaction was stirred for 24 h at 40 °C and then allowed to cool to room temperature. Water (3 µL, 0.17 mmol, 1.1 equiv.) was subsequently added and stirring was continued for 30 min to decompose excess 9-BBN, before the solution was transferred *via* syringe to a separate vessel which had been charged with a stirring bar, 4-iodoveratrole **109** (50.1 mg, 0.190 mmol, 1.3 equiv.), $Pd(dppf)Cl_2.CH_2Cl_2$ (3.0 mg, 3.7 µmol, 2.5 mol %) and Cs_2CO_3 (238 mg, 0.73 mmol, 5.0 equiv.) under argon and was stirred for 27 h at room temperature. Following this, $MgSO_4$ (18 mg, 0.15 mmol, 1.0 equiv.) was added and stirring was continued for 30 min to remove residual water. For deprotection, a solution of TBAF (1.0 M in THF, 0.22 mL, 0.22 mmol, 1.5 equiv.) was added *via* syringe and the mixture was finally stirred for 22 h at room temperature.

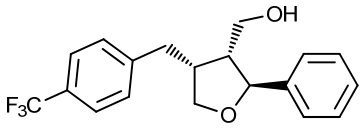
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 15 : 85 to 40 : 60 in 35 min) afforded the title compound **123**.

Yield:	24.5 mg, 51 % (over 4 steps from unprotected alcohol **114**)
Appearance:	light-brown oil
R_f (silica):	0.48 (EtOAc / LP, 2 : 1)
$[\alpha]_D^{20}$:	+10.1 (c 7.33, MeOH)
LC-HRMS (ESI):	calculated for $M+Na^+$: 351.1567, found: 351.1569, Δ: 0.57 ppm
(log *P*)$_{calc}$:	3.44 ± 0.54

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.71 (bs, 1H, OH), 2.41 (quint, ^3J = 6.6 Hz, 1H, H3), 2.56 (dd, ^2J = 12.7 Hz, ^3J = 10.3 Hz, 1H, C4-CH), 2.64 – 2.83 (m, 1H, H4), 2.92 (dd, ^2J = 12.7 Hz, ^3J = 4.6 Hz, 1H, C4-CH), 3.78 (dd, ^2J = 8.5 Hz, ^3J = 6.2 Hz, 1H, H5), 3.86 (s, 6H, Ar''-OCH_3), 3.81 – 3.99 (m, 2H, C3-CH_2), 4.08 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 4.89 (d, ^3J = 6.2 Hz, 1H, H2), 6.66 – 6.83 (m, 3H, Ar''-H), 7.20 – 7.40 (m, 5H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.2 (t, C4-C), 42.4 (d, C4), 52.9 (d, C3), 55.9 (q, Ar''-OCH_3), 56.0 (q, Ar''-OCH_3), 60.8 (t, C3-C), 73.1 (t, C5), 82.9 (d, C2), 111.4 (d, C5''*), 112.0 (d, C2''*), 120.6 (d, C6''), 125.7 (d, C2', C6'), 127.4 (d, C4'), 128.5 (d, C3', C5'), 133.1 (s, C1''), 143.3 (s, C1'), 147.5 (s, C4''), 149.0 (s, C3'').

D.3.27 ((2*S*,3*R*,4*R*)-2-Phenyl-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methanol (**147**)



147, $C_{19}H_{19}F_3O_2$
336.35 g mol^{-1}

Preparation: analogous to **123** (section D.3.26, page 184), using crude starting material TBDMS-**114** (44.5 mg, 0.118 mmol, 1.0 equiv.) and 1-bromo-4-(trifluoromethyl)benzene (34.6 mg, 0.154 mmol, 1.3 equiv.) as aryl halide coupling partner, and stirring for 42 in place of 27 h during the coupling step.

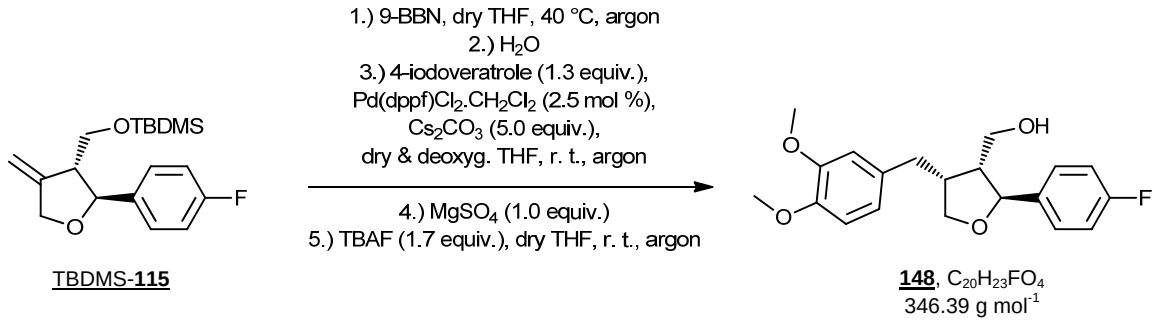
Work-up and purification: the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 40 : 60 in 35 min) afforded the title compound **147**.

Yield:	17.4 mg, 44 % (over 4 steps from unprotected alcohol **114**)
Appearance:	colorless oil
R_f (silica):	0.40 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{23}$:	+15.3 (c 1.61, MeOH)
(log *P*)$_{calc}$:	4.28 ± 0.55

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.57 (bs, 1H, OH), 2.42 (quint, ^3J = 6.5 Hz, 1H, H3), 2.61 – 2.87 (m, 2H, H4, C4-CH), 2.99 – 3.10 (m, 1H, C4-CH), 3.68 – 3.99 (m, 3H, C3-CH_2, H5), 4.01 – 4.12 (m, 1H, H5), 4.90 (d, ^3J = 6.1 Hz, 1H, H2), 7.25 – 7.37 (m, 7H, 5 x Ar'-H, H2'', H6''), 7.55 (d, ^3J = 8.1 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.5 (t, C4-C), 42.1 (d, C4), 52.8 (d, C3), 61.0 (t, C3-C), 72.9 (t, C5), 83.0 (d, C2), 124.4 (q, C4''-CF_3, $^1J_{C\text{-}F}$ = 271.9 Hz), 125.6 (dq, C3'', C5'', $^3J_{C\text{-}F}$ = 3.8 Hz), 125.8 (d, C2', C6'), 127.6 (d, C4'), 128.6 (d, C3', C5'), 128.8 (q, C4'', $^2J_{C\text{-}F}$ = 32.4 Hz), 129.1 (d, C2'', C6''), 143.1 (s, C1'), 144.8 (q, C1'', $^5J_{C\text{-}F}$ = 1.3 Hz).

D.3.28 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methanol (**148**)



TBDMS-**115** — **148**, $C_{20}H_{23}FO_4$, 346.39 g mol^{-1}

***Preparation**:* a reaction vessel was charged with a stirring bar and crude starting material TBDMS-**115** (169.3 mg, 0.467 mmol), and then evacuated and back-filled with argon using standard Schlenk technique. A solution of 9-BBN (0.5 M in THF, 1.40 mL, 0.70 mmol) was added *via* syringe, the reaction was stirred for 19 h at 40 °C and then allowed to cool to room temperature. Water (9 µL, 0.5 mmol) was subsequently added and stirring was continued for 15 min to decompose excess 9-BBN.

This mixture was then purged by bubbling argon into the solution through a needle, and dry and deoxygenated THF was added to produce a total volume of 2.7 mL, i.e. a 0.173 M solution of borylated intermediate, thus allowing the use of aliquots for subsequent coupling.

An aliquot (0.90 mL, 0.156 mmol, 1.0 equiv.) of this solution was transferred *via* syringe to a separate vessel which had been charged with a stirring bar, 4-iodoveratrole **109** (53.5 mg, 0.202 mmol, 1.3 equiv.), Pd(dppf)Cl_2.CH_2Cl_2 (3.2 mg, 3.9 µmol, 2.5 mol %) and Cs_2CO_3 (254 mg, 0.779 mmol, 5.0 equiv.) under argon and was stirred for 19.5 h at room temperature. Following this, $MgSO_4$ (19 mg, 0.16 mmol, 1.0 equiv.) was added and stirring was continued for 1.5 h to remove residual water. For deprotection, a solution of TBAF (1.0 M in THF, 0.26 mL, 0.26 mmol, 1.7 equiv.) was added *via* syringe and the mixture was finally stirred for 21 h at room temperature.

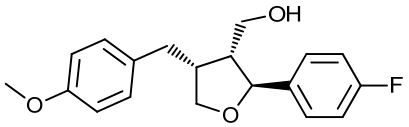
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 25 : 75 to 70 : 30 in 40 min) afforded the title compound **148**.

Yield:	31.5 mg, 58 % (over 4 steps from unprotected alcohol **115**)
Appearance:	slightly colored oil
R_f (silica):	0.60 (EtOAc)
$[\alpha]_D^{20}$:	+10.4 (c 0.69, MeOH)
LC-HRMS (APCI):	calculated for M+H$^+$: 347.1653, found: 347.1668, Δ: 4.32 ppm
(log *P*)$_{calc}$:	3.49 ± 0.60

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (bs, 1H, OH), 2.38 (quint, ^3J = 6.8 Hz, 1H, H3), 2.56 (dd, ^2J = 12.6 Hz, ^3J = 10.2 Hz, 1H, C4-CH), 2.65 – 2.83 (m, 1H, H4), 2.92 (dd, ^2J = 12.7 Hz, ^3J = 4.7 Hz, 1H, C4-CH), 3.77 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 3.86 (s, 3H, Ar''-OCH_3), 3.86 (s, 3H, Ar''-OCH_3), 3.79 – 4.00 (m, 2H, C3-CH_2), 4.07 (dd, ^2J = 8.5 Hz, ^3J = 6.3 Hz, 1H, H5), 4.87 (d, ^3J = 6.2 Hz, 1H, H2), 6.68 – 6.84 (m, 3H, Ar''-H), 6.95 – 7.08 (m, 2H, H3', H5'), 7.24 – 7.35 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.1 (t, C4-C), 42.4 (d, C4), 52.8 (d, C3), 56.00 (q, Ar''-OCH_3), 56.02 (q, Ar''-OCH_3), 60.7 (t, C3-C), 73.1 (t, C5), 82.4 (d, C2), 111.4 (d, C5''*), 112.0 (d, C2''*), 115.3 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 120.5 (d, C6''), 127.4 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 133.0 (s, C1''), 139.0 (d, C1', $^4J_{C\text{-}F}$ = 3.0 Hz), 147.5 (s, C4''), 149.0 (s, C3''), 162.2 (d, C4', $^1J_{C\text{-}F}$ = 245.1 Hz).

D.3.29 ((2*S*,3*R*,4*R*)-2-(4-Fluorophenyl)-4-(4-methoxybenzyl)tetrahydrofuran-3-yl)methanol (**149**)



149, $C_{19}H_{21}FO_3$
316.37 g mol^{-1}

***Preparation**:* analogous to **148** (section D.3.28, page 186), using 4-bromoanisole (37.8 mg, 0.202 mmol, 1.3 equiv.) as aryl halide coupling partner.

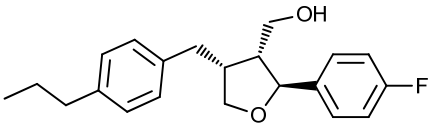
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 15 : 85 to 65 : 35 in 35 min) afforded the title compound **149**.

Yield:	28.1 mg, 58 % (over 4 steps from unprotected alcohol **115**)
Appearance:	light-brown oil
***R*$_f$ (silica)**:	0.36 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{23}$:	+8.3 (c 1.08, MeOH)
(log *P*)$_{calc}$:	3.67 ± 0.59

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (bs, 1H, OH), 2.35 (quint, ^3J = 6.5 Hz, 1H, H3), 2.57 (dd, ^2J = 12.4 Hz, ^3J = 9.8 Hz, 1H, C4-CH), 2.62 – 2.82 (m, 1H, H4), 2.89 (dd, ^2J = 12.4 Hz, ^3J = 4.6 Hz, 1H, C4-CH), 3.79 (s, 3H, C4''-OCH_3), 3.82 – 3.69 (m, 2H, C3-CH, H5), 3.93 (dd, ^2J = 10.6 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.06 (dd, ^2J = 8.5 Hz, ^3J = 6.3 Hz, 1H, H5), 4.89 (d, ^3J = 6.0 Hz, 1H, H2), 6.79 – 6.88 (m, 2H, H3'', H5''), 6.95 – 7.15 (m, 4H, H3', H5', H2'', H6''), 7.24 – 7.34 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 32.7 (t, C4-C), 42.4 (d, C4), 52.8 (d, C3), 55.4 (q, C4''-OCH_3), 61.0 (t, C3-C), 73.2 (t, C5), 82.6 (d, C2), 114.1 (d, C3'', C5''), 115.3 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.0 Hz), 129.6 (d, C2'', C6''), 132.4 (s, C1''), 139.1 (d, C1', $^4J_{C\text{-}F}$ = 3.0 Hz), 158.2 (s, C4''), 162.3 (d, C4', $^1J_{C\text{-}F}$ = 245.3 Hz).

D.3.30 ((2*S*,3*R*,4*R*)-2-(4-Fluorophenyl)-4-(4-propylbenzyl)tetrahydrofuran-3-yl)methanol (**150**)



150, $C_{21}H_{25}FO_2$
328.42 g mol^{-1}

***Preparation**:* analogous to **148** (section D.3.28, page 186), using 1-bromo-4-propylbenzene (45.8 mg, 0.230 mmol, 1.3 equiv.), as aryl halide coupling partner.

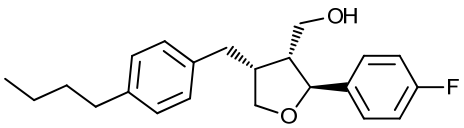
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (30 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 15 : 85 to 55 : 45 in 40 min) afforded the title compound **150**.

Yield:	40.0 mg, 69 % (over 4 steps from unprotected alcohol **115**)
Appearance:	pale brown oil
***R*$_f$ (silica)**:	0.48 (EtOAc / heptane, 1 : 1)
[α]$_D^{25}$:	+7.1 (c 1.01, MeOH)
LC-HRMS (ESI):	calculated for M+H$^+$: 329.1911, found: 329.1918, Δ: 2.13 ppm
(log *P*)$_{calc}$:	5.28 ± 0.58

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, ^3J = 7.3 Hz, 3H, C4''-$CH_2CH_2C\underline{H}_3$), 1.55 (bs, 1H, OH), 1.62 (sext, ^3J = 7.6 Hz, 2H, C4''-$CH_2C\underline{H}_2CH_3$), 2.35 (quint, ^3J = 6.8 Hz, 1H, H3), 2.51 – 2.63 (m, 3H, C4-CH, C4''-$C\underline{H}_2CH_2CH_3$), 2.68 – 2.79 (m, 1H, H4), 2.90 (dd, ^2J = 13.4 Hz, ^3J = 5.3 Hz, 1H, C4-CH), 3.70 – 3.79 (m, 2H, C3-CH, H5), 3.86 – 3.94 (m, 1H, C3-CH), 4.03 – 4.10 (m, 1H, H5), 4.89 (d, ^3J = 5.9 Hz, 1H, H2), 7.01 (dd, ^3J = 8.6 Hz, $^3J_{H\text{-}F}$ = 8.6 Hz, 2H, H3', H5'), 7.07 – 7.12 (m, 4H, Ar''-H), 7.24 – 7.31 (m, 2H, H2', H6').

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (q, C4''-$CH_2CH_2\underline{C}H_3$), 24.7 (t, C4''-$CH_2\underline{C}H_2CH_3$), 33.2 (t, C4-$\underline{C}$), 37.7 (t, C4''-$\underline{C}H_2CH_2CH_3$), 42.2 (d, C4), 52.8 (d, C3), 61.0 (t, C3-$\underline{C}$), 73.3 (t, C5), 82.6 (d, C2), 115.3 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 128.5 (d, C3''*, C5''*), 128.8 (d, C2''*, C6''*), 137.6 (s, C1''*), 139.1 (d, C1', $^4J_{C\text{-}F}$ = 3.0 Hz), 140.8 (s, C4''*), 162.2 (d, C4', $^1J_{C\text{-}F}$ = 245.1 Hz).

D.3.31 ((2*S*,3*R*,4*R*)-4-(4-Butylbenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methanol (**151**)



151, $C_{22}H_{27}FO_2$
342.45 g mol^{-1}

***Preparation**:* analogous to **148** (section D.3.28, page 186), using 1-bromo-4-butylbenzene (49.0 mg, 0.230 mmol, 1.3 equiv.) as aryl halide coupling partner.

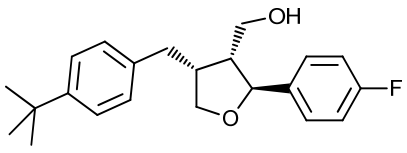
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (30 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 15 : 85 to 55 : 45 in 40 min) afforded the title compound **151**.

Yield:	38.7 mg, 64 % (over 4 steps from unprotected alcohol **115**)
Appearance:	pale brown oil
***R*$_f$ (silica)**:	0.49 (EtOAc / heptane, 1 : 1)
[α]$_D^{25}$:	+6.2 (c 0.91, MeOH)
LC-HRMS (ESI):	calculated for $M+H^+$: 343.2068, found: 343.2074, Δ: 1.79 ppm
(log *P*)$_{calc}$:	5.81 ± 0.58

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, ^3J = 7.3 Hz, 3H, C4''-$CH_2CH_2CH_2CH_3$), 1.35 (sext, ^3J = 7.4 Hz, 2H, C4''-$CH_2CH_2CH_2CH_3$), 1.51 – 1.63 (m, 3H, OH, C4''-$CH_2CH_2CH_2CH_3$), 2.35 (quint, ^3J = 6.8 Hz, 1H, H3), 2.53 – 2.63 (m, 3H, C4-CH, C4''-$CH_2CH_2CH_2CH_3$), 2.68 – 2.79 (m, 1H, H4), 2.90 (dd, ^2J = 13.4 Hz, ^3J = 5.3 Hz, 1H, C4-CH), 3.70 – 3.79 (m, 2H, C3-CH, H5), 3.87 – 3.95 (m, 1H, C3-CH), 4.03 – 4.10 (m, 1H, H5), 4.89 (d, ^3J = 5.9 Hz, 1H, H2), 6.97 – 7.04 (m, 2H, H3', H5'), 7.06 – 7.13 (m, 4H, Ar''-H), 7.24 – 7.32 (m, 2H, H2', H6').

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (q, C4''-$CH_2CH_2CH_2CH_3$), 22.5 (t, C4''-$CH_2CH_2CH_2CH_3$), 33.2 (t, C4-C), 33.8 (t, C4''-$CH_2CH_2CH_2CH_3$), 35.3 (t, C4''-$CH_2CH_2CH_2CH_3$), 42.2 (d, C4), 52.8 (d, C3), 61.0 (t, C3-C), 73.3 (t, C5), 82.6 (d, C2), 115.3 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 128.6 (d, C3''*, C5''*), 128.7 (d, C2''*, C6''*), 137.5 (s, C1''*), 139.1 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 141.0 (s, C4''*), 162.2 (d, C4', $^1J_{C\text{-}F}$ = 245.1 Hz).

D.3.32 ((2*S*,3*R*,4*R*)-4-(4-(*tert*-Butyl)benzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methanol (**152**)



152, $C_{22}H_{27}FO_2$
342.45 g mol^{-1}

***Preparation**:* analogous to **123** (section D.3.26, page 184), using crude starting material TBDMS-**115** (41.3 mg, 0.128 mmol, 1.0 equiv.) and 1-bromo-4-(*tert*-butyl)benzene (35.5 mg, 0.166 mmol, 1.3 equiv.) as aryl halide coupling partner, and stirring for 42 in place of 27 h during the coupling step.

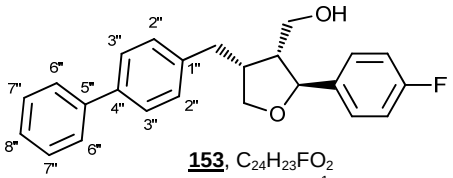
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 80 : 20 in 60 min) afforded the title compound **152**.

Yield:	13.5 mg, 31 % (over 4 steps from unprotected alcohol **115**)
Appearance:	nearly colorless oil
R_f (silica):	0.49 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{23}$:	+6.8 (c 1.07, MeOH)
LC-HRMS (ESI):	calculated for $M+H^+$: 343.2068, found: 343.2070, Δ: 0.62 ppm
(log *P*)$_{calc}$:	5.44 ± 0.59

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 9H, C4''-C(CH_3)$_3$), 1.93 (bs, 1H, OH), 2.32 (quint, ^3J = 6.4 Hz, 1H, H3), 2.56 (dd, ^2J = 12.4 Hz, ^3J = 9.8 Hz, 1H, C4-CH), 2.63 – 2.82 (m, 1H, H4), 2.88 (dd, ^2J = 12.5 Hz, ^3J = 4.7 Hz, 1H, C4-CH), 3.65 – 3.80 (m, 2H, C3-CH, H5), 3.87 (dd, ^2J = 10.7 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.06 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 4.88 (d, ^3J = 5.8 Hz, 1H, H2), 6.92 – 7.15 (m, 4H, H3', H5', H2'', H6''), 7.21 – 7.35 (m, 4H, H2', H6', H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 31.5 (q, C4''-C(<u>C</u>H_3)$_3$), 32.9 (t, C4-<u>C</u>), 34.5 (s, C4''-<u>C</u>(CH_3)$_3$), 42.1 (d, C4), 52.7 (d, C3), 60.8 (t, C3-<u>C</u>), 73.2 (t, C5), 82.5 (d, C2), 115.3 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 125.6 (d, C3'', C5''), 127.3 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.0 Hz), 128.3 (d, C2'', C6''), 137.3 (s, C1''), 139.1 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 149.2 (s, C4''), 162.2 (d, C4', $^1J_{C\text{-}F}$ = 245.1 Hz).

D.3.33 ((2*S*,3*R*,4*R*)-4-([1,1'-Biphenyl]-4-ylmethyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methanol (**153**)



153, $C_{24}H_{23}FO_2$
362.44 g mol^{-1}

***Preparation**:* analogous to **148** (section D.3.28, page 186), using 4-bromo-1,1'-biphenyl (160.9 mg, 0.690 mmol, 1.3 equiv.) as aryl halide coupling partner.

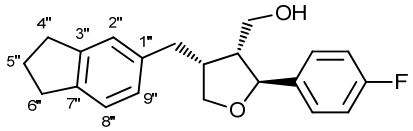
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (30 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / heptane, 20 : 80 to 60 : 40 in 40 min), followed by re-crystallization from EtOAc / heptane afforded the title compound **153**.

Yield:	130.1 mg, 68 % (over 4 steps from unprotected alcohol **115**)
Appearance:	off-white solid
Melting range:	137.0 – 140.0 °C
R_f (silica):	0.43 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{20}$:	+3.9 (c 0.74, MeOH)
(log *P*)$_{calc}$:	5.51 ± 0.60

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.57 (bs, 1H, OH), 2.38 (quint, ^3J = 6.5 Hz, 1H, H3), 2.66 (dd, ^2J = 12.2 Hz, ^3J = 10.1 Hz, 1H, C4-CH), 2.69 – 2.89 (m, 1H, H4), 2.99 (dd, ^2J = 12.3 Hz, ^3J = 4.4 Hz, 1H, C4-CH), 3.70 – 3.85 (m, 2H, C3-CH, H5), 3.87 – 4.01 (m, 1H, C3-CH), 4.10 (dd, ^2J = 8.5 Hz, ^3J = 6.3 Hz, 1H, H5), 4.91 (d, ^3J = 6.0 Hz, 1H, H2), 6.94 – 7.08 (m, 2H, H3', H5'), 7.20 – 7.61 (m, 11H, H2', H6', 9 x Ar''-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.2 (t, C4-C), 42.2 (d, C4), 52.8 (d, C3), 61.0 (t, C3-C), 73.2 (t, C5), 82.6 (d, C2), 115.4 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 127.1 (d, C3''*), 127.3 (d, C8''), 127.4 (d, C6''*), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 128.9 (d, C7''), 129.2 (d, C2''), 139.0 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 139.3 (s, C4''), 139.6 (s, C1''), 140.9 (s, C5''), 162.3 (d, C4', $^1J_{C\text{-}F}$ = 245.4 Hz).

D.3.34 ((2*S*,3*R*,4*R*)-4-((2,3-Dihydro-1H-inden-5-yl)methyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methanol (**154**)



154, $C_{21}H_{23}FO_2$
326.40 g mol^{-1}

***Preparation**:* analogous to **148** (section D.3.28, page 186), using 5-iodo-2,3-dihydro-1*H*-indene **266** (56.2 mg, 0.230 mmol, 1.3 equiv.) as aryl halide coupling partner.

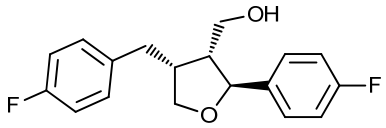
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (30 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 15 : 85 to 55 : 45 in 40 min) afforded the title compound **154**.

Yield:	37.9 mg, 66 % (over 4 steps from unprotected alcohol **115**)
Appearance:	pale brown oil
R_f (silica):	0.47 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{25}$:	+6.8 (c 0.55, MeOH)
LC-HRMS (ESI):	calculated for M+H$^+$: 327.1755, found: 327.1760, Δ: 1.57 ppm
$(\log P)_{calc}$:	4.88 ± 0.58

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (quint, ^3J = 7.4 Hz, 2H, H5''), 2.36 (quint, ^3J = 6.7 Hz, 1H, H3), 2.59 (dd, ^2J = 13.2 Hz, ^3J = 10.3 Hz, 1H, C4-CH), 2.68 – 2.79 (m, 1H, H4), 2.82 – 2.95 (m, 5H, C4-CH, 2 x H4'', 2 x H6''), 3.72 – 3.80 (m, 2H, C3-CH, H5), 3.93 (dd, ^2J = 10.6 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.04 – 4.11 (m, 1H, H5), 4.89 (d, ^2J = 5.9 Hz, 1H, H2), 6.92 – 7.07 (m, 4H, H3', H5', H2'', H9''*), 7.11 – 7.16 (m, 1H, H8''*), 7.29 (dd, ^3J = 8.3 Hz, $^4J_{H\text{-}F}$ = 5.6 Hz, 2H, H2', H6'). OH not visible.

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.6 (t, C5''), 32.6 (t, C6''*), 32.9 (t, C4''*), 33.5 (t, C4-C*), 42.4 (d, C4), 52.9 (d, C3), 61.0 (t, C3-C), 73.3 (t, C5), 82.5 (d, C2), 115.3 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 124.5 (d, C9''), 124.7 (d, C8''), 126.5 (d, C2''), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 138.2 (s, C1''*), 139.1 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 142.3 (s, C7''*), 144.9 (s, C3''*), 162.2 (d, C4', $^1J_{C\text{-}F}$ = 245.0 Hz).

D.3.35 ((2*S*,3*R*,4*R*)-4-(4-Fluorobenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methanol (**155**)



155, $C_{18}H_{18}F_2O_2$
304.33 g mol^{-1}

***Preparation**:* analogous to **148** (section D.3.28, page 186), using 1-bromo-4-fluorobenzene (35.4 mg, 0.202 mmol, 1.3 equiv.) as aryl halide coupling partner.

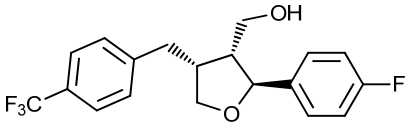
***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 60 : 40 in 35 min) afforded the title compound **155**.

Yield: 22.6 mg, 48 % (over 4 steps from unprotected alcohol **115**)
Appearance: light-brown oil
R_f (silica): 0.41 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{23}$: +12.9 (c 0.77, MeOH)
(log *P*)$_{calc}$: 3.81 ± 0.64

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (bs, 1H, OH), 2.36 (quint, ^3J = 6.5 Hz, 1H, H3), 2.52 – 2.82 (m, 2H, H4, C4-CH), 2.94 (dd, ^2J = 12.3 Hz, ^3J = 3.9 Hz, 1H, C4-CH), 3.67 – 3.98 (m, 3H, C3-CH_2, H5), 4.05 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.88 (d, ^3J = 6.0 Hz, 1H, H2), 6.92 – 7.19 (m, 6H, H3', H5', 4 x Ar''-H), 7.23 – 7.34 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 32.7 (t, C4-C), 42.6 (d, C4), 52.7 (d, C3), 60.7 (t, C3-C), 72.8 (t, C5), 82.7 (d, C2), 115.5 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 115.6 (dd, C3'', C5'', $^2J_{C\text{-}F}$ = 21.3 Hz), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.2 Hz), 130.2 (dd, C2'', C6'', $^3J_{C\text{-}F}$ = 7.7 Hz), 135.7 (d, C1'', $^4J_{C\text{-}F}$ = 3.3 Hz), 138.5 (d, C1', $^4J_{C\text{-}F}$ = 3.2 Hz), 161.7 (d, C4'', $^1J_{C\text{-}F}$ = 244.5 Hz), 162.3 (d, C4', $^1J_{C\text{-}F}$ = 245.8 Hz).

D.3.36 ((2*S*,3*R*,4*R*)-2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methanol (**156**)



156, $C_{19}H_{18}F_4O_2$
354.34 g mol^{-1}

***Preparation**:* analogous to **123** (section D.3.26, page 184), using crude starting material TBDMS-**115** (39.0 mg, 0.121 mmol, 1.0 equiv.) and 1-bromo-4-(trifluoromethyl)benzene (35.4 mg, 0.157 mmol, 1.3 equiv.) as aryl halide coupling partner, and stirring for 42 in place of 27 h during the coupling step.

***Work-up and purification**:* the heterogeneous reaction content was filtered and rinsed with CH_2Cl_2 (20 mL) and the solvents were evaporated. Flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 15 : 85 to 40 : 60 in 35 min) afforded the title compound **156**.

Yield:	17.5 mg, 41 % (over 4 steps from unprotected alcohol **115**)
Appearance:	pale yellow oil
R_f **(silica)**:	0.37 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{23}$:	+12.0 (c 1.36, MeOH)
(log *P*)$_{calc}$:	4.33 ± 0.62

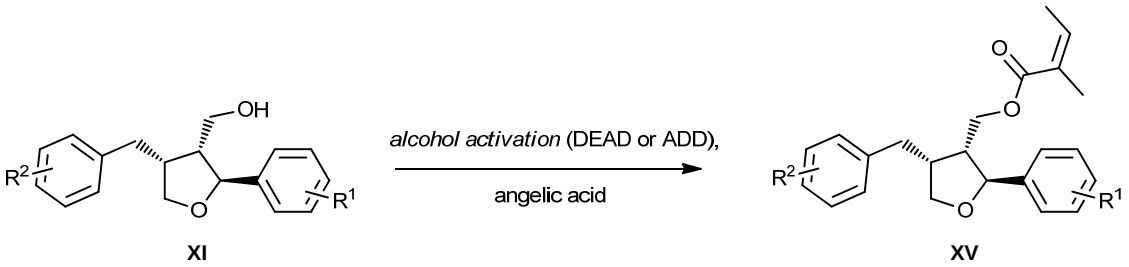
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.84 (bs, 1H, OH), 2.36 (quint, ^3J = 6.6 Hz, 1H, H3), 2.59 – 2.85 (m, 2H, H4, C4-CH), 2.90 – 3.11 (m, 1H, C4-CH), 3.64 – 3.96 (m, 3H, C3-CH_2, H5), 4.03 (dd, ^2J = 8.5 Hz, ^3J = 6.2 Hz, 1H, H5), 4.87 (d, ^3J = 6.1 Hz, 1H), 7.01 (dd, ^3J = 8.7 Hz, $^3J_{H\text{-}F}$ = 8.7 Hz, 2H, H3', H5'), 7.20 – 7.35 (m, 4H, H2', H6', H2'', H6''), 7.54 (d, ^3J = 8.2 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.4 (t, C4-C), 42.1 (d, C4), 52.6 (d, C3), 60.7 (t, C3-C), 72.8 (t, C5), 82.4 (d, C2), 115.4 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 124.4 (q, C4''-CF_3, $^1J_{C\text{-}F}$ = 271.9 Hz), 125.6 (dq, C3'', C5'', $^3J_{C\text{-}F}$ = 3.8 Hz), 127.4 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 128.8 (q, C4'', $^2J_{C\text{-}F}$ = 32.4 Hz), 129.1 (d, C2'', C6''), 138.8 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 144.7 (q, C1'', $^5J_{C\text{-}F}$ = 1.3 Hz), 162.3 (d, C4', $^1J_{C\text{-}F}$ = 245.4 Hz).

D.4 Modification of 3-(Hydroxymethyl)tetrahydrofuran-type Lignans

D.4.1 Mitsunobu Esterification

D.4.1.1 *General Outline* for Mitsunobu Esterification

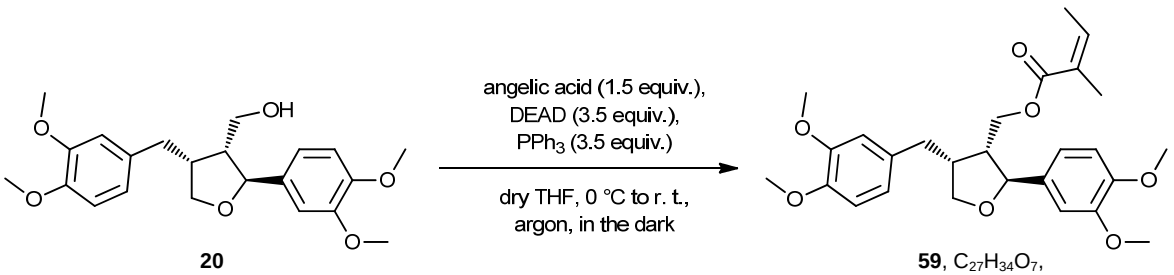


XI **XV**

All compounds of generic structure **XV** in this section were prepared according to the *General Outline* above, and are arranged such that compounds with the same R^1 are grouped together. Thus, for the ***Preparation*** of any particular compound, the experimental details are either given in full, or the reader is referred to an analogous procedure already described for a compound in this section. Generally, reaction progress was monitored by TLC or GC-MS, and the reaction was terminated when complete.

Details for ***Work-up and purification*** are given for each case individually to afford compounds of structure **XV**.

D.4.1.2 (*Z*)-((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (leoligin, **59**)



20

59, $C_{27}H_{34}O_7$, 470.55 g mol^{-1}

Preparation*:* a reaction vessel was charged with a stirring bar, starting material **20** (989 mg, 2.55 mmol, 1.0 equiv.), angelic acid (383 mg, 3.83 mmol, 1.5 equiv.) and PPh_3 (2.34 g, 8.93 mmol, 3.5 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry THF (20 mL) was then added and the solution cooled to 0 °C in an ice bath. To the stirred mixture was then added DEAD (1.40 mL, 8.93 mmol, 3.5 equiv.) dropwise *via* syringe, and the reaction stirred for 12 h while being kept away from light and allowed to warm slowly to room temperature.

***Work-up and purification**:* The solvent was evaporated, which was followed by the addition of $CHCl_3$ (15 mL), LP (300 mL) and water (200 mL). The layers were separated and the aqueous phase was re-extracted with LP (4 x 50 ml). The solvents were evaporated from the combined organic phases and then flash column chromatography was performed (180 g silica, flow rate 40 mL / min, EtOAc / LP, 25 : 75 to 50 : 50 in 60 min) to afford the title compound **59**. An analytical sample could be crystallized from a saturated solution of heptane and cooling it to -20 °C for several days.

Leoligin is a literature-known natural compound.[153]

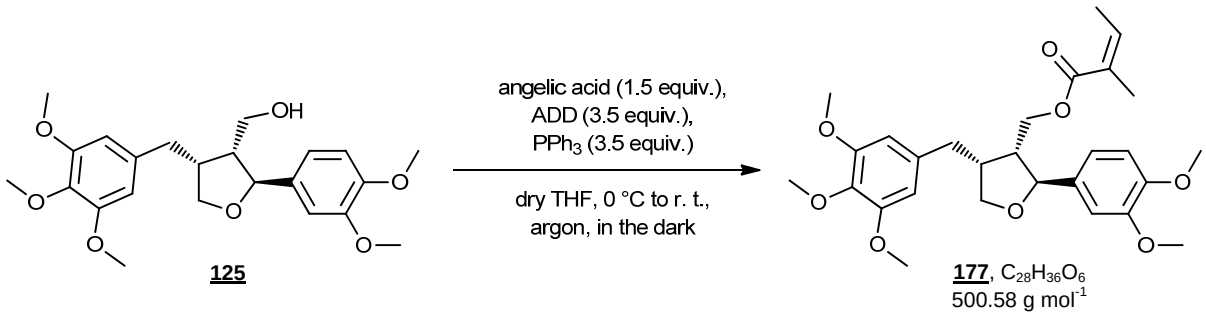
Yield:	1.124 g, 94 %
Appearance:	nearly colorless oil
Melting range:	45.0 – 46.5 °C; lit.[153] **melting range**: n/a (natural compound obtained as a colorless amorphous substance)
R_f **(silica)**:	0.57 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{25}$:	+23.4 (c 3.69, MeOH); lit.[153] $[\alpha]_D^{20}$: +25 (c 0.002, CH_2Cl_2)
LC-HRMS (ESI):	calculated for M+Na$^+$: 493.2197, found: 493.2201, Δ: 0.81 ppm
$(\log P)_{calc}$:	5.38 ± 0.48

GC-MS (EI, 70 eV, Method E): 23.65 min; 470.2 (M^+, 3), 219.1 (26), 189.1 (15), 177.1 (15), 165.1 (72), 151.0 (100), 107.1 (15).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 – 1.90 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.49 – 2.85 (m, 3H, H3, H4, C4-CH), 2.90 (dd, ^2J = 12.4 Hz, ^3J = 4.2 Hz, 1H, C4-CH), 3.78 (dd, ^2J = 8.6 Hz, ^3J = 6.0 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.08 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.28 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.42 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.3 Hz, 1H, H2), 6.10 (qq, ^3J = 7.2 Hz, ^4J = 1.3 Hz, 1H, H3'''), 6.67 – 6.75 (m, 2H, H2'', H6''), 6.77 – 6.90 (m, 4H, H2', H5', H6', H5'').

^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 33.3 (t, C4-C), 42.8 (d, C4), 49.3 (d, C3), 56.0 (q, 2 x Ar-OCH_3), 56.0 (q, Ar-OCH_3), 56.1 (q, Ar-OCH_3), 62.3 (t, C3-C), 72.8 (t, C5), 83.0 (d, C2), 109.0 (d, C2'), 111.2 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.6 (d, C6''), 127.5 (s, C2'''), 132.7 (s, C1''), 135.1 (s, C1'), 139.0 (d, C3'''), 147.6 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 167.8 (s, C1''').

D.4.1.3 (*Z*)-((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(3,4,5-trimethoxybenzyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**177**)



***Preparation**:* a reaction vessel was charged with a stirring bar, starting material **125** (25.3 mg, 0.051 mmol, 1.0 equiv.), angelic acid (7.6 mg, 0.076 mmol, 1.5 equiv.) and PPh_3 (46.5 mg, 0.177 mmol, 3.5 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry THF (0.75 mL) was then added *via* syringe and the solution cooled to 0 °C in an ice bath. To the stirred mixture was then added a solution of ADD (44.7 mg, 0.177 mmol, 3.5 equiv.) in dry THF (1.0 mL) *via* syringe over approximately 1 min, and the reaction stirred for 46 h while being kept away from light and allowed to warm slowly to room temperature.

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL). The solvents were evaporated and flash column chromatography was performed (9 g silica, flow rate 20 mL / min, EtOAc / heptane, 1 : 99 to 10 : 90 in 10 min, then to 70 : 30 in 50 min), followed by preparative HPLC (flow rate 21.2 mL / min, MeOH / water, isocratic steps of 40 : 60, then 60 : 40, then 80 : 20) to afford the title compound **177**.

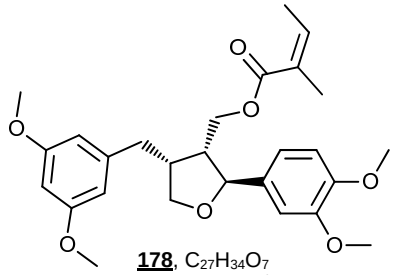
Yield:	17.2 mg, 68 %
Appearance:	pale yellow oil
R_f (silica):	0.39 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{25}$:	+25.1 (c 0.64, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 523.2308, found: 523.2319, Δ: 2.13 ppm
(log *P*)$_{calc}$:	4.95 ± 0.50

GC-MS (EI, 70 eV, Method J): 48.67 min; 500.3 (M^+, 17), 400.2 (35), 236.1 (23), 220.1 (22), 219.1 (100), 208.1 (20), 189.1 (19), 182.1 (59), 181.1 (76), 167.1 (17), 166.1 (17), 165.1 (96), 151.1 (88).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.83 – 1.91 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.47 – 2.82 (m, 3H, H3, H4, C4-CH), 2.90 (dd, ^2J = 12.5 Hz, ^3J = 4.1 Hz, 1H, C4-CH), 3.74 – 3.83 (m, 1H, H5), 3.82 (s, 3H, C4''-OCH_3), 3.84 (s, 6H, C3''-OCH_3, C5''-OCH_3), 3.86 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.09 (dd, ^2J = 8.6 Hz, ^3J = 6.1 Hz, 1H, H5), 4.27 (dd, ^2J = 11.3 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.42 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.83 (d, ^3J = 6.4 Hz, 1H, H2), 6.10 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.38 (s, 2H, H2'', H6''), 6.79 – 6.91 (m, 3H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 34.1 (t, C4-C), 42.8 (d, C4), 49.4 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 56.2 (q, C3''-OCH_3, C5''-OCH_3), 61.0 (q, C4''-OCH_3), 62.2 (t, C3-C), 72.8 (t, C5), 82.9 (d, C2), 105.7 (s, C2'', C6''), 109.0 (d, C2'), 111.2 (d, C5'), 118.2 (d, C6'), 127.4 (s, C2'''), 135.0 (s, C1'), 136.0 (s, C1''*), 136.6 (s, C4''*), 139.1 (d, C3'''), 148.6 (s, C4'), 149.2 (s, C3'), 153.4 (s, C3'', C5''), 167.8 (s, C1''').

D.4.1.4 (*Z*)-((2*S*,3*R*,4*R*)-4-(3,5-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**178**)



178, $C_{27}H_{34}O_7$
470.55 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **126** (28.4 mg, 0.073 mmol, 1.00 equiv.).

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL). The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / heptane, 1 : 99 to 10 : 90 in 10 min, then to 70 : 30 in 50 min) afforded the title compound **178**.

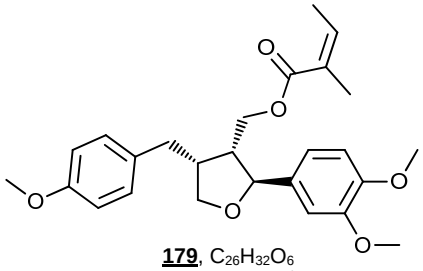
Yield:	30.2 mg, 88 %
Appearance:	colorless oil
R_f (silica):	0.29 (EtOAc / heptane, 1 : 2)
$[\alpha]_D^{25}$:	+24.4 (c 1.32, *i*-PrOH)
LC-HRMS (ESI):	calculated for M+Na^+: 493.2202, found: 493.2212, Δ: 1.99 ppm
(log *P*)$_{calc}$:	5.35 ± 0.47

GC-MS (EI, 70 eV, Method E): 20.97 min; 470.7 (M^+, 5), 219.3 (16), 165.8 (30), 164.9 (64), 152.1 (100), 151.1 (77), 90.8 (20).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 – 1.91 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.49 – 2.95 (m, 4H, H3, H4, C4-CH_2), 3.73 – 3.82 (m, 1H, H5), 3.78 (s, 6H, C3''-OCH_3, C5''-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.09 (dd, ^2J = 8.7 Hz, ^3J = 6.4 Hz, 1H, H5), 4.27 (dd, ^2J = 11.4 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.40 (dd, ^2J = 11.3 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.83 (d, ^3J = 6.4 Hz, 1H, H2), 6.10 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.33 (s, 3H, Ar''-H), 6.79 – 6.92 (m, 3H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 15.9 (q, C4'''), 20.7 (q, C5'''), 34.0 (t, C4-C), 42.4 (d, C4), 49.3 (d, C3), 55.4 (q, C3''-OCH_3, C5''-OCH_3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.3 (t, C3-C), 72.8 (t, C5), 82.9 (d, C2), 98.1 (d, C4''), 106.9 (d, C2'', C6''), 109.0 (d, C2'), 111.2 (d, C5'), 118.2 (d, C6'), 127.5 (s, C2'''), 135.0 (s, C1'), 139.0 (d, C3'''), 142.6 (s, C1''), 148.6 (s, C4'), 149.2 (s, C3'), 161.0 (s, C3'', C5''), 167.8 (s, C1''').

D.4.1.5 (*Z*)-((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(4-methoxybenzyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**179**)



179, $C_{26}H_{32}O_6$
440.53 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **127** (24.0 mg, 0.067 mmol, 1.0 equiv.) and stirring for 22 in place of 46 h.

***Work-up and purification**:* Et_2O (20 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (10 mL). The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 isocratically for 3 min, then to 40 : 60 in 30 min) afforded the title compound **179**.

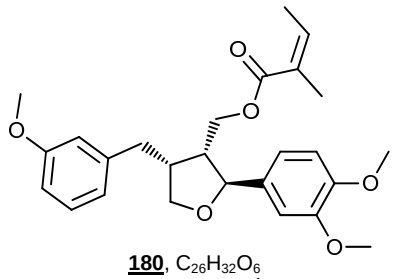
Yield:	24.0 mg, 81 %
Appearance:	colorless oil
R_f (silica):	0.67 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{25}$:	+25.1 (c 2.35, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 463.2091, found: 463.2058, Δ: -7.12 ppm
(log *P*)$_{calc}$:	5.56 ± 0.46

GC-MS (EI, 70 eV, Method F): 18.75 min; 440.2 (M^+, 3), 219.1 (31), 166.1 (17), 165.1 (89), 160.1 (17), 159.1 (20), 151.1 (17), 147.1 (23), 121.0 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 – 1.90 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.49 – 2.82 (m, 3H, H3, H4, C4-CH), 2.89 (dd, ^2J = 12.5 Hz, ^3J = 4.3 Hz, 1H, C4-CH), 3.76 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 3.79 (s, 3H, C4''-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.27 (dd, ^2J = 11.4 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.40 (dd, ^2J = 11.3 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.2 Hz, 1H, H2), 6.10 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.79 – 6.89 (m, 5H, 3 x Ar'-H, H3'', H5''), 7.09 (d, ^3J = 8.6 Hz, 2H, H2'', H6'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 32.8 (t, C4-C), 42.7 (d, C4), 49.3 (d, C3), 55.4 (q, C4''-OCH_3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.3 (t, C3-C), 72.8 (t, C5), 83.0 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 114.1 (d, C3'', C5''), 118.1 (d, C6'), 127.5 (s, C2'''), 129.6 (d, C2'', C6''), 132.2 (s, C1''), 135.1 (s, C1'), 139.0 (d, C3'''), 148.6 (s, C4'), 149.2 (s, C3'), 158.2 (s, C4''), 167.9 (s, C1''').

D.4.1.6 (*Z*)-((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(3-methoxybenzyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**180**)



180, $C_{26}H_{32}O_6$
440.53 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **128** (28.1 mg, 0.078 mmol, 1.00 equiv.) and stirring for 22 in place of 46 h.

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL). The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 10 : 90 in 5 min, then to 40 : 60 in 30) afforded the title compound **180**.

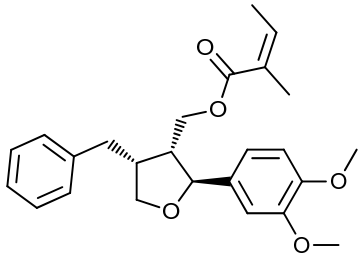
Yield:	31.2 mg, 90 %
Appearance:	colorless oil
R_f (silica):	0.68 (EtOAc / cyclohexane, 1 : 1)
$[\alpha]_D^{20}$:	+30.4 (c 1.21, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 463.2091, found: 463.2109, Δ: 3.89 ppm
(log *P*)$_{calc}$:	5.56 ± 0.46

GC-MS (EI, 70 eV, Method E): 17.63 min; 440.1 (M^+, 6), 340.1 (18), 219.1 (36), 174.1 (28), 173.1 (18), 166.1 (24), 165.0 (100), 159.1 (28), 151.0 (37), 147.1 (23), 121.1 (58), 91.1 (23).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 – 1.91 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.53 – 2.87 (m, 3H, H3, H4, C4-CH), 2.93 (dd, ^2J = 12.4 Hz, ^3J = 4.2 Hz, 1H, C4-CH), 3.77 (dd, ^2J = 8.7 Hz, ^3J = 6.3 Hz, 1H, H5), 3.80 (s, 3H, C3''-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.08 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.27 (dd, ^2J = 11.4 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.41 (dd, ^2J = 11.4 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.4 Hz, 1H, H2), 6.10 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.69 – 6.92 (m, 6H, 3 x Ar'-H, H2'', H4'', H6''), 7.23 (t, ^3J = 7.8 Hz, 1H, H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 33.7 (t, C4-C), 42.4 (d, C4), 49.3 (d, C3), 55.3 (q, C3''-OCH_3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.3 (t, C3-C), 72.8 (t, C5), 82.9 (d, C2), 108.9 (d, C2'), 111.1 (d, C5'*), 111.5 (d, C4''*), 114.6 (d, C2''), 118.2 (d, C6'), 121.1 (d, C6''), 127.5 (s, C2'''), 129.7 (d, C5''), 135.0 (s, C1'), 139.1 (d, C3'''), 141.8 (s, C1''), 148.6 (s, C4'), 149.2 (s, C3'), 159.9 (s, C3''), 167.8 (s, C1''').

D.4.1.7 (*Z*)-((2*S*,3*R*,4*R*)-4-Benzyl-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**181**)



181, $C_{25}H_{30}O_5$
410.50 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **129** (24.4 mg, 0.074 mmol, 1.00 equiv.) and stirring for 22 in place of 46 h.

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL). The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 35 : 65 in 30 min) afforded the title compound **181**.

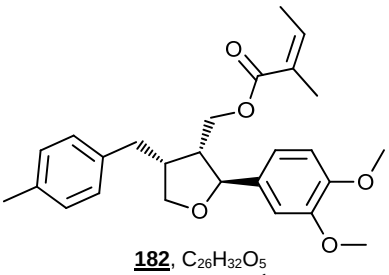
Yield:	26.4 mg, 86 %
Appearance:	colorless oil
R_f (silica):	0.74 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{25}$:	+31.6 (c 2.64, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 433.1985, found: 433.1968, Δ: -3.92 ppm
(log *P*)$_{calc}$:	5.64 ± 0.44

GC-MS (EI, 70 eV, Method F): 13.41 min; 410.2 (M^+, 2), 219.1 (22), 166.1 (55), 165.0 (100), 151.0 (19), 117.1 (23), 91.0 (68).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 – 1.91 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.3 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.70 – 2.53 (m, 2H, H3, C4-CH), 2.89 – 2.70 (m, 1H, H4), 2.95 (dd, ^2J = 12.5 Hz, ^3J = 4.1 Hz, 1H, C4-CH), 3.77 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.28 (dd, ^2J = 11.4 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.41 (dd, ^2J = 11.4 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.85 (d, ^3J = 6.3 Hz, 1H, H2), 6.10 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.92 – 6.79 (m, 3H, Ar'-H), 7.36 – 7.13 (m, 5H, Ar''-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 33.7 (t, C4-C), 42.5 (d, C4), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.3 (t, C3-C), 72.8 (t, C5), 83.0 (d, C2), 108.9 (d, C2'), 111.1 (d, C5'), 118.1 (d, C6'), 126.4 (d, C4''), 127.5 (s, C2'''), 128.7 (d, C2'', C6''; C3'', C5''; signal overlap), 135.1 (s, C1'), 139.1 (d, C3'''), 140.2 (s, C1''), 148.6 (s, C4'), 149.2 (s, C3'), 167.8 (s, C1''').

D.4.1.8 (*Z*)-((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(4-methylbenzyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**182**)



182, $C_{26}H_{32}O_5$
424.53 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **130** (29.4 mg, 0.086 mmol, 1.00 equiv.) and stirring for 22 in place of 46 h.

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (10 mL). The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 35 : 65 in 30 min) afforded the title compound **182**.

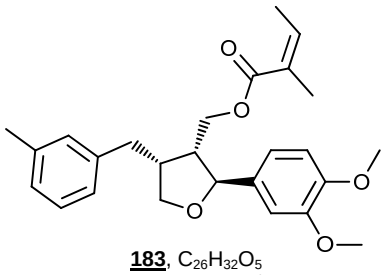
Yield:	30.8 mg, 84 %
Appearance:	colorless oil
R_f (silica):	0.75 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+27.1 (c 1.92, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 447.2142, found: 447.2149, Δ: 1.57 ppm
(log *P*)$_{calc}$:	6.10 ± 0.45

GC-MS (EI, 70 eV, Method E): 14.99 min; 424.3 (M^+, 3), 219.1 (26), 166.1 (50), 165.1 (100), 151.1 (19), 143.1 (18), 131.1 (27), 105.1 (76).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.84 – 1.90 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.32 (s, 3H, C4''-CH_3), 2.51 – 2.84 (m, 3H, H3, H4, C4-CH), 2.91 (dd, ^2J = 12.4 Hz, ^3J = 4.2 Hz, 1H, C4-CH), 3.76 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.27 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.41 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.2 Hz, 1H, H2), 6.10 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.78 – 6.91 (m, 3H, Ar'-H), 7.03 – 7.14 (m, 4H, Ar''-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 21.1 (q, C4''-$\underline{C}H_3$), 33.2 (t, C4-$\underline{C}$), 42.6 (d, C4), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.3 (t, C3-$\underline{C}$), 72.9 (t, C5), 83.0 (d, C2), 108.9 (d, C2'), 111.1 (d, C5'), 118.1 (d, C6'), 127.5 (s, C2'''), 128.6 (d, C2'', C6''), 129.4 (d, C3'', C5''), 135.1 (s, C1'), 135.9 (s, C4''), 137.1 (s, C1''), 139.0 (d, C3'''), 148.5 (s, C4'), 149.2 (s, C3'), 167.8 (s, C1''').

D.4.1.9 (*Z*)-((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(3-methylbenzyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**183**)



183, $C_{26}H_{32}O_5$
424.53 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **131** (23.5 mg, 0.069 mmol, 1.00 equiv.) and stirring for 22 in place of 46 h.

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (10 mL). The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 40 : 60 in 45 min) afforded the title compound **183**.

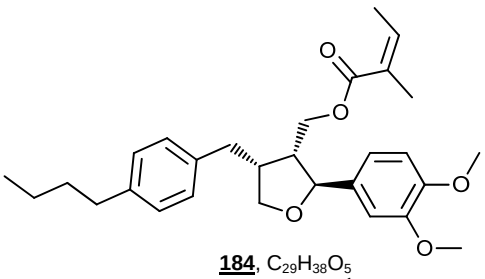
Yield:	24.6 mg, 85 %
Appearance:	colorless oil
R_f (silica):	0.40 (EtOAc / heptane, 1 : 2)
$[\alpha]_D^{25}$:	+25.7 (c 1.37, *i*-PrOH)
LC-HRMS (ESI):	calculated for M+H$^+$: 425.2322, found: 425.2316, Δ: -1.52 ppm
(log *P*)$_{calc}$:	6.10 ± 0.45

GC-MS (EI, 70 eV, Method E): 13.08 min; 166.2 (65), 165.4 (71), 164.8 (71), 150.9 (17), 143.1 (18), 130.8 (21), 105.0 (*m*-methylbenzyl, 100), 103.0 (16), 91.0 (19). M$^+$ not visible.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 – 1.92 (m, 3H, H5'''), 1.96 – 2.05 (m, 3H, H4'''), 2.33 (s, 3H, C3''-CH_3), 2.51 – 2.85 (m, 3H, H3, H4, C4-CH), 2.92 (dd, ^2J = 12.4 Hz, ^3J = 4.3 Hz, 1H, C4-CH), 3.77 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.28 (dd, ^2J = 11.4 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.41 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.3 Hz, 1H, H2), 6.10 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.78 – 7.07 (m, 6H, 3 x Ar'-H, H2'', H4'', H6''), 7.19 (t, ^3J = 7.8 Hz, 1H, H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 15.9 (q, C4'''), 20.7 (q, C5'''), 21.5 (q, C3''-$\underline{C}H_3$), 33.6 (t, C4-$\underline{C}$), 42.5 (d, C4), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.3 (t, C3-$\underline{C}$), 72.8 (t, C5), 83.0 (d, C2), 109.0 (d, C2'), 111.2 (d, C5'), 118.2 (d, C6'), 125.7 (d, C6''), 127.1 (d, C4''), 127.5 (s, C2'''), 128.6 (d, C5''), 129.6 (d, C2''), 135.1 (s, C1'), 138.3 (s, C3''), 139.0 (d, C3'''), 140.1 (s, C1''), 148.6 (s, C4'), 149.2 (s, C3'), 167.8 (s, C1''').

D.4.1.10 (*Z*)-((2*S*,3*R*,4*R*)-4-(4-Butylbenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**184**)



184, $C_{29}H_{38}O_5$
466.61 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **132** (31.8 mg, 0.083 mmol, 1.00 equiv.).

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL). The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 40 : 60 in 45 min) afforded the title compound **184**.

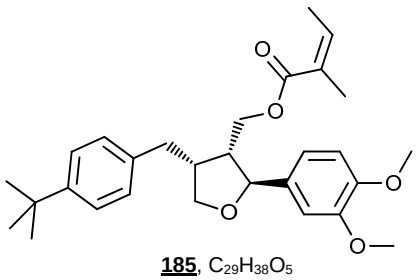
Yield:	29.8 mg, 77 %
Appearance:	colorless oil
R_f (silica):	0.43 (EtOAc / heptane, 1 : 2)
$[\alpha]_D^{25}$:	+17.1 (c 1.54, *i*-PrOH)
LC-HRMS (ESI):	calculated for M+H$^+$: 467.2792, found: 467.2815, Δ: 4.93 ppm
(log *P*)$_{calc}$:	7.69 ± 0.45

GC-MS (EI, 70 eV, Method E): 19.79 min; 466.0 (M$^+$, 4), 219.2 (22), 166.3 (28), 165.1 (100), 147.0 (28), 117.1 (29), 105.1 (25), 104.0 (52), 91.2 (27), 90.7 (20).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.92 (t, ^3J = 7.2 Hz, 3H, C4''-$CH_2CH_2CH_2\underline{C}H_3$), 1.35 (sext, ^3J = 7.2 Hz, 2H, C4''-$CH_2CH_2\underline{C}H_2CH_3$), 1.49 – 1.67 (m, 2H, C4''-$CH_2\underline{C}H_2CH_2CH_3$), 1.84 – 1.91 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.3 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.50 – 2.86 (m, 5H, H3, H4, C4-CH, C4''-$\underline{C}H_2CH_2CH_2CH_3$), 2.91 (dd, ^2J = 12.5 Hz, ^3J = 4.2 Hz, 1H, C4-CH), 3.77 (dd, ^2J = 8.5 Hz, ^3J = 6.3 Hz, 1H, H5), 3.86 (s, 3H, Ar'-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 4.08 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.28 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.41 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.2 Hz, 1H, H2), 6.09 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.78 – 6.92 (m, 3H, Ar'-H), 7.03 – 7.15 (m, 4H, Ar''-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (q, C4''-$CH_2CH_2CH_2\underline{C}H_3$), 16.0 (q, C4'''), 20.7 (q, C5'''), 22.5 (t, C4''-$CH_2CH_2\underline{C}H_2CH_3$), 33.3 (t, C4-C), 33.8 (t, C4''-$CH_2\underline{C}H_2CH_2CH_3$), 35.3 (t, C4''-$\underline{C}H_2CH_2CH_2CH_3$), 42.6 (d, C4), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.3 (t, C3-C), 72.9 (t, C5), 83.0 (d, C2), 109.0 (d, C2'), 111.2 (d, C5'), 118.2 (d, C6'), 127.5 (s, C2'''), 128.6 (d, C2''*, C6''*), 128.7 (d, C3''*, C5''*), 135.2 (s, C1'), 137.3 (s, C1''), 139.0 (d, C3'''), 141.0 (s, C4''), 148.6 (s, C4'), 149.2 (s, C3'), 167.8 (s, C1''').

D.4.1.11 (*Z*)-((2*S*,3*R*,4*R*)-4-(4-(*tert*-Butyl)benzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**185**)



185, $C_{29}H_{38}O_5$
466.61 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **133** (31.1 mg, 0.081 mmol, 1.00 equiv.) and stirring for 22 in place of 46 h.

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL). The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 7 : 93 isocratically for 3 min, then to 35 : 65 in 30 min) afforded the title compound **185**.

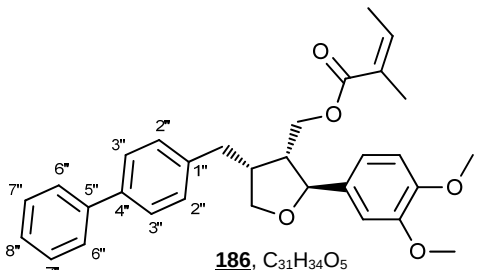
Yield:	25.4 mg, 67 %
Appearance:	colorless oil
R_f (silica):	0.78 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+21.4 (c 1.52, MeOH)
LC-HRMS (APCI):	calculated for M+Na^+: 489.2611, found: 489.2676, Δ: 13.29 ppm
(log *P*)$_{calc}$:	7.33 ± 0.46

GC-MS (EI, 70 eV, Method F): 19.94 min; 466.3 (M^+, 2), 219.1 (37), 185.1 (20), 180.1 (16), 166.1 (37), 165.1 (100), 151.1 (20), 147.1 (19), 132.1 (16), 131.1 (15), 117.1 (25).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 9H, C4''-$C(CH_3)_3$), 1.85 – 1.90 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.53 – 2.86 (m, 3H, H3, H4, C4-CH), 2.91 (dd, ^2J = 12.4 Hz, ^3J = 4.2 Hz, 1H, C4-CH), 3.80 (dd, ^2J = 8.5 Hz, ^3J = 6.3 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.09 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.28 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.42 (dd, ^2J = 11.4 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.3 Hz, 1H, H2), 6.10 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.79 – 6.92 (m, 3H, Ar'-H), 7.10 (d, ^3J = 8.3 Hz, 2H, H2'', H6''), 7.32 (d, ^3J = 8.3 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 31.5 (q, C4''-C($\underline{C}H_3)_3$), 33.1 (t, C4-$\underline{C}$), 34.5 (s, C4''-$\underline{C}(CH_3)_3$), 42.5 (d, C4), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.4 (t, C3-$\underline{C}$), 73.0 (t, C5), 83.0 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 118.2 (d, C6'), 125.6 (d, C3'', C5''), 127.5 (s, C2'''), 128.4 (d, C2'', C6''), 135.2 (s, C1'), 137.1 (s, C1''), 139.0 (d, C3'''), 148.6 (s, C4'), 149.18 (s, C3'*), 149.21 (s, C4''*), 167.9 (s, C1''').

D.4.1.12 (*Z*)-((2*S*,3*R*,4*R*)-4-([1,1'-Biphenyl]-4-ylmethyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**186**)



186, $C_{31}H_{34}O_5$
486.60 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **134** (24.9 mg, 0.062 mmol, 1.00 equiv.) and stirring for 22 in place of 46 h.

***Work-up and purification**:* The solvent was evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 35 : 65 in 30 min) afforded the title compound **186**.

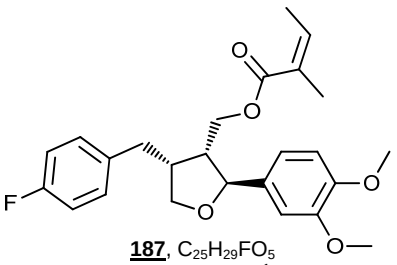
Yield:	29.3 mg, 98 %
Appearance:	colorless crystals
Melting range:	100.0 – 104.0 °C
R_f (silica):	0.73 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+1.1 (c 1.91, $CHCl_3$)
LC-HRMS (APCI):	calculated for M+H+: 487.2479, found: 487.2530, Δ: 10.47 ppm
(log *P*)$_{calc}$:	7.40 ± 0.48

GC-MS (EI, 70 eV, Method F): 49.66 min; 486.3 (M^+, 2), 219.1 (31), 207.1 (27), 193.1 (18), 167.1 (56), 166.1 (22), 165.1 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.87 – 1.92 (m, 3H, H5'''), 2.01 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.56 – 2.93 (m, 3H, H3, H4, C4-CH), 2.99 (dd, ^2J = 12.4 Hz, ^3J = 4.1 Hz, 1H, C4-CH), 3.81 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.12 (dd, ^2J = 8.7 Hz, ^3J = 6.2 Hz, 1H, H5), 4.30 (dd, ^2J = 11.4 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.44 (dd, ^2J = 11.4 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.87 (d, ^3J = 6.3 Hz, 1H, H2), 6.11 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.80 – 6.92 (m, 3H, Ar'-H), 7.21 – 7.61 (m, 9H, Ar''-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 33.4 (t, C4-C), 42.5 (d, C4), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.3 (t, C3-C), 72.9 (t, C5), 83.0 (d, C2), 109.0 (d, C2'), 111.2 (d, C5'), 118.2 (d, C6'), 127.1 (d, C3''*), 127.3 (d, C8''), 127.4 (d, C6''*), 127.5 (s, C2'''), 128.9 (d, C2''*), 129.2 (d, C7''*), 135.1 (s, C1'), 139.1 (d, C3'''), 139.3 (s, C4''*), 139.4 (s, C5''*), 140.9 (s, C1''*), 148.6 (s, C4'), 149.2 (s, C3'), 167.8 (s, C1''').

D.4.1.13 (*Z*)-((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(4-fluorobenzyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**187**)



187, $C_{25}H_{29}FO_5$
428.49 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **136** (29.8 mg, 0.086 mmol, 1.0 equiv.) and stirring for 22 in place of 46 h.

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL). The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 35 : 65 in 30 min) afforded the title compound **187**.

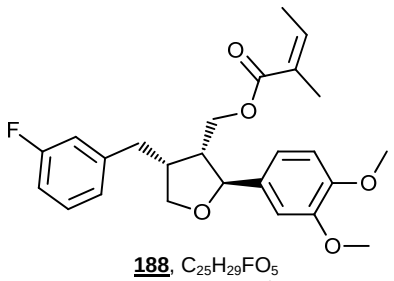
Yield:	27.8 mg, 75 %
Appearance:	colorless oil
R_f (silica):	0.73 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{25}$:	+34.0 (c 1.04, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 451.1891, found: 451.1909, Δ: 3.99 ppm
(log *P*)$_{calc}$:	5.69 ± 0.52

GC-MS (EI, 70 eV, Method F): 13.23 min; 428.2 (M^+, 3), 328.2 (15), 219.1 (24), 166.1 (48), 165.0 (100), 151.0 (17), 135.1 (22), 109.0 (68).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.83 – 1.91 (m, 3H, H5'''), 2.00 (d, ^3J = 7.8 Hz, 3H, H4'''), 2.51 – 2.85 (m, 3H, H3, H4, C4-CH), 2.92 (dd, ^2J = 12.5 Hz, ^3J = 3.9 Hz, 1H, C4-CH), 3.74 (dd, ^2J = 8.6 Hz, ^3J = 6.1 Hz, 1H, H5), 3.87 (s, 6H, Ar'-OCH_3), 4.06 (dd, ^2J = 8.6 Hz, ^3J = 6.1 Hz, 1H, H5), 4.26 (dd, ^2J = 11.3 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.40 (dd, ^2J = 11.4 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.2 Hz, 1H, H2), 6.11 (q, ^3J = 7.0 Hz, 1H, H3'''), 6.79 – 6.90 (m, 3H, Ar'-H), 6.98 (dd, ^3J = 8.6 Hz, $^3J_{H-F}$ = 8.6 Hz, 2H, H3'', H5''), 7.13 (dd, ^3J = 8.4 Hz, $^4J_{H-F}$ = 5.6 Hz, 2H, H2'', H6'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 32.9 (t, C4-C), 42.6 (d, C4), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.2 (t, C3-C), 72.7 (t, C5), 82.9 (d, C2), 108.9 (d, C2'), 111.2 (d, C5'), 115.5 (dd, C3'', C5'', $^2J_{C-F}$ = 21.2 Hz), 118.1 (d, C6'), 127.4 (s, C2'''), 130.1 (dd, C2'', C6'', $^3J_{C-F}$ = 7.8 Hz), 135.0 (s, C1'), 135.8 (d, C1'', $^4J_{C-F}$ = 3.3 Hz), 139.2 (d, C3'''), 148.6 (s, C4'), 149.2 (s, C3'), 161.6 (d, C4'', $^1J_{C-F}$ = 244.2 Hz), 167.8 (s, C1''').

D.4.1.14 (*Z*)-((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(3-fluorobenzyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**188**)



188, $C_{25}H_{29}FO_5$
428.49 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **137** (29.3 mg, 0.085 mmol, 1.00 equiv.) and stirring for 22 in place of 46 h.

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL). The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 40 : 60 in 40 min) afforded the title compound **188**.

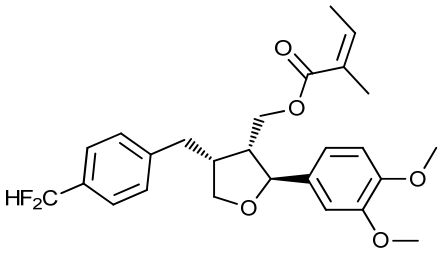
Yield:	32.8 mg, 91 %
Appearance:	colorless oil
R_f (silica):	0.73 (EtOAc / cyclohexane, 1 : 1)
$[\alpha]_D^{20}$:	+31.3 (c 1.17, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 451.1891, found: 451.1910, Δ: 4.21 ppm
(log *P*)$_{calc}$:	5.69 ± 0.52

GC-MS (EI, 70 eV, Method E): 13.06 min; 428.1 (M^+, 3), 328.1 (15), 219.1 (23), 166.1 (49), 165.0 (100), 151.1 (16), 135.1 (17), 109.0 (43).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 – 1. 90 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.54 – 2.87 (m, 3H, H3, H4, C4-CH), 2.95 (dd, ^2J = 12.6 Hz, ^3J = 3.9 Hz, 1H, C4-CH), 3.74 (dd, ^2J = 8.7 Hz, ^3J = 6.1 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.08 (dd, ^2J = 8.7 Hz, ^3J = 6.1 Hz, 1H, H5), 4.27 (dd, ^2J = 11.4 Hz, ^3J = 6.7 Hz, 1H, C3-CH), 4.39 (dd, ^2J = 11.4 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.83 (d, ^3J = 6.3 Hz, 1H, H2), 6.11 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.75 – 7.01 (m, 6H, 3 x Ar'-H, H2'', H4'', H6''), 7.17 – 7.33 (m, 1H, H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 33.5 (td, C4-C, $^4J_{C\text{-}F}$ = 1.5 Hz), 42.3 (d, C4), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.1 (t, C3-C), 72.7 (t, C5), 82.9 (d, C2), 108.9 (d, C2'), 111.1 (d, C5'), 113.4 (dd, C4'', $^2J_{C\text{-}F}$ = 21.1 Hz), 115.5 (dd, C2'', $^2J_{C\text{-}F}$ = 21.0 Hz), 118.2 (d, C6'), 124.4 (dd, C6'', $^4J_{C\text{-}F}$ = 2.8 Hz), 127.4 (s, C2'''), 130.2 (dd, C5'', $^3J_{C\text{-}F}$ = 8.4 Hz), 134.9 (s, C1'), 139.2 (d, C3'''), 142.7 (d, C1'', $^3J_{C\text{-}F}$ = 7.2 Hz), 148.6 (s, C4'), 149.2 (s, C3'), 163.1 (d, C3'', $^1J_{C\text{-}F}$ = 246.0 Hz), 167.8 (s, C1''').

D.4.1.15 (*Z*)-((2*S*,3*R*,4*R*)-4-(4-(Difluoromethyl)benzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**189**)



189, $C_{26}H_{30}F_2O_5$
460.51 g mol^{-1}

***Preparation**:* Preparation analogous of **177** (section D.4.1.3, page 196), using starting material **138** (24.3 mg, 0.064 mmol, 1.00 equiv.).

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL). The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 40 : 60 in 50 min) afforded the title compound **189**.

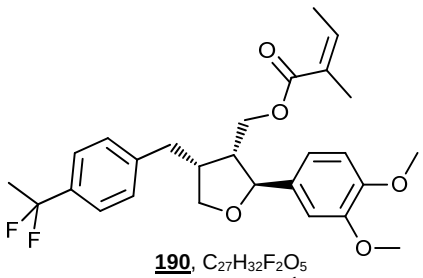
Yield:	23.3 mg, 79 %
Appearance:	colorless oil
R_f (silica):	0.33 (EtOAc / heptane, 1 : 2)
$[\alpha]_D^{25}$:	+20.4 (c 1.16, *i*-PrOH)
LC-HRMS (ESI):	calculated for M+H$^+$: 461.2134, found: 461.2165, Δ: 6.71 ppm
(log *P*)$_{calc}$:	6.01 ± 0.63

GC-MS (EI, 70 eV, Method E): 13.57 min; 460.5 (M$^+$, 3), 166.3 (36), 165.4 (65), 164.7 (51), 154.2 (17), 141.4 (20), 140.9 (42), 122.1 (17), 91.0 (41), 55.0 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 – 1.91 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.55 – 2.90 (m, 3H, H3, H4, C4-CH), 2.92 – 3.05 (m, 1H, C4-CH), 3.74 (dd, ^2J = 8.7 Hz, ^3J = 6.0 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.07 (dd, ^2J = 8.7 Hz, ^3J = 6.0 Hz, 1H, H5), 4.28 (dd, ^2J = 11.4 Hz, ^3J = 6.7 Hz, 1H, C3-CH), 4.41 (dd, ^2J = 11.4 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.3 Hz, 1H, H2), 6.11 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.62 (t, $^2J_{H\text{-}F}$ = 56.5 Hz, 1H, C4''-CF_2H), 6.78 – 6.91 (m, 3H, Ar'-H), 7.26 (d, ^3J = 8.0 Hz, 2H, H2''*, H6''*), 7.45 (d, ^3J = 8.0 Hz, 2H, H3''*, H5''*).

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 33.6 (t, C4-C), 42.4 (d, C4), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.2 (t, C3-C), 72.7 (t, C5), 82.9 (d, C2), 109.0 (d, C2'), 111.2 (d, C5'), 114.8 (dt, C4''-CF_2H, $^1J_{C\text{-}F}$ = 238.5 Hz), 118.1 (d, C6'), 126.0 (dt, C3'', C5'', $^3J_{C\text{-}F}$ = 6.0 Hz), 127.4 (s, C2'''), 129.1 (d, C2'', C6''), 132.7 (s, C4''), 134.9 (s, C1'), 139.2 (d, C3'''), 143.1 (t, C1'', $^5J_{C\text{-}F}$ = 2.0 Hz), 148.7 (s, C4'), 149.2 (s, C3'), 167.8 (s, C1''').

D.4.1.16 (*Z*)-((2*S*,3*R*,4*R*)-4-(4-(1,1-Difluoroethyl)benzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**190**)



190, $C_{27}H_{32}F_2O_5$
474.54 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **139** (23.2 mg, 0.059 mmol, 1.00 equiv.).

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL) The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 40 : 60 in 40 min) afforded the title compound **190**.

Yield:	21.8 mg, 78 %
Appearance:	colorless oil
R_f (silica):	0.34 (EtOAc / heptane, 1 : 2)
$[\alpha]_D^{25}$:	+19.9 (c 1.22, *i*-PrOH)
LC-HRMS (ESI):	calculated for M+H$^+$: 475.2291, found: 475.2324, Δ: 7.04 ppm
(log *P*)$_{calc}$:	6.36 ± 0.63

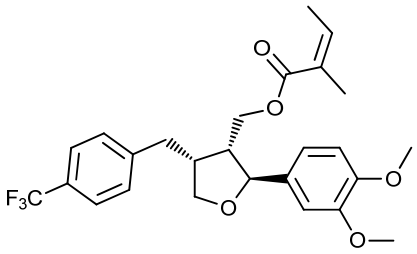
GC-MS (EI, 70 eV, Method D): 14.37 min; 474.6 (M$^+$, 5), 219.4 (16), 218.8 (20), 166.4 (34), 165.7 (48), 165.0 (100), 155.2 (26), 154.6 (21), 150.9 (17), 139.8 (26), 135.2 (21), 134.6 (19), 114.9 (24).

The compound partially eliminated hydrogen fluoride from its difluoroethyl moiety under the GC conditions used, furnishing a broad peak at 16.08 min; 454.9 (M-HF$^+$, 6), 219.1 (18), 206.7 (18), 166.2 (31), 165.2 (100), 160.8 (15), 151.3 (15), 148.2 (20), 136.0 (16), 135.3 (52), 134.8 (65), 132.8 (25), 115.0 (39).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 – 1.90 (m, 3H, H5'''), 1.91 (t, ^{3}J = 18.2 Hz, 3H, C4''-CF_2CH_3), 2.00 (dq, ^{3}J = 7.2 Hz, ^{5}J = 1.5 Hz, 3H, H4'''), 2.55 – 2.88 (m, 3H, H3, H4, C4-CH), 2.91 – 3.03 (m, 1H, C4-CH), 3.75 (dd, ^{2}J = 8.7 Hz, ^{3}J = 6.0 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.07 (dd, ^{2}J = 8.7 Hz, ^{3}J = 6.1 Hz, 1H, H5), 4.28 (dd, ^{2}J = 11.3 Hz, ^{3}J = 6.8 Hz, 1H, C3-CH), 4.41 (dd, ^{2}J = 11.4 Hz, ^{3}J = 7.1 Hz, 1H, C3-CH), 4.84 (d, ^{3}J = 6.3 Hz, 1H, H2), 6.11 (qq, ^{3}J = 7.2 Hz, ^{4}J = 1.4 Hz, 1H, H3'''), 6.80 – 6.91 (m, 3H, Ar'-H), 7.23 (d, ^{3}J = 8.1 Hz, 2H, H2''*, H6''*), 7.44 (d, ^{3}J = 8.1 Hz, 2H, H3''*, H5''*).

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 26.0 (qt, C4''-$CF_2\underline{C}H_3$, $^{2}J_{C\text{-}F}$ = 30.0 Hz), 33.5 (t, C4-<u>C</u>), 42.4 (d, C4), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.2 (t, C3-<u>C</u>), 72.7 (t, C5), 82.9 (d, C2), 109.0 (d, C2'), 111.2 (d, C5'), 118.2 (d, C6'), 121.9 (s, C4''-$\underline{C}F_2CH_3$), 125.1 (dt, C3'', C5'', $^{3}J_{C\text{-}F}$ = 6.0 Hz), 127.4 (s, C2'''), 128.8 (s, C2'', C6''), 134.9 (s, C1'), 136.4 (s, C4''), 139.2 (d, C3'''), 142.0 (t, C1'', $^{5}J_{C\text{-}F}$ = 1.7 Hz), 148.7 (s, C4'), 149.2 (s, C3'), 167.8 (s, C1''').

D.4.1.17 (*Z*)-((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**<u>191</u>**)



<u>191</u>, $C_{26}H_{29}F_3O_5$
478.50 g mol^{-1}

***Preparation**:* analogous to **<u>177</u>** (section D.4.1.3, page 196), using starting material **<u>140</u>** (32.7 mg, 0.082 mmol, 1.00 equiv.) and stirring for 22 in place of 46 h.

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL) The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 40 : 60 in 40 min) afforded the title compound **<u>191</u>**.

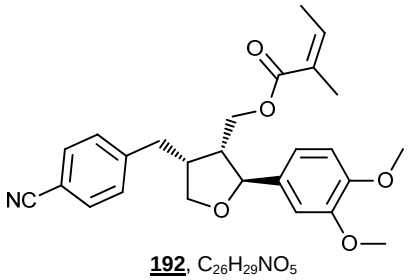
Yield:	34.3 mg, 87 %
Appearance:	colorless oil
R_f (silica):	0.74 (EtOAc / cyclohexane, 1 : 1)
$[\alpha]_D^{20}$:	+28.5 (c 0.97, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 501.1859, found: 501.1882, Δ: 4.59 ppm
(log *P*)$_{calc}$:	6.21 ± 0.49

GC-MS (EI, 70 eV, Method E): 12.47 min; 478.1 (M^+, 2), 219.0 (28), 166.1 (39), 165.0 (100), 159.0 (25).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 – 1.90 (m, 3H, H5'''), 2.00 (dq, ^{3}J = 7.2 Hz, ^{5}J = 1.5 Hz, 3H, H4'''), 2.55 – 2.89 (m, 3H, H3, H4, C4-CH), 2.95 – 3.07 (m, 1H, C4-CH), 3.74 (dd, ^{2}J = 8.7 Hz, ^{3}J = 5.9 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.07 (dd, ^{2}J = 8.8 Hz, ^{3}J = 6.0 Hz, 1H, H5), 4.28 (dd, ^{2}J = 11.4 Hz, ^{3}J = 6.6 Hz, 1H, C3-CH), 4.40 (dd, ^{2}J = 11.4 Hz, ^{3}J = 7.1 Hz, 1H, C3-CH), 4.84 (d, ^{3}J = 6.4 Hz, 1H, H2), 6.12 (qq, ^{3}J = 7.2 Hz, ^{4}J = 1.3 Hz, 1H, H3'''), 6.79 – 6.92 (m, 3H, Ar'-H), 7.30 (d, ^{3}J = 8.1 Hz, 2H, H2'', H6''), 7.56 (d, ^{3}J = 8.1 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 33.6 (t, C4-C), 42.3 (d, C4), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.1 (t, C3-C), 72.6 (t, C5), 82.9 (d, C2), 108.9 (d, C2'), 111.2 (d, C5'), 118.2 (d, C6'), 124.3 (q, C4''-CF_3, $^{1}J_{C\text{-}F}$ = 272.0 Hz), 125.7 (dq, C3'', C5'', $^{3}J_{C\text{-}F}$ = 3.8 Hz), 127.4 (s, C2'''), 128.9 (q, C4'', $^{2}J_{C\text{-}F}$ = 32.3 Hz), 129.1 (d, C2'', C6''), 134.8 (s, C1'), 139.3 (d, C3'''), 144.4 (q, C1'', $^{5}J_{C\text{-}F}$ = 1.3 Hz), 148.7 (s, C4'), 149.2 (s, C3'), 167.8 (s, C1''').

D.4.1.18 (*Z*)-((2*S*,3*R*,4*R*)-4-(4-Cyanobenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**192**)



192, $C_{26}H_{29}NO_5$
435.51 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **141** (28.7 mg, 0.081 mmol, 1.00 equiv.) and stirring for 26 in place of 46 h.

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL) The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 25 : 75 in 22 min, then 25 : 75 isocratically) afforded the title compound **192**.

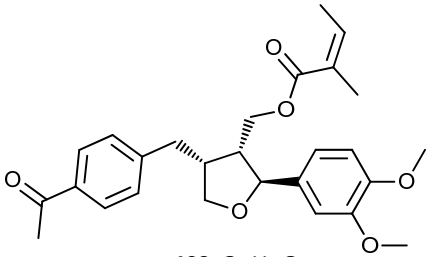
Yield:	22.8 mg, 64 %
Appearance:	colorless oil
R_f (silica):	0.64 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+21.3 (c 0.99, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 458.1938, found: 458.1958, Δ: 4.36 ppm
(log *P*)$_{calc}$:	5.08 ± 0.49

GC-MS (EI, 70 eV, Method E): 22.28 min; 435.3 (M^+, 2), 219.1 (27), 166.1 (34), 165.1 (100), 116.1 (26).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 – 1.90 (m, 3H, H5'''), 2.00 (dq, ^{3}J = 7.2 Hz, ^{5}J = 1.5 Hz, 3H, H4'''), 2.56 – 2.85 (m, 3H, H3, H4, C4-CH), 2.96 – 3.06 (m, 1H, C4-CH), 3.71 (dd, ^{2}J = 8.7 Hz, ^{3}J = 5.8 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.07 (dd, ^{2}J = 8.7 Hz, ^{3}J = 5.9 Hz, 1H, H5), 4.26 (dd, ^{2}J = 11.4 Hz, ^{3}J = 6.5 Hz, 1H, C3-CH), 4.39 (dd, ^{2}J = 11.4 Hz, ^{3}J = 7.2 Hz, 1H, C3-CH), 4.83 (d, ^{3}J = 6.4 Hz, 1H, H2), 6.11 (qq, ^{3}J = 7.2 Hz, ^{4}J = 1.4 Hz, 1H, H3'''), 6.79 – 6.90 (m, 3H, Ar'-H), 7.29 (d, ^{3}J = 8.3 Hz, 2H, H2'', H6''), 7.60 (d, ^{3}J = 8.2 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 34.0 (t, C4-C), 42.2 (d, C4), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.0 (t, C3-C), 72.5 (t, C5), 82.8 (d, C2), 108.9 (d, C2'), 110.5 (s, C4''), 111.2 (d, C5'), 118.1 (d, C6'), 118.9 (s, C4''-CN), 127.3 (s, C2'''), 129.5 (d, C2'', C6''), 132.6 (d, C3'', C5''), 134.6 (s, C1'), 139.5 (d, C3'''), 145.9 (s, C1''), 148.7 (s, C4'), 149.2 (s, C3'), 167.7 (s, C1''').

D.4.1.19 (*Z*)-((2*S*,3*R*,4*R*)-4-(4-Acetylbenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**193**)



193, $C_{27}H_{32}O_6$
452.54 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **142** (29.0 mg, 0.078 mmol, 1.00 equiv.) and stirring for 26 in place of 46 h.

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL) The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 25 : 75 in 14 min, then 25 : 75 isocratically) afforded the title compound **193**.

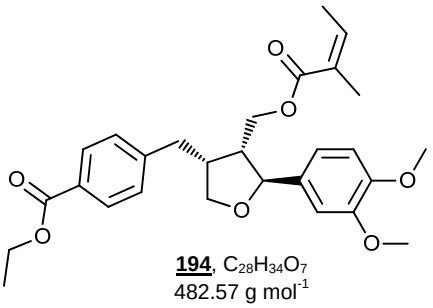
Yield:	27.6 mg, 78 %
Appearance:	colorless oil
R_f (silica):	0.58 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+20.3 (c 1.13, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 475.2091, found: 475.2112, Δ: 4.42 ppm
$(\log P)_{calc}$:	5.09 ± 0.47

GC-MS (EI, 70 eV, Method E): 25.39 min; 452.3 (M^+, 1), 219.1 (26), 166.1 (42), 165.1 (100), 105.1 (15).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.86 – 1.91 (m, 3H, H5'''), 1.99 (dq, ^{3}J = 7.3 Hz, ^{5}J = 1.5 Hz, 3H, H4'''), 2.50 – 2.92 (m, 3H, H3, H4, C4-CH), 2.59 (s, 3H, C4''-$COCH_3$), 2.95 – 3.08 (m, 1H, C4-CH), 3.74 (dd, ^{2}J = 8.7 Hz, ^{3}J = 5.9 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.07 (dd, ^{2}J = 8.7 Hz, ^{3}J = 6.1 Hz, 1H, H5), 4.28 (dd, ^{2}J = 11.4 Hz, ^{3}J = 6.7 Hz, 1H, C3-CH), 4.41 (dd, ^{2}J = 11.4 Hz, ^{3}J = 7.1 Hz, 1H, C3-CH), 4.84 (d, ^{3}J = 6.4 Hz, 1H, H2), 6.12 (qq, ^{3}J = 7.3 Hz, ^{4}J = 1.5 Hz, 1H, H3'''), 6.80 – 6.91 (m, 3H, Ar'-H), 7.28 (d, ^{3}J = 8.2 Hz, 2H, H2'', H6''), 7.90 (d, ^{3}J = 8.3 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 26.7 (q, C4''-CO<u>C</u>H_3), 33.8 (t, C4-<u>C</u>), 42.3 (d, C4), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.1 (t, C3-<u>C</u>), 72.6 (t, C5), 82.9 (d, C2), 108.9 (d, C2'), 111.2 (d, C5'), 118.1 (d, C6'), 127.4 (s, C2'''), 128.9 (d, C2''*, C6''*), 129.0 (d, C3''*, C5''*), 134.8 (s, C1'), 135.6 (s, C4''), 139.3 (d, C3'''), 145.9 (s, C1''), 148.7 (s, C4'), 149.2 (s, C3'), 167.7 (s, C1'''), 197.8 (s, C4''-<u>C</u>OCH_3).

D.4.1.20 Ethyl 4-(((3*R*,4*R*,5*S*)-5-(3,4-dimethoxyphenyl)-4-((((*Z*)-2-methylbut-2-enoyl)oxy)methyl)tetrahydrofuran-3-yl)methyl)benzoate (**<u>194</u>**)



<u>194</u>, $C_{28}H_{34}O_7$
482.57 g mol^{-1}

***Preparation**:* analogous to **<u>177</u>** (section D.4.1.3, page 196), using starting material **<u>143</u>** (26.7 mg, 0.067 mmol, 1.00 equiv.) and stirring for 22 in place of 46 h.

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL). The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 5 : 95 to 40 : 60 in 30 min) afforded the title compound **<u>194</u>**.

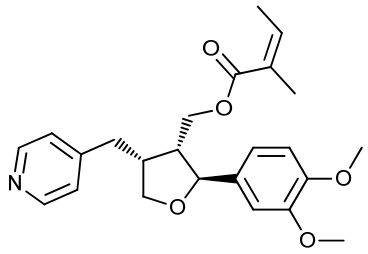
Yield:	28.8 mg, 89 %
Appearance:	colorless oil
R_f (silica):	0.65 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{25}$:	+18.4 (c 1.66, MeOH)
LC-HRMS (APCI):	calculated for $M+H^+$: 483.2377, found: 483.2354, Δ: -4.76 ppm
(log *P*)$_{calc}$:	6.15 ± 0.46

GC-MS (EI, 70 eV, Method E): 29.29 min; 482.3 (M^+, 1), 219.1 (32), 166.1 (47), 165.1 (100), 151.1 (14).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39 (t, ^{3}J = 7.1 Hz, 3H, C4''-$CO_2CH_2C\underline{H}_3$), 1.84 – 1.92 (m, 3H, H5'''), 2.00 (d, ^{3}J = 7.3 Hz, 3H, H4'''), 2.55 – 2.90 (m, 3H, H3, H4, C4-CH), 2.94 – 3.06 (m, 1H, C4-CH), 3.74 (dd, ^{2}J = 8.7 Hz, ^{3}J = 6.0 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH_3), 3.87 (s, 3H, Ar'-OCH_3), 4.06 (dd, ^{2}J = 8.7 Hz, ^{3}J = 6.0 Hz, 1H, H5), 4.20 – 4.46 (m, 4H, C3-CH_2, C4''-$CO_2C\underline{H}_2CH_3$), 4.84 (d, ^{3}J = 6.4 Hz, 1H, H2), 6.11 (q, ^{3}J = 7.3 Hz, 1H, H3'''), 6.79 – 6.91 (m, 3H, Ar'-H), 7.25 (d, ^{3}J = 7.9 Hz, 2H, H2'', H6''), 7.98 (d, ^{3}J = 8.1 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.5 (q, C4''-$CO_2CH_2\underline{C}H_3$), 16.0 (q, C4'''), 20.7 (q, C5'''), 33.8 (t, C4-$\underline{C}$), 42.3 (d, C4), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 61.0 (t, C4''-$CO_2\underline{C}H_2CH_3$), 62.1 (t, C3-$\underline{C}$), 72.6 (t, C5), 82.9 (d, C2), 108.9 (d, C2'), 111.2 (d, C5'), 118.2 (d, C6'), 127.4 (s, C2'''), 128.7 (d, C2''*, C6''*), 128.9 (s, C4''), 130.1 (d, C3''*, C5''*), 134.8 (s, C1'), 139.2 (d, C3'''), 145.5 (s, C1''), 148.6 (s, C4'), 149.2 (s, C3'), 166.6 (s, C1'''), 167.8 (s, C4''-$\underline{C}O_2CH_2CH_3$).

D.4.1.21 (*Z*)-((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(pyridin-4-ylmethyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**195**)



195, $C_{24}H_{29}NO_5$
411.49 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **144** (31.2 mg, 0.095 mmol, 1.00 equiv.) and stirring for 22 in place of 46 h.

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL). The solvents were evaporated and flash column chromatography was performed (9 g silica, flow rate 20 mL / min, EtOAc / LP, 50 : 50 to 100 : 0 in 30 min), followed by preparative HPLC (flow rate 20.0 mL / min, MeOH / water, 54 : 46 to 58 : 42 in 40 min, then to 60 : 40 in 12 min, 63 : 37 in 9 min) to afford the title compound **195**.

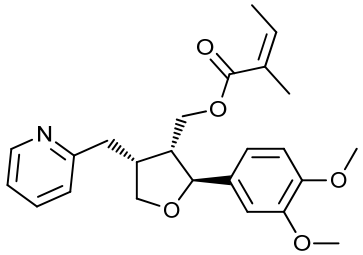
Yield:	26.5 mg, 68 %
Appearance:	colorless oil
R_f (silica):	0.32 (EtOAc)
$[\alpha]_D^{23}$:	+36.5 (c 1.15, MeOH)
LC-HRMS (ESI):	calculated for $M+H^+$: 412.2118, found: 412.2100, Δ: -4.37 ppm
(log *P*)$_{calc}$:	4.15 ± 0.45

GC-MS (EI, 70 eV, Method F): 15.34 min; 411.2 (M^+, 3), 219.1 (24), 192.1 (15), 166.1 (40), 165.0 (100), 146.1 (19), 93.1 (36).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 – 1.90 (m, 3H, H5'''), 2.00 (dq, ^{3}J = 7.2 Hz, ^{5}J = 1.5 Hz, 3H, H4'''), 2.56 – 2.90 (m, 3H, H3, H4, C4-CH), 2.95 (dd, ^{2}J = 12.6 Hz, ^{3}J = 4.0 Hz, 1H, C4-CH), 3.72 (dd, ^{2}J = 8.7 Hz, ^{3}J = 6.0 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.09 (dd, ^{2}J = 8.8 Hz, ^{3}J = 6.1 Hz, 1H, H5), 4.27 (dd, ^{2}J = 11.4 Hz, ^{3}J = 6.6 Hz, 1H, C3-CH), 4.38 (dd, ^{2}J = 11.5 Hz, ^{3}J = 7.2 Hz, 1H, C3-CH), 4.83 (d, ^{3}J = 6.4 Hz, 1H, H2), 6.12 (qq, ^{3}J = 7.2 Hz, ^{4}J = 1.4 Hz, 1H, H3'''), 6.80 – 6.89 (m, 3H, Ar'-H), 7.12 (d, ^{3}J = 5.8 Hz, 2H, H2'', H6''), 8.53 (d, ^{3}J = 4.2 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 33.2 (t, C4-C), 41.6 (d, C4), 49.2 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.0 (t, C3-C), 72.5 (t, C5), 82.8 (d, C2), 108.9 (d, C2'), 111.2 (d, C5'), 118.1 (d, C6'), 124.1 (d, C2'', C6''), 127.3 (s, C2'''), 134.6 (s, C1'), 139.4 (d, C3'''), 148.7 (s, C4'), 149.2 (s, C3'), 150.1 (d, C3'', C5''), 167.7 (s, C1''').

D.4.1.22 (*Z*)-((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(pyridin-2-ylmethyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**196**)



196, $C_{24}H_{29}NO_5$
411.49 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **145** (21.9 mg, 0.066 mmol, 1.00 equiv.) and stirring for 22 in place of 46 h.

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL) The solvents were evaporated and flash column chromatography was performed (9 g silica, flow rate 20 mL / min, EtOAc / LP, 20 : 80 to 50 : 50 in 40 min), followed by preparative HPLC (flow rate 20.0 mL / min, MeOH / water, 60 : 40) to afford the title compound **196**.

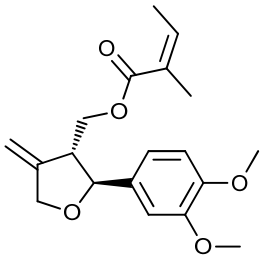
Yield:	14.2 mg, 52 %
Appearance:	colorless oil
R_f (silica):	0.61 (EtOAc)
$[\alpha]_D^{23}$:	+33.0 (c 0.80, MeOH)
LC-HRMS (ESI):	calculated for $M+H^+$: 412.2118, found: 412.2107, Δ: -2.67 ppm
$(\log P)_{calc}$:	4.15 ± 0.45

GC-MS (EI, 70 eV, Method F): 14.00 min; 411.2 (M^+, 1), 146.1 (24), 120.1 (26), 118.1 (15), 93.0 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.82 – 1.89 (m, 3H, H5'''), 1.98 (dq, ^{3}J = 7.2 Hz, ^{5}J = 1.5 Hz, 3H, H4'''), 2.64 (quint, ^{3}J = 6.7 Hz, 1H, H3), 2.86 (dd, ^{2}J = 15.2 Hz, ^{3}J = 11.9 Hz, 1H, C4-CH), 2.98 – 3.19 (m, 2H, H4, C4-CH), 3.77 (dd, ^{2}J = 8.5 Hz, ^{3}J = 6.9 Hz, 1H, H5), 3.86 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.15 (dd, ^{2}J = 8.5 Hz, ^{3}J = 6.5 Hz, 1H, H5), 4.27 (dd, ^{2}J = 11.4 Hz, ^{3}J = 7.0 Hz, 1H, C3-CH), 4.42 (dd, ^{2}J = 11.4 Hz, ^{3}J = 6.7 Hz, 1H, C3-CH), 4.85 (d, ^{3}J = 6.2 Hz, 1H, H2), 6.08 (qq, ^{3}J = 7.2 Hz, ^{4}J = 1.3 Hz, 1H, H3'''), 6.78 – 6.90 (m, 3H, Ar'-H), 7.12 – 7.21 (m, 2H, H4'', H6''), 7.64 (td, ^{3}J = 7.7 Hz, ^{4}J = 1.7 Hz, 1H, H5''), 8.56 (d, ^{3}J = 4.5 Hz, 1H, H3'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 36.0 (t, C4-C), 40.9 (d, C4), 49.1 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.4 (t, C3-C), 73.1 (t, C5), 83.2 (d, C2), 109.0 (d, C2'), 111.2 (d, C5'), 118.3 (d, C6'), 121.7 (d, C4''), 123.5 (d, C6''), 127.5 (s, C2'''), 135.0 (s, C1'), 137.1 (d, C5''), 139.1 (d, C3'''), 148.6 (s, C4'), 149.2 (s, C3'), 149.2 (d, C3''), 159.9 (s, C1''), 167.8 (s, C1''').

D.4.1.23 (*Z*)-((2*S*,3*R*)-2-(3,4-Dimethoxyphenyl)-4-methylenetetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**205**)



205, $C_{19}H_{24}O_5$
332.39 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **106** (55.9 mg, 0.223 mmol, 1.00 equiv.) and stirring for 19 in place of 46 h.

***Work-up and purification**:* Brine (4 mL) was added to the reaction content and then extracted with Et_2O (3 x 10 mL). The combined organic phases were dried with Na_2SO_4, filtered and the solvents were evaporated. Purification by flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 40 : 60 in 40 min) afforded the title compound **205**.

Yield:	58.9 mg, 79 %
Appearance:	colorless oil
R_f (silica):	0.73 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{25}$:	+28.8 (c 5.43, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 355.1516, found: 355.1511, Δ: -1.41 ppm
(log *P*)$_{calc}$:	3.89 ± 0.47

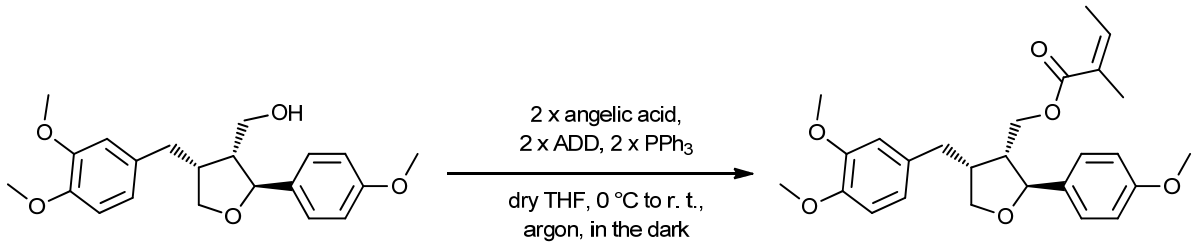
GC-MS (EI, 70 eV, Method D): 7.72 min; 332.1 (M^+, 3), 232.1 (62), 201.1 (24), 166.1 (24), 165.0 (94), 151.0 (23).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.73 – 1.80 (m, 3H, H5'''), 1.94 (dq, ^{3}J = 7.3 Hz, ^{5}J = 1.5 Hz, 3H, H4'''), 2.93 – 3.09 (m, 1H, H3), 3.87 (s, 3H, Ar'-OCH_3), 3.88 (s, 3H, Ar'-OCH_3), 4.31 (d, ^{3}J = 6.0 Hz, 2H, H3a), 4.43

(ddd, ^{2}J = 13.3 Hz, $^{4}J_{cis\text{-allyl}}$ = 2.2 Hz*, $^{4}J_{trans\text{-allyl}}$ = 4.5 Hz*, 1H, H5), 4.57 – 4.68 (m, 1H, H5), 4.71 (d, ^{3}J = 7.7 Hz, H2), 5.06 – 5.13 (m, 2H, H4a), 6.05 (qq, ^{3}J = 7.2 Hz, ^{4}J = 1.4 Hz, 1H), 6.79 – 6.95 (m, 3H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 15.8 (q, C4'''), 20.5 (q, C5'''), 50.5 (d, C3), 55.9 (q, Ar'-OCH_3), 56.0 (q, Ar'-OCH_3), 63.5 (t, C3a), 71.4 (t, C5), 84.3 (d, C2), 105.6 (t, C4a), 109.4 (d, C2'), 111.0 (d, C5'), 119.1 (d, C6'), 127.5 (s, C2'''), 133.1 (s, C1'), 138.8 (d, C3'''), 148.3 (s, C4*), 148.9 (s, C4'*), 149.2 (s, C3'), 167.8 (s, C1''').

D.4.1.24 (*Z*)-((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(4-methoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**197**)



146 **197**, $C_{26}H_{32}O_6$, 440.53 g mol^{-1}

***Preparation**:* a reaction vessel was charged with a stirring bar, starting material **146** (20.6 mg, 0.057 mmol, 1.0 equiv.), angelic acid (8.6 mg, 0.086 mmol, 1.5 equiv.) and PPh_3 (52.7 mg, 0.201 mmol, 3.5 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry THF (0.75 mL) was then added and the solution cooled to 0 °C in an ice bath. To the stirred mixture was then added a solution of ADD (50.7 mg, 0.201 mmol, 3.5 equiv.) in dry THF (1.0 mL) *via* syringe over approximately 1 min, and the reaction stirred for 46 h while being kept away from light and allowed to warm slowly to room temperature (first leg). Then the reaction was cooled in an ice bath again, and there was added more angelic acid (4.3 mg, 0.043 mmol, 0.8 equiv.) and PPh_3 (26.3 mg, 0.100 mmol, 1.8 equiv.) in dry THF (0.75 mL) *via* syringe, followed by the addition of more ADD (25.3 mg, 0.100 mmol, 1.8 equiv.) in dry THF (1.0 ml) *via* syringe over approximately 1 min, and the reaction stirred for 24 h while being kept away from light and allowed to warm slowly to room temperature again (second leg).

***Work-up and purification**:* Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL) The solvents were evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / heptane, 1 : 99 to 10 : 90 in 10 min, then 70 : 30 in 50 min) afforded the title compound **197**.

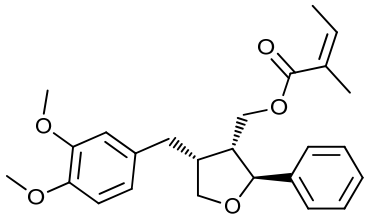
Yield:	22.6 mg, 89 %
Appearance:	colorless oil
R_f (silica):	0.32 (EtOAc / heptane, 1 : 2)
$[\alpha]_D^{25}$:	+13.5 (c 1.22, *i*-PrOH)
LC-HRMS (ESI):	calculated for $M+H^+$: 441.2272, found: 441.2293, Δ: 4.81 ppm
(log *P*)$_{calc}$:	5.56 ± 0.46

GC-MS (EI, 70 eV, Method E): 16.59 min; 440.4 (M^+, 1), 189.3 (31), 188.8 (29), 152.2 (19), 151.4 (96), 150.8 (100), 137.1 (27), 136.2 (28), 135.4 (82), 134.8 (97), 120.8 (26), 107.0 (39), 106.0 (26).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.84 – 1.90 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.48 – 2.84 (m, 3H, H3, H4, C4-CH), 2.89 (dd, ^2J = 12.6 Hz, ^3J = 4.1 Hz, 1H, C4-CH), 3.72 – 3.82 (m, 1H, H5), 3.80 (s, 3H, C4'-OCH_3), 3.86 (s, 3H, Ar''-OCH_3), 3.86 (s, 3H, Ar''-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.1 Hz, 1H, H5), 4.26 (dd, ^2J = 11.3 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.41 (dd, ^2J = 11.3 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.85 (d, ^3J = 6.3 Hz, 1H, H2), 6.08 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.65 – 6.92 (m, 5H, H3', H5', 3 x Ar''-H), 7.24 (d, ^3J = 7.9 Hz, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 33.3 (t, C4-C), 42.8 (d, C4), 49.4 (d, C3), 55.4 (q, C4'-OCH_3), 55.99 (q, Ar''-OCH_3), 56.04 (q, Ar''-OCH_3), 62.3 (t, C3-C), 72.8 (t, C5), 82.8 (d, C2), 111.5 (d, C5''*), 112.0 (d, C2''*), 114.0 (d, C3', C5'), 120.6 (d, C6''), 127.1 (d, C2', C6'), 127.6 (s, C2'''), 132.8 (s, C1''), 134.6 (s, C1'), 138.9 (d, C3'''), 147.6 (s, C4''), 149.1 (s, C3''), 159.2 (s, C4'), 167.9 (s, C1''').

D.4.1.25 (*Z*)-((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-phenyltetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**198**)



198, $C_{25}H_{30}O_5$
410.50 g mol^{-1}

***Preparation**:* analogous to **59** (section D.4.1.2, page 194), using starting material **123** (40.4 mg, 0.123 mmol, 1.0 equiv.), and stirring for 18 in place of 12 h.

***Work-up and purification**:* the solvent was evaporated, which was followed by the addition of $CHCl_3$ (1.0 mL), LP (10 mL) and water (10 mL). The layers were separated and the aqueous phase was re-extracted with LP. The solvents were evaporated from the combined organic phases and flash column chromatography was performed (90 g silica, flow rate 30 mL / min, EtOAc / LP, 5 : 95 isocratically for 5 min, then to 10 : 90 in 20 min, then to 30 : 70 in 20 min, finally to 100 : 0 in 10 min), followed by preparative HPLC (flow rate 20.0 mL / min, MeOH / water, 73 : 27 isocratically for 25 min, then to 77 : 23 in 15 min) to afford the title compound **198**.

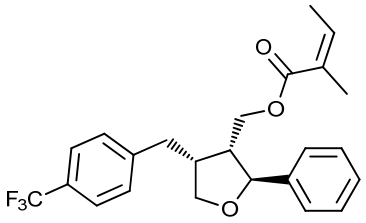
Yield:	24.0 mg, 48 %
Appearance:	colorless oil
R_f (silica):	0.52 (EtOAc / LP, 1 : 2)
$[\alpha]_D^{20}$:	+17.2 (c 1.13, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 433.1985, found: 433.1993, Δ: 1.85 ppm
(log *P*)$_{calc}$:	5.64 ± 0.44

GC-MS (EI, 70 eV, Method E): 13.43 min; 410.2 (M^+, 5), 194.1 (27), 190.1 (18), 189.1 (20), 164.1 (20), 159.1 (47), 152.1 (31), 151.1 (100), 107.1 (22), 105.0 (59), 91.1 (42).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.84 – 1.91 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4''''), 2.50 – 2.85 (m, 3H, H3, H4, C4-CH), 2.89 (dd, ^2J = 12.3 Hz, ^3J = 4.2 Hz, 1H, C4-CH), 3.81 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 3.86 (s, 6H, Ar''-OCH_3), 4.10 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.28 (dd, ^2J = 11.3 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.44 (dd, ^2J = 11.3 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.93 (d, ^3J = 5.8 Hz, 1H, H2), 6.10 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.66 – 6.75 (m, 2H, H2'', H6''*), 6.80 (d, ^3J = 7.9 Hz, 1H, H5''*), 7.21 – 7.39 (m, 5H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 33.2 (t, C4-C), 42.7 (d, C4), 49.5 (d, C3), 55.99 (q, Ar''-OCH_3), 56.03 (q, Ar''-OCH_3), 62.3 (t, C3-C), 72.9 (t, C5), 83.2 (d, C2), 111.4 (d, C5''*), 112.0 (d, C2''*), 120.6 (d, C6''), 125.8 (d, C2', C6'), 127.5 (s, C2'''), 127.6 (d, C4'), 128.6 (d, C3', C5'), 132.7 (s, C1''), 139.0 (d, C3'''), 142.8 (s, C1'), 147.6 (s, C4''), 149.1 (s, C3''), 167.8 (s, C1''').

D.4.1.26 (*Z*)-((2*S*,3*R*,4*R*)-2-Phenyl-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**199**)



199, $C_{24}H_{25}F_3O_3$
418.45 g mol^{-1}

***Preparation**:* analogous to **197** (section D.4.1.24, page 217), using starting material **147** (15.3 mg, 0.045 mmol, 1.0 equiv.). First leg: angelic acid (6.8 mg, 0.068 mmol, 1.5 equiv.), ADD (40.1 mg, 0.159 mmol, 3.5 equiv.), PPh_3 (41.7 mg, 0.159 mmol, 3.5 equiv.), stirring for 16 h. Second leg: angelic acid (6.8 mg, 0.068 mmol, 1.5 equiv.), ADD (40.1 mg, 0.159 mmol, 3.5 equiv.), PPh_3 (41.7 mg, 0.159 mmol, 3.5 equiv.), stirring for 16 h.

***Work-up and purification**:* the solvent was evaporated and flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 2 : 98 to 10 : 90 in 30 min) afforded the title compound **199**.

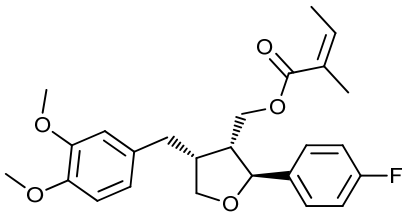
Yield:	13.6 mg, 72 %
Appearance:	colorless oil
R_f (silica):	0.80 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{20}$:	+16.3 (c 0.74, *i*-PrOH)
LC-HRMS (APCI):	calculated for $M+H^+$: 419.1829, found: 419.1840, Δ: 2.62 ppm
(log *P*)$_{calc}$:	6.47 ± 0.46

GC-MS (EI, 70 eV, Method E): 8.19 min; 159.0 (*p*-trifluoromethylbenzyl, 100), 146.1 (15), 115.0 (15), 107.0 (34), 105.0 (77), 91.1 (21). M^+ not visible.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.85 – 1.91 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.56 – 2.91 (m, 3H, H3, H4, C4-CH), 2.94 – 3.05 (m, 1H, C4-CH), 3.77 (dd, ^2J = 8.7 Hz, ^3J = 6.1 Hz, 1H, H5), 4.09 (dd, ^2J = 8.7 Hz, ^3J = 6.0 Hz, 1H, H5), 4.29 (dd, ^2J = 11.3 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.42 (dd, ^2J = 11.4 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.93 (d, ^3J = 5.9 Hz, 1H, H2), 6.11 (qq, ^3J = 7.2 Hz, ^4J = 1.3 Hz, 1H, H3'''), 7.22 – 7.40 (m, 7H, 5 x Ar'-H, H2'', H6''), 7.55 (d, ^3J = 8.2 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 33.6 (t, C4-C), 42.3 (d, C4), 49.6 (d, C3), 62.1 (t, C3-C), 72.7 (t, C5), 83.1 (d, C2), 124.3 (q, C4''-CF_3, $^1J_{C\text{-}F}$ = 271.9 Hz), 125.7 (dq, C3'', C5'', $^3J_{C\text{-}F}$ = 3.8 Hz), 125.8 (d, C2', C6'), 127.4 (s, C2'''), 127.8 (d, C4'), 128.9 (q, C4'', $^2J_{C\text{-}F}$ = 32.5 Hz), 128.7 (d, C3', C5'), 129.1 (d, C2'', C6''), 139.3 (d, C3'''), 142.6 (s, C1'), 144.4 (q, C1'', $^5J_{C\text{-}F}$ = 1.2 Hz), 167.8 (s, C1''').

D.4.1.27 (*Z*)-((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**200**)



200, $C_{25}H_{29}FO_5$
428.49 g mol^{-1}

***Preparation**:* analogous to **59** (section D.4.1.2, page 194), using starting material **148** (36.4 mg, 0.105 mmol, 1.0 equiv.) and stirring for 18 in place of 12 h.

***Work-up and purification**:* The solvent was evaporated, which was followed by the addition of $CHCl_3$ (1.0 mL), LP (10 mL) and water (10 mL). The layers were separated and the aqueous phase was re-extracted with LP. The solvents were evaporated from the combined organic phases and flash column chromatography was performed (45 g silica, flow rate 30 mL / min, EtOAc / LP, 3 : 97 isocratically for 3 min, then to 50 : 50 in 40 min), followed by preparative HPLC (flow rate 20.0 mL / min, MeOH / water, 73 : 27 isocratically for 25 min, then to 77 : 23 in 15 min), to afford the title compound **200**.

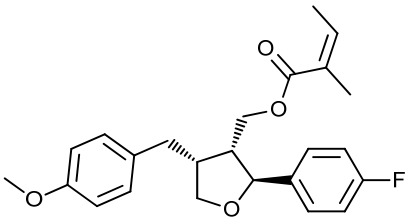
Yield:	24.7 mg, 55 %
Appearance:	colorless oil
R_f (silica):	0.47 (EtOAc / LP, 1 : 2)
$[\alpha]_D^{23}$:	+15.9 (c 0.90, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 451.1891, found: 451.1892, Δ: 0.22 ppm
(log *P*)$_{calc}$:	5.69 ± 0.52

GC-MS (EI, 70 eV, Method E): 13.03 min; 428.2 (M$^+$, 4), 194.1 (21), 190.1 (18), 189.1 (19), 177.1 (38), 164.1 (23), 163.1 (15), 152.1 (29), 151.0 (100), 123.0 (55), 109.0 (37), 107.1 (22).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.83 – 1.89 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.49 – 2.84 (m, 3H, H3, H4, C4-CH), 2.89 (dd, ^2J = 12.5 Hz, ^3J = 4.2 Hz, 1H, C4-CH), 3.79 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 3.86 (s, 3H, Ar''-OCH_3), 3.86 (s, 3H, Ar''-OCH_3), 4.08 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.27 (dd, ^2J = 11.3 Hz, ^3J = 7.3 Hz, 1H, C3-CH), 4.43 (dd, ^2J = 11.3 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.89 (d, ^3J = 6.1 Hz, 1H, H2), 6.10 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.65 – 6.84 (m, 3H, Ar''-H), 6.95 – 7.08 (m, 2H, H3', H5'), 7.23 – 7.34 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 33.2 (t, C4-C), 42.8 (d, C4), 49.5 (d, C3), 56.00 (q, Ar''-OCH_3), 56.02 (q, Ar''-OCH_3), 62.2 (t, C3-C), 72.9 (t, C5), 82.7 (d, C2), 111.5 (d, C5''*), 112.0 (d, C2''*), 115.4 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 120.6 (d, C6''), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 132.6 (s, C1''), 138.5 (d, C1', $^4J_{C\text{-}F}$ = 3.0 Hz), 139.2 (d, C3'''), 147.7 (s, C4''), 149.1 (s, C3''), 162.4 (d, C4', $^1J_{C\text{-}F}$ = 245.6 Hz), 167.8 (s, C1'''); C2''' not visible due to signal overlap with C2', C6'.

D.4.1.28 (*Z*)-((2*S*,3*R*,4*R*)-2-(4-Fluorophenyl)-4-(4-methoxybenzyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**201**)



201, $C_{24}H_{27}FO_4$
398.47 g mol^{-1}

***Preparation**:* analogous to **197** (section D.4.1.24, page 217), using starting material **149** (27.9 mg, 0.088 mmol, 1.0 equiv.). First leg: angelic acid (13.2 mg, 0.132 mmol, 1.5 equiv.), ADD (77.9 mg, 0.309 mmol, 3.5 equiv.), PPh_3 (81.0 mg, 0.309 mmol, 3.5 equiv.), stirring for 16 h. Second leg: angelic acid (13.2 mg, 0.132 mmol, 1.5 equiv.), ADD (77.9 mg, 0.309 mmol, 3.5 equiv.), PPh_3 (81.0 mg, 0.309 mmol, 3.5 equiv.), stirring for 21 h.

***Work-up and purification**:* the solvent was evaporated and flash column chromatography was performed in two sequential runs (first run: 18 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 35 : 65 in 35 min; second run: 18 g silica, flow rate 20 mL / min, EtOAc / LP, 1 : 99 to 20 : 80 in 35 min) to afford the title compound **201**.

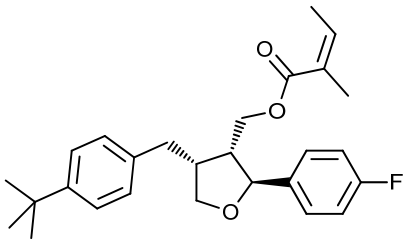
Yield:	16.7 mg, 48 %
Appearance:	colorless oil
R_f (silica):	0.76 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{20}$:	+9.2 (c 0.75, *i*-PrOH)
LC-HRMS (APCI):	calculated for $M+H^+$: 399.1966, found: 399.1972, Δ: 1.50 ppm
(log *P*)$_{calc}$:	5.87 ± 0.51

GC-MS (EI, 70 eV, Method E): 9.97 min; 398.0 (M^+, < 1), 177.0 (24), 164.1 (25), 160.1 (25), 159.1 (22), 134.1 (19), 123.0 (43), 121.0 (*p*-methoxybenzyl, 100), 109.0 (15).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.83 – 1.90 (m, 3H, H5'''), 1.96 – 2.03 (m, 3H, H4'''), 2.49 – 2.93 (m, 4H, H3, H4, C4-CH_2), 3.72 – 3.83 (m, 4H, H5, Ar''-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.26 (dd, ^2J = 11.3 Hz, ^3J = 7.3 Hz, 1H, C3-CH), 4.41 (dd, ^2J = 11.3 Hz, ^3J = 6.7 Hz, 1H, C3-CH), 4.88 (d, ^3J = 6.0 Hz, 1H, H2), 6.10 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.79 – 6.88 (m, 2H, H3'', H5''), 6.95 – 7.13 (m, 4H, H3', H5', H2'', H6''), 7.22 – 7.34 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 32.7 (t, C4-C), 42.7 (d, C4), 49.5 (d, C3), 55.4 (q, C4''-OCH_3), 62.2 (t, C3-C), 72.9 (t, C5), 82.7 (d, C2), 114.2 (d, C3'', C5''), 115.4 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.5 Hz), 127.5 (s, C2'''), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 129.6 (d, C2'', C6''), 132.1 (s, C1''), 138.5 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 139.2 (d, C3'''), 158.3 (s, C4''), 162.4 (d, C4', $^1J_{C\text{-}F}$ = 245.3 Hz), 167.8 (s, C1''').

D.4.1.29 (*Z*)-((2*S*,3*R*,4*R*)-4-(4-(*tert*-Butyl)benzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**202**)



202, $C_{27}H_{33}FO_3$
424.55 g mol^{-1}

***Preparation**:* analogous to **197** (section D.4.1.24, page 217), using starting material **152** (10.5 mg, 0.031 mmol, 1.0 equiv.). First leg: angelic acid (4.6 mg, 0.046 mmol, 1.5 equiv.), ADD (27.1 mg, 0.108 mmol, 3.5 equiv.), PPh_3 (28.2 mg, 0.108 mmol, 3.5 equiv.), stirring for 18.5 h. Second leg: angelic acid (4.6 mg, 0.046 mmol, 1.5 equiv.), ADD (27.1 mg, 0.108 mmol, 3.5 equiv.), PPh_3 (28.2 mg, 0.108 mmol, 3.5 equiv.), stirring for 47 h.

***Work-up and purification**:* the solvent was evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 2 : 98 to 10 : 90 in 40 min) afforded the title compound **202**.

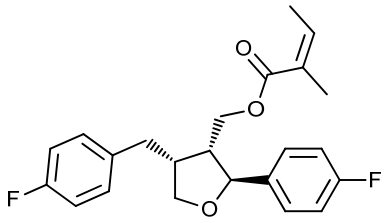
Yield:	4.9 mg, 37 %
Appearance:	colorless oil
R_f (silica):	0.83 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{20}$:	+9.2 (c 0.69, *i*-PrOH)
LC-HRMS (APCI):	calculated for $M+H^+$: 425.2486, found: 425.2503, Δ: 4.00 ppm
(log *P*)$_{calc}$:	7.64 ± 0.50

GC-MS (EI, 70 eV, Method E): 10.35 min; 185.1 (42), 177.0 (68), 175.1 (36), 147.1 (*p*-*tert*-butylbenzyl, 30), 145.1 (30), 132.1 (42), 131.1 (29), 129.1 (46), 123.0 (100), 117.0 (57), 109.0 (33). M^+ not visible.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 9H, C4''-C(CH_3)$_3$), 1.83 – 1.90 (m, 3H, H5'''), 1.99 (dq, ^{3}J = 7.2 Hz, ^{5}J = 1.5 Hz, 3H, H4'''), 2.49 – 2.85 (m, 3H, H3, H4, C4-CH), 2.90 (dd, ^{2}J = 12.5 Hz, ^{3}J = 4.2 Hz, 1H, C4-CH) , 3.78 (dd, ^{2}J = 8.6 Hz, ^{3}J = 6.4 Hz, 1H, H5), 4.09 (dd, ^{2}J = 8.6 Hz, ^{3}J = 6.3 Hz, 1H, H5), 4.28 (dd, ^{2}J = 11.3 Hz, ^{3}J = 7.3 Hz, 1H, C3-CH), 4.42 (dd, ^{2}J = 11.3 Hz, ^{3}J = 6.7 Hz, 1H, C3-CH), 4.89 (d, ^{3}J = 5.9 Hz, 1H, H2), 5.98 – 6.21 (m, 1H, H3'''), 6.95 – 7.15 (m, 4H, H3', H5', H2'', H6''), 7.22 – 7.37 (m, 4H, H2', H6', H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 31.5 (q, C4''-C(<u>C</u>H_3)$_3$), 33.1 (t, C4-<u>C</u>), 34.5 (s, C4''-<u>C</u>(CH_3)$_3$), 42.5 (d, C4), 49.6 (d, C3), 62.3 (t, C3-<u>C</u>), 73.0 (t, C5), 82.7 (d, C2), 115.4 (dd, C3', C5', $^{2}J_{C\text{-}F}$ = 21.5 Hz), 125.7 (d, C3'', C5''), 127.5 (s, C2'''), 127.5 (dd, C2', C6', $^{3}J_{C\text{-}F}$ = 8.1 Hz), 128.4 (d, C2'', C6''), 137.0 (s, C1''), 138.6 (d, C1', $^{4}J_{C\text{-}F}$ = 3.1 Hz), 139.2 (d, C3'''), 149.3 (s, C4''), 162.4 (d, C4', $^{1}J_{C\text{-}F}$ = 245.5 Hz), 167.9 (s, C1''').

D.4.1.30 (*Z*)-((2*S*,3*R*,4*R*)-4-(4-Fluorobenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**<u>203</u>**)



<u>203</u>, $C_{23}H_{24}F_2O_3$
386.43 g mol^{-1}

***Preparation**:* analogous to **<u>197</u>** (section D.4.1.24, page 217), using starting material **<u>155</u>** (20.9 mg, 0.069 mmol, 1.0 equiv.). First leg: angelic acid (10.3 mg, 0.103 mmol, 1.5 equiv.), ADD (60.7 mg, 0.241 mmol, 3.5 equiv.), PPh_3 (63.1 mg, 0.241 mmol, 3.5 equiv.), stirring for 16 h. Second leg: angelic acid (10.3 mg, 0.103 mmol, 1.5 equiv.), ADD (60.7 mg, 0.241 mmol, 3.5 equiv.), PPh_3 (63.1 mg, 0.241 mmol, 3.5 equiv.), stirring for 21 h.

***Work-up and purification**:* the solvent was evaporated and flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 0 : 100 to 10 : 90 in 50 min) afforded the title compound **<u>203</u>**.

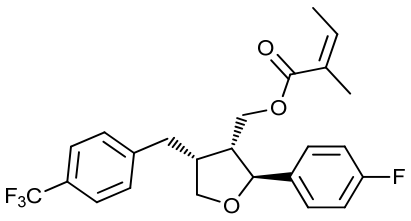
Yield:	17.1 mg, 64 %
Appearance:	colorless oil
R_f (silica):	0.75 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{25}$:	+15.2 (c 1.13, *i*-PrOH)
LC-HRMS (APCI):	calculated for M+Na^+: 421.1786, found: 421.1791, Δ: 1.19 ppm
(log *P*)$_{calc}$:	6.01 ± 0.56

GC-MS (EI, 70 eV, Method E): 8.29 min; 286.0 (21), 177.0 (43), 164.0 (14), 162.1 (24), 148.1 (37), 147.1 (42), 135.0 (34), 123.0 (67), 122.1 (18), 109.0 (*p*-fluorobenzyl, 100). M^+ not visible.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.83 – 1.90 (m, 3H, H5'''), 1.99 (dq, ^3J = 7.3 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.49 – 2.83 (m, 3H, H3, H4, C4-CH), 2.91 (dd, ^2J = 12.2 Hz, ^3J = 3.7 Hz, 1H, C4-CH), 3.75 (dd, ^2J = 8.7 Hz, ^3J = 6.2 Hz, 1H, H5), 4.06 (dd, ^2J = 8.7 Hz, ^3J = 6.1 Hz, 1H, H5), 4.26 (dd, ^2J = 11.4 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.40 (dd, ^2J = 11.4 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.88 (d, ^3J = 6.1 Hz, 1H, H2), 6.11 (qq, ^3J = 7.3 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.92 – 7.18 (m, 6H, H3', H5', 4 x Ar''-H), 7.23 – 7.34 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 16.0 (q, C4'''), 20.7 (q, C5'''), 32.9 (t, C4-C), 42.7 (d, C4), 49.5 (d, C3), 62.1 (t, C3-C), 72.8 (t, C5), 82.7 (d, C2), 115.5 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.5 Hz), 115.6 (dd, C3'', C5'', $^2J_{C\text{-}F}$ = 21.3 Hz), 127.4 (s, C2'''), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.3 Hz), 130.1 (dd, C2'', C6'', $^3J_{C\text{-}F}$ = 7.8 Hz), 135.7 (d, C1'', $^4J_{C\text{-}F}$ = 3.3 Hz), 138.4 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 139.3 (d, C3'''), 161.7 (d, C4'', $^1J_{C\text{-}F}$ = 244.4 Hz), 162.4 (d, C4', $^1J_{C\text{-}F}$ = 245.8 Hz), 167.8 (s, C1''').

D.4.1.31 (*Z*)-((2*S*,3*R*,4*R*)-2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**204**)



204, $C_{24}H_{24}F_4O_3$
436.44 g mol^{-1}

***Preparation**:* analogous to **177** (section D.4.1.3, page 196), using starting material **156** (13.3 mg, 0.038 mmol, 1.0 equiv.) and stirring for 18.5 in place of 46 h.

***Work-up and purification**:* the solvent was evaporated and flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 2 : 98 to 10 : 90 in 30 min) afforded the title compound **204**.

Yield:	10.1 mg, 61 %
Appearance:	colorless oil
R_f (silica):	0.79 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{20}$:	+13.8 (c 1.02, *i*-PrOH)
LC-HRMS (ESI):	calculated for M+H$^+$: 437.1734, found: 437.1756, Δ: 5.03 ppm
(log *P*)$_{calc}$:	6.53 ± 0.54

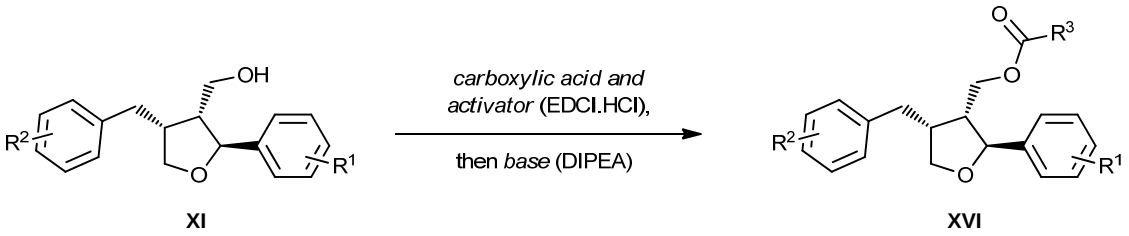
GC-MS (EI, 70 eV, Method E): 8.11 min; 336.0 (20), 212.0 (16), 185.0 (16), 177.0 (78), 164.1 (20), 159.0 (*p*-trifluoromethylbenzyl, 73), 125.0 (39), 123.0 (100), 109.0 (35). M$^+$ not visible.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.83 – 1.90 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.50 – 2.96 (m, 3H, H3, H4, C4-CH), 2.93 – 3.06 (m, 1H, C4-CH), 3.75 (dd, ^2J = 8.7 Hz, ^3J = 6.0 Hz, 1H, H5), 4.07 (dd, ^2J = 8.7 Hz, ^3J = 6.0 Hz, 1H, H5), 4.27 (dd, ^2J = 11.4 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.41 (dd, ^2J = 11.4 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.89 (d, ^3J = 6.2 Hz, 1H, H2), 6.12 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.95 – 7.11 (m, 2H, H3', H5'), 7.22 – 7.36 (m, 4H, H2', H6', H2'', H6''), 7.56 (d, ^3J = 8.2 Hz, 2H, H3'', H5'').

^{13}C NMR (100 MHz, $CDCl_3$): δ 15.8 (q, C4'''), 20.6 (q, C5'''), 33.4 (t, C4-C), 42.2 (d, C4), 49.4 (d, C3), 61.9 (t, C3-C), 72.5 (t, C5), 82.5 (d, C2), 115.4 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.5 Hz), 124.2 (q, C4''-CF_3, $^1J_{C\text{-}F}$ = 271.9 Hz), 125.6 (dq, C3'', C5'', $^3J_{C\text{-}F}$ = 3.7 Hz), 127.2 (s, C2'''), 127.3 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 128.8 (q, C4'', $^2J_{C\text{-}F}$ = 32.5 Hz), 128.9 (d, C2'', C6''), 138.0 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 139.3 (d, C3'''), 144.1 (q, C1'', $^5J_{C\text{-}F}$ = 1.1 Hz), 162.3 (d, C4', $^1J_{C\text{-}F}$ = 245.8 Hz), 167.6 (s, C1''').

D.4.2 **Steglich Esterification**

D.4.2.1 *General Outline* for Steglich Esterification

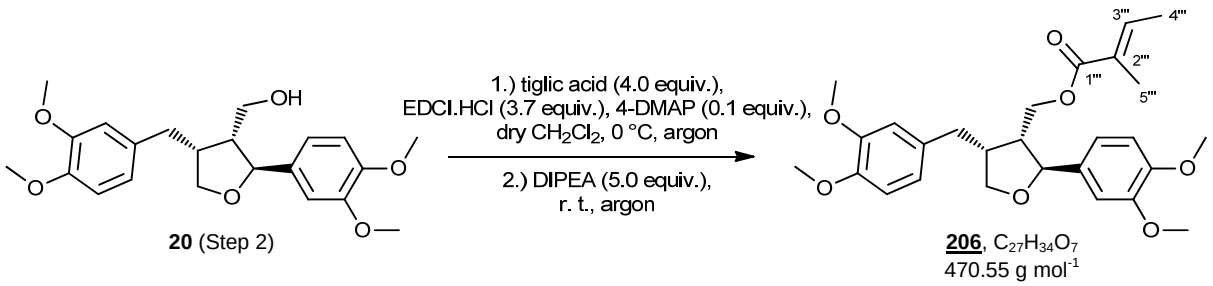


XI **XVI**

All compounds of generic structure **XVI** in this section were prepared according to the *General Outline* above, and are arranged such that compounds with the same R^1 are grouped together. Thus, for the ***Preparation*** of any particular compound, the experimental details are either given in full, or the reader is referred to an analogous procedure already described for a compound in this section. Generally, reaction progress was monitored by TLC or GC-MS, and the reaction was terminated when complete.

Details for ***Work-up and purification*** are given for each case individually to afford compounds of structure **XVI**.

D.4.2.2 (*E*)-((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (**<u>206</u>**)



20 (Step 2)

<u>206</u>, $C_{27}H_{34}O_7$
470.55 g mol^{-1}

Preparation*:* a reaction vessel was charged with a stirring bar, tiglic acid (36.0 mg, 0.360 mmol, 4.0 equiv.) and 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry CH_2Cl_2 (1.0 mL) was then added *via* syringe and the solution was cooled to 0 °C in an ice bath. The vessel was briefly opened, EDCI.HCl (63.8 mg, 0.333 mmol, 3.7 equiv.) added in one go and the mixture was stirred for 3 h at 0 °C. Meanwhile, a second vessel was charged with a stirring bar and starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.), evacuated and back-filled with argon (3 x), and DIPEA (78 µL, 0.45 mmol, 5.0 equiv.) was added *via* syringe. After 3 h, the solution containing the activated carboxylic acid was transferred to the second vial *via* syringe and stirred for 16 h at room temperature.

Work-up and purification*:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 50 : 50 in 30 min) to afford the title compound **<u>206</u>**.

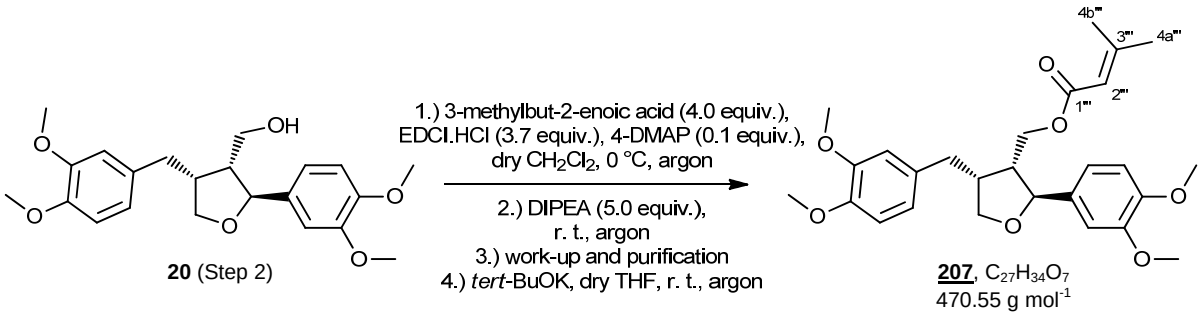
Yield:	40.3 mg, 95 %
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.57 (EtOAc / LP, 1 : 1)
[α]$_D^{20}$:	+17.5 (c 2.48, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 493.2197, found: 493.2204, Δ: 1.42 ppm
(log *P*)$_{calc}$:	5.38 ± 0.48

GC-MS (EI, 70 eV, Method E): 26.18 min; 470.2 (M$^+$, 2), 219.1 (30), 189.1 (16), 177.1 (16), 166.1 (15), 165.1 (90), 151.1 (100), 107.1 (16).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.73 – 1.84 (m, 6H, 3 x H4''', 3 x H5'''), 2.48 – 2.97 (m, 4H, H3, H4, C4-CH_2), 3.77 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.09 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.26 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.43 (dd, ^2J = 11.3 Hz, ^3J = 6.6 Hz, 1H, C3-CH), 4.83 (d, ^3J = 6.3 Hz, 1H, H2), 6.67 – 6.88 (m, 7H, 6 x Ar-H, H3''').

^{13}C NMR (50 MHz, $CDCl_3$): δ 12.1 (q, C5'''), 14.5 (q, C4'''), 33.4 (t, C4-C), 42.8 (d, C4), 49.3 (d, C3), 55.98 (q, Ar-OCH_3), 56.01 (q, Ar-OCH_3), 56.03 (q, Ar-OCH_3), 56.1 (q, Ar-OCH_3), 62.8 (t, C3-C), 72.9 (t, C5), 83.3 (d, C2), 109.1 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.3 (d, C6'), 120.6 (d, C6''), 128.4 (s, C2'''), 132.8 (s, C1''), 135.1 (s, C1'), 137.9 (d, C3'''), 147.6 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 168.0 (s, C1''').

D.4.2.3 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 3-methylbut-2-enoate (**207**)



20 (Step 2)

207, $C_{27}H_{34}O_7$
470.55 g mol^{-1}

***Preparation**:* a reaction vessel was charged with a stirring bar, 3-methylbut-2-enoic acid (36.0 mg, 0.360 mmol, 4.0 equiv.) and 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique (1 x). Dry CH_2Cl_2 (1.0 mL) was then added *via* syringe and the solution was cooled to 0 °C in an ice bath. The vessel was briefly opened, EDCI.HCl (63.8 mg, 0.333 mmol, 3.7 equiv.) added in one go and the mixture was stirred for 3 h at 0 °C. Meanwhile, a second vessel was charged with a stirring bar and starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.), evacuated and back-filled with argon (3 x), and DIPEA (78 µL, 0.45 mmol, 5.0 equiv.) was added *via* syringe. After 3 h, the solution containing the activated carboxylic acid was transferred to the second vial *via* syringe and stirred for 16 h at room temperature. The reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc /

LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 62 : 38 in 30 min) to give a mixture of the targeted compound **207**, as well as β-γ double bond isomerization compound **207'** (approximate ratio 3 : 1, by NMR, 34.4 mg).[s] Thus, a new reaction vessel was charged with a stirring bar and part of the so obtained material (24.7 mg, 0.052 mmol), evacuated and back-filled with argon. To this was then added *tert*-BuOK (2.9 mg, 0.026 mmol) in dry THF (1.0 mL) *via* syringe and the solution stirred at room temperature for 18 h.

Work-up and purification: THF (1.0 mL) was added, followed by Et_2O (15 mL) and a solution of $KHSO_4$ (0.029 mmol, 3.9 mg) in brine (2 mL). Water (1.5 mL) was added to dissolve the salts, the layers were separated, the aqueous phase was re-extracted with Et_2O (2 x 10 mL), the combined organic phases were dried with Na_2SO_4, filtered and the solvents were evaporated. Finally, flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 50 : 50 in 30 min) afforded the title compound **207**.

Yield:	17.0 mg, 40 % (with respect to the amount of starting material **20**), 56 % (with respect also to the amount of α-β- and β-γ- mixture applied for de-isomerization), respectively
Appearance:	nearly colorless oil
R_f **(silica)**:	0.50 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+29.2 (c 1.63, MeOH)
LC-HRMS (ESI):	calculated for $M+Na^+$: 493.2197, found: 493.2201, Δ: 0.81 ppm
(log *P*)$_{calc}$:	5.38 ± 0.48

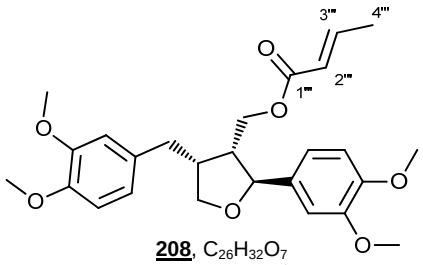
GC-MS (EI, 70 eV, Method E): 25.73 min; 470.2 (M^+, 2), 219.1 (29), 189.1 (17), 177.1 (16), 166.1 (15), 165.0 (89), 152.1 (15), 151.1 (100), 107.0 (18).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.90 (d, ^4J = 1.1 Hz, 3H, H4b'''), 2.17 (d, ^4J = 1.1 Hz, 3H, H4a'''), 2.47 – 2.84 (m, 3H, H3, H4, C4-CH), 2.89 (dd, ^2J = 12.6 Hz, ^3J = 4.3 Hz, 1H, C4-CH), 3.75 (dd, ^2J = 8.6 Hz, ^3J = 6.4 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.07 (d, ^2J = 8.5 Hz, ^3J = 6.2 Hz, 1H, H5), 4.21 (dd, ^2J = 11.3 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.37 (dd, ^2J = 11.3 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.81 (d, ^3J = 6.3 Hz, 1H, H2), 5.62 – 5.68 (m, 1H, H2'''), 6.67 – 6.91 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 20.4 (q, C4b'''), 27.6 (q, C4a'''), 33.3 (t, C4-C), 42.7 (d, C4), 49.3 (d, C3), 55.97 (q, Ar-OCH_3), 55.99 (q, Ar-OCH_3), 56.02 (q, Ar-OCH_3), 56.1 (q, Ar-OCH_3), 61.8 (t, C3-C), 72.9 (t, C5), 83.1 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.5 (d, C5''*), 112.1 (d, C2''*), 115.7 (d, C2'''), 118.2 (d, C6'), 120.6 (d, C6''), 132.9 (s, C1''), 135.2 (s, C1'), 147.6 (s, C4''), 148.5 (s, C4'), 149.1 (s, C3''), 149.1 (s, C3'), 157.7 (s, C3'''), 166.6 (s, C1''').

[s] *Cf*. **Scheme 59** (section B.1.2, page 75).

D.4.2.4 (*E*)-((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl but-2-enoate (**208**)



208, $C_{26}H_{32}O_7$
456.53 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.) and crotonic acid (31.0 mg, 0.360 mmol, 4.0 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 50 : 50 in 30 min) to afford the title compound **208**.

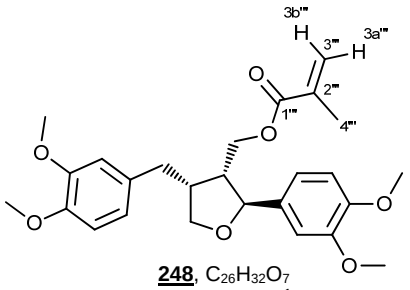
Yield:	32.0 mg, 78 %
Appearance:	colorless oil
R_f (silica):	0.54 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+24.6 (c 0.63, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 479.2040, found: 479.2046, Δ: 1.25 ppm
(log *P*)$_{calc}$:	4.83 ± 0.45

GC-MS (EI, 70 eV, Method E): 22.96 min; 456.2 (M$^+$, 3), 219.1 (27), 189.1 (17), 177.1 (15), 166.1 (15), 165.0 (87), 151.0 (100), 107.0 (18).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.88 (dd, ^3J = 6.9 Hz, ^4J = 1.5 Hz, 3H, H4'''), 2.48 – 2.94 (m, 4H, H3, H4, C4-CH_2), 3.75 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.08 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.25 (dd, ^2J = 11.3 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.43 (dd, ^2J = 11.3 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.81 (d, ^3J = 6.3 Hz, 1H, H2), 5.82 (dd, ^3J = 15.6 Hz, ^4J = 1.6 Hz, 1H, H2'''), 6.66 – 7.01 (m, 7H, 6 x Ar-H, H3''').

^{13}C NMR (50 MHz, $CDCl_3$): δ 18.2 (q, C4'''), 33.3 (t, C4-C), 42.7 (d, C4), 49.2 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 62.5 (t, C3-C), 72.9 (t, C5), 83.2 (d, C2), 109.1 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.6 (d, C6''), 122.4 (d, C2'''), 132.8 (s, C1''), 135.1 (s, C1'), 145.4 (d, C3'''), 147.6 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.1 (s, C3'), 166.4 (s, C1''').

D.4.2.5 ((2*S*,3*R*,4*R*)-4-(3,4-dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl methacrylate (**248**)



248, $C_{26}H_{32}O_7$
456.53 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.) and methacrylic acid (31.0 mg, 0.360 mmol, 4.0 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 62 : 38 in 30 min) to afford the title compound **248**.

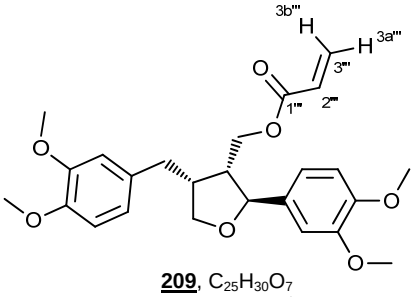
This compound polymerized before characterization (**$[\alpha]_D$**, **LC-HRMS, GC-MS**) could be completed.

Yield: 32.9 mg, 80 %
Appearance: nearly colorless oil
R_f (silica): 0.53 (EtOAc / LP, 1 : 1)
(log *P*)$_{calc}$: 4.83 ± 0.45

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.90 – 1.94 (m, 3H, H4'''), 2.50 – 2.97 (m, 4H, H3, H4, C4-CH_2), 3.77 (dd, ^2J = 8.5 Hz, ^3J = 6.2 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.09 (dd, ^2J = 8.5 Hz, ^3J = 6.2 Hz, 1H, H5), 4.28 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.44 (dd, ^2J = 11.3 Hz, ^3J = 6.7 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.2 Hz, 1H, H2), 5.56 (dd, ^2J = 1.3 Hz, ^4J = 1.3 Hz, 1H, H3a'''), 6.03 – 6.08 (m, 1H, H3b'''), 6.65 – 6.92 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 18.4 (q, C4'''), 33.4 (t, C4-C), 42.8 (d, C4), 49.2 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 63.1 (t, C3-C), 72.9 (t, C5), 83.2 (d, C2), 109.0 (d, C2'), 111.2 (d, C5'), 111.5 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.6 (d, C6''), 126.0 (t, C3'''), 132.7 (s, C1''), 135.1 (s, C1'), 136.2 (s, C2'''), 147.7 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 167.4 (s, C1''').

D.4.2.6 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl acrylate (**209**)



209, $C_{25}H_{30}O_7$
442.50 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.) and acrylic acid (25.9 mg, 0.360 mmol, 4.0 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 62 : 38 in 30 min) to afford the title compound **209**.

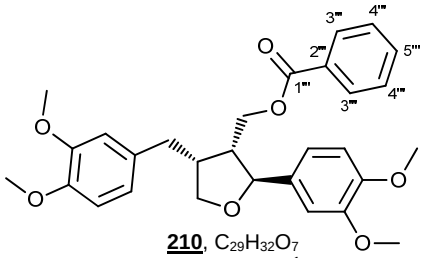
Yield:	29.3 mg, 74 %
Appearance:	nearly colorless oil
R_f (silica):	0.54 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+10.5 (c 1.68, $CHCl_3$)
LC-HRMS (ESI):	calculated for M+Na$^+$: 465.1889, found: 465.1911, Δ: 4.73 ppm
(log *P*)$_{calc}$:	4.30 ± 0.45

GC-MS (EI, 70 eV, Method D): 18.25 min; 442.2 (M$^+$, 4), 219.1 (22), 208.1 (19), 207.0 (86), 191.0 (17), 189.1 (16), 177.1 (18), 165.1 (74), 151.0 (100), 133.1 (16), 107.1 (18), 96.0 (18), 91.1 (15).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.49 – 2.96 (m, 4H, H3, H4, C4-CH_2), 3.76 (dd, ^2J = 8.5 Hz, ^3J = 6.3 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.09 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.28 (dd, ^2J = 11.3 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.46 (dd, ^2J = 11.3 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.82 (d, ^3J = 6.2 Hz, 1H, H2), 5.84 (dd, ^2J = 1.6 Hz, ^3J = 10.3 Hz, 1H, H3a'''), 6.09 (dd, $^3J_{cis}$ = 10.3 Hz, $^3J_{trans}$ = 17.2 Hz, 1H, H2'''), 6.37 (dd, ^2J = 1.6 Hz, ^3J = 17.2 Hz, 1H, H3b'''), 6.64 – 6.91 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.3 (t, C4-C), 42.6 (d, C4), 49.2 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 62.9 (t, C3-C), 72.9 (t, C5), 83.2 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.5 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.6 (d, C6''), 128.3 (d, C2'''), 131.3 (t, C3'''), 132.7 (s, C1''), 135.0 (s, C1'), 147.7 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 166.1 (s, C1''').

D.4.2.7 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl benzoate (**<u>210</u>**)



<u>210</u>, $C_{29}H_{32}O_7$
492.56 g mol^{-1}

***Preparation**:* analogous to **<u>206</u>** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.) and benzoic acid (44.0 mg, 0.360 mmol, 4.0 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 62 : 38 in 30 min) to afford the title compound **<u>210</u>**.

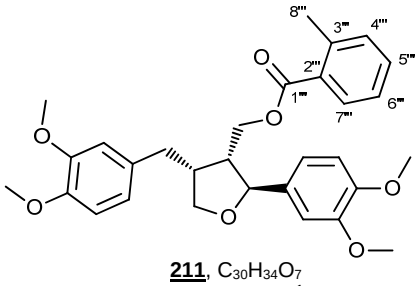
Yield:	40.4 mg, 91 %
Appearance:	colorless oil
R_f (silica):	0.54 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+20.2 (c 2.04, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 515.2040, found: 515.2050, Δ: 1.94 ppm
(log *P*)$_{calc}$:	5.70 ± 0.44

GC-MS (EI, 70 eV, Method F): 46.13 min; 492.2 (M^+, 3), 219.1 (24), 207.0 (24), 189.1 (16), 177.1 (15), 165.1 (72), 151.1 (94), 107.1 (18), 106.1 (15), 105.0 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.55 – 3.02 (m, 4H, H3, H4, C4-CH_2), 3.76 – 3.83 (m, 1H, H5), 3.84 (s, 3H, Ar-OCH_3), 3.85 (s, 6H, Ar-OCH_3), 3.86 (s, 3H, Ar-OCH_3), 4.13 (dd, ^2J = 8.6 Hz, ^3J = 6.1 Hz, 1H, H5), 4.46 (dd, ^2J = 11.2 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.63 (dd, ^2J = 11.3 Hz, ^3J = 6.3 Hz, 1H, C3-CH), 4.91 (d, ^3J = 6.2 Hz, 1H, H2), 6.66 – 6.95 (m, 6H, 3 x Ar'-H, 3 x Ar''-H), 7.42 (t, ^3J = 7.4 Hz, 2H, H4'''), 7.50 – 7.62 (m, 1H, H5'''), 7.89 – 7.97 (m, 2H, H3''').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.5 (t, C4-<u>C</u>), 42.8 (d, C4), 49.3 (d, C3), 55.9 (q, Ar-OCH_3), 55.99 (q, Ar-OCH_3), 56.02 (q, Ar-OCH_3), 56.1 (q, Ar-OCH_3), 63.4 (t, C3-<u>C</u>), 73.0 (t, C5), 83.5 (d, C2), 109.1 (d, C2'), 111.2 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.3 (d, C6'), 120.6 (d, C6''), 128.5 (d, C4'''), 129.7 (d, C3'''), 130.0 (s, C2'''), 132.6 (s, C1''), 133.3 (d, C5'''), 135.0 (s, C1'), 147.7 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 166.5 (s, C1''').

D.4.2.8 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbenzoate (**211**)



211, $C_{30}H_{34}O_7$
506.59 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (29.5 mg, 0.076 mmol, 1.00 equiv.), 2-methylbenzoic acid (41.4 mg, 0.304 mmol, 4.0 equiv.), EDCI.HCl (53.9 mg, 0.281 mmol, 3.7 equiv.), 4-DMAP (0.9 mg, 7.6 µmol, 0.1 equiv.) and DIPEA (66 µL, 0.38 mmol, 5.0 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 7 : 93 to 50 : 50 in 30 min) to afford the title compound **211**.

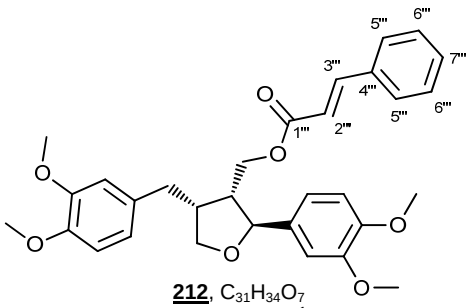
Yield:	28.9 mg, 75 %
Appearance:	colorless oil
R_f (silica):	0.44 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{25}$:	+19.1 (c 2.89, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 529.2197, found: 529.2234, Δ: 6.99 ppm
(log *P*)$_{calc}$:	6.16 ± 0.44

GC-MS (EI, 70 eV, Method F): 50.43 min; 506.3 (M$^+$, 4), 219.1 (31), 207.0 (35), 189.1 (18), 177.1 (16), 166.1 (15), 165.1 (79), 152.1 (15), 151.1 (100), 119.0 (88), 107.1 (15), 91.1 (58).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.53 – 2.90 (m, 3H, H3, H4, C4-CH), 2.60 (s, 3H, H8'''), 2.95 (dd, ^2J = 12.5 Hz, ^3J = 4.2 Hz, 1H, C4-CH), 3.72 – 3.82 (m, 1H, H5), 3.83 (s, 3H, Ar-OCH_3), 3.85 (s, 6H, Ar-OCH_3), 3.86 (s, 3H, Ar-OCH_3), 4.12 (dd, ^2J = 8.6 Hz, ^3J = 6.0 Hz, 1H, H5), 4.42 (dd, ^2J = 11.2 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.60 (dd, ^2J = 11.3 Hz, ^3J = 6.6 Hz, 1H, C3-CH), 4.90 (d, ^3J = 6.3 Hz, 1H, H2), 6.66 – 6.94 (m, 6H, Ar-H), 7.15 – 7.27 (m, 2H, H4''', H6'''), 7.41 (td, ^3J = 7.5 Hz, ^4J = 1.3 Hz, 1H, H5'''), 7.76 (dd, ^3J = 7.6 Hz, ^4J = 1.3 Hz, 1H, H7''').

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9 (q, C8'''), 33.4 (t, C4-C), 42.8 (d, C4), 49.4 (d, C3), 55.91 (q, Ar-OCH_3), 55.94 (q, Ar-OCH_3), 55.98 (q, Ar-OCH_3), 56.02 (q, Ar-OCH_3), 63.1 (t, C3-C), 72.9 (t, C5), 83.3 (d, C2), 109.1 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.3 (d, C6'), 120.6 (d, C6''), 125.8 (d, C6'''), 129.2 (s, C2'''), 130.6 (d, C4'''), 131.9 (d, C7'''*), 132.3 (d, C5'''*), 132.6 (s, C1''), 135.0 (s, C1'), 140.6 (s, C3'''), 147.6 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 167.3 (s, C1''').

D.4.2.9 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl cinnamate (**212**)



212, $C_{31}H_{34}O_7$
518.60 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.) and cinnamic acid (53.3 mg, 0.360 mmol, 4.0 equiv.).

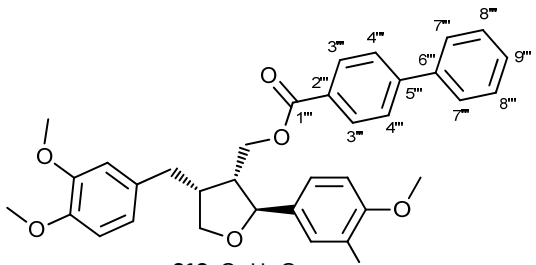
***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 62 : 38 in 30 min) to afford the title compound **212**.

Yield:	45.1 mg, 97 %
Appearance:	colorless oil
R_f (silica):	0.43 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{25}$:	+35.4 (c 4.24, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 541.2197, found: 541.2205, Δ: 1.48 ppm
(log *P*)$_{calc}$:	5.69 ± 0.45

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.50 – 3.00 (m, 4H, H3, H4, C4-CH_2), 3.78 (dd, ^2J = 8.6 Hz, ^3J = 5.8 Hz, 1H, H5), 3.83 (s, 3H, Ar-OCH_3), 3.85 (s, 3H, Ar-OCH_3), 3.86 (s, 3H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.11 (dd, ^2J = 8.6 Hz, ^3J = 6.1 Hz, 1H, H5), 4.34 (dd, ^2J = 11.3 Hz, ^3J = 7.2 Hz, 1H, C3-CH), 4.52 (dd, ^2J = 11.3 Hz, ^3J = 6.6 Hz, 1H, C3-CH), 4.85 (d, ^3J = 6.4 Hz, 1H, H2), 6.38 (d, ^3J = 16.1 Hz, 1H, H2'''), 6.68 – 6.95 (m, 6H, 3 x Ar'-H, 3 x Ar''-H), 7.35 – 7.44 (m, 3H, Ar'''-H), 7.44 – 7.54 (m, 2H, Ar'''-H), 7.57 (d, ^3J = 16.1 Hz, 1H, H3''').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.3 (t, C4-C), 42.7 (d, C4), 49.1 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 62.9 (t, C3-C), 72.9 (t, C5), 83.4 (d, C2), 109.1 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 117.6 (d, C2'''), 118.4 (d, C6'), 120.5 (d, C6''), 128.2 (d, C5'''), 129.0 (d, C6'''), 130.6 (d, C7'''), 132.7 (s, C1''), 134.3 (s, C4'''), 135.0 (s, C1'), 145.3 (d, C3'''), 147.6 (s, C4''), 148.6 (s, C4'), 149.0 (s, C3''), 149.1 (s, C3'), 166.8 (s, C1''').

D.4.2.10 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl) tetrahydrofuran-3-yl)methyl [1,1'-biphenyl]-4-carboxylate (**213**)



213, $C_{35}H_{36}O_7$
568.66 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.) and [1,1'-biphenyl]-4-carboxylic acid (71.4 mg, 0.360 mmol, 4.0 equiv.).

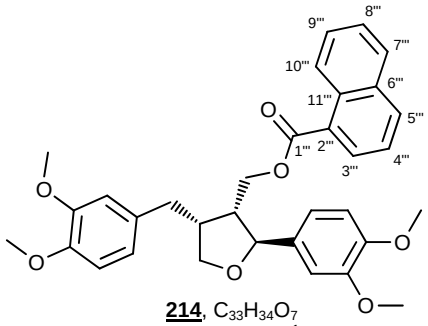
***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 15 : 85 in 10 min, then to 22 : 78 in 6 min, then to 50 : 50 in 10 min) to afford the title compound **213**.

Yield:	42.8 mg, 84 %
Appearance:	colorless oil
R_f (silica):	0.46 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{25}$:	+11.0 (c 4.28, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 591.2353, found: 591.2348, Δ: -0.85 ppm
(log *P*)$_{calc}$:	7.35 ± 0.48

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.64 (dd, ^2J = 12.2 Hz, ^3J = 9.5 Hz, 1H, C4-CH), 2.69 – 3.03 (m, 3H, H3, H4, C4-CH), 3.73 – 3.83 (m, 1H, H5), 3.85 (s, 12H, Ar-OCH_3), 4.14 (dd, ^2J = 8.5 Hz, ^3J = 6.0 Hz, 1H, H5), 4.48 (dd, ^2J = 11.2 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.65 (dd, ^2J = 11.2 Hz, ^3J = 6.3 Hz, 1H, C3-CH), 4.92 (d, ^3J = 6.2 Hz, 1H, H2), 6.68 – 6.96 (m, 6H, Ar-H), 7.36 – 7.53 (m, 3H, 2 x H8'''*, H9'''), 7.57 – 7.68 (m, 4H, 2 x H4''', 2 x H7'''*), 7.99 (d, ^3J = 8.4 Hz, 2H, H3''').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.5 (t, C4-C), 42.8 (d, C4), 49.3 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 63.4 (t, C3-C), 73.0 (t, C5), 83.5 (d, C2), 109.1 (d, C2'), 111.2 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.4 (d, C6'), 120.6 (d, C6''), 127.2 (d, C7'''*), 127.4 (d, C4'''*), 128.4 (d, C9'''), 128.7 (s, C2'''), 129.1 (d, C3'''), 130.2 (d, C8'''), 132.7 (s, C1''), 135.0 (s, C1'), 140.0 (s, C6'''), 146.0 (s, C5'''), 147.7 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 166.4 (s, C1''').

D.4.2.11 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 1-naphthoate (**214**)



214, $C_{33}H_{34}O_7$
542.62 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.) and 1-naphthoic acid (62.0 mg, 0.360 mmol, 4.0 equiv.).

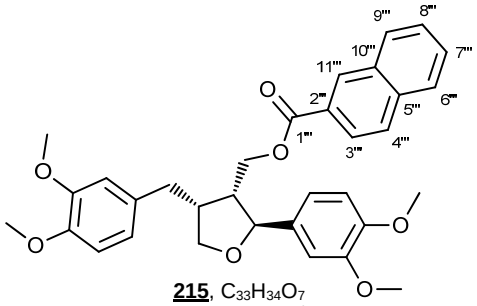
***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 8 : 92 to 50 : 50 in 30 min) to afford the title compound **214**.

Yield:	44.6 mg, 91 %
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.43 (EtOAc / LP, 1 : 1)
[α]$_D^{25}$:	+7.0 (c 3.99, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 565.2197, found: 565.2207, Δ: 1.77 ppm
(log *P*)$_{calc}$:	6.94 ± 0.44

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.65 (dd, ^2J = 12.3 Hz, ^3J = 9.6 Hz, 1H, C4-CH), 2.72 – 2.94 (m, 2H, H3, H4), 2.99 (dd, ^2J = 12.6 Hz, ^3J = 3.8 Hz, 1H, C4-CH), 3.70 – 3.82 (m, 1H, H5), 3.79 (s, 3H, Ar-OCH_3), 3.83 (s, 3H, Ar-OCH_3), 3.84 (s, 6H, Ar-OCH_3), 4.14 (dd, ^2J = 8.6 Hz, ^3J = 5.9 Hz, 1H, H5), 4.54 (dd, ^2J = 11.2 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.73 (dd, ^2J = 11.2 Hz, ^3J = 6.2 Hz, 1H, C3-CH), 4.95 (d, ^3J = 6.0 Hz, 1H, H2), 6.67 – 6.84 (m, 4H, Ar-H), 6.86 – 6.96 (m, 2H, Ar-H), 7.44 (t, ^3J = 7.7, 1H, H4'''), 7.49 – 7.67 (m, 2H, H8''', H9'''), 7.89 (d, ^3J = 7.6 Hz, 1H, H7'''), 7.98 (dd, ^3J = 7.4 Hz, ^4J = 1.2 Hz, 1H, H5'''*), 8.02 (d, ^3J = 8.3 Hz, 1H, H3'''*), 8.92 (d, ^3J = 8.3 Hz, 1H, H10''').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.4 (t, C4-C), 42.9 (d, C4), 49.4 (d, C3), 55.92 (q, Ar-OCH_3), 55.94 (q, Ar-OCH_3), 56.00 (q, Ar-OCH_3), 56.02 (q, Ar-OCH_3), 63.4 (t, C3-C), 73.0 (t, C5), 83.5 (d, C2), 109.1 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.3 (d, C6'), 120.6 (d, C6''), 124.5 (d, C4'''), 125.8 (d, C10'''), 126.4 (d, C8'''), 126.7 (s, C2'''), 128.0 (d, C9'''), 128.7 (d, C7'''), 130.4 (d, C3'''), 131.5 (s, C11'''), 132.6 (s, C1''), 133.8 (d, C5'''), 133.9 (s, C6'''), 135.0 (s, C1'), 147.6 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 167.4 (s, C1''').

D.4.2.12 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-naphthoate (**215**)



215, $C_{33}H_{34}O_7$
542.62 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.) and 2-naphthoic acid (62.0 mg, 0.360 mmol, 4.0 equiv.).

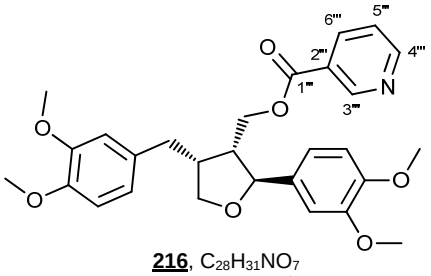
***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 8 : 92 to 50 : 50 in 30 min) to afford the title compound **215**.

Yield:	43.7 mg, 90 %
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.40 (EtOAc / LP, 1 : 1)
[α]$_D^{20}$:	+17.6 (c 2.38, MeOH)
LC-HRMS (APCI):	calculated for M+Na$^+$: 565.2197, found: 565.2211, Δ: 2.48 ppm
(log *P*)$_{calc}$:	6.94 ± 0.44

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.58 – 3.04 (m, 4H, H3, H4, C4-CH_2), 3.81 (s, 3H, Ar-OCH_3), 3.81 – 3.90 (m, 1H, H5), 3.83 (s, 3H, Ar-OCH_3), 3.84 (s, 3H, Ar-OCH_3), 3.84 (s, 3H, Ar-OCH_3), 4.15 (dd, ^2J = 8.5 Hz, ^3J = 6.0 Hz, 1H, H5), 4.52 (dd, ^2J = 11.2 Hz, ^3J = 7.3 Hz, 1H, C3-CH), 4.71 (dd, ^2J = 11.2 Hz, ^3J = 6.0 Hz, 1H, C3-CH), 4.94 (d, ^3J = 6.2 Hz, 1H, H2), 6.77 (m, 4H, Ar-H), 6.87 – 6.98 (m, 2H, Ar-H), 7.49 – 7.65 (m, 2H, H7''', H8'''), 7.80 – 7.98 (m, 4H, H3''', H4''', H6''', H9'''), 8.40 (s, 1H, H11''').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.5 (t, C4-C), 42.9 (d, C4), 49.2 (d, C3), 55.9 (q, 4 x Ar-OCH_3), 63.6 (t, C3-C), 73.0 (t, C5), 83.8 (d, C2), 109.2 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.5 (d, C6'), 120.6 (d, C6''), 125.1 (d, C3'''*), 126.9 (d, C8'''*), 127.1 (s, C2'''), 127.9 (d, C6'''*), 128.3 (d, C4'''*), 128.5 (d, C7'''*), 129.4 (d, C9'''*), 131.2 (d, C11'''*), 132.5 (s, C10'''), 132.6 (s, C1''), 134.9 (s, C1'), 135.7 (s, C5'''), 147.6 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 166.7 (s, C1''').

D.4.2.13 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl nicotinate (**216**)



216, $C_{28}H_{31}NO_7$
493.55 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (36.5 mg, 0.094 mmol, 1.00 equiv.) and nicotinic acid (46.3 mg, 0.376 mmol, 4.0 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 40 : 60 to 100 : 0 in 30 min) to afford the title compound **216**.

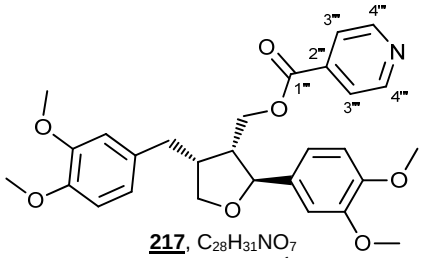
Yield:	33.1 mg, 71 %
Appearance:	colorless oil
R_f (silica):	0.33 (EtOAc)
$[\alpha]_D^{20}$:	+27.8 (c 1.56, MeOH)
LC-HRMS (APCI):	calculated for $M+H^+$: 494.2173, found: 494.2148, Δ: -5.06 ppm
(log *P*)$_{calc}$:	4.39 ± 0.45

GC-MS (EI, 70 eV, Method F): 50.36 min; 493.2 (M^+, 5), 219.1 (34), 207.0 (20), 166.1 (15), 165.0 (67), 152.1 (15), 151.1 (100), 124.0 (38), 107.1 (21), 106.0 (75).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.54 – 3.02 (m, 4H, H3, H4, C4-CH_2), 3.79 (dd, ^2J = 8.6 Hz, ^3J = 2.7 Hz, 1H, H5), 3.85 (s, 3H, Ar-OCH_3), 3.86 (s, 9H, Ar-OCH_3), 4.15 (dd, ^2J = 8.6 Hz, ^3J = 6.1 Hz, 1H, H5), 4.49 (dd, ^2J = 11.3 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.66 (dd, ^2J = 11.3 Hz, ^3J = 6.5 Hz, 1H, C3-CH), 4.88 (d, ^3J = 6.4 Hz, 1H, H2), 6.66 – 6.94 (m, 6H, Ar-H), 7.36 (dd, ^3J = 7.9 Hz, ^3J = 4.9 Hz, 1H, H5'''), 8.11 (dt, ^3J = 8.0 Hz, ^4J = 1.9 Hz, 1H, H6'''), 8.78 (dd, ^3J = 4.8 Hz, ^4J = 1.6 Hz, 1H, H4'''), 9.14 (d, ^4J = 2.0 Hz, 1H, H3''').

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.6 (t, C4-C), 42.6 (d, C4), 49.1 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 63.8 (t, C3-C), 73.0 (t, C5), 83.4 (d, C2), 109.1 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 111.9 (d, C2''*), 118.4 (d, C6'), 120.5 (d, C6''), 123.4 (d, C5'''), 125.8 (s, C2'''), 132.4 (s, C1''), 134.7 (s, C1'), 137.1 (d, C6'''), 147.7 (s, C4''), 148.7 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 150.9 (d, C3'''), 153.7 (d, C4'''), 165.2 (s, C1''').

D.4.2.14 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl isonicotinate (**217**)



217, $C_{28}H_{31}NO_7$
493.55 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (32.6 mg, 0.084 mmol, 1.00 equiv.) and isonicotinic acid (41.4 mg, 0.336 mmol, 4.0 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 40 : 60 to 55 : 45 in 8 min, then to 100 : 0 in 18 min) to afford the title compound **217**.

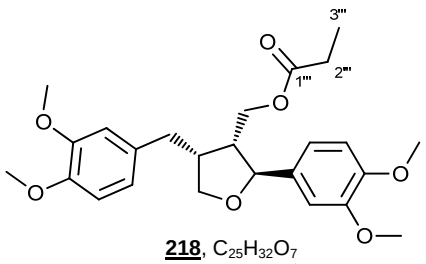
Yield:	32.8 mg, 79 %
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.33 (EtOAc)
[α]$_D^{20}$:	+25.1 (c 1.77, MeOH)
LC-HRMS (APCI):	calculated for M+H$^+$: 494.2173, found: 494.2152, Δ: -4.25 ppm
(log *P*)$_{calc}$:	4.39 ± 0.45

GC-MS (EI, 70 eV, Method F): 46.96 min; 493.3 (M$^+$, 3), 219.2 (18), 207.1 (61), 165.1 (57), 152.1 (15), 151.1 (100), 107.1 (22), 106.1 (75), 96.1 (15).

^{1}H NMR (200 MHz, CDCl$_3$): δ 2.53 – 2.98 (m, 4H, H3, H4, C4-CH$_2$), 3.77 (dd, ^2J = 8.3 Hz, ^3J = 2.5 Hz, 1H, H5), 3.83 (s, 3H, Ar-OCH$_3$), 3.85 (s, 9H, Ar-OCH$_3$), 4.14 (dd, ^2J = 8.7 Hz, ^3J = 6.1 Hz, 1H, H5), 4.47 (dd, ^2J = 11.2 Hz, ^3J = 7.3 Hz, 1H, C3-CH), 4.66 (dd, ^2J = 11.3 Hz, ^3J = 6.3 Hz, 1H, C3-CH), 4.86 (d, ^3J = 6.4 Hz, 1H, H2), 6.64 – 6.92 (m, 6H, Ar-H), 7.62 – 7.70 (m, 2H, H3'''), 8.74 (d, ^3J = 5.8 Hz, 2H, H4''').

^{13}C NMR (50 MHz, CDCl$_3$): δ 33.5 (t, C4-C), 42.6 (d, C4), 49.0 (d, C3), 56.0 (q, 4 x Ar-OCH$_3$), 64.2 (t, C3-C), 73.0 (t, C5), 83.5 (d, C2), 109.1 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 111.9 (d, C2''*), 118.5 (d, C6'), 120.5 (d, C6''), 122.8 (d, C3'''), 132.3 (s, C1''), 134.6 (s, C1'), 137.0 (s, C2'''), 147.7 (s, C4''), 148.8 (s, C4'), 149.1 (s, C3''), 149.3 (s, C3'), 150.7 (d, C4'''), 165.0 (s, C1''').

D.4.2.15 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl propionate (**218**)



218, $C_{25}H_{32}O_7$
444.52 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.), propionic acid (15.3 mg, 0.207 mmol, 2.3 equiv.), EDCI.HCl (34.5 mg, 0.180 mmol, 2.0 equiv.), 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.) and DIPEA (39 µL, 0.23 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 62 : 38 in 30 min) to afford the title compound **218**.

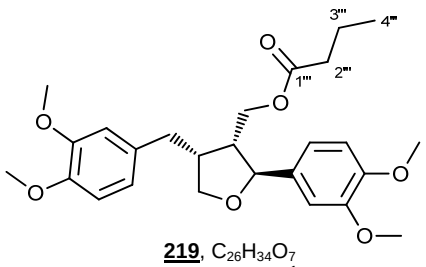
Yield:	36.4 mg, 91 %
Appearance:	colorless oil
R_f (silica):	0.32 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{20}$:	+19.8 (c 1.75, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 467.2040, found: 467.2047, Δ: 1.50 ppm
(log *P*)$_{calc}$:	4.22 ± 0.44

GC-MS (EI, 70 eV, Method E): 18.46 min; 444.2 (M$^+$, 7), 219.1 (18), 165.1 (53), 152.1 (15), 151.0 (100), 107.1 (15).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.13 (t, ^3J = 7.6 Hz, 3H, H3'''), 2.30 (q, ^3J = 7.6 Hz, 2H, H2'''), 2.47 – 2.94 (m, 4H, H3, H4, C4-CH_2), 3.75 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.20 (dd, ^2J = 11.2 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.37 (dd, ^2J = 11.2 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.79 (d, ^3J = 6.4 Hz, 1H, H2), 6.66 – 6.90 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 9.2 (q, C3'''), 27.7 (t, C2'''), 33.3 (t, C4-C), 42.6 (d, C4), 49.1 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 62.6 (t, C3-C), 72.9 (t, C5), 83.1 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.5 (d, C6''), 132.7 (s, C1''), 135.0 (s, C1'), 147.6 (s, C4''), 148.6 (s, C4'), 149.0 (s, C3''), 149.1 (s, C3'), 174.4 (s, C1''').

D.4.2.16 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl butyrate (**219**)



219, $C_{26}H_{34}O_7$
458.54 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.), butyric acid (18.2 mg, 0.207 mmol, 2.3 equiv.), EDCI.HCl (34.5 mg, 0.180 mmol, 2.0 equiv.), 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.) and DIPEA (39 µL, 0.23 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 62 : 38 in 30 min) to afford the title compound **219**.

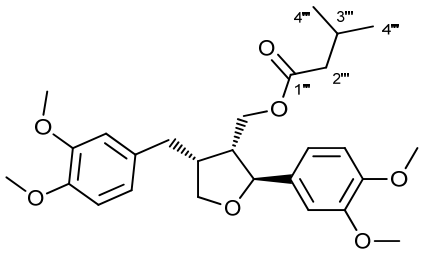
Yield:	35.1 mg, 85 %
Appearance:	colorless oil
R_f (silica):	0.44 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+20.3 (c 1.77, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 481.2197, found: 481.2207, Δ: 2.08 ppm
(log *P*)$_{calc}$:	4.75 ± 0.44

GC-MS (EI, 70 eV, Method E): 20.50 min; 458.2 (M$^+$, 6), 219.1 (21), 165.1 (52), 152.1 (15), 151.1 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.94 (t, ^3J = 7.4 Hz, 3H, H4'''), 1.64 (sext, ^3J = 7.4 Hz, 2H, H3'''), 2.26 (t, ^3J = 7.4 Hz, 2H, H2'''), 2.47 – 2.93 (m, 4H, H3, H4, C4-CH_2), 3.75 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.19 (dd, ^2J = 11.2 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.38 (dd, ^2J = 11.2 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.79 (d, ^3J = 6.4 Hz, 1H, H2), 6.64 – 6.92 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8 (q, C4'''), 18.5 (t, C3'''), 33.3 (t, C4-C), 36.3 (t, C2'''), 42.6 (d, C4), 49.1 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 62.5 (t, C3-C), 72.8 (t, C5), 83.0 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.5 (d, C6''), 132.7 (s, C1''), 135.0 (s, C1'), 147.6 (s, C4''), 148.6 (s, C4'), 149.0 (s, C3''), 149.1 (s, C3'), 173.6 (s, C1''').

D.4.2.17 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 3-methylbutanoate (**220**)



220, $C_{27}H_{36}O_7$
472.57 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (22.8 mg, 0.059 mmol, 1.00 equiv.) and 3-methylbutanoic acid (13.8 mg, 0.135 mmol, 2.3 equiv.), EDCI.HCl (22.5 mg, 0.117 mmol, 2.0 equiv.), 4-DMAP (0.7 mg, 5.9 µmol, 0.1 equiv.) and DIPEA (26 µL, 0.15 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 30 : 70 in 30 min) to afford the title compound **220**.

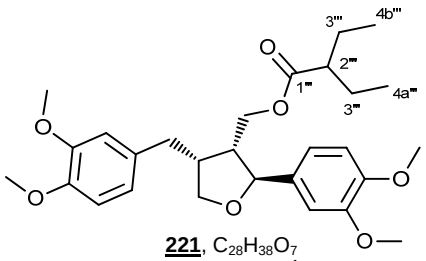
Yield:	22.0 mg, 96 %
Appearance:	colorless oil
R_f (silica):	0.45 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{23}$:	+22.9 (c 0.90, MeOH)
LC-HRMS (APCI):	calculated for M+Na$^+$: 495.2353, found: 495.2371, Δ: 3.63 ppm
(log *P*)$_{calc}$:	5.10 ± 0.45

GC-MS (EI, 70 eV, Method F): 21.28 min; 472.1 (M$^+$, 9), 219.1 (25), 189.1 (15), 165.0 (55), 152.1 (15), 151.0 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.96 (d, ^3J = 6.4 Hz, 6H, H4'''), 1.97 – 2.22 (m, 3H, 2 x H2''', H3'''), 2.47 – 2.64 (m, 2H, H3, C4-CH), 2.64 – 2.81 (m, 1H, H4), 2.87 (dd, ^2J = 12.5 Hz, ^3J = 4.3 Hz, 1H, C4-CH), 3.75 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.18 (dd, ^2J = 11.3 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.38 (dd, ^2J = 11.2 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.79 (d, ^3J = 6.4 Hz, 1H, H2), 6.66 – 6.90 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.6 (q, 2 x C4'''), 25.8 (d, C3'''), 33.3 (t, C4-C), 42.6 (d, C4), 43.5 (t, C2'''), 49.2 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 62.5 (t, C3-C), 72.8 (t, C5), 83.0 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.5 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.6 (d, C6''), 132.7 (s, C1''), 135.1 (s, C1'), 147.6 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 173.1 (s, C1''').

D.4.2.18 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-ethylbutanoate (**221**)



221, $C_{28}H_{38}O_7$
486.60 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (20.3 mg, 0.052 mmol, 1.00 equiv.) and 2-ethylbutanoic acid (14.0 mg, 0.120 mmol, 2.3 equiv.), EDCI.HCl (20.0 mg, 0.105 mmol, 2.0 equiv.), 4-DMAP (0.6 mg, 5.2 µmol, 0.1 equiv.) and DIPEA (23 µL, 0.13 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 30 : 70 in 30 min) to afford the title compound **221**.

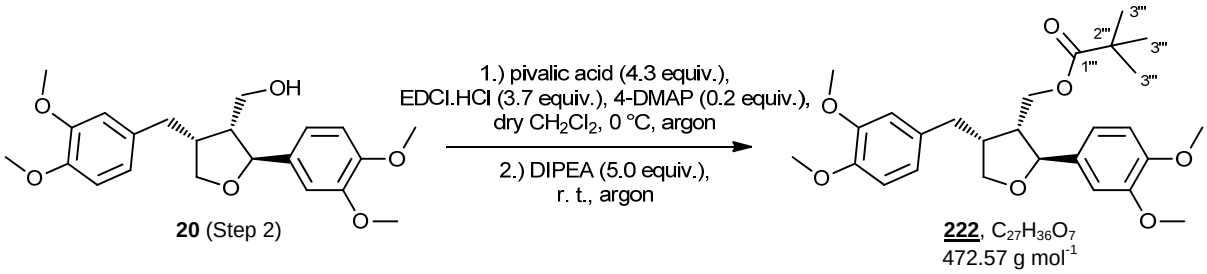
Yield:	22.2 mg, 87 %
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.44 (EtOAc / heptane, 1 : 1)
[α]$_D^{23}$:	+23.3 (c 0.88, MeOH)
LC-HRMS (APCI):	calculated for M+Na$^+$: 509.2510, found: 509.2533, Δ: 4.52 ppm
(log *P*)$_{calc}$:	5.63 ± 0.45

GC-MS (EI, 70 eV, Method F): 23.47 min; 486.2 (M$^+$, 7), 219.1 (32), 189.1 (15), 165.1 (56), 151.0 (100).

^{1}H NMR (200 MHz, CDCl$_3$): δ 0.90 (t, ^3J = 7.4 Hz, 6H, 3 x H4a''', 3 x H4b'''), 1.42 – 1.75 (m, 4H, H3'''), 2.15 – 2.30 (m, 1H, H2'''), 2.47 – 2.82 (m, 3H, H3, H4, C4-CH), 2.88 (dd, ^2J = 12.6 Hz, ^3J = 4.0 Hz, 1H, C4-CH), 3.76 (dd, ^2J = 8.6 Hz, ^3J = 6.1 Hz, 1H, H5), 3.87 (s, 6H, Ar-OCH$_3$), 3.87 (s, 3H, Ar-OCH$_3$), 3.89 (s, 3H, Ar-OCH$_3$), 4.06 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.18 (dd, ^2J = 11.3 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.41 (dd, ^2J = 11.3 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.81 (d, ^3J = 6.4 Hz, 1H, H2), 6.64 – 6.91 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, CDCl$_3$): δ 12.0 (q, C4a'''*), 12.1 (q, C4b'''*), 25.1 (t, 2 x C3'''), 33.2 (t, C4-C), 42.7 (d, C4), 49.2 (d, C3*), 49.4 (d, C2'''*), 55.99 (q, Ar-OCH$_3$), 56.01 (q, Ar-OCH$_3$), 56.04 (q, Ar-OCH$_3$), 56.1 (q, Ar-OCH$_3$), 62.4 (t, C3-C), 72.8 (t, C5), 83.0 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.5 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.6 (d, C6''), 132.7 (s, C1''), 135.1 (s, C1'), 147.6 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 176.2 (s, C1''').

D.4.2.19 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl pivalate (**222**)



20 (Step 2)

222, $C_{27}H_{36}O_7$
472.57 g mol^{-1}

***Preparation**:* a reaction vessel was charged with a stirring bar, pivalic acid (21.1 mg, 0.207 mmol, 2.3 equiv.) and 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry CH_2Cl_2 (1.0 mL) was then added *via* syringe and the solution was cooled to 0 °C in an ice bath. The vessel was briefly opened, EDCI.HCl (34.5 mg, 0.180 mmol, 2.0 equiv.) added in one go and the mixture was stirred for 3 h at 0 °C. Meanwhile, a second vessel was charged with a stirring bar and **20** (35.0 mg, 0.090 mmol, 1.00 equiv.), evacuated and back-filled with argon (3 x), and DIPEA (39 µL, 0.23 mmol, 2.5 equiv.) was added *via* syringe. After 3 h, the solution containing the activated carboxylic acid was transferred to the second vial *via* syringe and stirred for 70 h at room temperature. To complete the reaction, more of the activated carboxylic acid was prepared in a separate vessel in the same way as above (using pivalic acid (18.3 mg, 0.180 mmol, 2.0 equiv.), 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.) and EDCI.HCl (30.0 mg, 0.157 mmol, 1.7 equiv.)) and then, after 3 h at 0 °C, added to the reaction vial, followed by more DIPEA (39 µL, 0.23 mmol, 2.5 equiv.) *via* syringe, and the mixture was stirred for another 96 h at room temperature.

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 38 : 62 in 12 min, then to 100 : 0 in 10 min) to afford the title compound **222**.

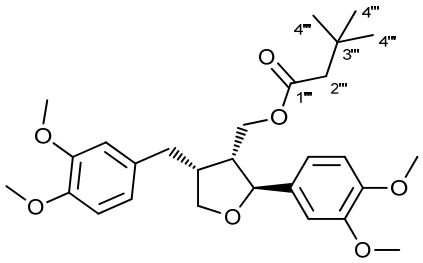
Yield:	32.2 mg, 76 %
Appearance:	colorless oil
R_f (silica):	0.49 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{23}$:	+22.5 (c 2.72, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 495.2353, found: 495.2351, Δ: -0.40 ppm
(log *P*)$_{calc}$:	4.91 ± 0.45

GC-MS (EI, 70 eV, Method E): 19.53 min; 472.2 (M^+, 5), 219.1 (25), 165.1 (54), 152.1 (15), 151.1 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (s, 9H, H3'''), 2.45 – 2.81 (m, 3H, H3, H4, C4-CH), 2.87 (dd, ^2J = 12.4 Hz, ^3J = 4.1 Hz, 1H, C4-CH), 3.77 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 3.88 (s, 9H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.17 (dd, ^2J = 11.3 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.36 (dd, ^2J = 11.3 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.82 (d, ^3J = 6.3 Hz, 1H, H2), 6.66 – 6.90 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.3 (q, 3 x C3'''), 33.3 (t, C4-C), 38.9 (s, C2'''), 42.8 (d, C4), 49.4 (d, C3), 55.98 (q, Ar-OCH_3), 56.00 (q, Ar-OCH_3), 56.03 (q, Ar-OCH_3), 56.1 (q, Ar-OCH_3), 62.7 (t, C3-C), 72.8 (t, C5), 82.9 (d, C2), 109.0 (d, C2'), 111.2 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.1 (d, C6'), 120.6 (d, C6''), 132.7 (s, C1''), 135.1 (s, C1'), 147.6 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 178.5 (s, C1''').

D.4.2.20 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 3,3-dimethylbutanoate (**223**)



223, $C_{28}H_{38}O_7$
486.60 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (30.0 mg, 0.077 mmol, 1.00 equiv.) and 3,3-dimethylbutanoic acid (20.6 mg, 0.178 mmol, 2.3 equiv.), EDCI.HCl (29.6 mg, 0.154 mmol, 2.0 equiv.), 4-DMAP (0.9 mg, 7.7 µmol, 0.1 equiv.) and DIPEA (34 µL, 0.19 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 30 : 70 in 30 min) to afford the title compound **223**.

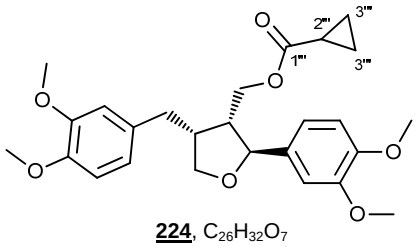
Yield:	19.5 mg, 51 %
Appearance:	colorless oil
R_f (silica):	0.43 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{23}$:	+24.7 (c 1.01, MeOH)
LC-HRMS (APCI):	calculated for $M+Na^+$: 509.2510, found: 509.2512, Δ: 0.39 ppm
(log *P*)$_{calc}$:	5.45 ± 0.45

GC-MS (EI, 70 eV, Method E): 18.75 min; 486.1 (M^+, 4), 219.0 (17), 166.0 (17), 165.0 (45), 152.1 (15), 151.0 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03 (s, 9H, H4'''), 2.20 (s, 2H, H2'''), 2.47 – 2.63 (m, 2H, H3, C4-CH), 2.64 – 2.82 (m, 1H, H4), 2.88 (dd, ^2J = 12.5 Hz, ^3J = 4.2 Hz, 1H, C4-CH), 3.76 (dd, ^2J = 8.6 Hz, ^3J = 6.1 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 3H, Ar-OCH_3), 3.87 (s, 3H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.06 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.16 (dd, ^2J = 11.3 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.36 (dd, ^2J = 11.3 Hz, ^3J = 7.2 Hz, 1H, C3-CH), 4.80 (d, ^3J = 6.4 Hz, 1H, H2), 6.66 – 6.90 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 29.8 (q, 3 x C4'''), 30.9 (s, C3'''), 33.2 (t, C4-C), 42.6 (d, C4), 48.1 (t, C2'''), 49.3 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 62.3 (t, C3-C), 72.8 (t, C5), 82.9 (d, C2), 109.0 (d, C2'), 111.2 (d, C5'), 111.5 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.6 (d, C6''), 132.7 (s, C1''), 135.1 (s, C1'), 147.7 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 172.4 (s, C1''').

D.4.2.21 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl cyclopropanecarboxylate (**224**)



224, $C_{26}H_{32}O_7$
456.53 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.), cyclopropanecarboxylic acid (17.8 mg, 0.207 mmol, 2.3 equiv.), EDCI.HCl (34.5 mg, 0.180 mmol, 2.0 equiv.), 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.) and DIPEA (39 µL, 0.23 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 62 : 38 in 30 min) to afford the title compound **224**.

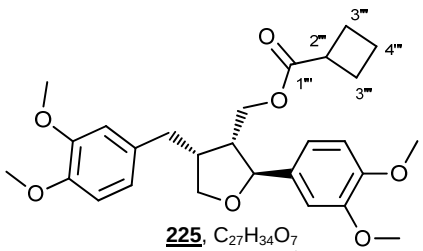
Yield:	37.4 mg, 91 %
Appearance:	colorless oil
R_f (silica):	0.54 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+17.8 (c 1.89, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 479.2040, found: 479.2048, Δ: 1.67 ppm
(log *P*)$_{calc}$:	4.05 ± 0.44

GC-MS (EI, 70 eV, Method D): 23.81 min; 456.2 (M^+, 5), 219.1 (27), 189.1 (16), 165.1 (67), 152.1 (15), 151.0 (100), 107.1 (16).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.80 – 1.02 (m, 4H, H3'''), 1.50 – 1.64 (m, 1H, H2'''), 2.46 – 2.94 (m, 4H, H3, H4, C4-CH_2), 3.75 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.08 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.19 (dd, ^2J = 11.2 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.37 (dd, ^2J = 11.2 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.81 (d, ^3J = 6.3 Hz, 1H, H2), 6.68 – 6.91 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 8.6 (t, 2 x C3'''), 13.0 (d, C2'''), 33.3 (t, C4-C), 42.6 (d, C4), 49.2 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 62.8 (t, C3-C), 72.9 (t, C5), 83.1 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.5 (d, C6''), 132.7 (s, C1''), 135.1 (s, C1'), 147.6 (s, C4''), 148.6 (s, C4'), 149.0 (s, C3''), 149.1 (s, C3'), 174.8 (s, C1''').

D.4.2.22 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl cyclobutanecarboxylate (**225**)



225, $C_{27}H_{34}O_7$
470.55 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (21.5 mg, 0.055 mmol, 1.00 equiv.), cyclobutanecarboxylic acid (12.7 mg, 0.127 mmol, 2.3 equiv.), EDCI.HCl (21.2 mg, 0.111 mmol, 2.0 equiv.), 4-DMAP (0.7 mg, 5.5 µmol, 0.1 equiv.) and DIPEA (24 µL, 0.14 mmol, 2.5 equiv.), and stirring the reaction for 24 in place of 16 h.

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 15 : 85 in 10 min, then to 25 : 75 in 5 min, then to 50 : 50 in 7 min) to afford the title compound **225**.

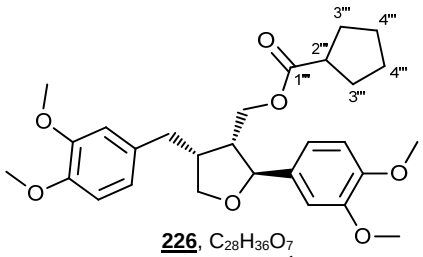
Yield:	21.5 mg, 83 %
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.37 (EtOAc / heptane, 1 : 1)
[α]$_D^{23}$:	+22.8 (c 1.27, MeOH)
LC-HRMS (APCI):	calculated for M+Na$^+$: 493.2197, found: 493.2214, Δ: 3.45 ppm
(log *P*)$_{calc}$:	4.62 ± 0.44

GC-MS (EI, 70 eV, Method E): 22.60 min; 470.1 (M$^+$, 4), 207.0 (52), 177.1 (16), 166.1 (17), 165.1 (50), 151.0 (100), 107.1 (15).

^{1}H NMR (200 MHz, CDCl$_3$): δ 1.79 – 2.06 (m, 2H, H4'''), 2.07 – 2.37 (m, 4H, H3'''), 2.47 – 2.93 (m, 4H, H3, H4, C4-CH$_2$), 3.11 (quint, ^3J = 8.6 Hz, 1H, H2'''), 3.75 (dd, ^2J = 8.5 Hz, ^3J = 6.3 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH$_3$), 3.87 (s, 6H, Ar-OCH$_3$), 3.89 (s, 3H, Ar-OCH$_3$), 4.07 (dd, ^2J = 8.5 Hz, ^3J = 6.3 Hz, 1H, H5), 4.19 (dd, ^2J = 11.2 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.38 (dd, ^2J = 11.2 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.80 (d, ^3J = 6.4 Hz, 1H, H2), 6.66 – 6.90 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, CDCl$_3$): δ 18.6 (t, C4'''), 25.4 (t, 2 x C3'''), 25.4 (t, C3'''), 33.3 (t, C4-C), 38.2 (d, C2'''), 42.7 (d, C4), 49.2 (d, C3), 56.0 (q, 4 x Ar-OCH$_3$), 62.6 (t, C3-C), 72.9 (t, C5), 83.1 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.5 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.6 (d, C6''), 132.7 (s, C1''), 135.1 (s, C1'), 147.6 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 175.4 (s, C1''').

D.4.2.23 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl cyclopentanecarboxylate (**226**)



226, $C_{28}H_{36}O_7$
484.58 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.), cyclopentanecarboxylic acid (23.6 mg, 0.207 mmol, 2.3 equiv.), EDCI.HCl (34.5 mg, 0.180 mmol, 2.0 equiv.), 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.) and DIPEA (39 µL, 0.23 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 62 : 38 in 30 min) to afford the title compound **226**.

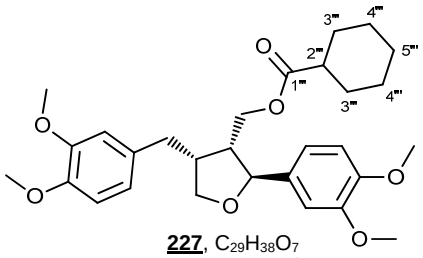
Yield:	38.7 mg, 89 %
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.59 (EtOAc / LP, 1 : 1)
[α]$_D^{20}$:	+17.4 (c 2.47, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 507.2353, found: 507.2358, Δ: 0.99 ppm
(log *P*)$_{calc}$:	5.18 ± 0.44

GC-MS (EI, 70 eV, Method F): 33.28 min; 484.2 (M$^+$, 3), 219.1 (24), 165.1 (57), 151.0 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 – 1.97 (m, 8H, 4 x H3''', 4 x H4'''), 2.47 – 2.93 (m, 5H, H3, H4, C4-CH_2, H2'''), 3.76 (dd, ^2J = 8.5 Hz, ^3J = 6.3 Hz, 1H, H5), 3.87 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.18 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.37 (dd, ^2J = 11.2 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.80 (d, ^3J = 6.3 Hz, 1H, H2), 6.66 – 6.91 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.9 (t, 2 x C4'''), 30.1 (t, 2 x C3'''), 33.3 (t, C4-C), 42.7 (d, C4), 44.0 (d, C2'''), 49.3 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 62.6 (t, C3-C), 72.8 (t, C5), 83.0 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.6 (d, C6''), 132.7 (s, C1''), 135.1 (s, C1'), 147.6 (s, C4''), 148.6 (s, C4'), 149.0 (s, C3''), 149.2 (s, C3'), 176.7(s, C1''').

D.4.2.24 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl cyclohexanecarboxylate (**227**)



227, $C_{29}H_{38}O_7$
498.61 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.), cyclohexanecarboxylic acid (26.5 mg, 0.207 mmol, 2.3 equiv.), EDCI.HCl (34.5 mg, 0.180 mmol, 2.0 equiv.), 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.) and DIPEA (39 µL, 0.23 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 62 : 38 in 30 min) to afford the title compound **227**.

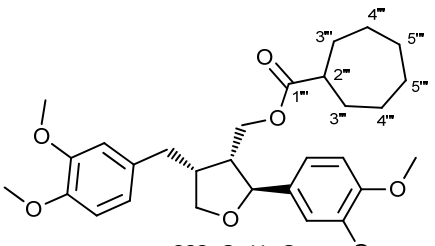
Yield:	33.3 mg, 74 %
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.62 (EtOAc / LP, 1 : 1)
[α]$_D^{20}$:	+16.8 (c 1.62, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 521.2510, found: 521.2516, Δ: 1.15 ppm
(log *P*)$_{calc}$:	5.75 ± 0.44

GC-MS (EI, 70 eV, Method E): 40.73 min; 498.2 (M$^+$, 3), 219.1 (26), 165.1 (53), 151.1 (100).

^{1}H NMR (200 MHz, CDCl$_3$): δ 1.12 – 1.96 (m, 10H, 4 x H3''', 4 x H4''', 2 x H5'''), 2.18 – 2.35 (m, 1H, H2'''), 2.46 – 2.83 (m, 3H, H3, H4, C4-CH), 2.86 (dd, ^2J = 12.4 Hz, ^3J = 4.3 Hz, 1H, C4-CH), 3.76 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 3.87 (s, 3H, Ar-OCH$_3$), 3.87 (s, 6H, Ar-OCH$_3$), 3.89 (s, 3H, Ar-OCH$_3$), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.17 (dd, ^2J = 11.3 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.37 (dd, ^2J = 11.3 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.80 (d, ^3J = 6.4 Hz, 1H, H2), 6.66 – 6.91 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, CDCl$_3$): δ 25.5 (t, 2 x C4'''), 25.8 (t, C5'''), 29.1 (t, 2 x C3'''), 29.1 (t, C3'''), 33.3 (t, C4-C), 42.7 (d, C4), 43.3 (d, C2'''), 49.3 (d, C3), 56.0 (q, 4 x Ar-OCH$_3$), 62.4 (t, C3-C), 72.9 (t, C5), 83.0 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.6 (d, C6''), 132.7 (s, C1''), 135.1 (s, C1'), 147.6 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 176.0 (s, C1''').

D.4.2.25 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl cycloheptanecarboxylate (**228**)



228, $C_{30}H_{40}O_7$
512.63 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.), cycloheptanecarboxylic acid (29.4 mg, 0.207 mmol, 2.3 equiv.), EDCI.HCl (34.5 mg, 0.180 mmol, 2.0 equiv.), 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.) and DIPEA (39 µL, 0.23 mmol, 2.5 equiv.).

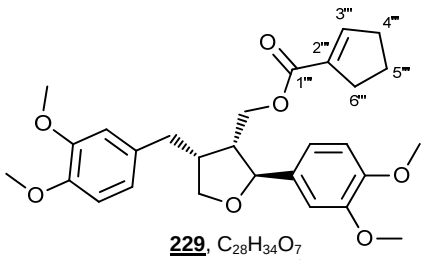
***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 15 : 85 in 10 min, then to 25 : 75 in 7 min, then to 50 : 50 in 12 min) to afford the title compound **228**.

Yield:	38.8 mg, 84 %
Appearance:	colorless oil
R_f (silica):	0.53 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{25}$:	+20.0 (c 3.74, MeOH)
LC-HRMS (ESI):	calculated for $M+H^+$: 513.2847, found: 513.2842, Δ: -0.87 ppm
(log *P*)$_{calc}$:	6.31 ± 0.44

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36 – 1.80 (m, 10H, 2 x H3''', 4 x H4''', 4 x H5'''), 1.80 – 1.99 (m, 2H, 2 x H3'''), 2.36 – 2.82 (m, 4H, H3, H4, C4-CH, H2'''), 2.86 (dd, ^2J = 12.4 Hz, ^3J = 4.1 Hz, 1H, C4-CH), 3.76 (dd, ^2J = 8.6 Hz, ^3J = 6.1 Hz, 1H, H5), 3.87 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.16 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.37 (dd, ^2J = 11.2 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.80 (d, ^3J = 6.4 Hz, 1H, H2), 6.66 – 6.90 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.4 (t, 2 x C4'''), 28.4 (t, 2 x C5'''), 30.9 (t, 2 x C3'''), 33.3 (t, C4-C), 42.7 (d, C4), 45.2 (d, C2'''), 49.3 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 62.5 (t, C3-C), 72.8 (t, C5), 83.1 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.6 (d, C6''), 132.7 (s, C1''), 135.1 (s, C1'), 147.6 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 176.9 (s, C1''').

D.4.2.26 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl cyclopent-1-enecarboxylate (**229**)



229, $C_{28}H_{34}O_7$
482.57 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.) and cyclopent-1-enecarboxylic acid (40.4 mg, 0.360 mmol, 4.0 equiv.), but stirred for 24 in place of 16 h.

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 62 : 38 in 30 min) to afford the title compound **229**.

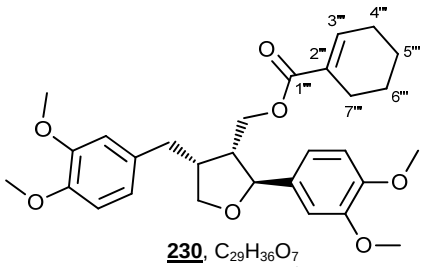
Yield:	39.4 mg, 91 %
Appearance:	colorless oil
R_f (silica):	0.43 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+20.0 (c 3.49, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 505.2197, found: 505.2200, Δ: 0.59 ppm
(log *P*)$_{calc}$:	5.38 ± 0.45

GC-MS (EI, 70 eV, Method F): 37.45 min; 482.2 (M$^+$, 2), 219.1 (28), 207.1 (17), 189.1 (16), 177.1 (16), 165.1 (81), 152.1 (15), 151.1 (100), 107.1 (17), 95.1 (73).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.95 (quint, ^3J = 7.4 Hz, 2H, H5'''), 2.40 – 2.85 (m, 7H, H3, H4, C4-CH, 2 x H4''', 2 x H6'''), 2.89 (dd, ^2J = 12.4 Hz, ^3J = 4.3 Hz, 1H, C4-CH), 3.76 (dd, ^2J = 8.6 Hz, ^3J = 6.4 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.09 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.27 (dd, ^2J = 11.2 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.43 (dd, ^2J = 11.3 Hz, ^3J = 6.7 Hz, 1H, C3-CH), 4.83 (d, ^3J = 6.3 Hz, 1H, H2), 6.63 – 6.91 (m, 7H, 6 x Ar-H, H3''').

^{13}C NMR (50 MHz, $CDCl_3$): δ 23.2 (t, C5'''), 31.4 (t, C4'''*), 33.3 (t, C4-C), 33.5 (t, C6'''*), 42.7 (d, C4), 49.2 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 62.5 (t, C3-C), 72.9 (t, C5), 83.2 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.5 (d, C6''), 132.8 (s, C1''), 135.1 (s, C1'), 136.3 (s, C2'''), 144.5 (d, C3'''), 147.6 (s, C4''), 148.5 (s, C4'), 149.0 (s, C3''), 149.1 (s, C3'), 165.2 (s, C1''').

D.4.2.27 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl cyclohex-1-enecarboxylate (**230**)



230, $C_{29}H_{36}O_7$
496.59 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.) and cyclohex-1-enecarboxylic acid (45.4 mg, 0.360 mmol, 4.0 equiv.), but stirred for 24 in place of 16 h.

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 62 : 38 in 30 min) to afford the title compound **230**.

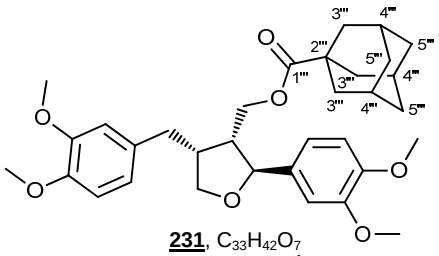
Yield:	27.0 mg, 60 %
Appearance:	colorless oil
R_f (silica):	0.47 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+20.5 (c 2.64, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 519.2353, found: 519.2378, Δ: 4.81 ppm
(log *P*)$_{calc}$:	5.95 ± 0.45

GC-MS (EI, 70 eV, Method F): 48.95 min; 496.3 (M$^+$, 1), 370.2 (15), 219.1 (32), 207.0 (24), 206.1 (16), 189.1 (17), 177.1 (17), 166.1 (15), 165.1 (89), 152.1 (16), 151.1 (100), 109.1 (39), 107.1 (19).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 – 1.71 (m, 4H, 2 x H5''', 2 x H6'''), 2.10 – 2.27 (m, 4H, 2 x H4''', 2 x H7'''), 2.50 – 2.95 (m, 4H, H3, H4, C4-CH_2), 3.76 (dd, ^2J = 8.5 Hz, ^3J = 6.2 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.08 (dd, ^2J = 8.5 Hz, ^3J = 6.2 Hz, 1H, H5), 4.26 (dd, ^2J = 11.3 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.42 (dd, ^2J = 11.3 Hz, ^3J = 6.5 Hz, 1H, C3-CH), 4.83 (d, ^3J = 6.3 Hz, 1H, H2), 6.67 – 6.92 (m, 7H, 6 x Ar-H, H3''').

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.5 (d, C6'''*), 22.1 (d, C5'''*), 24.2 (d, C7'''*), 25.9 (d, C4'''*), 33.4 (t, C4-C), 42.8 (d, C4), 49.2 (d, C3), 56.00 (q, Ar-OCH_3), 56.02 (q, Ar-OCH_3), 56.03 (q, Ar-OCH_3), 56.04 (q, Ar-OCH_3), 62.6 (t, C3-C), 72.9 (t, C5), 83.3 (d, C2), 109.1 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.3 (d, C6'), 120.6 (d, C6''), 130.1 (s, C2'''), 132.8 (s, C1''), 135.1 (s, C1'), 140.5 (d, C3'''), 147.6 (s, C4''), 148.5 (s, C4'), 149.1 (s, C3''), 149.1 (s, C3'), 167.5 (s, C1''').

D.4.2.28 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl adamantane-1-carboxylate (**231**)



231, $C_{33}H_{42}O_7$
550.68 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.) and adamantane-1-carboxylic acid (64.9 mg, 0.360 mmol, 4.0 equiv.), with additional stirring for 12 days at 40 °C.

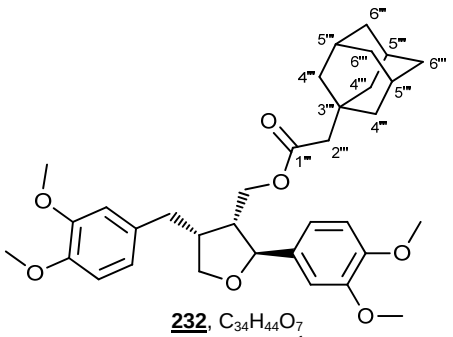
***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 15 : 85 in 10 min, then to 25 : 75 in 5 min, then to 50 : 50 in 7 min) to afford the title compound **231**.

Yield:	42.0 mg, 85 %
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.43 (EtOAc / LP, 1 : 1)
[α]$_D^{23}$:	+19.3 (c 4.09, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 573.2823, found: 573.2842, Δ: 3.31 ppm
(log *P*)$_{calc}$:	6.57 ± 0.47

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.59 – 2.06 (m, 15H, 6 x H3''', 3 x H4''', 6 x H5'''), 2.46 – 2.93 (m, 4H, H3, H4, C4-CH_2), 3.78 (dd, ^2J = 8.5 Hz, ^3J = 6.1 Hz, 1H, H5), 3.87 (s, 9H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.07 (dd, ^2J = 8.4 Hz, ^3J = 6.1 Hz, 1H, H5), 4.15 (dd, ^2J = 11.1 Hz, ^3J = 6.7 Hz, 1H, C3-CH), 4.36 (dd, ^2J = 11.3 Hz, ^3J = 6.7 Hz, 1H, C3-CH), 4.81 (d, ^3J = 6.5 Hz, 1H, H2), 6.66 – 6.91 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.0 (d, 3 x C4'''), 33.4 (t, C4-C), 36.6 (t, 3 x C5'''), 39.0 (t, 3 x C3'''), 40.9 (s, C2'''), 42.9 (d, C4), 49.4 (d, C3), 55.97 (q, Ar-OCH_3), 55.99 (q, Ar-OCH_3), 56.03 (q, Ar-OCH_3), 56.1 (q, Ar-OCH_3), 62.4 (t, C3-C), 72.9 (t, C5), 83.0 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.6 (d, C6''), 132.8 (s, C1''), 135.1 (s, C1'), 147.6 (s, C4''), 148.6 (s, C4'), 149.1 (s, C3''), 149.2 (s, C3'), 177.6 (s, C1''').

D.4.2.29 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl) methyl 2-(adamantan-1-yl)acetate (**232**)



232, $C_{34}H_{44}O_7$
564.71 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **20** (35.0 mg, 0.090 mmol, 1.00 equiv.), 2-(adamantan-1-yl)acetic acid (40.2 mg, 0.207 mmol, 2.3 equiv.), EDCI.HCl (34.5 mg, 0.180 mmol, 2.0 equiv.), 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.) and DIPEA (39 µL, 0.23 mmol, 2.5 equiv.).

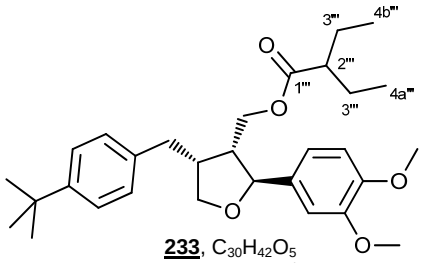
***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 15 : 85 in 10 min, then to 25 : 75 in 5 min, then to 48 : 52 in 7 min) to afford the title compound **232**.

Yield:	40.5 mg, 80 %
Appearance:	colorless oil
R_f (silica):	0.55 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{25}$:	+18.3 (c 4.05, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 587.2979, found: 587.3000, Δ: 3.58 ppm
(log *P*)$_{calc}$:	7.10 ± 0.47

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52 – 1.77 (m, 12H, 6 x H4''', 6 x H6'''), 1.89 – 2.03 (m, 3H, H5'''), 2.07 (s, 2H, H2'''), 2.46 – 2.64 (m, 2H, H3, C4-CH), 2.64 – 2.81 (m, 1H, H4), 2.89 (dd, ^2J = 12.7 Hz, ^3J = 4.2 Hz, 1H, C4-CH), 3.76 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.06 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.16 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.36 (dd, ^2J = 11.2 Hz, ^3J = 7.1 Hz, 1H, C3-CH), 4.81 (d, ^3J = 6.3 Hz, 1H, H2), 6.65 – 6.91 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 28.7 (d, 3 x C5'''), 32.9 (s, C3'''), 33.2 (t, C4-C), 36.8 (t, 3 x C6'''), 42.6 (t, 3 x C4'''), 49.1 (t, C2'''), 49.2 (d, C3), 55.99 (q, Ar-OCH_3), 56.01 (q, Ar-OCH_3), 56.02 (q, Ar-OCH_3), 56.04 (q, Ar-OCH_3), 62.2 (t, C3-C), 72.7 (t, C5), 82.9 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.5 (d, C6''), 132.7 (s, C1''), 135.1 (s, C1'), 147.6 (s, C4''), 148.6 (s, C4'), 149.0 (s, C3''), 149.1 (s, C3'), 171.8 (s, C1'''); C4 not visible due to signal overlap with C4'''.

D.4.2.30 ((2*S*,3*R*,4*R*)-4-(4-(*tert*-Butyl)benzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-ethylbutanoate (**233**)



233, $C_{30}H_{42}O_5$
482.65 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **133** (16.1 mg, 0.042 mmol, 1.00 equiv.), 2-ethylbutanoic acid (11.2 mg, 0.097 mmol, 2.3 equiv.), EDCI.HCl (16.1 mg, 0.084 mmol, 2.0 equiv.), 4-DMAP (0.5 mg, 4.2 µmol, 0.1 equiv.) and DIPEA (19 µL, 0.11 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / heptane, 3 : 97 isocratically for 5 min, then to 30 : 70 in 30 min) to afford the title compound **233**.

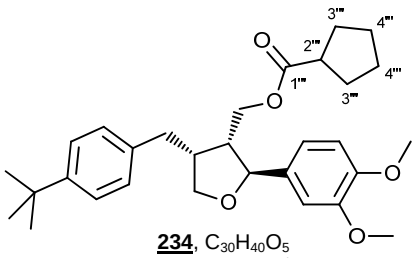
Yield:	16.5 mg, 81 %
Appearance:	colorless oil
R_f (silica):	0.65 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{25}$:	+12.3 (c 0.67, *i*-PrOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 505.2930, found: 505.2942, Δ: 2.40 ppm
(log *P*)$_{calc}$:	7.58 ± 0.43

GC-MS (EI, 70 eV, Method E): 17.71 min; 481.9 (M+, 9), 219.0 (24), 166.2 (36), 165.3 (48), 164.8 (41), 146.8 (17), 132.2 (100), 131.4 (40), 130.7 (17), 118.8 (18), 117.2 (48), 116.7 (29), 115.0 (16).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, ^3J = 7.4 Hz, 6H, 3 x H4a''', 3 x H4b'''), 1.31 (s, 9H, C4''-C(CH$_3$)$_3$), 1.44 – 1.72 (m, 4H, H3'''), 2.23 (tt, ^3J = 8.1 Hz, ^3J = 5.9 Hz, 1H, H2'''), 2.48 – 2.65 (m, 2H, H3, C4-CH), 2.67 – 2.84 (m, 1H, H4), 2.90 (dd, ^2J = 12.5 Hz, ^3J = 4.0 Hz, 1H, C4-CH), 3.76 (dd, ^2J = 8.6 Hz, ^3J = 6.4 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH$_3$), 3.89 (s, 3H, Ar'-OCH$_3$), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.19 (dd, ^2J = 11.3 Hz, ^3J = 6.7 Hz, 1H, C3-CH), 4.39 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.80 (d, ^3J = 6.3 Hz, 1H, H2), 6.80 – 6.91 (m, 3H, Ar'-H), 7.10 (d, ^3J = 8.3 Hz, 2H, H2'', H6''), 7.27 – 7.36 (m, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 12.1 (q, C4a'''*), 12.1 (q, C4b'''*), 25.1 (t, 2 x C3'''), 31.5 (q, C4''-C(CH_3)$_3$), 33.1 (t, C4-C), 34.5 (s, C4''-C(CH$_3$)$_3$), 42.5 (d, C4), 49.2 (d, C3*), 49.4 (d, C2'''*), 56.0 (q, 4 x Ar'-OCH$_3$), 62.5 (t, C3-C), 73.0 (t, C5), 83.0 (d, C2), 109.0 (d, C2'), 111.2 (d, C5'), 118.2 (d, C6'), 125.6 (d, C3'', C5''), 128.4 (d, C2'', C6''), 135.2 (s, C1'), 137.1 (s, C1''), 148.6 (s, C4'), 149.2 (s, C3'*), 149.3 (s, C4''*), 176.3 (s, C1''').

D.4.2.31 ((2*S*,3*R*,4*R*)-4-(4-(*tert*-Butyl)benzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl cyclopentanecarboxylate (**234**)



234, $C_{30}H_{40}O_5$
480.64 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **133** (16.7 mg, 0.043 mmol, 1.00 equiv.), cyclopentanecarboxylic acid (11.4 mg, 0.100 mmol, 2.3 equiv.), EDCI.HCl (16.6 mg, 0.087 mmol, 2.0 equiv.), 4-DMAP (0.5 mg, 4.3 µmol, 0.1 equiv.) and DIPEA (19 µL, 0.11 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 3 : 97 isocratically for 3 min, then to 30 : 70 in 30 min) to afford the title compound **234**.

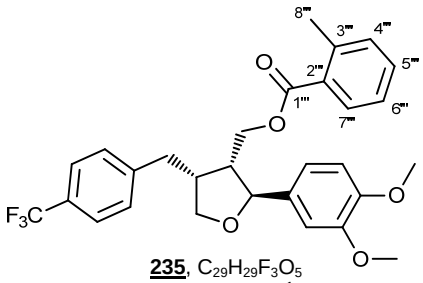
Yield:	16.6 mg, 79 %
Appearance:	colorless oil
R_f (silica):	0.65 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{25}$:	+14.2 (c 1.07, *i*-PrOH)
LC-HRMS (APCI):	calculated for M+Na$^+$: 503.2768, found: 503.2751, Δ: -3.38 ppm
(log *P*)$_{calc}$:	7.13 ± 0.43

GC-MS (EI, 70 eV, Method D): 22.61 min; 480.1 (M$^+$, 6), 219.0 (36), 192.0 (15), 185.1 (23), 180.0 (17), 167.0 (16), 166.0 (49), 165.0 (100), 151.0 (26), 147.1 (21), 132.1 (41), 131.0 (24), 117.0 (43).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (s, 9H, C4''-C(CH_3)$_3$), 1.48 – 1.96 (m, 8H, 4 x H3''', 4 x H4'''), 2.48 – 2.96 (m, 5H, H3, H4, C4-CH_2, H2'''), 3.75 (dd, ^2J = 8.5 Hz, ^3J = 6.5 Hz, 1H, H5), 3.87 (s, 3H, Ar'-OCH_3), 3.89 (s, 3H, Ar'-OCH_3), 4.08 (dd, ^2J = 8.6 Hz, ^3J = 6.4 Hz, 1H, H5), 4.19 (dd, ^2J = 11.3 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.36 (dd, ^2J = 11.2 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.80 (d, ^3J = 6.3 Hz, 1H, H2), 6.78 – 6.92 (m, 3H, Ar'-H), 7.10 (d, ^3J = 8.3 Hz, 2H, H2'', H6''), 7.32 (d, ^3J = 8.3 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.9 (t, 2 x C4'''), 30.1 (t, 2 x C3'''), 31.5 (q, C4''-C($\underline{C}H_3$)$_3$), 33.1 (t, C4-$\underline{C}$), 34.5 (s, C4''-$\underline{C}$(CH_3)$_3$), 42.5 (d, C4), 44.0 (d, C2'''), 49.3 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.7 (t, C3-$\underline{C}$), 73.0 (t, C5), 83.1 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 118.2 (d, C6'), 125.6 (d, C3'', C5''), 128.4 (d, C2'', C6''), 135.2 (s, C1'), 137.1 (s, C1''), 148.6 (s, C4'), 149.2 (s, C4''*), 149.2 (s, C3'*), 176.7 (s, C1''').

D.4.2.32 ((2*S*,3*R*,4*R*)-2-(3,4-Dimethoxyphenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl 2-methylbenzoate (**235**)



235, $C_{29}H_{29}F_3O_5$
514.53 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **140** (33.6 mg, 0.085 mmol, 1.00 equiv.) and 2-methylbenzoic acid (46.1 mg, 0.339 mmol, 4.0 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / heptane, 5 : 95 to 40 : 60 in 40 min) to afford the title compound **235**.

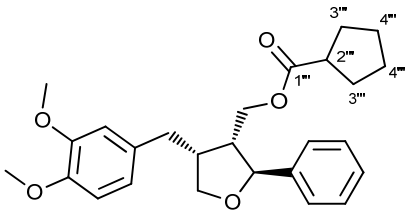
Yield:	27.6 mg, 63 %
Appearance:	colorless oil
R_f (silica):	0.54 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{25}$:	+17.0 (c 0.83, *i*-PrOH)
LC-HRMS (ESI):	calculated for M+H$^+$: 515.2040, found: 515.2056, Δ: 3.13 ppm
(log *P*)$_{calc}$:	7.00 ± 0.46

GC-MS (EI, 70 eV, Method F): 19.11 min; 514.1 (M$^+$, 4), 218.9 (17), 166.0 (22), 165.4 (54), 164.8 (52), 159.3 (35), 158.7 (34), 135.2 (15), 119.3 (56), 118.8 (86), 117.9 (33), 91.0 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.59 (s, 3H, H8'''), 2.65 – 2.96 (m, 3H, H3, H4, C4-CH), 3.05 (dd, ^2J = 12.5 Hz, ^3J = 3.6 Hz, 1H, C4-CH), 3.77 (dd, ^2J = 8.8 Hz, ^3J = 5.8 Hz, 1H, H5), 3.83 (s, 3H, Ar'-OCH_3), 3.86 (s, 3H, Ar'-OCH_3), 4.11 (dd, ^2J = 8.8 Hz, ^3J = 6.0 Hz, 1H, H5), 4.43 (dd, ^2J = 11.3 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.58 (dd, ^2J = 11.3 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.91 (d, ^3J = 6.3 Hz, 1H, H2), 6.78 – 6.93 (m, 3H, Ar'-H), 7.15 – 7.35 (m, 4H, H2'', H6'', H4''', H6'''), 7.41 (td, ^3J = 7.4 Hz, ^4J = 1.5 Hz, 1H, H5'''), 7.55 (d, ^3J = 8.1 Hz, 2H, H3'', H5''), 7.76 (dd, ^3J = 7.9 Hz, ^4J = 1.4 Hz, 1H, H7''').

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9 (q, C8'''), 33.7 (t, C4-C), 42.4 (d, C4), 49.4 (d, C3), 56.0 (q, Ar'-OCH_3), 56.1 (q, Ar'-OCH_3), 62.9 (t, C3-C), 72.7 (t, C5), 83.3 (d, C2), 109.1 (d, C2'), 111.2 (d, C5'), 118.3 (d, C6'), 124.3 (q, C4''-CF_3, $^1J_{C\text{-}F}$ = 271.9 Hz), 125.7 (dq, C3'', C5'', $^3J_{C\text{-}F}$ = 3.8 Hz), 125.9 (d, C6'''), 128.9 (q, C4'', $^2J_{C\text{-}F}$ = 32.5 Hz), 129.1 (d, C2'', C6''; s, C2'''; signal overlap), 130.6 (d, C4'''), 132.0 (d, C7'''*), 132.4 (d, C5'''*), 134.8 (s, C1'), 140.6 (s, C3'''), 144.3 (q, C1'', $^5J_{C\text{-}F}$ = 1.1 Hz), 148.7 (s, C4'), 149.3 (s, C3'), 167.3 (s, C1''').

D.4.2.33 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-phenyltetrahydrofuran-3-yl)methyl cyclopentanecarboxylate (**236**)



236, $C_{26}H_{32}O_5$
424.53 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **123** (20.0 mg, 0.061 mmol, 1.00 equiv.), cyclopentanecarboxylic acid (27.8 mg, 0.244 mmol, 4.0 equiv.), EDCI.HCl (23.3 mg, 0.122 mmol, 2.0 equiv.), 4-DMAP (0.7 mg, 6.1 µmol, 0.1 equiv.) and DIPEA (25 µL, 0.15 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 15 : 85 in 10 min, then to 22 : 78 in 5 min, then to 60 : 40 in 15 min) to afford the title compound **236**.

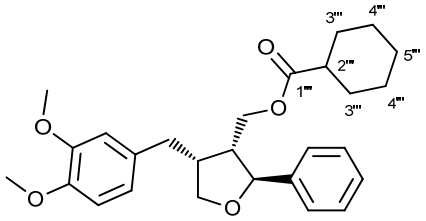
Yield:	22.3 mg, 86 %
Appearance:	colorless oil
R_f (silica):	0.76 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{25}$:	+16.7 (c 2.20, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 447.2142, found: 447.2148, Δ: 1.34 ppm
(log *P*)$_{calc}$:	5.44 ± 0.42

GC-MS (EI, 70 eV, Method E): 17.45 min; 424.2 (M$^+$, 7), 194.1 (28), 190.1 (21), 189.1 (22), 164.1 (19), 159.1 (51), 152.1 (32), 151.0 (100), 107.1 (19), 105.0 (54), 91.1 (36).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 – 1.99 (m, 8H, 4 x H3''', 4 x H4'''), 2.48 – 2.91 (m, 5H, H3, H4, C4-CH_2, H2'''), 3.78 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 3.86 (s, 3H, Ar''-OCH_3), 3.87 (s, 3H, Ar''-OCH_3), 4.09 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.19 (dd, ^2J = 11.2 Hz, ^3J = 7.2 Hz, 1H, C3-CH), 4.39 (dd, ^2J = 11.2 Hz, ^3J = 6.7 Hz, 1H, C3-CH), 4.89 (d, ^3J = 5.9 Hz, 1H, H2), 6.65 – 6.75 (m, 2H, H2'', H6''*), 6.80 (d, ^3J = 7.9 Hz, 1H, H5''*), 7.40 – 7.21 (m, 5H, Ar'-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.9 (t, 2 x C4'''), 30.1 (t, 2 x C3'''), 33.2 (t, C4-C), 42.7 (d, C4), 44.0 (d, C2'''), 49.5 (d, C3), 55.99 (q, Ar''-OCH_3), 56.4 (q, Ar''-OCH_3), 62.6 (t, C3-C), 73.0 (t, C5), 83.2 (d, C2), 111.4 (d, C5''*), 112.0 (d, C2''*), 120.6 (d, C6''), 125.8 (d, C2', C6'), 127.6 (d, C4'), 128.6 (d, C3', C5'), 132.8 (s, C1''), 142.8 (s, C1'), 147.6 (s, C4''), 149.1 (s, C3''), 176.7 (s, C1''').

D.4.2.34 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-phenyltetrahydrofuran-3-yl)methyl cyclohexanecarboxylate (**237**)



237, $C_{27}H_{34}O_5$
438.56 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **123** (19.4 mg, 0.059 mmol, 1.00 equiv.), cyclohexanecarboxylic acid (30.3 mg, 0.236 mmol, 4.0 equiv.), EDCI.HCl (22.7 mg, 0.118 mmol, 2.0 equiv.), 4-DMAP (0.7 mg, 5.9 µmol, 0.1 equiv.) and DIPEA (25 µL, 0.15 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 12 : 88 in 10 min, then to 19 : 81 in 5 min, then to 57 : 43 in 15 min) to afford the title compound **237**.

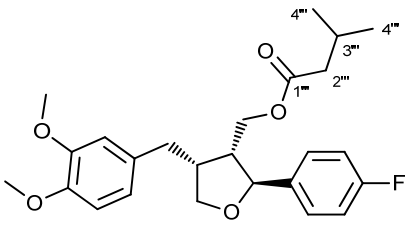
Yield:	21.7 mg, 84 %
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.78 (EtOAc / LP, 1 : 1)
[α]$_D^{25}$:	+17.9 (c 2.10, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 461.2298, found: 461.2302, Δ: 0.87 ppm
(log *P*)$_{calc}$:	6.01 ± 0.42

GC-MS (EI, 70 eV, Method E): 20.50 min; 438.2 (M$^+$, 6), 194.1 (31), 190.1 (23), 189.1 (23), 164.1 (20), 159.1 (56), 152.1 (33), 151.0 (100), 107.1 (19), 105.0 (57), 91.1 (39).

^{1}H NMR (200 MHz, CDCl$_3$): δ 1.15 – 1.96 (m, 10H, 4 x H3''', 4 x H4''', 2 x H5'''), 2.18 – 2.35 (m, 1H, H2'''), 2.47 – 2.91 (m, 4H, H3, H4, C4-CH$_2$), 3.78 (dd, ^2J = 8.5 Hz, ^3J = 6.3 Hz, 1H, H5), 3.86 (s, 6H, Ar''-OCH$_3$), 4.09 (dd, ^2J = 8.5 Hz, ^3J = 6.2 Hz, 1H, H5), 4.18 (dd, ^2J = 11.2 Hz, ^3J = 7.2 Hz, 1H, C3-CH), 4.39 (dd, ^2J = 11.2 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.88 (d, ^3J = 6.0 Hz, 1H, H2), 6.65 – 6.75 (m, 2H, H2'', H6''*), 6.80 (d, ^3J = 7.9 Hz, 1H, H5''*), 7.22 – 7.40 (m, 5H, Ar'-H).

^{13}C NMR (50 MHz, CDCl$_3$): δ 25.5 (t, 2 x C4'''), 25.8 (t, C5'''), 29.1 (t, 2 x C3'''), 29.1 (t, C3'''), 33.2 (t, C4-C), 42.7 (d, C4), 43.3 (d, C2'''), 49.5 (d, C3), 56.00 (q, Ar''-OCH$_3$), 56.04 (q, Ar''-OCH$_3$), 62.5 (t, C3-C), 73.0 (t, C5), 83.2 (d, C2), 111.4 (d, C5''*), 112.0 (d, C2''*), 120.6 (d, C6''), 125.8 (d, C2', C6'), 127.6 (d, C4'), 128.6 (d, C3', C5'), 132.8 (s, C1''), 142.8 (s, C1'), 147.6 (s, C4''), 149.1 (s, C3''), 176.0 (s, C1''').

D.4.2.35 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl 3-methylbutanoate (**238**)



238, $C_{25}H_{31}FO_5$
430.51 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **148** (23.7 mg, 0.068 mmol, 1.00 equiv.), 3-methylbutanoic acid (16.1 mg, 0.157 mmol, 2.3 equiv.), EDCI.HCl (26.2 mg, 0.137 mmol, 2.0 equiv.), 4-DMAP (0.8 mg, 6.8 µmol, 0.1 equiv.) and DIPEA (30 µL, 0.17 mmol, 2.5 equiv.), and stirring for 24 in place of 16 h.

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 9 : 91 to 25 : 75 in 60 min) to afford the title compound **238**.

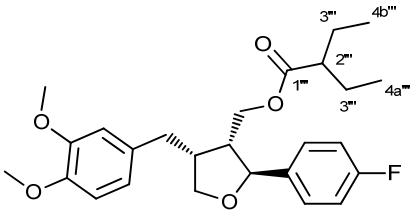
Yield:	18.6 mg, 63 %
Appearance:	colorless oil
R_f (silica):	0.65 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{23}$:	+15.6 (c 0.48, MeOH)
LC-HRMS (APCI):	calculated for M+H$^+$: 431.2228, found: 431.2247, Δ: 4.41 ppm
(log *P*)$_{calc}$:	5.41 ± 0.49

GC-MS (EI, 70 eV, Method E): 10.80 min; 430.0 (M$^+$, 3), 190.0 (16), 189.1 (18), 178.1 (15), 177.0 (38), 164.0 (19), 152.1 (30), 151.1 (100), 123.0 (47), 109.1 (23), 107.0 (17).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (d, ^3J = 6.3 Hz, 6H, H4'''), 1.96 – 2.21 (m, 3H, 2 x H2''', H3'''), 2.43 – 2.62 (m, 2H, H3, C4-CH), 2.63 – 2.80 (m, 1H, H4), 2.85 (dd, ^2J = 12.4 Hz, ^3J = 4.3 Hz, 1H C4-CH), 3.76 (dd, ^2J = 8.6 Hz, ^3J = 6.4 Hz, 1H, H5), 3.86 (s, 3H, Ar''-OCH_3), 3.87 (s, 3H, Ar''-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.18 (dd, ^2J = 11.2 Hz, ^3J = 7.5 Hz, 1H, C3-CH), 4.39 (dd, ^2J = 11.2 Hz, ^3J = 6.7 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.0 Hz, 1H, H2), 6.65 – 6.84 (m, 3H, Ar''-H), 6.96 – 7.09 (m, 2H, H3', H5'), 7.22 – 7.34 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 22.6 (q, 2 x C4'''), 25.8 (d, C3'''), 33.2 (t, C4-C), 42.6 (d, C4), 43.5 (t, C2'''), 49.5 (d, C3), 55.96 (q, Ar''-OCH_3), 55.99 (q, Ar''-OCH_3), 62.4 (t, C3-C), 72.9 (t, C5), 82.8 (d, C2), 111.5 (d, C5''*), 112.0 (d, C2''*), 115.4 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 120.6 (d, C6''), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 132.6 (s, C1''), 138.5 (d, C1', $^4J_{C\text{-}F}$ = 3.2 Hz), 147.7 (s, C4''), 149.1 (s, C3''), 162.3 (d, C4', $^1J_{C\text{-}F}$ = 245.5 Hz), 173.1 (s, C1''').

D.4.2.36 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl 2-ethylbutanoate (**239**)



239, $C_{26}H_{33}FO_5$
444.54 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **148** (15.2 mg, 0.044 mmol, 1.00 equiv.), 2-ethylbutanoic acid (11.7 mg, 0.101 mmol, 2.3 equiv.), EDCI.HCl (16.8 mg, 0.088 mmol, 2.0 equiv.), 4-DMAP (0.5 mg, 4.4 µmol, 0.1 equiv.) and DIPEA (19 µL, 0.110 mmol, 2.5 equiv.), and stirring for 13 in place of 16 h.

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 0 : 100 to 10 : 90 in 60 min) to afford the title compound **239**.

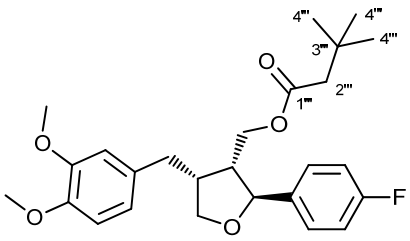
Yield:	16.2 mg, 83 %
Appearance:	colorless oil
R_f (silica):	0.66 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{23}$:	+14.2 (c 0.65, MeOH)
LC-HRMS (APCI):	calculated for M+Na$^+$: 467.2204, found: 467.2197, Δ: -1.50 ppm
(log *P*)$_{calc}$:	5.94 ± 0.49

GC-MS (EI, 70 eV, Method E): 11.51 min; 444.0 (M$^+$, 5), 194.0 (18), 190.1 (18), 189.1 (18), 178.1 (15), 177.0 (42), 164.1 (19), 163.1 (15), 152.1 (28), 151.0 (100), 123.0 (46), 109.0 (23), 107.0 (16).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, ^3J = 7.4 Hz, 3H, H4a'''*), 0.90 (t, ^3J = 7.4 Hz, 3H, H4b'''*), 1.44 – 1.70 (m, 4H, H3'''), 2.14 – 2.29 (m, 1H, H2'''), 2.45 – 2.61 (m, 2H, H3, C4-CH), 2.62 – 2.81 (m, 1H, H4), 2.87 (dd, ^2J = 12.5 Hz, ^3J = 4.1 Hz, 1H, C4-CH), 3.77 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 3.86 (s, 6H, Ar''-OCH_3), 4.06 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.17 (dd, ^2J = 11.2 Hz, ^3J = 7.2 Hz, 1H, C3-CH), 4.41 (dd, ^2J = 11.3 Hz, ^3J = 6.7 Hz, 1H, C3-CH), 4.85 (d, ^3J = 6.1 Hz, 1H, H2), 6.65 – 6.84 (m, 3H, Ar''-H), 6.97 – 7.09 (m, 2H, H3', H5'), 7.24 – 7.34 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 12.0 (q, C4a'''*), 12.1 (q, C4b'''*), 25.1 (t, 2 x C3'''), 33.2 (t, C4-C), 42.8 (d, C4), 49.1 (d, C2'''), 49.6 (d, C3), 56.0 (q, Ar''-OCH_3), 56.1 (q, Ar''-OCH_3), 62.3 (t, C3-C), 72.9 (t, C5), 82.7 (d, C2), 111.5 (d, C5''*), 112.0 (d, C2''*), 115.4 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 120.6 (d, C6''), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 132.6 (s, C1''), 138.5 (d, C1', $^4J_{C\text{-}F}$ = 3.0 Hz), 147.7 (s, C4''), 149.1 (s, C3''), 162.4 (d, C4', $^1J_{C\text{-}F}$ = 245.5 Hz), 176.2 (s, C1''').

D.4.2.37 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl 3,3-dimethylbutanoate (**240**)



240, $C_{26}H_{33}FO_5$
444.54 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **148** (22.0 mg, 0.064 mmol, 1.00 equiv.), 3,3-dimethylbutanoic acid (16.9 mg, 0.146 mmol, 2.3 equiv.), EDCI.HCl (24.3 mg, 0.127 mmol, 2.0 equiv.), 4-DMAP (0.8 mg, 6.4 µmol, 0.1 equiv.) and DIPEA (28 µL, 0.16 mmol, 2.5 equiv.), and stirring for 13.5 in place of 16 h.

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 9 : 91 to 25 : 75 in 60 min) to afford the title compound **240**.

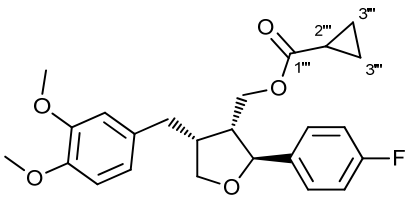
Yield:	25.8 mg, 92 %
Appearance:	colorless oil
R_f (silica):	0.66 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{23}$:	+15.7 (c 2.07, MeOH)
LC-HRMS (APCI):	calculated for $M+H^+$: 445.2385, found: 445.2398, Δ: 2.92 ppm
(log *P*)$_{calc}$:	5.76 ± 0.50

GC-MS (EI, 70 eV, Method E): 11.19 min; 444.1 (M^+, 7), 194.0 (15), 190.1 (17), 189.1 (19), 177.0 (39), 164.1 (19), 152.0 (28), 151.0 (100), 123.0 (42), 109.0 (24), 107.0 (16).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03 (s, 9H, H4'''), 2.19 (s, 2H, H2'''), 2.43 – 2.62 (m, 2H, H3, C4-CH), 2.62 – 2.82 (m, 1H, H4), 2.86 (dd, ^2J = 12.5 Hz, ^3J = 4.2 Hz, 1H, C4-CH), 3.77 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 3.86 (s, 3H, Ar''-OCH_3), 3.86 (s, 3H, Ar''-OCH_3), 4.06 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.16 (dd, ^2J = 11.1 Hz, ^3J = 7.2 Hz, 1H, C3-CH), 4.37 (dd, ^2J = 11.3 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.85 (d, ^3J = 6.1 Hz, 1H, H2), 6.64 – 6.84 (m, 3H, Ar''-H), 6.96 – 7.09 (m, 2H, H3', H5'), 7.23 – 7.34 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 29.8 (q, 3 x C4'''), 30.9 (s, C3'''), 33.1 (t, C4-C), 42.6 (d, C4), 48.1 (t, C2'''), 49.5 (d, C3), 56.00 (q, Ar''-OCH_3), 56.04 (q, Ar''-OCH_3), 62.2 (t, C3-C), 72.9 (t, C5), 82.7 (d, C2), 111.5 (d, C5''*), 112.0 (d, C2''*), 115.4 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 120.6 (d, C6''), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 132.6 (s, C1''), 138.5 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 147.7 (s, C4''), 149.1 (s, C3''), 162.4 (d, C4', $^1J_{C\text{-}F}$ = 245.5 Hz), 172.4 (s, C1''').

D.4.2.38 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl cyclopropanecarboxylate (**241**)



241, $C_{24}H_{27}FO_5$
414.47 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **148** (18.5 mg, 0.053 mmol, 1.00 equiv.), cyclopropanecarboxylic acid (10.6 mg, 0.123 mmol, 2.3 equiv.), EDCI.HCl (20.4 mg, 0.107 mmol, 2.0 equiv.), 4-DMAP (0.6 mg, 5.3 µmol, 0.1 equiv.) and DIPEA (23 µL, 0.13 mmol, 2.5 equiv.), and stirring for 13 in place of 16 h.

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 0 : 100 to 10 : 90 in 60 min) to afford the title compound **241**.

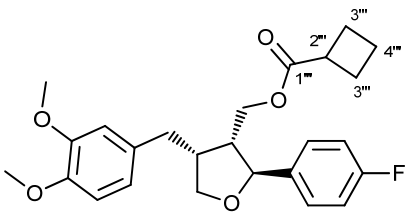
Yield:	16.6 mg, 75 %
Appearance:	colorless oil
R_f (silica):	0.60 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{20}$:	+6.8 (c 1.02, *i*-PrOH)
LC-HRMS (APCI):	calculated for $M+H^+$: 415.1915, found: 415.1932, Δ: 4.09 ppm
(log *P*)$_{calc}$:	4.37 ± 0.49

GC-MS (EI, 70 eV, Method E): 11.39 min; 414.0 (M^+, 6), 194.0 (17), 190.0 (16), 189.0 (17), 177.0 (41), 164.1 (19), 163.0 (15), 152.1 (27), 151.0 (100), 123.0 (53), 109.0 (23), 107.0 (20).

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.77 – 1.02 (m, 4H, H3'''), 1.47 – 1.66 (m, 1H, H2'''), 2.42 – 2.63 (m, 2H, H3, C4-CH), 2.63 – 2.93 (m, 2H, H4, C4-CH), 3.76 (dd, ^2J = 8.6 Hz, ^3J = 6.5 Hz, 1H, H5), 3.86 (s, 3H, Ar''-OCH_3), 3.87 (s, 3H, Ar''-OCH_3), 4.08 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.19 (dd, ^2J = 11.2 Hz, ^3J = 7.6 Hz, 1H, C3-CH), 4.38 (dd, ^2J = 11.2 Hz, ^3J = 6.6 Hz, 1H, C3-CH), 4.86 (d, ^3J = 6.1 Hz, 1H, H2), 6.65 – 6.84 (m, 3H, Ar''-H), 6.96 – 7.09 (m, 2H, H3', H5'), 7.24 – 7.35 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 8.7 (t, 2 x C3'''), 13.0 (d, C2'''), 33.2 (t, C4-C), 42.6 (d, C4), 49.4 (d, C3), 55.97 (q, Ar''-OCH_3), 55.99 (q, Ar''-OCH_3), 62.7 (t, C3-C), 73.0 (t, C5), 82.8 (d, C2), 111.5 (d, C5''*), 112.0 (d, C2''*), 115.4 (dd, C3', C5', $^2J_{C-F}$ = 21.4 Hz), 120.6 (d, C6''), 127.5 (dd, C2', C6', $^3J_{C-F}$ = 8.1 Hz), 132.6 (s, C1''), 138.5 (d, C1', $^4J_{C-F}$ = 3.1 Hz), 147.7 (s, C4''), 149.1 (s, C3''), 162.2 (d, C4', $^1J_{C-F}$ = 245.6 Hz), 174.9 (s, C1''').

D.4.2.39 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl cyclobutanecarboxylate (**242**)



242, $C_{25}H_{29}FO_5$
428.49 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **148** (17.0 mg, 0.049 mmol, 1.00 equiv.), cyclobutanecarboxylic acid (11.3 mg, 0.113 mmol, 2.3 equiv.), EDCI.HCl (18.8 mg, 0.098 mmol, 2.0 equiv.), 4-DMAP (0.6 mg, 4.9 µmol, 0.1 equiv.) and DIPEA (21 µL, 0.12 mmol, 2.5 equiv.), and stirring for 13.5 in place of 16 h.

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 9 : 91 isocratically for 20 min, then to 25 : 75 in 60 min) to afford the title compound **242**.

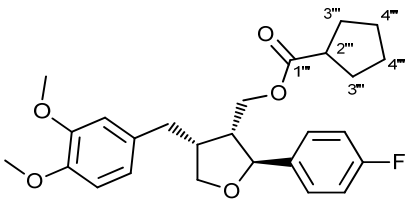
Yield:	15.8 mg, 75 %
Appearance:	colorless oil
R_f (silica):	0.60 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{23}$:	+14.2 (c 1.25, MeOH)
LC-HRMS (APCI):	calculated for M+H$^+$: 429.2072, found: 429.2085, Δ: 3.03 ppm
(log *P*)$_{calc}$:	4.93 ± 0.49

GC-MS (EI, 70 eV, Method E): 12.61 min; 428.0 (M$^+$, 7), 207.0 (15), 194.0 (17), 190.0 (18), 189.1 (18), 177.1 (36), 164.1 (20), 152.1 (25), 151.1 (100), 123.0 (49), 109.1 (20), 107.0 (18).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78 – 2.07 (m, 2H, H4'''), 2.07 – 2.36 (m, 4H, H3'''), 2.44 – 2.91 (m, 4H, H3, H4, C4-CH_2), 3.10 (quint, ^3J = 8.3 Hz, 1H, H2'''), 3.75 (dd, ^2J = 8.6 Hz, ^3J = 6.4 Hz, 1H, H5), 3.86 (s, 3H, Ar''-OCH_3), 3.87 (s, 3H, Ar''-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.19 (dd, ^2J = 11.2 Hz, ^3J = 7.5 Hz, 1H, C3-CH), 4.39 (dd, ^2J = 11.2 Hz, ^3J = 6.6 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.0 Hz, 1H, H2), 6.65 – 6.85 (m, 3H, Ar''-H), 6.95 – 7.09 (m, 2H, H3', H5'), 7.21 – 7.35 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 18.6 (t, C4'''), 24.39 (t, 2 x C3'''), 25.42 (t, C3'''), 33.2 (t, C4-C), 38.1 (d, C2'''), 42.7 (d, C4), 49.4 (d, C3), 55.99 (q, Ar''-OCH_3), 56.03 (q, Ar''-OCH_3), 62.6 (t, C3-C), 72.9 (t, C5), 82.8 (d, C2), 111.5 (d, C5''*), 112.0 (d, C2''*), 115.4 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 120.6 (d, C6''), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 132.6 (s, C1''), 138.5 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 147.7 (s, C4''), 149.1 (s, C3''), 162.3 (d, C4', $^1J_{C\text{-}F}$ = 245.6 Hz), 175.4 (s, C1''').

D.4.2.40 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl cyclopentanecarboxylate (**243**)



243, $C_{26}H_{31}FO_5$
442.52 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **148** (31.2 mg, 0.090 mmol, 1.00 equiv.), cyclopentanecarboxylic acid (23.6 mg, 0.207 mmol, 2.3 equiv.), EDCI.HCl (34.5 mg, 0.180 mmol, 2.0 equiv.), 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.) and DIPEA (39 µL, 0.23 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 0 : 100 to 15 : 85 in 16 min, then to 22 : 78 in 4 min) to afford the title compound **243**.

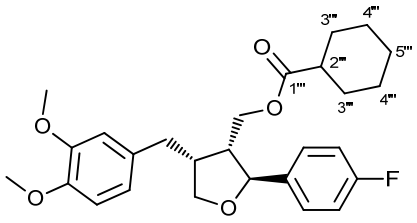
Yield:	38.2 mg, 96 %
Appearance:	colorless oil
R_f (silica):	0.73 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+13.8 (c 2.46, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 465.2048, found: 465.2024, Δ: -5.16 ppm
(log *P*)$_{calc}$:	5.50 ± 0.49

GC-MS (EI, 70 eV, Method D): 16.70 min; 442.3 (M$^+$, 4), 194.1 (22), 190.1 (22), 189.1 (21), 177.1 (41), 164.1 (23), 163.1 (15), 152.1 (30), 151.1 (100), 123.0 (48), 109.1 (32), 107.1 (18).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 – 1.98 (m, 8H, 4 x H3''', 4 x H4'''), 2.44 – 2.79 (m, 4H, H3, H4, C4-CH, H2'''), 2.85 (dd, ^2J = 12.4 Hz, ^3J = 4.3 Hz, 1H, C4-CH), 3.76 (dd, ^2J = 8.5 Hz, ^3J = 6.4 Hz, 1H, H5), 3.86 (s, 3H, Ar''-OCH_3), 3.87 (s, 3H, Ar''-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 4.18 (dd, ^2J = 11.2 Hz, ^3J = 7.4 Hz, 1H, C3-CH), 4.38 (dd, ^2J = 11.2 Hz, ^3J = 6.6 Hz, 1H, C3-CH), 4.85 (d, ^3J = 6.0 Hz, 1H, H2), 6.65 – 6.75 (m, 2H, H2'', H6''*), 6.80 (d, ^3J = 7.9 Hz, 1H, H5''*), 7.02 (dd, ^3J = 8.7 Hz, $^3J_{H-F}$ = 8.7 Hz, 2H, H3', H5'), 7.29 (dd, ^3J = 8.6 Hz, $^4J_{H-F}$ = 5.4 Hz, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.9 (t, 2 x C4'''), 30.1 (t, 2 x C3'''), 33.2 (t, C4-C), 42.7 (d, C4), 43.9 (d, C2'''), 49.5 (d, C3), 55.98 (q, Ar''-OCH_3), 56.00 (q, Ar''-OCH_3), 62.5 (t, C3-C), 72.9 (t, C5), 82.7 (d, C2), 111.4 (d, C5''*), 111.9 (d, C2''*), 115.4 (dd, C3', C5', $^2J_{C-F}$ = 21.5 Hz), 120.5 (d, C6''), 127.5 (dd, C2', C6', $^3J_{C-F}$ = 8.1 Hz), 132.6 (s, C1''), 138.5 (d, C1', $^4J_{C-F}$ = 3.1 Hz), 147.7 (s, C4''), 149.1 (s, C3''), 162.3 (d, C4', $^1J_{C-F}$ = 245.4 Hz), 176.7 (s, C1''').

D.4.2.41 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl cyclohexanecarboxylate (**244**)



244, $C_{27}H_{33}FO_5$
456.55 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **148** (31.2 mg, 0.090 mmol, 1.00 equiv.), cyclohexanecarboxylic acid (26.5 mg, 0.207 mmol, 2.3 equiv.), EDCI.HCl (34.5 mg, 0.180 mmol, 2.0 equiv.), 4-DMAP (1.1 mg, 9.0 µmol, 0.1 equiv.) and DIPEA (39 µL, 0.23 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 0 : 100 to 15 : 85 in 16 min, then to 22 : 78 in 4 min) to afford the title compound **244**.

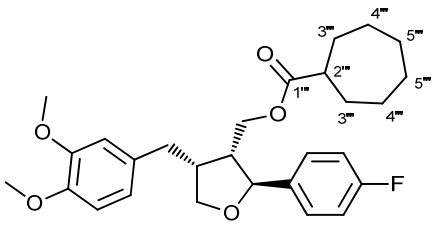
Yield:	37.2 mg, 91 %
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.76 (EtOAc / LP, 1 : 1)
[α]$_D^{20}$:	+15.1 (c 2.10, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 479.2204, found: 479.2185, Δ: -3.96 ppm
(log *P*)$_{calc}$:	6.06 ± 0.49

GC-MS (EI, 70 eV, Method D): 19.53 min; 456.3 (M$^+$, 4), 194.1 (24), 190.1 (24), 189.1 (23), 177.1 (44), 164.1 (26), 163.1 (16), 152.1 (30), 151.1 (100), 123.0 (47), 109.1 (33), 107.1 (18).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.11 – 1.95 (m, 10H, 4 x H3''', 4 x H4''', 2 x H5'''), 2.17 – 2.34 (m, 1H, H2'''), 2.42 – 2.62 (m, 2H, H3, C4-CH), 2.62 – 2.79 (m, 1H, H4), 2.85 (dd, ^2J = 12.4 Hz, ^3J = 4.3 Hz, 1H, C4-CH), 3.77 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 3.86 (s, 3H, Ar''-OCH_3), 3.87 (s, 3H, Ar''-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.17 (dd, ^2J = 11.3 Hz, ^3J = 7.3 Hz, 1H, C3-CH), 4.38 (dd, ^2J = 11.3 Hz, ^3J = 6.7 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.2 Hz, 1H, H2), 6.65 – 6.75 (m, 2H, H2'', H6''*), 6.81 (d, ^3J = 7.9 Hz, 1H, H5''*), 7.02 (dd, ^3J = 8.7 Hz, $^3J_{H\text{-}F}$ = 8.7 Hz, 2H, H3', H5'), 7.29 (dd, ^3J = 8.6 Hz, $^4J_{H\text{-}F}$ = 5.4 Hz, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.5 (t, 2 x C4'''), 25.8 (t, C5'''), 29.1 (t, 2 x C3'''), 29.1 (t, C3'''), 33.2 (t, C4-C), 42.7 (d, C4), 43.3 (d, C2'''), 49.5 (d, C3), 55.97 (q, Ar''-OCH_3), 56.00 (q, Ar''-OCH_3), 62.3 (t, C3-C), 72.9 (t, C5), 82.7 (d, C2), 111.4 (d, C5''*), 111.9 (d, C2''*), 115.4 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 120.5 (d, C6''), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 132.6 (s, C1''), 138.5 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 147.7 (s, C4''), 149.1 (s, C3''), 162.3 (d, C4', $^1J_{C\text{-}F}$ = 245.7 Hz), 176.0 (s, C1''').

D.4.2.42 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl cycloheptanecarboxylate (**245**)



245, $C_{28}H_{35}FO_5$
470.57 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **148** (28.3 mg, 0.082 mmol, 1.00 equiv.), cycloheptanecarboxylic acid (26.7 mg, 0.188 mmol, 2.3 equiv.), EDCI.HCl (31.3 mg, 0.163 mmol, 2.0 equiv.), 4-DMAP (1.0 mg, 8.2 µmol, 0.1 equiv.) and DIPEA (36 µL, 0.20 mmol, 2.5 equiv.), and stirring for 24 in place of 16 h.

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 9 : 91 to 25 : 75 in 30 min) to afford the title compound **245**.

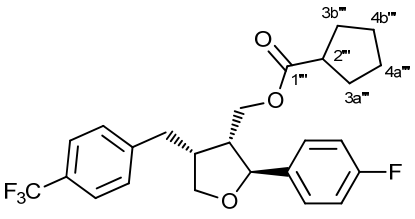
Yield:	32.6 mg, 88 %
Appearance:	colorless oil
R_f (silica):	0.66 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{23}$:	+14.9 (c 0.90, MeOH)
LC-HRMS (APCI):	calculated for M+H$^+$: 471.2541, found: 471.2553, Δ: 2.55 ppm
(log *P*)$_{calc}$:	6.62 ± 0.49

GC-MS (EI, 70 eV, Method E): 20.03 min; 470.0 (M$^+$, 4), 207.0 (15), 194.1 (18), 190.1 (18), 189.1 (17), 177.0 (39), 164.1 (22), 152.1 (26), 151.0 (100), 123.0 (41), 109.0 (23), 97.2 (22).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 – 1.98 (m, 12H, 4 x H3''', 4 x H4''', 4 x H5'''), 2.35 – 2.62 (m, 3H, H3, C4-CH, H2'''), 2.63 – 2.92 (m, 2H, H4, C4-CH), 3.76 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 3.86 (s, 3H, Ar''-OCH_3), 3.87 (s, 3H, Ar''-OCH_3), 4.07 (dd, ^2J = 8.6 Hz, ^3J = 6.3 Hz, 1H, H5), 4.16 (dd, ^2J = 11.3 Hz, ^3J = 7.4 Hz, 1H, C3-CH), 4.38 (dd, ^2J = 11.3 Hz, ^3J = 6.6 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.2 Hz, 1H, H2), 6.63 – 6.85 (m, 3H, Ar''-H), 6.94 – 7.11 (m, 2H, H3', H5'), 7.20 – 7.36 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$): δ 26.4 (t, 2 x C4'''), 28.4 (t, 2 x C5'''), 30.9 (t, 2 x C3'''), 33.2 (t, C4-C), 42.7 (d, C4), 45.2 (d, C2'''), 49.5 (d, C3), 55.99 (q, Ar''-OCH_3), 56.01 (q, Ar''-OCH_3), 62.5 (t, C3-C), 72.9 (t, C5), 82.8 (d, C2), 111.5 (d, C5''*), 112.0 (d, C2''*), 115.4 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.5 Hz), 120.6 (d, C6''), 127.6 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 132.6 (s, C1''), 138.5 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 147.7 (s, C4''), 149.1 (s, C3''), 162.4 (d, C4', $^1J_{C\text{-}F}$ = 245.5 Hz), 176.9 (s, C1''').

D.4.2.43 ((2*S*,3*R*,4*R*)-2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl cyclopentanecarboxylate (**246**)



246, $C_{25}H_{26}F_4O_3$
450.47 g mol^{-1}

***Preparation**:* analogous to **206** (section D.4.2.2, page 226), using starting material **156** (37.9 mg, 0.107 mmol, 1.00 equiv.), cyclopentanecarboxylic acid (28.1 mg, 0.246 mmol, 2.3 equiv.), EDCI.HCl (41.0 mg, 0.214 mmol, 2.0 equiv.), 4-DMAP (1.3 mg, 11 µmol, 0.1 equiv.) and DIPEA (48 µL, 0.27 mmol, 2.5 equiv.).

***Work-up and purification**:* the reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 2 : 98 to 10 : 90 in 30 min) to afford the title compound **246**.

Yield:	38.2 mg, 79 %
Appearance:	colorless oil
R_f (silica):	0.58 (EtOAc / heptane, 1 : 2)
$[\alpha]_D^{20}$:	+17.1 (c 0.79, MeOH)
LC-HRMS (ESI):	calculated for M+H$^+$: 451.1891, found: 451.1915, Δ: 5.35 ppm
(log *P*)$_{calc}$:	6.33 ± 0.51

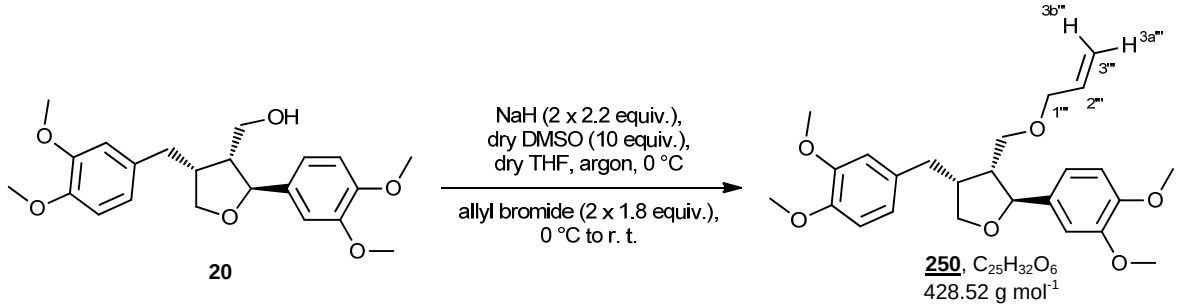
GC-MS (EI, 70 eV, Method D): 9.48 min; 336.6 (34), 335.7 (27), 212.1 (36), 197.0 (29), 185.1 (21), 177.1 (100), 159.02 (*p*-trifluoromethylbenzyl, 52), 125.0 (46), 123.0 (89), 109.0 (29), 97.0 (21). M$^+$ not visible.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 – 2.00 (m, 8H, 2 x H3a''', 2 x H3b''', 2 x H4a''', 2 x H4b'''), 2.54 (quint, ^3J = 6.6 Hz, 1H, H3), 2.60 – 2.90 (m, 3H, H4, C4-CH, H2'''), 2.90 – 3.03 (m, 1H, C4-CH), 3.73 (dd, ^2J = 8.7 Hz, ^3J = 6.3 Hz, 1H, H5), 4.06 (dd, ^2J = 8.7 Hz, ^3J = 6.1 Hz, 1H, H5), 4.19 (dd, ^2J = 11.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 4.36 (dd, ^2J = 11.3 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.85 (d, ^3J = 6.1 Hz, 1H, H2), 6.96 – 7.10 (m, 2H, H3', H5'), 7.23 – 7.35 (m, 4H, H2', H6', H2'', H6''), 7.56 (d, ^3J = 8.1 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$): δ 25.9 (t, C4a'''; C4b'''; signal overlap), 30.1 (t, C3a'''*), 30.1 (t, C3b'''*), 33.5 (t, C4-C), 42.3 (d, C4), 43.9 (d, C2'''), 49.5 (d, C3), 62.3 (t, C3-C), 72.7 (t, C5), 82.7 (d, C2), 115.5 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.5 Hz), 124.3 (q, C4''-CF_3, $^1J_{C\text{-}F}$ = 271.9 Hz), 125.7 (dq, C3'', C5'', $^3J_{C\text{-}F}$ = 3.8 Hz), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 129.0 (q, C4'', $^2J_{C\text{-}F}$ = 32.4 Hz), 129.0 (d, C2'', C6''), 138.2 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 144.3 (q, C1'', $^5J_{C\text{-}F}$ = 1.1 Hz), 162.4 (d, C4', $^1J_{C\text{-}F}$ = 245.7 Hz), 176.7 (d, C1''').

D.4.3 **Etherification**

D.4.3.1 (2*S*,3*R*,4*R*)-3-((Allyloxy)methyl)-4-(3,4-dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran (**250**)



20

250, $C_{25}H_{32}O_6$
428.52 g mol^{-1}

***Preparation**:* a reaction vessel was charged with a stirring bar, NaH mineral oil dispersion (approximately 60 %, 8.8 mg, 0.22 mmol, 2.2 equiv.) and then evacuated and back-filled with argon using standard Schlenk technique. Then, dry THF (0.5 mL) was added, followed by dry DMSO (71 µL, 1.0 mmol, 10 equiv.), both *via* syringe, and the stirred suspension was cooled to 0 °C in an ice bath. This was followed by the dropwise addition of starting material **20** (38.8 mg, 0.100 mmol, 1.0 equiv.) in dry THF (1.0 mL), subsequent stirring of the reaction for 15 min at 0 °C, and finally by allyl bromide (16 µL, 0.18 mmol, 1.8 equiv.), both *via* syringe. The ice bath was removed and the mixture was stirred for 18 h at room temperature, before the vessel was briefly opened to add more NaH dispersion (8.8 mg, 0.22 mmol, 2.2 equiv.). 1 h after that, more allyl bromide (16 µL, 0.18 mmol, 1.8 equiv.) was added *via* syringe, and the mixture was stirred for 25 h at room temperature.

***Work-up and purification**:* the reaction was quenched by the addition of saturated aqueous NH_4Cl (1.0 mL) and extracted with Et_2O (2 x 10 mL). The combined organic phases were dried with Na_2SO_4, filtered, the solvents evaporated and the residual material purified by flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 90 : 10 in 60 min) to afford the title compound **250**.

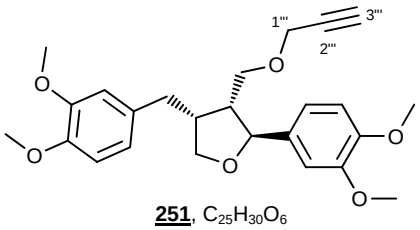
Yield:	31.8 mg, 74 %
Appearance:	colorless oil
R_f (silica):	0.57 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+19.6 (c 1.63, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 451.2091, found: 451.2096, Δ: 1.11 ppm
(log *P*)$_{calc}$:	4.25 ± 0.47

GC-MS (EI, 70 eV, Method D): 15.97 min; 428.2 (M$^+$, 7), 205.1 (15), 165.1 (53), 152.1 (16), 151.1 (100), 107.1 (16).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.41 – 2.60 (m, 2H, H3, C4-CH), 2.63 – 2.82 (m, 1H, H4), 2.93 (dd, ^2J = 13.0 Hz, ^3J = 4.2 Hz, 1H, C4-CH), 3.52 (dd, ^2J = 9.3 Hz, ^3J = 6.3 Hz, 1H, C3-CH), 3.60 – 3.81 (m, 2H, C3-CH, H5), 3.87 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 3.95 – 4.09 (m, 3H, H5, 2 x H1'''), 4.80 (d, ^3J = 6.6 Hz, 1H, H2), 5.20 (ddt, ^2J = 1.7 Hz, ^3J = 10.3 Hz, ^4J = 1.3 Hz, 1H, H3a'''), 5.30 (ddt, ^2J = 1.7 Hz, ^3J = 17.3 Hz, ^4J = 1.6 Hz, 1H, H3b'''), 5.93 (dddd, $^3J_{cis}$ = 10.3 Hz, $^3J_{trans}$ = 17.3 Hz, $^3J_{vic}$ = 5.9 Hz*, $^3J_{vic}$ = 5.0 Hz*, 1H, H2'''), 6.67 – 6.92 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.2 (t, C4-C), 42.7 (d, C4), 50.5 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 68.2 (t, C3-C), 72.3 (t, C1'''), 72.9 (t, C5), 82.8 (d, C2), 109.1 (d, C2'), 111.0 (d, C5'), 111.3 (d, C5''*), 112.0 (d, C2''*), 117.1 (t, C3'''), 118.1 (d, C6'), 120.6 (d, C6''), 133.3 (s, C1''), 134.8 (d, C2'''), 135.7 (s, C1'), 147.5 (s, C4''), 148.4 (s, C4'), 149.0 (s, C3''), 149.1 (s, C3').

D.4.3.2 (2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)-3-((prop-2-yn-1-yloxy)methyl)tetrahydrofuran (**251**)



251, $C_{25}H_{30}O_6$
426.50 g mol^{-1}

***Preparation**:* analogous to **250** (section D.4.3.1, page 269), using propargyl bromide (2 x 20 µL, 2 x 0.18 mmol, 2 x 1.8 equiv.) in place of allyl bromide.

***Work-up and purification**:* the reaction was quenched by the addition of saturated aqueous NH_4Cl (1.0 mL) and extracted with Et_2O (2 x 10 mL). The combined organic phases were dried with Na_2SO_4, filtered, the solvents evaporated and the residual material purified by flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 90 : 10 in 60 min) to afford the title compound **251**.

Yield:	23.2 mg, 54 %
Appearance:	colorless oil
R_f (silica):	0.46 (EtOAc / LP, 1 : 1)
$[\alpha]_D^{20}$:	+25.1 (c 1.49, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 449.1935, found: 449.1940, Δ: 1.11 ppm
(log *P*)$_{calc}$:	3.81 ± 0.50

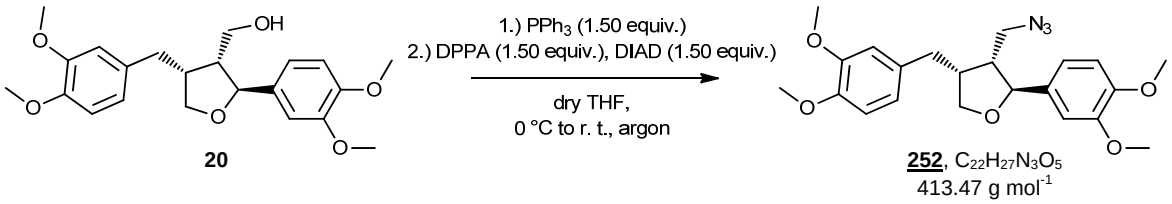
GC-MS (EI, 70 eV, Method E): 16.84 min; 426.2 (M^+, 8), 165.1 (44), 152.1 (16), 151.0 (100), 107.1 (17).

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.41 – 2.61 (m, 2H, H3, C4-CH), 2.45 (t, ^4J = 2.4 Hz, 1H, H3'''), 2.62 – 2.83 (m, 1H, H4), 2.95 (dd, ^2J = 13.0 Hz, ^3J = 4.2 Hz, 1H, C4-CH), 3.60 (dd, ^2J = 9.1 Hz, ^3J = 6.2 Hz, 1H, C3-CH), 3.81 – 3.69 (m, 2H, C3-CH, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.03 (dd, ^2J = 8.5 Hz, ^3J = 6.3 Hz, 1H, H5), 4.18 (t, ^4J = 2.1 Hz, 2H, H1'''), 4.80 (d, ^3J = 6.7 Hz, 1H, H2), 6.92 – 6.66 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.2 (t, C4-C), 42.7 (d, C4), 50.4 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 58.6 (t, C1'''), 68.0 (t, C3-C), 72.9 (t, C5), 74.8 (d, C3'''; *J*-mod spectrum shows antipodal signal due to a large $^1J_{C\text{-}H}$ of approximately 250 Hz), 79.7 (s, C2'''), 82.8 (d, C2), 109.1 (d, C2'), 111.0 (d, C5'), 111.4 (d, C5''*), 112.1 (d, C2''*), 118.2 (d, C6'), 120.7 (d, C6''), 133.3 (s, C1''), 135.5 (s, C1'), 147.5 (s, C4''), 148.5 (s, C4'), 149.0 (s, C3''), 149.1 (s, C3').

D.4.4 **Conversion to *N*-Analogs**

D.4.4.1 (2*S*,3*R*,4*R*)-3-(Azidomethyl)-4-(3,4-dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran (**252**)



***Preparation**:* a reaction vessel was charged with a stirring bar, starting material **20** (35.0 mg, 0.095 mmol, 1.00 equiv.) and triphenylphosphine (35.4 mg, 0.135 mmol, 1.50 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Then, dry THF (1.0 mL) was added *via* syringe, the solution was cooled to 0 °C in an ice bath and to the stirred mixture was added DPPA (37.2 mg, 0.135 mmol, 1.50 equiv.) in dry THF (0.5 mL), followed by the dropwise addition of DIAD (27.3 mg, 0.135 mmol, 1.50 equiv.) in dry THF (0.5 mL), both *via* syringe. The reaction was stirred for 17 h while being allowed to warm to room temperature.

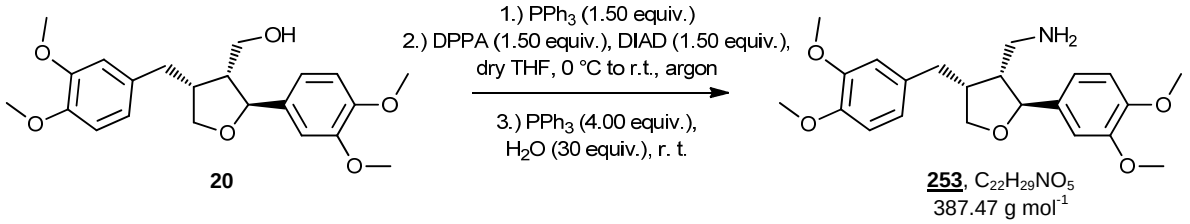
***Work-up and purification**:* Water (0.05 mL) was added and the solvent was evaporated, followed by flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 22 : 78 in 9 min, then 22 : 78 isocratically for 6 min, then to 62 : 38 in 30 min) to afford the title compound **252**.

Yield:	27.8 mg, 75 %
Appearance:	nearly colorless oil
R_f (silica):	0.78 (EtOAc)
LC-HRMS (ESI):	calculated for M+Na$^+$: 436.1848, found: 436.1835, Δ: -3.07 ppm
(log *P*)$_{calc}$:	3.70 ± 0.45

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35 – 2.59 (m, 2H, H3, C4-CH), 2.63 – 2.83 (m, 1H, H4), 2.89 (dd, ^2J = 12.7 Hz, ^3J = 4.4 Hz, 1H, C4-CH), 3.44 (dd, ^2J = 12.3 Hz, ^3J = 7.0 Hz, 1H, C3-CH), 3.60 (dd, ^2J = 12.3 Hz, ^3J = 7.9 Hz, 1H, C3-CH), 3.76 (dd, ^2J = 8.7 Hz, ^3J = 5.8 Hz, 1H, H5), 3.87 (s, 3H, Ar-OCH_3), 3.88 (s, 6H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.07 (dd, ^2J = 8.7 Hz, ^3J = 6.3 Hz, 1H, H5), 4.75 (d, ^3J = 6.7 Hz, 1H, H2), 6.66 – 6.91 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.2 (t, C4-C), 42.4 (d, C4), 49.7 (t, C3-C), 50.1 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 72.6 (t, C5), 83.2 (d, C2), 108.9 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.7 (d, C6''), 132.4 (s, C1''), 134.6 (s, C1'), 147.7 (s, C4''), 148.7 (s, C4'), 149.1 (s, C3''), 149.3 (s, C3').

D.4.4.2 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methanamine (**253**)



Preparation**:* Following the ***Preparation of **252** (section D.4.4.1, page 272), the crude azide intermediate was treated with water (0.05 mL, 2.7 mmol, 30 equiv.), then stirred for 5 min, followed by the addition of PPh_3 (94.4 mg, 0.360 mmol, 4.00 equiv.) and stirring was continued for 12 h at room temperature.

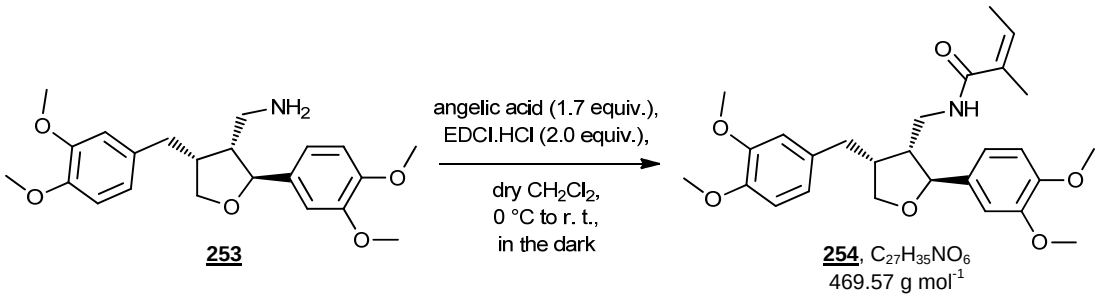
***Work-up and purification**:* The solvent was evaporated, the residue taken up in Et_2O (10 mL) and extracted with aqueous HCl (0.25 M, 2 x 10 mL). To the combined aqueous phases was added CH_2Cl_2, followed by the careful addition of Na_2CO_3 (1.5 g). The layers were separated and then extracted with more CH_2Cl_2 (2 x 10 mL). The combined organic phases were treated with brine (3 mL), dried with Na_2SO_4, filtered and the solvent was evaporated. Purification by flash column chromatography (9 g silica, flow rate 20 mL / min, MeOH / CH_2Cl_2, 1 : 99 to 20 : 80 in 40 min) afforded the title compound **253**.

Yield:	17.0 mg, 49 %
Appearance:	pale brown oil
***R*$_f$ (silica)**:	0.73 (EtOAc)
[α]$_D^{20}$:	+37.8 (c 1.54, MeOH)
LC-HRMS (ESI):	calculated for M+H$^+$: 388.2118, found: 388.2132, Δ: 3.49 ppm
(log *P*)$_{calc}$:	2.84 ± 0.43

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (bs, 2H, NH_2*), 2.30 (quint, ^3J = 7.0 Hz, 1H, H3), 2.52 (dd, ^2J = 12.7 Hz, ^3J = 10.8 Hz, 1H, C4-CH), 2.61 – 3.13 (m, 4H, H4, C4-CH, C3-CH_2), 3.78 (dd, ^2J = 8.6 Hz, ^3J = 4.5 Hz, 1H, H5), 3.87 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.05 (dd, ^2J = 8.5 Hz, ^3J = 5.9 Hz, 1H, H5), 4.70 (d, ^3J = 7.5 Hz, 1H, H2), 6.68 – 6.97 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.2 (t, C4-C), 42.6 (d, C4), 56.0 (q, 4 x Ar-OCH_3), 72.7 (t, C5), 83.6 (d, C2), 109.2 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.1 (d, C2''*), 118.5 (d, C6'), 120.8 (d, C6''), 133.0 (s, C1''), 135.6 (s, C1'), 147.5 (s, C4''), 148.6 (s, C4'), 149.0 (s, C3''), 149.2 (s, C3'). C3 and C3-C not visible.

D.4.4.3 (*Z*)-*N*-(((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl)-2-methylbut-2-enamide (**254**)



Procedure: a reaction vessel was charged with a stirring bar, starting material **253** (16.4 mg, 0.042 mmol, 1.0 equiv.), angelic acid (7.2 mg, 0.072 mmol, 1.7 equiv.) and EDCI.HCl (16.2 mg, 0.085 mmol, 2.0 equiv.), and then cooled in an ice bath to 0 °C. Subsequently, dry CH_2Cl_2 (1.0 mL) was added *via* syringe and the mixture was stirred for 45 h while being kept away from light and allowed to warm to room temperature. The reaction solution was used directly for flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 40 : 60 to 100 : 0 in 30 min) to afford the title compound **254**.

Yield:	15.1 mg, 76 %
Appearance:	nearly colorless oil
R_f (silica):	0.22 (EtOAc / LP, 2 : 1)
$[\alpha]_D^{23}$:	+20.0 (c 1.25, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 492.2357, found: 492.2335, Δ: -4.47 ppm
(log *P*)$_{calc}$:	3.90 ± 0.49

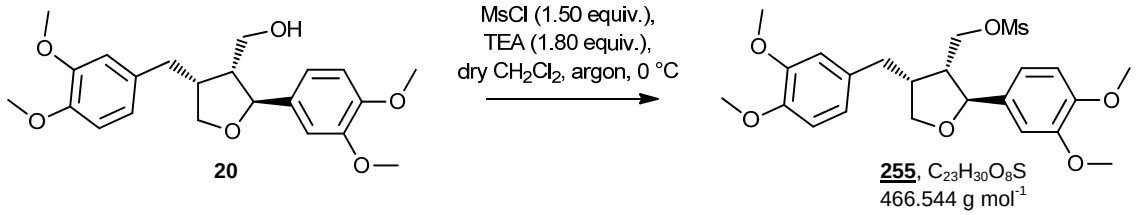
GC-MS (EI, 70 eV, Method E): 32.99 min; 469.2 (M$^+$, 6), 357.2 (25), 275.1 (20), 219.1 (30), 207.0 (24), 194.1 (25), 177.1 (19), 176.1 (22), 165.1 (50), 151.1 (77), 124.1 (16), 113.1 (24), 98.0 (100).

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.63 – 1.79 (m, 6H, H4''', H5'''), 2.43 – 2.81 (m, 3H, H3, H4, C4-CH), 2.94 (dd, ^2J = 12.7 Hz, ^3J = 4.1 Hz, 1H, C4-CH), 3.29 – 3.47 (m, 1H, C3-CH), 3.72 – 3.94 (m, 2H, C3-CH, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.07 (dd, ^2J = 8.8 Hz, ^3J = 6.0 Hz, 1H, H5), 4.72 (d, ^3J = 7.4 Hz, 1H, H2), 5.34 (t, ^3J = 5.2 Hz, 1H, NH), 5.51 – 5.67 (m, 1H, H3'''), 6.67 – 6.97 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 15.3 (q, C5'''), 20.8 (q, C4'''), 33.6 (t, C4-C), 38.2 (t, C3-C), 43.2 (d, C4), 50.2 (d, C3), 56.0 (q, 4 x Ar-OCH_3), 72.7 (t, C5), 84.3 (d, C2), 109.3 (d, C2'), 111.3 (d, C5'), 111.5 (d, C5''*), 112.1 (d, C2''*), 118.6 (d, C6'), 120.7 (d, C6''), 129.1 (d, C3'''), 132.1 (s, C2'''), 132.7 (s, C1''), 134.7 (s, C1'), 147.7 (s, C4''), 148.9 (s, C4'), 149.1 (s, C3''), 149.4 (s, C3'), 169.9 (s, C1''').

D.4.5 **C_1-Homologization**

D.4.5.1 ((2*S*,3*R*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl methanesulfonate (**255**)



20 **255**, $C_{23}H_{30}O_8S$, 466.544 g mol^{-1}

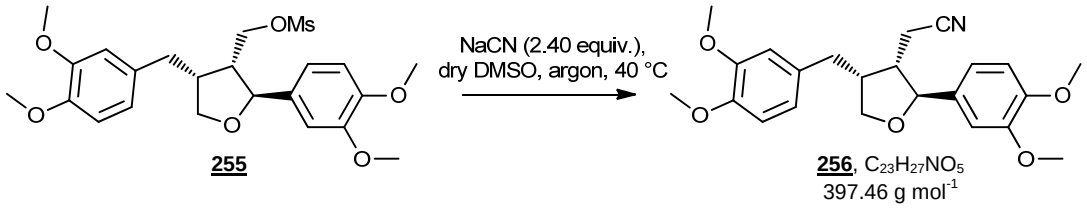
***Procedure**:* a reaction vessel was charged with a stirring bar, starting material **20** (108.4 mg, 0.279 mmol, 1.00 equiv.) and evacuated and back-filled with argon using standard Schlenk technique. Dry CH_2Cl_2 (1 mL) and triethylamine (70 µL, 0.502 mmol, 1.80 equiv.) were then added *via* syringe and the mixture was cooled to 0 °C in an ice bath. This was followed by the addition of mesyl chloride (32 µL, 0.419 mmol, 1.50 equiv.) *via* syringe and the reaction then stirred for 2 h while allowed to warm to room temperature. Aqueous HCl (0.5 M, 10 mL) was added dropwise, followed by extraction with Et_2O (4 x 20 mL) and EtOAc (2 x 20 mL). The combined organic phases were treated with water (10 mL), brine (10 mL), dried with Na_2SO_4, filtered and the solvent was evaporated. To the residue was again added Et_2O (10 mL) and then sonicated for approximately 3 min, which caused the reaction product to crystallize. Evaporation at room temperature then afforded the title compound **255**.

Yield:	130.1 mg, > 99 %
Appearance:	slightly off-white crystals
Melting range:	114.0 – 116.0 °C
R_f (silica):	0.62 (EtOAc)
$[\alpha]_D^{25}$:	+19.9 (c 0.64, MeOH / $CHCl_3$, 5 : 1)
LC-HRMS (ESI):	calculated for M+Na^+: 489.1559, found: 489.1568, Δ: 1.82 ppm
(log *P*)$_{calc}$:	2.77 ± 0.51

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.49 – 2.97 (m, 4H, H3, H4, C4-CH_2), 2.99 (s, 3H, OSO_2CH_3), 3.75 (dd, ^2J = 8.7 Hz, ^3J = 6.4 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.09 (dd, ^2J = 8.7 Hz, ^3J = 6.4 Hz, 1H, H5), 4.32 (dd, ^2J = 9.9 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 4.51 (dd, ^2J = 10.0 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 4.84 (d, ^3J = 6.1 Hz, 1H, H2), 6.67 – 6.91 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 33.2 (t, C4-C), 37.6 (q, OSO_2CH_3), 42.3 (d, C4), 49.6 (d, C3), 56.1 (q, 4 x Ar-OCH_3), 67.7 (t, C3-C), 72.8 (t, C5), 82.6 (d, C2), 109.0 (d, C2'), 111.2 (d, C5'), 111.5 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.6 (d, C6''), 132.2 (s, C1''), 134.3 (s, C1'), 147.8 (s, C4''), 148.8 (s, C4'), 149.2 (s, C3''), 149.3 (s, C3').

D.4.5.2 2-((2*S*,3*S*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)acetonitrile (**256**)



255 **256**, $C_{23}H_{27}NO_5$, 397.46 g mol^{-1}

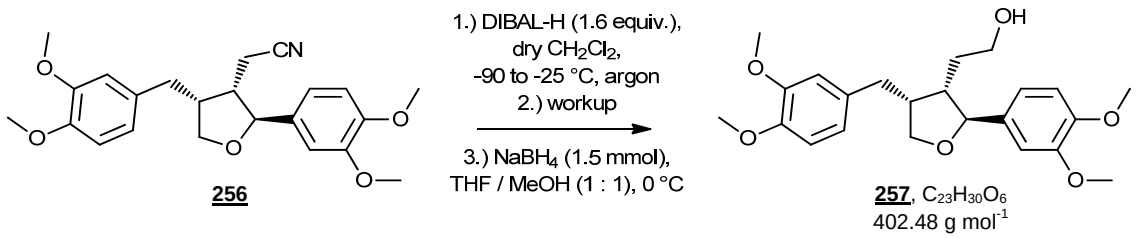
***Procedure**:* a reaction vessel was charged with a stirring bar, starting material **255** (95.9 mg, 0.206 mmol, 1.00 equiv.), dried NaCN (14.1 mg, 0.288 mmol, 1.40 equiv.) and evacuated and back-filled with argon using standard Schlenk technique. Then, dry DMSO (1.5 mL) was added *via* syringe, the mixture was stirred at 40 °C for 27 h and then allowed to remain at room temperature overnight. Water (5 mL) was added, followed by Et_2O (25 mL), the layers were separated and the aqueous phase was re-extracted with Et_2O (3 x 15 mL). The combined organic phases were treated with brine (3 mL), dried with Na_2SO_4, filtered and the solvent was evaporated. Purification by flash column chromatography (18 g silica, flow rate 20 mL / min, EtOAc / LP, 10 : 90 to 60 : 40 in 60 min) afforded the title compound **256**.

Yield:	71.6 mg, 88 %
Appearance:	colorless oil
R_f (silica):	0.53 (EtOAc)
$[\alpha]_D^{23}$:	+28.4 (c 0.67, MeOH)
LC-HRMS (APCI):	calculated for M+Na^+: 420.1781, found: 420.1789, Δ: 1.90 ppm
$(\log P)_{calc}$:	3.06 ± 0.44

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.66 – 2.42 (m, 4H, H3, C3-CH_2, C4-CH), 2.97 – 2.71 (m, 2H, H4, C4-CH), 3.79 (dd, ^2J = 8.9 Hz, ^3J = 5.6 Hz, 1H, H5), 3.87 (s, 3H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 3.90 (s, 3H, Ar-OCH_3), 4.12 (dd, ^2J = 8.9 Hz, ^3J = 6.6 Hz, 1H, H5), 4.70 – 4.76 (m, 1H, H2), 6.89 – 6.68 (m, 6H, Ar-H).

^{1}H NMR (50 MHz, $CDCl_3$): δ 16.3 (t, C3-C), 33.2 (t, C4-C), 42.5 (d, C4), 47.3 (d, C3), 56.1 (q, 4 x Ar-OCH_3), 72.3 (t, C5), 84.6 (d, C2), 108.8 (d, C2'), 111.2 (d, C5'), 111.5 (d, C5''*), 112.0 (d, C2''*), 118.3 (d, C6'), 118.8 (s, C3-CH_2-CN), 120.7 (d, C6''), 131.6 (s, C1''), 133.3 (s, C1'), 147.9 (s, C4''), 149.1 (s, C4'), 149.2 (s, C3''), 149.5 (s, C3').

D.4.5.3 2-((2*S*,3*S*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)ethanol (**257**)



256 **257**, $C_{23}H_{30}O_6$, 402.48 g mol^{-1}

***Procedure**:* a reaction vessel was charged with a stirring bar, starting material **256** (55.5 mg, 0.140 mmol, 1.00 equiv.) and evacuated and back-filled with argon using standard Schlenk technique. Then, dry CH_2Cl_2 (3.5 mL) was added *via* syringe and the mixture was cooled to -85 °C in a MeOH / liquid N_2 bath. A solution of DIBAL-H (1 M in heptane, 0.36 ml, 0.36 mmol, 2.60 equiv.) was added dropwise *via* syringe and the mixture allowed to warm to -50 °C over 90 min. This was followed by the dropwise addition of aqueous NaOH (2 M, 0.42 mL, 6.0 equiv.) and stirring for another 3 min. The cooling bath was removed and upon warming, water (3 mL) and CH_2Cl_2 (20 mL) was added, the layers were separated and the aqueous phase was re-extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered into a new reaction vessel, and the solvent was evaporated to obtain a residue of crude aldehyde intermediate (54.5 mg).

To this residue was added a stirring bar, MeOH (2.0 mL) and THF (1.5 mL), and the vessel closed without further provisions for inert conditions. After cooling to 0 °C in an ice bath, $NaBH_4$ (7.9 mg, 0.209 mmol, 1.50 equiv.) was added in one go and the mixture was stirred at 0 °C for 50 min.

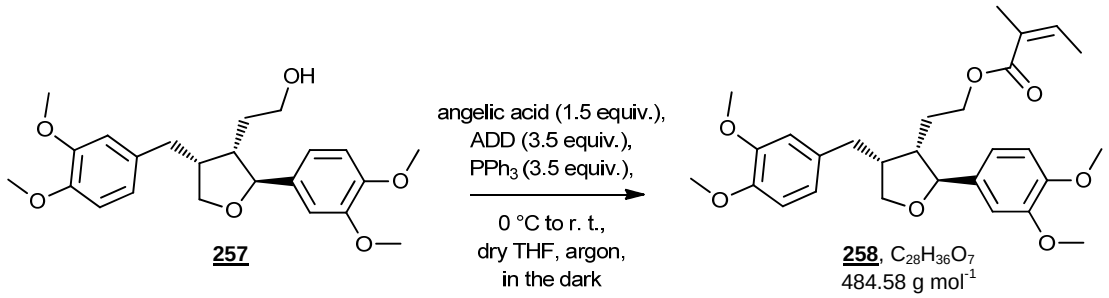
Saturated aqueous NH_4Cl (0.5 mL) was then added slowly, the cooling bath was removed and stirring was continued for another 5 min. CH_2Cl_2 (25 mL) and brine (2 mL) was added, the layers were separated and the aqueous phase was re-extracted with CH_2Cl_2 (2 x 10 ml). The combined organic phases were dried with Na_2SO_4, filtered and the solvent was evaporated. Purification by flash column chromatography (9 g silica, flow rate 20 mL / min, EtOAc / LP, 40 : 60 to 100 : 0 in 30 min) afforded the title compound **257**.

Yield:	20.5 mg, 36 %
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.40 (EtOAc)
[α]$_D^{25}$:	+39.5 (c 0.90, *i*-PrOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 425.1940, found: 425.1958, Δ: 4.21 ppm
(log *P*)$_{calc}$:	2.93 ± 0.42

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36 (bs, 1H, OH), 1.66 (dq, ^2J = 13.4 Hz, ^3J = 6.6 Hz, 1H, C3-CH), 1.87 (dq, ^2J = 14.0 Hz, ^3J = 6.8 Hz, 1H, C3-CH), 2.24 – 2.42 (m, 1H, H3), 2.46 (dd, ^2J = 12.5 Hz, ^3J = 11.4 Hz, 1H, C4-CH), 2.47 – 2.71 (m, 1H, H4), 2.88 (dd, ^2J = 12.6 Hz, ^3J = 3.2 Hz, 1H, C4-CH), 3.67 (t, ^3J = 6.7 Hz, 2H, C3-CH_2C$\underline{H}_2$), 3.80 (dd, ^2J = 8.6 Hz, ^3J = 3.4 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.89 (s, 3H, Ar-OCH_3), 4.01 (dd, ^2J = 8.6 Hz, ^3J = 5.4 Hz, 1H, H5), 4.62 (d, ^3J = 8.3 Hz, 1H, H2), 6.67 – 6.92 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 29.7 (t, C3-C), 33.1 (t, C4-C), 43.3 (d, C4), 47.5 (d, C3), 55.9 (q, 4 x Ar-OCH_3), 61.5 (t, C3-CH_2-C), 72.3 (t, C5), 84.8 (d, C2), 109.3 (d, C2'), 110.9 (d, C5'), 111.3 (d, C5''*), 112.2 (d, C2''*), 118.7 (d, C6'), 120.8 (d, C6''), 133.0 (s, C1''), 135.0 (s, C1'), 147.4 (s, C4''), 148.6 (s, C4'), 148.9 (s, C3''), 149.1 (s, C3').

D.4.5.4 (*Z*)-2-((2*S*,3*S*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)ethyl 2-methylbut-2-enoate (**258**)



257 **258**, $C_{28}H_{36}O_7$, 484.58 g mol^{-1}

***Procedure**:* a reaction vessel was charged with a stirring bar, starting material **257** (17.5 mg, 0.043 mmol, 1.00 equiv.), angelic acid (6.5 mg, 0.065 mmol, 1.50 equiv.) and PPh_3 (39.8 mg, 0.152 mmol, 3.50 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry THF (0.75 mL) was then added and the solution cooled to 0 °C in an ice bath. To the stirred mixture was then added a solution of ADD (38.3 mg, 0.152 mmol, 3.50 equiv.) in dry THF (1.0 mL) *via* syringe over approximately 1 min, and the reaction stirred for 23 h while being kept away from light and allowed to warm slowly to room temperature. Et_2O (5 mL) was then added to the reaction content, which was then filtered and rinsed with more Et_2O (15 mL). The solvents were evaporated and flash column chromatography was performed (9 g silica, flow rate 20 mL / min, EtOAc / heptane, 10 : 90 to 40 : 60 in 30 min), followed by preparative HPLC (flow rate 21.2 mL / min, MeOH / water, 63 : 37 to 70 : 30 in 60 min) to afford the title compound **258**.

Yield:	12.0 mg, 47 %
Appearance:	colorless oil
***R*$_f$ (silica)**:	0.47 (EtOAc)
$[\alpha]_D^{20}$:	+49.9 (c 0.31, MeOH)
LC-HRMS (ESI):	calculated for M+Na^+: 507.2359, found: 507.2365, Δ: 1.25 ppm
(log *P*)$_{calc}$:	5.52 ± 0.47

GC-MS (EI, 70 eV, Method J): 46.61 min; 484.2 (M^+, 20), 205.1 (100), 165.1 (14), 151.0 (58).

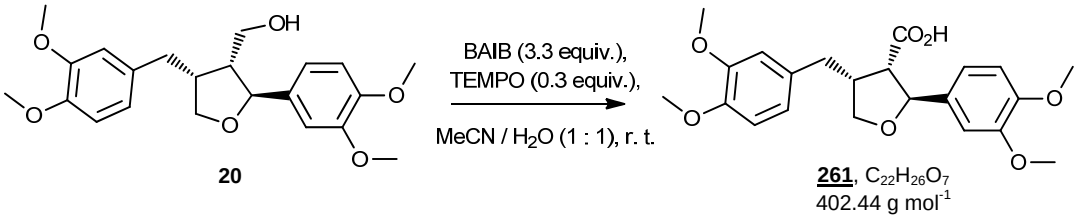
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (dq, ^2J = 13.8 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 1.83 – 1.86 (m, 3H, H5'''), 1.93 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 1.99 (dq, ^2J = 13.8 Hz, ^3J = 6.9 Hz, 1H, C3-CH), 2.25 – 2.35 (m, 1H, H3), 2.49 (dd, ^2J = 13.2 Hz, ^3J = 11.7 Hz, 1H, C4-CH), 2.59 – 2.69 (m, 1H, H4), 2.89 (dd, ^2J = 13.4 Hz, ^3J = 4.2 Hz, 1H, C4-CH), 3.80 (dd, ^2J = 8.7 Hz, ^3J = 3.9 Hz, 1H, H5), 3.87 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.03 (dd, ^2J = 8.7 Hz, ^3J = 5.8 Hz, 1H, H5), 4.19 (dt, ^2J = 11.1 Hz, ^3J = 6.9 Hz, 1H, C3-CH_2-CH), 4.23 (dt, ^2J = 11.1 Hz, ^3J = 6.9 Hz, 1H, C3-CH_2-CH), 4.65 (d, ^3J = 8.0 Hz, 1H, H2),

6.05 (qq, ^{3}J = 7.2 Hz, ^{4}J = 1.4 Hz, 1H, H3'''), 6.71 (d, ^{4}J = 1.9 Hz, 1H, H2''), 6.73 (dd, ^{3}J = 8.1 Hz, ^{4}J = 1.9 Hz, 1H, H6''), 6.81 (d, ^{3}J = 8.1 Hz, 1H, H5''), 6.81 – 6.88 (m, 3H, H2', H5', H6').

^{13}C NMR (100 MHz, $CDCl_3$): δ 15.9 (q, C4'''), 20.7 (q, C5'''), 26.0 (t, C3-C), 33.3 (t, C4-C), 43.0 (d, C4), 47.9 (d, C3), 56.0 (q, Ar-OCH_3), 56.09 (q, Ar-OCH_3), 56.11 (q, Ar-OCH_3), 56.14 (q, Ar-OCH_3), 62.8 (t, C3-CH_2-C), 72.4 (t, C5), 84.8 (d, C2), 109.4 (d, C2'), 111.1 (d, C5'), 111.5 (d, C5''*), 112.3 (d, C2''*), 118.8 (d, C6'), 120.9 (d, C6''), 127.9 (s, C2'''), 132.9 (s, C1''), 135.0 (s, C1'), 138.2 (d, C3'''), 147.6 (s, C4''), 148.8 (s, C4'), 149.1 (s, C3''), 149.3 (s, C3'), 168.1 (s, C1''').

D.4.6 **Ester Inversion**

D.4.6.1 (2*S*,3*S*,4*R*)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-carboxylic acid (**<u>261</u>**)



20 **<u>261</u>**, $C_{22}H_{26}O_7$, 402.44 g mol^{-1}

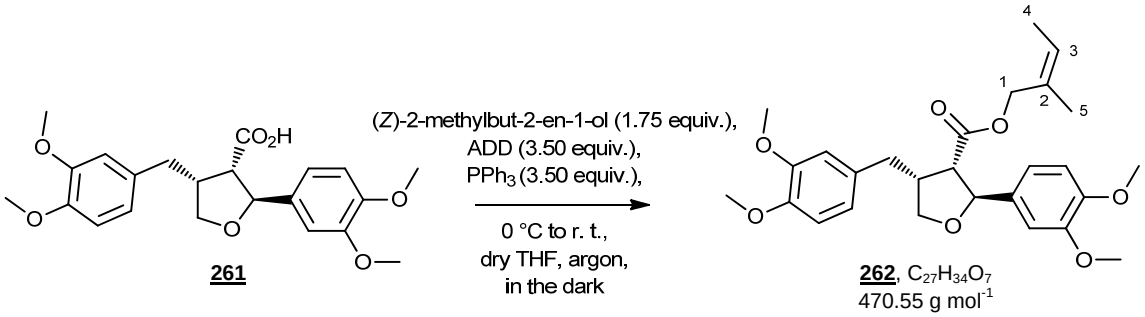
***Procedure**:* a reaction vessel was charged with a stirring bar, starting material **20** (277.3 mg, 0.714 mmol, 1.00 equiv.), MeCN (2.0 mL) and water (2.0 ml). To this stirred mixture was added BAIB (505.8 mg, 1.570 mmol, 2.20 equiv.) in small portions over approximately 30 sec, followed by TEMPO (22.3 mg, 0.143 mmol, 0.20 equiv.) in one go. More MeCN (0.5 mL) was added to flush residual oxidant from the sides of the vessel. The reaction mixture warmed noticeably, and stirring was continued for 80 min at room temperature. More BAIB (252.9 mg, 0.785 mmol, 1.10 equiv.) and TEMPO (11.2 mg, 0.072 mmol, 0.10 equiv.) was added in the same fashion, and stirring was continued for 100 min. Then, Et_2O (5 mL) and heptane (10 mL) were added, followed by a solution of Na_2CO_3 (600 mg) in water (20 mL). The layers were separated and the aqueous phase was treated again (2 x) with a mixture of Et_2O (5 mL) and heptane (10 mL). Then CH_2Cl_2 (15 mL) and aqueous HCl (2 M, 10 ml) were added cautiously, the layers were separated and the aqueous phase was re-extracted with CH_2Cl_2 (2 x 15 mL). To remove residual mineral acid, the combined organic phases were treated with brine (5 mL) to which $NaHCO_3$ (1 spatula) had been added beforehand. After separation of the layers, the pH of the brine layer was adjusted to 6-7 with NH_4Cl and then also extracted with CH_2Cl_2 (15 mL). The combined organic phases were dried with Na_2SO_4, filtered and the solvent was evaporated to afford the title compound **<u>261</u>** in pure form according to NMR without further purification.

Yield:	285 mg, 99 %
Appearance:	colorless oil
R_f (silica):	0.55 (EtOAc / AcOH, 200 : 1)
$[\alpha]_D^{20}$:	+32.4 (c 0.55, MeOH)
LC-HRMS (ESI):	calculated for M+Na$^+$: 425.1576, found: 425.1588, Δ: 2.78 ppm
(log *P*)$_{calc}$:	3.24 ± 0.53

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.63 (dd, ^2J = 14.2 Hz, ^3J = 12.0 Hz, 1H, C4-CH), 2.82 – 3.07 (m, 2H, H4, C4-CH), 3.18 (t, ^3J = 7.6 Hz, 1H, H3), 3.80 – 3.90 (m, 10H, H5, 3 x Ar-OCH_3), 3.87 (s, 3H, Ar-OCH_3), 4.11 (dd, ^2J = 8.6 Hz, ^3J = 6.2 Hz, 1H, H5), 5.29 (d, ^3J = 7.0 Hz, 1H, H2), 6.66 – 6.96 (m, 6H, Ar-H), 11.02 (bs, 1H, CO_2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 34.3 (t, C4-<u>C</u>), 44.2 (d, C4), 56.0 (q, 4 x Ar-OCH_3; d, C3; signal overlap), 72.8 (t, C5), 82.1 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.4 (d, C5''*), 112.0 (d, C2''*), 118.2 (d, C6'), 120.8 (d, C6''), 131.8 (s, C1''), 133.8 (s, C1'), 147.7 (s, C4''), 148.7 (s, C4'), 149.0 (s, C3''), 149.1 (s, C3'), 177.6 (s, C3-<u>C</u>O_2).

D.4.6.2 (2*S*,3*S*,4*R*)-(*Z*)-2-Methylbut-2-en-1-yl 4-(3,4-dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-carboxylate (**262**)



***Procedure**:* a reaction vessel was charged with a stirring bar, starting material **261** (43.0 mg, 0.107 mmol, 1.00 equiv.) and PPh_3 (98.1 mg, 0.374 mmol, 3.50 equiv.), and then evacuated and back-filled with argon using standard Schlenk technique. Dry THF (1.5 mL) and a solution of (*Z*)-2-methylbut-2-en-1-ol **260** (0.154 M in pentane, 1.21 mL, 0.187 mmol, 1.75 equiv.) was added *via* syringe and the solution cooled to 0 °C in an ice bath. To the stirred mixture was then added dropwise a solution of ADD (94.4 mg, 0.374 mmol, 3.50 equiv.) in dry THF (2.0 mL) *via* syringe over approximately 1 min, and the reaction stirred for 16 h while being kept away from light and allowed to warm slowly to room temperature. Then, Et_2O (5 mL) was added to the reaction content, which was then filtered and rinsed with more Et_2O (20 mL) The solvents were evaporated and flash column chromatography was performed (9 g silica, flow rate 20 mL / min, EtOAc / heptane, 10 : 90 to 50 : 50 in 40 min), followed by preparative HPLC (flow rate 21.2 mL / min, MeCN / water, 50 : 50 isocratically for 20 min, then to 53 : 47 in 40 min) to afford the title compound **262**.

Yield:	27.7 mg, 55 %
Appearance:	colorless crystals
Melting range:	97.0 – 98.0 °C
R_f **(silica)**:	0.40 (EtOAc / heptane, 1 : 1)
$[\alpha]_D^{25}$:	+26.3 (c 0.79, MeOH)
LC-HRMS (ESI):	calculated for $M+Na^+$: 493.2202, found: 493.2215, Δ: 2.60 ppm
(log *P*)$_{calc}$:	5.45 ± 0.52

GC-MS (EI, 70 eV, Method I): 34.75 min; 470.3 (M^+, 4), 401.2 (24), 194.1 (19), 177.1 (16), 166.1 (14), 165.1 (100), 151.1 (52).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 (d, ^3J = 6.8 Hz, 3H, H4'''), 1.74 (s, 3H, H5'''), 2.59 (dd, ^2J = 13.4 Hz, ^3J = 11.2 Hz, 1H, C4-CH), 2.81 (dd, ^2J = 13.6 Hz, ^3J = 4.8 Hz, 1H, C4-CH), 2.86 – 2.97 (m, 1H, H4), 3.13 (t, ^3J = 8.0 Hz, 1H, H3), 3.80 – 3.85 (m, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 9H, Ar-OCH_3), 4.04 – 4.11 (m, 1H, H5), 4.64 (d, ^2J = 12.6 Hz, 1H, H1'''), 4.66 (d, ^2J = 12.6 Hz, 1H, H1'''), 5.27 (d, ^3J = 7.3 Hz, 1H, H2), 5.50 (q, ^3J = 6.7 Hz, 1H, H3'''), 6.66 – 6.74 (m, 2H, H2'', H6''), 6.77 – 6.85 (m, 2H, H5'', Ar'-H), 6.86 – 6.92 (m, 2H, Ar'-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (q, C4'''), 21.7 (q, C5'''), 34.4 (t, C4-C), 44.5 (d, C4), 56.0 (q, 4 x Ar-OCH_3), 56.3 (d, C3), 63.4 (t, C1'''), 73.0 (t, C5), 82.4 (d, C2), 109.0 (d, C2'), 111.2 (d, C5'), 111.4 (d, C5''*), 112.1 (d, C2''*), 118.1 (d, C6'), 120.7 (d, C6''), 125.8 (d, C3'''), 130.2 (s, C2'''), 132.2 (s, C1''), 134.3 (s, C1'), 147.7 (s, C4''), 148.7 (s, C4'), 149.1 (s, C3''), 149.1 (s, C3'), 172.2 (s, C3-CO_2).

D.5 Pharmacological Evaluation

This section contains the materials and methods which were used in the cell-based *in vitro* assays for the pharmacological evaluation of leoligin and its (synthetic) analogs. These assays and the statistical calculations were conducted by Dr. Atanas G. Atanasov and co-workers of the Molecular Targets Group (headed by Prof. Verena M. Dirsch) at the Department of Pharmacognosy, Faculty of Life Sciences, at the University of Vienna.

D.5.1 Macrophage Cholesterol Efflux Assay

For quantification of the cholesterol efflux enhancing-ability of the compounds to be tested, THP-1 cells were used. They were cultured in RPMI-1640 medium supplemented with penicillin (100 U / mL), L-glutamine (2 mM), streptomycin (100 µg / mL) and heat-inactivated FBS (10 %). The cells were differentiated in 24 well-plates (0.2×10^6 viable cells per mL; 1 mL suspension per well) with PMA (200 nM) for 72 h. After washing twice with PBS, the cells were labeled with [^{3}H]-cholesterol (0.2 µCi / mL) and unesterified cholesterol (20 µg / mL) for 24 h in the presence of the compounds to be tested in serum-free medium with BSA (0.1 %). Pioglitazone was used as a positive control, and the solvent vehicle (0.1 % DMSO) as a negative control. Thereafter, the cells were washed twice with PBS and the medium replaced with serum-free medium again which contained identical treatments in the presence or absence of apoAI (10 µg / mL). After 6 h, the medium was removed and centrifuged (500 g, 5 min), followed by lysing with NaOH (0.1 M) and the radioactivity was measured. Cholesterol efflux was calculated by dividing the radioactivity in the media by the sum of the radioactivity in both the media and the cells. The specific apoAI-mediated efflux was calculated as the difference between the efflux in the presence *vs.* absence of apoAI.

D.5.2 ABCA1 Expression Quantification

For protein extraction and western blotting, THP-1 cells (differentiated as described in section D.5.1) were treated with solvent vehicle (DMSO) or the compounds to be tested, and then incubated for 24 h. Following this, the cells were lysed using NP40 lysis buffer (150 mM NaCl, 50 mM HEPES at pH 7.4, 1 % NP40, 1 % protease inhibitor Complete (Roche), 1 % PMSF, 0.5 % Na_3VO_4 and 0.5 % NaF) for 30 min on ice. Total protein content in the lysates was quantified by Bradford assay; for SDS-PAGE, 20 µg of protein was loaded per lane and then resolved. Immunoblotting was used for visualization of ABCA1, using specific antibodies, ECL reagent, and an LAS-3000 luminescent image analyzer (Fujifilm) with AIDA image analyzer software (version 4.06, Raytest).

D.5.3 NF-κB Activity and Cell Viability Assay

As described previously,[325] HEK293/NF-κB-luc cells (RC0014, Panomics) were cultured at 37 °C and under CO_2 atmosphere (5 %) in DMEM, supplemented with hygromycin B (100 µg / mL), benzylpenicillin (100 U / mL), streptomycin (100 µg / mL), L-glutamine (2 mM) and FBS (10 %). The cells were stained for 1 h in serum-free medium supplemented with Cell Tracker Green CMFDA (C2925, 2 µM, Invitrogen; as this fluorescent probe is retained inside living cells, it was used to monitor cell membrane integrity to quantify the number of viable cells).[325-326] Then, the cells were re-seeded in 96-well plates (4×10^4 cells per well) in phenol red-free and FBS-free DMEM overnight. After that, the cells were pre-treated with the compounds to be tested or with the solvent vehicle DMSO (0.1 % in culture medium) for 30 min and subsequently stimulated with TNFα (2 ng / mL) for 4 h. The cells were then lysed in a luciferase lysis buffer (E1531, Promega) and the luminescence of

the firefly luciferase and the fluorescence of the Cell Tracker Green CMFDA were quantified (excitation wavelength: 485 nm; emission wavelength: 520 nm) with a Tecan GENios Pro plate reader (Tecan Group Ltd.). For quantification of the NF-κB activity, the luciferase-derived signal of the NF-κB reporter was normalized by the Cell Tracker Green CMFDA-derived fluorescence, accounting for differences in the cell number. Potential differences in cell viability were detected by comparing the Cell Tracker Green CMFDA fluorescence of the solvent vehicle-treated cells and the cells treated with the compounds to be tested. Parthenolide (as a known NF-κB inhibitor) was used as a positive control.

D.5.4 **SMC Proliferation Assay**

Viable rat aortic SMCs (0.5×10^4 cells per well) were seeded in SMC growth medium (DMEM/F12 medium containing serum (20 %), gentamicin (30 µg / mL) and amphotericin (15 ng / mL)) in 96-well plates. After 24 h, the medium was removed, the cells were washed once with SMC starvation medium (DMEM/F12 medium containing serum (0.1 %), BSA (0.2 %), gentamicin (30 µg / mL) and amphotericin (15 ng / mL)) and incubated in starvation medium for another 24 h. The quiescent cells were then pre-treated for 30 min with the compounds to be tested and then induced to proliferate with PDGF (20 ng / mL). Unstimulated cells were used for normalization and assessing of the basal level of proliferation. The final concentration of the solvent vehicle DMSO was identical (0.1 %) in all wells. 48 h on, SMC proliferation was quantified by conversion of resazurin dye for 2 h. The fluorescence was measured at 580 nm, with excitation at 535 nm in a Tecan GENios Pro plate reader (Tecan Group Ltd.) as described previously.[327]

D.5.5 **EC Proliferation Assay**

Human umbilical vein ECs (0.5×10^4 cells per well; immortalized[328] as described) were seeded in 96-well plates for 24 h in HUVEC Complete Medium (200 µL per well, EBM growth medium supplemented with FBS (10 %), EBM SingleQuots (Lonza), benzylpenicillin (100 U / mL), streptomycin (100 µg / mL), and amphotericin (1 %)). Then the medium was exchanged with fresh HUVEC Complete Medium and the cells were treated with the compounds to be tested for 48 h. Then the medium was removed, the cells were washed once with PBS (200 µL) and treated with HUVEC Complete Medium (150 µL), containing resazurin (10 µg / mL), for 2 h. The fluorescence was measured at 580 nm, with excitation at 535 nm in a Tecan GENios Pro plate reader (Tecan Group Ltd.) as described previously.[327]

D.5.6 **SMC Cytotoxicity Assay**

Rat aortic SMCs (5×10^3 cells per well) were seeded in 96-well plates. After 24 h, the cells were serum-starved for another 24 h to render them quiescent. The cells were then pre-treated for 30 min with the compounds to be tested or with the solvent vehicle DMSO (0.1 %), and then stimulated for 24 h with PDGF-BB (20 ng / mL). The loss of cell membrane integrity as an indication of cell death[305-306] was then quantified by the release of LDH. For this, the supernatant of the cells was assessed for LDH activity. For assessment of total LDH activity, identically treated samples were incubated for 45 min in the presence of Triton X-100 (1 %). Enzyme activity in both cases was measured for 30 min in the presence of L-lactic acid (4.5 mg / mL), NAD^+ (0.56 mg / mL), diaphorase (1.69 U / mL), BSA (0.004 w/v %), D-sucrose (0.15 w/v %) and INT (0.5 mM) in the dark. Enzyme activity was halted with oxamic acid (1.78 mg / mL) and the absorbance was measured at 490 nm. Effects on cell viability

were calculated as percentage of extracellular LDH enzyme activity. Digitonin (50 µg / mL) was used as a positive control.

D.5.7 **Statistical Analysis**

Statistical analysis was conducted with the ANOVA / Bonferroni test for significance determination, using GraphPad PRISM (version 4.03, GraphPad Software Inc.).

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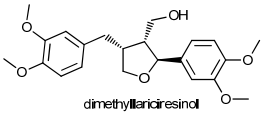
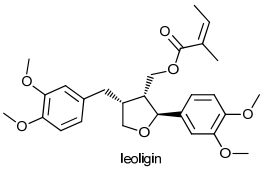
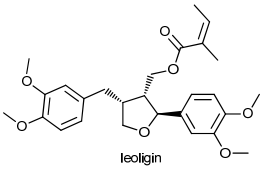
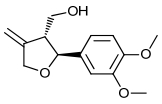
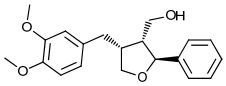
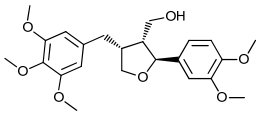
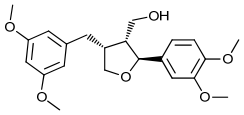
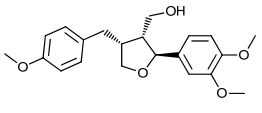
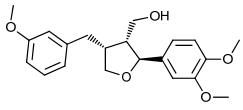
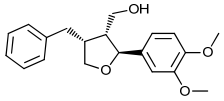
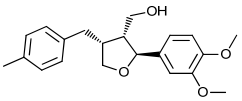
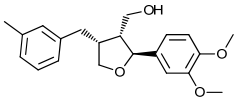
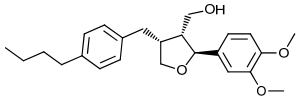
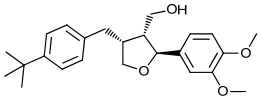
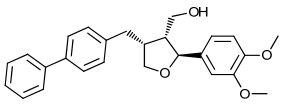
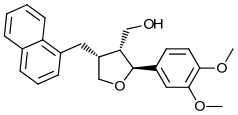
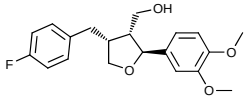
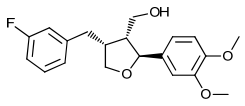
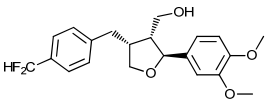
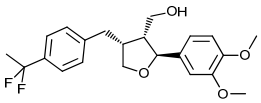
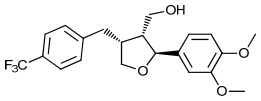
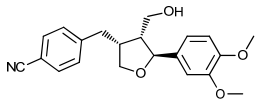
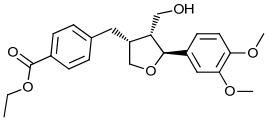
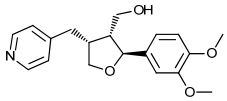
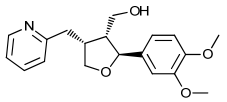
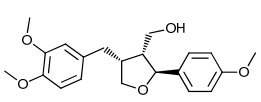
Appendix

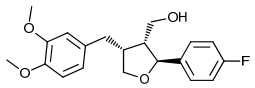
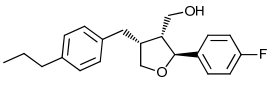
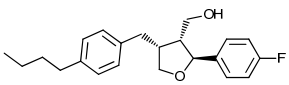
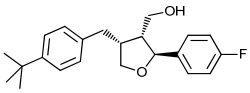
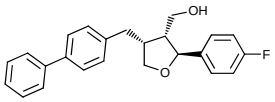
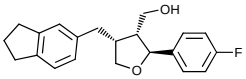
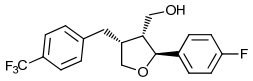
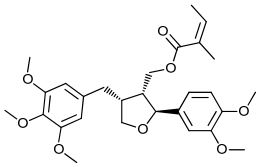
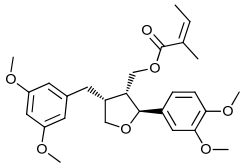
Complete dataset of the pharmacological evaluation of furan-type lignans

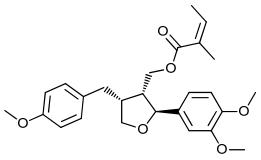
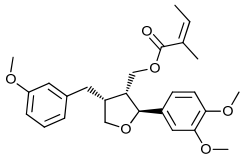
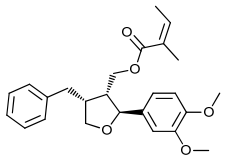
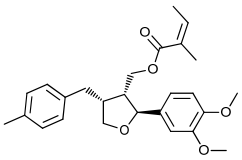
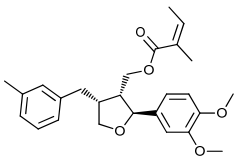
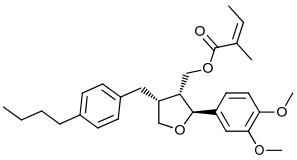
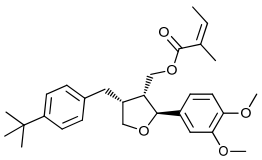
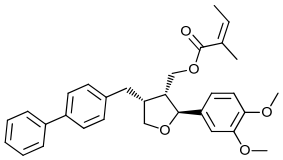
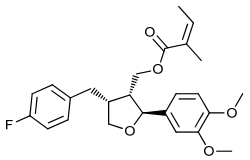
List:

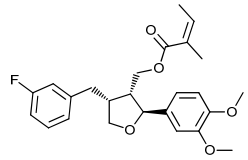
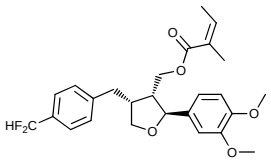
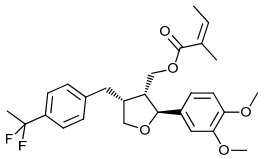
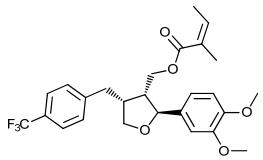
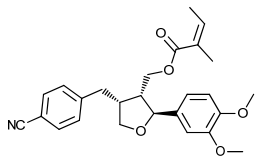
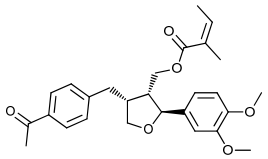
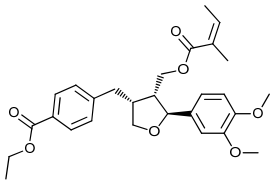
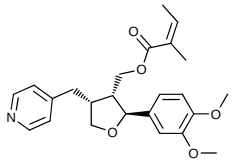
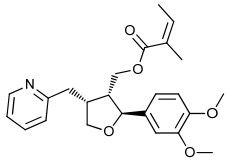
Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
 dimethyllariciresinol	**20**	**≥ 30**						
 leoligin	**59**	**32.1**	**51 ± 5 ***** **55 ± 6 *****	**19.7**	**87 ± 3**[e]	**2.53 ± 0.15 *****	**1.00**[h]	**3.1 ± 0.7 n.s.**
 leoligin	**59** (natural)[l]	**27.7**		**22.7**	**96 ± 1**[e]			
	**106**	**≥ 30**		**≥ 20**	**n/c**			
	**123**	**≥ 30**		**≥ 20**	**94 ± 7**			
	**125**	**≥ 30**		**≥ 20**	**112 ± 13**			
	**126**	**≥ 30**		**≥ 20**	**98 ± 6**			
	**127**	**≥ 30**		**≥ 20**	**101 ± 2**			

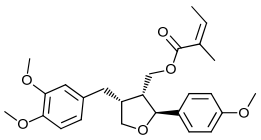
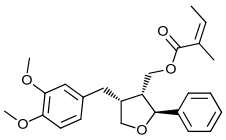
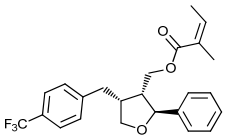
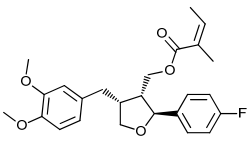
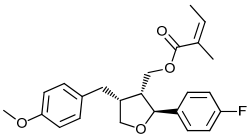
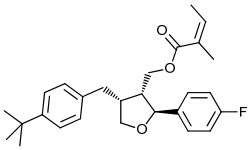
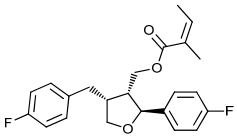
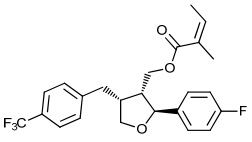
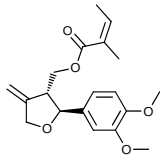
Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	**128**	≥ 30		≥ 20	111 ± 7			
	**129**	≥ 30		≥ 20	85 ± 9			
	**130**	≥ 30	101 ± 11 n.s.	≥ 20	98 ± 7			
	**131**	≥ 30		≥ 20	110 ± 16			
	**132**	9.5	80 ± 12 n.s.	9.4	83 ± 3			
				12.5	97 ± 2			
	**133**	5.0	50 ± 11 ***	≥ 20	104 ± 5			14.1 ± 7.1 n.s.
	**134**	40.7	37 ± 11 ***	≥ 20	100 ± 5			
	**135**	≥ 30	88 ± 6 n.s.	≥ 20	117 ± 8			
	**136**	≥ 30		≥ 20	100 ± 7			

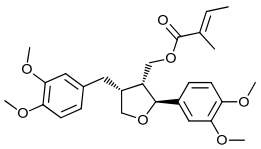
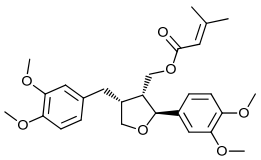
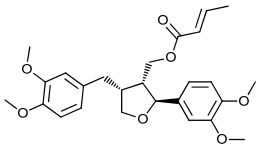
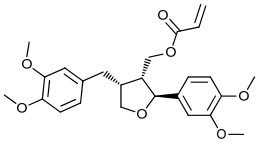
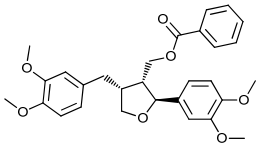
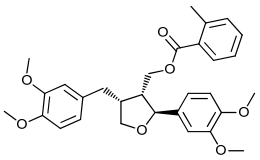
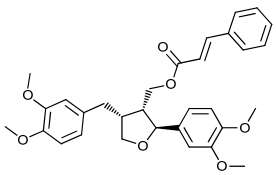
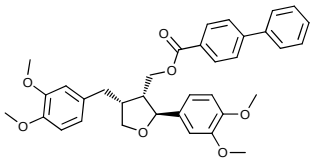
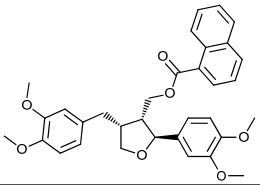
Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	**137**	≥ 30		≥ 20	87 ± 16			
	**138**	≥ 30		≥ 20	106 ± 3			
	**139**	≥ 30	93 ± 1 n.s.	≥ 20	109 ± 3			
	**140**	≥ 30	85 ± 7 n.s.	≥ 20	103 ± 4			
	**141**	≥ 30		≥ 20	112 ± 17			
	**143**	≥ 30		≥ 20	105 ± 6			
	**144**	≥ 30		≥ 20	124 ± 16			
	**145**	≥ 30		≥ 20	101 ± 16			
	**146**	≥ 30		≥ 20	95 ± 1			

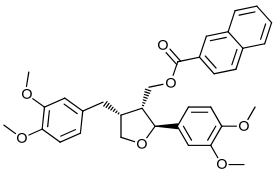
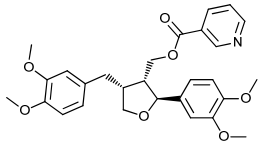
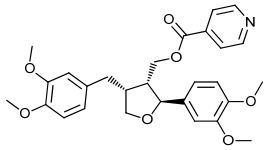
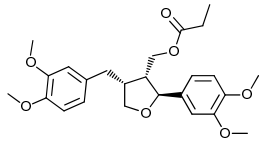
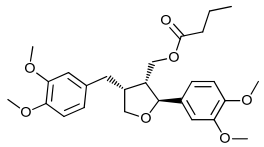
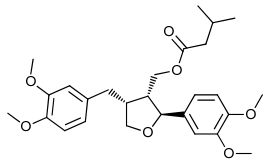
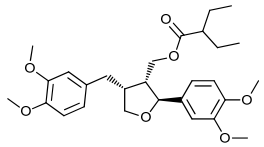
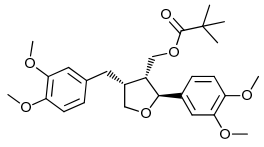
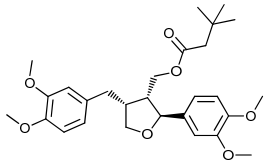
Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	**148**	≥ 30		≥ 20	91 ± 11			
	**150**	-149 ± 15[c] ***[a]						
	**151**	-172 ± 3[c] ***[a]						
	**152**	-172 ± 3[c] ***[a]						
	**153**	≥ 30		≥ 20	96 ± 6			
	**154**	-70 ± 36[c] ***[a]						
	**156**	10.9		≥ 20	94 ± 4			
	**177**	13.5						
	**178**	19.4	60 ± 11 **	4.7 5.7	92 ± 2 105 ± 11		1.05 ± 0.03	

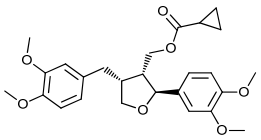
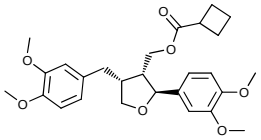
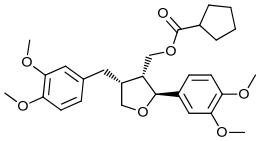
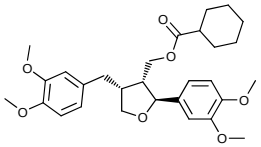
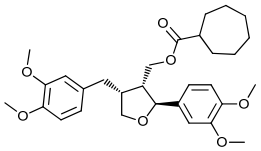
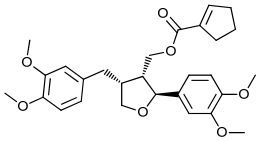
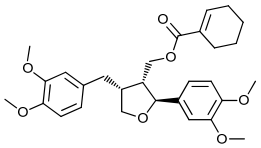
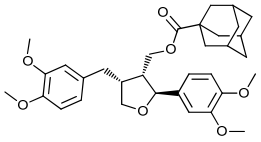
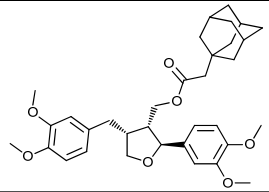
Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	179	23.9	29 ± 6 ***	5.8 9.9	98 ± 5 93 ± 1	2.60 ± 0.24 ***	0.84 ± 0.24	
	180	≥ 30	16 ± 7 ***	8.6	80 ± 11	2.55 ± 0.08 ***	1.00 ± 0.27	
	181	28.4	18 ± 0 ***	6.1 5.8	87 ± 6 70 ± 14	1.99 ± 0.05 ***	1.22 ± 0.71	
	182	≥ 30	34 ± 2 ***	7.9	72 ± 6	2.68 ± 0.09 ***	1.20 ± 0.25	
	183	≥ 30		4.1	106 ± 3			
	184	13.4	99 ± 7 n.s.	≥ 20	90 ± 5			7.2 ± 2.7 n.s.
	185	3.2	54 ± 2 *** 67 ± 8 **	≥ 20	68 ± 17	1.61 ± 0.22 n.s.	1.20 ± 0.22	16.3 ± 7.4 n.s.
	186	≥ 30		≥ 20	95 ± 26			
	187	26.0	16 ± 3 ***	4.3	81 ± 13	2.30 ± 0.16 ***	0.96 ± 0.03	

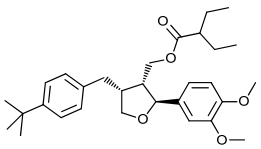
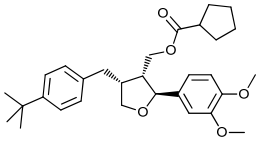
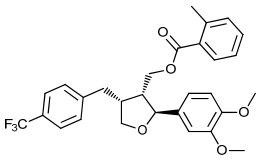
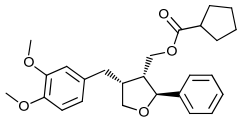
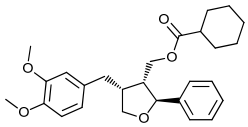
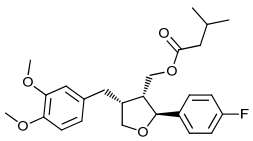
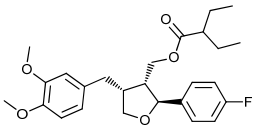
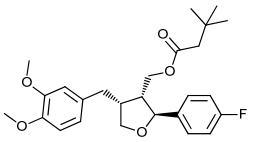
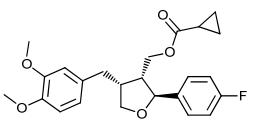
Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	188	≥ 30	38 ± 5 ***	10.5	83 ± 7			
	189	15.0	48 ± 1 ***	7.7 10.7	114 ± 12 100 ± 1		1.16 ± 0.39	
	190	8.8	67 ± 4 *	4.3	102 ± 1		1.22 ± 0.40	
	191	20.1	51 ± 9 ***	≥ 20	84 ± 17	3.14 ± 0.20 ***	1.22 ± 0.31	4.0 ± 1.1 n.s.
	192	31.0	8 ± 1 ***	9.8 9.9	92 ± 1 91 ± 2			
	193	≥ 30	39 ± 4 ***	14.0	98 ± 2			
	194	31.0	69 ± 2 *	≤ 20 ≥ 20	107 ± 36 93 ± 4			
	195	≥ 30		≥ 20	88 ± 22	1.43 ± 0.05 n.s.	0.84 ± 0.17	
	196	≥ 30	94 ± 5 n.s.	≥ 20 ≤ 20	99 ± 18 94 ± 3			

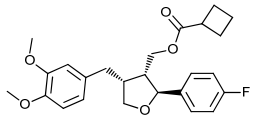
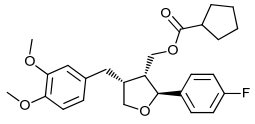
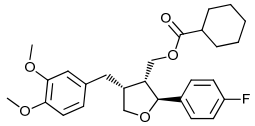
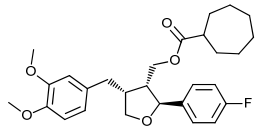
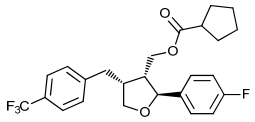
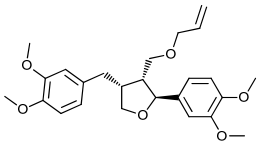
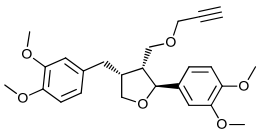
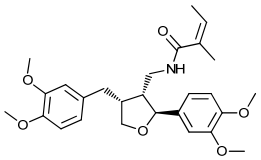
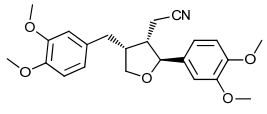
Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	**197**	10.0	61 ± 8 n.s.	7.7	100 ± 2		1.21 ± 0.34	
	**198**	19.8 20.7	37 ± 5 ***	4.2	93 ± 14	1.78 ± 0.20 **	1.06 ± 0.21	
	**199**	4.2	104 ± 4 n.s.	≥ 20	85 ± 18			6.0 ± 2.4 n.s.
	**200**	8.9 5.4	49 ± 7 ***	≥ 20 10.2	66 ± 8 88 ± 7	1.94 ± 0.10 ***	1.11 ± 0.57	
	**201**	≥ 30	81 ± 8 n.s.	≥ 20	119 ± 27			
	**202**	4.9	102 ± 7 n.s.	≥ 20	95 ± 10			41.4 ± 3.7 ***
	**203**	4.7	105 ± 5 n.s.	≥ 20	86 ± 12			5.9 ± 3.5 n.s.
	**204**	1.9 4.0	102 ± 3 n.s.	≥ 20	90 ± 22			6.0 ± 1.4 n.s.
	**205**	10.3	62 ± 10 ***	≥ 20	100 ± 8	1.37 ± 0.15 n.s.	1.24 ± 0.20	41.0 ± 25.0 ***

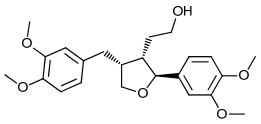
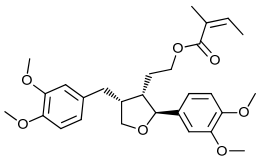
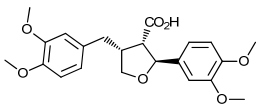
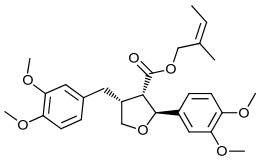
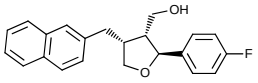
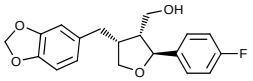
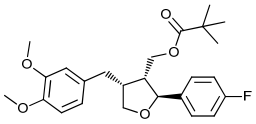
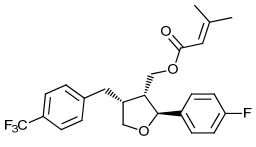
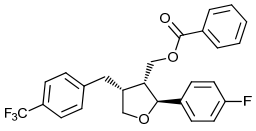
Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	206	20.4	68 ± 10 n.s.	≥ 20	107 ± 0	1.42 ± 0.09 n.s.	0.92 ± 0.07	
	207	34.3	79 ± 10 n.s.	5.3	108 ± 5	1.53 ± 0.20 n.s.	1.51 ± 0.45	
	208	29.9	91 ± 8 n.s.	7.0	106 ± 3			
	209	3.4	0 ± 0 ***	6.2	98 ± 3			71.2 ± 5.2 ***
	210	60.3	35 ± 4 ***	≥ 20 12.7	80 ± 10 91 ± 10	1.39 ± 0.10 n.s.	0.75 ± 0.19	
	211	≥ 30	42 ± 11 ***	≤ 20 ≥ 20	113 ± 28 98 ± 1	2.49 ± 0.21 ***	1.05 ± 0.23	
	212	32.8	83 ± 2 n.s.	≥ 20	74 ± 17			
	213	≥ 30		≥ 20	100 ± 26			
	214	≥ 30		≥ 20	168 ± 61		1.50 ± 0.50	

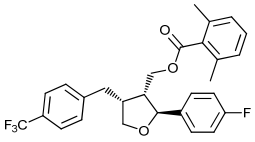
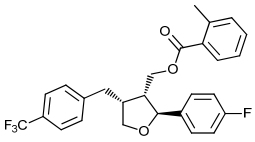
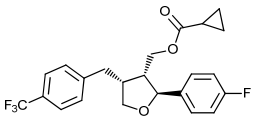
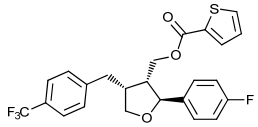
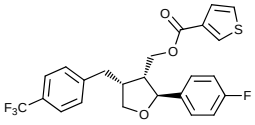
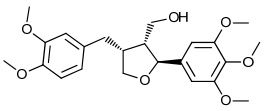
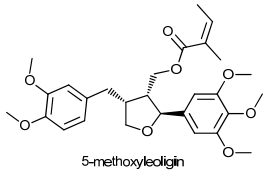
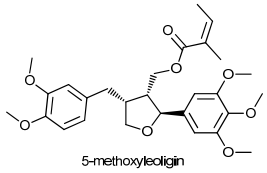
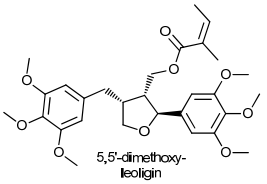
Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	**215**	≥ 30	62 ± 6 ** 55 ± 18 ***	≥ 20	143 ± 59			
	**216**	≥ 30		≥ 20	97 ± 14			
	**217**	≥ 30		13.1	101 ± 9			
	**218**	≥ 30		10.7	104 ± 6			
	**219**	≥ 30		6.3	61 ± 7			
	**220**	31.0	52 ± 7 ***	4.4 4.8	119 ± 6 99 ± 1			
	**221**	18.3	43 ± 7 ***	5.1 4.6	105 ± 6 72 ± 8			
	**222**	24.3	53 ± 5 *** 38 ± 4 ***	2.2	84 ± 7			
	**223**	23.6	39 ± 11 ***	5.2 4.3	103 ± 0 67 ± 10			

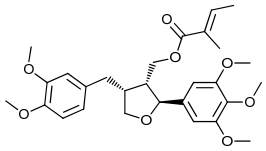
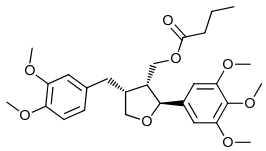
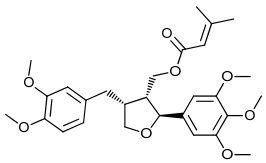
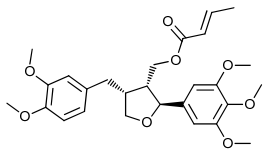
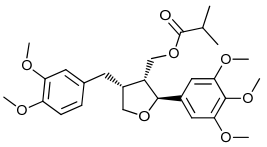
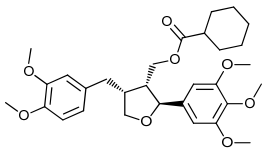
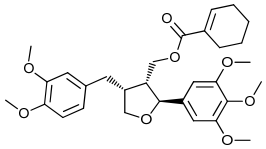
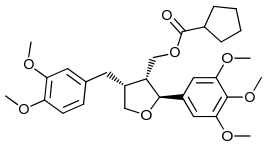
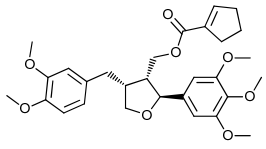
Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	**224**	71.1	55 ± 8 ***	9.6	70 ± 10	1.20 ± 0.21 n.s.	0.67 ± 0.15	
	**225**	≥ 30	49 ± 6 ***	6.4	75 ± 1			
	**226**	9.8 17.5	43 ± 5 ***	8.0	85 ± 7			
	**227**	11.4	34 ± 4 ***	3.2	93 ± 8	1.19 ± 0.08 n.s.	0.63 ± 0.12	
	**228**	10.3	35 ± 8 ***	1.6	87 ± 4			
	**229**	15.9	29 ± 4 ***	6.5	98 ± 2			
	**230**	13.0	33 ± 8 ***	5.1 4.7	103 ± 2 99 ± 6			
	**231**	15.3	39 ± 2 ***	≥ 20	117 ± 17			
	**232**	≥ 30	91 ± 2 n.s.	≥ 20	180 ± 59			

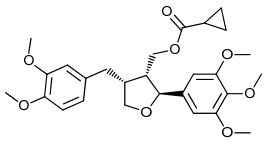
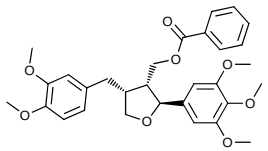
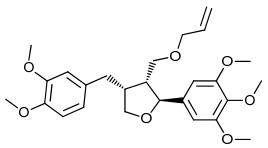
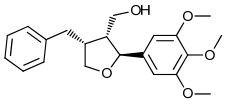
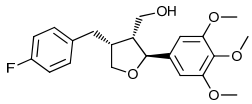
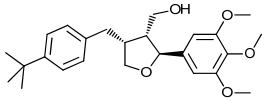
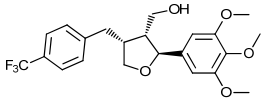
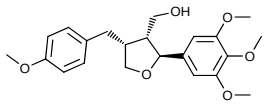
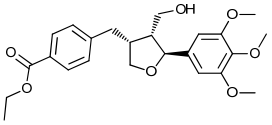
Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	**233**	≥ 30	84 ± 3 n.s.	≥ 20	107 ± 18			
	**234**	3.4 14.6	43 ± 14 *** 60 ± 4 ***	≥ 20 ≥ 20 15.5	134 ± 38 89 ± 19 104 ± 15			14.1 ± 7.0 n.s.
	**235**	≥ 30	90 ± 5 n.s.	≥ 20	123 ± 31		1.02 ± 0.20	
	**236**	20.7	68 ± 9 **	5.7	87 ± 12			
	**237**	14.6	68 ± 14 *	6.5 5.3	96 ± 3 100 ± 3			
	**238**	10.4	93 ± 10 n.s.	4.3	91 ± 3			7.7 ± 2.7 n.s.
	**239**	≥ 30	75 ± 11 n.s.	5.3	94 ± 12			
	**240**	13.2	55 ± 10 *	3.7	101 ± 2			
	**241**	≥ 30	62 ± 8 n.s.	≥ 20	93 ± 7			

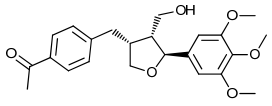
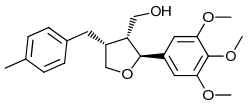
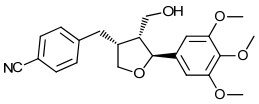
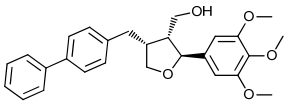
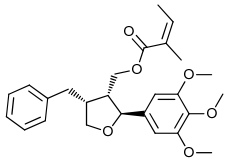
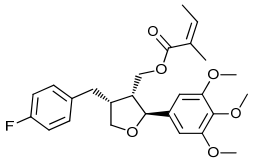
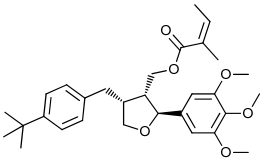
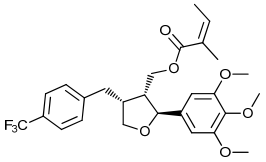
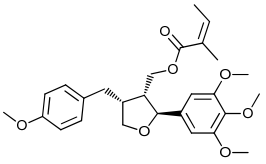
Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	**242**	32.0	113 ± 10 n.s.	5.2	85 ± 16			
	**243**	18.7	60 ± 9 ***	3.9	79 ± 16			
	**244**	≥ 30	51 ± 9 ***	6.3 5.7	83 ± 2 87 ± 1			
	**245**	≥ 30		≤ 20 ≥ 20	104 ± 15 93 ± 1			
	**246**	17.6		≥ 20	97 ± 6			
	**250**	27.8	101 ± 6 n.s.	≥ 20	79 ± 12			
	**251**	34.6	78 ± 5 n.s.	≥ 20	95 ± 4			
	**254**	≥ 30		≥ 20	78 ± 15	1.68 ± 0.24 n.s.		
	**256**	≥ 30		≥ 20	78 ± 19			

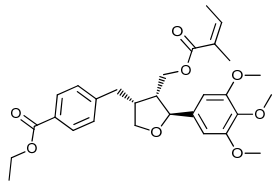
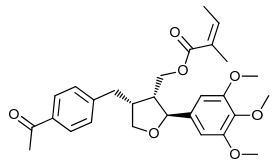
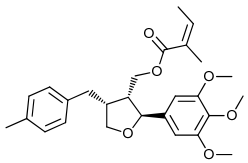
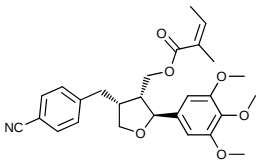
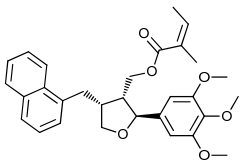
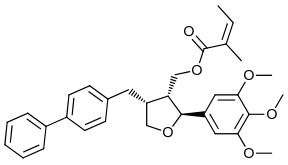
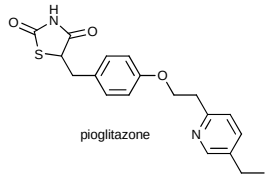
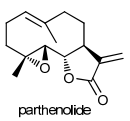
Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	**257**	≥ 30	111 ± 1 n.s.	≥ 20	74 ± 17			
	**258**	≥ 30						
	**261**	≥ 30						
	**262**	8.3						
	**KH-85**	-149 ± 7[c] ***[a]						
	**KH-86 A**	≥ 30						
	**KH-97**	12.9						
	**KH-99 A**	4.4						
	**KH-101**	12.1						

Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	**KH-102**	**≥ 30**						
	**KH-103**	**7.5**						
	**KH-104**	**-131 ± 8**[c] *******[a]						
	**KH-105**	**18.8**						
	**KH-106**	**5.7**						
	**SOGE-8**	**≥ 30**		**≥ 20**	**103 ± 2**			
 5-methoxyleoligin	**60**, **SOGE-9**	**15.1**	**80 ± 9 n.s.**	**≥ 20**	**85 ± 21**			
 5-methoxyleoligin	**60**, **SOGE-9** (natural)[l]			**10.6**	**105 ± 3**	**1.39 ± 0.20 n.s.**		
 5,5'-dimethoxy-leoligin	**61** (natural)[l]			**15.4**	**109 ± 6**	**2.16 ± 0.12 *****		

Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	SOGE-10	24.2	107 ± 6 n.s.	≥ 20	96 ± 3			
	SOGE-11	≥ 30	104 ± 6 n.s.	≥ 20	99 ± 3			
	SOGE-12	≥ 30	98 ± 6 n.s.	≥ 20	100 ± 3			
	SOGE-13	≥ 30		≥ 20	97 ± 6			
	SOGE-14	30.0	99 ± 12 n.s.	≥ 20	95 ± 5			
	SOGE-16	14.4	57 ± 11 ***	7.3	95 ± 3			
	SOGE-17	18.0	52 ± 5 ***	≥ 20	95 ± 6			
	SOGE-18	11.6 22.1	77 ± 6 n.s.	9.3	102 ± 6			6.2 ± 2.8 n.s.
	SOGE-19	12.6	71 ± 2 *	≤ 20 ≥ 20	121 ± 28 89 ± 6			

Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	SOGE-20	11.7	80 ± 11 n.s.	≥ 20	88 ± 9			
	SOGE-21	18.9	67 ± 7 ***	≤ 20 ≥ 20	127 ± 28 95 ± 4			
	SOGE-22	≥ 30		≥ 20	126 ± 43			
	SOGE-24	≥ 30	97 ± 5 n.s.	≥ 20	109 ± 12			
	SOGE-25	≥ 30		≥ 20	106 ± 0			
	SOGE-26	15.8	51 ± 8 ***	≥ 20	105 ± 1			5.8 ± 1.3 n.s.
	SOGE-27	≥ 30	99 ± 15 n.s.	≥ 20	105 ± 1			
	SOGE-28	≥ 30		≥ 20	106 ± 4			
	SOGE-29	≥ 30		≥ 20	99 ± 10			

Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	SOGE-31	≥ 30		≥ 20	97 ± 9			
	SOGE-32	≥ 30		≥ 20	96 ± 7			
	SOGE-33	≥ 30		≥ 20	101 ± 10			
		11.0	81 ± 12 n.s.	≥ 20	100 ± 2			5.8 ± 3.8 n.s.
	SOGE-35	16.7		9.1	92 ± 6			
				9.2	74 ± 9			
	SOGE-36	≥ 30	41 ± 4 ***	≥ 20	100 ± 5			
	SOGE-37	≥ 30	37 ± 6 ***	19.0	104 ± 5			
	SOGE-38	19.6	81 ± 6 n.s.	≥ 20	144 ± 60			
	SOGE-39	≥ 30	54 ± 12 ***	≥ 20	100 ± 7			
	SOGE-40	24.7	44 ± 9 ***	≥ 20	97 ± 6			

Chemical Structure	Cmpd.[j, k]	SMC inhibition: IC_{50} / µM	EC inhibition: residual signal / %[a, b]	NF-κB inhibition: IC_{50} / µM	NF-κB inhibition: viability signal / %[d]	MCE enhancement: fold increase[a, f]	ABCA1 enhancement: protein expression[g]	SMC cytotoxicity: extracellular LDH / %[i]
	**SOGE-41**	**≥ 30**	**77 ± 5 n.s.**	**10.4**	**95 ± 4**			
	**SOGE-43**	**≥ 30**	**83 ± 6 n.s.**	**≥ 20**	**93 ± 10**			
	**SOGE-44**	**27.5**	**43 ± 6 *****	**10.5**	**97 ± 2**			
	**SOGE-45**	**≥ 30**	**54 ± 14 *****	**≥ 20**	**86 ± 27**			
	**SOGE-46**	**≥ 30**	**31 ± 5 *****	**6.1**	**89 ± 5**			
	**SOGE-47**	**≥ 30**		**≥ 20**	**150 ± 65**			
	**267**[l, m]					**2.04 ± 0.13 *****		
	**268**[l, m]			**1.7**				

pioglitazone

parthenolide

Notes:

[a]ANOVA / Bonferroni (***: $p < 0.001$; **: $p < 0.01$; *: $p < 0.05$; n.s.: not significant).

[b]Single-dose value, measured at 30 µM: given is the residual signal (of compound-treated cells ± standard error of the mean) in % relative to untreated (100 %) cells.

[c]IC_{50} was not determined; single-dose value only, measured at 30 µM: given is the residual signal (of PDGF-stimulated and compound-treated cells ± standard deviation) in % relative to unstimulated (100 %) and stimulated but untreated (0 %) cells. This means that 50 % of residual signal would correspond to IC_{50} = 30.0 µM; a lower residual signal value would mean a lower IC_{50}, a higher residual signal value a higher IC_{50}. This was done in order to account for variations in basal proliferation, *cf.* section B.2.3 (page 106). Negative values suggest a toxic effect.

[d]Single-dose value, measured at 20 µM: given is the viability signal (of stimulated and compound-treated cells ± standard error of the mean) in % relative to stimulated but untreated (100 %) cells.

[e]Measured at 30 µM.

[f]Single-dose value, measured at 10 µM: given is the fold increase of (MCE) macrophage cholesterol efflux (activation of compound-treated cells ± standard error of the mean) relative untreated (1.00) cells. Shown is the mean value over all available data for a given compound. For variations between assay rounds and the resulting limited comparability, *cf.* section B.2.1 (page 94).

[g]Single-dose value, measured at 5 µM: given is the effect on ABCA1 protein expression (activation of compound-treated-cells ± standard deviation) relative to leoligin-treated (1.00) cells.

[h]Reference value at 5 µM.

[i]Single-dose value, measured at 30 µM: given is the ratio of extracellular lactate dehydrogenase (of compound-treated cells ± standard deviation) in % relative to untreated (≤ 5 %) cells.

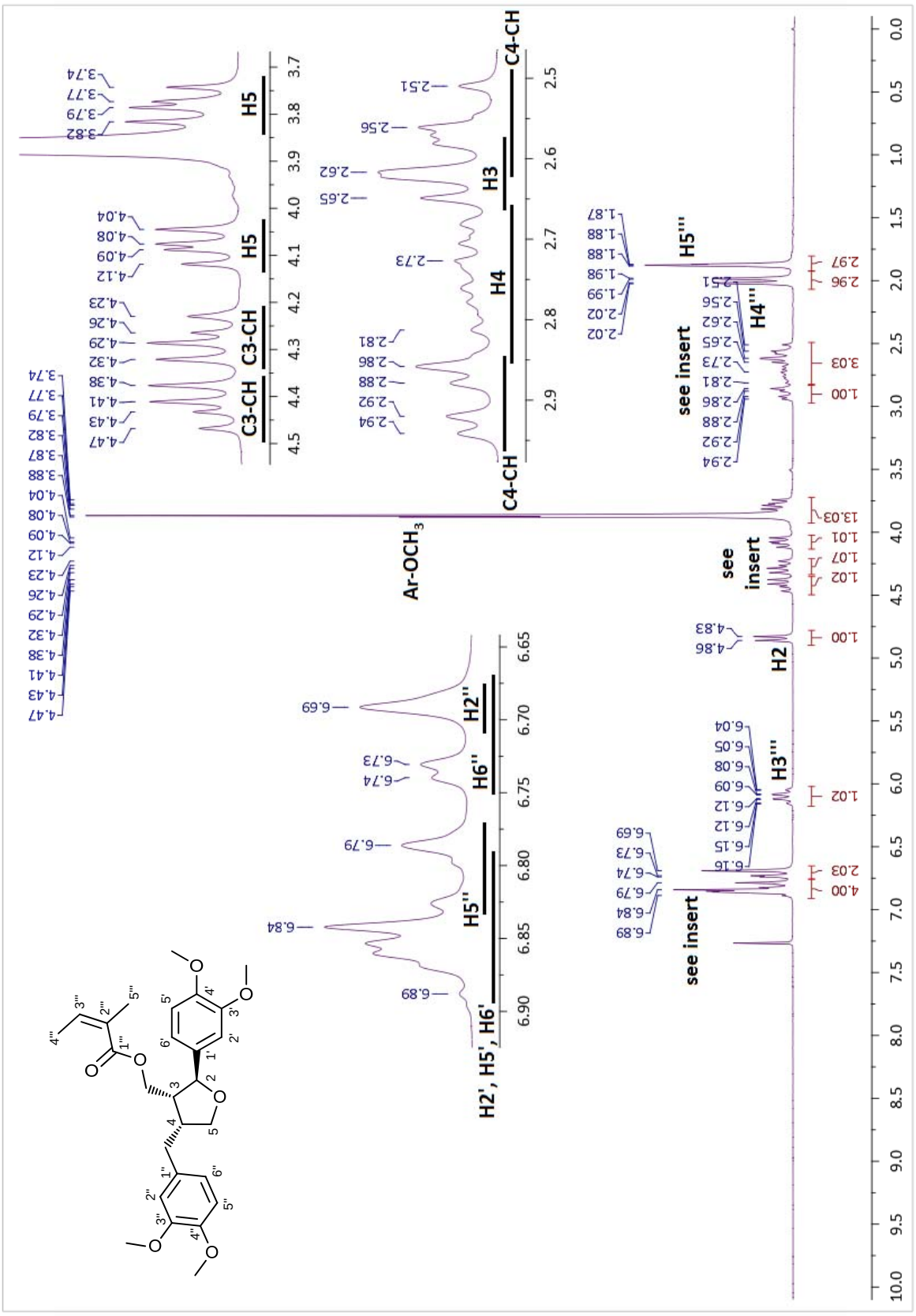
[j]For compounds **KH**, *cf.* related work.[290]

[k]For compounds **SOGE**, *cf.* related work.[163]

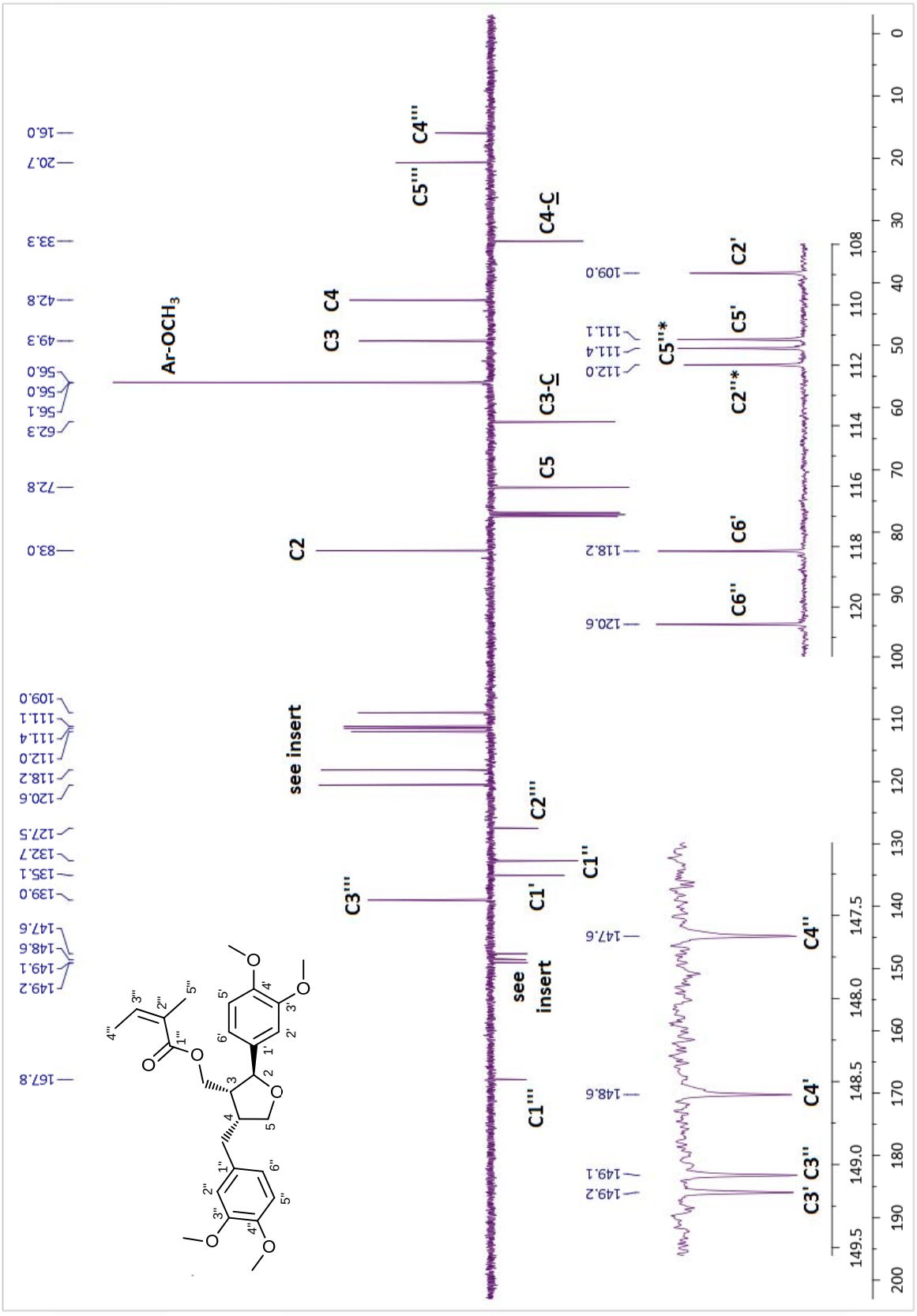
[l]For comparison.

[m]Compound was used as positive control.

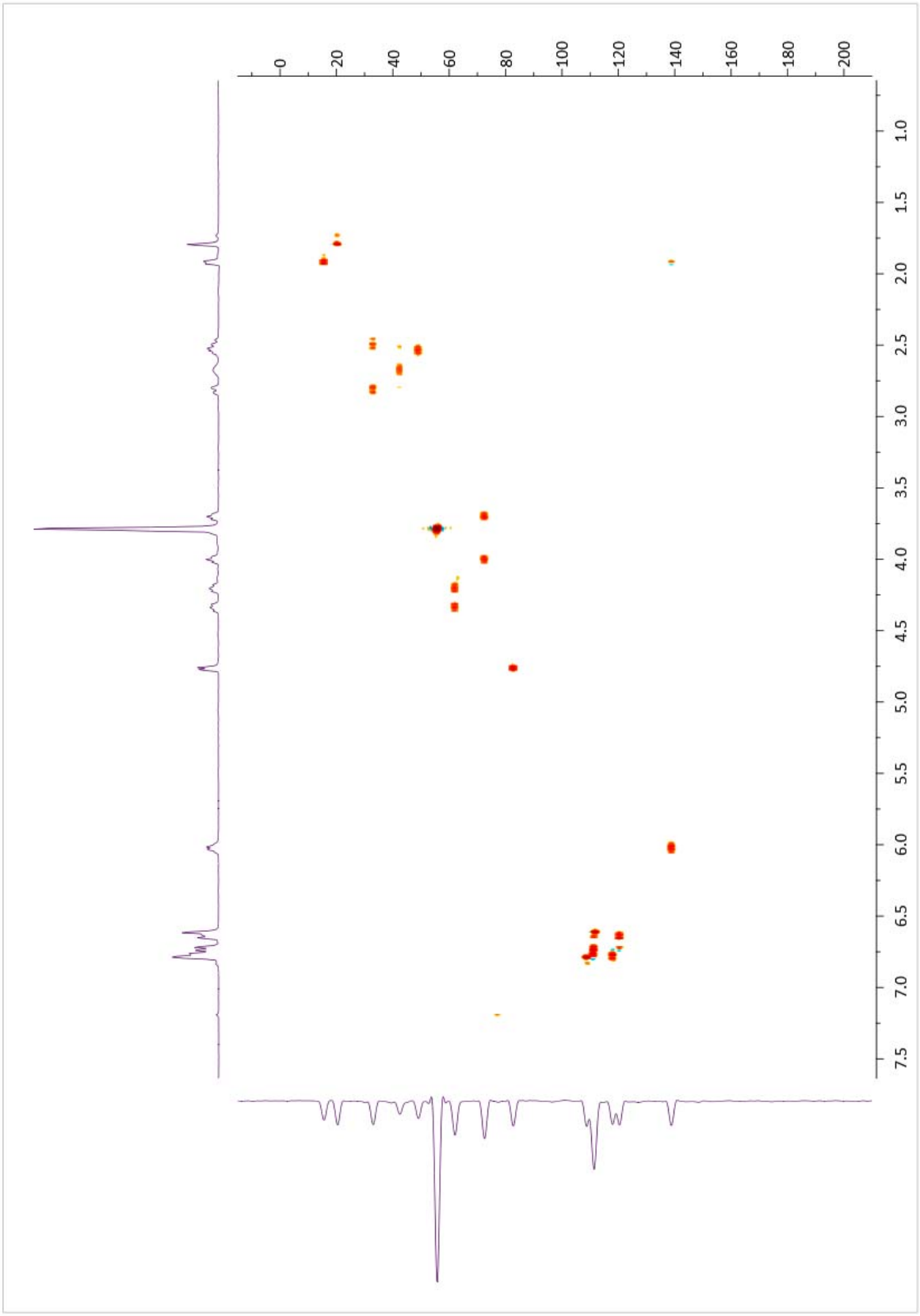
NMR spectra of synthetic leoligin



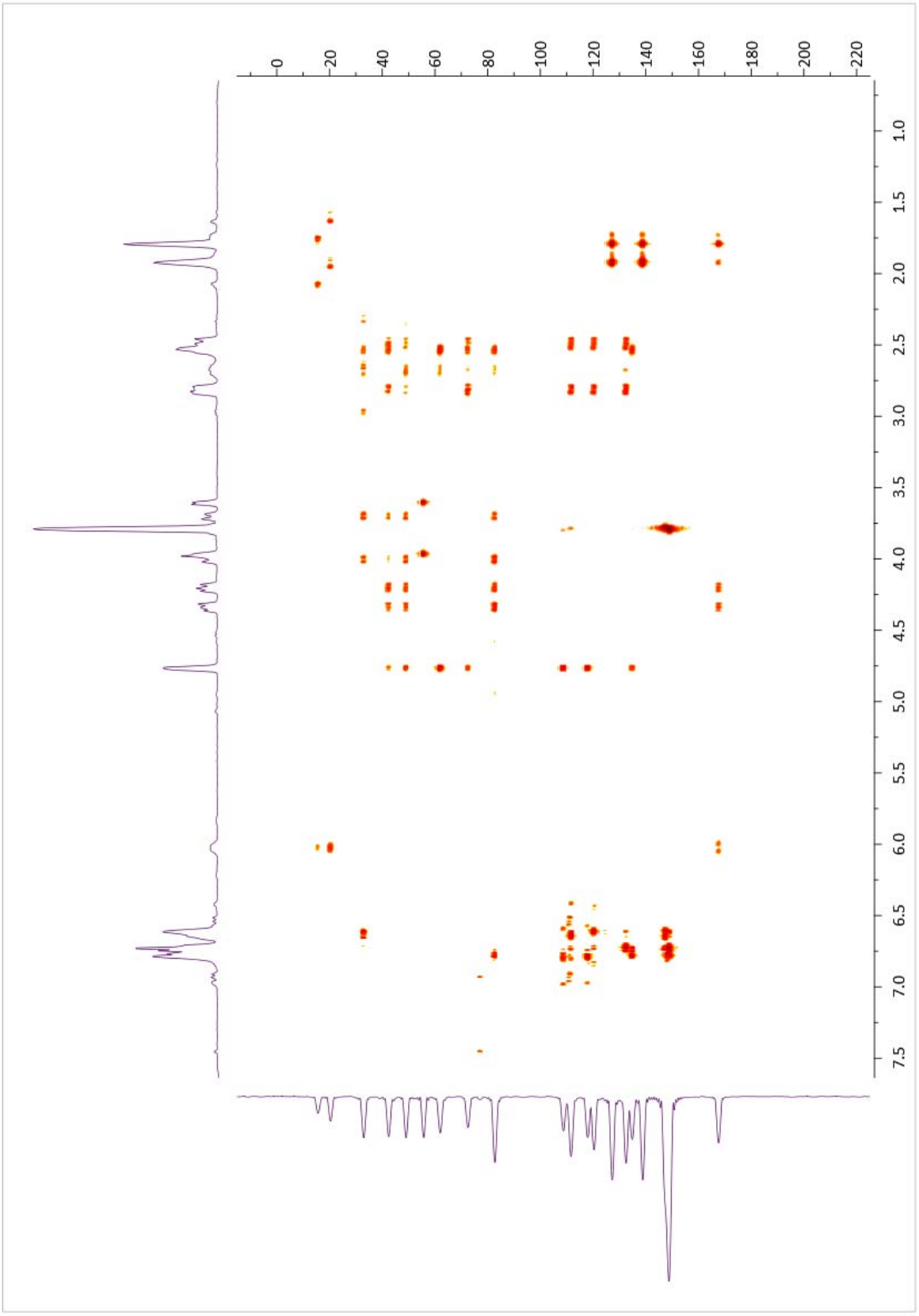
^{1}H NMR (200 MHz, $CDCl_3$): assignments according to the General Notes (section D.1, page 117).



***J*-mod ^{13}C NMR (100 MHz, $CDCl_3$):** assignments according to the General Notes (section D.1, page 117).



Heteronuclear Single Quantum Coherence (HSQC) spectrum.



Heteronuclear Multiple-Bond Correlation (HMBC) spectrum.

Resume

Thomas Linder

Schönburgstraße 33 / 13
A-1040 Vienna, Austria

thomas.linder@tuwien.ac.at

Education

begun in June 2011	**Ph.D. studies** at **Vienna University of Technology** • Thesis entitled *Synthetic Lignans Targeting Cardiovascular Diseases* under the supervision of Prof. Marko D. Mihovilovic • Received *inventum* Award in silver for Patent of the Year 2012 (AT 511441) by the Austrian Patent Office
Oct. 2004 – Feb. 2011	**Master's degree program** ("Diplomstudium") in **Technical Chemistry** at **Vienna University of Technology** • Coursework included analytical, physical, synthetic and biochemistry; chemical engineering • Major in applied synthetic chemistry • Thesis entitled *Synthesis and Biological Evaluation of Heterocyclic Retinoic Acid Analogs* under the supervision of Prof. Marko D. Mihovilovic • Graduated (*summa cum laude*) March 10, 2011
June 2003	Passed **A-levels** with distinction

Professional Experience

Sept. 2015 – present	**R&D Process Chemist** at **Patheon**, Linz, Austria
June 2011 – Dec. 2014	**Research position** at the **Institute of Applied Synthetic Chemistry**, **Vienna University of Technology**, Vienna, Austria
Sept. 2010 – Apr. 2011	**Tutoring position** at **Vienna University of Technology**, Vienna, Austria
June 2008 – Dec. 2008	**Internship** at **CSIRO Molecular and Health Technologies**, Clayton, Melbourne, Australia
Aug. 2006 – Sept. 2006	**Internship** at **DuPont Performance Coatings**, Guntramsdorf, Austria

Scientific Contributions

Turner, M.; Linder, T.; Schnürch, M.; Mihovilovic, M.D.; Stanetty, P., Investigation of the regioselectivity of the Hurd-Mori reaction for the formation of bicyclic 1,2,3-thiadiazoles. *Tetrahedron* **2010,** *66*, 5472-5478.

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Linder, T.; Schnürch, M.; Mihovilovic, M.D., Construction of Heterocyclic Lignans in Natural Product Synthesis and Medicinal Chemistry. In: *Targets In Heterocyclic Systems - Vol. XXIX: Chemistry and Properties*, Eds.: Attanasi, O. A.; Merino, P.; Spinelli, D.; The Royal Society of Chemistry, 2015 (*accepted, in press*).

Wang, L.; Ladurner, A.; Latkolik, S.; Schwaiger, S.; Linder, T.; Hošek, J.; Palme, V.; Schilcher, N.; Polanský, O.; Heiss, E.; Stangl, H.; Mihovilovic, M.; Stuppner, H.; Dirsch, V.; Atanasov, A., Leoligin, the Major Lignan from Edelweiss (*Leontopodium nivale* ssp. *alpinum*), Promotes Cholesterol Efflux from THP-1 Macrophages. *J. Nat. Prod.* (*submitted*).

Mihovilovic, M.D.; Schnürch, M.; Hilber, K.; Koenig, X.; Linder, T.; Mike, A., Triazine derivatives as differentiation accelerators. WO 2013/040622.

Mihovilovic, M.D.; Linder, T.; Atanasov, A.; Dirsch, V.; Stuppner, H.; Schweiger, S.; Bernhard, D., Preparation of leoligin derivatives as smooth muscle cell proliferation inhibitors. WO 2015/196228.

Linder, T.; Koley, M.; Mike, A.; Heher, P.; König, X.; Schnürch, M.; Hilber, K.; Weitzer, G.; Mihovilovic, M.D., Towards Small Molecule-Induced Cardiomyogenesis: Focusing On *N*-Containing Heterocyclic Scaffolds. Poster presentation: 15th Blue Danube Symposium on Heterocyclic Chemistry, Sept. 1-5, 2013, Olomouc, Czech Republic.

Linder, T.; Geyrhofer, S.; Atanasov, A.; Dirsch, V.; Stuppner, H.; Schnürch, M.; Mihovilovic, M.D., Synthetic Lignans Targeting Cardiovascular Diseases. Poster presentation: XXIII International Symposium on Medicinal Chemistry and 1st EFMC Young Medicinal Chemist Symposium, Sept. 7-11, 2014, Lisbon, Portugal.

Linder, T.; Geyrhofer, S.; Atanasov, A.; Dirsch, V.; Stuppner, H.; Schnürch, M.; Mihovilovic, M.D., Synthetic Lignans Targeting Cardiovascular Diseases: Structure Motifs and Biological Activity. Short Lecture: International Symposium: Natural products and drug discovery - future perspectives, Nov. 13-14, 2014, Vienna, Austria.