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TECHNISCHE UNIVERSITÄT WIEN
Vienna University of Technology

MASTER THESIS

Synthesis of biologically active tool compounds: mephedrone derivatives and the key fragment of leoligin

Conducted at the

Institute of Applied Synthetic Chemistry

TU Wien

under the supervision of

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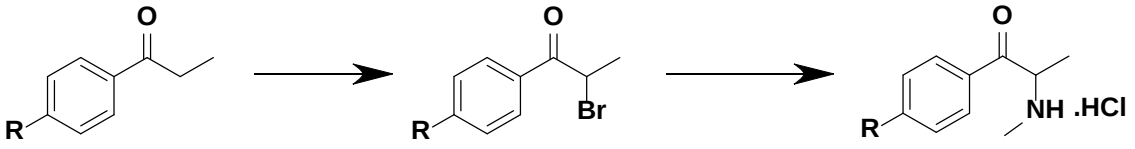
I want to thank my family for supporting me the whole way, from the crib until today. Especially my sister Zahra. Thank you.

And special thanks to “Ibe from Karlsplatz”.

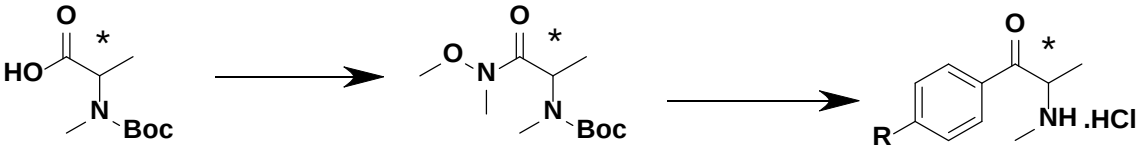
Abstract

The present thesis has two major subjects; the synthesis of i) mephedrone derivatives and ii) the key fragment of leoligin and leoligin analogs.

i) Methcathinones are widely used recreational drugs. These inhibitors of monoamine transporters are typically consumed as racemic mixtures. One of the most commonly used methcathinones is mephedrone. In this work, racemic mixtures as well as enantiomerically pure samples of representative mephedrone derivatives were prepared. Therefore, different strategies were employed.

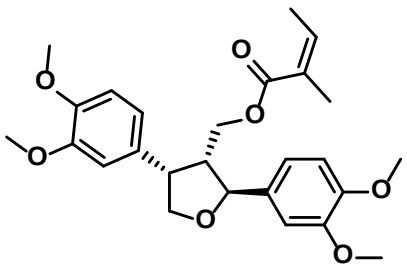


Racemic derivative



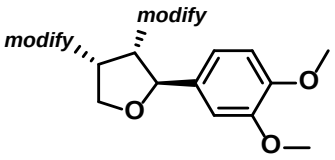
enantiomeric pure derivative

ii) 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.



Leoligin

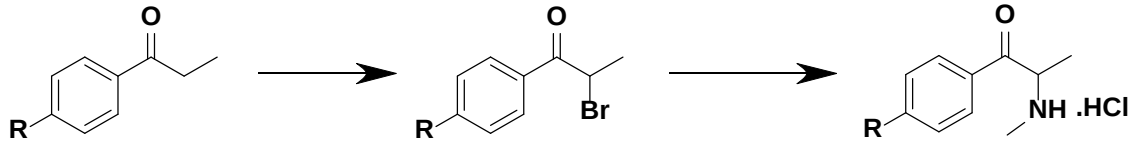
This work is based on a previously developed approach, which permitted the synthesis of a sufficiently diverse array of leoligin-like compounds to selectively improve on the biological activities of this plant-derived natural product. All these compounds have one fragment in common, which is synthesized within this work for further modifications.



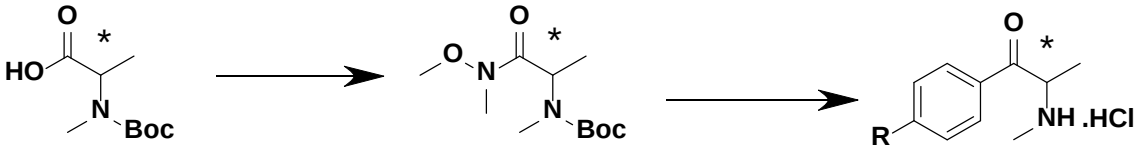
Kurzfassung

Die vorliegende Arbeit umspannt zwei Themengebiete; die Synthese von i) Mephedron-Derivaten und ii) das Schlüsselfragment von Leoligin und Leoligin Analoga.

i) Methcathinone werden weitgehend als Designer-Drogen eingesetzt. Diese Transportprotein-Inhibitoren werden üblicherweise in Form racemischer Mischungen konsumiert. Eines der am meisten verbrauchte Methcathinon ist Mephedron. In dieser Arbeit wurden sowohl racemische Mischungen als auch enantiomerenreine Proben repräsentativer Mephedron-Derivate hergestellt. Zu diesem Zweck wurden verschiedene Strategien angewendet.

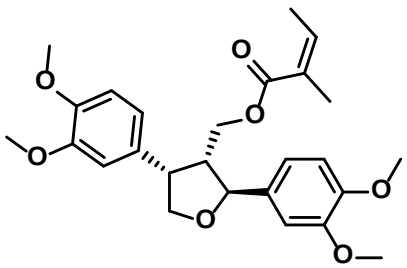


racemische Derivate



enantiomerenreine Derivate

ii) Leoligin, das Hauptlignan aus dem Edelweiß (*Leontopodium nivale* ssp. *alpinum*), ist in der Lage die Ausschüttung 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.



Leoligin

Diese Arbeit basiert auf einer unlängst entwickelten Methode, welche die Darstellung einer hinreichend vielfältigen Sammlung leoliginartiger Verbindungen erlaubte um die biologische Aktivität dieses pflanzlichen Naturstoffes selektiv zu verbessern. All diese Verbindungen haben ein einheitliches Fragment, welches im Rahmen dieser Arbeit hergestellt und für weitere Modifikationen bereitgestellt wurde.

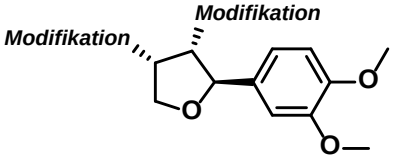
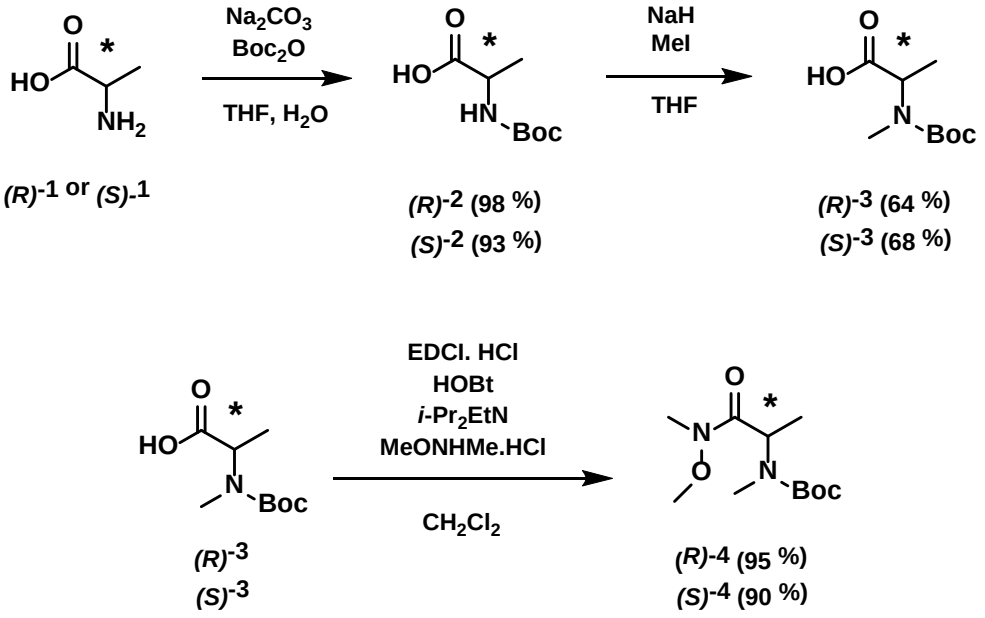


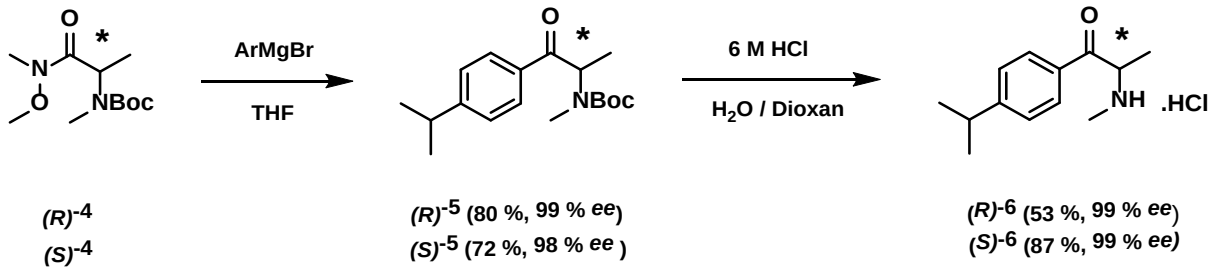
Table of contents

General schemes

Synthesis of mephedrone derivatives via Boc-protected Weinreb amides

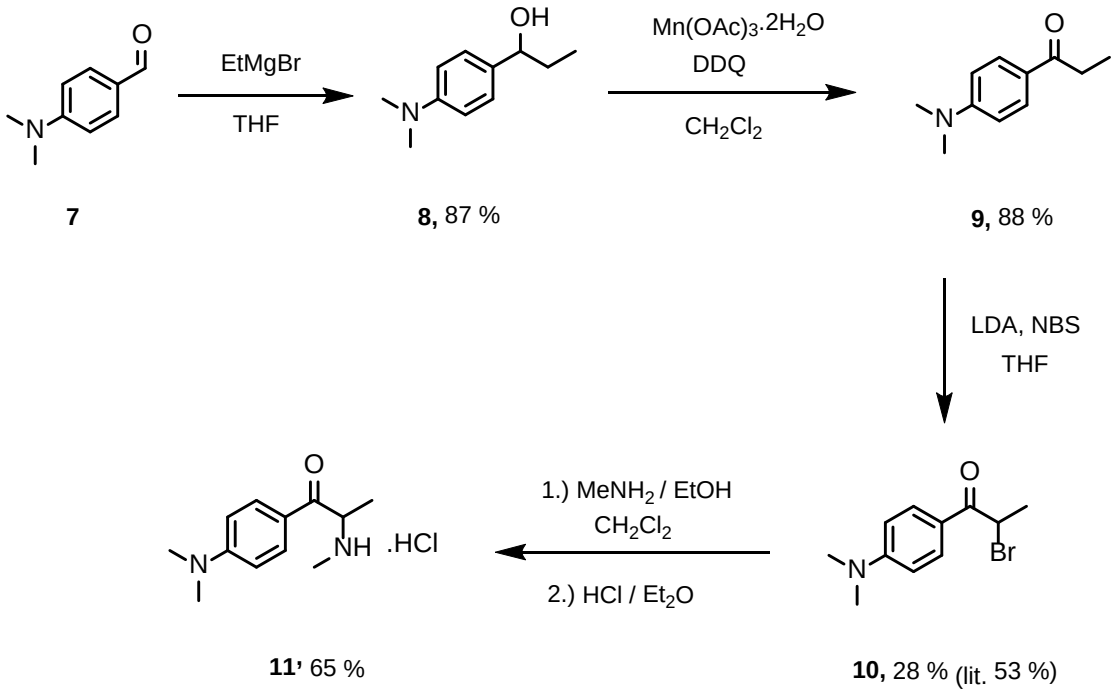


Scheme 1: Synthesis of Boc-protected Weinreb amides

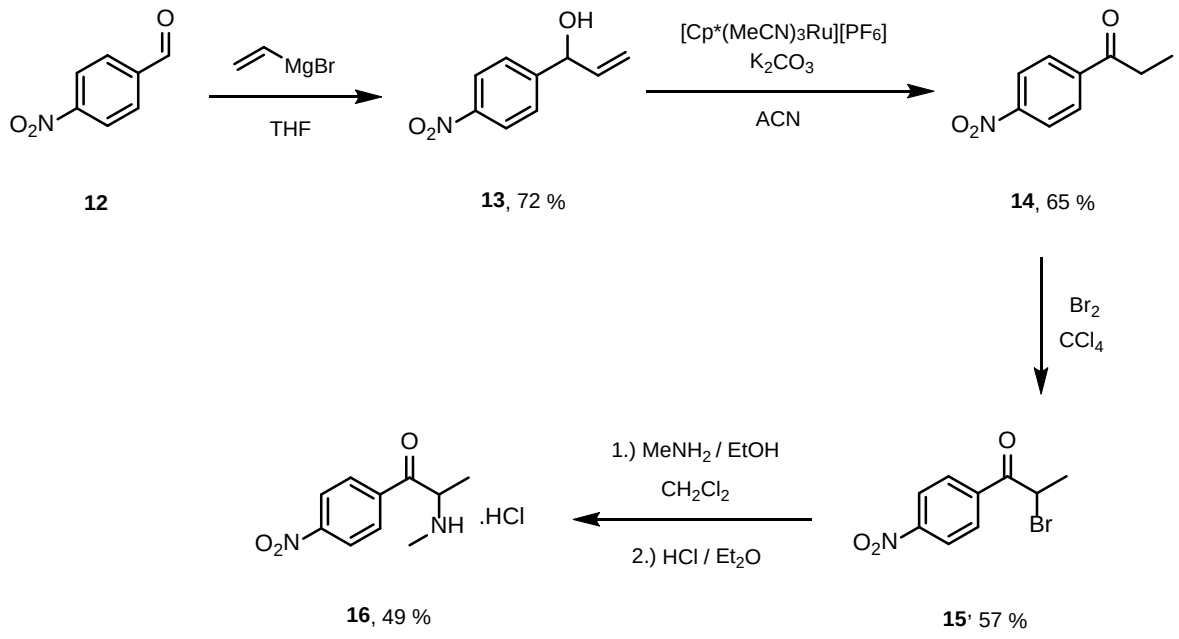


Scheme 2: Gringnard addition and deprotection

Racemic synthesis of mephedrone derivatives

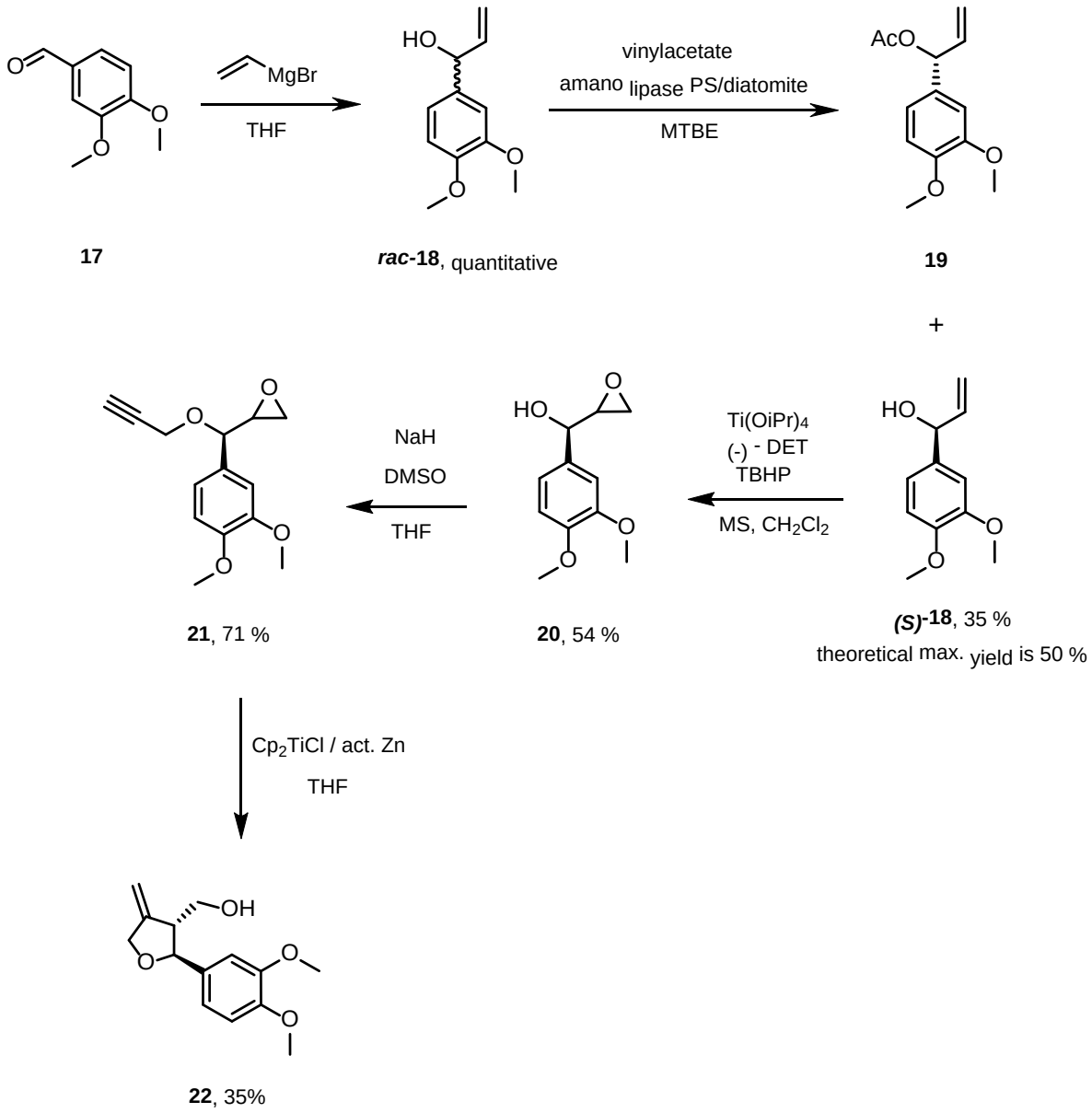


Scheme 3: Racemic synthesis of 4-dimethylamino-MCAT



Scheme 4: Racemic synthesis of 4-nitro-MCAT

Synthesis of the key fragment of leoligin



Scheme 5: Synthesis of the key fragment in the total synthesis of leoligin and leoligin analogs

Key

All compounds prepared or used as starting materials in this thesis are labeled with bold Arabic numbers. Compounds unknown to the literature are additionally underlined.

Generic structures are labelled with bold Roman numerals.

Literature citations are indicated by superscript Arabic numbers. Footnotes are indicated by superscript Roman numerals.

A Introduction

The present work is organized in two parts, which will be introduced individually below.

A.1 Mephedrone derivatives

A.1.1 Monoamine transporters

Neurotransmission, also called synaptic transmission, is the process by which signaling molecules called neurotransmitters are released by the axon terminal of a neuron (the presynaptic neuron) and bind to and activate the receptors on the dendrites of another neuron (the postsynaptic neuron).[1]

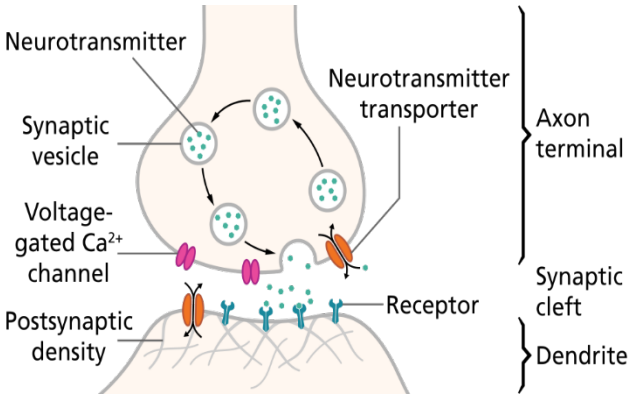


Fig. 1: Structure of a typical chemical synapse

Neurotransmission is essential for the process of communication between two neurons. Synaptic transmission relies on: the availability of the neurotransmitter; the release of the neurotransmitter by exocytosis; the binding of the postsynaptic receptor by the neurotransmitter; the functional response of the postsynaptic cell; and the subsequent removal or deactivation of the neurotransmitter (Figure 1).

In response to a threshold action potential or graded electrical potential, a neurotransmitter is released at the presynaptic terminal. The released neurotransmitter may then move across the synapse to be detected by and bind with receptors in the postsynaptic neuron. Binding of neurotransmitters may influence the postsynaptic neuron in either an inhibitory or excitatory way. The binding of neurotransmitters to receptors in the postsynaptic neuron can trigger either short term changes, such as changes in the membrane potential called postsynaptic potentials, or longer-term changes by the activation of signaling cascades.

Neurons form elaborate networks through which nerve impulses (action potentials) travel. Each neuron has as many as 15000 connections with other neurons. Neurons do not touch each other (except in the case of an electrical synapse through a gap junction); instead, neurons interact at close contact points called synapses. A neuron transports its information by way of an action potential. When the nerve impulse arrives at the synapse, it may cause the release of neurotransmitters, which influence another (postsynaptic) neuron. The postsynaptic neuron may receive inputs from many additional neurons, both excitatory and inhibitory. The excitatory and inhibitory influences are summed, and if the net effect is inhibitory, the neuron will be less likely to "fire" (i.e., generate an action potential), and if the net effect is excitatory, the neuron will be more likely to fire. How likely a neuron is to fire depends on how far its membrane potential is from the threshold potential, the voltage at which an action potential is triggered because enough voltage-dependent sodium channels are activated so that the net inward sodium current exceeds all outward currents. Excitatory inputs bring a neuron closer to threshold, while inhibitory inputs bring the neuron farther from threshold. An action potential is an "all-or-none" event; neurons whose membranes have not reached threshold will not fire, while those that do must fire. Once the action potential is initiated, it will propagate along the axon, leading to release of neurotransmitters at the synaptic bouton to pass along information to yet another adjacent neuron.[2]

Neurotransmitters, also known as chemical messengers, are endogenous chemicals that enable neurotransmission. They transmit signals across a chemical synapse, from one neuron (nerve cell) to another "target" neuron, muscle cell, or gland cell.[1] Monoamine neurotransmitters are neurotransmitters and neuromodulators that contain one amino group that is connected to an aromatic ring by a two-carbon chain[3] (Figure 2).

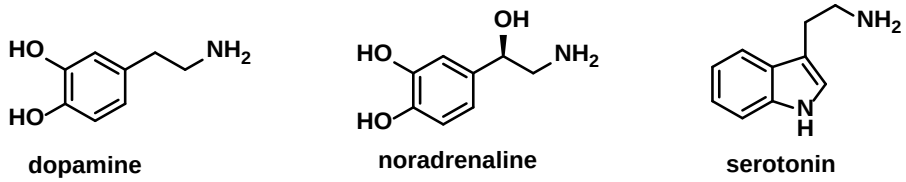


Fig. 2: Structure of dopamine, noradrenaline and serotonine

Monoamine transporters (MATs) are protein structures that function as integral plasma-membrane transporters to regulate concentrations of extracellular monoamine neurotransmitters. Three major classes of MATs namely dopamine-, norepinephrine- and serotonin transporters (DAT, NET, SERT) are responsible for the reuptake of their associated amine neurotransmitters (serotonin, dopamine, norepinephrine). MATs are located just outside the synaptic cleft (peri-synaptically), transporting monoamine transmitter overflow from the synaptic cleft back to the cytoplasm of the pre-synaptic neuron.[4]

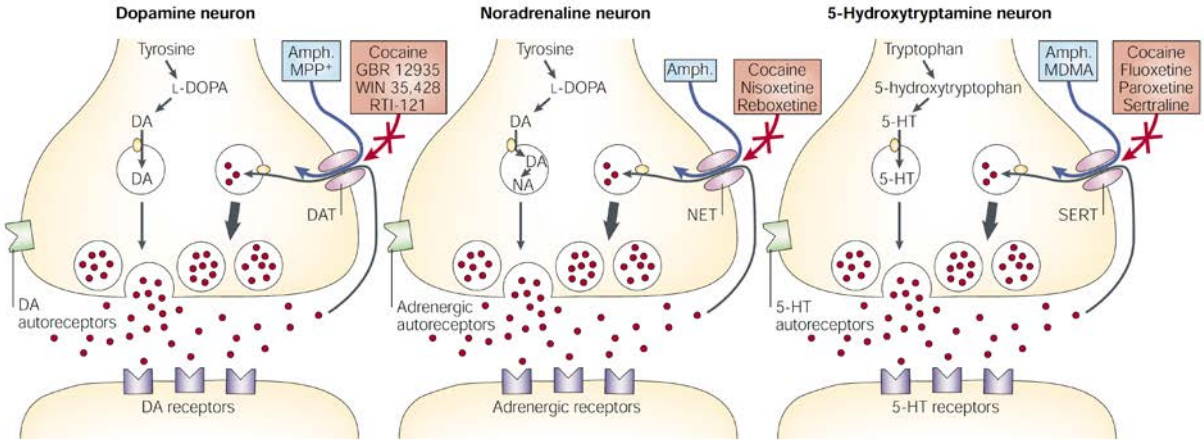


Fig. 3: Schematic representation of dopamine, noradrenaline and serotonine synaptic terminals[5]

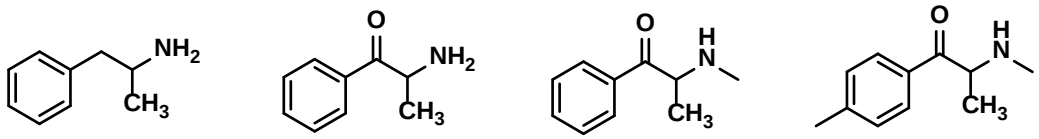
As depicted in **Figure 3**, monoamine transporters are almost exclusively expressed in neurons that use their cognate neurotransmitter. The psychostimulants cocain and amphetamine interact with DAT, NET and SERT. While cocain and cocain-derivatives are non-selective blockers of monoamine transporters, amphetamine-like compounds are substrates and can be taken up into the neuron. Inside the synaptic terminal they can cause reverse transport of neurotransmitter, leading to massive release of neurotransmitter into the extracellular space.[5]

A.1.2 Cathinone-derivatives as recreational drugs

Stimulants (also referred to as psychostimulants) is an overarching term that covers many drugs including those that increase activity of the body[6], drugs that are pleasurable and invigorating, or drugs that have sympathomimetic effects.[7] Stimulants are widely used throughout the world as prescription medicines as well as without a prescription (either legally or illicitly) as performance-enhancing or

recreational drugs. It is estimated that the percent of the population that has abused amphetamines, cocaine and MDMA combined is between 0.8 % and 2.1 %.[8]

Methcathinone (MCAT), the β-keto analog of methamphetamine, is the parent compound of an emerging class of abused designer drugs. Like its amphetamine analog, MCAT functions as a monoamine releaser that selectively increases release of dopamine over that of serotonin. Mephedrone (4-CH_3 MCAT) is the *para*-methyl analog of MCAT and was recently popularized in Europe and the United States as one of the primary components of *bath salts*. Because of its rapid rise to international notoriety as a designer drug of abuse, as well as its cocaine- and methamphetamine-like discriminative stimulus effects, 4-CH_3 MCAT was added to the list of controlled drugs in both the United States and the United Kingdom in 2010–2011.[9]



amphetamine | **cathinone** | **methcathinone (MCAT)** | **mephedrone (4-CH_3 MCAT)**

Fig. 4: Structure of amphetamine, cathinone, methcathinone and mephedrone

In comparison with MCAT, which has high in vitro selectivity to increase dopamine rather than 5-HT release, 4-CH_3 MCAT has lower potency to release dopamine, higher potency to release 5-HT, and is less effective than MCAT in producing abuse-related behavioural effects. In further studies, the *para* substituent on the benzene ring of the MCAT scaffold, was manipulated to include substituents that varied systematically along three physicochemical dimensions [steric (E_s), electronic (σ_p), and lipophilic (π_p)], and **Table 1** shows quantitative measures for each substituent on each parameter.[9]

Physicochemical parameters				*In vitro* release EC_{50}		
Drug name	**E_s**	**σ_p**	**π_p**	**DAT (nM)**	**SERT (nM)**	**DAT selectivity[a]**
MCAT	1.24	0.00	0.00	12.5 ± 1.1	3,860 ± 520	309
4-F MCAT	0.78	0.06	0.14	83.4 ± 6.0	1,290 ± 220	15.4
4-OCH3 MCAT	0.69	-0.27	-0.02	506 ± 62	120 ± 18	0.24
4-Cl MCAT	0.27	0.23	0.71	42.2 ± 5.2	144 ± 22	3.40
4-Br MCAT	0.08	0.23	0.86	59.4 ± 5.1	60.2 ± 6.7	1.01
4-CH_3 MCAT	0.00	-0.17	0.56	49.1 ± 8.3	118 ± 26	2.41
4-CF_3 MCAT	-1.16	0.54	0.88	2,700 ± 300	190 ± 30	0.07

Table 1: Physicochemical parameters and *in vitro* release activities of MCAT and its *para*-substituted analogs.
[a]DAT selectivity calculated as SERT EC50 ÷ DAT EC50.

In contrast to the significant correlations obtained for E_s values, neither lipophilic (π_p) nor electronic (σ_p) parameters of the para substituent correlated with in vitro or in vivo drug effects. The non-significant correlations of these values with DAT versus SERT selectivity suggest that, within the ranges studied recently, these parameters are less important than steric hindrance as determinants of abuse-related neurochemical and behavioral effects of MCAT analogs.[9]

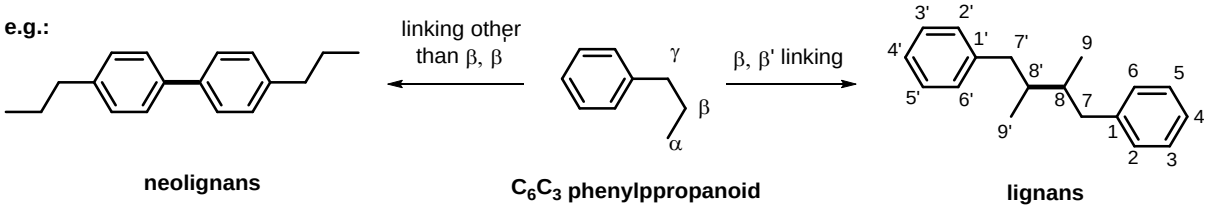
A.1.3 Objective

According to section A.1.2, there were no significant correlations for the lipophilic or electronic parameters of the para substituent on the benzene ring of the MCAT scaffold with in vitro or in vivo drug effects. However, more extreme lipophilic and/or electronic values beyond the ranges studied until now, might influence neurochemical and behavioral effects, and lipophilic and electronic parameters might also influence other aspects of pharmacology, such as pharmacokinetics. Thus, to follow the mode of action of monoamine transporters the aim of this part was to produce novel MCAT analogs with different para substituents in order to understand their associated effects on biological activity with the aim of identifying prospective novel candidates for medical applications. Further, the effect of these compounds on monoamine transporters will be studied. If procurable, these derivatives should be prepared in enantiopure form to enable the investigation of differences in activity of *(R)*- and *(S)*-enantiomer.

A.2 The leoligin key fragment

A.2.1 Lignans

Lignans form a wide range of natural compounds which occur in both herbaceous plants (herbs) and woody plants (trees, shrubs and vines), consisting of at least two phenylpropanoid units (C_6C_3 building blocks).[10] The definition is often restricted to *dimeric* phenylpropanoids[11] because it is the most prominent form in which they are known to appear in nature.[12] 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.[12]



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

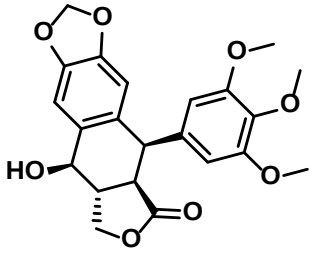
Phenylpropanoids in general protect plants in stress conditions like infections, wounding, exposure to UV radiation and ozone, pollutants and herbivores.[13] But they are not exclusively plant-derived compounds. For instance, podophyllotoxin (*vide infra*) and a glycoside thereof were isolated from the fungal endophyte *Trametes hirsuta*, normally residing inside its host plant *Podophyllum hexandrum*.[14] The physiological properties of lignans have been made use of, one way or another, for centuries. Aside from 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.[10, 15]

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)[16-18].

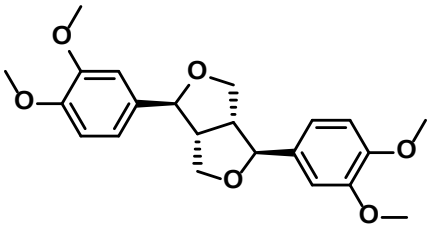
A.2.2 Lignans against cardiovascular disease

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

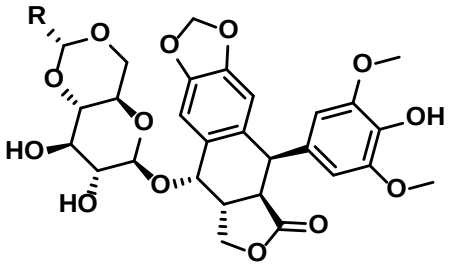
inner lining of the arterial walls) by lowering plasma and liver cholesterol levels (e.g.: (+)-sesamin and (+)-asarinin) and behaving as platelet activating factor (PAF) antagonists (e.g.: (+)-eudesmin (also called (+)-pinoresinol dimethyl ether) and (+)-syringaresinol dimethyl ether (also called (+)-lirioresinol-B dimethyl ether), **Figure 5**).[19-20]



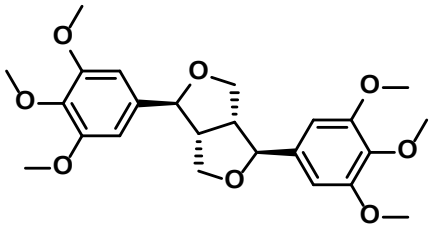
podophyllotoxin



(+)-eudesmin



R = CH_3: etoposide
2-thiophenyl: teniposide



(+)-lirioresinol-B dimethylether

Fig. 5: Pharmacologically relevant lignans.

Generally, the term atherosclerosis describes a condition in which plaque builds up inside the arteries causing narrowing of these vessels.[21] Atherosclerotic plaques are consisting of necrotic cores, calcified regions, accumulated modified lipids, smooth muscle cells (SMCs), endothelial cells[i] (EC), leukocytes and foam cells[22] and possess a fibrous cap of varying thickness and strength.[23]

Although atherosclerosis itself is seldom deadly but plaque rupture, defined as "a plaque with deep injury with a real defect or gap in the fibrous cap that had separated its lipid rich atheromatous core from the flowing blood, thereby exposing the thrombogenic core of the plaque", is the most common cause of potentially fatal thrombosis.[24]

A thrombus is capable to partially or completely block a blood vessel and therefore strongly limit or interrupt the oxygen supply to organs such as heart and brain, leading to severe and life threating complications.[25-26]

The atherosclerotic process is initiated by a variety of chemical, mechanical and immunological mechanisms causing endothelial dysfunction. As a result of this dysfunction inflammatory molecules promote the increased presence of macrophages in the subintima[ii] that turn into foam cells after

[i] Endothelial cells = A monolayer of cells covering the inside of the vessel and part of the intima
[ii] Intima = inner layer of a vessel wall

taking up low density lipoproteins. Subsequently foam cells and macrophages form a highly instable lipid-filled necrotic core. At the same time SMCs migrate from the medial to the intimal layer, where they form the fibrous cap along with collagen and elastin. Several factors can weaken the fibrous cap until it ruptures.[22]

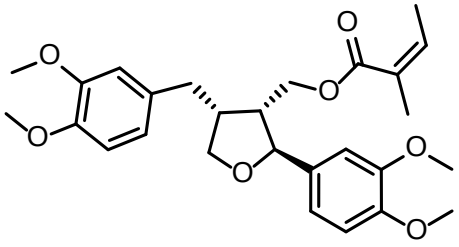


Fig. 6: Structure of leoligin

Previous research discovered that leoligin **(Figure 6)** displays the ability to promote macrophage cholesterol efflux, which causes the macrophages to release the lipoproteins and therefore preventing the emergence of the already mentioned foam cells and subsequently the highly instable necrotic core.[27]

A.2.3 Objective

As coronary heart disease is one of the leading causes of death worldwide, there is a high demand for treatment of atherosclerosis, but all known procedures are connected to major risks such as restenosis or late-stent thrombosis. Therefore, it is of high scientific interest to develop agents that could erase or significantly reduce these risks.

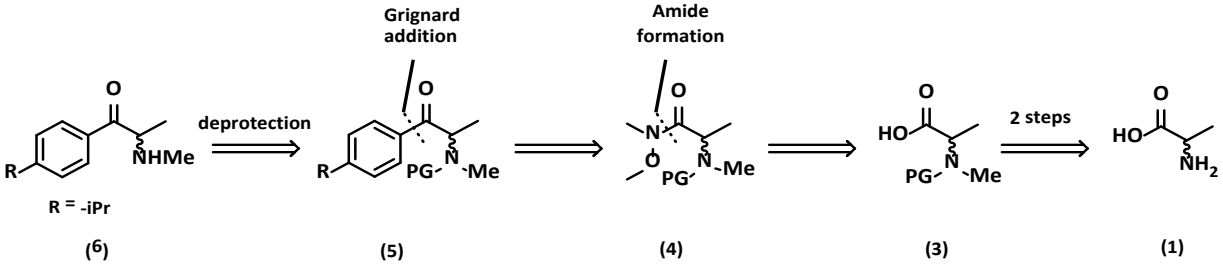
In the past, natural products proved to be an excellent pool for the identification of new drug lead compounds.[29] However, obtaining leoligin from its natural source is a rather tedious procedure.[28] For example, the initial isolation and purification afforded 38 mg of the compound from 804 g of dried root material,[30] 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, but although modified approaches are promising, they do not allow for variations of the chemical structure. For that reason, it was of interest to synthesize a library of synthetic leoligin analogs for biological testing to find a compound that is selectively inhibiting the proliferation of vascular SMCs. In addition to that, the extracted amount of leoligin fails to provide the compound in the required quantities for in depth biological testing or for the synthesis of derivatives for SAR studies. Since leoligin and a variety of analog structures can be prepared from the same fragment, the aim of this part was to produce this key fragment and make available this key building block for further transformations.

B Results and discussion

B.1 Chemistry

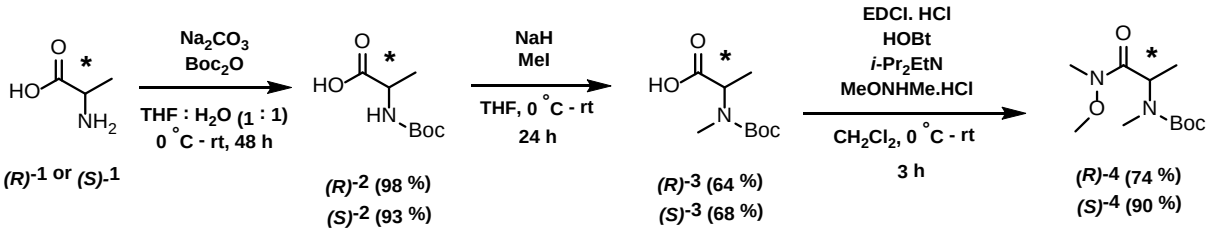
B.1.1 Synthesis of enantiomerically enriched mephedrone derivatives

The stereoselective synthesis of mephedrone derivatives was planned according to the retrosynthesis shown in **scheme B-1**. The desired product **6** can be traced back to a carbamate-protected aminoketone **5**. This ketone can be the product of a Weinreb ketone synthesis, the addition of a Grignard reagent onto Weinreb amide **4**. This compound in turn can be disconnected to the protected N-methylalanine **3**.



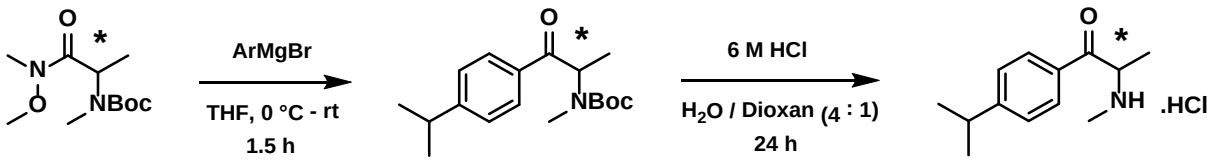
Scheme B-1: Retrosynthetic route to enantiomerically enriched methcathinones

tert-Butyloxycarbonyl (Boc) was chosen as protecting group. Previous studies had also used the benzyloxycarbonyl (Cbz) protecting-group, but lower e.e. values were obtained in comparison to the Boc-group.[31] Boc-protected Weinreb amides **4** were prepared from L- or D-alanine by protection, alkylation of the carbamate and amide coupling. (Since this work is part of a bigger project, the amide coupling was also done with **2** and the product served as precursor in other parts of the project.)



Scheme B-2: Synthesis of Boc-protected Weinreb amides

The Grignard reagent was prepared separately and 3 equivalents were used to achieve full conversion,[31] while keeping the temperature at 0 °C to avoid side reactions. The Boc-group was removed using 6 M HCl at 0 °C. Classical deprotection conditions were not used, since previous research showed that higher temperatures would lead to (partial) racemization.[31] To compensate low reaction rates caused by low temperatures, the concentration of the acid was increased. To achieve a better solubility of the substrates, a mixture of water / dioxane (4 : 1) was used.



(R)-4
(S)-4

(R)-5 (80 %),
(S)-5 (72 %)

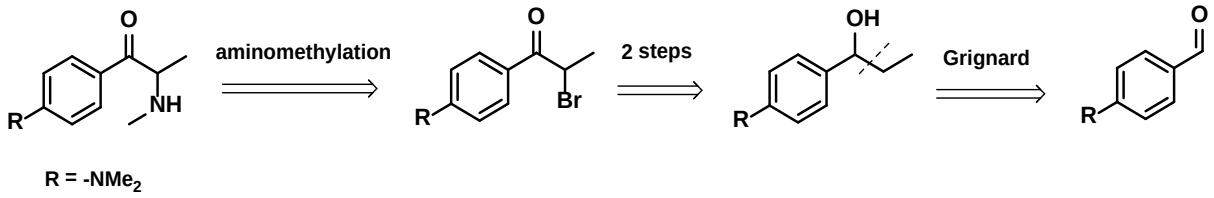
(R)-6 (53 %, 99 % *ee*)
(S)-6 (87 %, 99 % *ee)*

Scheme B-3: Grignard addition into Boc-Weinreb amides and deprotection to the final compound

B.1.2 Racemic synthesis of mephedrone derivatives

In the aim of the project, two more structures were supposed to be synthesized. One with the dimethylamino group in *para*-position and the other one with the nitro group in the same position. Both synthesis routes will be discussed below.

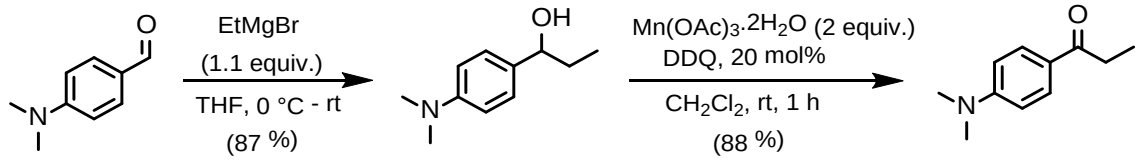
In the case of 4-dimethylaminomethcathinone, shortened 4-dimethylamino-MCAT, previous coworkers tried an enantioselective route, which failed due to problems caused by extremely reactive intermediates. Thus, a racemic route was carried out, depicted in **scheme B-4**.



(11) (10) (8) (7)

Scheme B-4: Retrosynthetic route towards 4-dimethylamino-MCAT

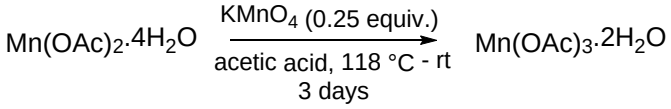
4-Dimethylamino-MCAT **11** can be synthesized through aminomethylation from the corresponding 2-haloketon **10**. The preparation of racemic mephedrone from haloketones has been described in the literature.[32] Preparation of compound **10** can be envisioned via α-halogenation and oxidation of the alcohol **8**, which leads back to an aldehyde as starting material to undergo a Grignard addition.
In the forward way, the Grignard addition proceeded smoothly to provide compound 8.



(7) (8) (9)

Scheme B-5: Grignard addition to 4-dimethylaminobenzaldehyde and oxidation

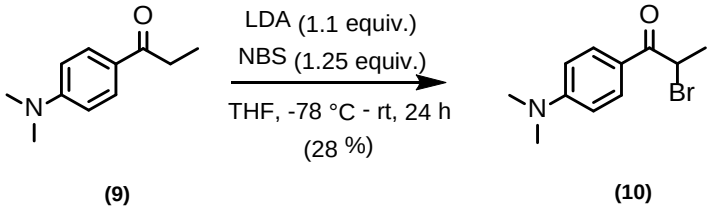
The oxidation step was performed using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidizing and Manganese(III) acetate dihydrate as co-oxidizing reagent. The latter one was introduced as follows[33]:



Scheme B-6: Preparation of the cooxidizing reagent

For the reaction itself (scheme B-6), different amounts of the co-oxidizing reagents were used. Using 6 equivalents of $Mn(OAc)_3.2H_2O$ as reported in literature[34] led to loss of one of the methyl groups of nitrogen (NMR). By using only 2 equivalents, this problem could be avoided (also shown by NMR).

The next step was the most critical one in the whole synthesis route (Scheme B-7). There was only one reaction reported with the same substrate for α-bromination of the ketone **(9)** using LDA as base and NBS as the bromo source.[35] Literature reported 53 % yield for this step, but the best yield achieved here was 28 %. A commercial solution of LDA in THF was used for the reaction, therefore it was titrated first and used according to its calculated purity. Although the purity was high, the little impurities might have led to side reactions which could prohibit the desired bromination.

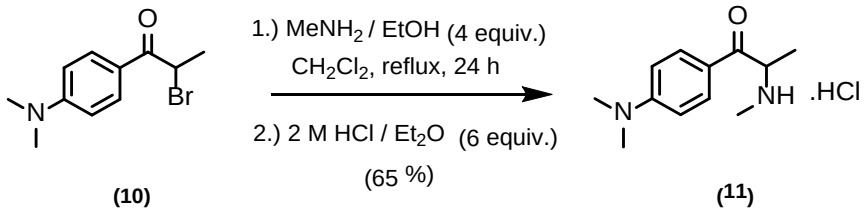


(9) **(10)**

Scheme B-7: α-bromination of 1-(4-(dimethylamino)phenyl)propan-1-one

In attempt to optimize the reaction, more equivalents of LDA were used. Literature used 1.1 equiv., using this amount of LDA, gave 24 % yield. Using 1.5 equiv. result in 28 %. As an alternative, other procedures reported for similar substrates were tested, using bromine in acetic acid[36] or bromine with $AlCl_3$.[31] None of them led to any product.

The last step was less problematic. Aminomethylation was performed using a methylamine solution, as reported for mephedrone.[36] Acidic work up was applied, and ethereal HCl was added dropwise to form the hydrogen chloride salt of the product (Scheme B-8).

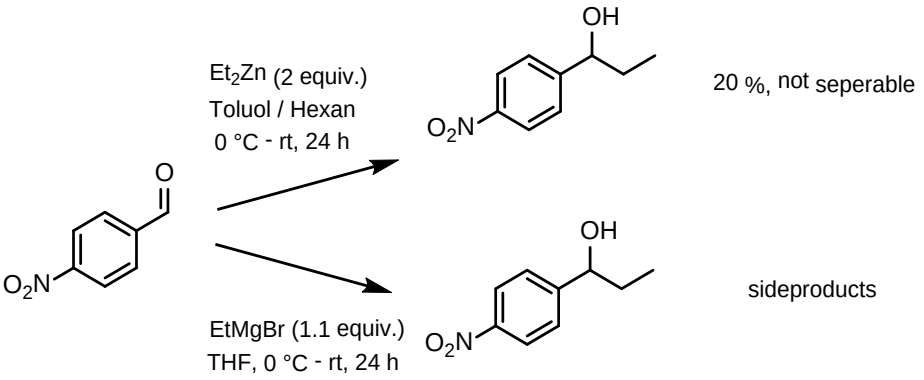


(10) **(11)**

Scheme B-8: nucleophilic substitution of the α-bromketon into the final product

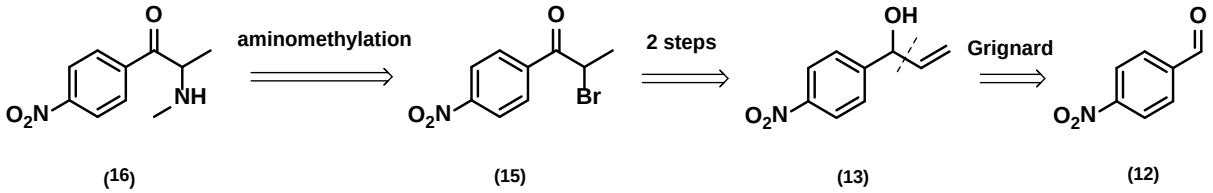
For the **nitro-substitued MCAT** the same retrosynthetic route shown in scheme B-4 was planned, initially. Starting with 4-nitrobenzaldehyde, there were a few reactions reported using diethylzinc as reagent.[37] All of them were enantioselective and employed chiral catalysts. Since enantioselectivity was not an issue in this part (and the fact that these catalysts had to be synthesized as well) this addition was performed in the absence of a catalyst. It resulted in impure product with only 20 % yield (Scheme B-8). The explanation is that these chiral catalysts do not only facilitate the desired stereoconfiguration, but also promote and catalyse the right reaction, as a catalyst does.

As an alternative, the addition with ethyl magnesium bromide as in scheme B-5 was conducted for 4-nitrobenazldehyde. This also led to a lot of sideproducts and about only 7 % of product according to the crude NMR. The mixture was not processed further (Scheme B-9).



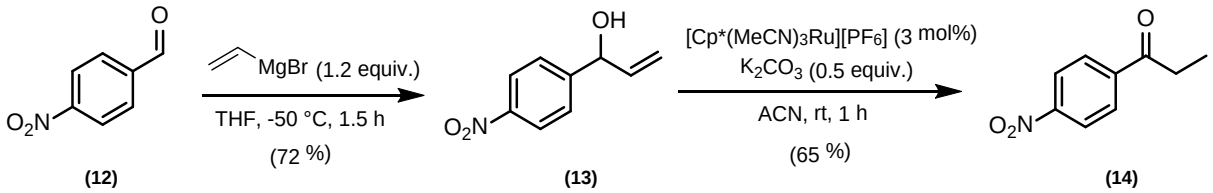
Scheme B-9: unsuccessful addition reactions to 4-nitrobenzaldehyde

Regarding these experiments, an alternative route had to be chosen, as depicted in Scheme B-10.



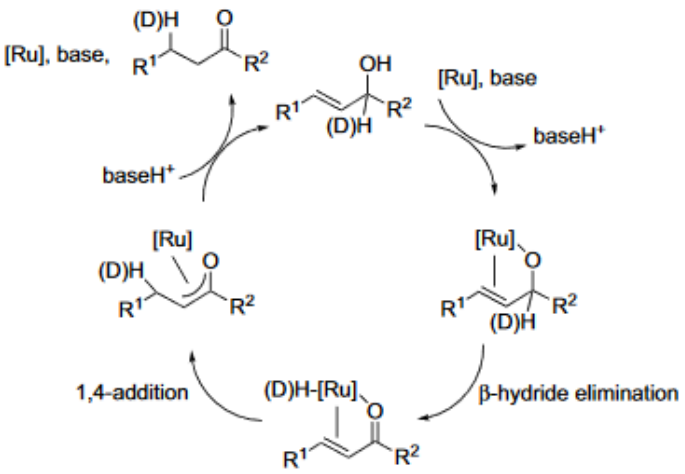
Scheme B-10: retrosynthetic route towards 4-nitro-MCAT

This retrosynthetic route does not look much different from the first one (Scheme B-4). Again, the final compound (**16**) can be synthesized through nucleophilic substitution from the corresponding α-bromketon **(15),** which can be accessed from the ketone via bromination. But here the difference comes: The keton traces back to its isomer – the enol **(13)** and the latter can be achieved utilizing another Grignard addition.



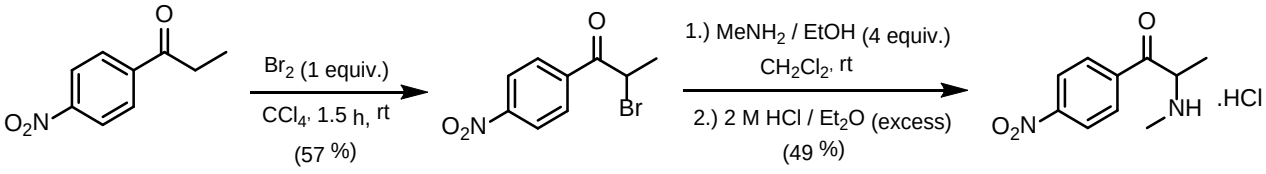
Scheme B-11: Grignard addition to 4-nitrobenzaldehyde and isomerization

As depicted in Scheme B-11, this time vinyl magnesium bromide was used as Grignard reagent,[38] which worked much better for 4-nitrobenzaldehyde than ethyl magnesium bromide. The isomerization step was catalysed by a commercially available pentamethylcyclopentadienyl ruthenium catalyst. The proposed mechanism of this isomerization in shown below **(Scheme B-12).** To gain information about this step, Bouziane and co-workers synthesized a deuterated allylic alcohol. Under the optimized reaction conditions, the isomerization led mainly to the formation of a monodeuterated saturated ketone. Due to the fact that deuterium is exclusively present at the β-position of the ketone function, the proposed mechanism involves two key steps: (i) a β-hydride elimination to form the α,β-unsaturated ketone, (ii) followed by the 1,4-addition of the ruthenium monohydride species.[39]



Scheme B-12: Proposed mechanism of the isomerization step

For the bromination another procedure was employed using bromine in tetrachlorocarbon.[40] The last step worked again with methylamine in ethanol. This time shorter reaction times were required, since after only 5 h some decomposition reactions appeared (NMR). The best time to stop the reaction seemed to be after 2 h and the reaction was performed at ambient temperatures. Again, after work up the hydrogen chloride salt was precipitated by adding dropwise ethereal HCl.

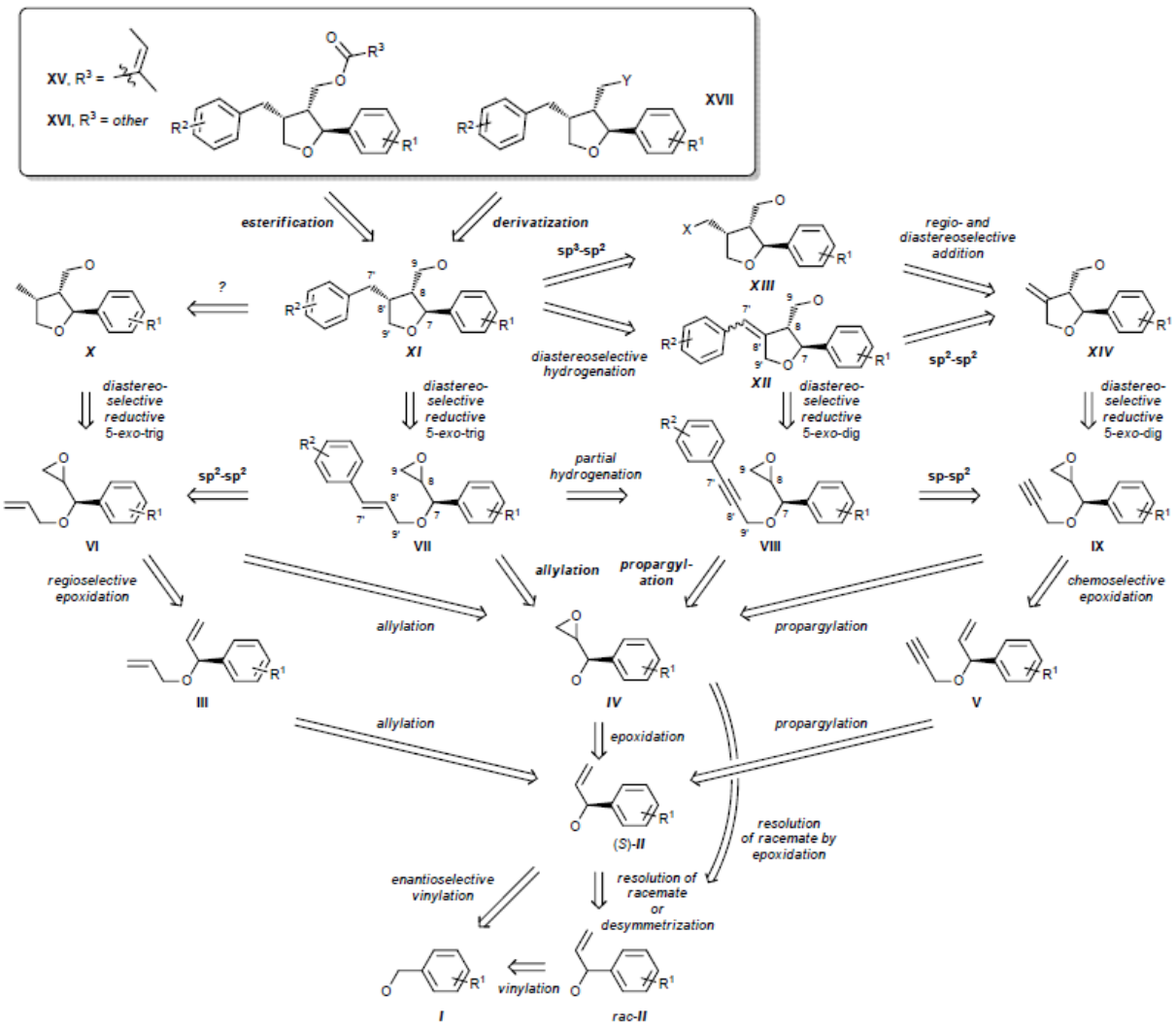


(14) **(15)** **(16)**

Scheme B-13: bromination and nucleophilic substitution of the nitro compound

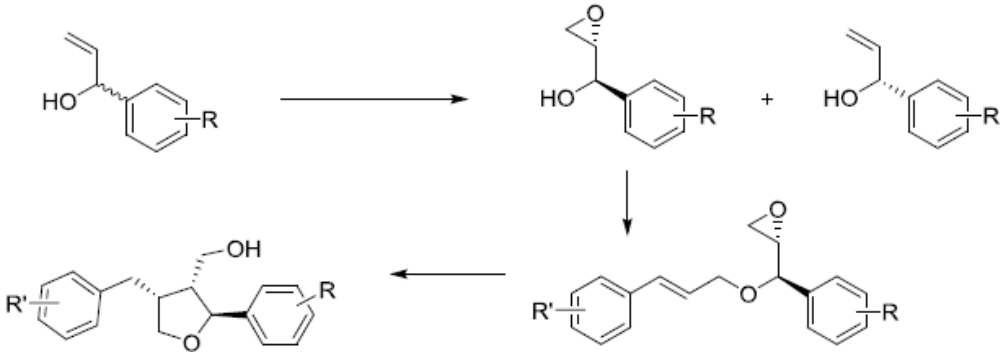
B.1.3 Synthesis of the leoligin key fragment

Scheme B-14 explores how leoligin-like compounds XV, XVI and XVII may be prepared. The general synthetic metodology 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 before-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 B-14 which promised swift access to leoligin and analogs and avoid many issues of the synthetic plans such as lengthy synthesis, poor diastereocontrol, racemic products and low yields.



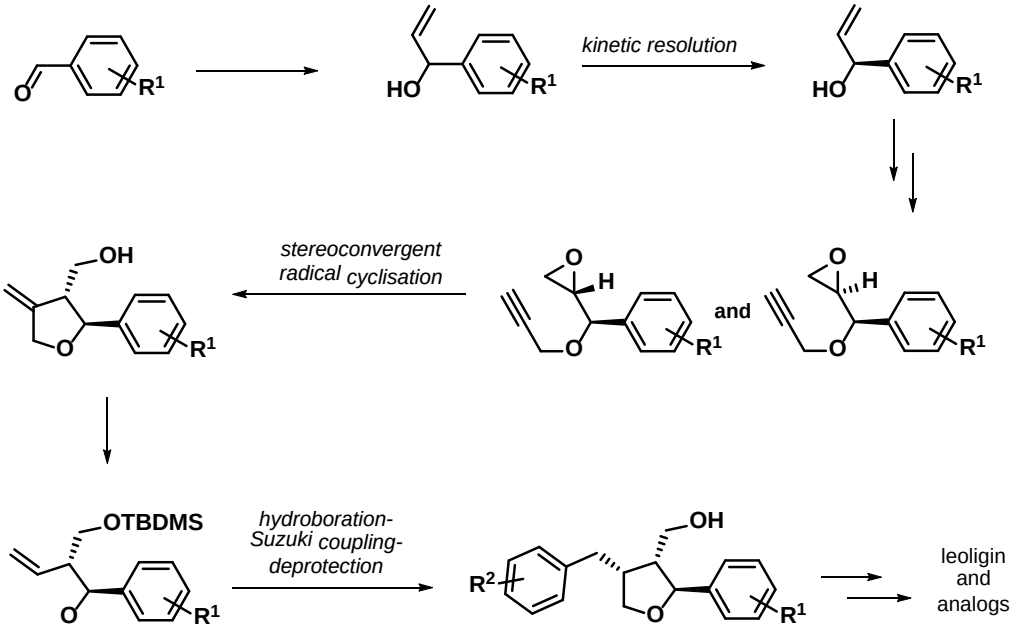
Scheme B-14: Retrosynthetic overview over possible routes to leoligin-like molecules. Steps in which the synthesis is divergent are indicated in bold. Synthons which are not actual chemical entities are labeled in italic. A distinction was made between (*Z*)-2-methylbut-2-enoates XV (esters of angelic acid) and other esters XIV due to the prominence of the former. For clarity, positions are numbered only in four structures, but the numbering applies throughout and is consistent with the IUPAC-recommended nomenclature for lignans.

The above road is key for orientation within the various possible routes. Banerjee et al.[41], who worked previously on structures related to the current leoligin project approached a route which included a kinetic resolution by Sharpless asymmetric epoxidation, a Williamson ether synthesis and a radical cyclization.



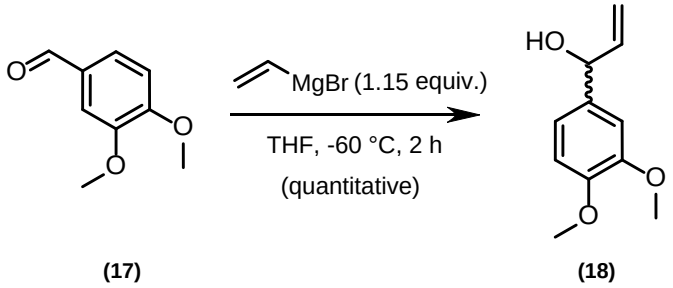
Scheme B-15: Pathway towards leoligin reported by Banerjee et al.

Thomas Linder developed this strategy towards a more modular synthesis (**Scheme B-16**), dismissing the initial Sharpless epoxidation as it led to poor yields, and instead first using Amano lipase PS. This led to an enantiomer-pure intermediate that needed to be epoxidized. But instead of the Sharpless epoxidation, a much simpler non-stereoselective mCPBA based protocol was used.[28]



Scheme B-16: Synthesis route developed and done by Thomas Linder

The first step of the total synthesis towards leoligin was a Grignard addition of vinylmagnesiumbromid to cheap and commercially available 3,4-dimethoxyaldehyde (veratraldehyde) and generated a racemic mixture of *rac*-**18** (Scheme B-17).



Scheme B-17: Grignard addition

Since only the (*S*)-allylic alcohol is relevant in further synthesis, a chiral resolution is required. A kinetic resolution *via* lipase-catalyzed enantioselective esterification was used. Lipases are triacylglycerol acyl hydrolases, i.e. their natural substrates are lipophilic triglycerides, which makes them versatile reagents for organic synthesis in non-aqueous media.[42] Most of them are built on an α / β hydrolase fold[43] and employ a chymotrypsin-like hydrolysis mechanism using a catalytic triad consisting of a serine nucleophile, a histidine base, and an acid residue (usually aspartic acid).[44-45] The mechanism of the lipase-catalyzed hydrolysis of a fatty acid ester consists of several steps **(Figure 8)**. It starts with a nucleophilic attack of the serine residue on the ester which results in a tetrahedral intermediate. The released proton of serin takes over to the imidazole residue of histidine, which is supported by the carboxylate anion of aspartic acid. The negatively charged intermediate, in turn, is stabilized by several amino acid esters in a region of the active site called the “oxyanion hole”. After elimination of an alcohol, an enzyme-substrate complex, the so-called acyl-enzyme, is formed. The nucleophilic attack

of water on the acylenzyme in the next step of the reaction leads again to a tetrahedral intermediate, which eventually breaks down into the free enzyme and the fatty acid.[43]

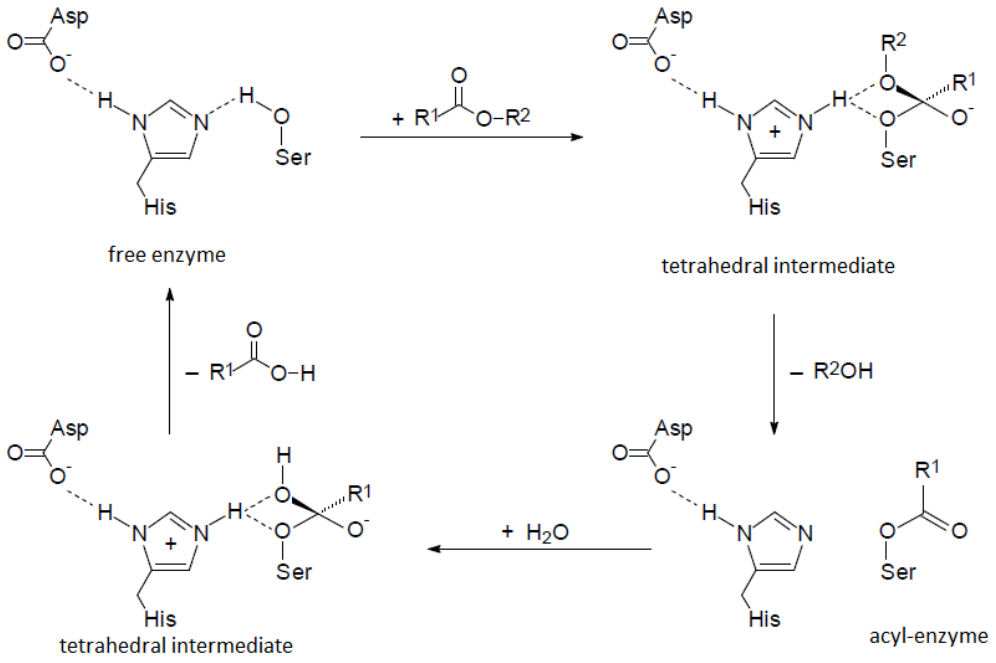


Fig. 8: Mechanism of the lipase-catalyzed hydrolysis of a fatty acid ester

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. **(Figure 9, top).**

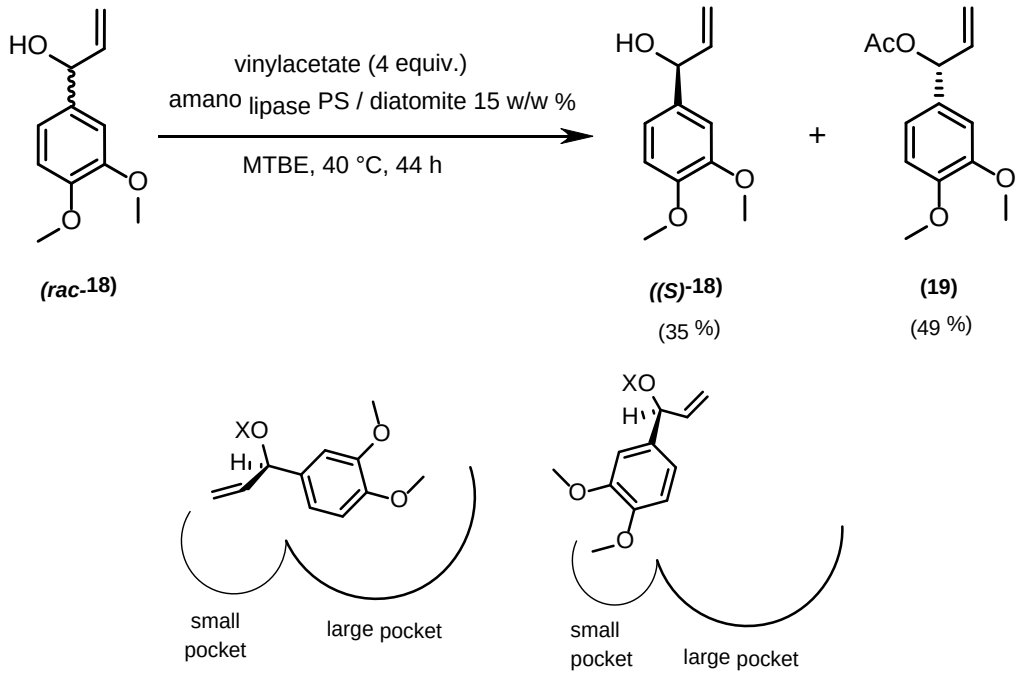


Fig. 9, top: Kinetic resolution. **Bottom:** Cartoon illustrating the mode of action of the enzyme.

Lipases generally obey Kazlauskas' rule[46], which translates well into a model where the active site of the enzyme consists of two pockets, a large and a small one (**Figure 9, bottom**). 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 alcohol **18**, the lipase is (*R*)-selective. The reaction was monitored on-the-fly by chiral HPLC and terminated when less than 1 % of the (*R*)-**18** enantiomer remained in the reaction mixture. Therefore, e.e. values for the isolated compound (*S*)-**18** were more than 98 %. Since this is not a dynamic kinetic resolution, the highest possible yield of the *(S)*-product is 50 %.

In previous work, 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 **(Figure 10).**

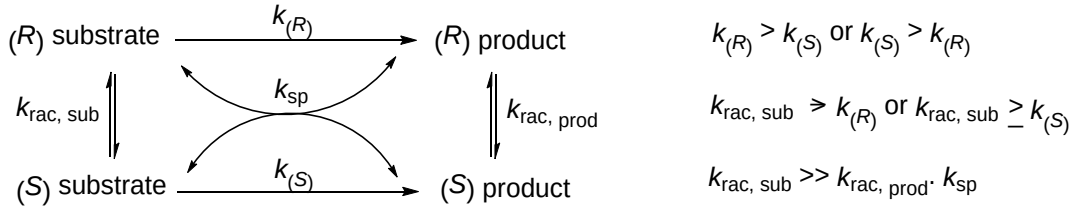
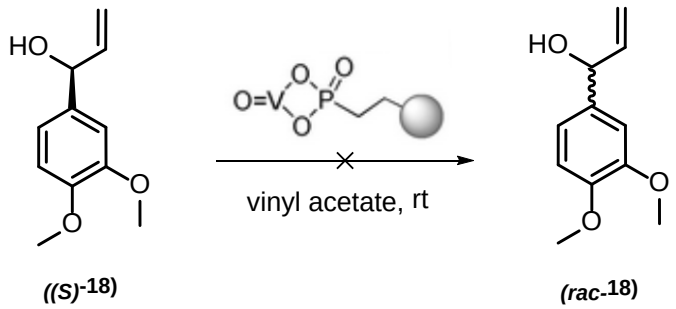


Fig. 10: Principle of dynamic kinetic resolution. $k_{rac,\ sub}$ and $k_{rac,\ prod}$: racemization rate constants for substrate and product, respectively. $k_{(R)}$ and $k_{(S)}$: rate constants for product formation from the (*R*) and (*S*) enantiomer, respectively. k_{sp}: spontaneous (non-catalyzed) interconversion.

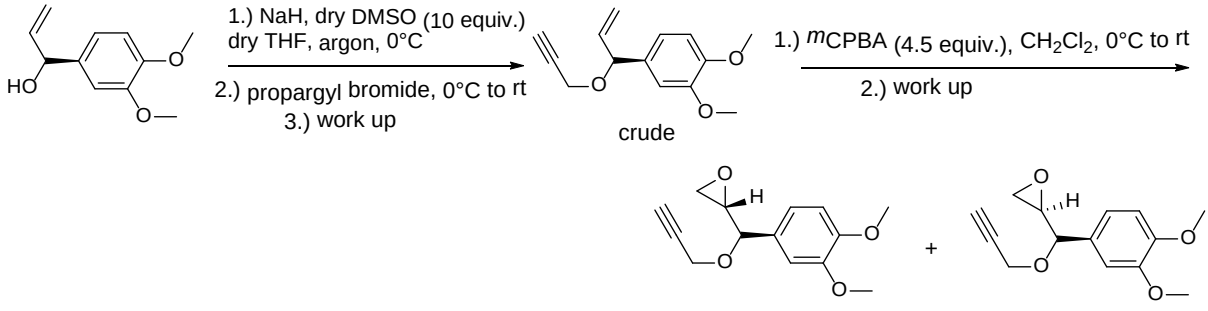
Combinations of enzymes for enantioselective, irreversible conversion to product with transition metal catalysts for substrate racemization have widely been used for dynamic kinetic resolution.[47] Therefore, a polymer-bound vanadyl phosphate was used as catalyst to see if it would convert (*S*)-**18** into a mixture of enantiomers. The reaction was carried out with 1- and 10 mol % of the catalyst in vinyl acetate as solvent (Scheme B-18). After 24 h there was no racemization observed in any of the samples (determination by chiral HPLC).



***((S)*-18)** ***(rac*-18)**

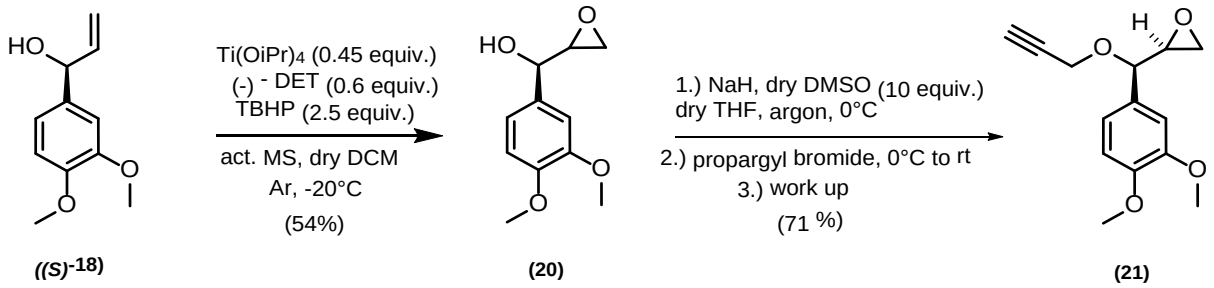
Scheme B-18: Attempted racemization of (*S*)-**18**

Having enantiopure compounds (*S*)-**18**—although not by *dynamic* kinetic resolution—in hand, the next step (*cf.* **Scheme B-16**, page 17) was the oxidation of the double bond to prepare the epoxides. To do so, Linder performed a nucleophilic substitution using propargyl bromide and afterwards an epoxidation with *m*CPBA.



Scheme B-19: Propargylation-epoxidation sequence by Linder

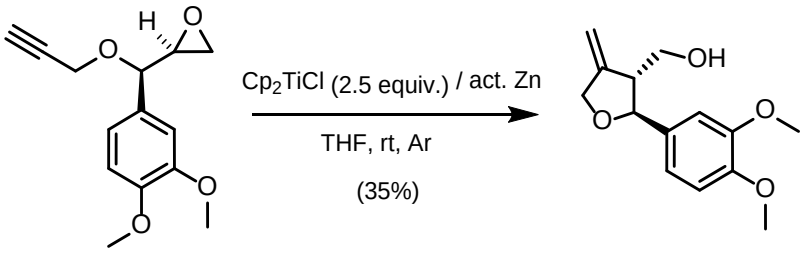
Using this method, only poor yields were obtained, since problems appeared during the work up of the epoxidation step. As an alternative, Sharpless epoxidation was applied, and therefore the epoxidation had to be done first:



***((S)*-18)** **(20)** **(21)**

Scheme B-20: Propargylation-epoxidation sequence done in this work

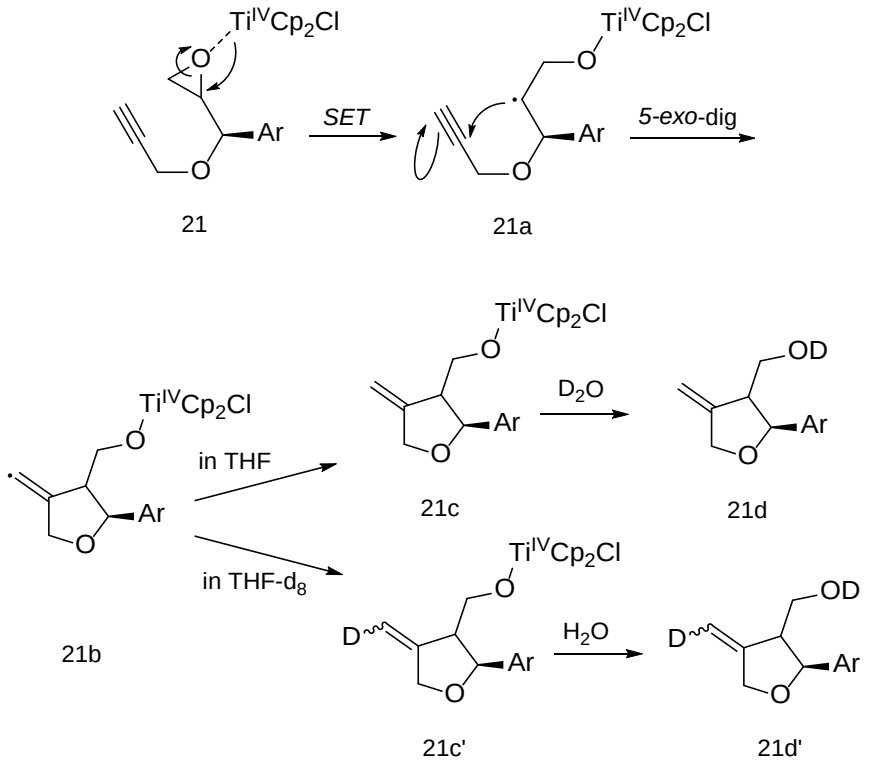
The Sharpless epoxidation was carried with optimizations done by previous coworkers for similar substrates.[48] The key step of the whole total synthesis, the radical cyclization, was carried out according to Saha and Roy[49] with a yield of 35 % of the desired diastereoisomer. The key step is known to yield in the range of just 40 % (Scheme B-21).



(21) **(22)**

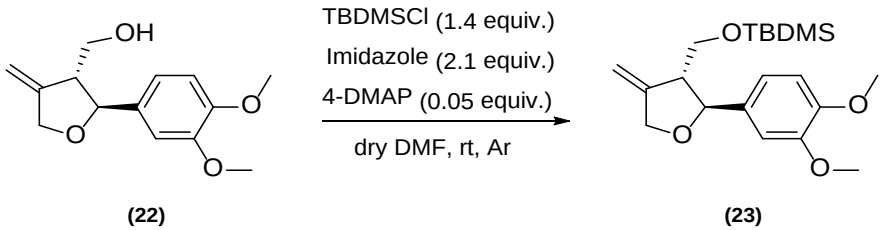
Scheme B-21: Radical cyclisation

In the first step, the titanium(III) reagent probably needs to coordinate to the oxygen of epoxide. (Scheme B-22). 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 **21a**. 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 **21b**. Deuterolysis of the experiment with triple bond-containing compound **21** as the starting material produced **21d** which did not contain any deuterium at the methylene group, suggesting that the highly reactive vinyl radical **21b** 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 (**21d'**). 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 37 % of **21d** had been obtained in these mechanistic studies by Nugent and RajanBabu.[50]



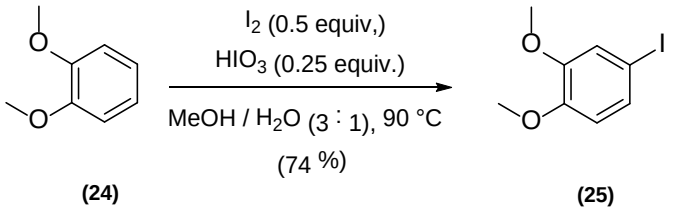
Scheme B-22: Mechanism of titanium(III)-promoted radical and reductive cyclization

In order to avoid side reactions and to control the selectivity of the hydroboration and subsequently of the Suzuki-Miyaura coupling, protection of the hydroxyl group as silyl ether was of importance. Therefore, key fragment **(22)** was protected with a tertbutyldimethylsilyl group by employing a standard protocol and work up (Scheme B-23).



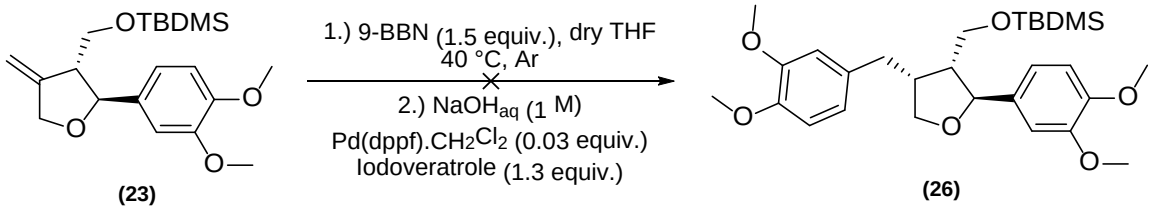
Scheme B-23: Sillyl protection

The next step (*cf*. **Scheme B-16**, page 17) would be the hydroboration-Suzuki coupling sequence and it was found that crude **(23)** can be used for this. Depending on the desired product, different coupling partners could be used. Some of them are commercially available, some need to be synthesized such as 4-iodoveratrole, whose coupling product with **(23)** would lead to leoligin. This was done[51] as with complete regioselectivity of iodine entry (Scheme B-24).



Scheme B-24: Synthesis of 4-iodoveratrole

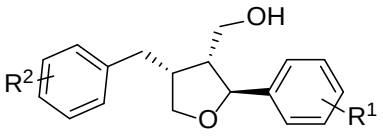
For the Suzuki reaction, 1,1'bis(diphenylphpsphino)ferrocene (dppf) appears to be a popular ligand for transformations with 9-BBN-derived coupling partners.[52-53] The coupling part of the reaction can be conducted in THF, which is convenient because 9-BBN is commercially available as a solution in this solvent. Attempts to do the coupling as explained above and conducted in Linders work[28] (Scheme B-25) did not show formation of any product (TLC and NMR).



Scheme B-25: attempted hydroboration-Suzuki coupling sequence

To recognize the problem, the reaction was quenched after the first step with NaOH (3 M) and H_2O_2 (30 % wt. in H_2O). TLC proved the formation of the alcohol and showed that the hydroboration step was not the critical one. Since the synthesis didn't go further, the leoligin project was handed to a more experienced member[i] of the working group. After many trials and errors and considering a lot of aspects during the synthesis, he found out that one possible cause of defect could be the solvent. The coupling is a catalytical step and the solvents used during this work (unless described otherwise) were technical solvents. As Linder worked on this project "pro analytics" solvents were used, which have much less impurities than technical solvents. Since catalysts can be poisoned by a small percentage of impurities, this might be a possible reason for the failure. Using "pro analytics" solvents for similar compounds led to the desired coupling product.

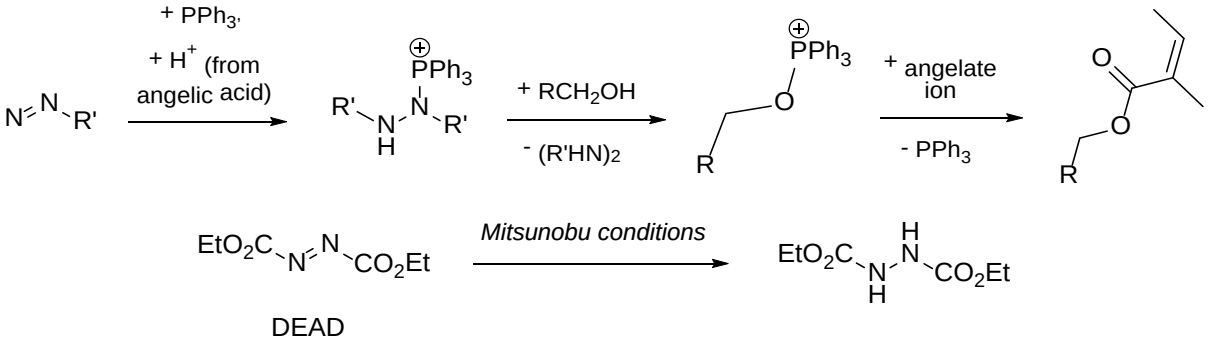
Continuing the synthesis of leoligin, the next step would be the deprotection of the silyl group. It was found that the sylil group can be removed *in situ* by simply adding TBAF solution after coupling. The last step in the syntheis of leoligin and analogs thereof is the acylation of the primary hydroxy group at C9. As for leoligin itself, esterification involving angelic acid needs to be carried out. Leoligin, and other angelic acid-containing esters of the structure **(I)** can be prepared by Mitsunobu reaction.[54]



(I)

There, the carboxylic acid, as its anion, merely reacts as a nucleophile with phosphonium alkoxide and displaces a phosphine oxide (Scheme B-26). The phosphonium alkoxide is generated from a phosphine (mostly triphenylphosphine) and a diazo compound. The most commonly employed diethyl azodicarboxylate (DEAD) can be used for this transformation.

[i] The author would like to acknowledge Dipl.-Ing. Dr. Laszlo Czollner for performing the experiments.



Scheme B-26: Mitsunobu reaction used for the generation of angelic acid-bearing lignans

C Conclusion and outlook

In this thesis, a valuable method for generating three novel mephedrone derivatives was presented. One in both enantiopure forms and the other two in their racemic form. The synthesized compounds in chapter B.1.1 and B.1.2 will be tested in the group of Harald Sitte at Medical University of Vienna. If the racemic compounds (chapter B.1.2) show interesting biological activities, a separation of the enantiomeres will be done, to prove their activity in their enantiomerically pure form. The latter is beyond the scope of this work.

Additionally, the key fragment for the synthesis of leoligin and a variety of leoligin analogs was prepared. As this work is part of a bigger project, having the key fragment in hand, the diastereoselective hydroboration and subsequent Suzuki-coupling will be done for the rapid generation of a compound library. By making synthetic decisions based on continually returning screening results, this method can be used to generate molecules diverse enough to gain insight into the structural requirements for improving the biological activities of leoligin.

D Experimental Section

D.1 General Notes

D.1.1 Chemicals

Chemicals were purchased from commercial suppliers and used without further purification, unless otherwise noted.

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 Et2O. After drying *in vacuo* at 60 °C the material was stored under argon.[55]

D.1.2 Dry solvents

Dry **toluene, CH_2Cl, Et_2O, THF** and **MeOH** were obtained by passing pre-dried material through a cartridge containing activated alumina (PURESOLV, Innovative Technology) via a solvent dispensing system unless otherwise noted and were stored under nitrogen.

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

Deoxygenated and dry THF was obtained by refluxing and distilling pre-dried material (as describes above) from sodium and benzophenone under argon.[56]

D.1.3 Chromatography (TLC, MPLC, HPLC)

Thin Layer Chromatography TLCs were performed on aluminum coated silica gel 60 F_{254} from Merck and spots were visualized with UV light (254 nm). 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). Amines were visualized with a ninhydrin solution (0.2 g ninhydrin in 100 ml ethanol).

Flash column chromatography was performed on a Büchi Sepacore™ MPLC system, using silica gel 60 (40-63 µm) from Merck.

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.

D.1.4 Melting points

Melting ranges were determined using or an SRS OptiMelt Automated Melting Point System. Temperatures are reported in intervals of 1 °C.

D.1.5 Specific rotation

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*).

D.1.6 GC-MS

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

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.

Method A: 160 °C (2 min), to 280 °C (12 °C / min)

Method B: 100 °C (2 min), to 280 °C (12 °C / min)

Data is reported in the form *retention time*; m/z_1 (*relative intensity in %*), m/z_2 (*relative intensity in %*), etc. Also, the molecular ion signal M+ is given.

D.1.7 HR-MS

All HR-MS measurements were carried out by Dr. Laszlo Czollner at University of Natural Resources and Life Sciences, Vienna.

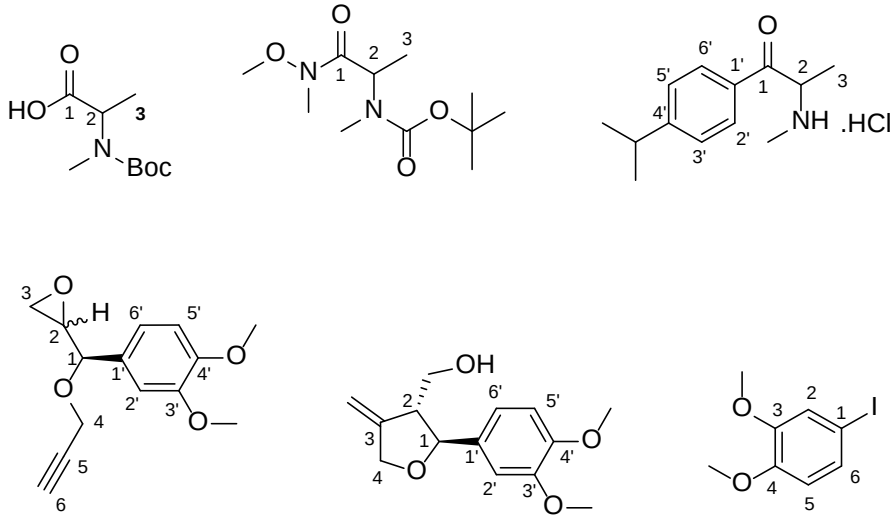
HR-MS analysis was carried out from methanol solutions (concentration: 10 µM) by using an HTC PAL system autosampler (CTC Analytics AG, Zwingen, Switzerland), an Agilent 1100/1200 HPLC with binary pumps, degasser and column thermostat (Agilent Technologies, Waldbronn, Germany) and Agilent 6230 AJS ESI–TOF mass spectrometer (Agilent Technologies, Palo Alto, United States).

Chromatography: Column: Phenomenex C-18, 2.1 ID, 1.7 µm particles, operated at 40 °C; Column flow: 0.5 ml/min; Injection volume: 5 µl; Gradient: A: H2O + 0.1 % formic acid, B: MeOH + 0.1 % formic acid – isocratic 70% phase B;

D.1.8 NMR spectroscopy

^{1}H- and ^{13}C-NMR spectra were recorded from $CDCl_3$ or D_2O solutions on a Bruker Avance UltraShield 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm relative to the nominal residual solvent signals: ^{1}H: 7.26 ppm, ^{13}C: 77.16 ppm (CDCl3) and ^{1}H: 4.79 ppm (D_2O).

D.1.9 NMR assignments



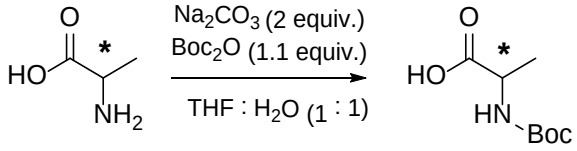
Signal multiplicities are denoted as: singlet (s), doublet (d), triplet (t), quartet (q) or unspecified multiplet (m).

D.10 Abbreviations

anh.	anhydrous
apoAI	apolipoprotein A1
DEA	diethylamine
4-DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
EtOH	ethanol
equiv.	equivalent(s)
EDCI.HCl	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
HOBt	benzotriazol-1-ol
i-PrOH	propan-2-ol
LDA	lithium diisopropylamide
LP	light petroleum
*m*CPBA	*meta*-chloroperbenzoic acid
MPLC	medium pressure liquid chromatography
MTBE	methyl *tert*-butyl ether
NBS	*N*-Bromosuccinimide
rac	racemic
rt	room temperature
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydroperoxide
*t*Bu	*tert*-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
SMC	smooth muscle cell

D.2 Synthesis of Weinreb amides

D.2.1 *(R)* and *(S)* (*tert*-Butoxycarbonyl)alanine



***(R)*-1 or *(S)*-1** ***(R)*-2 or *(S)*-2**

This compound was introduced according to the literature.[57]

A three-neck bottom flask was equipped with a thermometer, a septum rubber and a stirring bar. Alanine **(1)** (5 g, 56 mmol, 1 equiv.) was dissolved in an 1 : 1 mixture of H_2O and THF (75 mL) along with Na_2CO_3 (13 g, 123 mmol, 2 equiv.). The mixture was cooled to 0 °C and Boc_2O (13.5g, 50 mmol, 1.1 equiv.) was slowly added. The reaction was warmed up to rt and stirred overnight. After TLC showed full conversion, the pH of the mixture was adjusted to 2 by careful addition of 1M HCl (250 mL). The mixture was extracted with EtOAc (4 x 125 mL). The combined organic phases were washed with brine (80 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. Since NMR showed a purity over 95 %, no further purification was done.

(R)

Yield: 9.75 g (93 %)
Appearance: colorless solid
Specific rotation: $[\alpha]_D^{20}$: -24.2° (*c* 1, acetic acid), lit.[58]: -21.6° (*c* 1, acetic acid)

(S)

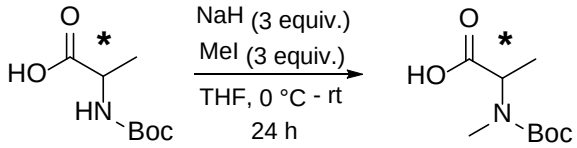
Yield: 10.33 g (98 %)
Appearance: colorless solid
Specific rotation: $[\alpha]_D^{20}$: +22.2° (*c* 1, acetic acid), lit.[58] for the *(R)*-isomer: -21.6° (*c* 1, acetic acid)

Molecular formula, m.w.: $C_8H_{15}NO_4$, 189.21
Melting point: 79 – 82 °C (lit.[57]: 79 – 81°C)
TLC: R_f (CH_2Cl_2 : MeOH, 95 : 5) = 0.1

^{1}H NMR (400 MHz, DMSO): δ = 1.21 (d, *J* = 7.3 Hz, 3H, H3), 1.37 (s, 9H, *t*Bu), 3.91 (q, *J* = 7.4 Hz, 1H, H2), 7.08 (d, *J* = 7.6 Hz, 1H NH), 12.40 (s, 1H, COOH).

^{13}C NMR (101 MHz, DMSO): δ = 17.6 (q, C3), 28.7 (q, *t*Bu), 49.3 (d, C2), 78.4 (s, *t*Bu), 155.7 (s, NCO), 175.1 (s, COOH).

D.2.2 *(R)* and *(S)* N-(tert-butoxycarbonyl)-N-methylalanine



(R)-**2** or *(S)*-**2** *(R)*-**3** or *(S)*-**3**

This compound was introduced according to the literature.[59]

A round bottom flask equipped with a septum rubber and a stirring bar was charged with tert-butoxycarbonyl)alanine **(2)** (5 g, 26.4 mmol, 1 equiv.), and then evacuated and back filled with argon using standard Schlenk-line technique. Anhydrous THF (88 mL) was added and the solution was cooled to 0 °C. NaH (60 % dispersion in mineral oil, 3.2 g, 79.3 mmol, 3 equiv.) was added in portions and the reaction was stirred for 1 h at 0 °C. Then MeI (13.1 mL, 211 mmol, 8 equiv.) was added dropwise via syringe at this temperature and the reaction mixture was allowed to warm to room temperature and stirred overnight. Reaction progress was monitored by TLC and the reaction was terminated when complete.

The reaction was quenched with water (170 mL) and extracted with Et_2O (170 mL). The organic phase was separated and washed a saturated solution of $NaHCO_3$ (170 mL). The aqueous phases were combined and pH was adjusted to 2 by careful addition of 6 M HCl. The now acidic phase was extracted with EtOAc (3 x 160) and the combined organic layers were washed with a saturated solution of $Na_2S_2O_3$ (110 mL), dried over anh. $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. Since NMR showed a purity over 95 %, no further purification was done.

(R)

Yield: 3.66 g (68 %)
Appearance: colorless solid
Specific rotation: $[\alpha]_D^{20}$: +46.8° (*c* 0.94, CH_2Cl_2), lit.[60] for the *(S)*-isomer: -41.8° (*c* 0.91, CH_2Cl_2)

(S)

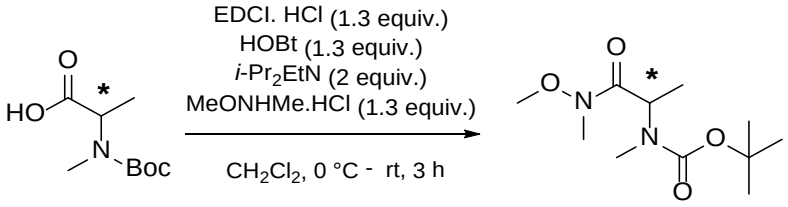
Reaction scale: 4.76 g (25.17 mmol)
Yield: 3.37 g (66 %)
Appearance: colorless solid
Specific rotation: $[\alpha]_D^{20}$: -41.7° (*c* 0.94, CH_2Cl_2), lit.[60]: -41.8° (*c* 0.91, CH_2Cl_2)

Molecular formula, m.w.: $C_9H_{17}NO_4$, 203.24
Melting point: 87 – 89 °C (lit.[61]: 89 °C)
TLC: R_f (CH_2Cl_2 : MeOH, 95 : 5) = 0.4

^{1}H NMR (400 MHz, DMSO): Mixture of rotamers. δ = 1.28 (d, *J* = 15.4 Hz, 3H H3,), 1.38 (s, 9H, *t*Bu), 2.73 (s, 3H, NMe), 4.27 (q, *J* = 7.2 Hz, 0.5 H, H2), 4.54 (q, *J* = 7.4 Hz, 0.5 H, H2), 12.66 (s, 1H, COO<u>H</u>).

^{13}C NMR (101 MHz, DMSO): Mixture of rotamers. δ = 15.1 (q, C3), 15.7 (q, C3), 28.4 (q, (<u>C</u>H_3)$_3$), 28.5 (q, *t*Bu), 31 (q, NMe), 31.8 (q, NMe), 53.7 (d, C2), 55.3 (d, C2), 79.4 (s, *t*Bu), 155.1 (s, NCO), 155.5 (s, NCO), 173.9 (<u>C</u>OOH).

D.2.3 *(R)* and *(S)* tert-Butyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl) (methyl)carbamate



***(R)*-3 or *(S)*-3** ***(R)*-4 or *(S)*-4**

This compound was introduced according to a modified literature procedure.[62]

A three-neck round bottom flask equipped with a thermometer, a rubber septum and a stirring bar was charged with N-(tert-butoxycarbonyl)-N-methylalanine **(3)** (1 g, 4.92 mmol, 1 equiv.), evacuated and backfilled with argon using standard Schlenk technique. Dry CH_2Cl_2 (20 mL) was added and 1-hydroxybenzotriazol (0.98 g, 6.4 mmol, 1.3 equiv.), *N,O*-dimethylhydroxylamine hydrochlorid (0.62 g, 6.4 mmol, 1.3 equiv.) and *i*-Pr_2EtN (1.7 mL, 9.84 mmol, 2 equiv.) were added successively. The reaction mixture was cooled to 0°C and EDCI hydrochloride (1.2 g, 6.4 mmol, 1.3 equiv.) was added. The reaction was allowed to warm to rt and stirred until TLC indicated full conversion.

After 3 h the reaction was quenched by addition of 30 mL water and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with HCl (1 M, 30 mL), a saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo.* Since NMR showed a purity over 95 %, no further purification was done.

(R)

Yield: 1.1 g (90 %)
Appearance: colorless oil
Specific rotation: $[\alpha]_D^{20}$: -58.8° (*c* 1.06, CH_2Cl_2), lit.[60]: -55.5° (*c* 1.06, CH_2Cl_2)

(S)

Reaction scale: 2.58 g (12.41 mmol)
Yield: 2.92 g (95 %)
Appearance: colorless oil
Specific rotation: $[\alpha]_D^{20}$: +61.8° (*c* 1.06, CH_2Cl_2), lit. [60] for the *(R)*-isomer: -55.5° (*c* 1.06, CH_2Cl_2)

Molecular formula, m.w.: $C_{11}H_{22}N_2O_4$, 246.31
TLC: R_f (CH_2Cl_2 : MeOH, 95 : 5) = 0.44

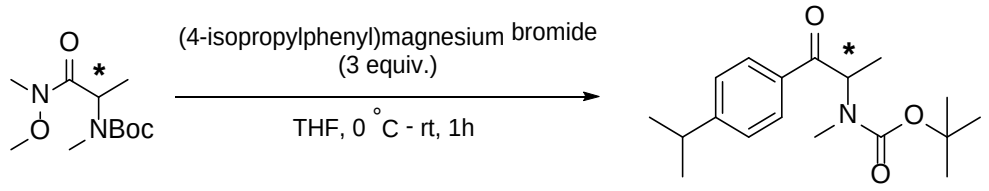
^{1}H NMR (400 MHz, $CDCl_3$): Mixture of rotamers. δ = 1.28 (d, *J* = 7.1 Hz, 3H, H3), 1.43 (s, 9H, *t*Bu), 2.83 (s, 3H, ONC$\underline{H}_3$), 3.16 (s, 3H, NC$\underline{H}_3$), 3.67 (s, 1.5H, OMe), 3.71 (s, 1.5H, OMe), 4.84 – 4.94 (m, 0.5H, H2), 5.15 – 5.23 (m, 0.5H, H2).

^{13}C NMR (101 MHz, $CDCl_3$): Mixture of rotamers. δ = 14.7 (q, C3), 28.6 (q, *t*Bu), 30 (q, ONC$\underline{H}_3$), 32.3 (q, NC$\underline{H}_3$), 50 (d, C2), 51.8 (d, C2), 61.4 (q, OMe), 61.6 (q, OMe), 79.8 (s, *t*Bu), 80.1 (s, *t*Bu), 155.2 (s, CO), 155.9 (s, CO).

D.3 Synthesis of 4-MCATs

D.3.1 para-^{i}Pr-MCAT

D.3.1.1 (*R*) and (*S*) tert-Butyl (1-(4-isopropylphenyl)-1-oxopropan-2-yl)(methyl)carbamate



(R)-4 or *(S)*-4 *(R)*-5 or *(S)*-5

This compound was introduced according to a literature procedure.[31]

Preparation of the Grignard reagent: A three-neck round bottom flask equipped with a thermometer, a rubber septum, a condenser and a stirring bar was charged with magnesium turnings (1 equiv.), evacuated and backfilled with argon using standard Schlenk technique. 1mL of THF was added, followed by a small amount of 1-bromo-4-isopropylbenzene until a color change and exotherm were observed. Then the rest of solvent (4 mL to create a 1M solution) was added, followed by dropwise addition of rest of 1-bromo-4-isopropylbenzene (overall 1 equiv.) and stirred at 50 °C until magnesium fully dissolved.

tert-Butyl (1-(methoxy(methyl)amino)-1-oxopropan-2-yl)(methyl)carbamate (208 mg, 0.82 mmol, 1 equiv.) was dissolved in anhydrous THF (5 mL) under argon and cooled to 0°C. Freshly prepared (4-isopropylphenyl)magnesium bromide (2.5 mL, 2.5 mmol, 3 equiv.) was added dropwise. The reaction was stirred at 0°C for 1 hour, then warmed to rt and stirred for additional 30 minutes. When TLC indicated full conversion, the reaction was quenched with a saturated aqueous NH_4Cl solution (4 mL) and water (8 mL). The mixture was extracted wit Et_2O (4 x 8 mL), combined organic phases were washed with brine (8 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*.

The crude product was purified by flash column chromatography (15 g silica, LP / EtOAc, isocratically 95 : 5) to afford the title compound **(5).**

(R)

Yield: 200 mg (80 %)
Appearance: colorless oil
Specific rotation: $[\alpha]_D^{20}$: +138° (*c* 0.81, CH_2Cl_2)
ee.: 99 % (HPLC)
HPLC: 5.3 min; Diacel Chiralpak AS-H; flowrate 1 ml / min, hexane / EtOH, 99.7 : 0.3, 25 °C, detection at 254 nm.

LC-HRMS (ESI): calculated for $M+H^+$: 306.2064, found: 306.2063, Δ = 0.39 ppm

(S)

Reaction scale: 200 mg
Yield: 181 mg (72 %)

Appearance: colorless oil
Specific rotation: $[\alpha]_D^{20}$: **-**114° (*c* 0.81, CH_2Cl_2)
ee.: 98 % (HPLC)

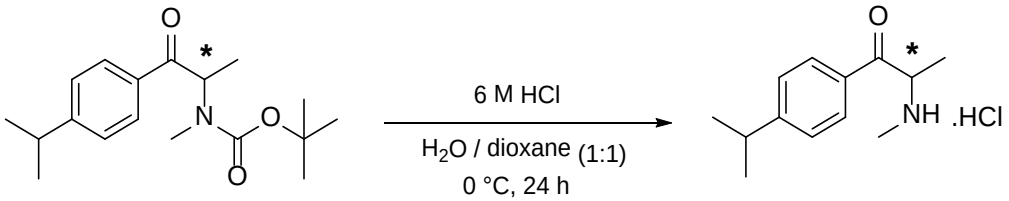
HPLC: 6.2 min; Diacel Chiralpak AS-H; flowrate 1 ml / min, hexane / EtOH, 99.7 : 0.3, 25 °C, detection at 254 nm.

LC-HRMS (ESI): calculated for $M+H^+$: 306.2064, found: 306.2066, Δ = -0.77 ppm
Molecular formula, m.w.: $C_{18}H_{27}NO_3$, 305.42
TLC: R_f (LP: EtOAc, 3 : 1) = 0.85

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of rotamers. δ 1.26 (d, *J* = 6.9 Hz, 6H, $(CH_3)_2$), 1.34 (d, *J* = 6.9 Hz, 1.8H, H3), 1.37 (d, 1.2H, H3), 1.44 (d, *J* = 6.3 Hz, 9H, *t*Bu), 2.64 (s, 1.8H, NMe), 2.78 (s, 1.2H, NMe), 2.95 (q, *J* = 6.9 Hz, 1H, C<u>H</u>$(CH_3)_2$), 5.20 (q, *J* = 7.0 Hz, 0.4H, H2), 5.68 (q, *J* = 6.9 Hz, 0.6H, H2), 7.28 (d, *J* = 6.5 Hz, 2H, H2', H6'), 7.89 (dd, *J* = 35.8, 7.9 Hz, 2H, H3', H5').

^{13}C NMR (101 MHz, $CDCl_3$): Mixture of rotamers. δ 13.6 (q, C3), 13.9 (q, C3), 23.8 (q, $(CH_3)_2$), 28.5 (q, *t*Bu), 29.7 (q, NMe), 30.6 (q, NMe), 34.4 (d, <u>C</u>H$(CH_3)_2$), 54.5 (d, C2), 56.8 (d, C2), 80.2 (s, *t*Bu), 80.7 (s, *t*Bu), 126.8 (d, C2', C6'), 128.6 (d, C3'), 128.9 (d, C5'), 133.4 (s, C1'), 154.8 (s, C=O / C4'), 155.6 (s, C=O / C4'), 199.4 (s, C1).

D.3.1.2 (*R*) and (*S*)-1-(4-Isopropylphenyl)-2-(methylamino)propan-1-one hydrochloride



***(R)*-5 or *(S)*-5** ***(R)*-6 or *(S)*-6**

The title compound was prepared according to a modified literature procedure.[36]

In an 8 mL screw-cap vial **<u>(5)</u>** (130 mg, 0.49 mmol, 1 equiv.) was added dropwise to pre-cooled solution of 6 M HCl in H_2O / dioxane 4 : 1 (2.5 mL, this solution was prepared by mixing 50 mL conc. HCl and 20 mL of dioxane and diluting the mixture to 100 mL with deionised water) at 0 °C and stirred over night at this temperature. After TLC indicated full conversion, the reaction mixture was extracted with 2 x 2 mL of Et_2O and the aqueous layer was evaporated in a stream of pressurized air. The residue was taken up in deionised water, filtered and lyophilized.
Analytical protocol for the determination of enantiomeric excess using chiral HPLC:

For the analysis of the enantiomeric composition of **<u>(6)</u>** samples on normal-phase chiral HPLC, an analytical protocol from the literature[63] was adapted.
In a screw-cap vial 1.5 mg of the corresponding hydrochloride were dissolved in water (1 mL). Then 10 µl of 2 M NaOH were added and the free base was extracted with dichloromethane (1 mL). The organic layer was dried over anh. sodium sulfate, filtered and evaporated in a stream of air. The oily residue was taken up in an HPLC-grade mixture of n-heptane / i-PrOH (97 : 3), filtered and immediately subjected to HPLC analysis.

(R)

Yield: 62 mg (52%)
Appearance: white powder
Specific rotation: $[\alpha]_D^{20}$: +47.0° (*c* 0.79, MeOH)
ee.: 99 % (HPLC)

HPLC: 9.7 min; Diacel Chiralpak AS-H; flowrate 1 ml / min, heptane / i-PrOH / DEA, 97 : 3: 0.1, 25 °C, detection at 254 nm.

LC-HRMS (ESI): calculated for $M+H^+$: 206.1539, found: 206.1541, Δ = -0.69 ppm

(S)

Reaction scale: 150 mg
Yield: 97 mg (87 %)
Appearance: white powder
Specific rotation: $[\alpha]_D^{20}$: -40.1° (*c* 0.85, MeOH)
ee.: 99 % (HPLC)

HPLC: 6.8 min; Diacel Chiralpak AS-H; flowrate 1 ml / min, heptane / i-PrOH / DEA, 97 : 3: 0.1, 25 °C, detection at 254 nm.

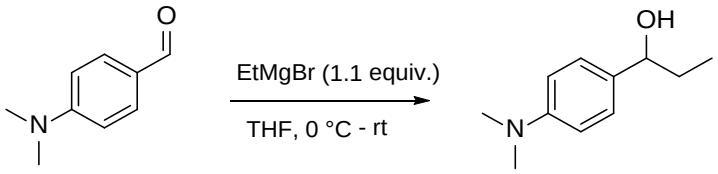
LC-HRMS (ESI): calculated for $M+H^+$: 206.1539, found: 206.1543, Δ = 1.96 ppm
Molecular formula, m.w.: $C_{13}H_{20}ClNO$, 241.76
Melting point: decomposition > 175 °C

^{1}H NMR (400 MHz, D_2O): δ 1.27 (d, *J* = 6.9 Hz, 6H, $(CH_3)_2$), 1.61 (d, *J* = 7.3 Hz, 3H, H3), 2.81 (s, 3H, NMe), 3.05 (q, *J* = 6.9 Hz, 1H, C<u>H</u>$(CH_3)_2$), 5.09 (q, *J* = 7.3 Hz, 1H, H2), 7.55 (d, *J* = 8.4 Hz, 2H, H2‘, H6‘), 7.98 (d, *J* = 8.4 Hz, 2H, H3‘, H5‘).

^{13}C NMR (101 MHz, D_2O): δ 15.4 (q, C3), 22.7 (q, CH_3), 22.8 (q, CH_3), 30.9 (q, NMe), 33.9 (d, <u>C</u>H$(CH_3)_2$), 59.5 (d, C2), 127.4 (d, C3‘, C5‘), 129.3 (d, C2‘, C6‘), 130 (C1‘), 157.9 (C4‘), 197.1 (C1).

D.3.2 Synthesis of 4-dimethylamino-MCAT

D.3.2.1 1-(4-(Dimethylamino)phenyl)propan-1-ol



(7) **(8)**

This compound was prepared according to the literature.[34]

A three-neck bottom flask equipped with a thermometer, a septum rubber, a stirring bar was evacuated and backfilled with argon using standard Schlenk technique. Ethylmagnesium bromide (1 M in THF, 7.4 mL, 1.1 equiv.) was cooled to 0 °C and 4-(dimethylamino)benzaldehyde (1 g, 6.7 mmol, 1.0 equiv.) in THF (6.6 mL) was added dropwise. The reaction mixture was allowed to warm to rt and stirred over night. After TLC showed full conversion, the reaction was quenched by adding 1 mL of a saturated NH_4Cl solution. Water (27 mL) was added and the mixture was added with 4 x 27 mL of Et_2O and 2 x 27 mL of EtOAc. The combined organic phases were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*.

The crude product was purified through flash column chromatography (90 g silica, 9 g precolumn, LP / EtOAc, isocratically 85 : 15) to afford the title compound **(8)**.

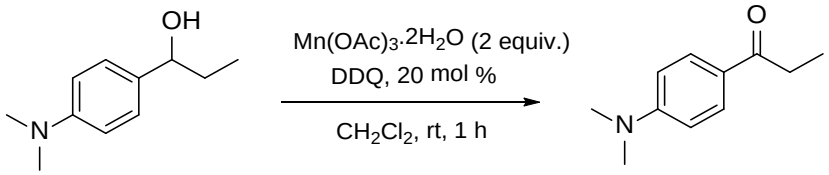
This compound is literature-known.[34]

Yield: 1.04 g (87 %)
Appearance: pale yellow oil which solidifies when stored refrigerated
Melting point: compound obtained as a liquid, lit.[34]: 37 – 38 °C
Molecular formula, m.w.: $C_{11}H_{17}NO$, 179.26
TLC: R_f (LP: EtOAc, 85 : 15) = 0.11

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.4 Hz, 3H, H3), 1.68 – 1.88 (m, 2H, H2), 2.95 (s, 6H, NMe), 4.49 (t, *J* = 6.7 Hz, 1H, H1), 6.73 (d, *J* = 8.7 Hz, 2H, H3‘, H5‘), 7.22 (d, *J* = 8.5 Hz, 2H, H2‘, H6‘).

^{13}C NMR (101 MHz, $CDCl_3$): δ 10.5 (q, C3), 31.6 (t, C2), 40.9 (q, NMe), 76 (d, C1), 112.7 (d, C3‘, C5‘), 127.1 (d, C2‘, C6‘), 132.8 (s, C1‘), 150.3 (s, C4‘).

D.3.2.2 1-(4-(Dimethylamino)phenyl)propan-1-one



(8) **(9)**

The title compound was prepared according to a modified literature procedure.[34]

Preparation of the co-oxidizing agent[33]: In a three-neck bottom flask equipped with a thermometer, a septum rubber and a stirring bar $Mn(OAc)_2.4H_2O$ (6.86 g, 28 mmol, 1 equiv.) was added to boiling glacial acetic acid (70 mL). Once most of the material was dissolved, $KMnO_4$ (1.1 g, 7 mmol, 0.25 equiv.) was added in portions over several minutes. Stirring was maintained at the boiling point for 30 min. The solution was then cooled to rt and 1.05 mL water was added. Stirring was continued for additional 24 hours, after which the dark colored solution was allowed to stand for 2 days. The product was filtered, washed with glacial acetic acid and Et_2O, and allowed to air-dry to a constant weight, furnishing 5.76 g (77 %) of $Mn(OAc)_3.H_2O$ as a dark red colored solid (decomposition > 120 °C, lit.: melting point: 115 °C).

Precursor **(8)** (500 mg, 2.79 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (28 mL) in an open round bottom flask and stirred at rt. $Mn(OAc)_3.H_2O$ (1.5 g, 5.58 mmol, 2 equiv.) was added as a single portion, followed by the addition of DDQ (126 mg, 0.56 mmol, 20 mol %). The reaction progress was monitored

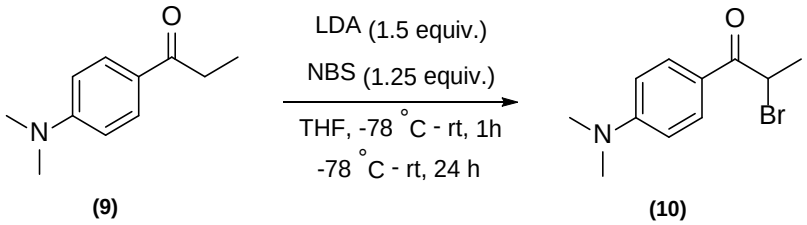
by TLC until complete consumption of the starting material was observed (Color change from dark purple to red brown). After 1 h it was filtered through a pad of Celite, washed with a saturated NH_4Cl solution and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (30 g silica, CH_2Cl_2 / EtOAc, isocratically 95 : 5) to afford the title compound **(9)**.

Yield: 437 mg (88.4 %)
Appearance: red solid
Melting point: 104 °C (lit.[64]: 104.3 °C)
Molecular formula, m.w.: $C_{11}H_{15}NO$, 177.25
TLC: R_f (LP: EtOAc, 85 : 15) = 0.34

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, *J* = 7.3 Hz, 3H, H3), 2.91 (q, *J* = 7.4 Hz, 2H, H2), 3.05 (s, 6H, NMe), 6.66 (dd, *J* = 9.1, 2.1 Hz, 2H, H3', H5'), 7.85 – 7.93 (m, 2H, H2', H6').

^{13}C NMR (101 MHz, $CDCl_3$): δ 9 (q, C3), 31.1 (t, C2), 40.2 (q, NMe), 110.8 (d, C3', C5'), 125.2 (s, C1'), 130.3 (d, C2', C6'), 153.4 (s, C4'), 199.3 (s, C1).

D.3.2.3 2-Bromo-1-(4-(dimethylamino)phenyl)propan-1-one



(9) **(10)**

This compound was prepared according to the literature.[35]

A reaction vial was evacuated and backfilled with argon using standard Schlenk technique. Freshly titrated LDA (0.7 mL, 0.78 M in THF, 1.5 equiv.) was dissolved in THF (1.4 mL) and cooled to -78 °C. Compound **(9)** (64 mg, 0.36 mmol, 1 equiv.) was dissolved in THF (1.5 mL) and added dropwise to the LDA solution. The mixture was stirred at -78°C for 30 min and warmed to 0 °C over 30 min. It was cooled again to -78 °C and NBS (63 mg, 0.35 mmol, 1.25 equiv.) was added. After 1 h stirring at this temperature it was slowly warmed to rt and stirred overnight. After TLC showed no further conversion, the reaction was quenched with water and extracted with Et_2O (4 x 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure.

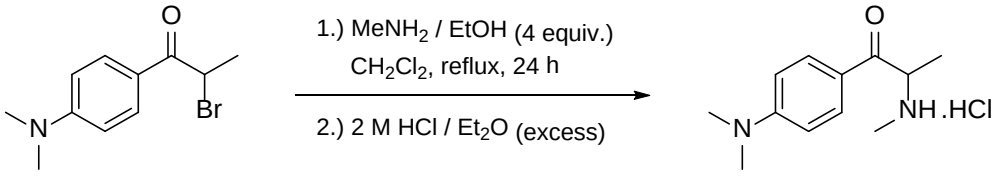
The crude product was purified through flash column chromatography (6.2 g silica, CH_2Cl_2 / LP, isocratically 80 : 20) to afford the title compound **(10)**.

Yield: 26.1 mg (28.3 %, lit.[35]: 53 %)
Appearance: green solid
Melting range: 136 – 138 °C, no melting point found in lit.[35]
Molecular formula, m.w.: $C_{11}H_{14}BrNO$, 256.14
TLC: R_f (CH_2Cl_2 : LP, 80 : 20) = 0.37
GC-MS (EI, 70 eV, Method B): 10.9 min; 254.9 (M+, 4), 149.01 (10), 147.98 (100), 103.97 (6), 76.96 (10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88 (d, *J* = 6.6 Hz, 3H, H3), 3.08 (s, 6H, NMe), 5.28 (q, *J* = 6.6 Hz, 1H, H2), 6.67 (d, *J* = 9.1 Hz, 2H, H3', H5'), 7.94 (d, *J* = 9.1 Hz, 2H, H2', H6').

^{13}C NMR (101 MHz, $CDCl_3$): δ 20.7 (q, C3), 40.1 (q, NMe), 41.9 (d, C2), 110.9 (d, C3', C5'), 121.6 (s, C1'), 131.3 (d, C2', C6'), 153.8 (s, C4'), 191.6 (s, C1).

D.3.2.4 1-(4-(Dimethylamino)phenyl)-2-(methylamino)propan-1-one hydrochloride



(10) **(11)**

The title compound was prepared according to a modified literature procedure.[36]

In an 8 mL screw-cap vial 2-bromo-1-(4-(dimethylamino)phenyl)propan-1-one (30 mg, 0.117 mmol, 1 equiv.) was dissolved in d_6-dichloromethane (1.2 mL) and a solution of methyl amine (33 % in EtOH, 24.2 µL, 2.2 equiv.) was added dropwise. The mixture was heated to reflux. Reaction progress was monitored by NMR. Since after 5 h starting material was observed, methyl amine (20 µL, 2 equiv.) was added and the mixture was stirred at rt overnight. After completion of the reaction, the excess amount of methyl amine was removed by bubbling argon through the solution. Solvent was added and the mixture was extracted with 1 M HCl (0.5 mL then 0.2 mL, pH = 1). The combined aqueous phases were washed with CH_2Cl_2 and the aqueous phase was basified with 2 M K_2CO_3. It was extracted twice with CH_2Cl_2, and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$ and filtered in a new reaction vial.

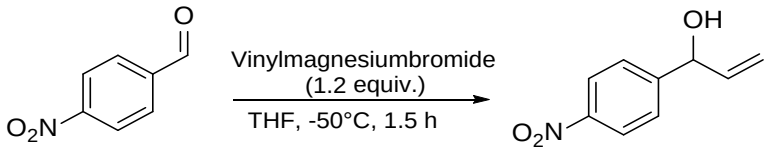
HCl (2 M solution in Et_2O, 0.5 mL, 8.5 equiv.) was added dropwise after which the product precipitated. The solvent was removed under reduced pressure to afford the title compound **(11)**.

Yield: 18.6 mg (65.4 %)
Appearance: colorless solid
Melting point: sublimation > 100 °C
Molecular formula, m.w.: $C_{12}H_{19}ClN_2O$, 242.75
TLC: R_f (CH_2Cl_2 : MeOH, 95 : 5) = 0.29
LC-HRMS (ESI): calculated for M+H$^+$: 206.1419, found: 207.1495, Δ = -1.7 ppm.
^{1}H NMR (400 MHz, D_2O): δ 1.60 (d, *J* = 7.2 Hz, 3H, H3), 2.76 (s, 3H, NMe), 3.12 (s, 6H, N($C\underline{H}_3$)$_2$), 4.98 (q, *J* = 7.2 Hz, 1H, H2), 6.90 (d, *J* = 8.5 Hz, 2H, H3', H5'), 7.93 (d, *J* = 9.2 Hz, 2H, H2', H6').

^{13}C NMR (101 MHz, D_2O): δ 16 (q, C3), 31 (q, NMe), 40.1 (q, N($\underline{C}H_3$)$_2$), 58.8 (d, C2), 112.5 (d, C3', C5'), 120.6 (s, C1'), 131.5 (d, C2', C6'), 154.3 (s, C4'), 194.3 (s, C1).

D.3.3 Synthesis of 4-nitro-MCAT

D.3.3.1 1-(4-Nitrophenyl)prop-2-en-1-ol



(12) **(13)**

This compound was prepared according to the literature.[39]

A three-neck bottom flask equipped with a thermometer, a septum rubber, a stirring bar was evacuated and backfilled with argon using standard Schlenk technique. It was charged with vinyl magnesium bromide (1 M in THF, 1.2 equiv.) and cooled to -78 °C. 4-Nitrobenzaldehyde **(12)** (1 g, 6.61 mmol, 1 equiv.) was dissolved in freshly redistilled THF (23.4 mL) and added dropwise to the Grignard reagent. The reaction was stirred at –50 °C and the reaction progress was monitored by TLC. After 90 min the reaction was quenched with a saturated solution of NH_4Cl (4 mL), water was added and the mixture was extracted with EtOAc (2 x 60 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo.*

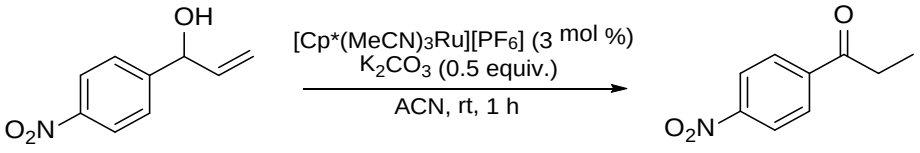
The crude product was purified through flash column chromatography (flow rate 50 mL / min, EtOAc / LP): 90 g silica with 9 g precolumn, from 5 : 95 to 50 : 50 in 24 min, then 50 : 50 isocratically for 2 min.

Yield: 858 mg (72.4 %)
Appearance: brown crystals
Melting range: 55.5 - 58.2 °C (lit.[39]: 54 - 55.5 °C)
Molecular formula, m.w.: $C_9H_9NO_3$, 179.18
TLC: R_f (LP : EtOAc, 70 : 30) = 0.43
GC-MS (EI, 70 eV, Method A): 3.67 min; 179.06 (M^+, 12), 150.01 (40), 132.08 (88), 91.08 (32), 78.07 (41), 77.05 (100).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 1H, OH), 5.27 (dt, *J* = 10.2, 1.1 Hz, 1H, H3), 5.31 (d, *J* = 6.3 Hz, 1H, H1), 5.40 (dt, *J* = 17.1, 1.2 Hz, 1H, H3), 5.99 (ddd, *J* = 16.9, 10.2, 6.5 Hz, 1H, H2), 7.55 (d, *J* = 8.3 Hz, 2H, H2‘, H6‘), 8.20 (d, *J* = 8.8 Hz, 2H, H3‘, H5‘).

^{13}C NMR (101 MHz, $CDCl_3$): δ 74.7 (d, C1), 117 (t, C3), 123.9 (d, C3‘, C5‘), 127.1 (d, C2‘, C6‘), 139.3 (d, C2), 147.5 (s, C4‘), 149.7 (s, C1‘).

D.3.3.2 1-(4-Nitrophenyl)propan-1-one



(13) **(14)**

This compound was prepared according to the literature.[39]

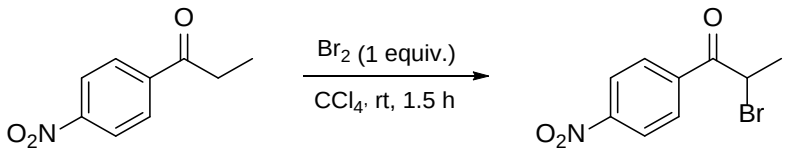
A reaction vial was charged with 1-(4-nitrophenyl)prop-2-en-1-ol **(13)** (1.347 g, 7.52 mmol, 1 equiv.) and K_2CO_3 (520 mg, 3.76 mmol, 0.5 equiv.) and evacuated and backfilled with argon using standard Schlenk technique. Acetonitrile (20 mL) and the ruthenium catalyst (114 mg, 3 mol %) were added under an inert atmosphere and the mixture was heated to reflux for 1 h. It was allowed to cool to rt, after which the solvent was removed *in vacuo*.

The crude product was purified through flash column chromatography (flow rate 50 mL / min, EtOAc / LP): 90 g silica with 9 g precolumn, 5 : 95 isocratically for 6 min, then 10 : 90 isocratically for 38 min.

Yield: 1.1 g (81.7 %)
Appearance: yellow solid
Melting range: 86 – 88 °C (lit.[39]: 89 – 91 °C)
Molecular formula, m.w.: $C_9H_9NO_3$, 179.18
TLC: R_f (LP : EtOAc, 70 : 30) = 0.84
GC-MS (EI, 70 eV, Method A): 3.37 min; 179.04 (M^+, 5.28), 151.05 (7.4), 150 (100), 120.01 (12), 103.98 (37), 76.05 (27).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.2 Hz, 2H, H3), 3.05 (q, *J* = 7.2 Hz, 2H, H2), 8.10 (d, *J* = 9.0 Hz, 2H, H2‘, H6‘), 8.29 (d, *J* = 8.9 Hz, 2H, H3‘, H5‘).
^{13}C NMR (101 MHz, $CDCl_3$): δ 8 (q, C3), 32.6 (t, C2), 123.9 (d C3‘, C5‘), 129.1 (d, C2‘, C6‘), 141.4 (s, C1‘), 150.3 (s, C4‘), 199.2 (s, C1).

D.3.3.3 2-Bromo-1-(4-nitrophenyl)propan-1-one



(14) **(15)**

This compound was prepared according to the literature.[40]

A reaction vessel was evacuated and backfilled with argon using standard schlenk technique. Bromine (0.35 mL, 6.84 mmol, 1.2 equiv.) was dissolved in CCl_4 (4.5 mL) and a solution of 1-(4-nitrophenyl)propan-1-one **(14)** (1.025 g, 5.72 mmol, 1 equiv.) in CCl_4 (7.5 mL) was added. The mixture was stirred at rt and the reaction progress was monitored by TLC. After 2 h the reaction was quenched with a 10 % solution of $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo.*

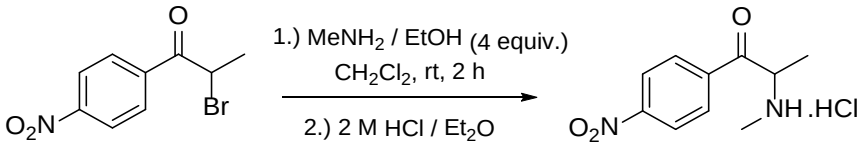
The crude product was purified through flash column chromatography (90 g silica with 9 g precolumn, CH_2Cl_2 / LP, isocratically 40 : 60) to afford the title compound **(15)**.

Yield: 839 mg (56.8 %)
Appearance: yellow oil
Molecular formula, m.w.: $C_9H_8BrNO_3$, 258.07
TLC: R_f (LP : EtOAc, 50 : 50) = 0.56
GC-MS (EI, 70 eV, Method A): 4.43 min; 256.94 (M^+, 0.28), 210.95 (0.22), 179.07 (0.16), 151.06 (8), 150.01 (100), 120.01 (9), 104.02 (26), 76.04 (16).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94 (d, *J* = 6.6 Hz, 3H, H3), 5.25 (q, *J* = 6.6 Hz, 1H, H2), 8.18 (d, *J* = 9.0 Hz, 2H, H2‘, H6‘), 8.34 (d, *J* = 8.9 Hz, 2H, H3‘, H5‘).

^{13}C NMR (101 MHz, $CDCl_3$): δ 19.9 (q, C3), 41.5 (d, C2), 124 (d, C3‘, C5‘), 130.1 (d, C2‘, C6‘), 138.9 (s, C1‘), 150.7 (s, C4‘), 191.8 (s, C1).

D.3.3.4 2-(Methylamino)-1-(4-nitrophenyl)propan-1-one hydrochloride



(15) **(16)**

The title compound was prepared according to a modified literature procedure.[36]

In a reaction vessel vial 2-bromo-1-(4-nitrophenyl)propan-1-one **(15)** (812 mg, 3.15 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (31 mL) and a solution of methyl amine (33 % in EtOH, 1.18 mL, 4 equiv.) was added dropwise. It was stirred at rt for 2 h after which most of the starting material was converted (according to NMR). The reaction mixture was extracted with 1 M HCl (3 x 4 mL, pH control). The combined aqueous phases were washed with CH_2Cl_2 (20 mL) and the aqueous phase was basified with K_2CO_3 (2 M, 8 mL). It was extracted with CH_2Cl_2 (3 x 40 mL), the combined organic phases were dried over anhydrous $MgSO_4$ and filtered in a new reaction vessel.
HCl (2 M solution in Et_2O, 10 mL, 6 equiv.) was added dropwise after which the product precipitated. The solvent was removed under reduced pressure to afford the title compound **(16)**.

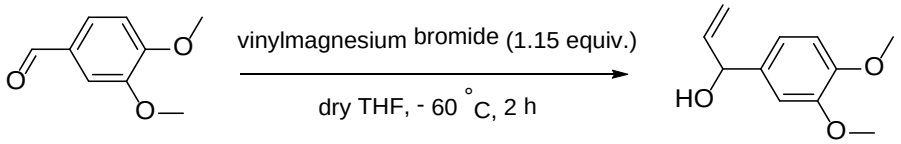
Yield: 376 mg (48.8 %)
Appearance: colorless solid
Melting point: decomposition > 178 °C
Molecular formula, m.w.: $C_{10}H_{13}ClN_2O_3$, 244.68
LC-HRMS (ESI): calculated for $M+H^+$: 208.0848, found: 209.093, Δ = -4.33 ppm.

^{1}H NMR (400 MHz, D_2O): δ 1.64 (d, *J* = 7.3 Hz, 3H, H3), 2.85 (s, 3H, NMe), 5.18 (q, *J* = 7.3 Hz, 1H, H2), 8.24 (d, *J* = 6.8 Hz, 2H, H2‘, H6‘), 8.44 (d, *J* = 8.7 Hz, 2H, H3‘, H5‘).

^{13}C NMR (101 MHz, D_2O): δ 14.71 (q, C3), 30.90 (q, NMe), 60.02 (d, C2), 124.25 (d, C3‘, C5‘), 130.13 (d, C2‘, C6‘), 137.12 (s, C1‘), 150.99 (s, C4‘), 196.21 (s, C1).

D.4 Synthesis of the key fragment for leoligin

D.4.1 1-(3,4-dimethoxyphenyl)prop-2-en-1-ol



(17) ***rac*-(18)**

This compound was prepared according to the literature.[28]

A reaction vessel was charged with a stirring bar, dimethoxybenzaldehyde **(17)** (14.45 g, 86.95 mmol, 1 equiv.) and was then evacuated and back-filled with argon using standard Schlenk technique. Dry THF (120 mL) was added *via* syringe and the stirred mixture was cooled to -60 °C in a MeOH / liquid N_2 bath. Vinylmagnesium bromide (100 mL, 1 M in THF, 1.15 equiv.) was added within 1 h, while keeping the reaction at this temperature. Reaction progress was monitored by TLC the reaction was terminated when complete. After 1 h stirring at -60 °C, the reaction mixture was slowly warmed up to 10 °C.

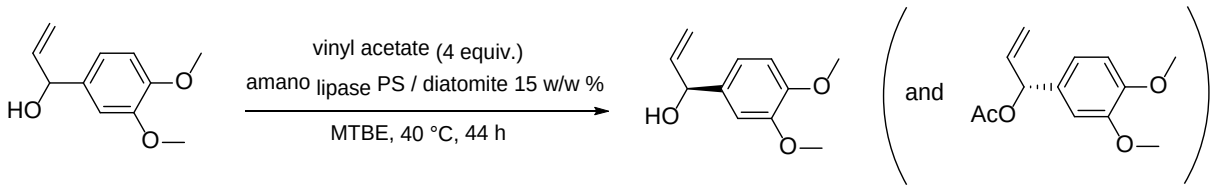
A saturated aqueous NH_4Cl solution (20 mL) was added slowly while providing additional cooling to prevent the temperature from rising over +10 °C during the exothermic hydrolysis. To dissolve the magnesium salts, water (100 mL) was added and the mixture was extracted with Et_2O (1 x 100 mL, 4 x 50 mL). The combined organic phases were treated with saturated aqueous $NaHCO_3$ solution (25 mL) and brine (20 mL), followed by drying with anhydrous $MgSO_4$. The solution was filtered through a pad of celite and the solvent was removed under reduced pressure to afford the title compound ***rac*-(18).**

Yield: 16.806 g (99.5 %)
Appearance: yellow oil
Molecular formula, m.w.: $C_{11}H_{14}O_3$, 194.23
TLC: R_f (LP : EtOAc, 75 : 25) = 0.31
GC-MS (EI, 70 eV, Method A): 4.02 min; 194.06 (M^+, 100), 163.03 (29), 139.03 (98), 138.03 (30), 124.01 (23), 76.99 (29), 54,93 (78).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (d, *J* = 3.6 Hz, 1H, OH), 3.88 (s, 3H, Ar'-OCH_3), 3.89 (s, 3H, Ar'-OCH_3), 5.17 (d, *J* = 4.0 Hz, 1H, H1), 5.20 (dt, *J* = 10.3, 1.4 Hz, 1H, H3^{cis}), 5.35 (dt, *J* = 17.1, 1.4 Hz, 1H, H3^{trans}), 6.05 (ddd, *J* = 17.1, 10.3, 5.9 Hz, 1H, H2), 6.85 (d, *J* = 8.0 Hz, 1H, H5'), 6.87 – 6.95 (m, 2H, H2', H6').

For additional characterization see chapter D.4.2.

D.4.2 *(S)*-1-(3,4-Dimethoxyphenyl)prop-2-en-1-ol



***rac*-(18)** **(*S*)-(18)** **(19)**

This compound was prepared according to the literature.[28]

A round bottom flask was charged with racemic 1-(3,4-dimethoxyphenyl)prop-2-en-1-ol ***rac*-(18)** (15.71 g, 80.9 mmol, 1 equiv.) and vinyl acetate (29.8 mL, 32.4 mmol, 4 equiv.). MTBE (442 mL) and Amano lipase PS (immobilized on diatomite, 2.36 g, 15 w/w %) were added. The suspension was stirred at 40 °C until conversion of the undesired enantiomer *rac*-alcohol to its acetate (*R*)-acetate was complete, as monitored by chiral HPLC. After 44 h the mixture was filtered through a pad of celite, rinsed with Et_2O (100 mL) and the solvent was evaporated. Flash column chromatography was then performed (flow rate 50 mL / min, EtOAc / LP) under following conditions:

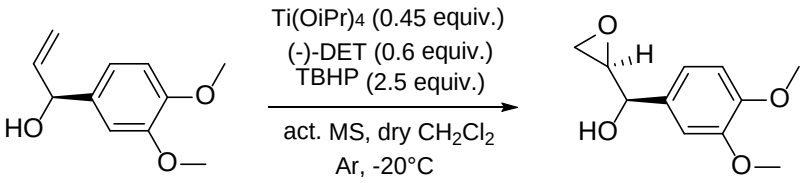
90 g silica with 9 g precolumn, 15 : 85 isocratically for 45 min, then to 25 : 75 in 5 min, then to 44 : 56 in 30 min. This resulted in a pale-yellow oil which crystallized upon standing to afford the title compound ***(S)*-18**.

Yield: 5.92 g, 35 % (theoretical maximum yield is 50 %)
Appearance: pale-yellow oil which crystallized upon standing
Melting range: n/a as compound obtained as a liquid (lit.[67] 51 – 53.5 °C)
Molecular formula, m.w.: $C_{11}H_{14}O_3$, 194.23
TLC: R_f (LP : EtOAc, 75 : 25) = 0.29
GC-MS (EI, 70 eV, Method B): 7.30 min; 194.06 (M^+, 69), 163.05 (53), 139.07 (100), 91.05 (26), 77.05 (32), 55.02 (87).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (s, OH), 3.87 (s, 3H, Ar'OCH_3), 3.89 (s, 3H, Ar'-OCH_3), 5.16 (d, *J* = 5.9 Hz, 1H, H1), 5.20 (dt, *J* = 10.3, 1.4 Hz, 1H, $H3^{cis}$), 5.35 (dt, *J* = 17.1, 1.4 Hz, 1H, H_3^{trans}), 6.05 (ddd, *J* = 17.1, 10.3, 5.8 Hz, 1H, H2), 6.84 (d, *J* = 8.1 Hz, 1H, H5'), 6.86 – 6.95 (m, 2H, H2', H6').

^{13}C NMR (101 MHz, $CDCl_3$): δ = 55.9 (s, Ar'-O<u>C</u>H_3), 56 (s, Ar'-O<u>C</u>H_3), 75.2 (d, C1), 109.5 (d, C2'), 111.1 (d, C5'), 115 (t, C3), 118.7 (d, C6'), 135.3 (s, C1'), 140.3 (d, C2), 148.7 (s, C3' / C4'), 149.2 (s, C3' / C4').

D.4.3 *(R)*-(3,4-Dimethoxyphenyl)(*(R)*-oxiran-2-yl)methanol



***(S)*-(18)** **(20)**

This compound was prepared according to the literature.[48]

Dry CH_2Cl_2 (140 mL), (-)-DET (2.69 g, 13.06 mmol, 0.6 equiv.) and the alcohol ***(S)*-(18)** (4.23 g, 21.76 mmol, 1 equiv.) were (additionally) dried over activated MS overnight under argon atmosphere. (-)-DET was dissolved in dry CH_2Cl_2 (1 mL) and cooled to -20 °C *via* a cryostat. $Ti(OiPr)_4$ (2.9 mL, 9.79 mmol, 0.45 equiv.) in dry CH_2Cl_2 (70 mL, 0.14 M) was added and the reaction mixture was stirred for 15 min.

Then TBHP (5.5 M in decane, 9.9 mL, 54.4 mmol, 2.5 equiv.) was added slowly. After 30 min the solution of the substrate was added and the resulting mixture was stirred for 96 h at -20 °C. Reaction progress was monitored by TLC. When the reaction was finished, a solution of Na_2SO_3 (20 g in 100 mL water) was added as well as 500 mL water. The aqueous layer was extracted with CH_2Cl_2 (3 x 500 mL) and the

combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed in *vacuo* and the compound was purified through flash column chromatography in two successive runs:

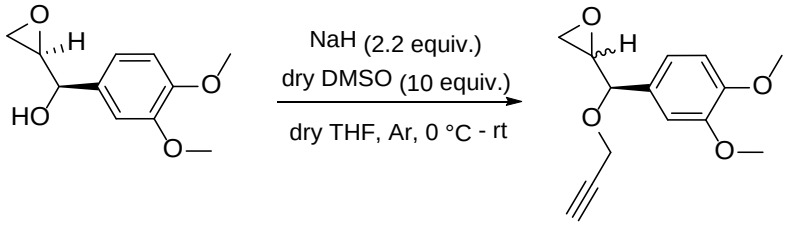
14.22 g crude: 45 g silica, isocratically 100 % EtOAc → gave 5.3 g crude material.
5.3 g crude (flow rate 50 mL / min, EtOAc / LP): 90 g silica with 9 g pre-column, from 5 : 50 to 50 : 50 in 30 min, then 50 : 50 isocratically for 20 min. This resulted in a yellow oil which crystallized upon standing to afford the title compound **(20)**.

Yield: 2.45 g, 53.6 %
Appearance: yellow oil which crystallized upon standing
Melting range: compound obtained as a liquid (lit.[65]: 75.5 – 77 °C)
Molecular formula, m.w.: $C_{11}H_{14}O_4$, 210.23
TLC: R_f (LP : EtOAc, 50 : 50) = 0.25
GC-MS (EI, 70 eV, Method A): 5.37 min; 210 (M^+, 41), 168.03 (10), 166.99 (100), 138.95 (64), 123.99 (18), 108.01 (12).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21 – 2.27 (m, 1H, OH), 2.79 (dd, *J* = 5.0, 4.0 Hz, 1H, H3), 2.96 (ddd, *J* = 5.0, 2.8, 0.6 Hz, 1H, H3), 3.22 (dt, *J* = 4.0, 2.9 Hz, 1H, H2), 3.88 (s, 3H, Ar'-OCH_3), 3.90 (s, 3H, Ar'-OCH_3), 4.87 (t, *J* = 2.4 Hz, 1H, H1), 6.83 – 6.90 (m, 1H, H5'), 6.90 – 6.98 (m, 2H, H2', H6').

^{13}C NMR (101 MHz, $CDCl_3$): δ = 43.8 (t, C3), 55.2 (d, C2), 56 (q, Ar'-O<u>C</u>H3), 56.1 (q, Ar'-O<u>C</u>H3), 70.8 (d, C1), 109.6 (d, C2'), 111.2 (d, C5'), 118.9 (d, C6'), 132 (s, C1'), 149.1 (s, C4' / C3'), 149.3 (s, C4' / C3').

D.4.4 2-(*(R)*-(3,4-Dimethoxyphenyl)(prop-2-yn-1-yloxy)methyl)oxirane



(21) **(22)**

This compound was prepared according to the literature.[28]

A round bottom flask was charged with a stirring bar, NaH (60 % dispersion in mineral oil, 811 mg, 2.2 equiv.) and then evacuated and back-filled with argon using standard Schlenk technique. Dry THF (20.3 mL) and dry DMSO (6.6 mL, 92.2 mml, 10.00 equiv.) were then added in this order *via* syringe and the resulting suspension was cooled to 0 °C in an ice bath. Starting material **(21)** (1.94 g, 9.22 mmol, 1 equiv.), as a beforehand prepared solution in dry THF (23.1 mL) 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, 2.47 mL, 16.56 mmol, 1.8 equiv.), both *via* syringe. The ice bath was then removed and the reaction continued at room temperature. Progress of this substitution reaction was monitored by TLC.

After 72 h, the mixture was cooled in an ice bath again and hydrolyzed, while still under argon, by careful addition of 1 M HCl (9.22 mL). Most of the THF was then evaporated, followed by the addition of water (80 mL) and extraction with Et_2O (4 x 40 mL). The combined organic phases were treated with brine (20 mL), dried with $MgSO_4$, filtered and the solvents were evaporated.

The crude product was purified through flash column chromatography (flow rate 50 mL / min, EtOAc / LP): 90 g silica with 9 g precolumn, from 5 : 95 to 50 : 50 in 42 min, then 50 : 50 isocratically for 3 min.

Yield: 1.549 g, 67.7 % (779 mg major isomer, 770 mg minor isomer)
Appearance: yellow solid
Molecular formula, m.w.: $C_{14}H_{16}O_4$, 248.28
Melting range: 53 – 55 °C (compound obtained as a liquid in lit.[28])
TLC: R_f (LP : EtOAc, 50 : 50) = 0.69 (major isomer), 0.62 (minor isomer)
GC-MS (EI, 70 eV, Method A): 4.69 min; 248.04 (M^+, 30), 218.03 (5), 206.05 (13), 205.02 (100), 179.02 (12), 166.02 (40), 165 (53), 151.01 (15), 91 (7), 76.99 (13).

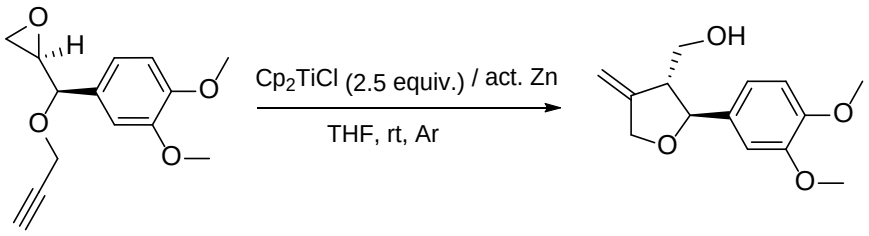
^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ = 2.43 (t, *J* = 2.4 Hz, 1H, H6), 2.71 (dd, *J* = 5.2, 2.6 Hz, 1H, H3), 2.81 (dd, *J* = 5.2, 3.9 Hz, 1H, H3), 3.20 (td, *J* = 4.2, 2.6 Hz, 1H, H2), 3.88 (s, 3H, Ar'-OCH_3), 3.90 (s, 3H, Ar'-OCH_3), 3.97 (dd, *J* = 15.8, 2.4 Hz, 1H, H4), 4.20 (dd, *J* = 15.8, 2.4 Hz, 1H, H4), 4.49 (d, *J* = 4.4 Hz, 1H, H1), 6.86 (d, *J* = 8.7 Hz, 1H, H5'), 6.90 (m, 2H, H2', H6').

minor isomer: δ = 2.44 (t, *J* = 2.4 Hz, 1H, H6), 3.61 (dd, *J* = 10.5, 6.5 Hz, 1H, H3), 3.67 (dd, *J* = 10.5, 3.5 Hz, 1H, H3), 3.88 (d, *J* = 2.4 Hz, 1H, H4), 3.89 (s, 3H, Ar'-OCH_3), 3.90 (s, 3H, Ar'-OCH_3), 3.91 (d, *J* = 2.4 Hz, 1H, H4), 3.96 (dt, *J* = 7.3, 3.4 Hz, 1H, H2), 4.14 (dd, *J* = 15.7, 2.4 Hz, 1H, H4), 4.50 (d, *J* = 7.1 Hz, 1H, H1), 6.87 (d, *J* = 8.1 Hz, 1H, H5'), 6.91 (m, 2H, H2', H6').

^{13}C NMR (101 MHz, $CDCl_3$) major isomer: δ = 45.4 (t, C3), 54.2 (d, C2), 56 (t, C4), 56 (q, Ar'-O<u>C</u>H_3), 56 (q, Ar'-O<u>C</u>H_3), 74.9 (d, C6), 79.4 (d, C1), 79.5 (s, C5), 110.4 (d, C2'), 111 (d, C5'), 120.5 (d, C6'), 129.4 (s, C1'), 149.3 (s, C3' / C4'), 149.4 (s, C3' / C4').

minor isomer: δ = 36.3 (t, C3), 55.8 (t, C4), 55.9 (q, Ar'-O<u>C</u>H_3), 56 (q, Ar'-O<u>C</u>H_3), 73.6 (d, C2), 74.8 (d, C6), 79.3 (d, C1), 81.2 (s, C5), 110.2 (d, C2'), 111 (d, C5'), 120.9 (d, C6'), 128.8 (s, C1'), 149.4 (s, C3' / C4'), 149.4 (s, C3' / C4').

D.4.5 (*(2S,3R)*-2-(3,4-dimethoxyphenyl)-4-methylenetetrahydrofuran-3-yl)methanol



(22) **(23)**

This compound was prepared according to the literature.[49]

A round bottom flask was charged with activated Zinc (1.12 g, 16.38 mmol, 7 equiv.) and Cp_2TiCl_2 (1.46 g, 5.85 mmol, 2.5 equiv.) under argon. Deoxygenated THF (32.5 mL, distilled from Na / benzophenone) was added. After 1 h of stirring at rt, the Zinc was allowed to settle for 5 min and the solution (without the Zinc) was transferred to a solution of starting material **(22)** (583 mg, 2.34 mmol, 1 equiv.) in deoxygenated THF (16.3 mL) over a period of 10 min. Stirring was continued overnight at rt and reaction progress was monitored by TLC.

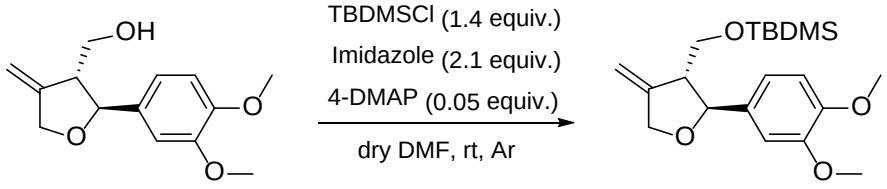
When the reaction was complete, diluted sulfuric acid (10 % in water, 16.2 mL) was added and the major amount of THF was evaporated at 40 °C and 150 mbar. Water (150 mL) was added to the crude product and the aqueous layer was extracted with Et2O (4 x 50 mL) and EtOAc (2 x 50 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*.

The crude product was purified through flash column chromatography (45 g silica, flow rate 35 mL / min, EtOAc / LP): isocratocally 15 : 85 for 30 min, then to 30 : 70 in 12 min, isocratically 30 : 70 for 31 min, from 30 : 70 to 50 : 50 in 7 min, isocratically 50 : 50 for 6 min.

Yield: 205.4 mg, 35 %
Appearance: yellow solid
Molecular formula, m.w.: $C_{14}H_{18}O_4$, 250.29
TLC: R_f (LP : EtOAc, 50 : 50) = 0.15
GC-MS (EI, 70 eV, Method B): 10.22 min; 250.04 (M^+, 64), 219.03 (20), 150.99 (67), 139 (100), 123.98 (23), 94.99 (9), 76.98 (19).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.78 (qd, *J* = 4.8, 2.1 Hz, 1H, H2), 3.73 (dd, *J* = 11.3, 4.7 Hz, 1H, C2-C$\underline{H}_2$), 3.82 – 3.87 (m, 1H, C2-C$\underline{H}_2$), 3.87 (s, 3H, Ar'-OCH_3), 3.89 (s, 3H, Ar'-OCH_3), 4.42 (dq, *J* = 13.4, 2.3 Hz, 1H, H4), 4.61 (dt, *J* = 13.4, 2.4 Hz, 1H, H4), 4.79 (d, *J* = 7.5 Hz, 1H, H1), 5.07 (q, *J* = 2.4 Hz, 1H, C3=C$\underline{H}_2$), 5.11 (q, *J* = 2.2 Hz, 1H, C3=C$\underline{H}_2$), 6.84 (d, *J* = 8.0 Hz, 1H, H5'), 6.88 – 6.97 (m, 2H, H2', H6').

D.4.6 *tert*-butyl(((2S,3R)-2-(3,4-dimethoxyphenyl)-4-methylenetetrahydrofuran-3-yl)methoxy)dimethylsilane



(23) **(24)**

This compound was prepared according to the literature.[28]

Starting material **(23)** (205.4 g, 0.82 mmol, 1 equiv.), imidazole (117 mg, 1.72 mmol, 2.1 equiv.) and 4-DMAP (5 mg, 0.041 mmol, 0.05 equiv) were dissolved in DMF (4.76 mL, 0.17 M) under argon. TBDMSCl (3M in THF, 0.37 mL, 1.12 mmol, 1.37 equiv.) was added to the solution and the mixture was stirred for 15 h at rt. Reaction progress was monitored by TLC. After completion, the reaction was quenched with a saturated NH_4Cl solution (4.5 mL) and extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure.

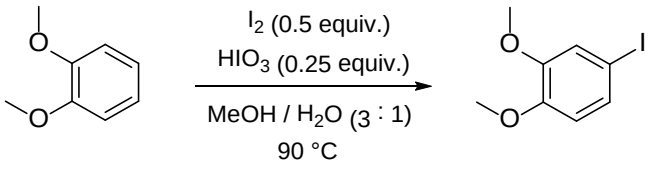
The crude product was purified through flash column chromatography (9 g silica, 20 mL / min, EtOAc / LP): gradually from 5 : 95 to 15 : 95 in 11 min.

Yield: 169 mg, 57 %
Appearance: yellow solid
Molecular formula, m.w.: $C_{20}H_{32}O_4Si$, 364.21

TLC: R_f (LP : EtOAc, 70 : 30) = 0.65

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 9H, *t*Bu), 2.73 – 2.83 (m, 1H, H2), 3.68 – 3.77 (m, 2H, C2-C$\underline{H}_2$), 3.87 (s, 3H, Ar'-OCH$_3$), 3.88 (s, 3H, Ar'-OCH$_3$), 4.41 (dq, *J* = 13.1, 2.2 Hz, 1H, H5), 4.56 (dt, *J* = 13.1, 2.1 Hz, 1H, H5), 4.85 (d, *J* = 6.3 Hz, 1H, H1), 5.03 (dq, *J* = 4.3, 2.2 Hz, 2H, C3-C$\underline{H}_2$), 6.83 (d, *J* = 8.0 Hz, 1H, C5'), 6.86 – 6.94 (m, 2H, C2', C6').

D.4.7 4-Iodo-1,2-dimethoxybenzene (4-Iodoveratrole)



(25) **(26)**

This compound was prepared according to the literature.[28]

A reaction vessel was charged with a stirring bar, veratrole **(25)** (2.76 g, 20 mmol, 1 equiv.), iodine (2.54 g, 10 mmol, 0.5 equiv.) and iodic acid (0.88 g, 5 mmol, 0.25 equiv.), followed by the addition of a mixture of MeOH / water (3 : 1, 200 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, 15 mL). More water (70 mL) was added and then the mixture was extracted with CH_2Cl_2 (1 x 35 mL, 2 x 50 mL). The combined organic phases were treated with brine (35 mL), dried with Na_2SO_4, filtered through a short plug of silica and the solvent was evaporated.

High vacuum distillation at 1 mbar and 90 °C then afforded the title compound**.**

Yield: 3.89 g, 73.7 %
Appearance: yellow oil which solidifies when stored refrigerated
Molecular formula, m.w.: $C_8H_9IO_2$, 264.06
Boiling range: 99 - 107 °C at 1 mbar; lit.[66]: 83 – 88 °C at 0.05 mmHg (0.067 mbar)
TLC: R_f (MTBE : heptane, 1 : 10) = 0.29
GC-MS (EI, 70 eV, Method A): 3.55 min; 263.85 ($M+H^+$, 100), 248.82 (47), 220.84 (14), 202.08 (8), 106.93 (9), 93.9 (56), 78.83 (33).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3H, Ar-OCH$_3$), 3.86 (s, 3H, Ar-OCH$_3$), 6.62 (d, *J* = 8.5 Hz, 1H, H6), 7.12 (d, *J* = 2.0 Hz, 1H, H5), 7.22 (dd, *J* = 8.4, 2.0 Hz, 1H, H3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 56 (q, Ar-O$\underline{C}$H$_3$), 56.2 (q, Ar-O$\underline{C}$H$_3$), 82.4 (s, C4), 113.3 (d, C6), 120.4 (d, C3), 129.9 (d, C5), 149.3 (s, C1 / C2), 149.9 (s, C1 / C2).

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