TECHNISCHE UNIVERSITÄT WIEN
Vienna University of Technology

DIPLOMARBEIT

TOTAL SYNTHESIS OF POTENTIAL ANTI-INFLAMMATORY DRUG LEAD CANDIDATE (±)-KADSURENIN-F

ausgeführt zum Zwecke der Erlangung des akademischen Grades eines Diplomingenieurs der technischen Wissenschaften unter der Leitung von

Prof. Dr. Marko D. Mihovilovic

Institut für Angewandte Synthesechemie, E163

eingereicht an der Technischen Universität Wien

Fakultät für Technische Chemie

durch

Sebastian Hecko, BSc

Bauernfeldgasse 12/5, 1190 Wien

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Science, my lad, is made up of mistakes,
but they are mistakes which it is useful to make,
because they lead little by little to the truth.

Jules Verne

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Acknowledgements

Looking back at the year I spent working on this thesis, I can definitely say it was one of the most challenging, but also most exciting times of my life. Hence, I would like to take the opportunity to thank those who were company and support, and who have contributed, directly and indirectly, to this thesis.

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Last of all I want to express my deepest gratitude to my family, in particular to my mother. I would not have arrived at this point if it were not for you. Thank you for being there!

Abstract

The importance of novel natural sources in the quest for potential drug lead discovery has increasingly drawn the emphasis to historical records or ancient treatment techniques as demonstrated by the bestowal of the Nobel Prize in Physiology or Medicine 2015 for the discovery of anti-malaria drug artemisinin. Hence, many research groups have placed their focus on evaluation and derivatization of natural product derived drug lead candidates.

In recent studies extracts from the stem of the Japanese pepper plant *Piper Futokadsura* that were historically known for their beneficial properties and are to this day used in Traditional Chinese Medicine for the treatment of asthma or arthritic conditions, were shown to have interesting anti-inflammatory activities. Among several isolated secondary metabolites, Kadsurenin F, structurally a neolignan, proved to be the most potent, inhibiting the release of major pro-inflammatory cytokines IL-1β, TNF-α and MCP-1, as well as anti-inflammatory cytokine IL-10 at µM level. These play a major role in the primary up-regulation of the immune system and are often associated with the pathogenesis of IBDs (inflammatory bowel diseases) as Crohn's disease or Ulcerative colitis.

For that reason, the target within the frame of this thesis was to establish and evaluate an easy accessible synthetic route towards this neolignan-scaffold.

104 (±)-Kadsurenin F   Key fragment **1**   Key fragment **2**
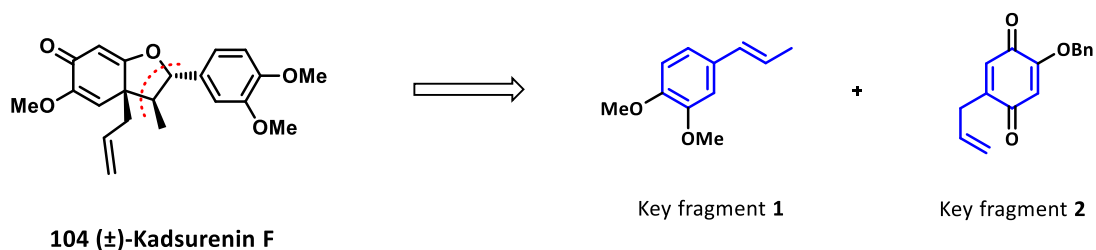
The assembly of such substituted benzofurane core units has been studied by Engler et al. forming the target structures that are derived from two phenylpropanoid fragments in a Lewis acid assisted formal [2+5]-cycloaddition, enabling the simultaneous installation of all three stereocenters in a single step.

For the decoration of these desired key fragments several approaches were examined, relying either on substrates from the natural pool, having the synthetically more demanding allyl-moiety already in place or a modular strategy by stepwise assembly of the designated structure. Summarizing, three different synthetic routes towards fragment **1** and five different synthetic routes towards fragment **2** were investigated and evaluated, allowing the synthesis of (±)-Kadsurenin F in 9 steps with an overall yield of 6%.

Kurzfassung

Die Herausforderung, immer neue natürliche Quellen für die Weiterentwicklung von Arzneimittel-Leitstrukturen zu finden, hat die Aufmerksamkeit in den letzten Jahren wieder zurück auf alte Aufzeichnungen und historische Behandlungsmethoden gelenkt, wie vor allem durch die Verleihung des Nobelpreises für Physiologie oder Medizin für die Entdeckung des Malariamedikaments Artemisinin im Jahre 2015 gezeigt hat. Infolgedessen verlagerten viele Forschungsgruppen ihren Schwerpunkt auf die Entwicklung und Derivatisierung auf Naturstoff basierenden Arzneimittel-Leitstrukturen.

Neue Studien zeigen, dass der Extrakt des Stammes der japanisches Pfefferpflanze *Piper Futokadsura*, welcher historisch für sein gesundheitsfördernden Eigenschaften bekannt war und bis heute in der traditionellen chinesischen Medizin zur Behandlung von Asthma und Arthritis verwendet wird, auch interessante anti-inflammatorische Eigenschaften aufweist. Neben vieler anderer isolierter Sekundärmetaboliten wies Kadsurenin F, welches strukturell den Neolignanen zuzuordnen ist, bereits beim Einsatz im µM Bereich die stärkste Wirkung bei der Inhibierung der Ausschüttung der wichtigsten pro- (IL-1β, TNF-α und MCP-1) und anti-inflammatorischen Cytokine (IL-10) auf. Diese spielen vor allem in der primären Aktivierung der Immunantwort eine Rolle und stehen oft mit Pathogenese von CEDs (chronisch-entzündlichen Darmerkrankungen), wie Morbus Crohn und Colitis ulcerosa, im Zusammenhang.

Daraus entwickelte sich als grundlegende Zielsetzung dieser Arbeit die Entwicklung und Evaluierung einer leicht zugänglichen Synthese dieser Neolignanstruktur.

104 (±)-Kadsurenin F Schlüsselfragment **1** Schlüsselfragment **2**
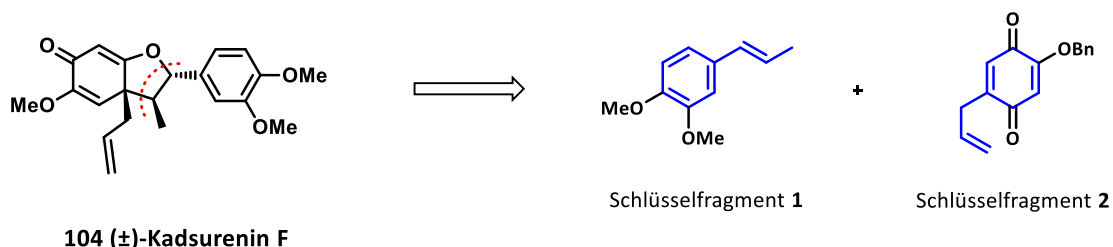
Im Zuge der Synthese solcher substituierter Benzofuran-Grundstrukturen ermöglichte Engler et al. durch das Heranziehen einer Lewis-Säure unterstützten [2+5]-Cycloaddition, ausgehend von zwei Phenylpropan-Fragmenten, die gleichzeitige Einführung aller drei Stereozentren in einem einzigen Schritt. Für die Gestaltung dieser geforderten Schlüsselfragmente wurden verschiedene Ansätze getestet, in welchen die entsprechenden Strukturen entweder basierend auf einer modularen Synthese stufenweise zusammengesetzt wurden, oder welche auf Naturstoffen aufbauten, bei welchen die synthetisch anspruchsvollere Allyl-Gruppe bereits entsprechend installiert war. In Summe wurden drei verschiedene synthetische Routen zu Fragment **1** und fünf zu Fragment **2** aufgestellt und evaluiert, was schlussendlich zu einer neunstufigen Totalsynthese von (±)-Kadsurenin F mit einer Gesamtausbeute von 6% führte.

A   Synthetic schemes

All compounds prepared or used as starting materials as well as unisolated intermediates in this thesis are numbered in bold Arabic numerals. Compounds unknown to the literature are additionally underscored. General structures and compounds presented as literature examples are numbered in bold Roman numerals. Literature citations are indicated by superscript Arabic numbers.

A I   Synthesis of key fragment 1
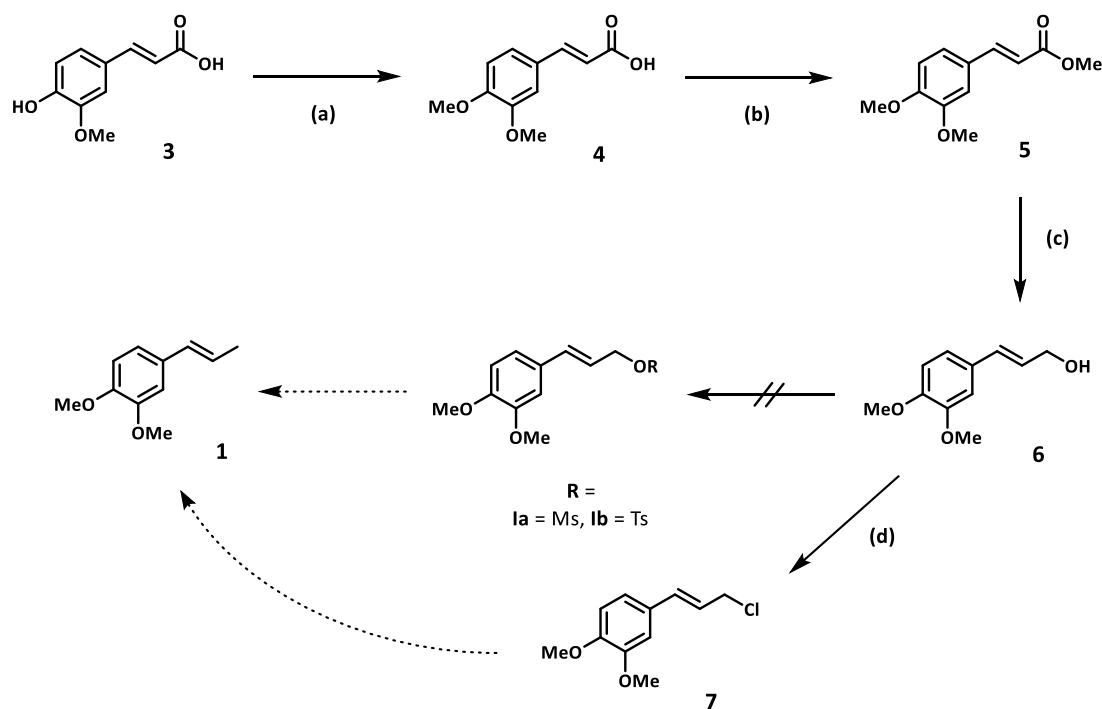
Scheme A-1: Reagents and conditions: a) DMS, 4N NaOH, rf, 76 %; b) c. H_2SO_4, MeOH, rf, 97 %; c) DIBAL-H, CH_2Cl_2, 0 °C, quant; d) $SOCl_2$, 10:1 $Et_2O:CH_2Cl_2$, 0 °C, not isolated.
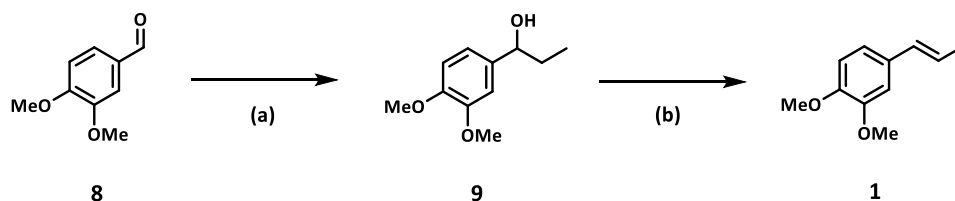
Scheme A-2: Reagents and conditions: a) EtMgBr, 4:7 Et_2O:toluene, 0 °C - rt, 95 %; b) mw, [hmim]Br, 140 °C, (E/Z = 93/7).
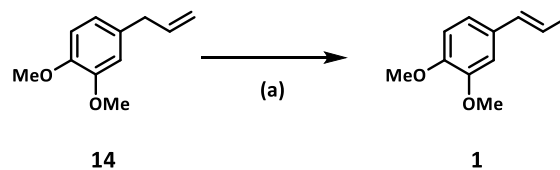
Scheme A-3: Reagents and conditions: a) 0.5 mol% [{RuCl(μ-Cl)(η^3:η^3-C$_{10}$H$_{16}$)}$_2$], MeOH, 80 °C, 4 d, 84 % (*E/Z* = 99/1).

A II   Synthesis of key fragment 2
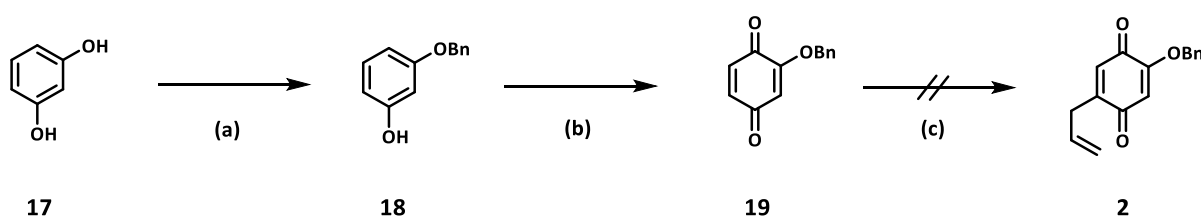
Scheme A-4: Reagents and conditions: a) BnBr, K$_2$CO$_3$, acetone, rf, 40 %; b) Fremy's salt **VIII**, KH$_2$PO$_4$, acetone/H$_2$O, rt, 70 %; c) TiCl$_4$, TMS-allyl, CH$_2$Cl$_2$, -78 °C.
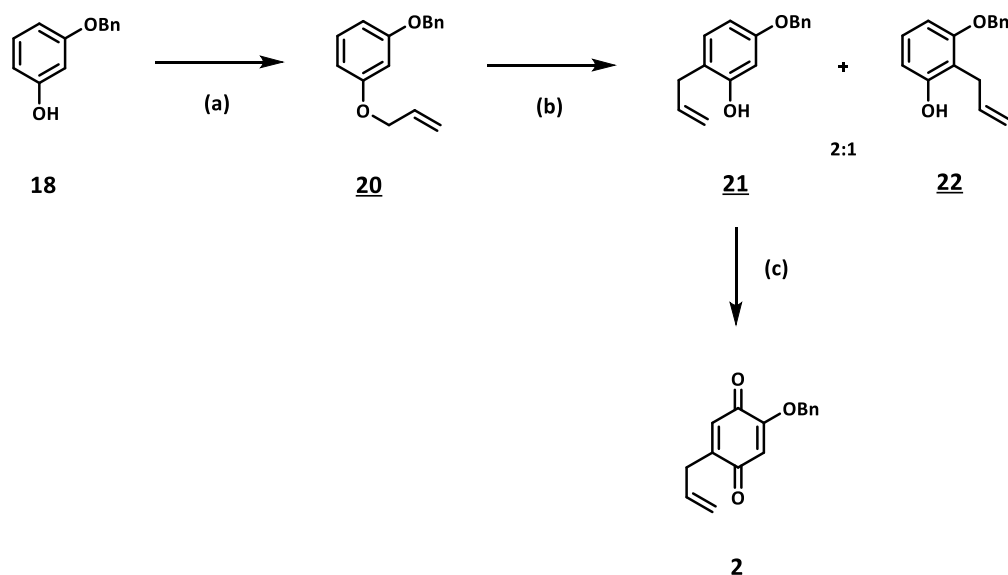
Scheme A-5: Reagents and conditions: a) allylBr, K$_2$CO$_3$, acetone, rf, 85 %; b) only **21**: 200 °C, neat, 45 %; c) 15 equiv. Fremy's salt **VIII**, 0.14 M KH$_2$PO$_4$ buffer, acetone/H$_2$O, rt, 60 %.
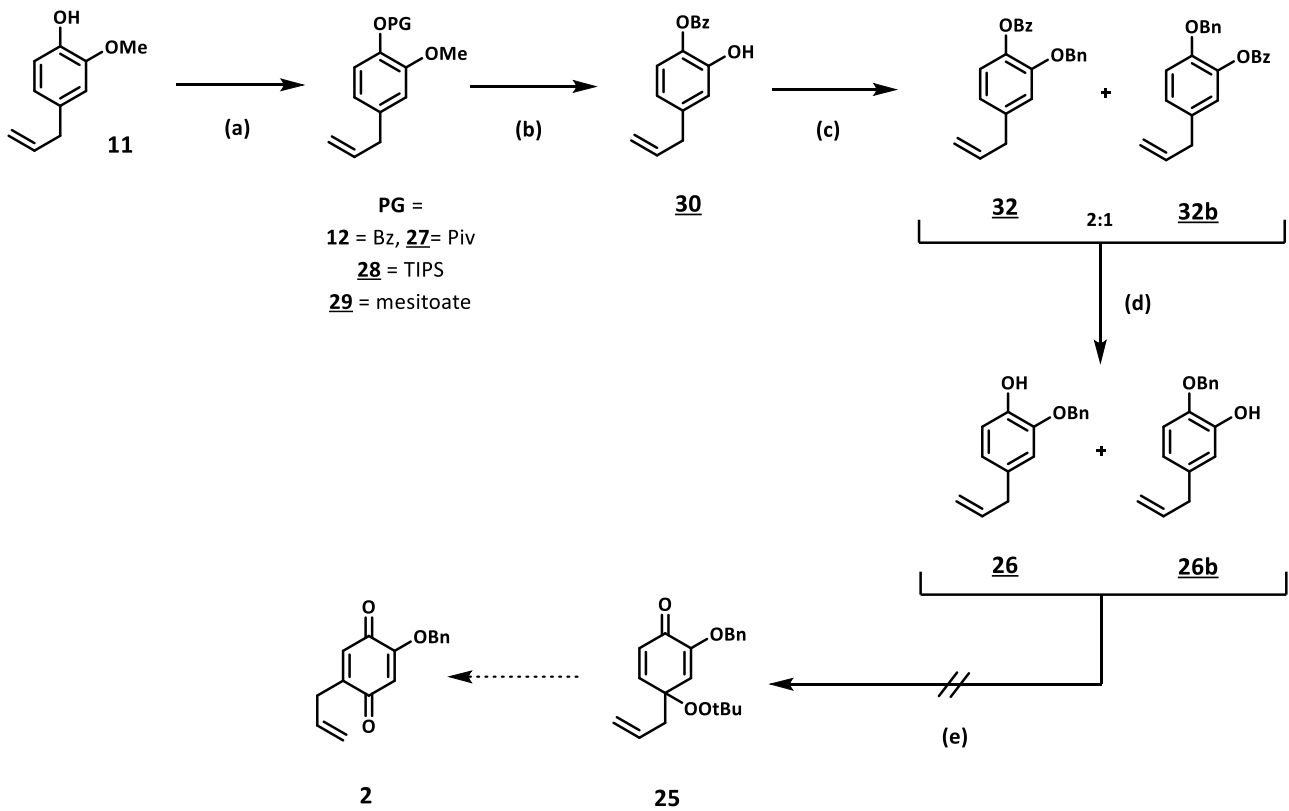
Scheme A-6: Reagents and conditions: a) only **12**: BzCl, N(Et)$_3$, DMAP, CH$_2$Cl$_2$, 0 °C – rt, 94 %; b) AlCl$_3$, S(Me)$_2$, CH$_2$Cl$_2$, 0 °C – rt, 90 %; c) BnBr, K$_2$CO$_3$, acetone, rf, 80 %; d) 2N NaOH, acetone, rf, 71 %; e) RuCl$_2$(PPh$_3$)$_3$, aqueous TBHP, DCE, 0 °C – rt.
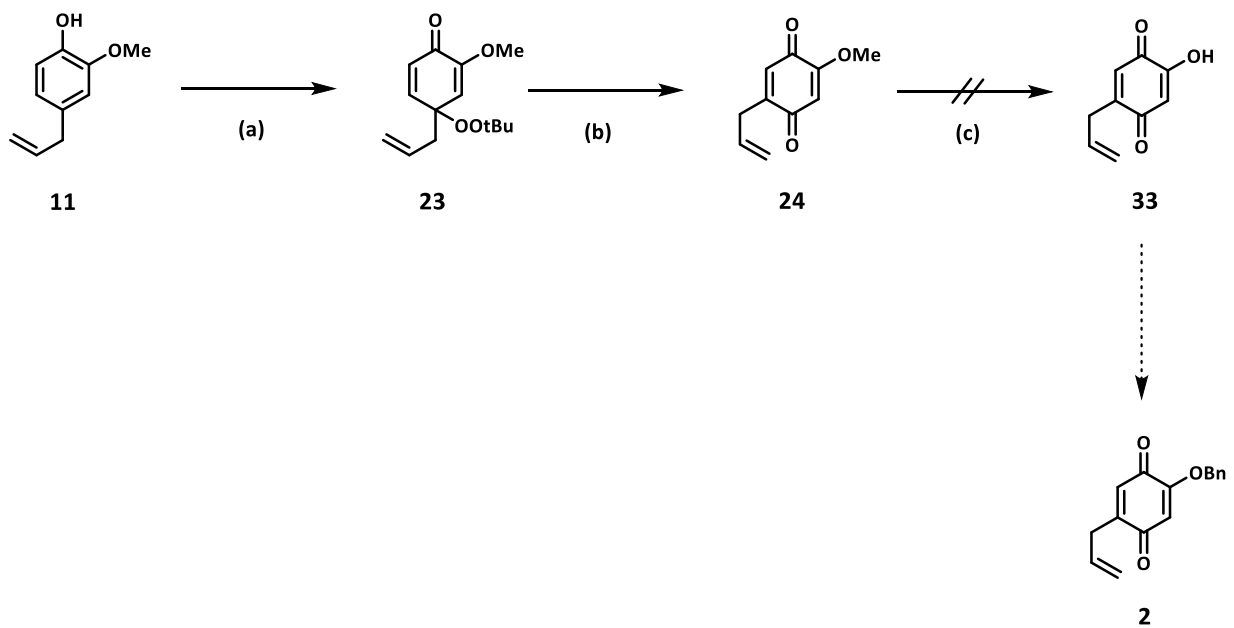
Scheme A-7: Reagents and conditions: a) RuCl$_2$(PPh$_3$)$_3$, aqueous TBHP, DCE, 0 °C – rt, 22 %; b) TiCl$_4$, CH$_2$Cl$_2$, -78 °C – rt, 81 %; c) 2N NaOH, EtOH, 70 °C.
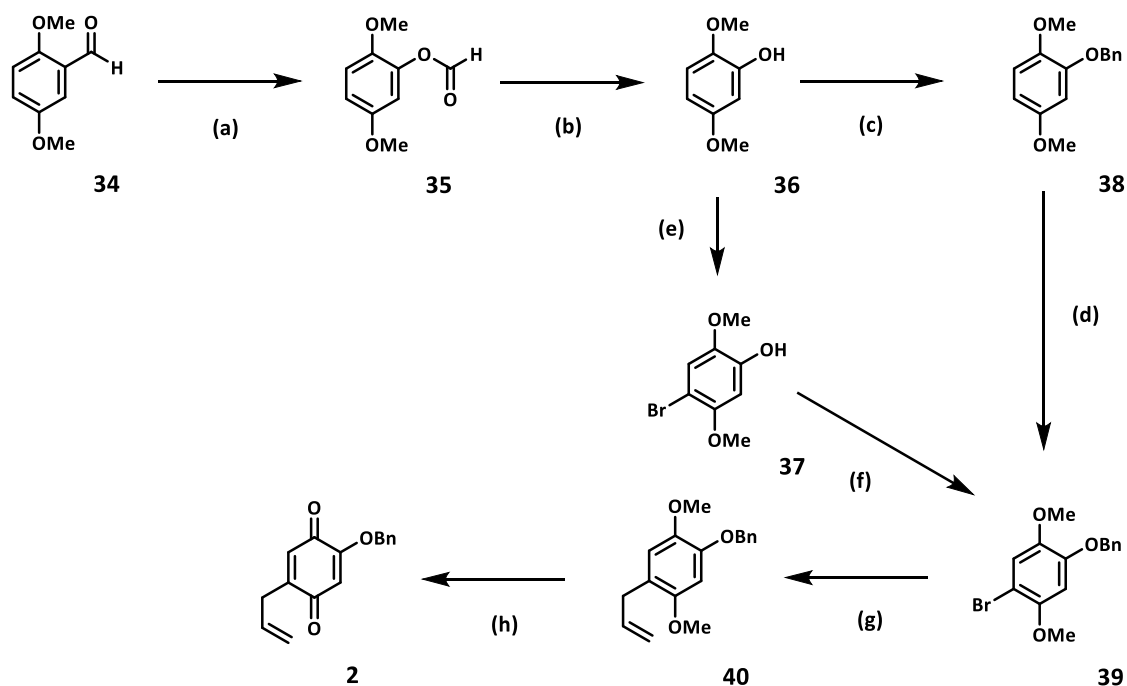
Scheme A-8: Reagents and conditions: a) mCPBA, CH$_2$Cl$_2$, 0 °C - rt, 88 %; b) 4N KOH, MeOH, rt, 92 %; c) BnBr, K$_2$CO$_3$, ACN, rf, 95 %; d) NBS, CH$_2$Cl$_2$, 0 °C, 91 %; e) NBS, CH$_2$Cl$_2$, 0 °C, 80 %; f) BnBr, K$_2$CO$_3$, NaI, acetone, rt – 50 °C, 14 %; g) PdCl$_2$(dppf)·CH$_2$Cl$_2$, allylB(pin), CsF, 1,4-dioxane, 85 °C, 88 %; h) CAN, 4:1 ACN/H$_2$O, 0 °C, 40 %.
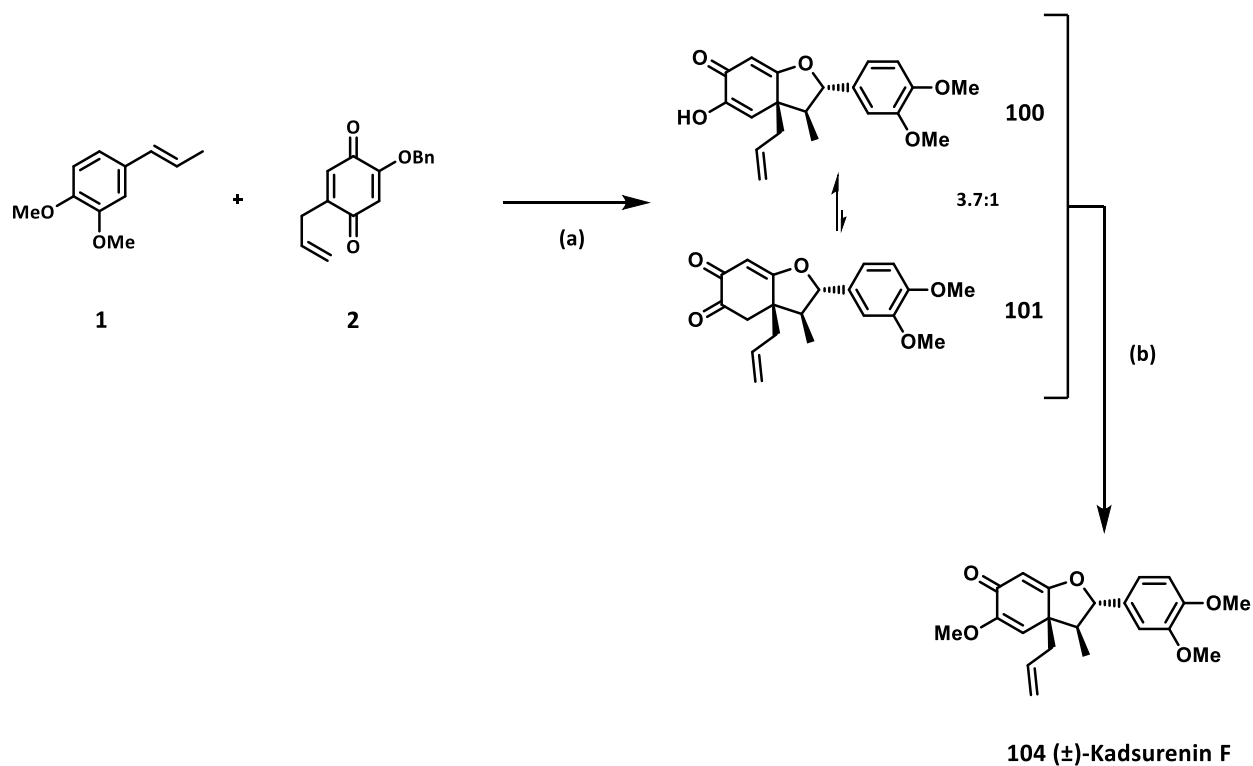
Scheme A-9: Reagents and conditions: a) SnCl$_4$, CH$_2$Cl$_2$, -78 °C – rt, 33 %; b) CH$_3$I, K$_2$CO$_3$, acetone, rt, 71 %.

B   Introduction

B I   Lignans and Neolignans

Lignans and their subclass neolignans belong to a large class of predominantly plant derived natural products originating from oxidative coupling of two C_6C_3 units.[1-2] These dimeric secondary metabolites are known to act on an ecological level in plant-plant or plant-insect interactions as a means of defense against herbivores or other microorganisms by disruption of the endocrine system.[3-4] Additional protective properties in response to stress conditions like trauma, infections or exposure to UV radiation and pollutants are also documented.[4-5]

The structures typically coupled by a β,β'-linkage between two C_6C_3 units are termed lignans, whereas neolignans are composed of any other connection between these sub-units (Scheme B-1). For the purpose of nomenclature these C_6C_3-subunits are treated as phenylpropanes and are numbered from 1 to 6 in the aromatic ring, starting from the propyl group, whereas the propyl group is numbered from 7 to 9, starting from the benzene ring.[6]
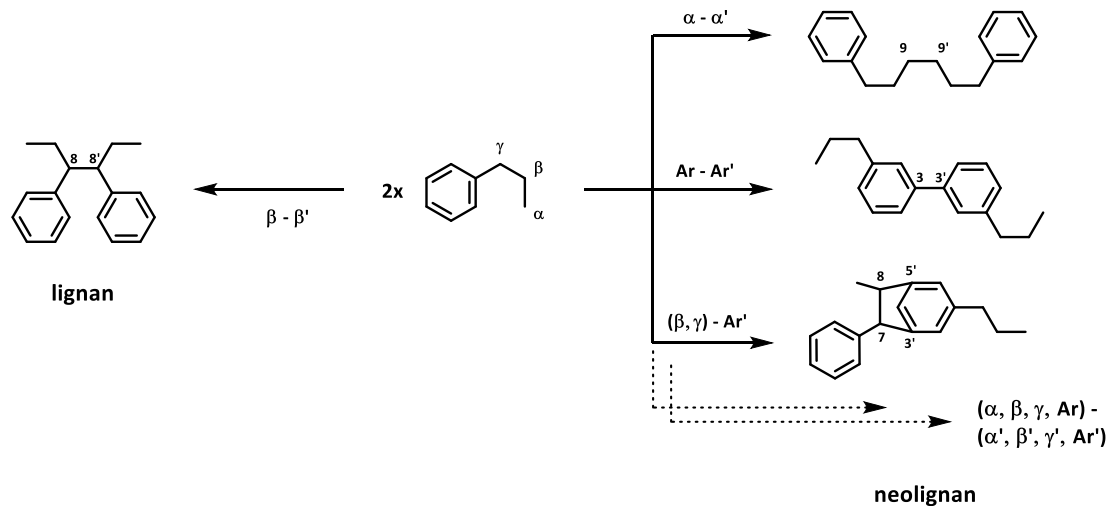
Scheme B-1: Exemplary coupling of two phenylpropane units to form lignan or neolignan structures

These dimeric structures display a high structural variety, encompassing diverse substitution patterns on the aromatic system and different degrees of oxidation on the propane side-chain. These features emerge from the biogenesis of these compounds, originating in the Shikimate pathway.[7]

The biosynthesis, as illustrated in Scheme B-2, is initiated by the deamination of phenylalanine by phenylalanine ammonialyase (PAL) to form cinnamic acid, followed by the hydroxylation to p-coumaric

acid by cytochrome P-450 (CYP). The synthetic path continues through alternating steps of methylation with S-adenosyl methionine (SAM) and further hydroxylation to form caffeic acid, ferulic acid and sinapic acid. The final alcohol species are ultimately derived by reduction of the corresponding acids *via* formation of the coenzyme A-ester and further reduction in the presence of NADPH.[8-9]
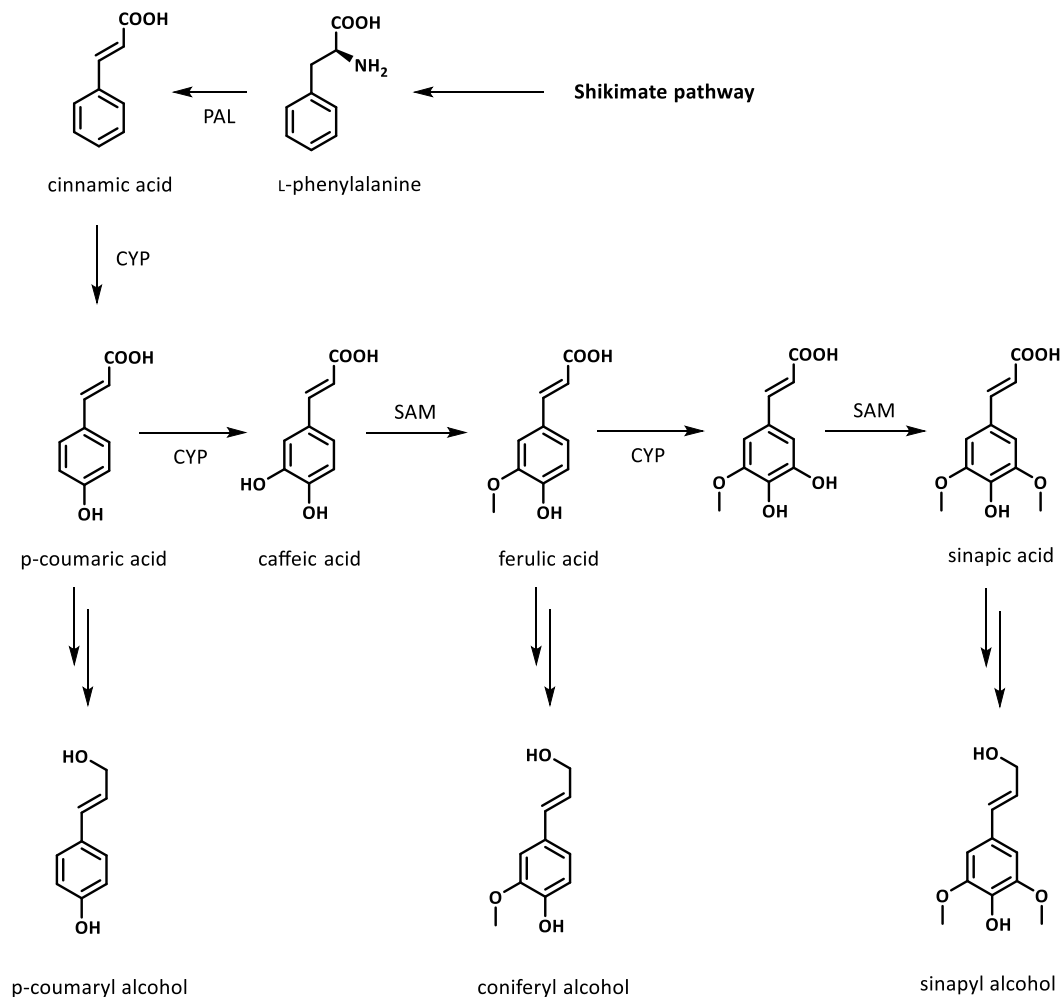
Scheme B-2: Biogenesis of phenylpropanoid precursors for lignan and neolignan structures

The para-relationship between the electron-rich olefin and the phenol-group represents the common structural feature of these compounds. This arrangement enables certain oxidoreductases to abstract both a proton and an electron from these substrates to form resonance-stabilized quinone radicals as shown in Scheme B-3. These can either pair by β,β'-linkage and form lignan-class structures or collapse *via* different recombination sites at the resonance structures to yield different types of neolignans. A dirigent protein (DIR) enables herein the diastereoselectivity of the radical-coupling and ensures the optical purity of the final dimers.[10]
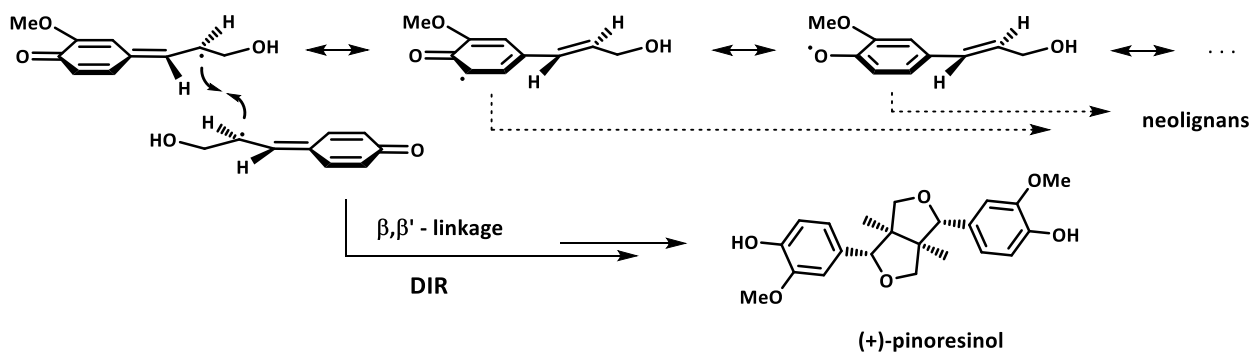
Scheme B-3: Resonance stabilization of quinone radicals and formation of (+)-pinoresinol *via* β,β'-linkage

The structural variety of potential reaction partners and the possibility of resonance stabilization of the quinone-species enable the formation of an enormous structural diversity. Hence, many different types of lignans and neolignans are already known in the literature as shown in Figure B-1, which depicts only a small selection of known natural products. Dibenzyloctadienes, benzofurane, biphenyl, aryl-alkyl ethers, all consist of these dimeric core structures, but show different types of connectivity, arising from the choice of coupling partners and the corresponding dirigent enzymes.[11]
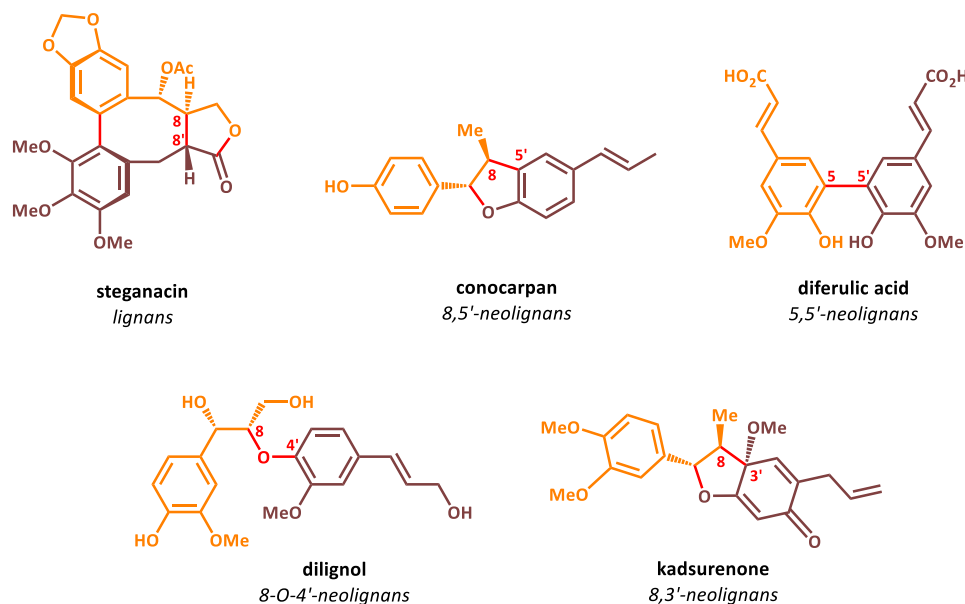
Figure B-1: Selection of known lignan and neolignan natural products [12]

Depending on the structural features, these natural products demonstrate a broad range of biological activities, having e.g. cardiovascular[13], anticancer, antiangiogenic, antiviral, antibacterial, antioxidative or anti-inflammatory properties.[14-15] Within the frame of this thesis the focus will be placed on the effects on inflammatory regulation of these compounds.

B II   Inflammation

Acute inflammation in general is the innate immune system's reaction to different types of external or internal stimuli. These can be either pathogens entering the body, trauma or a variety of physical agents, such a radiation or heat.[16]

Clinically, the immune response is characterized by five signs consisting of redness, heat, pain, swelling and loss of function, which are indicating an inflammatory process. This prompt non-specific response of the body is termed acute phase response (APR) and is caused by local or systematic disturbances in its homeostasis. At the origin of the aforementioned stimuli a number of actions are initiated by the affected tissue, triggering the activation of the vascular system and inflammatory cells, as well as the release of pro-inflammatory cytokines (Figure B-2).[17]

trauma/pathogen   macrophage   cytokine release
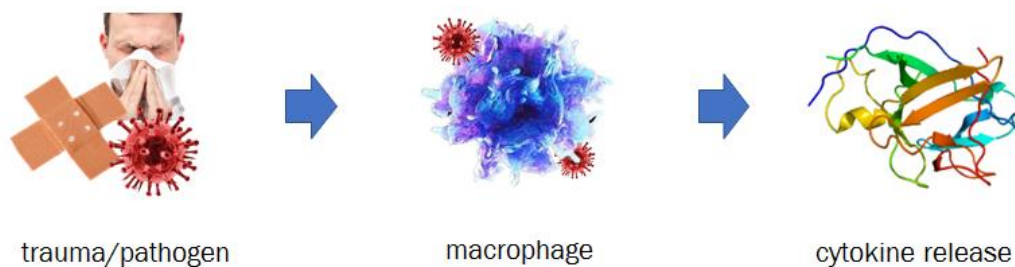
Figure B-2: Simplified inflammatory response *via* different stimuli

These cytokines initiate vasodilation and cause an increase in vascular permeability, leading to an elevated blood flow, thus allowing nutrients, plasma proteins and leukocytes that are normally restricted to enter blood vessels to gain access to the source of the inflammation. Furthermore, they stimulate the release of fibroblasts, the structural framework cells of the body to aid in the wound healing process and lead to the increased production of ROS (reactive oxygen species) or RNS (reactive nitrogen species) as a potent tool for non-specific antimicrobial defense.[18-19]

This innate immune response to invaders is triggered by the interaction and recognition of pathogen-associated molecular patterns (PAMPs) like e.g. LPS (lipopolysaccharide) present in many Gram negative bacteria, lipoproteins or RNA fragments with toll-like receptor (TLR) proteins as illustrated in Figure B-3. These TLR represent a family of 13 membrane-spanning, pattern recognition receptors (PRR), usually expressed in antigen-presenting cells such as macrophages and dendritic cells.[20]
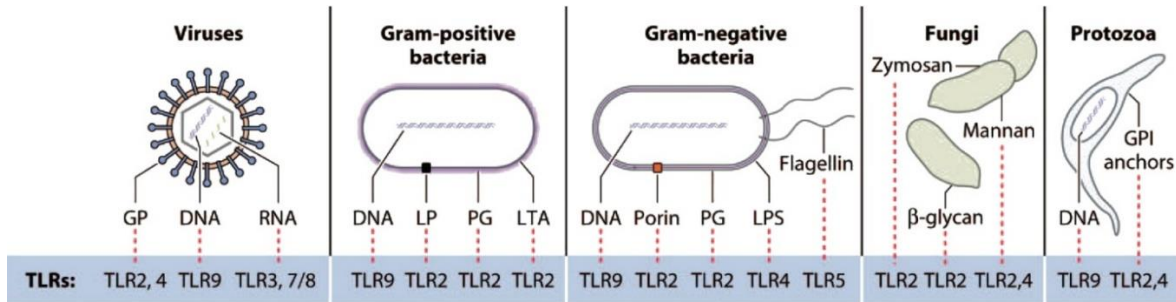
Figure B-3: TLR recognition of pathogen-associated molecular patterns (PAMPs)[21]

Upon recognition of the foreign entity with the receptor, the production of pro-inflammatory cytokines is initiated by a signaling cascade as illustrated in the simplified TLR signaling pathway in Figure B-4.
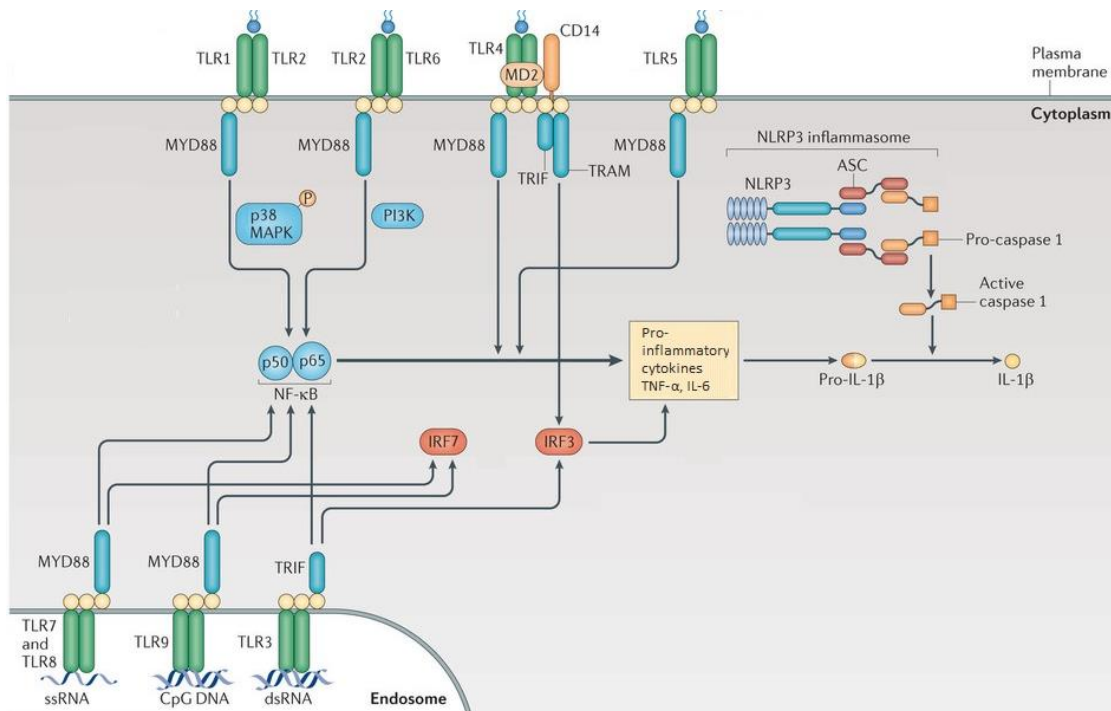
Figure B-4: TLR signaling pathway (modified from Shaw et al.)[22]

The cytoplasmic domains of the TLR-ligands recruit signaling adaptor proteins MyD88 (myeloid differentiation primary response protein 88), TIRAP (toll-interleukin 1 receptor domain containing adaptor protein), TRAM (translocation associated membrane protein 1), and/or TRIF (toll-interleukin 1 receptor-domain-containing adapter-inducing interferon-β). Depending on the type of receptor, stimulation of the downstream signaling pathway, involving phosphorylation, ubiquitination or protein-protein interaction, converges into the activation of transcription factor NF-κB (nuclear factor-kappaB). This process ultimately drives the inflammatory gene expression of pro-inflammatory cytokines TNF-α and IL-6. These additionally induce Caspase 1 catalyzed conversion of the IL-1β precursor, to furnish the release of active pro-

inflammatory cytokine IL-1β.[22] The secretion of these cytokines into the bloodstream ultimately mediates the acute-phase response of the body, which causes the inflammatory symptoms.

B II.1 Cytokines in inflammatory bowel disease (IBD)

Inflammatory bowel disease comprises two major forms (Ulcerative Colitis – UC and Crohn's disease – CD) that represent a group of chronic autoimmune disorders, in which the organism attacks elements of its own digestive system. Although the mechanism for the pathogenesis of these inflammatory conditions is not entirely understood, it was found that an imbalance in cytokine regulatory processes plays a fundamental role as shown in Table B-1.[23]

Table B-1: Dysregulation of cytokines in IBSs and cell lines involved in their production

Cytokine	UC	CD	Cells involved in the production
TNF-α	Up-regulated	Up-regulated	Macrophages
TL1α	Unknown	Up-regulated	Th1
IL-1β	IL-1ra/IL-1 ratio	IL-1ra/IL-1 ratio	Macrophages
IL-6	Up-regulated	Up-regulated	Macrophages, DC, Th17 and others
IL-18	Not	Yes, not in all patients	Macrophages
TGF-β	Not clear, maybe defective signalling	Not clear, maybe defective signalling	Th0, Th3, Treg
IL-10	Not clear	Yes, up-regulated	Tr1 and Breg
IL-4	Not clear	Not clear	Th2, NK
IL-12	Up-regulated	Up-regulated	Macrophages, DC
IL-23	Yes	Yes	Macrophages, DC
IL-27	Not clear	Up-regulated	APCs
IL-17	Up-regulated	Up-regulated	Th17
IL-13	Up-regulated	Not	Th1, NK
IL-5	Up-regulated	Not	Th2, NK

Especially the upregulation of cytokines responsible for the acute-phase response, namely IL-1β, and TNF-α, have a major role in driving intestinal inflammation.[24] Clinical evidence suggests that a deficiency in the enzyme Caspase 1 protected mice from Ulcerative colitis by disabling the proteolytic cleavage of Pro-IL-1β into its active form.[25] Moreover, recent experimental studies showed that neutralization of TNF-α with certain monoclonal antibodies effected T-cell apoptosis *in vivo* and led to an effective suppression of induced colitis.[26] Similar anti-inflammatory effects have recently been reported by lignan or neolignan structures from plant extracts, displaying either inhibitory properties on the release of pro-inflammatory cytokines[27-28], the expression of NF-κB[29], or ROS production[30]. These findings evidently signify the enormous potential of these lignanoid structures as potential drug lead candidates.

B II.2 Pharmacology of benzofurane-neolignans

Several structural analogues of the target molecule Kadsurenin F are already known in the literature with various substitution patterns encompassing a benzofurane core (Scheme B-4).

α = kadsurenone
β = denudatin B

porosin

burchellin
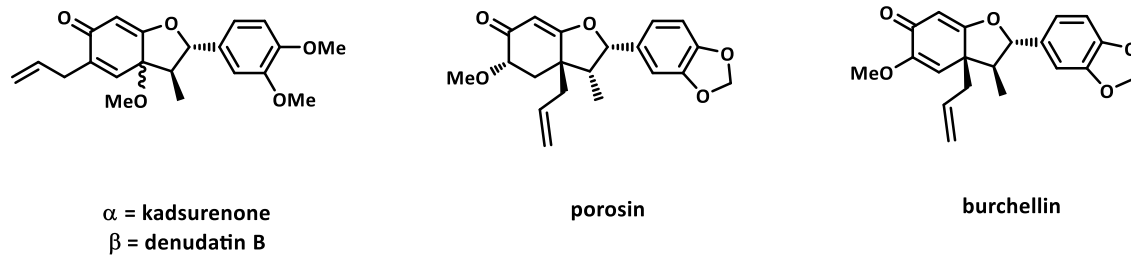
Scheme B-4: Selection of structural analogues of Kadsurenin F

Among these only few have been tested for biological activity, furthermore in particular for having anti-inflammatory properties. Kadsurenone as being one of these examples displays potent PAF (platelet-activating factor) agonism that was proven to indirectly interfere with LPS induced TNF-α production.[31] On the other hand structures displaying higher similarity to Kadsurenin F were not yet proven to be biologically active.

Nevertheless, collaboration partners at the university of Innsbruck with the focus on natural product evaluation, isolated Kadsurenin F from extracts of the Japanese pepper plant *Piper Futokadsura* and proved it to be a potent inhibitor for the release of major pro-inflammatory cytokines IL-1β, TNF-α and MCP-1, as well as anti-inflammatory cytokine IL-10 at µM level. This could be shown in an *in vivo* mice model by employing the neolignan in the treatment of a hapten-induced colitis.

B III Objective

Based on the promising pharmacological results, the need for a synthetic approach towards Kadsurenin F was desired. This would enable the eventual creation of a structural library that would give access to analogues for further biological testing. Hence, the target of this thesis was to establish a concise route towards the neolignan scaffold, mainly focusing on the reliability of the chemistry and potential diversification of the target molecule.

C   Results and Discussion

C I   Retrosynthetic analysis
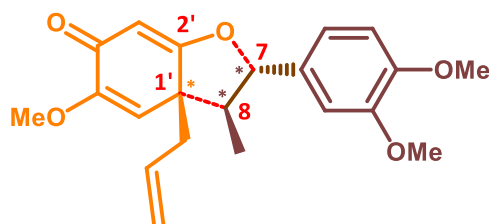
Figure C-1: Structure of target molecule Kadsurenin F

The analysis of the target structure reveals an oxidatively masked benzofurane core, sharing a connection between two phenylpropanoid fragments, in a manner typically found as a motif in the neolignan-class. This dimeric structure depicted in Figure C-1, applying the nomenclature for said compounds, bears a 8,1'-linkage with an additional 2',7-epoxy bridge. Three successive stereocenters on the bridging positions on the furane-unit, with defined 7S, 8S, 1'R configuration in addition to the quaternary center, represent the synthetically most demanding moieties on this molecule.
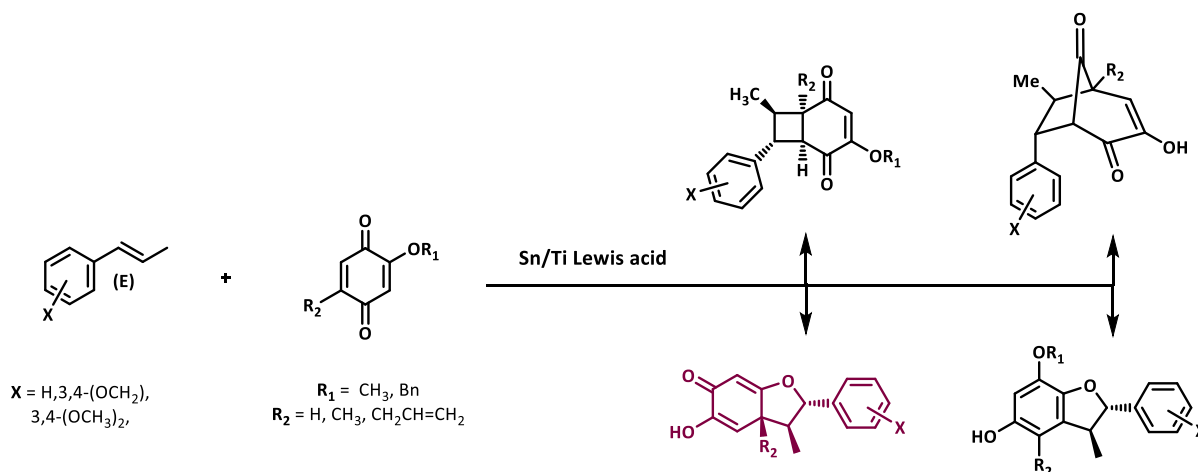
Scheme C-1: Lewis assisted [2+5] cyclisation devised by Engler et al. with substituted styrenes and 2-alkoxy-1,4-benzoquinones – different products depending on reaction conditions[32]

Fortunately, Engler et al. developed individual strategies[32] towards these benzofurane-neolignans based upon earlier studies of Büchi[33]. By mimicking nature's way of assembling these structures, they devised the synthesis of several analogues using a Lewis acid assisted diastereoselective [2+5]-cycloaddition between 2-alkoxy-substituted 1,4-benzoquinones and styrene units. This enabled the synthesis of

different structural motifs by careful control of the applied reaction conditions (Scheme C-1). The mechanistical intricacies of this reaction will be discussed in greater detail on a later stage in chapter C IV.

Benefiting from this approach, the retrosynthetic cut divides the molecule into the key fragments *(E)*-methylisoeugenol (**1**) and 2-allyl-5-(benzyloxy)cyclohexa-2,5-diene-1,4-dione (**2**).

104 (±)-Kadsurenin F

Key fragment **1**   Key fragment **2**
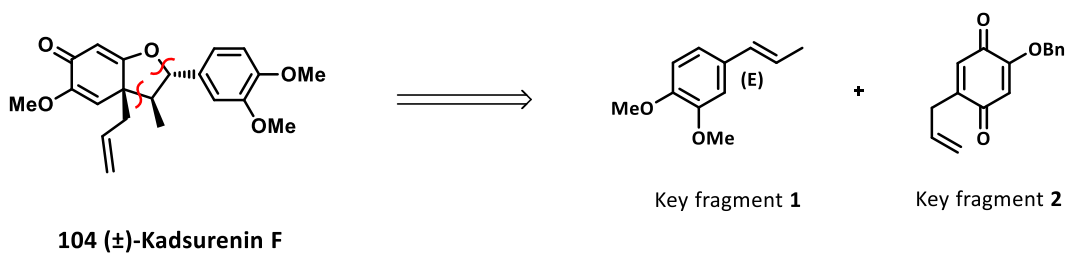
Scheme C-2: Biomimetic retrosynthetic cut of Kadsurenin F

To accomplish the synthesis of these two building blocks, several strategies (A to H) were developed and evaluated, always taking into account aspects of a possible quick assembly, reliability of the chemistry and modularity of the synthetic approach with regards to the subsequent derivatization potential.
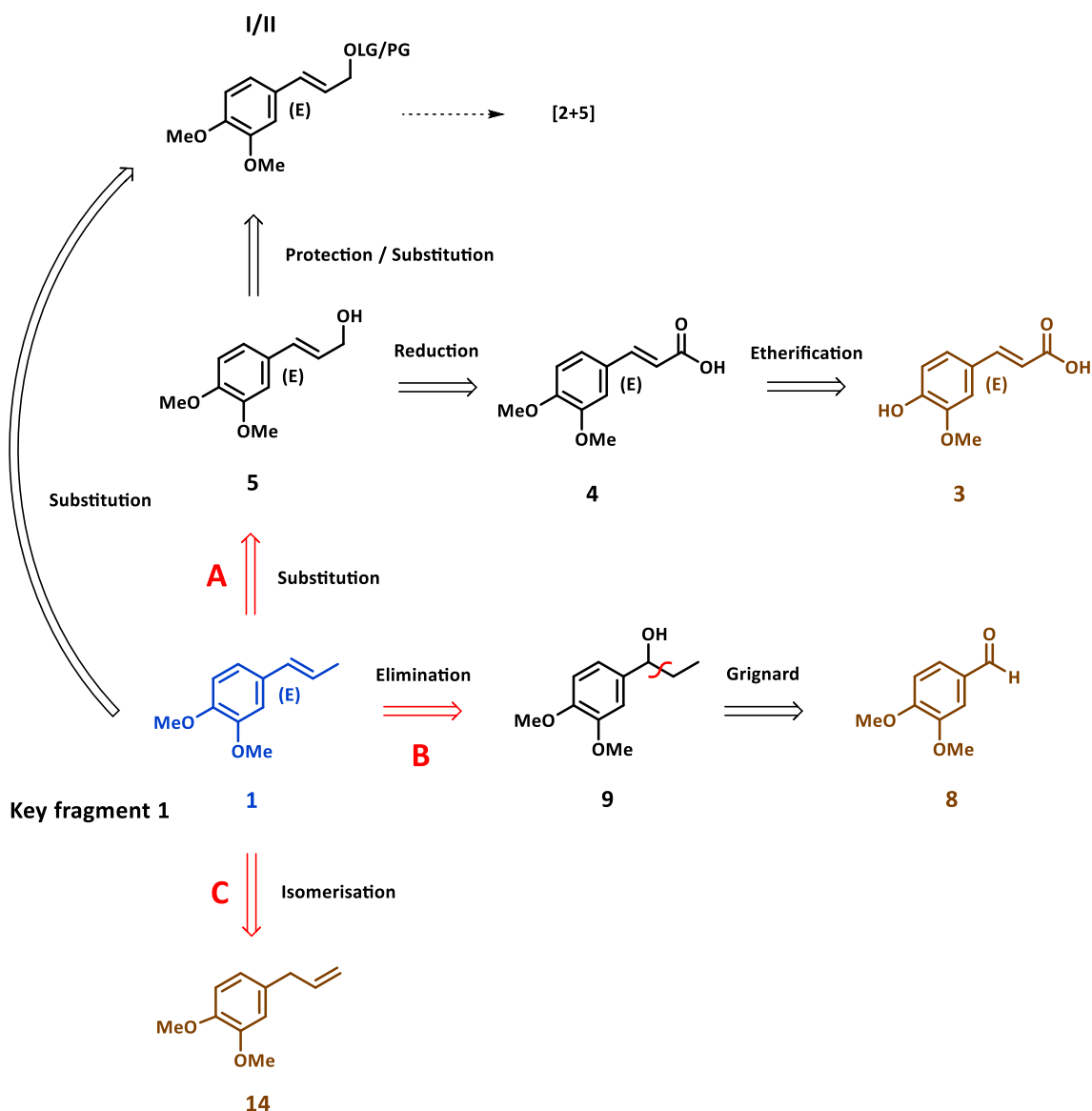
Scheme C-3: Retrosynthetic analysis of key fragment **1** (Synthetic strategies are designated with red letters, starting materials are brown colored)

Scheme C-3 summarizes the retrosynthetic analysis of key fragment I. As the geometry of the olefin has a major influence on the resulting stereochemistry of the neolignan[32-34], the synthetic route had to account for the stereospecific formation of the *(E)*-olefin.

   (A) Hence, one approach towards the target was to exploit structures that had the wanted motif already incorporated, such as commercially available *(E)*-ferulic acid **3**. Methylation of the phenol position leading to **4** and subsequent reduction to form the *(E)*-dimethoxycinnamyl alcohol **5** would moreover display a possibility for further structural modifications. This could be achieved *via* the installation of a leaving (**I**) or protecting group (**II**) that would enable further derivatization on the C9 carbon of the neolignan-scaffold. Deoxygenation of allylic alcohol or hydride-substitution of the terminal leaving group[35] would finally give access to the key fragment **1**. Several methods could be envisioned for this step including Barton-McCombie[36], a stepwise oxidation to the carbonyl and Wolff-Kischner reduction[37],

photocatalytic Garegg–Samuelsson[38] reaction or recently published Ir-catalysed one-pot Wolff-Kischner deoxygenation[39].

The other two approaches would omit the necessity for methylation on the aromatic ring, but would encompass installation of the *(E)*-olefin as main challenge. This could be either envisioned *via* elimination **(B)** of the benzylic alcohol **9**, which would be derived from veratryl aldehyde **8** by Grignard addition or by transition metal (Ru) catalyzed isomerization[40] **(C)** from commercial methyleugenol **14**.

Scheme C-4: Retrosynthetic analysis of key fragment **2** (Synthetic strategies are designated with red letters, starting materials are brown colored).

The synthetic outline for the assembly of key fragment **2** is depicted in Scheme C-4, displaying a multitude of possible approaches, each entailing the synthetic challenge of introducing the allyl moiety in para-position to the alkoxy-group, yet enabling the oxidation to the 1,4-benzoquinone.

(D) A possible retrosynthetic cut can be made between the side chain and the ring, by introducing the allyl-moiety *via* Lewis acid assisted allylation[32, 41] from the 2-benzyloxy-1,4-benzoquinone **19,** which can be derived from an atypical phenol oxidation[42] of **18,** leading back to resorcinol **17**.

(E) A different approach would use the same oxidation protocol, but introduce the allyl-group *via* Claisen rearrangement from allyloxy-ether **20**, enabling the synthesis of the key fragment *via* the phenolic oxidation of **21**. As we are dealing with a meta-substituted, unsymmetrical ether, two regioisomers should be expected in this step, possibly limiting the yield.

Following a rather quick approach towards such structural motifs, Murahashi et al. reported the synthesis of 1,4-benzoquinones in a two-step procedure from p-substituted phenols *via* peroxidation and [1,2]-rearrangement.[43] As eugenol **11** was already used as substrate in the abovementioned protocol to give the methoxy version **24** of the target compound *via* rearrangement of **23**, two convergent studies emerged from the use of **11** as starting material.

(F) Demethylation of protected eugenol **XXI,** forming intermediate **XXII,** followed by etherification and deprotection, would facilitate the formation of Bn-Eugenol **26**. This would enable synthesis of the target by applying Murahashi's methodology *via* rearrangement of peroxide **25**.

(G) The alternative to strategy F would be direct hydrolysis of masked ester **24** (colored in orange) and simple esterification with benzyl alcohol, to arrive at key fragment **2**.

(H) The final strategy comprises a more classical approach by stepwise assembly of the core structure, starting from 2,5-dimethoxybenzaldehyde **34**. Hence, Dakin oxidation could be applied to form phenol **36**, which would enable the preparation of the coupling precursor **39,** either *via* etherification and bromination or in reversed order. Final oxidative demethylation[44] of **40** would deliver the key fragment **2**.

C II   Synthesis of key fragment 1

C II.1   Strategy A
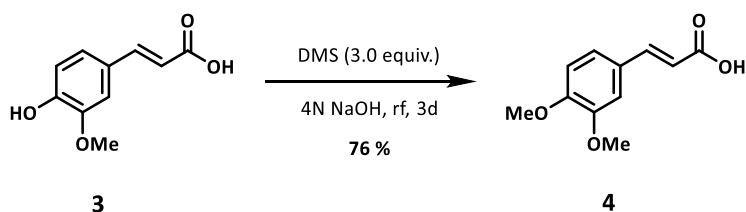
Scheme C-5

The first step in the synthetic sequence towards key fragment **1** was the methylation of commercially available *(E)*-ferulic acid **3** with DMS (dimethyl sulfate) in refluxing 4N NaOH (Scheme C-5). Contrary to the literature[45] a prolonged reaction time and more equivalents of DMS were needed to accomplish full consumption of the starting material. Recrystallisation from acetone or 70% EtOH afforded the acid in moderately high yields.
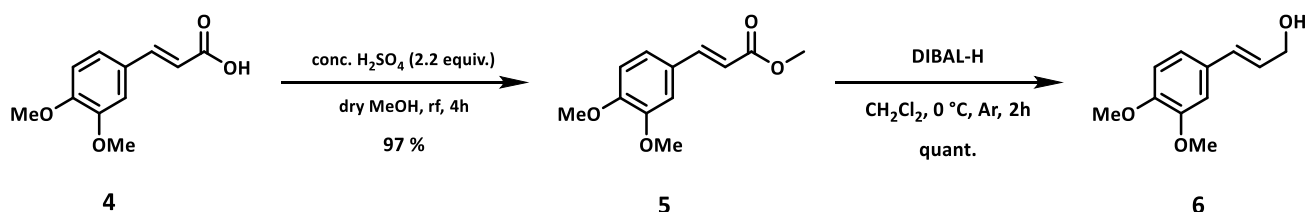
Scheme C-6

For the reaction towards cinnamyl alcohol **6**, DIBAL-H was selected as the reagent of choice, representing a milder hydride than e.g. LAH or $NaBH_4$ usually allowing for a cleaner reduction of highly electron rich α,β-unsaturated acids or esters[46] and possibly minimizing competing 1,4-addition. To enable clean reduction, preceding acidic esterification with MeOH derived ester **5**, which was directly subjected to the next step without purification. Finally, DIBAL-H facilitated unproblematic synthesis of allylic alcohol **6** in nearly quantitative yield over two steps (Scheme C-6).

For the final reduction of the alcohol, a possible radical derived deoxygenation approach was considered to be implausible, considering the highly conjugated structure of the consequently resulting radical species, which could allow for various side reactions to take place (*cf.* biogenesis of neolignan-structures in Scheme B-3). Therefore, a standard substitution procedure with a conventional sulfonate leaving group was applied (Scheme C-7).
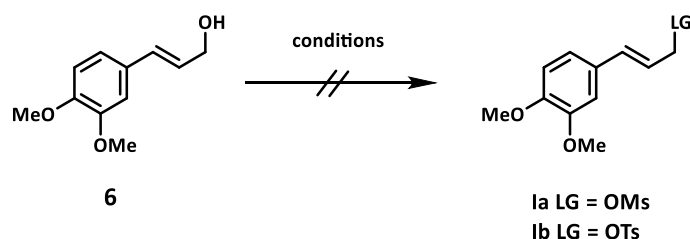
Scheme C-7

Regrettably, all attempts towards intermediate **1**, as judged from TLC and crude ^{1}H-NMR analysis, were unsuccessfull even after full consumption of the starting material (Table C-1). Either evident complete decomposition or signals that could be attributed to the methyl-group of the resulting mesylate were missing in the spectra. However, all reactions employing the sulfonyl chloride and triethylamine as base showed a predominant formation of a structurally similar product to alcohol **6** with only minor shifts in the ^{1}H-NMR-spectrum (entry 1 and 2).

Table C-1: Attempted installation of leaving group

entry	conditions	observed results
1	MsCl (2.5 equiv.), N(Et)$_3$ (3.0 equiv.), dry CH$_2$Cl$_2$, 0 °C to rt, Ar, < 15 min	unstable side product
2	MsCl (1.5 equiv.), N(Et)$_3$ (3.0 equiv.), dry CH$_2$Cl$_2$, -78 °C to rt, Ar, 30 min	unstable side product
3	MsCl (1.5 equiv.), K$_2$CO$_3$ (3.0 equiv.), dry CH$_2$Cl$_2$, -78 °C to rt, Ar, 30 min	no reaction
4	MsCl (1.5 equiv.), Ag$_2$CO$_3$ (3.0 equiv.), dry CH$_2$Cl$_2$, -78 °C to rt, Ar, 30 min	no reaction
5	TsCl (1.5 equiv.), N(Et)$_3$ (3.0 equiv.), dry CH$_2$Cl$_2$, -78 °C to rt, Ar, 1 d	unstable side product
6	TsCl (1.2 equiv.), NaH (1.5 equiv.), dry Et$_2$O, 0 °C to rt, Ar, 30 min	decomposition
7	TsCl (1.2 equiv.), dry pyridine, 0 °C to rt, Ar, 5 h	decomposition
8	Ms$_2$O (1.5 equiv.), N(Et)$_3$ (3.0 equiv.), dry CH$_2$Cl$_2$, -78 °C, Ar, < 15 min	decomposition
9	Ts$_2$O (1.5 equiv.), N(Et)$_3$ (3.0 equiv.), dry CH$_2$Cl$_2$, -78 °C to rt, Ar, 1 h	decomposition

As the inherent instability of the main reaction product could be verified *via* 2D-TLC, showing evident decomposition, quantitative analysis of the NMR proved to be quite difficult. Nevertheless three different structures were envisioned as possible reaction products matching the spectral data, which would arise from the substitution of the mesylate (Figure C-2).

Figure C-2: Possible side products from the mesylation of **5** with N(Et)$_3$ as base.

To verify the most plausible hypothesis, cinnamyl chloride **7** was synthesized using thionyl chloride and subjected to crude NMR analysis, thereby proving the suggested structure to match the formed by-product.

Scheme C-8

Considering the strongly electron rich structure of the compound due to the mesomeric effect of the methoxy groups of the aryl ring, installation of the leaving group might be extremely short-lived and/or unstable. This would either enable the chloride to quickly replace (a) mesylate **Ia** acting as the stronger nucleofuge, or furnishing the synthesis of **7** by addition (b) to intermediate cationic species **V** (Scheme C-9).[47]

Scheme C-9

To counteract this problem, inorganic carbonate bases were used to facilitate immediate precipitation of any formed chloride ions as highly insoluble Ag or K-salts (entry 3 and 4). As reactions under these conditions did not show any significant conversion, the leaving group was switched to a tosylate **Ib**, as this should display higher stability compared the mesylate species **Ia**.

The application of standard mesylation conditions (entry 5) exhibited only minimal progress even at elevated temperatures, which was contributed to the lower reactivity of the tosyl chloride with alcohols. Thus, different conditions employing pyridine or NaH as bases were tested (entrys 6 and 7), which did not give product or left over starting material after work-up. In two last attempts, increasing the reactivity, in addition to an exclusion of chloride as nucleophile source, inherently more active tosic and mesic anhydrides were employed (entrys 8 and 9). Unfortunately no isolation of product or recovery of starting material was possible also in this case, thus proving the instability of **Ia/Ib,** therefore having the need to adapt the strategy for the synthesis of **1**.
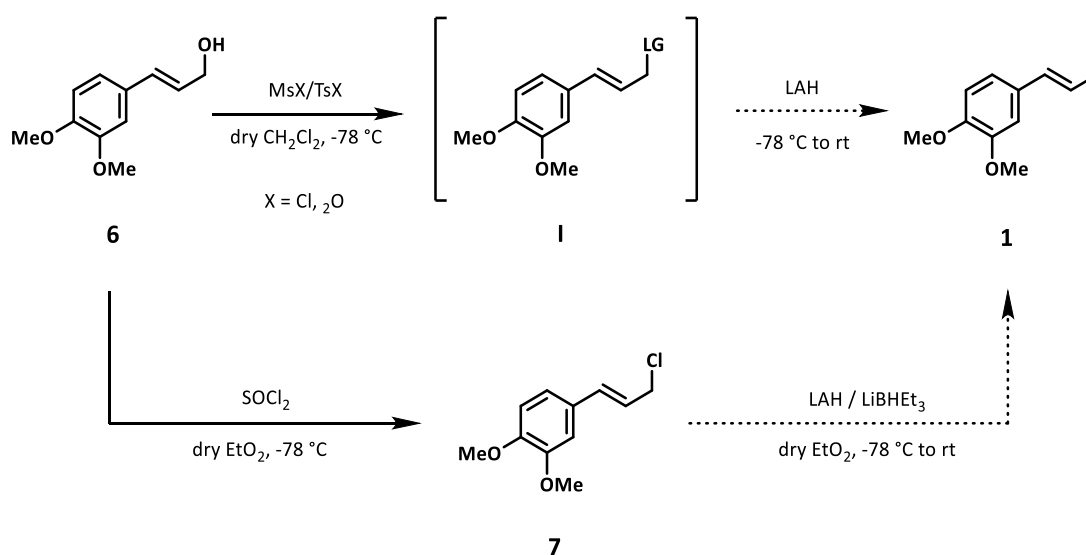
Scheme C-10

A possible, yet not tested approach would be the *in situ* reduction of the intermediates **I** in a one-pot reaction with LAH or by reducing the less unstable chloride, thus enabling a sequential approach (Scheme C-10). Realizing that these methods would not allow for further derivatization on the final structure as the handle for modifications would be inevitably lost, this approach was abandoned, moreover as an alternative had meanwhile been found (see Strategy C).

C II.2   Strategy B

The rationale behind strategy B was the rather quick access towards the required key fragment **1**, with the leading question, whether a stereospecific elimination of benzyl alcohol **9** was possible and, if not, if separation of the isomers would be feasible. Thus, as a first step, benzyl alcohol **9** was prepared *via* Grignard addition to veratryl aldehyde **8** in excellent yield.
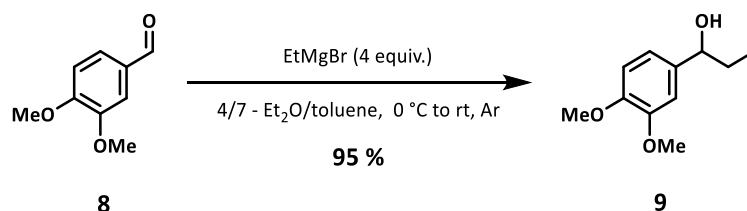
Scheme C-11

As the dehydration of alcohols is an extensively studied transformation in organic chemistry, various synthetic approaches are known to the literature, either employing mineral acids[48], anhydrous CuSO$_4$[49], oxalyl chloride[50] or SiO$_2$[51], just to mention some commonly used techniques. The problem with these approaches arises with their insufficient selectivity towards the formation of the respective (*E*)-olefins in the reported examples. As already mentioned (*cf.* C I – necessity for (*E*)-geometry of **1**), a sterospecific synthesis towards the key fragment was sought after, thus limiting the search to highly selective methods.
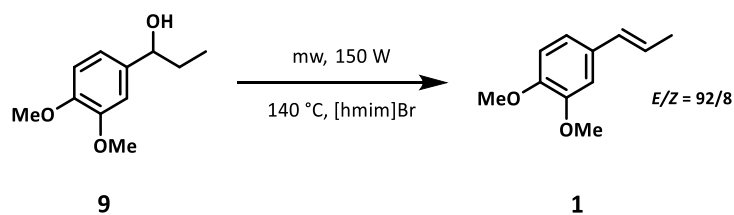
Scheme C-12

One of the investigated protocols employed an ionic liquid as solvent in a microwave assisted dehydration of benzylic alcohols, which claimed to cleanly produce the corresponding (*E*)-arylalkenes in high yields (Scheme C-12).[52] As the results from this approach, judging from crude ^{1}H-NMR analysis, merely gave rise to (*E/Z*)-ratios of 92/8, separation of these isomers was subsequently attempted. After several unsuccessful efforts of chromatographic separation, employing various eluents and combinations thereof (LP, cyclohexane, toluene, EtOAc, CH$_2$Cl$_2$, Et$_2$O, MeOH), as well as preimpragnation of the silica with silver nitrate[53], which is known to increase the retention of the *trans*-olefin, also this approach towards an *E*-specific synthesis of key fragment **1** was abandoned.

C II.3   **Strategy C**

The last attempt towards a clean, stereospecific formation of key fragment **1** was envisioned *via* isomerization of a terminal double bond. Several literature protocols using methyl-eugenol **14** as substrate were already documented, applying either Ru[54-55] or Pt[56]-catalysis to furnish the transformation. To our disappointment, none of these catalysts met the set criteria, either displaying only minimally better selectivity than the dehydrative approach or by having the need for a highly expensive, moreover lengthy synthesis towards the catalytic species.

Thus, by expanding the literature search for similar substrates, one particular catalyst, namely commercially available bis(allyl)-ruthenium(IV) **10** was found to be used for the stereospecific isomerization of eugenol-esters **VII** (Scheme C-13).[40]

VIa-d: R = Ph, Me, Et, iPr   **VIIa-d: R = Ph, Me, Et, iPr**   **10**
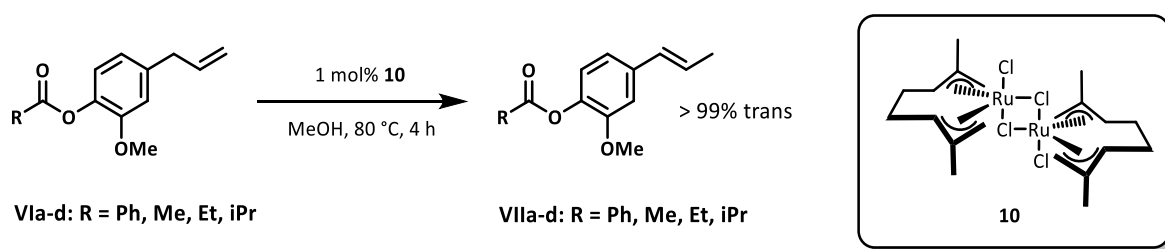
Scheme C-13: Isomerisation protocol for eugenol-esters devised by Díaz-Álvarez et al.

Since the literature conditions could be verified by rapid synthesis of Bz-eugenol **12** and subsequent isomerization to facilitate **13** with 99% *trans*-selectivity (Scheme C-14), the same conditions were subsequently applied on methyl-eugenol **14.**
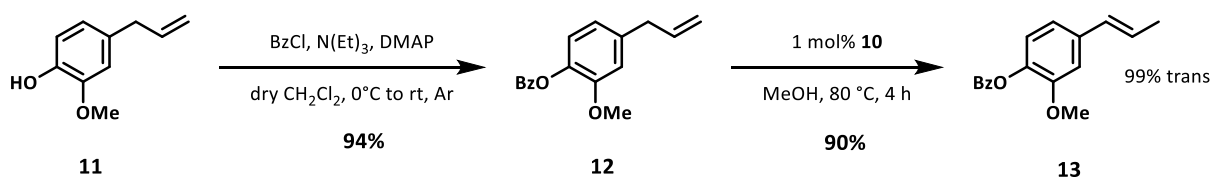
Scheme C-14

Unfortunately, preliminary tests gave discouraging results, as even after a prolonged reaction time of 24 h (sixfold compared to the literature examples), only 70% conversion could be observed based on crude ^{1}H-NMR analysis, moreover with inferior selectivity (entry 1). Consequently, catalyst loading was increased, which enabled not only an improvement in the reaction rate, but had additionally a beneficial effect on the selectivity of the isomerization (entry 2). However, due to the identical R_f value of substrate and product, complete conversion of the starting material was required.

Table C-2: Isomerization of of methyleugenol **14**
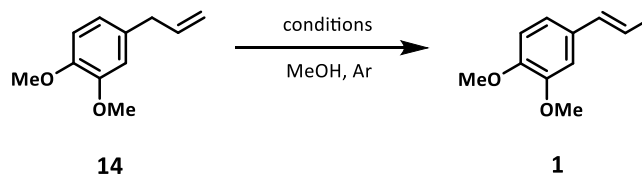
entry	catalyst mol%	temperature	time		conversion	E/Z
1	1	80	24 h		70%	95/5
2	2.5	80	44 h		90%	98.5/1.5
3	2.5	100[a]	7 h		96%	97.5/2.5
4	2.5	120[a]	1 h		90%	97/3
5	2.5	160[a]	1 h		100%	93/7
6	**0.5**	**80**	**72 h**		**100%**	**> 99/1**
7	1	80	72 h		100%	98.5/1
8	2.5	80	72 h		100%	98/2

By increasing the temperature, reaction times could be efficiently reduced, unfortunately at the expense of the final purity of the product (entries 3-5). Thus, by accepting prolonged reaction times, the influence of the catalyst loading on the selectivity was tested (entries 6-9). This led to the suprising observation that by decreasing catalyst loading to half amount, perfect *trans*-selectivity could be accomplished, allowing for a quick one-step synthesis of **1**, which yielded 84% of the product after purification.
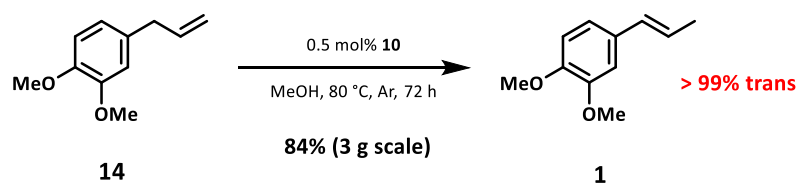
Scheme C-15

C III   Synthesis of key fragment 2

C III.1   Strategy D

Considering the retrosynthetic analysis, one of the possibilities for the assembly of key fragment **2** was to install the allyl moiety in the last step. As there was a literature precedence for the regioselective allylation of 2-methoxybenzoquinone **15** by Engler et al.[32], the goal was to set out to apply these conditions on required substrate **19**.
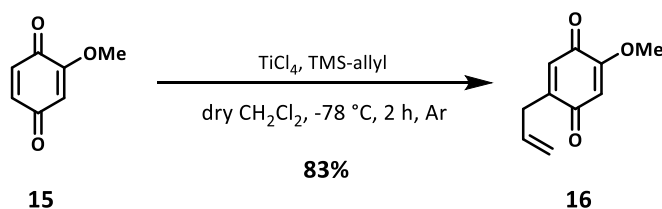
Scheme C-16: Original report by Engler et al.[32]

Thus, the first step in the synthetic sequence was the mono-benzylation of resorcinol **17**, which resulted, despite the equimolar use of BnBr, in only mediocre yields due to reasonable amounts of double-benzylated product (Scheme C-17). As no time was invested in the optimization of this protocol, further oxidation of the resulting phenol **18** was conducted.
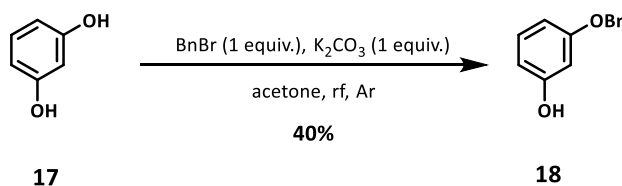
Scheme C-17

Since the usual approach towards 1,4-benzoquinones involves oxidation of the hydroquinone-species, this transformation does not have a vast amount of literature precedence with general applicability. Two historic communications for this oxidation report the use of either heavy metals in large molar excess[57] or Fremy's salt[42]. More recent studies involve the employment of catalytic systems like $KHSO_5$ with iron phthalocyanine tetrasulfonate[58], Co-salen (salcomine) and molecular oxygen[59] or the usage of hypervalent iodine reagents[60].

Suprisingly Fremy's salt **VIII**, a persistent, long-lived radical species, although being a strong oxidizing agent, displays a certain degree of functional group tolerance and is commonly used even for

late stage oxidation[61-62]. Most importantly, no oxidation towards ortho-quinones, no dimerization and a tolerance towards benzylic ethers had been reported.[42, 63-64]

With these considerations in mind, Fremy's salt **VIII** was synthesized as reported in the literature[42] with 68% yield. The bright orange crystals displayed the already documented instability to air & bases (*moderate*) as well as acids (*high*), as slow decomposition of the salt was evident by bleaching of the orange color after several days or weeks in the dessicator.[65] Nevertheless, a freshly prepared batch of Fremy's salt was used for the oxidation of phenol **18** according to a literature protocol by Guillonneau et al.[63] Since two protons are liberated during the process, all oxidations need to be neutrally buffered to counteract the decomposition of the reagent. The mechanism for the named Teuber oxidation is depicted in Scheme C-18.

Reaction of phenol **18** with the free radical *via* hydrogen abstraction leads to the formation of resonance stabilized phenoxy radical **IX**, which due to resonance stabilization can be depicted as the more stable quinone radical species **X**. This can react with another equivalent of Fremy's salt to form intermediate **XI**, which yields bright yellow benzoquinone **19** after loss of imidobissulfate.
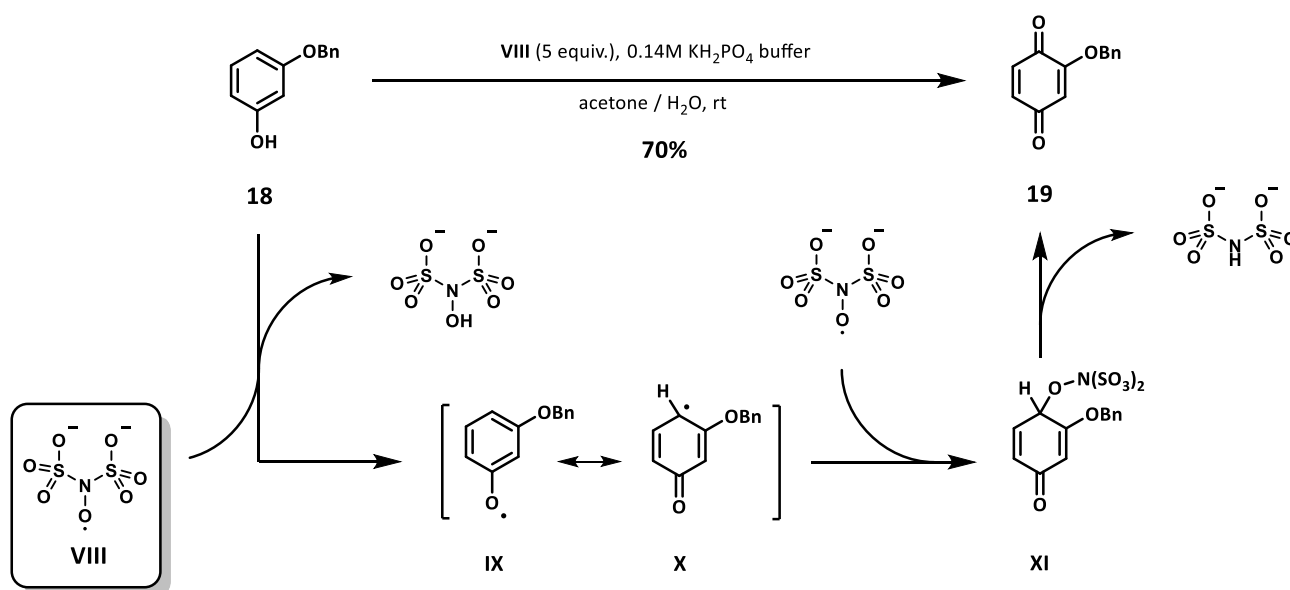
Scheme C-18

Following the successful oxidation, allylation of **19** was further investigated. Contrary to the abovementioned literature (*cf.* first paragraph C III.1), several other reports on allylation on unsymmetric benzoquinones report the formation of regioisomeric mixtures[66-67] and side-products[68]. The classical conditions for this transformation employ Lewis acids, most commonly BF$_3$.OEt$_2$[66, 69], with allylsilanes[70] or allylstannes[68-69] , which are typically employed in cases with symmetrical structures or substrates with only one possible reaction site.

Nevertheless, two different protocols were tested if any selectivity towards the 2,5-disubstituted benzoquinone **2** could be achieved (Table C-3).

Table C-3: Allylation of of benzoquinone **19**
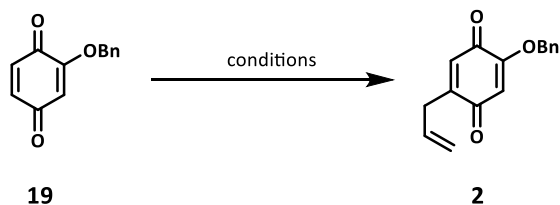
entry	conditions	observed results
1[32]	**19** (2.0 equiv.), TiCl$_4$ (2.0 equiv.), (Me)$_3$Si-allyl (1.0 equiv)	massive side product formation
2[69]	**19** (2.0 equiv.), BF$_3$.OEt$_2$ (2.0 equiv.), (nBu)$_3$Sn-allyl (1.0 equiv.)	complete decomposition

Entry 1 represents the abovementioned protocol, which was stated to proceed with full stereocontrol that enabled the synthesis of the benzoquinone **16** in 83% yield. Applying these conditions on benzoquinone **19** resulted unfortunately in massive side product formation, which could be determined by TLC and GC-MS analysis.
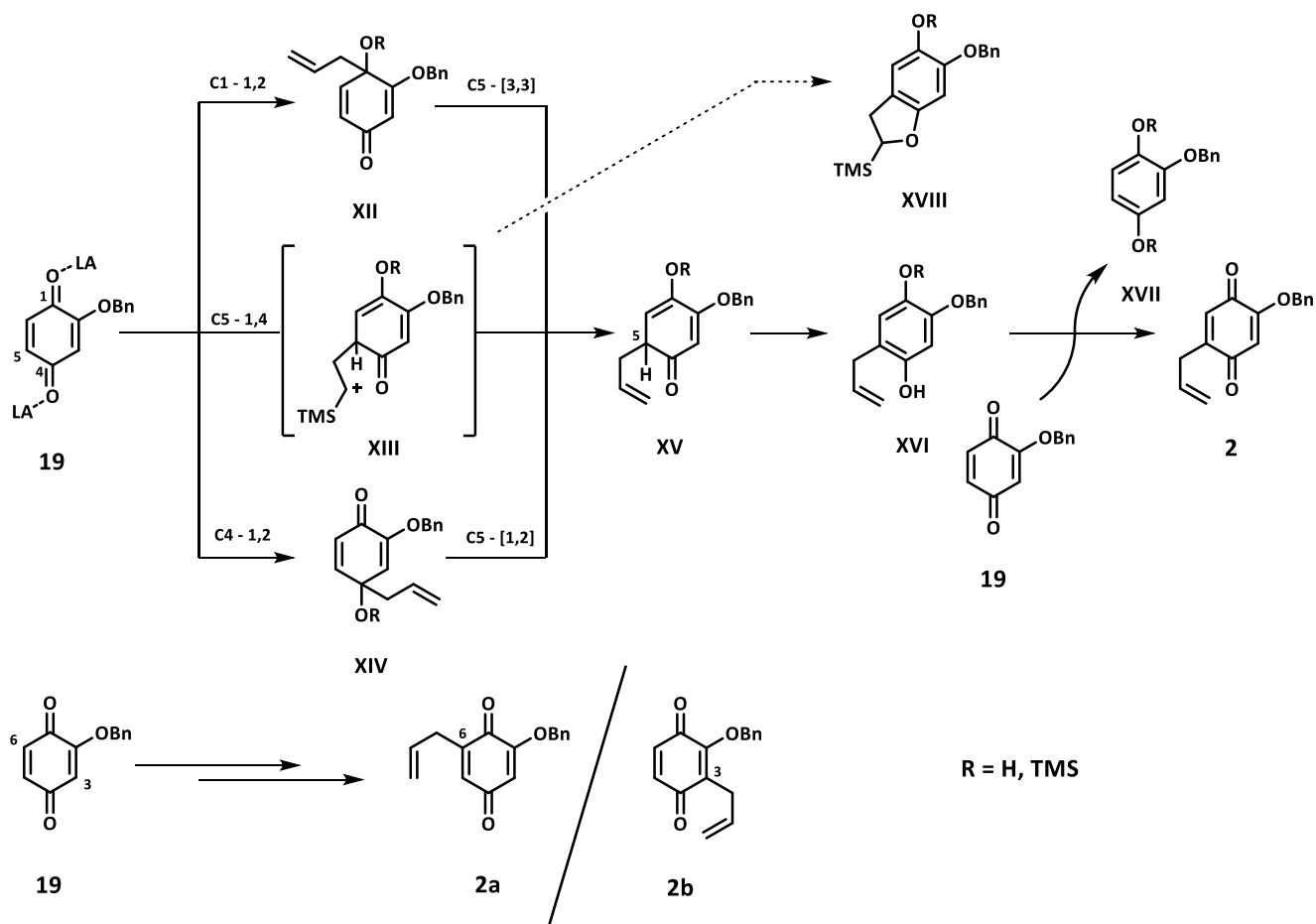
Scheme C-19

Especially in the mass spectrum several identical m/z-values could be arbitrarily assigned to different regioisomers (**2**, **2a**, **2b**) as well as intermediate products (**XVI**) and literature-mentioned side-products (**XVII**, **XVIII**).

The rationale behind these results can be conceived by analyzing the mechanistic scheme for the allylation as depicted in Scheme C-19. With the coordination of the Lewis-acid to one of the two present carbonyls all positions (except for C2 due to mesomeric electron donation of the benzyl-group) get activated, thus enabling the nucleophilic attack of allylating agent. 1,2-Addition to either C1 (**XII**) followed by [3,3]-shift or to C4 (**XIV**) followed by a [1,2]-shift as well as 1,4-addition to C5 (**XIII**), would ultimately converge to intermediate **XV**, which after rearomatization would give hydroquinone **XVI**. Final oxidation with a second equivalent of starting material would conclude the synthetic path towards **12**, thus explaining the need for two equivalents of **19** and the detection of **XVII** in the mass spectrum.

As both possibilities, either 1,2-addition and 1,4-addition to quinones are already reported in the literature[69], several different pathways enable thereby the formation of all regioisomers, rendering the isolation impossible.

Furthermore, the formation of **XVIII,** as one of major side products in the reaction, can be attributed to the unsuffienct leaving group capability of TMS, which allows for the intermediate charge of **XIII** to be traped by the carbonyl. To counteract this problem, the allylation was attempted with more reactive allyltributyltinstannane, which is known to eliminate faster than the corresponding silanes under acidic conditions (entry 2)[71]. Unfortunatelly, by doing so formation of a black viscous oil that could not be dissolved by any means, rendered any isolation of product or recovery of starting material impossible.

Hence, with these findings and no further literature source supporting the claim of the regioselective allylation, this approach was abandoned.

C III.2   Strategy E

To enable the regioselective installation of the allyl-group a reversed order of oxidation and allylation was investigated. This could be realized by classical Claisen-rearrangement of allyl-oxy ether **20** and subsequent oxidation of the phenol **21** *via* the already applied Fremy's salt protocol. As the required precursor **18** had been already synthesized, simple Williamson etherification with allyl bromide delivered **20** in good yields (Scheme C-20). Subsequently, Claisen rearrangement under neat conditions yielded the products in a 65/35 ratio in favour of the desired regioisomer **21**. Although several solvents (diphenylether, N,N-dimethylaniline, diethylenglycol, decaline) were tested, solvent free conditions proved to be the most selective.
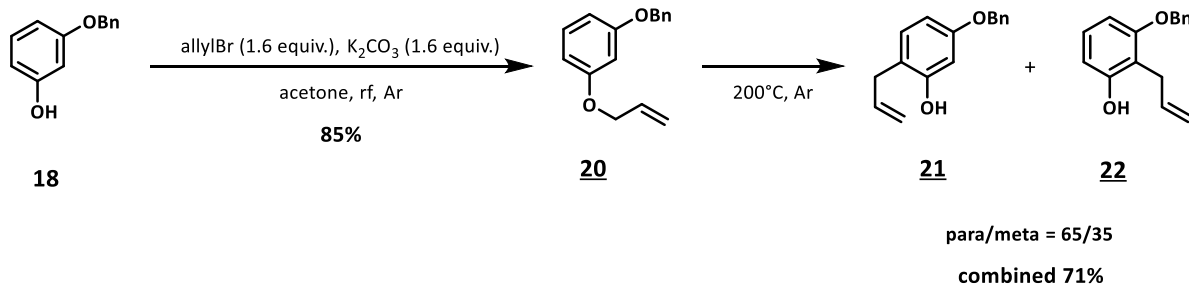
Scheme C-20

Before oxidation could be attempted, separation of the regioisomers proved to be a difficult problem, as these did not exhibit any difference in retention behavior using standard chromatographic solvent mixtures. Solely the use of mixtures of CH_2Cl_2 with LP enabled a minimal difference between the R_f values. Although a ratio of 400:1 silica gel : substrate was used, chromatography of the regioisomers needed to be repeated several times to enable full isolation of both species, thus making this approach unsuitable for large scale synthesis.

Nevertheless, with the successful isolation of 45% of compound **21** following the Claisen rearrangement, the applicability of the oxidation protocol with Fremy's salt **VIII** (*cf.* Scheme C-18) on the resulting product was tested. Unfortunately, only traces of the product could be verified *via* GC-MS analysis, after full consumption of the reagent (Scheme C-21). The depletion could be easily observed, as the reagent in its active form displayed a distinct violet color in solution, which faded as it was degraded Only after further addition of 10 equivalents of the radical species and a total reaction time of two days, full conversion of the starting material was confirmed, yielding at best 60% of key fragment **2**. These findings represent a poor mass balance, considering the need of nearly 1 g of the reagent (**VIII**) for the oxidation of 50 mg of phenol (**20**).

Furthermore, results of these oxidation experiments were hardly reproducible due to the unstable nature of the reagent rendering this approach towards the final product to be only used as a back-up plan if any other strategy would fail.
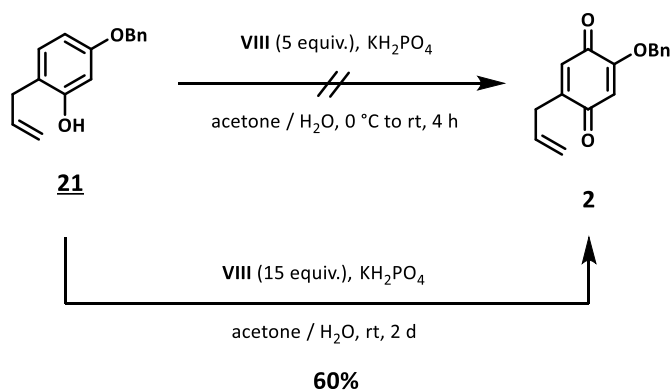
Scheme C-21

C III.3   Strategy F

Following a rather unusual approach, Murahashi et al. devised a strategy towards 4-(tert-butyldioxy)cyclohexadienones *via* Ru-catalyzed oxidation with tert-butyl hydroperoxide (TBHP) under anhydrous conditions[43]. The interesting feature of this transformation is that it allows for a rapid synthesis of 2-substituted benzoquinones by Lewis acid assisted [1,2]-alkylmigration of the corresponding peroxides (Scheme C-22).
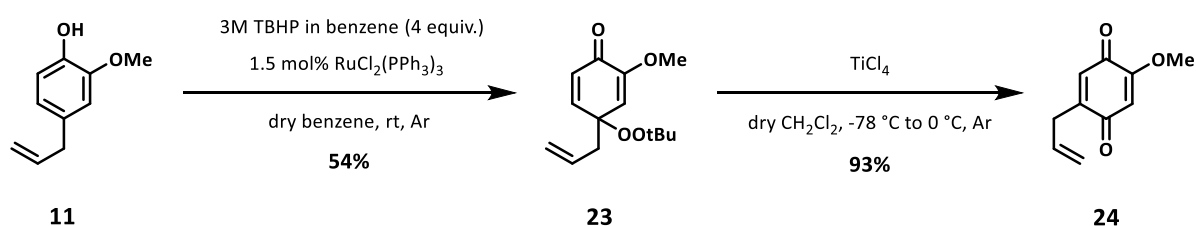
Scheme C-22: Original report by Murahashi et al.[43]

As this approach would enable the rather quick synthesis of the wanted core structure, a possible strategy involved the replacement of the methoxy ether of eugenol **11** with a benzyloxy-group and by the adoption of this protocol, ultimately enabling the final transformation to key fragment **2**. (Scheme C-23)
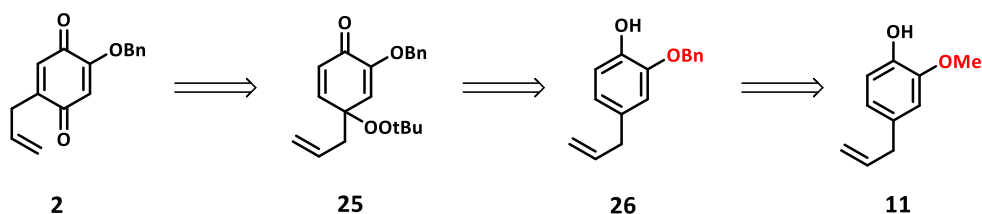
Scheme C-23

Regretfully, the abovementioned catalytic system employs anhydrous TBHP in benzene that is not commercially available and needs to be prepared by azeotropic distillation as described by Sharpless[72]; due to its explosive nature, this represent a highly dangerous task. Fortunately, Ratnikov et al. investigated further catalytic species (Rh, Cu) for this oxidation with different phenols, while comparing them in some cases to the efficacy of Murahashi's catalyst, only to realize that the already applied Ru-species does not necessary loose its activity in contact with commercial aqueous 70% TBHP (T-HYDRO).[73](Scheme C-24)
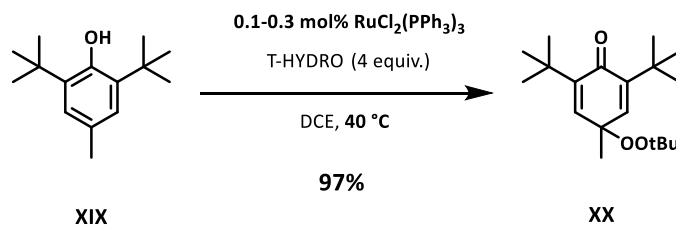
Scheme C-24: Original report by Ratnikov et al.[73]

With these findings, both oxidation procedures were tested with slight modifications, either employing 1.5 mol% of the catalyst at room temperature, or reducing the amount of catalyst to 0.1 mol% while raising the temperature to 40 °C. Unfortunately, any of the two cases resulted in thermal runaway (TR) of the T-HYDRO (T > 100 °C) with concomitant strong gas evolution, causing immediate decomposition of the product (entry 1-2). In both reactions T-HYDRO was added dropwise in approximately 5 minutes to the reddish colored solutions containing all reagents. This led to an immediate deep green discoloration (possibly a Ru=O, Ru-OH species), which after TR of the peroxide-solution, turned bright orange.

Table C-4: Peroxidation of eugenol **11**
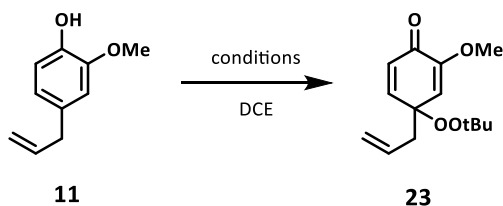
entry	conditions	observed results
1	**11** (1.0 equiv.), T-HYDRO (4 equiv.), RuCl$_2$(PPh$_3$)$_3$ (1.5 mol%.), rt, Ar	TR after 1 h
2	**11** (1.0 equiv.), T-HYDRO (4 equiv.), RuCl$_2$(PPh$_3$)$_3$ (0.2 mol%.), 40 °C	TR after 10 min
3	**11** (1.0 equiv.), T-HYDRO (4 equiv.), RuCl$_2$(PPh$_3$)$_3$ (0.2 mol%.), 0 °C to rt, Ar	13 %
4	**11 (1.0 equiv.), T-HYDRO (10 equiv.), RuCl$_2$(PPh$_3$)$_3$ (0.4 mol%.), 0 °C to rt, Ar**	**23 %**
5	**11** (1.0 equiv.), T-HYDRO (10 equiv.), RuCl$_2$(PPh$_3$)$_3$ (0.8 mol%.), 0 °C to rt, Ar	TR after reaching rt

As these two approaches seemed to represent too extreme conditions for the reaction with these modifications, the reaction was consequently executed at 0 °C with a slow temperature gradient towards room temperature. Furthermore lower amounts of catalyst were applied, thus enabling isolation of the product after confirming full conversion of **11** *via* TLC. This was done by extraction with CH$_2$Cl$_2$ and subsequent column chromatography, which yielded peroxide **23** with an abysmal yield of 13% (entry 3). An increase of the T-HYDRO amount to 10 equivalents, as stated by the authors should drastically increase the yield[73], still only resulted in 23% product formation (entry 4). Further increase in catalyst loading was

attempted, but was accompanied by TR after warming the reaction to room temperature, which was necessary for full consumption of the starting material.

By still having a sufficient amount of product at hand, the resulting peroxide **23** was subsequently subjected to the Lewis acid assisted [1,2]-migration to yield benzoquinone **24** as the only regioisomer (Scheme C-25)**.**

		TiCl₄ (1.2 equiv.)	
not observed	**23**	dry CH₂Cl₂, -78 °C to 0 °C, Ar **81%**	**24**
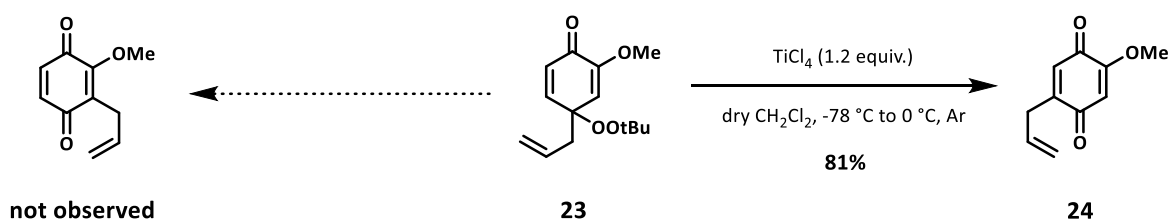
Scheme C-25

With a working but far from perfect protocol at hand, we then turned to the synthesis of Bn-eugenol **26** to test if further screening would pay off. As the complete deprotection of **11** and subsequent etherification would lead to an inseparable mixture of **26** and its regioisomer, an orthogonal protecting group strategy was required, that would allow for the selective deprotection of the methoxy-group (Scheme C-26). Hence, a collection of protected eugenol-derivates according to Table C-5 were synthesized.

PG =
10 = Bz, **27** = Piv
28 = TIPS, **29** = mesitoate
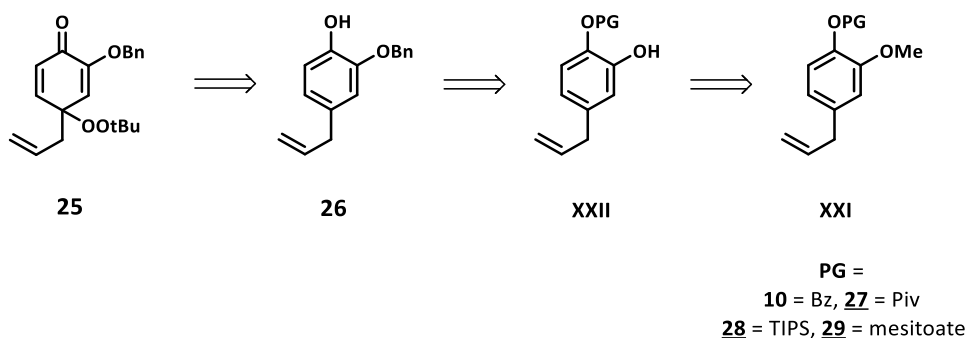
Scheme C-26

Although various methods for demethylative cleavage in the presence of a variety of protecting groups are known in the literature[74], only limited precedence could be found concerning a general functional group tolerance for phenolic ester- or silyl-protecting groups. Limiting the search even further to account for the 1,2-diphenolic relationship, ultimately gave no literature results.

Table C-5: Protection of eugenol **11**

compound	conditions	yield
27	**11**, PivCl (1.1 equiv.), N(Et)$_3$ (2 equiv.), 10 mol% DMAP, CH$_2$Cl$_2$, 0 °C to rt, Ar	90 %
28	**11**, TIPSCl (1.5 equiv.), imidazole (2 equiv.), CH$_2$Cl$_2$, 0 °C to rt, Ar	94 %
29	1. Mesitoic acid (1 equiv,) (COCl)$_2$ (1.1 equiv.), cat. DMF, CH$_2$Cl$_2$, 0 °C to rf, Ar 2. (1.) + **11** (1.1 equiv.), N(Et)$_3$ (3 equiv.), rf, Ar	79 %

The closest resemblance to the protected phenol was a literature report by Lee et al.[75] which mentioned a selective demethylation of a 1,3-disubstituted phenol in the presence of a substituted benzoyl-group with a combination of AlCl$_3$ and dimethyl sulfide representing a milder Lewis acidic environment as the usually applied reagents BBr$_3$ or BCl$_3$[76]. With this protocol in mind, all protected eugenol-derivates **XXI** were tested with the presented conditions and monitored *via* GC-MS.

Table C-6: Demethylation of protected eugenol **XXI**
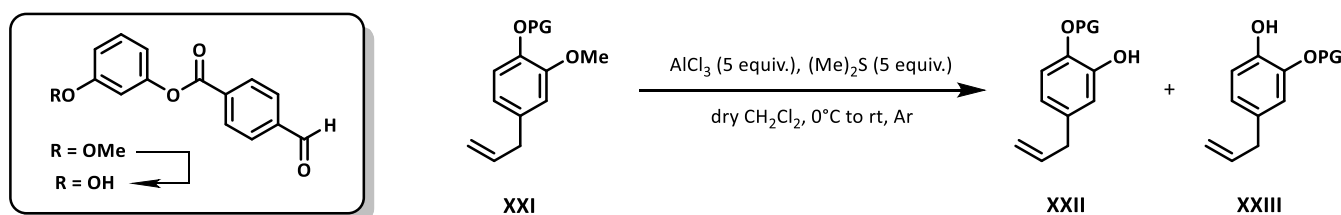
entry	compound	observed result – XXII/XXIII	comments
1	**12** – Bz-eugenol	PG-migration after workup – 65/35	NH$_4$Cl-workup
2	**27** – Piv-eugenol	PG-migration during reaction – 60/40	NH$_4$Cl-workup
5	**28** – mesitoate-eugenol	complete deprotection	-
4	**29** – TIPS-eugenol	PG-migration during reaction – 78/22	NH$_4$Cl-workup
6	**12** – Bz-eugenol	PG-migration after workup – 68/32	NaHCO$_3$-workup
7	**12** – Bz-eugenol	PG-migration after workup – 65/35	EtOAc/NaHCO$_3$-workup
8	**12** – Bz-eugenol	**No migration – 100/0 – 94% yield**	EtOAc/NH$_4$Cl-workup

The rationale behind the choice of the protecting groups can be given in view of the inherent instability of esters in close proximity to adjacent hydroxy groups. This motif enables especially base labile esters to undergo migration to the vicinal position.[77] Hence, by emposing greater steric hindrance with the use of bulky esters the attack of the neighboring nucleophile and therefore migration of the protecting group should be prohibited.

Suprisingly only the least bulky Bz-eugenol **12** was shown to be the only species to retain the position of the protecting group throughout the reaction (entries 1-4), several different work-up conditions were tested to assess feasibility of compound isolation (entry 6-8). Fortunately dilution of the reaction mixture with EtOAc, which may have acted as a Lewis acid scavenger, followed by quenching with NH_4Cl, delivered the desired demethylated species (**30**) in excellent yield (entry 8). However, further purification by column chromatography on silica had to be avoided, as the acidity of the column caused immediate migration of the protecting group.
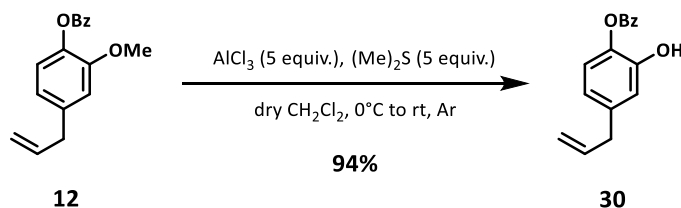
Scheme C-27

Based on the finding, that even minor Brønsted basicity or moderate Brønsted acidity caused migration of the benzoyl-group, classic benzylation employing solid potassium carbonate and benzyl bromide was shown to exhibit immediate migration (Scheme C-27). Even by increasing the amounts of benzyl bromide and additionally employing Finkelstein[78] conditions to form inherently more active benzyl iodide *in situ* failed to avoid migration of the protecting group. Furthermore, since both retained and migrated product exhibited the same R_f value in any tested solvent mixture, separation of these two species was not possible.
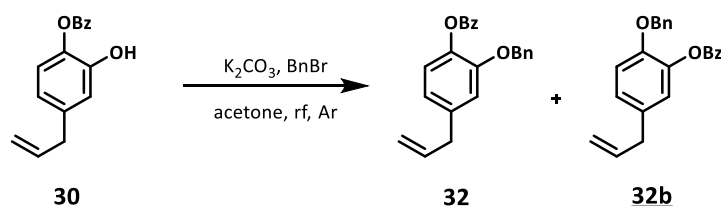
Scheme C-28

Thus, one last attempt was to employ a Lewis acid catalyzed benzylation protocol[79] to install the benzyl group, as it was evident, that the substrate exhibited tolerance towards Lewis acids. The class of the substrates that are used for this transformations, which are mostly applied in in sugar chemistry, are 2,2,2,-trichloroacetimidates[80]. Herein, activation of the acetimidate moiety with a catalytic amount of Lewis acid enables a substitution on the benzylic position of the reagent with concomitant release of the 2,2,2-trichloracetamide as strong nucleofuge, which is the major driving force for this reaction.

1.05 - 3 equiv.

1 - 10 mol% TMS-OTf

dry CH$_2$Cl$_2$, 0°C to rt, Ar

30   **31**   **32**
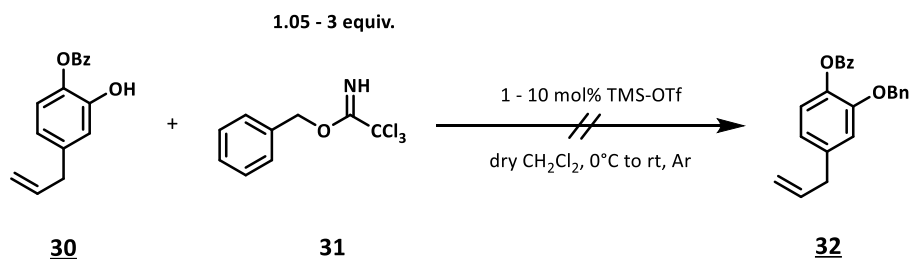
Scheme C-29

Although the reaction employing benzyl 2,2,2-trichloroacetimidate **31** was shown to proceed without migration of protecting group, as was judged from GC-MS analysis, the ultimate isolation of the product was rendered impossible due to the formation of three or even more different side-products that exhibited the same R$_f$-value. This can be exemplified by looking at the ß-hydrogen, usually displaying a well defined ddt-coupling ($^3J_{trans,\ Ha-Hb}$ = 17 Hz, $^3J_{cis,\ Ha-Hc}$ = 10 Hz, $^3J_{vic,\ Ha-Hd}$ = 7 Hz) from the starting material **30** on the left and the columned product after the benzylation on the right.
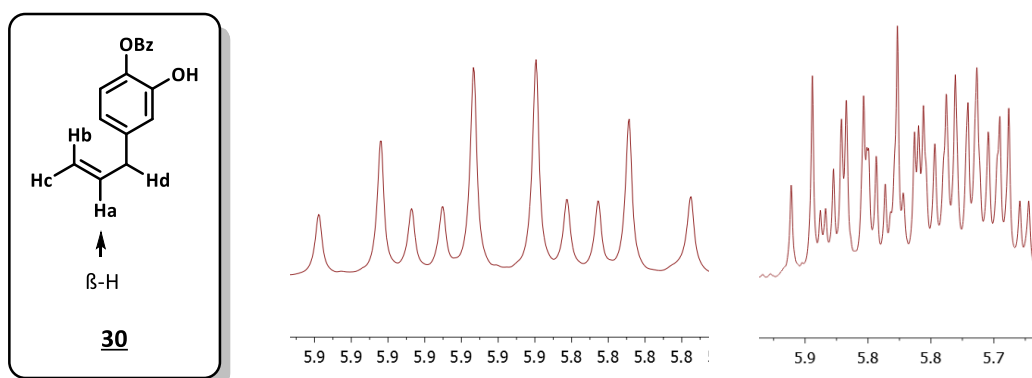
Figure C-3

Hence, the focus was shifted back to the classical basic benzylation as this reaction delivered the protected benzylated products without any side products in a 65:35 ratio of **32** (major) and its regioisomer **32b.** It was decided to simply continue with the synthetic plan and to see if either separation would be feasible after deprotection or the difference in reactivity in the peroxidation step might lead to a differentiation.

Subsequently deprotection of the mixture delivered the two benzylated phenols in a combined yield of 81% over two steps starting from the demethylated product **30** in an unchanged ratio.
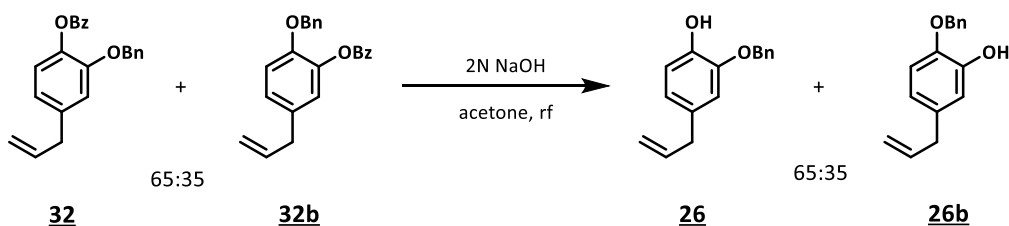
Scheme C-30

As no separation of the regioisomers was feasible even at this stage, subsequent oxidation of the phenol with the newly established peroxidation-protocol was investigated. The proposed mechanism for this transformation[43] is believed to be initiated by a Ru-catalyzed single-electron oxidation of **26** to form radical intermediate **XXIV**, whose resonance strcuture **XXVII** is ultimately trapped by a TBHP-radical to yield peroxide **25**. As oxidation of **26b** would lead to intermediate **XXVI**, which should not have the possibility to react towards the intermediates of the upper reaction pathway, formation of **25** should be impossible. Separation of the two regioisomers would be thereby theoretically possible, if any interference between these two reaction pathways could be excluded.
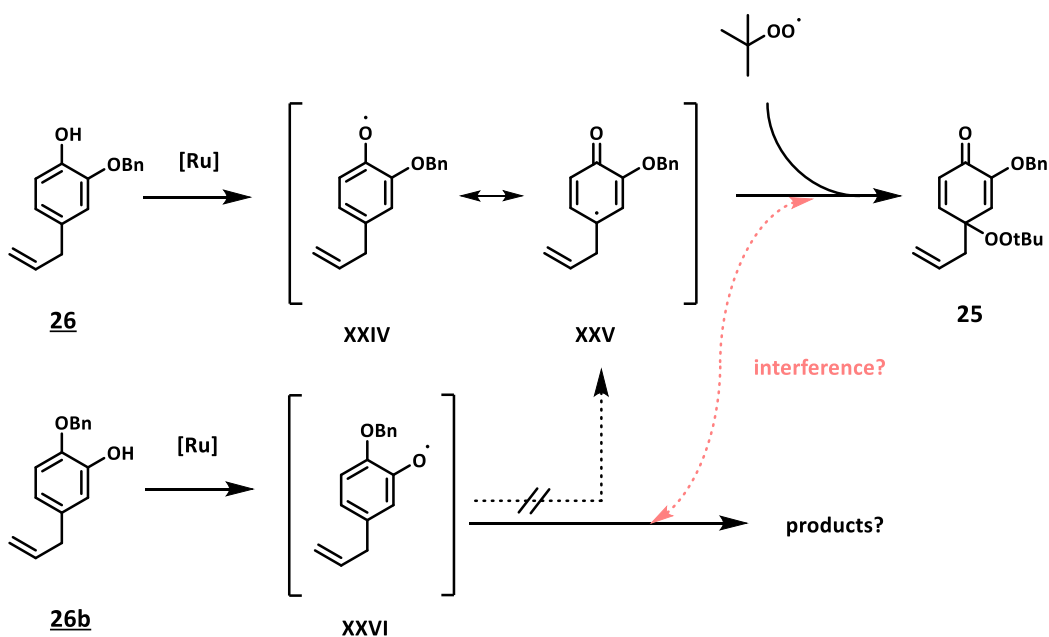
Scheme C-31

Unfortunately, the application of the oxidation conditions on the regioisomeric mixture only led to inseparable amount of side product formation. Lowering of the catalyst loading or the amount of TBHP did not lead to any improvements. As stated this could be possibly addressed to the adverse interference of intermediates or even products with either pathway, consequently this approach was abandoned.

C III.4   Strategy G

A viable second approach deriving from the accomplished synthesis of **24** would be the use of simple hydrolysis or demethylation conditions to lead to 2-hydroxy substituted quinone **33,** which could be esterified with benzyl alcohol to give key fragment **2**. The rationale behind this approach comes from the properties of these hydroxy-benzoquinones, which at their core represent masked conjugated carboxylic acids[81].

Scheme C-32

The usual literature conditions for this kind of transformation employ either strong bases[82] or strong Lewis acid like BBr$_3$[83] to accomplish this transformation, usually facing a lack in generality for certain substitution patterns.

Nevertheless two protocols for the methyl-cleavage were tested, either refluxing the benzoquinone in 2N sodium hydroxide[84] or by using the already tested demethylation[75] conditions that were used for the demethylation of protected eugenols **XXIII** (*cf.* Table C-6).

Scheme C-33

As even the addition of a small drop of base to the solution of **24** caused an immediate intense darkening of the solution even at room temperature, no further heating was applied. Following the complete addition of base, the reaction mixture was allowed to stir for 10 minutes at room temperature, after which TLC analysis already confirmed full consumption of the starting material. Subsequent acidic

workup of the dark mixture failed to deliver any extraction into the organic phase, even after acidification to pH <2, so this approach was abandoned.

A different effect was caused by addition of the benzoquinone to the solution of Lewis acid. Here the first contact with the liquid caused immediate formation of an orange viscous oil that immediately blocked stirring, effectively clogging the vial. Full consumption of the starting material was immediately evident *via* TLC analysis, thus work-up of the orange gel was attempted. As no dissolution of the solid could be achieved by any means of applied solvent (CH₂Cl₂, EtOAc, CH₃Cl, MeOH, H₂O) also this attempt was abandoned.

No further investigated was done on the behalf of this approach, moreover as an effective alternative had meanwhile been found.

C III.5   Strategy H

The last presented strategy in this thesis exemplifies a more modular approach toward the formation of the key fragment **2**. Since a demethylative oxidation represents the final step for this synthetic path, preceding 1,4-dimethoxybenzene derivates can be seen as protected versions of those benzoquinone-structures, thereby enabling a stepwise assembly of the wanted elements with the application of classical "aromatic chemistry".

Consequently, 2,5-dimethoxybenzaldehyde **34** was set as a starting point for this route, which was rapidly converted to 2,5-dimethoxyphenol **36** *via* two step protocol employing a Baeyer-Villiger oxidation with subsequent hydrolysis of the resulting formate **35** (Scheme C-34)[85]. By conducting this functional group transformation two succeeding modifications are enabled: Firstly by changing the nature of the directing group, introduction of the bromine into the envisioned *para*-position is rendered possible, thus creating the anchor point for the subsequent coupling reaction. Secondly the immediate possibility of installing the desired benzyloxy-ether in the required position is opened, thereby enabling a rapid approach towards the 2-alkoxy motif.
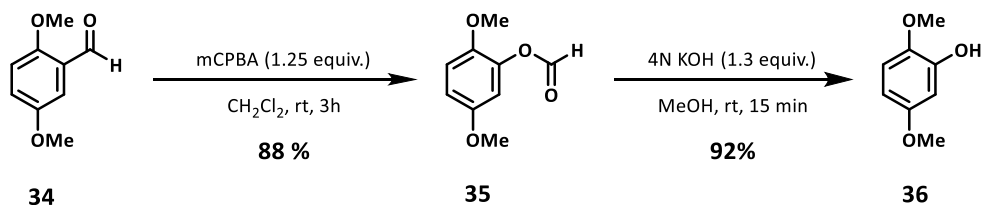
Scheme C-34

A one-step process, namely the Dakin oxidation[86] could be also envisioned for this transformation, by employing H₂O₂ as the oxidant and strongly basic aqueous solution as the reaction medium. Given that both products in the multi-step procedure were synthesized in high yields, moreover

with minimal contaminations which limited purification to simple extraction, no further investigations were done on this behalf.

Continuing along the synthetic outline, two different routes were envisioned for coupling-precursor **39**, using either direct bromination of the phenol **36** and subsequent esterification or the reversed synthetic order (Scheme C-35). Since phenolic brominations represent the classical electrophilic aromatic substitutions, the former was investigated first. As the molecule has two highly electron-rich sites due to the mesomeric effects of the two methoxy groups as well as the phenolic group itself, certain amounts of ortho or double brominated products were expected.
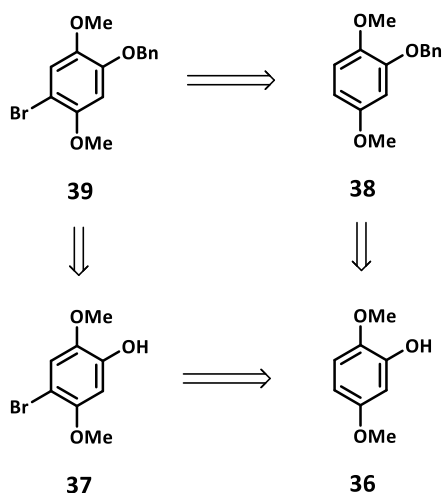
Scheme C-35

Fortunately by applying the literature protocol of Kakde et al.[87] employing only equimolar amounts of NBS in aprotic media, the formation of proclaimed side-products could be entirely suppressed, yielding 80 % of bromophenol **37** after column chromatography. The remaining 20 % could be addressed to the observed instability of the product, as decomposition of the columned product could be detected on TLC and by slow deep green discoloration of the yellow solid in the fridge, already after several hours.
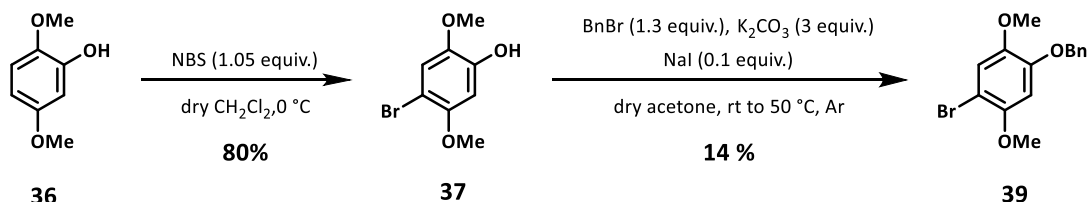
Scheme C-36

Hence, to account for the instability, the subsequent benzylation was only stirred at room temperature, with the addition of 10 mol% NaI, to enhance reactivity[78] and to limit possible losses due to

thermal decomposition. However, to furnish full conversion of the starting material an increase in temperature was nonetheless needed on the next day. Since column chromatography of **39** yielded in only 14% product formation, the reverse protocol was investigated.

Since phenol **36** did not show any instability issues, classical benzylation conditions were used, followed by the application of the identical protocol for the bromination to afford in **38** and **39** in excellent 95 % and 91 % yield respectively (Scheme C-37).
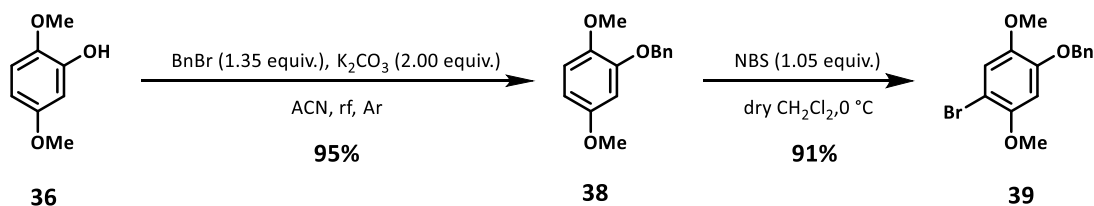
Scheme C-37

By comparing these two approaches it becomes evident, that the later, possibly due the instability of the electron rich p-bromophenol **36**, proved to be the more robust pathway (a) giving a combined yield of 86 %, compared to 11% of the former (b) over these two steps (Scheme C-38).
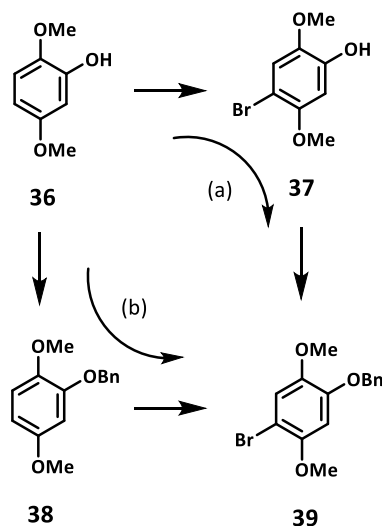
Scheme C-38: Combined yield over two steps – (a) 11%; (b) 86%

The succeeding step in the sequence was the allylation of the aryl bromide **39** where either Suzuki-Miyaura or Stille-coupling were envisioned. Published literature[88] using allylboronic acid pinacol ester in Suzuki-couplings with similar highly activated aryl systems accomplished nearly quantitative yields. Consequently, preliminary testing of the applicability of these conditions for the allylation of the aryl bromide **39** were tested and resulted in the successful formation of allylated product **40.** Since this approach was used in a late-stage synthesis on low mg-scale, scalability of the reaction was also

investigated and led surprisingly to increased yields, delivering the fully decorated 1,4-dimethoxybenzene **40** in 88% on 2,5 g scale. (Scheme C-39).
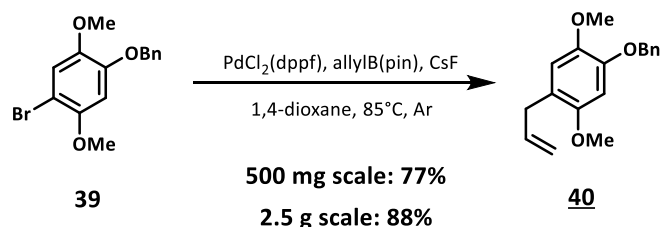
Scheme C-39

Arriving at the last step of this synthetic plan it was found that he overwhelming majority of literature data, especially for the structurally similar substrates like ubiquinones[89], employed the already historical, but to this day unchanged conditions for this transformation, namely using highly potent CAN (ceric ammonium nitrate) in acetonitrile/water mixtures. As these transformations are even regularly employed in late stage modifications and exhibit a suprisigly high fuctional group tolerance, with next to no alternatives, the proposed conditions were applied in this step, derlivering the envisioned benzoquinone in 40% yield.
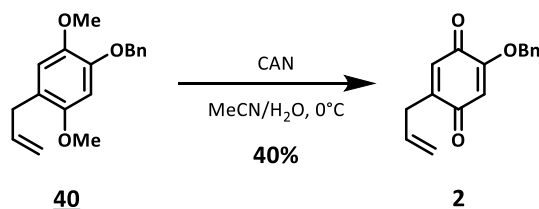
Scheme C-40

Hence, synthesis of key fragment **2** was enabled in 6 steps, resulting in a total yield of 25%.

C IV   Synthesis of conjugate

With viable synthetic routes established for both building blocks, the most important reaction was the synthesis of the final conjugate as devised by Engler et al.[32] (*cf.* Scheme C-1). As depicted in Scheme C-41, the authors developed a one-step approach towards these decorated neolignan-scaffolds by employing a Lewis assisted [2+5]-cycloaddition, thus enabling the formation of racemic keto-enol tautomers in a diastereoselective fashion.
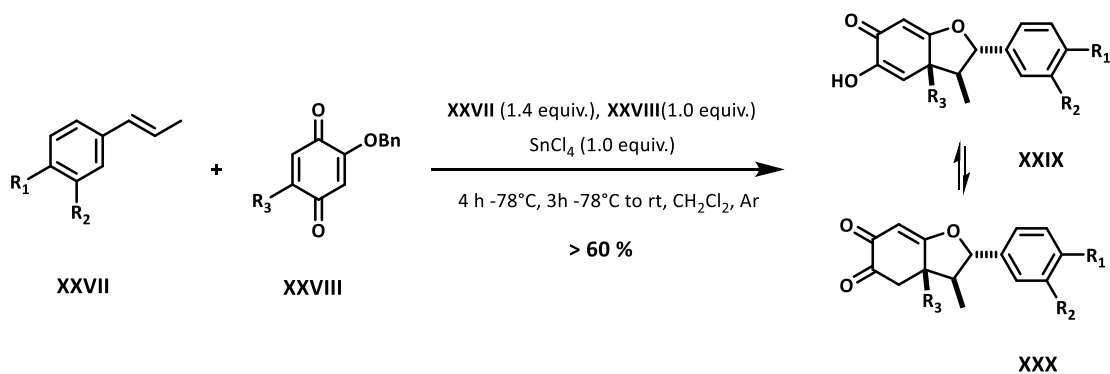
Scheme C-41: [2+5]-cycloaddition protocol devised by Engler et al.[32]

As the concept for this reaction was already established, proof of the reaction conditions as stated, as well as further investigations were envisioned. Thus with the two key fragments at hand, different reaction conditions were screened in order to ascertain the credibility of the protocol (Table C-7).

Table C-7: [2+5]-cycloaddition between *(E)*-methylisoeugenol **1** and 2-allyl-5-(benzyloxy)cyclohexa-2,5-diene-1,4-dione **2**
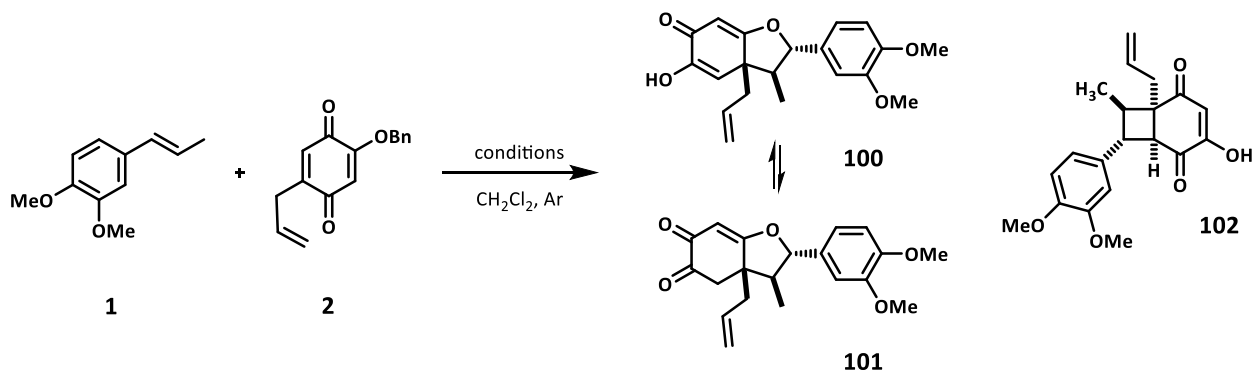
entry	conditions	observed results
1	**1** (1.4 equiv.), **2** (1.0 equiv.), SnCl₄ (1.0 equiv.), 4 h -78°C, 3h -78°C to rt (40mg)	37 % **100/101**, 8 % **102**
2	**1** (1.4 equiv.), **2** (1.0 equiv.), SnCl₄ (1.0 equiv.), 4 h -78°C to rt	5 % **100/101**, - **102**
3	**1** (1.4 equiv.), **2** (1.0 equiv.), SnCl₄ (2.0 equiv.), 4 h -78°C, 3h -78°C to rt	0 % **100/101**, 10% **102**
4	**1** (1.4 equiv.), **2** (1.0 equiv.), SnCl₄ (1.0 equiv.), 4 h -78°C, 3h -78°C to rt (200 mg)	33 % **100/101**, 10 % **102**

Fortunately, by applying the devised protocol, a synthesis towards the two keto-enol tautomers **100/101** (keto:enol 1:3.7) was not only possible, but also scalable. However, in every case except for entry 3, where the majority of the material had decomposed upon immediate warming of the reaction to room temperature, substantial amounts of side-product formation occurred (*cf.* Scheme C-1). To understand the rationale behind the formation of these stereodefined products, as well as any side-products, the mechanism of the assembly needed to be understood.

As the authors claim, the [2+5]-cycloaddition is initated by the coordination of the Lewis acid to benzoquinone **2**. By employing a bidentate Lewis acid, as SnCl$_4$ and low temperatures, the complexation will be thereby predominantly directed to the C5 carbonyl and C4 alkoxy group, thus forming the pentadienyl carbocation **LA-2**. Following the activation, this species can undergo a formal [2π+4π]-cycloadditon with **1** to produce bicyclic carbocation **XXXI**, in which, due to steric reasons, the aryl group takes on *endo*-orientation to the carbonyl at C2, thus forcing the methyl group to adopt *syn*-configuration with the allyl-moeity. This relative configuration of these two chiral centers is heavily dependent on the geometry of the applied propenylbenzene, as the *(Z)*-isomer would lead to *anti*-configuration. Subsequent rearrangement to the more stable the benzylic carbocation **XXXII**, leads up to two possible succeeding pathways, which strongly depend on the alkoxy-moeity at C4 and temperature of the reaction.
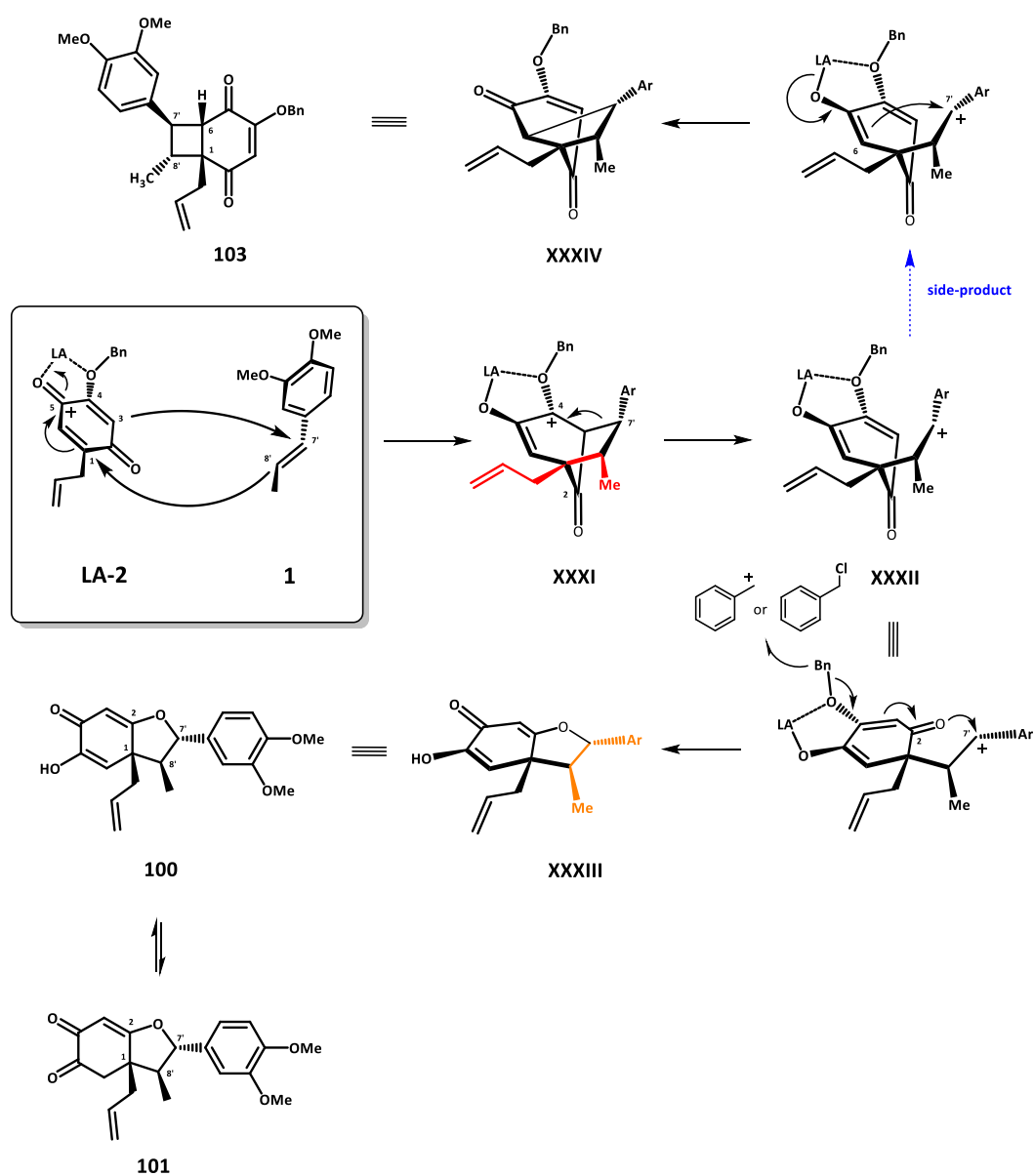
Scheme C-42

Installation of a strong electrofuge or increased temperatures that enable tautomerisation of the α,β-unsaturated ketone, promote dealkylation and C-O bond formation, thus giving the required keto-enol tautomers **100/101**. Keeping the reaction at low temperatues and employing worse alkoxy-leaving group (e.g. methoxy) allow for a competing reaction pathway to take place. Under these conditions C-C bond formation is preferred that leads to the formation of cyclobutane **103**, also belonging to the structural class of 8,1'-neolignans**.**

Suprisingly, in all experiments **103** could not be detected. Only debenzylated <u>**102**</u> could be found, that might have originated from a Lewis assisted process, similar to the demethylation of **XXI** (*cf.* Table C-6). This observation might also provide an explanation for the reaction where two equivalents of Lewis acid were used (entry 3), as premature debenzylation should inhibit the formation of the products.

With enough keto-enol tautomers as hand, the last step towards Kadsurenin F (**104**) employed methylation of the tautomers **100/101** with a large excess of methyl iodide to yield 71% final product.
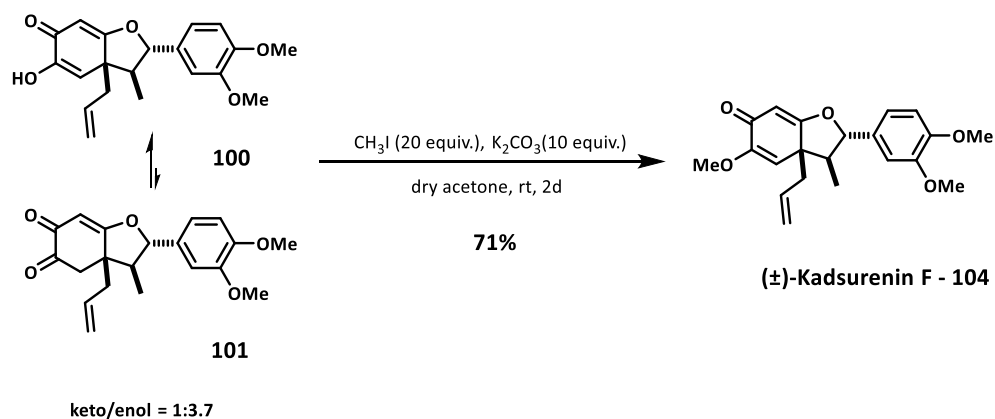
Scheme C-43

To verify the final structure of the product, NMR data of the synthetic Kadsurenin F was compared to already published literature and to the naturally isolated product (Figure E-1). HMBC and NOESY correlations are depicted in the appendix in (Figure F-4 & Figure F-8).

D   Conclusion and Outlook

The central task of this thesis was the development of a concise strategy towards the plant derived neolignan Kadsurenin F. The focus was placed either on the modularity of the assembly, enabling the eventual creation of a structural library that would give access to structural analogues for biological testing or on the swiftness of the assembly, for quick access to sizable amounts of Kadsurenin F.

Fortunately the construction of such neolignan scaffolds, which are derived from two phenylpropanoid fragments, had already been studied by Engler et al., generating these structures in a Lewis acid assisted formal [2+5]-cycloaddition. These two fragments could be established to be (*E*)-methylisoeugenol (**1**) and 2-allyl-5-(benzyloxy)cyclohexa-2,5-diene-1,4-dione (**2**).

Hence several strategies towards these key fragments were elaborated, which are shortly summarized in Table D-1.

Table D-1: Summary of developed strategies

strategy	comments	Successful strategy?
1 - A	Modular strategy – 5 steps – derivatization on O4 and C9 possible	No – but plausible
1 - B	Quick access strategy – 2 steps	No
1 - C	**Quick access strategy – 1 step**	Yes – 84 %
2 - D	Quick access strategy – 4 steps	No
2 - E	**Quick access strategy – 4 steps**; unsuited for large scale synthesis	Yes – 6%
2 - F	Quick access strategy – 5 steps	No
2 - G	Quick access strategy – 4 steps	No
2 - H	**Modular strategy – 6 step** – derivatization on C7' and maybe C6' possible	Yes – 25%

As can be seen, only three of these devised strategies are applicable towards the synthesis of one of the two key fragments, whereas only one viable strategy enabled a modular synthetic approach towards fragment **2**. Since a modular approach for the decoration of fragment **1** is still missing, further studies concerning strategy A, by employing protected versions of the cinnamyl alcohol **6,** would need to be tested in the final cyclization, thus allowing late stage modifications on C9. Derivatization on O4 could be also enabled in this approach, by installing different ether or ester functionalities in the first step (cf. Scheme C-3). (Scheme D-1)
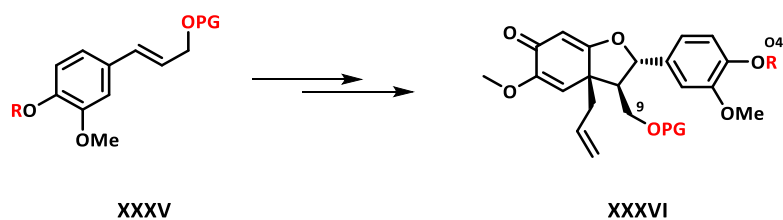
Scheme D-1

Concerning strategy H, several different modifications could be envisioned with the chosen substrate, by either using the inherent directing capabilities of the aldehyde or by applying a C-H activation protocol[90] for selective ortho-bromination. Hence all possible decoration patterns could be covered with the same methodology (Scheme D-2).
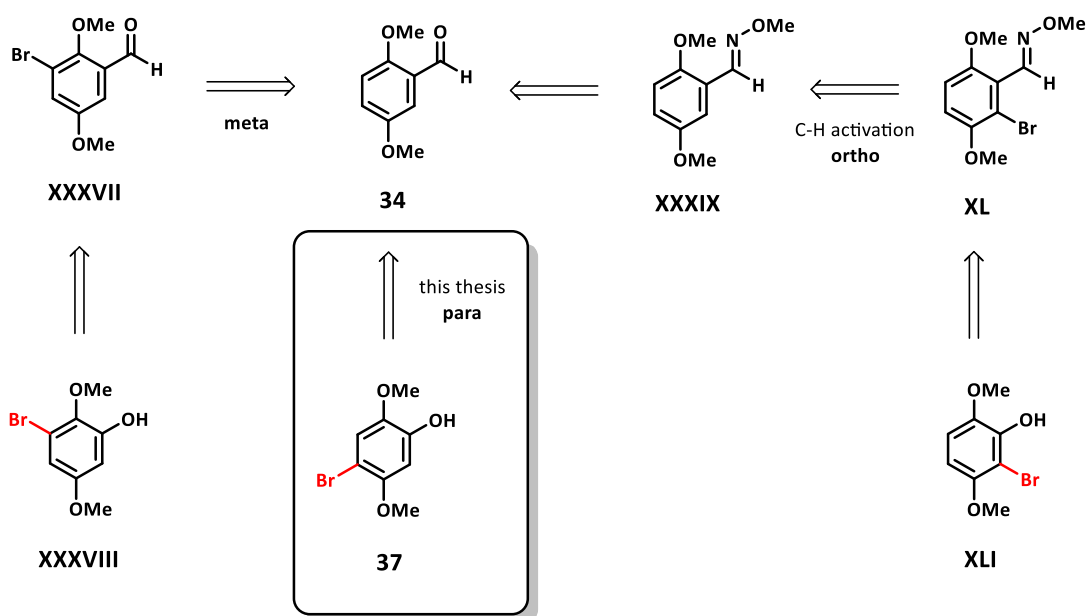
Scheme D-2

In summary by using these two modular approaches, further modifications could be enabled for the generation of diverse structural analogues as depicted in Figure D-1.
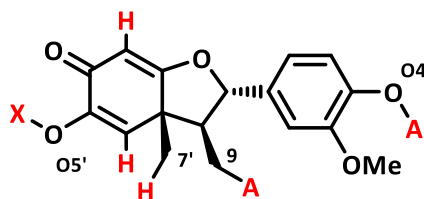
Figure D-1: Red colored letters represent the corresponding strategies; modification on position X due to dealkylation possible in any chosen approach

As these modifications would still only allow racemic product synthesis, an enantioselective approach would need to be covered in further studies. This could be achieved by employing chiral ligands for the final Lewis acid assisted cyclisation step, as was shown in preliminary tests by[91] employing BINOL. As these experiments were done in 1991, the expanded present-day ligand-library could be applied to screen for highest enantioselectivity.

To conclude this thesis, the racemic synthesis of (±)-Kadsurenin F (**104**) was ultimately enabled, by employing the key fragments (*E*)-methylisoeugenol (**1**) and 2-allyl-5-(benzyloxy)cyclohexa-2,5-diene-1,4-dione (**2**). This could be achieved either with the application of strategies C + E or C + H resulting in an overall yield of (±)-Kadsurenin F in **2% (7 steps)** or **6% (9 steps)** respectively.
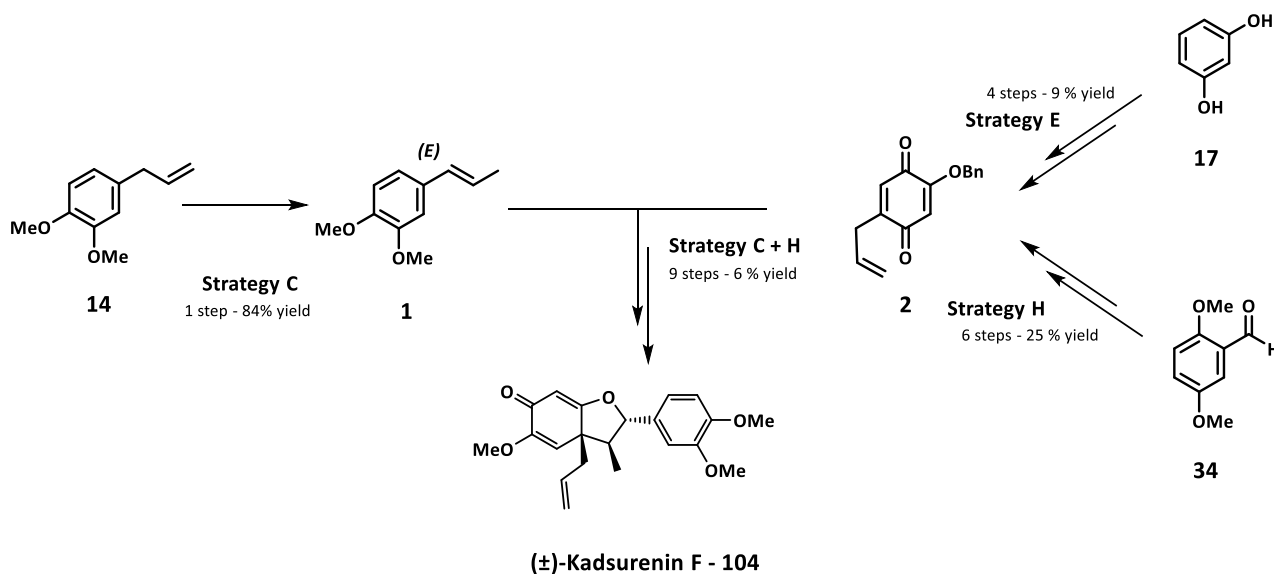
Scheme D-3

E   Experimental part

E I   Materials and methods – chemical synthesis

Unless noted otherwise, all reagents were purchased from commercial suppliers and used without further purification. CH_2Cl_2, Et_2O, 1,4-dioxane, MeOH, THF and toluene intended for water-free reactions were pre-distilled and then desiccated on Al_2O_3 columns (PURESOLV, Innovative Technology). Chromatography solvents were distilled prior to use. For all other solvents quality grade is given in the reaction procedures.

Column chromatography was performed on a Büchi Sepacore Flash System (2x Büchi Pump Module C-605, Büchi Pump Manager C-615, Büchi UV Photometer C-635, Büchi Fraction Collector C-660) or standard manual glass columns using silica gel from Merck (40-63 µm) using LP/EtOAc or LP/CH_2Cl_2 mixtures.

Table E-1: Recipes for TLC staining solutions used in this thesis.

TLC staining solution 1 (general purpose)		TLC staining solution 2 (general purpose)		TLC staining solution 3 (general purpose)		TLC staining solution 4 for acidic compounds	
6 g	$KMnO_4$	10 g	phosphomolybdic acid hydrate	3.5 g	p-anisaldehyde	40 mg	bromocresol green
0.5 g	KOH	1 g	ceric ammonium nitrate	1.5 mL	acetic acid	100 mL	dry EtOH
40 g	K_2CO_3	20 g	H_2SO_4 conc.	5 mL	H_2SO_4 conc.	0.1 M	NaOH until blue color appears
600 mL	deion. H_2O	300 mL	EtOH	120 mL	EtOH		

Desiccation of organic solvents after extraction in reaction work-up was performed using anhydrous sodium sulfate and subsequent filtration.

Melting points were determined by Büchi Melting Point B-545.

Microwave reactions were performed using a Biotage Initiator EXP EU Microwave Synthesizer.

NMR spectra were recorded from $CDCl_3$, d_6-DMSO solutions on a Bruker Advance UltraShield 400 (400 MHz) or Avance III HD 600 (600 MHz) spectrometer and chemical shifts are reported in ppm using tetramethylsilane as an internal standard. Whenever possible calibration *via* residual solvent peaks was performed. Peak assignment is based on correlation experiments or software prediction (ChemDraw Professional 15 or MestReNova 9.0.1). Annotations of the structures were carried out in accordance with IUPAC nomenclature, unless otherwise noted.

General conversion control were conducted with a Thermo Scientific Trace 1300 / ISQ LT Single Quadrupole Mass Spectrometer device using a standard capillary column BGB 5 (30 m x 0.25 mm ID) with helium flow of 1.5 mL / min, analyzing an m/z range from 50 to 550 and the following temperature profile: 100-300 °C, 2 min at 100 °C, 35 °C/min until 300 °C, 6 min at 300 °C

HR-MS analysis was carried out from acetonitrile 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).

E II   Chemical synthesis

E II.1   (E)-3,4-Dimethoxycinnamic acid (4)

3
M = 194.19

4
M = 208.21
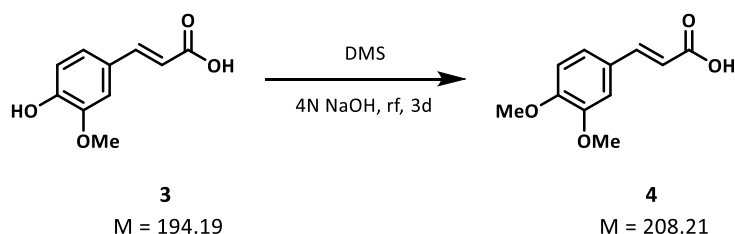
(E)-3,4-Dimethoxycinnamic acid **4** was synthesized according to a literature protocol.[45]

Procedure: (E)-Ferulic acid **3** (5.00 g, 25.75 mmol, 1.00 equiv.) in 4N NaOH (25 mL) was cooled to 10 °C, followed by the dropwise addition of dimethyl sulfate (2.5 mL, 26.36 mmol, 1.00 equiv.), forming a cloudy emulsion. The mixture was heated to reflux for 1 h, whereupon another portion dimethyl sulfate (1.25 mL, 13.18 mmol, 0.50 equiv.) was added to the now clear solution. The reaction was refluxed for another 1 h and the addition was repeated once again resulting in a total volume of DMS of 5 mL. The mixture refluxed overnight. For completion of the reaction two additional 1.25 mL portions of DMS and 5 mL 4N NaOH were added on the next day and stirred for one more day until full consumption of the starting material could be confirmed *via* TLC.

Work-up: The orange solution was cooled to room temperature and poured into a beaker with 2N HCl (200 mL) to precipitate the product. Excess dimethyl sulfate was destroyed by stirring the orange suspension for 15 min and the product was collected by suction filtration through a sinter funnel (por. 3). The solids were washed with water until the filtrate was acid free and subjected to final two washings with n-hexane to leave an ocher, waxy solid that was further purified by recrystallization from acetone (60 mL / 5 g crude) or 70% EtOH yielding 4.10 g (76%) of **4** as ocher crystals. Spectral data and melting point are in accordance with the literature.[45]

Appearance	ocher crystalline solid
TLC	R_f (CHCl$_3$/MeOH - 5/1) = 0.64
Yield	4.10 g (76%)
Reaction scale	5.00 g (25.75 mmol **3**)
Reaction time	3 d
Substrate concentration	1.03 M
Purification	recrystallization from acetone
Molecular formula, m.w.	C$_{11}$H$_{12}$O$_4$, 208.21
M.p.	179 – 181 °C (lit.[45]: 180 – 182 °C)
^{1}H-NMR (400 MHz, DMSO-d_6)	δ = 3.79 (s, 3H, -OCH$_3$), 3.81 (s, 3H, -OCH$_3$), 6.45 (d, J = 15.9 Hz, 1H, =CH-COOH), 6.98 (d, J = 8.4 Hz, 1H, H5), 7.21 (dd, J = 8.4, 2.0 Hz, 1H, H6), 7.32

(d, J = 2.0 Hz, 1H, H2), 7.53 (d, J = 15.9 Hz, 1H, Ar-CH=), 12.22 (s, 1H, COOH) ppm.

^{13}C-NMR (101 MHz, DMSO-d_6) δ = 55.5 (q, -OCH$_3$), 55.6 (q, -OCH$_3$), 110.3 (d, C2), 111.5 (d, C5), 116.7 (d, =<u>CH</u>-COOH), 122.6 (d, C6), 127.0 (s, C1), 144.1 (d, Ar-CH=), 149.0 (s, C3 or C4), 150.8 (s, C3 or C4), 167.9 (s, COOH) ppm.

E II.2   (E)-3,4-Dimethoxycinnamic acid methyl ester (5)

4
M = 208.21

5
M = 222.24
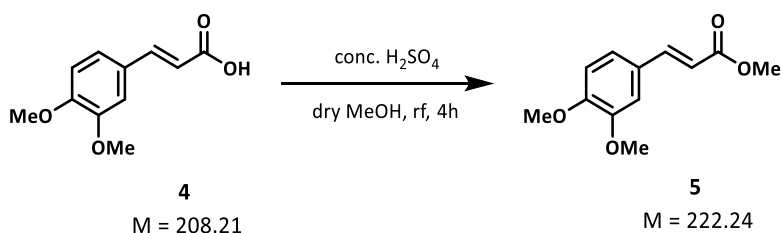
(E)-3,4-Dimethoxycinnamic acid methyl ester **5** was synthesized according to a literature protocol.[92]

Procedure: An oven-dried, argon flushed three-neck round bottom flask was charged with (E)-dimethoxycinnamic acid **4** (2.50 g, 12.01 mmol, 1.00 equiv.), which was dissolved in 30 mL dry MeOH. The resulting suspension was stirred for 15 min at room temperature to dissolve a major fraction of the cinnamic acid followed by the dropwise addition of conc. H$_2$SO$_4$ (1.4 mL, 26.26 mmol, 2.20 equiv.) over a period of 5 min. The mixture was then heated to reflux for 4 h, until full consumption of the staring material was confirmed *via* TLC.

Work-up: The mixture was cooled to room temperature and solid NaHCO$_3$ (2.85 g) was added in portions which caused vigorous bubbling of the solution. The mixture was stirred for additional 10 min and was subsequently diluted with CH$_2$Cl$_2$ (100 mL) and water (100 mL). The phases were separated and the aqueous phase was extracted twice with small portions of CH$_2$Cl$_2$. The combined organic layers were washed twice with water and brine, dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure yielding 2.50 g (97%) of **5** as light yellow solid. The resulting material was subjected to the next step without further purification. Spectral data[92] and melting point[93] are in accordance with the literature.

Appearance	light yellow solid
TLC	**R$_f$** (LP/EtOAc - 3/1) = 0.22
Yield	2.60 g (97%)
Reaction scale	2.50 g (12.01 mmol **4**)
Reaction time	4 h
Substrate concentration	0.40 M
Purification	product was obtained pure after work-up

Molecular formula, m.w.	$C_{12}H_{14}O_4$, 222.24
M.p.	66 – 68 °C (lit.[93]: 68 – 69 °C)
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 3.79 (s, 3H, -COOCH$_3$), 3.91 (s, 6H, 2x -OCH$_3$), 6.31 (d, J = 15.9 Hz, 1H, =C<u>H</u>-COOMe), 6.86 (d, J = 8.3 Hz, 1H, H5), 7.04 (d, J = 2.0 Hz, 1H, H2), 7.10 (dd, J = 8.3, 2.0 Hz, 1H, H6), 7.63 (d, J = 15.9 Hz, 1H, Ar-CH=) ppm.

E II.3   (E)-3-(3,4-Dimethoxyphenyl)prop-2-en-1-ol (6)

5
M = 222.24

6
M = 194.23
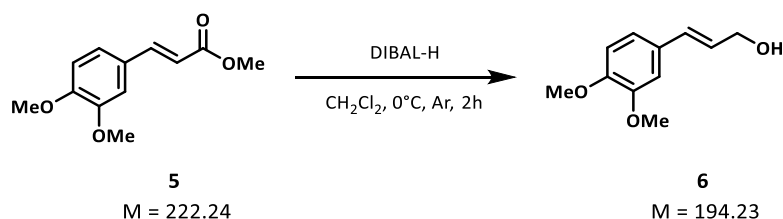
(E)-3,4-Dimethoxycinnamyl alcohol **6** was synthesized according to a literature protocol.[92]

Procedure: An oven-dried, argon flushed three-neck round bottom flask was charged with (E)-3,4-dimethoxycinnamic acid methyl ester **5** (2.30 g, 10.35 mmol, 1.00 equiv.), which was dissolved in 110 mL dry CH$_2$Cl$_2$. The solution was cooled to 0 °C with an ice bath to and treated with DIBAL-H (27.20 mL, 1M in heptane, 27.20 mmol, 2.60 equiv.) dropwise over a period of 10 min causing a deep yellow color change that faded over the course of the reaction. The ice bath was removed and the solution was allowed to stir at room temperature for 2 h, until full consumption of the staring material was confirmed *via* TLC.

Work-up: MeOH (18 mL) was added very slowly to the solution, causing immediate refluxing and formation of a voluminous colorless precipitate. The resulting slurry was stirred for 5 min and then 1N HCl (80 mL) was added dropwise over 15 min, dissolving any formed solids. The phases were separated and the aqueous layer was extracted twice with small portions of CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure leaving a crude yellow solid that was further purified by column chromatography (crude mass/SiO$_2$ = 1/50) eluting 2.5:1 to 1:1 LP/EtOAc to yield 2.00 g (quant.) of **6** as colorless solid. Spectral data are in accordance with the literature.[92]

Appearance	colorless solid
TLC	**R$_f$** (LP/EtOAc - 1/1) = 0.28
Yield	2.00 g (quant.)
Reaction scale	2.30 g (10.35 mmol **5**)
Reaction time	2 h
Substrate concentration	0.09 M
Purification	column chromatography LP/EtOAc gradient 2.5:1 to 1:1

Molecular formula, m.w.	$C_{11}H_{14}O_3$, 194.23
M.p.	77 – 79 °C (lit.[94]: 78.8 – 79.2 °C)
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 1.40 (t, J = 5.9 Hz, 1H, -OH), 3.89 (s, 3H, -OCH$_3$), 3.90 (s, 3H, -OCH$_3$), 4.31 (td, J = 5.9, 1.5 Hz, 2H, -CH$_2$-OH), 6.25 (dt, J = 15.8, 5.9 Hz, 1H, =C̲H̲-CH$_2$), 6.56 (dt, J = 15.8, 1.4 Hz, 1H, Ar-CH=), 6.82 (d, J = 8.2 Hz, 1H, H5), 6.93 (dd, J = 8.2, 2.0 Hz, 1H, H6), 6.95 (d, J = 2.0 Hz, 1H, H2) ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 55.9 (q, -OCH$_3$), 56.0 (q, -OCH$_3$), 63.9 (t, -CH$_2$-OH), 109.0 (d, C2), 111.2 (d, C5), 119.8 (d, C6), 126.7 (d, =C̲H̲-CH$_2$), 129.9 (s, C1), 131.3 (d, Ar-CH=), 149.0 (s, C3 or C4), 149.1 (s, C3 or C4) ppm.

E II.4   1-(3,4-Dimethoxyphenyl)propan-1-ol (9)

8
M = 166.18

9
M = 196.25
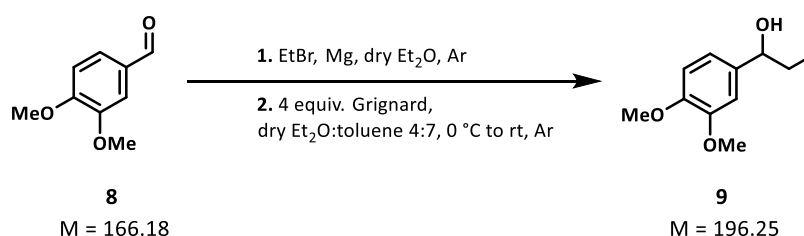
1-(3,4-Dimethoxyphenyl)propan-1-ol **9** was synthesized according to a literature protocol.[51]

Procedure: An oven-dried, argon flushed three-neck round bottom flask was charged with magnesium chips (3.51 g, 144.42 mmol, 4.00 equiv.) and 30 mL dry Et$_2$O. Under argon, ethyl bromide (10.78 mL, 144.42 mmol, 4.00 equiv.) dissolved in 120 mL of dry Et$_2$O dropping funnel was added and the reaction was started by slow addition of the bromide to the reaction mixture and small amounts of I$_2$. The addition speed was adjusted for a gentle reflux. Following the complete addition of the substrate the reaction mixture was kept on reflux for another 2 h, until only minimal amounts of magnesium remained in the flask.

The freshly prepared Grignard-solution was added dropwise to a solution of veratryl aldehyde **8** (6.00 g, 36.11 mmol, 1.00 equiv.) in a mixture of 300 mL 4:7 Et$_2$O:toluene at 0 °C over a period of 30 min. The mixture was taken from the cooling bath and the slightly yellowish suspension was allowed to stir overnight at room temperature, until full consumption of the staring material was confirmed *via* TLC.

Work-up: The reaction was hydrolyzed with saturated aqueous NH$_4$Cl (150 mL) and stirred for 15 min. The phases were separated and the aqueous layer was extracted three times with small portions of EtOAc. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure to leave a crude yellow oil that was further purified by column chromatography (crude mass/SiO$_2$ = 1/50) eluting 2:1 to 1:1 LP/EtOAc + 1% N(Et)$_3$ to yield 6.72 g (95%) of **9** as colorless oil. Spectral data are in accordance with the literature.[51]

Appearance	colorless oil
TLC	R_f (LP/EtOAc - 1/1) = 0.38
Yield	6.72 g (95%)
Reaction scale	6.00 g (36.11 mmol **8**)
Reaction time	1 d
Substrate concentration	0.12 M
Purification	column chromatography 2:1 to 1:1 LP/EtOAc + 1% N(Et)$_3$
Molecular formula, m.w.	$C_{11}H_{14}O_2$, 196.25
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 0.90 (t, J = 7.4 Hz, 3H, -CH$_3$), 1.63 – 1.89 (m, 2H, -CH$_2$-), 1.92 (s, 1H, -OH), 3.86 (s, 3H, -OCH$_3$), 3.88 (s, 3H, -OCH$_3$), 4.52 (t, J = 6.7 Hz, 1H, -CH-), 6.82 (d, J = 8.2 Hz, 1H, H5), 6.85 (dd, J = 8.2, 1.8 Hz, 1H, H6), 6.90 (d, J = 1.8 Hz, 1H, H2) ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 10.4 (q, -CH$_3$), 32.0 (t, -CH$_2$-), 56.0 (q, -OCH$_3$), 56.1 (q, -OCH$_3$), 76.1 (d, -CH-), 109.1 (d, C2), 111.0 (d, C5), 118.4 (d, C6), 137.4 (s, C1), 148.5 (s, C3 or C4), 149.2 (s, C3 or C4) ppm.

E II.5   4-Allyl-2-methoxyphenyl benzoate (12)

11
M = 164.20

12
M = 268.31
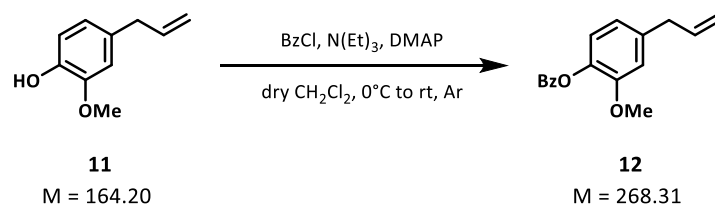
4-Allyl-2-methoxyphenyl benzoate **12** was synthesized according to a literature protocol.[40]

Procedure: An oven-dried, argon flushed three-neck round bottom flask was charged with freshly distilled eugenol **11** (5.00 g, 30.45 mmol, 1.00 equiv.), which was dissolved in 25 mL dry CH$_2$Cl$_2$. The solution was cooled to 0 °C with an ice bath followed by addition of triethylamine (8.47 mL, 60.90 mmol, 2.00 equiv.) and DMAP (0.41 g, 3.05 mmol, 0.1 equiv.) dissolved in 2 mL dry CH$_2$Cl$_2$. Afterwards benzoyl chloride (3.86 mL, 33.49 mmol, 1.10 equiv.) was added dropwise over a period of 5 min to the light orange solution, which led to the immediate formation of a voluminous colorless precipitate. The mixture was removed from the cooling bath and stirred for 2 h at room temperature, until full consumption of the staring material was confirmed *via* TLC.

Work-up: The solvent was removed *in vacuo* and the resulting solids were dissolved in Et$_2$O and water. The organic phase was collected and the aqueous phase was extracted three times with small portions of Et$_2$O. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure leaving crude off-colorless solid product that was further purified by

recrystallization from MeOH (3 mL / 1 g) to yield 7.64 g (94%) of **12** as colorless crystalline solid. Spectral data and melting point are in accordance with the literature.[40]

Appearance	colorless crystalline solid
TLC	R_f (LP/EtOAc - 5/1) = 0.58
Yield	7.64 g (94%)
Reaction scale	5.00 g (30.45 mmol **11**)
Reaction time	2 h
Substrate concentration	0.47 M
Purification	recrystallization from MeOH
Molecular formula, m.w.	$C_{17}H_{16}O_3$, 268.31
M.p.	66.8 – 67.5 C (lit.[40]: 66 – 67 °C)
^{1}H-NMR (400 MHz, CDCl₃)	δ = 3.42 (dd, J = 6.7, 1.5 Hz, 2H, -C$\underline{H_2}$-CH=), 3.81 (s, 3H, -O-CH₃), 5.07 – 5.19 (m, 2H, =CH₂), 6.00 (ddt, J = 16.8, 10.1, 6.7 Hz, 1H, -C$\underline{H}$=CH₂), 6.83 (dd, J = 7.9, 1.9 Hz, 1H, H5), 6.85 (d, J = 1.9 Hz, 1H, H3), 7.08 (d, J = 7.9 Hz, 1H, H6), 7.46 – 7.56 (m, 2H, H3', H5'), 7.63 (ddt, J = 7.9, 6.9, 1.3 Hz, 1H, H4'), 8.19 – 8.27 (m, 2H, H2', H6') ppm.
^{13}C-NMR (101 MHz, CDCl₃)	δ = 40.3 (t, -C$\underline{H_2}$-CH=), 56.0 (q, -O-CH₃), 112.9 (d, C3), 116.3 (t, =CH₂), 120.8 (d, C5), 122.8 (d, C6), 128.6 (d, 2C, C3', C5'), 129.6 (s, C1'), 130.4 (d, 2C, C2', C6'), 133.5 (d, C4'), 137.2 (d, -C$\underline{H}$=CH₂), 138.3 (s, C4), 139.2 (s, C1), 151.2 (s, C2), 165.0 (s, -OCO-) ppm.

E II.6 (E)-Methylisoeugenol (1)
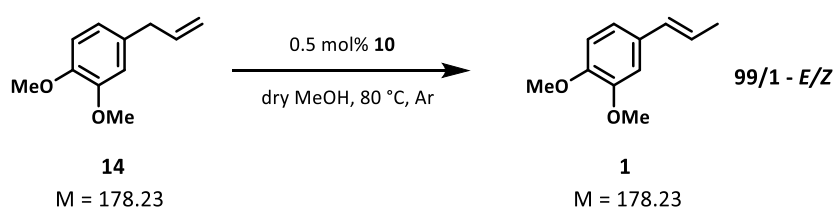
(E)-Methylisoeugenol **1** was synthesized according to a modified literature protocol.[40]

Procedure: An oven-dried, argon flushed screw cap vial was charged with [[{RuCl(μ-Cl)(η³:η³-C₁₀H₁₆)}₂] **10** (25 mg, 0.04 mmol, 0.5 mol% of Ru), eugenol methyl ester **14** (2.92 g, 16.38 mmol, 1.00 equiv.) and 4 mL dry MeOH. This mixture was tightly capped and heated to 80 °C for 72 h, until full consumption of the staring material was confirmed *via* GCMS and H-NMR.

Work-up: The reaction mixture was flushed over a short pad of silica with EtOAc and was then directly adsorbed onto Celite to be purified by flash chromatography (crude mass/SiO₂ = 1/100) eluting 10:1 to 5:1

LP/EtOAc yielding 2.46 g (84%; 99/1 - *E/Z*) of **1** as colorless oil. Spectral data are in accordance with the literature.[40]

Appearance	colorless oil
TLC	$\mathbf{R_f}$ (LP/EtOAc - 5/1) = 0.51
Yield	2.46 g (84%)
Reaction scale	2.92 g (16.38 mmol **14**)
Reaction time	3 d
Substrate concentration	4.0 M
Purification	column chromatography LP/EtOAc gradient 10:1 to 5:1 (250 g silica)
Molecular formula, m.w.	$C_{11}H_{14}O_2$, 178.23
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 2.32 (s, 3H, p-CH$_3$), 2.50 (s, 6H, o-CH$_3$), 3.42 (dt, *J* = 6.8, 1.5 Hz, 2H, -<u>CH$_2$</u>-CH=), 3.87 (s, 3H, -OCH$_3$), 5.08 – 5.20 (m, 2H, =CH$_2$), 5.99 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H, -<u>CH</u>=CH$_2$), 6.83 (dd, *J* = 8.0, 1.9 Hz, 1H, H5), 6.87 (d, *J* = 1.9 Hz, 1H, H3), 6.92 (s, 2H, H3', H5'), 7.08 (d, *J* = 8.0 Hz, 1H, H6) ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 20.1 (q, 2C, o-CH$_3$), 21.3 (q, p-CH$_3$), 40.2 (t, -<u>CH$_2$</u>-CH=), 55.8 (q, -OCH$_3$), 112.9 (d, C3), 116.3 (t, =CH$_2$), 120.9 (d, C5), 122.6 (d, C6), 128.7 (d, 2C, C3', C5'), 130.1 (s, C1'), 136.0 (s, 2C, C2', C6'), 137.2 (d, -<u>CH</u>=CH$_2$), 138.0 (s, -C4), 139.3 (s, C4'), 139.8 (s, C1), 151.2 (s, C2), 168.1 (s, COOAr) ppm.
GCMS	**1** - t_R = 5.34 min, main fragments 178 (100, M$^+$), 163 (42), 107 (44), 91 (29). **(Z)-1** - t_R = 5.15 min, main fragments 178 (100, M$^+$), 163 (41), 107 (62), 91 (43).
HRMS (ESI)	calc. for $C_{11}H_{15}O_2^+$ [M+H]$^+$ 179.1067, found 179.1068 – Δ = 0.68 ppm.

## E II.7   3-(Benzyloxy)phenol (18)

17
M = 110.11

18
M = 200.24
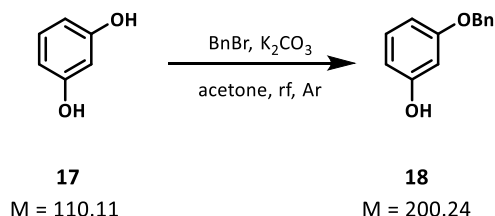
Procedure: An oven-dried, argon flushed three-neck round bottom flask was charged with resorcinol **17** (5.00 g, 45.41 mmol, 1.00 equiv.), K$_2$CO$_3$ (6.28 g, 45.41 mmol, 1.00 equiv.) and 200 mL acetone. The solution was heated to reflux followed by the addition of benzyl bromide (5.39 mL, 45.41 mmol,

1.00 equiv.) dissolved in 100 mL acetone to the heated solution under argon over a period of 1 hour. The reaction was refluxed overnight, until full consumption of benzyl bromide was confirmed *via* TLC.

Work-up: The crude mixture was filtered through a cotton plug to remove the bulk solids followed by subsequent removal of the solvent in *vacuo*. The oily residue was taken up in CH_2Cl_2 and extracted several times with 2N NaOH. The collected aqueous phases were acidified with conc. aqueous HCl and reextracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to leave a crude orange viscous oil that was further purified by column chromatography (crude mass/SiO_2 = 1/100) eluting LP/EtOAc 10:1 to 5:1 to yield 3.64 g (40%) of **18** as light yellow viscous oil. Spectral data are in accordance with the literature.[95]

Appearance	light yellow viscous oil
TLC	R_f (LP/EtOAc - 10/1) = 0.18
Yield	3.64 g (40%)
Reaction scale	5.00 g (45.41 mmol **17**)
Reaction time	1 d
Substrate concentration	0.15 M
Purification	column chromatography 10:1 to 5:1 LP/EtOAc
Molecular formula, m.w.	$C_{13}H_{12}O_2$, 200.24
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 5.04 (s, 2H, -O-CH$_2$-), 5.09 (s, 1H, -OH), 6.44 (ddd, J = 8.0, 2.4, 0.8 Hz, 1H, H5), 6.49 (t, J = 2.3 Hz, 1H, H2), 6.58 (ddd, J = 8.3, 2.4, 0.8 Hz, 1H, H4), 7.14 (t, J = 8.2 Hz, 1H, H5), 7.30 − 7.36 (m, 1H, H4'), 7.36 − 7.41 (m, 2H, H3', H5'), 7.41 − 7.45 (m, 2H, H2', H6') ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 70.2 (t, -O-CH$_2$-), 102.6 (d, C2), 107.5 (d, C4), 108.2 (d, C5), 127.6 (d, 2C, C2', C5'), 128.1 (d, C4'), 128.7 (d, 2C, C3', C5'), 130.3 (d, C5), 136.9 (s, C1'), 156.7 (s, C1), 160.2 (s, C3) ppm.

E II.8   Potassium nitrosodisulfonate - Fremy's salt (VIII)
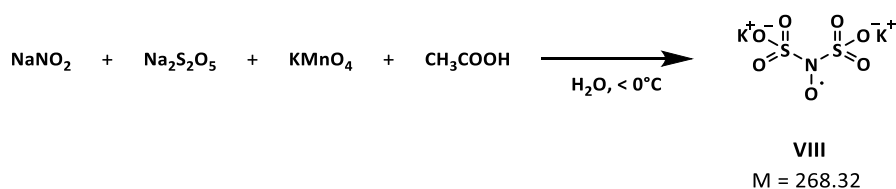
VIII
M = 268.32

Potassium nitrosodisulfonate **VIII** was synthesized according to a literature protocol.[42]

Procedure: For this synthesis several solutions needed to be prepared in advance.

Na$_2$S$_2$O$_5$ (16.00 g, 84.16 mmol, 1.00 equiv.) dissolved in 52 mL water. (**A**)

NaNO$_2$ (17.25 g, 250.00 mmol, 2.97 equiv.) dissolved in 50 mL water. (**B**)

KMnO$_4$ (6.32 g, 59.25 mmol, 0.48 equiv.) dissolved in 300 mL water. (**C**)

A freshly prepared solution **B** was cooled in a 1 L beaker to ≤ 0 °C *via* ice/salt bath and chopped ice was added to ensure a maximum temperature of 0 °C. Subsequently a precooled solution of **A** was added over a period of 2 min, following the dropwise addition of glacial acetic acid (10.00 mL, 174.85 mmol, 2.07 equiv.) causing the solution to turn light orange. The mixture was stirred for 10 min and 25% aqueous NH$_3$ (35 mL, 375 mmol, 4.45 equiv.) was then added increasing the pH to 14, while keeping the temperature below 0 °C. Finally, oxidation of the formed intermediate hydroxylamine-N,N-disulfonate was achieved by dropwise addition of solution **C** to the strongly stirred mixture over a period of 1 h, triggering the precipitation of massive amounts of solid MnO$_2$. To keep the solution at the required temperature, chopped ice was also added here to aid with the cooling process.

Work-up: Concluding the addition of the permanganate solution, the final mixture was stirred for 10 min and was then subsequently filtered over a Buchner funnel quickly into a precooled (< 0°) flask. Saturated aqueous KCl (200 mL) was then added to the clear violet solution dropwise while maintaining the temperature, causing the Fremy's salt **VIII** to precipitate as bright orange crystals. The suspension was allowed to stir for 1 h after complete addition of the potassium salt, to ensure full precipitation of the product. The orange solids were then collected *via* filtration over a sintered glass funnel and washed twice with 5% ammoniacal saturated aqueous KCl (50 mL), twice with 5% ammoniacal MeOH (50 mL) and twice with acetone (50 mL). During the whole filtration process drying by drawing air current through the solids should be thoroughly avoided. The wet solid product was spread out on a watch glass and was allowed to dry for 15 min. Finally, the orange crystals were stored in a desiccator over calcium oxide, in the presence of ammonium carbonate in a separate dish to provide an ammoniacal atmosphere. Total yield 15.5 g (68%) of **VIII**.

Appearance	bright orange crystalline solid
Yield	15.5 g (68%)
M.p.	rapid decomposition

Reaction scale	16.00 g (84.16 mmol Na$_2$S$_2$O$_5$)
Reaction time	5 h
Molecular formula, m.w.	K$_2$NO$_7$S$_2$, 268.32

E II.9   2-(Benzyloxy)cyclohexa-2,5-diene-1,4-dione (19)

18
M = 200.24

19
M = 214.22
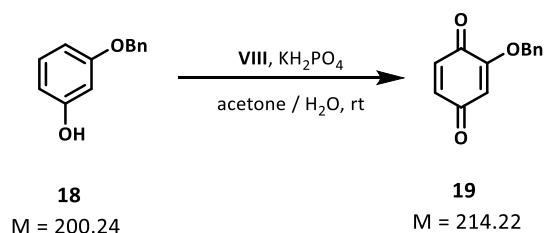
2-(Benzyloxy)cyclohexa-2,5-diene-1,4-dione **19** was synthesized according to a literature protocol.[63]

Procedure: A single-neck round bottom flask was charged with 3-(benzyloxy)phenol **18** (1.00 g, 4.99 mmol, 1.00 equiv.), which was dissolved in a mixture of 25 mL acetone and 75 mL 0.1 M KH_2PO_4 buffer-solution that led to minor precipitation of the buffer-salt. In a separate beaker a solution of Fremy's salt **VIII** (5.00 g, 18.73 mmol, 3.75 equiv.) dissolved in 300 mL 0.06 M KH_2PO_4 buffer was prepared resulting in a deep violet colored solution that was cooled to 0 °C. The freshly prepared reagent was subsequently added to the round bottom flask over a period of 1 hour. The reaction was then stirred for 3 h, until full consumption of the starting material was confirmed *via* TLC.

Work-up: The solution was directly extracted three times with small portions of EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure leaving a yellow amorphous solid. For further purification the crude material was purified by flash chromatography (crude mass/SiO_2 = 1/50) eluting LP/EtOAc 10:1 to 4:1 to yield 0.75 g (70%) of **19** as yellow crystalline solid. Spectral data are in accordance with the literature.[63]

Appearance	yellow crystalline solid
TLC	R_f (LP/EtOAc – 3/1) = 0.44
Yield	0.75 g (70%)
Reaction scale	1.00 g (4.99 mmol **18**)
Reaction time	3 h
Substrate concentration	0.05 M
Purification	column chromatography 10:1 to 4:1 LP/EtOAc
Molecular formula, m.w.	$C_{13}H_{10}O_3$, 214.22
M.p.	116 °C (decomposition)
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 5.05 (s, 2H, -O-CH$_2$-), 6.00 (d, *J* = 2.1 Hz, 1H, H3), 6.69 (dd, *J* = 10.1, 2.1 Hz, 1H, H5), 6.73 (d, *J* = 10.1 Hz, 1H, H6), 7.33 – 7.43 (m, 5H, H2'-H6') ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 71.2 (t, -O-CH$_2$-), 109.1 (d, C3), 127.8 (d, 2C, C2', C6'), 129.0 (d, C4'), 129.0 (d, 2C, C3', C5'), 134.1 (s, C1'), 134.7 (d, C6), 137.1 (d, C5), 157.6 (s, C2), 181.7 (s, C4), 187.6 (s, C1) ppm.

E II.10 1-(Allyloxy)-3-(benzyloxy)benzene (<u>20</u>)

18
M = 200.24

<u>20</u>
M = 240.30
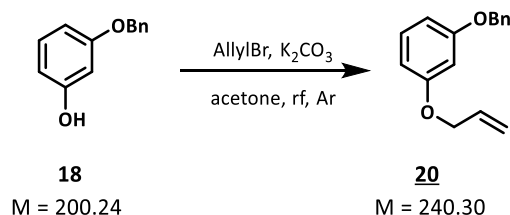
1-(Allyloxy)-3-(benzyloxy)benzene <u>20</u> was synthesized according to a modified literature protocol.[96]

Procedure: An oven-dried, argon flushed three-neck round bottom flask was charged with 3-(benzyloxy)phenol **18** (2.04 g, 10.19 mmol, 1.00 equiv.), K_2CO_3 (1.83 g, 16.30 mmol, 1.60 equiv.), allyl bromide (1.42 mL, 16.30 mmol, 1.60 equiv.) and 10 mL acetone. After heating the reaction mixture to reflux for 1 day, full consumption of the starting material was confirmed *via* TLC.

Work-up: The reaction was diluted with CH_2Cl_2 (100 mL) and quenched by addition of 2N NaOH (50 mL). The phases were separated and the aqueous layer was extracted twice with small portions of CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure leaving a light yellow oil. For further purification the crude material was adsorbed onto Celite and purified by flash chromatography (crude mass/SiO_2 = 1/60) eluting LP/EtOAc 30:1 to yield 2.08 g (85%) of **<u>20</u>** as colorless oil. Spectral data are in accordance with the literature.[96]

Appearance	colorless oil
TLC	**R_f** (LP/EtOAc – 10/1) = 0.59
Yield	2.08 g (85%)
Reaction scale	2.04 g (10.19 mmol **18**)
Reaction time	1 d
Substrate concentration	1.0 M
Purification	column chromatography 30:1 LP/EtOAc
Molecular formula, m.w.	$C_{16}H_{16}O_2$, 240.30
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 4.53 (dt, *J* = 5.3, 1.5 Hz, 2H, -O-<u>CH$_2$</u>-CH=), 5.06 (s, 2H, -O-CH$_2$-Ar), 5.30 (ddt, *J* = 10.5, 1.5 Hz, 1H, =CH$_2^{cis}$), 5.43 (ddt, *J* = 17.3, 1.6 Hz, 1H, =CH$_2^{trans}$), 6.07 (ddt, *J* = 17.3, 10.6, 5.3 Hz, 1H, -<u>CH</u>=CH$_2$), 6.54 – 6.63 (m, 3H, H2, H4, H6), 7.17 – 7.23 (m, 1H, H5), 7.32 – 7.37 (m, 1H, H4'), 7.37 – 7.43 (m, 2H, H3', H5'), 7.43 – 7.48 (m, 2H, H2', H6') ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 69.0 (t, -O-<u>CH$_2$</u>-CH=), 70.2 (t, -O-CH$_2$-Ar), 102.3 (d, C2), 107.4 (d, C4 or C6), 107.5 (d, C4 or C6), 117.8 (t, =CH$_2$), 127.6 (d, 2C, C2', C6'), 128.1 (d, C4'), 128.7 (d, 2C, C3', C5'), 130.0 (d, C5), 133.4 (d, -<u>CH</u>=CH$_2$), 137.1 (s, C1'), 160.0 (s, C1 or C3), 160.2 (s, C1 or C3) ppm.

E II.11   2-Allyl-5-(benzyloxy)phenol (<u>21</u>)

20
M = 240.13

21
M = 240.13
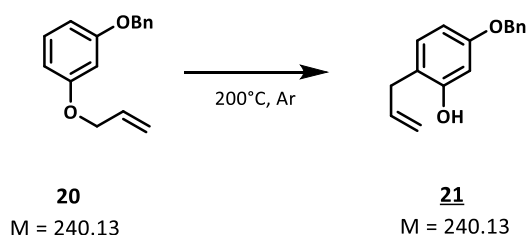
The Claisen rearrangement was conducted according to a literature protocol.[97]

Procedure: An oven-dried, screw cap vial was charged with 1-(allyloxy)-3-(benzyloxy)benzene <u>20</u> (1.00 g, 4.16 mmol, 1.00 equiv.), tightly capped and carefully purged with argon. The reaction was heated to 200 °C for 4 h, until full consumption of the starting material was confirmed *via* TLC.

Work-up: The crude material was directly adsorbed onto Celite and purified by repeated column chromatography (crude mass/SiO$_2$ = 1/400) eluting CH$_2$Cl$_2$/LP 2.5:1 to 4:1 to yield 448 mg (45%) of <u>21</u> as light yellow and 260 mg (26%) of <u>22</u> as colorless solid (m/p-ratio = 65/35).

       Main product from the Claisen rearrangement (<u>21</u>):

Appearance	light yellow solid
TLC	**R$_f$** (CH$_2$Cl$_2$/LP − 3/1) = 0.24
Yield	448 mg (45%)
Reaction scale	1000 mg (10.19 mmol <u>20</u>)
Reaction time	4 h
Substrate concentration	neat
Purification	column chromatography 2.5:1 to 4:1 CH$_2$Cl$_2$/LP
Molecular formula, m.w.	C$_{16}$H$_{16}$O$_2$, 240.30
M.p.	54 − 55 °C
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 3.35 (dt, *J* = 6.3, 1.7 Hz, 2H, -<u>CH$_2$</u>-CH=), 4.99 (s, 1H, -OH), 5.02 (s, 2H, -O-CH$_2$-), 5.13 − 5.20 (m, 2H, =CH$_2$), 6.00 (ddt, *J* = 16.7, 10.3, 6.3 Hz, 1H, -<u>CH</u>=CH$_2$), 6.49 (d, *J* = 2.5 Hz, 1H, H6), 6.53 (dd, *J* = 8.3, 2.5 Hz, 1H, H4), 6.99 (d, *J* = 8.3 Hz, 1H, H3), 7.29 − 7.35 (m, 1H, H4'), 7.35 − 7.39 (m, 2H, H3', H5'), 7.39 − 7.44 (m, 2H, H2', H6') ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 34.5 (t, -<u>CH$_2$</u>-CH=), 70.1 (t, -O-CH$_2$-), 103.0 (d, C6), 107.3 (d, C4), 116.3 (t, =CH$_2$), 118.0 (s, C2), 127.6 (d, 2C, C2', C6'), 128.0 (d, C4'), 128.6 (d, 2C, C3', C5'), 130.9 (d, C3), 136.9 (d, -<u>CH</u>=CH$_2$), 137.0 (s, C1'), 154.9 (s, C1), 158.7 (s, C5) ppm.
HRMS (ESI)	<u>c</u>alc. for C$_{16}$H$_{17}$O$_2^+$ [M+H]$^+$ 241.1223, found 241.1230 − Δ = 4.66 ppm.

E II.12   2-Allyl-3-(benzyloxy)phenol (**22**)

A second product that emerged from the Claisen rearrangement was regioisomer **22**.

22
M = 240.13

Appearance	colorless solid
TLC	R_f (CH_2Cl_2/LP – 3/1) = 0.31
Yield	260 mg (26 %)
Molecular formula, m.w.	$C_{16}H_{16}O_2$, 240.30
M.p.	57 – 58 °C
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 3.57 (dt, J = 6.2, 1.7 Hz, 2H, -CH$_2$-CH=), 5.04 (s, 1H, -OH), 5.09 (s, 2H, -O-CH$_2$-), 5.10 – 5.20 (m, 2H, =CH$_2$), 6.03 (ddt, J = 16.9, 10.0, 6.1 Hz, 1H, -CH=CH$_2$), 6.53 (dd, J = 8.2, 1.0 Hz, 1H, H4), 6.59 (dd, J = 8.3, 0.9 Hz, 1H, H6), 7.09 (t, J = 8.2 Hz, 1H, H5), 7.32 – 7.38 (m, 1H, H4'), 7.38 – 7.44 (m, 2H, H3', H5'), 7.44 – 7.48 (m, 2H, H2', H6') ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 27.7 (t, -CH$_2$-CH=), 70.5 (t, -O-CH$_2$-), 104.9 (d, C6), 109.2 (d, C4), 114.3 (s, C2), 115.6 (t, =CH$_2$), 127.3 (d, 2C, C2', C6'), 127.7 (d, C5), 127.9 (d, C4'), 128.6 (d, 2C, C3', C5'), 136.4 (d, -CH=CH$_2$), 137.4 (s, C1'), 155.3 (s, C1), 157.4 (s, C3) ppm.
HRMS (ESI)	calc. for $C_{16}H_{17}O_2^+$ [M+H]$^+$ 241.1223, found 241.1226 – Δ = 1.22 ppm.

E II.13   4-Allyl-4-(tert-butylperoxy)-2-methoxycyclohexa-2,5-dien-1-one (23)
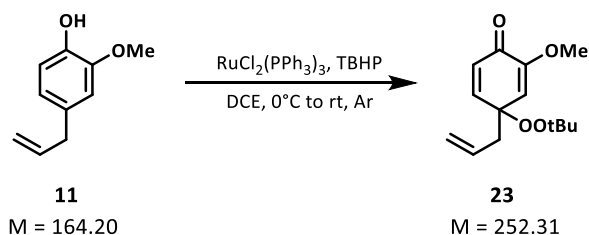
4-Allyl-4-(tert-butylperoxy)-2-methoxycyclohexa-2,5-dien-1-one **23** was synthesized according to a modified literature procedure.[73]

Procedure: An oven-dried, argon flushed screw cap vial was charged with $RuCl_2(PPh_3)_3$ (5.8 mg, 0.006 mmol, 0.4 mol% of Ru) and 3 mL degassed DCE. Then, freshly distilled eugenol **11** (260 μL, 1.50 mmol, 1.00 equiv.) was added at 0 °C to the resulting orange solution, followed by the dropwise addition of aqueous 70% TBHP (2.10 mL, 15.00 mmol, 10.00 equiv.) over a period of 5 min, which led to the formation of a deep green, two-phasic solution. The mixture was stirred for 1 h at 0 °C then it was allowed to warm to room temperature to continue stirring for additional 2 h. During this time a color change from green to orange and a clearing of the opaque solution could be observed.

Work-up: The reaction was diluted with water (20 mL) and CH_2Cl_2 (20 mL). The phases were separated and the aqueous layer was extracted with small portions of CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure leaving crude yellow amorphous solid. This was adsorbed onto Celite and purified by flash chromatography (crude mass/SiO_2 = 1/100) eluting 5:1 to 3:1 to yield 85 mg (22%) of **23** as colorless amorphous solid. Spectral data are in accordance with the literature.[43]

Appearance	colorless amorphous solid
TLC	R_f (LP/EtOAc - 5/1) = 0.49
Yield	83 mg (22%)
Reaction scale	230 mg (1.50 mmol **11**)
Reaction time	3 h
Substrate concentration	0.50 M
Purification	column chromatography 5:1 to 3:1 LP/EtOAc
Molecular formula, m.w.	$C_{14}H_{20}O_3$, 252.31
¹H-NMR (400 MHz, CDCl₃)	δ = 1.19 (s, 9H, -C(CH₃)₃), 2.41 − 2.57 (m, 2H, -<u>CH₂</u>-CH=), 3.67 (s, 3H, -OCH₃), 5.01 − 5.15 (m, 2H, =CH₂), 5.66 (ddt, J = 17.4, 10.1, 7.3 Hz, 1H, -<u>CH</u>=CH₂), 5.71 (d, J = 2.6 Hz, 1H, H3), 6.25 (d, J = 10.1 Hz, 1H, H6), 6.88 (dd, J = 10.1, 2.7 Hz, 1H, H5) ppm.
¹³C-NMR (101 MHz, CDCl₃)	δ = 26.6 (q, 3C, -C(CH₃)₃), 42.1 (t, -<u>CH₂</u>-CH=), 55.1 (q, -OCH₃), 80.2 (s, -C(CH₃)₃ or C4), 80.2 (s, -C(CH₃)₃ or C4), 116.2 (d, -<u>CH</u>=CH₂), 119.9 (t, =CH₂), 128.9 (d, C6), 131.0 (d, C3), 150.5 (d, C5), 151.5 (s, C2), 181.4 (s, C1) ppm.

E II.14   2-Allyl-5-methoxycyclohexa-2,5-diene-1,4-dione (24)

23
M = 252.31

24
M = 178.19
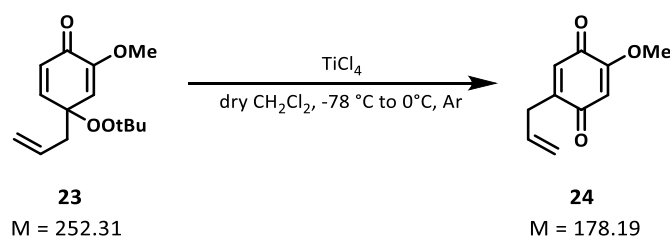
2-Allyl-5-methoxycyclohexa-2,5-diene-1,4-dione **4** was synthesized according to a literature protocol.[43]

Procedure: An oven-dried, argon flushed three-neck round bottom flask was charged with 25 mL dry CH_2Cl_2 and cooled to -78 °C *via* liquid N_2/MeOH-bath. Then, titanium(IV)chloride (118 µL, 1.08 mmol, 1.20 equiv.) was added to the cooled solution in one portion, which led to partial freezing of the Lewis acid on the side of the flask. Further stirring did not improve the dissolution process, therefore peroxide **23** (226 mg, 0.89 mmol, 1.00 equiv.) dissolved in 2 mL dry CH_2Cl_2 was added dropwise to the solution. The reaction was stirred for 30 min at that temperature causing a slow violet color change and was then warmed to 0 °C. The darkened solution was kept at this temperature for 1 h, until full consumption of the starting material was confirmed *via* TLC.

Work-up: The mixture was diluted with CH_2Cl_2 (10 mL) and quenched with saturated aqueous $NaHCO_3$ (6 mL). This resulting suspension was stirred for 30 min and was subsequently filtered through a pad of Celite. The clear yellow solution was directly dried over Na_2SO_4 and the solvent was removed under reduced pressure leaving crude dark-yellow solid that was further purified by column chromatography (crude mass/SiO_2 = 1/40) eluting LP/EtOAc 5:1 to yield 130 mg (81%) of **24** as yellow crystalline solid. Spectral data and melting point are in accordance with the literature.[43]

Appearance	yellow crystalline solid
TLC	R_f (LP/EtOAc - 3/1) = 0.35
Yield	130 mg (81%)
Reaction scale	226 mg (1.50 mmol **23**)
Reaction time	2 h
Substrate concentration	0.03 M
Purification	column chromatography 5:1 LP/EtOAc
Molecular formula, m.w.	$C_{10}H_{10}O_3$, 178.19
M.p.	92 – 93 °C (lit.[43]: 92.5 – 93.5 °C)
¹H-NMR (400 MHz, CDCl₃)	δ = 3.18 (apparent dq, J = 6.8, 1.4 Hz, 2H, -$\underline{CH_2}$-CH=), 3.81 (s, 3H, -OCH₃), 5.10 – 5.23 (m, 2H, =CH₂), 5.80 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H, -$\underline{CH}$=CH₂), 5.93 (s, 1H, H3), 6.50 (t, J = 1.6 Hz, 1H, H6) ppm.

^{13}C-NMR (101 MHz, CDCl$_3$) δ = 33.0 (t, -$\underline{CH_2}$-CH=), 56.4 (q, -OCH$_3$), 107.7 (d, C3), 119.1 (t, =CH$_2$), 131.0 (d, C6), 132.9 (d, -$\underline{CH}$=CH$_2$), 148.7 (s, C5), 158.7 (s, C2), 182.3 (s, C1), 187.1 (s, C4) ppm.

E II.15   4-Allyl-2-methoxyphenyl pivalate (<u>27</u>)
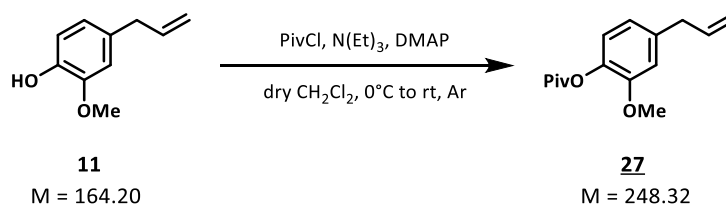
11
M = 164.20

27
M = 248.32

Procedure: An oven-dried, argon flushed three-neck round bottom flask was charged with freshly distilled eugenol **11** (6.06 g, 30.45 mmol, 1.00 equiv.), which was dissolved in 25 mL dry CH$_2$Cl$_2$. The solution was cooled to 0 °C with an ice bath followed by the addition of triethylamine (10.26 mL, 73.81 mmol, 2.00 equiv.) and DMAP (0.49 g, 4.06 mmol, 0.1 equiv.) dissolved in 2 mL dry CH$_2$Cl$_2$. Afterwards pivaloyl chloride (5.00 mL, 40.59 mmol, 1.1 equiv.) dissolved in 3 mL dry CH$_2$Cl$_2$ was added dropwise over a period of 5 min to the light orange solution, which led to the immediate formation of a voluminous colorless precipitate. The mixture was removed from the cooling bath and stirred for additional 2 h at room temperature, until full consumption of the staring material was confirmed *via* TLC.

Work-up: The solvent was removed *in vacuo* and the resulting solids dissolved in Et$_2$O and water. The organic phase was collected and the aqueous phase was extracted three times with small portions of Et$_2$O. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure leaving crude colorless solid product that was further purified by recrystallization from MeOH (5 mL / 1 g) to yield 8.21g (90%) of **27** as colorless crystalline solid.

Appearance	colorless crystalline solid
TLC	**R$_f$** (LP/EtOAc - 10/1) = 0.54
Yield	8.21 g (90%)
Reaction scale	6.06 g (39.91 mmol **11**)
Reaction time	2 h
Substrate concentration	0.46 M
Purification	recrystallization from MeOH
Molecular formula, m.w.	C$_{15}$H$_{20}$O$_3$, 248.32
M.p.	50.0 – 50.5 °C
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 1.36 (s, 9H, -C(CH$_3$)$_3$), 3.37 (dt, J = 6.6, 1.5 Hz, 2H, -$\underline{CH_2}$-CH=), 3.79 (s, 3H, -OCH$_3$), 5.05 – 5.13 (m, 2H, =CH$_2$), 5.96 (ddt, J = 16.9, 10.1, 6.7 Hz, 1H, -$\underline{CH}$=CH$_2$), 6.73 – 6.80 (m, 2H, H3, H5), 6.91 (d, J = 7.8 Hz, 1H, H6) ppm.

^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 27.4 (q, 3C, -C($\underline{CH_3})_3$), 39.2 (s, -$\underline{C}$(CH$_3$)$_3$), 40.2 (t, -$\underline{CH_2}$-CH=), 56.0 (q, -OCH$_3$), 112.9 (d, C3), 116.1 (t, =CH$_2$), 120.8 (d, C5), 122.5 (d, C6), 137.3 (d, -$\underline{CH}$=CH$_2$), 138.6 (s, C1 or C4), 138.7 (s, C1 or C4), 151.1 (s, C2), 177.0 (s, -OCO-) ppm.

E II.16   (4-Allyl-2-methoxyphenoxy)triisopropylsilane (**28**)
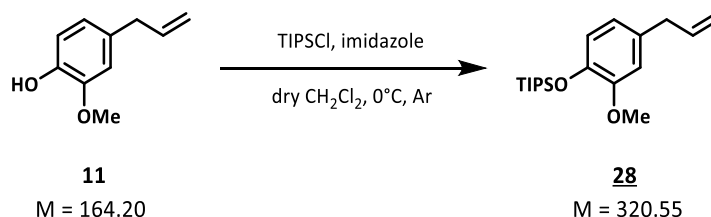
11
M = 164.20

28
M = 320.55

Procedure: An oven-dried, argon flushed three-neck round bottom flask was charged with freshly distilled eugenol **11** (2.00 g, 12.18 mmol, 1.00 equiv.) and dissolved in 25 mL dry CH$_2$Cl$_2$. The solution was cooled to 0 °C with an ice bath followed by the addition of imidazole (1.66 g, 24.36 mmol, 2.00 equiv.) dissolved in 2.5 mL dry CH$_2$Cl$_2$. Afterwards TIPSCl (3.91 mL, 18.27 mmol, 1.50 equiv.) dissolved in 3 mL dry CH$_2$Cl$_2$ was added dropwise over a period of 5 min to the light orange solution, which led to the immediate formation of a voluminous colorless precipitate. The mixture was removed from the cooling bath and stirred for 4 h at room temperature, until full consumption of the staring material was confirmed *via* TLC.

Work-up: The resulting suspension was directly filtered through a cotton plug and the solids were carefully washed with CH$_2$Cl$_2$. After quenching the collected filtrate with saturated aqueous NH$_4$Cl (50 mL), the phases were separated and the aqueous layer was extracted three times with small portions of CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure giving a colorless oil that had a strong TIPSCl smell. To further purify the product the oil was adsorbed onto Celite and flashed over silica (crude mass/SiO$_2$ = 1/60). To remove unreacted silyl species or formed TIPSOTIPS-ether the column was first flushed with pure LP (twice the volume of the column) and then continued to elute the product with LP/EtOAc 50:1 to 40:1 to yield 3.65 g (94%) of **28** as colorless oil.

Appearance	colorless oil
TLC	**R$_f$** (LP/EtOAc - 25/1) = 0.47
Yield	3.65 g (94%)
Reaction scale	2.00 g (12.18 mmol **11**)
Reaction time	4 h
Substrate concentration	0.49 M
Purification	column chromatography LP/EtOAc 50:1 to 40:1
Molecular formula, m.w.	C$_{19}$H$_{32}$O$_2$Si, 320.22

¹H-NMR (400 MHz, CDCl₃) δ = 1.09 (d, J = 7.3 Hz, 18H, TIPS-CH₃), 1.17 − 1.33 (m, 3H, TIPS-CH), 3.32 (dt, J = 6.7, 1.5 Hz, 2H, -C̲H₂-CH=), 3.79 (s, 3H, -OCH₃), 5.00 − 5.10 (m, 2H, =CH₂), 5.89 − 6.04 (m, 1H, -C̲H=CH₂), 6.61 (dd, J = 8.0, 2.0 Hz, 1H, H5), 6.66 (d, J = 2.1 Hz, 1H, H3), 6.79 (d, J = 8.0 Hz, 1H, H6) ppm.

¹³C-NMR (101 MHz, CDCl₃) δ = 13.0 (d, 3C, TIPS-CH), 18.1 (q, 6C, TIPS-CH₃), 40.0 (t, -C̲H₂-CH=), 55.6 (q, -OCH₃), 112.8 (d, C3), 115.5 (t, =CH2), 120.3 (d, C6), 120.6 (d, C5), 133.1 (s, C4), 138.0 (d, -C̲H=CH₂), 143.8 (s, C1), 150.8 (s, C2) ppm.

E II.17   4-Allyl-2-methoxyphenyl 2,4,6-trimethylbenzoate (29)

11
M = 164.20

29
M = 310.39
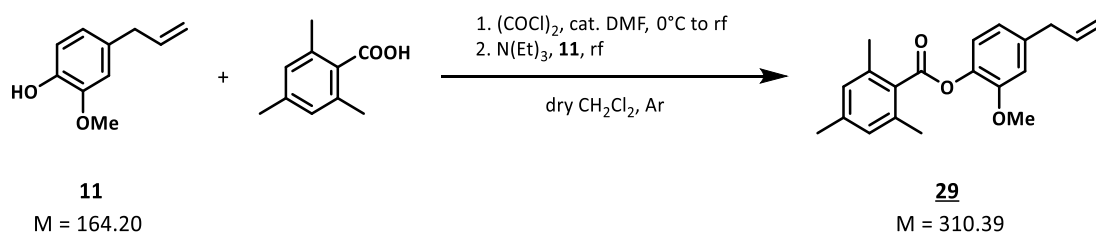
Procedure: An oven-dried, argon flushed three-neck round bottom flask was charged with 2,4,6-trimethylbenzoic acid (4.10 g, 24.97 mmol, 1.00 equiv.) in 100 ml dry CH₂Cl₂. The resulting clear solution was cooled to 0 °C with an ice bath and the whole reaction apparatus was carefully purged with argon. Afterwards 0.1 mL DMF and oxalyl chloride (2.36 g, 27.47 mmol, 1.10 equiv.) were added dropwise over a period of 5 min. The mixture was removed from the cooling bath and stirred for 2 h at room temperature and was then heated to reflux during which an intense yellow color developed. As a reaction control, samples of the reaction mixture were heated in pure MeOH and analyzed *via* TLC until full consumption of the acid was confirmed (TLC stain solution 4). Hence, triethylamine (10.40 mL, 74.91 mmol, 3.00 equiv.) was added, causing a deep red color change followed by the dropwise addition of freshly distilled eugenol **11** (4.25 mL, 27.47 mmol, 1.10 equiv.) over a period of 5 min, causing the formation of voluminous colorless precipitate. The mixture was removed from the cooling bath and stirred at room temperature overnight. For completion of the reaction, the solution was finally heated to reflux for 4 h, until full consumption of the staring material was confirmed *via* TLC.

Work-up: The mixture was diluted with CH₂Cl₂ (100 mL) and quenched with saturated aqueous NaHCO₃ (100 mL). The phases were separated and the aqueous layer was extracted three times with small portions of CH₂Cl₂. The combined organic layers were washed with saturated aqueous NaHCO₃, 1N HCl, brine, dried over Na₂SO₄ and the solvent was removed under reduced pressure leaving a crude brown oil that was further purified by recrystallization from MeOH (5 mL / 1 g) to yield 6.10 g (79%) of **29** as light brown crystalline solid.

Appearance	light brown crystalline solid
TLC	**R$_f$** (LP/EtOAc - 10/1) = 0.45
Yield	6.10 g (79%)

Reaction scale	4.10 g (24.97 mmol 2,4,6-trimethylbenzoic acid)
Reaction time	2 d
Substrate concentration	0.25 M
Purification	recrystallization from MeOH
Molecular formula, m.w.	$C_{20}H_{22}O_3$, 310.39
M.p.	73.9 – 74.2 °C
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 2.32 (s, 3H, p-CH$_3$), 2.50 (s, 6H, 2x o-CH$_3$), 3.42 (dt, J = 6.8, 1.5 Hz, 2H, -CH$_2$-CH=), 3.87 (s, 3H, -OCH$_3$), 5.08 – 5.20 (m, 2H, =CH$_2$), 5.99 (ddt, J = 16.8, 10.0, 6.7 Hz, 1H, -CH=CH$_2$), 6.83 (dd, J = 8.0, 1.9 Hz, 1H, H4), 6.87 (d, J = 1.9 Hz, 1H, H6), 6.92 (s, 2H, H3', H5'), 7.08 (d, J = 8.0 Hz, 1H, H3) ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 20.1 (q, 2C, o-CH$_3$), 21.3 (q, p-CH$_3$), 40.2 (t, -CH$_2$-CH=), 55.8 (q, -OCH$_3$), 112.9 (d, C6), 116.3 (t, =CH$_2$), 120.9 (d, C4), 122.6 (d, C3), 128.7 (d, 2C, C3', C5'), 130.1 (s, C1'), 136.0 (s, 2C, C2', C6'), 137.2 (s, C5), 138.0 (d, -CH=CH$_2$), 139.3 (s, C4'), 139.8 (s, C1), 151.2 (s, C2), 168.1 (s, -COOAr) ppm.
GCMS	t_R = 8.13 min, main fragments 148 (11), 147 (100), 119 (17)
HRMS (ESI)	calc. for $C_{20}H_{23}O_3^+$ [M+H]$^+$ 311.1642, found 311.1640 – Δ = 0.49 ppm.

E II.18   4-Allyl-2-hydroxyphenyl benzoate (<u>30</u>)

12
M = 268.31

30
M = 254.29
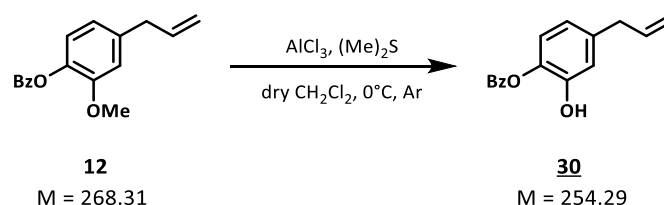
4-Allyl-2-hydroxyphenyl benzoate **30** was synthesized according to a modified literature protocol.[75]

Procedure: An oven-dried, argon flushed three-neck round bottom flask was charged with anhydrous aluminum(III)chloride (6.61 g, 49.57 mmol, 5.00 equiv.) and 60 mL dry CH$_2$Cl$_2$. The yellow suspension was cooled to 0 °C and dimethyl sulfide (3.62 mL, 49.57 mmol, 5.00 equiv.) was added to the mixture causing the yellow solids to quickly dissolve. The solution was stirred for another 15 min at this temperature, following the addition of Bz-eugenol **12** (2.66 g, 9.91 mmol, 1.00 equiv.) dissolved in 25 mL dry CH$_2$Cl$_2$ slowly over a period of 40 min. The reaction was stirred at 0 °C for 1 h and was then allowed to warm to room temperature over the period of 2 h by keeping it in the melting ice bath allowing for a mild temperature gradient. Full consumption of the starting material could be confirmed *via* TLC after a total of 3 h.

Work-up: For the work-up the solution was cooled to 0 °C, diluted with EtOAc (250 mL) and quenched by slow addition of saturated aqueous NH$_4$Cl (100 mL), causing the formation of a voluminous colorless

precipitate. The solids were dissolved by addition of saturated aqueous NH_4Cl, until two clear phases were obtained. These were subsequently separated and the aqueous layer was extracted three times with small portions of EtOAc. The combined organic layers were washed with saturated aqueous NH_4Cl, brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure leaving a green oil with residual colorless solids. The crude material was taken up in CH_2Cl_2 and centrifuged enabling a decantation of the clear solution, which after removal of the solvent yielded 2.28 g (90%) of **30** as slightly greenish oil that crystallized upon standing.

Appearance	light green solid
TLC	R_f (LP/EtOAc – 5/1) = 0.32
Yield	2.28 g (90%)
Reaction scale	2.66 g (10.19 mmol **12**)
Reaction time	4 h
Substrate concentration	0.15 M
Purification	no purification possible – leads to migration of the protecting group
Molecular formula, m.w.	$C_{16}H_{14}O_3$, 254.29
M.p.	58 – 60 °C
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 3.35 (dt, J = 6.8, 1.5 Hz, 2H, -$\underline{CH_2}$-CH=), 5.04 – 5.16 (m, 2H, =CH$_2$), 5.74 (s, 1H, -OH), 5.95 (ddt, J = 16.8, 10.1, 6.7 Hz, 1H, -$\underline{CH}$=CH$_2$), 6.79 (dd, J = 8.2, 2.0 Hz, 1H, H5), 6.91 (d, J = 2.0 Hz, 1H, H3), 7.10 (d, J = 8.2 Hz, 1H, H6), 7.47 – 7.57 (m, 2H, H3', H5'), 7.61 – 7.70 (m, 1H, H4'), 8.17 – 8.25 (m, 2H, H2', H6') ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 39.8 (t, -$\underline{CH_2}$-CH=), 116.3 (t, =CH$_2$), 118.2 (d, C3), 121.3 (d, C5), 122.4 (d, C6), 128.8 (d, 2C, C3', C5'), 129.0 (s, C1'), 130.5 (d, 2C, C2', C6'), 134.1 (d, C4'), 137.1 (d, -$\underline{CH}$=CH$_2$), 137.2 (s, C4), 139.6 (s, C1), 147.2 (s, C2), 165.3 (s, -COO-) ppm.
HRMS (ESI)	calc. for $C_{16}H_{15}O_3^+$ [M+H]$^+$ 254.1016, found 255.1011 – Δ = 1.8 ppm.

E II.19   2,5-Dimethoxyphenyl formate (35)

34
M = 166.18

35
M = 182.18
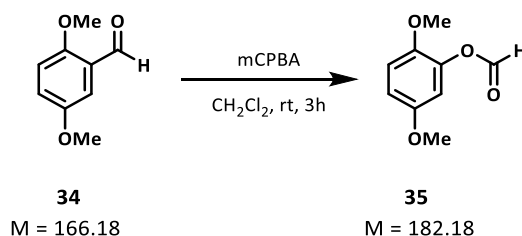
2,5-Dimethoxyphenyl formate **35** was synthesized according to a modified literature protocol.[85]

Procedure: A three-neck round bottom flask was charged with 77% mCPBA (16.86 g, 75.22 mmol, 1.25 equiv.), which was dissolved in 170 mL CH_2Cl_2. 2,5-Dimethoxybenzaldehyde **34** (10.00 g, 60.18 mmol, 1.00 equiv.) dissolved in 35 mL CH_2Cl_2 was then added dropwise over a period of 10 min, to the clear solution, causing a light yellow color change and a slight increase in temperature. A cold water bath was used to keep the the solution at room temperature. The reaction was stirred for 2 h, until full consumption of the starting material was confirmed *via* TLC.

Work-up: The precipitated m-chlorobenzoic acid was removed by filtration and the solution was quenched by the addition of saturated aqueous Na_2SO_3 (100 mL). The phases were separated and the aqueous layer was extracted three times with small portions of CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield 9.65 g (88%) of **35** as orange oil. The resulting material was subjected to the next step without further purification. Spectral data are in accordance with the literature.[98]

Appearance	orange oil
TLC	R_f (LP/EtOAc $-$ 3/1) = 0.49
Yield	9.65 g (88%)
Reaction scale	10.00 g (60.18 mmol **34**)
Reaction time	2 h
Substrate concentration	0.29 M
Purification	product was obtained pure after work-up
Molecular formula, m.w.	$C_9H_{10}O_4$, 182.18
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 3.76 (s, 3H, -OCH$_3$), 3.80 (s, 3H, -OCH$_3$), 6.70 (d, J = 3.0 Hz, 1H, H6), 6.77 (dd, J = 9.0, 3.0 Hz, 1H, H4), 6.93 (d, J = 9.0 Hz, 1H, H3), 8.26 (s, 1H, -OCHO) ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	56.0 (q, -OCH$_3$), 56.7 (q, -OCH$_3$), 109.3 (d, C6), 112.0 (d, C4), 113.7 (d, C3), 139.4 (s, C2), 145.1 (s, C1), 153.9 (s, C5), 159.2 (d, -OCHO) ppm.
GCMS	t_R = 5.01 min, main fragments 182 (16, M$^+$), 154 (27), 139 (100), 111 (68).

E II.20   2,5-Dimethoxyphenol (36)
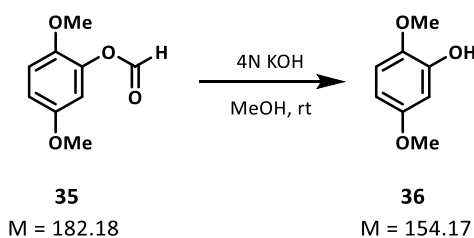

35
M = 182.18

36
M = 154.17

2,5-Dimethoxyphenol **36** was synthesized according to a modified literature protocol.[85]

Procedure: A single-neck round bottom flask was charged with 2,5-dimethoxyphenyl formate **35** (9.86 g, 54.12 mmol, 1.00 equiv.), which was dissolved in 130 mL MeOH, followed by the addition of KOH (3.95 g, 70.36 mmol, 1.30 equiv.) dissolved in 20 mL water, causing immediate darkening of the solution. The reaction was stirred for 15 min, until full consumption of the starting material was confirmed *via* TLC and GCMS.

Work-up: The solvent was removed under reduced pressure leaving a black oily residue that was dissolved under heavy stirring in water (200 mL) and was acidified with conc. HCl (pH < 2). After the addition of CH_2Cl_2 (100 mL) the phases were separated and the aqueous layer was extracted four times with small portions of CH_2Cl_2. The combined organic layers were washed with brine until the washings remained pH neutral, dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield 7.65 g (88%) of **36** as orange oil. The resulting material was subjected to the next step without further purification. Spectral data are in accordance with the literature.[98]

Appearance	orange oil
TLC	R_f (LP/EtOAc – 3/1) = 0.46
Yield	7.65 g (92%)
Reaction scale	9.86 g (54.12 mmol **35**)
Reaction time	15 min
Substrate concentration	0.40 M
Purification	product was obtained pure after work-up
Molecular formula, m.w.	$C_8H_{10}O_3$, 154.17
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 3.75 (s, 3H, -OCH$_3$), 3.84 (s, 3H, -OCH$_3$), 5.68 (s, 1H, -OH), 6.38 (dd, *J* = 8.8, 2.9 Hz, 1H, H4), 6.56 (d, *J* = 2.9 Hz, 1H, H6), 6.77 (d, *J* = 8.8 Hz, 1H, H3) ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 55.8 (q, -OCH$_3$), 56.7 (q, -OCH$_3$), 101.9 (d, C6), 104.4 (d, C4), 111.6 (d, C3), 141.1 (s, C2), 146.5 (s, C1), 154.7 (s, C5) ppm.
GCMS	t_R = 4.58 min, main fragments 154 (34, M$^+$), 139 (69), 111 (100), 69 (23).

E II.21   4-Bromo-2,5-dimethoxyphenol (37)

36
M = 154.17

37
M = 233.06
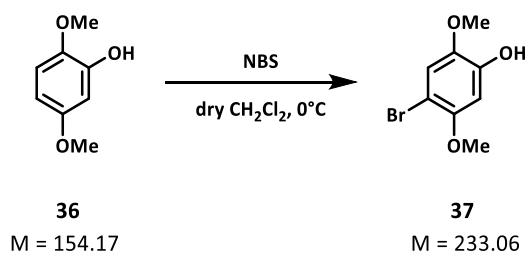
4-Bromo-2,5-dimethoxyphenol **37** was synthesized according to a modified literature protocol.[87]

Procedure: An oven-dried, argon flushed three-neck round bottom flask was charged with 2,5-dimethoxyphenol **36** (5.00 g, 32.43 mmol, 1.00 equiv.), which was dissolved in 60 mL dry CH_2Cl_2. The solution was cooled to 0 °C *via* ice bath followed by the addition of NBS (1.95 g, 10.98 mmol, 1.05 equiv.) in two portions causing an immediate green color change. The mixture was stirred for 10 min, until full consumption of the starting material was confirmed *via* TLC and GCMS.

Work-up: The reaction was quenched by the addition of saturated aqueous Na_2SO_3 (40 mL) at room temperature. The mixture was stirred for 5 min rendering the solution deep orange. The phases were separated and the aqueous layer was extracted twice with small portions of CH_2Cl_2. The combined organic layers were washed with three times with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give a green viscous oil. For further purification the crude material was adsorbed onto Celite and purified by column chromatography (crude mass/SiO_2 = 1/50) eluting LP/EtOAc 3:1 to yield 6.05 g (80%) of **37** as yellow oil that solidified upon standing. Spectral data are in accordance with the literature.[99]

Appearance	yellow solid
TLC	R_f (LP/EtOAc − 5/1) = 0.27
Yield	6.05 g (80%)
Reaction scale	5.00 g (32.43 mmol **36**)
Reaction time	10 min
Substrate concentration	0.54 M
Purification	column chromatography 3:1 LP/EtOAc
Molecular formula, m.w.	$C_8H_9BrO_3$, 233.06
M.p.	68.2 − 68.4 °C
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 3.81 (s, 3H, -OCH$_3$), 3.83 (s, 3H, -OCH$_3$), 5.65 (s, 1H, -OH), 6.61 (s, 1H, H6), 7.02 (s, 1H, H3) ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 56.8 (q, -OCH$_3$), 56.9 (q, -OCH$_3$), 99.9 (s, C4), 100.6 (d, C6), 115.8 (d, C3), 141.0 (s, C2), 145.8 (s, C1), 150.7 (s, C5) ppm.
GCMS	t_R = 5.75 min, main fragments 234 (69, M$^+$), 232 (71, M$^+$), 219 (97), 217 (100), 191 (65), 189 (70).

E II.22   2-(Benzyloxy)-1,4-dimethoxybenzene (38)

36
M = 154.17

38
M = 244.29

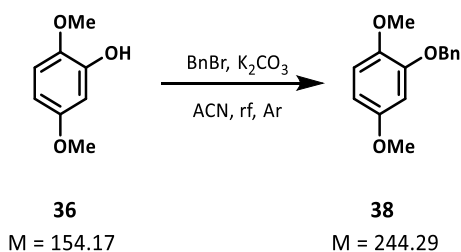2-(Benzyloxy)-1,4-dimethoxybenzene **38** was synthesized according to a literature protocol.[100]

Procedure: An oven-dried, argon flushed three-neck round bottom flask was charged with 2,5-dimethoxyphenol **36** (2.00 g, 12.97 mmol, 1.00 equiv.), K_2CO_3 (4.19 g, 32.43 mmol, 2.50 equiv.), benzyl bromide (2.54 mL, 20,75 mmol, 1.65 equiv.) and 40 mL acetonitrile. The solution was heated to reflux overnight, until full consumption of the starting material was confirmed *via* TLC.

Work-up: The solvent was removed under reduced pressure leaving an orange oily residue that was dissolved with EtOAc and saturated aqueous NH_4Cl. The phases were separated and the aqueous layer was extracted twice with small portions of EtOAc. The combined organic layers were washed with saturated aqueous NH_4Cl, brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give a crude orange oil. For further purification the oil was adsorbed onto Celite and purified by flash chromatography (crude mass/SiO_2 = 1/80) eluting LP/EtOAc 13:1 to 10:1 to yield 3.00 g (95%) of **38** as colorless oil that solidified upon standing. Spectral data and melting point are in accordance with the literature.[100]

Appearance	colorless solid
TLC	R_f (LP/EtOAc – 10/1) = 0.38
Yield	3.00 g (95%)
Reaction scale	2.00 g (23.97 mmol **36**)
Reaction time	1 d
Substrate concentration	0.32 M
Purification	column chromatography 13:1 to 10:1 LP/EtOAc
Molecular formula, m.w.	$C_{15}H_{16}O_3$, 244.29
M.p.	38 – 39 °C (lit. [100]: 36 °C)
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 3.72 (q, 3H, -OCH$_3$), 3.85 (q, 3H, -OCH$_3$), 5.14 (s, 2H, -O-CH$_2$-), 6.42 (dd, J = 8.8, 2.9 Hz, 1H, H5), 6.54 (d, J = 2.8 Hz, 1H, H3), 6.82 (d, J = 8.7 Hz, 1H, H6), 7.27 – 7.33 (m, 1H, H4'), 7.34 – 7.40 (m, 2H, H3', H5'), 7.43 – 7.47 (m, 2H, H2', H6') ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 55.7 (q, -OCH$_3$), 56.9 (q, -OCH$_3$), 71.1 (t, -O-CH$_2$-), 102.7 (d, C3), 103.9 (d, C5), 112.9 (d, C6), 127.4 (d, 2C, C2', C6'), 128.0 (d, C4'), 128.7 (d, 2C, C3', C5'), 137.1 (s, C1'), 144.2 (s, C2), 149.2 (s, C1), 154.2 (s, C5) ppm.

E II.23   1-(Benzyloxy)-4-bromo-2,5-dimethoxybenzene (39)

37
M = 233.06

39
M = 323.19
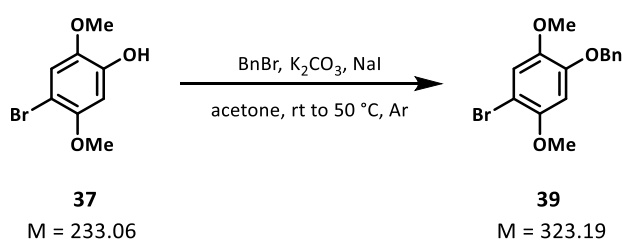
Procedure A: An oven-dried, argon flushed three-neck round bottom flask was charged with 4-bromo-2,5-dimethoxyphenol **37** (4.00 g, 17.16 mmol, 1.00 equiv.), which was dissolved in 30 ml acetone. Then K_2CO_3 (7.12 g, 51.49 mmol, 3.00 equiv.), benzyl bromide (2.65 mL, 22.31 mmol, 1.30 equiv.) and NaI (256 mg, 1.72 mmol, 0.10 equiv.) was added, which caused an immeditate red discoloring. Since the starting material exhibited definite decomposition on TLC, the solution was stirred only at room temperature overnight. However, for completion of the reaction the reaction was heated to 50 °C for 3 h, until full consumption of the starting material was confirmed *via* TLC and GC-MS.

Work-up: The reaction was filtered through a Buchner funnel and the solvent was directly removed under reduced pressure to leave an orange, cloudy oil. For further purification the crude material was adsorbed onto Celite and purified by flash chromatography (crude mass/SiO_2 = 1/100) eluting LP/EtOAc 10:1 to 8:1 to yield 0.75 g (14%) of **39** as colorless oil that solidified upon standing.

38
M = 244.29

39
M = 323.19
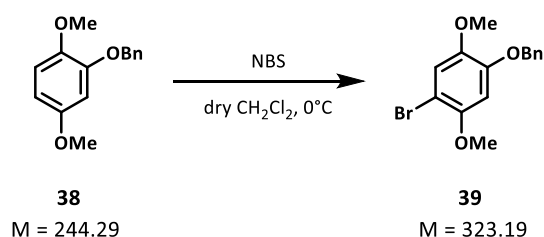
1-(Benzyloxy)-4-bromo-2,5-dimethoxybenzene **39** was synthesized according to a modified literature protocol.[87]

Procedure B: An oven-dried, argon flushed three-neck round bottom flask was charged with 2-(benzyloxy)-1,4-dimethoxybenzene **38** (2.55 g, 10.46 mmol, 1.00 equiv.), which was dissolved in 20 mL dry CH_2Cl_2. The solution was cooled to 0 °C with an ice bath followed by the addition of NBS (1.95 g, 10.98 mmol, 1.05 equiv.) in one portion. The resulting colorless suspension was removed from the cooling bath and allowed to warm to room temperature, which caused immediate dissolution of NBS by subsequent precipitation of a colorless solid. The mixture was stirred for 10 min, until full consumption of the starting material was confirmed *via* TLC and GCMS.

Work-up: The reaction was quenched by the addition of saturated aqueous Na_2SO_3 (40 mL) at room temperature and was then stirred at this temperature for another 5 min. The phases were separated and the aqueous layer was extracted twice with small portions of CH_2Cl_2. The combined organic layers were washed twice with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to give a light yellow oil that solidified upon standing. For further purification the crude material was adsorbed onto Celite and purified by flash chromatography (crude mass/SiO_2 = 1/100) eluting LP/EtOAc 8:1 to yield 3.07 g (91%) of **39** as colorless oil that solidified upon standing.

Spectral data are in accordance with the literature.[101]

**Appearance**   colorless solid

TLC	R_f (LP/EtOAc – 10/1) = 0.34
Yield	procedure A: 0.75 g (14%); procedure B: 3.07 g (91%)
Reaction scale	procedure A: 4.00 g (14.16 mmol **37**); procedure B: 2.55 g (10.46 mmol **38**)
Reaction time	procedure A: 2 d; procedure B: 10 min
Substrate concentration	procedure A: 0.57 M**;** procedure B: 0.52 M
Purification	column chromatography 8:1 LP/EtOAc
Molecular formula, m.w.	$C_{15}H_{15}BrO_3$, 323.19
M.p.	100.2 – 100.4 °C
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 3.73 (s, 3H, -OCH$_3$), 3.80 (s, 3H, -OCH$_3$), 5.12 (s, 2H, -O-CH$_2$-), 6.56 (s, 1H, H6), 7.06 (s, 1H, H3), 7.28 – 7.33 (m, 1H, H4'), 7.34 – 7.39 (m, 2H, H3', H5'), 7.41 – 7.47 (m, 2H, H2', H6') ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 56.6 (q, -OCH$_3$), 56.8 (q, -OCH$_3$), 71.5 (t, -O-CH$_2$-), 101.5 (d, C6), 101.6 (s, C4), 117.0 (d, C3), 127.3 (d, 2C, C2', C6'), 128.0 (d, C4'), 128.5 (d, 2C, C3', C5'), 136.6 (s, C1'), 144.4 (s, C2), 148.0 (s, C1), 150.0 (s, C5) ppm.
GCMS	t_R = 7.74 min, main fragments 324 (3, M$^+$), 322 (3, M$^+$), 92 (8), 91 (100), 65 (8).

E II.24   1-Allyl-4-(benzyloxy)-2,5-dimethoxybenzene (<u>40</u>)

39
M = 323.19

40
M = 284.36
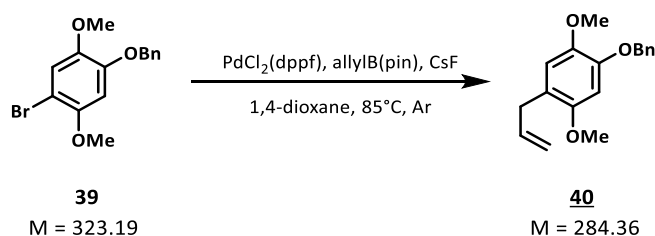
1-Allyl-4-(benzyloxy)-2,5-dimethoxybenzene **40** was synthesized according to a modified literature protocol.[88]

Procedure: An oven-dried, argon flushed three-neck round bottom flask equipped with thermometer and balloon was charged with 1-(benzyloxy)-4-bromo-2,5-dimethoxybenzene **39** (2.50 g, 7.74 mmol, 1.00 equiv.), which was dissolved with 125 mL dry, degassed 1,4-dioxane. The solvent was degassed by slowly bubbling argon through the liquid for 4 h. Then, CsF (5.60 g, 36.89 mmol, 4.77 equiv.) and Pd(dppf)Cl$_2$·CH$_2$Cl$_2$ (0.63 g, 0.77 mmol, 0.10 equiv.) was added to the clear solution. The suspension was stirred for 5 min allowing the catalyst to partially dissolve, followed by the dropwise addition allylboronic acid pinacol ester (3.45 mL, 18.41 mmol, 2.38 equiv.) over a period of 2 min. The solution was then heated to 85 °C under argon and stirred for 1 hour. During this time the suspension started to partially clear up, resulting in a less cloudy red solution, which after heating for another 3 h turned into a bright orange viscous slurry. At this point another portion of Pd(dppf)Cl$_2$·CH$_2$Cl$_2$ (0.63 g, 0.77 mmol, 0.10 equiv.) was

added and the suspension was stirred overnight, after which possible darkening and decomposition of the catalyst might occur. For completion of the reaction, another portion of allylboronic acid pinacol ester (0.86 mL, 4.60 mmol, 0.60 equiv.) was added and the suspension was heated to 85 °C for additional 2 h, until full consumption of the starting material was confirmed *via* TLC.

Work-up: The solvent was removed in *vacuo* and the resulting dark dry residue was filtered through a short pad of silica (40 g) with CH_2Cl_2 as eluent, giving a light yellow oil that solidified upon standing. For further purification the crude material was adsorbed onto Celite and purified by flash chromatography (crude mass/SiO_2 = 1/100) eluting LP/EtOAc 20:1 to 10:1 to yield 1.93 g (88%) of **40** as colorless oil that crystallized upon standing.

Appearance	colorless crystalline solid
TLC	R_f (LP/EtOAc – 51) = 0.62
Yield	1.93 g (88%)
Reaction scale	2.50 g (7.74 mmol **39**)
Reaction time	1 d
Substrate concentration	0.06 M
Purification	column chromatography 20:1 to 10:1 LP/EtOAc
Molecular formula, m.w.	$C_{18}H_{20}O_3$, 284.36
M.p.	69.9 – 70.2 °C
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 3.31 (dt, J = 6.5, 1.5 Hz, 2H, -$\underline{CH_2}$-CH=), 3.69 (s, 3H, -OCH$_3$), 3.84 (s, 3H, -OCH$_3$), 4.99 – 5.09 (m, 2H, =CH$_2$), 5.14 (s, 2H, -O-CH$_2$-), 5.96 (ddt, J = 15.6, 10.7, 6.5 Hz, 1H, -$\underline{CH}$=CH$_2$), 6.53 (s, 1H, H3), 6.72 (s, 1H, H6), 7.26 – 7.35 (m, 1H, H4'), 7.33 – 7.42 (m, 2H, H3', H5'), 7.41 – 7.49 (m, 2H, H2', H6') ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 33.8 (t, -$\underline{CH_2}$-CH=), 56.5 (q, -OCH$_3$), 57.0 (q, -OCH$_3$), 72.0 (t, -O-CH$_2$-), 101.2 (d, C3), 114.9 (d, C6), 115.4 (t, =CH$_2$), 121.1 (s, C1), 127.5 (d, 2C, C2', C6'), 128.0 (d, C4'), 128.7 (d, 2C, C3', C5'), 137.3 (d, -$\underline{CH}$=CH$_2$), 137.5 (s, C1'), 143.9 (s, C5), 147.2 (s, C4), 151.3 (s, C2) ppm.
GCMS	t_R = 7.48 min, main fragments 284 (13, M$^+$), 193 (25), 165 (19), 91 (100), 65 (18).
HRMS (ESI)	calc. for $C_{18}H_{21}O_3^+$ [M+H]$^+$ 285.1485, found 285.1484 – Δ = 0.25 ppm.

E II.25   2-Allyl-5-(benzyloxy)cyclohexa-2,5-diene-1,4-dione (2)

40
M = 284.36

2
M = 254.29
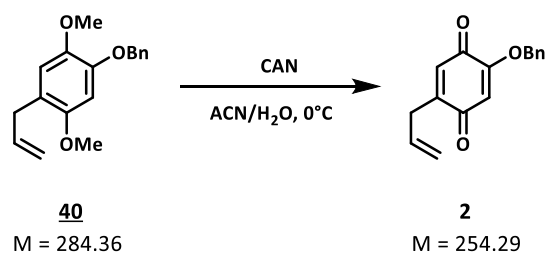
2-Allyl-5-(benzyloxy)cyclohexa-2,5-diene-1,4-dione **2** was synthesized from **40** according to a modified literature protocol.[85]

Procedure A: A single-neck round bottom flask was charged with 1-allyl-4-(benzyloxy)-2,5-dimethoxybenzene **40** (1.26 g, 4.43 mmol, 1.00 equiv.), which was dissolved in 55 mL 4:1 mixture ACN/water. Solid CAN (4.86 g, 8.86 mmol, 2.00 equiv.) was subsequently added to the slightly cloudy mixture in small portions at 0 °C, which caused immediate darkening of the solution. The reaction was stirred for 30 min at this temperature, until full consumption of the starting material was confirmed *via* TLC.

Work-up: The solution was diluted with CH_2Cl_2 (100 mL) and water (100 mL). The phases were separated and the aqueous layer was extracted twice with small portions of CH_2Cl_2. The combined organic layers were washed twice with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to leave an orange oil. For further purification the crude material was adsorbed onto Celite and purified by flash chromatography (crude mass/SiO_2 = 1/100) eluting LP/EtOAc 7.5:1 to 6:1 to yield 0.36 g (32%) of **2** as yellow crystalline solid.

As a second possibility 2-allyl-5-(benzyloxy)cyclohexa-2,5-diene-1,4-dione **2** was synthesized according to a different modified literature protocol starting from 2-allyl-5-(benzyloxy)phenol **21**.[32]

21
M = 240.13

2
M = 254.29
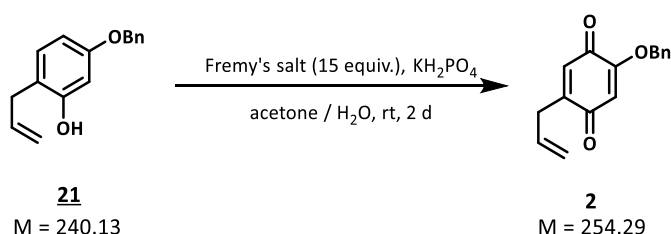
Procedure B: A single-neck round bottom flask was charged with Fremy's salt **VIII** (279 mg, 1.04 mmol, 5.00 equiv.), which was dissolved in 20 mL 0.14 M KH_2PO_4 buffer at room temperature resulting in a deep violet solution. Subsequently, 2-allyl-5-(benzyloxy)phenol **21** (50 mg, 0.21 mmol, 1.00 equiv.) dissolved in 20 ml acetone was added dropwise over a period of 5 min, which led to partial precipitation of **VIII**. Therefore additional water (10 mL) was used to achieve homogeneity of the solution. The reaction was then stirred until no violet color was evident, indicating full consumption of the oxidizing agent. Therefore

another portion of the Fremy's salt **VIII** (279 mg, 1.04 mmol, 5.00 equiv.) was added with 7 mL buffer and the solution was stirred overnight. The addition of the reagent was repeated once more on the next day and the solution was stirred, until full consumption of the starting material was confirmed *via* TLC and GCMS after totaling a time of 2 days.

Work-up: The solution was directly extracted three times with small portions of EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure leaving a yellow amorphous solid. For further purification the crude material was purified by flash chromatography (crude mass/SiO_2 = 1/50) eluting LP/EtOAc 7:1 to yield 32 mg (60%) of **2** as yellow crystalline solid.

Spectral data and melting point are in accordance with the literature.[32]

Appearance	yellow crystalline solid
TLC	R_f (LP/EtOAc – 5/1) = 0.40
Yield	procedure A: 0.36 g (32%); procedure B: 32 mg (60%)
Reaction scale	procedure A: 1.26 g (4.43 mmol **40**); procedure B: 50 mg (0.21 mmol **21**)
Reaction time	procedure A: 30 min; procedure B: 24 h
Substrate concentration	procedure A: 0.08 M; procedure B: 0.006 M
Purification	column chromatography 7.5:1 to 6:1 LP/EtOAc
Molecular formula, m.w.	$C_{16}H_{14}O_3$, 254.29
M.p.	96.5 – 97.5 °C (lit.[32]: 96 – 97 °C)
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 3.17 (apparent dq, J = 6.8, 1.4 Hz, 2H, -<u>CH$_2$</u>-CH=), 5.03 (s, 2H, -O-CH$_2$-Ar'), 5.10 – 5.23 (m, 2H, =CH$_2$), 5.80 (ddt, J = 17.0, 10.1, 6.8 Hz, 1H, -<u>CH</u>=CH$_2$), 5.98 (s, 1H, H6), 6.51 (t, J = 1.6 Hz, 1H, H3), 7.32 – 7.42 (m, 5H, H2'-H6') ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 33.0 (t, -<u>CH$_2$</u>-CH=), 71.1 (t, -O-CH$_2$-Ar'), 109.0 (d, C6), 119.1 (t, =CH$_2$), 127.7 (d, 2C, C2', C6'), 128.9 (d, C4'), 129.0 (d, 2C, C3', C5'), 131.1 (d, C3), 132.9 (d, -<u>CH</u>=CH$_2$), 134.2 (s, C1'), 148.4 (s, C2), 157.6 (s, C5), 182.2 (s, C4), 187.2 (s, C1) ppm
GCMS	t_R = 7.49 min, main fragments 254 (2, M$^+$), 239 (2), 92 (10), 91 (100), 69 (12).
HRMS (ESI)	calc. for $C_{16}H_{15}O_3^+$ [M+H]$^+$ 255.1016, found 255.1021 – Δ = 2.06 ppm.

E II.26   (2S*,3S*,3aR*)-3a-Allyl-2-(3,4-dimethoxyphenyl)-5-hydroxy-3-methyl-3,3a-dihydrobenzofuran-6(2H)-one (100/101)
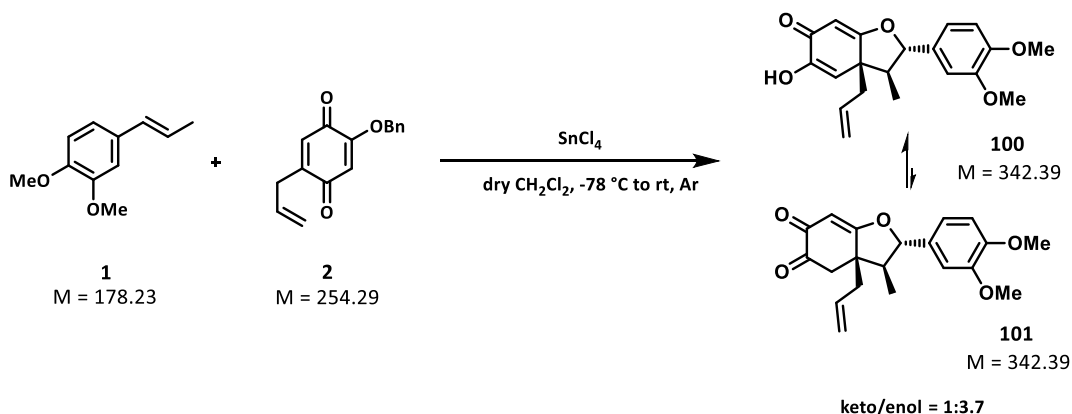
The Lewis acid assisted [2+5]-cycloaddition was done according to a literature protocol by Engler et. al.[32]

Procedure: A oven dried, argon flushed single-neck round bottom flask was charged with 2-allyl-5-(benzyloxy)cyclohexa-2,5-diene-1,4-dione **2** (200 mg, 0.79 mmol, 1.00 equiv.), which was dissolved in 13.5 mL dry CH_2Cl_2. The solution was cooled to -80 °C *via* LN/MeOH bath and stirred for 10 min at this temperature, followed by the dropwise addition of tin(IV)chloride (92 μL, 0.79 mmol, 1.00 equiv.) causing the yellow solution to darken and minor formation of reddish solids on the wall of the vial. After stirring the mixture for 15 min, (E)-methylisoeugenol **1** (187 μL, 1.10 mmol, 1,40 equiv.) was added slowly over a period of 2 min. The reaction was stirred for 3 h in a temperature range between -80 °C and -65 °C, during which the mixture turned gradually red and was then allowed to warm to room temperature over a period of 4 h.

Work-up: The now dark orange suspension was then cooled to 0 °C and quenched with the addition of solid $NaHCO_3$ (2 g) followed by iPrOH (10 mL). The mixture was diluted with water (50 mL) causing the formation of a voluminous precipitate. The cloudy solution was filtered through a large pad of Celite and was then extracted three times with small portions of CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure leaving a yellow viscous oil that was further purified by flash chromatography eluting n-hexane/EtOAc 2:1 to 1:1 to yield 90 mg (33%) of **100/101** as a mixture of off-white amorphous solid keto-enol-tautomers (keto/enol = 1:3.7) and 26 mg (10%) of __102__ as a colorless amorphous solid side product.

Main products from the [2+5] cycloaddition (**100/101**):

Appearance	off-white amorphous solid
TLC	R_f (LP/EtOAc − 1/1) = 0.44
Yield	90 mg (33%)
Reaction scale	200 mg (0.79 mmol **2**)

Reaction time	7 h
Substrate concentration	0.06 M
Purification	column chromatography 2:1 to 1:1 n-hexane/EtOAc
Molecular formula, m.w.	$C_{20}H_{22}O_5$, 342.39
^{1}H-NMR (400 MHz, CDCl$_3$)	Keto-tautomer signals were omitted due to unfavorable keto-enol ratio
	δ = 1.11 (d, J = 6.9 Hz, 3H, -CH$_3$), 2.26 – 2.40 (m, 2H, H3, -CH$_2$-CH=), 2.53 (dd, J = 13.1, 7.3 Hz, 1H, -CH$_2$-CH=), 3.85 (s, 3H, -OCH$_3$), 3.86 (s, 3H, -OCH$_3$), 4.95 – 5.10 (m, 2H, =CH$_2$), 5.22 (d, J = 10.0 Hz, 1H, H2), 5.51 (ddt, J = 17.3, 10.1, 7.3 Hz, 1H, -CH=CH$_2$), 5.73 (s, 1H, H4 or H7), 5.82 (s, 1H, H4 or H7), 6.72 (s, 1H, -OH), 6.73 (d, J = 1.1 Hz, 1H, H6'), 6.84 (d, J = 1.2 Hz, 2H, H2', H5') ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 8.4 (q, -CH$_3$), 36.4 (t, -CH$_2$-CH=), 49.2 (d, C3), 51.8 (s, C3a), 56.0 (q, -OCH$_3$), 56.0 (q, -OCH$_3$), 91.6 (d, C2), 100.0 (d, C4 or C7), 108.3 (d, C4 or C7), 109.4 (d, C6'), 111.1 (d, C2' or C5'), 119.6 (d, C2' or C5'), 120.1 (t, =CH$_2$), 129.8 (s, C1'), 130.8 (d, -CH=CH$_2$), 148.5 (s, C5 or C3' or C4'), 149.4 (s, C5 or C3' or C4'), 149.9 (s, C5 or C3' or C4'), 183.3 (s, C6 or C7a), 184.5 (s, C6 or C7a) ppm.
HRMS (ESI)	**100:** calc. for $C_{20}H_{23}O_5^+$ [M+H]$^+$ 342.1540, found 342.1555 – Δ = 4.51 ppm.
	101: calc. for $C_{20}H_{23}O_5^+$ [M+H]$^+$ 342.1540, found 342.1554 – Δ = 3.91 ppm.

E II.27   (1R*,6S*,7R*,8R*)-1-Allyl-7-(3,4-dimethoxyphenyl)-4-hydroxy-8-methylbicyclo[4.2.0]oct-3-ene-2,5-dione (102)

A second product that emerged from the [2+5]-cycloaddition was cyclobutane **102**.
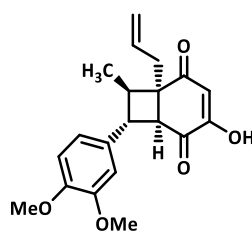
102
M = 342.39

Appearance	colorless amorphous solid
TLC	**R$_f$** (LP/EtOAc – 1/1) = 0.68
Yield	26 mg (10 %)

Molecular formula, m.w.	$C_{20}H_{22}O_5$, 342.39
^{1}H-NMR (400 MHz, CDCl$_3$)	δ = 1.15 (d, J = 7.0 Hz, 3H, -CH$_3$), 2.42 (ddt, J = 14.7, 7.1, 1.3 Hz, 1H, -C<u>H$_2$</u>-CH=), 2.51 – 2.66 (m, 2H, H8, -<u>CH$_2$</u>-CH=), 3.16 (dd, J = 7.6, 5.6 Hz, 1H, H7), 3.80 (d, J = 7.6 Hz, 1H, H6), 3.82 (s, 3H, -OCH$_3$), 3.83 (s, 3H, -OCH$_3$), 5.21 – 5.33 (m, 2H, =CH$_2$), 5.83 (s, 1H, -OH), 5.92 (ddt, J = 17.2, 10.1, 7.1 Hz, 1H, -<u>CH</u>=CH$_2$), 6.55 (d, J = 2.2 Hz, 1H, H5'), 6.61 (s, 1H, H3), 6.62 (dd, J = 8.3, 2.2 Hz, 1H, H6'), 6.76 (d, J = 8.3 Hz, 1H, H2') ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 18.1 (q, -CH$_3$), 32.5 (t, -<u>CH$_2$</u>-CH=), 44.7 (d, C8), 49.7 (d, C7), 55.7 (s, C1), 55.9 (q, -OCH$_3$), 55.9 (q, -OCH$_3$), 67.6 (d, C6), 111.3 (d, C2'), 111.5 (d, C5'), 119.9 (t, =CH$_2$), 120.5 (d, C3'), 123.7 (d, C3), 130.4 (s, C1'), 133.0 (d, -<u>CH</u>=CH$_2$), 148.6 (s, C4 or C3' or C4'), 149.1 (s, C4 or C3' or C4'), 149.3 (s, C4 or C3' or C4'), 191.7 (s, C5), 201.0 (s, C2) ppm.

E II.28   [2S*,3S*,3aR*]-3a-Allyl-2-(3,4-dimethoxyphenyl)-5-methoxy-3-methyl-3,3a-dihydrobenzofuran-6(2H)-one – (±)-Kadsurenin F (104)
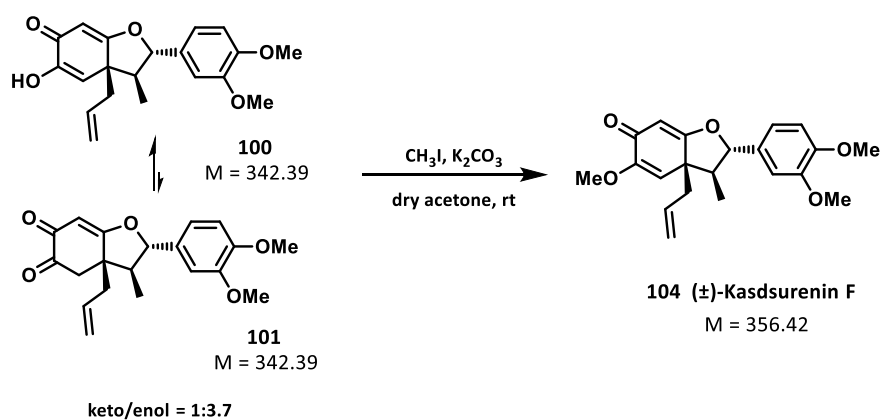
The procedure was conducted according to a literature protocol.[32]

Procedure: An oven-dried, argon flushed, screw cap vial was charged with keto-enol tautomer **100/101** (40 mg, 0.12 mmol, 1.00 equiv.), which was dissolved in 1 mL dry acetone. Following the addition of K$_2$CO$_3$ (161 mg, 1.17 mmol, 10.00 equiv.) and methyl iodide (145 µl, 2.34 mmol, 20.00 equiv.) the vial was tightly capped and the suspension was stirred for 2 d at room temperature, until full consumption of the starting material was confirmed *via* TLC.

Work-up: The yellow suspension was filtered through a pad of Celite and the solvent as well as unreacted methyl iodide was removed by reduced pressure to leave a yellow solid residue. Further purification was done by flash chromatography eluting LP/EtOAc 1:1 to 2:1 to yield 30 mg (71%) **104 (±)-Kadsurenin F** as colorless amorphous solid. Spectral data are in accordance with the literature.[102]

Appearance	colorless amorphous solid
TLC	R_f (LP/EtOAc − 1/2) = 0.31
Yield	30 mg (71%)
Reaction scale	40 mg (0.79 mmol **100/101**)
Reaction time	2 d
Substrate concentration	0.12 M
Purification	column chromatography 1:1 to 1:2 LP/EtOAc
Molecular formula, m.w.	$C_{21}H_{24}O_5$, 356.42
^{1}H-NMR (600 MHz, CDCl$_3$)	δ = 1.14 (d, J = 6.9 Hz, 3H, -CH$_3$), 2.27 − 2.33 (m, 1H, H3), 2.33 (dd, J = 13.2, 7.3 Hz, 1H, -C̲H̲$_2$-CH=), 2.55 (dd, J = 13.4, 7.0 Hz, 1H, -C̲H̲$_2$-CH=), 3.67 (s, 3H, -OCH$_3$), 3.87 (s, 3H, Ar-OCH$_3$), 3.87 (s, 3H, Ar-OCH$_3$), 4.99 (apparent dq, J = 16.9, 1.4 Hz, 1H, =CH$_2$^{trans}), 5.07 (ddt, J = 10.0, 1.7, 0.8 Hz, 1H, =CH$_2$^{cis}), 5.20 (d, J = 9.9 Hz, 1H, H2), 5.42 (s, 1H, H4), 5.53 (ddt, J = 17.2, 10.0, 7.2 Hz, 1H, -C̲H̲=CH$_2$), 5.79 (s, 1H, H7), 6.75 (s, 1H, Ar-H), 6.85 (s, 1H, Ar-H), 6.85 (s, 1H, Ar-H) ppm.
^{13}C-NMR (101 MHz, CDCl$_3$)	δ = 8.6 (q, -CH$_3$), 36.8 (t, -C̲H̲$_2$-CH=), 49.5 (d, C3), 51.2 (s, C3a), 55.5 (q, -OCH$_3$), 56.1 (q, Ar-OCH$_3$), 56.1 (q, Ar-OCH$_3$), 91.3 (d, C2), 102.2 (d, C7), 108.0 (d, C4), 109.3 (d, C2'), 111.1 (d, C5'), 119.6 (d, C6'), 120.2 (t, =CH$_2$), 130.1 (s, C1'), 131.1 (d, -C̲H̲=CH$_2$), 149.5 (s, C3' or C4'), 149.9 (s, C3' or C4'), 153.6 (s, C5), 181.6 (s, C7a), 183.0 (s, C6) ppm.
HRMS (ESI)	calc. for $C_{21}H_{25}O_5^+$ [M+H]$^+$ 357.1697, found 357.1713 − Δ = 4.64 ppm.

proton	1	this thesis
2	5.21 (d)	5.20 (d)
3	2.31 (dq)	2.30 (m)
4	5.43 (s)	5.42 (s)
7	5.81 (s)	5.79 (s)
CH3	1.16 (d)	1.14 (d)
OCH3	3.69 (s)	3.67 (s)
Ar-OCH3	3.89 (s)	3.87 (s)
Ar-OCH3	3.89 (s)	3.87 (s)
2'	6.77 (s)	6.75 (s)
5'	or	or
6'	6.87 (s)	6.85 (s)
-CH2-	2.35 (dd)	2.33 (dd)
-CH2-	2.57 (dd)	2.55 (dd)
-CH=	5.56 (m)	5.53 (ddt)
=CH2	5.03 (dd)	4.99 (dq)
=CH2	5.09 (dd)	5.07 (ddt)

^{1}H-NMR shifts [ppm] [multiplicity] referenced to CDCl$_3$

carbon	1	2	this thesis
2	91.0	91.2	91.3
3	49.3	49.4	49.5
3a	51.0	51.0	51.2
4	107.8	107.9	108.0
5	153.3	153.5	153.6
6	182.6	182.9	193.0
7	101.9	102.1	102.2
7a	181.3	181.5	181.6
CH3	8.5	8.4	8.6
OCH3	55.2	55.3	55.5
1'	129.8	130.0	130.1
2'	109.1	109.3	109.4
3'	149.6	149.8	149.5
4'	149.2	149.4	149.9
5'	110.9	111.0	111.1
6'	119.3	119.5	119.6
-CH2-	36.7	36.7	36.8
-CH=	119.9	120.0	120.2
=CH2	130.7	130.9	131.1

^{13}C-NMR shifts [ppm] referenced to CDCl$_3$

Figure E-1: Comparison of NMR-data with reported literature **1**[32](synthetic Kadsurenin F), **2**[102] (naturally isolated Kadsurenin F)

F   Appendix

F I   List of abbreviations

[hmim]Br	1-butyl-3-methylimidazolium bromide
ACN	acetonitrile
allylB(pin)	allylboronic acid pinacol ester
APR	acute phase response
Bn	benzyl
Bz	benzoyl
CAN	ceric ammonium nitrate
CD	Crohn's disease
CED	Chronisch entzündliche Darmerkrankung
conc.	concentrated
DCE	1,2-dichloroethane
DIBAL-H	diisobutylaluminium hydride
DIR	dirigent protein
DMAP	4-(dimethylamino)-pyridine
DMF	dimethylformamide
DMS	dimethyl sulfate
DMSO	dimethyl sulfoxide
DNA/RNA	deoxyribonucleic acid / ribonucleic acid
EtOAc	ethyl acetate
IBD	inflammatory bowel disease
IL	interleukin
LAH	lithium aluminum hydride
LN	liquid nitrogen
LP	light petroleum (boiling point approx. 40 – 60 °C)
LPS	lipopolysaccharide
M.p.	melting point
m.w.	molecular weight
MCP-1	monocyte chemoattractant protein-1
mCPBA	meta-chloroperoxybenzoic acid
Ms/Ts	mesyl (methanesulfonyl) / tosyl (toluenesulfonyl)
NBS	N-bromosuccinimide
NF-κB	nuclear factor-kappaB
NMR	nuclear magnetic resonance
OTf	triflyl
PAMP	pathogen-associated molecular pattern
PG / LG	protecting group, leaving group
Piv	pivaloyl
PRR	pattern recognition receptors
quant.	quantitative
ROS/RNS	reactive oxygen species / reactive nitrogen species
TBHP	tert-butyl hydroperoxide
THF	tetrahydrofuran
TIPS	triisopropylsilyl ether
TLC	thin layer chromatography
TLR	toll-like receptor
TMS	trimethylsilyl, tetramethylsilane
TNFa	tumor necrosis factor alpha
TR	thermal runaway
UC	ulcerative colitis

F II   NMR spectra of synthetic (±)-Kadsurenin
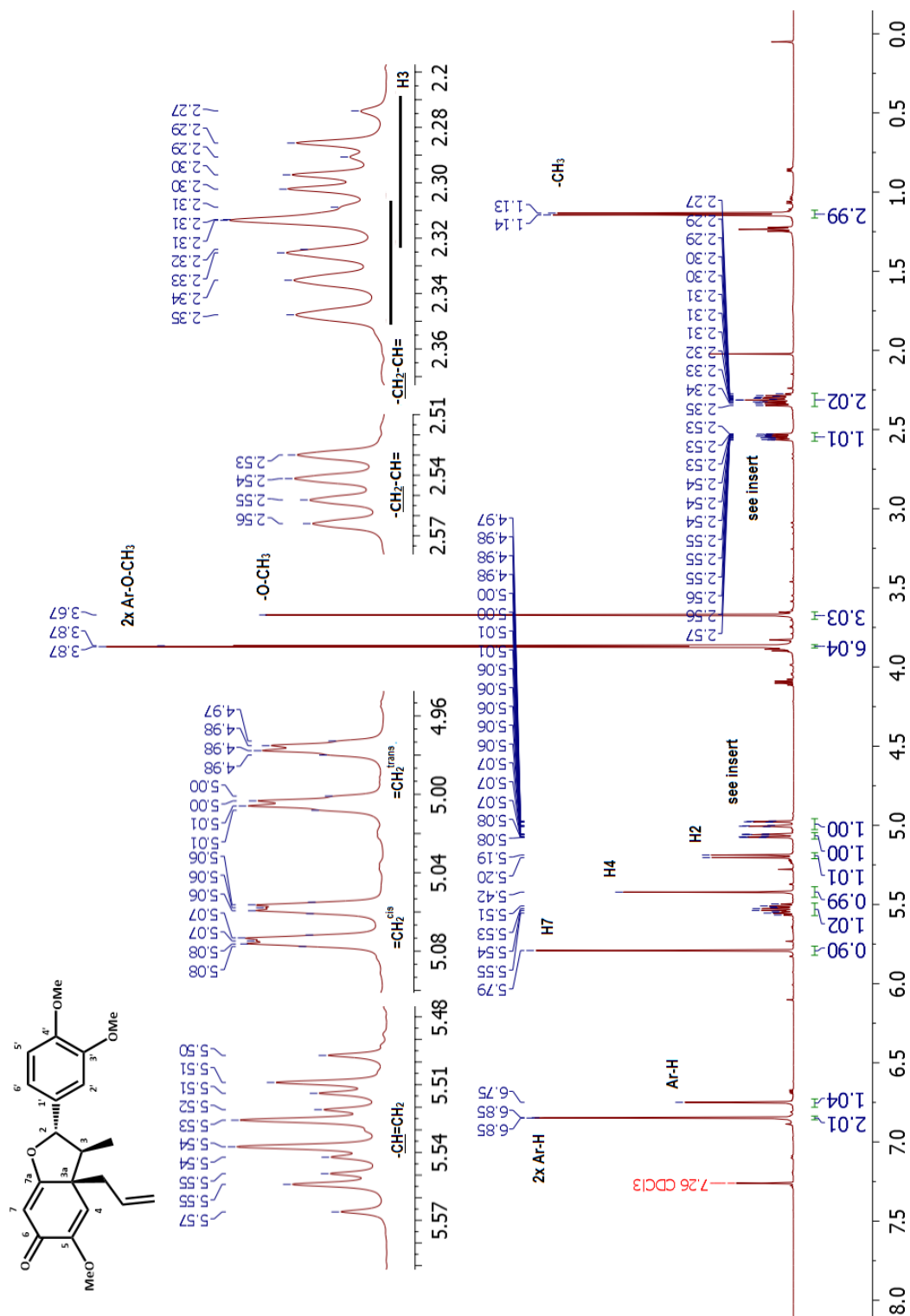
Figure F-1: ^{1}H-NMR (600 MHz, CDCl$_3$) of (±)-Kadsurenin F
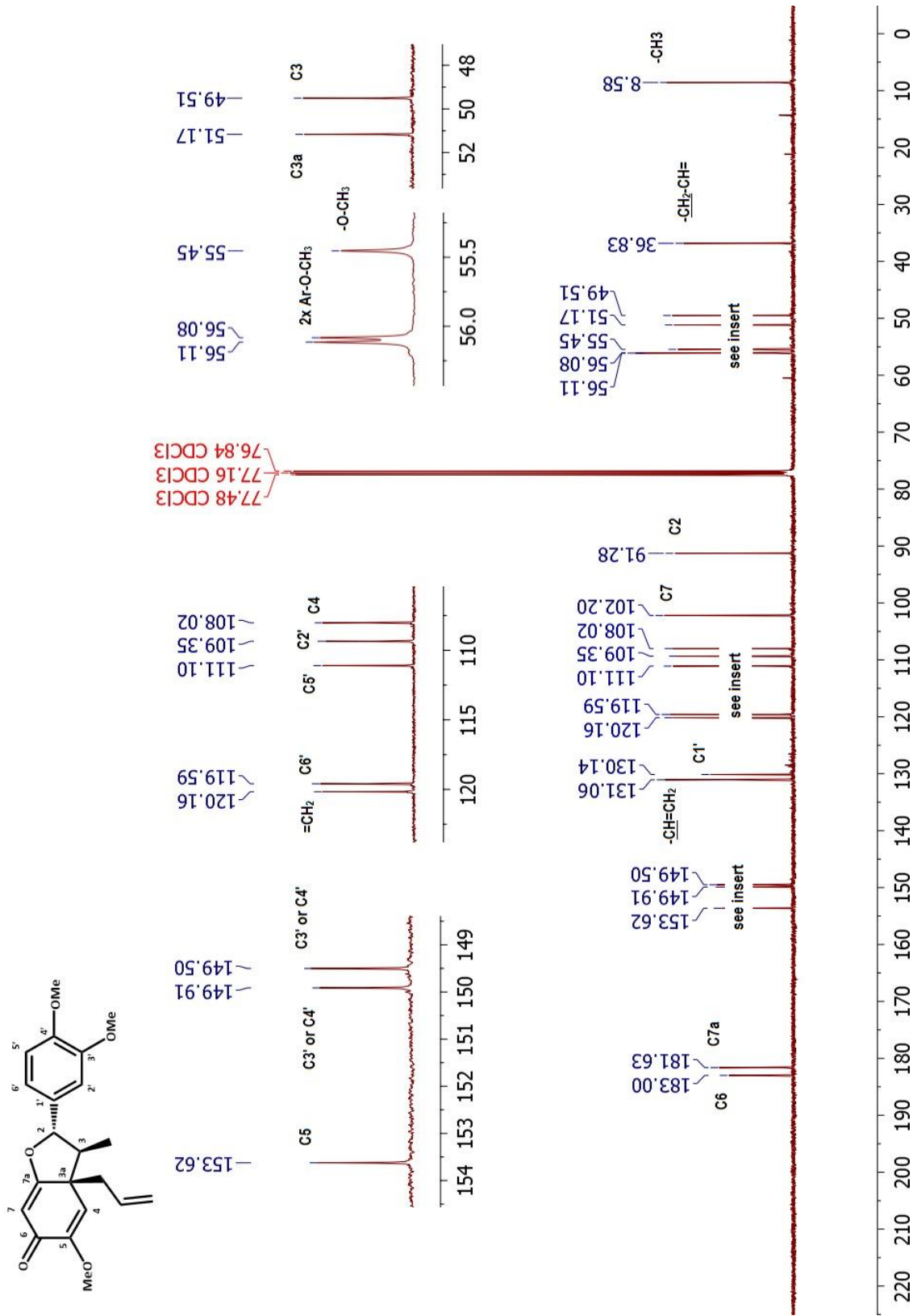
Figure F-2: ^{13}C-NMR (101 MHz, CDCl$_3$) of (±)-Kadsurenin F
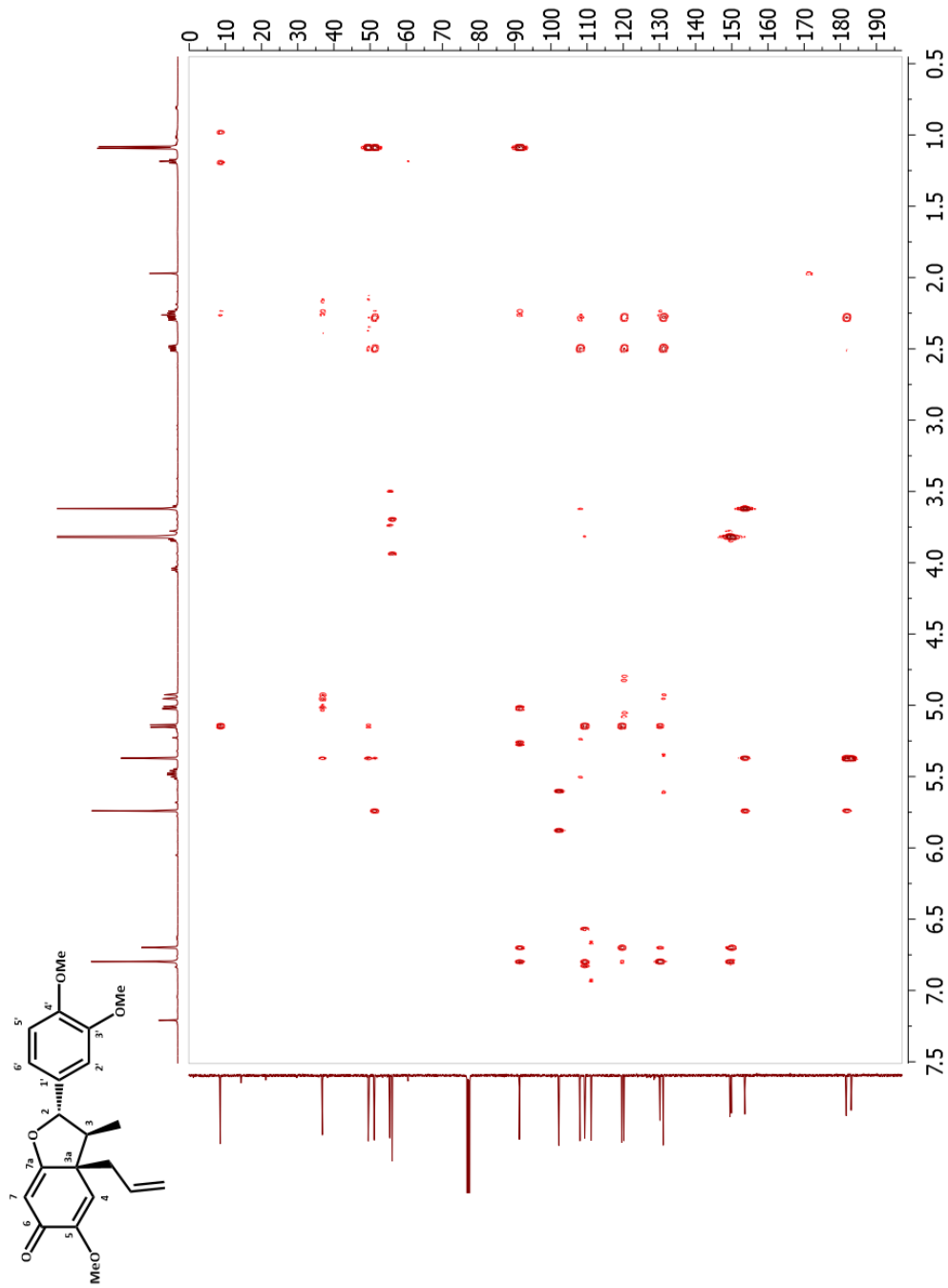
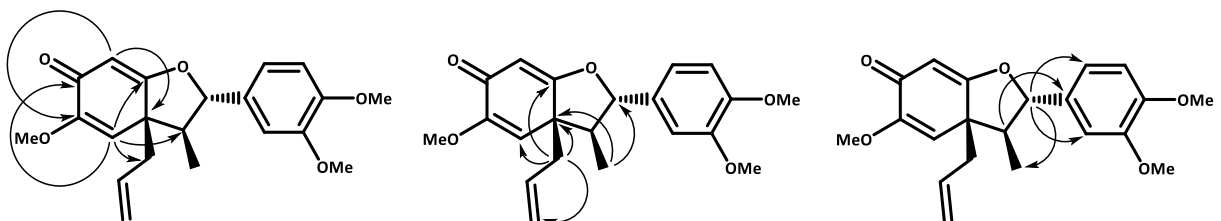**Figure F-3:** HMBC of (±)-Kadsurenin F

Figure F-4: Important correlations observed in **HMBC**-spectrum of (±)-Kadsurenin F
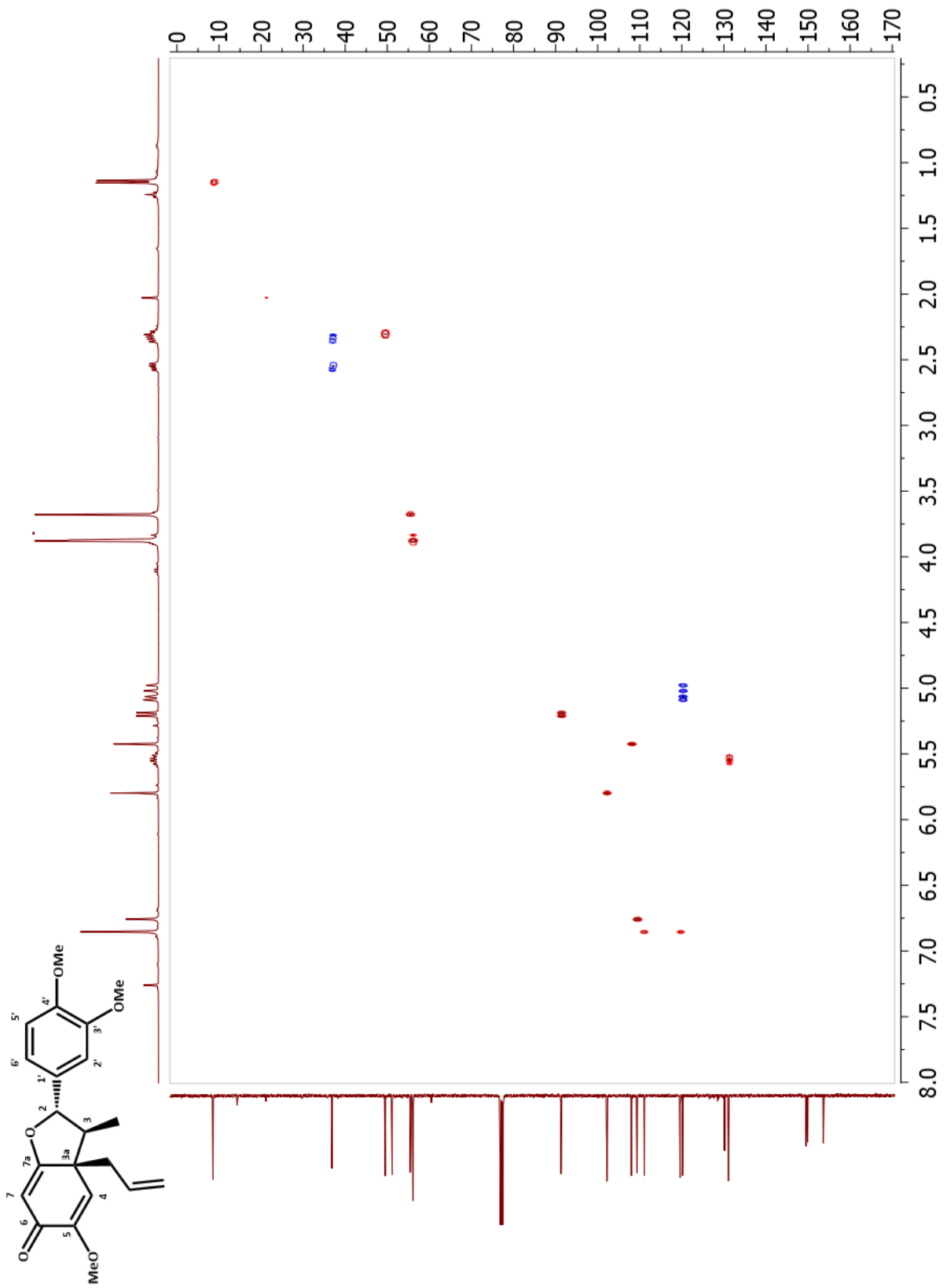
Figure F-5: HSQC of (±)-Kadsurenin F
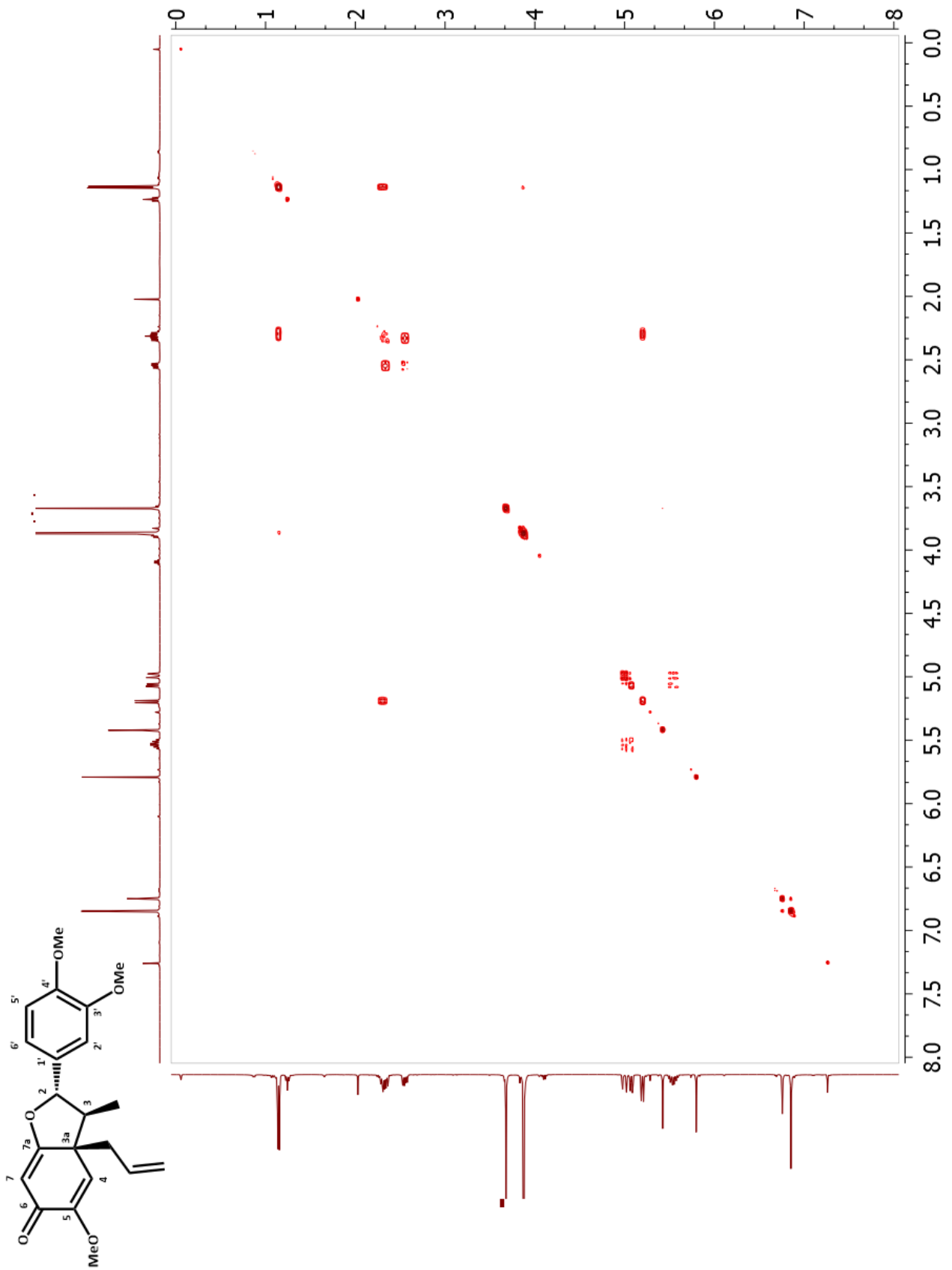
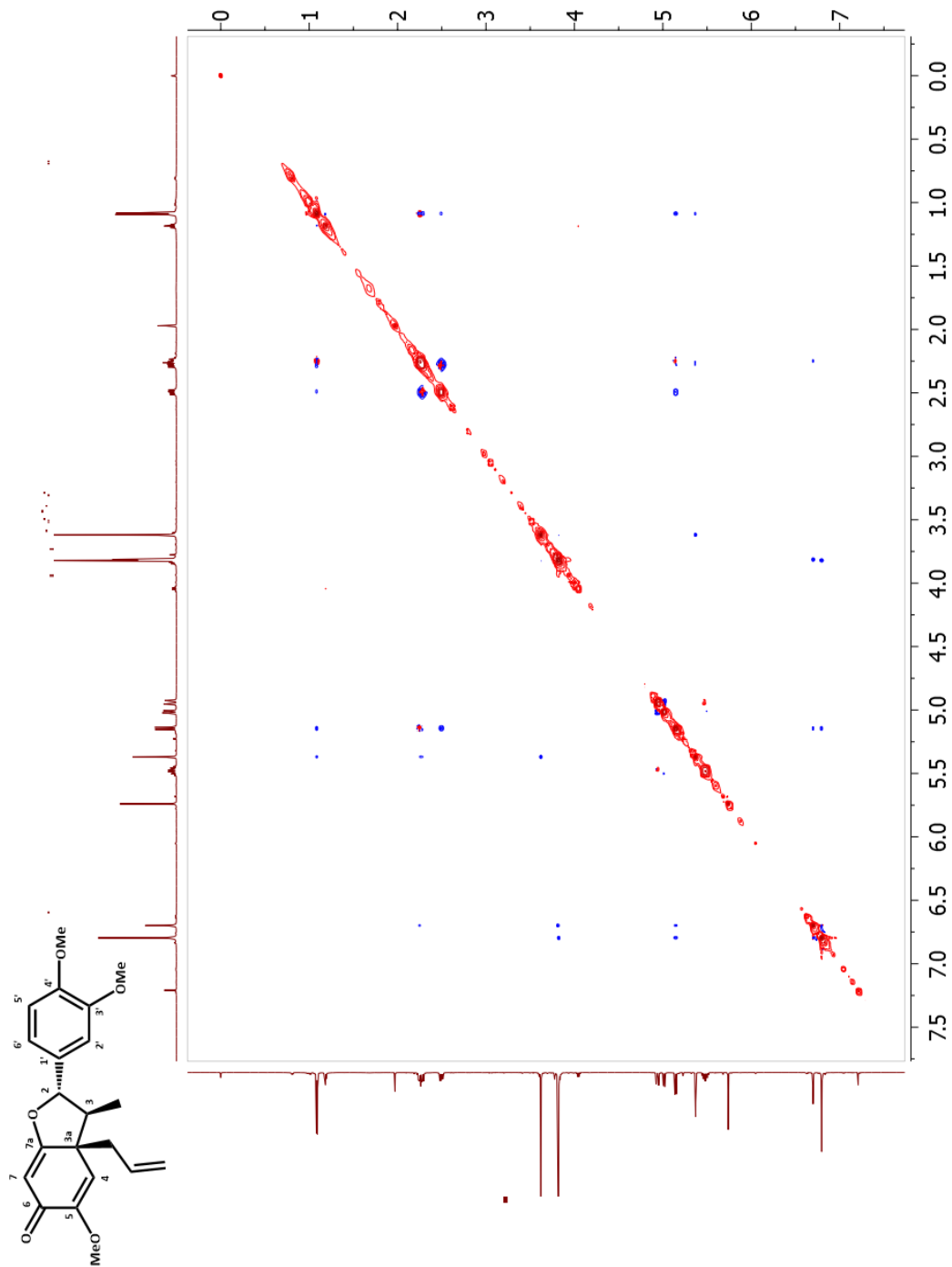**Figure F-6:** COSY of (±)-Kadsurenin F

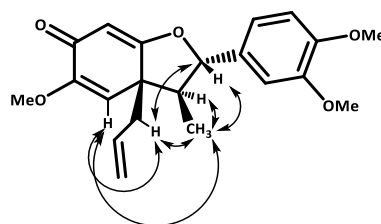**Figure F-7:** NOESY of (±)-Kadsurenin F

Figure F-8: Important correlations observed in **NOESY**-spectrum of (±)-Kadsurenin F

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