universität wien

MASTERARBEIT

Titel der Masterarbeit

„Design and Synthesis of a Compound Library Exploiting 5-Methoxyleoligin as Angiogenic Lead Structure“

verfasst von

Sophie Geyrhofer BSc

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universität wien

MASTER THESIS

Title of the Thesis

„Design and Synthesis of a Compound Library Exploiting 5-Methoxyleoligin as Angiogenic Lead Structure“

written by

Sophie Geyrhofer BSc

submitted in partial fulfillment of the requirements for the degree

Master of Science (MSc)

Vienna, June 2, 2013

Supervisor (formal): Univ.-Prof. Dr. Verena Dirsch

Supervisor (external): Ao.Univ.Prof. Dipl.-Ing. Dr.techn. Marko Mihovilovic

Dedicated to my friends Daniel, Lisa and Julia,

who always supported me and brought me back on track when I was lost.

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First I would like to thank Prof. Marko D. Mihovilovic, who decided to give me the chance to work in his group and to believe in me, which was surely a risk, because he did not know me before this thesis. Thank you for your trust and your support.

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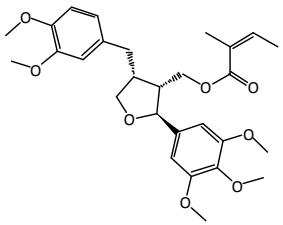
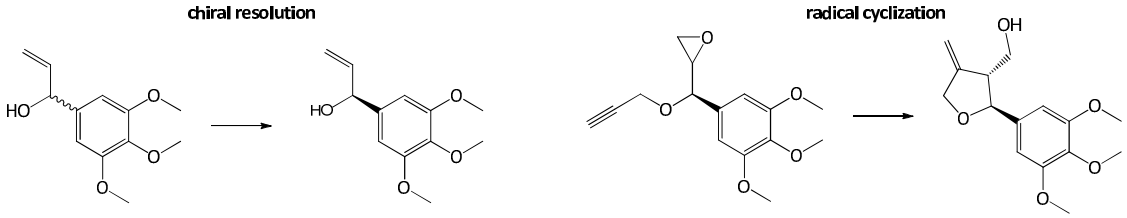
Last but not least, I want to thank my family for supporting me the whole way, from the crib until today. If not for you, I would not have arrived at this point. Thank you.

Abstract

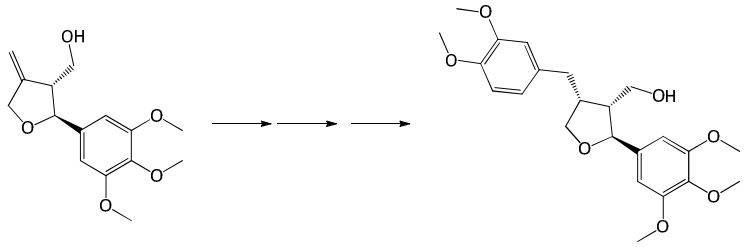
The aim of this thesis was to develop a method for the total synthesis of optically pure 5-methoxyleoligin, a naturally occurring furan lignan isolated from the roots of *Leontopodium alpinum* which showed proangiogenic activity in preliminary tests. Additionally, this synthesis should allow generating rapidly a compound library of structures similar to 5-methoxyleoligin for subsequent biological screening towards angiogenic and other biological activity.



The key steps of the synthesis are kinetic resolution using the enzyme amano lipase PS, which is essential to obtain optically pure 5-methoxyleoligin, and a radical cyclization reaction, which is used to generate the tetrahydrofuran core.



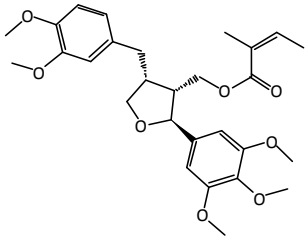
Furthermore, through combination of diastereoselective hydroboration and Suzuki coupling, the third stereocenter could be introduced with high diastereoselectivity.



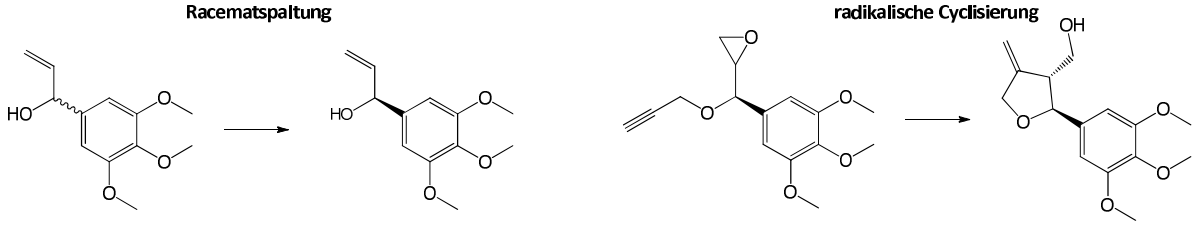
In total, 36 compounds were submitted for biological testing, including the lead structure 5-methoxyleoligin in synthetic form and the corresponding alcohol.

Deutsche Kurzfassung

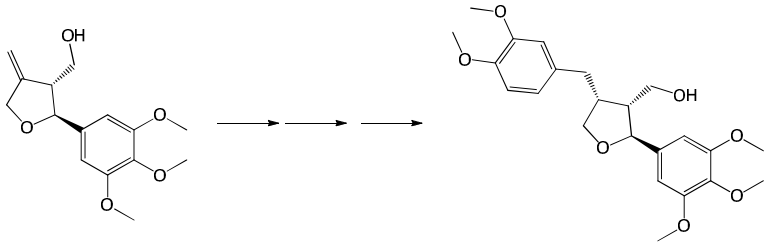
Das Ziel dieser Arbeit war es, eine Methode für die Totalsynthese von optisch reinem 5-Methoxyleoligin zu entwickeln, einem natürlich vorkommenden Furan-Lignan das aus den Wurzeln von *Leontopodium alpinum* isoliert wurde und in vorangegangenen Tests proangiogene Wirkung zeigte. Außerdem sollte die Synthese eine schnelle Herstellung von ähnlichen Verbindungen erlauben, die im Anschluss ebenfalls unter anderem auf proangiogene Aktivität getestet werden sollten.



Die Schlüsselschritte der Synthese sind eine kinetische Racematspaltung unter Verwendung des Enzyms Amano Lipase PS und eine radikalische Cyclisierungsmethode, um den Tetrahydrofuran-Kern mit der richtigen Stereoselektivität herzustellen.



Außerdem, durch Kombination einer diastereoselektiven Hydroborierung und einer Suzuki-Kupplung, kann das dritte Stereozentrum mit hoher Diaereoselektivität etabliert werden.



In Summe wurden 36 Verbindungen für biologische Tests übermittelt, darunter die Leitstruktur 5-Methoxyleoligin in synthetischer Form und der dazugehörige Alkohol.

Key

All compounds prepared in this thesis are labeled with bold Arabic numbers. Compounds unknown to the literature are additionally underlined. Literature citations are indicated by Arabic numbers in square brackets.

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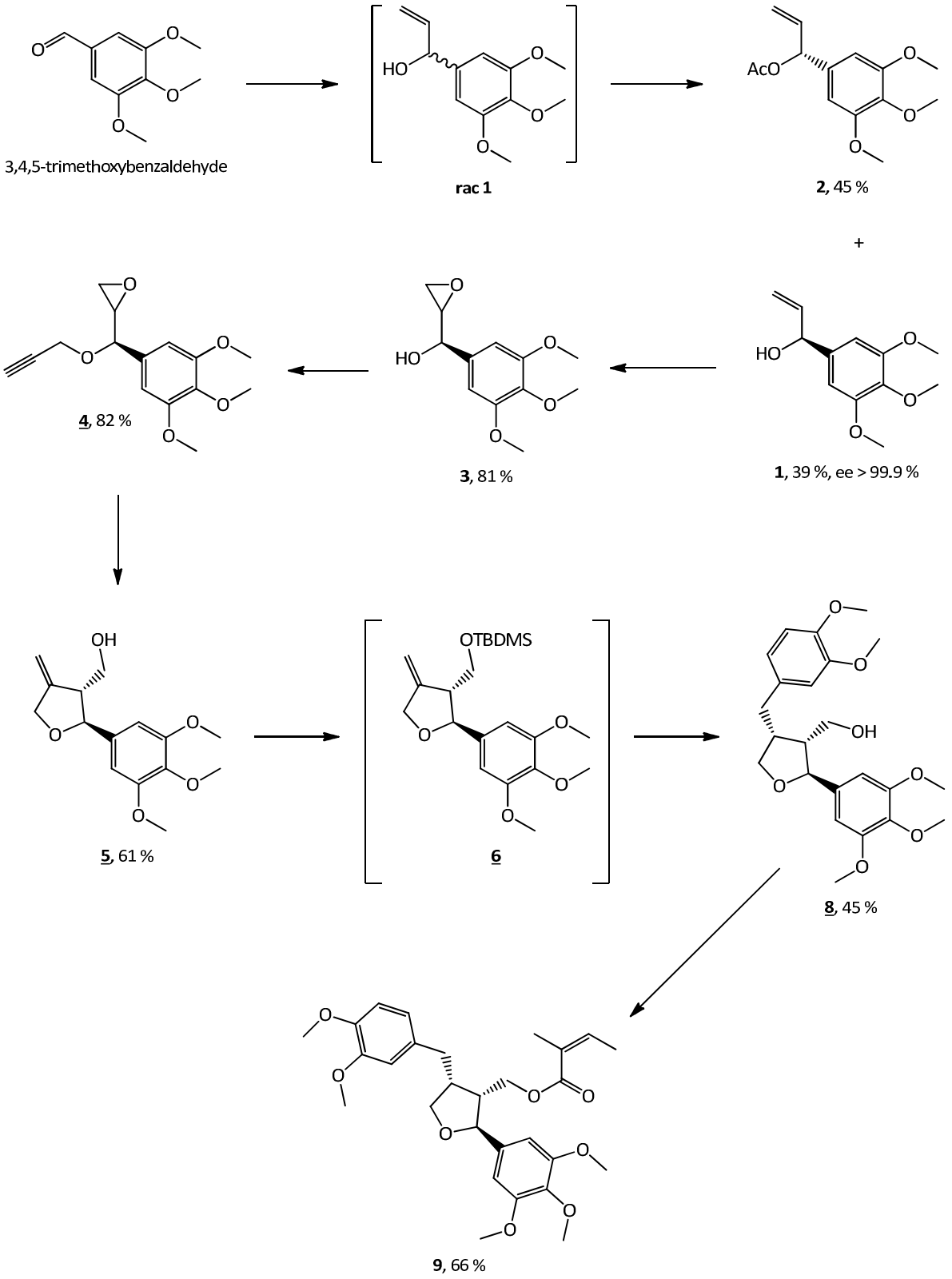
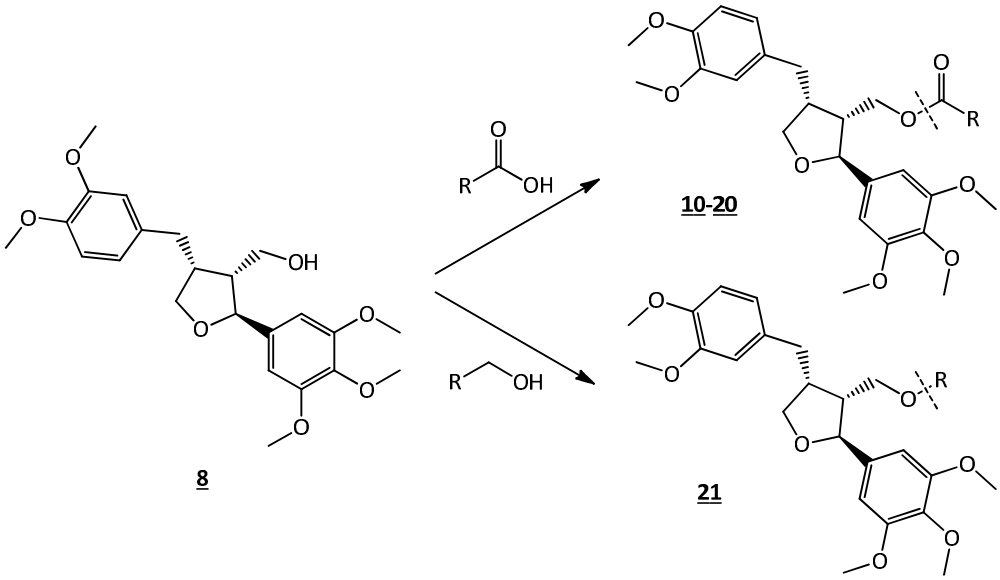
General Schemes

Total Synthesis of 5-Methoxyleoligin



Variation of the Ester Functionality



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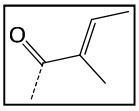
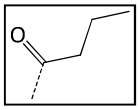
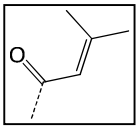
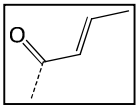
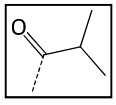
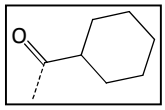
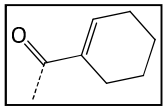
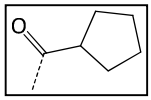
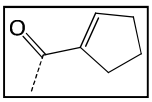
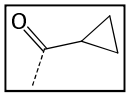
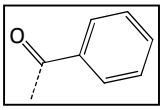
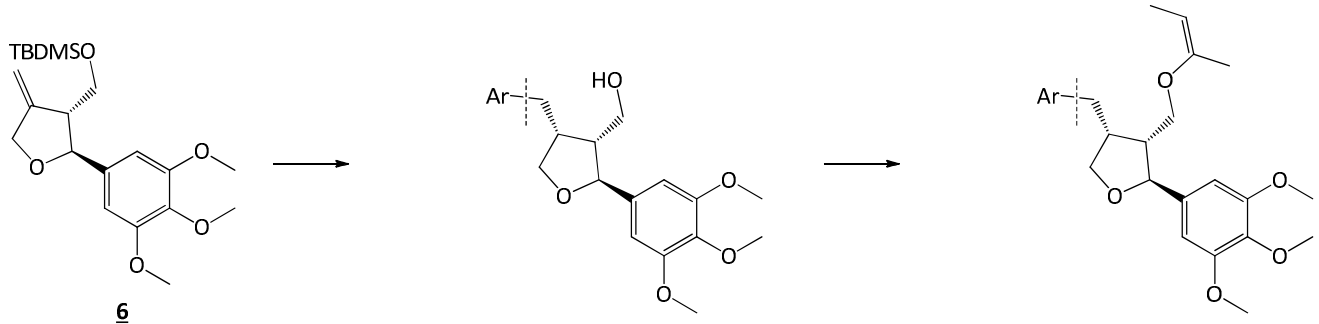
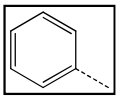
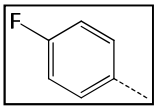
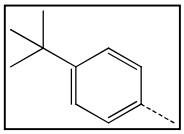
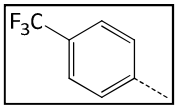
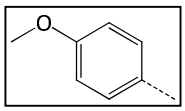
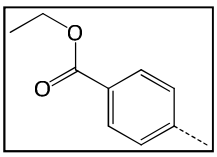
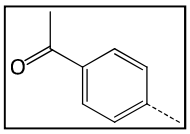
8		**10**	70
8		**11**	72
8		**12**	66
8		**13**	74
8		**14**	83

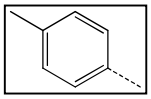
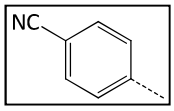
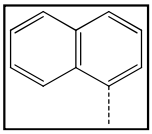
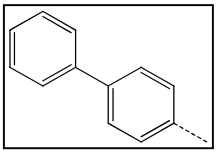
8		**15**	81
8		**16**	56
8		**17**	85
8		**18**	69
8		**19**	75
8		**20**	93
8		**21**	42

Variation of the Benzylic Moiety



6 **22**-**32** **33**-**43**

Starting Material	R	Compound	Yield / %	Compound	Yield / %
6		**22**	36	**33**	61
6		**23**	47	**34**	67
6		**24**	49	**35**	67
6		**25**	62	**36**	67
6		**26**	28	**37**	58
6		**27**	45	**38**	81
6		**28**	24	**39**	76

6		**29**	43	**40**	64
6		**30**	41	**41**	84
6		**31**	45	**42**	61
6		**32**	45	**43**	61

I. Introduction

1. Motivation for this work

Myocardial infarction (MI) caused by coronary artery disease (CAD) is one of the major causes of death worldwide [1]. Therefore, the scientific community has a great interest in developing new strategies for the treatment of CAD and prevention of MI, as well as the after-care of patients after they survived a MI.

1.1 Artherosclerosis and Coronary Artery Disease

Atherosclerosis is defined as a "multifocal, smoldering, immunoinflammatory disease of medium-sized and large arteries fuelled by lipids" [2]. As soon as arteries of the heart are concerned, there is the more specific term of coronary artery disease (also atherosclerotic heart disease). The main symptom of CAD is plaque formation at the inner walls of coronary arteries, which leads to stenosis. These atherosclerotic plaques (or atheromas) contain fibrous tissue, foam cells, a lipid rich core and calcium (**Figure 1**) and are often highly unstable.

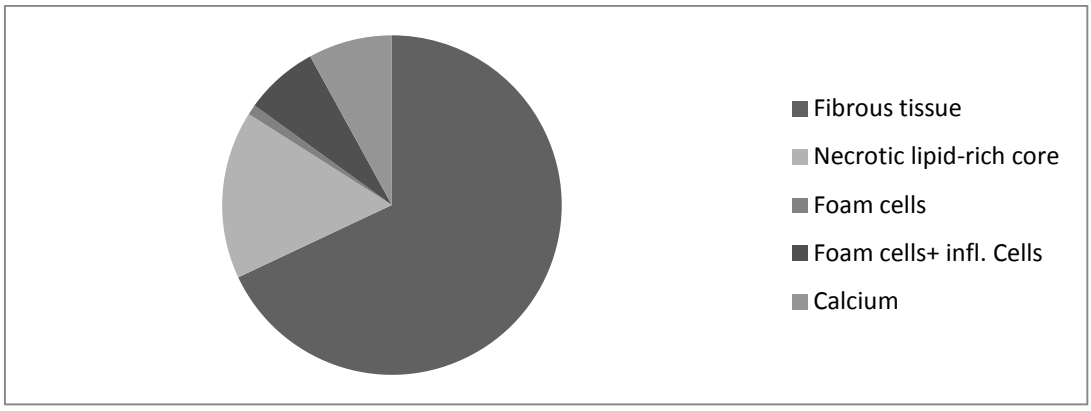


Figure 1 Representation of contents of an average atherosclerotic plaque [2]

The disease *per se* is only rarely fatal; however, events caused by it, usually involving plaque rupture, are much more dangerous. The term plaque rupture is used for "a plaque with deep injury with a real defect or gap in the fibrous cap that had separated its lipid-rich atheromatous core from the flowing blood, thereby exposing the thrombogenic core of the plaque" [3]. This process is the main cause for (acute) myocardial infarction.

1.2 Myocardial Infarction

Myocardial infarction, or acute myocardial infarction, commonly also known as heart attack, is defined as undersupply of the heart with blood (ischemia) and subsequent necrosis of heart muscle tissue [4]. The most common reason for such an undersupply of the heart with blood is, as mentioned above, the rupture of an atherosclerotic plaque. However, once the patient has survived the acute MI, there is still the risk of a following heart failure due to arrhythmias caused by myocardial scarring, recurrence of coronary occlusion and complications due to cardiomyocyte hypertrophy or contractility loss [5].

1.3. Therapeutic Options

There are two possible ways to decrease the number of deaths caused by CAD and MI

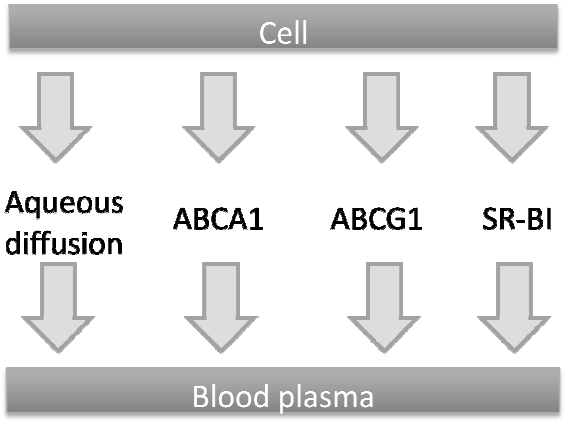
- Prevention: treating the symptoms of CAD, which means prevention of plaque building and the risk of their rupture
- After-care: improving the treatment directly after an infarction as well as decrease the permanent damage caused by it

<u>Prevention: Macrophage Cholesterol Efflux</u>

The first possibility seems to be feasible through activation of macrophage cholesterol efflux. If macrophages could be forced to release the accumulated lipids in order to decrease the formation of foam cells and to reduce the inflammatory response [6], then plaques would grow much slower, or maybe even stop growing and, additionally, the stability of the plaques should increase because of the smaller size of the instable lipid-rich core.

Macrophage cholesterol efflux occurs *via* four different pathways: aqueous diffusion, scavenger receptor class B type I (SR-BI) and two transporters of the adenosine triphosphate binding cassette superfamiliy, ABCA1 and ABCG1 (**Figure 2a**) [7]. A main process of macrophage cholesterol efflux is aqueous diffusion. Unfortunately, this is not a process that can be controlled, because it involves diffusion of spontaneously desorbed free cholesterol molecules through the aqueous phase and subsequent collision with HDL particles [8]. SR-BI is a CD36-related cell surface glycoprotein [9] and

is not a good target either, because its contribution to overall cholesterol efflux from macrophages is rather small. Its mechanism of action is not fully elucidated yet, but it is clear that SR-BI promotes bidirectional flux of cholesterol between HDL particles and SR-BI expressing cells (**Figure 2b**). Nevertheless, ABCA1 and ABCG1 use ATP to transport substrates from inside the cell to the outside, and therefore are active transporters [10]. Both are interesting targets, because they promote cholesterol efflux in an unidirectional way, either to lipid-poor apolipoproteins (e.g. apolipoprotein A-I (apoA-I)) or lipid-rich acceptors.



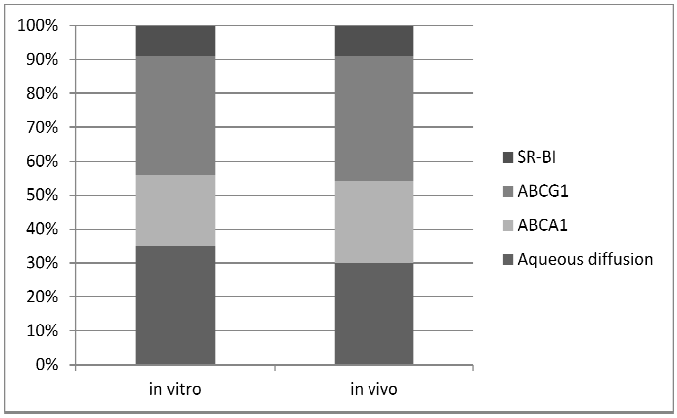


Figure 2a The four different pathways of cholesterol efflux [7] **Figure 2b Contribution of each pathway in vitro and in vivo [7]**

<u>After-care: Angiogenesis</u>

During MI the heart is undersupplied with blood, which causes a lack of oxygen and glucose in the tissue, called ischemia. Due to this undersupply, cardiomyocytes die; the amount of cell death depends on several factors, such as the size of the undersupplied tissue, the efficiency of reperfusion and the duration of ischemia [5]. An increased ischemic injury results in extended risk of heart failure.

Therefore, a promising intervention in an early stage after MI could be a proangiogenic therapy in order to accelerate the resupply of tissue, prevent necrosis of cardiomyocytes and salvage the ischemic myocardium [5]. Not only tissue loss due do ischemia can be decreased, but also the loss of contractile function in otherwise viable cardiomyocytes nearby the developing scar. Those cells suffer from increased physical load through the healing process, which is often followed by hypoperfusion, microvascular dysfunction and increased metabolic demand, as well as subsequent decrease of the ability to contract [11].

2. Lignans

Lignans are a very large class of secondary metabolites and are widely distributed in the plant kingdom. Already in 1984, more than 200 different lignans were known, and every year more of them are isolated from various plant species. The interest in this class of compounds has increased over time, not least because of their broad spectrum of biological activity [12].

2.1 Definition and Classification

A lignan is commonly defined as a dimer of two phenylpropane units linked by their C8 atoms. If a connection other than 8-8' (such as 8-1', 8-5', 8-*O*-4', 5-5', 3-*O*-4', 7-1', 8-7', 1-5', 2-*O*-3' etc.) is formed between the two units, terminologies like "neolignan" are used. However, Davin and Lewis propose that the term lignan should be enlarged to all skeletal types, because there is a relatively small number of possible linkages which can precisely be specified [13].

According to Suzuki and Umezawa classification of 8-8' lignans results in eight subclasses. In each subclass the oxidation state of the 9(9')-position and the aromatic rings differs between the associated lignans, which allows to further sub-classify them (**Figure 3**).

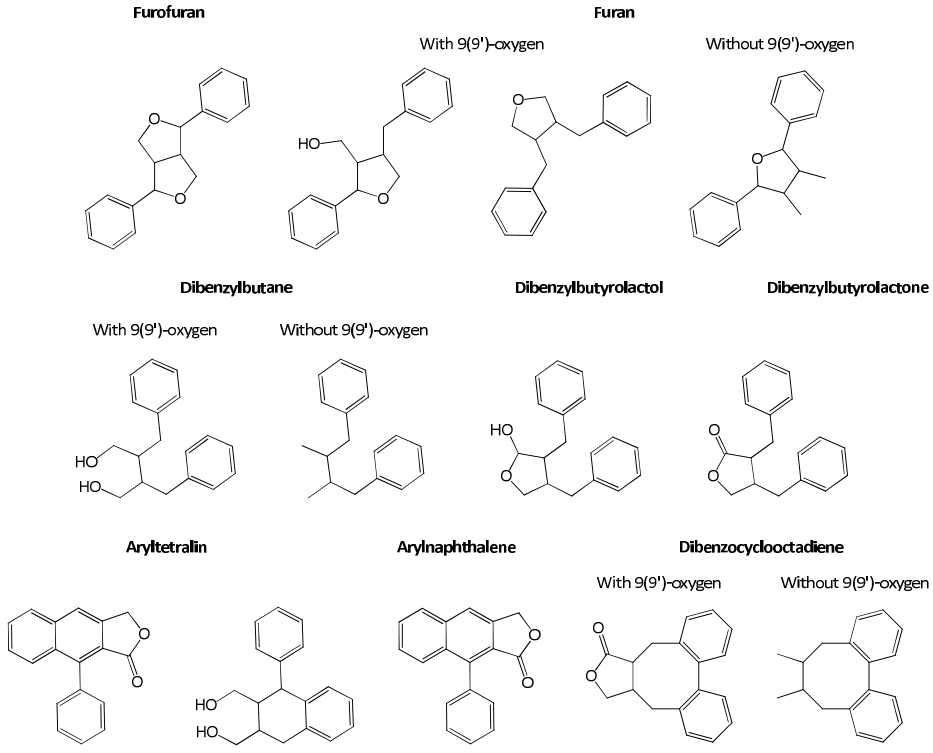
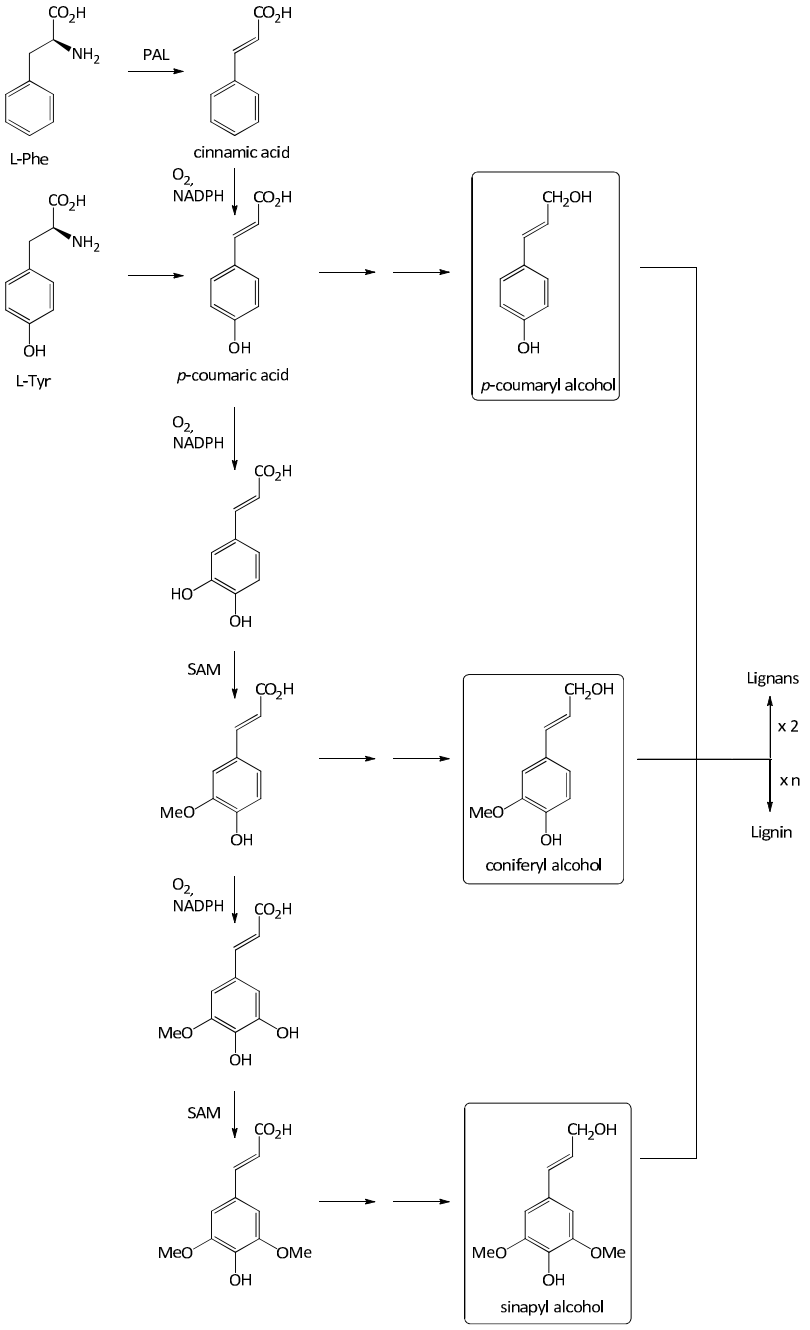


Figure 3 The eight subclasses of lignans according to Suzuki and Umezawa

2.2 Biosynthesis

Lignans are derived from three different building blocks: *p*-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol [14]. Biosynthesis of those starts with the elimination of ammonia in two aromatic amino acids, L-phenylalanine and L-tyrosine, which leads to formation of *p*-coumaric acid. Subsequently, the three building blocks for lignan synthesis are formed through alternating hydroxylation and methylation steps and the reduction of the acid moiety (**Scheme 1**).



Scheme 1 Schematic pathway of the biosynthesis of *p*-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol

Dimerization of the phenylpropane units is then initialized by the removal of a proton as well as the corresponding electron by a peroxidase, generating a radical and leading to different resonance forms (**Figure 4**). In case of the synthesis of 8-8' lignans with defined stereochemistry, a so-called dirigent protein (DIR) traps the free radical and allows stereoselective coupling. This was first shown in *Forsythia intermedia* for (+)-pinoresinol synthase [15].

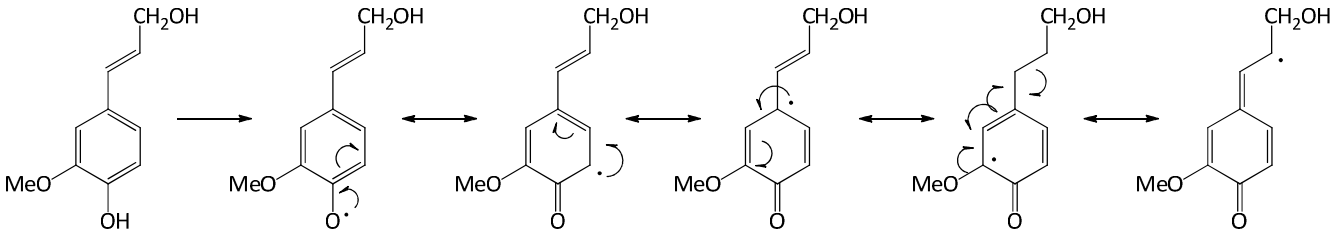


Figure 4 Resonance forms of coniferyl alcohol

2.3 Biological activities

Many biological activities have been reported over the last years, including

- antiviral [12, 16, 17]
- anticancer [12, 17-19]
- cancer prevention [20, 21]
- antioxidant [18, 19, 22]
- anti-inflammatory [19]
- antimicrobial [19]
- immunosuppressive [19]
- hepatoprotective [23]
- osteoporosis prevention

The probably best investigated lignan regarding its biological activity is podophyllotoxin (**Figure 5**). This compound was first isolated from *Podophyllum*, but later on also from *Linum* species and

others. Its semi-synthetic derivatives etoposide, teniposide and etophos are established drugs for cancer treatment [17].

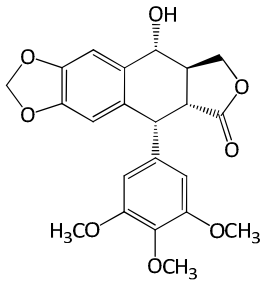


Figure 5 Structure of podophyllotoxin

3. Objective

CAD and subsequent MI are leading causes of death worldwide. Therefore, the need for new and better drugs and treatments is growing, and many researchers focus on these topics. As mentioned above, lignans are a huge class of compounds and show a very broad spectrum of biological activity. In addition, derivatives of podophyllotoxin already proved themselves as drugs for cancer treatment. However, no proangiogenic activity or ability to promote cholesterol efflux of lignans had been reported in the literature, until previously.

Recently, 5-methoxyleoligin, a furan-type lignan isolated from Edelweiss, showed promising results in first proangiogenic assays [24]. Therefore it represents an interesting target for treatment of patients after MI, creating a need for a synthetic pathway to obtain the compound in useful amounts.

The synthetic route should enable the efficient and optically pure preparation of 5-methoxyleolgin, as well as be designed for the rapid generating of a compound library of similar structures and extending the scope to lignan-type compounds not found in nature.

II. Results and Discussion

1. Chemistry

5-Methoxyleolgin was first isolated in 2004 from roots of *Leontopodium alpinum* at the University of Innsbruck [25]. This plant, commonly known as Edelweiss, grows e.g. in the Alps and was used a long time in folk medicine to treat fever, diarrhea, dysentery and abdominal aches. As it is a subject to nature conservancy protection, the roots of cultivated Edelweiss were used for isolation (1907.84 g). After several purification steps (including extraction, sephadex separation, silica column chromatography, and semi-preparative HPLC, **Figure 6**), 4.0 mg of 5-methoxyleoligin were isolated (2.1 x 10^{-6} w/w %).

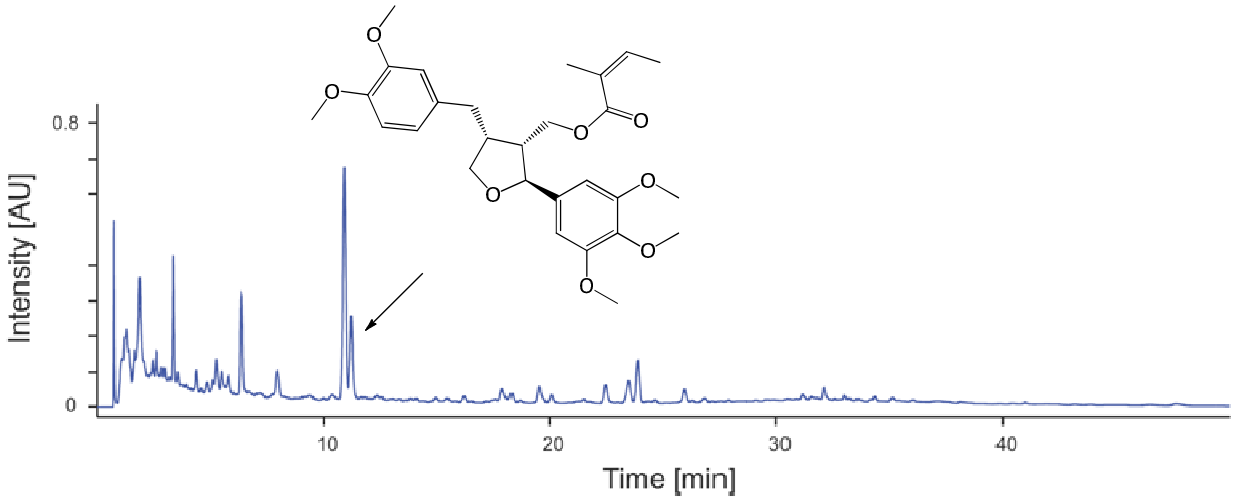


Figure 6 HPLC-analysis of the DCM-extract of the roots of *L. alpinum*

The structure of 5-methoxyleolgin was determined by FAB-HR, NMR techniques, and comparison with the previously isolated lignan leoligin [25]. FAB-HR (fast atom bombardement – high resolution) was used because it is a very mild ionization method [26]. The substance is embedded in a matrix (e.g. glycerine) and then bombarded with a beam of atoms, like Ar- or Xe-molecules. The substance is ionized *via* sputtering mechanisms giving mainly pseudo-molecular ions. This allows easy and exact determination of molecular weights.

5-Methoxyleoligin belongs to the class of furan lignans and bears two aromatic rings, a 3,4,5-trimethoxyphenyl and a 3,4-dimethoxybenzyl moiety. Additionally, it is esterified at the oxidized 9-position with angelic acid and exhibits optical activity, due to its three stereocenters.

As isolation is not a feasible method for obtaining this compound in useful amounts, the aim of this thesis was to develop a practicable total synthesis as well as to create a compound-library for medicinal chemistry investigations using 5-methoxyleoligin as lead structure. The reason for 5-methoxyleoligin to be an interesting target for total synthesis is primarily due to its biological activity. Briefly, it promotes macrophage cholesterol efflux and angiogenesis (see section II.2. Biology) and therefore it is a potential drug candidate for abatement of CAD and decreasing the risk of a CAD-induced MI, as well as treatment of patients after a MI.

There are a variety of lignan syntheses published in the scientific literature (**Figure 7**), addressing the problem *via* different routes. With respect to similarity to the tetrahydrofuran core of 5-methoxyleoligin, its substitution pattern and stereochemistry, the published routes may be classified (with decreasing degree of similarity) as affording

- the correct absolute configuration [27-30]
- the correct absolute configuration of the optical antipode [31]
- the correct relative configuration of 5-methoxyleolgin in racemic form [32-37]
- an epimeric form in non-racemic form [38-42]
- an epimeric form in racemic form [43, 44]
- any form using another (natural) lignan as starting material (partial synthesis) [45, 46]
- any other form similar to 5-methoxyleoligin not appertaining to the other points [47-53]

Although there are approaches that delivered scaffolds with the correct absolute configuration in enantiomerically pure form, they were not used for the synthesis of 5-methoxyleoligin due to the fact, that those approaches are relatively long and not modular enough, which is necessary if a compound library should be designed.

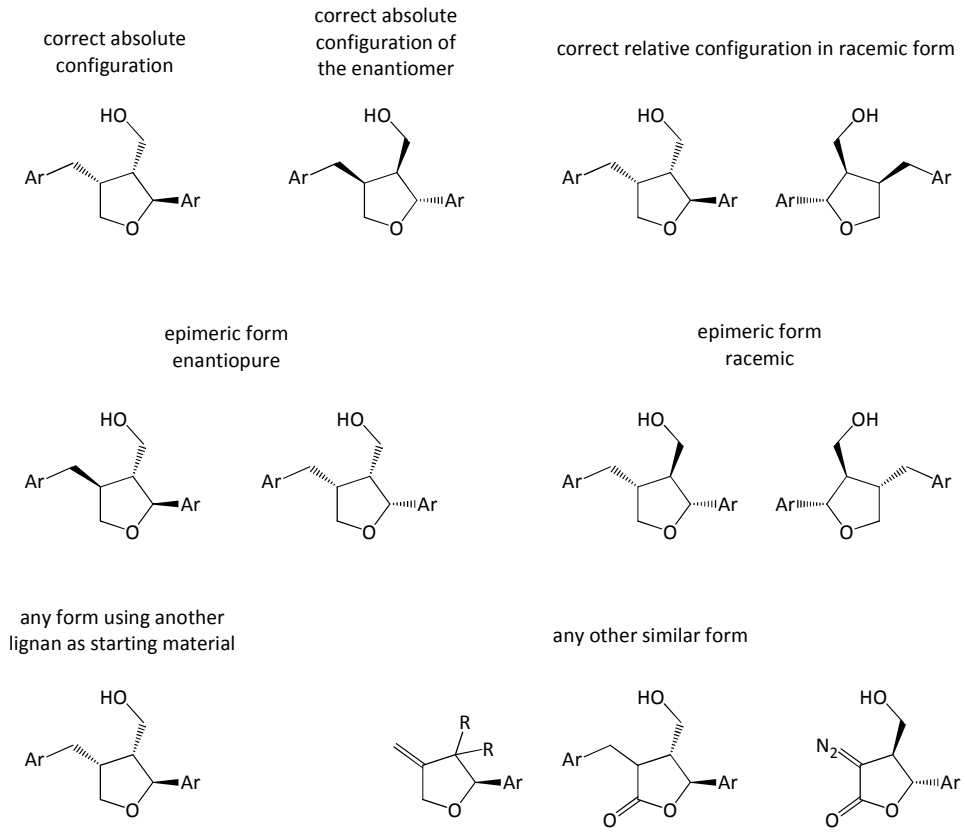
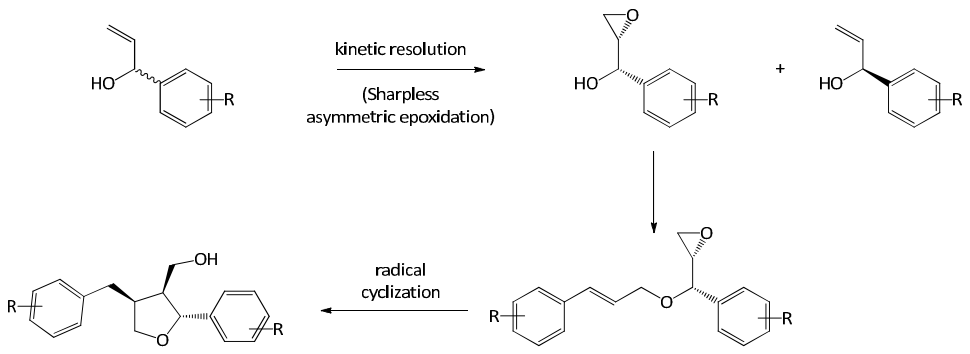


Figure 7 Lignan scaffolds synthesized so far

1.1 Total Synthesis of 5-Methoxyleoligin

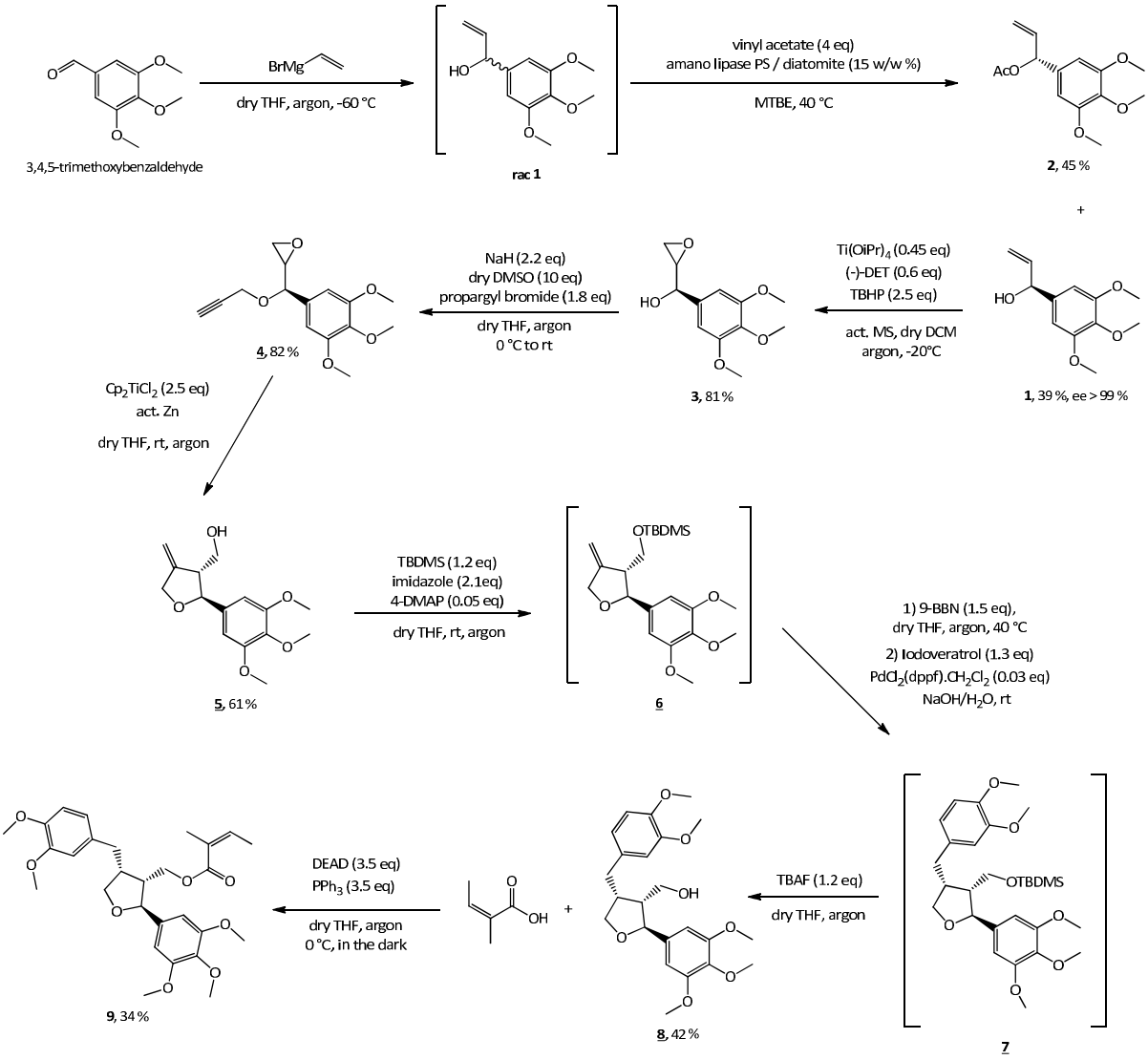
The original approach for total synthesis of 5-methoxyleoligin was based on a publication of Banerjee et al [31], involving a kinetic resolution by a Sharpless asymmetric epoxidation, a Williamson ether synthesis and a radical cyclization reaction, which was published earlier by Nugent et al (**Scheme 2**) [54]. This methodology was previously used as entry point for optimizing the synthesis of Leoligin in our group [55].



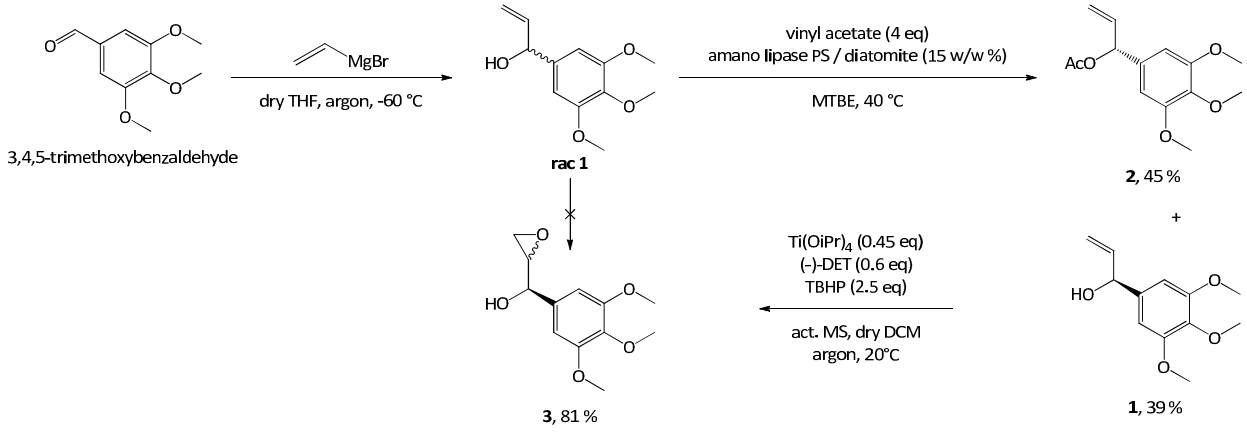
Scheme 2 Original literature route by Nugent et al

As the critical step, the radical cyclization reaction, did not work with our substrate in acceptable yield and all attempts to improve the situation failed, this approach was dismissed. Nevertheless, since both the Nugent [54] and Roy group had used this cyclization methodology to synthesize similar compounds, the reaction type was used on a different substrate, which finally worked. In **Scheme 3** the total synthesis of 5-methoxyleoligin based on the synthesis of Leoligin is shown [55].

The first step in the total synthesis of 5-methoxyleoligin **9** is a Grignard addition of vinylmagnesium bromide to commercially and cheaply available 3,4,5-trimethoxybenzaldehyde, producing a racemic mixture of the allylic alcohol **rac 1**. In order to synthesize 5-methoxyleolgin **9** in its enantiomerically pure form, a chiral resolution had to be performed. The first attempt was the subsequent Sharpless asymmetric epoxidation of the double bond. As this reaction is completely reagent controlled, it can be tuned to only convert the desired antipode, leaving the undesired one behind. The configuration of the newly generated stereocenter is not of importance, because it is lost in subsequent steps, again. Unfortunately, this method of chiral resolution did not work as well as expected as it suffered from low yields, hence another method based on the enzyme amano lipase PS was chosen (**Scheme 4**). This reaction was described before on this compound, although another enzyme was used [56]. With amano lipase PS, the selective acetylation worked with good yield and high ee for the alcohol (>99.9 %) and, additionally, this type of kinetic resolution has the potential to be transformed into a dynamic kinetic resolution [57-62].



Scheme 3 Original route for the total synthesis of 5-methoxyleoligin



Scheme 4 Grignard reaction, kinetic resolution and subsequent Sharpless asymmetric epoxidation

The advantage of a dynamic kinetic resolution is that it is, unlike a classic kinetic resolution, not limited to a theoretical yield of 50 % (**Figure 8**).

However, several factors have to be taken into consideration [63]:

- The kinetic resolution should be irreversible in order to ensure high enantioselectivity.
- The enantiomeric ratio (*E*-value, $E=k_R/k_S$) should be at least greater than 20.
- To avoid depletion of R, racemization (k_{rac}) should be at least equal or greater than the reaction rate of the fast enantiomer (k_R).
- In case the selectivities are only moderate, k_{rac} should be greater than k_R by a factor of 10.
- For obvious reasons, any spontaneous reaction involving the substrate enantiomers as well as racemization of the product should be absent.
- Dynamic resolution is generally limited to compounds possessing one single stereocenter

As this is tricky and a methodology has still to be developed, synthesis so far has only been performed with material derived from kinetic resolution.

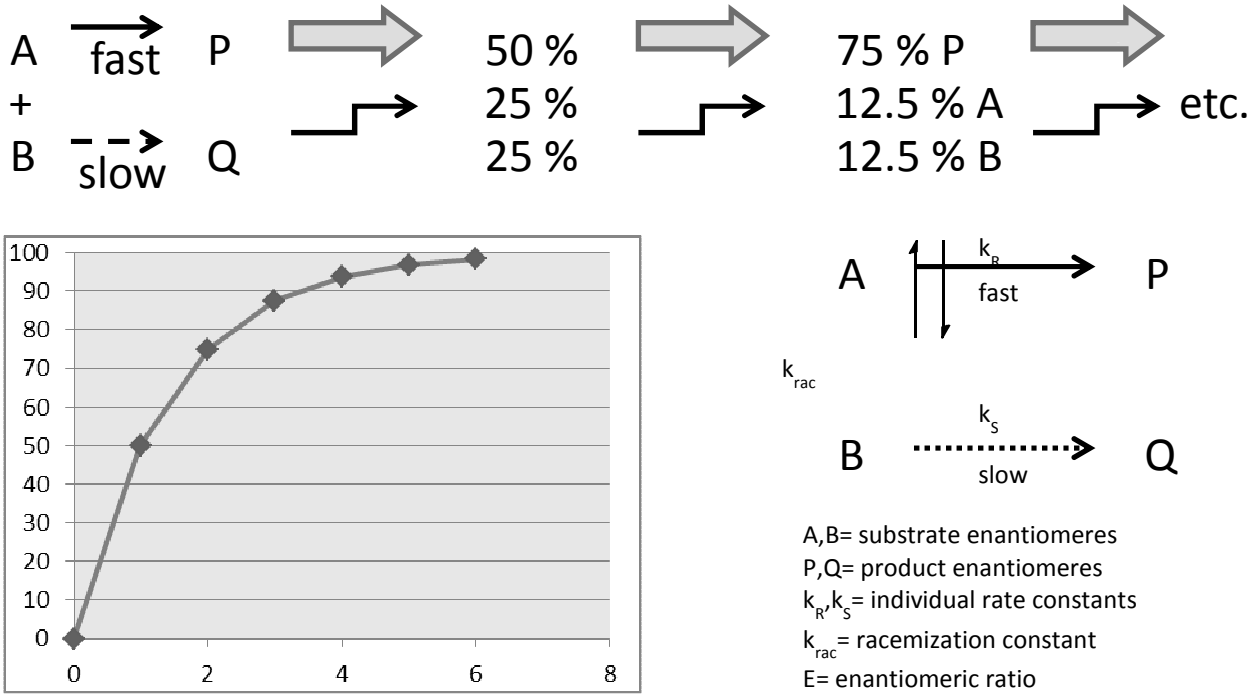


Figure 8 Scheme of the principle of dynamic kinetic resolution

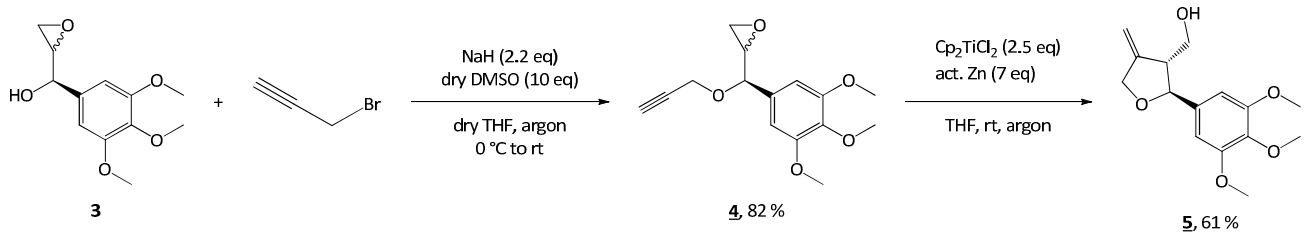
With the desired enantiomer in hand, the epoxidation of the double bond was the next step. As oxidation with different protocols (e.g. mCPBA-oxidation) were previously shown in our research group not to work on substrate **1** [55], Sharpless epoxidation was reconsidered. As it again suffered from low conversion and therefore low yields in the beginning (around 20 % according to GC), reaction conditions were screened regarding reaction temperature and time as well as catalyst loading. The first screening showed that -20 °C is the optimal setting, as at higher temperatures conversion increases, but yields are lower due to decomposition of the starting material. The second screen showed that the reaction is over after 22 h, while longer reaction times again only lead to decomposition. Regarding catalyst loading, 45 mol % of catalyst gave satisfactory conversion, while further increase showed no improvement any more. The results are compiled in **Table 1**.

Temperature (22h, 45 mol % catalyst, 100 mg)		
#	temperature / °C	yield / % (product/starting material)
1	-20	22/74
2	0	18/43
Time (45 mol % catalyst, -20 °C, 50 mg)		
#	time /h	conversion (GC) /%
3	6.75	66
4	21.75	82
5	30	80
6	70	80
Catalyst Loading (22 h, -20 °C, 50 mg)		
#	mol %	conversion (GC) /%
7	15	26
8	45	54
9	90	53
Batch Size Observation (45 % catalyst, -20 °C)		
#	starting material /g	yield / %
10	0.1	22
11	1	67
12	2	75
13	5	81

Table 1 Results of reaction condition optimization

With the results in hand, the reaction could then be performed with a yield of 81 %. Interestingly, also an increase of yield with magnitude of scale was observed.

The next step was a classical Williamson ether synthesis, which could be performed without any problems and a yield of 82 % (**Scheme 5**).



Scheme 5 Williamson ether synthesis and radical cyclization

The following radical cyclization was the key step of the whole synthesis, not least because it was the reason for discarding the first approach. This slightly different reaction (regarding the starting material) was performed according to Saha and Roy [52] in a yield of 57 % of the desired diastereomer. In this reaction, if starting from racemic material, formation of four different products is possible (**Figure 9A**); however, in case of the synthesis of 5-methoxyleoligin, only two diastereomers could be formed due to performing the reaction with enantiopure starting material. The proposed mechanism for this reaction is shown in **Figure 9B**. It involves the selective opening of the epoxide (during which the stereocenter, formed through epoxidation, is lost due to hybridization change), addition of the titanium species and generation of the free radical. Ring closure follows, generating a tetrahydrofuran ring bearing an exocyclic double bond in position 4. The stereochemistry is controlled by the stereogenic center initially installed during the enzyme mediated kinetic resolution. A second titanium species adds at this position and the titanium species is cleaved through acidic work up to give **5** [64].

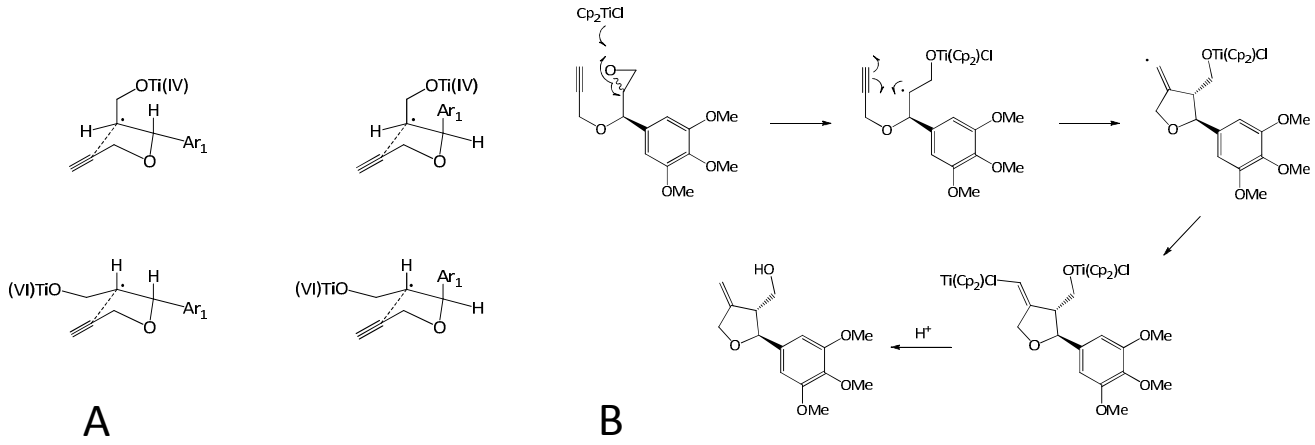
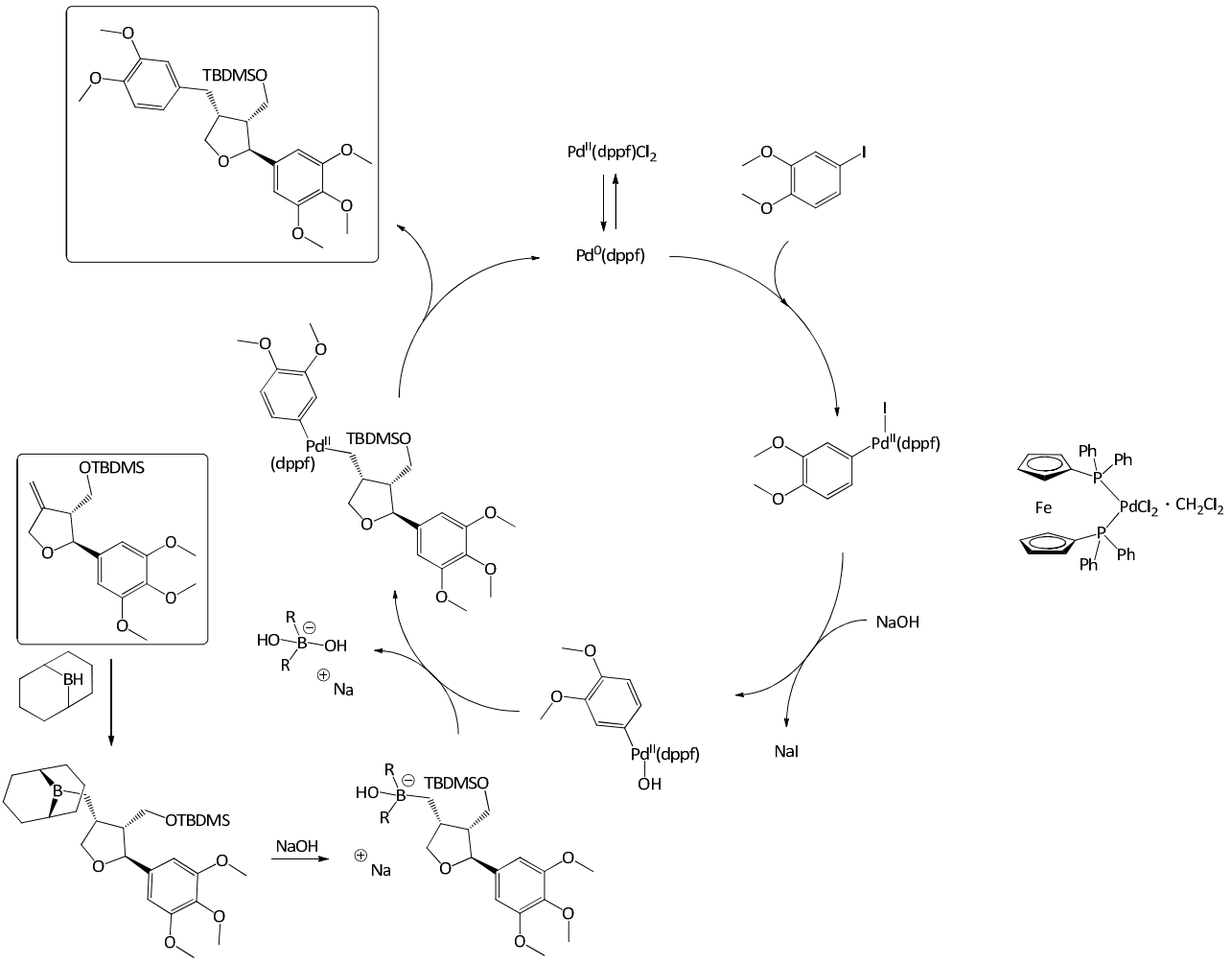


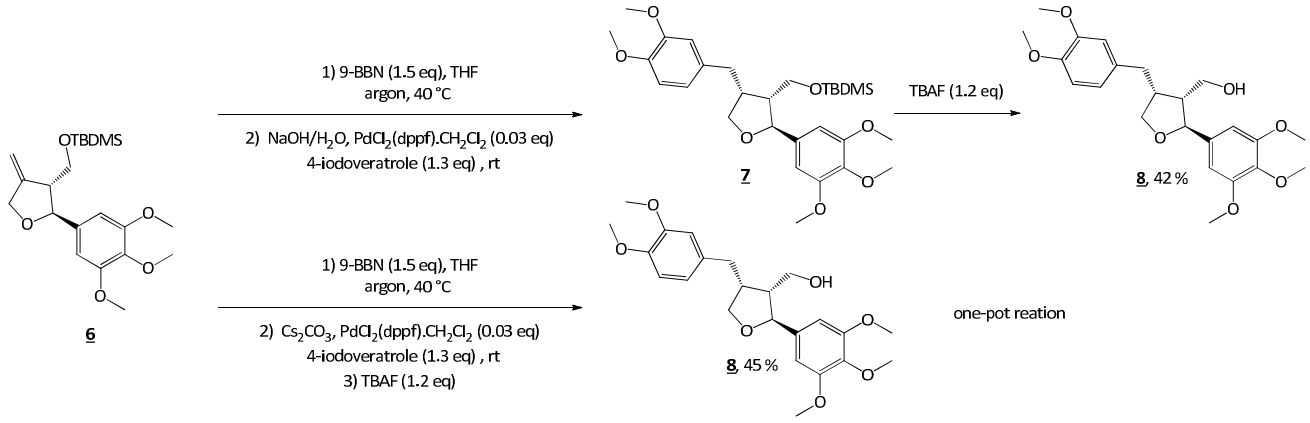
Figure 9 A: Possible products formed by radical cyclization (racemic precursor). B: Mechanism of the radical cyclization reaction

Next, the hydroxyl group had to be protected as silyl ether, not only to prevent side reactions in the subsequent hydroboration and Suzuki-Miyaura coupling, but also to control the selectivity of the coupling reaction. Preliminary experiments showed that all tested silyl groups (*tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, triisopropylsilyl) are large enough to provide sufficient sterical hindrance to yield mainly the desired 3,4-*cis*-diastereomer, whereas e.g. an acetyl group is not sufficient. Additionally, a silyl group only allows the distal carbon of the olefin to be attacked by the hydroboration reagent. For protection of the hydroxy functionality of **5**, tert-butyldimethylsilyl was used, the reaction was worked up and the protected crude product was used without further purification in the subsequent hydroboration step. Hydroboration was carried out with 9-BBN, and without any work up or isolation all reagents for Suzuki coupling (base, catalyst and halide) were added directly to the reaction mixture. The mechanism for transmetallation is shown in **Scheme 6**.



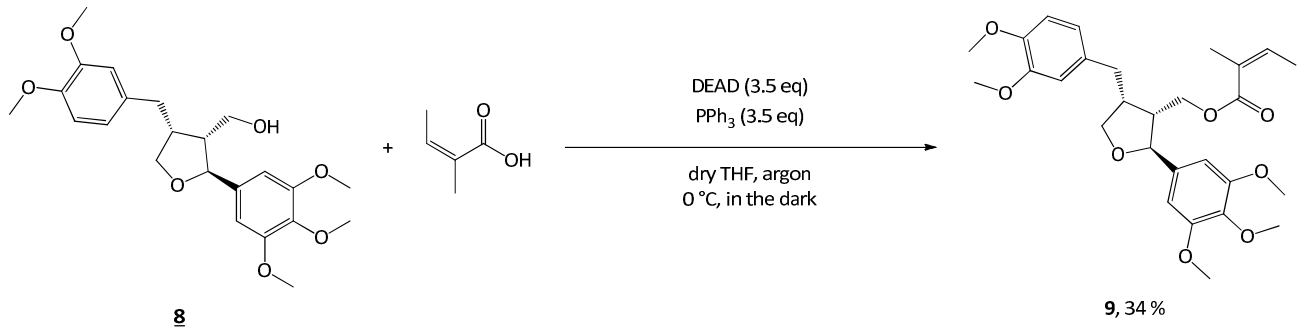
Scheme 6 Mechanism of Hydroboration and subsequent Suzuki coupling employing Pd-catalyst $Pd(dppf)Cl_2.CH_2Cl_2$

In case of 5-methoxyleoligin **9**, aqueous NaOH solution was used as base, which made work up necessary in order to get rid of the water before deprotection with TBAF. In a later stage of the thesis, an improved protocol was used. The aqueous NaOH solution was exchanged for dry Cs_2CO_3, which gave slightly better yields and, more importantly, allowed to do the deprotection without a work-up, extending the one-pot reaction (**Scheme 7**).



Scheme 7 Hydroboration, Suzuki coupling and deprotection as multi- and one-pot reaction

Finally, with 5-methoxyleoligin alcohol **8** in hand, the only functionality left to be introduced was the angelic acid moiety. To preserve the integrity of the Z configuration of the α,β-unsaturated system during the esterification, a Mitsunobu protocol with diethyl azodicarboxylate DEAD as reagent was used (**Scheme 8**). Additionally, the reaction was carried out in the dark to minimize the possibility of isomerization.



Scheme 8 Reactions condition for the Mitsunobu reaction using DEAD

However, the reaction product of the DEAD reagent had nearly the same retention time as the product, and after a separation on silica a second purification step was necessary, using reversed-phase preparative HPLC. In order to simplify purification, the Mitsunobu reaction was repeated

with another reagent, ADD, which gave rise to a different reaction product possessing a different behavior on silica than 5-methoxyleoligin due to different polarity (**Figure 10**).

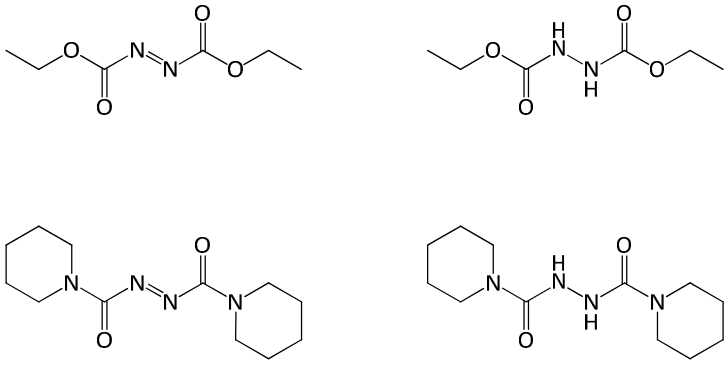
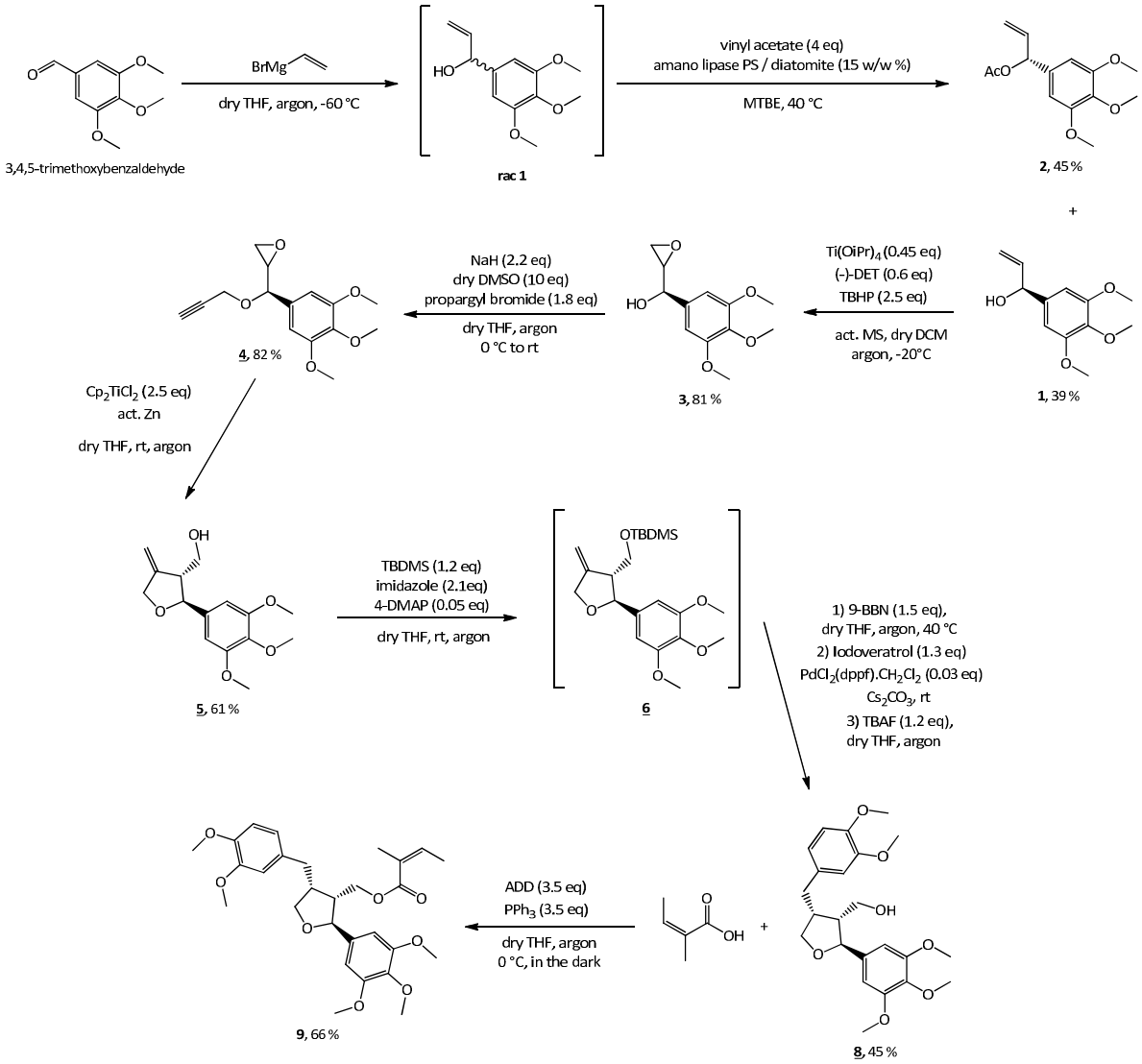


Figure 10 From left to right: structures of DEAD and its reaction product as well as ADD and its reaction product

Therefore, purification could easily be conducted *via* flash column chromatography in a single step and the product was obtained in 63 % and an overall yield of 4 % (starting from 25 g 3,4,5-trimethoxybenzldehyde). In **Scheme 9**, the total synthesis with optimized reactions is shown.



Scheme 9 Improved total synthesis of 5-methoxyleoligin

1.2 Variation of the 3-position

As soon as the methodology for the total synthesis was established, twelve derivatives with modifications at the ester moiety were synthesized (**Figure 11**).

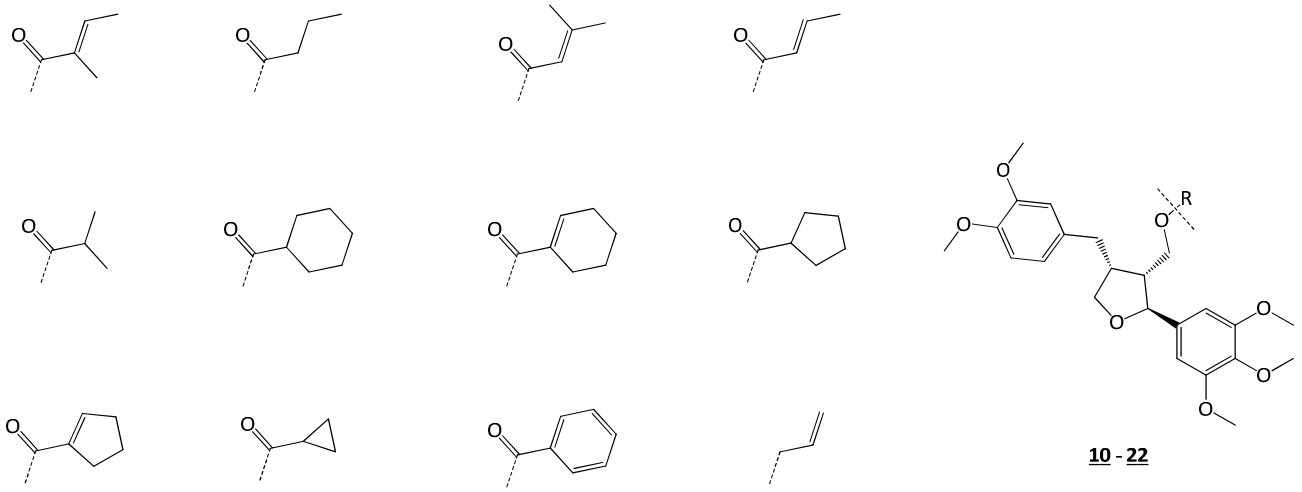
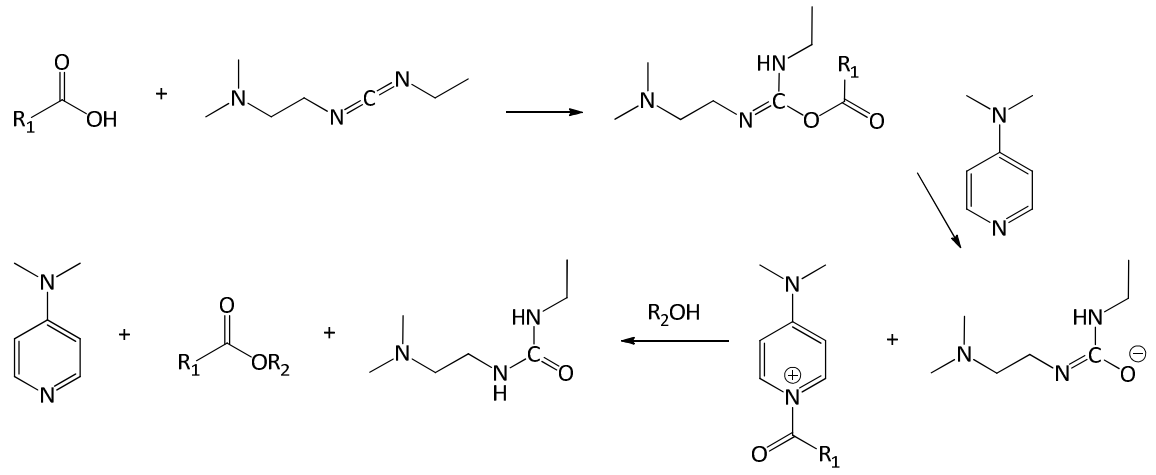


Figure 11 Survey of the synthesized derivatives

Four different reactions were used: two different Steglich reaction protocols for α,β-unsaturated as well as saturated acids, the above mentioned Mitsunobu protocol with ADD, and the before described Williamson ether synthesis protocol.

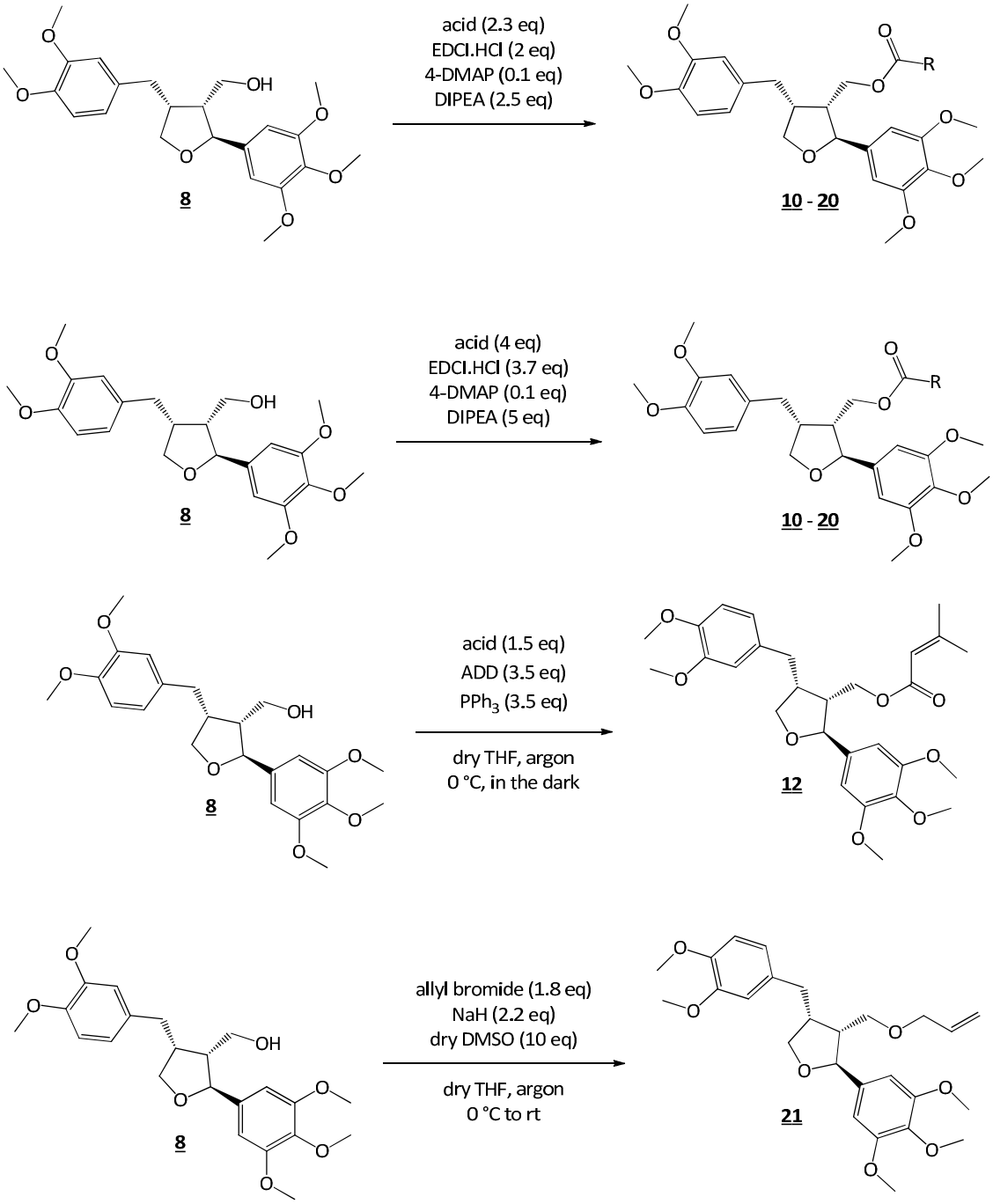
The Steglich reaction was used rather than the Mitsunobu reaction, because it is cheaper and easier concerning preparation und purification of products. The reaction mechanism is shown in **Scheme 10** [65].



Scheme 10 Reaction mechanism of the Steglich esterification with EDCI.HCl and 4-DMAP

The Mitsunobu protocol with ADD, and the before described Williamson ether synthesis protocol were both only used for one derivative, as shown in **Scheme 11**. Preferred application of a

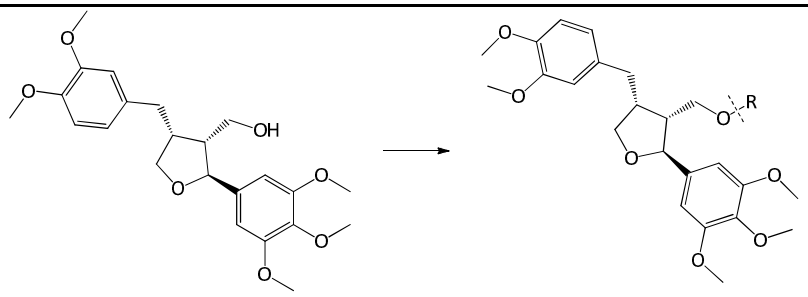
Mitsunobu rather than a Steglich reaction for the preparation of compound **12** was due to isomerization occurring during the Steglich protocol as earlier observed with angelic acid.



Scheme 11 From left to right: EDCI protocol for saturated and unsaturated acids, a Mitsunobu protocol, and a Williamson ether synthesis

For saturated acid derivatives yields were in a range between 72-85 %, for α,β-unsaturated precursors between 56-74 %, while the esterification of benzoic acid gave a yield of 93 %. The

Mitsunobu reaction gave a yield of 66 %, and the Williamson ether synthesis yielded 42 %, but some of the starting material could be recovered. The results are shown in **Table 2.**



8 **10-21**

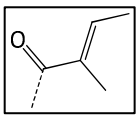
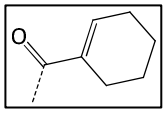
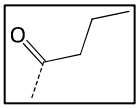
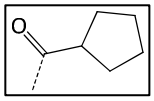
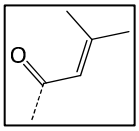
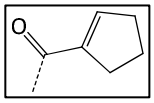
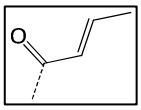
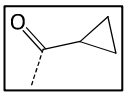
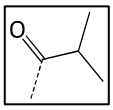
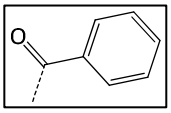
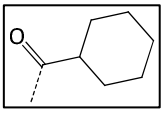
Compound	Yield / %	R	Compound	Yield / %	R
10	70		**16**	56	
11	72		**17**	85	
12	66		**18**	69	
13	74		**19**	75	
14	83		**20**	93	
15	81		**21**	42	

Table 2 Overview of all ester derivatives

1.3 Variation of the 4-position

Next, variation of the benzyl moiety was investigated. Eleven derivatives were synthesized (**Figure 12**), using the improved protocol for the hydroboration-coupling-deprotection sequence and employing the outlined halide reaction partners.

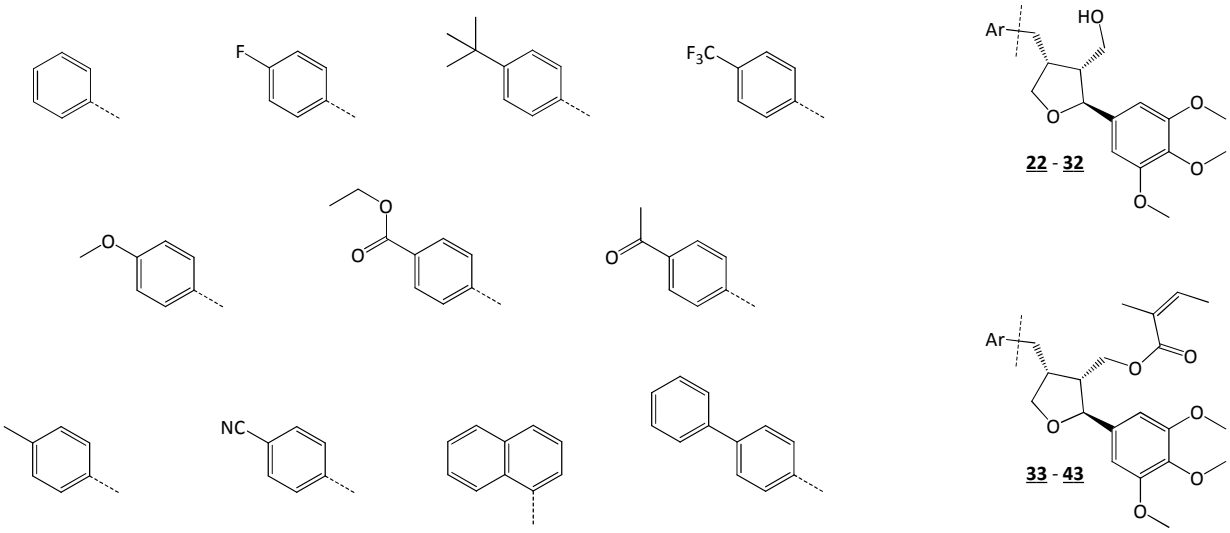
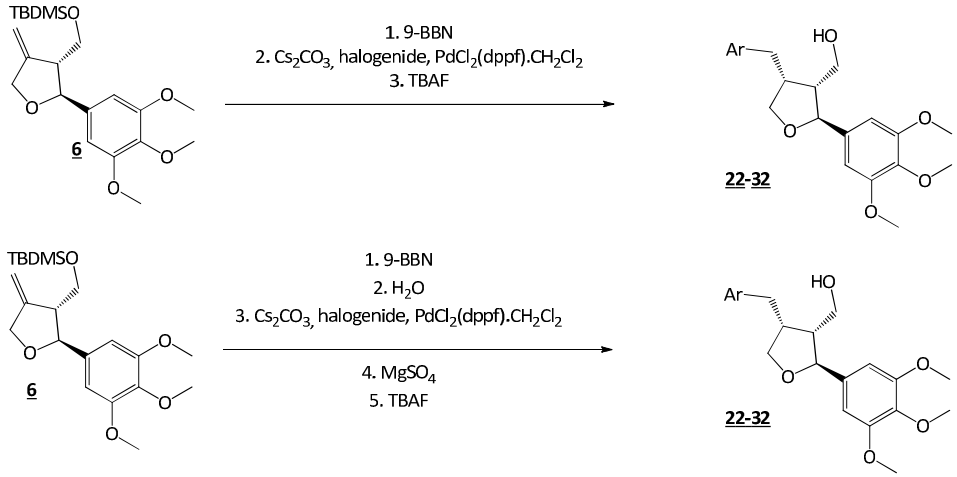


Figure 12 Survey of the synthesized derivatives

However, as 9-BBN is capable to reduce e.g. acetophenone (tested in preliminary experiments), coupling reactions were carried out slightly different in cases where the substituents at the aryl could be reduced. Prior to addition of the base, halide, and catalyst, 1 equiv of water was added to destroy residual 9-BBN. Furthermore, 1 equiv of $MgSO_4$ was added to catch residual water before starting the deprotection (**Scheme 12**).



Scheme 12 Improved reaction conditions for the reaction sequence of hydroboration, Suzuki coupling and deprotection

Yields for Suzuki couplings were on average around 40 %, and a positive correlation between yield and electron deficiency of the coupling partner was observed. Results are shown in **Table 3**. An improvement of this step with respect to the moderate yields would be eligible and probably possible, since conversion of the starting material is complete and no homocoupling can be observed.

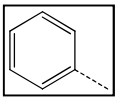
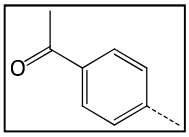
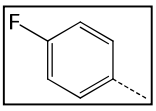
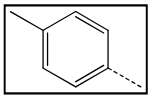
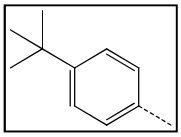
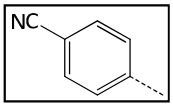
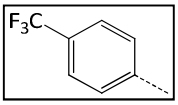
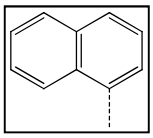
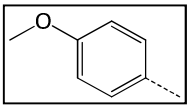
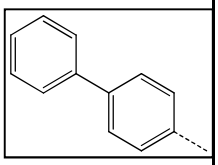
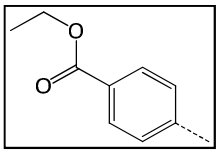
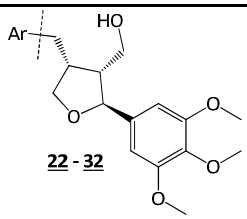
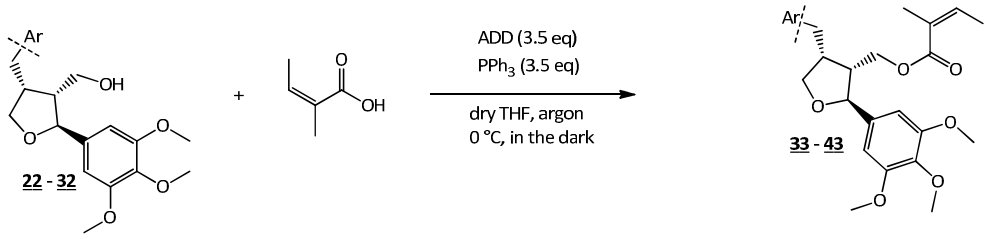
Compound	Yield / %	R	Compound	Yield / %	R
22	36		**28**	24	
23	47		**29**	43	
24	49		**30**	41	
25	62		**31**	45	
26	28		**32**	45	
27	45		 **22** - **32**		

Table 3 Overview of benzyl derivatives of 5-methoxyleoligin alcohol

Subsequent Mitsunobu reaction according to the improved conditions (**Scheme** 13) was performed on each alcohol derivative, giving products in yields between 60-85 %. The results are shown in **Table 4**.



Scheme 13 Mitsunobu reaction for synthesis of different derivatives

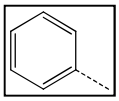
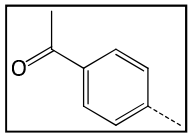
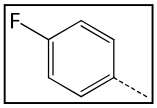
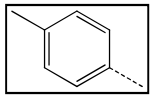
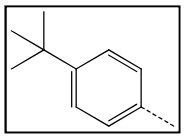
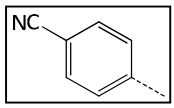
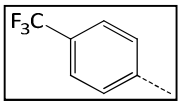
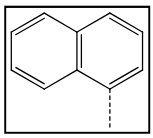
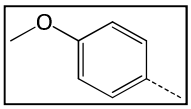
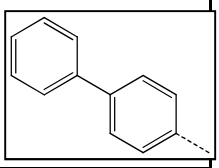
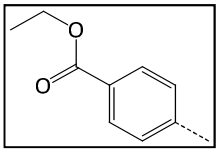
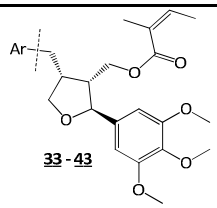
Compound	Yield / %	R	Compound	Yield / %	R
33	61		**39**	76	
34	67		**40**	64	
35	67		**41**	84	
36	67		**42**	61	
37	58		**43**	61	
38	81				

Table 4 Overview of benzyl derivatives of 5-methoxyleoligin

In total, twelve derivatives with varied ester position and eleven derivatives with variation of the benzyl moiety were synthesized and submitted for biological testing. Additionally, also the alcohols of the benzyl derivatives were submitted, in case the acid moiety has no or only small influence on biological activity.

2. Biology

Assays concerning macrophage cholesterol efflux were carried out in the Laboratory of Univ.-Prof. Dr. Verena Dirsch from the Department of Pharmacognosy at the University of Vienna. All other assays were performed at the Institute of Pharmacy / Pharmacognosy, University of Innsbruck, in the laboratory of Univ.-Prof. Dr. Hermann Stuppner [66].

2.1 Macrophage Cholesterol Efflux

This assay performed to test the ability of a substance to promote cholesterol efflux from macrophages to the surrounding and can, when using inhibitors or KO cells, also be used to determine the impact of different pathways to overall cholesterol efflux. Therefore appropriate cells, in this case THP-1 cells were cultured, differentiated and labeled for 24 h with ($1H^3$)-cholesterol and unesterified cholesterol in the presence of the indicated treatments (leoligin, 5-methoxyleoligin, and 5,5'-dimethoxyleoligin), dissolved in serum-free medium with 0.1 % bovine serum albumin (BSA). Cells were then incubated again for 6 h either in presence or absence of apoA-I, an apolipoprotein which is the major protein component of high density lipoprotein (HDL) and promotes cholesterol efflux. Cells and medium were separated and the radioactivity in both was determined. The percentage of cholesterol efflux was calculated by dividing the media-derived radioactivity by the sum of the radioactivity in the media and the cells. The specific apoA-I-mediated efflux was calculated as the difference between the efflux in the presence or absence of apoA-I (**Figure 13**). The solvent vehicle (DMSO, 0.1 %) served as negative control, whereas Pioglitazone (10 µM), was used as positive control.

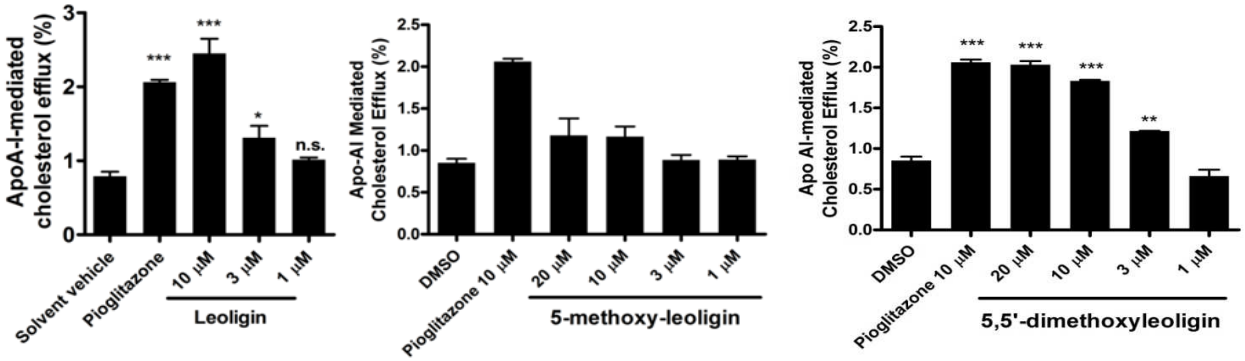


Figure 13 Results of leoligin, 5-methoxyleologin and 5,5'-dimethoxyleoligin tested in a macrophage cholesterol efflux activation assay in THP-1 cells. The bars represent means ± SD of three independent experiments. ***P<0.001, *P<0.05 vs. the solvent vehicle control (n=3, ANOVA/Bonferroni).

2.2 Wound scratch healing assay

Wound scratch healing assays are performed to investigate the ability of a substance to either inhibit or promote cell migration. A monolayer of confluent growing cells is wounded with a pin, the indicated treatments applied and cell movement is monitored over time [67]. In case of testing 5-methoxyleoligin, the percentage of migration was estimated 9 h after wounding the cell layer (**Figure 14**).

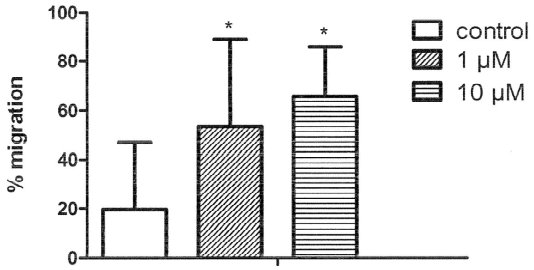


Figure 14 Percent migration of endothelial cells (HUVEC's) promoted by 5-methoxyleoligin. All experiments were performed in triplicates. Significant differences to the control are indicated by an asterisk (* $p<0.05$). [24]

Although the error bars are quite high, there is a clear indication that 5-methoxyleoligin promotes endothelial cell migration.

2.3 Capillary Tube Formation and Spheroid Sprouting Assay

The ability of endothelial cells to form three-dimensional structures can be tested with capillary tube formation and spheroid sprouting assays [68]. In these assays, endothelial cells are grown on plastic culture dishes coated with different matrices, like matrigel, collagen or fibrin clots, to simulate the particular *in vivo* situation. The process of forming tubes is a crucial step in angiogenesis, therefore it was important that 5-methoxyleoligin induced capillary formation of endothelial cells on matrigel. Already after 6 h of incubation a significant increase of capillaries per mm^2 was monitored (**Figure 15 A and C**). Additionally, a spheroid sprouting assay was performed, testing again endothelial cells, but this time in a three-dimensional collagen matrix. Also in this assay 5-methoxyleoligin was confirmed as proangiogenic substance, as it showed promotion of sprout number as well as sprout length after 24 h of incubation (**Figure 15B**).

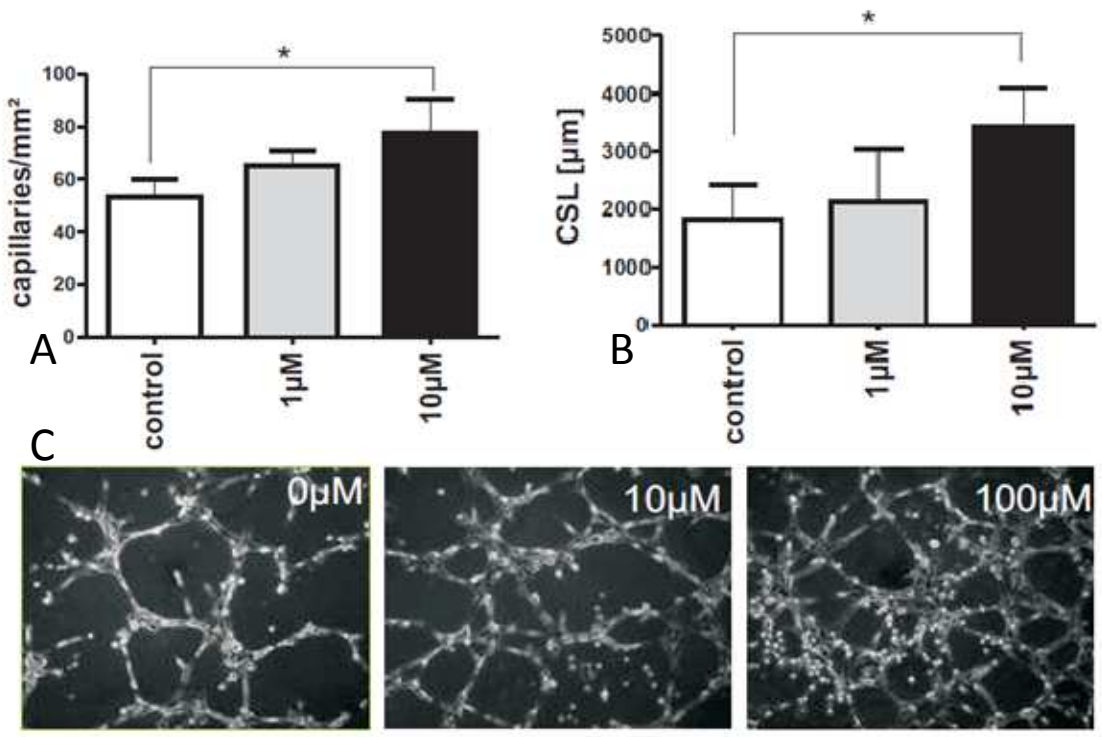


Figure 15 A: number of capillaries per mm² after treatment with different doses of 5-methoxyleoligin in matrigel. B: Cumulative sprout length in a spheroid sprouting assay testing 5-methoxyleoligin. C: Pictures of tube formation at different concentrations of 5-methoxyleoligin in matrigel (magnification: 100x). All experiments were performed in triplicates. Significant differences to the control are indicated by an asterisk (* $p<0.05$) [24, 66].

2.4 Chick chorioallantoic membrane (CAM) assay

The CAM assay is a whole-animal assay and therefore classified as *in vivo* experiment [68]. The contents of a whole chicken egg are transferred into a plastic culture dish and incubated for 4-days. After application of a graft containing 5-methoxyleoligin the egg is additionally incubated for 3 days and the blood vessel formation was analyzed in a specified ring area. 5-Methoxyleoligin increases blood vessel formation significantly in a dose dependent manner, as shown in **Figure 16 A, B** and **C**

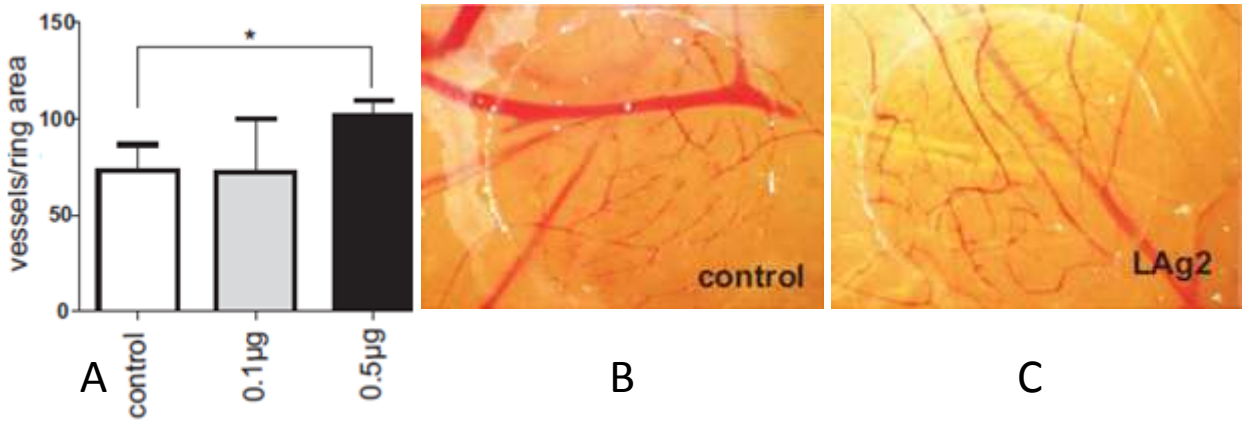


Figure 16 A: Number of vessels formed after incubation with different doses of 5-methoxyleoligin. B: Picture of the graft without 5-methoxyleoligin. C: Picture of the graft after incubation with 0.5 µg 5-methoxyleoligin. All experiments were performed in triplicates. Significant differences to the control are indicated by an asterisk (* p<0.05). [24, 66]

2.5 Rat MI Assay

The rat MI assay is used for the investigation of the impacts of MI, especially congestive heart failure [69]. Results are generally satisfactory comparable with studies in humans; however, there are some differences due to the trigger of MI. In humans, the most frequent cause is coronary artery disease, which is characterized by arterial lesions and complications after an MI include arrhythmias, transient ischemia and also recurrence of coronary occlusion. In the rat model, where infarction is normally induced by ligation of a coronary artery, those characteristics are absent.

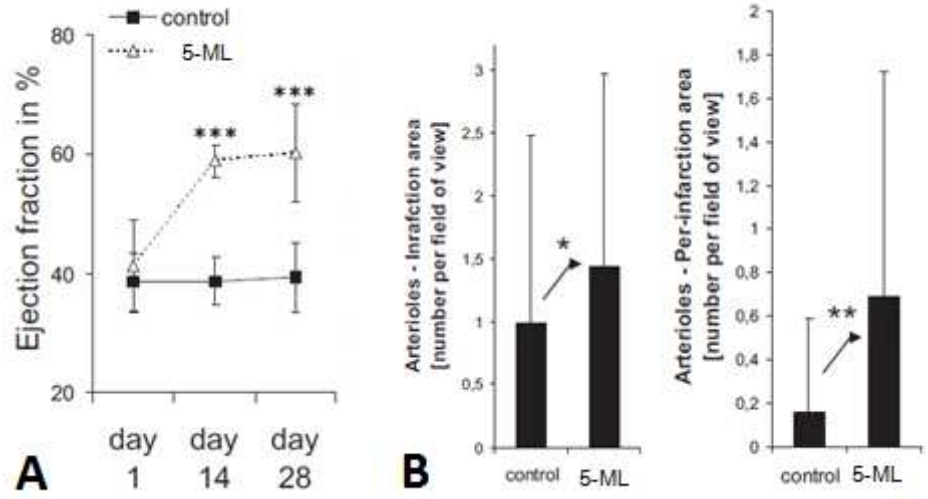


Figure 17 A: Ultrasound-based analysis of the ejection fraction in rats after MI (after 1, 14 and 28 days) and injection of either the solvent control or 5-methoxyleoligin. Significant differences compared to the control are indicated by asteriks (* p<0.001). B: Number of arterioles in the infarction and peri-infarction area after an induced MI in rats (n=7). Significant differences compared to the control are indicated by asteriks (* p<0.05; ** p<0.01) [66].**

For the testing of 5-methoxyleoligin, MI was induced in 8-10 weeks old male rats through left anterior descending coronary artery ligation. Animals treated according to the "Principles of Laboratory Animal Care" and the "Guide for the Care and Use of Laboratory Animals" [24]. The procedure involves anesthetization of the animal, ventilation by intubation, a minithoracotomy and the infarction was then induced by suture of the vessel [66]. 30 minutes after ligation solvent control or a 10 µM 5-methoxyleoligin solution were injected into the infarction zone (5 injections à 10 µl per animal), followed by closure of the operation situs. 5-Methoxyleoligin showed significant increase in the ejection fraction (**Figure 17 A**) after two and four weeks, which is important as prove of regaining heart function, with the ejection fraction in percent being defined as ([EDV-ESV]/EDV) x 100 with EDV = end-diastolic and ESV = endsystolic volume. Additionally, 5-methoxyleolgin could increase the number of arterioles in the infarction as well as the per-infarction area (**Figure 17B**).

3. Conclusions

In this thesis, a valuable method for the synthesis of 5-methoxyleoligin was presented, which can in addition easily be used to generate a compound library, using 5-methoxyleolgin as lead structure.

Although a compound with scaffold of **5** was already prepared in a similar manner in the literature, the kinetic resolution using Amano lipase PS was newly introduced, improving the ee of the product and facilitating the transformation into a dynamic kinetic resolution in the future. The diastereoselective hydroboration and subsequent Suzuki-coupling enables the rapid generation of a compound library, and is additionally not known on systems like 5-methoxyleoligin in the literature so far, therefore representing a new methodology. Concerning the last step, transforming the hydroxy functionality either into an ester or an ether, four different protocols could be established, again allowing a rapid generation of derivatives.

Furthermore, the strong proangiogenic activity of 5-methoxyleolgin could be demonstrated in several *in vitro* and *in vivo* assays, as well as the ability of this class of compounds to promote macrophage cholesterol efflux. Regarding both biological activities, the synthesized derivatives have to be tested in the near future to obtain an idea on structural motives essential for these activities. As soon as there is a lead in a certain direction, co-variation of both ester and benzyl moiety should be performed, in order to optimize the structure towards the particular activity.

III. Experimental

1. General Notes

1.1 Chemicals

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

1.2 Dry Solvents

Dry solvents were obtained by passing pre-dried material through a cartridge containing activated alumina *via* a solvent dispensing system unless otherwise noted and stored under nitrogen.

1.3 Cryostat

For low reaction temperatures and reactions that required cooling overnight a Cryostat RKT20 Lauda was used.

1.4 Chromatography (TLC, MPLC, HPLC)

TLC's were performed on aluminum coated silica gel 60 F_{254} from Merck and spots were visualized with UV light and/or staining with cerium ammonium nitrate dip reagent.

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

Preparative HPLC was performed on a Shimadzu LC-8A device with an SIL-10AP autosampler, SPD-20 detector and FRC-10A fraction collector. For separation the following conditions were used:

column: Phenomenex Luna RP18, 10 µm , 100A, 250x21.20 mm; injection volume: 1.5 mL; column flow: 20 mL/min; detection wavelength: 254 nm; eluent: MeOH/H_2O, gradient 70-72 % MeOH in 25 min, then 72-75 % MeOH in 15 min.

Analytical HPLC to determine the ee value of **1** and **2** was performed on a Thermo Dionex UltiMate 3000 device. For separation the following conditions were used:

Column: Daicel Chiralpak AS-H , 5 µm, 100A, 250x4.6 mm; injection volume: 1.5 µl; column flow: 1 mL/min; detection wavelength: 210 nm; eluent: *n*-heptane/*iso*-propanol=90/10

1.5 Specific rotation

An Anton Parr MCP500 polarimeter was used to measure specific rotation. Values were determined at 20 °C ± 0.05 °C and over an integration period of 20 sec.

1.6 GC-MS

A Thermo Finnigan Focus GC / DSQ II using a standard capillary column BGB 5 (30m x 0.32 mm ID) was used for GC-MS runs. The following settings were used as standard:

Ionization method: Electron ionization (70 eV)

Injection: 1 µL (hot needle-technique), split-injection (ratio 1:8)

Flow: 2 mL/min Helium

Injectorblock temperature: 250 °C

MS-transferline temperature: 280 °C

Method 1: 100 °C for 2 min, 100 - 280 °C in 10 min, 280 °C for 3 min

Method 2: 80 °C for 2 min, 80 - 280 °C in 10 min, 280 °C for 24 min

Method 3: 80 °C for 2 min, 80 - 280 °C in 10 min, 280 °C for 29 min

Method 4: 80 °C for 2 min, 80 - 280 °C in 10 min, 280 °C for 39 min

Reported are: all fragment signals at/over mass (m/z) 100 and at/over 10 % relative intensity

all molecular peaks (regardless the relative intensity)

all peaks with 100 % intensity (regardless the mass)

1.7 HR-MS

HR-MS was carried out by Prof. E. Rosenberg at Vienna University of Technology, Institute for Chemical Technologies and Analytics.

Analytical method: All samples were analyzed by LC-IT-TOF-MS in only positive ion detection mode upon recording of MS and MS/MS spectra. For the evaluation in the following, only positive ionization spectra were used (where the quasi-molecular ion is the one of $[M+NaH^+]$ or $[M+NaNa^+]$), and further data or information were not taken into consideration.

Instrumental parameters: Shimadzu Prominence HPLC, consisting of: solvent degassing unit (DGU-20 A3), binary gradient pump (2 x LC-20AD), auto-injector (SIL-20A), column oven (CTO-20AC), control module (CBM-20A), and diode array detector (SPD-M20A)

MS System: Shimadzu IT-TOF-MS with electrospray interface.

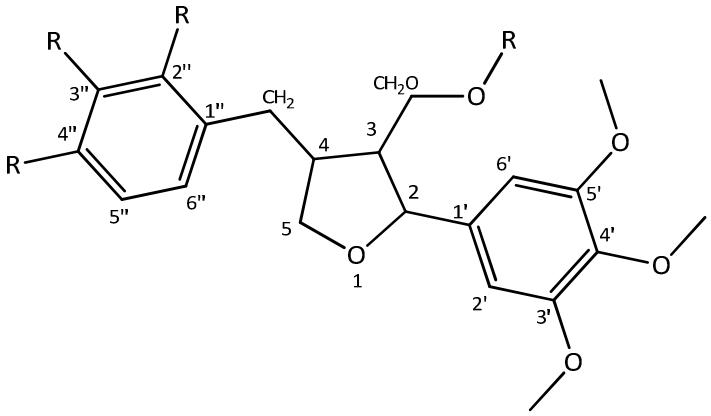
Chromatography (parameters: Short_Col_PI_NI_MS2):

Column: Phenomenex ODS(3), 4 mm x 4.6 mm, 5 µm particles, operated at 40 °C; Column flow: 0.5 ml/min; Injection volume: 2 µl; Gradient: A: H_2O + 0.1 % formic acid, B: MeOH; MS parameters as in autotune. Data recorded with detector voltage at autotune value. Scan range: 100-1000 amu for both, MS (PI and NI)-detection. ES ionization. Cycle time <0.6 s. CDL-temperature 200 °C, Heating block temperature: 200 °C, scan range 200-400 nm

1.8 NMR-Spectroscopy

^1H- and ^{13}C-NMR spectra were recorded from $CDCl_3$ solutions on a Bruker AC 200 (200 MHz) or on a Bruker Avance UltraShield 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm

relative to the nominal residual solvent signals: ^{1}H: 7.26 ppm, ^{13}C: 77.0 ppm. Allocations of the structures were carried out as follows:



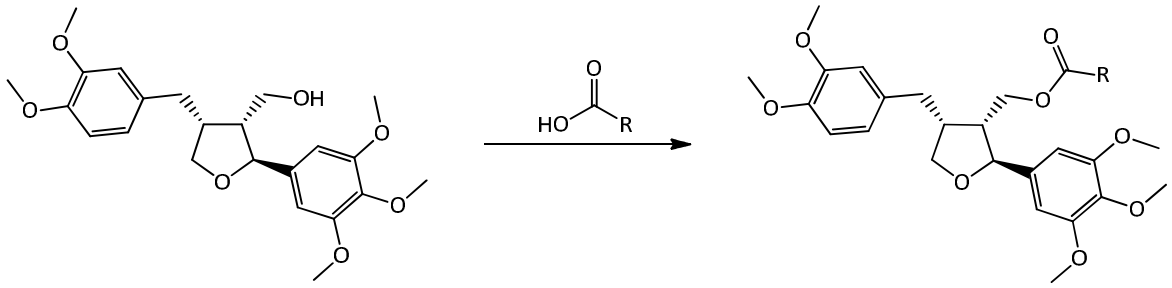
2. Abbreviations

4-DMAP	4-dimethylaminopyridine
9-BBN	9-borabicyclo[3.3.1]nonane
act.	activated
ADD	1,1'-(azodicarbonyl)dipiperidine
aqu.	Aqueous
BSA	Bovine serum albumin
CAD	coronary artery disease
CAM	chorioallantoic membrane
cp	cyclopentadienyl
CSL	cumulative sprout length
DCM	dichloromethane
DEAD	diethyl diazenedicarboxylate
DET	diethyl tartrate
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EDCI.HCl	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
EtOAc	ethyl acetate
equiv	equivalent
GC-MS	gas chromatography - mass spectroscopy

HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectroscopy
HUVEC	human umbilical vein endothelial cell
MI	myocardial infarction
MPLC	medium pressure liquid chromatography
MTBE	2-methoxy-2-methylpropane
NMR	nuclear magnetic resonance
PE	petroleum ether
ppm	parts per million
rac.	racemic
rt	room temperature
satd.	saturated
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydroperoxide
THF	tetrahydrofuran
TLC	thin layer chromatography

3. General Procedures

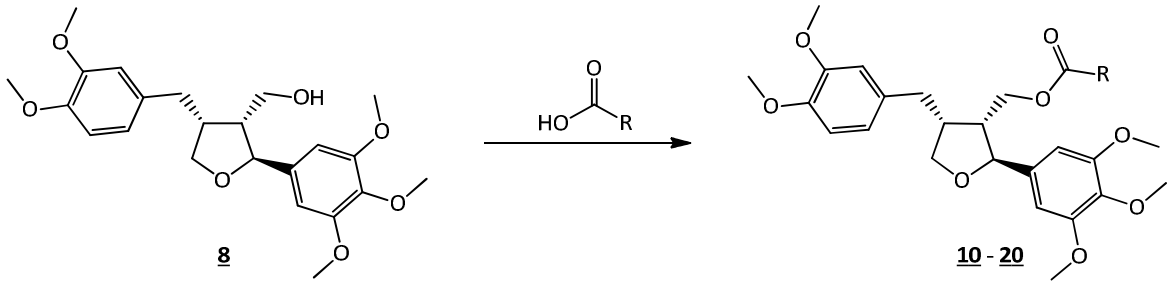
3.1 General Procedure A



8 **10** - **20**

The acid (4 equiv) and 4-DMAP (0.1 equiv) were dissolved in dry DCM (0.3 M with respect to acid) under argon at 0 °C and EDCI.HCl (3.7 equiv) was added. The solution was stirred for 3 h, then it was transferred to a mixture of **8** (1 equiv) and DIPEA (5 equiv) under argon. The resulting suspension was stirred for 20 h at rt and reaction progress was monitored by TLC. When the reaction was finished the suspension was directly applied to column chromatography (MPLC, 9 g silica, 20 mL/min flow rate, first 10-22 % EtOAc in 10 min, then 22 % EtOAc for 6 min, then 22 - 65 % in 30 min. 9 g silica cartridges were routinely used for reactions using less than 40 mg of **8**).

3.2 General Procedure B

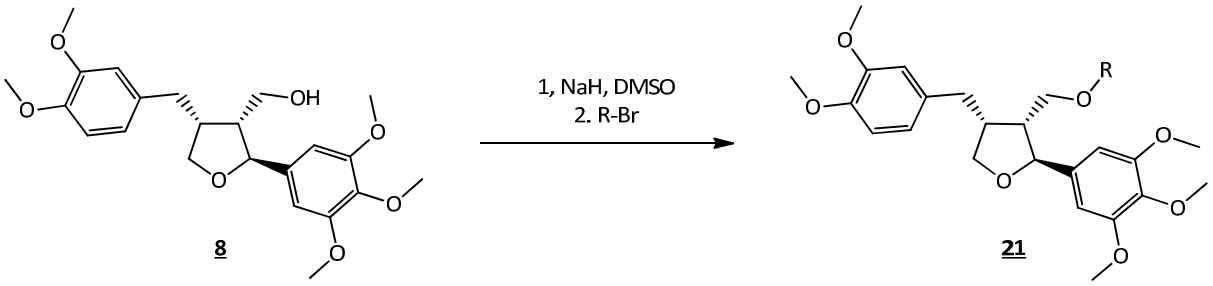


8 **10** - **20**

The acid (2.3 equiv) and 4-DMAP (0.1 equiv) were dissolved in dry DCM (0.1 M with respect to acid) under argon at 0 °C and EDCI.HCl (2 equiv) was added. The solution was stirred for 3 h, before being transferred to a mixture of **8** (1 equiv) and DIPEA (2.5 equiv) under argon. The resulting suspension was then stirred for 20 h at rt and the reaction progress monitored by TLC. When the reaction was finished the suspension was directly applied to column chromatography (MPLC, 9 g silica,

20 mL/min flow rate, first 10-22 % EtOAc in 10 min, then 22 % EtOAc for 6 min, then 22 - 65 % in 30 min. 9 g silica cartridges were routinely used for reactions using less than 40 mg of **8**).

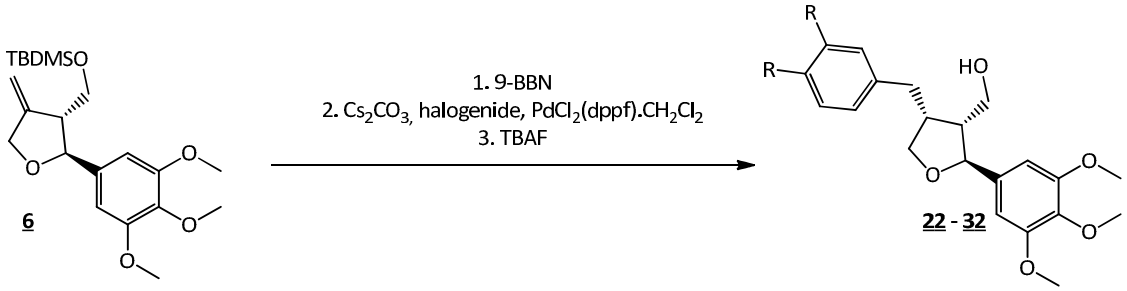
3.3 General Procedure C



8 **21**

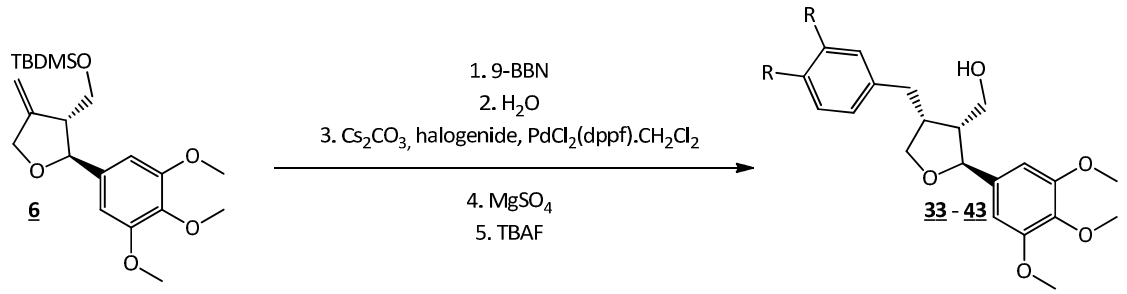
NaH (60 % dispersion in mineral oil, 2.2 equiv) was dissolved in dry THF (1M with respect to NaH) under argon atmosphere and cooled with an ice bath. Dry DMSO (10 equiv) was added. To this suspension substrate **8** (1 equiv) added slowly as a solution in dry THF (0.4 M with respect to **8**). After stirring for 15 min a solution of alkylbromide in THF was added slowly, usually followed by additional THF to dissolve the formed slurry. The ice bath was then removed and the reaction mixture was stirred for 48 h. Progress of the reaction was monitored by TLC until complete conversion was indicated. The solution was cooled to 0 °C again and HCl (1M, 1 equiv) was added drop wise. Most of the THF was then removed *in vacuo* and water was added. The aqueous layer was extracted with 4 x Et_2O, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the solvent was removed. The crude product was purified *via* column chromatography (MPLC, 9 g silica, 20 mL/min flow rate, first 10-22 % EtOAc in 10 min, then 22 % EtOAc for 6 min, then 22 - 65 % in 30 min. 9 g silica cartridges were routinely used for reactions using less than 40 mg of **8**).

3.4 General Method D



A flask was charged with substrate **7** (1 equiv) under argon atmosphere followed by 9-BBN (0.5 M in THF, 1.5 equiv). After 24 h, the solution was transferred into an 8 mL thermoblock vial charged with Cs_2CO_3 (5 equiv), $PdCl_2(dppf).CH_2Cl_2$ (0.025 equiv) and halide (1.3 equiv) under argon atmosphere. The resulting suspension was stirred for 27 h before TBAF (1.5 equiv) was added. After 22 h deprotection was complete (monitored by TLC and GC-MS) and Et_2O as well as water were added. The layers were separated and the aqueous layer was extracted with 4 x Et_2O and 2 x EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed in *vacuo*. The crude product was purified *via* column chromatography (MPLC, 9 g silica, 15-70 % EtOAc in 45 min. 9 g silica cartridges were routinely used for reactions using less than 60 mg of **6**).

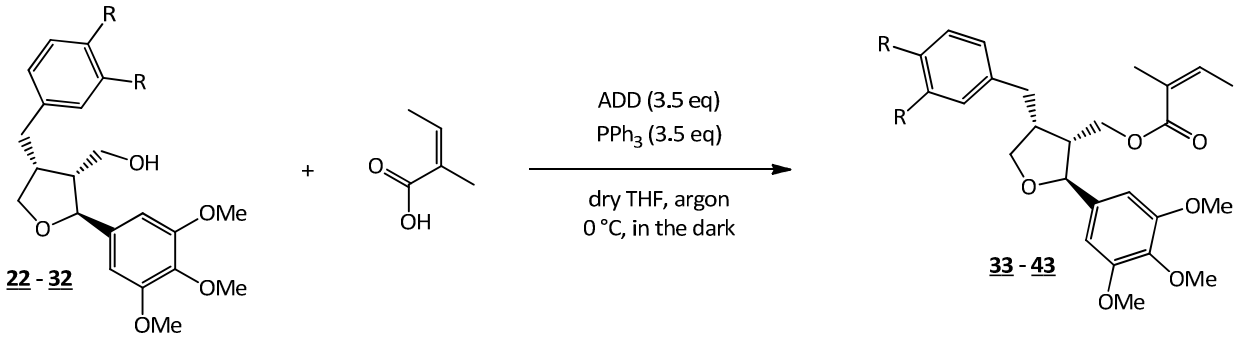
3.5 General Method E



A flask was charged with substrate **6** (1 equiv) and 9-BBN (0.5 M in THF, 1.5 equiv) was added under argon atmosphere. After 24 h, water (1 equiv) was added and stirring was continued for 30 min, before the solution was transferred into an 8 mL thermoblock vial charged with Cs_2CO_3 (5 equiv), $PdCl_2(dppf).CH_2Cl_2$ (0.025 equiv) and halide (1.3 equiv) under argon atmosphere. The resulting suspension was stirred for 27 h then $MgSO_4$ (1 equiv) was added and stirring was continued for 30 in. Finally, TBAF (1.5 equiv) was added. After 22 h deprotection was complete (monitored by TLC

and GC-MS) and Et_2O and water were added. The layers were separated and the aqueous layer was extracted with 4 x Et_2O and 2 x EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed in *vacuo*. The crude product was purified *via* column chromatography (MPLC, 9 g silica, 15-70 % EtOAc in 45 min. 9 g silica cartridges were routinely used for reactions using less than 60 mg of **6**).

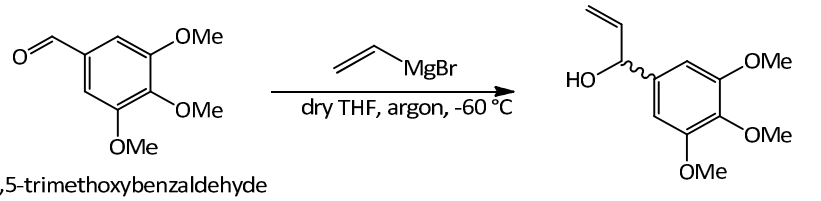
3.6 General Method F



The substrate (1 equiv), angelic acid (1.5 equiv) and PPh_3 (3.5 equiv) were charged under argon, cooled with an ice bath and dissolved in THF (0.13 M). ADD (3.5 equiv) was added slowly and the reaction was stirred for 18.5 h in the dark while being allowed to warm to rt. Reaction progress was monitored by TLC. When the reaction was finished, brine was added, the layers separated and the aqueous phase was extracted with 3 x Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed via evaporation. The crude product was purified *via* column chromatography (MPLC, 9 g silica, 20 mL/min flow rate, first 10-22 % EtOAc in 10 min, then 22 % EtOAc for 6 min, then 22 - 65 % in 30 min. 9 g silica cartridges were routinely used for reactions using less than 40 mg of **8**).

4. Synthesis of 5-Methoxyleoligin

4.1 (±)-1-(3,4,5-Trimethoxyphenyl)prop-2-en-1-ol (rac 1)



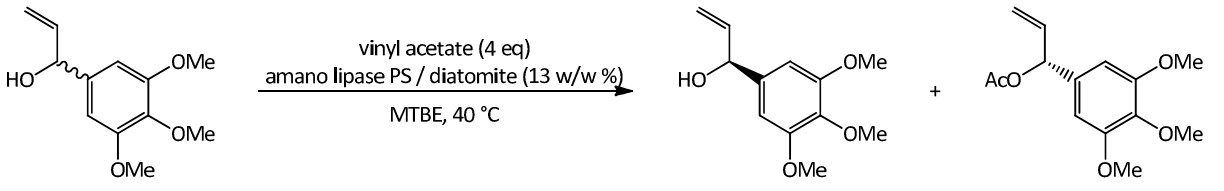
3,4,5-trimethoxybenzaldehyde
Chemical Formula: $C_{10}H_{12}O_4$
Molecular Weight: 196,20

rac 1
Chemical Formula: $C_{12}H_{16}O_4$
Molecular Weight: 224,25

A round bottomed flask was charged with 3,4,5-trimethoxybenzaldehyde (25 g, 127.4 mmol, 1 equiv) under argon atmosphere. Dry THF (175 mL, 0.73 M) was added and the solution was cooled to -60 °C. Vinylmagnesium bromide (146.5 mL, 146.5 mmol, 1.15 equiv) was added drop wise via a dropping funnel over 2 h while the temperature was kept nearly constant (± 5 °C). Reaction progress was monitored by TLC. When the reaction was finished, the mixture was then allowed to warm to -10 °C. Satd. aqu. NH_4Cl solution (30 mL) was added drop wise over 15 min and the temperature was maintained below +10 °C. Subsequently water (130 mL) was added to dissolve the magnesium salts and the product was extracted with Et_2O (1 x 150 mL, 2 x 75 mL). The combined organic layers were washed with satd. aqu. $NaHCO_3$ solution (45 mL) and brine (30 mL), dried over Na_2SO_4 and filtered through a plug of silica (5 g, preconditioned with Et_2O). The solvent was removed in *vacuo* and the product was dried in *vacuo* without further purification. The purity of the product was determined by H-NMR (> 95 %).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.95 (s, 1H, OH), 3.82 (s, 3H, OCH_3), 3.86 (s, 6H, 2xOCH_3), 5.13 (d, J= 5.87 Hz, 1H, H2), 5.16-5.43 (m, 2H, H4), 5.93-6.13 (m, 1H, H3), 6.59 (s, 2H, H2' & H6')

4.2 Enantiomeric separation of (R)- and (S)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-ol (1 & 2)



rac 1
Chemical Formula: $C_{12}H_{16}O_4$
Molecular Weight: 224,25

1
Chemical Formula: $C_{12}H_{16}O_4$
Molecular Weight: 224,25

2
Chemical Formula: $C_{14}H_{18}O_5$
Molecular Weight: 266,29

Rac 1 (28.3 g, 126.2 mmol, 1 equiv) was dissolved in MTBE (690 mL, 0.18 M) and vinyl acetate (40.5 mL, 504.8 mmol, 4 equiv). The solution was kept at 40.5 °C and Amano lipase PS on diatomite (3.68 g, 13 w/w %) was added. Reaction progress was monitored by chiral HPLC. After 76 h at this temperature the enantiomeric separation was complete and the mixture was filtered through Celite 545. The solvent was removed in *vacuo* and the compounds were separated by column chromatography (MPLC, 2 x 90 g silica in sequence, 50 mL/min flow rate, 12 % EtOAc for 50 min, then 12-100 % in 60 min).

(**S)-1-(3,4,5-Trimethoxyphenyl)prop-2-en-1-ol (1):**

Yield: 11.17 g (39 %, >99.9 % ee)

Appearance: slightly yellow oil [70]

TLC: Rf(PE/EtOAc = 0/1) = 0.28

Specific rotation: $[\alpha]_D^{20}$ = +8.74 (MeOH; c 1.000)

GC-MS (EI, 70 eV): Method 1; Retention time: 8.38 min; Main fragments (relative intensity): 224 (M^+, 81), 193 (38), 181 (25), 169 (100), 154 (24), 151 (24), 149 (25), 139 (19), 138 (52), 123 (18), 121 (31)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.95 (bs, 1H, OH), 3.82 (s, 3H, OCH_3), 3.86 (s, 6H, 2xOCH_3), 5.13 (d, J= 5.87 Hz, 1H, C<u>H</u>-OH), 5.16-5.43 (m, 2H, CH=C<u>H</u>$_2$), 5.93-6.13 (m, 1H, CH-CH_2), 6.59 (s, 2H, C<u>H</u>-C-C<u>H</u>)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 56.01 (q 3' OCH_3 & 5' OCH_3), 60.76 (q, 4' OCH_3), 75.34 (d, <u>C</u>H-OH), 103.08 (d, <u>C</u>H-C-<u>C</u>H), 115.19 (t, CH=<u>C</u>H$_2$), 138.31 (s, C_q), 139.97 (d, <u>C</u>H=CH_2), 153.24 (s, *m*-C_{aryl}). One C_q not visible.

(R)-1-(3,4,5-Trimethoxyphenyl)allyl acetate (2):

Yield: 15.17 g (45 %, 86 % ee)

Appearance: nearly colorless oil [71]

TLC: Rf(PE/EtOAc = 1/2) = 0.27

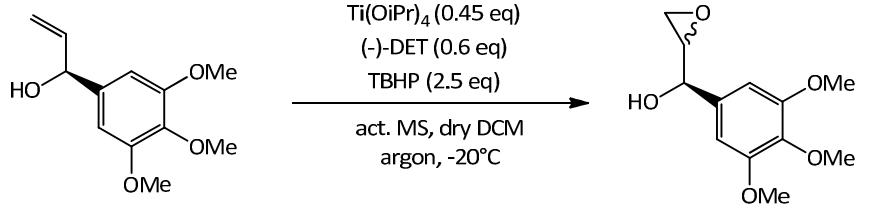
Specific rotation: $[\alpha]_D^{20}$ = +45.308 (MeOH; c 1.2531)

GC-MS (EI, 70 eV): Method 1; Retention time: 8.76 min; Main fragments (relative intensity): 266 (M^+, 36), 224 (73), 207 (30), 206 (27), 191 (69), 177 (27), 176 (100), 163 (23), 161 (41), 149 (31), 148 (23), 133 (24), 121 (19), 106 (27), 105 (21), 103 (19)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.11 (s, 3H, $COCH_3$), 3.82 (s, 3H, OCH_3), 3.85 (s, 6H, 2xOCH_3), 5.19-5.36 (m, 2H, CH=CH_2), 5.88-6.07 (m, 1H, CH=CH_2), 6.18 (d, J=5.67 Hz, 1H, OCH), 6.56 (s, 2H, CH-C-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 21.3 (q, CO$\underline{C}H_3$), 56.1 (q, 2xOCH_3), 60.8 (q, OCH_3), 76.1 (d, OCH), 104.3 (d, $\underline{C}$H-C-$\underline{C}$H), 116.8 (t, CH=$\underline{C}H_2$), 134.4 (s, *p*-C_{aryl}), 136.0 (d, $\underline{C}$H=CH_2), 137.8 (s, CH-$\underline{C}$(CH)-CH), 153.3 (s, *m*-C_{aryl}), 169.9 (s, C=O).

4.3 (1R)-Oxiran-2-yl(3,4,5-trimethoxyphenyl)methanol (3)



1
Chemical Formula: $C_{12}H_{16}O_4$
Molecular Weight: 224,25

3
Chemical Formula: $C_{12}H_{16}O_5$
Molecular Weight: 240,25

Dry DCM (150 mL), (-)-DET (2.789 g, 12.536 mmol, 0.6 equiv) and **1** (5.085 g, 22.676 mmol, 1 equiv) were (additionally) dried over activated MS over night under argon atmosphere. (-)-DET was dissolved in dried DCM (1 mL) and cooled to -20 °C *via* a cryostat. $Ti(OiPr)_4$ (3.00 mL, 10.145 mmol, 0.45 equiv) in dry DCM (70 mL, 0.14 M) was added and the reaction mixture was stirred for 15 min. Then TBHP (5.5 M in decane, 10.31 mL, 56.689 mmol, 2.5 equiv) was added slowly. After 30 min the solution of **1** was added and the resulting mixture was stirred for 70 h at -20 °C. Reaction progress

was monitored by TLC. When the reaction was finished, a solution of sodium sulfite (20 g in 100 mL water) was added as well as 1000 mL DCM and 500 mL water. The aqueous layer was extracted with DCM (4 x 500 mL) and the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed in *vacuo* and the compound was purified *via* column chromatography (MPLC, product rotated on BULK Isolute Sorbent, 90 g silica, 50 mL/min flow rate, 8 % EtOAc for 15 min, then 8 -50 % EtOAc in 25 min, then 50-100 % EtOAc in 10 min, then 100 % for 10 min).

Yield: 4.431 g (81 %)

Appearance: orange oil [70, 72]

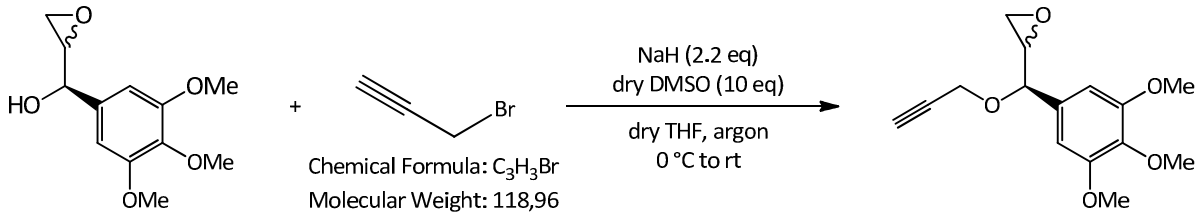
TLC: Rf(PE/EtOAc = 0/1) = 0.08

Specific rotation: $[\alpha]_D^{20}$ = -13.748 (MeOH; c 1.3092)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.36 (d, J=2.16 Hz, 1H, OH), 2.77 (dd, J=4.89 & 4.10 Hz, 1H, CH_2O), 2.93 (dd, J=5.09 & 2.74 Hz, 1H, CH_2O), 3.16-3.24 (m, 1H, CH_2-C<u>H</u>-O), 3.82 (s, 3H, OCH_3), 3.85 (s, 6H, 2xOCH_3), 4.77-4.83 (m, 1H, CH-<u>CH</u>-O), 6.60 (s, 2H, C<u>H</u>-C-C<u>H</u>)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 43.7 (t, CH_2), 55.0 (d, <u>CH</u>-O-CH_2), 56.1 (q, 2xOCH_3), 60.8 (q, OCH_3), 71.1 (d, <u>CH</u>-OH), 103.2 (d, <u>C</u>H-C-<u>C</u>H), 135.2 (s, C_q), 153.4 (s, 2C, *m*-C_{aryl}). One C_q not visible.

4.4 2-((R)-(Prop-2-yn-1-yloxy)(3,4,5-trimethoxyphenyl)methyl)oxiran (<u>4</u>)



3
Chemical Formula: $C_{12}H_{16}O_5$
Molecular Weight: 240,25

<u>4</u>
Chemical Formula: $C_{15}H_{18}O_5$
Molecular Weight: 278,30

Prepared according to procedure C using **3** as starting material (4.431 g, 18.443 mmol). Modification: Purification *via* column chromatography (MPLC, 90 gsilica, 50 ml/min flow rate, 3 % EtOAc for 10 min, then 3-30 % EtOAc in 20 min, then 30-100 % EtOAc in 20 min, then 100 % EtOAc for 10 min).

Yield: 4.211 g (82 %)

Appearance: slightly yellow oil

TLC: Rf (PE/EtOAc = 4/1) = 0.19

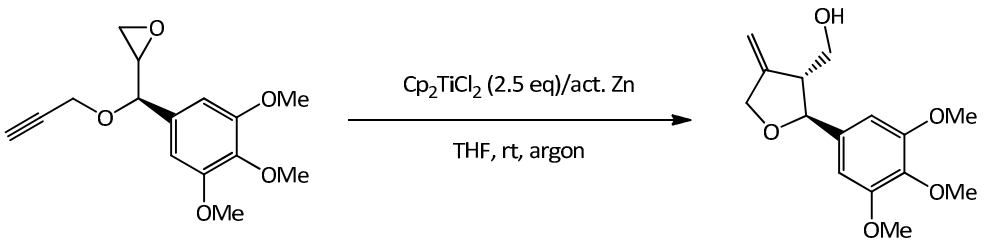
Specific rotation: $[\alpha]_D^{20}$ = -118.8 (MeOH; c 1.0163)

GC-MS (EI, 70 eV): Method 1; Retention time: 9.97 min; Main fragments (relative intensity): 278 (M^+, 57), 248 (56), 235 (93), 209 (96), 196 (70), 195 (44), 193 (17), 192 (16), 181 (65), 179 (22), 178 (100), 176 (33), 168 (16), 166 (21), 163 (31), 161 (17), 156 (32), 151 (27), 135 (18), 121 (17)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.46 (t, J=2.35 Hz, 1H, CH≡C-CH_2), 2.76 (dd, J= 5.19 & 2.54, 1H, CH-CH_2-O), 2.84 (dd, J= 5.19 & 3.91, 1H, CH-CH_2-O), 3.12-3.20 (m, 1H, CH-CH_2-O), 3.85 (s, 3H, OCH_3), 3.88 (s, 6H, 2xOCH_3), 4.01 (dd, J=15.66 & 2.35 Hz, 1H, C-CH_2-O), 4.24 (dd, J=15.66 & 2.34 Hz, 1H, C-CH_2-O), 4.43 (d, J=4.70 Hz, 1H, CH-CH-O), 6.60 (s, 2H, CH-C-CH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 45.5 (t, CH-CH_2-O), 54.0 (d, CH-CH_2-O), 56.1 (t, C-CH_2-O), 56.1 (q, 2xOCH_3), 60.8 (q, OCH_3), 74.9 (d, C≡CH), 79.2 (s, C≡CH), 79.7 (d, CH-CH-O), 104.2 (d, CH-C-CH), 132.7 (s, *p*-C_{aryl}), 138.0 (s, CH-C-CH), 153.4 (s, *m*-C_{aryl}).

4.5 ((2S,3R)-4-Methylene-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methanol (5)



4
Chemical Formula: $C_{15}H_{18}O_5$
Molecular Weight: 278,30

5
Chemical Formula: $C_{15}H_{20}O_5$
Molecular Weight: 280,32

A flask was charged with act. Zn (6.612 g, 101.139 mmol, 7 equiv) and Cp_2TiCl_2 (8.993 g, 36.121 mmol, 2.5 equiv) under argon; deoxygenated THF (200 mL, distilled from Na/benzophenone) was added. After 1 h of stirring at rt, the Zn was allowed to settle for 5 min and the solution (without the Zn) was transferred to a solution of **4** (4.021 g, 14.448 mmol, 1 equiv) in

deoxygenated THF (100 mL) over a period of 25 min. Stirring was continued for 70 min at rt and reaction progress was monitored by TLC. When the reaction was completed, diluted sulfuric acid (10 % in water, 83 mL) was added and the major amount of THF was evaporated. Water was added to the crude product and the aqueous layer was extracted with Et_2O (4 x 600 mL). The combined organic layers were washed with satd. $NaHCO_3$ solution, brine, dried over Na_2SO_4, filtered and the solvent was removed in *vacuo*. The crude product was purified *via* column chromatography (MPLC, 90 g silica, 50 mL/min flow rate, 10-50 % EtOAc for 20 min, then 50-100 % in 15 min, then 100 % for 15 min).

Yield: 2.325 g (57 %)

Appearance: yellow oil

TLC: Rf(PE/EtOAc = 2/1) = 0.07

Specific rotation: $[\alpha]_D^{20}$ = +6.2 (MeOH; c 1.0791)

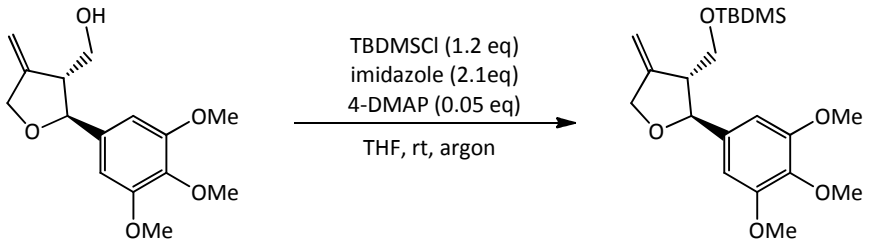
HRMS (ESI$^+$): exact mass calculated for $C_{15}H_{20}O_5$: 303.1203. Found: 303.1203. $[M+Na]^+$, Δ = 0.00 ppm

GC-MS (EI, 70 eV): Method 1; Retention time: 11 min; Main fragments (relative intensity): 280 (17), 197 (12), 196 (11), 195 (11), 182 (37), 181 (100), 169 (57), 154 (31), 139 (13), 138 (45), 125 (13), 115 (12), 110 (10)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.62 (bs, 1H, OH), 2.69-85 (m, 1H, H3), 3.82 (s, 3H, OCH_3), 3.85 (s, 8H, 2x OCH_3 & CH_2O), 4.35-4.69 (m, 2H, H5), 4.78 (d, J=7.44 Hz, 1H, H2), 5.02-5.16 (m, 2H, CH_2), 6.63 (s, 2H, H2' & H6').

^{13}C-NMR (50 MHz, $CDCl_3$): δ 54.0 (d, C4), 56.0 (q, 2xOCH_3), 60.7 (q, OCH_3), 61.9 (t, CH_2O), 71.4 (d, C3), 83.4 (d, C2), 103.5 (d, C2' & C6'), 105.0 (t, CH_2), 136.8 (s, C_q), 148.5 (d, C3), 153.5 (s, C3' & C5'). One C_q not visible

4.6 *tert*-Butyldimethyl(((2S,3R)-4-methylene-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methoxy)silane (6)

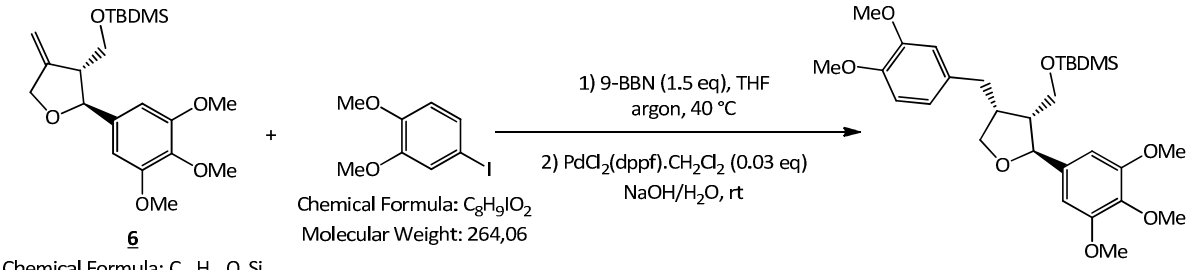


5
Chemical Formula: $C_{15}H_{20}O_5$
Molecular Weight: 280,32

6
Chemical Formula: $C_{21}H_{34}O_5Si$
Molecular Weight: 394,58

Substrate **5** (1.014 g, 3.617 mmol, 1 equiv), imidazole (0.518 g, 7.596 mmol, 2.1 equiv) and 4-DMAP (23.1 mg, 0.181 mmol, 0.05 equiv) were dissolved in DMF (21 mL, 0.17 M) under argon. TBDMSCl (3M in THF, 1.45 mL, 4.341 mmol, 1.2eq) was added to the solution and the mixture was stirred for 16 h at rt. Reaction progress was monitored by TLC. When the reaction was finished, Et_2O (50 mL) and satd. NH_4Cl solution (20 mL) were added and the aqueous phase was extracted with Et_2O (4 x 30 mL). The combined organic layers were washed with satd. $NaHCO_3$ solution (10 mL) and brine (10 mL), dried over Na_2SO_4 and filtered. The solvent was evaporated and the crude product used without purification in the next step.

4.7 *tert*-Butyl(((2S,3R,4R)-4-(3,4-dimethoxybenzyl)-2-(3,4,5-trimethoxyphenyl) tetrahydrofuran-3-yl)methoxy)dimethylsilane (7)



6
Chemical Formula: $C_{21}H_{34}O_5Si$
Molecular Weight: 394,58

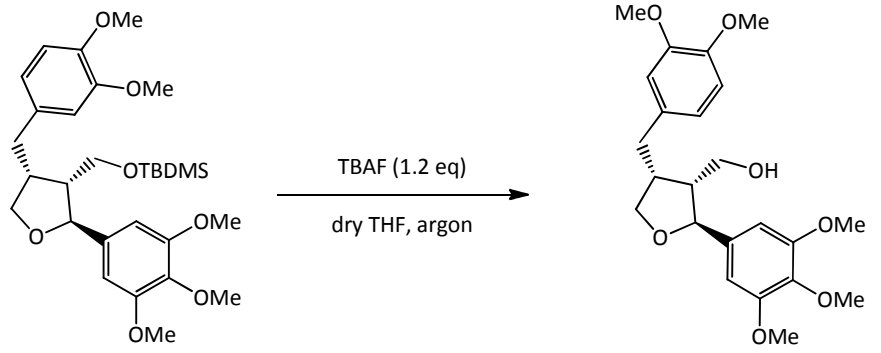
Chemical Formula: $C_8H_9IO_2$
Molecular Weight: 264,06

7
Chemical Formula: $C_{29}H_{44}O_7Si$
Molecular Weight: 532,74

A flask was charged with **6** (3.617 mmol, 1 equiv) under argon and 9-BBN (0.5 M in THF, 10.85 mL, 5.426 mmol, 1.5 equiv) was added. The resulting mixture was stirred for 22.5 h at 40 °C. On the next day, it was allowed to warm to rt and aqueous NaOH solution (1 M, 10 mL) was added. Stirring

was continued for another 15 min and 4-iodoveratrole (1.248 g, 4.792 mmol, 1.3 equiv) and $PdCl_2(dppf).CH_2Cl_2$ (88.5 mg, 0.109 mmol, 0.03 equiv) were added. The mixture became biphasic and was stirred for another 24 h at rt, then Et_2O (100 mL) and brine (25 mL) were added. Reaction progress was monitored by TLC. The layers were separated and the aqueous phase was extracted with Et_2O (4 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated. The crude product was used without further purification in the next step.

4.8 ((2S,3R,4S)-4-(3,4-Dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methanol (8)



7
Chemical Formula: $C_{29}H_{44}O_7Si$
Molecular Weight: 532,74

8
Chemical Formula: $C_{23}H_{30}O_7$
Molecular Weight: 418,48

A flask was charged with **7** (3.617 mmol, 1 equiv) under argon and TBAF (1 M in THF, 4.34 mL, 4.341 mmol) was added. The reaction was stirred for 20 h at rt. Reaction progress was monitored by TLC. When the reaction was finished, Et_2O (100 mL) and brine (25 mL) were added and the aqueous phase was extracted with Et_2O (4 x 30 mL) and EtOAc (2 x 35 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated. The compound was purified *via* column chromatography (MPLC, 90 g silica, 40 mL/min flow rate, 30 EtOAc for 5 min, then 30-100 % EtOAc in 45 min)

Yield: 0.631 g (42 % over 3 steps)

Appearance: yellow oil

TLC: Rf(PE/EtOAc = 1/1) = 0.27

Specific rotation: $[\alpha]_D^{20}$ = +7.1 (MeOH; c 2.143)

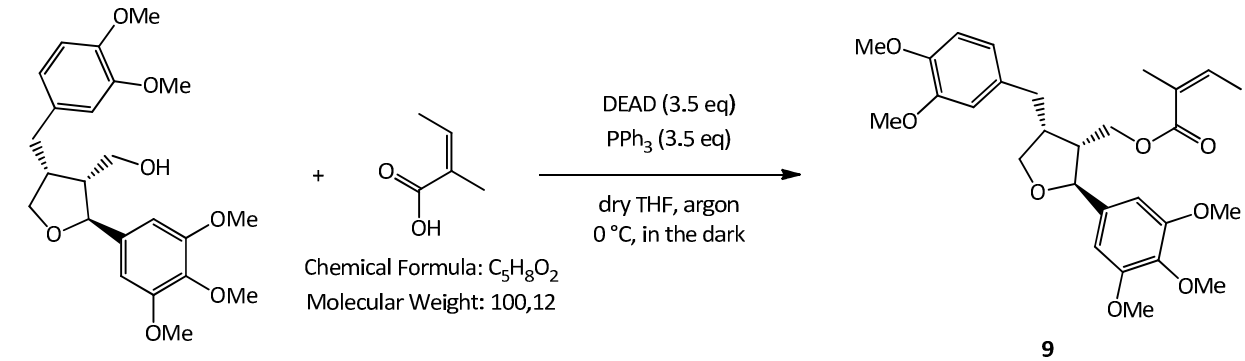
HRMS (ESI$^+$): exact mass calculated for $C_{23}H_3O_7$: 441.1884. Found: 441.1903. $[M+Na]^+$, Δ = 4.31 ppm

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.68 (bs, 1H, OH), 2.32-2.82 (m, 3H, H3 & H4 & CH_2), 2.92 (dd, J=12.82 & 4.60 Hz, 1H, CH_2), 3.83 (s, 3H, OCH_3), 3.85 (s, 15H, 4xOCH_3, CH_2O, H5), 4.07 (dd, J=8.41 & 6.45 Hz, 1H, H5), 4.84 (d, J=6.06 Hz, 1H, H2), 6.56 (s, 2H, H2' & H6'), 6.67-6-83 (m, 3H, H2'' & H5'' & H6'').

^{13}C-NMR (50 MHz, $CDCl_3$): δ 33.1 (t, CH_2), 42.2 (d, C4), 52.4 (d, C3), 55.8 (q, 2xOCH_3), 56.1 (q, 2xOCH_3), 60.8 (q, OCH_3), 60.9 (t, CH_2OH), 73.0 (t, C5), 82.9 (d, C2), 102.5 (d, C2' & C6'), 111.2 (d, CH), 111.8 (d, CH), 120.4 (d, C6''), 132.9 (s, C1''), 137.05 (s, C_q), 138.7 (s, C_q), 147.4 (s, C4''), 148.9 (s, C3''), 153.2 (s, C3' & C5').

4.9 (Z)-((2S,3R,4S)-4-(3,4-Dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (9)

Method 1:



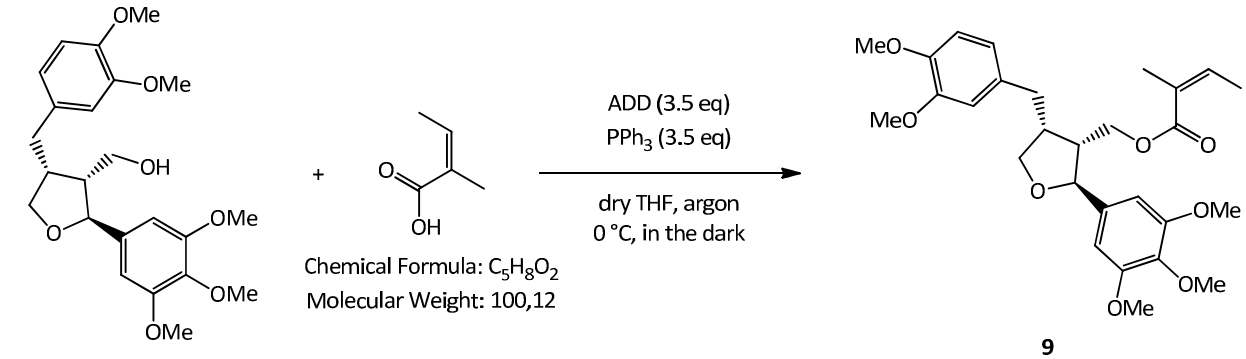
8
Chemical Formula: $C_{23}H_{30}O_7$
Molecular Weight: 418,48

Chemical Formula: $C_5H_8O_2$
Molecular Weight: 100,12

9
Chemical Formula: $C_{28}H_{36}O_8$
Molecular Weight: 500,58

Prepared according to procedure F using **8** as starting material (75.1 mg, 0.179 mmol). Modification: Instead of ADD, DEAD was used. Purification *via* column chromatography (MPLC, 2 x 9 g silica in sequence, 10 ml/min flow rate, 20 - 50 % EtOAc in 30 min), then by preparative HPLC (20 ml/min flow rate, 70 % MeOH for 25 min, then 72-75 % MeOH in 15 min, then 75 % MeOH for 5 min).

Method 2:



8
Chemical Formula: $C_{23}H_{30}O_7$
Molecular Weight: 418,48

Chemical Formula: $C_5H_8O_2$
Molecular Weight: 100,12

9
Chemical Formula: $C_{28}H_{36}O_8$
Molecular Weight: 500,58

Prepared according to procedure F using **8** as starting material (152.6 mg, 0.365 mmol). Modification: The crude product was purified *via* column chromatography (MPLC, 40 g silica, 50 mL/min flow rate, 10-22 % EtOAc in 10 min, then 22 % EtOAc for 10 min, then 22-65 % EtOAc in 40 min)

Yield: Method 1: 30.2 mg (34 %), Method 2: 134.2 mg (74 %)

Appearance: slightly yellow viscous oil [25]

TLC: Rf(PE/EtOAc = 2/1) = 0.25

Specific rotation: $[\alpha]_D^{20}$ = +19.7 (MeOH; c 1.5415). According to literature: $[\alpha]_D^{20}$ = +20.86 (MeOH; 0.302) [25]

HRMS (ESI$^+$): exact mass calculated for $C_{28}H_{36}O_8$: 523.2302. Found: 523.2311. $[M+Na]^+$, Δ = 1.72 ppm

GC-MS (EI, 70 eV): Method 2; Retention time: 31.04 min; Main fragments (relative intensity): 500 (M^+, 12), 249 (24), 203 (13), 196 (11), 195 (61), 190 (11), 189 (15), 181 (23), 178 (11), 177 (14), 152 (15), 151 (100), 107 (14)

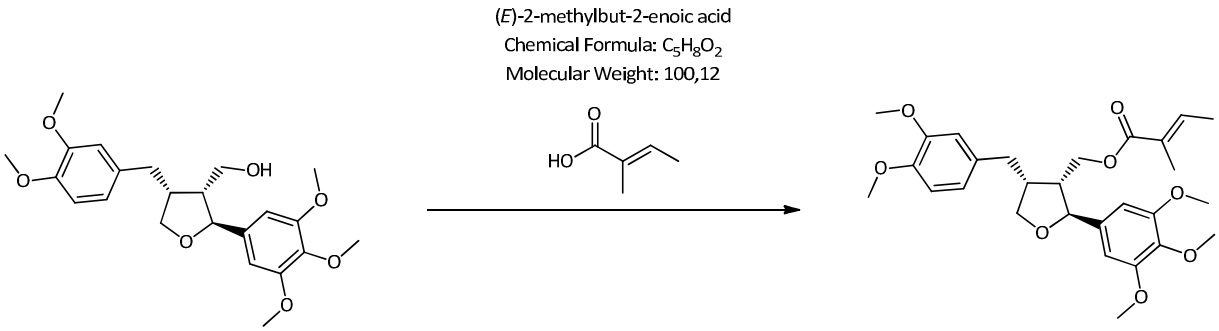
^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.83-1.90 (m, 3H, α-CH_3), 1.95-2.04 (m, 3H, β-CH_3), 2.47-2.81 (m, 3H, H3 & H4 & CH_2), 2.88 (dd, 1H, CH_2), 3.77 (dd, J= 8.70 & 6.26 Hz, 1H, H5), 3.81 (s, 3H, OCH_3), 3.84 (s, 6H, 2xOCH_3), 3.85 (s, 6H, 2xOCH_3), 4.07 (dd, J=8.70 & 6.07 Hz, 1H, H5), 4.29 (dd, J=11.35 & 7.14, 1H,

CH_2O), 4.43 (dd, J=11.35 & 6.56 Hz, 1H, CH_2O), 4.83 (d, J=5.87, 1H, H2), 6.02-6.17 (m, 1H, β-CH), 6.54 (s, 2H, H2' & H6'), 6.64-6.83 (m, 3H, H2'' & H5'' & H6'').

^{13}C-NMR (50 MHz, $CDCl_3$): δ 15.8 (q, β-CH_3), 20.5 (q, α-CH_3), 33.12 (t, CH_2), 42.56 (d, C4), 49.2 (d, C3), 55.8 (q, OCH_3), 55.9 (q, OCH_3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 62.2 (t, CH_2O), 72.8 (t, C5), 83.1 (d, C2), 102.5 (d, C2' & C6'), 111.3 (d, C2''), 111.8 (d, C5''), 120.4 (d, C6''), 127.2 (s, α-C), 132.7 (s, C1''), 138.2 (s, C_q), 139.0 (d, β-CH), 147.5 (s, C4''), 148.9 (s, C3''), 153.3 (s, C3' & C5'), 167.6 (s, C=O). One C_q not visible.

5. Variation of the Ester Functionality

5.1 (E)-((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (<u>10</u>)



<u>8</u>
Chemical Formula: $C_{23}H_{30}O_7$
Molecular Weight: 418,48

<u>10</u>
Chemical Formula: $C_{28}H_{36}O_8$
Molecular Weight: 500,58

Prepared and purified according to General Procedure A using **<u>8</u>** as starting material (30 mg, 0.074 mmol) and (E)-2-methylbut-2-enoic acid as reagent.

Yield: 25.4 mg (70 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 1/1) = 0.66

Specific rotation: $[\alpha]_D^{20}$ = +19.2 (MeOH; c 1.925)

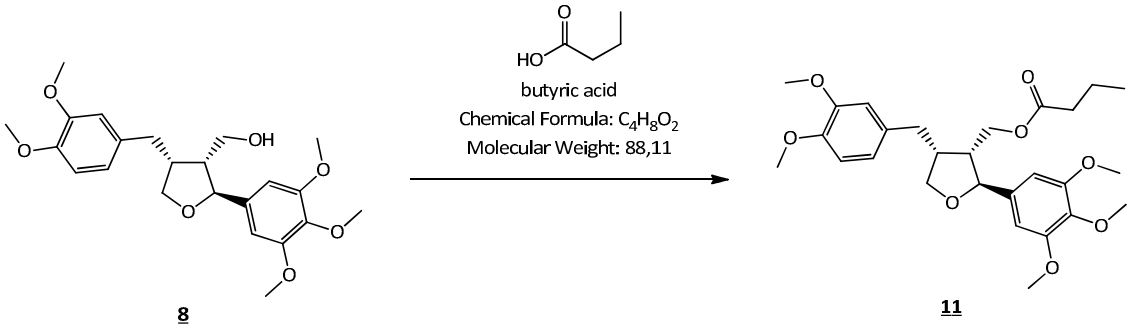
HRMS (ESI$^+$): exact mass calculated for $C_{28}H_{37}O_8$: 523.2302. Found: 523.2311. $[M+Na]^+$, Δ = 1.72 ppm

GC-MS (EI, 70 eV): Method 4; Retention time: 33.79 min; Main fragments (relative intensity): 515 (M^+, 12), 249 (26), 203 (12), 196 (10), 195 (61), 190 (11), 189 (15), 181 (23), 178 (10), 177 (14), 159 (10), 152 (14), 151 (100), 107 (18)

^{1}H-NMR (200 MHz, $CDCl_3$): 1.69-1.85 (m, 6H, α-CH_3 & β-CH_3), 2.46-2.95 (m, 4H, H3 & H4 & CH_2), 3.81 (s, 3H, OCH_3), 3.83 (s, 7H, 2xOCH_3, H5), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.07 (dd, J=8.51 & 6.17 Hz, 1H, H5), 4.27 (dd, J=11.25 & 7.33 Hz, 1H, CH_2O), 4.43 (dd, J=11.25 & 6.36 Hz, 1H, CH_2O), 4.81 (d, J=6.07 Hz, 1H, H2), 6.53 (s, 2H, H2' & H6'), 6.64-6.84 (m, 4H, H2'' & H5'' & H6'' & β-CH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 12.0 (q, β-CH_3), 14.4 (q, α-CH_3), 33.1 (t, CH_2), 42.6 (d, C4), 49.1 (d, C3), 55.8 (q, 2x OCH_3), 56.0 (q, 2x OCH_3), 60.8 (q, OCH_3), 62.7 (t, CH_2O), 72.9 (t, C5), 83.4 (d, C2), 102.6 (d, C2' & C6'), 111.3 (d, C2'), 111.8 (d, C5'), 120.4 (d, C6'), 128.2 (s, α-C), 132.5 (s, C1''), 137.2 (s, C_q), 137.8 (d, β-CH), 138.2 (s, C_q), 147.5 (s, C4''), 148.9 (s, C3''), 153.2 (s, C3' & C5'), 167.8 (s, C=O)

5.2 ((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl butyrate (<u>11</u>)



<u>8</u>
Chemical Formula: $C_{23}H_{30}O_7$
Molecular Weight: 418,48

<u>11</u>
Chemical Formula: $C_{27}H_{36}O_8$
Molecular Weight: 488,57

Prepared and purified according to General Procedure B using **<u>8</u>** as starting material (30 mg, 0.074 mmol) and butyric acid as reagent.

Yield: 25.1 mg (72 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 1/1) = 0.66

Specific rotation: $[\alpha]_D^{20}$ = +19.2 (MeOH; c 1.948)

HRMS (ESI$^+$): exact mass calculated for $C_{27}H_{36}O_8$: 511.2302. Found: 511.2282. $[M+Na]^+$, Δ = 3.91 ppm

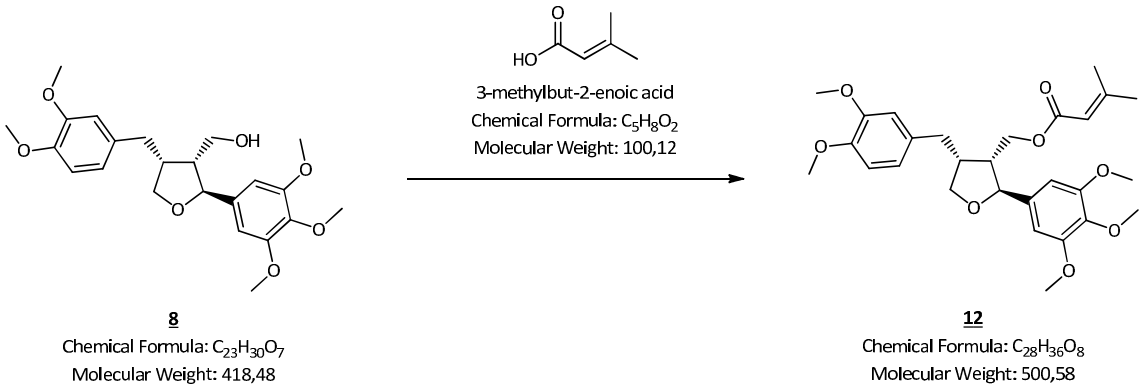
GC-MS (EI, 70 eV): Method 4; Retention time: 33.79 min; Main fragments (relative intensity): 515 (M^+, 12), 249 (26), 203 (12), 196 (10), 195 (61), 190 (11), 189 (15), 181 (23), 178 (10), 177 (14), 159 (10), 152 (14), 151 (100), 107 (18)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.94 (t, J=7.43, 3H, CH_3), 1.64 (tq, J=7.43 & 7.44, 2H, <u>CH_2</u>CH_3), 2.26 (t, J=7.44, 2H, (CO)<u>CH_2</u>), 2.46-2-92 (m, 4H, H3 & H4 & CH_2), 3.74 (dd, J=8.61 & 6.45 Hz, 1H, H5), 3.82 (s,

3H, OCH_3), 3.85 (s, 9H, 3xOCH_3), 3.88 (s, 3H, OCH_3), 4.06 (dd, J=8.61 & 6.26 Hz, 1H, H5), 4.20 (dd, J=11.15 & 7.24 Hz, 1H, CH_2O), 4.38 (dd, J=11.15 & 6.75 Hz, CH_2O), 4.77 (d, J=5.87 Hz, 1H, H2), 6.53 (s, 2H, H2' & H6'), 6.64-6.83 (m, 3H, H2'' & H5'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 13.7 (q, CH_3), 18.4 (t, $\underline{CH_2}CH_3$), 33.1 (t, CH_2), 36.2 (t, (CO)$\underline{CH_2}$), 42.4 (d, C4), 49.0 (d, C3), 55.9 (q, 2xOCH_3), 56.1 (q, 2xOCH_3), 60.8 (q, OCH_3), 62.5 (t, CH_2O), 72.8 (t, C5), 83.2 (d, C2), 102.6 (d, C2' & C6'), 111.3 (d, C2''), 111.8 (d, C5''), 120.4 (d, C6''), 132.5 (s, C1''), 138.2 (s, C_q), 147.5 (s, C4''), 148.9 (s, C3''), 153.3 (s, C3' & C5'), 173.5 (s, C=O). One C_q not visible.

5.3 ((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl 3-methylbut-2-enoate (12)



8
Chemical Formula: $C_{23}H_{30}O_7$
Molecular Weight: 418,48

12
Chemical Formula: $C_{28}H_{36}O_8$
Molecular Weight: 500,58

Prepared and purified according to General Procedure F using **8** as starting material (21.2 mg, 0.051 mg) and 3-methylbut-2-enoic acid as reagent.

Yield: 16.6 mg (66 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 1/1) = 0.64

Specific Rotation: $[\alpha]_D^{20}$ = +29.9 (MeOH; c 1.194)

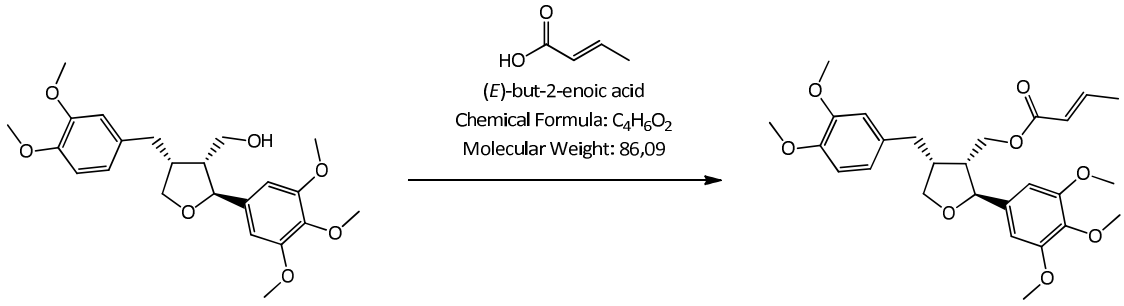
HRMS (ESI$^+$): exact mass calculated for $C_{28}H_{36}O_8$: 523.2302. Found: 523.2310. $[M+Na]^+$, Δ = 1.53 ppm

GC-MS (EI, 70 eV): Method 4; Retention time: 32.13 min; Main fragments (relative intensity): 500 (M^+, 5), 249 (18), 208 (10), 207 (50), 195 (40), 191 (10), 189 (10), 181 (16), 177 (12), 151 (62), 133 (12), 107 (13), 83 (100)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.89 (d, J=0.97 Hz, 3H, β-CH_3), 2.18 (d, J=1.18 Hz, 3H, β-CH_3), 2.46-2.94 (m, 3H, H3 & H4 & CH_2), 3.87 (dd, J=12.62 & 4.21 Hz, 1H, CH_2), 3.74 (dd, J=8.60 & 6.66 Hz, 1H, H5), 3.81 (s, 3H, OCH_3), 3.84 (s, 9H, 3 x 3xOCH_3), 3.86 (s, 3H, OCH_3), 4.06 (dd, J=8.60 & 6.26 Hz, 1H, H5), 4.22 (dd, J=11.34 & 7.24 Hz, 1H, CH_2O), 4.39 (dd, J=11.34 & 6.65 Hz, 1H, CH_2O), 4.79 (d, J=5.87 Hz, 1H, H2), 5.65 (m, 1H, (<u>CH</u>=$C(CH_3)_2$), 6.54 (s, 2H, H2' & H6'), 6.65-6.84 (m, 3H, H2'' & H5'' & H6'').

^{13}C-NMR (50 MHz, $CDCl_3$): δ 20.3 (q, β-CH_3), 27.5 (q, α-CH_3), 33.1 (t, CH_2), 42.5 (d, C4), 49.1 (d, C3), 55.9 (q, 2C, OCH_3), 56.1 (q, 2C, OCH_3), 60.8 (q, C4' OCH_3), 61.7 (t, OCH_2), 72.8 (d, C5), 83.2 (d, C2), 102.5 (d, C2' & C6'), 111.3 (d, C2''), 111.9 (d, C5''), 115.5 (s, α-C), 120.4 (d, C6''), 132.6 (s, C1''), 138.3 (s, C_q), 147.4 (s, C4''), 148.9 (s, C3''), 153.2 (s, C3' & C5'), 157.7 (s, β-C), 166.4 (s, C=O). One C_q is not visible.

5.4 (E)-((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl but-2-enoate (<u>13</u>)



<u>8</u>
Chemical Formula: $C_{23}H_{30}O_7$
Molecular Weight: 418,48

<u>13</u>
Chemical Formula: $C_{27}H_{34}O_8$
Molecular Weight: 486,55

Prepared and purified according to General Procedure A using **<u>8</u>** as starting material (30 mg, 0.074 mmol) and (E)-but-2-enoic acid as reagent.

Yield: 26.1 mg (74 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 1/1) = 0.57

Specific rotation: $[\alpha]_D^{20}$ = +23.9 (MeOH; c 1.738)

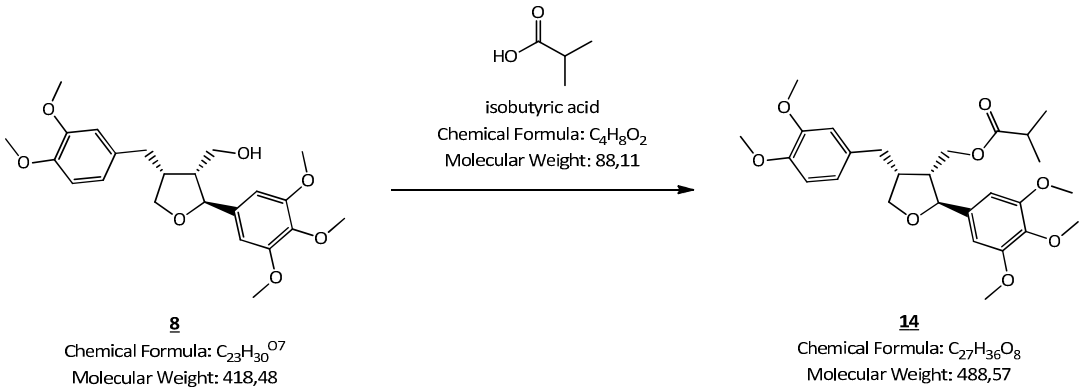
HRMS (ESI$^+$): exact mass calculated for $C_{27}H_{34}O_8$: 509.2146. Found: 509.2124. $[M+Na]^+$, Δ = 4.32 ppm

GC-MS (EI, 70 eV): Method 3; Retention time: 29.32 min; Main fragments (relative intensity): 486 (M^+, 14), 249 (27), 207 (17), 204 (12), 203 (14), 196 (11), 195 (69), 190 (13), 189 (18), 182 (10), 181 (24), 178 (11), 177 (16), 159 (11), 152 (14), 151 (93), 107 (16), 69 (100)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.88 (dd, J=7.06 & 1.54, 3H, CH_3), 2.46-2.93 (m, 4H, H3 & H4 & CH_2), 3.75 (dd, J =8.61 & 6.85 Hz, 1H, H5), 3.82 (s, 3H, OCH_3), 3.85 (s, 9H, 3xOCH_3), 3.86 (s, 3H, OCH_3), 4.07 (dd, J=8.61 & 6.16 Hz, 1H, H5), 4.26 (dd, J=11.35 & 7.14 Hz, 1H, CH_2O), 4.44 (dd, J=11.35 & 6.65 Hz, 1H, CH_2O), 4.80 (d, J=5.87, 1H, H2), 5.75-5.88 (m, 1H, α-CH), 6.53 (s, 2H, H2' & H6'), 6.64-6.84 (m, 3H, H2'' & H5'' & H6''), 6.85-7.00 (m, 1H, β-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 18.1 (q, CH_3), 33.1 (t, CH_2), 42.5 (d, C4), 49.0 (d, C3), 55.9 (q, 2xOCH_3), 56.1 (q, 2xOCH_3), 60.8 (q, OCH_3), 62.5 (t, CH_2O), 72.9 (t, C5), 83.4 (d, C2), 102.6 (d, C2' & C6'), 111.3 (d, C2''), 111.9 (d, C5''), 120.4 (d, C6''), 122.3 (s, α-CH), 132.5 (s, C1''), 138.2 (s, C_q), 145.4 (d, β-CH), 147.5 (s, C4''), 148.9 (s, C3''), 153.3 (s, C3' & C5'), 166.3 (s, C=O). One C_q not visible

5.5 ((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl isobutyrate (<u>14</u>)



Prepared and purified according to General Procedure B using **<u>8</u>** as starting material (30 mg, 0.074 mmol) and isobutyric acid as reagent.

Yield: 29.1 mg (83 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 1/1) = 0.64

Specific rotation: $[\alpha]_D^{20}$ = +19.9 (MeOH; c 2.190)

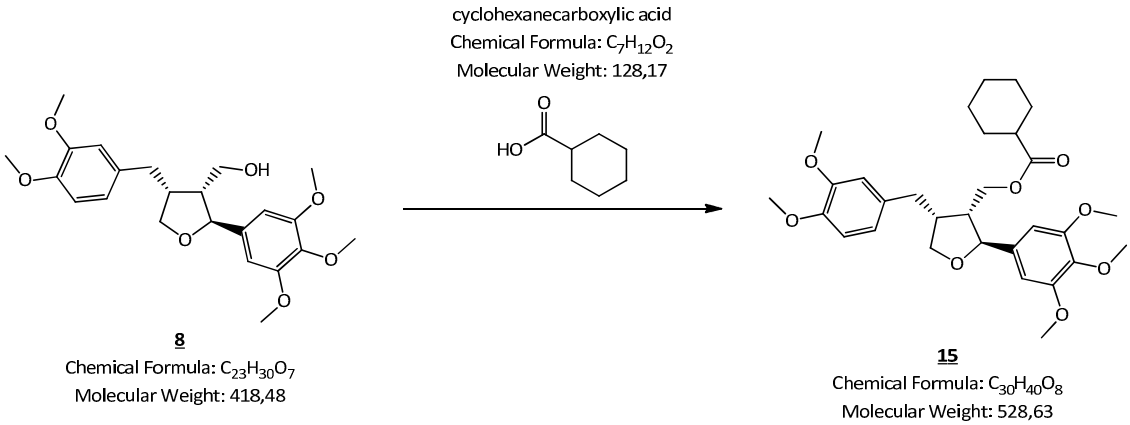
HRMS (ESI$^+$): exact mass calculated for $C_{27}H_{36}O_8$: 511.2302. Found: 511.2309. $[M+Na]^+$, Δ = 1.37 ppm

GC-MS (EI, 70 eV): Method 3; Retention time: 25.04 min; Main fragments (relative intensity): 488 (M^+, 19), 249 (19), 203 (10), 195 (36), 189 (13), 182 (11), 181 (22), 177 (11), 152 (14), 151 (100), 107 (14)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.16 (d, J=6.85 Hz, 6H, 2xCH_3), 2.45-2.91 (m, 5H, H3 & H4 & CH_2 & β-CH_3), 3.75 (dd, J=8.61 & 6.46 Hz, 1H, H5), 3.81 (s, 3H, OCH_3), 3.85 (s, 12H, 4xOCH_3), 4.06 (dd, J= 8.61 & 6.26 Hz, 1H, H5), 44.19 (dd, J=11.35 & 7.05 Hz, 1H, CH_2O), 4.38 (dd, J=11.35 & 6.65 Hz, 1H, CH_2O), 4.79 (d, J=5.87 Hz, 1H, H2), 6.53 (s, 2H, H2' & H6'), 6.63-6.84 (m, 3H, H2'' & H5'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 18.9 (q, 2xCH_3), 33.1 (t, CH_2), 34.0 (d, α-CH), 42.5 (d, C4), 49.1 (d, C3), 55.8 (q, 2C, OCH_3), 56.1 (q, 2C, OCH_3), 60.8 (q, C4' OCH_3), 62.5 (t, CH_2O), 72.8 (t, CH_2), 83.1 (d, C2), 102.5 (d, C2' & C6'), 111.3 (d, C2''), 111.8 (d, C5''), 120.4 (d, C6''), 132.5 (s, C1''), 138.2 (s, C_q), 147.5 (s, C4''), 148.9 (s, C3''), 153.3 (s, C3' & C5'), 176.8 (s, C=O). One C_q not visible

5.6 ((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl cyclohexanecarboxylate (<u>15</u>)



Prepared and purified according to General Procedure B using **<u>8</u>** as starting material (30 mg, 0.074 mmol) and cyclohexanecarboxylic acid as reagent.

Yield: 16.5 mg (42 %)

Appearance: slightly yellow viscous oil

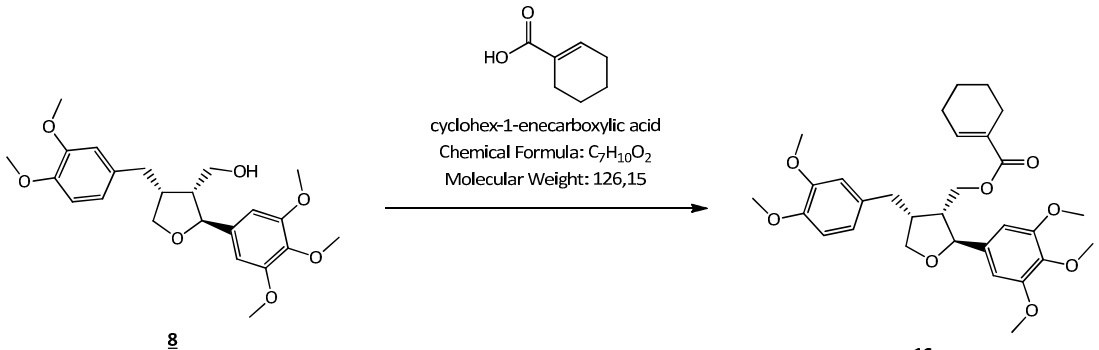
TLC: Rf(PE/EtOAc = 1/1) = 0.71

Specific rotation: $[\alpha]_D^{20}$ = +18.9 (MeOH; c 2.100)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.13-1.97 (m, 10H, 5 x cyhex CH_2), 2.18-2.35 (m, 1H, (CO)<u>CH</u>), 2.44-2.93 (m, 4H, H3 & H4 & CH_2), 3.75 (dd, J=8.61 & 6.65 Hz, 1H, H5) , 3.81 (s, 3H, OCH_3), 3.85 (s, 12H, OCH_3), 4.05 (dd, J=8.61 & 6.17 Hz, 1H, H5), 4.18 (dd, J=11.15 & 7.14 Hz, 1H, CH_2O), 4.38 (dd, J=11.15 & 6.65 Hz, 1H, CH_2O), 4.78 (d, J=6.06, 1H, H2), 6.53 (s, 2H, H2' & H6'), 6.63-6.84 (m, 3H, H2'' & H5'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 25.4 (t, 2C, cyhex-CH_2), 25.7 (t, cyhex-CH_2), 29.0 (t, 2C, cyhex-CH_2), 33.1 (t, CH_2), 42.5 (d, α-CH), 43.2 (d, C4), 49.1 (d, C3), 55.8 (q, OCH_3), 55.9 (q, OCH_3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 62.4 (t, CH_2O), 72.8 (t, C5), 83.1 (d, C2), 102.5 (d, C2' & C6'), 111.3 (d, C2''), 111.8 (d, C5''), 120.4 (d, C6''), 132.5 (s, C1''), 137.2 (s, C_q), 138.2 (s, C_q), 147.5 (s, C4''), 148.9 (s, C3'), 153.3 (s, C3' & C5'), 175.8 (s, C=O)

5.7 ((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl cyclohex-1-enecarboxylate (<u>16</u>)



<u>8</u>
Chemical Formula: $C_{23}H_{30}O_7$
Molecular Weight: 418,48

<u>16</u>
Chemical Formula: $C_{30}H_{38}O_8$
Molecular Weight: 526,62

Prepared and purified according to General Procedure A using **<u>8</u>** as starting material (30 mg, 0.074 mmol) and cyclohex-1-enecarboxylic acid as reagent.

Yield: 21.3 mg (56 %)

Appearance: slightly yellow viscous oil

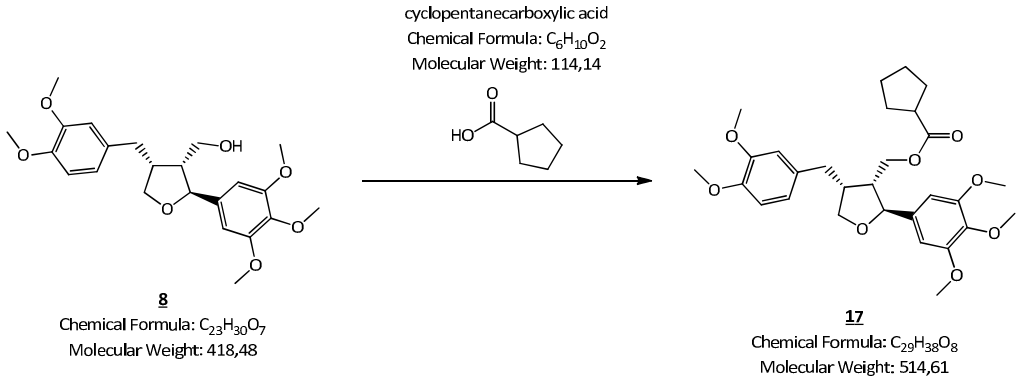
TLC: Rf(PE/EtOAc = 1/1) = 0.65

Specific rotation: $[\alpha]_D^{20}$ = +17.9 (MeOH; c 1.157)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.49-1.70 (m, 4H, <u>CH_2</u>-CH-C(CO)-<u>CH_2</u>), 2.07-2.29 (m, 4H, CH-CH_2-<u>CH_2</u>-<u>CH_2</u>), 2.48-2.93 (m, 4H, H3 & H4 & CH_2), 3.50 (MeOH), 3.69-3.80 (m, 1H, H5), 3.83 (s, 3H, OCH_3), 3.85 (s, 6H, OCH_3), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.02-4.14 (m, 1H, H5), 4.21-4.34 (m, 1H, CH_2O), 4.37-4.50 (m, 1H, CH_2O), 4.82 (d, J=6.06 Hz, 1H, H2), 6.55 (s, 2H, H2' & H6'), 6.64-6.83 (m, 3H, H2'' & H5'' & H6''), 6.90 (m, 1H, (CO)C-<u>CH</u>)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 21.3 (t, CH-<u>CH_2</u>-CH_2), 22.0 (t, CH-CH_2-<u>CH_2</u>), 24.1 (t, C-CH_2-<u>CH_2</u>), 25.8 (t, C-<u>CH_2</u>-CH_2), 33.1 (t, CH_2), 42.6 (d, C4), 49.1 (d, C3), 55.8 (q, OCH_3), 55.9 (q, OCH_3), 56.0 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 62.5 (t, CH_2O), 72.9 (t, C5), 83.5 (d, C2), 102.6 (d, C2' & C6'), 111.3 (d, C2''), 111.8 (d, C5''), 120.4 (d, C6''), 129.5 (s, (CO)<u>C</u>), 130.3 (s, C_q), 132.5 (s, C_q), 138.3 (s, C_q), 140.4 (d, (CO)C-<u>CH</u>), 147.5 (s, C4''), 148.9 (s, C3''), 153.2 (s, C3' & C5'), 167.3 (s, C=O).

5.8 ((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl cyclopentanecarboxylate (<u>17</u>)



<u>8</u>
Chemical Formula: $C_{23}H_{30}O_7$
Molecular Weight: 418,48

<u>17</u>
Chemical Formula: $C_{29}H_{38}O_8$
Molecular Weight: 514,61

Prepared and purified according to General Procedure B using **<u>8</u>** as starting material (30 mg, 0.074 mmol) cyclopentanecarboxylic acid as reagent.

Yield: 31.4 mg (85%)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 1/1) = 0.67

Specific rotation: $[\alpha]_D^{20}$ = +20.5 (MeOH; c 2.045)

HRMS (ESI^+): exact mass calculated for $C_{29}H_{38}O_8$: 537.2459. Found: 537.2477. $[M+Na]^+$, Δ = 3.35 ppm

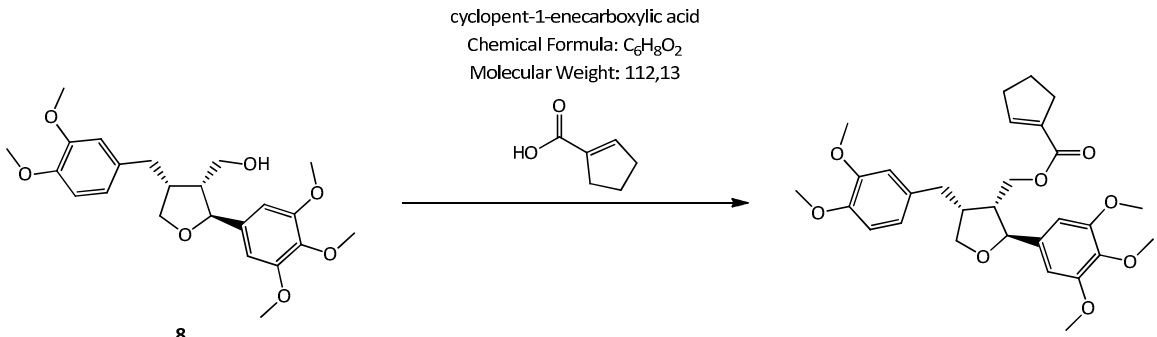
GC-MS (EI, 70 eV): Method 4; Retention time: 39.96 min; Main fragments (relative intensity): 514 (M^+, 12), 249 (25), 208 (14), 107 (66), 203 (13), 195 (45), 191 (13), 189 (15), 181 (17), 177 (17), 152 (16), 151 (100), 132 (15), 107 (18)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.45-1.96 (m, 8H, cypent-CH_2), 2.45-2.91 (m, 5H, m, 4H, H3 & H4 & CH_2 & C(CO)<u>CH</u>), 3.75 (dd, J=8.61 & 6.45 Hz, 1H, H5), 3.82 (s, 3H, OCH_3), 3.85 (s, 9H, 3xOCH_3), 3.86 (s, 3H, OCH_3), 4.06 (dd, J=8.61 & 6.45 Hz,1H, H5), 4.19 (dd, J=11.35 & 7.04 Hz,1H, CH_2O), 4.38 (dd, J=11.35 & 6.65 Hz, 1H, CH_2O), 4.78 (d, J=6.07, 1H, H2), 6.53 (s, 2H, H2' & H6'), 6.64-6.84 (m, 3H, H2'' & H5'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 25.6 (t, CH_2-<u>CH_2</u>-<u>CH_2</u>-CH_2), 29.9 (t, <u>CH_2</u>-CH_2-CH_2-<u>CH_2</u>), 33.1 (t, CH_2), 42.5 (d, C4), 43.8 (d, C(CO)<u>CH</u>), 49.1 (d, C3), 50.1 (q, C3' OCH_3 & C5' OCH_3), 55.8 (q, OCH_3), 55.9 (q, OCH_3),

60.8 (q, C4' OCH_3), 62.5 (t, CH_2O), 72.8 (t, C5), 83.1 (d, C2), 102.5 (d, C2' & C6'), 111.3 (d, C2''), 111.8 (d, C5''), 120.4 (d, C6''), 128.6 (s, C_q), 132.5 (s, C_q), 138.2 (s, C_q), 147.5 (s, C4''), 148.9 (s, C3''), 153.3 (s, C3' & C5'), 176.5 (s, C=O).

5.9 ((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl cyclopent-1-enecarboxylate (<u>18</u>)



<u>8</u>
Chemical Formula: $C_{23}H_{30}O_7$
Molecular Weight: 418,48

<u>18</u>
Chemical Formula: $C_{29}H_{36}O_8$
Molecular Weight: 512,59

Prepared and purified according to General Procedure A using **<u>8</u>** as starting material (30 mg, 0.074 mmol) and cyclopent-1-enecarboxylic acid as reagent.

Yield: 25.7 mg (69 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 1/1) = 0.65

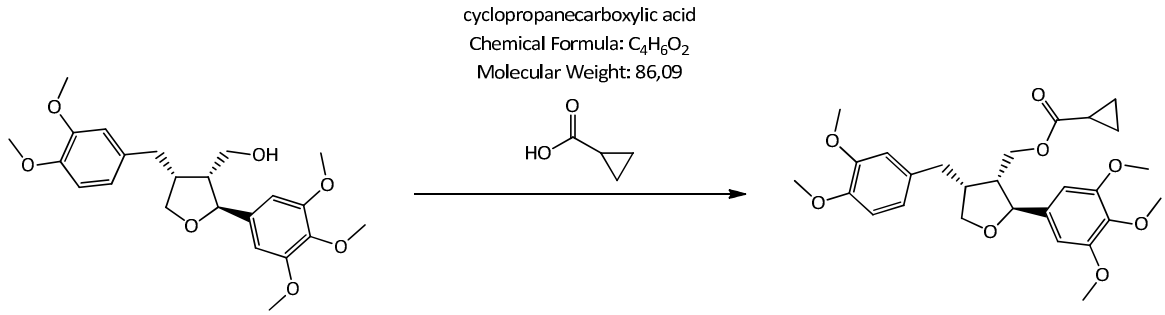
Specific rotation: $[\alpha]_D^{20}$ = +21.4 (MeOH; c 1.713)

HRMS (ESI^+): exact mass calculated for $C_{29}H_{36}O_8$: 535.2302. Found: 535.2311. $[M+Na]^+$, Δ = 1.68 ppm

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.85-2.04 (m, 2H, CH-CH_2-<u>CH_2</u>), 2.39-2.95 (m, 8H, H3 & H4 & CH_2 & CH-<u>CH_2</u>-CH_2), 3.76 (dd, J=8.61 & 6.75 Hz, 1H, H5), 3.81 (s, 3H, OCH_3), 3.84 (s, 6H, 2xOCH_3), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.08 (dd, J=8.61 & 6.45 Hz, 1H, H5), 4.28 (dd, J=11.15 & 7.24 Hz, 1H, CH_2O), 4.44 (dd, J=11.15 & 6.36 Hz, 1H, CH_2O), 4.81 (d, J=5.87 Hz, 1H, H2), 6.53 (s, 2H, H2' & H6'), 6.64-6.84 (m, 3H, H2'' & H5'' & H6''& C(CO)-C-<u>CH</u>).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 23.0 (t, CH-CH_2-$\underline{CH_2}$), 31.3 (t, C(CO)-$\underline{CH_2}$), 33.1 (t, CH-$\underline{CH_2}$-CH_2), 33.4 (t, CH_2), 42.6 (d, C4), 49.0 (d, C3), 55.8 (q, OCH_3), 55.9 (q, OCH_3), 56.0 (q, 2xOCH_3), 60.8 (q, OCH_3), 62.4 (t, CH_2O), 72.9 (t, C5), 83.4 (d, C2), 102.8 (d, C2' & C6'), 111.3 (d, C2''), 111.8 (d, C5''), 120.4 (d, C6''), 132.5 (s, $\underline{C}$(CO)), 136.2 (s, C1''), 137.2 (s, C_q), 138.2 (s, C_q), 144.5 (d, C(CO)-$\underline{CH}$), 147.5 (s, C4''), 148.9 (s, C3''), 153.2 (s, C3' & C5'), 165.1 (s, C=O).

5.10 ((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl cyclopropanecarboxylate (<u>19</u>)



<u>8</u>
Chemical Formula: $C_{23}H_{30}O_7$
Molecular Weight: 418,48

<u>19</u>
Chemical Formula: $C_{27}H_{34}O_8$
Molecular Weight: 486,55

Prepared and purified according to General Procedure B using **<u>8</u>** as starting material (30 mg, 0.074 mmol) and cyclopropanecarboxylic acid as reagent.

Yield: 26.2 mg (75 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 1/1) = 0.64

Specific rotation: $[\alpha]_D^{20}$ = +20.4 (MeOH; c 1.785)

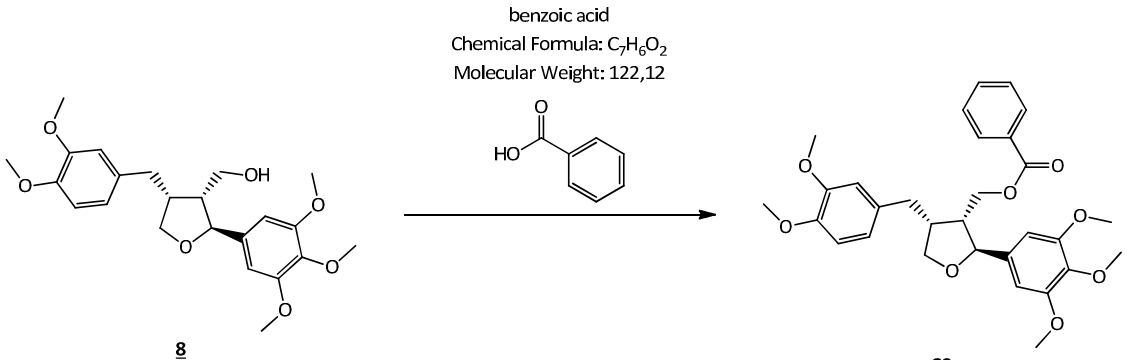
HRMS (ESI$^+$): exact mass calculated for $C_{27}H_{34}O_8$: 509.2146. Found: 509.2148. $[M+Na]^+$, Δ = 0.39 ppm

GC-MS (EI, 70 eV): Method 4; Retention time: 30.35 min; Main fragments (relative intensity): 486 (M^+, 18), 249 (23), 207 (13), 203 (12), 195 (47), 189 (15), 182 (10), 181 (23), 178 (10), 177 (13), 152 (14), 151 (100), 107 (15)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.78-1.03 (m, 4H, CH-$\underline{CH_2}$), 1.49-1.65 (m, 1H, $\underline{CH}$(CO)), 2.47-2.93 (m, 4H, H3 & H4 & CH_2), 3.74 (dd, J=8.61 & 6.46 Hz, 1H, H5), 3.82 (s, 3H, OCH_3), 3.85 (s, 9H, 3xOCH_3), 3.86 (s, 3H, OCH_3), 4.07 (dd, J=8.61 & 6.17 Hz, 1H, H5), 4.20 (dd, J=11.15 & 7.24 Hz, 1H, CH_2O), 4.38 (dd, J=11.15 & 6.75 Hz, 1H, CH_2O), 4.79 (d, J=6.07 Hz, 1H, H2), 6.54 (s, 2H, H2' & H6'), 6.64-6.84 (m, 3H, H2'' & H5'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 8.5 (t, 2C, CH-$\underline{CH_2}$), 12.8 (d, $\underline{CH}$(CO)), 33.1 (t, CH_2), 42.4 (d, C4), 49.0 (d, C3), 55.8 (q, 2C, OCH_3), 56.1 (q, 2C, OCH_3), 60.8 (q, C4' OCH_3), 62.7 (t, CH_2O), 72.8 (t, C5), 83.2 (d, C2), 102.5 (d, C2' & C6'), 111.3 (d, C2''), 111.8 (d, C5''), 120.4 (d, C6''), 132.5 (s, C1''), 138.2 (s, C_q), 147.5 (s, C4''), 148.9 (s, C3''), 153.2 (s, C3' & C5'), 174.7 (s, C=O). One C_q not visible

5.11 ((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl benzoate (<u>20</u>)



Prepared and purified according to General Procedure A using **<u>8</u>** as starting material (30 mg, 0.074 mmol) and benzoic acid as reagent.

Yield: 34.5 mg (93 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 1/1) = 0.65

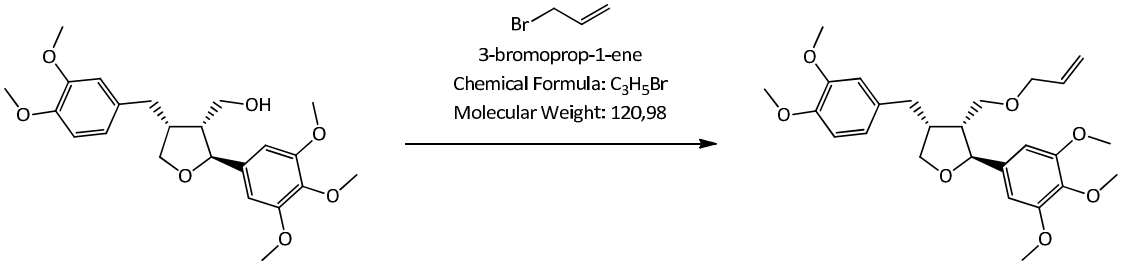
Specific rotation: $[\alpha]_D^{20}$ = +23.3 (MeOH; c 2.170)

HRMS (ESI$^+$): exact mass calculated for $C_{30}H_{34}O_8$: 545.2146. Found: 545.2152. $[M+Na]^+$, Δ = 1.10 ppm

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.47-2.54 (m, 4H, H3 & H3 & CH_2), 3.80 (s, 6H, 2xOCH_3), 3.81 (s, 3H, OCH_3), 3.85 (s, 6H, 2xOCH_3), 4.14 (dd, J=8.02 & 6.06 Hz, 1H, H5), 4.48 (dd, J=11.35 & 7.34 Hz, 1H, CH_2O), 4.66 (dd, J=11.35 & 6.17 Hz, 1H, CH_2O), 4.91 (d, J=5.87 Hz, 1H, H4), 6.57 (s, 2H, H2' & H6'), 6.64-6.84 (m, 3H, H2'' & H5'' & H6''), 7.37-7.49 (m, 2H, C(CO)-CH), 7.58 (tt, J=7.34 & 1.37 Hz, 1H, C(CO)-CH-CH-CH), 7.90-8.00 (m, 2H, C(CO)-CH-CH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 33.2 (t, CH_2), 42.6 (d, C4), 49.1 (d, C3), 55.8 (q, 2C, OCH_3), 56.0 (q, 2C, OCH_3), 60.8 (q, C4' OCH_3), 63.3 (t, CH_2O), 72.9 (t, C5), 83.6 (d, C2), 102.6 (d, C2' & C6'), 111.3 (d, C2''), 111.8 (d, C5''), 120.4 (d, C6''), 128.4 (d, C(CO)-C=CH), 129.5 (s, C(CO)-C), 129.7 (s, C(CO)), 132.4 (s, C1''), 133.3 (d, C(CO)-CH-CH-CH), 137.2 (s, C_q), 138.1 (s, C_q), 148.9 (s, C4''), 147.5 (s, C3''), 153.3 (s, C3' & C5'), 166.3 (s, C=O).

5.12 (2S,3R,4R)-3-((Allyloxy)methyl)-4-(3,4-dimethoxybenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran (21)



8
Chemical Formula: $C_{23}H_{30}O_7$
Molecular Weight: 418,48

21
Chemical Formula: $C_{26}H_{34}O_7$
Molecular Weight: 458,54

Prepared and purified according to General Procedure C using **8** as starting material (35 mg, 0.087 mmol) and 3bromoprop-1-ene as reagent.

Yield: 16.5 mg (42 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 1/1) = 0.51

Specific rotation: $[\alpha]_D^{20}$ = +15.2 (MeOH; c 1.383)

HRMS (ESI$^+$): exact mass calculated for $C_{26}H_{34}O_7$: 481.2197. Found: 481.2206. $[M+Na]^+$, Δ = 1.87 ppm

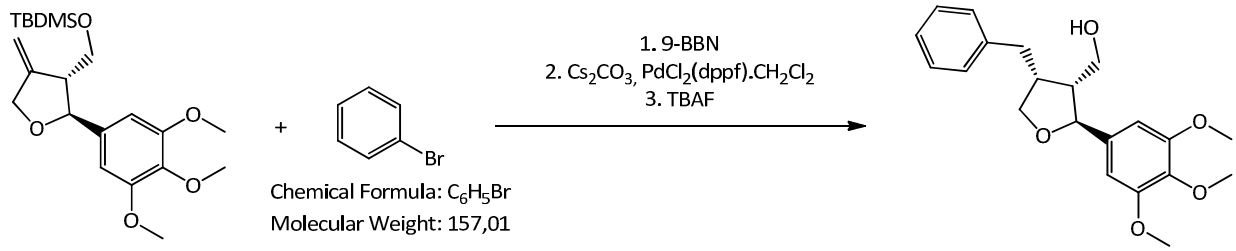
GC-MS (EI, 70 eV): Method 4; Retention time: 21.76 min; Main fragments (relative intensity): 458 (M^+, 11), 235 (15), 208 (11), 107 (44), 195 (29), 191 (11), 181 (24), 177 (15), 152 (14), 151 (100), 133 (11), 107 (18)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.40-2.97 (m, 4H, H3 & H4 & CH_2), 3.47-3.78 (m, 3H, H5 & CH_2O), 3.82 (s, 3H, OCH_3), 3.84 (s, 6H, 2xOCH_3), 3.85 (s, 6H, 2xOCH_3), 3.94-4.07 (m, 3H, CH_2O & O-$\underline{CH_2}$-CH), 4.81 (d, J=6.07 Hz, 1H, H2), 5.13-5.37 (m, 2H, O-CH_2-CH=$\underline{CH_2}$), 5.82-6.04 (m, 1H, O-CH_2-$\underline{CH}$=CH_2), 6.56 (s, 2H, H2' & H6'), 6.64-6.84 (m, 3H, H2'' & H5'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 33.0 (t, CH_2), 42.6 (d, C4), 50.3 (d, C3), 55.8 (q, OCH_3), 55.9 (q, OCH_3), 56.1 (q, 2C, OCH_3), 60.8 (q, C4' OCH_3), 68.3 (t, CH_2O), 72.2 (t, O-CH_2), 72.8 (t, C5), 83.1 (d, C2), 102.9 (d, C2' & C6'), 111.2 (d, C2''), 111.9 (d, C5''), 117.0 (t, O-CH_2-CH=$\underline{CH_2}$), 120.5 (d, C6''), 133.1 (s, C1''), 134.6 (d, O-CH_2-$\underline{CH}$=CH_2), 131.0 (s, C_q), 138.9 (s, C_q), 147.4 (s, C4''), 148.9 (s, C3''), 153.2 (s, C3' & C5').

6. Variation of the Benzylic Position

6.1 (2S,3R,4R)-(4-Benzyl-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methanol (22)



6
Chemical Formula: $C_{21}H_{34}O_5Si$
Molecular Weight: 394,58

Chemical Formula: C_6H_5Br
Molecular Weight: 157,01

22
Chemical Formula: $C_{21}H_{26}O_5$
Molecular Weight: 358,43

Prepared and purified according to General Procedure D using **6** as starting material (52 mg, 0.132 mmol) and phenylbromide as aryl halide.

Yield: 22.2 mg (36 %)

Appearance: orange oil

TLC: Rf(PE/EtOAc = 1/1) = 0.38

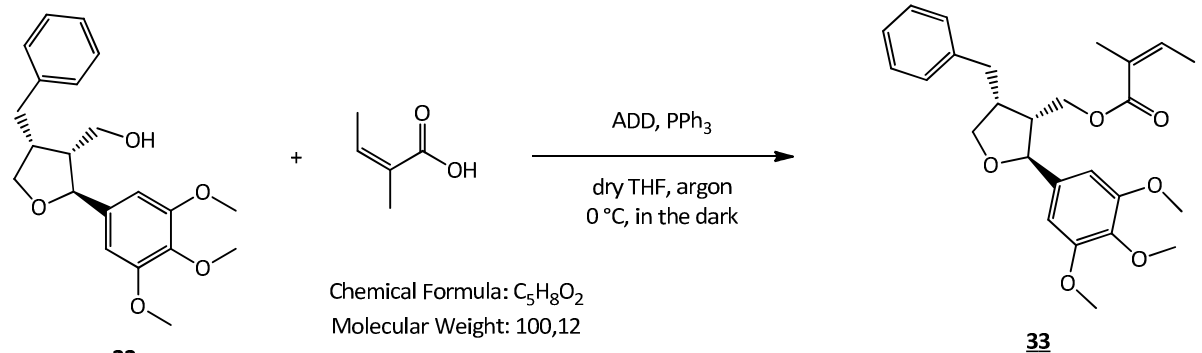
Specific rotation: $[\alpha]_D^{20}$ = +7.8 (MeOH; c 1.961)

HRMS (ESI^+): exact mass calculated for $C_{21}H_{26}O_5$: 381.1672. Found: 381.1667. $[M+Na]^+$, Δ = 1.31 ppm

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.91 (bs, 1H, OH), 2.31-3.01 (m, 4H, H3 & H4 & CH_2), 3.81 (s, 3H, 4' OCH_3), 3.84 (s, 6H, 3' & 5' OCH_3), 4.85 (d, J=5.87 Hz, 1H, H2), 6.54 (s, 2H, H2' & H6'), 7.12-7.35 (m, 5H, H2'' - H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 33.5 (t, CH_2), 42.1 (d, C4), 52.4 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 60.8 (t, CH_2OH), 73.0 (t, C5), 83.0 (d, C2), 102.5 (d, C2' & C6'), 126.2 (d, C2'' & C6''), 128.6 (d, C3''& C5''), 138.8 (s, C1''), 140.4 (s, C_q), 153.3 (s, C3' & C5'). One C_q not visible

6.2 (Z)- (2S,3R,4R)-4-Benzyl-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (<u>33</u>)



<u>22</u>
Chemical Formula: $C_{21}H_{26}O_5$
Molecular Weight: 358,43

Chemical Formula: $C_5H_8O_2$
Molecular Weight: 100,12

<u>33</u>
Chemical Formula: $C_{26}H_{32}O_6$
Molecular Weight: 440,53

Prepared and purified according to General Procedure F using **<u>22</u>** as starting material (16.1 mg, 0.045 mmol).

Yield: 12.1 mg (61 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 2/1) = 0.64

Specific rotation: $[\alpha]_D^{20}$ = +28.1 (MeOH; c 0.7021)

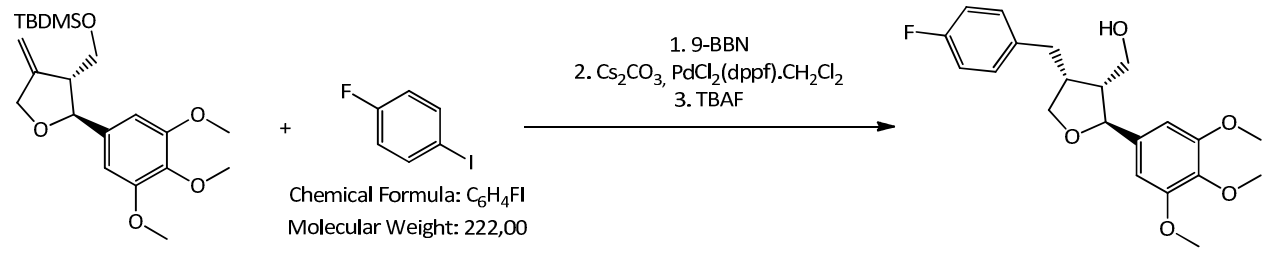
GC-MS (EI, 70 eV): Method 4; Retention time: 20.30 min; Main fragments (relative intensity): 440 (M^+, 12), 340 (10), 249 (27), 222 (10), 197 (13). 196 (40), 195 (85), 182 (12), 181 (41), 169 (12), 143 (9 (129 (13), 117 (33), 115 (12), 105 (10), 91 (100)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.85-1.89 (m, 3H, α-CH_3), 1.97-2.02 (m, 3H, β-CH_3), 2.58-2.67 (m, 2H, H3 & CH_2), 2.72-2.83 (m, 1H, H4), 2.93 (dd, J=13.30 & 4.82 Hz, 1H, CH_2), 3.77 (dd, J= 8.47 & 7.01 Hz, 1H, H5), 3.82 (s, 3H, 4' OCH_3), 3.84 (s, 6H, 3' & 5' OCH_3), 4.07 (dd, J=8.47 & 6.73 Hz, 1H, H5), 4.30 (dd, J=11.40 & 7.30, 1H, CH_2O), 4.42 (dd, J=11.40 & 7.02 Hz, 1H, CH_2O), 4.83 (d, J=6.14, 1H, H2), 6.06-6.14 (m, 1H, β-CH), 6.53 (s, 2H, H2' & H6'), 7.15-7.32 (m, 5H, H2''-H6'')

^{13}C-NMR (100 MHz, $CDCl_3$): δ 15.8 (q, β-CH_3), 20.6 (q, α-CH_3), 33.5 (t, CH_2), 42.3 (d, C4), 49.2 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 62.2 (t, CH_2O), 72.8 (t, C5), 83.2 (d, C2), 102.5 (d,

C2' & C6'), 126.3 (s, C4''), 127.3 (s, α-C), 128.6 (d, C2'' & C6''), 128.6 (d, C3'' & C5''), 137.2 (s, C_q), 138.2 (s, C_q), 139.1 (d, β-CH), 134.0 (s, C_q), 153.3 (s, C3' & C5'), 167.7 (s, C=O)

6.3 (2S,3R,4R)-(4-(4-Fluorobenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methanol (23)



6
Chemical Formula: $C_{21}H_{34}O_5Si$
Molecular Weight: 394,58

23
Chemical Formula: $C_{21}H_{25}FO_5$
Molecular Weight: 376,42

Prepared and purified according to General Procedure D using **6** as starting material (52 mg, 0.132 mmol) and 1-fluoro-4-iodobenzene as aryl halide.

Yield: 30.4 mg (47 %)

Appearance: yellow oil

TLC: Rf(PE/EtOAc = 1/1) = 0.29

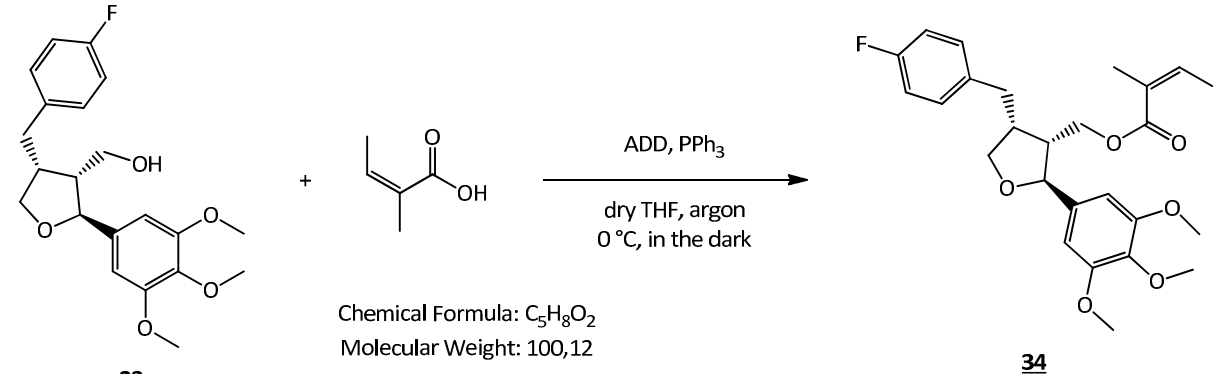
Specific rotation: $[\alpha]_D^{20}$ = +7.4 (MeOH; c 2.176)

HRMS (ESI$^+$): exact mass calculated for $C_{21}H_{25}O_5F$: 399.1078. Found: 399.1582. $[M+Na]^+$, Δ = 1.00 ppm

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.70 (bs, 1H, OH), 2.29-3.02 (m, 4H, H3 & H4 & CH_2), 3.59-3.93 (m, 3H, H5 & CH_2O), 3.81 (s, 3H, 4' OCH_3), 3.84 (s, 6H, 3' OCH_3 & 5' OCH_3), 3.96-4.09 (m, 1H, CH_2O), 4.83 (d, J=5.87 Hz, 1H, H2), 6.54 (s, 2H, H2' & H6'), 6.89-7.04 (m, 2H, H2'' & H6''), 7.06-7.19 (m, 2H, H3'' & H5'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 32.6 (t, CH_2), 42.2 (d, C4), 52.3 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 60.9 (t, CH_2O), 72.8 (t, C5), 83.0 (d, C2), 102.5 (d, C2' & C6'), 115.3 (dd, J=20.84 Hz, C3'' & C5''), 123.0 (dd, J=7.77 Hz, C2'' & C6''), 136.0 (s, C_q), 137.1 (s, C_q), 138.7 (s, C_q '), 153.2 (s, C3' & C5'), 161.4 (d, J=244.43 Hz, C4'')

6.4 (Z)- (2S,3R,4R)-(4-(4-Fluorobenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (<u>34</u>)



<u>23</u>
Chemical Formula: $C_{21}H_{25}FO_5$
Molecular Weight: 376,42

Chemical Formula: $C_5H_8O_2$
Molecular Weight: 100,12

<u>34</u>
Chemical Formula: $C_{26}H_{31}FO_6$
Molecular Weight: 458,52

Prepared and purified according to General Procedure F using **<u>23</u>** as starting material (21.6 mg, 0.057 mmol).

Yield: 17.6 mg (67 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 2/1) = 0.87

Specific rotation: $[\alpha]_D^{20}$ =+28.6 (MeOH; c 1.255)

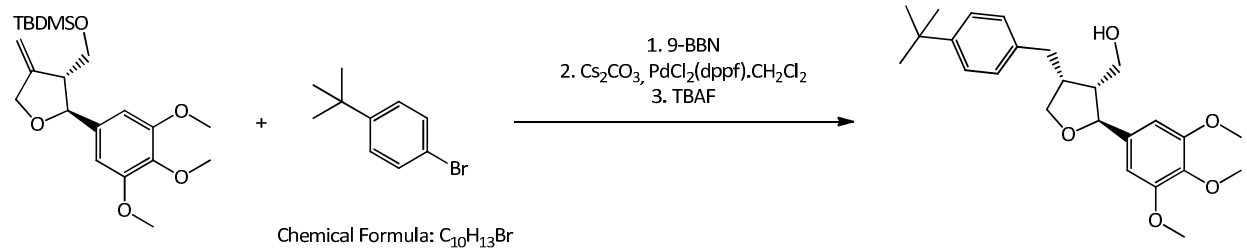
HRMS (ESI$^+$): exact mass calculated for $C_{26}H_{31}O_6F$: 481.1997. Found: 481.2001. $[M+Na]^+$, Δ = 0.83 ppm

GC-MS (EI, 70 eV): Method 4; Retention time: 18.65 min; Main fragments (relative intensity): 458 (M^+, 12), 249 (20), 196 (23), 195 (60), 181 (25), 135 (25), 110 (12), 109 (100)

^{1}H -NMR (200 MHz, $CDCl_3$): δ 1.82-1.90 (m, 3H, α-CH_3), 1.94-2.04 (m, 3H, β-CH_3), 2.51-2.83 (m, 3H, H3 & H4 & CH_2), 2.90 (dd, J=12.33 & 3.91 Hz, 1H, CH_2), 3.73 (dd, J= 8.60 & 6.17 Hz, 1H, H5), 3.81 (s, 3H, 4' OCH_3), 3.84 (s, 6H, 3' & 5' OCH_3), 4.06 (dd, J=8.60 & 6.06 Hz, 1H, H5), 4.28 (dd, J=11.34 & 7.05, 1H, CH_2O), 4.41 (dd, J=11.34 & 6.65 Hz, 1H, CH_2O), 4.83 (d, J=5.87, 1H, H2), 6.03-6.18 (m, 1H, β-CH), 6.52 (s, 2H, H2' & H6'), 6.90-7.04 (m, 2H, H3'' & H5''), 7.07-7.17 (H2'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 15.8 (q, β-CH_3), 20.6 (q, α-CH_3), 32.8 (t, CH_2), 42.5 (d, C4), 49.1 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 62.1 (t, CH_2O), 72.7 (t, C5), 83.1 (d, C2), 102.5 (d, C2' & C6'), 115.4 (dd, J=21.20 Hz, C3'' & C5''), 127.2 (s, α-C), 129.9 (dd, J=7.77 Hz, C2'' & C6''), 135.5 (s, C1'), 135.6 (s, C1''), 138.1 (s, C4'), 139.2 (d, β-CH), 153.3 (s, C3' & C5'), 165.8 (dd, J=186.86 Hz, C4'), 170.3 (C=O)

6.5 (2S,3R,4R)-(4-(4-(*tert*-Butyl)benzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methanol (24)



6
Chemical Formula: $C_{21}H_{34}O_5Si$
Molecular Weight: 394,58

Chemical Formula: $C_{10}H_{13}Br$
Molecular Weight: 213,11

24
Chemical Formula: $C_{25}H_{34}O_5$
Molecular Weight: 414,53

Prepared and purified according to General Procedure D using **6** as starting material (57.7 mg, 0.206 mmol) and 1-bromo-4-(*tert*-butyl)benzene as aryl halide.

Yield: 41.6 mg (49 %)

Appearance: nearly colorless oil

TLC: Rf(PE/EtOAc = 1/1) = 0.31

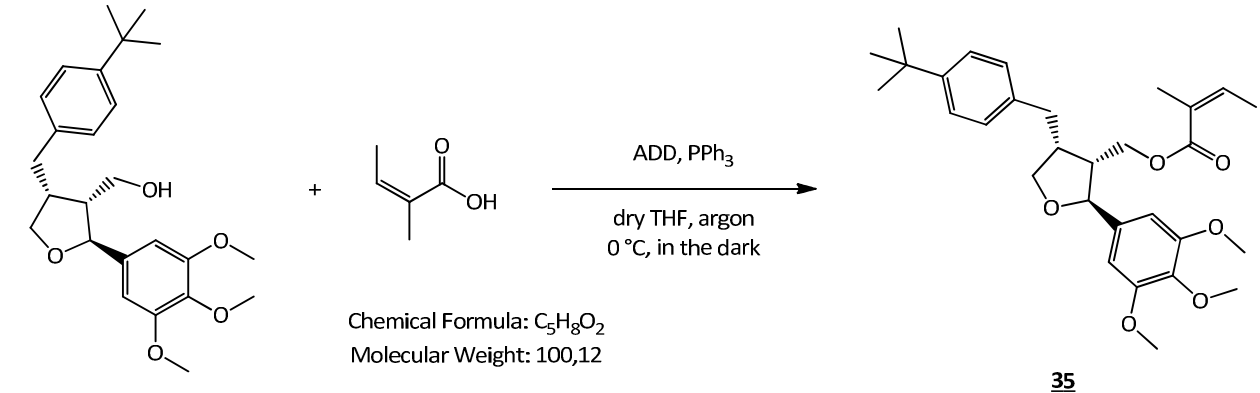
Specific rotation: $[\alpha]_D^{20}$ = +11.0 (MeOH; c 1.704)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 9H, $C(CH_3)_3$), 2.32-2.48 (m, 1H, H4), 2.58 (dd, J=12.43 & 9.59 Hz, 1H, CH_2), 2.68-2.82 (m, 1H, H3), 2.91 (dd, J=12.43 & 4.90 Hz, 1H, CH_2), 3.75 (dd, J=8.61 & 6.75 Hz, 1H, CH_2O), 3.81 (s, 3H, 4' OCH_3), 3.84 (s, 6H, 3' OCH_3 & 5' OCH_3), 3.93 (dd, J=10.47 & 6.75 Hz, 1H, H5), 3.93 (dd, J=8.61 & 6.36 Hz, 1H, CH_2O), 4.85 (d, J=5.67 Hz, 1H, H2), 6.55 (s, 2H, H2' & H6'), 7.11 (d, J=8.31 Hz, 2H, H2' & H6'), 7.30 (d, J=8.31 Hz, 2H, H3' & H5')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 31.3 (q, $C(\underline{C}H_3)_3$), 32.9 (t, CH_2), 34.3 (s, $\underline{C}(CH_3)_3$), 42.0 (d, C4), 52.3 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 60.9 (t, CH_2O), 73.1 (t, C5), 83.0 (d, C2), 102.5

(d, C2' & C6'), 145.4 (s, C3' & C5'), 128.2 (s, C2' & C5'), 137.2 (s, C1''), 138.9 (s, C_q), 149.0 (s, C4''), 153.2 (s, C3' & C5'). One C_q not visible

6.6 (Z)- (2S,3R,4R)-(4-(4-(*tert*-Butyl)benzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (<u>35</u>)



<u>24</u>
Chemical Formula: $C_{25}H_{34}O_5$
Molecular Weight: 414,53

Chemical Formula: $C_5H_8O_2$
Molecular Weight: 100,12

<u>35</u>
Chemical Formula: $C_{30}H_{40}O_6$
Molecular Weight: 496,63

Prepared and purified according to General Procedure F using <u>**24**</u> as starting material (23.7 mg, 0.057 mmol).

Yield: 19.1 mg (76 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 2/1) = 0.69

Specific rotation: $[\alpha]_D^{20}$ = +22.4 (MeOH; c 0.1.486)

HRMS (ESI$^+$): exact mass calculated for $C_{30}H_{40}O_6$: 519.2717. Found: 519.2717. $[M+Na]^+$, Δ = 0.00 ppm

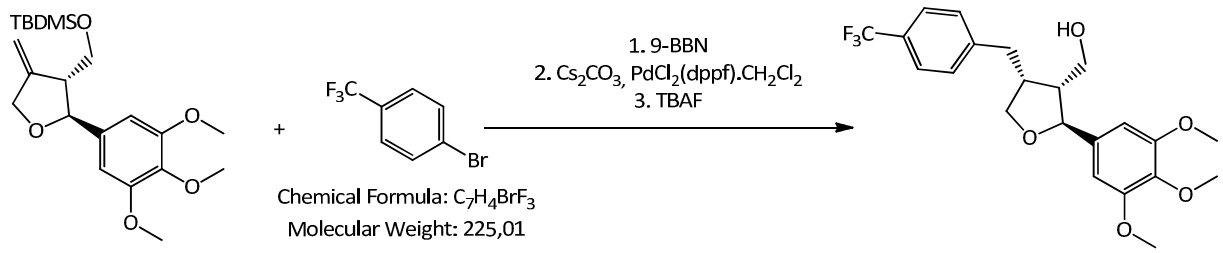
GC-MS (EI, 70 eV): Method 4; Retention time: 28.61 min; Main fragments (relative intensity): 496 (M^+, 14), 396 (10), 249 (41), 210 (15), 197 (17), 196 (43), 195 (100), 182 (18), 181 (47), 169 (15), 147 (36), 143 (14), 132 (32), 131 (23), 129 (14), 119 (14), 117 (46), 105 (17)

^{1}H -NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 9H, $C(CH_3)_3$), 1.82-1.92 (m, 3H, α-CH_3), 1.94-2.05 (m, 3H, β-CH_3), 2.51-2.97 (m, 4H, H3 & H4 & CH_2), 3.81 (s, 4H, 4' OCH_3 & H5), 3.83 (s, 6H, 3' & 5' OCH_3), 4.09

(dd, J=8.61 & 6.26 Hz, 1H, H5), 4.29 (dd, J=11.35 & 7.24 Hz, 1H, CH_2O), 4.43 (dd, J=11.35 & 6.75 Hz, 1H, CH_2O), 4.83 (d, J=5.87 Hz, 1H, H2), 6.02-6.17 (m, 1H,β-CH), 6.54 (s, 2H, H2' & H6'), 7.05-7.14 (m, 2H, H3'' & H5''), 7.27-7.36 (m, 2H, H2'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 15.8 (s, β-CH_3), 20.8 (s, α-CH_3), 31.4 (s, 3C, C($\underline{C}H_3)_3$), 33.0 (s, CH_2), 34.4 (s, $\underline{C}(CH_3)_3$), 42.3 (d, C4), 49.2 (d, C3), 56.1 (s, C3' OCH_3 & C5' OCH_3), 60.8 (s, C4' OCH_3), 62.3 (s, CH_2O), 72.9 (t, C5), 83.2 (d, C2), 102.6 (d, C2' & C6'), 125.5 (d, C2'' & C6''), 127.3 (s, α-C), 128.2 (d, C3'' & C5''), 136.9 (s, C1''), 138.3 (s, C_q), 139.6 (s, β-CH), 149.2 (s, C4''), 153.3 (s, C3' & C5'), 167.7 (s, C=O). One C_q not visible.

6.7 (2S,3R,4R)-(4-(4-(Trifluoromethyl)benzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methanol (<u>25</u>)



<u>6</u>
Chemical Formula: $C_{21}H_{34}O_5Si$
Molecular Weight: 394,58

Chemical Formula: $C_7H_4BrF_3$
Molecular Weight: 225,01

<u>25</u>
Chemical Formula: $C_{22}H_{25}F_3O_5$
Molecular Weight: 426,43

Prepared and purified according to General Procedure D using **<u>6</u>** as starting material (52 mg, 0.132 mmol) and 1-bromo-4-(trifluoromethyl)benzene as aryl halide.

Yield: 40.2 mg (62 %)

Appearance: slightly yellow oil

TLC: Rf(PE/EtOAc = 1/1) = 0.32

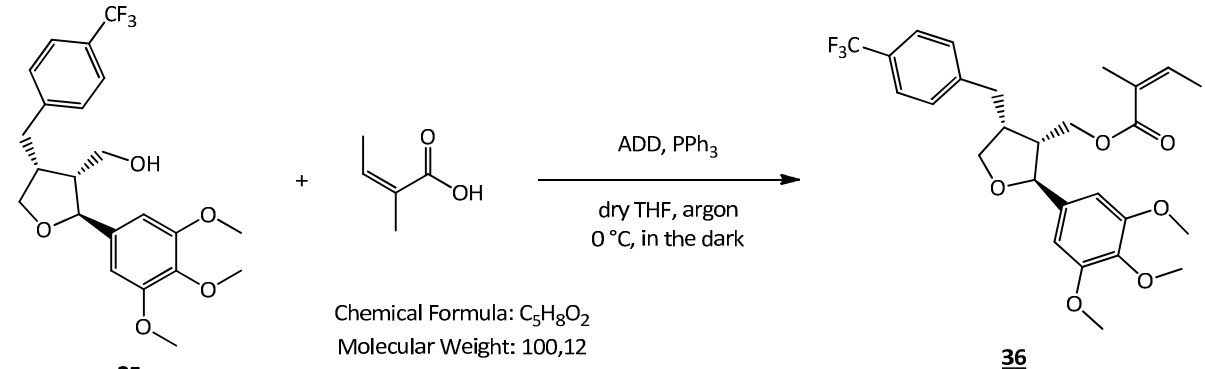
Specific rotation: $[\alpha]_D^{20}$ = +15.5 (MeOH; c 0.1.721)

HRMS (ESI$^+$): exact mass calculated for $C_{22}H_{25}O_5F_3$: 449.1546. Found: 449.1551. $[M+Na]^+$, Δ = 1.11 ppm

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.74 (bs, 1H, OH), 2.33-2.49 (m, 1H, H4), 2.57-3.10 (m, 3H, H3 & CH_2), 3.63-4.10 (m, 4H, H5 & CH_2O), 3.81 (s, 3H, 4' OCH_3), 3.84 (s, 6H, 3' OCH_3 & 5' OCH_3), 4.83 (d, J=5.87 Hz, 1H, H2), 6.54 (s, 2H, H2' & H6'), 7.30 (d, J=8.02 Hz, 2H, H2'' & H6''), 7.54 (d, J=8.02 Hz, 2H, H3'' & H5'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 33.3 (t, CH_2), 41.9 (d, C4), 52.2 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, OCH_3), 60.8 (t, CH_2O), 72.7 (t, C5), 82.9 (d, C2), 102.5 (d, C2' & C6'), 118.6 (q, J=289.29 Hz, CF_3), 125.5 (dq, J=3.89 Hz, C3'' & C5''), 128.9 (d, C2'' & C6''), 133.3 (q, J=48.39 Hz, C4''), 137.1 (s, C_q), 138.6 (s, C_q), 144.6 (s, C_q), 153.3 (s, C3' & C5').

6.8 (Z)-(2S,3R,4R)-4-(4-(Trifluoromethyl)benzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (<u>36</u>)



<u>25</u>
Chemical Formula: $C_{22}H_{25}F_3O_5$
Molecular Weight: 426,43

Chemical Formula: $C_5H_8O_2$
Molecular Weight: 100,12

<u>36</u>
Chemical Formula: $C_{27}H_{31}F_3O_6$
Molecular Weight: 508,53

Prepared and purified according to General Procedure F using **<u>25</u>** as starting material (35.2 mg, 0.083 mmol).

Yield: 31.2 mg (74 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 2/1) = 0.67

Specific rotation: $[\alpha]_D^{20}$ = +26.2 (MeOH; c 1.295)

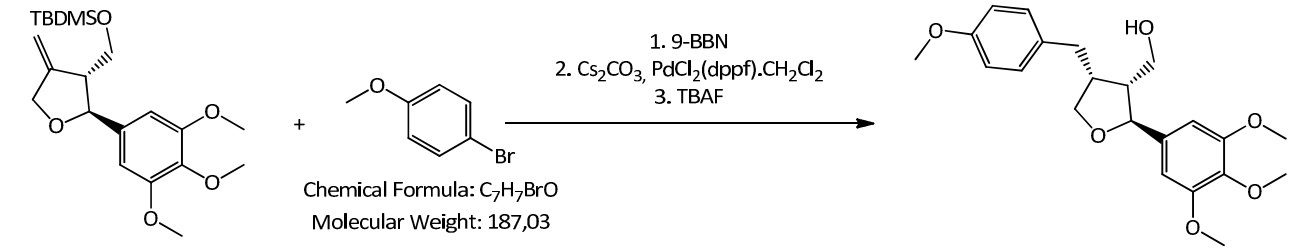
HRMS (ESI$^+$): exact mass calculated for $C_{27}H_{31}O_6F_3$: 531.1965. Found: 531.1973. $[M+Na]^+$, Δ = 1.51 ppm

GC-MS (EI, 70 eV): Method 4; Retention time: 17.85 min; Main fragments (relative intensity): 508 (17), 408 (14), 249 (38), 222 (10), 207 (22), 197 (13), 196 (34), 195 (95), 191 (10), 182 (12), 181 (24), 169 (14), 165 (10), 159 (44), 153 (11), 109 (14), 55 (100)

^{1}H -NMR (200 MHz, $CDCl_3$): δ 1.85-1.88 (m, 3H, $\underline{CH_3}$-C(CO)=CH-CH_3), 1.97-2.02 (m, 3H, C=CH-$\underline{CH_3}$), 2.59-2.83 (m, 3H, H3 & H4 & CH_2), 2.99 (dd, J=12.86 & 4.09 Hz, 1H, CH_2), 3.74 (dd, J= 8.63 & 6.85 Hz, 1H, H5), 3.82 (s, 3H, 4' OCH_3), 3.84 (s, 6H, OCH_3), 4.06 (dd, J=8.63 & 6.29 Hz, 1H, H5), 4.30 (dd, J=11.40 & 7.02 Hz, 1H, CH_2O), 4.41 (dd, J=11.40 & 7.02 Hz, 1H, CH_2O), 4.83 (d, J=6.14 Hz, 1H, H2), 6.07-6.15 (m, 1H, C=$\underline{CH}$-CH_3), 6.53 (s, 2H, H2' & H6'), 7.29 (d, J=8.05 Hz, 2H, H3'' & H5''), 7.55 (d, J=8.05 Hz, 2H, H2'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 15.8 (q, C=CH-$\underline{CH_3}$), 20.6 (q, $\underline{CH_3}$-C(CO)=CH-CH_3), 33.5 (t, CH_2), 42.4 (d, C4), 49.2 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 62.0 (t, CH_2O), 72.6 (t, C5), 83.1 (d, C2), 102.5 (d, C2' & C6'), 125.7 (q, J=293.3 Hz, CF_3), 125.6 (dq, J=3.84 Hz, C3'' & C5''), 127.2 (s, $\underline{C}$=CH-CH_3), 128.9 (d, C2'' & C6''), 137.3 (s, C_q), 137.9 (s, C_q), 139.3 (d, C=$\underline{CH}$-CH_3), 144.1 (s, C1''), 153.3 (s, C3' & C5'), 167.6 (s, C=O). C4'' not visible.

6.9 (2S,3R,4R)-(4-(4-Methoxybenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methanol (**26**)



6
Chemical Formula: $C_{21}H_{34}O_5Si$
Molecular Weight: 394,58

Chemical Formula: C_7H_7BrO
Molecular Weight: 187,03

26
Chemical Formula: $C_{22}H_{28}O_6$
Molecular Weight: 388,45

Prepared and purified according to General Procedure D using **6** as starting material (52 mg, 0.132 mmol) and 1-bromo-4-methoxybenzene as aryl halide.

Yield: 19.3 mg (28 %)

Appearance: orange oil

TLC: Rf(PE/EtOAc = 1/1) = 0.20

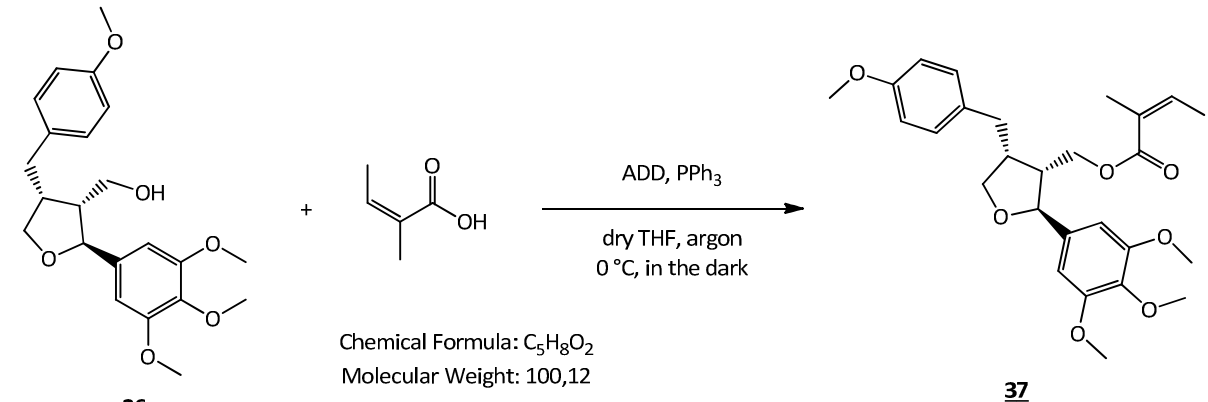
Specific rotation: $[\alpha]_D^{20}$ = +3.4 (MeOH; c 0.742)

HRMS (ESI$^+$): exact mass calculated for $C_{22}H_{28}O_6$: 411.1778. Found: 411.1785. $[M+Na]^+$, Δ = 1.70 ppm

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.54 (bs, 1H, OH), 2.31-2.96 (m, 4H, H3 & H4 & CH_2), 3.76-3.99 (m, 3H, H5 & CH_2O), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.84 (s, 6H, 3' OCH_3 & 5' OCH_3), 4.00-4.11 (m, 1H, CH_2O), 4.84 (d, J=5.87 Hz, 1H, H2), 6.54 (s, 2H, H2' & H6'), 6.77-6.78 (m, 2H, H3'' & H5''), 7.04-7.15 (m, 2H, H2'' & H6'')

^{13}C-NMR (^{13}C, 50 MHz, $CDCl_3$): δ 32.6 (t, CH_2), 42.2 (d, C4), 52.4 (d, C3), 55.2 (q, OCH_3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 61.0 (t, CH_2O), 73.0 (t, C5), 83.0 (d, C2), 102.5 (d, C2' & C6'), 114.0 (d, C3'' & C5''), 129.5 (d, C2'' & C6''), 132.3 (s, C1''), 137.1 (s, C_q), 138.8 (s, C_q), 153.2 (s, C3' & C5'), 158.0 (s, C4'')

6.10 (Z)- (2S,3R,4R)-(4-(4-Methoxybenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (<u>37</u>)



<u>26</u>
Chemical Formula: $C_{22}H_{28}O_6$
Molecular Weight: 388,45

Chemical Formula: $C_5H_8O_2$
Molecular Weight: 100,12

<u>37</u>
Chemical Formula: $C_{27}H_{34}O_7$
Molecular Weight: 470,55

Prepared and purified according to General Procedure F using **<u>26</u>** as starting material (14.3 mg, 0.037 mmol).

Yield: 10.1 mg (58 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 2/1) = 0.67

Specific rotation: $[\alpha]_D^{20}$ = +20.1 (MeOH; c 1.000)

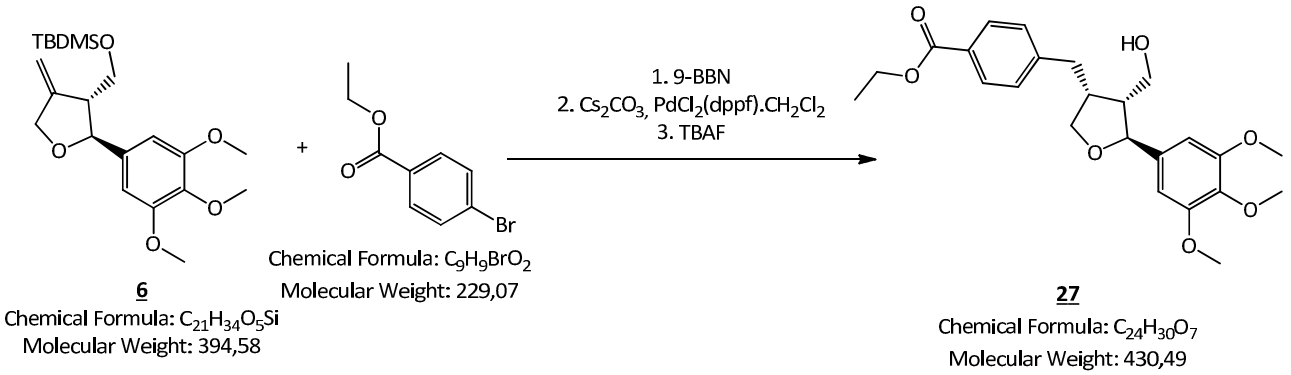
HRMS (ESI$^+$): exact mass calculated for $C_{27}H_{34}O_7$: 493.2197. Found: 493.2203. $[M+Na]^+$, Δ = 1.22 ppm

GC-MS (EI, 70 eV): Method 4; Retention time: 24.86 min; Main fragments (relative intensity): 470 (M^+, 6), 281 (11), 249 (15), 208 (11), 107 (54), 195 (38), 181 (16), 135 (11), 147 (19), 133 (14), 122 (10), 121 (100)

^{1}H -NMR (200 MHz, $CDCl_3$): δ 1.82-1.91 (m, 3H, α-CH_3), 1.94-2.04 (m, 3H, β-CH_3), 2.48-2.80 (m, 3H, H3 & H4 & CH_2), 2.87 (dd, J=12.42 & 4.21 Hz, 1H, CH_2), 3.78 (s, 4H, OCH_3 & H5), 3.81 (s, 3H, OCH_3), 3.84 (s, 6H, OCH_3), 4.07 (dd, J=8.61 & 6.26 Hz, 1H, H5), 4.28 (dd, J=11.35 & 7.24 Hz, 1H, CH_2O), 4.42 (dd, J=11.35 & 6.66, 1H, CH_2O), 4.83 (d, J=5.67, 1H, H2), 6.10 (m, 1H, β-CH), 6.53 (s, 2H, H2' & H6'), 6.78-6.87 (m, 2H, H3'' & H5''), 7.03-7.13 (m, 2H, H2'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 15.8 (q,β-CH_3), 20.6 (q, α-CH_3), 32.6 (t, CH_2), 42.5 (d, C4), 49.1 (d, C3), 55.2 (q, C4'' OCH_3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 62.2 (t, CH_2O), 72.8 (t, C5), 83.2 (d, C2), 102.5 (d, C2' & C6'), 114.0 (d, C3'' & C5''), 127.3 (s, α-C), 129.5 (d, C2'' & C6''), 131.9 (s, C1''), 138.3 (s, C_q), 139.1 (d, β-CH), 153.3 (s, C4''), 158.1 (s, C3' & C5'), 167.7 (s, C=O). One C_q not visible.

6.11 Ethyl 4-(((3R,4R,5S)-4-(Hydroxymethyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl)benzoate (<u>27</u>)



<u>6</u>
Chemical Formula: $C_{21}H_{34}O_5Si$
Molecular Weight: 394,58

Chemical Formula: $C_9H_9BrO_2$
Molecular Weight: 229,07

<u>27</u>
Chemical Formula: $C_{24}H_{30}O_7$
Molecular Weight: 430,49

Prepared and purified according to General Procedure E using **<u>6</u>** as starting material (57.7 mg, 0.206 mmol) and ethyl 4-bromobenzoate as aryl halide.

Yield: 40.0 mg (45 %)

Appearance: slightly yellow oil

TLC: Rf(PE/EtOAc = 1/1) = 0.17

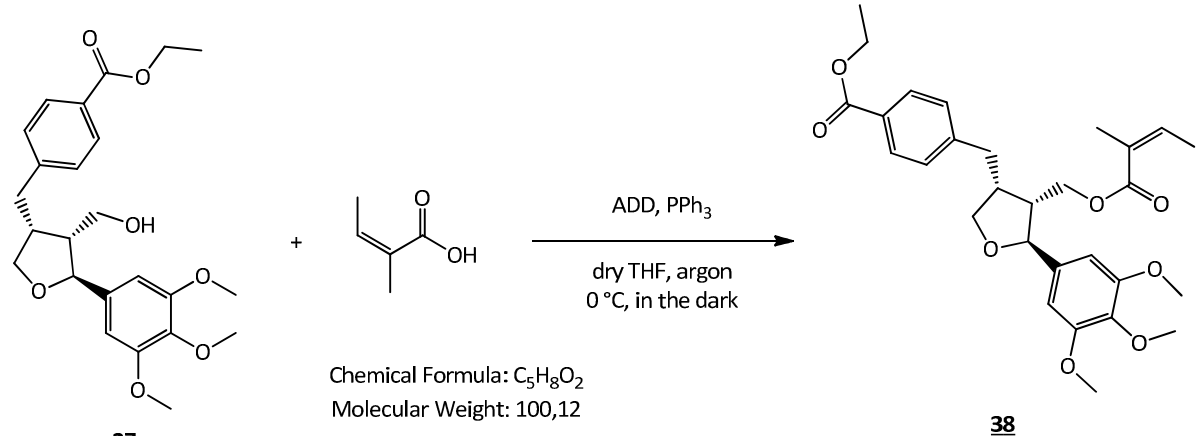
Specific rotation: $[\alpha]_D^{20}$ = +7.7 (MeOH; c 2.021)

HRMS (ESI^+): exact mass calculated for $C_{24}H_{30}O_7$: 453.1884. Found: 453.1886. $[M+Na]^+$, Δ = 0.44 ppm

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.39 (t, J=7.43 Hz, 3H, O-CH_2-<u>CH_3</u>), 1.94 (bs, 1H, OH), 2.38-2.46 (m, 1H, H4), 2.69 (dd, J=12.91 & 10.96, 1H, CH_2), 2.72-2.82 (m, 1H, H3), 3.07 (dd, J=8.61 & 4.30, 1H, CH_2), 3.72 (dd, J=8.21 & 6.65 Hz, 1H, CH_2O), 3.83 (s, 3H, 4' OCH_3), 3.85 (s, 6H, 3' OCH_3 & 5' OCH_3), 3.92 (dd, J=10.4 & 6.8 Hz, 1H, H5), 4.04 (dd, J=8.61 & 6.65 Hz, 1H, CH_2O), 4.37 (q, J=7.43 Hz, 2H, O-<u>CH_2</u>-CH_3) 4.85 (d, J=5.87, 1H, H2), 6.55 (s, 2H, H2' & H6'), 7.27 (d, J=8.22 Hz, 2H, H2'' & H6''), 7.97 (d, J=8.22 Hz, 2H, H3'' & H5'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 14.3 (q, O-CH_2-<u>CH_3</u>), 33.5 (t, CH_2), 41.9 (d, C4), 52.3 (d, C3), 56.0 (q, 2C, C3' OCH_3 & C5' OCH_3), 60.7 (t, CH_2O), 60.7 (q, C4' OCH_3), 60.9 (t, O-<u>CH_2</u>-CH_3), 72.7 (t, C5), 82.9 (d, C2), 102.4 (d, C2' & C6'), 128.5 (s, C4''), 128.8 (d, C2'' & C6''), 129.9 (d, C3'' & C5''), 137.0 (s, C_q), 138.6 (s, C_q), 145.8 (s, C1''), 153.2 (s, C3' & C5'), 166.5 (s, C=O)

6.12 (Z)-Ethyl 4-(((3R,4R,5S)-4-(((2-methylbut-2-enoyl)oxy)methyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl)benzoate (38)



27
Chemical Formula: $C_{24}H_{30}O_7$
Molecular Weight: 430,49

Chemical Formula: $C_5H_8O_2$
Molecular Weight: 100,12

38
Chemical Formula: $C_{29}H_{36}O_8$
Molecular Weight: 512,59

Prepared and purified according to General Procedure F using **27** as starting material (34.0 mg, 0.079 mmol).

Yield: 29.8 mg (74 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 2/1) = 0.59

Specific rotation: $[\alpha]_D^{20}$ = +17.7 (MeOH; c 1.228)

HRMS (ESI^+): exact mass calculated for $C_{29}H_{36}O_8$: 535.2302. Found: 535.2319. $[M+Na]^+$, Δ = 3.18 ppm

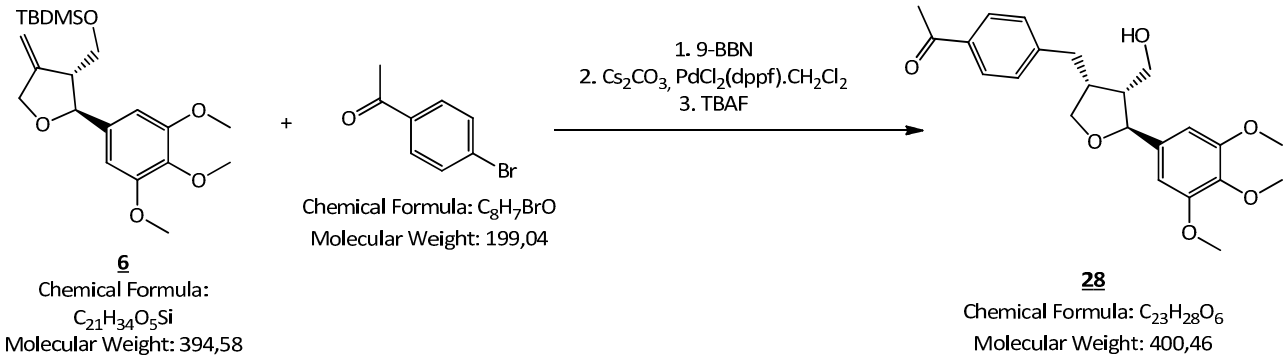
GC-MS (EI, 70 eV): Method 4; Retention time: 36.22 min; Main fragments (relative intensity): 512 (M^+, 11), 381 (11), 249 (31), 207 (20), 196 (33), 195 (93), 181 (33), 169 (11), 163 (17), 143 (14), 135 (17), 118 (13), 117 (19), 113 (13), 107 (16), 55 (100)

^{1}H -NMR (400 MHz, $CDCl_3$): δ 1.39 (t, J=7.16 Hz, 3H, $OCH_2\underline{CH_3}$), 1.85-1.91 (m, 3H α-CH_3), 1.98-2.04 (m, 3H, β-CH_3), 2.59-2.85 (m, 3H, H3 & H4 & CH_2), 3.00 (dd, J=13.01 & 4.54 Hz, 1H, CH_2), 3.75 (dd, J= 8.48 & 6.73 Hz, 1H, H5), 3.83 (s, 3H, OCH_3), 3.85 (s, 6H, OCH_3), 4.06 (dd, J=8.48 & 6.58 Hz, 1H, H5),

4.27-4.46 (m, 4H, CH_2O, $O\underline{CH_2}CH_3$), 4.84 (d, J=6.14, 1H, H2), 6.08-6.16 (m, 1H, β-CH), 6.54 (s, 2H, H2' & H6'), 7.25 (d, J= 8.48 Hz, 2H, H3'' & H5''), 7.99 (d, J= 8.48 Hz, 2H, H2'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 14.3 (q, $OCH_2\underline{CH_3}$), 15.8 (q, β-CH_3), 20.5 (q, α-CH_3), 33.6 (t, CH_2), 42.1 (d, C4), 49.2 (d, C3), 56.0 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 60.9 (t, $O\underline{CH_2}CH_3$), 62.0 (t, CH_2O), 72.6 (t, C5), 83.0 (d, C2), 102.5 (d, C2' & C6'), 127.2 (d, α-CH), 128.5 (d, C2'' & C6''), 128.7 (s, C4''), 129.9 (d, C3'' & C5''), 137.2 (s, C_q), 138.0 (s, C_q), 139.2 (d, β-CH), 142.3 (s, C_q), 153.3 (s, C3' & C5'), 166.4 (s, C=O), 167.6 (s, C=O).

6.13 1-(4-(((3R,4R,5S)-4-(Hydroxymethyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl)phenyl)ethanone (28)



6
Chemical Formula: $C_{21}H_{34}O_5Si$
Molecular Weight: 394,58

Chemical Formula: C_8H_7BrO
Molecular Weight: 199,04

28
Chemical Formula: $C_{23}H_{28}O_6$
Molecular Weight: 400,46

Prepared and purified according to General Procedure E using **6** as starting material (57.7 mg, 0.206 mmol) and 1-(4-bromophenyl)ethanone as aryl halide.

Yield: 19.5 mg (24 %)

Appearance: yellow oil

TLC: Rf(PE/EtOAc = 1/1) = 0.31

Specific rotation: $[\alpha]_D^{20}$ = +10.9 (MeOH; c 1.552)

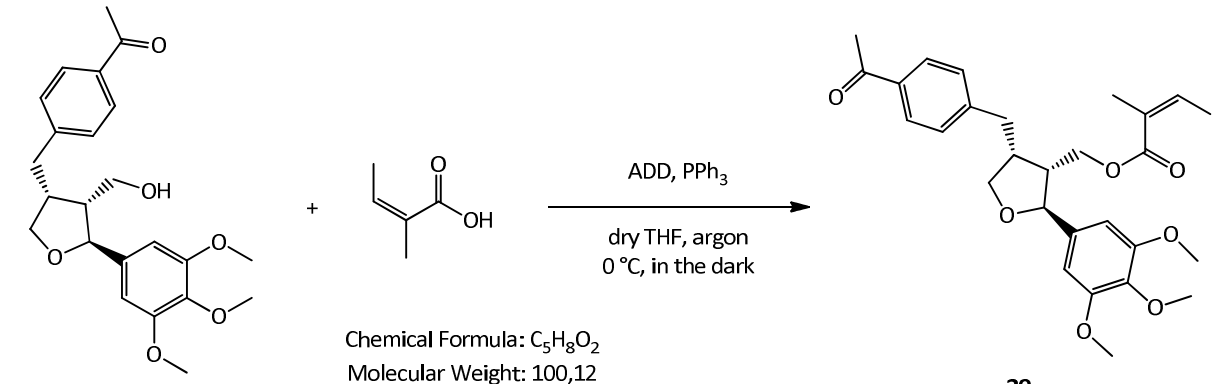
HRMS (ESI$^+$): exact mass calculated for $C_{23}H_{28}O_6$: 423.1778. Found: 423.1785. $[M+Na]^+$, Δ = 1.65 ppm

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.73 (bs, 1H, OH), 2.30-2.59 (m, 1H, H4), 2.65 (s, 3H, C(CO)-$\underline{CH_3}$), 2.59 - 2.83 (m, 2H, H3 & CH_2), 2.96-3.08 (m, 1H, CH_2), 3.64-3.95 (m, 3H, H5 & CH_2O), 3.80 (s, 3H, 4' OCH_3),

3.83 (s, 6H, 3' OCH_3 & 5' OCH_3), 3.97-4.06 (m, 1H, CH_2O), 4.82 (d, J=6.06, 1H, H2), 6.53 (s, 2H, H2' & H6'), 7.28 (d, J=8.42 Hz, 2H, H2'' & H6''), 7.88 (d, J=8.42 Hz, 2H, H3'' & H5'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 26.5 (q, (CO)$\underline{CH_3}$), 36.3 (t, CH_2), 41.9 (d, C4), 52.3 (d, C3), 50.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 60.7 (t, CH_2O), 72.7 (t, C5), 82.9 (d, C2), 102.5 (d, C2' & C6'), 128.7 (d, C3'' & C5''), 128.8 (d, C2'' & C6''), 135.3 (s, C_q), 137.1 (s, C_q), 138.6 (s, C4'), 146.3 (s, C1''), 153.2 (s, C3' & C5'), 197.8 (s, C=O)

6.14 (Z)- (2S,3R,4R)-(4-(4-Acetylbenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (<u>39</u>)



<u>28</u>
Chemical Formula: $C_{23}H_{28}O_6$
Molecular Weight: 400,46

Chemical Formula: $C_5H_8O_2$
Molecular Weight: 100,12

<u>39</u>
Chemical Formula: $C_{28}H_{34}O_7$
Molecular Weight: 482,57

Prepared and purified according to General Procedure F using **<u>32</u>** as starting material (14.3 mg, 0.036 mmol).

Yield: 13.1 mg (76 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 2/1) = 0.23

Specific rotation: $[\alpha]_D^{20}$ = +19.7 (MeOH; c 1.276)

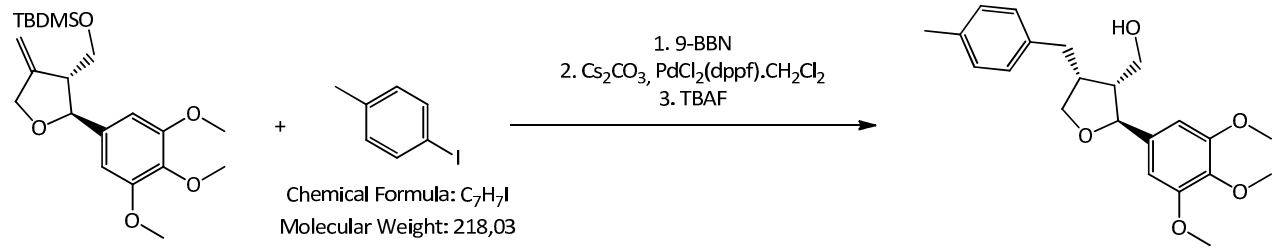
HRMS (ESI$^+$): exact mass calculated for $C_{28}H_{34}O_7$: 505.2197. Found: 505.2204. $[M+Na]^+$, Δ = 1.39 ppm

GC-MS (EI, 70 eV): Method 4; Retention time: 35.38 min; Main fragments (relative intensity): 482 (M^+, 10). 351 (13), 249 (29), 217 (16), 207 (25), 197 (11), 196 (35), 195 (100), 182 (13), 181 (39), 169 (14), 133 (25), 118 (14), 115 (11), 105 (29)

^{1}H -NMR (200 MHz, $CDCl_3$): δ 1.82-1.92 (m, 3H, α-CH_3), 1.94-2.05 (m, 3H, β-CH_3), 2.58 (s, 3H, CH_3CO), 2.61-2.91 (m, 3H, H3 & H4 & CH_2), 2.92-3.05 (m, 1H, CH_2), 3.74 (dd, J= 8.80 & 6.17 Hz, 1H, H5), 3.81 (s, 3H, 4' OCH_3), 3.84 (s, 6H, 3' & 5' OCH_3), 4.06 (dd, J=8.80 & 6.06 Hz, 1H, H5), 4.29 (dd, J=11.35 & 7.04, 1H, CH_2O), 4.41 (dd, J=11.35 & 6.85 Hz, 1H, CH_2O), 4.83 (d, J=6., 1H, H2), 6.03-6.19 (m, 1H, β-CH), 6.52 (s, 2H, H2' & H6'), 7.27 (d, J= 8.22 Hz, 2H, H3'' & H5''), 7.89 (d, J= 8.22 Hz, 2H, H2'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 15.8 (q, β-CH_3), 20.6 (q, α-CH_3), 26.5 (q, CO<u>CH_3</u>), 33.6 (t, CH_2), 42.8 (d, C4), 49.2 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 62.0 (t, CH_2O), 72.6 (t, C5), 83.1 (d, C2), 102.5 (d, C2' & C6'), 128.8 (d, C2'' & C6''), 128.8 (d, C3'' & C5''), 127.2 (s, α-C), 135.5 (s, C_q), 136.9 (s, C_q), 137.3 (s, C_q), 137.9 (C4'), 139.3 (d, β-CH), 153.3 (s, C3' & C5'), 167.6 (s, C=O), 197.6 (s, <u>C</u>OCH_3)

6.15 (2S,3R,4R)-(4-(4-Methylbenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methanol (<u>29</u>)



<u>6</u>
Chemical Formula: $C_{21}H_{34}O_5Si$
Molecular Weight: 394,58

Chemical Formula: C_7H_7I
Molecular Weight: 218,03

<u>29</u>
Chemical Formula: $C_{22}H_{28}O_5$
Molecular Weight: 372,45

Prepared and purified according to General Procedure D using **<u>6</u>** as starting material (57.7 mg, 0.206 mmol) and 1-iodo-4-methylbenzene as aryl halide.

Yield: 33.2 mg (43 %)

Appearance: slightly yellow oil

TLC: Rf(PE/EtOAc = 1/1) = 0.35

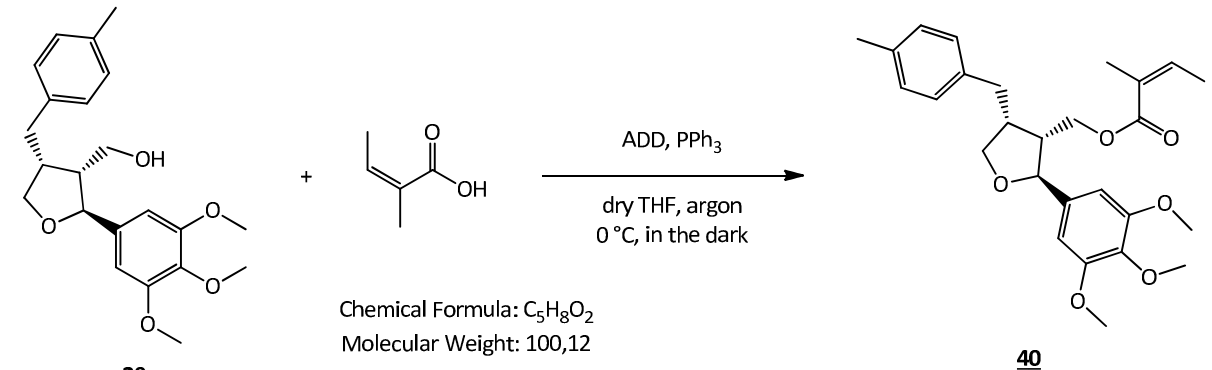
Specific rotation: $[\alpha]_D^{20}$ = +12.3 (MeOH; c 1.219)

HRMS (ESI$^+$): exact mass calculated for $C_{22}H_{28}O_5$: 395.1829. Found: 395.1829. $[M+Na]^+$, Δ = 0.00 ppm

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.73 (bs, 1H, OH), 2.31 (s, 3H, CH_3), 2.33-2.79 (m, 4H, H3 & H4 & CH_2), 2.83-2.98 (dd, J= 12.52 & 4.70 Hz, 1H, CH_2), 3.68-3.98 (m, 3H, H5 & CH_2O), 3.81 (s, 3H, 4' OCH_3), 3.84 (s, 6H, 3' OCH_3 & 5' OCH_3), 4.00-4.11 (m, 1H, CH_2O), 4.84 (d, J=5.67 Hz, 1H, H2), 6.54 (s, 2H, H2' & H6'), 7.08 (s, 4H, H2'' & H3'' & H5'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 20.9 (q, CH_3), 33.0 (t, CH_2), 42.1 (d, C4), 52.4 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 60.9 (t, CH_2O), 73.0 (t, C5), 82.8 (d, C2), 102.5 (d, C2' & C6'), 128.4 (d, C3'' & C5''), 129.2 (d, C2'' & C6''), 135.7 (s, C_q), 137.1 (s, C_q), 137.2 (s, C_q), 138.8 (s, C_q), 153.2 (s, C3' & C5').

6.16 (Z)- (2S,3R,4R)-(4-(4-Methylbenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (40)



29
Chemical Formula: $C_{22}H_{28}O_5$
Molecular Weight: 372,45

Chemical Formula: $C_5H_8O_2$
Molecular Weight: 100,12

40
Chemical Formula: $C_{27}H_{34}O_6$
Molecular Weight: 454,56

Prepared and purified according to General Procedure F using **32** as starting material (23.7 mg, 0.064 mmol).

Yield: 18.6 mg (64 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 2/1) = 0.78

Specific rotation: $[\alpha]_D^{20}$ = +25.3 (MeOH; c 1.404)

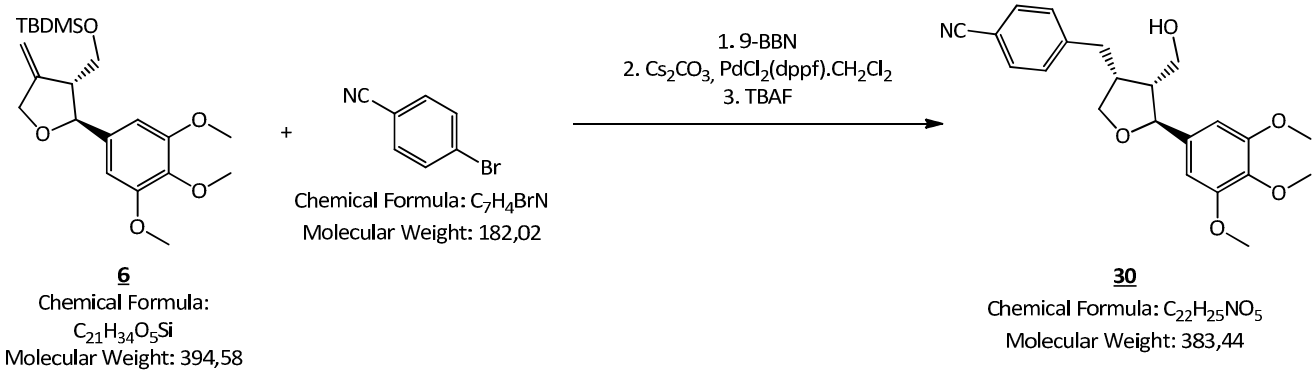
HRMS (ESI$^+$): exact mass calculated for $C_{27}H_{34}O_6$: 477.2248. Found: 477.2250. $[M+Na]^+$, Δ = 0.42 ppm

GC-MS (EI, 70 eV): Method 4; Retention time: 20.72 min; Main fragments (relative intensity): 454 (M^+, 14), 249 (22), 196 (25), 195 (58), 180 (26), 143 (11), 131 (27), 117 (10), 106 (10), 105 (100)

^{1}H -NMR (200 MHz, $CDCl_3$): δ 1.84-1.92 (m, 3H, α-CH_3), 1.96-2.05 (m, 3H, β-CH_3), 2.32 (s, 3H, 4'' CH_3), 2.51-2.83 (m, 3H, H3 & H4 & CH_2), 2.90 (dd, J=12.33 & 4.12 Hz, 1H, CH_2), 3.77 (dd, J= 8.61 & 6.45 Hz, 1H, H5), 3.82 (s, 3H, 4' OCH_3), 3.85 (s, 6H, 3' & 5' OCH_3), 4.08 (dd, J=8.61 & 6.36 Hz, 1H, H5), 4.30 (dd, J=11.35 & 7.24, 1H, CH_2O), 4.43 (dd, J=11.35 & 6.65 Hz, 1H, CH_2O), 4.84 (d, J=5.87, 1H, H2), 6.03-6.19 (m, 1H, β-CH), 6.54 (s, 2H, H2' & H6'), 7.00-7.18 (m, 4H, H2'' & H3'' & H5'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 15.8 (q, β-CH_3), 20.6 (q, α-CH_3), 20.9 (q, C4'' CH_3), 33.1 (t, CH_2), 42.4 (d, C4), 49.2 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 62.3 (t, CH_2O), 72.8 (t, C5), 83.18 (d, C2), 102.5 (d, C2' & C6'), 127.3 (s, α-C), 128.5 (d, C2'' & C6''), 129.3 (d, C3'' & C5''), 135.9 (s, C_q), 136.9 (s, C_q), 138.3 (s, C_q), 139.0 (d, β-CH), 153.3 (s, C3' & C5'), 167.7 (s, C=O). One C_q not visible.

6.17 4-(((3R,4R,5S)-4-(Hydroxymethyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl)benzonitrile (<u>30</u>)



<u>6</u>
Chemical Formula: $C_{21}H_{34}O_5Si$
Molecular Weight: 394,58

<u>30</u>
Chemical Formula: $C_{22}H_{25}NO_5$
Molecular Weight: 383,44

Prepared and purified according to General Procedure E using **<u>6</u>** as starting material (57.7 mg, 0.206 mmol) and 4-bromobenzonitrile as aryl halide.

Yield: 32.1 mg (41 %)

Appearance: orange oil

TLC: Rf(PE/EtOAc = 1/1) = 0.27

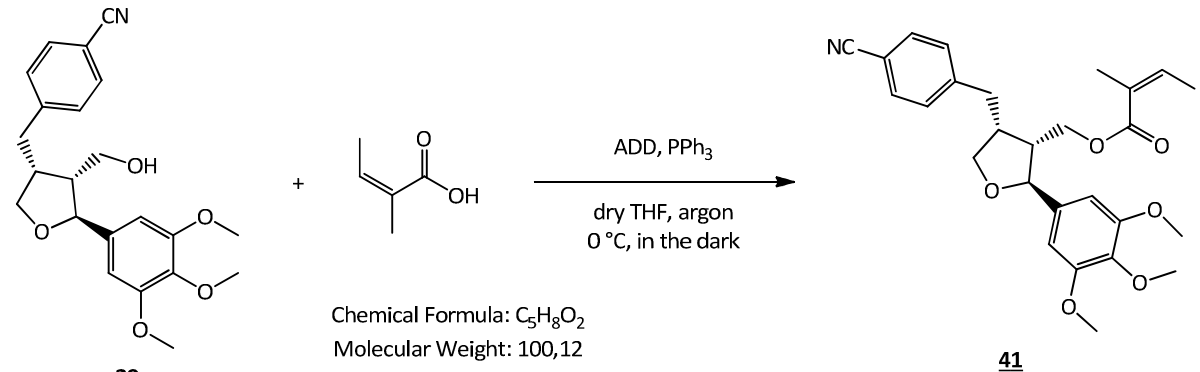
Specific rotation: $[\alpha]_D^{20}$ = +11.0 (MeOH; c 1.291)

HRMS (ESI$^+$): exact mass calculated for $C_{22}H_{25}NO_5$: 406.1625. Found: 406.1633. $[M+Na]^+$, Δ = 1.97 ppm

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.63 (bs, 1H, OH), 2.32-2.48 (m, 1H, H4), 2.59 -2.79 (m, 2H, H3 & CH_2), 2.95-3.14 (m, 1H, CH_2), 3.61-3.94 (m, 3H, H5 & CH_2O), 3.80 (s, 3H, 4' OCH_3), 3.83 (s, 6H, 3' OCH_3 & 5' OCH_3), 3.95-4.04 (m, 1H, CH_2O), 4.80 (d, J=6.06 Hz, 1H, H2), 6.52 (s, 2H, H2' & H6'), 7.30 (d, 2H, H2'' & H6''), 7.57 (d, 2H, H3'' & H5'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 33.6 (t, CH_2), 41.8 (d, C4), 52.2 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.6 (t, CH_2O), 60.7 (q, C4' OCH_3), 72.5 (t, C5), 82.8 (d, C2), 102.4 (d, C2' & C6'), 110.1 (s, C4''), 118.8 (s, CN), 129.4 (d, C3'' & C5''), 132.3 (d, C2'' & C6''), 137.1 (s, C_q), 138.4 (s, C_q), 146.2 (s, C_q), 153.2 (s, C3' & C5').

6.18 (Z)-(2S,3R,4R)-(4-(4-Cyanobenzyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (<u>41</u>)



<u>30</u>
Chemical Formula: $C_{22}H_{25}NO_5$
Molecular Weight: 383,44

Chemical Formula: $C_5H_8O_2$
Molecular Weight: 100,12

<u>41</u>
Chemical Formula: $C_{27}H_{31}NO_6$
Molecular Weight: 465,54

Prepared and purified according to General Procedure F using **<u>30</u>** as starting material (17.1 mg, 0.045 mmol).

Yield: 18.0 mg (87 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 2/1) = 0.28

Specific rotation: $[\alpha]_D^{20}$ = +20.7 (MeOH; c 1.239)

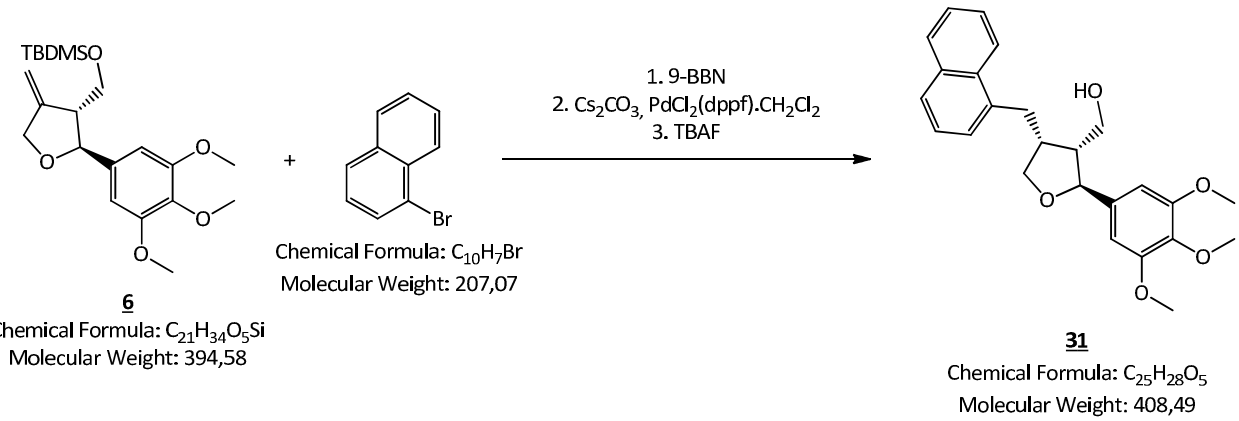
HRMS (ESI$^+$): exact mass calculated for $C_{27}H_{31}NO_6$: 488.2044. Found: 488.2058. $[M+Na]^+$, Δ = 2.87 ppm

GC-MS (EI, 70 eV): Method 4; Retention time: 31.73 min; Main fragments (relative intensity): 465 (M^+, 12), 365 (9), 249 (30), 207 (11), 197 (11), 196 (31), 195 (100), 182 (11), 181 /32), 169 (16), 168 (11), 154 (11), 153 (12), 142 (11), 116 (51)

^{1}H -NMR (200 MHz, $CDCl_3$): δ 1.81-1.89 (m, 3H, α-CH_3), 1.94-2.07 (m, 3H, β-CH_3), 2.54-2.83 (m, 3H, H3 & H4 & CH_2), 2.93-3.05 (m, 1H, CH_2), 3.71 (dd, J= 8.70 & 5.77 Hz, 1H, H5), 3.81 (s, 3H, 4' OCH_3), 3.84 (s, 6H, 3' & 5' OCH_3), 4.05 (dd, J=8.70 & 6.06 Hz, 1H, H5), 4.27 (dd, J=11.35 & 6.65, 1H, CH_2O), 4.39 (dd, J=11.35 & 6.75 Hz, 1H, CH_2O), 4.82 (d, J=6.07, 1H, H2), 6.04-6.20 (m, 1H, β-CH), 6.52 (s, 2H, H2' & H6'), 7.28 (d, J= 8.02 Hz, 2H, H3'' & H5''), 7.59 (d, J= 8.02 Hz, 2H, H2'' & H6'')

^{13}C-NMR (50 MHz, $CDCl_3$): δ 15.8 (q, β-CH_3), 20.5 (q, α-CH_3), 33.78 (t, CH_2), 42.0 (d, C4), 49.2 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 61.9 (t, CH_2O), 72.4 (t, C5), 83.0 (d, C2), 102.3 (d, C2' & C6'), 110.4 (s, C4''), 118.4 (s, C≡N), 127.1 (s, α-C), 129.7 (d, C3'' & C5''), 132.5 (d, C2'' & C6''), 127.1 (s, C=CH-CH_3), 137.3 (s, C_q), 137.7 (s, C_q), 139.4 (d, β-CH), 145.6 (s, C1''), 153.3 (s, C3' & C5'), 167.5 (s, C=O).

6.19 (2S,3R,4R)-(4-(Naphthalen-1-ylmethyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methanol (<u>31</u>)



<u>6</u>
Chemical Formula: $C_{21}H_{34}O_5Si$
Molecular Weight: 394,58

Chemical Formula: $C_{10}H_7Br$
Molecular Weight: 207,07

<u>31</u>
Chemical Formula: $C_{25}H_{28}O_5$
Molecular Weight: 408,49

Prepared and purified according to General Procedure D using **<u>6</u>** as starting material (57.7 mg, 0.206 mmol) and 1-bromonaphthalene as aryl halide.

Yield: 38.3 mg (45 %)

Appearance: slightly yellow oil

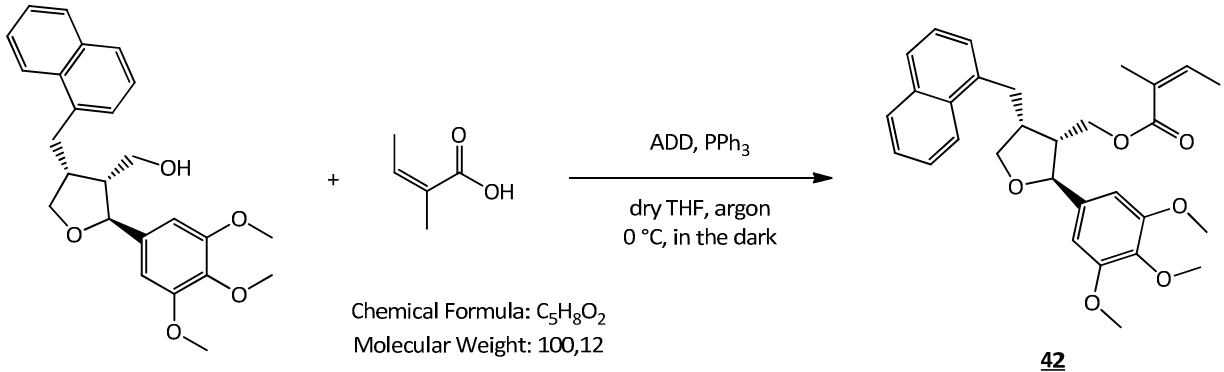
TLC: Rf(PE/EtOAc = 1/1) = 0.47

Specific rotation: $[\alpha]_D^{20}$ = +33.0 (MeOH; c 1.666)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.81 (bs, 1H, OH), 2.44-2.60 (m, 1H, 4), 2.84-3.03 (m, 2H, H3 & CH_2), 3.48-3.64 (m, 1H, CH_2), 3.72-4.13 (m, 4H, H5 & CH_2O), 3.82 (s, 3H, 4' OCH_3), 3.83 (s, 6H, 3' OCH_3 & 5' OCH_3), 4.84 (d, J= 7.07 Hz, 1H, H2), 6.56 (s, 2H, H2' & H6'), 7.28-7.59 (4H, naphtyl), 7.69-7.79 (m, 1H, naphtyl), 7.81-7.91 (m, 1H, naphtyl), 8.05-8.17 (m, 1H, naphtyl)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 30.3 (t, CH_2), 41.5 (d, C4), 52.9 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 60.8 (t, CH_2O), 72.9 (t, C5), 82.7 (d, C2), 102.6 (d, C2' & C6'), 123.7 (d, CH), 125.4 (d, CH), 125.6 (d, CH), 126.0 (d, CH), 126.6 (d, CH), 127.1 (d, CH), 128.8 (d, CH), 131.8 (s, C2''), 133.9 (s, C3''), 136.4 (s, C_q), 137.2 (s, C_q), 138.7 (s, C_q), 153.3 (s, C3' & C5').

6.20 (Z)-(2S,3R,4R)-(4-(Naphthalen-1-ylmethyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (<u>42</u>)



<u>31</u>
Chemical Formula: $C_{25}H_{28}O_5$
Molecular Weight: 408,49

Chemical Formula: $C_5H_8O_2$
Molecular Weight: 100,12

<u>42</u>
Chemical Formula: $C_{30}H_{34}O_6$
Molecular Weight: 490,59

Prepared and purified according to General Procedure F using **<u>31</u>** as starting material (16.2 mg, 0.040 mmol).

Yield: 11.9 mg (61 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 2/1) = 0.55

Specific rotation: $[\alpha]_D^{20}$ = +39.3 (MeOH; c 1.188)

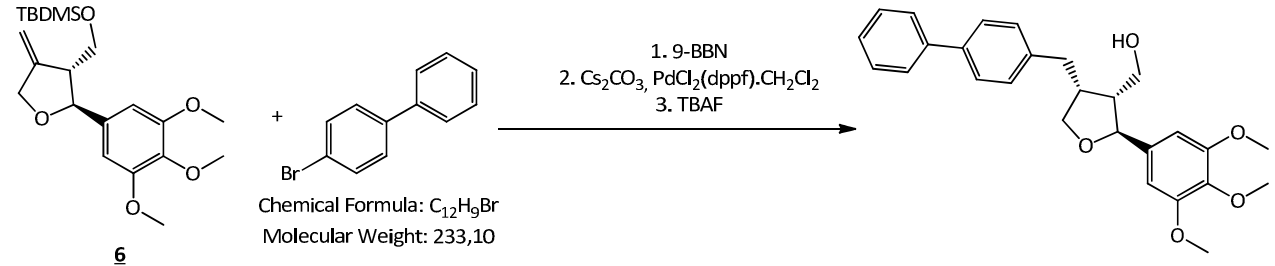
HRMS (ESI$^+$): exact mass calculated for $C_{30}H_{34}O_6$: 513.2248. Found: 513.2242. $[M+Na]^+$, Δ = 1.17 ppm

GC-MS (EI, 70 eV): Method 4; Retention time: 41.68 min; Main fragments (relative intensity): 490 (M^+, 8), 249 (27), 207 (21), 196 (16), 195 (68), 194 (15), 193 (11), 182 (13), 181 (30), 179 (26), 168 (11), 167 (28), 166 (13), 165 (27), 153 (24), 152 (11), 142 (14), 141 (100), 115 (26)

^{1}H -NMR (400 MHz, $CDCl_3$): δ 1.92-1.96 (m, 3H, α-CH_3), 1.99-2.05 (m, 3H, β-CH_3), 2.69-2.79 (m, 1H, H3), 2.89-3.02 (m, 2H, H4 & CH_2), 3.42-3-61 (m, 1H, CH_2), 3.82 (s, 3H, OCH_3), 3.84 (s,7, OCH_3, H5), 3.96 (dd, J= 8.61 & 5.28 Hz, 1H, H5), 4.43 (dd, J=11.35 & 6.65 Hz, 1H, CH_2O), 4.58 (dd, J=11.35 & 7.72, 1H, CH_2O), 4.86 (d, J=7.04, 1H, H2), 6.11-6.19 (m, 1H, β-CH), 6.55 (s, 2H, H2' & H6'), 7.31-7.36 (m, 1H, naphtyl), 7.37-7.44 (m, 1H, naphtyl), 7.45-7.52 (m, 2H, naphtyl), 7.72-7.78 (m, 1H, naphtyl), 7.83-7.90 (m, 1H, naphtyl), 7.97-8.03 (m, 1H, naphtyl).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 15.9 (q, β-CH_3), 20.6 (q, α-CH_3), 30.5 (t, CH_2), 41.6 (d, C4), 49.7 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 62.1 (t, CH_2O), 72.8 (t, C5), 82.9 (d, C2), 102.6 (d, C2' & C6'), 123.4 (d, C2''-CH-CH), 125.5 (d, C6''), 125.7 (d, C3''-CH-CH), 126.0 (d, C5''), 126.7 (d, C2''-CH-CH), 127.3 (s, C4''), 127.3 (d, C2''), 129.5 (d, C3''-CH-CH), 131.5 (s, C1''), 134.0 (s, α-C), 135.9 (s, C3''), 137.3 (s, C_q), 138.1 (s, C_q) 139.2 (d, β-CH), 153.3 (s, C3' & C5'), 167.7 (s, C=O)

6.21 (2S,3R,4R)-(4-([1,1'-Biphenyl]-4-ylmethyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methanol (32)



6
Chemical Formula: $C_{21}H_{34}O_5Si$
Molecular Weight: 394,58

Chemical Formula: $C_{12}H_9Br$
Molecular Weight: 233,10

32
Chemical Formula: $C_{27}H_{30}O_5$
Molecular Weight: 434,52

Prepared and purified according to General Procedure D using **6** as starting material (57.7 mg, 0.206 mmol) and 4-bromo-1,1'-biphenyl as aryl halide.

Yield: 40.3 mg (45 %)

Appearance: yellow oil

TLC: Rf(PE/EtOAc = 1/1) = 0.34

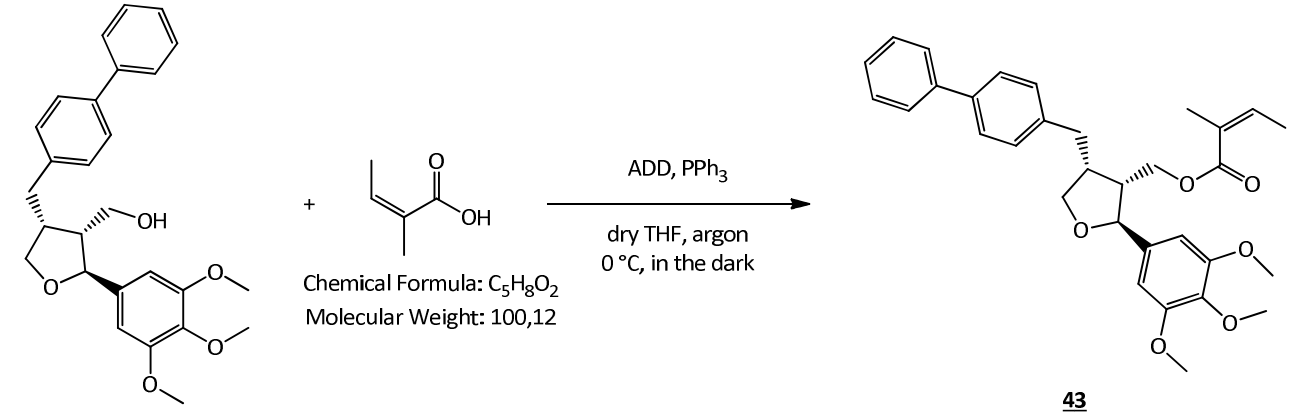
Specific rotation: $[\alpha]_D^{20}$ = +7.1 (MeOH; c 1.716)

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.78 (bs, 1H, OH), 2.35-2.52 (m, 1H, H4), 2.58-2.90 (m, 2H, H3 & CH_2), 2.93-3.06 (m, 1H, CH_2), 3.72-3.89 (m, 3H, H5 & CH_2O), 3.82 (s, 3H, 4' OCH_3), 3.85 (s, 6H, 3' OCH_3 & 5' OCH_3), 3.91-4.02 (m, 1H, CH_2O), 4.87 (d, J=5.86 Hz, 1H, H2), 6.56 (s, 2H, H2' & H6'), 7.19-7.64 (m, 9H, biphenyl)

^{13}C-NMR (50 MHz, $CDCl_3$): δ 33.1 (t, CH_2), 42.0 (d, C4), 52.3 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 60.9 (t, CH_2O), 73.0 (t, C5), 83.0 (d, C2), 102.5 (d, C2' & C6'), 126.9 (d, 2C, CH),

127.1 (d, CH), 127.2 (d, 2C, CH), 128.7 (d, 2C, CH), 129.0 (d, 2C, CH), 137.0 (s, C_q), 138.9 (s, C_q), 139.1 (s, C_q), 139.4 (s, C_q), 140.7 (s, C_q), 153.2 (s, C3' & C5')

6.22 (Z)- (2S,3R,4R)-(4-([1,1'-Biphenyl]-4-ylmethyl)-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran-3-yl)methyl 2-methylbut-2-enoate (<u>43</u>)



<u>32</u>
Chemical Formula: $C_{27}H_{30}O_5$
Molecular Weight: 434,52

<u>43</u>
Chemical Formula: $C_{32}H_{36}O_6$
Molecular Weight: 516,62

Prepared and purified according to General Procedure F using **<u>32</u>** as starting material (32.1 mg, 0.076 mmol).

Yield: 23.4 mg (61 %)

Appearance: slightly yellow viscous oil

TLC: Rf(PE/EtOAc = 2/1) = 0.57

Specific rotation: $[\alpha]_D^{20}$ = +9.3 (MeOH; c 1.7820)

HRMS (ESI^+): exact mass calculated for $C_{32}H_{36}O_6$: 539.2404. Found: 539.2495. $[M+Na]^+$, Δ = 0.19 ppm

^{1}H -NMR (200 MHz, $CDCl_3$): δ 1.84-1.92 (m, 3H, α-CH_3), 1.95-2.07 (m, 3H, β-CH_3), 2.57-2.89 (m, 3H, H3 & H4 & CH_2), 2.98 (dd, J=12.53 & 4.11 Hz, 1H, CH_2), 3.82 (s, 3H, 4' OCH_3), 3.85 (s, 7H, 3' & 5' OCH_3, H5), 4.12 (dd, J=8.61 & 6.26 Hz, 1H, H5), 4.32 (dd, J=11.35 & 7.04, 1H, CH_2O), 4.46 (dd, J=11.35 & 6.85 Hz, 1H, CH_2O), 4.86 (d, J=5.87, 1H, H2), 6.04-6.18 (m, 1H, β-CH), 6.55 (s, 2H, H2' & H6'), 7.18-7.63 (m, 9H, biphenyl).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 15.8 (q, β-CH_3), 20.6 (q, α-CH_3), 33.2 (t, CH_2), 42.3 (d, C4), 49.2 (d, C3), 56.1 (q, C3' OCH_3 & C5' OCH_3), 60.8 (q, C4' OCH_3), 62.2 (t, CH_2O), 72.8 (t, C5), 83.2 (d, C2), 102.5 (d, C2' & C6'), 126.9 (d, 2C, *ortho* CH), 127.2 (d, *para* CH), 127.3 (d, C2'' & C6''), 128.8 (d, C3'' & C5''), 129.0 (d, 2C, *meta* CH), 138.2 (s, C4''), 139.0 (s, C4'), 139.1 (d, β-CH), 139.3 (s, α-C), 140.7 (s, C1''), 153.3 (s, C3' & C5'), 167.7 (s, C=O). Two C_q not visible.

IV. Literature

1. WHO, *Global status report on noncommunicable diseases* 2010.
2. Falk, E., *Pathogenesis of atherosclerosis.* J. Am. Coll. Cardiol., 2006. **47**(8, Suppl. C): p. C7-C12.
3. Schaar, J.A., et al., *Terminology for high-risk and vulnerable coronary artery plaques. Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, Santorini, Greece.* Eur Heart J, 2004. **25**(12): p. 1077-82.
4. Thygesen, K., J.S. Alpert, and H.D. White, *Universal definition of myocardial infarction.* Eur Heart J, 2007. **28**(20): p. 2525-38.
5. Cochain, C., K.M. Channon, and J.-S. Silvestre, *Angiogenesis in the Infarcted Myocardium.* Antioxid. Redox Signaling, 2013. **18**(9): p. 1100-1113.
6. Zhang, L. and A. Chawla, *Role of PPARγ in macrophage biology and atherosclerosis.* Trends Endocrinol. Metab., 2004. **15**(10): p. 500-505.
7. Adorni, M.P., et al., *The roles of different pathways in the release of cholesterol from macrophages.* J. Lipid Res., 2007. **48**(11): p. 2453-2462.
8. Tall, A.R., P. Costet, and N. Wang, *Regulation and mechanisms of macrophage cholesterol efflux.* J. Clin. Invest., 2002. **110**(7): p. 899-904.
9. Ji, A., et al., *Scavenger receptor SR-BI in macrophage lipid metabolism.* Atherosclerosis (Amsterdam, Neth.), 2010. **217**(1): p. 106-112.
10. Higgins, C.F. and K.J. Linton, *The ATP switch model for ABC transporters.* Nat. Struct. Mol. Biol., 2004. **11**(10): p. 918-926.
11. Frangogiannis, N.G., *The Mechanistic Basis of Infarct Healing.* Antioxid. Redox Signaling, 2006. **8**(11 & 12): p. 1907-1939.
12. MacRae, W.D. and G.H.N. Towers, *Biological activities of lignans.* Phytochemistry, 1984. **23**(6): p. 1207-20.
13. Davin, L.B. and N.G. Lewis, *An historical perspective on lignan biosynthesis: monolignol, allylphenol and hydroxycinnamic acid coupling and downstream metabolism.* Phytochem. Rev., 2004. **2**(3): p. 257-288.
14. Dewick, P.M., *Medicinal natural products: a biosynthetic approach.* 2002.
15. Suzuki, S. and T. Umezawa, *Biosynthesis of lignans and norlignans.* J. Wood Sci., 2007. **53**(4): p. 273-284.
16. Cos, P., et al., *Plant-derived leading compounds for chemotherapy of human immunodefiency virus (HIV) infection - an update (1998-2007).* Planta Med., 2008. **74**(11): p. 1323-1337.
17. Yousefzadi, M., et al., *Podophyllotoxin: current approaches to its biotechnological production and future challenges.* Eng. Life Sci. **10**(4): p. 281-292.
18. Pan, J.-Y., et al., *An update on lignans: natural products and synthesis.* Nat. Prod. Rep., 2009. **26**(10): p. 1251-1292.
19. Saleem, M., et al., *An update on bioactive plant lignans.* Nat. Prod. Rep., 2005. **22**(6): p. 696-716.
20. Huang, W.-Y., Y.-Z. Cai, and Y. Zhang, *Natural Phenolic Compounds From Medicinal Herbs and Dietary Plants: Potential Use for Cancer Prevention.* Nutr. Cancer, 2010. **62**(1): p. 1-20.

21. Webb, A.L. and M.L. McCullough, *Dietary lignans: Potential role in cancer prevention.* Nutr. Cancer, 2005. **51**(2): p. 117-131.

22. Faure, M., et al., *Antioxidant activities of lignans and flavonoids.* Phytochemistry, 1990. **29**(12): p. 3773-5.

23. Negi, A.S., et al., *Recent advances in plant hepatoprotectives: a chemical and biological profile of some important leads.* Med. Res. Rev., 2008. **28**(5): p. 746-772.

24. Bernhard, D., et al., *Pharmaceutical compositions comprising lignans and their derivatives for the medical management of angiogenesis and hypovascularity*. 2011, (Medizinische Universitaet Wien, Austria; Universitaet Innsbruck; Medizinische Universitaet Innsbruck). Application: WO p. 71pp.

25. Schwaiger, S., et al., *New constituents of Leontopodium alpinum and their in vitro leukotriene biosynthesis inhibitory activity.* Planta Med., 2004. **70**(10): p. 978-985.

26. Barber, M., et al., *Fast atom bombardment of solids (F.A.B.): a new ion source for mass spectrometry.* J. Chem. Soc., Chem. Commun., 1981(7): p. 325-7.

27. Xia, Y.-M., W.-H. Bi, and Y.-Y. Zhang, *Synthesis of dibenzylbutanediol lignans and their anti-HIV, anti-HSV, antitumor activities.* J. Chil. Chem. Soc., 2009. **54**(4): p. 428-431.

28. Yamauchi, S., T. Tanaka, and Y. Kinoshita, *First highly stereoselective synthesis of (+)-dihydrosesamin, a trisubstituted tetrahydrofuran-type of lignan, by using highly erythro-selective aldol condensation.* J. Chem. Soc., Perkin Trans. 1, 2001(18): p. 2158-2160.

29. Raffaelli, B., K. Wahala, and T. Hase, *Asymmetric synthesis, stereochemistry and rearrangement reactions of naturally occurring 7'-hydroxylignano-9,9'-lactones.* Org. Biomol. Chem., 2006. **4**(2): p. 331-341.

30. Nishiwaki, H., et al., *Stereoselective syntheses of all stereoisomers of lariciresinol and their plant growth inhibitory activities.* J. Agric. Food Chem., 2011. **59**(24): p. 13089-13095.

31. Banerjee, B. and S.C. Roy, *Concise enantioselective synthesis of furan lignans (-)-dihydrosesamin and (-)-acuminatin and furofuran lignans (-)-sesamin and (-)-methyl piperitol by radical cyclization of epoxides.* Synthesis, 2005(17): p. 2913-2919.

32. Roy, S.C., K.K. Rana, and C. Guin, *Short and Stereoselective Total Synthesis of Furano Lignans (±)-Dihydrosesamin, (±)-Lariciresinol Dimethyl Ether, (±)-Acuminatin Methyl Ether, (±)-Sanshodiol Methyl Ether, (±)-Lariciresinol, (±)-Acuminatin, and (±)-Lariciresinol Monomethyl Ether and Furofuran Lignans (±)-Sesamin, (±)-Eudesmin, (±)-Piperitol Methyl Ether, (±)-Pinoresinol, (±)-Piperitol, and (±)-Pinoresinol Monomethyl Ether by Radical Cyclization of Epoxides Using a Transition-Metal Radical Source.* J. Org. Chem., 2002. **67**(10): p. 3242-3248.

33. Stevens, D.R. and D.A. Whiting, *Synthesis of the lignan (+-)-dihydrosesamin: problems of stereocontrol in the formation of 2,3,4-trisubstituted tetrahydrofurans and tetrahydrofuranones.* J. Chem. Soc., Perkin Trans. 1, 1990(2): p. 425-426.

34. Maiti, G., S. Adhikari, and S.C. Roy, *Short and stereoselective synthesis of (+-)-dihydrosesamin by a radical cyclization reaction.* Tetrahedron Lett., 1994. **35**(23): p. 3985-3986.

35. Maiti, G., S. Adhikari, and S.C. Roy, *Radical cyclization route to furanolignans: short and stereoselective synthesis of (+-)-dihydrosesamin and (+-)-lariciresinol.* J. Chem. Soc., Perkin Trans. 1, 1995(7): p. 927-929.

36. Lu, F. and J. Ralph, *Novel tetrahydrofuran structures derived from beta -beta -coupling reactions involving sinapyl acetate in Kenaf lignins.* Org. Biomol. Chem., 2008. **6**(20): p. 3681-3694.

37. Mondiere, A., et al., *Efficient Rhodium-Catalyzed Conjugate Addition of Arylboronic Acids to Unsaturated Furano Esters for the Highly Stereoselective Synthesis of Four Natural Trisubstituted Furanolignans.* Eur. J. Org. Chem., 2009(25): p. 4225-4229.

38. Yoda, H., K. Kimura, and K. Takabe, *Asymmetric syntheses of trisubstituted tetrahydrofuran lignans, sesaminone and 4-epidihydrosesamin.* Synlett, 2001(3): p. 400-402.

39. Yamauchi, S., et al., *Synthesis and antioxidant activity of olivil-type lignans.* Biosci. Biotechnol. Biochem., 2005. **69**(1): p. 113-122.

40. Nakato, T. and S. Yamauchi, *Enantioselective Synthesis of the Tetrahydrofuran Lignans (-)- and (+)-Magnolone.* J. Nat. Prod., 2007. **70**(10): p. 1588-1592.

41. Raffaelli, B., et al., *Stereochemistry and rearrangement reactions of hydroxylignanolactones.* Org. Biomol. Chem., 2008. **6**(14): p. 2619-2627.

42. Pandey, G., et al., *Synthesis of optically pure 2,3,4-trisubstituted tetrahydrofurans via a two-step sequential Michael-Evans aldol cyclization strategy: total synthesis of (+)-magnolone.* Tetrahedron Lett., 2010. **51**(22): p. 2975-2978.

43. Takahashi, M., et al., *First total syntheses of new phenylpropanoid lignans, (+-)-aglacin K stereoisomer and analogue of (+-)-arborone.* Heterocycles, 2007. **71**(10): p. 2113-2118.

44. Nasveschuk, C.G. and T. Rovis, *A rapid total synthesis of (+-)-sylvone.* Synlett, 2008(1): p. 126-128.

45. Eklund, P., R. Sillanpaeae, and R. Sjoeholm, *Synthetic transformation of hydroxymatairesinol from Norway spruce (Picea abies) to 7-hydroxysecoisolariciresinol, (+)-lariciresinol and (+)-cyclolariciresinol.* J. Chem. Soc., Perkin Trans. 1, 2002(16): p. 1906-1910.

46. Eklund, P.C., et al., *Reactions of the natural lignan hydroxymatairesinol in basic and acidic nucleophilic media: formation and reactivity of a quinone methide intermediate.* Org. Biomol. Chem., 2004. **2**(15): p. 2229-2235.

47. Bottex, M., et al., *A Versatile Palladium-Mediated Three-Component Reaction for the One-Pot Synthesis of Stereodefined 3-Arylidene-(or 3-Alkenylidene-)tetrahydrofurans.* J. Org. Chem., 2001. **66**(1): p. 175-179.

48. Swain, N.A., R.C.D. Brown, and G. Bruton, *A Versatile Stereoselective Synthesis of endo,exo-Furofuranones: Application to the Enantioselective Synthesis of Furofuran Lignans.* J. Org. Chem., 2004. **69**(1): p. 122-129.

49. Wardrop, D.J. and J. Fritz, *Total Synthesis of (±)-Magnofargesin.* Org. Lett., 2006. **8**(17): p. 3659-3662.

50. Angle, S.R., I. Choi, and F.S. Tham, *Stereoselective Synthesis of 3-Alkyl-2-aryltetrahydrofuran-4-ols: Total Synthesis of (±)-Paulownin.* J. Org. Chem., 2008. **73**(16): p. 6268-6278.

51. Jongkol, R., et al., *Syntheses of methylenolactocin and nephrosterinic acid via diastereoselective acylation and chemoselective reduction-lactonization.* Tetrahedron, 2009. **65**(32): p. 6382-6389.

52. Saha, S. and S.C. Roy, *Titanocene (III) chloride mediated radical induced synthesis of (-)-methylenolactocin and (-)-protolichesterinic acid.* Tetrahedron, 2010. **66**(24): p. 4278-4283.

53. Sun, H.L., et al., *Synthesis, chiral resolution, and determination of novel furan lignan derivatives with potent anti-tumor activity.* Bioorg. Med. Chem. Lett., 2010. **20**(6): p. 1961-1964.

54. RajanBabu, T.V. and W.A. Nugent, *Selective Generation of Free Radicals from Epoxides Using a Transition-Metal Radical. A Powerful New Tool for Organic Synthesis.* J. Am. Chem. Soc., 1994. **116**(3): p. 986-997.

55. Linder, T., *PhD thesis,* Vienna University of Technology, in progress.

56. Stambasky, J., A.V. Malkov, and P. Kocovsky, *Synthesis of Enantiopure 1-Arylprop-2-en-1-ols and Their tert-Butyl Carbonates.* J. Org. Chem., 2008. **73**(22): p. 9148-9150.

57. Martin-Matute, B., et al., *Highly compatible metal and enzyme catalysts for efficient dynamic kinetic resolution of alcohols at ambient temperature.* Angew. Chem. Int. Ed., 2004. **43**(47): p. 6535-6539.

58. Martin-Matute, B., et al., *Combined Ruthenium(II) and Lipase Catalysis for Efficient Dynamic Kinetic Resolution of Secondary Alcohols. Insight into the Racemization Mechanism.* J. Am. Chem. Soc., 2005. **127**(24): p. 8817-8825.

59. Bogar, K. and J.-E. Bäckvall, *High-yielding metalloenzymatic dynamic kinetic resolution of fluorinated aryl alcohols.* Tetrahedron Lett., 2007. **48**(31): p. 5471-5474.

60. Bogar, K., et al., *Chemoenzymatic Dynamic Kinetic Resolution of Allylic Alcohols: A Highly Enantioselective Route to Acyloin Acetates.* Org. Lett., 2007. **9**(17): p. 3401-3404.

61. Träff, A., et al., *Highly Efficient Route for Enantioselective Preparation of Chlorohydrins via Dynamic Kinetic Resolution.* Org. Lett., 2008. **10**(21): p. 4807-4810.

62. Träff, A., R. Lihammar, and J.-E. Bäckvall, *A Chemoenzymatic Dynamic Kinetic Resolution Approach to Enantiomerically Pure (R)- and (S)-Duloxetine.* J. Org. Chem., 2011. **76**(10): p. 3917-3921.

63. Strauss, U.T., U. Felfer, and K. Faber, *Biocatalytic transformation of racemates into chiral building blocks in 100% chemical yield and 100% enantiomeric excess.* Tetrahedron Asymmetry, 1999. **10**(1): p. 107-117.

64. Mandal, P.K., G. Maiti, and S.C. Roy, *Stereoselective Synthesis of Polysubstituted Tetrahydrofurans by Radical Cyclization of Epoxides Using a Transition-Metal Radical Source. Application to the Total Synthesis of (±)-Methylenolactocin and (±)-Protolichesterinic Acid.* J. Org. Chem., 1998. **63**(9): p. 2829-2834.

65. Hassner, A., L.R. Krepski, and V. Alexanian, *Aminopyridines as acylation catalysts for tertiary alcohols.* Tetrahedron, 1978. **34**(14): p. 2069-2076.

66. Messner, B., et al., *5-Methoxyleoligin, a Lignan from Edelweiss, Stimulates CYP26B1-Dependent Angiogenesis In Vitro and Induces Arteriogenesis in Infarcted Rat Hearts In Vivo.* PLoS ONE, 2013. **8**(3): p. e58342.

67. Hulkower, K.I. and R.L. Herber, *Cell migration and invasion assays as tools for drug discovery.* Pharmaceutics, 2011. **3**: p. 107-124.

68. Auerbach, R., et al., *Angiogenesis assays: a critical overview.* Clin. Chem. (Washington, DC, U. S.), 2003. **49**(1): p. 32-40.

69. Tucci Paulo, J.F., *Pathophysiological characteristics of the post-myocardial infarction heart failure model in rats.* Arq Bras Cardiol, 2010. **96**(5): p. 420-424.

70. Chakraborty, P., et al., *Titanocene(III) chloride mediated formal synthesis of magnofargesin and 7â€²-epimagnofargesin.* Tetrahedron Lett. **53**(48): p. 6584-6587.

71. Jiménez-Núñez, E., et al., *cis-Selective Single-Cleavage Skeletal Rearrangement of 1,6-Enynes Reveals the Multifaceted Character of the Intermediates in Metal-Catalyzed Cycloisomerizations.* Angewandte Chemie International Edition, 2008. **47**(41): p. 7892-7895.

72. Kumar Das, S., S. Kumar Das, and G. Panda, *Formal Total Synthesis of (–)-Raphidecursinol B.* Eur. J. Org. Chem. **2010**(26): p. 5100-5107.

Curriculum Vitae

Sophie Geyrhofer BSc

Education

10/2011 - today	**Master studies in chemistry at the University of Vienna**
	Main focus: synthetic organic chemistry, medicinal chemistry, spectroscopy
	Master's thesis: "Design and Synthesis of a Compound Library Exploiting 5-Methoxyleoligin as Angiogenic Lead Structure"
10/2008 – 07/2011	**Bachelor's degree in chemistry at the University of Vienna**
	Main focus: synthetic organic chemistry
	Bachelor's thesis: "Synthesis of a building block for total synthesis of Bielschowskysin"
09/2000 – 06/2008	Matura at Konrad – Lorenz Gymnasium Gänserndorf
	(equivalent to A-level)

Professional experience

10/2012–06/2013	**Tutor in the laboratories "Basics of Chemistry" and "Synthetic Chemistry" at Vienna University of Technology**
06/2005 –today	Salesperson at "Ideenbäckerei Geier" (bakery), side job
	Tasks: sales, presentation of wares, baking
08/2010 – 08/2010	**Internship at MA39 (in the chemistry lab of IFUM, laboratory for environmental medicine)**
	Tasks: chemical and physical analysis, photometric determinations, sampling of ground-, bathing and drinking water