MASTER THESIS

SYNTHETIC LIGNANS AGAINST CARDIOVASCULAR DISEASES

Conducted at the

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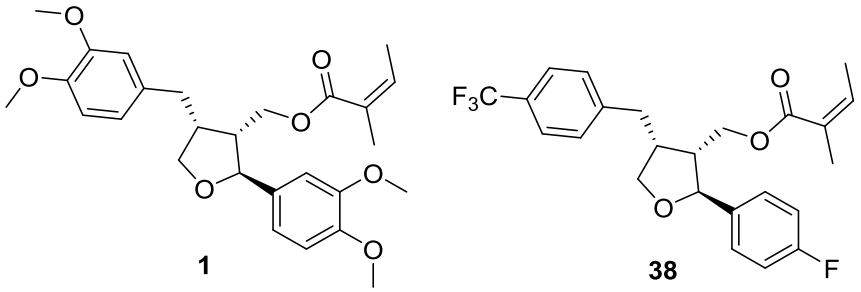
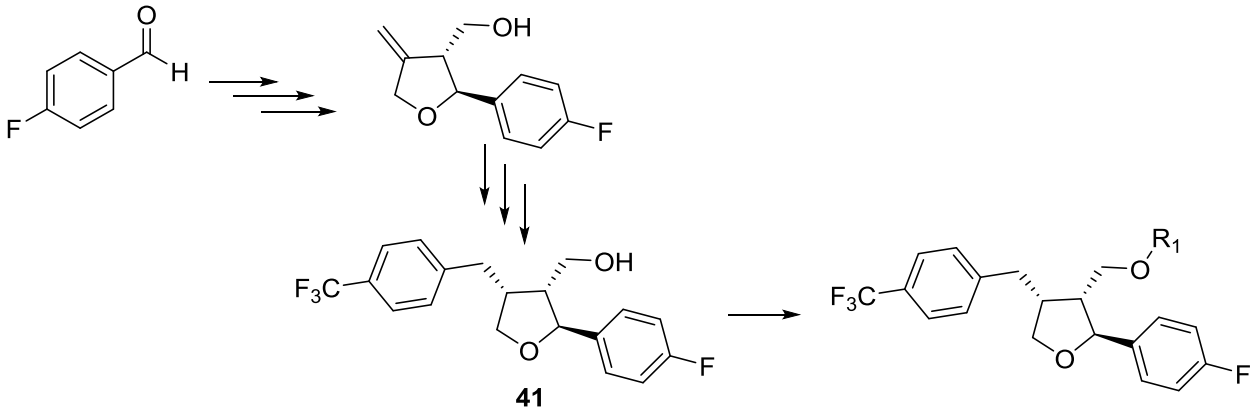
Abstract

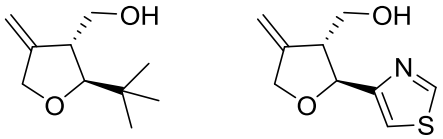
Previous research work revealed that a synthetic analog **35** of the lignan leoligin **1**, naturally occurring in *Leontopodium alpinum,* is capable to selectively inhibit the growth of vascular smooth cells without reducing the growth of endothelial cells.



As the scaffold **38** contained an ester containing a highly undesired Michael acceptor motive it was the aim of this work to conduct the total synthesis of the stage of the alcohol **41** in order to generate several different esters for biological testing. The key steps towards **41** include an enzymatically catalyzed kinetic resolution in order to obtain optically pure product, a radical cyclisation to sustain the tetrahydrofuran core and a combination of hydroboration and Suzuki coupling was utilized for the highly selective introduction of a third stereocenter. The last step of the total synthesis was a Mitsunobu esterification.

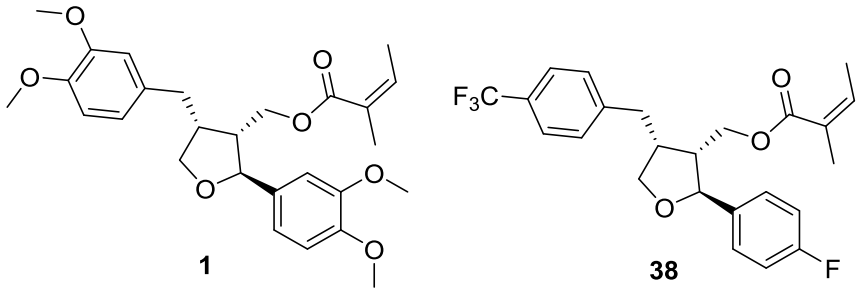


In addition to that the feasibility of the total synthesis of leoligin analogs, possessing a thiazole or a tert-butyl moiety in two position of the tetrahydrofuran ring (shown below) was to be investigated based on the already established protocols.

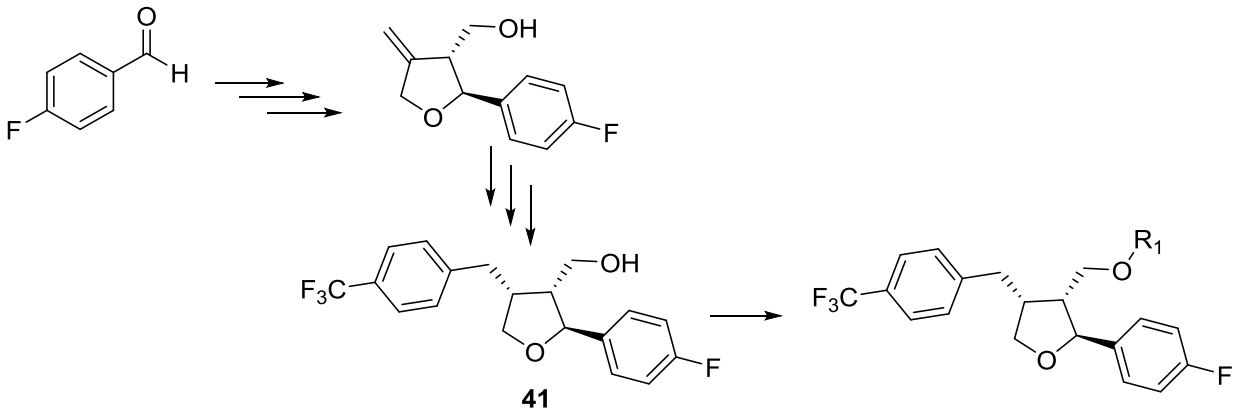


Deutsche Kurzfassung

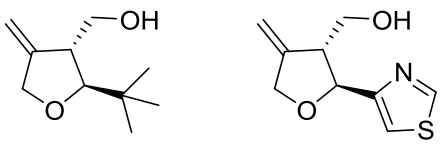
In vorangegangener Forschung wurde ein synthetisches Derivat **38** von Leoligin **1**, ein natürlich in *Leontopodium alpinum* vorkommenden Lignan, entdeckt, das selektiv das Wachstum von vaskulären Glattmuskelzellen hemmt, ohne dabei Endothelzellen zu beeinflussen.



Da in der Struktur dieses Lignans ein Ester enthalten ist, der sehr unerwünschte Michael Akzeptor Eigenschaften besitzt, war ein Ziel dieser Arbeit eine Totalsynthese bis zu der Stufe des Alkohols **41**, um in weiterer Folge verschiedene Ester für biologische Testungen zu synthetisieren. Zu den Schlüsselreaktionen der Synthese von **41** gehören unter anderem eine enzymatische kinetische Racematspaltung um ein optisch reines Produkt zu erhalten, eine radikalische Zyklisierung um den Tetrahydrofurankern herzustellen und die selektive Einführung eines dritten Stereozentrums wurde durch eine Kombination von einer Hydroborierung und Suzuki Kupplung bewirkt. Der letzte Schritt der Totalsynthese war eine Mitsunobu Veresterung.



Zusätzlich wurde die Durchführbarkeit der Totalsynthese eines Leoligin Analogs, welches einen Thiazol oder einen tert-Butyl Rest in der Position zwei des Tetrahydrofuran Ringes besitzt, unter Verwendung des etablierten Protokolls untersucht.



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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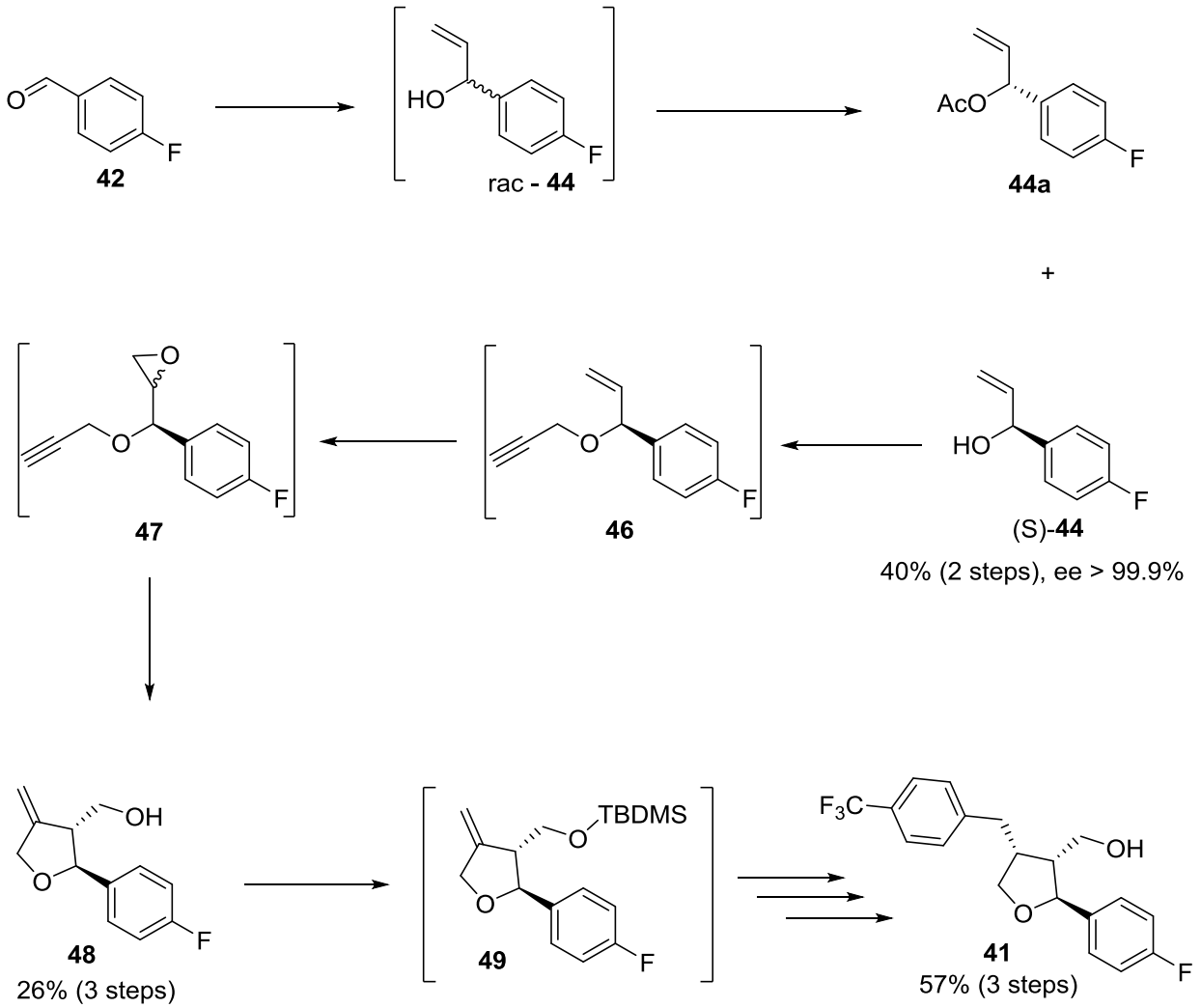
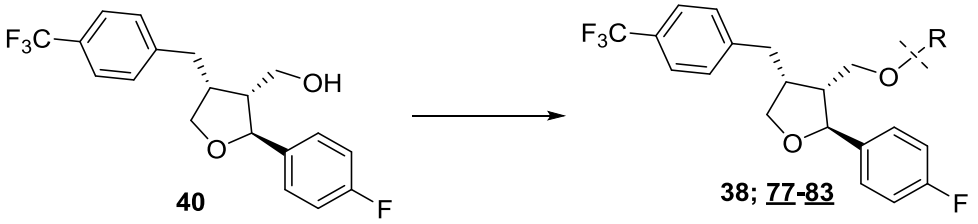
Total Synthesis of ((2S,3R,4R)-2-(4-fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methanol



Variation of Position 2 and 4



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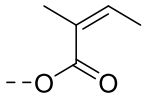
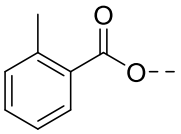
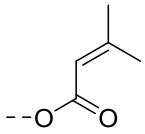
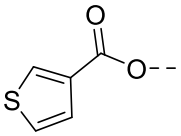
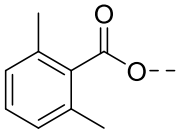
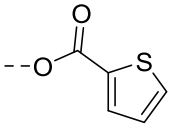
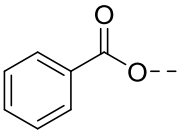
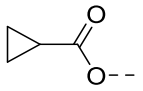
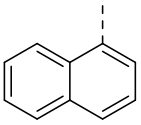
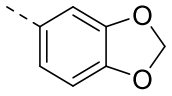
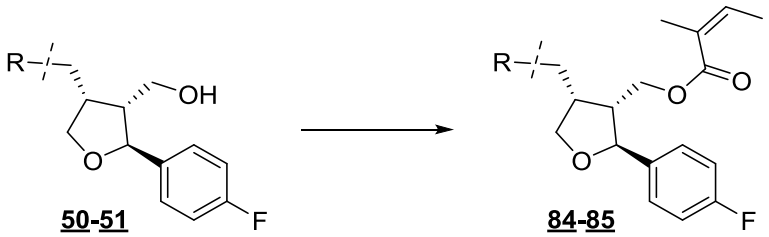
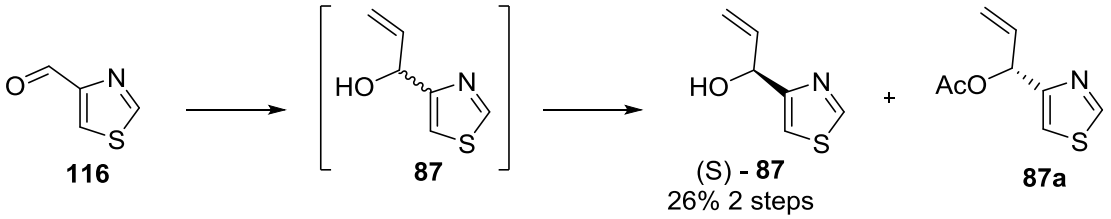
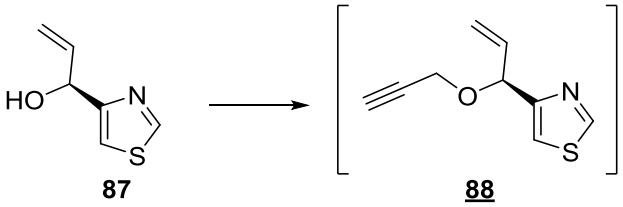
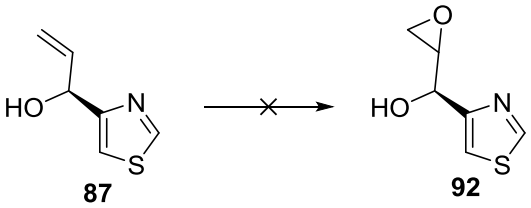
35	22		**80**	88	
77	86		**81**	83	
78	82		**82**	65	
79	78		**83**	70	
84	88		**85**	76	

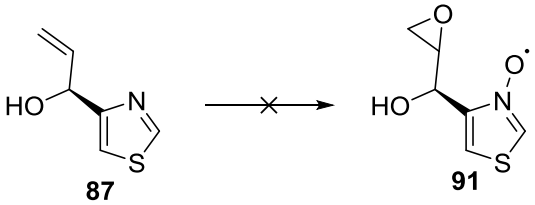


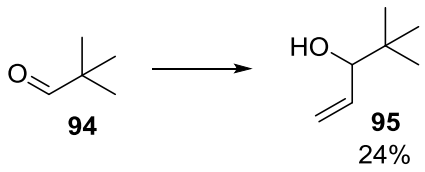
Variation of Position 2

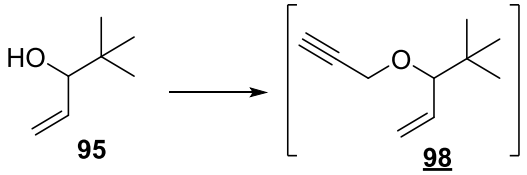


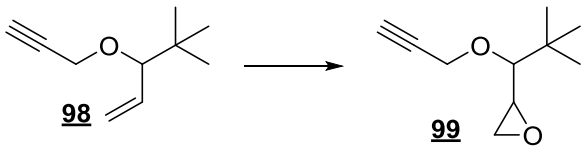












A. Introduction

A.1 Motivation

In 2012 an estimated 17.5 million people died worldwide as a result of cardiovascular diseases, making it the number one cause of death globally according to WHO. More than half of these deaths are estimated to be due to coronary heart disease (7.4 million) and stroke (6.7million).[1] For that reason treating and preventing coronary heart disease and therefore stroke are of high interest for the scientific community.

A.2 Atherosclerosis, Coronary Artery Disease – Definitions, Causes and Risks

Generally the term atherosclerosis describes a condition in which plaque builds up inside the arteries causing narrowing of these vessels, which is termed stenosis. Furthermore it can be referred to as "multifocal, smoldering, immunoinflammatory disease of medium-sized and large arteries fueled by lipids."[2]. Atherosclerotic plaques are consisting of necrotic cores, calcified regions, accumulated modified lipids, smooth muscle cells (SMCs), endothelial cells (EC)[I], leukocytes and foam cells [3] and possess a fibrous cap of varying thickness and strength.[4] As soon as coronary arteries, which are defined as the blood vessels delivering the oxygen rich blood to the heart muscle, [1] are affected one speaks of coronary artery disease. [2-3, 5].

However atherosclerosis itself is seldom deadly but plaque rupture, defined as "a plaque with deep injury with a real defect or gap in the fibrous cap that had separated its lipid rich atheromatous core from the flowing blood, thereby exposing the thrombogenic core of the plaque", is the most common cause of potentially fatal thrombosis.[6]
A thrombus is capable to partially or completely block a blood vessel and therefore strongly limit or interrupt the oxygen supply to organs such as heart and brain, leading to severe and life threating complications such as myocardial ischemia, cardiac arrhythmia, myocardial infarction (heart attack), cardiac arrest and stroke.[7-8]

The atherosclerotic process is initiated by a variety of chemical, mechanical and immunological mechanisms causing endothelial dysfunction. As a result of this dysfunction inflammatory molecules promote the increased presence of macrophages in the subintima[II] that turn into foam cells after taking up low density lipoproteins. Subsequently foam cells and macrophages form a highly instable lipid-filled necrotic core. At the same time SMCs migrate from the medial to the intimal layer, where they form the fibrous cap along with collagen and elastin. Several factors can weaken the fibrous cap until it ruptures.[3]

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

A.3 Therapeutic Options and Complications

Noninvasive treatment is stopping further growth of atherosclerotic plaque or even reversing the process. Previous research discovered that leoligin (figure 1) displays the ability to promote macrophage cholesterol efflux, which causes the macrophages to release the lipoproteins and therefore preventing the emergence of the already mentioned foam cells and subsequently the highly instable necrotic core. This feature of leoligin will not be discussed any further in this thesis as it had been subject in earlier leoligin related projects. [9]

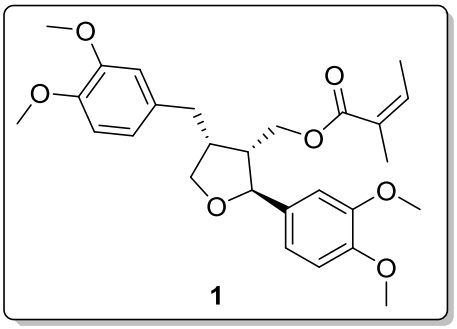


Figure 1 Leoligin

In addition to drug based prevention there are various invasive methods of treatment that are frequently used. Percutaneous coronary intervention (PCI) is a general term used for procedures such as percutaneous transluminal coronary angioplasty (PTCA) and coronary artery stenting (CAS). PTCA, first performed in 1977 by Andreas Grüntzig, represents a minimal invasive procedure that mechanically widens atherosclerotic blood vessels utilizing an inflatable ballon.[5] However this revolutionary method had a major drawback as the restenosis, a re-narrowing of the treated artery, occurred in up to 30-60% of patients in a timeframe of less than 6 months. In the late 80s the bare metal stent, which is a tiny mesh tube that is put into the artery after PTCA in order to keep the vessel open, was developed (figure 2). Originally stents were often made out of 316L stainless steel but today a second generation consisting of cobalt chromium alloy is available.[8]

Bare metal stents reduced the elastic recoil of the vessel significantly but also created new issues including thrombosis and intimal hyperplasia.[10] Intimal Hyperplasia (IH) is defined as “a distinctive state of vascular remodeling that results in a gradual diminution of the vessel lumen due to migration and proliferation of vascular smooth muscle cells (VSMC) into the vessel intimal region” [11] (figure 3).

In normal uninjured vessels the intima is comprised of a monolayer of ECs forming a nonthrombogenic barrier, which prevents and protects against clotting, inflammation and is additionally responsible for signaling the underlying medial layer [11-12]. During the intervention of PCI the already dysfunctioning ECs are stripped off the vessel wall and therefore enlarges the possibility of the formation of thrombi. However this issue can be handled by systematic administration of anticoagulants. [5]

Furthermore, the probability of IH is additionally increased by damaged ECs and once occurring is difficult to manage medicinally and leading to restenosis as shown in figure 3. This condition is often requiring a second more sophisticated surgical intervention. For that reason, IH is the leading cause of long term failure not only in PTCA and CAS but also in coronary artery bypass vain grafting and allograft transplantation[11].

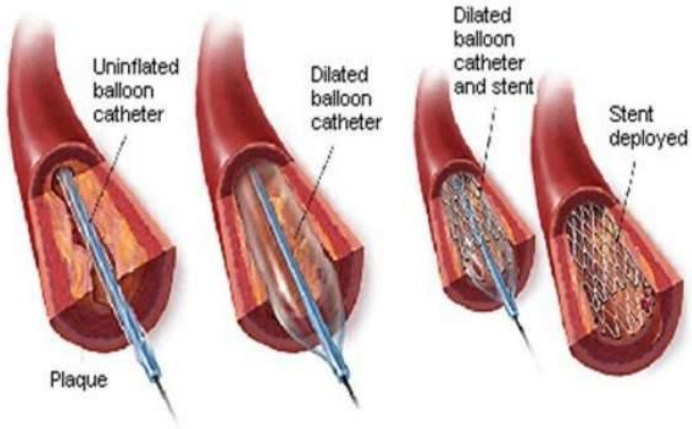


Figure 2 Procedure of percutaneous transluminal coronary angioplasty (PTCA) and coronary artery stenting (CAS)[8]

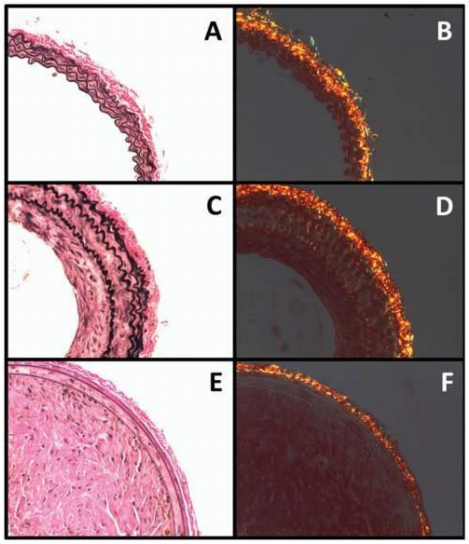


Figure 3 Progressing Intimal Hyperplasia; left is showing mouse carotid arteries using Verhoeff stain for elastin (dark brown/black) and right the same using picroSirus red and visualized under polarized light to reveal collagen fibers (yellow/orange). A and B are control, C and D show intimal hyperplasia and E and F display complete luminal occlusion [11]

In order to minimize the problems encountered with PCI and bare metal stenting, drug eluting stents (DES) were invented. There are two different types: the drug is either directly applied on the stent or impregnated within polymer matrices. Especially the impregnated polymer matrices have been designed in order to provide a long-term release in vivo. Indeed the use of DES reduced restenosis by 37.5% but the occurrence of late-stent thrombosis due to incomplete endothelialization, delayed arterial healing

and local inflammation was a major drawback.[5] Only two drugs, paclitaxel (figure 4) and sirolimus (figure 5) are approved and used for DES and both do not only retard the proliferation of SMCs but also compromise the regrowth of ECs, which are, as already discussed, highly important for functioning vessels. [13] For that reason it is of great scientific interest to develop agents that are capable of selectively inhibiting SMCs proliferation without affecting ECs.

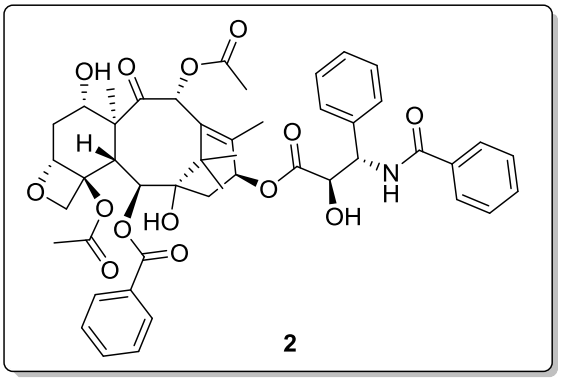


Figure 4 Paclitaxel

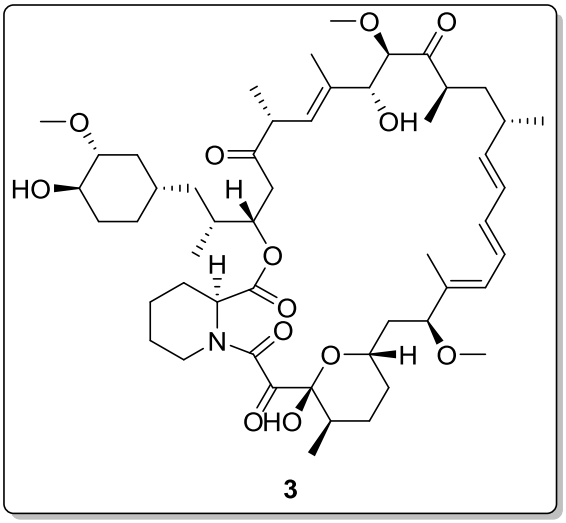


Figure 5 Sirolimus

A.4 Lignans

A.4.1 Definition and Classification

Lignans and norlignans are natural products, which are widely distributed in plants and have been known to possess several clinically important biological activities. Lignans are defined as "dimers of phenylpropanoid (C_6-C_3) units linked by the central carbons of their side chains"[14] and dimers "exhibiting linkages other than (C_8-$C_{8''}$)"[14] are referred to as neolignans. Neolignans will not be discussed any further. Based on cyclisation pattern and location of oxygen in the skeleton lignans can be classified into eight different subgroups and additionally evaluated depending on the oxidation state of the C9(C9') position (figure 6). [15]

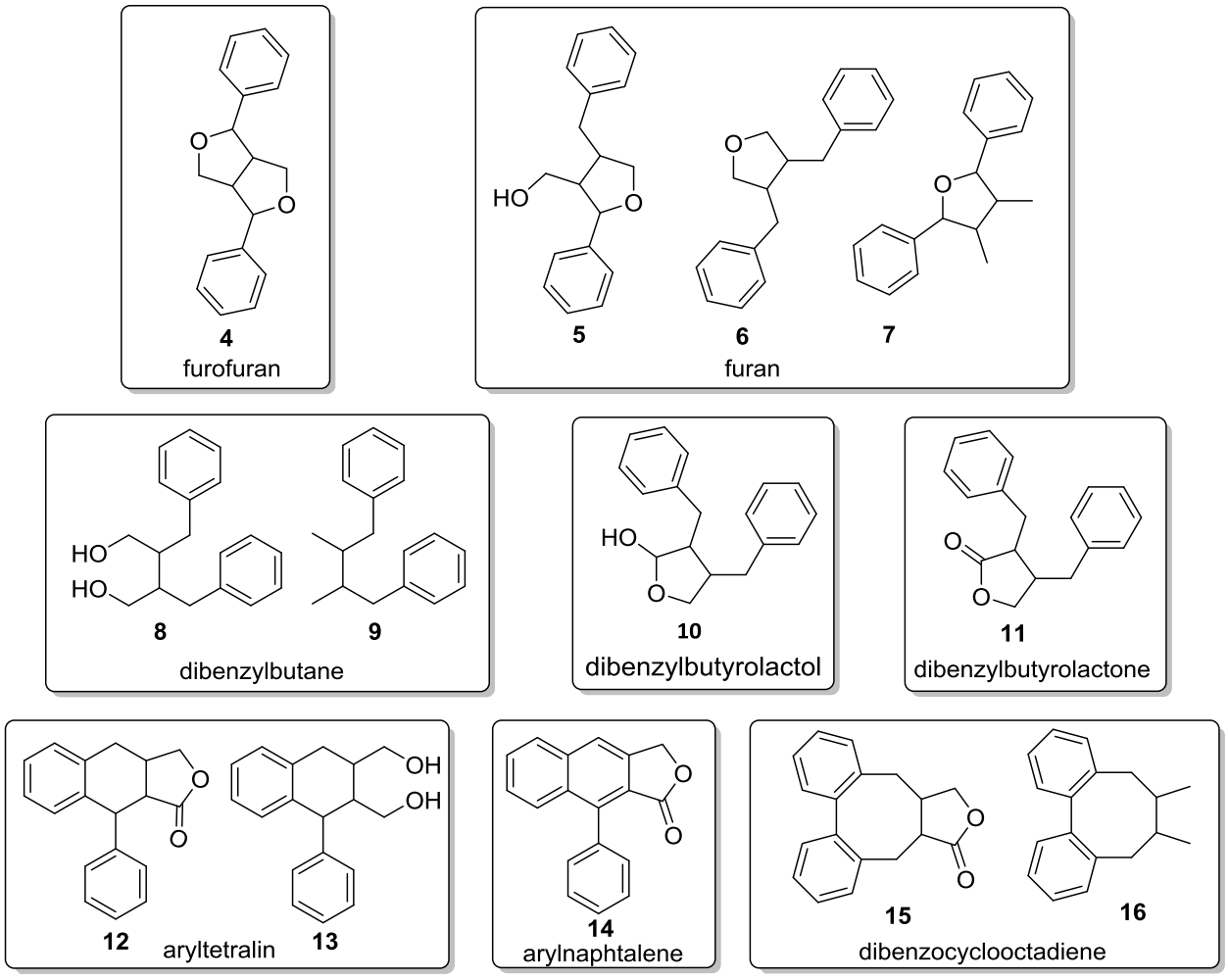
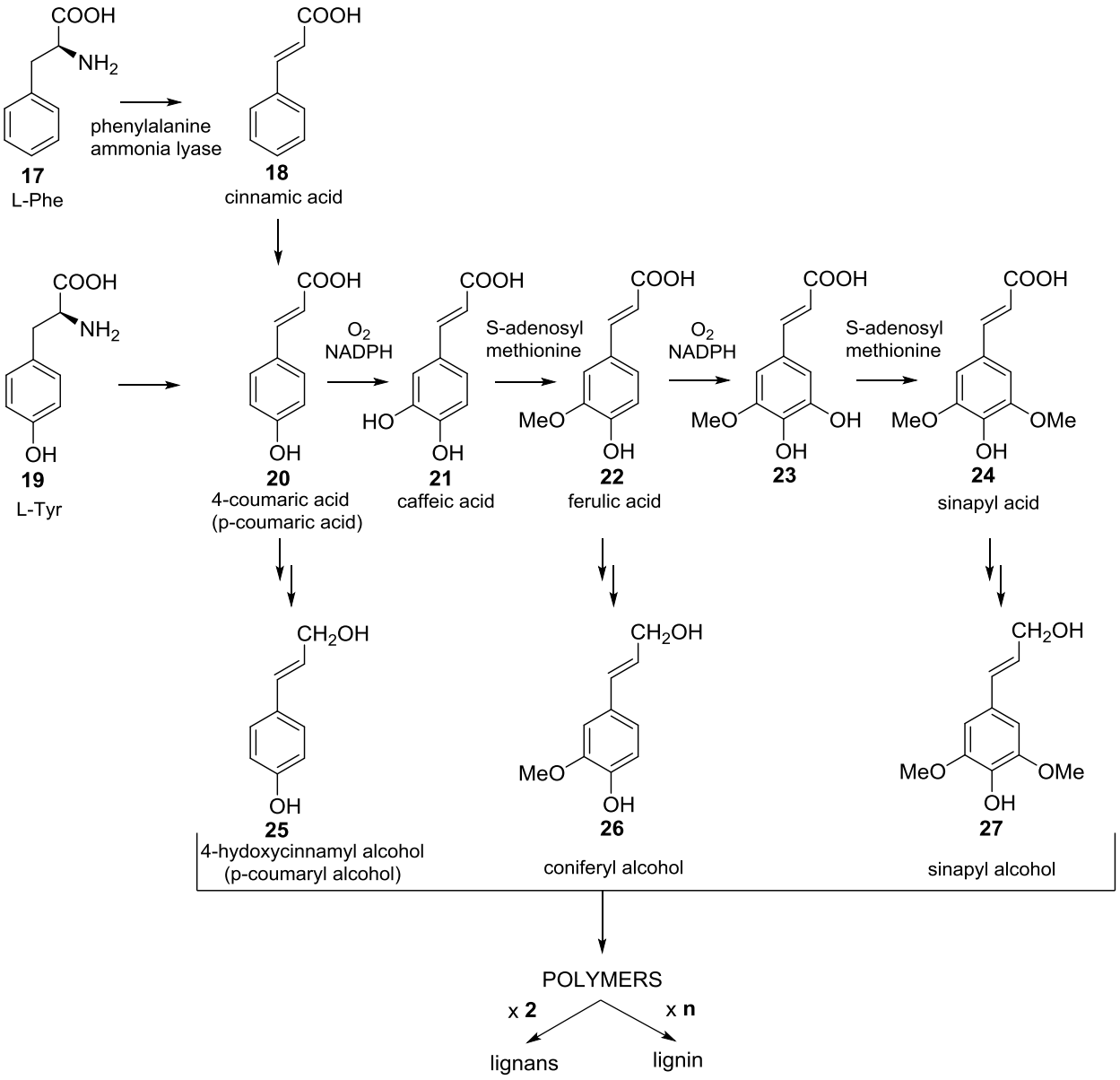


Figure 6 Structural classifications of lignans

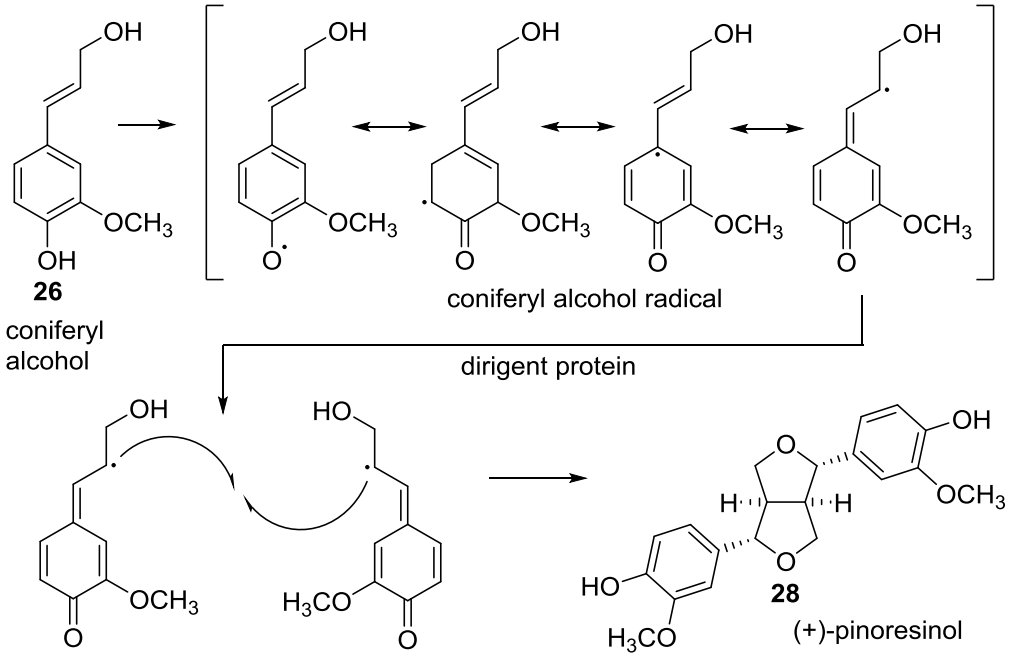
A.4.2 Biosynthesis

L-phenylalanine and L-tyrosine act as precursors for a large range of natural products, which include lignans. In the first step ammonia is eliminated from a side-chain in both L-phenylalanine and L-tyrosine. In the case of L-phenylalanine this is conducted via the enzyme phenylalanine ammonia lyase (PAL) resulting in cinnamic acid. Although the transformation of L-tyrosine to *p*-coumaric acid is similar, it is not entirely clear whether a separate enzyme exists or whether PAL is capable of deamination of L-tyrosine as well. Subsequently the most important monomers, p-coumaryl alcohol, coniferyl alcohol and sinapyl alcohol, for the formation of dimeric lignans and polymeric lignins are produced. In this process *p*-coumaric acid is altered through hydoroxylation, methylation and reduction of the acid. The overview of this pathway is found in scheme 1.

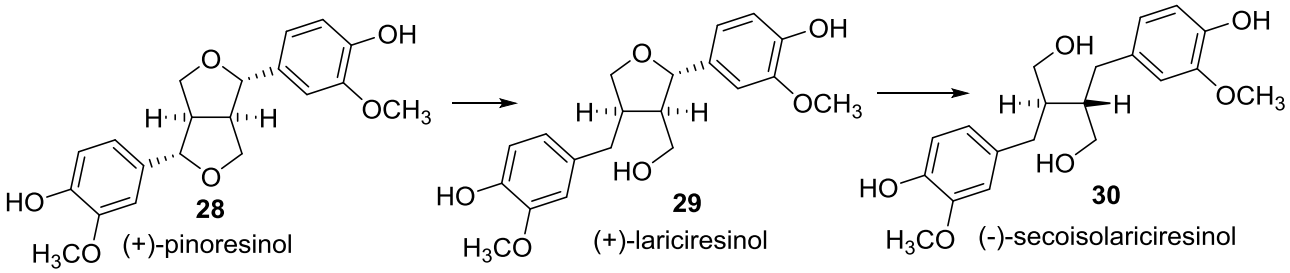


Scheme 1 Pathway towards the formation of lignans [16]

After the formation of the monomers, a peroxidase enzyme performs a one-electron oxidation of the phenol moiety and thereby creating a radical and enabling different resonance structures[17]. In contrast to lignin, lignans naturally occur in only one enantiomeric configuration or at least with one configuration being in excess and exhibit optical activity as a result. This leads to the conclusion that lignans are synthesized under strictly stereoselective controlled coupling. pinoresinol synthase, an oxidase[18], was the first example of a so called dirigent protein. [15] This directing protein is capturing free radicals and therefore catalyzing the formation of a lignin called (+)-pinoresinol (scheme 2). In further steps (+)-pinoresinol is reduced to (-)-secoisolariciresinol via (+)-lariciresinol by a pinoresinol/lariciresinol reductase as shown in scheme 3. (+)-Lariciresinol belongs to the subgroup of furan lignans as well as (+)-lariciresinol dimethyl ether, which is the corresponding alcohol to leoligin (figure 7). As (+)-lariciresinol dimethyl ether is a derivative of (+)-lariciresinol it is quite probable that additional enzymes are present in the Edelweiss plant, which stop the reduction of (+)-pinoresinol at the stage of (+)-lariciresinol in order to form leoligin in subsequent steps.



Scheme 2 Stereoselective synthesis of the lignan (+)-pinoresinol



Scheme 3 Reduction of (+)-pinoresinol to (-)-secoisolariciresinol via (+)-lariciresinol catalyzed by pinoresinol/lariciresinol reductase

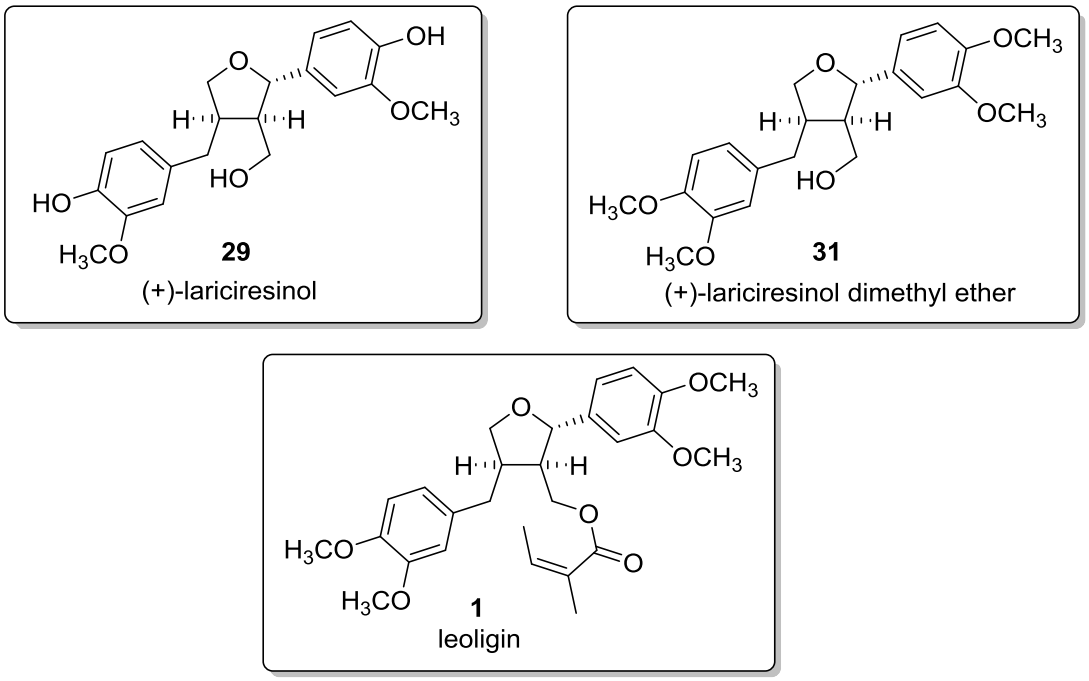


Figure 7 Comparison (+)-lariciresinol and (+)-lariciresinol dimethyl ether, which is the corresponding alcohol to leoligin

A.5 Biological Activities

Lignans have been reported to possess various biological activities, including:

- prevention of atherosclerotic cardiovascular disease [19]
- Inhibiting HIV-1 [20]
- anticancer [14, 21]
- cancer prevention [21-23]
- antiviral [14]
- antioxidant [23-25]
- anti-inflammatory [25-26]
- antimicrobial [25]
- immunosuppressive [25, 27]
- hepatoprotective [14]

One of the most remarkable lignans is podophyllotoxin (figure 8), which exhibited a strong inhibitory effect on tumor cell growth but its major side effects declined the hope of clinical use. However this discovery led to the development of etoposide, teniposide and a water soluble prodrug etoposide phosphate that are one of the most highly prescribed anticancer drugs.[28]

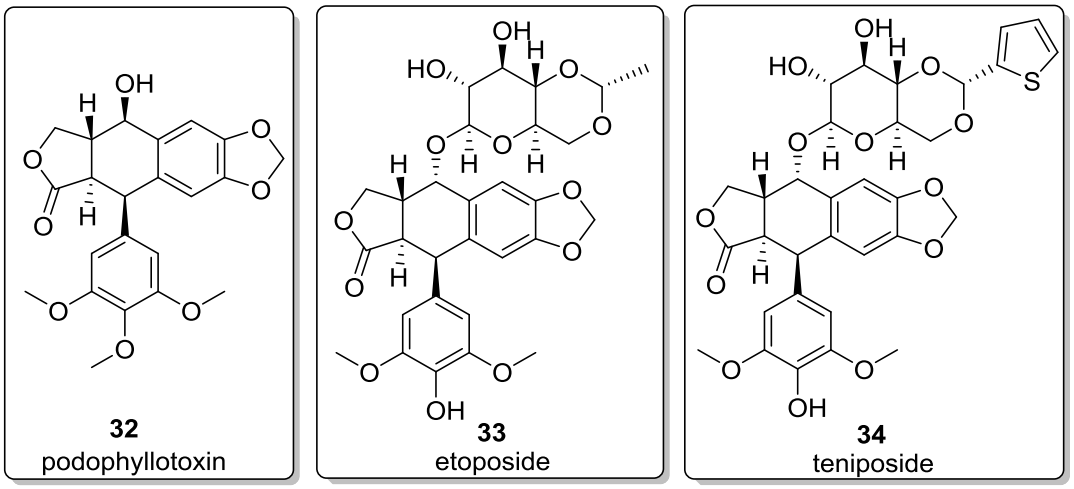
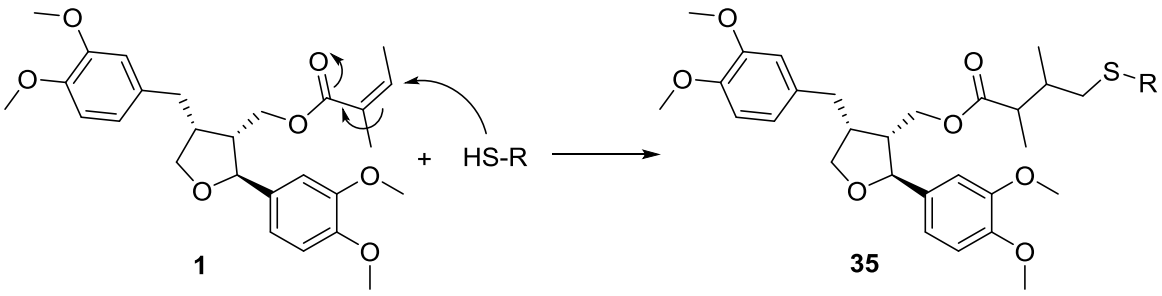


Figure 8 Anti-cancer drugs

A.6 Objective

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

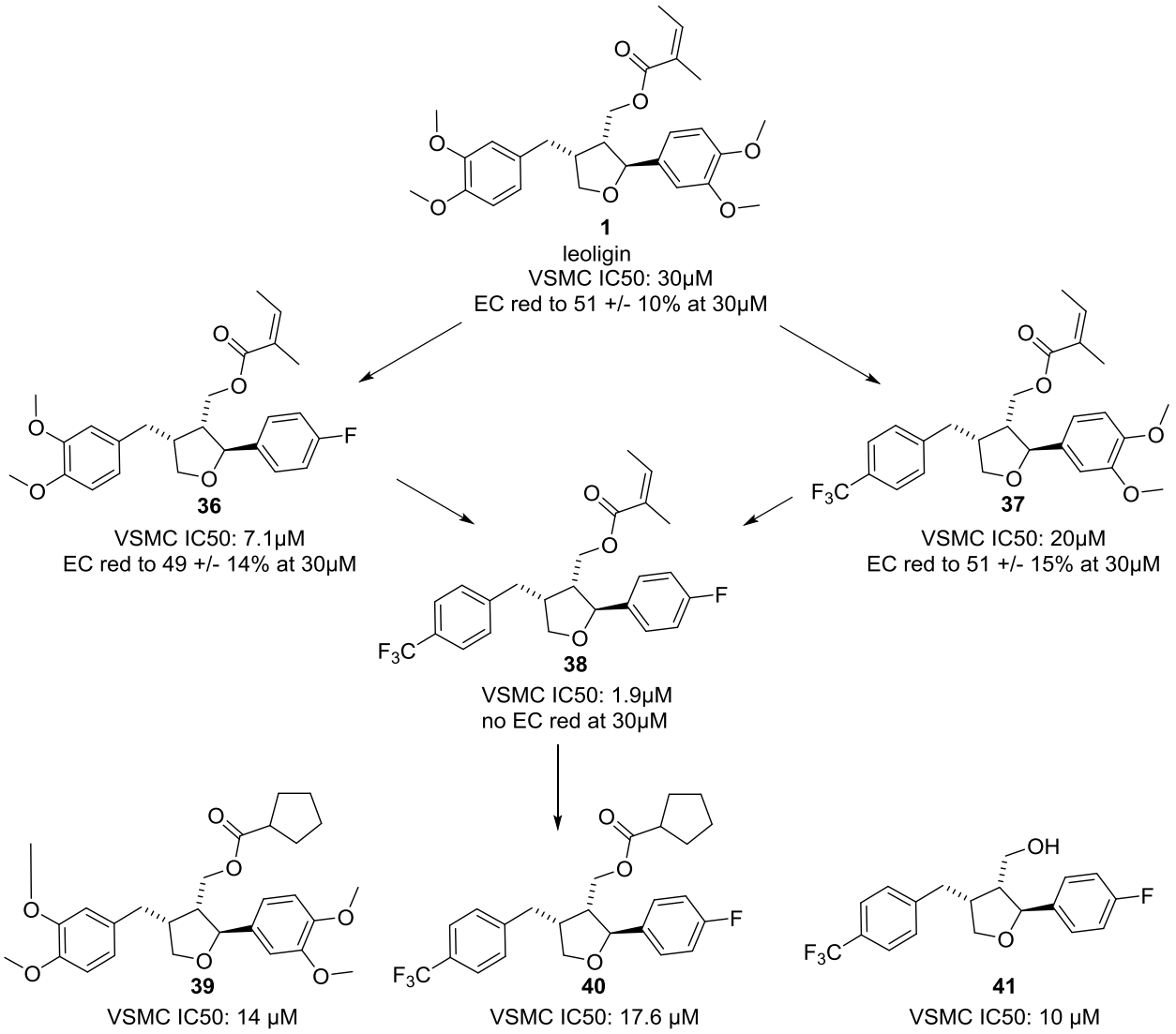
In 2003 leoligin was first isolated from the roots of Edelweiss (Leontopodium alpinum Cass.).[29] Six years later leoligin was discovered to inhibit intimal hyperplasia. This phenomenon is occurring in venous bypass grafts and PCI procedures and causing these procedures to fail.[30] However it was also found to inhibit the regrowth of ECs, which are crucial for functioning vessels, to the same extend as VSMCs that are responsible for intimal hyperplasia.
For that reason it was of interest to synthesize a library of synthetic analogs for biological testing in order to find a compound that is selectively inhibiting the proliferation of VSMCs. In addition to that the extracted amount of leoligin is in the range of 20mg per kg dried roots and fails to provide the compound in the required quantities for in depth biological testing or for the synthesis of derivatives for SAR studies. Consequently, in previous research conducted by Thomas Linder[9] a route towards synthetic leoligin and synthetic analogs was established that will be discussed in detail in subsequent chapters.
During the research two synthetic analogs were identified, each differing in one moiety to the original scaffold, that possessed a significantly better inhibitory activity than leoligin (scheme 5). Finally those two modifications were combined and the compound with the best biological activity was obtained. In addition to that the agent did not exhibit any EC reduction at 30µM unlike the other compounds. However the best analog still contains an ester derived from angelic acid, which possesses Michael acceptor properties. This property is highly unwanted as Michael acceptors can undergo non-selective binding with undesired targets such as ubiquitous glutathione.[31] The mechanistic rational is shown in scheme 4.



Scheme 4 Undesired reaction of a Michael acceptor

Because of the relatively high biological activity of the corresponding alcohol, cyclopentanecarboxylic acid was utilized for esterification. As the exchange of these particular esters on the original leoligin scaffold resulted in a substantial improvement of inhibitory activity, it was hoped to be able to achieve similar effects. Unfortunately that was not the case.

This disappointing result led to the conclusion that a pi system might be required in the ester position. The major aim of this thesis was to synthesize different esters, which contain a pi system but which cannot act as Michael acceptors in order to become a potential drug candidate.
In addition to that the feasibility of the total synthesis of a leoligin analog, possessing a thiazol or a tert-butyl moiety in 2-position of the tetrahydrofuran ring, using the established protocol should be investigated. As this thesis was a part of a larger project, some open ends had to be tied as well which had been started earlier in the project.



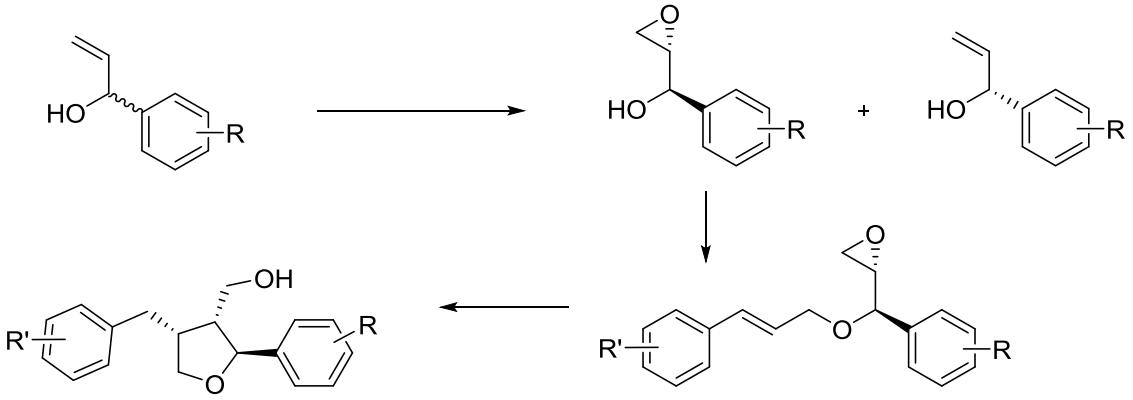
Scheme 5 Most important cornerstones in the development of the compound with the best biological activity (VSMC IC50: 1.9)

B. Results and Discussion

B.1 Chemisty

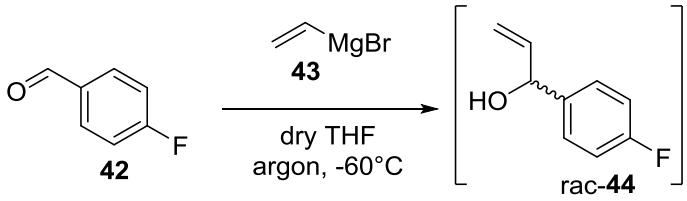
B.1.1 Total Synthesis of Synthetic Leoligin Analogs Bearing a 4-Fluorphenyl Moiety in 2 Position

In previous work on the leoligin project the original approach was inspired by work by Banerjee et al (scheme 6)[32], which included a kinetic resolution by Sharpless asymmetric epoxidation, a Williamson ether synthesis and a radical cyclization, has been optimized and further developed towards a more modular synthesis. Since the suggested kinetic resolution by Sharpless epoxidation resulted in non-acceptable poor yields this approach was dismissed and replaced by method using amano lipase PS.
Furthermore, the Williamson ether synthesis was no longer introducing the benzyl moiety located at the 4-position of the tetrahydrofuran ring and therefore represents the first step towards modularity. The Sharpless epoxidation was replaced with a much simpler non stereo selective mCPBA based protocol. This simplification was possible since the created stereocenter is lost in subsequent steps, anyways. The critical radical cyclization employed by both the Nugent [33] and Roy [34-35] group also required some refinement to deliver good results. As the key intermediate holds an exocyclic double bond, that can be hydroborated and used for stereoselective Suzuki coupling, it is very easy to introduce many different moieties in this position in a very short time. This modularity represents the biggest advantage in comparison with literature known routes towards related scaffolds in order to produce a large number of different compounds for biological testing. All this optimization work was done by Thomas Linder as part of his PhD thesis.[9]



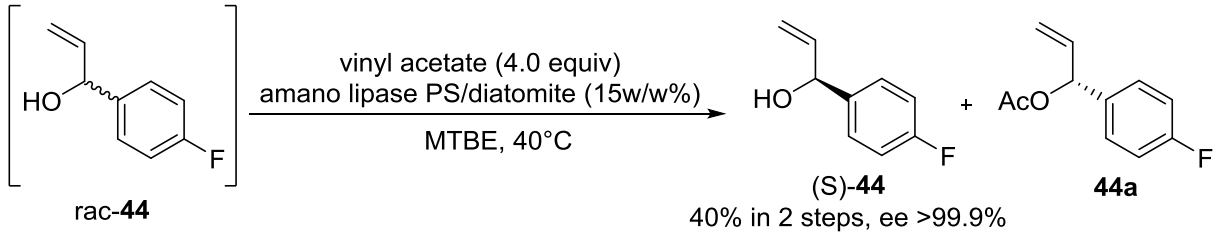
Scheme 6 Pathway towards leoligin analogs reported by Banerjee et al

The first step of the total synthesis towards leoligin analogs, which marked the start of this master thesis, was a Grignard addition of vinylmagnesiumbromid to cheap and commercially available 4-fluorobenzaldehyde and generated a racemic mixture of rac-**44**.



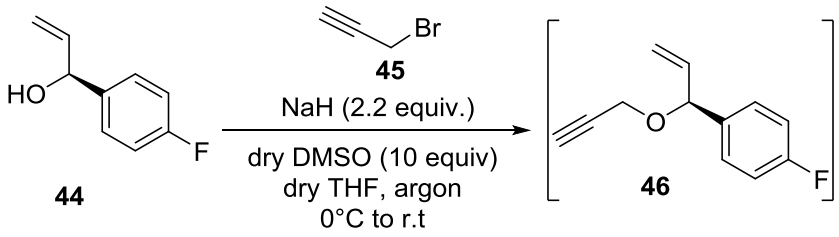
Scheme 7 Grignard Addition

This reaction is shown in scheme 7. Since only the (S)-allyl alcohol is relevant in further synthesis, a chiral resolution is required. Previous research suggested the use of a protocol based on amano lipase PS, which selectively acetylates the undesired (R)-allylalcohol (scheme 8) and for that reason the enantiomers can easily be separated via flash column chromatography. Since this is not a dynamic kinetic resolution, the highest possible yield of the (S)-product is 50%. In this example a good yield of 40% and ee > 99.9% was accomplished.



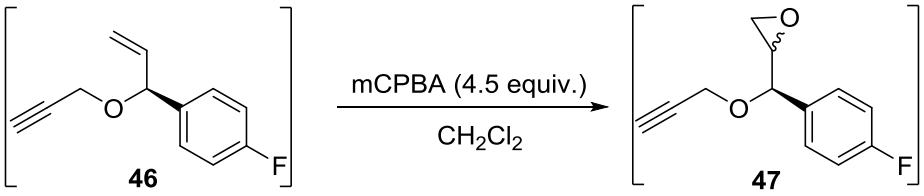
Scheme 8 Enzymatic Kinetic Resolution

The next step a Williamson ether synthesis (scheme 9) resulted in a neat spot to spot reaction. The product was used as crude without further purification.



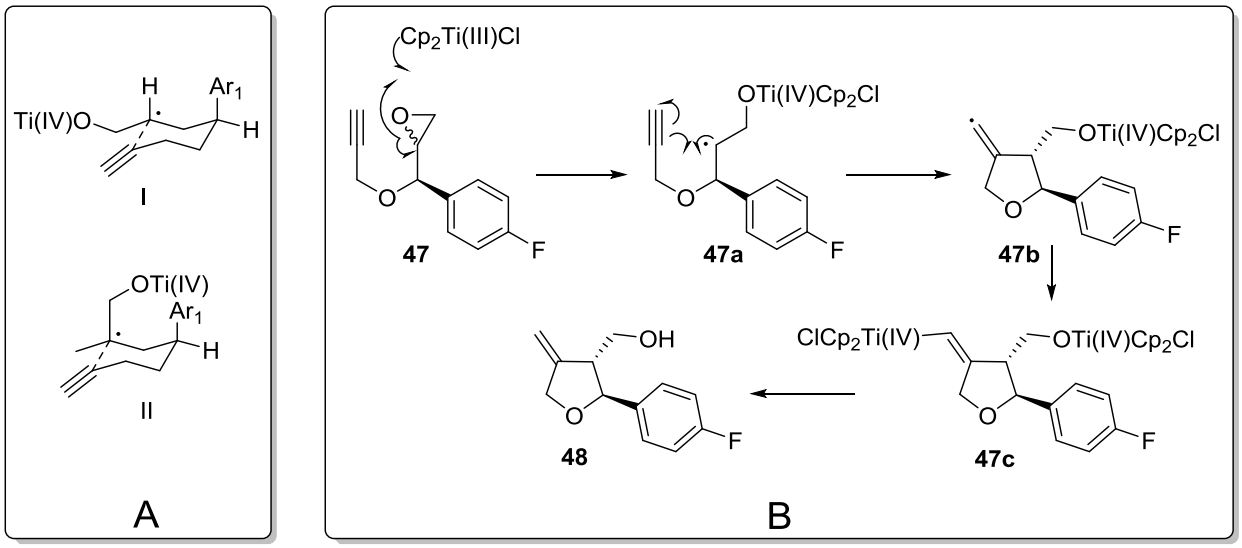
Scheme 9 Williamson Ethersynthesis

The subsequent epoxidation (scheme 10) was performed successfully using *meta*-chloroperoxybenzoic acid (mCPBA). However the byproduct *meta*-chlorobenzoic acid (mCBA) proved to be fairly difficult to remove. Due to sufficient differences in solubility of the product and mCBA most of the byproduct could be removed via precipitation. As small amounts of mCBA have no negative influence on further steps, a complete removal was not conducted in order to avoid low yields.



Scheme 10 Epoxidation

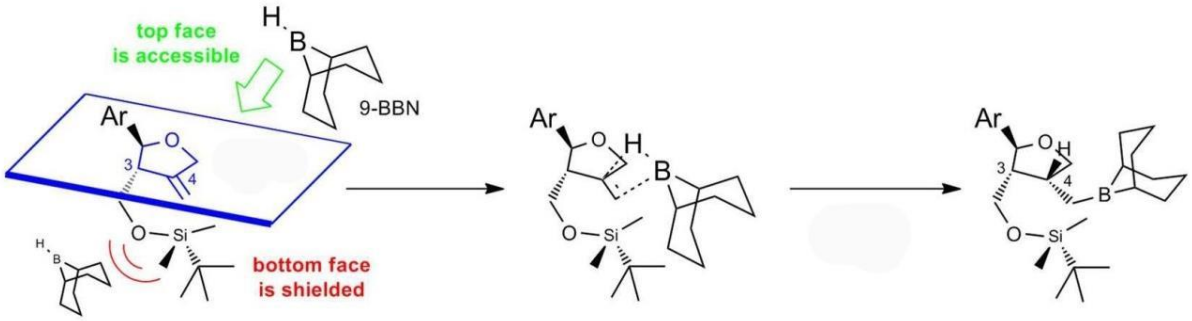
The key step of the whole total synthesis, the radical cyclization, was carried out according to Saha and Roy [36] with a yield of 26% of the desired diastereoisomer over 3 steps. The key step is known to yield in the range of just 40%. The ether synthesis and the epoxidation are typically performing a yield range of approximately 80%. This knowledge is derived of previous reactions with very similar substrates.[9]
In theory this reaction could proceed via two transition states shown in scheme 11A. However a very strong preference of desired configuration I can be expected due to steric hindrance in structure II. This was confirmed in the experiment as no follow up product of transition state II could be observed. The proposed mechanism for this reaction is shown in scheme 11B. The first stage includes the opening of the epoxide generating a free radical via addition of the titanium species. During this process the stereocenter of the epoxide is lost due to a change of hybridization. This is followed by ring closure and the formation of a tetrahydrofuran ring bearing an exocyclic double bond in position 4.
At this position a second titanium species is added, which is cleaved through acidic work up to give **48** [35].



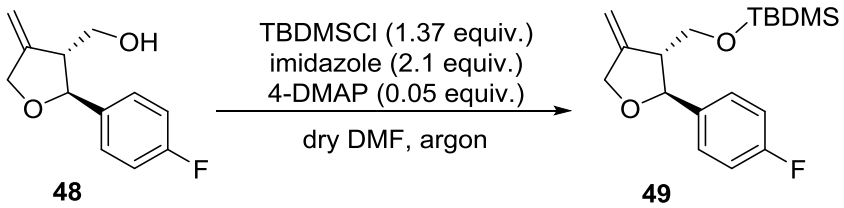
Scheme 11 A Possible products formed by radical cyclization **B** Proposed mechanism of radical cyclization

In order to avoid side reactions and to control the selectivity of the hydroboration and subsequently of the Suzuki-Miyaura coupling, the protection of the hydroxyl group as silyl ether was of importance (scheme 12). Earlier research showed that the tested silyl groups (tertbutyldimethylsilyl, tert-butyldiphenylsilyl, triisopropylsilyl) are of sufficient size to provide sterical hindrance to yield mainly the desired 3,4-*cis*-diastereomer (ratio typically about 95:5) while for example an acetyl group proved to be too small in size. Compound **48** was protected with a tertbutyldimethylsilyl group by employing a standard protocol and work up (scheme 13). Due to a mislabeled solvent flask, DMF with a very high

water content of 1.5% was accidentally used in this reaction, which caused hydroxylation of tert-butyldimethylsilylchloride (TBDMSCl) but did not lead to decomposition of **48**. For this reason the **48** was extracted from the reaction mixture and the reaction was repeated with DMF of sufficient quality (399ppm; 0.04% H_2O) that had been checked *via* Karl Fischer titration. Because of this unfortunately unusually high amounts of TBDMSOH were present in the crude product and MPLC flash column chromatography needed to be conducted. In this way the purity of the product was improved and afterwards determined utilizing ^{1}H NMR with toluene as internal standard and used in further steps. As a result of this unfavorable incidence an unusually low yield of only 77% could be obtained but a small test experiment done prior to the large scale experiment showed that it is possible to perform the protection on **48** with a yield >90%.



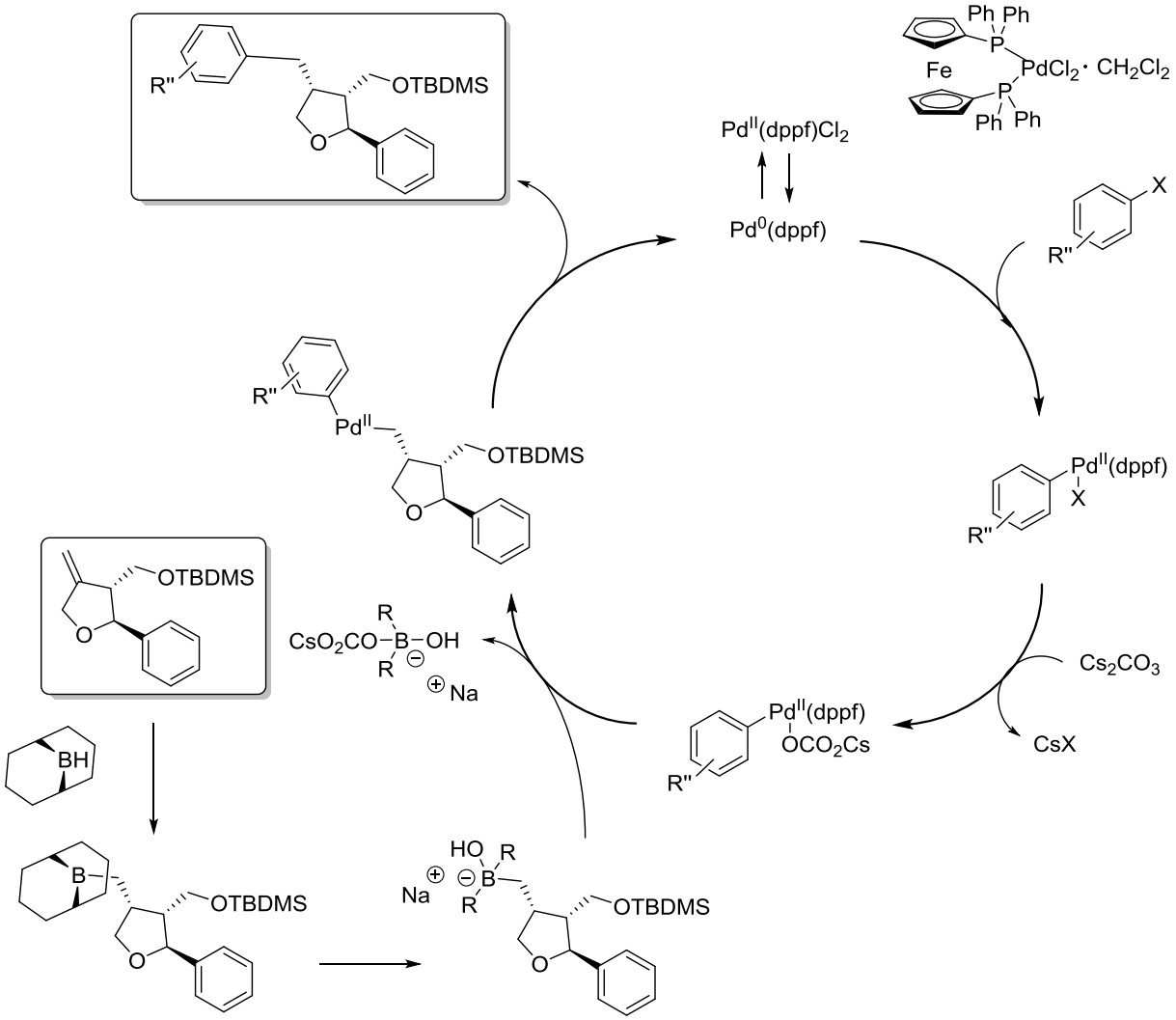
Scheme 12 Role of the protection group in the hydroboration



Scheme 13 Protection of the alcohol group of **48**

The following steps including hydroboration with 9-BBN, Suzuki coupling and deprotection with TBAF have been developed and refined to be a one pot reaction. In the past aqueous NaOH solution was utilized in the Suzuki coupling, which was unfavorable as the reaction had to be worked up in order to remove the water before the deprotection with TBAF. For that reason dry Cs_2CO_3 was used as base, which made it possible to perform a one pot reaction and therefore to avoid an unnecessary workup and prospective loss of yield.

The mechanism for transmetallation is displayed in scheme 14.



Scheme 14 Mechanism of Suzuki-Miyaura coupling

During this master thesis three derivatives were synthesized utilizing the already mentioned one pot hydrobration-coupling-deprotection sequence. Compound **41** was afforded in a good yield of 53% over three steps. Compound **50** was synthesized in the same manner with a slightly better yield of 63%. Product **51** was originally obtained in a yield of 43% with minor impurities after flash column chromatography. Due to experience earlier in the project[9], it was known that leoligin analogs bearing a naphtyl moiety in position 4 can be crystallized in MeOH, it was taken advantage of this property for further purification. In this way **51** was afforded in high purity but unfortunately in a low yield of 22%. It remains to further research to improve the yield and the purification of this intermediate product.

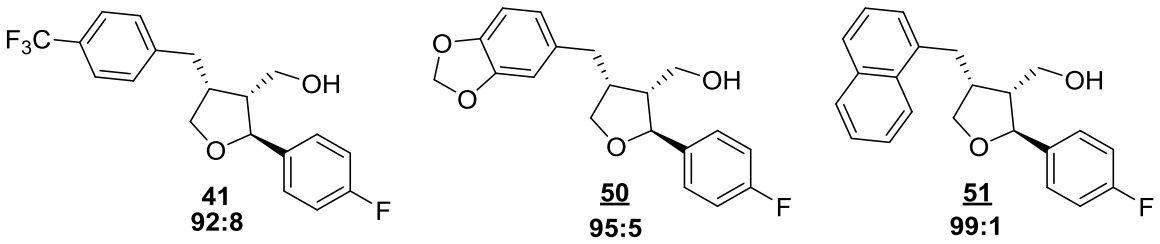
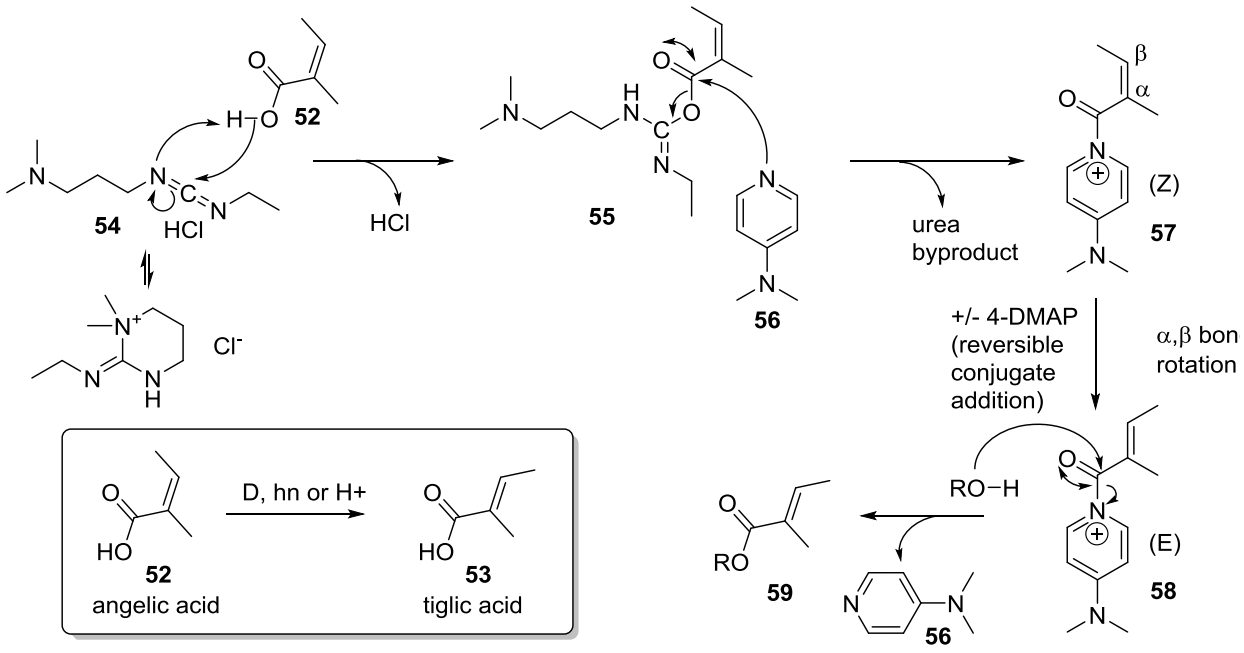


Figure 9 Synthesized coupling products with diastereomeric ratios

In the last step of this total synthesis the hydroxyl group is esterified. The scaffold of leoligin extracted from Edelweiss is carrying an angelic acid moiety and as the influence of each moiety in the three positions were to be explored independently, a suitable protocol for the introduction of the α,β-unsaturated acid in *Z* configuration had to be found.

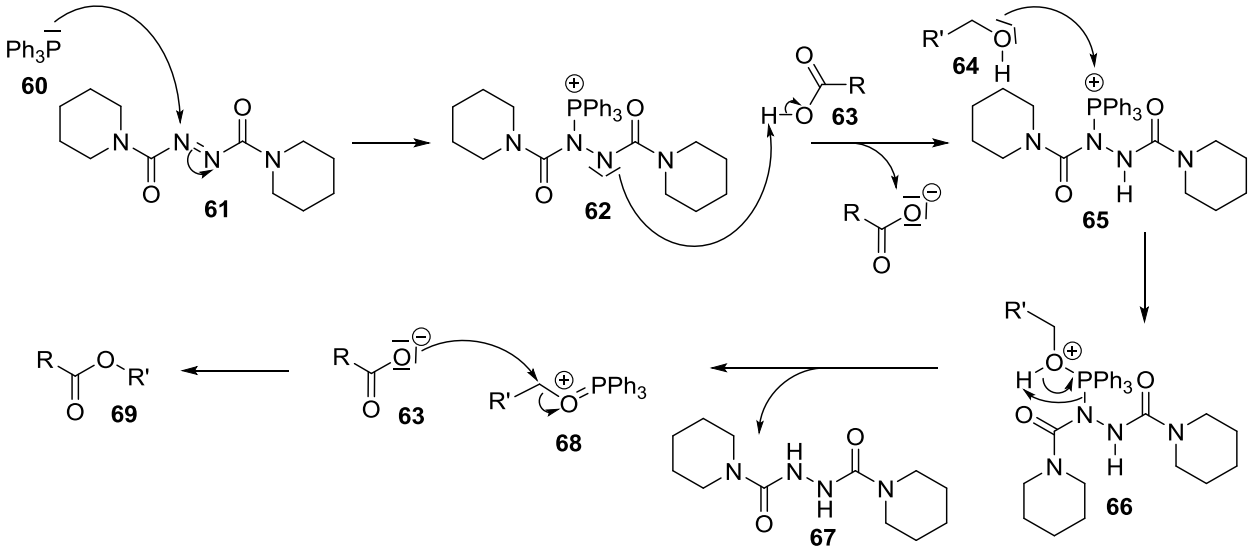
Angelic acid is a rather sensitive compound, which isomerizes to the thermodynamically more stable tiglic acid (*E* configuration) if exposed to heat, light or (strong) acid. For that reason brute force methods were not considered and instead the widely used 4-dimethylaminopyridine-catalyzed Steglich esterification was found to be a possible approach [37]. The Steglich esterification is performed utilizing a carbodiimide that is reacted with the carboxylic acid to give an *O*-acylisourea intermediate. Classically the used carboiimide is *N*,*N*'-diyclohexylcarbodiimide (DCC) or *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDCI.HCl), as the latter is resulting in a highly polar urea byproduct, which can be removed from the desired ester a lot easier than the corresponding dicyclohexylurea from DCC. The esterification subsequent to the formation of the *O*-acylisourea intermediate is very slow and for that reason the catalyst 4-dimethylaminopyridine (DMAP) was employed. This method has already been reported to be successful for the esterification of sensitive α,β-unsaturated carboxylic acids [38] and has also been used in group for this purpose in the past [39]. However in the case of angelic acid preliminary experiments revealed that an 8:2 isomeric mixture of ester product was formed. This was most likely caused by the reversible Michael addition of the catalyst to the intermediate and enabling the bond rotation to the thermodynamically favored (*E*) configuration [40-41] (scheme 15). As isomerization is a well-known problem [42] and one published approach is utilizing angelic anhydride and LiHMDS or $CsCO_3$ and avoiding pyridine bases. Although this protocol would have been suitable for the planned esterification it was not considered as commercial angelic anhydride is very expensive and in addition to that contains a few percent of angelic-tiglic mixed anhydride.



Scheme 15 Steglich reaction employing angelic acid, EDCl.HCl and benzylalcohol (R=Bn) and the proposed mechanism leading, which is affording both the desired angelic acid ester the unwanted tiglic acid ester **59**

For that reason a Mitsunobu protocol with diethyl azodicarboxylate DEAD as reagent was tested and found to be suitable for the task in question [43-44].

The reaction mechanism is shown in scheme 16. Via this methodology the alcohol is activated instead of the acid (Steglich esterification). In addition to that the reaction was performed in the dark to minimize the possibility of isomerization. Unfortunately it turned out that the byproduct derived from DEAD had a very similar retention time as the product causing serious purification problems (figure 10).



Scheme 16 Mitsunobu mechanism

For that reason DEAD was replaced with 1,1'-(azodicarbonyl)dipiperidine (ADD) earlier in the project by Sophie Geyrhofer during her master thesis [45] and as a result of that change, purification could easily be conducted via flash column chromatography in a single step. This optimization was applied to all Mitsunobu reactions conducted within this thesis.

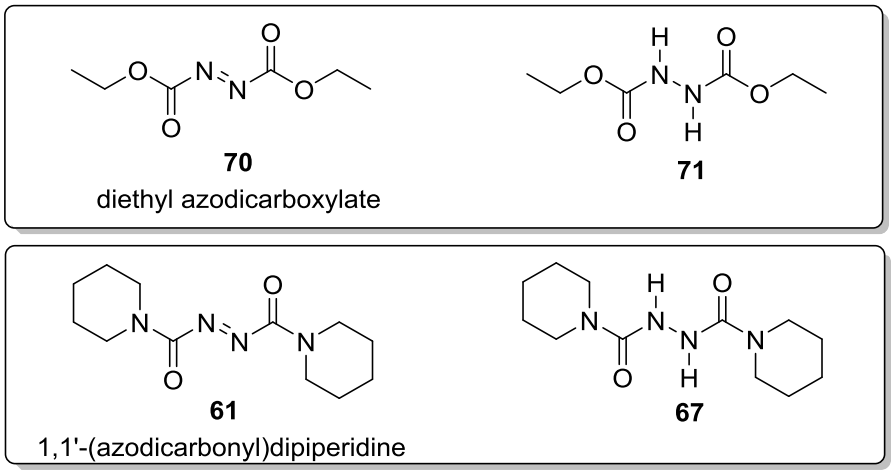
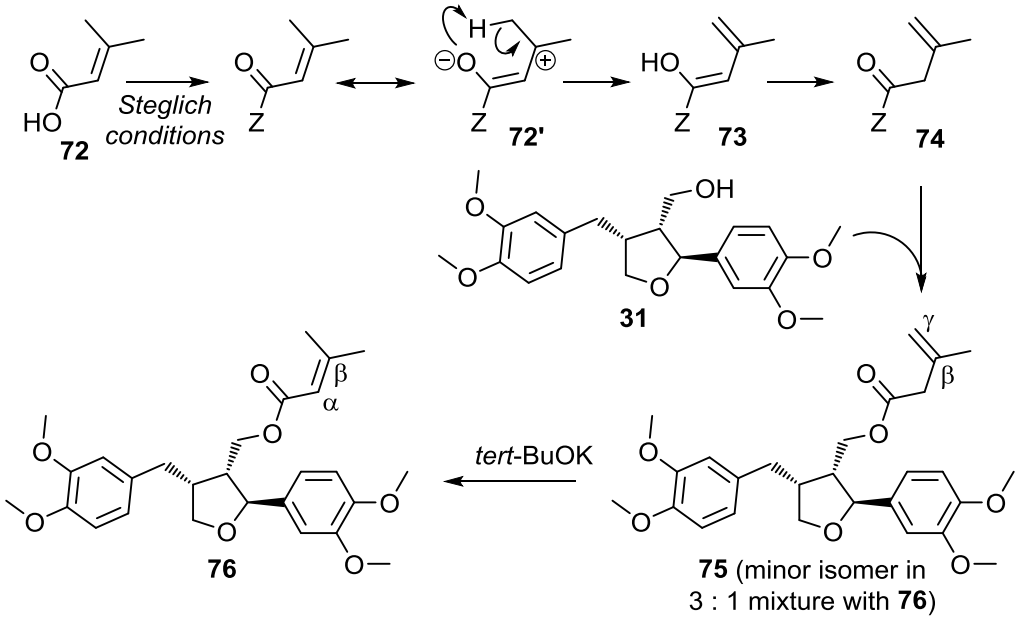


Figure 10 Reagents in the Mitsunobu reaction

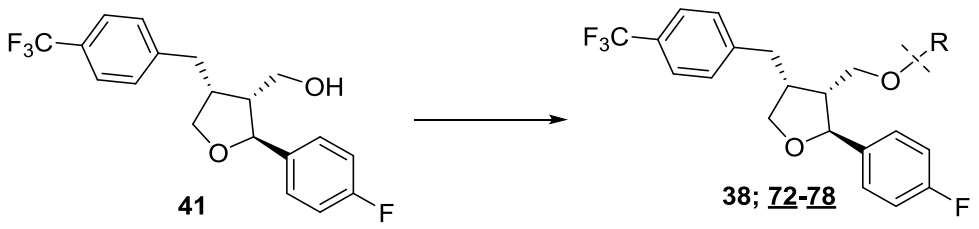
Eight different esters were synthesized (table 1) according to the Mitsunobu protocol achieving excellent yields of 78-88% in most cases. Besides esterifications with angelic acids, this methodology was also essential for sterically demanding 2,6-dimethyl benzoic acid thus the fact that the alcohol is activated instead of the acid. In the past the Steglich esterification turned out to be not ideal for 3,3-dimethyacrylic acid because the product was obtained in an 3:1 isomeric mixture as shown in scheme 17. Although the isomerization is reversible upon exposure to strong base [46] the problem can be avoided completely with the Mitsunobu protocol [45] as the results of this thesis revealed.

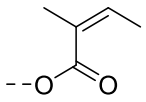
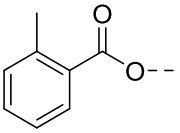
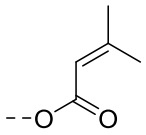
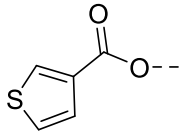
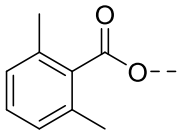
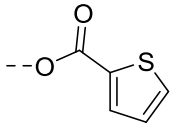
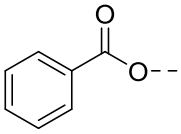
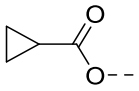
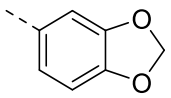
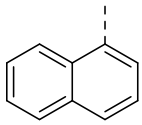


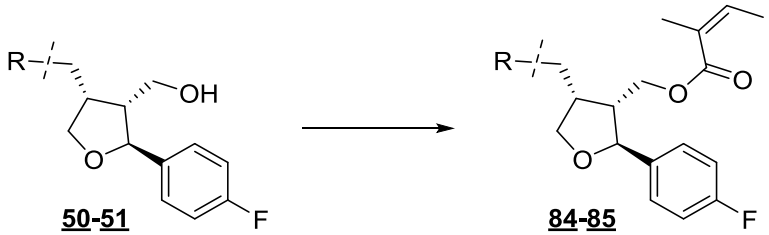
Scheme 17 Isomerization of 3,3-dimethyacrylic acid, which is probably due to the 1,5-shift in **72'**. Z is representing the isourea- or pyridinium moiety in the activated intermediates.

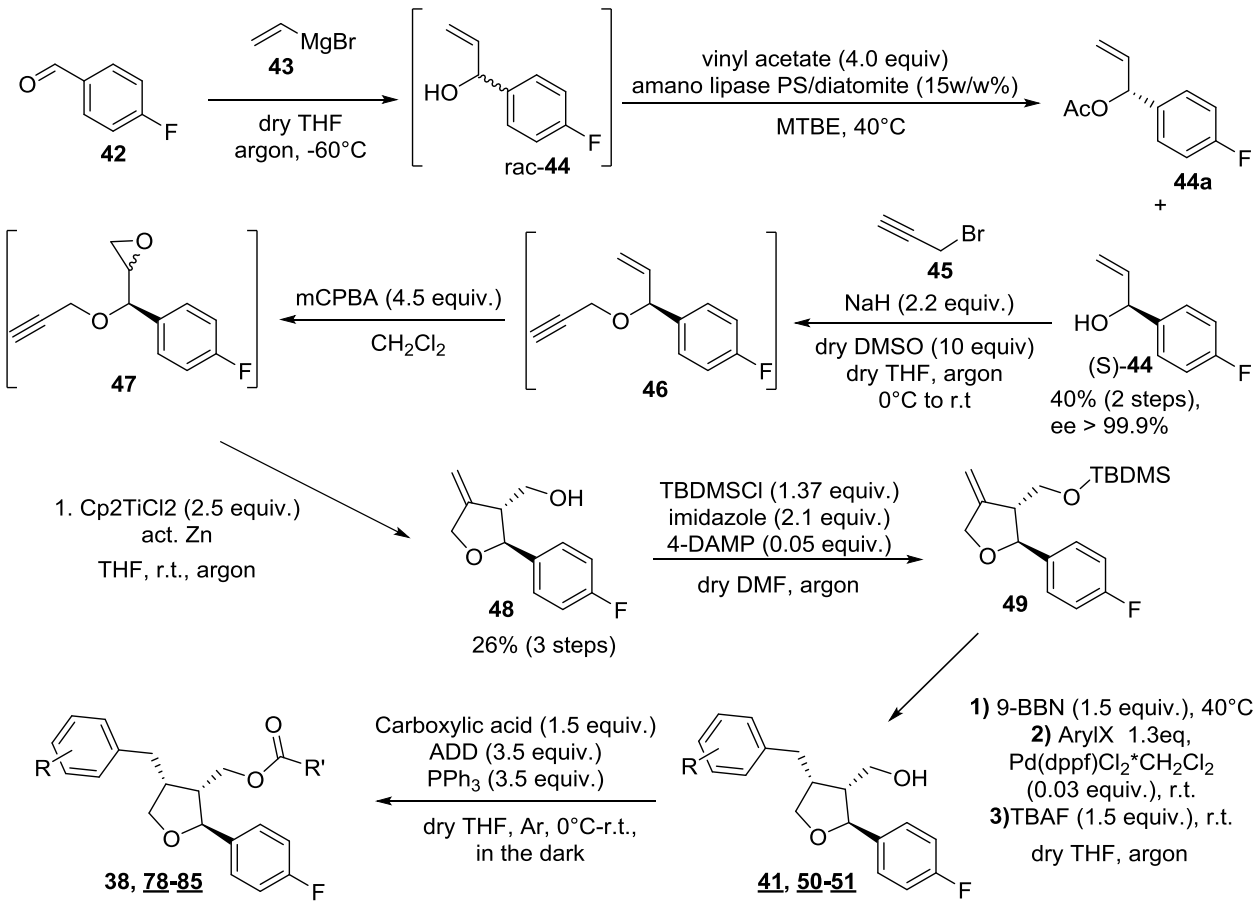
Since the Mitsunobu reaction is very easy to prepare and results in very good yields it was also used to obtain all remaining products. The results are shown in table 1. There is only one example of an unsatisfactory yield of just 22 %, which occurred due to unfavorable circumstances in the flash column chromatography. However the yield was sufficient for biological retesting and therefore it was renounced to repeat the synthesis that had been performed yielding in a rage of 75 % in the past. A summary of the optimized total synthesis is shown in scheme 18.

Table 1 Summary of Yields



Compound	Yield / %	R	Compound	Yield / %	R
38	22		**80**	88	
77	86		**81**	83	
78	82		**82**	65	
79	78		**83**	70	
84	76		**85**	88	



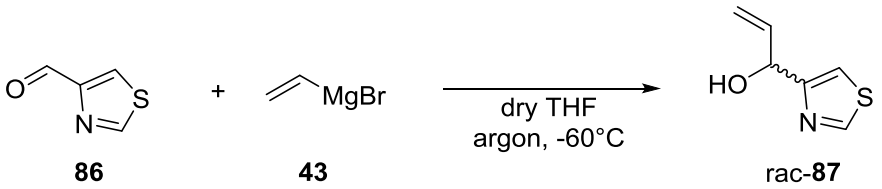


Scheme 18 Optimized total synthesis towards synthetic leoligin analogs

B.1.2 Attempted Total Synthesis of Synthetic Leoligin Analogs Bearing a Thiazole Moiety in 2 Positon

Another aim of this thesis was to show whether or not it was possible to synthesize Leoligin analogs carrying a heterocycle in 2-position of the tetrahydrofuran ring employing the established route (scheme 18). From a medicinal chemistry perspective this would enable to substantially broaden the scope of modification at the leoligin core with respect to changing the pharmacological properties of such analogs with respect to solubility and tissue distribution.

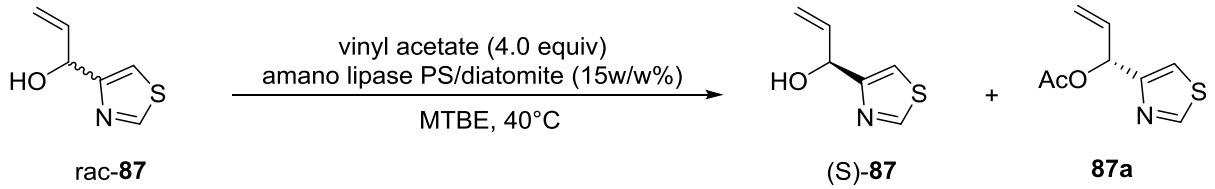
For that reason a Grignard addition of vinylmagnesiumbromid to commercially available 1,3-thiazol-4-carboxaldehyde was successfully performed affording a crude yield of 89 % (scheme 19), which was used in the next step without further purification.



86 **43** rac-**87**

Scheme 19 Gringard Addition

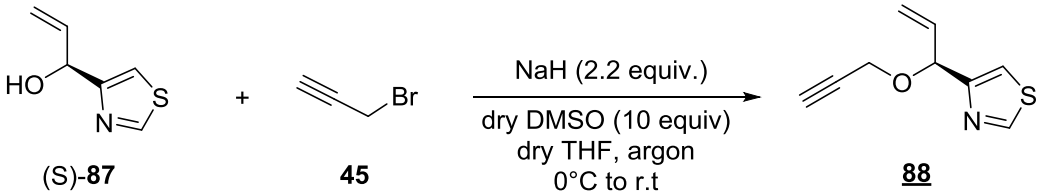
Subsequently a racemic resolution employing amano lipase PS was done and monitored *via* chiral HPLC that resulted in an acceptable yield of 26 %, ee > 99.9% (max possible 50 %) as shown in scheme 20.



rac-**87** (S)-**87** **87a**

Scheme 20 Racemic Resolution

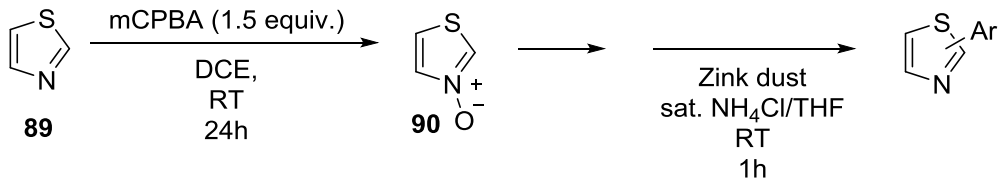
The Williamson ether synthesis was carried out without any problems in a spot to spot reaction (scheme 21). As the crude NMR showed only minor impurities, the crude product was used in the next step without further purification.



(S)-**87** **45** **88**

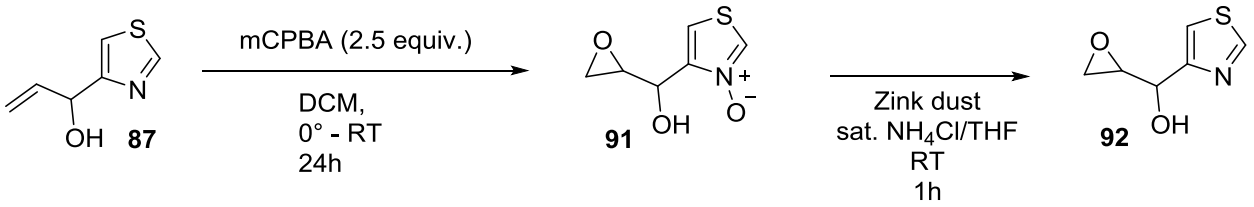
Scheme 21 Williamson Etherification

According to the publication by Campeau et al [47] it was known that thiazoles and thiazole derivatives form N-oxides when stirred with mCPBA for 24h at room temperature (scheme 22). Since it was reported that the formed N-oxides can be reduced very easily and quickly, it was planned to utilize this protocol to form both the epoxide and as intermediate step the N-oxide (scheme 23). Therefore the amount of mCPBA had to be adapted and increased from 1.5 to 2.5 equivalents.



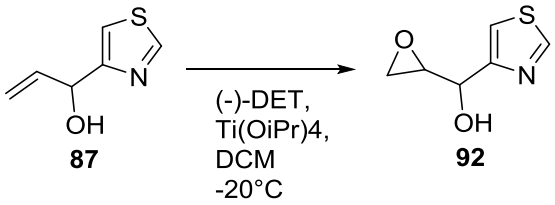
89 **90**

Scheme 22 Route published by Campeau et al



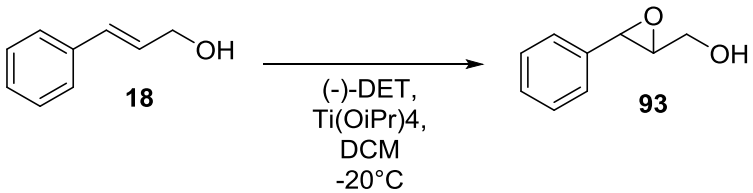
Scheme 23 Planned approach towards the epoxide

Unfortunately this epoxidation approach did not lead to the expected result. After the reaction was stirred for 24h a substance was formed that was no longer soluble in DCM and settled to the bottom of the reaction vial as brown sticky honey like substance, which is not consistent with the reported analog reactions performed by Campeau et al. According to TLC the conversion of the starting material was no longer present so the reaction was worked up as subsequently described. The reaction mixture was cooled with an ice bath and filtered in order to remove most of the mCBA. The solvent was carefully removed by reduced pressure and room temperature utilizing a rotary evaporator. NMR showed that the work up contained only mCBA and the obtained brown, high viscous substance was a mixture of decomposition products, which were impossible to identify. For that reason this approach was dismissed and the Sharpless epoxidation was reconsidered (scheme 24).



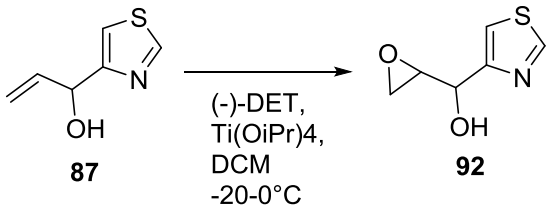
Scheme 24 Shapless Epoxidation

In the past the Sharpless epoxidation was successfully used for substrates, which were not accessible with the mCPBA protocol. So it was attempted to synthesize the epoxide in this way but unfortunately after 3 days stirring at -20°C no evidence for conversion could be found *via* TLC (scheme 24). After the reaction was worked up it was confirmed by NMR with naphtalene as internal standard that indeed neither conversion nor decomposition had occurred. In order to exclude the possibility of mistakes in the preparation or unsuitable chemicals a test reaction utilizing cinnamic acid was successfully performed according to crude NMR (scheme 25). It was renounced to conduct purification as the crude NMR confirmed the complete conversion of the starting material as well as the formation of the desired product.



Scheme 25 Literature known Shapless Epoxidation

Finally in a last attempt the Sharpless reaction was repeated with the starting material of interest and monitored with GC-MS and TLC. But again no conversion could be observed after 3 days so it was decided to allow the reaction mixture to warm to 0 °C for four hours prior to work up (scheme 26). Unfortunately, even that measure did not result in the desired product. NMR with internal standard revealed that some starting material was consumed but no epoxide was formed.



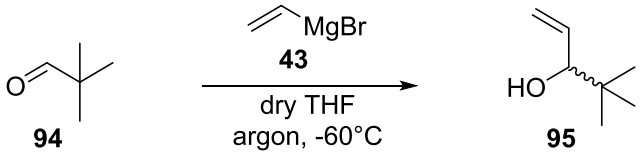
Scheme 26 Shapless Epoxidation allowed to warm up

At this point it became apparent, that the established route is not suitable to synthesize Leoligin analogs holding a thiazole in 2-position of the tetrahydrofuran ring and this work-package was discontinued.

B.1.3 Attempted Total Synthesis of Synthetic Leoligin Analogs Holding a Pivalyl Moiety in 2 Positon

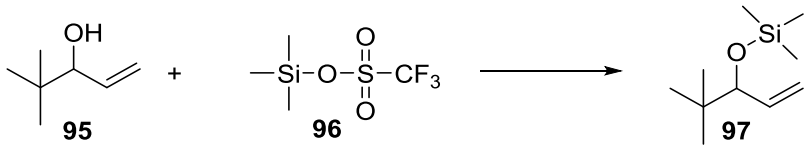
Besides testing if it was possible to synthesize Leoligin analogs starting form 1,3-thiazol-4-carboxaldehyde it was also attempted to do so starting from pivalaldehyde. The rationale behind this modification was based on generally improved biological activity by increasing lipophilicity of the molecule, which could be complemented by additional sterical bulk.

So the Grignard addition of vinylmagnesium bromide was successfully performed (scheme 27). Because the obtained 4,4-dimethylpent-1-en-3-ol is not UV active at a useable wavelength the progress of the racemic resolution could not be performed analog to previous examples utilizing chiral HPLC with UV detection. For that reason it was decided to perform flash column chromatography in order to obtain pure product for establishing a new analytical method. The first column was done using light petroleum and ethyl acetate but unfortunately only 11.4% product could be isolated. This was very surprising as the amount of crude product containing only minor impurities according to NMR provided no reason for a yield significantly worse than 85%. As ethyl acetate has a comparably high boiling point of 77°C and the product is a small and rather apolar molecule, which are factors pointing towards a volatile compound, it was concluded that the usage of diethylether instead of ethyl acetate could result in better yield. In doing so an improved yield of 24% could be obtained, which is still far below the expected. Due to this fact it was assumed that the product is forming an azeotrope with the solvents used for flash column chromatography.



Scheme 27 Grignard addition

The detection of the progress of the kinetic resolution turned out to be a major challenge. After the available IR detector connected to the HPLC system proved to be unsuitable, it was attempted to introduce a chromophore, in order to make UV detection possible. So an ether synthesis employing four equivalents 4-nitrobenzoylchloride and two equivalents DMAP at 50 °C was attempted. However the approach was dismissed due to insufficient conversion in reaction time of four hours. A suitable derivatization method has to be achievable in less than one hour in order to monitor the progress of a kinetic resolution occurring in an approximate 24h timeframe. After that it was decided to switch to GC detection as a chiral column designed for molecules like ketones, esters and lactones was available. Therefore it was tried to obtain the TBDMS protected alcohol using the established protocol, which also suffered from poor reactivity. Based on these insights TMS-triflate was used (scheme 28), which resulted in full conversion after five minutes but unfortunately the formed product was too volatile and for that reason the enantiomers were not separated on the column. Additionally it was discovered that TMS triflate is also reacting with MTBE, which is used as solvent in the kinetic resolution. So the solvent has to be removed prior to reaction, which may also result in problematic loss of analyte.



Scheme 28 Derivatisation with TMS triflate

Finally a derivatization of TBDMS triflate was attempted, which was also dismissed because of insufficient conversion within practicable time. As a suitable derivatization protocol had not been found it was decided to prove the general achievability of the subsequent steps of the total synthesis before continuing the research of this particular task. All further reactions shall be understood as pure feasibility study and for that reason the focus of this part of the work was put on the doubtless prove of existence of the desired intermediates.

So Williamson ether synthesis was performed according to the established protocol. However after two days of reaction time at room temperature only 54 % conversion according to GC-MS could be achieved and an additional 20 h stirring at 70 °C increased the conversion only by 10 %. After a quick literature search for etherification employing this particular substrate, three test reactions were conducted using 6 instead of 2.2 equivalents of NaH, which were stirred for 3.5 h in order to form the alkoxide prior to the addition of propargylbromide. Besides that the influence of 0.2 equivalents KI, which is capable of forming propargyliodide, was investigated. The exact reaction conditions and their outcome of the original protocol and test reactions are summarized in table 2. At this point it has to be mentioned that

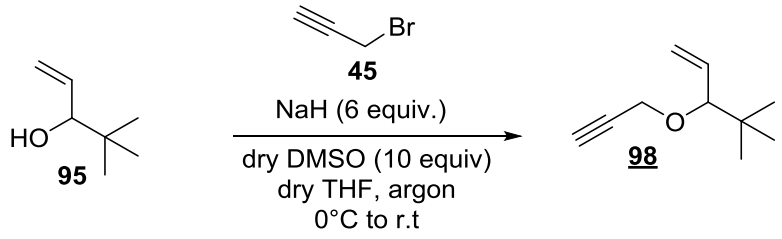
the conversion was checked *via* GC-MS 30min after the addition of propargylbromide, which caused a color change of the reaction mixture to almost black, and the conversion was neither increasing nor decreasing in the additional reaction time.

Table 2 Summary of the optimization screening

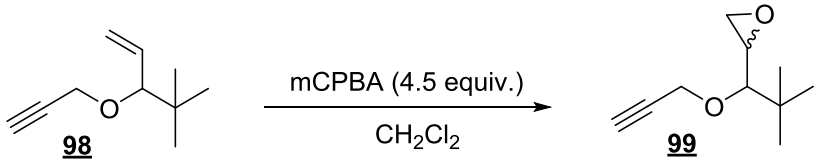
T	Equivalent NaH	Time NaH	Equivalent KI	Time	Equivalent DMSO	Outcome (GCMS Area)
RT/70°C	2.2	-	-	2d/20h	10	54%/64%
RT	6	3.5h	-	24h	10	88%
RT	6	3.5h	0.2	48h	10	25%
RT	6	3.5h	0.2	48h	-	16%

Unexpectedly, the results clearly demonstrate that the use of KI is not beneficial. To exclude the possibility of mistakes, the reactions (DMSO and DMSO/KI) were repeated and confirmed first findings. As 88% conversion is satisfying no further refinement work was done. However looking at the conditions required for etherification of the 4,4-dimethylpent-1-en-3-ol (scheme 29), it becomes obvious that fast derivatization, which is crucial for monitoring the progress of the kinetic resolution, is a very challenging task.

Since the obtained ether is very apolar and consequently very volatile, it was just possible to remove most of the solvent originating from work up *in vacuo* and for that reason no isolated yield could be determined in this step. As this is just a feasibility study and the existence of **98** could be proven beyond any doubt *via* NMR, it was renounced to obtain a product without a significant amount of solvent, which cause the tertbutyl group to be invisible on the NMR.



Scheme 29 Optimized Williamson etherification



Scheme 30 Epoxidation

The epoxidation was conducted with mCPBA (scheme 30). At first only 2 equivalents mCPBA were used in order to test if the 4.5 equivalent usually used are indeed required. After 14h reaction time GC-MS analysis revealed a conversion of only approximately 40% (area comparison), which shows that this previously established high amount of peroxy acid is indeed required for complete conversion within a reasonable timeframe. Finally full conversion of the starting material according to GC-MS could be

achieved after utilization of the original amount of mCPBA. As most of mCBA was removed via precipitation utilizing light petroleum and diethylether and it has proven not to be ideal in terms of yield to remove these solvents completely in the step of the Grignard addition and as this is a pure feasibility study, it was decided to just remove largest parts of solvent in order not to lose product. Since the crude NMR indicated the presence of the epoxide and the GC-MS showed typical fragments, a test radical cyclisation with a quarter of the volume containing the epoxide was conducted. As the etherification and the epoxidation were not isolated and the GC-MS conversions gave no reasons to suspect otherwise because no significant amounts of byproducts were apparent, it was assumed that those steps provided approximately quantitative yields.

However no desired cyclized product was formed in the test reaction according to GC MS and NMR. It was remarkable that no typical color change from green to red occurred, when the epoxide was added, indicating a change of oxidation states occurring during the ring closure (scheme 11 B). For that reason the epoxide was columned, which was originally avoided in order to avoid unnecessary losses of product, but afterwards the NMR (200MHz) still appeared mostly unchanged. So 400MHz and subsequently 600MHz NMR spectra (1H, 13C, APT, DEPT, COSY, HSQC) were measured, which confirmed the presence of the desired product and revealed that the irregular peaks which, were thought to be caused by overlaying impurities, were in fact just due to insufficient resolution of the 200MHz NMR. Figure 12 and figure 13 display the impressive difference of the same sample measured at different machines. The ratio of the formed enantiomers (figure 11) was determined to be 42% and 58%. Unfortunately only 25mg could be obtained, which turned out to be an approximately 1:1 mixture of product and mCBA. Past examples suggest an expected yield of about 40% in the radical cyclisation, so it was decided to stop the total synthesis at the stage of the epoxide as the amount yielding form this reaction is most likely not to be sufficient for characterization. The very disappointing yield of less than 20mg representing three quarters of the obtained material also offers an explanation why no color change, that is linked to the oxidation state could be observed, as the test reaction was thought to be at approximately 100mg scale.

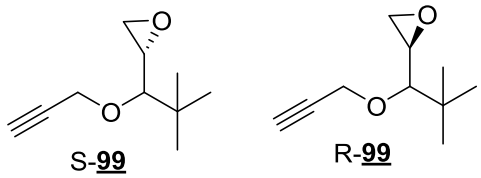


Figure 11 Enantiomeres of the formed epoxide **99**

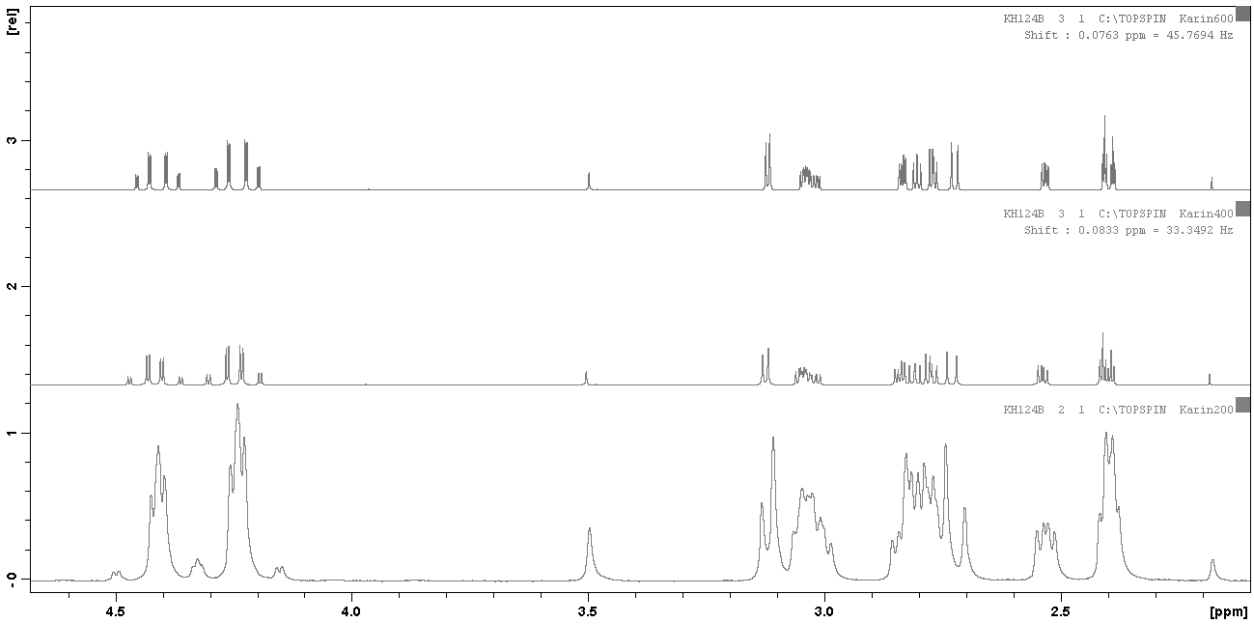


Figure 12 Comparison of NMR Spectra 200MHz (bottom) 400MHz (middle) 600MHz (top)

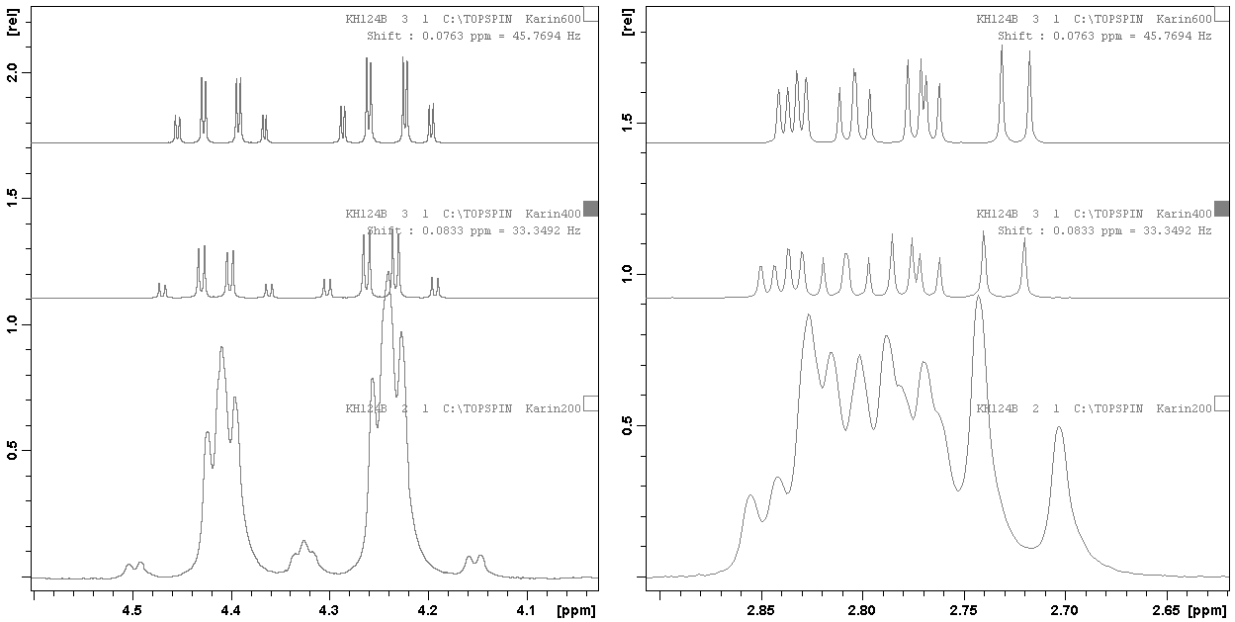
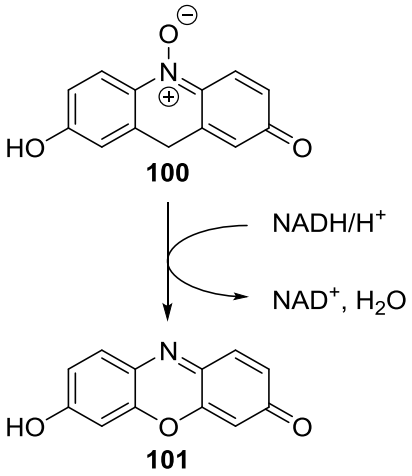


Figure 13 Comparison of NMR Spectra 200MHz (bottom) 400MHz (middle) 600MHz (top)

B.2 Biology

B.2.1 Vascular Smooth Muscle Cell Proliferation

Biological testing was conducted at the Department of Pharmacognosy, University of Vienna by the joint research groups of Prof. Verena Dirsch and Dr. Atanas Atanasov. The resazurin assay was used to test the ability of the compounds to inhibit the proliferation of the VSMC. This assay is based on the blue dye resazurin that is reduced to the fluorescent red resorufin (scheme 31) by metabolic conversion correlating with cell number [48].



Scheme 31 Blue dye resazurin (top) reduced to the fluorescent red resorufin (bottom)

In order to determine the extent of vascular SMC proliferation, rat aortic SMC (0.5 x 10^4 per well) were placed in SMC growth medium (DMEM/F12 medium with 20 % serum, 30 µg/mL Gentamicin and 15 ng/mL Amphotericin) in 96-well plates. After 24h the cells were washed once with SMC starvation medium (DMEM/F12 medium with 0.1 % serum, 0.2 % BSA, 30 µg/mL Gentamicin and 15 ng/mL Amphotericin) and further incubated in starvation medium for additional 24h.
Subsequently the quiescent cells were treated for 30 min with the test compounds and the proliferation was induced adding 20 ng/mL platelet-derived growth factor (PDGF). Unstimulated cells were used for normalization and estimation of the basal level of proliferation. Finally all wells contained the same final concentration (0.1%) of the solvent vehicle, dimethyl sulfoxide (DMSO). After another 48h, the SMC proliferation was quantified utilizing resazurin conversion for 2h [48].

The results of the biological testing are summarized in table 3. Compound **38** is the most active leoligin analog in terms of inhibiting smooth muscle cells known prior to this thesis without being toxic. IC50 of this compound was estimated twice resulting in 1.9µM and 4µM. The rather large relative difference between those two values is a normal result of biological factors within cells (e.g. different batch of SMC). Unfortunately **38** carries the angelic acid moiety, which is a highly undesired good Michael acceptor. As a result of that the ester moiety was varied considering that previous testing (**103** - IC50

17.6µM) showed that a pi system within that position is very likely to be required for good biological results. Compound **77** exhibits almost the same results (IC50 4.4µM) as structurally very similar **38**. Obviously the slight change in the scaffold just reduces the ability to act as Michael acceptor but does not affect inhibitory activities.

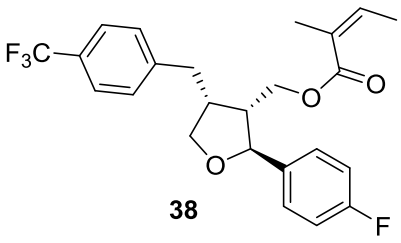
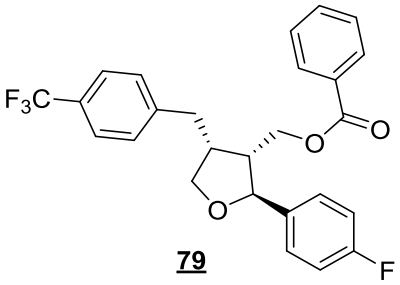
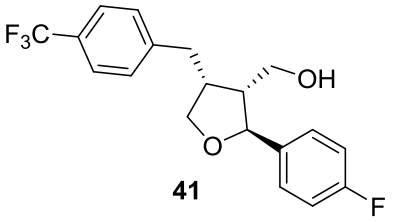
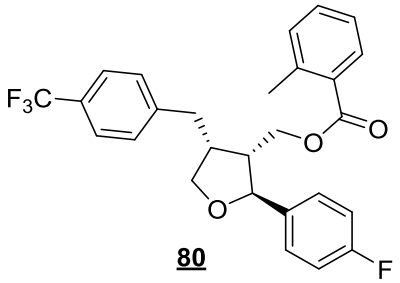
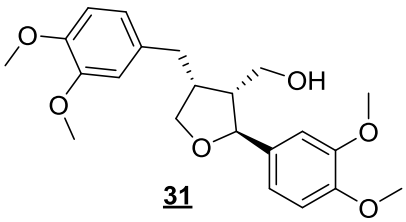
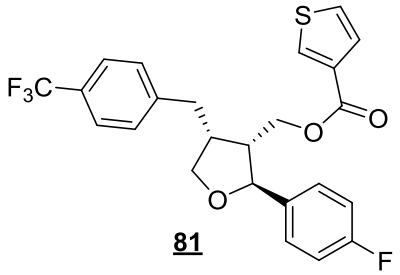
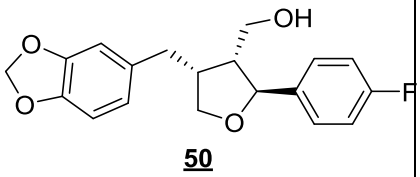
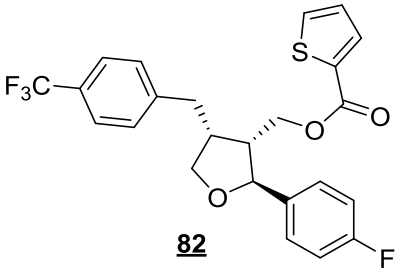
A more interesting result was obtained with compound **81**, which is almost in the same range of activity with IC50 of 5.7µM and has no Michael acceptor properties. Analog **80** (IC50 7.5µM) is slightly less active but still satisfying. Product **79** (IC50 12.1µM) possess a similar activity as the corresponding alcohol **41** (IC50 10µM). At this point it should be mentioned that such comparatively good biological properties in a corresponding alcohol are remarkable and not found in many leoligin analogs. Compound **82** (IC50 18.8µM) is as active as **103** (IC50 17.6µM), which is the compound that led to the conclusion that a pi system is beneficial. The difference in biological activity of esters containing a thiophene ring (5.7µM and 18.8µM) is noteworthy suggesting that the orientation of the sulfur within the (unfortunately unknown) binding site has a significant influence.

Compound **83** has reduced VSMC proliferation to only 0.16 units, in comparison to cells treated with PDGF and DMSO, at agent concentration of 30µM, which has proven to be a hint towards cytotoxicity in the past. The alcohol **51** showed an even worse reduction to 0.1 units.

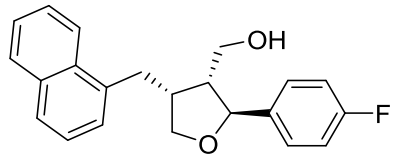
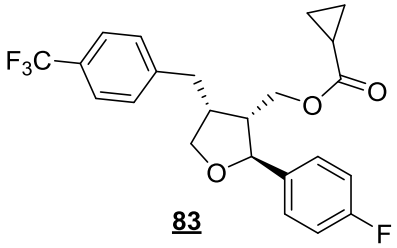
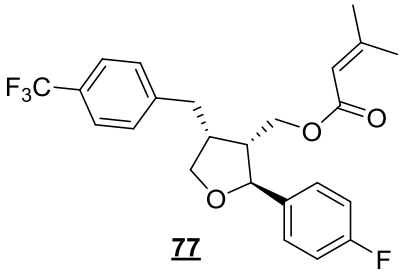
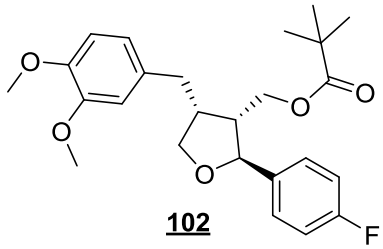
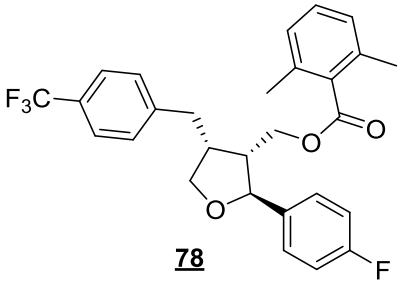
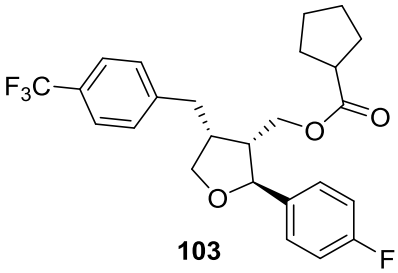
In contrary to that **78** does not show any inhibiting properties at 30µM. As leoligin **1** has an IC50 of 30µM no further investigations were conducted. Cause of that inactivity might be due to steric reasons. Product **50** also showed no activity at 30µM. This phenomenon of inactive alcohols could be observed in the corresponding alcohol of leoligin, lariciresinol dimethyl ether **31**, as well as in several other synthetic analogs.

Additionally a different analog **102** was synthesized in order to complete the compound library. When tested, **102** displayed a medium activity of IC50 12.9µM.

Table 3 Summary of the biological testing

 **38**	IC50 1.9µM 4.0µM	 **79**	IC50 12.1µM
 **41**	IC50 10µM	 **80**	IC50 7.5µM
 **31**	not active[III]	 **81**	IC50 5.7µM
 **50**	not active[IV]	 **82**	IC50 18.8µM

[III] No sign of inhibitory activity at agent concentration of 30µM. Therefore no further tests were conducted.
[IV] No sign of inhibitory activity at agent concentration of 30µM. Therefore no further tests were conducted.

 **51**	toxic[V]	 **83**	toxic[VI]
 **77**	IC50 4.4µM	 **102**	IC50 12.9µM
 **78**	not active[VII]	 **103**	IC50 17.6µM

[V] **VSMC proliferation of only 0.10 units in comparison to cells treated with PDGF and DMSO at agent concentration of 30µM, which has proven to be a sign of cytotoxicity in the past. Therefore no further tests were conducted.**

[VI] **VSMC proliferation of only 0.16 units in comparison to cells treated with PDGF and DMSO at agent concentration of 30µM, which has proven to be a sign of cytotoxicity in the past. Therefore no further tests were conducted.**

[VII] No sign of inhibitory activity at agent concentration of 30µM. Therefore no further tests were conducted.

C. Conclusion

The variation of the ester moiety based on the scaffold of the compound **35** possessing the best biological activity was conducted successfully. The biological result revealed that two of the new compounds exhibit biological activities in the same range as **35** but having lower or no Michael acceptor properties. Therefore the aim of this part of the thesis was fulfilled.

Unfortunately the synthesis of a synthetic analog to leoligin starting from 1,3-thiazole-2-carbaldehyde was not so successful as the synthesis failed at the step of epoxidation. For that reason it was found not to be within the scope of the established protocol.

The same task starting from pivalyl aldehyde was found to be a major challenge as the crucial monitoring of the established way of racemic resolution via lipase has not yet been fully established. However the route, without conducting kinetic resolution, was found to be feasible but is still suffering from unacceptably low yield which requires further investigations.

D. Experimental Section

D.1 General Notes

D.1.1 Chemicals

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

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

Zinc dust was **activated** by treating commercially available zinc dust with aqueous HCl (2 M), followed by thorough washing with water, subsequently with MeOH and dry Et2O. After drying *in vacuo* at 60 °C the material was stored under argon.[35]

D.1.2 Dry Solvents

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

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

Deoxygenated and dry THF was obtained by refluxing and distilling pre-dried material (as describes above) from sodium and benzophenone under argon.[49]

D.1.3 Chromatography (TLC, MPLC, HPLC)

Thin Layer Chromatography TLCs were performed on aluminum coated silica gel 60 F_{254} from Merck and spots were visualized with UV light (254 nm) and/or staining with phosphormolybdic acid (5% phosphormolybdic acid in 96% ethanol) 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 a SIL-10AP autosampler, SPD-20 detector and FRC-10A fraction collector. For separation the following condition were used:

column: Phenomenex Luna RP18, 10 µm , 100A, 250x21.20 mm; flow: 21.2ml/min; eluent: MeOH/H_2O; method: 75-80% MeOH in 60min

Analytical HPLC to determine the ee value of **44** and **87** was performed on a Thermo Dionex UltiMate 3000 device.
Column: Daicel Chiralpak AS-H , 5 µm, 100A, 250x4.6 mm; injection volume: 1.5 µl; flow: 1 mL/min; eluent: n-heptane/iso-propanol: 90/10; detection wavelength: 210 nm

D.1.4 Melting Points

Melting ranges were determined using a Kofler-type Leica Galen III micro hot stage microscope. Temperatures are reported in intervals of 1 °C.

D.1.5 Specific rotation

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

D.1.6 GC-MS

A Thermo Finnigan Trace 1300/ISQ LT Single Quadrupole Mass Spectrometer device using a helium flow of 1.5 mL / min, analyzing an *m/z* range from 50 to 550 with a Rxi-5Sil MS (0.25 µm film; 30 m x 0.25 mm ID) column was utilized for GC-MS runs.

Method A: 150 °C for 2min, 150-300 °C in 5 min, 300 °C for 7min
Method B: 60 °C for 2 min, 60-300 °C in 7 min, 300 °C 2 min
Method C: 100 °C 2 min, 100-280 °C in 4.5 min, 280 °C 38 min
(column used in method C: TR-5 MS (0.50 µm film; 30 m x 0.25 mm ID))

Reported are:

- Fifteen fragment signals with highest relative intensity
- all molecular peaks (regardless the relative intensity) – in cases where M^+ was not visible due to excessive fragmentation, a characteristic fragment signal is identified instead

D.1.7 HR-MS

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

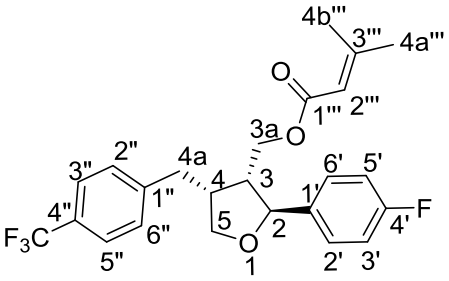
HR-MS analysis was carried out from methanol solutions (concentration: 10 µM) by using an HTC PAL system autosampler (CTC Analytics AG, Zwingen, Switzerland), an Agilent 1100/1200 HPLC

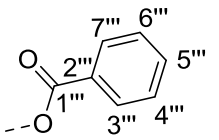
with binary pumps, degasser and column thermostat (Agilent Technologies, Waldbronn, Germany) and Agilent 6230 AJS ESI–TOF mass spectrometer (Agilent Technologies, Palo Alto, United States).
Chromatography: Column: Phenomenex C-18, 2.1 ID, 1.7 µm particles, operated at 40 °C; Column flow: 0.5 ml/min; Injection volume: 5 µl; Gradient: A: H_2O + 0.1 % formic acid, B: MeOH + 0.1 % formic acid – isocratic 70% phase B;

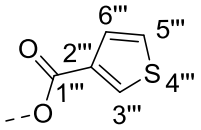
D.1.8 NMR Spectroscopy

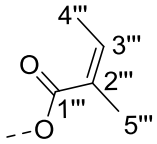
^{1}H- and ^{13}C-NMR spectra were recorded from $CDCl_3$ solutions on a Bruker AC 200 (200 MHz) or on a Bruker Avance UltraShield 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm relative to the nominal residual solvent signals: ^{1}H: 7.26 ppm, ^{13}C: 77.16 ppm.

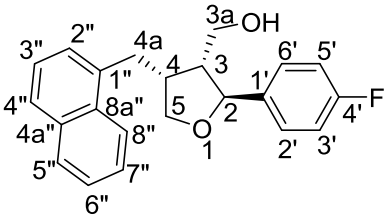
D.1.9 NMR Assignments

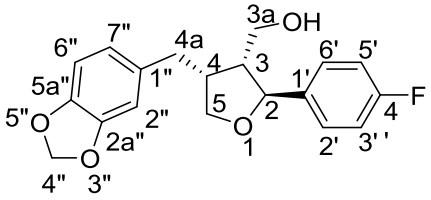


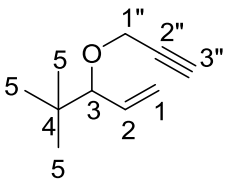


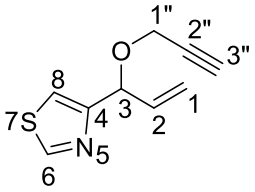


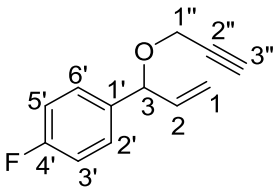












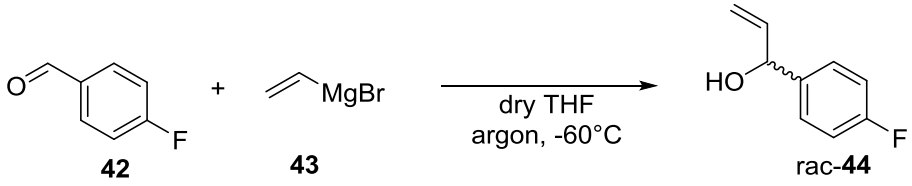
Assignments, which could not be stated without doubt, are marked with an asterix (*).

D.2 Abbreviations

ADD	1,1′-(azodicarbonyl)dipiperidine
9-BBN	9-borabicyclo[3.3.1]nonane
d	doublet
DCM	dichloromethan
DIPEA	diisopropylethylamine
4-DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
equiv.	equivalent(s)
dppf	1,1′-bis(diphenylphosphino)ferrocene
EDCI.HCl	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
LP	light petroleum
m	unspecified multiplet
*m*CBA	*meta*-chlorobenzoic acid
*m*CPBA	*meta*-chloroperbenzoic acid
MPLC	medium pressure liquid chromatography
MTBE	methyl *tert*-butyl ether
q	quartet
quint	quintet
rac	racemic
s	singlet
sext	sextet
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography

D.3 Synthesis of ((2S,3R,4R)-2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methanol

D.3.1 1-(4-Fluorophenyl)prop-2-en-1-ol (44)

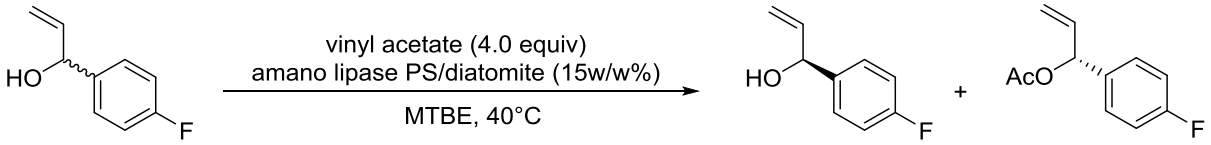


42 **43** rac-**44**

C_7H_5FO MW: 124.11 | C_2H_3BrMg MW: 131.26 | C_9H_9FO MW: 152.17

A 500 mL flask equipped with a stirring bar, dropping funnel, quick-fit and low temperature thermometer was evacuated and back-filled with argon using standard Schlenk technique (3 x). After that a solution of **42** (6.82 g, 55 mmol, 1.00 equiv.) in dry THF (100 mL) was added *via* septum and cooled to -65 °C using a MeOH/N_2 slurry. Vinylmagnesium bromide solution (1 M in THF, 63.3 mL, 63.3 mmol, 1.15 equiv.) was added *via* a dropping funnel over a period of 30min while the temperature of – 65°C was kept within ±3 °C. Afterwards the mixture was allowed to warm to -30 °C within 2h, then a saturated aqueous NH_4Cl solution (12.5 mL) was added dropwise while providing additional cooling to prevent the temperature from rising above -20°C during the exothermic hydrolysis. Water (160 mL) was added to dissolve magnesium salts and the product was extracted with Et_2O (1 x 70 mL, 5 x 40 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (1 x 20 mL) and saturated brine (1 x 13 mL) and dried with Na_2SO_4. The solution was filtered through a plug of silica (10 g, pre-conditioned with Et_2O) and the solvents were removed *in vacuo* (min pressure 100 mbar). This reaction was monitored via TLC and resulted in a spot to spot reaction. R*ac*-**44**, a pale yellow oil (10 g – pure according to TLC), was used directly in the next step without further purification.

D.3.2 (S)-1-(4-Fluorophenyl)prop-2-en-1-ol (44)



rac-**44** | (S)-**44** | **44a**

C_9H_9FO MW: 152.17 | C_9H_9FO MW: 152.17 | $C_{11}H_{11}FO_2$ MW: 194.21

Rac-**44** (8.36 g, 55 mmol, 1.00 equiv.), amano lipase PS (immobilized on diatomite, 1.25 g, 15 w/w%) and vinyl acetate (18.94 g, 20.4 mL, 220 mmol, 4.00 equiv.) in MTBE (300 mL) were charged into a flask with stirring bar. The resulting suspension was stirred at 40 °C for 26 h, while being monitored using chiral HPLC. After that the mixture was filtered through celite 545 and the solvent was removed *in vacuo*. Flash

column chromatography was performed using the following method: 90 g SiO_2 separation column, 50 L/min, EtOAc in LP: 1 to 5 % within 40 min, then 5 to 20 % within 40 min.

Yield: 3.34 g (40 % over 2 steps)

Appearance: pale yellow oil

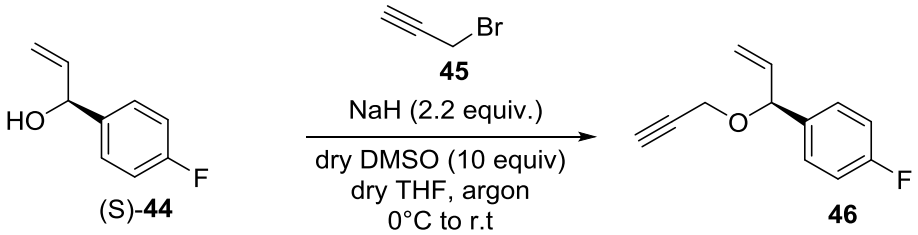
TLC: R_f (heptane : EtOAc, 3 : 1)= 0.33

Specific rotation: $[\alpha]_D^{20}$: +5.36° (MeOH; 2.7389 g/100 mL)

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.04 (bs, OH) 5.11 – 5.28 (m, 2H, H2,H1, H3), 5.24 – 5.42 (m, 1H, H1), 6.02 (ddd, *J* = 16.8, 10.2, 6.1 Hz, 1H, H2), 6.90 – 7.12 (m, 2H, H3', H5'), 7.24 – 7.42 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$) δ 74.6 (d, C3), 115.3 (t, C1), 115.3 (dd, $^2J_{C\text{-}F}$ = 21.5 Hz, C3', C5'), 128.0 (dd, $^3J_{C\text{-}F}$ = 8.2 Hz, C2', C6'), 138.3 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, C1'), 140.1 (d, C2), 162.3 (d, $^1J_{C\text{-}F}$ = 245.7 Hz, C4').

D.3.3 (S)-1-Fluoro-4-(1-(prop-2-yn-1-yloxy)allyl)benzene (46)



(S)-**44**
C_9H_9FO
MW: 152.17

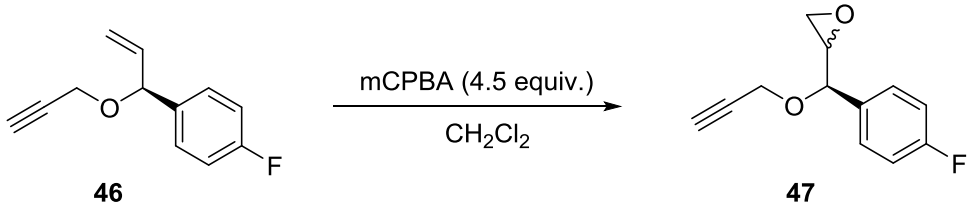
46
$C_{12}H_{11}FO$
MW: 190.22

NaH (approximately 60 % dispersion in mineral oil, 1.79 g, 44.87 mmol, 2.20 equiv.) was weight in a 250 mL three neck flask and set under argon using standard Schlenk technique (4x), then dry THF (35 mL) and dry DMSO (14.5 mL, 203.9 mol, 10.00 equiv.) were added and the resulting stirred suspension was cooled using an ice bath. After that a solution of (*S*)-**44** (3.1 g, 20.4 mmol, 1.00 equiv.) in dry THF (15 mL) was added *via* a dropping funnel over a period of 10 min, still using an ice bath for cooling. Stirring was continued at under those conditions for 15 min, then a solution of propargyl bromide (80 % in toluene, 4.09 mL, 36.7 mmol, 1.80 equiv.) was added over a period of 15 min. To disperse the so formed slurry, dry THF (10 mL) was added. After that the ice bath was removed and the reaction was stirred for 15 h. The mixture was then cooled in an ice bath again under argon atmosphere and hydrolyzed by dropwise addition of aqueous HCl solution (1 M, 12 mL) over 17 min. Most of the THF was removed *in vacuo* (300 mbar/50 °C), followed by the addition of water (50 mL). The aqueous phase was extracted with Et_2O (4 x 50 mL), the combined organic phases were washed with saturated brine (1 x 50 mL), dried over Na_2SO_4

and the solvent was removed *in vacuo* to afford crude pale yellow oil **46** (5.09 g, pure according to TLC) to be used directly in the next step.

TLC: R_f (heptane : EtOAc, 2 : 1) = 0.66

D.3.4 2-((R)-(4-Fluorophenyl)(prop-2-yn-1-yloxy)methyl)oxirane (47)



46 $C_{12}H_{11}FO$ MW: 190.22

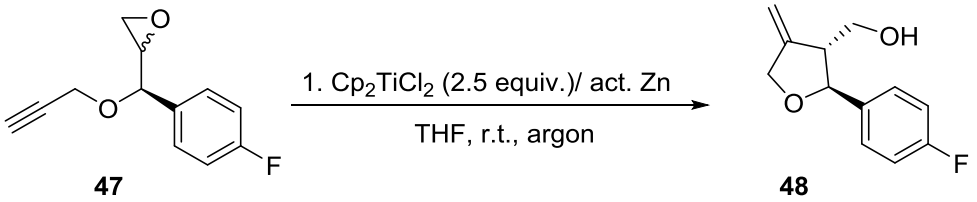
47 $C_{12}H_{11}FO_2$ MW: 206.22

A stirred solution of crude **46** (3.88 g) in CH_2Cl_2 (500 mL) was cooled with an ice bath and *m*CPBA (approximately 77 %, 20.5 g, 91.8 mmol, 4.5 equiv.) was added in small portions over 30 min. The reaction was allowed to warm to room temperature while stirring was continued for 31 h. As conversion was not complete according to TLC more mCPBA was added (purity approximately 77 %, 4.5 g, 20.4 mmol, 1 equiv.) and stirring continued for another 14 h to complete the conversion. Then a sufficient amount of aqueous Na_2SO_3 solution was added to destroy residual peroxy acid, which required cooling using an ice bath. In order to prove the absence of peroxide an iodine test was performed. Then an aqueous solution of Na_3PO_4 (30 g) in water (90 mL) was added to the mixture to adjust the pH to 8. The crude product was extracted with Et_2O (1 x 120 mL, 6 x 80 mL), the combined organic phases were washed with saturated brine (30 mL), dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. Then 100 mL Et_2O and 200 mL PE were added to the crude material and left in the fridge overnight in order to precipitate m-chlorbenzoic acid. After that the solid acid was filtered off with a sinter funnel and the solvent was evaporated *in vacuo*. This process was repeated once again using a mixture of 25 mL Et_2O and 75 mL PE and this afforded crude pale yellow oil **47**, purity approximately 80% according to NMR, which was directly used for the next step.

TLC: R_f (heptane : EtOAc, 2 : 1) = 0.48

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.44 (t, *J* = 2.4, 1H, H3'''), 2.46 – 2.91 (m, 2H, H1), 3.10-3.29 (m, 1H, H2), 3.88 – 4.38 (m, 2H, H1''), 4.55 (d, *J* = 4.4 Hz, 1H, H3), 6.97 – 7.15 (m, 2H, H3', H5'), 7.35 (dd, *J* = 8.2, 5.3, 2H, H2', H6').

D.3.5 ((2S,3R)-2-(4-Fluorophenyl)-4-methylenetetrahydrofuran-3-yl)methanol (48)



47 **48**

$C_{12}H_{11}FO_2$ MW: 206.22

$C_{12}H_{13}FO_2$ MW: 208.23

Bis(cyclopentadienyl)titanium(IV) dichloride (12.7 g, 51 mmol, 2.5 equiv.) and activated zinc dust (9.3 g, 142.8 mmol, 7.0 equiv.) were weight in and set under argon atmosphere *via* standard Schlenk technique (5x). Then dry and deoxygenated THF (275 mL) was added and the resulting suspension was stirred vigorously at room temperature for 1.5 h. After that the residual zinc was allowed to settle for 10 min, after which the green solution was transferred *via* a canula to a fast stirred solution of crude epoxide **47** (4.2 g) in dry and deoxygenated THF (150 mL) at room temperature over a period of 30 min. Stirring was continued for another 2 h, then dilute H_2SO_4 (10 %, 115 mL) was carefully added while the mixture was cooled with an ice bath. Afterwards most of the THF was removed *in vacuo* (down to 160 mbar at 50 °C). The obtained aqueous phase was extracted with Et_2O, the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (120 mL), saturated brine (120 mL), dried with Na_2SO_4, filtered and the solvent was removed from the filtrate *in vacuo*.

Flash column chromatography was performed on the entire batch in sequence as follows: 90 g SiO_2 separation column, 40 mL/min, EtOAc in LP: 0 to 30 % within 2 h.
After that a second flash column chromatography was conducted using the method: 90 g SiO_2 separation column, 40 mL/min, DCM in LP: 60 to 100 % for 40 min and immediately after completing 90 % DCM/1 0 % MeOH for 20 min was applied.

Yield: 1.1 g (26 % over 3 steps)

Appearance: light yellow oil

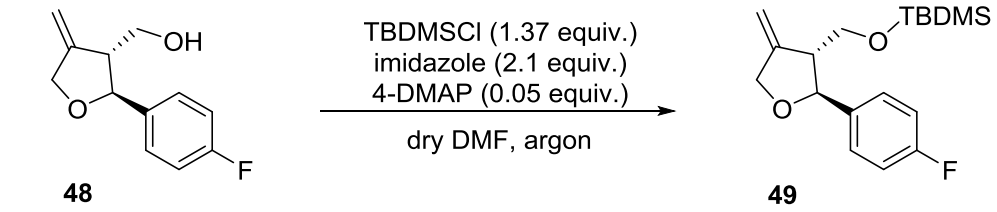
TLC: R_f (heptane : EtOAc, 1 : 1) = 0.50

Specific rotation: $[\alpha]_D^{25}$: +7.7° (MeOH; 0.96 g/100 mL)

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.66-2.83 (m, 1H, H3), 3.62 – 3.95 (m, 2H, H3a), 4.43 (dq, *J* = 13.4, 2.3 Hz, 1H, H5), 4.61 (dt, *J* = 13.2, 2.4 Hz, 1H, H5), 4.85 (d, *J* = 7.2 Hz, 1H, H2), 5.09 (dq, *J* = 9.8, 2.3 Hz, 2H, H4a), 6.93 – 7.15 (m, 2H, H3', H5'), 7.21 – 7.46 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$) δ 54.2 (d, C3), 62.0 (t, C3a), 71.5 (t, C5), 82.9 (d, C2), 105.4 (t, C4a), 115.5 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 128.1 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 137.1 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 148.6 (s, C4), 162.5 (d, C4', $^1J_{C\text{-}F}$ = 245.9 Hz).

D.3.6 tert-Butyl(((2S,3R)-2-(4-fluorophenyl)-4-methylenetetrahydrofuran-3-yl)methoxy)dimethylsilane (49)



48

$C_{12}H_{13}FO_2$
MW: 208.23

49

$C_{18}H_{27}FO_2Si$
MW: 322.50

To a 100 mL flask containing a stirred solution of **48** (1.1 g, 5.28 mmol, 1 equiv.), imidazole (755.2 mg, 11.09 mmol, 2.1 equiv) and 4-dimethylaminopyridine (32.3 mg, 2.64 mmol, 0.05 equiv.) in 33 mL dry DMF under Ar atmosphere a *tert*-butylchlorodimethylsilane solution (2.14 mL, 3 M in THF, 7.24 mmol, 1.37 equiv.) was added dropwise. The mixture was stirred at room temperature for 18.5 h. After that 80 mL Et_2O was added followed by 40 mL saturated aqueous NH_4Cl solution. The layers were separated and the aqueous phase was extracted four times with Et_2O. The combined layers were washed with saturated aqueous $NaHCO_3$ solution, brine and dried with Na_2SO_4, filtered and solvents were removed *in vacuo* to afford the crude **49**, which was directly used in the next step.

Yield: 1.5 g 85% purity containing 1.3g (78 %) product

Appearance: light yellow oil

TLC: R_f (heptane : EtOAc, 20 : 1) = 0.36

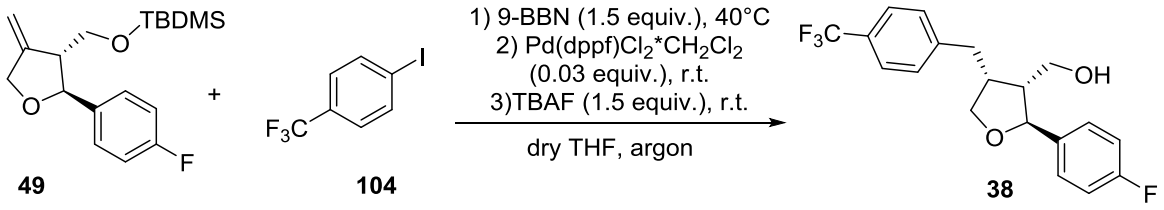
HRMS (ESI$^+$): exact mass calculated for $C_{12}H_{13}FO_2$+H^+: 323.1837, found: 323.1843, Δ = 1.93 ppm.

GC MS (EI, 70 eV) RT: 7.89 min (method B), main signals (rel. int.): 265 (68), 237 (19), 235 (25), 217 (25), 190 (53), 173 (75), 161 (100), 146 (34), 141 (28), 122 (47), 109 (38), 105 (15), 89 (20), 75 (39), 73 (46). M^+ not visible.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H, $OSi(CH_3)_2$), 0.88 (s, 9H, $OSiC(CH_3)_3$), 2.68 – 2.84 (m, 1H, H3), 3.69 – 3.78 (m, 2H, C3a), 4.35 – 4.47 (m, 1H, H5), 4.49 – 4.62 (m, 1H, H5), 4.89 (d, ^3J = 6.2 Hz, 1H, H2), 4.98 – 5.07 (m, 2H, C4a), 6.95 – 7.10 (m, 2H, H3', H5'), 7.26 – 7.41 (m, 2H, H2', H6').

D.4 Variation of the Benzylic Position

D.4.1 ((2S,3R,4R)-2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methanol (38)



49 $C_{18}H_{27}FO_2Si$ MW: 322.50

104 $C_7H_4F_3I$ MW: 272.01

38 $C_{19}H_{18}F_4O_2$ MW: 354.34

Compound **49** (588.22 mg, 1.55 mmol, 1 equiv.) was charged into a reaction flask equipped with a stirring bar and set under Ar atmosphere using standard Schlenk technique(4x). Then 9-BBN (4.64 mL, 0.5 M in THF, 2.32 mmol, 1.5 equiv.) was added *via* syringe and stirred at 40 °C for 24 hours. Then the reaction vessel was briefly opened to add Cs_2CO_3 (1.77 g, 5.43 mmol, 3.5 equiv.) and $Pd(dppf)Cl_2*CH_2Cl_2$ (31.66 g, 0.04 mmol, 0.025 equiv.). Afterwards 4-iodobenztrifluoride (296.18 µL, 2.02 mmol, 1.3 equiv.) was added using a syringe and the reaction mixture was stirred at room temperature for 48 h. Subsequently TBAF (0.94 mL, 1 M THF, 0.94 mmol, 1.5 euqiv.) was added *via* syringe and stirring was continued for another 24h at room temperature. After that DCM was added to the reaction mixture and the solution was filtered through a sinter funnel. All solvents were removed *in vacuo* and the resulting crude material was purified using MPLC column chromatography (90 g SiO_2, 40 mL/min, 15-35 % EtOAc in LP within 70 min – applied twice).

Purification: MPLC: 90 g SiO_2, 40 mL/min, 15-35 % EE in LP within 70 min; applied twice

Yield: 293.1 mg (53 %)

Appearance: off white crystals

Melting point: 104-106 °C

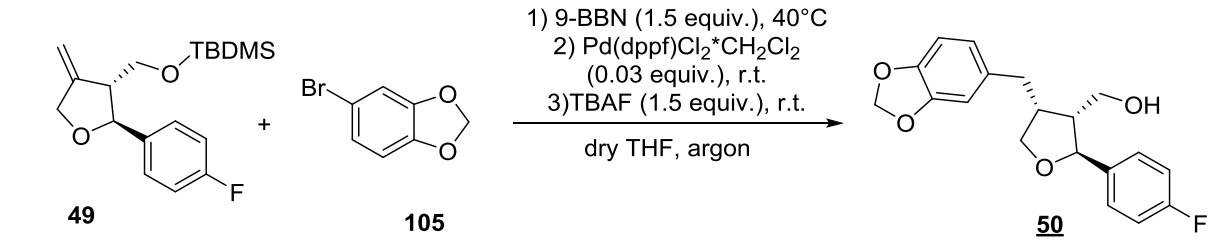
TLC: R_f (heptane : EtOAc, 1 : 1) = 0.50

Specific rotation: $[\alpha]_D^{23}$: +12.0° (MeOH; 1.36 g/100 mL)

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.84 (bs, 1H, OH), 2.36 (quint, ^3J = 6.6 Hz, 1H, H3), 2.59 – 2.85 (m, 2H, H4, H4a), 2.90 – 3.11 (m, 1H, H4a), 3.64 – 3.96 (m, 3H, 2 x H3a, H5), 4.03 (dd, ^2J = 8.5 Hz, ^3J = 6.2 Hz, 1H, H5), 4.87 (d, ^3J = 6.1 Hz, 1H), 7.01 (dd, ^3J = 8.7 Hz, $^3J_{H-F}$ = 8.7 Hz, 2H, H3', H5'), 7.20 – 7.35 (m, 4H, H2', H6', H2'', H6''), 7.54 (d, ^3J = 8.2 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$) δ 33.4 (t, C4a), 42.1 (d, C4), 52.6 (d, C3), 60.7 (t, C3a), 72.8 (t, C5), 82.4 (d, C2), 115.4 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.4 Hz), 124.4 (q, C4''$\underline{C}F_3$, $^1J_{C\text{-}F}$ = 271.9 Hz), 125.6 (dq, C3'', C5'', $^3J_{C\text{-}F}$ = 3.8 Hz), 127.4 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 128.8 (q, C4'', $^2J_{C\text{-}F}$ = 32.4 Hz), 129.1 (d, C2'', C6''), 138.8 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 144.7 (q, C1'', $^5J_{C\text{-}F}$ = 1.3 Hz), 162.3 (d, C4', $^1J_{C\text{-}F}$ = 245.4 Hz).

D.4.2 ((2S,3R,4R)-4-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methanol (<u>50</u>)



49
$C_{18}H_{27}FO_2Si$
MW: 322.50

105
$C_7H_5BrO_2$
MW: 201.02

<u>50</u>
$C_{19}H_{19}FO_4$
MW: 330.3554

49 (117.64 mg, 0.31 mmol, 1 equiv.) was weight in a reaction flask equipped with a stirring bar and set under Ar atmosphere using standard Schlenk (4x) technique. Then 9-BBN (0.9 mL, 0.5 M in THF, 0.47 mmol, 1.5 equiv.) was added *via* syringe and stirred at 40 °C for 24 hours. Then the reaction vessel was briefly opened to add Cs_2CO_3 (353.5 mg, 1.09 mmol, 3.5 equiv.) and $Pd(dppf)Cl_2*CH_2Cl_2$ (6.32 mg, 7.75 µmol, 0.025 equiv.). Afterwards, 5-bromobenzo-1,3-dioxol (48.5 µL, 0.40 mmol, 1.3 equiv.) was added using a syringe and the reaction mixture was stirred at room temperature for 48 h. Subsequently TBAF (0.47 mL, 1 M THF, 0.47 mmol, 1.5 euqiv.) was added *via* syringe and stirring continued for another 24 h at room temperature. After that DCM was added to the reaction mixture and the solution was filtered through a sinter funnel. All solvents were removed in vacuo and the resulting crude material was purified using MPLC column chromatography (18 g SiO_2, 20 mL/min, 10-25 % EtOAc in LP within 60min).

Yield: 64.5 mg (63 %)

Appearance: yellow oil

TLC: R_f (heptane : EtOAc, 1 : 1) = 0.38

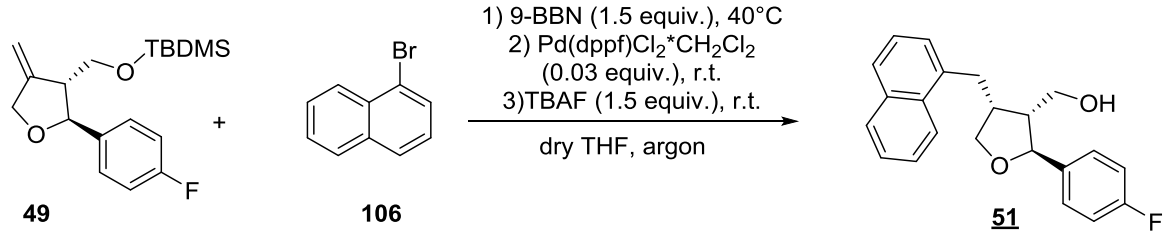
Specific rotation: $[\alpha]_D^{20}$: +3.3° (MeOH; 2.56 g/100 mL)

HRMS (ESI+): exact mass calculated for $C_{19}H_{19}FO_4$+H^+: 331.1340. Found: 331.1361. [M+ H^+], Δ = 6.41ppm

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (bs, 1H, OH), 2.28 (quint, *J* = 6.8 Hz, 1H, H3), 2.36 – 2.74 (m, 2H, H4, H4a), 2.80 (dd, *J* = 12.6, 4.6 Hz, 1H, H4a), 3.52 – 3.94 (m, 3H, 2 x H3a, H5), 3.99 (dd, *J* = 8.6, 6.4 Hz, 1H, H5), 4.80 (d, *J* = 6.0 Hz, 1H, H2), 5.86 (s, 2H, H4''), 6.45 – 6.73 (m, 3H, H2'', H6'', H7''), 6.80 – 7.06 (m, 2H, H3', H5'), 7.12 – 7.30 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$) δ 33.2 (t, C4a), 42.3 (d, C4), 52.6 (d, C3), 60.8 (t, C3a), 73.0 (t, C5), 82.4 (d, C2), 100.9 (t, C4''), 108.3 (d, C2''*), 108.9 (d, C6''*), 115.2 (dd, $^{2}J_{C\text{-}F}$ = 21.4 Hz, C3', C5'), 121.4 (d, C7''), 127.3 (dd, C2', C6', $^{3}J_{C\text{-}F}$ = 8.1 Hz), 134.1 (s, C1''), 138.8 (d, C1', $^{4}J_{C\text{-}F}$ = 3.0 Hz), 145.9 (s, C5a''), 147.8 (s, C2a''), C4' not visible.

D.4.3 ((2S,3R,4R)-2-(4-Fluorophenyl)-4-(naphthalen-1-ylmethyl)tetrahydrofuran-3-yl)methanol (51)



49 $C_{18}H_{27}FO_2Si$ MW: 322.50

106 $C_{10}H_7Br$ MW: 207.07

51 $C_{22}H_{21}FO_2$ MW: 336.41

87 (128.8mg, 0.4mmol, 1equiv.) was weight in a reaction flask equipped with a stirring bar and set under Ar atmosphere using standard Schlenk (4x) technique. Then 9-BBN (1.2mL, 0.5M in THF, 0.6mmol, 1.5equiv.) was added *via* syringe and stirred at 40 °C for 24 hours. Then the reaction vessel was briefly opened to add Cs_2CO_3 (456.15mg, 1.4mmol, 3.5equiv.) and $Pd(dppf)Cl_2*CH_2Cl_2$ (8.17mg, 0.01mmol, 0.025equiv.). Afterwards 1-bromonaphtalin (72.8µL, 0.52mmol, 1.3equiv.) was added using a syringe and the reaction mixture was stirred at room temperature for 48h. Subsequently TBAF (0.6mL, 1M THF, 0.6mmol, 1.5euqiv.) was added *via* syringe and the stirring continued for another 24h at room temperature. After that DCM was added to the reaction mixture and the solution was filtered through a sinter funnel. All solvents were removed in *vacuo* and the resulting crude material was purified using MPLC column chromatography (18g SiO_2, 20mL/min, 10-35% EtOAc in heptane within 70min). Following this step 1mL MeOH was added to the product with minor impurities and stored at -30°C for 7 days for crystallization. Afterwards the solvent was carefully removed using a Pasteur pipette and washed with 3 mL MeOH. Finally the product **45** was dried in *vacuo*.

Yield: 29.4mg (21.8%)

Appearance: off white crystals

Melting point: 131-132°C

TLC: R_f (heptane : EtOAc, 1 : 1) = 0.50

Specific rotation: $[\alpha]_D^{20}$: +19.1° (MeOH; 0.85 g/100mL)

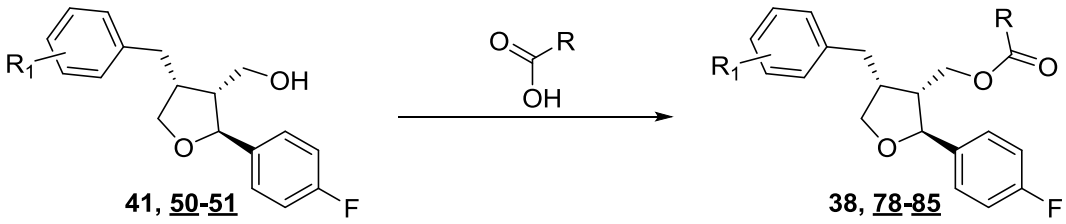
HRMS (ESI+): exact mass calculated for $C_{22}H_{21}FO_2+H^+$: 337.1599. Found: 337.1607. [M+ H^+], Δ = 2.44ppm

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (bs, 1H, OH), 2.47 (qint, ^3J = 6.9 Hz, 1H, H3), 2.85 – 3.00 (m, 2H, H4, H4a), 3.64 – 3.51 (m, 1H, H4a), 3.82 – 3.98 (m, 3H, 2 x H3a, H5), 3.99-4.10 (m, 1H, H5), 4.88 (d, *J* = 7.2 Hz, 1H, H2), 7.01 (t, ^3J = 8.7 Hz, $^3J_{H-F}$ = 8.7 Hz, 2H, H3', H5'), 7.20 – 7.38 (m, 3H, H2', H6', H2''), 7.32 – 7.46 (m, 1H, H3''), 7.50 (pd, *J* = 6.8, 1.5 Hz, 2H, H6'', H7''), 7.74 (d, *J* = 8.0 Hz, 1H, H4''), 7.86 (dd, *J* = 7.3, 2.1 Hz, 1H, H5''), 8.10 (dd, *J* = 7.7, 1.7 Hz, 1H, H8'')

^{13}C NMR (101 MHz, $CDCl_3$) δ 30.4 (t, C4a), 41.7 (d, C4), 53.4 (d, C3), 60.9 (t, C3a), 73.1 (t, C5), 82.3 (d, C2), 115.4 (dd, $^2J_{C-F}$ = 21.4 Hz, C3', C5'), 123.8 (d, C8''), 125.6 (d, C2''*), 125.8 (d, C3''*), 126.2 (d, C6''), 126.7 (d, C7''), 127.3 (d,C4''), 127.6 (dd, C2', C6', $^3J_{C-F}$ = 8.1 Hz), 129.0 (d, C5''), 132.0 (s, C8a''), 134.1 (s, C4a''), 136.5 (s, C1''), 139.0 (d, C1', $^4J_{C-F}$ = 3.1 Hz), 162.3 (d, C4', $^1J_{C-F}$ = 245.3 Hz)

D.5 General Procedure

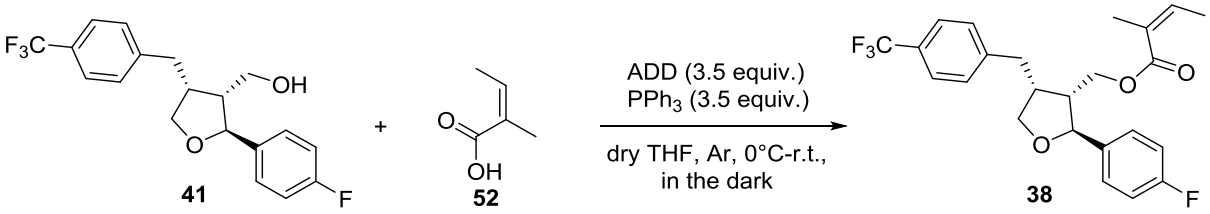
D.5.1 General Prodcedure A



The substrate (1 equiv.), carboxylic acid (1.5 equiv.) and PPh_3 (3.5 equiv.) were charged into a reaction vessel equipped with a stirring bar and set under Ar atmosphere using standard Schlenk technique (4 x) prior to adding THF. Afterwards ADD (3.5 equiv.) dissolved in 1.5 mL dry THF was added dropwise to the reaction mixture, which was cooled with an ice bath. The mixture stirred for two days while being allowed to warm up to room temperature. Subsequently DCM and SiO_2 were added, after that all solvents were removed *in* vacuo and further purification was carried out using MPLC flash column chromatography. The method used is noted at each product.

D.6 Variation of the Ester Functionality

D.6.1 ((2S,3R,4R)-2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl (Z)-2-methylbut-2-enoate (38)



$C_{19}H_{18}F_4O_2$ MW: 354.34 | $C_5H_8O_2$ MW: 100.12 | $C_{24}H_{24}F_4O_3$ MW: 436.45

Prepared according to general procedure A using **41** as starting material (35.1 mg, 99.05 µmol) and angelic acid as reagent in the dark.

Purification: MPLC: 9 g SiO_2, 20 mL/min, 2-10 % EE in LP within 30 min.

Yield: 21 mg (50.2 %)

Appearance: colorless oil

TLC: R_f (heptane : EtOAc, 3 : 1) = 0.42

HRMS (ESI+): exact mass calculated for $C_{19}H_{18}F_4O_2$+H^+:437.1734. Found: 437.1756. [M+ H^+], Δ = 5.03ppm

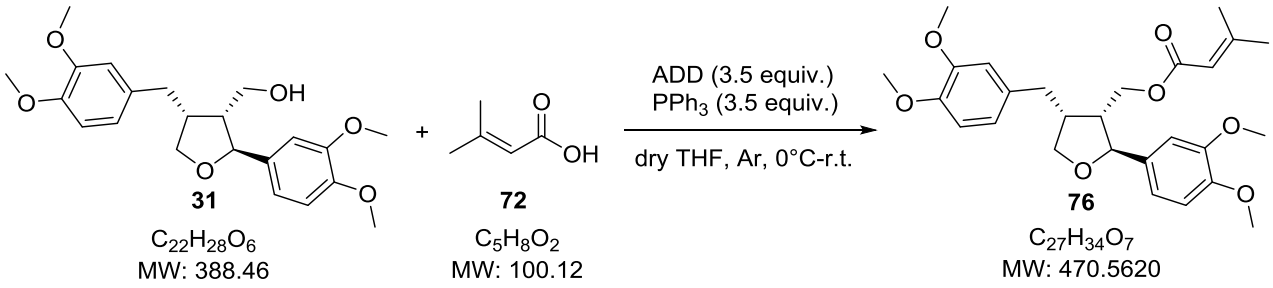
Specific rotation: $[\alpha]_D^{20}$: +13.8° (iPrOH; 1.02 g/100 mL)

GC-MS (EI, 70 eV): RT: 8.11 min (method C), Main signals (rel. int): 336 (20), 212 (16), 185 (16), 177 (78), 164 (20), 159 (*p*-trifluoromethylbenzyl, 73), 125 (39), 123 (100), 109 (35). M^+ not visible.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.83 – 1.90 (m, 3H, H5'''), 2.00 (dq, ^3J = 7.2 Hz, ^5J = 1.5 Hz, 3H, H4'''), 2.50 – 2.96 (m, 3H, H3, H4, H4a), 2.93 – 3.06 (m, 1H, H4a), 3.75 (dd, ^2J = 8.7 Hz, ^3J = 6.0 Hz, 1H, H5), 4.07 (dd, ^2J = 8.7 Hz, ^3J = 6.0 Hz, 1H, H5), 4.27 (dd, ^2J = 11.4 Hz, ^3J = 6.9 Hz, 1H, H3a), 4.41 (dd, ^2J = 11.4 Hz, ^3J = 6.9 Hz, 1H, H3a), 4.89 (d, ^3J = 6.2 Hz, 1H, H2), 6.12 (qq, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H, H3'''), 6.95 – 7.11 (m, 2H, H3', H5'), 7.22 – 7.36 (m, 4H, H2', H6', H2'', H6''), 7.56 (d, ^3J = 8.2 Hz, 2H, H3'', H5'').

^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8 (q, C4'''), 20.6 (q, C5'''), 33.4 (t, C4a), 42.2 (d, C4), 49.4 (d, C3), 61.9 (t, C3a), 72.5 (t, C5), 82.5 (d, C2), 115.4 (dd, C3', C5', $^2J_{C\text{-}F}$ = 21.5 Hz), 124.2 (q, C4''$\underline{C}F_3$, $^1J_{C\text{-}F}$ = 271.9 Hz), 125.6 (dq, C3'', C5'', $^3J_{C\text{-}F}$ = 3.7 Hz), 127.2 (s, C2'''), 127.3 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 128.8 (q, C4'', $^2J_{C\text{-}F}$ = 32.5 Hz), 128.9 (d, C2'', C6''), 138.0 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 139.3 (d, C3'''), 144.1 (q, C1'', $^5J_{C\text{-}F}$ = 1.1 Hz), 162.3 (d, C4', $^1J_{C\text{-}F}$ = 245.8 Hz), 167.6 (s, C1''').

D.6.2 ((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)tetrahydrofuran-3-yl)methyl 3-methylbut-2-enoate (76)



31 $C_{22}H_{28}O_6$ MW: 388.46 + **72** $C_5H_8O_2$ MW: 100.12 → **76** $C_{27}H_{34}O_7$ MW: 470.5620

Lariciresinol dimethyl ether (34mg, 87.5µmol, 1equiv.), 3,3-dimethylacrylic acid (13.2mg, 0.13mmol, 1.5equiv.) and PPh_3 (80.4mg, 0.31mmol, 3.5equiv.) were charged into a reaction vessel equipped with a stirring bar and set under Ar atmosphere using standard Schlenk technique (4x). Then THF was added and the mixture was cooled using an ice bath. ADD (77.3mg, 0.31mmol, 3.5equiv.) dissolved in 1.5 mL dry THF was added dropwise to the reaction mixture, which was stirred for two days while being allowed to warm up to room temperature. Subsequently DCM was added and the obtained mixture was purified using flash column chromatography (MPLC, 9g SiO_2 separation column, 20L/min, EtOAc in LP: 10 to 50% within 30 min – applied twice)

Yield: 23.7mg (57.6%) (yield after first column 35.1mg – 85.2% with minor impurities)

Apperience: pale yellow oil

TLC: R_f (heptane: EtOAc, 1:1)=0.38

HRMS (ESI+): exact mass calculated for $C_{27}H_{34}O_7$+Na^+: 493.2197. Found: 493.2201. [M+ Na^+], Δ = 0.81 ppm.

Specific rotation: $[\alpha]_D^{20}$: +29.2° (MeOH; 1.63 g/100mL)

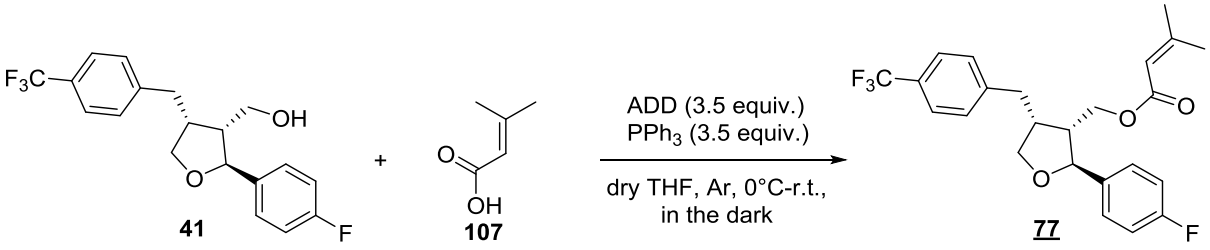
GC MS: (EI, 70 eV) RT: 25.73 min (method C), main signals (rel. int.): 470.2 (M^+, 2), 219.1 (29), 189.1 (17), 177.1 (16), 166.1 (15), 165.0 (89), 152.1 (15), 151.1 (100), 107.0 (18).

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.90 (d, ^4J = 1.1 Hz, 3H, H4b'''), 2.17 (d, ^4J = 1.1 Hz, 3H, H4a'''), 2.47 – 2.84 (m, 3H, H3, H4, H4a), 2.89 (dd, ^2J = 12.6 Hz, ^3J = 4.3 Hz, 1H, H4a), 3.75 (dd, ^2J = 8.6 Hz, ^3J = 6.4 Hz, 1H, H5), 3.86 (s, 3H, Ar-OCH_3), 3.87 (s, 6H, Ar-OCH_3), 3.88 (s, 3H, Ar-OCH_3), 4.07 (d, ^2J = 8.5 Hz, ^3J = 6.2 Hz, 1H, H5), 4.21 (dd, ^2J = 11.3 Hz, ^3J = 6.9 Hz, 1H, H3a), 4.37 (dd, ^2J = 11.3 Hz, ^3J = 7.1 Hz, 1H, H3a), 4.81 (d, ^3J = 6.3 Hz, 1H, H2), 5.62 – 5.68 (m, 1H, H2'''), 6.67 – 6.91 (m, 6H, Ar-H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 20.4 (q, C4b'''), 27.6 (q, C4a'''), 33.3 (t, C4a), 42.7 (d, C4), 49.3 (d, C3), 56.0 (q, Ar-OCH_3), 56.0 (q, Ar-OCH_3), 56.0 (q, Ar-OCH_3), 56.1 (q, Ar-OCH_3), 61.8 (t, C3a), 72.9 (t, C5), 83.1 (d, C2), 109.0 (d, C2'), 111.1 (d, C5'), 111.5 (d, C5''*), 112.1 (d, C2''*), 115.7 (d, C2'''), 118.2 (d, C6'), 120.6 (d,

C6''), 132.9 (s, C1''), 135.2 (s, C1'), 147.6 (s, C4''), 148.5 (s, C4'), 149.1 (s, C3''), 149.1 (s, C3'), 157.7 (s, C3'''), 166.6 (s, C1''').

D.6.3 ((2S,3R,4R)-2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl 3-methylbut-2-enoate (77)



$C_{19}H_{18}F_4O_2$
MW: 354.34

$C_5H_8O_2$
MW: 100.12

$C_{24}H_{24}F_4O_3$
MW: 436.45

Prepared according to general procedure A using **41** as starting material (35.8 mg, 0.10 mmol) and 3,3-dimethylacrylic acid as reagent in the dark.

Purification: MPLC: 9 g SiO_2, 20 mL/min, 2-10 % EtOAc in LP within 30 min.

Yield: 36.7 mg (83 %)

Appearance: colorless oil

TLC: R_f (heptane : EtOAc, 1 : 1) = 0.75

HRMS (ESI+): exact mass calculated for $C_{24}H_{24}F_4O_3+H^+$: 437.1735. Found: 473.1752. [M+ H^+], Δ = 3.94ppm

Specific rotation: $[\alpha]_D^{20}$: +8.5° (MeOH; 1.81 g/100 mL)

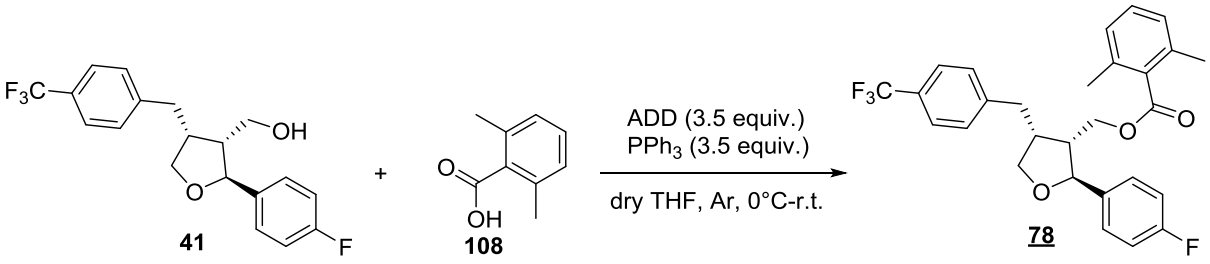
GC MS (EI, 70 eV): RT: 8.07 min (method A), Main signals (rel. int.): 353 (5), 336 (22), 212 (13), 198 (7), 197 (10), 185 (10), 177 (52), 164 (14), 159 (33), 143 (8), 138 (10), 125 (30), 123 (78), 109 (24), 83 (100), 55 (21). M^+ not visible.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.91 (d, *J* = 1.3 Hz, 3H, H4b'''), 2.17 (d, *J* = 1.3 Hz, 3H , H4a'''), 2.42 – 2.90 (m, 3H, H3, H4, H4a), 2.92 – 3.06 (m, 1H, H4a), 3.73 (dd, *J* = 8.7, 6.3 Hz, 1H, H5), 3.98 – 4.15 (m, 1H , H5), 4.21 (dd, *J* = 11.4, 7.0 Hz, 1H, H3a), 4.35 (dd, *J* = 11.4, 7.1 Hz, 1H, H3a), 4.86 (d, *J* = 6.1 Hz, 1H, H2), 5.63 (p, *J* = 1.3 Hz, 1H, H2'''), 7.02 (t, *J* = 8.7 Hz, 2H, H3', H5'), 7.20 – 7.42 (m, 4H, H2', H6', H2'', H6''), 7.55 (d, *J* = 8.1 Hz, 2H, H3'', H5'').

^{13}C NMR (50 MHz, $CDCl_3$) δ 20.4 (q, C4b'''), 27.6 (q, C4a'''), 33.5 (t, C4a), 42.2 (d, C4), 49.5 (d, C3), 61.5 (t, C3a), 72.8 (t, C5), 82.7 (d, C2), 115.4 (dd, $^2J_{C\text{-}F}$ = 21.5 Hz, C3', C5'), 115.4 (d, C2'''), 124.3 (q, C4''$\underline{C}F_3$, $^1J_{C\text{-}F}$ = 271.9 Hz), 125.7 (dq, C3'', C5'', $^3J_{C\text{-}F}$ = 3.7 Hz), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 128.9 (q, C4'', $^2J_{C\text{-}F}$ = 32.3

Hz), 129.0 (d, C2'', C6''), 138.3 (d, C1', $^{4}J_{C\text{-}F}$ = 3.1 Hz), 144.4 (q, C1'', $^{5}J_{C\text{-}F}$ = 1.2 Hz), 158.2 (s, C3'''), 162.4 (d, C4', $^{1}J_{C\text{-}F}$ = 245.5 Hz), 166.5 (s, C1''').

D.6.4 ((2S,3R,4R)-2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl 2,6-dimethylbenzoate (78)



$C_{19}H_{18}F_4O_2$ MW: 354.34 | $C_9H_{10}O_2$ MW: 150.18 | $C_{28}H_{26}F_4O_3$ MW: 486.51

Prepared according to general procedure A using **41** as starting material (32.2 mg, 0.09 mmol) and 2,6-dimethylbenzoic acid as reagent.

Purification: MPLC: 9 g SiO_2, 20mL/min, 2-10 % EE in LP within 30 min.

Yield: 36.2 mg (82 %)

Appearance: colorless oil

TLC: R_f (heptane : EtOAc, 1 : 1) = 0.75

HRMS (ESI-): exact mass calculated for $C_{28}H_{26}F_4O_3$+$COOH^-$: 533.1864. Found: 533.1869. [M+ $COOH^-$], Δ = 0.94ppm

Specific rotation: $[\alpha]_D^{20}$: +13.8° (MeOH; 1.20 g/100mL)

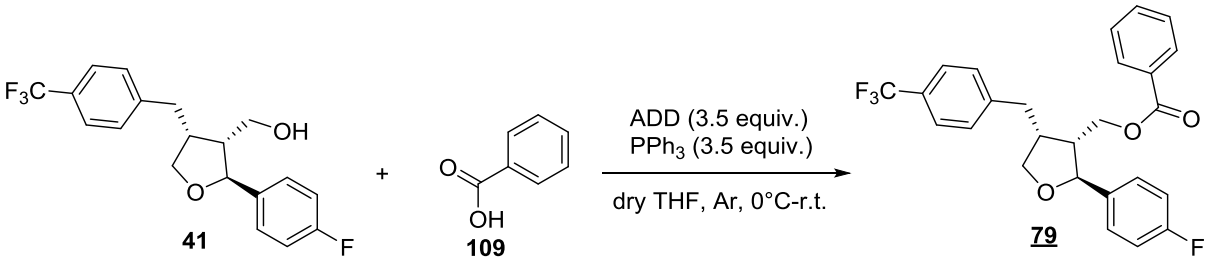
GC MS (EI, 70 eV) RT: 9.95 min (method A), main signals (rel. int.): 353 (7) 336 (35), 212 (16), 185 (13), 177 (59), 164 (16), 159 (55), 133 (100), 132 (21), 125 (37), 123 (71), 109 (24), 105 (40), 103 (12), 79 (14), 77 (13). M^+ not visible.

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.29 (s, 6H, C3'''$\underline{CH_3}$, C7'''$\underline{CH_3}$), 2.50 – 2.91 (m, 3H, H3, H4, H4a), 3.03 (m, 1H, H4a), 3.73 (dd, *J* = 8.8, 6.0 Hz, 1H, H5), 4.04 (dd, *J* = 8.8, 6.0 Hz, 1H, H5), 4.41 (dd, *J* = 11.3, 6.7 Hz, 1H, H3a), 4.62 (dd, *J* = 11.3, 7.2 Hz, 1H, H3a), 4.90 (d, *J* = 6.0 Hz, 1H, H2), 6.88 – 7.11 (m, 4H, H3', H5', H4''', H6'''), 7.12 – 7.39 (m, 5H, H2', H6', H2'', H6'', H5'''), 7.53 (d, *J* = 8.1 Hz, 2H, H3'', H5'').

^{13}C NMR (101 MHz, $CDCl_3$) δ – 20.0 (q, C3'''$\underline{CH_3}$, C7'''$\underline{CH_3}$), 33.5 (t, C4a), 42.2 (d, C4), 49.7 (d, C3), 62.9 (t, C3a), 72.6 (t, C5), 82.6 (d, C2), 115.6 (dd, $^{2}J_{C\text{-}F}$ = 21.4 Hz, C3', C5'), 124.3 (q, C4''$\underline{C}F_3$, $^{1}J_{C\text{-}F}$ = 271.8 Hz), 125.8

(dq, C3'', C5'', $^{3}J_{C\text{-}F}$ = 3.8 Hz), 127.4 (dd, C2', C6', $^{3}J_{C\text{-}F}$ = 8.1 Hz), 127.9 (d, C4''', C6'''), 129.0 (q, C4'', $^{2}J_{C\text{-}F}$ = 32.4 Hz), 129.0 (d, C2'', C6''), 129.7 (d, C5'''), 133.6 (s, C2'''), 135.0 (s, C3''', C7'''), 138.0 (d, C1', $^{4}J_{C\text{-}F}$ = 3.2 Hz), 144.1 (q, C1'', $^{5}J_{C\text{-}F}$ = 1.3 Hz), 162.5 (d, C4', $^{1}J_{C\text{-}F}$ = 245.8 Hz), 170.1 (s, C1'''=O)

D.6.5 ((2S,3R,4R)-2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl benzoate (79)



$C_{19}H_{18}F_4O_2$ MW: 354.34 | $C_7H_6O_2$ MW: 122.12 | $C_{26}H_{22}F_4O_3$ MW: 458.45

Prepared according to general procedure A using **41** as starting material (35.8 mg, 0.10 mmol) and benzoic acid as reagent.

Purification: MPLC: 9 g SiO_2, 20 mL/min, 2-10 % EE in LP within 30 min.

Yield: 37 mg (78 %)

Appearance: colorless crystals

Melting point: 106-107 °C

TLC: R_f (heptane : EtOAc, 1 : 1) = 0.75

HRMS (ESI+): exact mass calculated for $C_{26}H_{22}F_4O_3$+H^+: 459.1578. Found: 459.1574. [M+ H^+], Δ = -0.82ppm

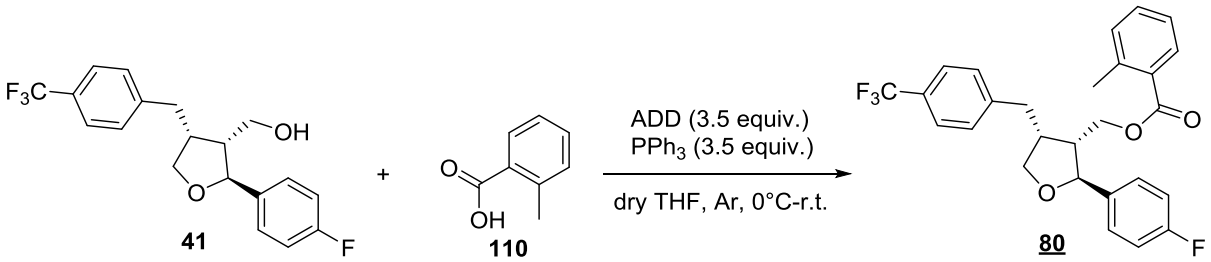
Specific rotation: $[\alpha]_D^{20}$: +13.9° (MeOH; 1.20 g/100mL)

GCMS (EI, 70 eV) RT: 8.07 min (method A), main signals (rel. int.): 353 (5), 336 (22), 212 (13), 198 (7), 197 (10), 185 (10), 177 (52), 164 (14), 159 (33), 143 (8), 138 (10), 125 (30), 123 (78), 109 (24), 83 (100), 55 (21). M^+ not visible.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 – 2.92 (m, 3H, H3, H4, H4a), 3.04 (dd, ^{2}J = 13.2, ^{3}J = 4.8 Hz, 1H, H4a), 3.79 (dd, ^{2}J = 8.7, ^{3}J = 6.5 Hz, 1H, H5), 4.12 (dd, ^{2}J = 8.8, ^{3}J = 6.4 Hz, 1H, H5), 4.46 (dd, ^{2}J = 11.4, ^{3}J = 7.2 Hz, 1H, H3a), 4.61 (dd, ^{2}J = 11.3, ^{3}J = 6.6 Hz, 1H, H3a), 4.95 (d, ^{3}J = 6.3 Hz, 1H, H2), 7.02 (t, J = 8.6 Hz, 2H, H3', H5'), 7.27 – 7.36 (m, 4H, H2', H6', H2'', H6''), 7.43 (t, ^{3}J = 7.8 Hz, 2H, H4''', H6'''), 7.49 – 7.61 (m, 3H, H3'', H5'', H5'''), 7.91 (dd, ^{3}J = 8.4, ^{4}J = 1.4 Hz, 2H, H3''', H7''')

^{13}C NMR (101 MHz, $CDCl_3$) δ 33.5 (t, C4a), 42.2 (d, C4), 49.4 (d, C3), 63.0 (t, C3a), 72.7 (t, C5), 82.9 (d, C2), 115.4 (dd, $^{2}J_{C\text{-}F}$ = 21.7 Hz, C3', C5'), 124.2 (q, C4''$\underline{C}F_3$, $^{1}J_{C\text{-}F}$ = 271.9 Hz), 125.6 (dq, C3'', C5'', $^{3}J_{C\text{-}F}$ = 3.8 Hz), 127.5 (dd, C2', C6', $^{3}J_{C\text{-}F}$ = 8.1 Hz), 128.5 (d, C4''', C6'''), 128.9 (q, C4'', $^{2}J_{C\text{-}F}$ = 32.4 Hz), 128.9 (d, C2'', C6''), 129.5 (d, C3''', C7'''), 129.7 (s, C2'''), 133.3 (d, C5'''), 138.0 (d, C1', $^{4}J_{C\text{-}F}$ = 3.0 Hz), 144.0 (q, C1'', $^{5}J_{C\text{-}F}$ = 1.1 Hz), 162.3 (d, C4', $^{1}J_{C\text{-}F}$ = 245.8 Hz), 166.4 (s, C1'''=O)

D.6.6 ((2S,3R,4R)-2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl 2-methylbenzoate (<u>80</u>)



$C_{19}H_{18}F_4O_2$
MW: 354.34

$C_8H_8O_2$
MW: 136.15

$C_{27}H_{24}F_4O_3$
MW: 472.48

Prepared according to general procedure A using **41** as starting material (35.8 mg, 0.10 mmol) and *o*-toluic acid as reagent.

Purification: MPLC: 9 g SiO_2, 20 mL/min, 2-10 % EtOAc in LP within 30 min.

Yield: 42 mg (88 %)

Appearance: colorless oil

TLC: R_f (heptane : EtOAc, 1 : 1) = 0.75

HRMS (ESI+): exact mass calculated for $C_{27}H_{24}F_4O_3$+H^+: 473.1735. Found: 473.1736. [M+ H^+], Δ = 0.26ppm

Specific rotation: $[\alpha]_D^{20}$: +13.3° (MeOH; 1.39 g/100mL)

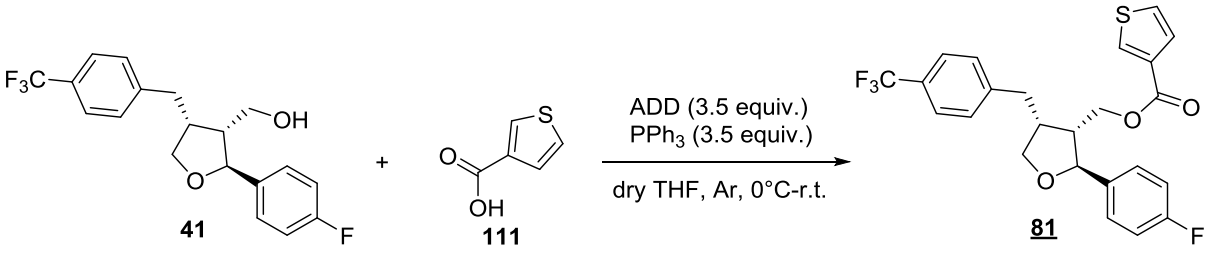
GC MS (EI, 70 eV) RT: 9.90 min (method A), main signals (rel. int.): 353 (4), 336 (22), 212 (15), 197 (11), 185 (11), 177 (56), 164 (15), 159 (44), 135 (11), 133 (13), 125 (34), 123 (76), 119 (100), 109 (26), 91 (50), 65 (12). M^+ not visible.

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.59 (s, 3H, C3'''$\underline{CH_3}$), 2.62 – 2.98 (m, 3H, H3, H4, H4a), 3.05 (dd, *J* = 11.9, 3.4 Hz, 1H, H4a), 3.78 (dd, *J* = 8.8, 5.9 Hz, 1H, H5), 4.11 (dd, *J* = 8.8, 5.9 Hz, 1H, H5), 4.42 (dd, *J* = 11.4, 7.0 Hz, 1H, H3a), 4.58 (dd, *J* = 11.4, 6.7 Hz, 1H, H3a), 4.95 (d, *J* = 6.2 Hz, 1H, H2), 7.01 (t, *J* = 8.7 Hz, 2H, H3', H5'),

7.13 – 7.41 (m, 6H, H2', H6', H2'', H6'', H4''', H6'''), 7.42 (td, *J* =7.5 Hz, *J* =1.6 Hz, 1H, H5'''), 7.55 (d, *J* = 8.1 Hz, 2H, H3'', H5''), 7.74 (dd, *J* = 7.7, 1.5 Hz, 1H, H7''').

^{13}C NMR (101 MHz, $CDCl_3$) - δ 21.9 (q, C3'''$\underline{C}H_3$), 33.6 (t, C4a), 42.4 (d, C4), 49.6 (d, C3), 62.8 (t, C3a), 72.7 (t, C5), 82.9 (d, C2), 115.6 (dd, $^2J_{C\text{-}F}$ = 21.5 Hz, C3', C5'), 124.3 (q, C4''$\underline{C}F_3$, $^1J_{C\text{-}F}$ = 271.7 Hz), 125.8 (dq, C3'', C5'', $^3J_{C\text{-}F}$ = 3.8 Hz), 125.9 (d, C6'''), 127.6 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 129.0 (s, C2'''), 129.0 (q, C4'', $^2J_{C\text{-}F}$ = 32.5 Hz), 129.1 (d, C2'', C6''), 130.6 (d, C4'''), 132.0 (d, C7'''*), 132.5 (d, C5'''*), 138.1 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 140.7 (s, C3'''), 144.2 (s, C1''), 162.5 (d, C4', $^1J_{C\text{-}F}$ = 245.8 Hz), 167.3 (s, C1'''=O)

D.6.7 ((2S,3R,4R)-2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl thiophene-3-carboxylate (<u>81</u>)



$C_{19}H_{18}F_4O_2$ MW: 354.34 | $C_5H_4O_2S$ MW: 128.15 | $C_{24}H_{20}F_4O_3S$ MW: 464.47

Prepared according to general procedure A using **41** as starting material (35.8 mg, 0.10 mmol) and 3-thiophenecarboxylic acid as reagent.

Purification: MPLC: 9 g SiO_2, 20 mL/min, 2-10 % EE in LP within 30 min.

Yield: 39.1 mg (83 %)

Appearance: colorless crystals

Melting point: 90-92 °C

TLC: R_f (heptane : EtOAc, 1 : 1) = 0.70

HRMS (ESI+): exact mass calculated for $C_{24}H_{20}F_4O_3S+H^+$: 465.1042. Found: 465.1149. [M+ H^+], Δ = 1.56ppm

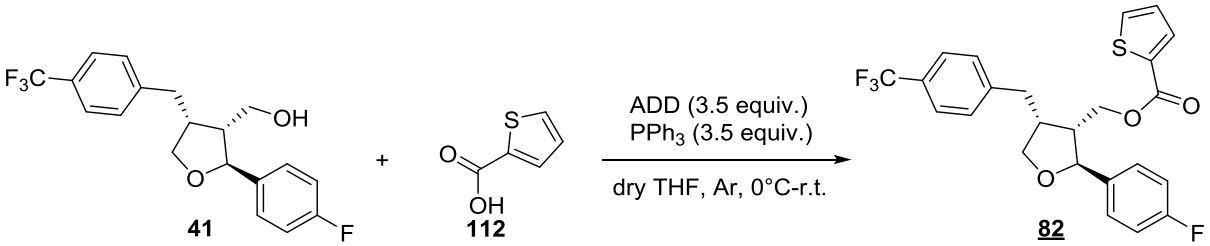
Specific rotation: $[\alpha]_D^{20}$: +11.5° (MeOH; 1.92 g/100mL)

GC MS (EI, 70 eV) RT: 8.86 min (method A), main signals (rel. int.): 353 (3), 336 (16), 212 (10), 197 (8), 185 (7), 177 (40), 164 (10), 159 (27), 138 (7), 125 (23), 123 (56), 112 (6), 110 (100), 109 (19), 83 (10). M^+ not visible.

^{1}H NMR (200 MHz, $CDCl_3$) δ 2.56 – 2.96 (m, 3H, H3, H4, H4a), 2.96 – 3.12 (m, 1H, H4a), 3.77 (dd, *J* = 8.7, 6.2 Hz, 1H, H5), 4.11 (dd, *J* = 8.7, 6.0 Hz, 1H, H5), 4.41 (dd, *J* = 11.3, 7.0 Hz, 1H, H3a), 4.56 (dd, *J* = 11.3, 6.5 Hz, 1H, H3a), 4.93 (d, *J* = 6.0 Hz, 1H, H2), 7.02 (t, *J* = 8.7 Hz, 2H, H3', H5'), 7.23 – 7.36 (m, 5H, H2', H6', H2'', H6'', H5'''), 7.43 (dd, *J* = 5.1, 1.2 Hz, 1H, H6'''), 7.55 (d, *J* = 8.1 Hz, 2H, H3'', H5''), 7.99 (dd, ^{4}J = 3.0, 1.3 Hz, 1H, H3''').

^{13}C NMR (50 MHz, $CDCl_3$) δ 33.5 (t, C4a), 42.2 (d, C4), 49.3 (d, C3), 62.7 (t, C3a), 72.7 (t, C5), 82.8 (d, C2), 115.4 (dd, $^{2}J_{C\text{-}F}$ = 21.5 Hz, C3', C5'), 122.7 (q, C4''$\underline{C}F_3$, $^{1}J_{C\text{-}F}$ = 276.9 Hz), 125.6 (dq, C3'', C5'', $^{3}J_{C\text{-}F}$ = 3.8 Hz), 126.3 (d, C5'''), 127.5 (dd, C2', C6', $^{3}J_{C\text{-}F}$ = 8.1 Hz), 127.7 (d, C6'''), 128.8 (q, C4'', $^{2}J_{C\text{-}F}$ = 32.6 Hz), 128.9 (d, C2'', C6''), 133.0 (d, C3'''), 133.0 (s, C2'''), 138.0 (d, C1', $^{4}J_{C\text{-}F}$ = 3.2 Hz), 144.0 (q, C1'', $^{5}J_{C\text{-}F}$ = 1.3 Hz), 162.3 (d, C4', $^{1}J_{C\text{-}F}$ = 245.8 Hz), 162.4 (s, C1'''=O)

D.6.8 ((2S,3R,4R)-2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl thiophene-2-carboxylate (<u>82</u>)



$C_{19}H_{18}F_4O_2$
MW: 354.34

$C_5H_4O_2S$
MW: 128.15

$C_{24}H_{20}F_4O_3S$
MW: 464.47

Prepared according to general procedure A using **41** as starting material (35.8 mg, 0.10 mmol) and 2-thiophenecarboxylic acid as reagent.

Purification: MPLC: 9 g SiO_2, 20 mL/min, 2-10 % EE in LP within 30 min.

Yield: 30.7 mg (65 %)

Appearance: colorless crystals

Melting Point: 68-69 °C

TLC: R_f (heptane : EtOAc, 1 : 1) = 0.70

HRMS (ESI+): exact mass calculated for $C_{24}H_{20}F_4O_3S+H^+$: 465.1042. Found: 465.1145. [M+ H^+], Δ = 0.70ppm

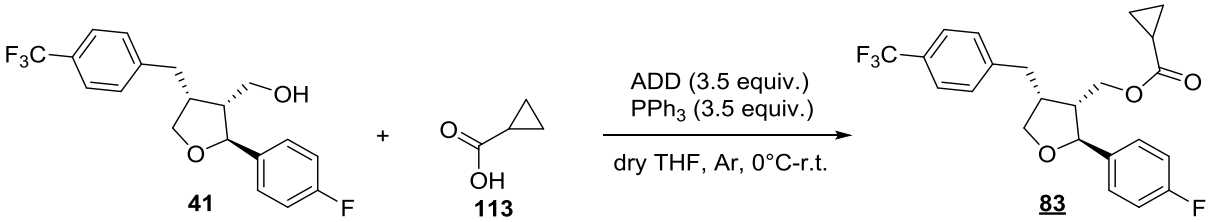
Specific rotation: $[\alpha]_D^{20}$: +14.8° (MeOH; 1.51 g/100 mL)

GC MS (EI, 70 eV) RT: 9.83 min (method A), main signals (rel. int.): 336 (12), 212 (11), 207 (13), 197 (9), 177 (40), 164 (10), 159 (27), 125 (23), 123 (58), 113 (11), 110 (100), 109 (21), 97 (13), 83 (10), 57 (14). M^+ not visible.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (qint, *J* = 6.9 Hz, 1H, H3), 2.72 – 2.90 (m, 2H, H4, H4a), 3.04 (dd, *J* = 12.9, 4.3 Hz, 1H, H4a), 3.78 (dd, *J* = 8.8, 6.6 Hz, 1H, H5), 4.10 (dd, *J* = 8.8, 6.3 Hz, 1H, H5), 4.44 (dd, *J* = 11.2, 7.1 Hz, 1H, H3a), 4.57 (dd, *J* = 11.3, 6.7 Hz, 1H, H3a), 4.94 (d, *J* = 6.0 Hz, 1H, H2), 6.95 (t, *J* = 8.6 Hz, 2H, H3', H5'), 7.12 (dd, *J* = 5.0, 3.6 Hz, 1H, H5'''), 7.23 – 7.41 (m, 4H, H2', H6', H2'', H6''), 7.55 (d, *J* = 8.1 Hz, 2H, H3'', H5''), 7.59 (dd, *J* = 5.0, 1.4 Hz, 1H, H4'''), 7.75 (dd, *J* = 3.7, 1.4 Hz, 1H, H6''').

^{13}C NMR (101 MHz, $CDCl_3$) δ 33.5 (t, C4a), 42.2 (d, C4), 49.4 (d, C3), 63.0 (t, C3a), 72.7 (t, C5), 82.6 (d, C2), 115.4 (dd, $^2J_{C\text{-}F}$ = 21.5 Hz, C3', C5'), 124.2 (q, C4''$\underline{C}F_3$, $^1J_{C\text{-}F}$ = 272.1 Hz), 125.6 (dq, C3'', C5'', $^3J_{C\text{-}F}$ = 3.7 Hz), 127.4 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 128.0 (d, C5'''*), 128.8 (q, C4'', $^2J_{C\text{-}F}$ = 32.4 Hz), 128.8 (d, C2'', C6''), 132.8 (d, C4'''*), 133.0 (s, C2'''), 133.8 (d, C6'''*), 138.0 (d, C1', $^4J_{C\text{-}F}$ = 3.2 Hz), 144.0 (q, C1'', $^5J_{C\text{-}F}$ = 1.2 Hz), 161.9 (s, C1'''=O), 162.3 (d, C4', $^1J_{C\text{-}F}$ = 245.8 Hz).

D.6.9 ((2S,3R,4R)-2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)benzyl)tetrahydrofuran-3-yl)methyl cyclopropanecarboxylate (<u>83</u>)



Prepared according to general procedure A using **41** as starting material (35.8 mg, 0.10 mmol) and cyclopropanecarboxylic acid as reagent.

Purification: MPLC: 9 g SiO_2, 20 mL/min, 2-10 % EE in LP within 30 min.

Yield: 30 mg (70 %)

Appearance: colorless oil

TLC: R_f (heptane : EtOAc, 1 : 1) = 0.67

HRMS (ESI-): exact mass calculated for $C_{23}H_{22}F_4O_3$+$COOH^-$: 467.1487. Found: 467.1480. [M+ $COOH^-$], Δ = -1.50ppm

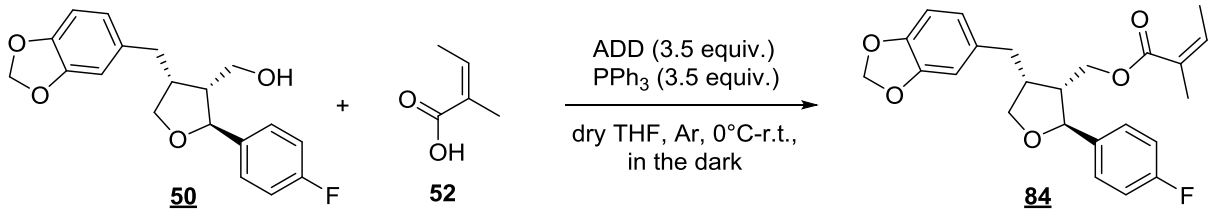
Specific rotation: $[\alpha]_D^{20}$: +14.0° (MeOH; 1.16 g/100 mL)

GC MS (EI, 70 eV) RT: 7.91 min (method A), main signals (rel. int.): 353 (4), 336 (25), 212 (18), 198 (10), 197 (16), 185 (13), 177 (73), 164 (19), 159 (40), 151 (10), 143 (17), 138 (13), 125 (40), 123 (100), 109 (32), 69 (95). M^+ not visible.

^{1}H NMR (200 MHz, $CDCl_3$) δ 0.77 – 1.07 (m, 4H, H3''', H4'''), 1.48 – 1.66 (m, 1H, H2'''), 2.43 – 2.91 (m, 3H, H3, H4, H4a), 2.88 – 3.06 (m, 1H, H4a), 3.73 (dd, *J* = 8.7, 6.2 Hz, 1H, H5), 4.07 (dd, *J* = 8.7, 6.1 Hz, 1H, H5), 4.20 (dd, *J* = 11.3, 7.2 Hz, 1H, H3a), 4.36 (dd, *J* = 11.3, 6.9 Hz, 1H, H3a), 4.85 (d, *J* = 6.2 Hz, 1H, H2), 7.03 (t, *J* = 8.7 Hz, 2H, H3', H5'), 7.19 – 7.43 (m, 4H, H2', H6', H2'', H6''), 7.56 (d, *J* = 8.0 Hz, 2H, H3'', H5'').

^{13}C NMR (101 MHz, $CDCl_3$) δ 8.6 (t, C3'''), 12.8 (d, C2'''), 33.4 (t, C4a), 42.1 (d, C4), 49.3 (d, C3), 62.4 (t, C3a), 72.6 (t, C5), 82.6 (d, C2), 115.3 (dd, $^2J_{C\text{-}F}$ = 21.4 Hz, C3', C5'), 124.2 (q, C4''$\underline{C}F_3$, $^1J_{C\text{-}F}$ = 271.4 Hz), 125.6 (dq, C3'', C5'', $^3J_{C\text{-}F}$ = 3.7 Hz), 127.4 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 128.8 (q, C4'', $^2J_{C\text{-}F}$ = 32.5 Hz), 128.8 (d, C2'', C6''), 138.1 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 144.1 (q, C1'', $^5J_{C\text{-}F}$ = 1.0 Hz), 162.5 (d, C4', $^1J_{C\text{-}F}$ = 245.6 Hz), 174.7 (s, C1'''=O)

D.6.10 ((2S,3R,4R)-4-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl (Z)-2-methylbut-2-enoate (84)



50 $C_{19}H_{19}FO_4$ MW: 330.36 + **52** $C_5H_8O_2$ MW: 100.12 → **84** $C_{24}H_{25}FO_5$ MW: 412.46

Prepared according to general procedure A using **50** (35 mg, 0.11 mmol) and angelic acid as reagent.

Purification: MPLC: 9 g SiO_2, 20 mL/min, 0-7 % EtOAc in LP within 30 min. Applied twice.

Yield: 33mg (75.5%)

Appearance: colourless oil

TLC: R_f (heptane : EtOAc, 5 : 1) = 0.50

HRMS (ESI+): exact mass calculated for $C_{24}H_{25}FO_5+H^+$: 413.1759. Found: 465.1771. [M+ H^+], Δ = 2.96ppm

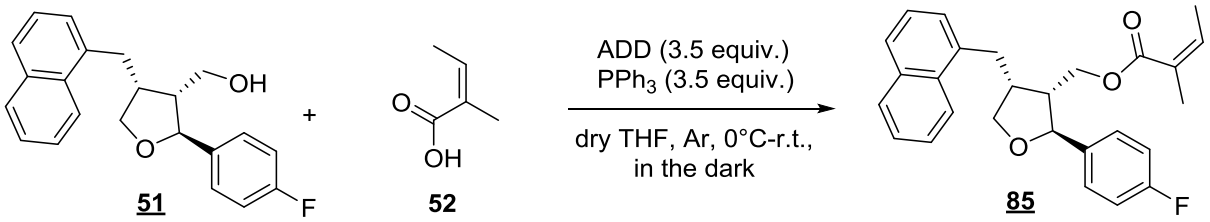
Specific rotation: $[\alpha]_D^{20}$: +13.5° (MeOH; 1.26g/100mL)

GC MS (EI, 70 eV) RT: 10.00 min (method A), main signals (rel. int.): 312 (26), 190 (12), 178 (41), 177 (36), 174 (25), 173 (23), 162 (13), 148 (26), 136 (26), 135 (100), 123 (48), 109 (33), 83 (37), 77 (25), 55 (40). M^+ not visible.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 – 1.89 (m, 3H, H5'''), 1.99 (dq, *J* = 7.1, 1.7 Hz, 3H, H4'''), 2.47 – 2.64 (m, 2H, H3, H4), 2.63 – 2.78 (m, 1H, H4a), 2.85 (dd, *J* = 13.5, 4.9 Hz, 1H, H4a), 3.76 (dd, *J* = 8.7, 6.8 Hz, 1H, H5), 4.07 (dd, *J* = 8.6, 6.6 Hz, 1H, H5), 4.26 (dd, *J* = 11.3, 7.3 Hz, 1H, H3a), 4.39 (dd, *J* = 11.3, 6.7 Hz, 1H, H3a), 4.87 (d, *J* = 6.2 Hz, 1H, H2), 5.93 (s, 2H, H5), 6.10 (qq, *J* = 7.1, 1.6 Hz, 1H, H3'''), 6.62 (dd, *J* = 7.8, 1.8 Hz, 1H, H7''), 6.65 (d, *J* = 1.8 Hz, 1H, H2''), 6.73 (d, *J* = 7.8 Hz, 1H, H6''), 7.02 (t, *J* = 8.6 Hz, 2H, H3', H5'), 7.24 – 7.34 (m, 2H, H2', H6').

^{13}C NMR (101 MHz, $CDCl_3$) δ 16.0 (q, C4'''), 20.7 (q, C5'''), 33.4 (t, C4a), 42.7 (d, C4), 49.5 (d, C3), 62.2 (t, C3a), 72.8 (t, C5), 82.7 (d, C2), 101.1 (t, C4''), 108.5 (d, C2''*), 109.0 (d, C6''*), 115.4 (dd, $^2J_{C\text{-}F}$ = 21.5 Hz, C3', C5'), 121.6 (d, C7''), 127.4 (s, C2'''), 127.5 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.3 Hz), 133.8 (C1''), 138.4 (d, C1', $^4J_{C\text{-}F}$ = 3.0 Hz), 139.2 (d, C3'''), 146.2 (C5a''), 147.9 (C2a''), 162.5 (d, C4', $^1J_{C\text{-}F}$ = 245.5 Hz), 167.8 (C1'''=O).

D.6.11 ((2S,3R,4R)-2-(4-Fluorophenyl)-4-(naphthalen-1-ylmethyl)tetrahydrofuran-3-yl)methyl (Z)-2-methylbut-2-enoate (85)



$C_{22}H_{21}FO_2$
MW: 336.41

$C_5H_8O_2$
MW: 100.12

$C_{27}H_{27}FO_3$
MW: 418.51

Prepared according to general procedure A using **51** as starting material (18 mg, 0.11mmol) and angelic acid as reagent.

Purification: MPLC: 9 g SiO_2, 20 mL/min, 0-5 % EtOAc in LP within 40 min.

Yield: 20.1 mg (88 %)

Appearance: colorless oil

TLC: R_f (heptane : EtOAc, 5 : 1) = 0.65

HRMS (ESI+): exact mass calculated for $C_{27}H_{27}FO_3$+H^+: 419.2017. Found: 419.2027. [M+ H^+], Δ = 2.44ppm

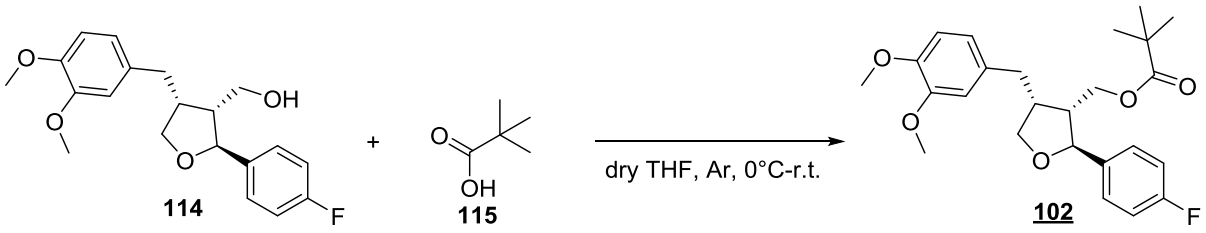
Specific rotation: $[\alpha]_D^{20}$: +11.5° ($CHCl_3$; 0.83 g/100mL)

GC MS (EI, 70 eV) RT: 11.47 min (method A), main signals (rel. int.): 318 (27), 179 (31), 178 (31), 177 (100), 167 (23), 166 (29), 165 (45), 153 (31), 142 (28), 141 (97), 123 (57), 115 (35), 109 (23), 83 (50), 55 (43). M^+ not visible.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (p, *J* = 1.5 Hz, 3H, H5'''), 2.02 (dq, *J* = 7.3, 1.5 Hz, 3H, H4'''), 2.70 (p, *J* = 7.1 Hz, 1H, H3), 2.92 – 3.04 (m, 2H, H4, H4a), 3.43 – 3.57 (m, 1H, H4a), 3.88 (dd, *J* = 8.8, 4.7 Hz, 1H, H5), 3.97 (dd, *J* = 8.8, 5.6 Hz, 1H, H5), 4.40 (dd, *J* = 11.4, 6.6 Hz, 1H, H3a), 4.57 (dd, *J* = 11.4, 7.8 Hz, 1H, H3a), 4.92 (d, *J* = 7.3 Hz, 1H, H2), 6.15 (qq, *J* = 7.3, 1.5 Hz, 1H, H3'''), 7.03 (t, *J* = 8.7 Hz, 2H, H3', H5'), 7.25 – 7.41 (m, 3H, H2', H6', H2''), 7.42 (dd, *J* = 8.2, 7.0 Hz, 1H, H3''), 7.46 – 7.54 (m, 2H, H5'', H6''), 7.76 (d, *J* = 8.1 Hz, 1H, H4''), 7.83 – 7.92 (m, 1H, H5''), 7.96 – 8.04 (m, 1H, H8'').

^{13}C NMR (101 MHz, $CDCl_3$) δ 16.0 (q, C4'''), 20.7 (q, C5'''), 30.6 (t, C4a), 41.8 (d, C4), 50.2 (d, C3), 62.1 (t, C3a), 72.9 (t, C5), 82.4 (d, C2), 115.5 (dd, $^2J_{C\text{-}F}$ = 21.5 Hz, C3', C5'), 123.5 (d, C8''), 125.6 (d, C2''*), 125.8 (d, C3''*), 126.1 (d, C5''), 126.9 (d, C6''), 127.4 (d, C4''), 127.5 (s, C2'''), 127.6 (dd, C2', C6', $^3J_{C\text{-}F}$ = 8.1 Hz), 129.1 (d, C5''), 131.9 (s, C8a''), 134.2 (s, C4a''), 136.0 (s, C1''), 138.4 (d, C1', $^4J_{C\text{-}F}$ = 3.1 Hz), 139.3 (d, C3'''), 162.5 (d, C4', $^1J_{C\text{-}F}$ = 245.5 Hz), 167.9 (s, C1'''=O)

D.6.12 ((2S,3R,4R)-4-(3,4-Dimethoxybenzyl)-2-(4-fluorophenyl)tetrahydrofuran-3-yl)methyl pivalate (102)



$C_{20}H_{23}FO_4$
MW: 346.40

$C_5H_{10}O_2$
MW: 102.13

$C_{25}H_{31}FO_5$
MW: 430.52

Preperation: A reaction vessel equipped with a stirring bar containing pivalic acid (37.4 mg, 36.6 mmol, 4 equiv.) and 4-DMAP (1.1 mg, 9.15 µmol, 0.1 equiv.) was set under argon atmosphere using standard Schlenk technique (4x) prior to adding 1mL dry DCM and cooling the mixture with an ice bath. Then the vessel was briefly opened and EDCI*HCl (63.8 mg, 33.86 mmol, 3.7 equiv.) was added in one go followed by stirring the mixture for 3 h at 0 °C. After that the solution was transferred dropwise *via* syringe to a second reaction vessel with a mixture of **114** (31.7 mg, 91.5 µmol, 1 equiv.) and DIPEA (78 µL, 45.75 mmol, 5 equiv.) under Ar. The reaction was stirred at room temperature for 7 days. The reaction solution was directly used for flash column chromatography (MPLC, 9 g SiO_2, 20 mL/min, 4-25 % EtOAc in LP within 80 min)

Yield: 23.1 mg (60.3 %)

Appearance: colorless oil

TLC: R_f (heptane : EtOAc, 1 : 1) = 0.60

HRMS (ESI+): exact mass calculated for $C_{25}H_{31}FO_5$+H^+: 431.2229. Found: 465.1142. [M+ H^+], Δ = 3.10ppm

Specific rotation: $[\alpha]_D^{20}$: +15.7° (MeOH; 0.77 g/100mL)

GC MS (EI, 70 eV) RT: 9.36 min (method A), main signals (rel. int.): 430 (M^+, 18), 194 (22), 190 (24), 189 (24), 178 (16), 176 (10), 164 (22), 163 (15), 159 (13), 152 (31), 151 (100), 123 (41), 109 (30), 107 (17), 57 (38).

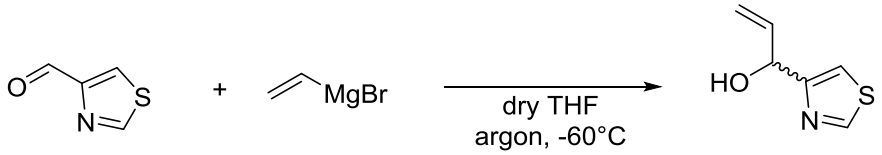
^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (s, 9H, H3'''), 2.44 – 2.80 (m, 3H, H3, H4a, H4), 2.86 (dd, *J* = 12.5, 4.2 Hz, 1H, H4a), 3.79 (dd, *J* = 8.6, 6.1 Hz, 1H, H5), 3.87 (s, 6H, Ar''-OCH_3), 4.08 (dd, *J* = 8.6, 6.2 Hz, 1H, H5), 4.18 (dd, *J* = 11.3, 7.1 Hz, 1H, H3a), 4.37 (dd, *J* = 11.3, 6.7 Hz, 1H, H3a), 4.86 (d, *J* = 6.1 Hz, 1H, H2), 6.63 – 6.88 (m, 3H, Ar''-H), 6.94 – 7.13 (m, 2H, H3', H5'), 7.22 – 7.38 (m, 2H, H2', H6').

^{13}C NMR (50 MHz, $CDCl_3$) δ 27.3 (q, 3C, C3'''), 33.3 (t, C4a), 38.9 (s, C2'''), 42.8 (d, C4), 49.6 (d, C3), 56.0 (q, Ar''-OCH_3), 56.1 (q, Ar''-OCH_3), 62.6 (t, C3a) , 72.9 (t,C5) , 82.6 (d, C2), 111.5 (d, C5''*), 112.0 (d, C2''*),

115.5 (dd, *J* = 21.4 Hz, C3', C5'), 120.6 (d, C6''), 127.5 (dd, *J* = 8.1 Hz, C2', C6'), 132.6 (C1''), 138.5 (d, *J* = 3.1 Hz, C1'), 147.7 (C4''), 149.1 (C3''), 178.5 (s, C1'''). C4' not visible

D.7 Variation of the 2-Postion

D.7.1 1-(Thiazol-4-yl)prop-2-en-1-ol (87)



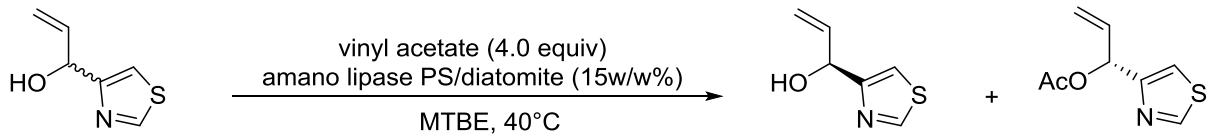
86
C_4H_3NOS
MW: 113.13

43
C_2H_3BrMg
MW: 131.26

rac-**87**
C_6H_7NOS
MW: 141.19

A 250 mL flask equipped with a stirring bar, dropping funnel, quick-fit and low temperature thermometer was evacuated and back-filled with argon using standard Schlenk technique (3x). After that a solution of 1,3-thiazol-4-carboxaldehyd (3.39 g, 30 mmol, 1.00 equiv.) in dry THF (100 mL) was added *via* syringe and cooled to -60 °C using a MeOH/N_2 slurry. Then vinylmagnesium bromide solution (1 M in THF, 42 mL, 42 mmol, 1.4 equiv.) was added *via* syringe over a period of 45 min while the temperature was kept within ±3 °C. Afterwards the mixture was allowed to warm to -20 °C within 4 h, followed by dropwise addition of a saturated aqueous NH_4Cl solution (12 mL) while providing additional cooling to prevent the temperature from rising over -20 °C during the exothermic hydrolysis. In addition water (100 mL) was added to dissolve magnesium salts and the product was extracted with Et_2O. The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (1 x 20 mL) and saturated brine (1 x 15 mL), dried with Na_2SO_4, filtered and the solvents were removed *in vacuo* (min pressure 100 mbar). The progress of this reaction was monitored via TLC and resulted in a spot to spot reaction. R*ac*-**87**, yellow oil (3.77 g), was used directly in the next step without further purification.

D.7.2 (S)-1-(Thiazol-4-yl)prop-2-en-1-ol (87)



rac-**87**
C_9H_9FO
MW: 152.17

(S)-**87**
C_6H_7NOS
MW: 141.19

87a
$C_8H_9NO_2S$
MW: 183.23

Rac-**87** (3.77 g, 26.7 mmol, 1.00 equiv.), amano lipase PS (immobilized on diatomite, 0.57g, 15 w/w %) and vinyl acetate (9.18 g, 9.88 mL, 106.8 mmol, 4.00 equiv.) in MTBE (150 mL) were charged into a flask with stirring bar. The resulting suspension was stirred at 40 °C for 28 h, then the mixture was filtered through celite 545 and the solvent was removed *in vacuo*.
MPLC flash column chromatography was performed using the following method: 180 g SiO_2 separation column, 50 mL/min, EtOAc in LP: 10 to 45 % within 2 h.

Yield: 1.00 g (26 %)

Appearance: yellow oil

TLC: R_f (heptane : EtOAc, 1 : 1)= 0.24

HRMS (ESI+): exact mass calculated for $C_6H_7NOS+H^+$: 142.0321. Found: 142.0341. [M+ H^+], Δ = 14.25ppm

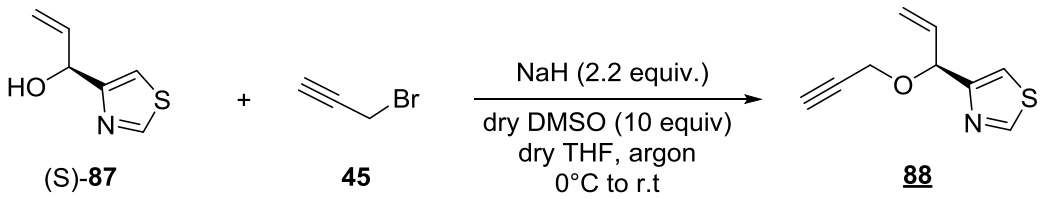
Specific rotation: $[\alpha]_D^{20}$: +1.5° (MeOH; 1.41 g/100 mL)

GC MS (EI, 70 eV) RT: 5.17 min (method B), main signals (rel. int.): 141 (M^+, 8), 140 (7), 125 (8), 124 (100), 114 (29), 113 (32), 112 (80), 97 (14), 86 (25), 85 (64), 84 (7), 59 (18), 58 (12), 56 (11), 55 (7).

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.14 (bs, OH), 5.22 (d, *J* = 10.3 Hz, 1H, H1), 5.29 – 5.48 (m, 2H, H1, H3), 6.12 (ddd, *J* = 17.6, 10.2, 5.7 Hz, 1H, H2), 7.23 (d, *J* = 2.0 Hz, 1H, H8), 8.74 (d, *J* = 2.2 Hz, 1H, H6).

^{13}C NMR (50 MHz, $CDCl_3$) δ 71.4 (d, C3), 114.4 (d, C8), 116.2 (t, C1), 138.7 (d, C2), 153.6 (d, C6), 159.1 (s, C4).

D.7.3 (S)-4-(1-(Prop-2-yn-1-yloxy)allyl)thiazole (88)



(S)-**87** | **45** | **88**

C_6H_7NOS MW: 141.19 | C_3H_3Br MW: 118.96 | C_9H_9NOS MW: 179.24

NaH (approximately 60 % dispersion in mineral oil, 563.2 mg, 14.08 mmol, 2.20 equiv.) was weight in a 250 mL three neck flask and set under argon using standard Schlenk technique (4x), then dry THF (15 mL) and dry DMSO (4.5 mL, 64 mol, 10.00 equiv.) were added and the resulting stirred suspension was cooled using an ice bath. After that a solution of (*S*)-**87** (0.9 g, 6.4 mmol, 1.00 equiv.) in dry THF (15 mL) was added *via* a dropping funnel over a period of 10min. Stirring was continued at that temperature for 15 min, then a solution of propargyl bromide (80 % in toluene, 1.01 mL, 11.5 mmol, 1.80 equiv.) was added over a period of 15min. To suspend the so formed slurry, more dry THF (10 mL) was added. The ice bath was removed and the reaction was stirred for 19 h. The mixture was then cooled in an ice bath again under argon atmosphere and hydrolyzed by dropwise addition of aqueous HCl solution (1 M, 12 mL) over 17 min. Most of the THF was then removed *in vacuo* (50 °C), followed by the addition of water (15 mL). The aqueous phase was extracted with Et_2O (4 x 15 mL), the combined organic phases were washed with saturated brine (1 x 15 mL), dried over Na_2SO_4 and the solvent was removed from the filtrate *in vacuo* to afford crude yellow oil **88** (1.32 g).

Appearance: yellow oil

TLC: R_f (heptane : EtOAc, 1 : 1)= 0.50

Specific rotation (crude material): $[\alpha]_D^{20}$: +1.7° (MeOH; 0.49 g/100 mL)

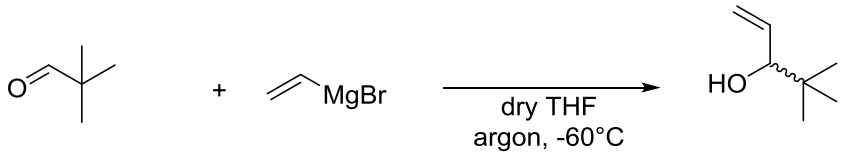
HRMS (crude material) (ESI_+): exact mass calculated for $C_9H_9NOS+H^+$: 180.0478. Found: 180.0488. [M+ H^+], Δ = 5.68ppm

GC MS (EI, 70 eV) RT: 5.83 min (method B), main signals (rel. int.): 179 (M^+, 1), 178 (7), 150 (37), 149 (21), 140 (51), 136 (20), 125 (55), 124 (75), 114 (13), 112 (100), 98 (22), 97 (77), 85 (26), 84 (16), 57 (13), 55 (19), 53 (19).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (t, *J* = 2.3 Hz, 1H, H3''), 4.25 (d, *J* = 2.4 Hz, 2H, H1''), 5.31 (d, *J* = 7.6 Hz, 1H, H3), 5.38 (dt, *J* = 10.2, 1.1 Hz, 1H, H1), 5.47 (dt, *J* = 17.3, 1.4 Hz, 1H, H1), 6.00 (ddd, *J* = 17.3, 10.2, 7.3 Hz, 1H, H2), 7.32 – 7.37 (m, 1H, H8), 8.80 (d, *J* = 2.1 Hz, 1H, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.8 (t, C1''), 74.9 (d, C3''), 78.0 (d, C3), 79.7 (s, C2''), 115.7 (d, C8), 119.2 (t, C1), 136.1 (d, C2), 153.4 (d, C6), 156.8 (s, C4).

D.7.4 4,4-Dimethylpent-1-en-3-ol (95)



94	**43**	**95**
$C_5H_{10}O$	C_2H_3BrMg	$C_7H_{14}O$
MW: 86.13	MW: 131.26	MW: 114.19

A 250 mL three neck flask equipped with a stirring bar, dropping funnel, quick-fit and low temperature thermometer was evacuated and back-filled with argon using standard Schlenk technique (3x). After that a solution of pivalyaldehyde (2 g, 23 mmol, 1.00 equiv.) in dry THF (40 mL) was added *via* septum and cooled to -80 °C using a MeOH/N_2 slurry. Vinylmagnesium bromide solution (1 M in THF, 32.5 mL, 33 mmol, 1.4 equiv.) was added *via* a dropping funnel over a period of 30min while the temperature of -80 °C was kept within ±5 °C. Afterwards the mixture was allowed to warm to -10 °C within 4.5 h, and then a saturated aqueous NH_4Cl solution (10 mL) was added dropwise while providing additional cooling to prevent the temperature from rising above -20 °C during the exothermic hydrolysis. Water (150 mL) was added to dissolve magnesium salts and the aqueous layer was extracted six times with Et_2O. The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (1 x 20 mL) and saturated brine (1 x 13 mL) and dried with Na_2SO_4. The solution was filtered and the solvents were removed *in vacuo* (min pressure 350 mbar). The crude product was purified using MPLC and the following method: 90 g SiO_2, 50 mL/min, 0-15 % Et_2O in LP within 60 min.

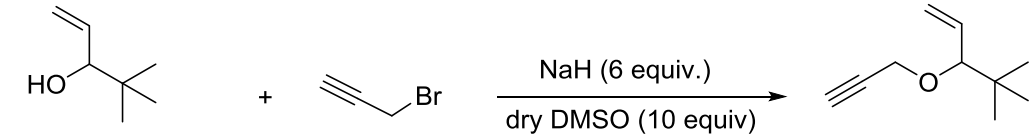
Yield: 645.7 mg (24 %)

Appearance: colorless oil

TLC: R_f (heptane : EtOAc, 3 : 1) = 0.49

^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (s, 9H, H5), 3.64 – 3.88 (m, 1H, H3), 5.05 – 5.39 (m, 2H, H1), 5.93 (ddd, *J* = 17.2, 10.4, 6.7 Hz, 1H, H2). OH not visible in this resolution

D.7.5 4,4-Dimethyl-3-(prop-2-yn-1-yloxy)pent-1-ene (98)



95
$C_7H_{14}O$
MW: 114.19

85
C_3H_3Br
MW: 118.96

98
$C_{10}H_{16}O$
MW: 152.24

NaH was washed with dry heptane (HPLC grade, additionally dried for two days using 3Å molsieves) and dried *in vacuo*. After that NaH (479 mg, 19.9 mmol, 6 equiv.) was quickly weight in a 25 mL flask equipped with a stirring bar and set under Ar atmosphere using standard Schlenk technique (4x). While cooling was provided by an ice-bath, 5 mL dry and desoxygenated THF and DMSO (2.36 mL, 33.28 mmol, 10 equiv.) were added. Then **95** (380 mg, 3.32 mmol, 1 equiv.) was added slowly and the mixture was stirred 5min until removing the ice bath. The stirring was continued for 2 hours at room temperature followed by dropwise addition of propargylbromide (0.73 mL, 80 % in toluene, 6.65 mmol, 2 equiv.) to the cooled mixture. The mixture was stirred for 15 h at room temperature, then 5mL HCl was added dropwise to the cooled mixture, followed by 10 mL Et_2O. The layers were separated and the aqueous layer was extracted five times with Et_2O, dried with Na_2SO_4, filtered and most of the solvents were removed *in vacuo* (min pressure 800 mbar). The crude product **98** was used in the next step without further purification.
A small amount was submitted to MPLC chromatography 9 g SiO_2, 20 mL/min, LP within 15 min in order to obtain a NMR sample free of Et_2O.

TLC: R_f (LP) = 0.24

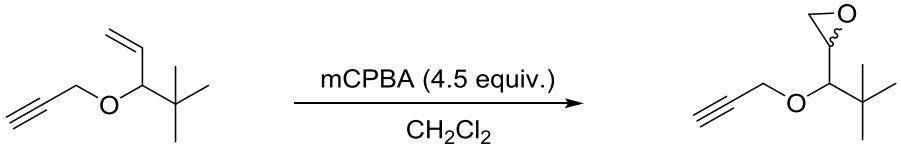
Appearance: colorless oil

GC MS (EI, 70 eV) RT: 4.10 min (method B), main signals (rel. int.): 97 (5), 96 (44), 95 (100), 91 (8), 88 (6), 85 (37), 83 (54), 81 (33), 68 (8), 67 (81), 66 (8), 65 (19), 57 (50), 55 (25), 51 (14). M^+ not visible.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (t, *J* = 2.4 Hz, 1H, H3''), 3.54 (d, *J* = 8.3 Hz, 1H, H3), 4.01 (dd, *J* = 15.8, 2.3 Hz, 1H, H1''), 4.22 (dd, *J* = 15.8, 2.4 Hz, 1H, H1''), 5.25 (ddd, $^3J_{Trans}$ = 17.2, $^4J_{H1\text{-}H3}$ = 2.0 Hz, J = 0.8Hz, 1H, H1), 5.32 (dd, $^3J_{Cis}$ = 10.4, $^4J_{H1\text{-}H3}$ = 2.0 Hz, 1H, H1), 5.71 (ddd,$^3J_{Trans}$ = 17.2, $^3J_{Cis}$ = 10.4, $^3J_{H2\text{-}H3}$ = 8.3 Hz, 1H, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 55.7(t, C1''), 73.3 (d, C3''), 80.8 (s, C2''), 88.1(d, C3), 119.5 (t, C1), 135.4 (d,C2).

D.7.6 2-(2,2-Dimethyl-1-(prop-2-yn-1-yloxy)propyl)oxirane (99)



98
$C_{10}H_{16}O$
MW: 152.24

99
$C_{10}H_{16}O_2$
MW: 168.24

A stirred solution of crude **98** (400 mg) in CH_2Cl_2 (10 mL) was cooled with an ice bath and *m*CPBA (purity approximately 77 %, 1.18 g, 5.25 mmol, 2 equiv.) was added in small portions over 15 min. The reaction was allowed to warm to room temperature while stirring was continued for 18 h. As the conversion was incomplete according to TLC and GCMS more mCPBA was added (purity approximately 77%, 1.47 g, 6.56 mmol, 2.5 equiv.) and stirring continued for another 15h until >90% of starting material was used up according to GC MS area. Then a sufficient amount aqueous Na_2SO_3 solution (1.6 g, 13.15 mmol, 5 equiv.) was added to destroy residual peroxy acid, which required cooling using an ice bath. This was followed by an aqueous solution of Na_3PO_4 (7 g, 18.41 mmol, 7 equiv.) in water (30 mL) to adjust the pH to 8. The crude product was extracted with Et_2O (1x 20 mL, 4x 15 mL), the combined organic phases were washed with saturated brine (10 mL), dried with Na_2SO_4, filtered and the solvent was removed *in vacuo*. Then 7 mL Et_2O and 70 mL PE were added to the crude material and left in the fridge overnight in order to precipitate m-chlorobenzoic acid. After that the solid acid was separated by filtration with a sinter funnel and the solvent was evaporated in vacuo. This process was repeated once again using a mixture of 3 mL Et_2O and 70 mL PE and this afforded crude colorless oil **99**. The crude product was purified by chromatography using MPLC and the following method: 18 g SiO_2, 20 mL/min, 0-20 % Et_2O in LP within 90 min.

TLC: R_f (heptane : EtOAc, 5 : 1) = 0.60

GC MS (EI, 70 eV) RT: 5.08 min (method B), main signals (rel. int.): 125 (29), 111 (53), 95 (13), 83 (34), 82 (14), 81 (72), 73 (32), 71 (26), 69 (23), 67 (18), 66 (12), 57 (100), 56 (13), 55 (66), 53 (28). M^+ not visible.

^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91 (s, H5a), 0.92 (s, H5b), 2.31 (t, ^4J = 2.4 Hz, 1H, H3''a), 2.33 (t, ^4J = 2.4 Hz, 1H, H3''b), 2.46 (dd, ^2J = 4.8, $^3J_{Trans}$ = 2.8 Hz, 1H, H1a), 2.65 (d, ^3J = 8.0 Hz, 1H, H3a), 2.69 (dd, ^2J = 5.4, $^3J_{Cis}$ = 3.9 Hz, 1H, H1b), 2.71 – 2.75 (m, 1H, H1a), 2.76 (dd, ^2J = 5.5 Hz, $^3J_{Trans}$ = 2.7 Hz, 1H, H1b), 2.92 – 2.96 (m, 1H, H2a), 2.97 – 3.00 (m, 1H, H2b), 3.04 (d, *J* = 4.8 Hz, 1H, H3b), 4.13 (dd, *J* = 16.1, 2.4 Hz, 1H, H1''b), 4.20 (dd, *J* = 15.9, 2.4 Hz, 1H, H1''b), 4.30 (dd, *J* = 15.9, 2.4 Hz, 1H, H1''a), 4.36 (dd, *J* = 15.9, 2.4 Hz, 1H, H1''a).
The indices a and b are marking the two present enantiomers.

^{13}C NMR (151 MHz, $CDCl_3$) δ 26.4 (q, 3C, C5b), 26.7 (q, 3C, C5a), 35.1 (C4a), 35.2 (C4b), 44.3 (t, C1a), 44.5 (t, C1b), 50.7 (d, C2b), 52.8 (d, C2a), 58.1 (t, C1''b), 58.8 (t, C1''a), 73.8 (d, C3''a), 74.3 (d, C3''b), 80.4 (C2''b), 80.7 (C2''a), 83.9 (d, C3b), 87.4 (d, C3a)

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