TECHNISCHE UNIVERSITÄT WIEN
Vienna University of Technology

Dr. Valentin Enev

Master Thesis

Towards the total synthesis of elisabethin A – an enantioselective approach

Submitted at the

Institute of Applied Synthetic Chemistry
of the Vienna University of Technology

Supervised by

Priv.Doz. Dipl.-Ing. Dr. Valentin Enev

And

Ao.Univ.Prof. Dipl.-Ing. Dr.techn. Peter Gärtner

Submitted by

Maximilian Benedikt Kaiser BSc.
Liechtensteinstraße 80/3
A-1090 Vienna

Date

Maximilian Benedikt Kaiser

Wer Jogginghosen trägt, hat die Kontrolle über sein Leben verloren.

Karl Lagerfeld

Acknowledgements

I would like to thank

Ao. Univ.Prof. Dipl.-Ing. Dr.techn. Peter Gärtner for the opportunity to work in his group and all the advice during the seminar.

my Supervisor Dipl.-Ing. Dr. Valentin Enev for continuous encouragement and advice throughout my thesis.

the NMR service team (Dipl.-Ing. Dr. techn. Katharina Schragl, Dipl.-Ing. Dr. techn. Maria Vasiloiu, Dipl.-Ing. Anna Ressmann, Dipl.-Ing. Sebastian Steiner) for measurement of NMR spectra.

my lab colleagues Dipl.-Ing. Dr. techn. Katharina Schragl, Dipl.-Ing. Dr. techn. Maria Vasiloiu, Dipl.-Ing. Anna Ressmann, Dipl.-Ing. Sebastian Steiner, Nicolas Kratena BSc. and David Schönbauer BSc. for the constructive and pleasant work atmosphere.

my colleagues Dominik, Drasko, Jürgen, Stoffl (aka Stoffl Unterweger), and Martin for countless hours of chemistry talks.

my very good friends Aaron, Bene, Claudio, Josh, Marka, Pfanner, Stoffl and Wuggi (aka The Wugglord).

my mother and father for their support and encouragement throughout my entire life.

the FWF for the generous funding of the elisabethin A project

Dedicated to my parents

Table of Contents

1 Introduction 3

2 State of the art 5

2.1 Heckrodt and Mulzer 2003[4] 5

2.1.1 *E,Z* configuration of the diene and an *exo* transition state 10

2.1.2 *E,Z* configuration of the diene and *endo* transition state 10

2.1.3 *E,E* configuration of the diene and *exo* transition state 11

2.1.4 *E,E* configuration of the diene and *endo* transition state 11

2.2 Waizumi and Rawal 2003[5] 13

2.2.1 *Z,E* configuration of the diene and *endo* transition state 17

2.3 Preindl and Mulzer 2014[6] 17

2.4 Steiner 2014[13] 20

4 Own Synthesis 25

4.1 Retrosynthetic analysis 25

4.2 Preliminaries 27

4.3 Chiral orthoester approach 28

4.4 Lactone alkylation approach 33

4.5 Double protection approach 35

4.6 Lactone approach 39

4.7 Determination of the enantiomeric excess 41

4 Conclusion 44

6 Experimental Part 45

6.1 General 45

6.2 Preliminaries 46

6.2.1 1-(2,4-dimethoxy-3-methylphenyl)ethan-1-one (76) 46

6.2.3 2,4-dimethoxy-3-methylphenyl acetate (77) 47

6.2.5 2,4-dimethoxy-3-methylphenol (78) 48

6.2.6 2-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (47) 48

6.2.7 2,2,6-trimethoxy-7-methyl-2,3-dihydrobenzofuran-5-ol (74b) 49

6.2.8 (*R*)-2-(((4-methoxybenzyl)oxy)methyl)oxirane (80) 49

6.2.9 (*R*)-1-((4-methoxybenzyl)oxy)pent-4-yn-2-ol 50

6.2.11 (*R*)-1-((4-methoxybenzyl)oxy)pent-3-yn-2-ol (81) 51

6.2.13 (*R,E*)-1-((4-methoxybenzyl)oxy)pent-3-en-2-ol (82) 52

6.2.15 (*S,E*)-2,2,6-trimethoxy-5-((1-((4-methoxybenzyl)oxy)pent-3-en-2-yl)oxy)-7-methyl-2,3-dihydrobenzofuran (83) 53

6.2.16 Methyl(*S,E*)-2-(2-hydroxy-4-methoxy-5-((1-((4-methoxybenzyl)oxy)pent-3-en-2-yl)oxy)-3-methylphenyl)acetate (84) 54

6.2.18 Methyl 2-(2,5-dihydroxy-4-methoxy-3-methylphenyl)acetate (87) 55

6.2.19 5-hydroxy-6-methoxy-7-methylbenzofuran-2(3*H*)-one (88) 55

6.2.20 6-methoxy-7-methyl-5-((triisopropylsilyl)oxy)benzofuran-2(3*H*)-one (89) 56

6.2.21 tert-butyldimethyl((2,2,6-trimethoxy-7-methyl-2,3-dihydrobenzofuran-5-yl)oxy)silane (90) 57

6.2.22 methyl 2-(5-((tert-butyldimethylsilyl)oxy)-2-hydroxy-4-methoxy-3-methylphenyl)acetate (91) 58

6.2.24 methyl 2-(5-((tert-butyldimethylsilyl)oxy)-4-methoxy-3-methyl-2-((triisopropylsilyl)oxy)phenyl)acetate (92) 59

6.2.25 5-((tert-butyldimethylsilyl)oxy)-6-methoxy-7-methylbenzofuran-2(3*H*)-one (94) 60

6.2.26 2-(5-((tert-butyldimethylsilyl)oxy)-2-hydroxy-4-methoxy-3-methylphenyl)acetic acid (95) 61

6.2.27 Triisopropylsilyl 2-(5-((tert-butyldimethylsilyl)oxy)-4-methoxy-3-methyl-2-((triisopropylsilyl)oxy)phenyl)acetate (96) 61

6.2.28 2-(5-((tert-butyldimethylsilyl)oxy)-4-methoxy-3-methyl-2-((triisopropylsilyl)oxy)phenyl)acetic acid (97) 62

6.2.29 2-(5-((tert-butyldimethylsilyl)oxy)-4-methoxy-3-methyl-2-((triisopropylsilyl)oxy)phenyl)-N-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-N-methylacetamide (98) 63

6.2.30 (*S*)-3-(benzyloxy)-2-(5-((tert-butyldimethylsilyl)oxy)-4-methoxy-3-methyl-2-((triisopropylsilyl)oxy)phenyl)-N-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-N-methylpropanamide (99) 64

6.2.32 (*R*)-3-(benzyloxy)-2-(5-((tert-butyldimethylsilyl)oxy)-4-methoxy-3-methyl-2-((triisopropylsilyl)oxy)phenyl)propan-1-ol (101) 65

6 References 66

7 Appendices 68

7.1 Abbreviations 68

7.2 Selected Spectra 70

1 Introduction

Marine terpenoids attracted enormous attention during the last two decades not only due to their unusual carbon-skeleton architecture but also because of their biological activity. Especially extracts from the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae* are rich of bioactive secondary metabolites.[1] A few dozen have been isolated so far. Properties possessed by these compounds vary but some could be beneficial for humanity like the ones following below:

- Anti-inflammatory [1,2,3]
- Analgesic [1,]
- Anti-bacterial (anti tuberculosis e.g.) [2]
- Anti-cancer [2]
- Anti-plasmodium (parasite causing malaria)

Though, all these compounds are derived from one "super family" their chemical structures sometimes vary extensively, ranging from bi- tri- cyclic over tetra cyclic compounds to di terpene-pentose-glycosides. This wealth of structural novelty paired with a challenging synthesis made these compounds interesting targets for total synthesis. For some, a total synthesis was necessary due to the lack of material for biological testing. One of these target molecules is elisabethin A which was isolated from the abovementioned sea whip in quantity of 25 mg by Rodriguez *et al.* in 1998.[1] This was on one hand enough for characterisation by X-ray, HRMS and extensive NMR studies which allowed the confirmation of the relative stereo chemistry (absolute configuration could not be assured with 100% certainty) on the other hand 25 mg only allowed limited testing which makes the synthetic production very important. The structure revealed by the spectroscopic experiments is given in Figure 1.

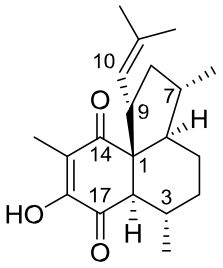
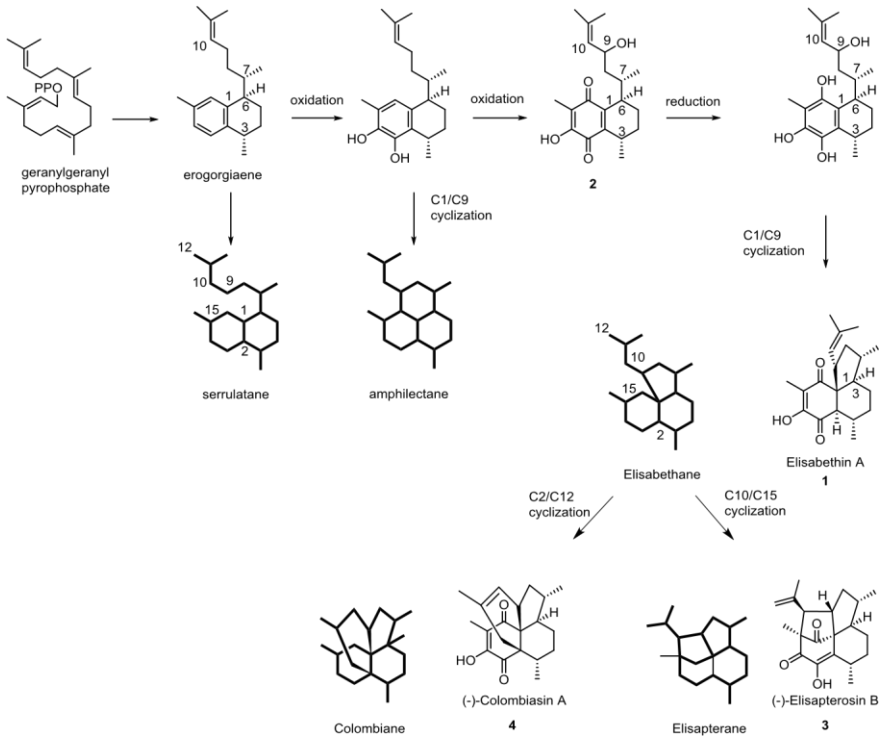


Figure 1: Elisabethin A (**1**)

This diterpenoid consists of a tricyclic *cis, trans* 5,6,6 ring system with six contiguous stereo centres - one of them quaternary at the juncture of the three cycles. In addition, the fully substituted enedione functionality completes the complexity of the structure.

Since this specimen was isolated more than 15 years ago it is still not accessible by means of total synthesis, although notable groups have tackled it.[4,5,6] This, in fact, makes it on one hand more interesting going along with higher motivation and ambition to succeed, on the other hand it appears to have a daunting impact too, which would explain why only three approaches have been reported in over 15 years.

Ferns and Kerr proposed a possible biological pathway in 2005 trying to give an insight how the sequence towards different polycyclic carbon framework formation (including the elisabethane-skeleton) might take place in nature.[7]



Scheme 1: Proposed biosynthesis of elisabethane and its isomers the colombianes and Elisapteranes

This biosynthesis is as of yet neither entirely clear nor certified, but isolations of different quinones, who have a similar structure as bicyclic quinone **2** indicate at least partial correctness. The sequence starts from geranylgeranyl phosphate which possesses the serrulatane skeleton after bicyclic ring formation. This serrulatane skeleton is believed to be nature's precursor to the elisabethan skeleton which could be formed via a C1/C9 cyclisation. Elisabethan on the other hand is thought to be the precursor for its structural isomers colombiane and elisapterane, both accessible by a cyclisation the first via C2/C12 the second mentioned by C10/C15 forming a forth ring.

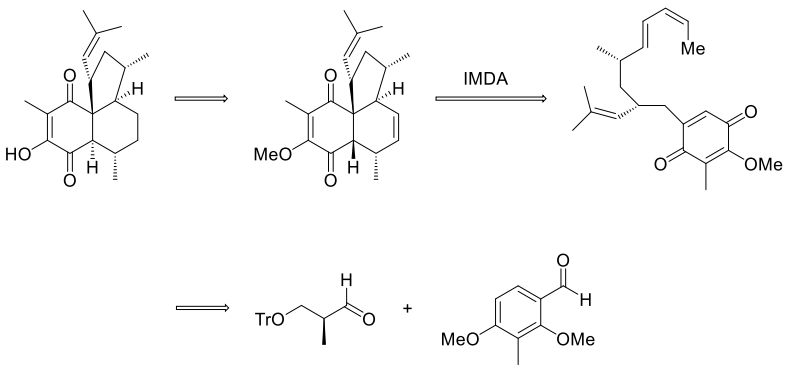
2 State of the art

As stated before not many attempts have been reported exclusively dedicating their work to this single molecule. Therefore they will be discussed quite detailed in this chapter. In advance it must be said that none of them was successful by means of synthesising the target molecule but revealing insights were by every single synthetic approach. Mulzer's[4] and Rawal's[5] approach, both published in 2003, relied on a crucial **i**ntra**m**olecular **D**iels-**A**lder reaction (referred to as IMDA in further course of this work) which due to its diastereospecific nature should create most of the chiral information of the final product in one step.

2.1 Heckrodt and Mulzer 2003[4]

The retrosynthetic analysis (Scheme 2) shows that the proposed reaction sequence does not appear to be very challenging except for the IMDA. The end game after the IMDA is a relatively simple three step sequence including an olefin-reduction, an epimerisation and a demethylation. The IMDA is meant to create the second six membered and the five membered ring in one step, together with four out of six stereocentres. The precursor for the IMDA is built up by two chiral building blocks, which can both be derived from quite simple molecules.

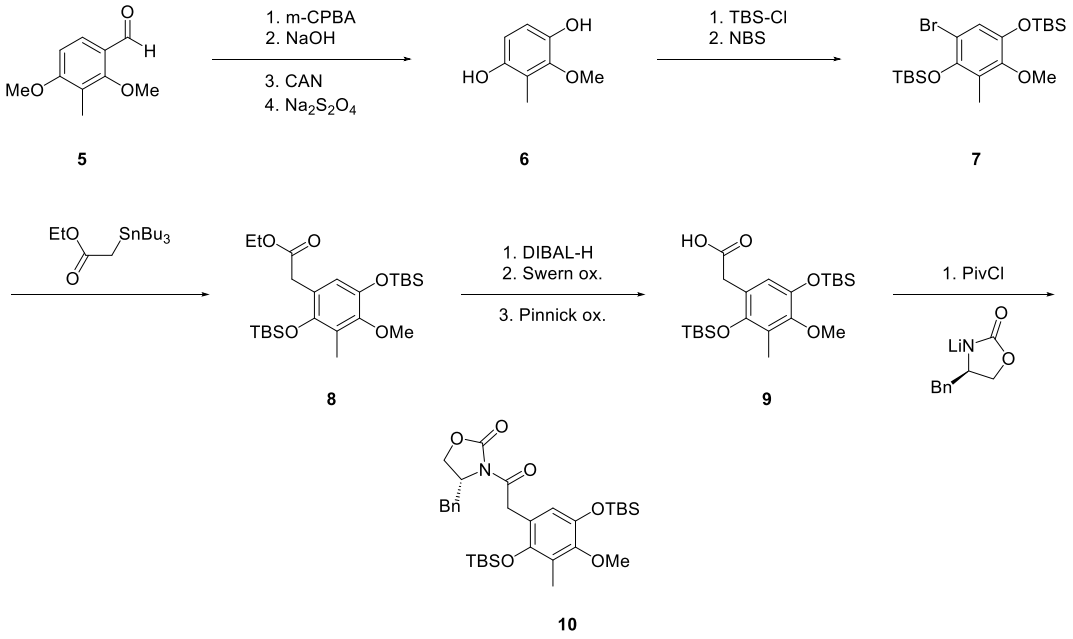
It must be stated that relying that much on one crucial reaction takes not only away flexibility but is also risky regarding continuing steps of the total synthetic approach.



Scheme 2: Mulzer's retrosynthetic analysis

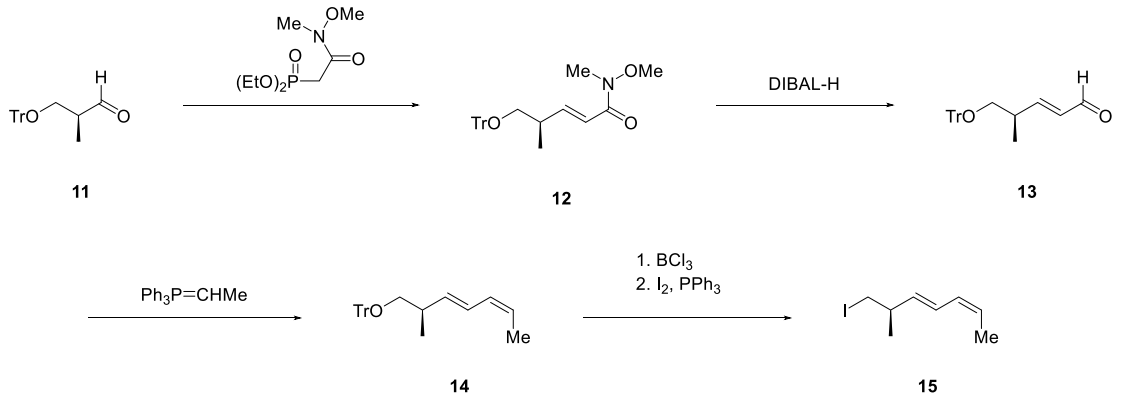
One of the building blocks was derived from 2,4 -dimethoxy-3-methylbenzaldehyde (**5**).

It was converted in a four step sequence to hydroquinone **6**, which was then TBS protected and brominated resulting in compound **7**. The next step was a Negishi-Reformatsky coupling to yield ethyl ester **8** which was converted to the free acid **9** *via* a three step reduction/oxidation sequence. This was necessary because the ethyl ester was said to be inert towards regular basic hydrolysis. The next two steps were the activation of the free acid by converting into the mixed anhydride and the installation of the chiral Evans' oxazolidinone auxiliary **10** resulting in an overall yield of 47% over 12 steps (Scheme 3).



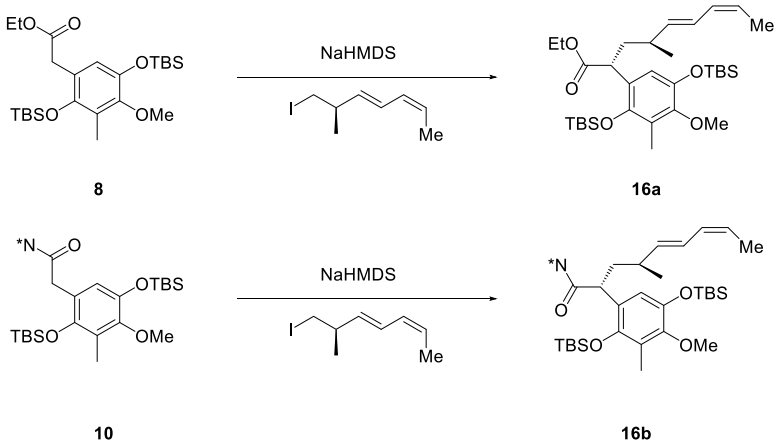
Scheme 3: Chiral oxazolidinone building block

The sequence towards the second building block started from the known aldehyde **11**, which was converted to the (*E*)-Weinreb-enamide **12**. This amide was reduced to the corresponding α,β-unsaturated aldehyde **13**, which was subsequently olefinated *via* "salt-free" Wittig reaction to install the (*Z*)-diene **14**. Subsequently, the triphenylmethyl protecting group was cleaved off and the resulting primary alcohol was converted into iodide **15** in an overall yield of 55% over five steps (Scheme 4).



Scheme 4: Chiral iodide building block

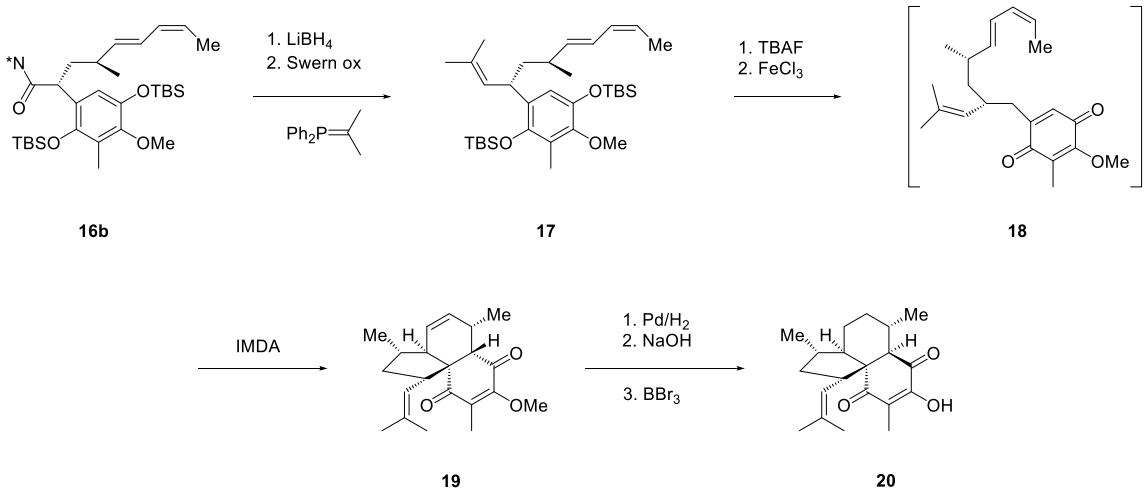
The first asymmetric reaction to install the chiral centre on C9 (elisabethin numbering) was conducted with ester **8** and iodine **15**. As the substrate control selectivity for **16a** was too low (42%), they use the chiral auxiliary **10** which gave **16b** in a moderate yield of 69% but with significantly better *de* of 86% (Scheme 5).



Scheme 5: Asymmetric alkylation

The cleavage of the auxiliary was achieved by reduction to the primary alcohol, followed by oxidation and Wittig reaction bringing the isobutene group in place **17**. The next two step reaction sequence was crucial as the whole synthetic plan relies on it. At first the TBS group was removed from protected hydroquinone and then the corresponding *para* quinone was formed by oxidation. This compound was never isolated but detected *via* TLC and NMR.

Now this intermediate **18** readily underwent the intramolecular Diels- Alder reaction to give the 5,6,6 ring system **19** which was only a reduction, an epimerization and a demethylation away from the final product **20** which was received in a yield of 21% over the last seven steps (Scheme 6).



Scheme 6: Preparation for the IMDA and final steps

Even though the total synthesis of such a challenging molecule must be seen as a great success, the authors did not share all the synthetic and analytic information they should have gathered during their work. This fact makes it hard to realise what might have gone wrong, but leaves room for speculation about the final structure which compared to the isolated elisabethin A[1] might have the right constitution but wrong configuration. The spectra of their final product was described to be "in agreement" with the spectra recorded by the Rodriguez group. Figure 2 depicts the ^{1}H-NMR spectra which clearly are not superimposable.

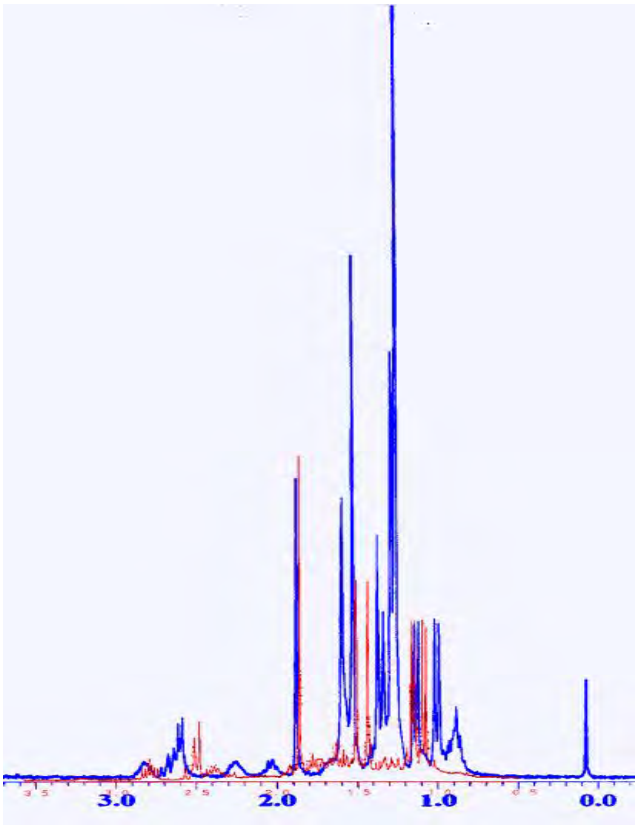


Figure 2: Comparison of ^{1}H-NMR: Mulzer[4] (blue) and Rodríguez [1](red)

However, this is not the only disagreement. Another evidence is revealed in the paper published by Rawal *et al.*[5] which will be discussed in more detail in the following chapter.

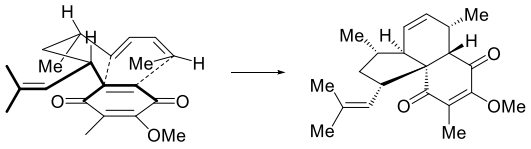
A close insight into what could have gone wrong with the IMDA is given in a review by Zanoni and Franzini.[8] They discuss different aspects of the synthesis, but most notably the crucial IMDA. They focused on the two most important questions which are:

How did the precursor look like right before the IMDA and
via what transition state could the reaction have proceeded?

Four different major possibilities were considered:

1) *E,Z* configuration of the diene and *exo* transition state
2) *E,Z* configuration of the diene and *endo* transition state
3) *E,E* configuration of the diene and *exo* transition state
4) *E,E* configuration of the diene and *endo* transition state

2.1.1 *E,Z* configuration of the diene and an *exo* transition state

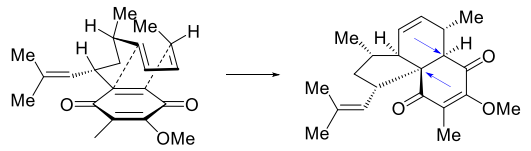


18 **19a**

Figure 3

This *exo* transition state proposed by Mulzer *et al.* (Figure 3) would lead to a structure possessing six correctly installed stereocentres, only missing minor structural changes to result in the final elisabethin A. Due to the reported reaction conditions (tenfold amount of $FeCl_3$, room temperature) applied in the oxidation step which then triggered the IMDA, one can assume that the $FeCl_3$ acted as Lewis-acid. [9]This led then to the favoured *endo* instead of *exo* transition state.[10]

2.1.2 *E,Z* configuration of the diene and *endo* transition state

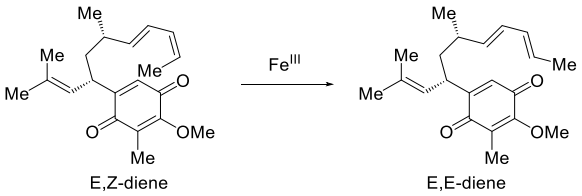


18 **19b**

Figure 4

The favoured *endo* transition state would lead to a structure where two out of four new stereocentres have the wrong configuration.[9] Nevertheless, the "wrong" configuration on C2 could solve the problem of the C2-epimerization which is very difficult according to Rawal. On the other hand, wrong configuration on C1 is not correctable leading to a diastereomer in the end.

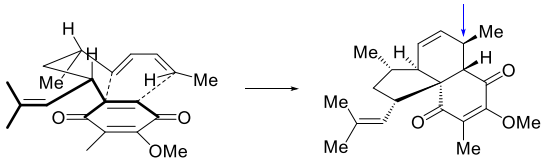
Besides favouring one or another transition state, the presence of the Lewis-acid in the reaction mixture is thought to enable *Z/E* isomerisation.[11] This could cause the reaction to a different IMDA precursor.



18 **18a**

Figure 5

2.1.3 *E,E* configuration of the diene and *exo* transition state

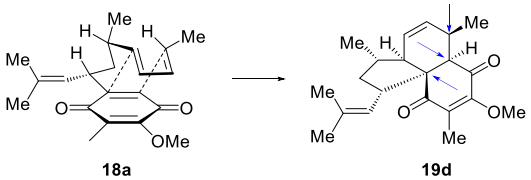


18a **19c**

Figure 6

A combination of the *exo* transition state and a wrong diene isomer could lead to structure **19c** which is a C3 epimer of the desired molecule. Now the same problem as in **19b** occurs: namely, the C2 centre would already have the correct stereochemistry of the final target molecule, but an inversion of the wrong C3 configuration is almost impossible.

2.1.4 *E,E* configuration of the diene and *endo* transition state



18a **19d**

Figure 7

The fourth scenario is the *endo* transition state with the *E,E* isomer where even three out of six centres (C1,C2 and C3) are assembled in the wrong configuration.

As a conclusion it can be stated that there are well-funded literature based reasons which make it seem much more probable that the synthesised structure is one of the diastereomers **19b**, **19c** or **19d**. Which one of those was actually synthesised cannot be told with certainty but there are several arguments which make some structures more and others less likely. One is the presence of $FeCl_3$ which could lead to *Z/E* isomerisation resulting in the *E,E*-diene system, which would then proceed *via* the *endo* transition state (preferably under low temperature and Lewis-acidic conditions) to **19d**.

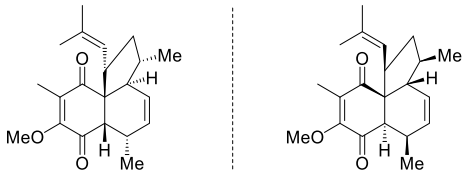


Figure 8: Intermediates: Mulzer (left) and Rawal (right)

As the Rawal synthesis targeted (*ent*)-elisabethin A both strategies proceeded *via* the same intermediate, but are enantiomers. Theoretically, the spectra of two enantiomers are not distinguishable. In this case however, they are. Although they look quite similar there are some signals in Mulzer's ^{1}H-spectra which show deviation up to 0.5 ppm. One possibility is that Rawal's structure is incorrect. Nevertheless, this is highly unlikely because after his failed approach to generate (*ent*)-elisabethin A he rerouted his synthesis and succeeded in the formation of (*ent*)-elisapterosin B.[12] Elisapterosin B has already been synthesised by that time and a comparison of the analytical data confirmed his correct stereochemistry. This allows the assumption that Mulzer's intermediate does not have the proposed structure.[4] The reason why Rawal was not able to synthesise (*ent*)-elisabethin A was the epimerisation at C2 which C2 did not succeed. While Mulzer reported a successful epimerisation of C2 using five equivalents of NaOH in refluxing MeOH/H_2O for five hours Rawal's epimerisation did not give any conversion despite the rougher conditions (NaOEt in refluxing EtOH). One possibility is that Mulzer did not succeed in epimerising C2 this could possibly lead to another argument which diastereomer Mulzer got in the end. Therefore a comparison of the four diastereomers and Rawals intermediate is shown in Figure 9.

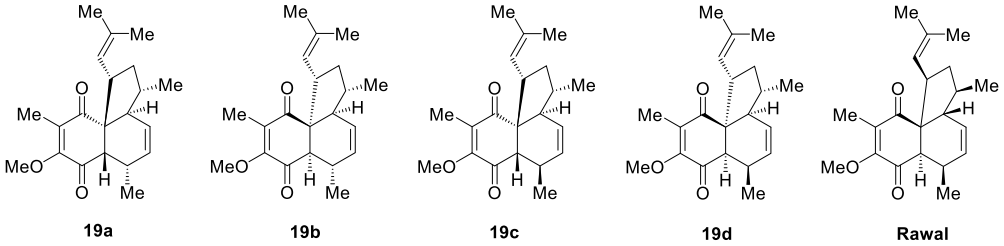


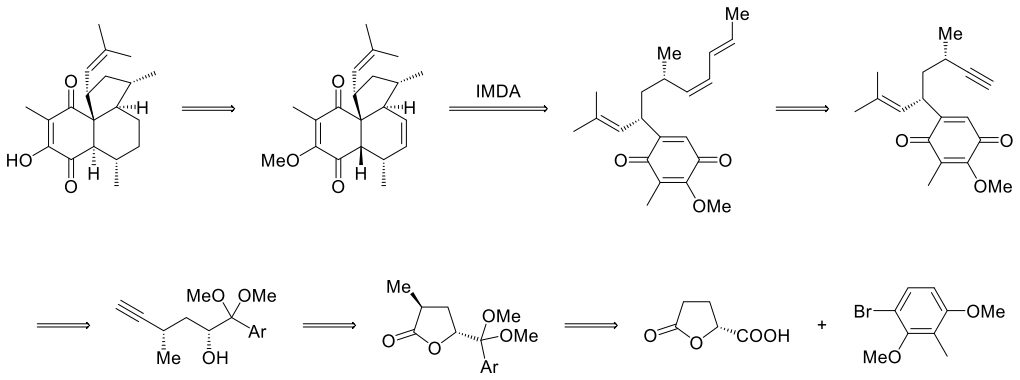
Figure 9: Mulzer's possible diastereomers (**19a-d**) and Rawal's (assured) intermediate

A successful epimerization of C2 in **19a** would have led to the correct final product. Besides the already mentioned disagreements in the spectra, a comparison of the optical rotation of the final and the isolated product [Mulzer: $[\alpha]^{25}_{D}$ +129.7 (c 0.05, $CHCl_3$); Rodríguez: $[\alpha]^{25}_{D}$ +133.0 (c 0.45, $CHCl_3$)] reveals that Mulzer's measured value cannot be seen as proof of the right structure. These facts make it very unlikely that the epimerisation of compound **19a** succeeded which leaves **19b-d** as possible diastereomers.[8]

2.2 Waizumi and Rawal 2003[5]

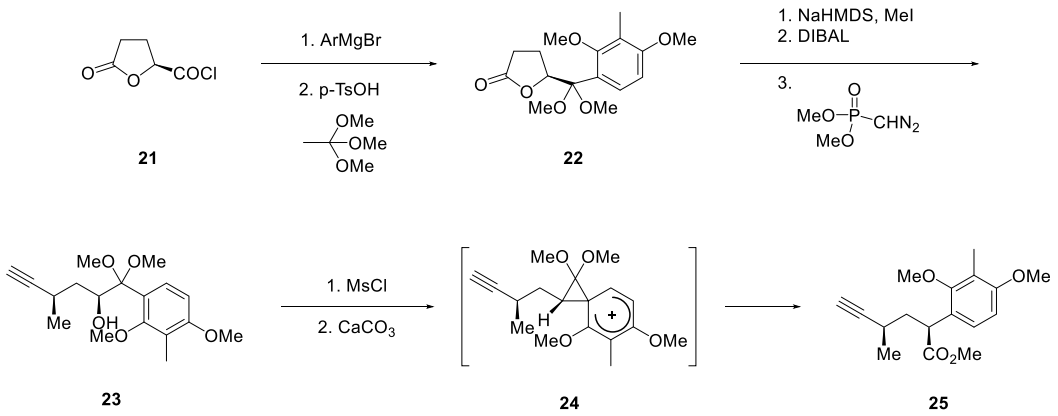
A few months after the synthesis of Heckrodt and Mulzer, Rawal published his synthesis of the enantiomer of elisabterosin B.[12] His original plan was the synthesis of (*ent*)-elisabethin A, the retro synthetic analysis (Scheme 7) is although described for the natural elisabethin A.

This strategy also relies on an IMDA reaction. The key step is very similar to Mulzer's because the IMDA is supposed to build up the five and the second six membered ring. Besides, both precursors for the IMDA carry two out of six necessary stereo centres. A small difference with huge consequence is the structure of the quinoidal IMDA precursor. Instead of an *E,Z* diene Rawal used a *Z,E* diene which might be the reason for the success of his key step. Furthermore, $FeCl_3$ was not used in this oxidation. This *Z,E* diene was installed *via* a Negishi coupling of an alkyne and a Z-bromoalkene. In addition, the quinone functionality was established *via* a copper catalysed O_2 oxidation of the position *para* to the phenol OH position of the aryl ring system. Then the isobutene group was brought in place *via* an elegant Pinacol-type rearrangement followed by reduction and Wittig reaction. The precursor of the open form could be derived from a lactone containing two stereocentres of which one was installed *via* substrate controlled methylation. The starting materials therefore can be assigned as derivative of glutamic acid and 3-brom-2,6-di methoxy toluene.



Scheme 7: Rawal's retrosynthetic analysis

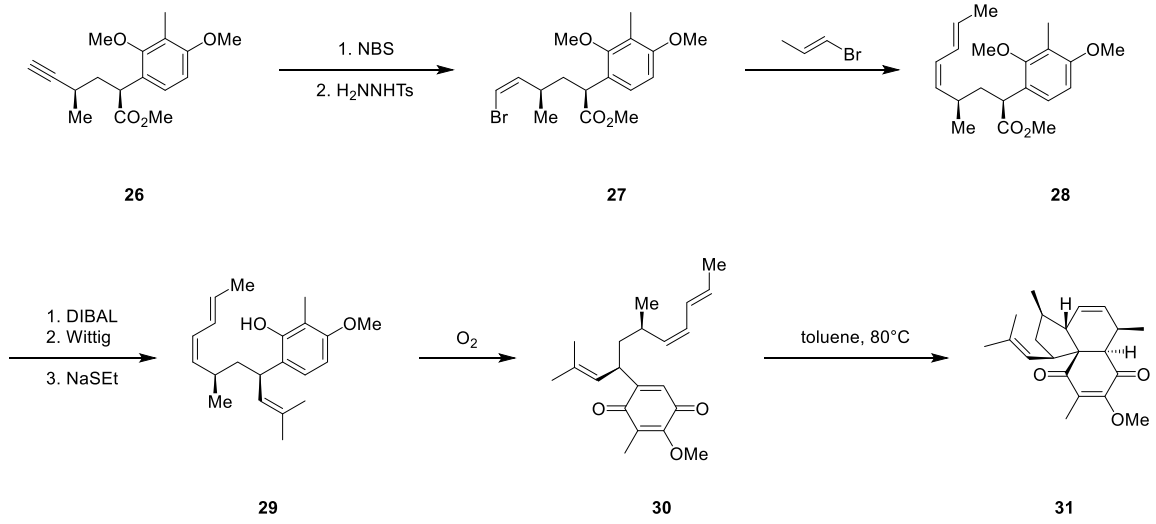
Due to this retrosynthetic analysis, the forward synthesis should be viable for both, elisabethin A and (*ent*)-elisabethin A, but as the natural occurring L-enantiomer of glutamic acid is cheaper than the D-enantiomer, the decision which elisabethin A enantiomer should be targeted was made by money. First, L-glutamic acid was converted to (*S)*-(+)-tetrahydro-5-oxo-2-furancarboxylic chloride (**21**) which was the reported starting material. It was coupled to the Grignard reagent of 1-bromo-2,4-dimethoxy-3-methylbenzene, mediated by $ZnCl_2$ and conducted under Pd catalysis. The received ketone was reacted with trimethyl orthoacetate under acidic conditions giving ketal **22**. Substrate controlled installation of the methyl group (C6 position in (*ent*)-elisabethin A) was achieved in a *dr* of 8:1 with NaHMDS and MeI. The following reduction of the lactone to the corresponding lactol (aldehyde) and treatment with Seyferth reagent afforded open chained alkyne **23**. Then the secondary alcohol was mesylated followed by triggering the Pinacol-type rearrangement *via* heating in MeOH with an excess of $CaCO_3$ acting as acid scavenger. The reaction was believed to proceed *via* intermediate **24** before forming methyl ester **25** in a yield of 27 % over seven steps (Scheme 8).



Scheme 8: Diastereoselective methylation and pinacol-type rearrangement

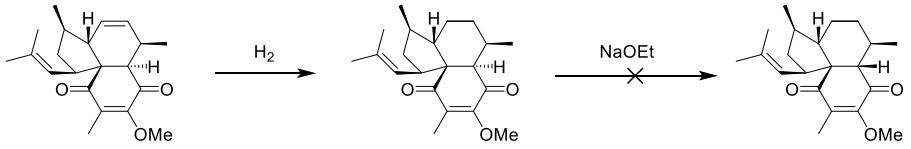
Subsequently, the alkyne group of ester **25** was brominated and reduced giving *Z*-bromoalkene **27**. Pd catalysed cross coupling of *Z*-bromoalkene with *E*-bromopro-1-ene resulted in the *Z,E* compound **28** crucial for the success of the later IMDA.

The installation of the isobutene group was achieved in a two-step sequence starting with DIBAL reduction to result in aldehyde formation. It was then reacted with the corresponding Wittig reagent to give the isobutene side chain. In addition, a selective demethylation of the more hindered methoxy group was achieved by the usage of NaSEt resulting in phenol **29**. Salcomine catalysed oxidation of the position *para* to the free phenol OH of the aryl system resulted in the selective formation of quinone **30**. In the end, the IMDA was triggered by heating in toluene giving compound **31** as single diastereomer in an overall yield of 13 % over eight steps (Scheme 9).



Scheme 9: *Z,E* diene installation and IMDA

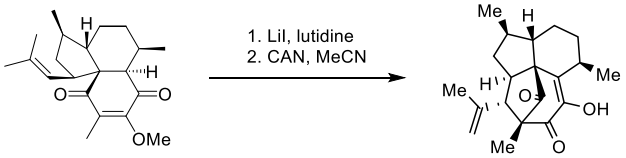
As the key step of the synthetic strategy worked smoothly, there were only reactions of minor difficulty. The first was the olefin hydrogenation, which was accomplished in quantitative yield while using Wilkinson's catalyst to receive alkane **32**. The second last step, the epimerisation of C2 from (*ent-1β*)-elisabethin A to (*ent*)-elisabethin A did not work even though it was expected to. As application of harsh conditions like NaOEt in refluxing EtOH did not lead to any formation of desired product, the last resort was to reroute the synthesis. In this case it was successfully done generating (*ent*)-elisapterosin B (Scheme 10).



31 32 33

Scheme 10: Hydrogenation and failed epimerisation

(*ent*)-Elisapterosin B could be synthesised in a two-step sequence beginning with the demethylation resulting in a secondary allylic alcohol. The necessary final C10/C15 cyclisation was then achieved by a nature-inspired strategy using two equivalents of cerium ammonium nitrate (CAN). Each equivalent was able to do a single electron transfer (SET) of which the first oxidised the C14, forming a ketone and the second generated a radical on C15. This radical was now believed to attack C10 forming the ketone-bridge while leaving a radical on C11. The second equivalent of CAN oxidised C11 forming a tertiary carbocation. Deprotonation resulting in the final olefin **34** could now have occurred at C10 or at one of the C12 methyl groups. Generally, the higher branched olefin is formed, however, in this case it was believed that due to stereo electronic reasons the lower substituted olefin was formed (Scheme 11).

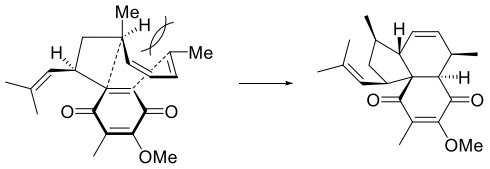


32 34

Scheme 11: Rerouting to (*ent*)-elisapterosin B

Comparison of the final (*ent*)-elisapterosin B and elisapterosin B synthesis by Kim and Rychnovsky [12]revealed that the suggested structure for (*ent-1β*)-elisabethin A **32** was correct. As already mentioned above the fact that the stereo chemistry of the final product is correct is thereby proof for the correct structure of compound **31**. The comparison of both enantiomers in Figure 2 now leaves only one conclusion: Mulzer's „enantiomer" has a different configuration and is therefore most likely a diastereomer of Rawal's intermediate. Rawal's correctly assembled stereochemistry was achieved *via* an *endo* transition state.

2.2.1 *Z,E* configuration of the diene and *endo* transition state



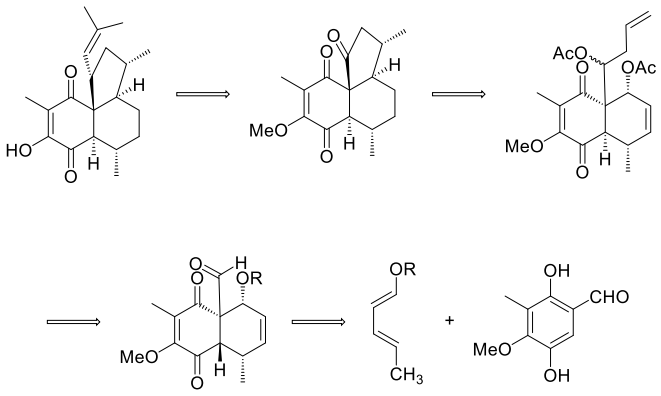
31

Figure 10

In contrary to Mulzer's IMDA only one transition state was described as possible by Zanoni and Franzini, which is in agreement with the proposed structure.[8] This arrangement avoids the 1,3 allylic strain between the C7 methyl group and the propenyl chain of the *Z* double bond. Besides steric reasons this *endo* transition state is also plausible because the conditions and reagents applied in the preparation of the IMDA precursor do not indicate any possibility of isomerisation.

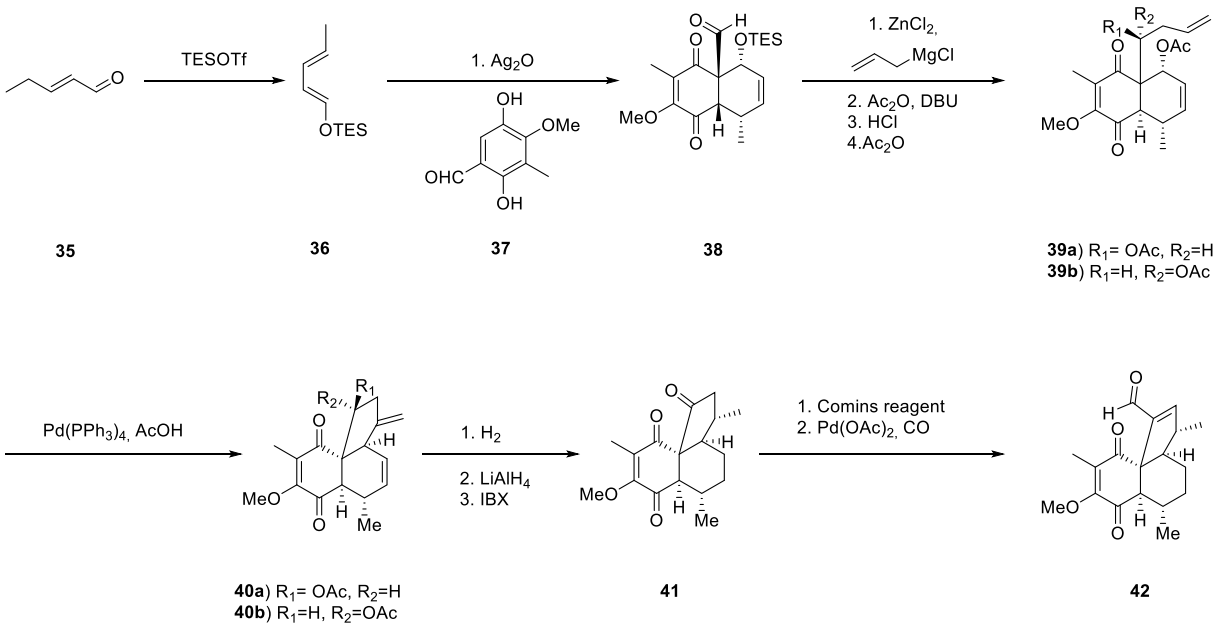
2.3 Preindl and Mulzer 2014[6]

As the final compound of the first approach from 2003 was "met with criticism from outside" the Mulzer group decided to tackle elisabethin A again. This time they planned to not rely on such a restrictive key step as in 2003. Having learned the lesson the idea was to establish the molecule centre by centre which should give the possibility to assert the configuration of every chiral carbon individually. The retrosynthetic analysis (Scheme 12) reveals that the installation of the isobutene group was meant to be one of the last steps. The ketone which should be olefinated was not carrying six but only five stereo centres which means that not only the isobutene group needed to be installed but it needed to be done in an diastereoselective way. The annulation of the five membered ring was then achieved using a palladium ene cyclisation. The allyl group on the other hand was brought into the molecule attacking the aldehyde with the corresponding zinc reagent. This aldehyde could now easily be generated *via* a Diels-Alder reaction, this time in an intermolecular way, leading to two quite simple building blocks.



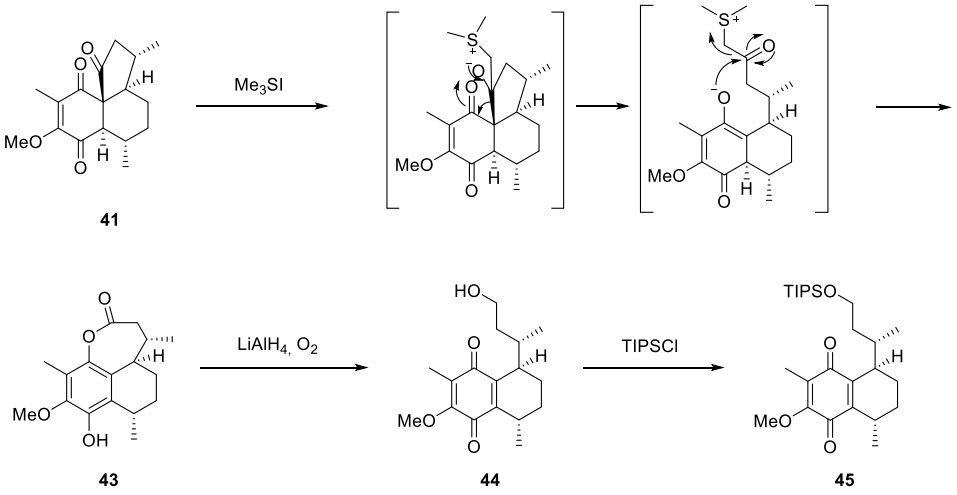
Scheme 12: Mulzer's retrosynthetic analysis, second approach

The first building block was synthesised starting from *α,β*-unsaturated aldehyde **35**. It was reacted with TESOTf under basic conditions generating the silylated diene **36**. The crude mixture of *E* and *Z* diene then underwent a clean diastereoselective Diels-Alder reaction with known hydroquinone **37** in the presence of silver(I) oxide resulting in the single diastereomer **38**. As preparation of the five membered ring formation elongation on C9 was necessary, the corresponding allyl zinc reagent was reacted with the aldehyde functionality. The next steps were the protection of the just generated secondary alcohol with Ac_2O using DBU as base which also epimerised C2 resulting in the correct configuration. A protecting group switch was executed using HCl to cleave TES followed by OAc protection using Ac_2O resulting in compound **39a/b** which showed a diastereomer ratio of 4:1. Subsequently, the five membered ring was formed using a palladium ene cyclisation obtaining the tricyclic ring system **40a/b**. Next on the agenda was the hydrogenation of the olefins. In case of the C7 methylene group it fortunately occurred from the right direction giving the correct stereochemistry for the methyl group. Similar to their first approach ester hydrolysis appeared to be problematic which is why a general reduction/oxidation strategy could not be avoided using $LiAlH_4$ and Dess-Martin- periodinane resulting in ketone **41**. Due to the fact that the reduction/oxidation sequence "destroyed" chiral information on C9, the moderate diastereomer ratio of 4:1 was not of importance any more. The further procedure accepted the fact that the installation of the last stereocentre might not be diastereoselective. Therefore the idea was to get to the final compound doing a racemic reaction followed by separation of the diastereomers. After all attempts introducing the isobutene group *via* direct CC coupling failed, ketone **41** was transformed into the enol triflate using Comins' reagent. Carbonylation using tetrakis(triphenylphosphine)palladium(0) and CO led to the *α,β*-unsaturated aldehyde **42** in an overall yield of 15-18 % over 12 steps (Scheme 13). The double bond of the unsaturated system was said to be inert towards reduction, which meant that the correct product could not be reached in the end. Every other attempt of generating a different carbonyl functionality, like an ester, from enol triflate led to epimerisation of C2.



Scheme 13: Consecutive installation of five stereo centres

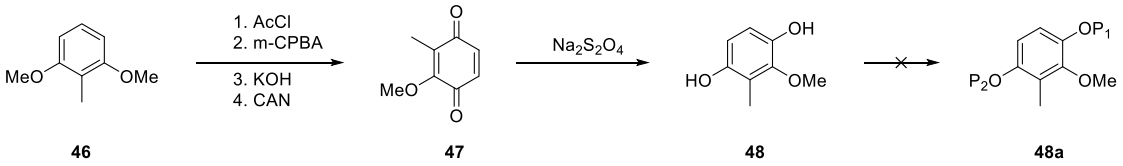
As aldehyde **42** was not useful towards rerouting the synthesis, the authors turned back on ketone **41** which was synthesised in an overall yield of 23-26 %. The geometry of the tricyclic system especially the position of the C1-C9 bond was said to be advantageous for a Grob-Eschenmoser fragmentation like retro-Claisen cleavage. Therefore trimethyl sulfonium iodide was used to cleave the C1-C9 bond leading to the seven membered phenolic lactone **43**. Reduction with $LiAlH_4$ and oxidative workup resulted in the primary alcohol **44** which was only a TIPS protection away from final bicyclic quinone **45**, resulting in 76 % yield over three steps (Scheme 14). The spectra of compound **45** and the corresponding intermediate in Rychnovsky's (elisapterosin B) synthesis matched, which was proof of the correct stereochemistry of the remaining three centres. Mulzer's intermediate could be converted to colombiasin A and elisapterosin B following the course of Rychnovsky's synthetic plan, which was reported but not executed.[12]



Scheme 14: Generating Rychnovsky's intermediate to proof stereo chemistry[12]

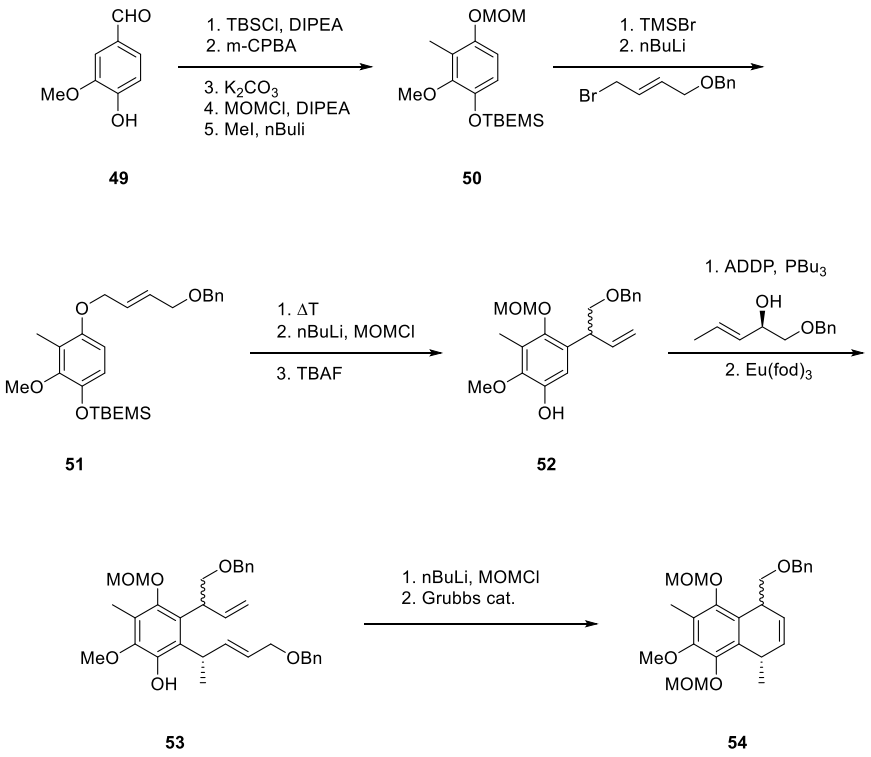
2.4 Steiner 2014[13]

(Retrosynthetic analysis given in Scheme 22, 23)



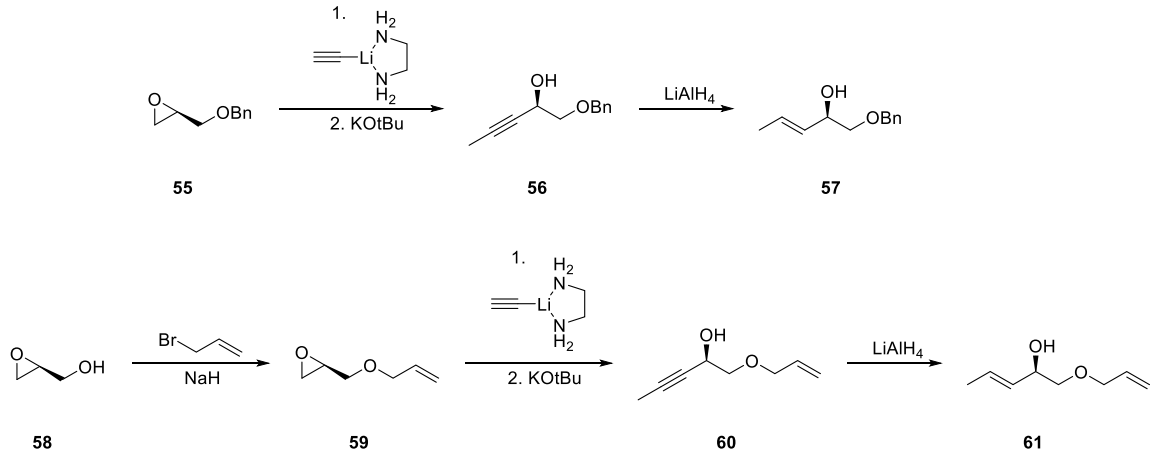
Scheme 15: Approach towards orthogonally protected hydroquinone

First, commercially available 2,6-di methoxy toluene (**46**) was transferred into quinone **47** in a straight forward four step sequence (Scheme 15). In contrary to literature, generating hydro quinone **48** was said to result in very low yield. Additionally, differentiation of the so obtained two phenol OH groups was not possible which in consequence made a mono protection impossible and always led to a mixture of three inseparable compounds of one double and two mono protected. Therefore this approach to receive an orthogonally protected hydro quinone was abandoned quickly in favour of another literature known procedure starting from commercially available vanillin (**49**).



Scheme 16: From vanillin to bicyclic ring system

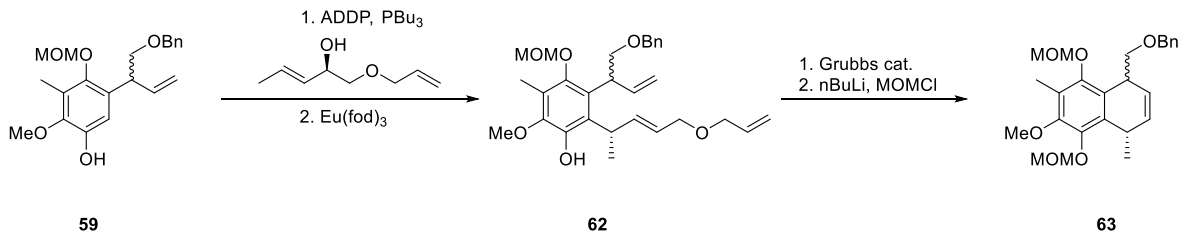
The second approach started with TBS protection of phenol **49** before converting the aldehyde to an ester. This gave the second phenol OH after basic hydrolysis. The next steps were a MOM protection and the installation of the methyl group. This interestingly went along with methylation of the TBS protecting group yielding in a **t**ert **b**utyl, **e**thyl, **m**ethyl silyl (TBEMS instead of TBS) protecting group **50**. Usage of TMSBr assured selective MOM cleavage allowing the attachment of the first vinyl ether group using n-BuLi and (*E*)-(((4-bromobut-2-en-1-yl)oxy)methyl)benzene. Ether **51** then underwent a thermally induced Claisen rearrangement followed by MOM protection of the phenol and cleavage of the silyl group using fluoride. Mitsunobu reaction of phenol **52** with a chiral alcohol followed by Lewis-acid catalysed Claisen rearrangement using Europium(III)-tris(1,1,1,2,2,3,3- heptafluoro-7,7-dimethyl-4,6-octanedionate) (throughout this work referred to as $Eu(fod)_3$) yielded in diene **53**. After MOM protection a ring closing metathesis (RCM) allowed the formation of bicyclic compound **54** in 6 % yield over 13 steps (Scheme 16). At this point it must be said that the yield was satisfying for the first 12 steps (75% or higher for 11 steps) but the RCM only yielded in 51 % product while consuming 17 % catalyst. Such circumstances demanded changes before scale-up.



Scheme 17: Chiral alcohol synthesis

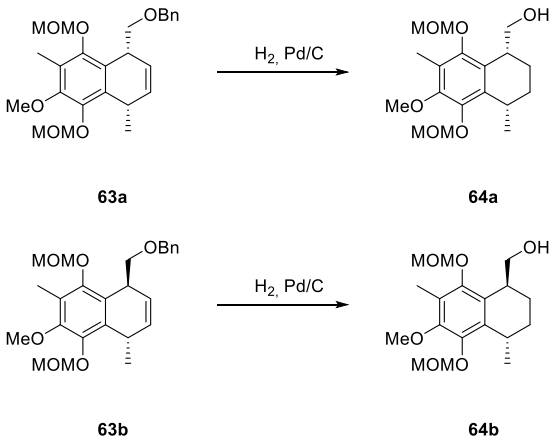
Therefore, the chiral alcohol was modified simply by exchanging the OBn group with an O-allyl group by reacting the commercially available (*S*)-glycidol (**58)** with allyl bromide instead of benzyl chloride. The next steps were the opening of epoxide **59** using lithium acetylide followed by basic alkyne isomerisation giving **60** before $LiAlH_4$ reduction led to the final compound (*R,E*)-1-(allyloxy)pent-3-en-2-ol (**61**) in 66 % yield (Scheme 17). This chiral alcohol with its modified relay arm in place should achieve better yields while demanding less catalyst. With this superior building block in hand the sequence beginning at phenol **52** was repeated.

This four step sequence in comparison to the first approach (**52** to **54**) resulted only a little more satisfying yield (16 vs 21 %) but the ring closing metathesis was improved from 51 % yield and 17 % catalyst consumption to 83 % yield while only requiring 8 % catalyst (Scheme 18).



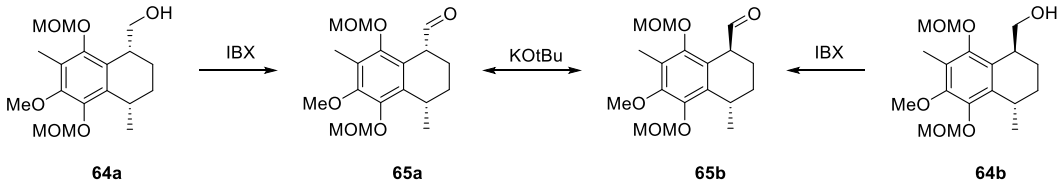
Scheme 18: Modified sequence towards bicyclic ring system

The two diastereomers **63** were separated by means of column chromatography isolating *cis* and *trans* diastereomer in pure form **63a/b**. Reduction of the olefin and deprotection of the benzyl group could be achieved by hydrogenation resulting in primary alcohol **64a** respectively **64b** (Scheme 19).



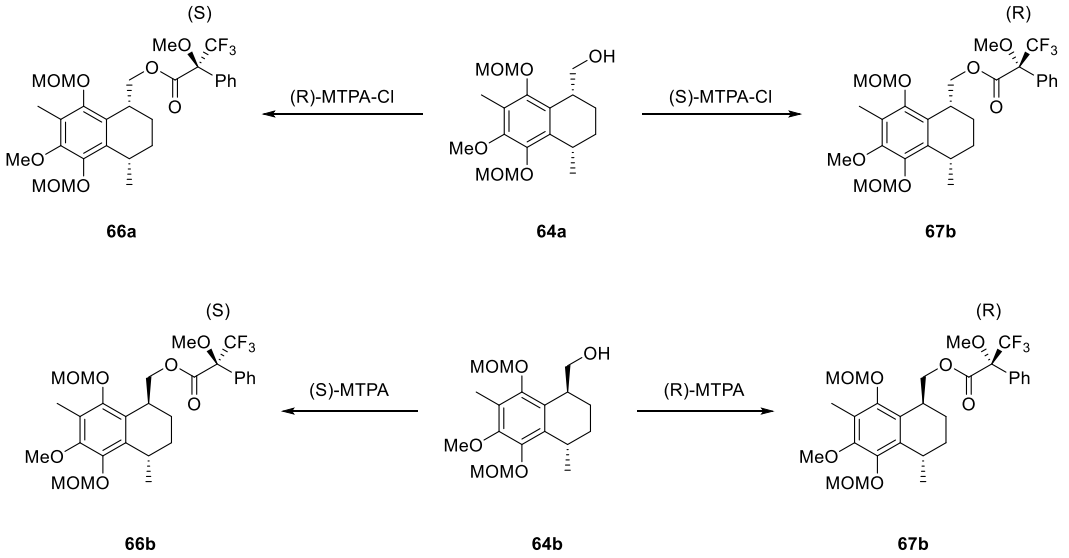
Scheme 19

Having the pure desired and undesired primary alcohol in hand the next target was the oxidation to the corresponding aldehyde using Dess-Martin- periodinane and epimerisation of C6. Therefore *cis* diastereomer **64a** was oxidised to aldehyde **65a**, which was further reacted with KOtBu expecting full epimerisation. MM2 energy minimizations revealed only small energy differences between *cis* and *trans* diastereomer **65a** and **65b** which might have been the reason for unsuccessful epimerisation.



Scheme 20: Failed epimerisation at C6

For confirmation of stereoselectivity, both alcohols were converted into their corresponding (*R*) - and (*S*) - Mosher ester derivatives which was accomplished either *via* using Mosher's acid or the Mosher's acid chloride (Scheme 21).



Scheme 21: Generating Mosher's esters

Comparison of this resulting set of diastereomers respectively enantiomers allowed the determination of enantiomer excess of 96% (undesired Claisen rearrangement product with (*R*)-configuration on C3 not shown due to clarity reasons).

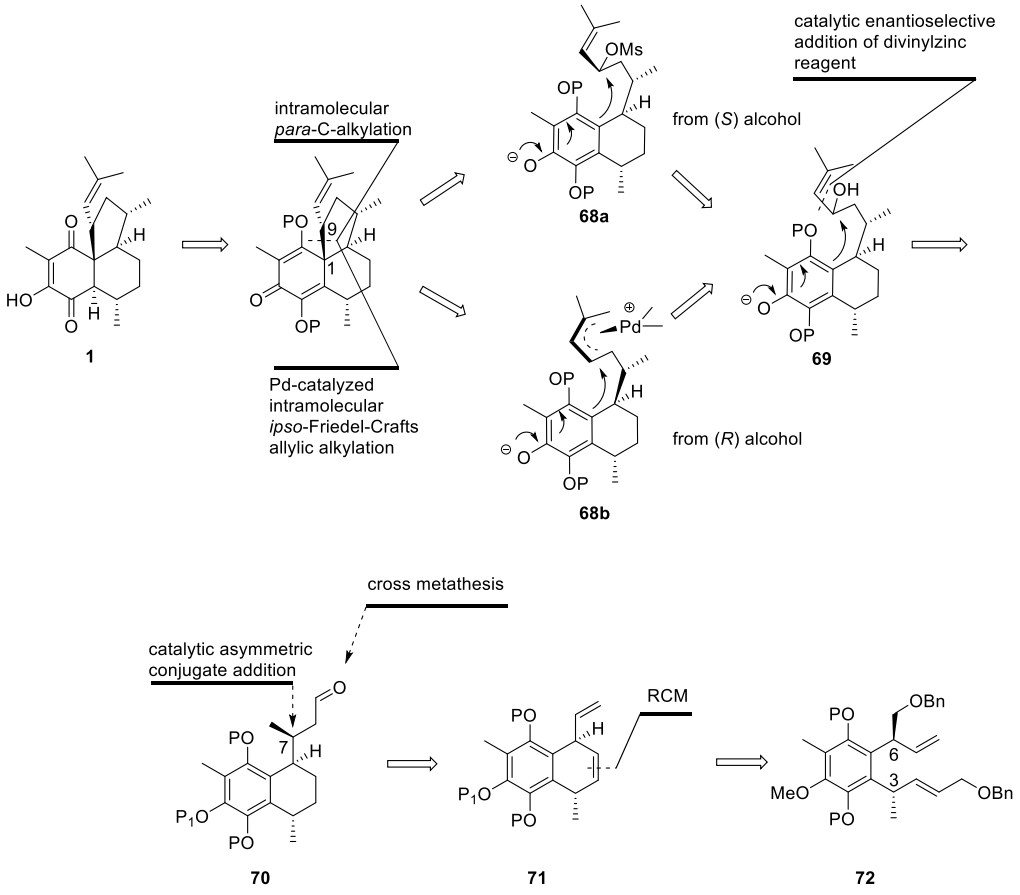
In conclusion it must be said that this work provided vital information regarding my own synthetic approach:

1. The modification of the chiral alcohol and as result the improvements of the ring closing metathesis
2. Crossing the epimerisation off the list of possibilities to adjust correct C6 configuration
3. Proofing the stereoselective nature of the Lewis-acid catalysed Claisen rearrangement by determining an ee of 96 %.

3 Own Synthesis

3.1 Retrosynthetic analysis

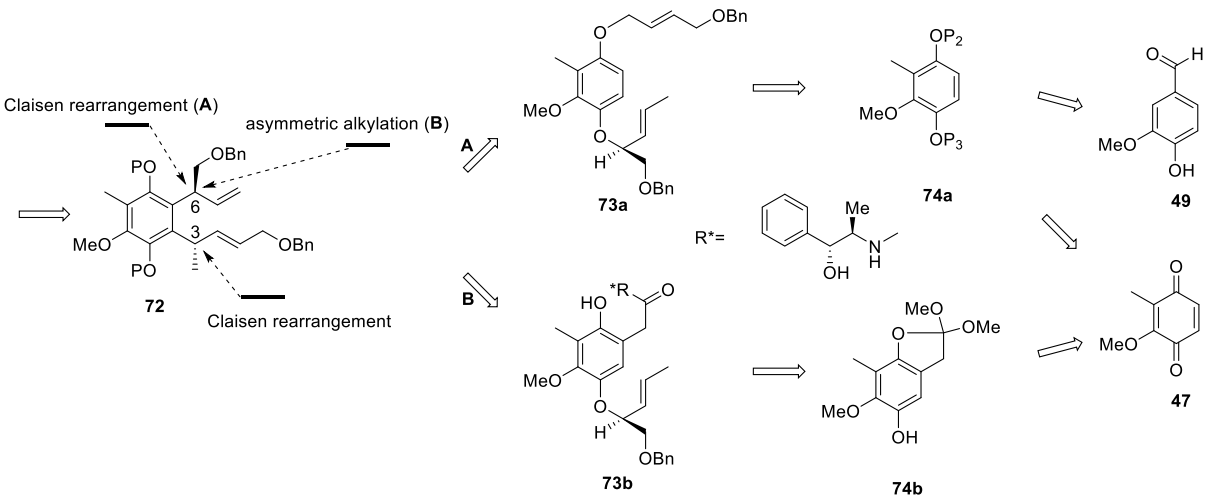
As we claim our synthesis to be biomimetic the strategy was more or less dictated by nature. Thus, some structures discussed in the retrosynthetic analysis are looking quite similar to those shown in Scheme 1. Among them, the open chained bicyclic precursor for the C1-C9 cyclisation step has to be highlighted as it is almost identical to intermediate **68a/b** aside from OH protection.



Scheme 22: Retrosynthetic analysis; from elisabethin A to diene

The formation of the five membered ring performing abovementioned C1-C9 cyclisation should be accomplished either *via* an intramolecular *para*-C-alkylation or a Pd/Ir- catalysed *ipso*- Friedel-Crafts allylic alkylation (Scheme 22).[14,15,16,17,18,19] Both intermediates **68a/b** could be derived from the same alcohol, determined by the choice of cyclisation conditions the (*R*) - or (*S*) - form.

The installation of the isobutene (2-methylprop-1-ene) group could be achieved by a catalytic enantioselective addition of the corresponding divinyl zinc reagent.[20] Which alcohol will be obtained after the addition to the aldehyde is determined by the configuration of the catalyst. The C7 methyl group could be brought in place conducting a catalytic asymmetric 1,4- addition of the *α,β*-unsaturated carbonyl **70** which could an ester.[21] The just mentioned carbonyl functionality and the chain elongation could be accomplished applying a cross metathesis (CM) using methyl acrylate.[22] The non-aromatic ring in the bicyclic compound **71** could be constructed *via* a Ring Closing Metathesis (RCM) which would lead to the diene **72**.[23]



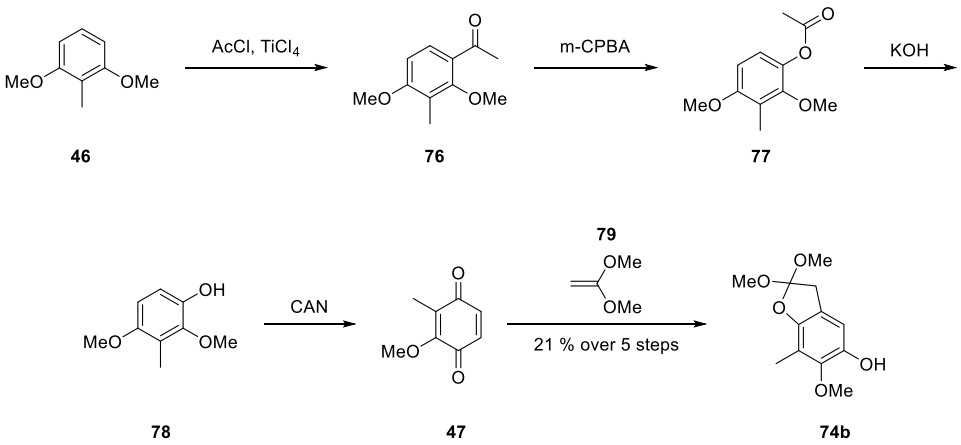
Scheme 23: Retrosynthetic analysis; from starting material to diene

The lower carbon chain carrying chiral centre C3 could be brought in place *via* Claisen rearrangement of the corresponding ether which was installed by means of Mitsunobu reaction (Scheme 23).[24] Both strategies (A/B) use the same procedure while differing for the upper carbon chain. Strategy (A) introduces C6 *via* a second Claisen rearrangement resulting in a racemic compound which could be derived from diether system **73a**. Then the upper ether could be installed performing a Williamson ether synthesis, the lower by the just mentioned Mitsunobu reaction. The precursor for this is meant to be an orthogonally protected hydroquinone **74a** which again could be derived from either quinone **47** or commercially available vanillin (**49**).[25] Strategy B, on the other hand, is meant to bring in centre C6 early before doing an asymmetric alkylation using a chiral auxiliary **73b** assuring the correct configuration. The auxiliary chosen for this purpose was (*R*,*R*) pseudoephedrine.[26] The precursor for this strategy would be literature known orthoester **74b** which could be generated from the easily accessible quinone **47** *via* Michael addition.[27]

The chiral alcohol used in the Mitsunobu reaction could be synthesised starting from commercially available (*S*)-glycidol (**58**).[28] The (*R*)-glycidol does not differ much in price, which would make (*ent*)-elisabethin A accessible without facing significant additional costs.

3.2 Preliminaries

Our synthetic approach will be enantioselective to avoid running into the same problems regarding C6 as Steiner did in 2014. Therefore, strategy B was chosen, starting from easily accessible quinone **47** which can be converted in a one-step reaction into orthoester **74b**.[25,27] Said orthoester was our "key starting material" because several different approaches discussed in the course of this work started from this very compound.

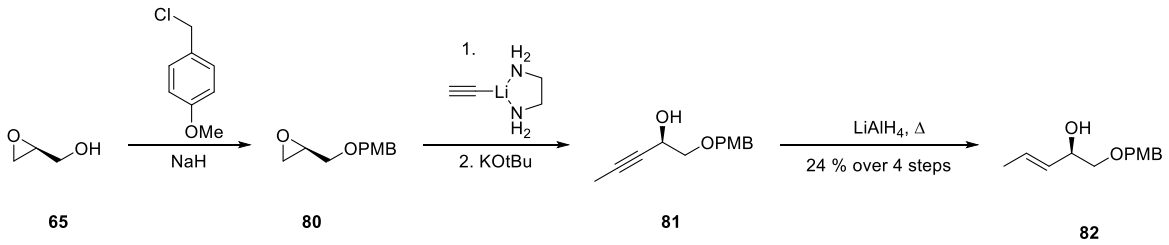


Scheme 24: Synthesis of orthoester **74b**

The sequence initiated from commercially available 2,6-dimethoxy toluene (**46**), which underwent a Friedel-Crafts acylation resulting in ketone **76**. The following Bayer-Villiger oxidation led to ester **77** which was subjected to basic ester hydrolysis giving phenol **78**.[25] Subsequent oxidation using cerium ammonium nitrate yielded in quinone **47**. Finally, Michael addition with literature known ketal **79** resulted in orthoester **74b**.[27] This five step sequence represented a reliable route to generate the "key starting material" (Scheme 24).

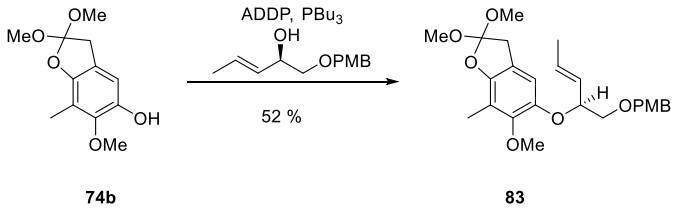
3.3 Chiral orthoester approach

The requirements to this starting material **74b** were principally the same as for Steiner's compound **50**. It should enable to react one of the phenol OH's selectively while leaving the other one untouched. Instead of doing an orthogonal protection of a hydroquinone followed by selective deprotection, the performed Michael addition already provided a mono protected hydro quinone. Before proceeding further towards intermediate **73b** chiral alcohol **82** needed to be synthesised.[28] Said alcohol was derived from commercially available (*S*)-glycidol (**65**) in a four step sequence. After PMB installation, opening of epoxide **80** was achieved using lithium acetylide. Following basic isomerisation gave compound **81**, which was subjected to $LiAlH_4$ reduction resulting in **82** in 24 % yield over four steps (Scheme 25).



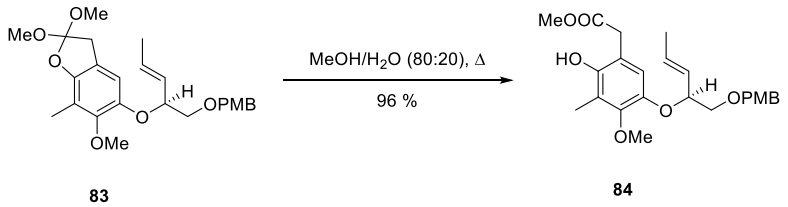
Scheme 25: Synthesis of chiral alcohol (**82**)[28]

In the next step, orthoester **74b** was converted into ether **83** using alcohol **82**, ADDP and PBu_3.[29]



Scheme 26: Mitsunobu reaction

With chiral ether **83** in hand, the next goals were the opening of the orhtoester and the protection of the free OH group. Therefore, ether **83** was refluxed in a mixture of $MeOH/H_2O$ for four hours obtaining phenol **84** (Scheme 27).[27]

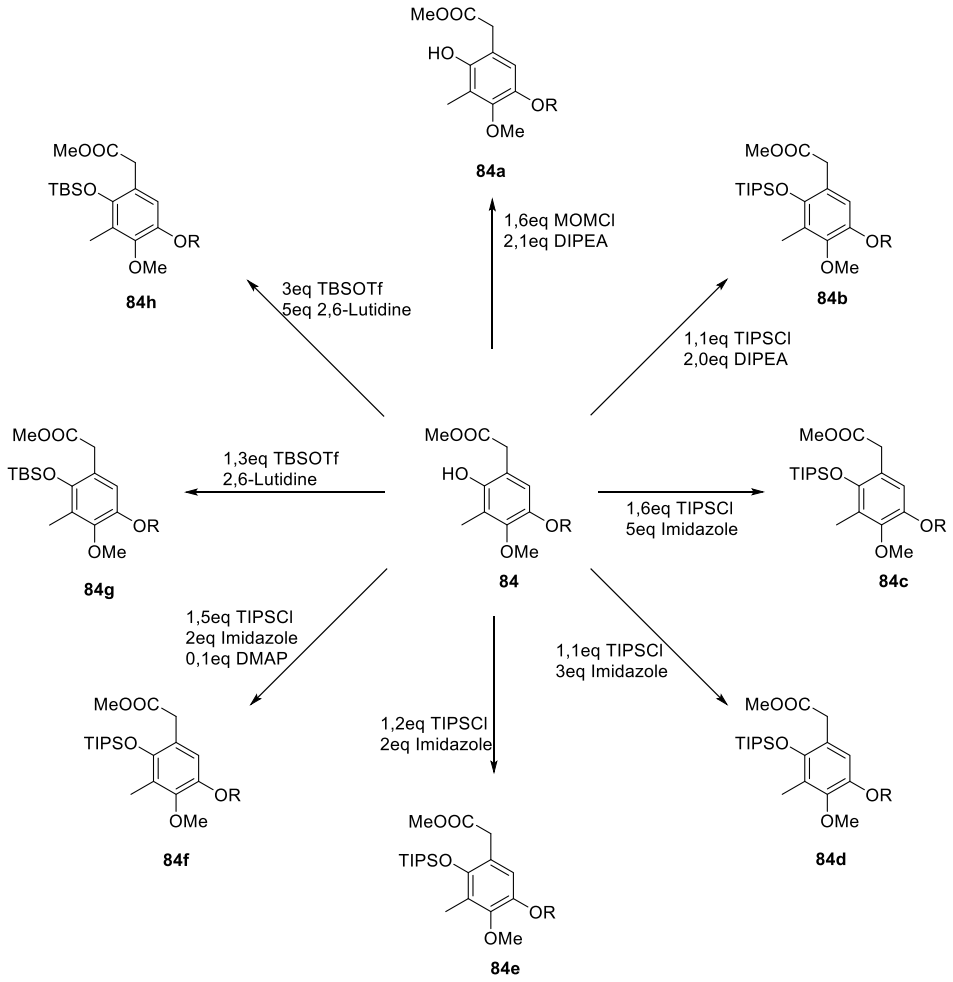


83 **84**

Scheme 27

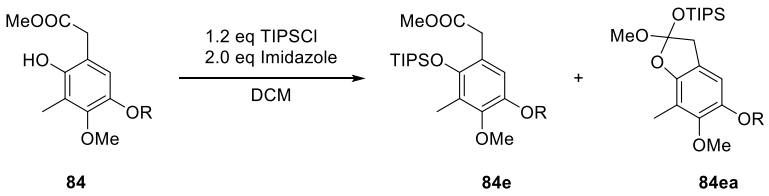
Said phenol needed to be protected, therefore several reactions were conducted applying different conditions, but none gave satisfying results. The chiral ether is referred to as OR in Scheme 28.

The first four experiments gave product **84a**-**d** in yields of approximately 30-65 %.



Scheme 28: Different protecting approaches

These low yields made it necessary to look for an optimisation of the reactions. As the equivalents of TIPSCl and imidazole as well as the nature of base had already been modified in said four reactions next selected parameter for variation was the solvent. Thus, DMF was exchanged by DCM.

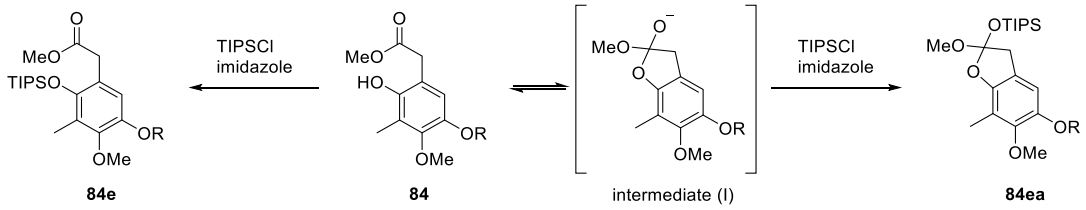


84 **84e** **84ea**

Scheme 29: Unexpected side product formation

This switch of solvent had the effect that not only a starting material product mixture was obtained, but formation of side product was observed as well (Scheme 29).

This side product formation left room for speculation. It could be explained by a lowered nucleophilicity of the phenol OH towards external electrophiles due to the electron donating abilities of the ether group in *para* position. This would make an intramolecular attack on the methyl ester group much more likely. Intermediate (I) could be formed in such a manner, which would be in an equilibrium with the phenolic form (Scheme 30).

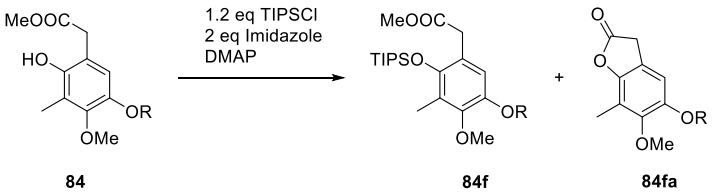


84e **84** intermediate (I) **84ea**

Scheme 30: Possible side product formation

Accordingly, the structure given in Scheme 30 was an assumption and could not be proven but an indication was the isolated side product **84ea** which represented the silyl protected (trapped) form of intermediate (I).

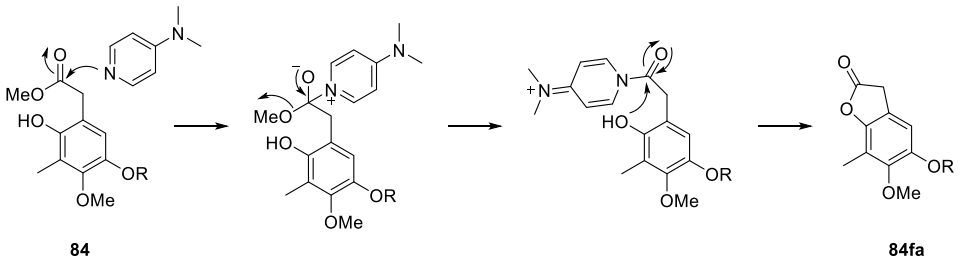
To avoid intramolecular reaction, the attack on the external electrophile needed to be promoted. Therefore, with the idea in mind of increasing the reactivity of TIPSCl, DMAP was added. The other parameters remained the same.



84 84f 84fa

Scheme 31: Unexpected side product formation

After separation by means of column chromatography, a mixture of lactone side product **84fa** and desired product **84f** was obtained in a mixture of almost 1:1 (Scheme 31).[30]



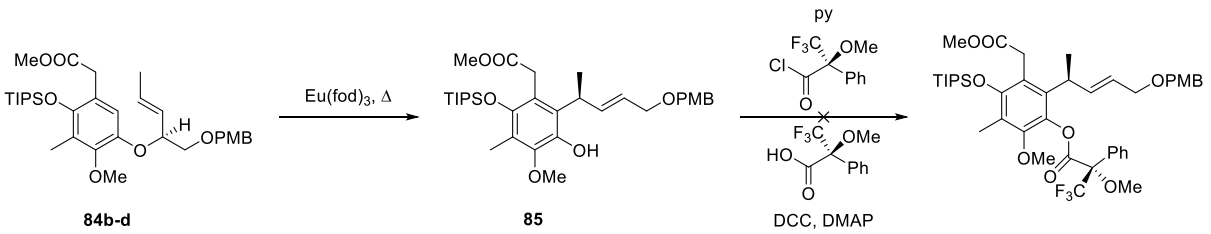
84 84fa

Scheme 32: Possible mechanism of lactone formation

Unfortunately, it seemed that DMAP activated not only TIPSCl but also the ester group, leading to lactone **84fa**. A possible activation mechanism is given in Schema 32. The structures shown are highly speculative as there was no proof except for side product formation. If the reaction at least proceeded in a similar way, this would give an explanation for the lactone formation in such quantities.

As the conducted TIPS installations did not turn out as we wanted, the next reactions were TBS protections. The first attempt did not give any conversion at all, the second one gave a mixture of starting material 84 and desired product **84h** in a ratio of 1:1.

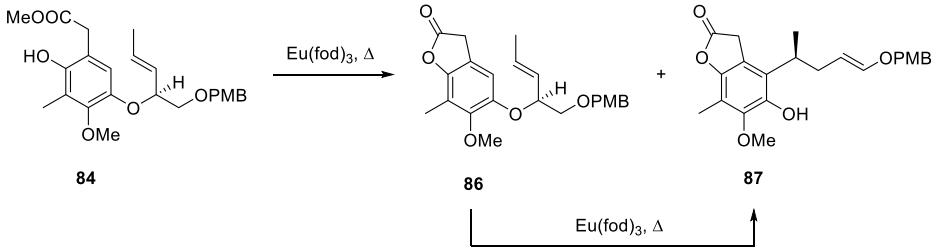
In summary, none of these results were satisfying enough to consider the OH protecting a possible strategy in the course of this synthesis. Nevertheless, enough TIPS protected product **84b**-**d** was generated to do some further experiments which should give essential information about the reactivity of the chiral ether group and the corresponding free phenol OH. This would be helpful when reaching again this point of synthesis while applying a different protecting strategy.



Scheme 33: Claisen rearrangement

One of the abovementioned further experiments was a Lewis-acid catalysed Claisen rearrangement of the chiral ether. Heating in toluene using 10 molar % $Eu(fod)_3$ gave slightly more than 20% yield of desired product **85** showing that the protocol works.[31] The low yield due to low conversion was not the major concern but the stereoselectivity of the rearrangement which was suggested to proceed *via* chair transition state.[32] Therefore, the idea was to generate the corresponding Mosher esters to determine the diastereomer ratio (Scheme 33). Unfortunately, none of the conducted ester formations gave the desired product.[33,34]

As the TIPS protection strategy failed, another way to proceed further had to be found. With a working Claisen rearrangement in hand, this reaction was repeated without OH protection.



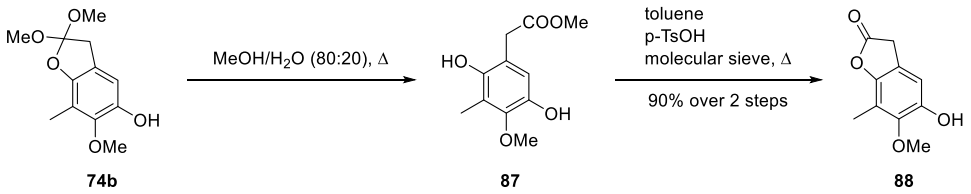
Scheme 34: Claisen rearrangement without free OH

Accordingly, phenol **84** was heated in toluene in the presence of 10 % $Eu(fod)_3$ resulting in a mixture of lactone **86** and **87** in a ratio 3:2. After separation, undesired product **86** was subjected to the same conditions to give lactone **87** (Scheme 34). This lactone formation could be explained in a similar way as the lactone **84fa** formation *via* an in an intramolecular nucleophilic attack of the phenol OH at the (Lewis-acid) activated carbonyl species.[35] This proved that the Lewis-acid catalysed Claisen rearrangement worked, but due to Eu^{3+}-activated lactone formation the percentage of $Eu(fod)_3$ needed, might be higher than necessary.

These results triggered the idea how to overcome the troubles of phenol protection. Due to lactone formation, phenol protection was obsolete. This superior route was at the same time the end of the "chiral orthoester approach".

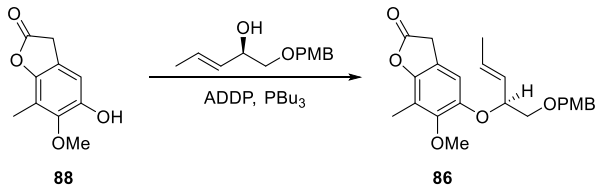
3.4 Lactone alkylation approach

The phenol with "lactone" protecting group could fortunately be synthesised in a two-step sequence starting from orthoester **74b**.



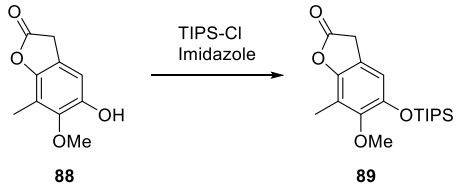
Scheme 35: Lactone formation

Refluxing in MeOH/H_2O (80:20) mixture for two hours afforded hydro quinone **87** which was then subjected to lactone formation conditions by heating a mixture of toluene, *para*- toluene sulfonic acid and molecular sieve for four hours resulting in product **88** (Scheme 35).[35] The following Mitsunobu reaction gave the chiral lactone ether **86** (Scheme 36).[29]



Scheme 36

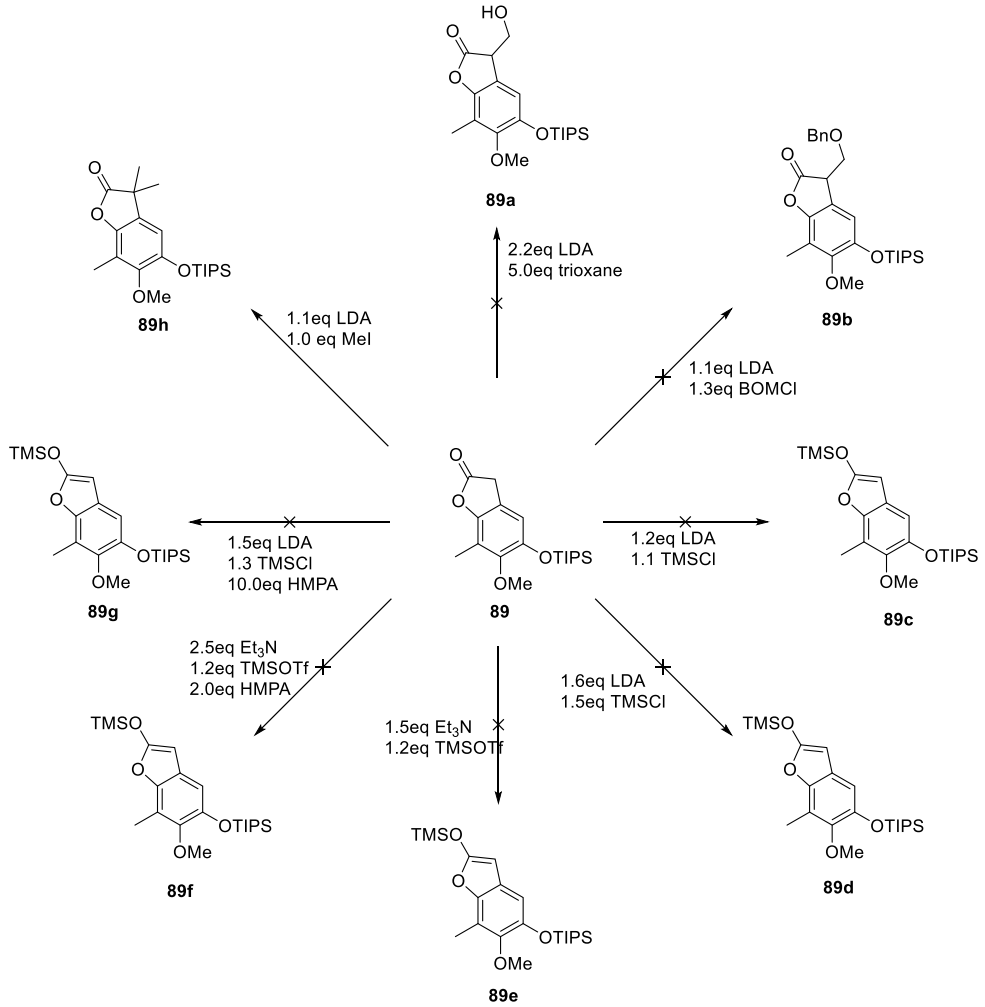
As it was mentioned above Mitsunobu reaction and the Claisen rearrangement worked out, the next task was the α-alkylation. Yet, protection of lactone **88** with TIPS gave compound **89** (Scheme 37) which was subjected to α-alkylation.



88 89

Scheme 37: Phenol TIPS protection

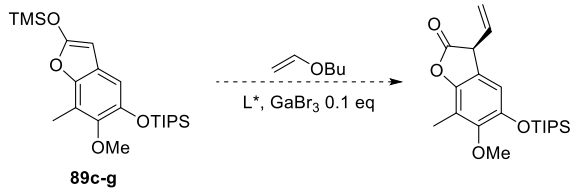
Several different reagents and protocols were applied for the alkylation of **89**, but none of them worked the way we had expected (Scheme 38).



Scheme 38: Failed lactone alkylation approaches

Therefore the first two approaches were meant to create a primary alcohol functionality **89a**, respectively protected primary alcohol **89b** as precursor for the aldehyde.[36] It must be stated that, at this point of the synthesis it was not known yet that the later epimerisation of C6 *via* basic treatment of the aldehyde functionality (**65a**) would not be successful.

As these alkylations did not give any conversion, a different strategy was aspired which should allow selective alkylation using a chiral ligand. To apply the above mentioned protocol, lactone **89** needed to be transferred into the corresponding TMS enol ether **89c**-**g** and could then react further to desired olefin shown in Scheme 39.[37]

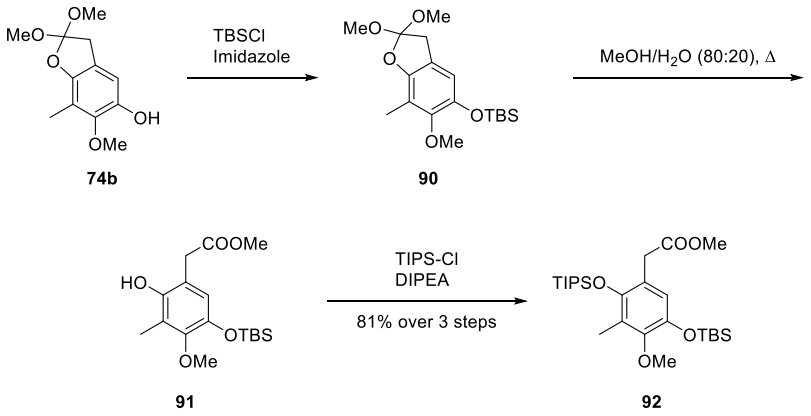


Scheme 39: Selective alkylating possibility

As it was not possible to generate the necessary enol ether **89c**-**g** this reaction could never be conducted, however, the starting material could be recovered. The only reaction in Scheme 37 that worked resulted in the double alkylated lactone **89h**. Therefore this approach was abandoned and we focused on the "double protection approach" which was applied on simultaneously.

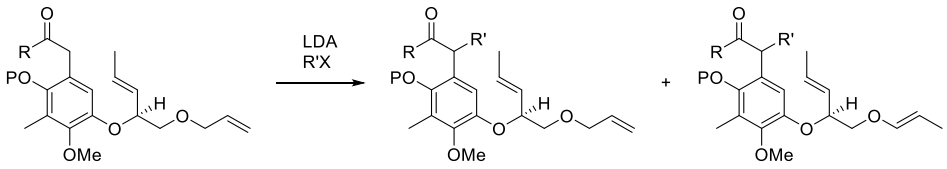
3.5 Double protection approach

This approach had his roots again in "key starting material" **74b**. Treatment with TBSCl and imidazole resulted in TBS protected orthoester **90** which was opened in the same manner by refluxing in MeOH/H_2O (80:20) for four hours to give phenol **91** which was subjected to TIPS protection forming methyl ester **92** (Scheme 40).[27]



Scheme 40: Orthogonal phenol protection

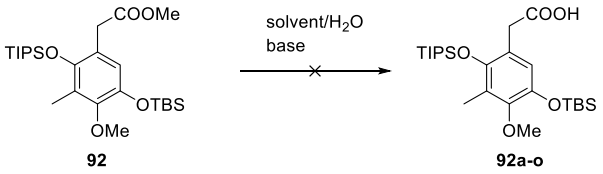
This strategy was chosen for two reasons: First, to avoid the problematic TIPS protection of phenol **84.** The second reason, was the modified chiral alcohol, carrying a relay arm. In Steiner's synthesis this modification improved the RCM, making it a RRCM, producing more yield, while consuming less catalyst Scheme 17,18). Our synthetic plan though, was based on an (eventual enantioselective) alkylation of a carbonyl compound, which would require the use of a strong base like LDA. Such conditions paired with the modified chiral alcohol could lead to partial or full rearrangement of olefin functionality of the relay arm. An exemplary reaction what could happen is given below showing a not further specified carbonyl compound (Scheme 41).



Scheme 41: Side reaction during α-alkylation

This was the main reason for selecting this strategy. Besides, installing the upper C-chain was the only option left. Hence, the next steps were the installation of the chiral auxiliary and the asymmetric alkylation before bringing the modified chiral alcohol in place. For this reason the methyl ester needed to by hydrolysed to the corresponding acid. This could then be further reacted to the chiral amide either *via* activation of the free acid by forming the corresponding acyl chloride or *via* using DCC and DMAP as coupling reagents.

Nevertheless, the methyl ester needed to be hydrolysed first (Scheme 42).



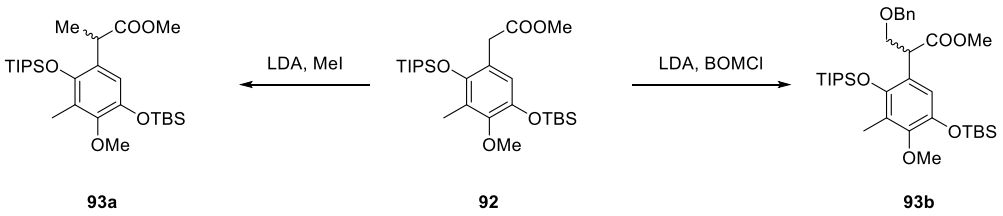
Scheme 42: Unsuccessful ester hydrolysis

Therefore, several different conditions were applied. [38,39] The results are given in Table 1.

product	solvent/H_2O	c [mmol/ml]	base	ester hydrolysis	TBS cleavage
92a	MeOH	0,047	K_2CO_3	-	-
92b	MeOH	0,013	K_2CO_3	-	-
92c	MeOH	0,097	K_2CO_3	+	+
92d	CH_3CN	0,033	K_2CO_3	-	-
92e	THF	0,200	K_2CO_3/LiOH	-	+
92f	DMF	0,043	K_2CO_3/LiOH	-	+
92g	DMF	0,130	K_2CO_3	-	-
92h	DMF	0,091	LiOH	-	+
92i	DMF	0,091	LiOH	-	+
92j	DMF	0,100	LiOH	-	+
92k	DMF	0,071	LiOH	-	+
92l	DMF	0,125	LiOH	-	+
92m	DMF	0,100	LiOH	-	+
92n	DMF	0,071	LiOH	-	+
92o	THF	0,100	LiOH	-	+

Table 1

To sum up, no conversion was observed when K_2CO_3 was used as base and full cleavage of the TBS protecting group occurred when K_2CO_3 was exchanged by LiOH. Mulzer had a similar problem in his first approach, solving it by simply conducting a general reduction/oxidation sequence resulting in free acid formation. As this was not an option for us, another pathway towards the carboxylic acid needed to be established. Before this approach was abandoned in favour for another strategy, the material available was used to do some further experiments which should give an insight into α-alkylation behaviour.



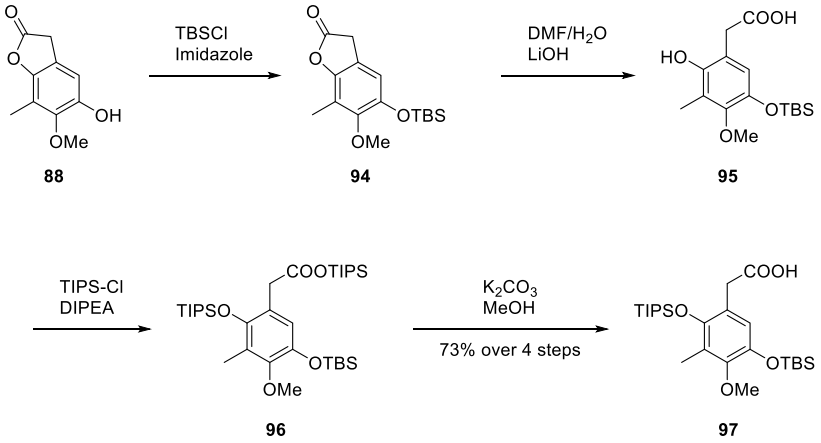
Scheme 43: Alkylation test reactions

Although, no exact yields were determined for these alkylation reactions it must be stated that both reached almost full conversion (according to NMR) and in contrary to the lactone methylation, only mono alkylated product **93a** was observed (Scheme 43). This result was quite a relief, knowing that the general applied protocol for alkylation reactions was working. Therefore, the reason for unsuccessful previous attempts must be the unique reactivity of the lactone species towards α-alkylation.

Both conversions shown in Scheme 43 were simply test reactions, but as product **93b** played a more or less important role in the later course of the synthesis it should be mentioned at this point. These two reactions were the last ones conducted in this approach. It was abandoned in favour of a more promising one.

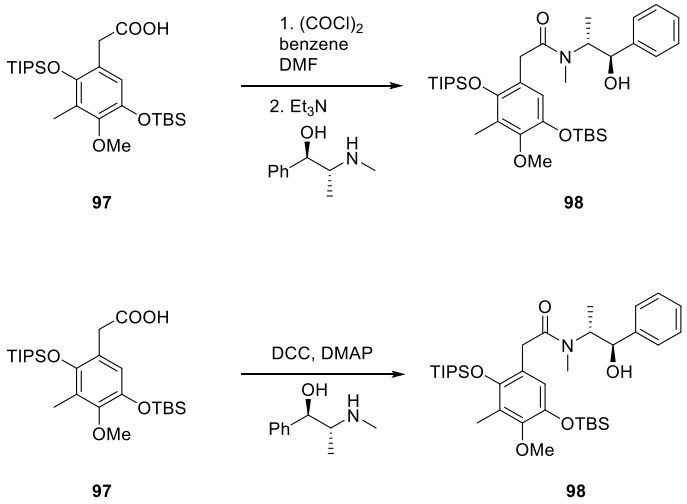
3.6 Lactone approach

This attempt started again from lactone **88** which underwent a similar reaction sequence as orthoester **74b** in the previous approach.



Scheme 44: Detour towards the free acid functionality

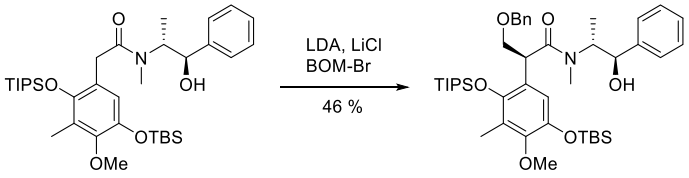
Installation of TBS ether went along with full conversion giving lactone 94, followed by basic hydrolysis of crude material to yield acid **95**. Although, applying similar conditions as shown in Table 1, TBS deprotection was not observed. Both functionalities were TIPS protected resulting in compound **96**, whereby the TIPS on the acid was selectively cleaved *via* stirring in MeOH in the presence of K_2CO_3 giving acid **97** in good yields over four steps (Scheme 44).



Scheme 45: Introduction of the chiral auxiliary

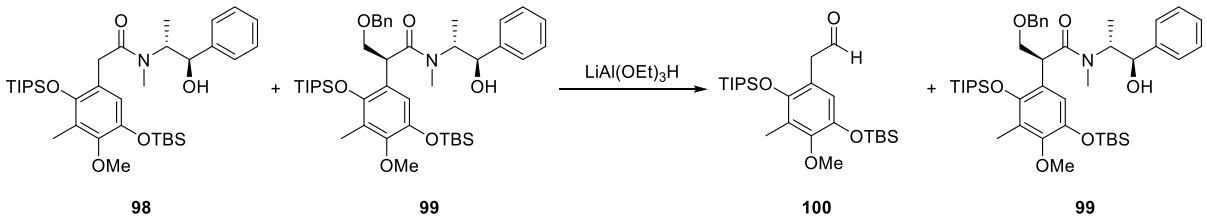
With acid **97** in hand, we turned our attention to the installation of the chiral auxiliary. Therefore, two different methods for activation of the acyl group were conducted. First, *via* acyl chloride, followed by addition of (*R*,*R*)-pseudoephedrine and base. Second *via* DCC followed by and (*R*,*R*)-pseudoephedrine in the presence of DMAP.[26] Both reactions led to amide **98**. The second approach, however, gave better yields (67 vs 81 %) (Scheme 45).[40]

With this chiral auxiliary installed, the crucial asymmetric alkylation was tackled.[26]



Scheme 46: Asymmetric alkylation

The reaction was quenched at approximately 70 % conversion and after separation by means of column chromatography compound **99** was obtained in 46 % yield (Scheme 46). In the next step amid **99** was to be reduced to the corresponding aldehyde, which would only need a Wittig reaction to install the olefin group **72**. According to literature, reduction to the corresponding aldehyde was possible using $LiAl(OEt)_3H$, which was *in situ* generated by reaction of $LiAlH_4$ and ethyl acetate. When this protocol was applied to a mixture of **98** and **99** the outcome was surprising (Scheme 46).[26]

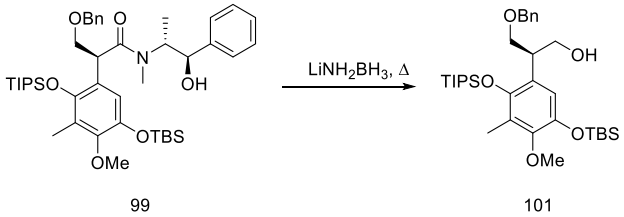


Scheme 47

It turned out that the unalkylated compound **98** was more susceptible to reduction than product **99.** This could be ascribed to the sterically rather demanding structure of **99** in combination with the bulky reducing reagent. Therefore, the reduction step allowed the removal of compound **98** and the isolation of desired benzyl ether **99** in almost pure form.

This sort of purification was not suitable, due to two reasons. First, conversion of **98** to aldehyde **100** prohibits the recovery of starting material. Second, benzyl ether **99** is not inert towards reduction and therefore, small amounts are also converted to the corresponding aldehyde, which has a negative effect on the yield.

As this reduction did not give the desired results, another cleavage was conducted. Treatment of pure amid **99** with *in situ* generated $LiNH_2BH_3$ and heating led to full conversion to primary alcohol **101** (Scheme 48).[26]



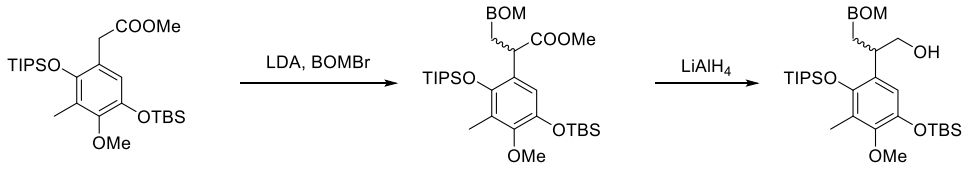
99 101

Scheme 48: Reductive cleavage of chiral auxiliary yielding in primary alcohol

As this reduction went quite smoothly the next goal was the determination of the enantiomeric excess.

3.7 Determination of the enantiomeric excess

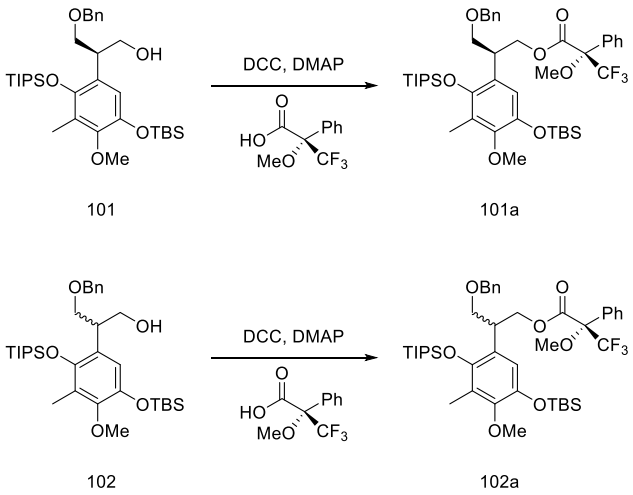
The enantiomeric excess was measured by chiral HPLC. Therefore, the corresponding racemic primary alcohol needed to be synthesised. This was achieved by alkylation of methyl ester **92** using BOMBr, leading to full conversion to compound **93b**. Said ester was subjected crude to $LiAlH_4$ reduction resulting in primary alcohol **102** (Scheme 49).



92 93b 102

Scheme 49: Generating racemic alcohol

Subsequent, the comparison of the retention times revealed an ee of > 99%. An ee this high was somehow surprising. Therefore, to confirm the high ee both alcohols were converted into their corresponding Mosher ester derivatives (Scheme 50) and the crude mixture was submitted to NMR.[33]



Scheme 50: Forming a set of Mosher esters

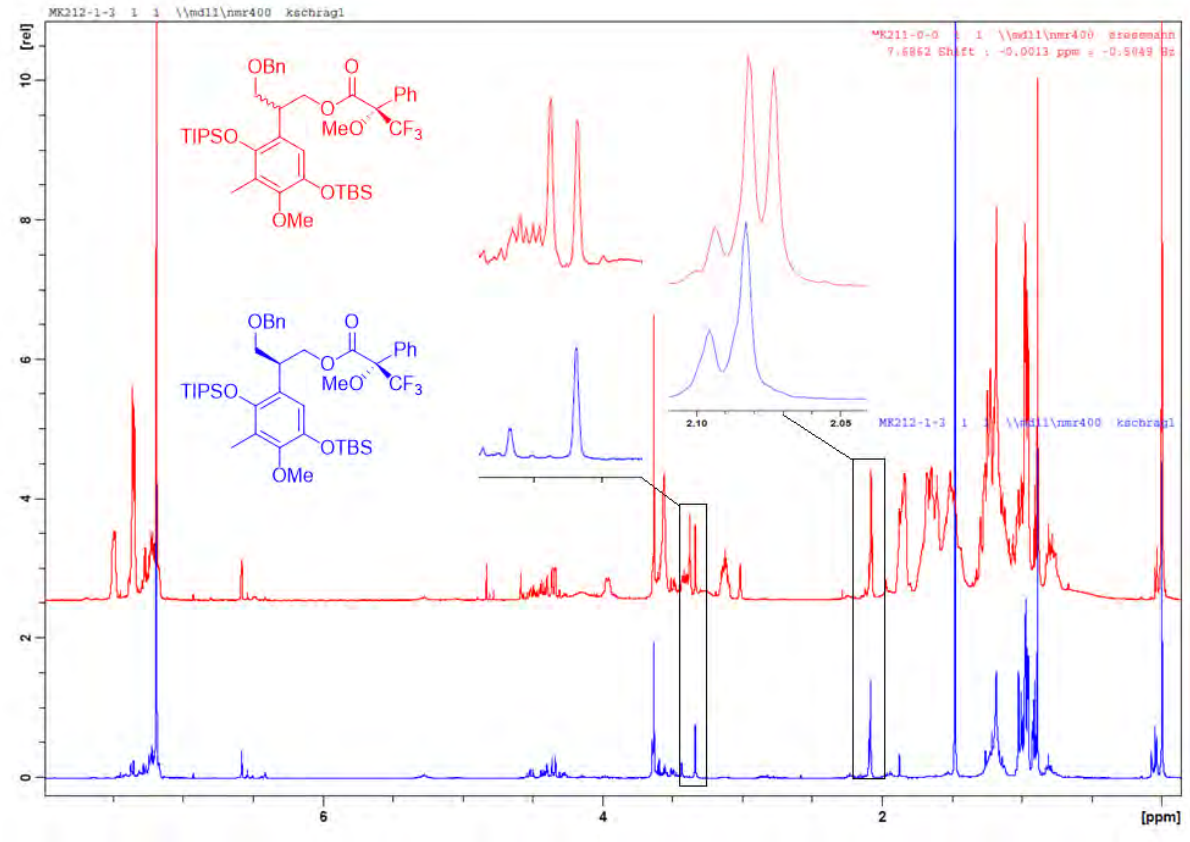


Figure 11: ^{1}H spectra Mosher ester

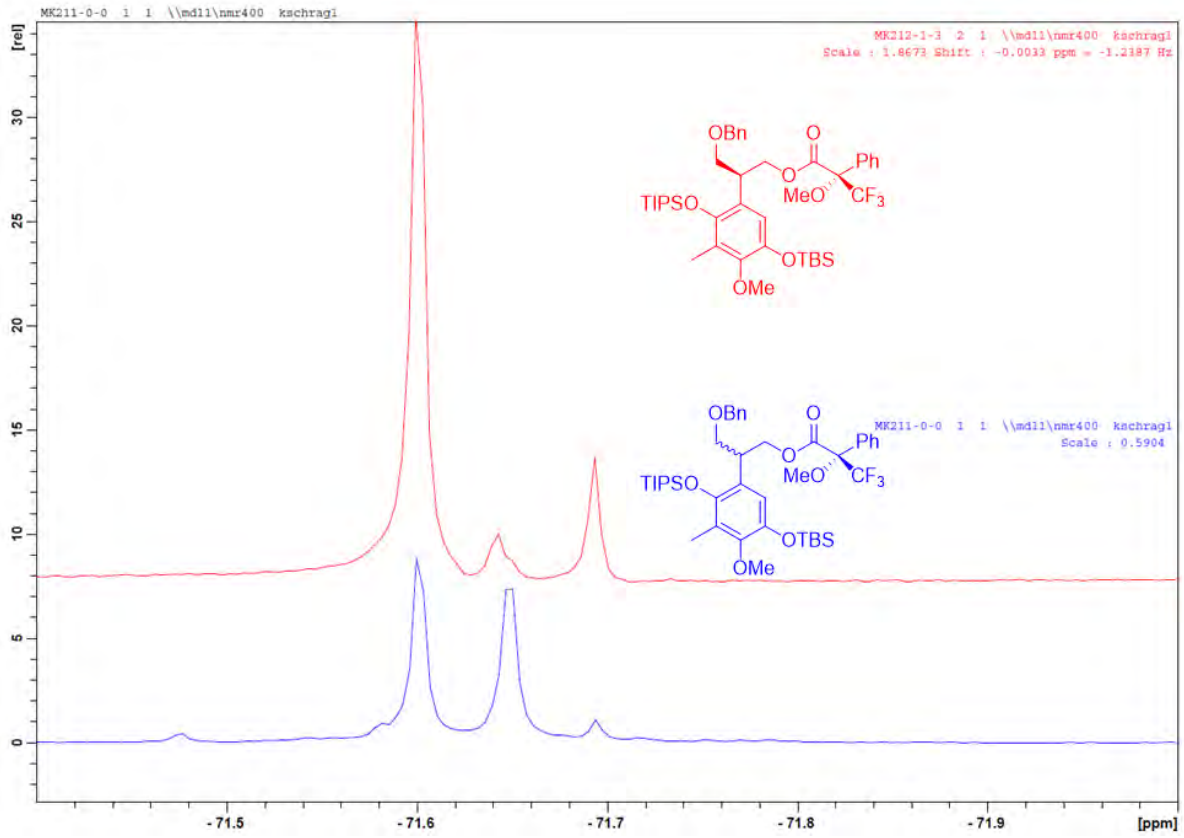


Figure 12: ^{19}F spectra Mosher ester

The comparison of the NMR spectra of the resulting Mosher esters **101a** and **102a** is shown in Figure 11 and Figure 12.

In Figure 11 two regions of the ^{1}H spectrum are enlarged: The methoxy group next to the chiral centre corresponds to the region at 3.5 ppm and the aromatic CH_3 group to the region at 2.0 ppm. In comparison to the diastereomeric mixture of the Mosher esters (red) only one singlet appears for the enantiopure compound (blue).

Additionally, analysis of the ^{19}F spectrum, shown in Figure 12, leads to the same conclusion. Again, two signals with equal intensity for the diastereomeric mixture and only one signal for the enantiomer. These results therefore confirm the high ee determined by chiral HPLC.

4 Conclusion

We were able to synthesis chiral alcohol **101** in 14 steps from commercially available 2,6-dimethoxy toluene with an excellent ee of >99 %. The sequence thereby included an asymmetric alkylation and the following reduction of the chiral auxiliary. Accordingly, we proofed this route to be a reliable path towards the correct installation of C6, which makes it ready for scale up.

Other routes towards intermediate **72** applying a different method to introduce chirality were unfortunately unsuccessful, though provided important insight into the reactivity of lactone **88** respectively **89**.

The problems regarding hydrolysis of ester **92** could be avoided by exchanging the TBS protecting group with MOM. This should enable a quicker path to generate acid **92a-o**

5 Experimental Part

5.1 General

The following general procedures were used in all reactions unless otherwise noted. Glassware was oven-dried at 115°C and assembled while still hot. Schlenk flasks were flame-dried. Oxygen- and moisture sensitive reactions were carried out under a slight argon overpressure using Schlenk techniques and in dry solvents. Sensitive liquids and solutions were transferred *via* double tipped cannula or syringes through rubber septa. All reactions were stirred magnetically unless otherwise stated.

The solvents used were purified and dried according to common procedures as follows.

- **Dry methylene chloride and diethyl ether** were retrieved from an Innovative Technologies PureSolv system.
- **Dry tetrahydrofurane** was pre-dried using an Innovative Technologies PureSolv system, refluxed over sodium/benzophenone and freshly distilled.
- **Dry toluene, hexane, ethy acetate and acetonitrile** were p.a. and HPLC grade, respectively, refluxed over sodium and freshly distilled.
- **Dry DMF and DMSO** were used as purchased.
- **Ethyl acetate, petroleum ether and diethyl ether (technical grade)** were distilled prior to use.
- **Methylene chloride (technical grade)** was distilled from potassium carbonate prior to use.

All other solvents used were p.a. or HPLC grade.

All reagents were used as received, except diisopropylamine (iPr_2NH), which was freshly distilled from CaH_2. Bromomethoxy methyl benzene (BOMBr) and ketal **79** were prepared according to literature procedures. [41,27]

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 at 200 and 50 MHz or on a Bruker AC 400 at 400 and 100 MHz, using the solvent peak as reference. ^{13}C NMR spectra were run in proton-decoupled mode. Multiplicities of ^{1}H signals were referred to as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet) and m (multiplet).

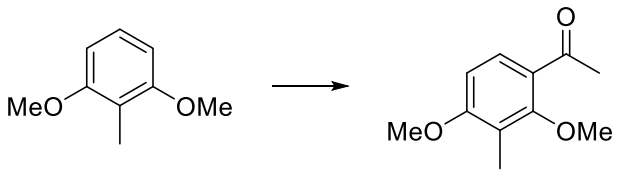
IR spectra were recorded on a Perkin Elmer Spectrum 65 FT IR Spectrometer equipped with a specac MK II Golden Gate Single Reflection ATR unit.

TLC-analysis was done with precoated aluminium-backed plates (Silica gel 60 F_{254}, Merck). Compounds were visualised by submerging in an acidic phosphormolybdic acid / Cerium sulphate solution and heating. Column chromatography was carried out with silica gel Merck 60. **Specific rotations** were measured on an Anton Parr MCP 500 polarimeter in at 20°C and 589nm.

Chiral HPLC measurements were conducted on a DAICEL CHIRALPAK IB (250x 4.60 mm, 5µ) as stationary phase and a 99.5:0.5 mixture of *n*-heptane/iPrOH a solvent. Flow rate 0.7ml/min.

5.2 Preliminaries

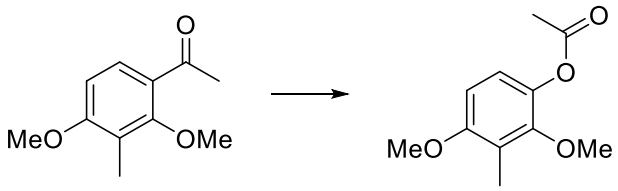
5.2.1 1-(2,4-dimethoxy-3-methylphenyl)ethan-1-one (76)



Acetyl chloride (9.37 mL, 130 mmol, 2.0 equiv) and $TiCl_4$ (14.25 mL, 130 mmol, 2.0 equiv) were placed in a three necked round bottom flask equipped with a septum, Ar inlet and dropping funnel. The solution was cooled to 0°C and 2,6-dimethoxy toluene (10.05 g, 66 mmol, 1.0 equiv) dissolved in benzene (50 mL) was added over a period of 45 min. Stirring continued for 1.5 hours before the reaction was quenched by cautious addition of HCl (5%) to give a strong yellow colour. The organic layer was washed successively with H_2O and brine, dried over Na_2SO_4 before being concentrated *in vacuo* to rsult in quantitative yield. The product was used for further reactions without purification. Spectroscopic data were identical to that reported in the literature.

R_f: (toluene/EA: 20:1) 0.29

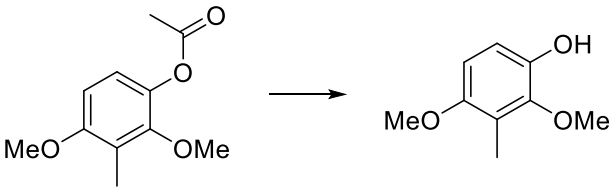
5.2.3 2,4-dimethoxy-3-methylphenyl acetate (77)



M-CPBA (20.44 g, 86 mmol, 1.34 equiv) was added to a cooled (0°C) solution of ketone (**76**) (12.78 g, 66 mmol, 1.0 equiv) and p-toluene sulfonic acid (0.40 g, 2.3 mol, 0.035 equiv) in CH_2Cl_2 (50 mL) in several portions over 45 min. whereat the colour changed from orange to green. The reaction was allowed to warm to r.t and stirred overnight. Reaction NMR showed significant amount of unreacted starting material which is why more m-CPBA (7.26 g, 75%, 32 mmol 0.48 equiv) was added over 40 min. together with p-toluene sulfonic acid (0.22 g, 1.2 mmol, 0.019 equiv). The reaction mixture was stirred overnight and diluted with saturated $NaHCO_3$ solution. The layers were separated and the organic phase was washed several times with saturated $NaHCO_3$ to remove benzoic acid. The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo* to yield 11.71 g (84%) of crude product which was used for further reactions without purification. Spectroscopic data were identical to that reported in the literature.

R_f: (toluene/EA: 20:1) 0.38

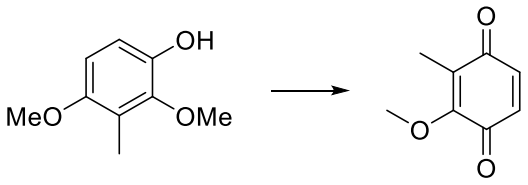
5.2.5 2,4-dimethoxy-3-methylphenol (78)



Ester (**77**) (10.71 g, 51 mmol, 1.0 equiv) was dissolved in MeOH (40 mL) and placed in a round bottom flask equipped with a reflux condenser. KOH (5.72 g, 102 mmol, 2.0 equiv) dissolved in a mixture of MeOH/H_2O (50 mL, 1:1) was added and the reaction mixture was heated to reflux for 2 hours. pH= 2 was adjusted by addition of HCl (6M) before the aqueous layer was extracted with Et_2O. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to yield quantitative product. Spectroscopic data identical to that reported in the literature.

R_f: (toluene/EA: 20:1) 0.32

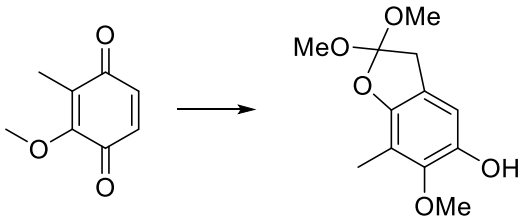
5.2.6 2-methoxy-3-methylcyclohexa-2,5-diene-1,4-dione (47)



To a vigorously stirred solution of phenol (**78**) (8.57 g, 51 mmol, 1.0 equiv) in CH_3CN (120 mL) was added CAN (56.06 g, 102 mmol, 2.0 equiv) dissolved in H_2O (80 mL) *via* dropping funnel over a period of 30 min. and stirred for an additional 1 hour. The layers were separated, the aqueous layer was extracted with CH_2Cl_2, washed successively with H_2O, saturated $NaHCO_3$ solution, H_2O and brine. The organic phase was dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (PE/EA 6:1) yielding 4.01 g (40% over 4 steps) of pure product. Spectroscopic data identical to that reported in the literature.

R_f (PE/EA: 1:1) 0.43

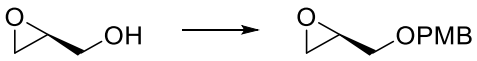
5.2.7 2,2,6-trimethoxy-7-methyl-2,3-dihydrobenzofuran-5-ol (74b)



A pressure vessel was equipped with quinone (**47**) (2.00 g, 13 mmol, 1.0 equiv), ketal (5.27 g, 60 mmol, 4.6 equiv), toluene (12 mL) and a magnetic stirrer. The reaction mixture was heated in an oil bath (temperature: 115°C) for 24 hours. Subsequent, the solvent and remaining ketal were removed *in vacuo* and the residue was purified by column chromatography (PE/EE 95:5) to yield 1.59 g (51 %) of desired product. Spectroscopic data identical to that reported in the literature.

R_f: (PE/EA: 2:1) 0.20

5.2.8 (*R*)-2-(((4-methoxybenzyl)oxy)methyl)oxirane (80)



To a cooled (0°C) suspension of NaH (1.76 g, 60% in mineral oil, 44 mmol, 1.1 equiv) in dry DMF (35 mL) was added 4-methoxybenzyl chloride (5.47 mL, 44 mmol, 1.1 equiv) and the solution was stirred for 30 min. at the same temperature. Subsequent, (*S*)- glycidol (**65**) (2.69 mL, 40 mmol, 1.0 equiv) was added drop wise over a period of 1 hour, accompanied by vigorous gas formation. The reaction mixture was allowed to warm to r.t and was stirred overnight. After TLC confirmed full conversion, the reaction was quenched by addition of saturated NH_4Cl and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and H_2O, dried over Na_2SO_4 and the solvent removed *in vacuo*. Purification by means of column chromatography yielded 6.6 g (85%) of pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.25 (2H, dd, *J* = 6.6, 1.9); 6.86 (2H, dd, *J* = 6.7, 2.0); 4.49 (2H, q, *J* = 11.6); 3.78 (3H, s); 3.71 (1H, dd, *J* = 11.4, 3.1); 3.40 (1H, dd, *J* = 11.4, 5.8); 3.13-3.18 (1H, m); 2.75-2.80 (1H, m); 2.59 (1H, dd, *J* = 5.0, 2.7)

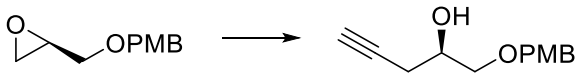
^{13}C-NMR (100MHz, $CDCl_3$): δ= 159.2, 129.9, 129.4, 113.8, 72.9, 70.5, 55.2, 50.8, 44.3

IR [cm^{-1}]: ν = 2998, 2837, 1715, 1612, 1586, 1512, 1464, 1421, 1385, 1336, 1302, 1244, 1173, 1087, 1031, 900, 818, 767, 710, 637, 583, 517.

R_f: 0.30 (PE/EA 3:1)

$[\alpha]^{20}_D$ = +3.4 (c=1.01, $CHCl_3$)

5.2.9 (*R*)-1-((4-methoxybenzyl)oxy)pent-4-yn-2-ol



Epoxide (**80**) (6.50 g, 34 mmol, 1.0 equiv) was placed in a Schlenk flask and dissolved in dry DMSO (60 mL) before lithium acetylide ethylenediamine complex was added in 2 portions in an interval of 2 hours. The reaction mixture was stirred for another 2 hours until TLC confirmed full conversion. HCl (12M) was added until pH= 7 was reached, then the aqueous layer was extracted with Et_2O and the combined organic layers were dried over Na_2SO_4. Removal of the solvent yielded 6.2 g (85%) of yellow oil. Product was used crude for the next step.

R_f: 0.22 (PE/EA 3:1)

5.2.11 (*R*)-1-((4-methoxybenzyl)oxy)pent-3-yn-2-ol (81)

Crude (*R*)-1-((4-methoxybenzyl)oxy)pent-4-yn-2-ol (5.94 g, 27 mmol, 1.0 equiv) was placed in a Schlenk flask and dissolved in dry DMSO (60 mL) under Ar atmosphere. After the addition of KOtBu (6.05 g, 54 mmol, 2.0 equiv) the reactions mixture was stirred for 2 hours. Subsequent, the mixture was quenched with saturated NH_4Cl and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification was achieved by column chromatography to yield 2.9 g (48%) of desired product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.28 (2H, d, *J* = 7.3), 6.89 (2H, d, *J* = 8.6), 4.59-4.46 (1H, m), 4.54 (2H, dd, *J* = 16.6, 11.5), 3.81 (3H, s), 3.58 (1H, dd, *J* = 9.8, 3.5), 3.50 (1H, dd, *J* = 9.6, 7.9), 1.84 (3H, d, *J* = 2.0).

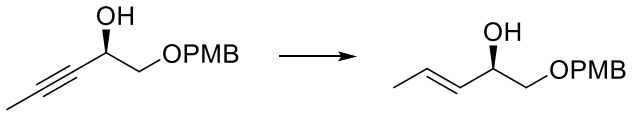
^{13}C-NMR (100MHz, $CDCl_3$): δ= 159.4, 129.8, 129.6, 113.9, 82.0, 77.1, 73.7, 73.1, 61.8, 55.3, 3.7.

IR [cm^{-1}]: ν = 3399, 2917, 2858, 2242, 1612, 1586, 1512, 1464, 1442, 1361, 1302, 1244, 1174, 1145, 1102, 1075, 1030, 952, 895, 818, 757, 708, 637, 580

R_f: 0.22 (PE/EA 3:1)

$[\alpha]^{20}_D$ = -6.2 (c 1.22, CH_2Cl_2)

5.2.13 (*R*,*E*)-1-((4-methoxybenzyl)oxy)pent-3-en-2-ol (82)



$LiAlH_4$ was weighed into a dry 3-necked round bottom flask and dissolved in dry THF (15 mL) and stirred under Ar atmosphere. Yn-ol (**81**) dissolved in THF (23 mL) was added *via* septum over a period of 50 min., the resulting reaction mixture was refluxed for 2 hours, subsequently, allowed to cool to r.t and stirred overnight. The next day, the reaction was quenched with Et_2O and saturated potassium sodium tartrate solution and stirred overnight. The aqueous layer was extracted with Et_2O, the combined organic layers were washed with H_2O and Brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification was achieved by column chromatography to yield 2.0 g (69%) desired product.

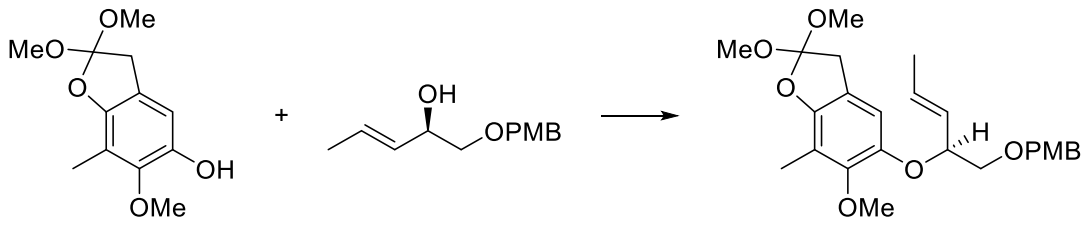
^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.25 (2H, dd, *J* = 8.6), 6.87 (2H, dd, *J* = 8.6), 5.71-5.81 (1H, m), 5.39 - 5.47(1H, m), 4.48 (2H, s), 4.22 -4.28 (1H, m), 3.79 (3H, s), 3.45 (1H, dd, *J* = 9.6, 3.2), 3.31 (1H, dd, *J* = 9.5), 2.49 (1H, broad s), 1.68 (3H, d, *J* = 6.6)

^{13}C-NMR (100MHz, $CDCl_3$): δ= 159.4, 130.1, 129.5(3), 129.5(0), 128.7, 113.9, 74.1, 73.1, 71.4, 55.4, 17.9.

IR [cm^{-1}]: ν = 3425, 2914, 2856, 1676, 1612, 1586, 1512, 1454, 1361, 1302, 1245, 1173, 1092, 1032, 966, 917, 818, 757, 637, 564, 516.

$[\alpha]^{20}_D$ = -11.1 (c 0.62, CH_2Cl_2)

5.2.15 (*S*,*E*)-2,2,6-trimethoxy-5-((1-((4-methoxybenzyl)oxy)pent-3-en-2-yl)oxy)-7-methyl-2,3-dihydrobenzofuran (83)



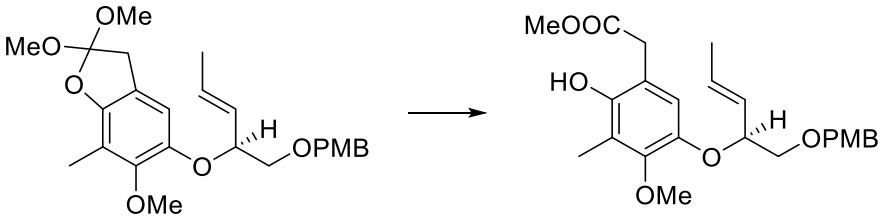
Orthoester (**74b**) (578 mg, 2.41 mmol, 1.0 equiv), en-ol (**82**) (634 mg, 2.85 mmol, 1.2 equiv) and PBu_3 (770 mg, 3.8 mmol, 1.6 equiv) were placed in a Schlenk flask and dissolved in benzene (12 mL). The mixture was cooled *via* ice bath until benzene started to get solid, subsequently, ADDP dissolved in benzene (2 mL) was added *via* septum. After 10 min. the reaction mixture was allowed to warm to r.t and was stirred over the weekend. The reaction was quenched by the addition of toluene and flashed (PE/EA 15:1) to get rid of excess of PBu_3. The fractions without PBu_3 were combined and concentrated *in vacuo*, taken up in petroleum ether and washed with 2M NaOH, NH_4Cl, H_2O, Brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by means of column chromatography yielded 550 mg (52%) of desired product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.25 (2H, dd, *J* =8.5), 6.86 (2H, dd, *J* =8.5), 6.60 (1H, s), 5.67-5.77 (1H, m) 5.49-5.57 (1H, m), 4.58-4.65 (1H, m), 4.53 (2H, d, *J* =1.8), 3.79 (3H, s), 3.77 (3H, s), 3.68 (1H, dd, *J* =10.4, 6.6), 3.58 (1H, dd, *J* =10.4, 4.2), 3.41 (6H, s), 3.17 (2H, s), 2.14 (3H,s), 1.68 (3H, broad d, *J* =6.4)

^{13}C-NMR (100MHz, $CDCl_3$): δ= 159.4, 129.8, 129.6, 113.9, 82.0, 77.1, 73.7, 73.1, 61.8, 55.3, 3.7.

R_f: (PE/EA 3:1) 0.43

5.2.16 Methyl(*S*,*E*)-2-(2-hydroxy-4-methoxy-5-((1-((4-methoxybenzyl)oxy)pent-3-en-2-yl)oxy)-3-methylphenyl)acetate (84)



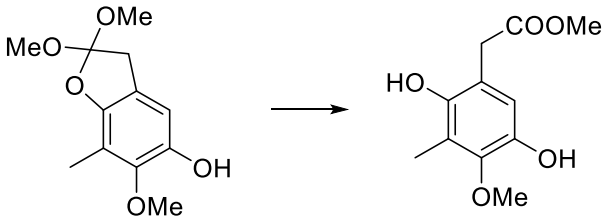
Ether (**83**) (405 mg, 0.91 mmol, 1.0 equiv) was dissolved in a mixture of MeOH/H_2O (80:20) and heated under reflux for 4 hours. Subsequent, the solvents were evaporated *in vacuo* to yield 376 mg (96%) of desired product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.25 (2H, dd, *J* =9.1), 7.11 (1H, s), 6.86 (2H, dd, *J* =8.8), 6.53 (1H, s), 5.67-5.78 (1H,m), 5.48-5.56 (1H, m), 4.65 (1H, dd, *J* =11.1, 6.4), 4.53 (2H, d, *J* =1.5), 3.80 (3H, s), 3.78 (3H, s), 3.73 (3H, s), 3.68 (1H, dd, *J* =10.4, 6.6), 3.58 (1H, dd, *J* =10.4, 4.3), 3.55 (2H, d J =2.6), 2.18 (3H, s), 1.68 (3H, broad d, *J* =6.4)

^{13}C-NMR (100MHz, $CDCl_3$): δ= 174.6, 159.3, 149.3, 148.3, 145.0, 130.5, 129.8, 129.4, 128.2, 121.2, 117.3, 115.1, 113.8, 80.1, 73.1, 72.8, 60.6, 55.4, 52.8, 37.9, 18.0, 9.5.

R_f: (PE/EA 3:1) 0.26

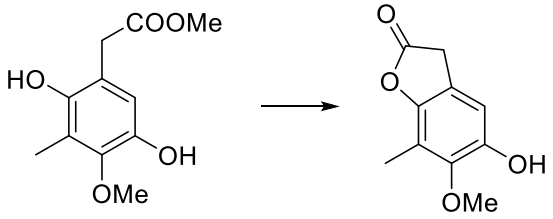
5.2.18 Methyl 2-(2,5-dihydroxy-4-methoxy-3-methylphenyl)acetate (87)



Orthoester (**74b**) (3.38 g, 14 mmol, 1.0 equiv) was dissolved in a mixture of MeOH/H_2O (80:20, 125 mL) and heated under reflux for 4 hours. Subsequent, the solvents were evaporated *in vacuo* to give quantitative yield. Spectroscopic data identical to that reported in the literature.

R_f: (PE/EA: 2:1) 0.24

5.2.19 5-hydroxy-6-methoxy-7-methylbenzofuran-2(3*H*)-one (88)



Hydroquinone (**87**) (3.18 g, 14 mmol, 1.0 equiv) was dissolved in toluene (40 mL) and *para*-toluene sulfonic acid (catalytic amount) was added. The mixture was placed in a round bottom flask equipped with a soxhlet extractor filled with molecular sieve. The reaction was heated to reflux for 3 hours, subsequently, the mixture was washed with saturated $NaHCO_3$ solution,the organic layer was dried over Na_2SO_4 before the solvent was removed *in vacuo* yielding 2.46 g (90 %) as a brown solid.

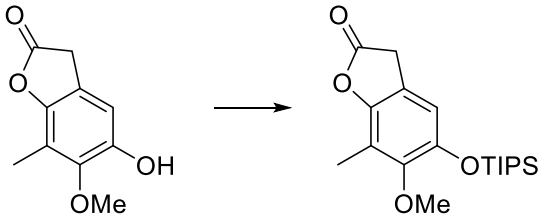
^{1}H-NMR (400 MHz, $CDCl_3$): δ= 6.66 (1H, s), 5.61 (1H, s), 3.73 (3H, s), 3.60 (2H, s), 2.18 (3H, s)

^{13}C-NMR (100MHz, $CDCl_3$): δ= 174.7, 146.9, 145.7, 145.4, 118.1, 115.1, 108.7, 61.2, 33.7, 9.5

IR [cm^{-1}]: ν = 3441, 3007, 2959, 2928, 2837, 1796, 1736, 1634, 1610, 1464, 1447, 1426, 1387, 1363, 1323, 1262, 1237, 1212, 1190, 1140, 1074, 1007, 984, 946, 892, 870, 826, 771, 694, 669, 652, 587, 570, 552, 528

R_f: (PE/EA: 2:1) 0.18

5.2.20 6-methoxy-7-methyl-5-((triisopropylsilyl)oxy)benzofuran-2(3*H*)-one (89)



A Schlenk flask was charged with lactone (**88**) (200 mg, 1.03 mmol, 1.0 equiv), imidazole (206 mg, 3.03 mmol, 3.0 equiv) and the solids were dissolved in dry DMF (1.0 mL). Subsequently, TIPSCl (0.24 mL, 1.13 mmol, 1.1 equiv) was added and the reaction mixture was stirred overnight. The reaction was quenched by the addition of saturated $NaHCO_3$ solution and toluene. Layers were separated and the organic layer was dried over Na_2SO_4 and afterwards concentrated *in vacuo*. Purification was achieved by column chromatography (PE/EA 6:1) to give 325 mg (90%) product as a brown- reddish solid.

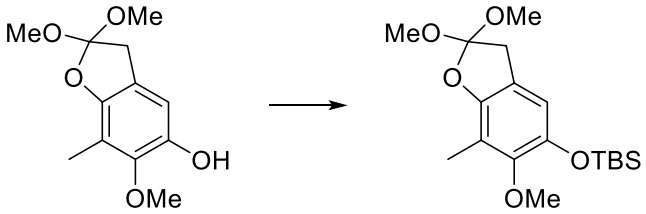
^{1}H-NMR (400 MHz, $CDCl_3$): δ= 6.64 (1H, s), 3.77 (3H, s), 3.66 (2H, s), 2.22 (3H, s), 1.20-1.32 (3H, m), 1.10 (18H, d, *J* =7.3)

^{13}C-NMR (100MHz, $CDCl_3$): δ= 174.8, 149.6, 147.6, 146.0, 116.9, 116.4, 113.2, 60.4, 33.8, 17.9, 12.8, 9.3

IR [cm^{-1}]: ν = 2945, 2866, 1797, 1628, 1455, 1384, 1355, 1278, 1234, 1142, 1092, 1063, 1011, 943, 902, 883, 850, 834, 783, 747, 687, 669, 656, 587, 556, 537, 507.

R_f: (PE/EA: 2:1) 0.79

5.2.21 tert-butyldimethyl((2,2,6-trimethoxy-7-methyl-2,3-dihydrobenzofuran-5-yl)oxy)silane (90)



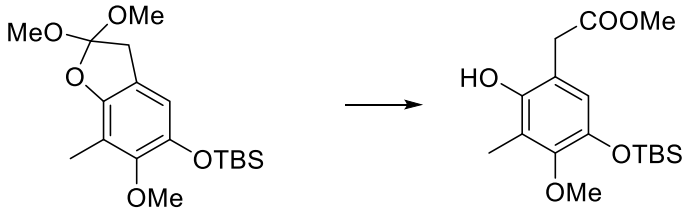
Orthoester (**74b**) (200 mg, 0.83 mmol, 1.0 equiv), imidazole (170 mg, 2.5 mmol, 3.0 equiv) and dry DMF (1.0 mL) were placed in a Schlenk flask. Subsequently TBSCl (1.50 mL of 0.1M solution in DMF, 1.2 mmol, 1.2 equiv) was added and the reaction mixture was stirred overnight. The next day, another portion of TBSCl (0.25 mL of 0.1M solution in DMF, 0.20 mmol, 0.20 equiv) was added and after 2 hours the reaction was quenched by addition of saturated $NaHCO_3$ solution and toluene. The aqueous layer was extracted with Et_2O, the combined organic layers were washed with H_2O, dried over Na_2SO_4. Removal of the solvent resulted in quantitative yield of desired product.

^{1}H-NMR (400 MHz, CD_2Cl_2): δ= 6.53 (1H, s), 3.70 (3H, s), 3.38 (6H, s), 3.15 (2H, s), 2.11 (3H, s), 1.01 (9H, s), 0.15 (6H, s)

^{13}C-NMR (100MHz, CD_2Cl_2): δ= 150.6, 149.9, 143.5, 125.7, 119.3, 114.7, 60.5, 50.7, 37.9, 26.1, 18.7, 9.5, -4.4

IR [cm^{-1}]: ν = 2930, 2858, 1611, 1472, 1458, 1390, 1359, 1287, 1252, 1233, 1203, 1118, 1087, 1060, 1023, 1003, 991, 951, 892, 832, 816, 780, 754, 739, 681, 577, 548, 518, 505

5.2.22 methyl 2-(5-((tert-butyldimethylsilyl)oxy)-2-hydroxy-4-methoxy-3-methylphenyl)acetate (91)



Orthoester (**90**) (270 mg, 0.76 mmol, 1.0 equiv) was dissolved in a mixture of MeOH/H_2O (80:20, 20 mL) and heated under reflux for 4 hours. Subsequent, the solvents were evaporated *in vacuo* to give 238 mg (92 %).

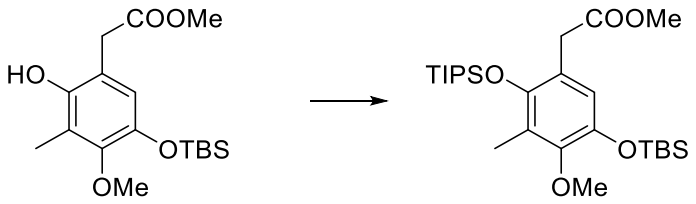
^{1}H-NMR (400 MHz, $CDCl_3$): δ= 6.45 (1H, s), 3.74 (3H, s), 3.72 (3H, s), 3.56 (2H, s), 2.19 (3H, s), 1.00 (9H, s), 0.15 (6H, s).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 174.5, 149.6, 147.9, 142.4, 121.1, 119.7, 115.5, 59.9, 52.7, 37.6, 25.7, 18.2, 9.4

IR [cm^{-1}]: ν = 3348, 2955, 2930, 2858, 1708, 1606, 1483, 1439, 1389, 1329, 1249, 1165, 1121, 1057, 1006, 939, 880, 830, 815, 780, 748, 705, 670, 634, 548, 522, 510

R_f: (PE/EA: 3:1) 0.73

5.2.24 methyl 2-(5-((tert-butyldimethylsilyl)oxy)-4-methoxy-3-methyl-2-((triisopropylsilyl)oxy)phenyl)acetate (92)



A Schlenk flask charged with phenol (**91**) (877 mg, 2.58 mmol, 1.0 equiv), dissolved in dry DMF (8.5 mL), Hünig's base (0.90 mL, 5.15 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 5 min. Subsequently TIPSCl (0.66 mL, 1.20 mmol, 1.2 equiv) was added and stirred overnight. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution and toluene. Layers were separated and the organic layer was dried over Na_2SO_4 and afterwards concentrated *in vacuo*. Purification was achieved by column chromatography (toluene) to give 1.12 g (88%) of desired product as a yellow oil.

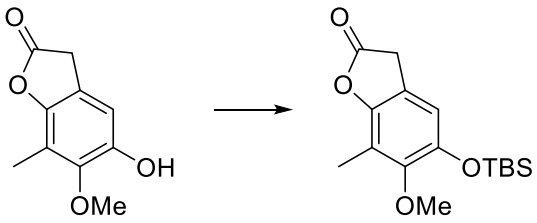
^{1}H-NMR (400 MHz, $CDCl_3$): δ= 6.40 (1H, s), 3.74 (3H, s), 3.72 (3H, s), 3.56 (2H, s), 2.19 (3H, s), 1.32-1.39 (3H, m) 1.05 (18H, s), 1.00 (9H, s), 0.14 (6H, s)

^{13}C-NMR (100MHz, $CDCl_3$): δ= 174.5, 149.6, 147.9, 142.2, 121.1, 119.7, 115.5, 59.9, 52.7, 37.6, 25.7, 17.7, 12.3, 9.5, -4.6

IR [cm^{-1}]: ν = 2930, 2867, 1741, 1481, 1434, 1390, 1362, 1324, 1249, 1222, 1152, 1127, 1059, 1015, 917, 883, 837, 781, 746, 681, 652, 545, 528, 513, 505

R_f: (toluene/EA: 20:1) 0.67

5.2.25 5-((tert-butyldimethylsilyl)oxy)-6-methoxy-7-methylbenzofuran-2(3*H*)-one (94)



A Schlenk flask was charged with lactone (**88**) (200 mg, 1.03 mmol, 1.0 equiv), imidazole (208 mg, 3.06 mmol, 3.0 equiv) and the solids were dissolved in dry DMF (1.0 mL). TBSCl (1.86 mL of 0.1M solution in DMF, 1.2 mmol, 1.2 equiv) was added and stirred for 4h at 35°C. Another portion of TBSCl (0.7 mL of 0.1M solution in DMF, 0.46 mmol, 0.45 equiv) was added and the mixture was stirred overnight. The reaction mixture was quenched by addition of saturated $NaHCO_3$ solution and toluene. The aqueous layer was extracted Et_2O, the combined organic layers were washed with H_2O, dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to yield 311 mg (98%) desired product.

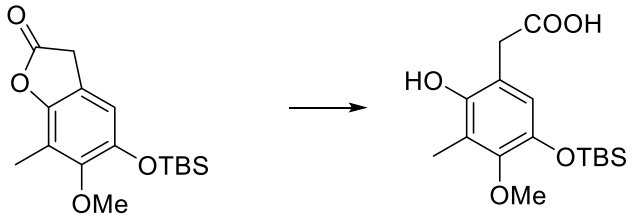
^{1}H-NMR (400 MHz, $CDCl_3$): δ= 6.63 (1H, s), 3.74 (3H, s), 3.66 (2H, s), 2.21 (3H, s), 1.00 (9H, s), 0.16 (6H, s)

^{13}C-NMR (100MHz, $CDCl_3$): δ= 174.8, 150.0, 148.0, 145.6, 117.3, 116.4, 114.3, 60.3, 33.8, 25.8, 18.3, 9.4, -4.6

IR [cm^{-1}]: ν = 2955.1, 2929.61, 2885.52, 2857.62, 1804.34, 1792.00, 1626.53, 1606.36, 1470.82, 1454.88, 1417.53, 1389.55, 1356.13, 1280.64, 1247.9, 1234.93, 1201.40, 1177.63, 1140.18, 1086.64, 1063.46, 1007.81, 944.09, 902.35

R_f: (toluene/EA) 20:1) 0.71

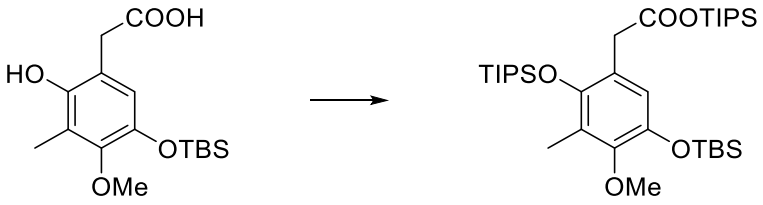
5.2.26 2-(5-((tert-butyldimethylsilyl)oxy)-2-hydroxy-4-methoxy-3-methylphenyl)acetic acid (95)



A round bottom flask was charged with TBS lactone (**94**) (202 mg, 0.65 mmol, 1.0 equiv) and dissolved in a 1:1 mixture of DMF/H_2O (6 mL). Several crystals of LiOH were added to the reaction mixture and it was stirred for 2 hours. The reaction was quenched by addition of NH_4Cl. DMF and H_2O were evaporated *in vacuo,* the residue was dissolved in ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The product was used crude without further purification. A yield of 98% according to NMR (crude product still contained DMF) was achieved.

^{1}H-NMR (400 MHz, $CDCl_3$): δ= 6.49 (1H, s), 3.72 (3H, s), 3.58 (2H, s), 2.17 (3H, s), 1.00 (9H, s), 0.15 (6H, s)

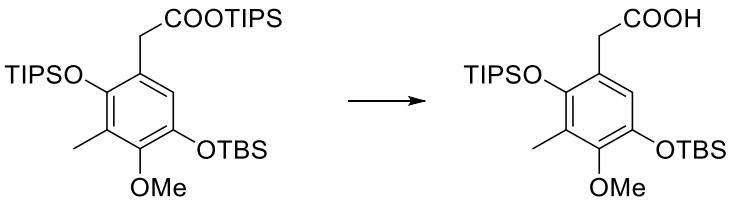
5.2.27 Triisopropylsilyl 2-(5-((tert-butyldimethylsilyl)oxy)-4-methoxy-3-methyl-2-((triisopropylsilyl)oxy)phenyl)acetate (96)



A Schlenk flask was charged with crude acid (**95**) (359 mg, 1.1 mmol, 1.0 equiv), Hünig's base (0.75 mL, 4.4 mmol, 4.0 equiv) and dry DMF (5.0 mL). Subsequently TIPSCl (0.47 mL, 2.2 mmol, 2.0 equiv) was added and the reaction mixture stirred overnight. The reaction was quenched by the addition of saturated $NaHCO_3$ solution and toluene. Layers were separated and the organic layer was washed with H_2O, dried over Na_2SO_4, afterwards concentrated *in vacuo* to yield 639 mg crude product.

R_f: (toluene/EA 20:1) 0.97

5.2.28 2-(5-((tert-butyldimethylsilyl)oxy)-4-methoxy-3-methyl-2-((triisopropylsilyl)oxy)phenyl)acetic acid (97)



Crude acid (**96**) (639 mg, 1.0 mmol, 1.0 equiv) was dissolved in MeOH (30 mL) and K_2CO_3 (276 mg, 2.0 mmol, 2.0 equiv) was added. After 1 hour of stirring the reaction was quenched by the addition of solid NH_4Cl, the solvent was evaporated under reduced pressure, the residue was taken up in ethyl acetate and washed with H_2O. The organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo* to yield 404 mg (76% over 2 steps).

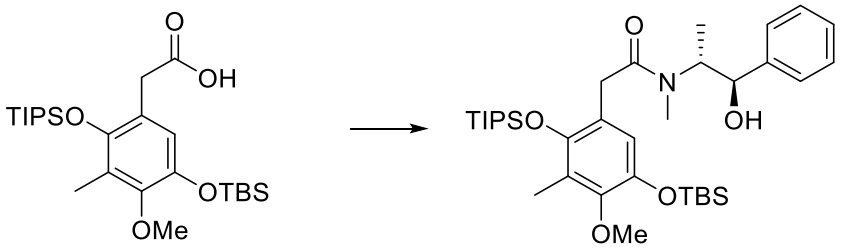
^{1}H-NMR (400 MHz, $CDCl_3$): δ= 9.75 (1H, broad s), 6.46 (1H, s), 3.58 (3H, s), 3.46 (2H, s), 2.03 (3H, s), 1.08-1.19 (3H, m), 0.94 (18H, d, *J* = 7.5), 0.85 (9H, s), 0.00 (6H, s).

^{13}C-NMR (100MHz, $CDCl_3$): δ= 177.9, 149.4, 147.9, 142.8, 123.1, 120.0, 119.1, 59.9, 35.8, 25.9, 18.4, 18.1, 14.4, 11.4, -4.6

IR [cm^{-1}]: ν = 2947, 2927, 2867, 1734, 1709, 1481, 1433, 1390, 1347, 1248, 1220, 1127, 1097, 1058, 1014, 915, 883, 836, 799, 780, 732, 680, 650, 617, 577, 560, 528, 511, 502.

R_f: (DCM/MeOH 95:5) 0.15

5.2.29 2-(5-((tert-butyldimethylsilyl)oxy)-4-methoxy-3-methyl-2-((triisopropylsilyl)oxy)phenyl)-N-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-N-methylacetamide (98)



Acid (**97**) (521 mg, 1.08 mmol, 1.0equiv) was dissolved in benzene (12 mL), the solution was cooled to 5°C and oxalyl chloride (0.12 mL, 1.40 mmol, 1.3 equiv) was added, accompanied by slight gas formation. After stirring for 10 min., the addition of DMF (1 drop) was followed by vigorous gas formation. The reaction mixture was stirred for another 10 min at 5°C, was then allowed to warm to r.t and stirred for one additional 1 hour. Subsequent, the excess of oxalyl chloride was removed *via* azeotropic destillation *in vacuo* to give acetyl chloride.

(1*R*,2*R*)-(-)-Pseudoephedrine (158 mg, 0.94 mmol, 1.0 equiv) and Et_3N (0.17 mL, 1.22 mmol, 1.3 equiv) were placed in a Schlenk flask, dissolved in THF (6 mL) and cooled to 0°C.

The freshly prepared acetyl chloride was dissolved in THF (10 mL) and added *via* syringe to the Pseudoephedrine/Et_3N solution over 20 min. The solution was allowed to warm to r.t and stirred overnight. The reaction was quenched by the addition of H_2O, the aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. Purification was achieved by column chromatography (PE/EA 15:1) yielding 404 mg (67%) of yellow solid.

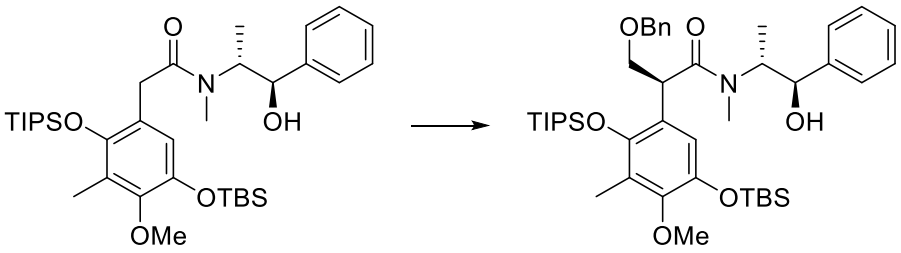
^{1}H-NMR (5.5: 4.5 rotamer ratio, asterisk denotes minor rotamer signal, 400 MHz, $CDCl_3$): δ= 7.27-7.34 (5H, m), 6.67* (1H, s), 6.57 (1H, s), 4.57-4.63 (1H, m), 4.27-4.41 (2H, m), 3.71 (3H, s), 3.66* (3H, s), 3.60 (2H, s), 2.88* (3H, s), 2.65 (3H, s), 2.23* (3H, s), 2.16 (3H, s), 1.21-1.32 (3H, m), 1.06-1.12 (18H, m), 0.98 (9H, s), 0.96* (9H, s)

^{13}C-NMR (100MHz, $CDCl_3$): δ= 174.2, 173.1*, 147.2, 146.5*, 143.7*, 143.2, 142.5, 141.2*, 128.8*, 128.5, 128.4*, 127.8, 127.2*, 126.6, 123.7*, 123.0, 121.2*, 120.2, 118.0, 117.7*, 76.7, 75.4*, 60.0, 59.9*, 58.4, 37.0, 36.6*, 26.6, 25.9, 24.0, 18.1, 18.0* 18.4, 15.2*, 14.4, 14.3, 14.2*, 11.4, -4.5, -4.6*

IR [cm^{-1}]: ν = 3368, 2930, 2867, 1622, 1480, 1431, 1344, 1298, 1235, 1123, 1057, 1014, 917, 883, 837, 805, 781, 731, 700, 681, 649, 620, 587, 541

R_f: (PE/EA 2:1) 0.61

5.2.30 (*S*)-3-(benzyloxy)-2-(5-((tert-butyldimethylsilyl)oxy)-4-methoxy-3-methyl-2-((triisopropylsilyl)oxy)phenyl)-N-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-N-methylpropanamide (99)



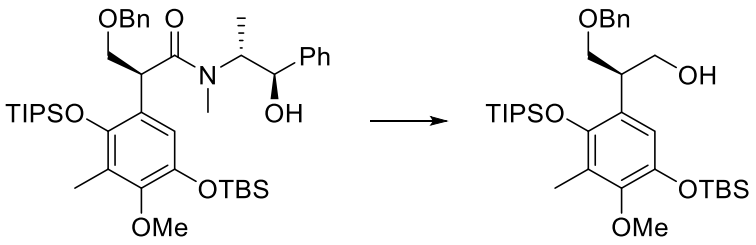
LiCl (62 mg, 1.47 mmol, 7.0 equiv) was placed in a Schlenk flask, LDA (1.1 mL, 0.5M stock solution, 0.53 mmol, 2.5 equiv) was added and the resulting suspension was cooled to -78°C. Amid (**98**) (130 mg, 0.21 mmol, 1.0 equiv) was dissolved in THF (0.4 mL) and added in two portions *via* syringe. The reaction mixture was allowed to warm to r.t overnight and was quenched using saturated NH_4Cl. Purification was achieved by column chromatography (toluene/CH_3CN 25:1) yielding 72 mg (46 %) of pure product.

^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.09-7.29 (10H, m), 6.63 (1H, s), 3.89- 4.67 (7H, m), 3.64 (3H, s), 2.55 (3H, s), 2.08 (3H, s), 0.95- 1.24 (24H, m), 0.91 (9H, s), 0.08 (6H, d, *J* =2.4)

^{13}C-NMR (100MHz, $CDCl_3$): δ= 174.9, 149.4, 146.5, 143.3, 142.5, 138.7, 128.4, 128.3, 128.1, 127.6, 127.5, 126.7, 122.7, 121.2, 117.2, 76.7, 73.6, 71.7, 59.9, 43.3, 29.8, 25.9, 18.7, 18.5, 18.4, 14.5, 14.0, 11.8, -4.4, -4.5

R_f: (PE/EA 2:1) 0.67

5.2.32 (*R*)-3-(benzyloxy)-2-(5-((tert-butyldimethylsilyl)oxy)-4-methoxy-3-methyl-2-((triisopropylsilyl)oxy)phenyl)propan-1-ol (101)



Amid (**99**) (18 mg, 0.024 mmol, 1.0 equiv) was dissolved in THF (0.3 mL) and placed in a flame dried microwave veil under Ar atmosphere. LiH_2NBH_3 (0.5 mL, 0.22mmol/mL in THF stock solution, 0.11 mmol, 4.6 equiv) was added *via* syringe, the veil was closed and the reaction mixture was heated in an oil bath (T= 55°C) overnight. After TLC confirmed full conversion, the reaction was cooled to 0°C and HCl (1M) was added over a period of 40 min. to quench excess of hydride accompanied by gas formation. The aqueous phase was extracted with Et_2O and the combined organic layers were washed with HCl (1M) and Na_2CO_3 (2M) before it was dried over Na_2SO_4 and concentrated under reduced pressure. Purification via column chromatography (PE/EA 20:1) gave 7 mg (42%) product as a colourless oil. The ee was determined *via* chiral HPLC. The retention time of the diastereomeric mixture appears at 9.83min., respectively at 10.45min. , whereat the intensity is 50 % for both. The retention of the enantiomer was 10.45min and the corresponding intensity > 99 %.

^{1}H-NMR (400 MHz, $CDCl_3$): δ= 7.28-7.37 (5H, m), 6.43 (1H, s), 4.56 (1H, d, J = 12.1), 4.51 (1H, d, *J* =12.1), 3.95 (1H, dd, *J* = 10.9, 7.8), 3.72-3.81 (2H, m), 3.70 (3H, s), 3.64 (1H, t, *J* =8.76), 3.53-3.60 (1H, m), 2.16 (3H, s), 1.24-1.36 (3H, m), 1.10 (18H, dd, *J* = 7.4, 1.6), 0.98 (9H, s), 0.11 (6H, s)

^{13}C-NMR (100MHz, $CDCl_3$): δ= 148.7, 147.6, 142.8, 138.1, 128.6, 127.9, 127.8, 124.9, 123.1, 116.8, 74.5, 73.7, 66.9, 59.9, 40.0, 25.9, 18.2, 18.1, 14.4, 11.5, -4.5

IR [cm^{-1}]: ν = 2929, 2866, 1481, 1431, 1362, 1250, 1220, 1063, 1015, 919, 883, 838, 782, 735, 681, 548, 525, 507

R_f: (PE/EA 2:1) 0.67

6 References

(1) Rodríguez, A. D.; González, Eduvigis. *J. Am. Chem. Soc.* **1998**, *63* (20), 7083.
(2) Srikrishna, A.; Pardeshi, V. H.; Satyanarayana, G. *Tetrahedron Lett.* **2007**, *48* (23), 4087.
(3) Rodríguez, I. I.; Shi, Y.-P.; García, O. J.; Rodríguez, A. D.; Mayer, A. M. S.; Sánchez, J. A.; Ortega-Barria, E.; González, J. *J. Nat. Prod.* **2004**, *67* (10), 1672.
(4) Heckrodt, T. J.; Mulzer, J. *J. Am. Chem. Soc.* **2003**, *125* (16), 4680.
(5) Waizumi, N.; Stankovic, A. R.; Rawal, V. H. *J. Am. Chem. Soc.* **2003**, *125* (43), 13022.
(6) Preindl, J.; Leitner, C.; Baldauf, S.; Mulzer, J. *Org. Lett.* **2014**, *16* (16), 4276.
(7) Ferns, T.; Kerr, R. G. *Tetrahedron* **2005**, *61* (52), 12358.
(8) Zanoni, G.; Franzini, M. *Angew. Chem. Int. Ed.* **2004**, *43* (37), 4837.
(9) Yakelis, N. A.; Roush, W. R. *Org. Lett.* **2001**, *3* (6), 957.
(10) Gorman, D. B.; Tomlinson, I. A. *Chem. Commun.* **1998**, No. 1, 25.
(11) Matikainen, J.; Hase, T. *Tetrahedron* **1997**, *53* (12), 4531.
(12) Kim, A. I.; Scott D. Rychnovsky. *Angew. Chem. Int Ed* **2003**, *42* (11), 1267.
(13) Steiner, S. *Diploma Thesis* **2015**.
(14) jackson, S. R.; Johnson, M. G.; Mikami, M.; Carreira, E. M. *Angew Chem Int Ed* **2001**, *40* (14), 2694.
(15) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem Commun* **2007**, No. 7, 675.
(16) Ritter, T.; Zarotti, P.; Carreira, E. M. *Org. Lett.* **2004**, *6* (23), 4371.
(17) Wu, Q.-F.; Liu, W.-B.; Zhuo, C.-X.; Rong, Z.-Q.; Ye, K.-Y.; You, S.-L. *Angew. Chem. Int. Ed.* **2011**, *50* (19), 4455.
(18) Nemoto, T.; Ishige, Y.; Yoshida, M.; Kohno, Y.; Kanematsu, M.; Hamada, Y. *Org. Lett.* **2010**, *12* (21), 5020.
(19) Rousseaux, S.; García-Fortanet, J.; Del Aguila Sanchez, M. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133* (24), 9282.
(20) Lurain, A. E.; Maestri, A.; Kelly, A. R.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126* (42), 13608.
(21) Wang, S.-Y.; Loh, T.-P. *Chem. Commun.* **2010**, *46* (46), 8694.
(22) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125* (37), 11360.
(23) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34* (1), 18.
(24) Kanematsu, M.; Soga, K.; Manabe, Y.; Morimoto, S.; Yoshida, M.; Shishido, K. *Tetrahedron* **2011**, *67* (26), 4758.
(25) Siddiqi, S.; Heckrodt, T. J. *Z. Fuer Naturforschung B Chem. Sci.* **2003**, *58* (4), 328.
(26) Myers, A. G.; Yang, B. H. *J. Am. Chem. Soc.* **1997**, *119*, 6496.
(27) Kesteleyn, B.; De Kimpe, N. *J. Org. Chem.* **2000**, *65* (3), 635.
(28) Takano, S.; Sekiguchi, Y.; Sato, N. *Synthesis* **1987**, 139.
(29) Quartieri, F.; Mesiano, L. E.; Borghi, D.; Desperati, V.; Gennari, C.; Papeo, G. *Eur. J. Org. Chem.* **2011**, *2011* (33), 6794.
(30) Guo, X.; Yu, R.; Li, H.; Li, Z. *J. Am. Chem. Soc.* **2009**, *131* (47), 17387.
(31) Ramadhar, T. R.; Kawakami, J.; Lough, A. J.; Batey, R. A. *Org. Lett.* **2010**, *12* (20), 4446.
(32) Trost, B. M.; Toste, F. D. *J Am Chem Soc* **1998**, *120*, 815.
(33) Chavda, S.; Coulbeck, E.; Dingjan, M.; Eames, J.; Motevalli, M. *Tetrahedron Asymmetry* **2008**, *19* (10), 1274.
(34) Cordero, F. M.; Pisaneschi, F.; Salvati, M.; Valenza, S.; Faggi, C.; Brandi, A. *Chirality* **2005**, *17* (3), 149.
(35) Rasapalli, S.; Jarugumilli, G.; Yarrapothu, G. R.; Golen, J. A.; Rheingold, A. L. *Tetrahedron Lett.* **2013**, *54* (21), 2615.

(36) Grieco, P. A.; Hiroi, K. *J. Chem. Soc. Chem. Commun.* **1972**, *24*, 1317.
(37) Nishimoto, Y.; Ueda, H.; Yasuda, M.; Baba, A. *Angew. Chem. Int. Ed.* **2012**, *51* (32), 8073.
(38) Chen, Q.-H.; Praveen Rao, P. N.; Knaus, E. E. *Bioorg. Med. Chem.* **2006**, *14* (23), 7898.
(39) Taylor, S. R.; Ung, A. T.; Pyne, S. G. *Tetrahedron* **2007**, *63* (45), 10896.
(40) Gaich, T.; Mulzer, J. *Org. Lett.* **2010**, *12* (2), 272.
(41) Connor, D. S.; Klein, G. W. *Org. Synth.* **1972**, *52*, 16.

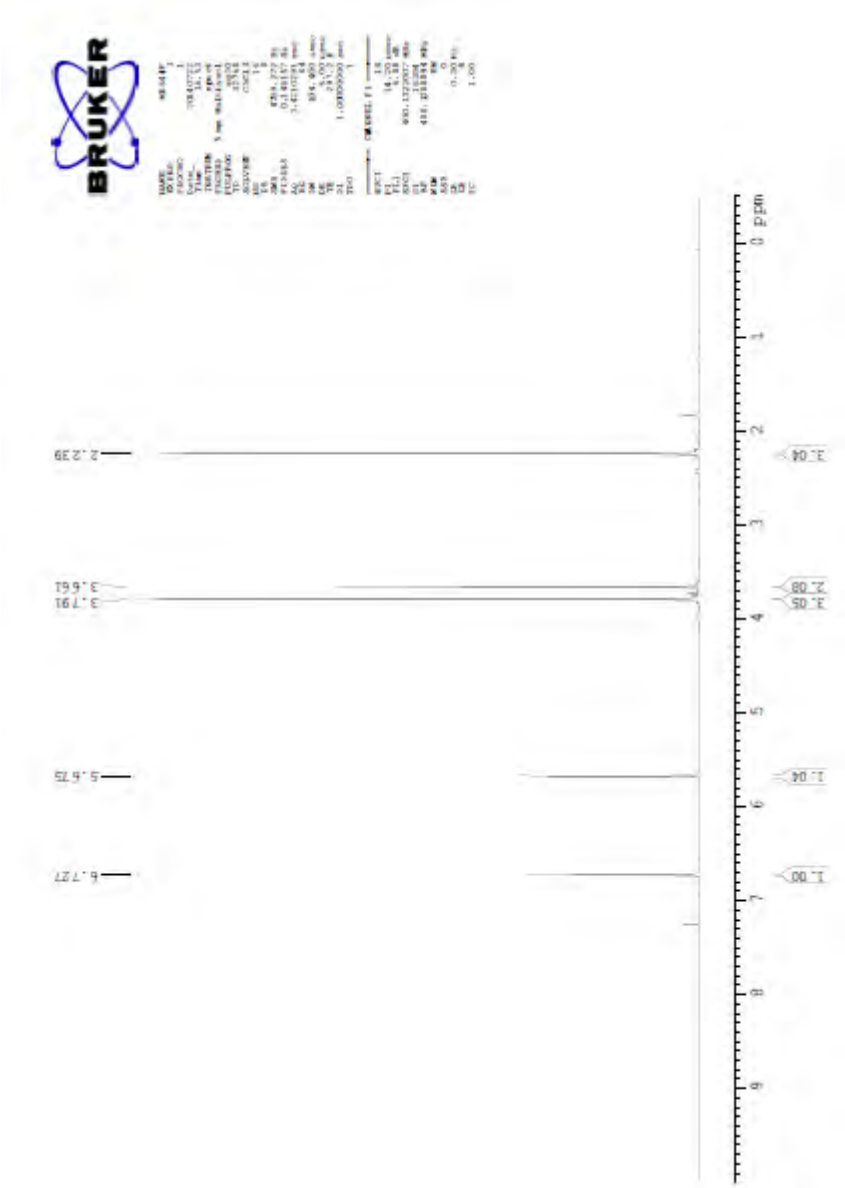
7 Appendices

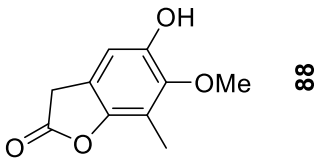
7.1 Abbreviations

ADDP	1,1'-(Azodicarbonyl)-dipiperidine
APT	attached proton test
BOMBr	((bromomethoxy)methyl)benzene
Bn	benzyl
CaH_2	calcium hydride
CAN	Cerium ammonium nitrate
DCC	*N,N'-Dicyclohexylcarbodiimide*
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine (Hünig's base)
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EA	ethyl acetate
ee	enantiomeric excess
equiv.	equivalent(s)
EtOH	ethanol
Eu(fod)3	Europium(III)-tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate)
HPLC	high performance liquid chromatography
IMDA	intramolecular Diels-Alder reaction
iPr	isopropyl
IR	infrared
KOtBu	potassium *tert*-butoxide
mCPBA	m-chloroperoxybenzoic acid
MeI	methyl iodide
MeOH	methanol
MOM	methoxymethyl
MOMCl	chloromethyl methyl ether
NaH	sodium hydride
NaHMDS	sodium bis(trimethylsilyl)amide
NaOEt	sodium ethoxide

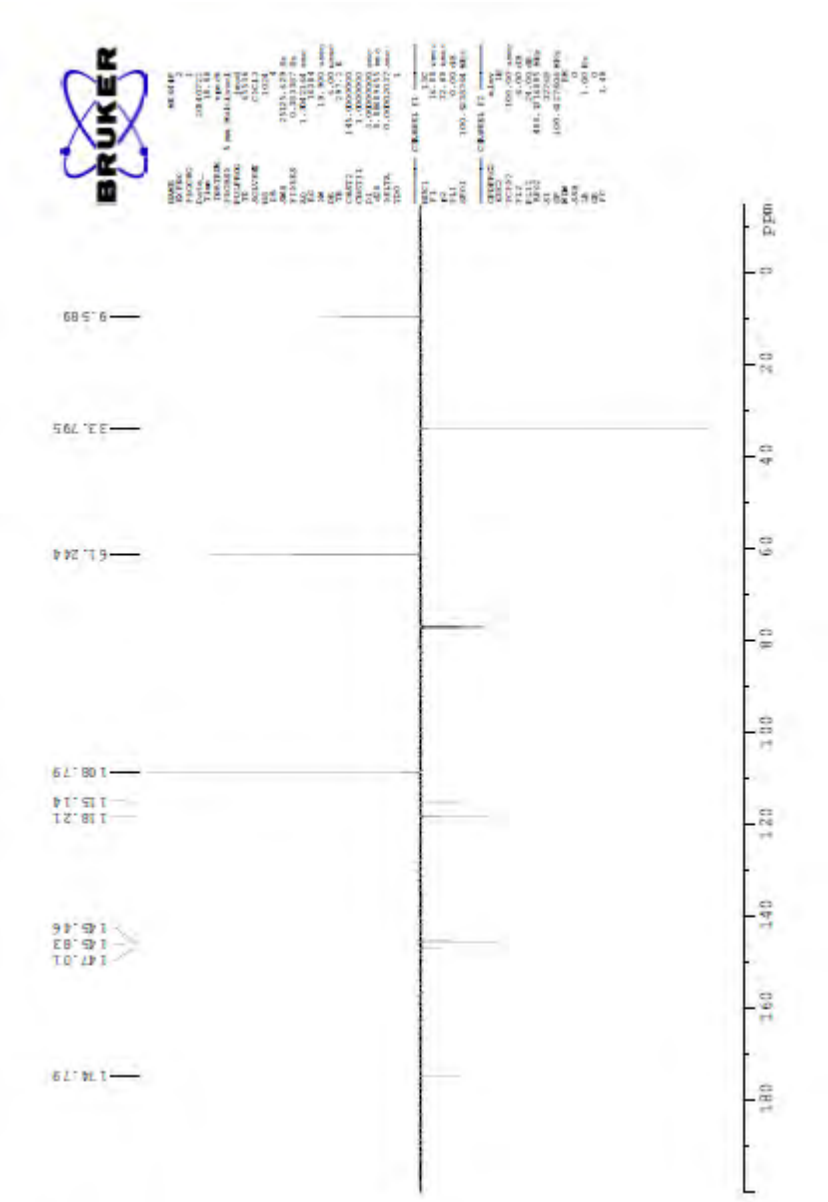
nBuLi	n-butyllithium
NEt_3	triethylamine
NMR	nuclear magnetic resonance
P, PG	protecting group
PE	petroleum ether
PMB	para-methoxybenzyl (4-methoxybenzyl)
PMBCl	para-methoxybenzyl chloride (4-methoxybenzyl chloride)
pTsOH	p-toluenesulfonic acid, p-toluenesulfonate
RCM	ring closing metathesis
RRCM	relay ring closing metathesis
TBAF	tetra-N-butylammonium fluoride
TBEMS	tert-butylethylmethylsilyl
TBS	tert-butyldimethylsilyl group
TBSCl	tert-butyldimethylsilyl chloride
TBSOTf	tert-butyldimethylsilyl triflate
TESOTf	triethylsilyl trifluoromethanesulfonate
THF	tetrahydrofurane
TIPS	triisopropyl silyl
TIPSCl	triisopropyl silyl chloride
TLC	thin layer chromatography
TS	transition state

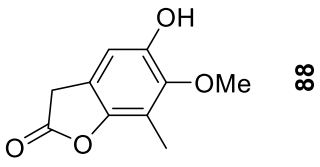
7.2 Selected Spectra



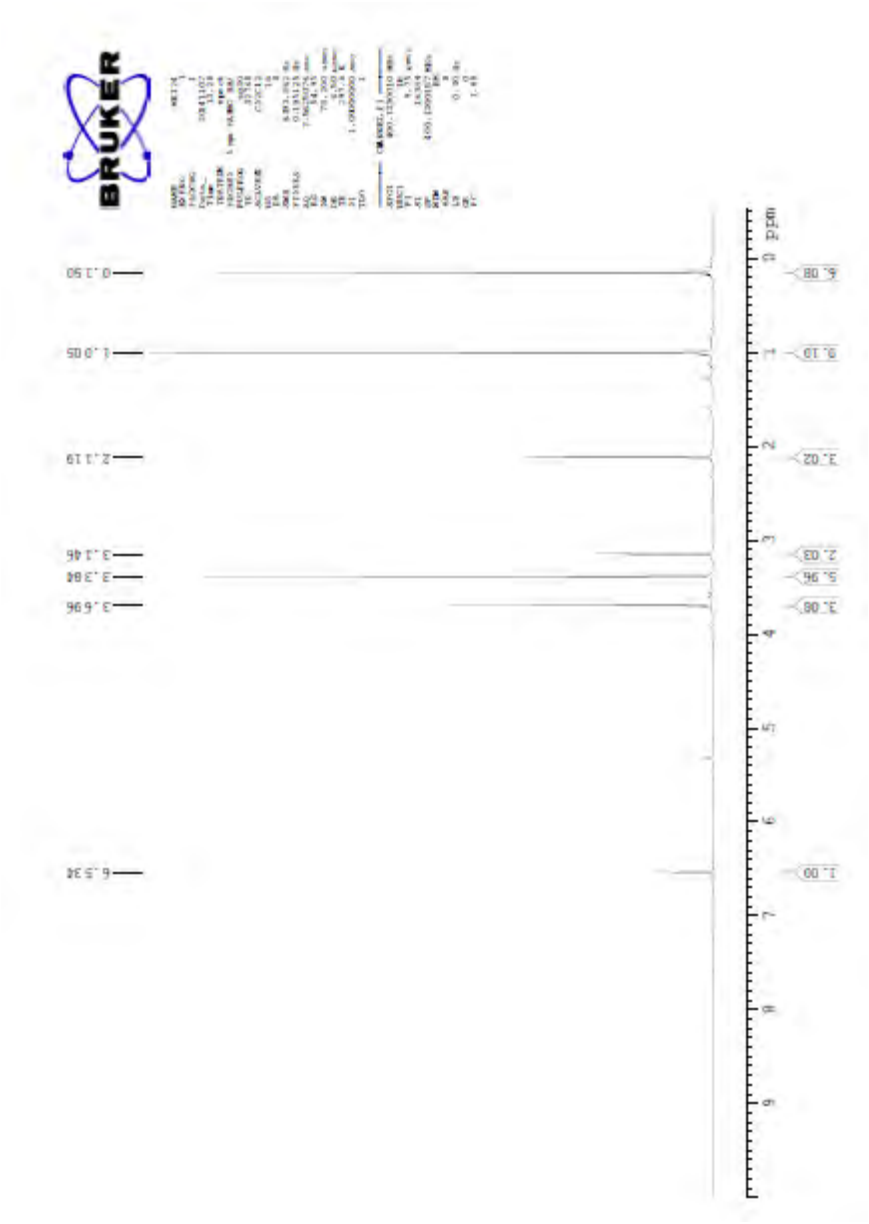


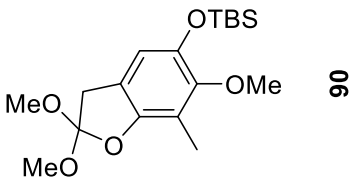
88



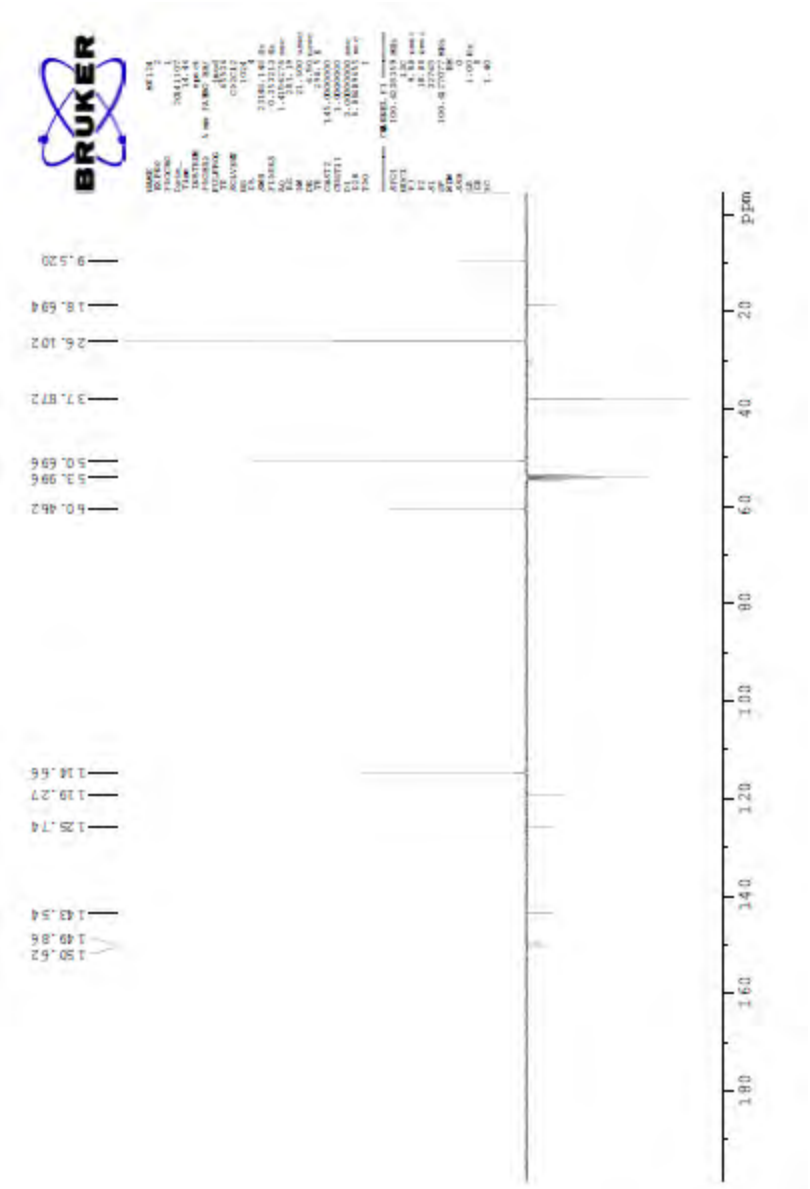


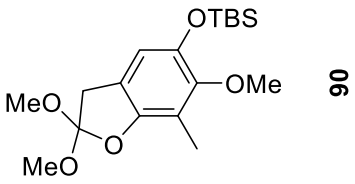
88



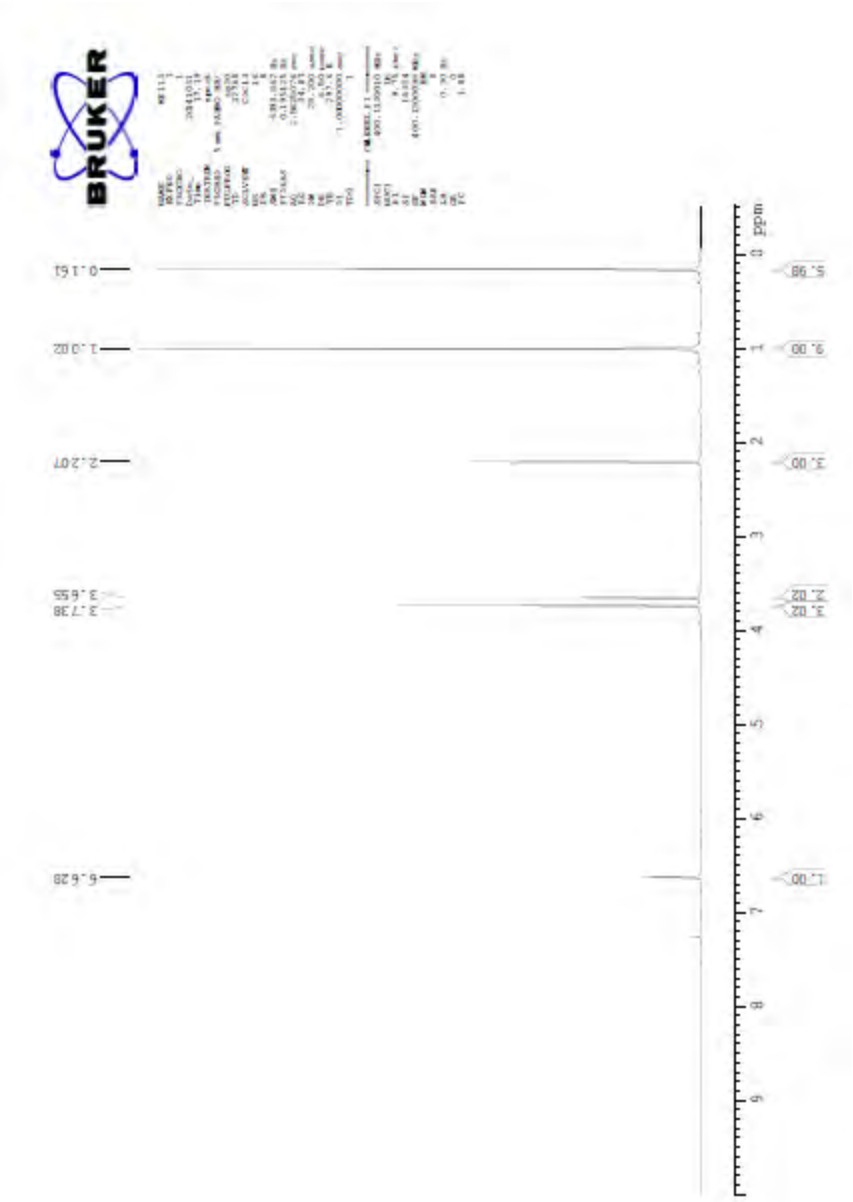


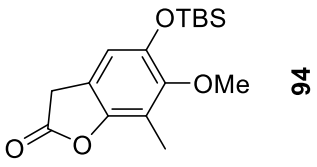
90



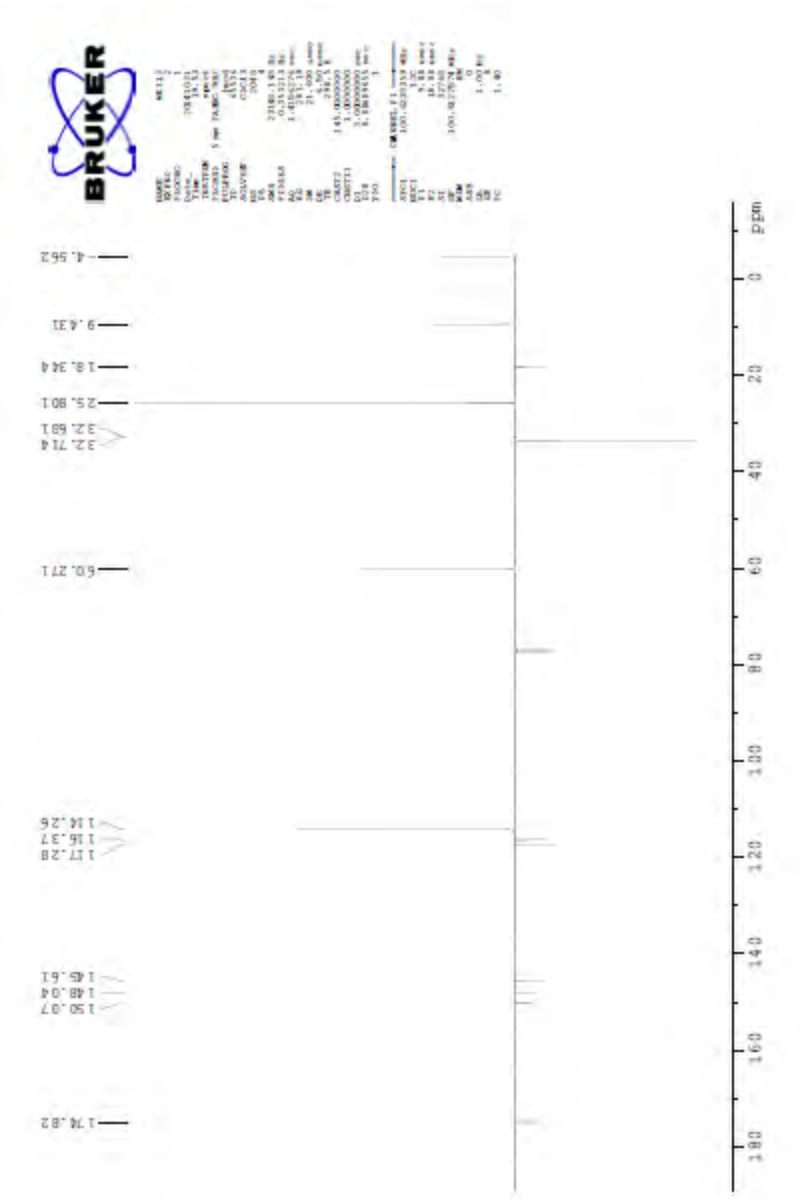


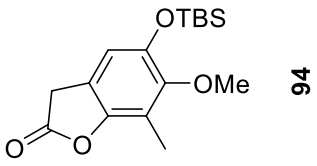
90



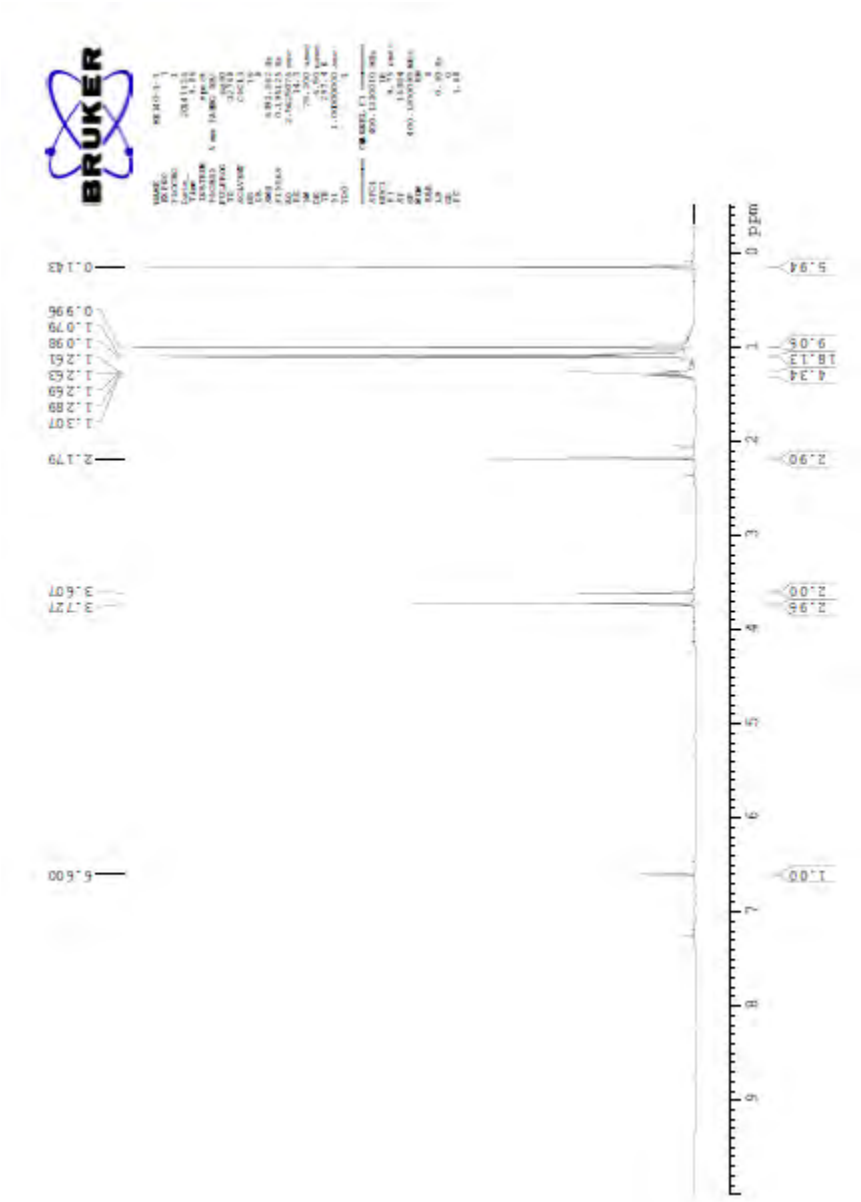


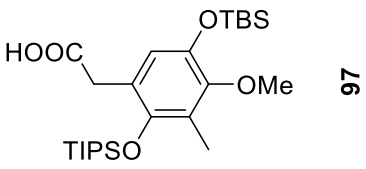
94



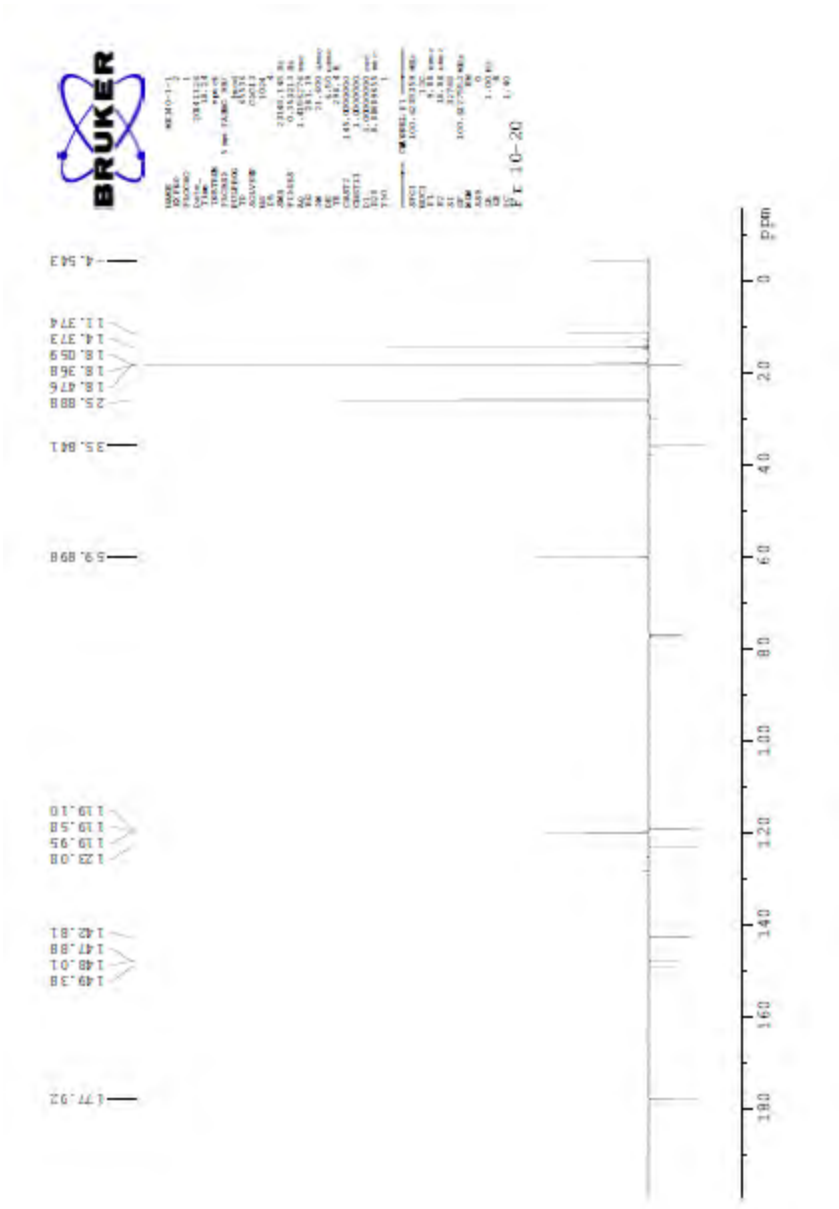


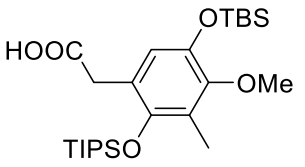
94



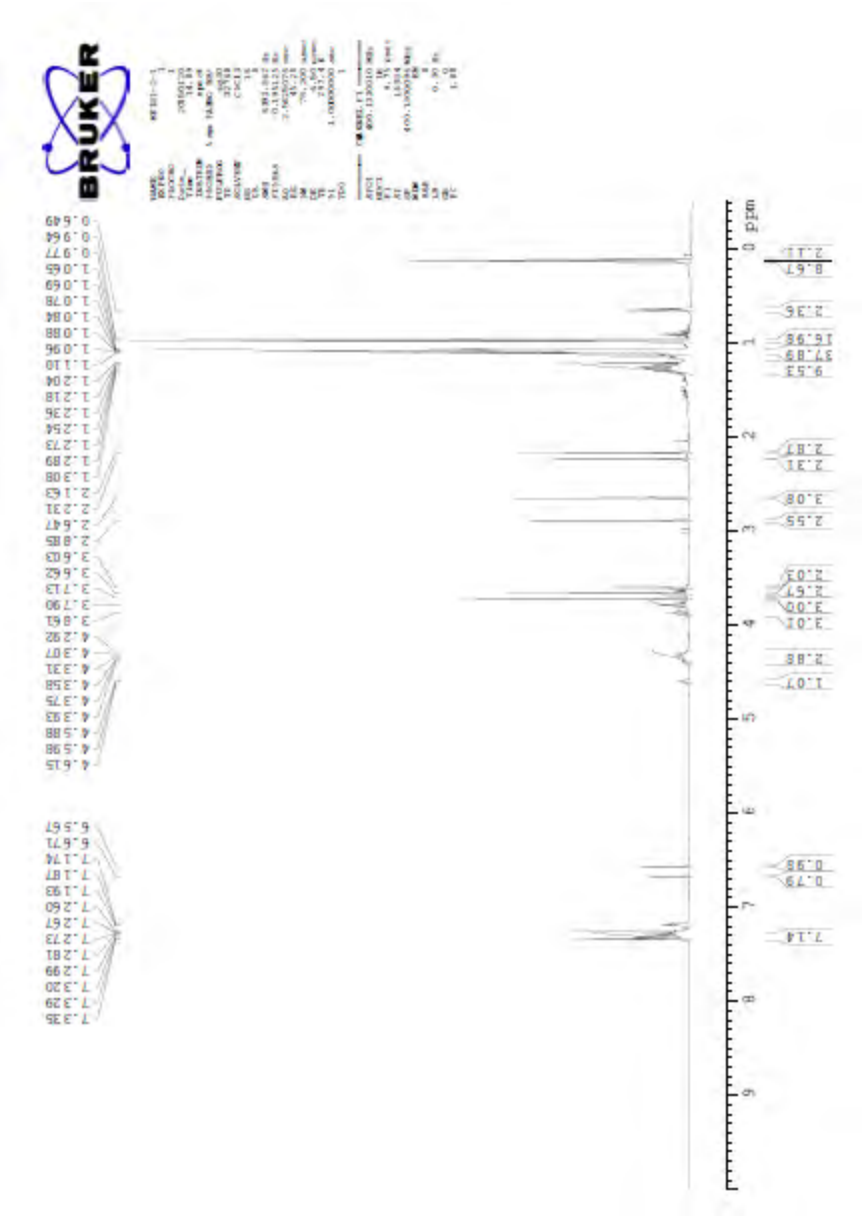


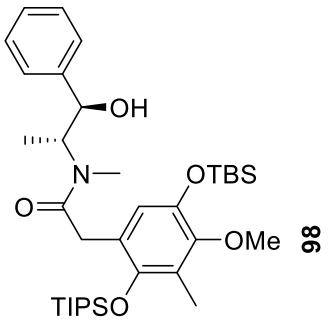
97



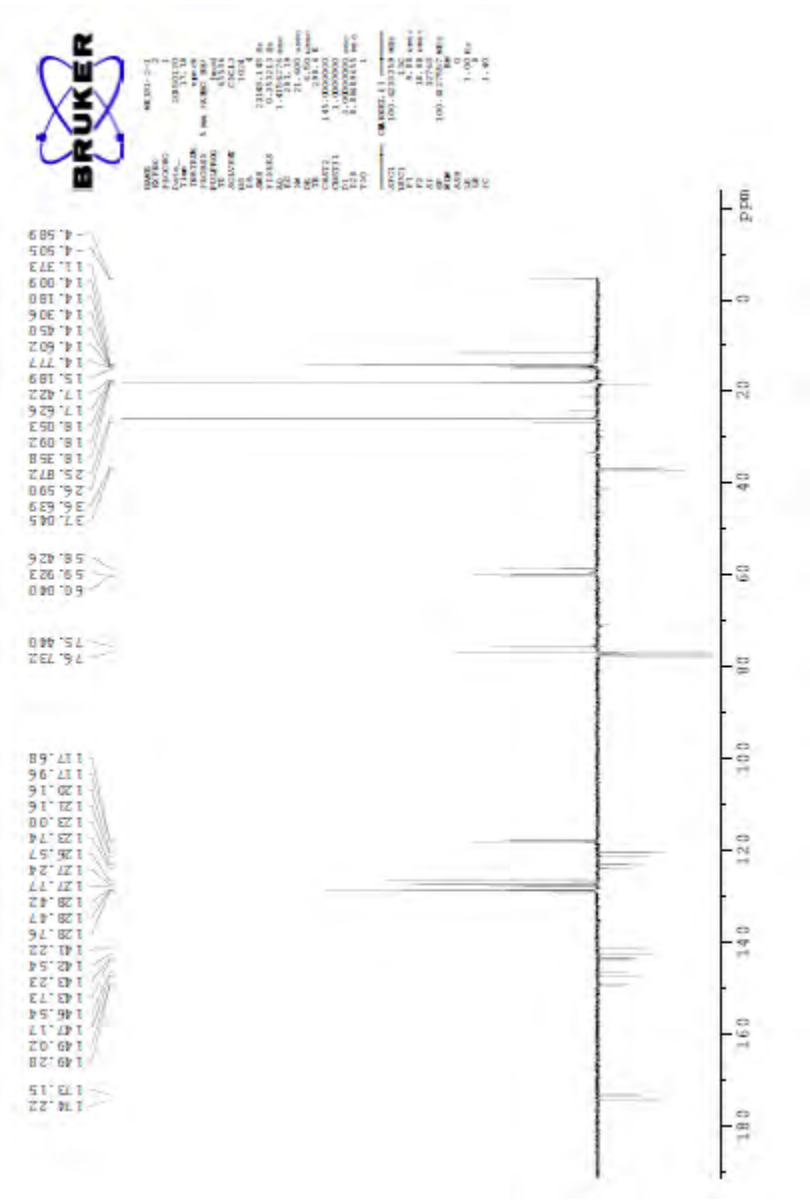


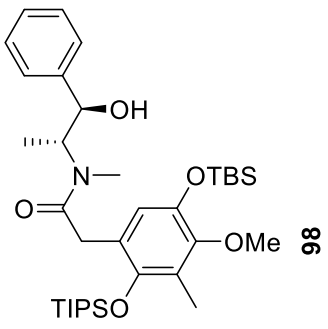
97



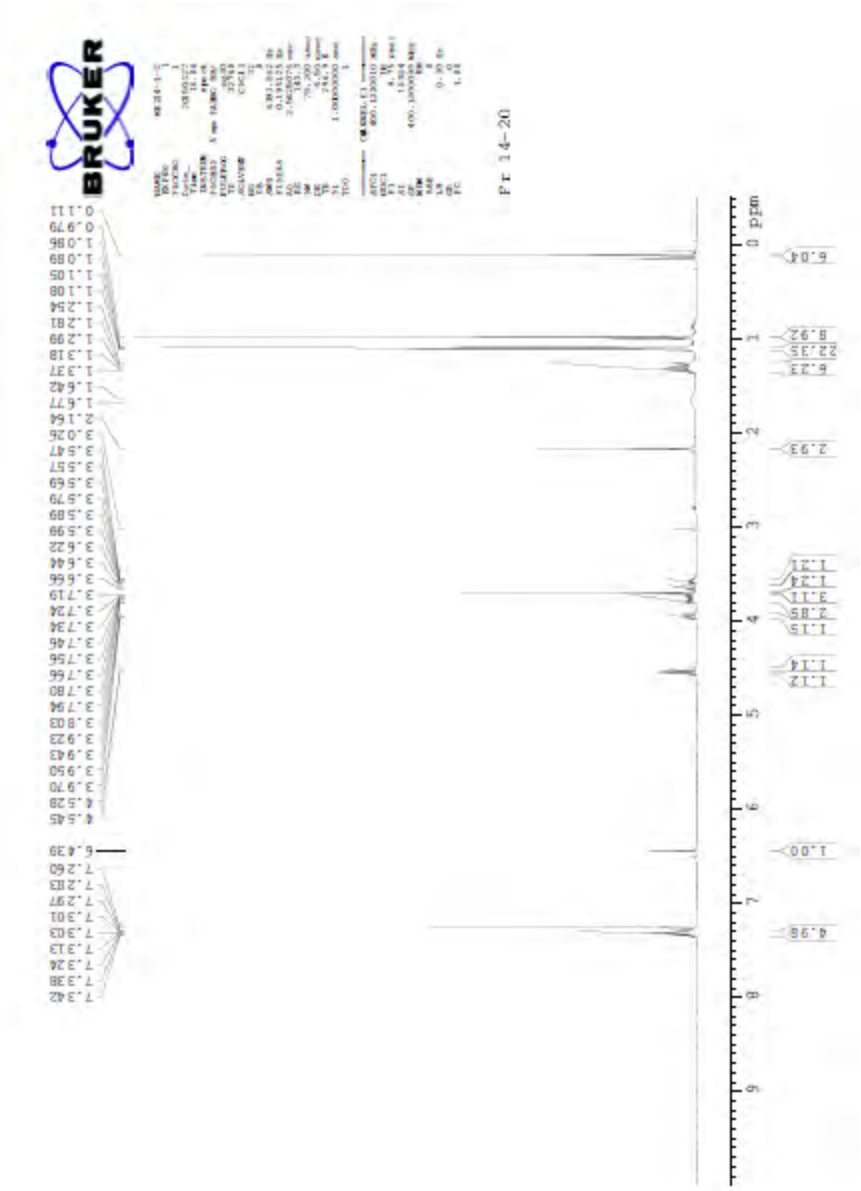


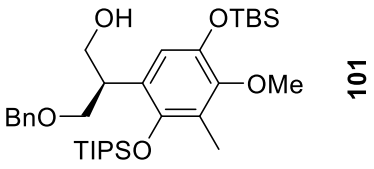
98



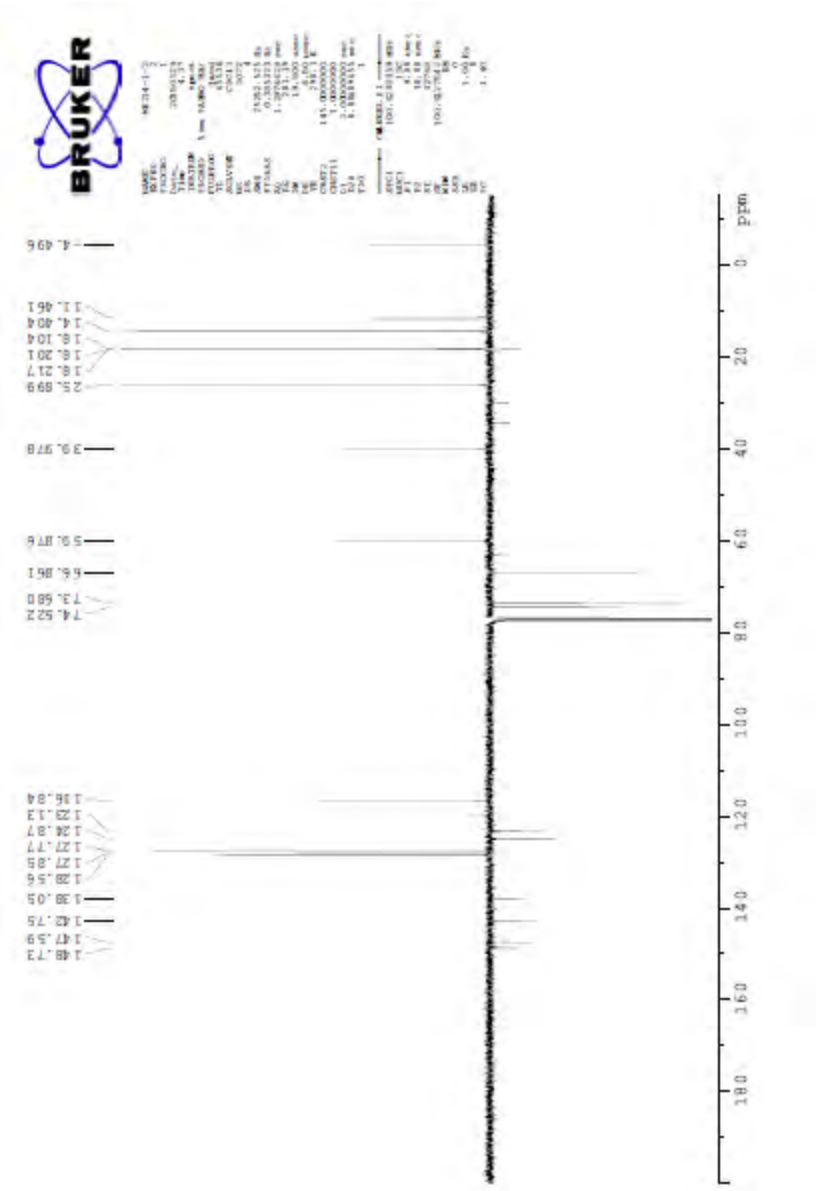


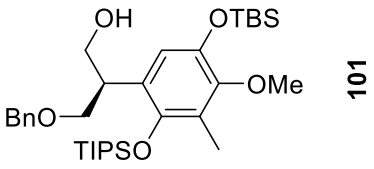
98





101





101