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Stereoselective synthesis of Bis-Tetrahydrofurans

Master thesis in material science

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Tartu 2014

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Abbreviations

Ac - acetyl

ACG – acetogenin

AKR – aminolytic kinetic resolution

Bn - benzyl

Boc - tert-butoxy carbonyl

DCM - dichlorometane

d.r – diastereomeric ratio

cat. – catalyst

Cbz - benzyloxycarbonyl

m-CPBA – meta-chloroperoxybenzoic acid

eq. - equivalents

e.r – enantiomeric ratio

Et – Ethyl

HKR – hydrokinetic resolution

Me - Methyl

NMO – N-methylene morpholine oxide

NMR – Nuclear magnetic resonance

Nu – nucleophile

PG – protecting group

PMO – pyridine-N-oxide

rt – room temperature

TBAF – tetrabutylammonium fluoride

THF – tetrahydrofuran

THP – tetrahydropyran

TLC – thin layer chromatography

TPAP – tetrapropyl ammonium perruthenate

Introduction

In nature chirality plays a big role due to the different biological activity of enantiomers. Nearly all biological polymers have to be homochiral to function – either left handed as amino acids or right handed as sugars. Yet when synthesized in laboratory we mostly produce a racemic mixture of both enantiomers. While it is possible to separate enantiomers from each other it is often too expensive and difficult, and additionally, half of the material becomes useless. A more useful approach would be to synthesize only one isomer. Such approach is called asymmetric/stereoselective synthesis and it is the key step in modern chemistry to produce only the wanted enantiomer.

Bis-tetrahydrofuran (THF) units, with four chiral centers (highlighted in Figure 1), have been of great interest since they are the key unit of *Annonaceus* acetogenins. Acetogenins are naturally occurring compounds with broad spectrum of biological activities such as cytotoxic, antitumor, antimicrobial, antimalarian, antifeedant, pesticidal, and immunosuppressive effects.¹

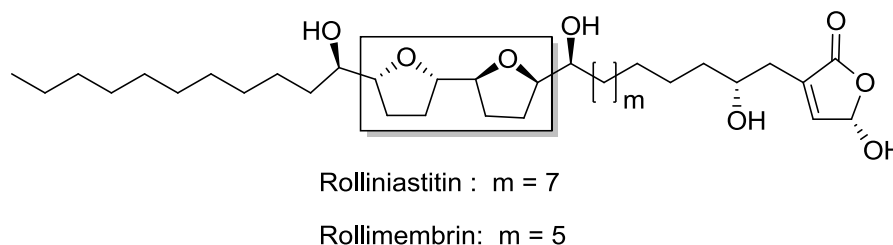
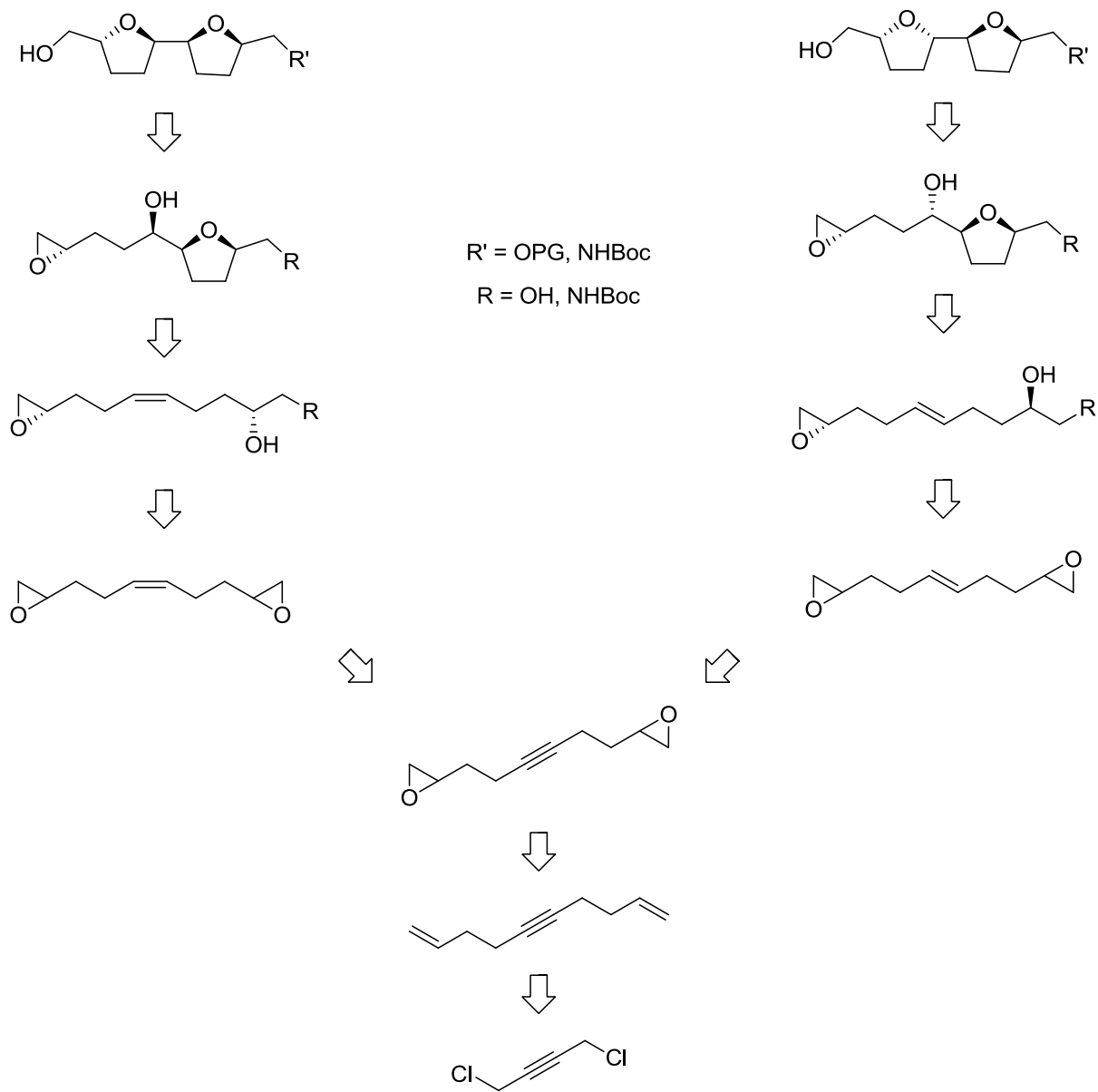


Figure 1. Acetogenins containing bis-THF rings.

Due to difficulties to separate these compounds from plant material and due to interesting biological properties, considerable effort has been made to synthesize acetogenins and their analogues.

The main purpose of this thesis was to develop a stereoselective synthesis route to such bis-THF motifs. The main retrosynthetic steps are shown on Scheme 1. The key steps are stereoselective reduction of triple bond, kinetic resolution of bis-epoxide and oxidative cyclization.



Scheme 1. Retrosynthetic scheme for the synthesis of bis-THF compounds.

Stereochemistry

Stereochemistry describes how the atoms of a molecule are arranged in three-dimensional space. Many of the descriptions for stereogenic units begin with assigning priorities to the attached ligands, higher atomic number getting higher priority. There are various rules for assigning descriptors to stereocenters, here we provide a brief review of the terminology that is used in this thesis.

R,S System – for tetracoordinated carbon and related structures the Cahn-Ingold-Prelog system is used. The center is termed R, if moving from the highest to the lowest priority ligands involves a clockwise direction. A counterclockwise direction implies S (Figure 2).

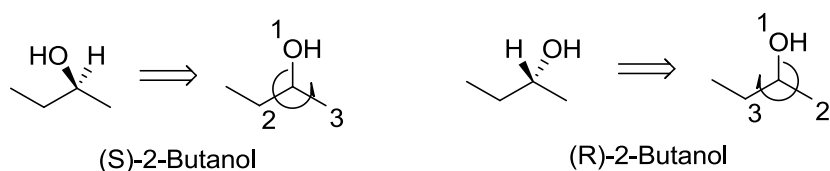


Figure 2. Determining of S and R stereochemistry.

E, Z System – For olefins and related structures the double bond is divided in half and two sides are compared. If the two high priority ligands are on the same side of the double bond, the system is Z; if they are on opposite sides, the system is E (Figure 3). If an H atom is on each carbon of the double bond, however, traditional „cis“ and „trans“ descriptors are used.

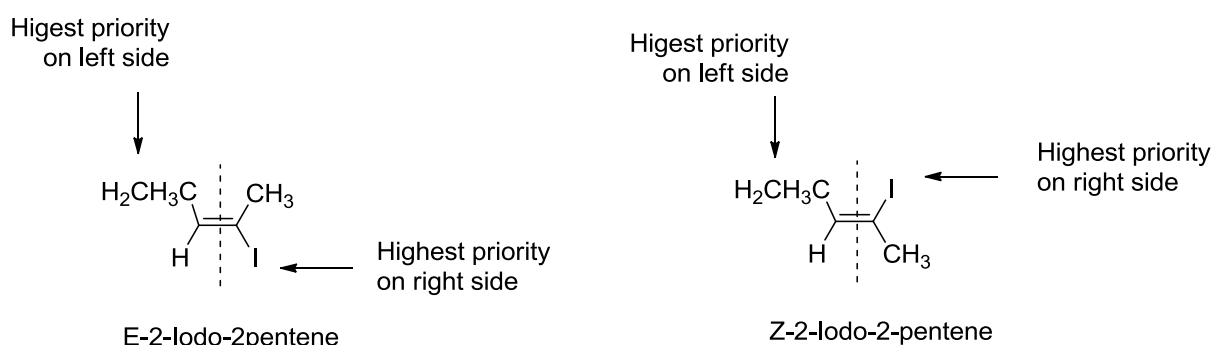


Figure 3. Labeling alkene stereochemistry

Erythro and Threo – This is the basis of a nomenclature system for compounds with two stereogenic centers. If the two stereogenic centers have two groups in common, erythro and threo terms can be assigned. If the groups that are the same are both on one side, the

compound is called erythro; if they are on opposite sides, the compound is called threo (Figure 4).²



Figure 4. Determination of erythro and threo diastereomers.

Acetogenins

Annonaceus acetogenins (ACGs), a new class of polyketides, are natural products isolated exclusively from *Annonaceae* species that are widely distributed in tropical and subtropical regions. Since uvaricin (Figure 5) was isolated in 1982³ from the roots of *Uvaria accuminata*, more than 400 members of this family of compounds have been isolated and characterized from 51 different species.^{4,5}

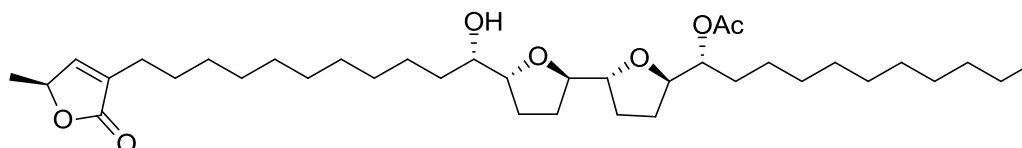


Figure 5. Uvaricin was the first *Annonaceus* acetogenin discovered.

Much attention has also been paid to acetogenins' broad range of bioactivity; e.g., their immunosuppressive, pesticidal, antimalarial, insecticidal, antifeedant, and probably most important, antitumor activities. In this respect they are known to be very potent cytotoxic compounds, targeting the reduced nicotinamide adenine dinucleotide (NADH) (also known as complex I). Some acetogenins show growth inhibitory activity against multidrug resistant (MDR) cancer cells.

Chemically, the ACGs are white, waxy, derivatives of long unbranched aliphatic (C₃₂ or C₃₄) fatty acids that have been combined with a 2-propanol unit at C-2 to form a terminal methyl-substituted α,β -unsaturated- γ -lactone ring. One, two, or three tetrahydrofuran (THF) or tetrahydropyran (THP) rings are located along the hydrocarbon chain and a number of

oxygenated moieties (hydroxyls, acetoxy, ketones, epoxides) and double or triple bonds may be present.⁶

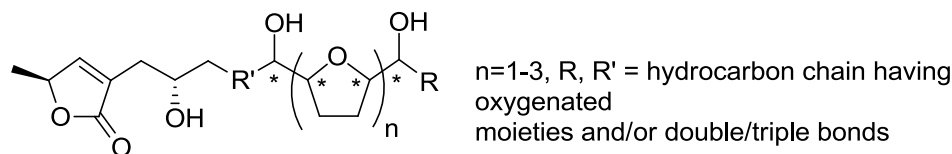


Figure 6. Representative structure of the *Annonaceous* acetogenins.

Generally, all ACGs belong to two broad groups:⁷

- 1) classical ACGs, which involve ACGs comprising none to three THF units along with a terminal γ -lactone.
- 2) Nonclassical ACGs, which include ACGs containing a THP ring or hydroxylated THF ring along with a terminal γ -lactone.

Due to the large number of annonaceous acetogenins that have been isolated and characterized, a system of classification has been introduced, which groups them according to their core structure (Figure 7).^{7,8} These include mono-THF, adjacent bis-THF, nonadjacent bis-THF, tri-THF, non-THF ring, adjacent THF and THP, non-adjacent THF and THP, mono-THP, and acetogenins containing only γ -lactones.

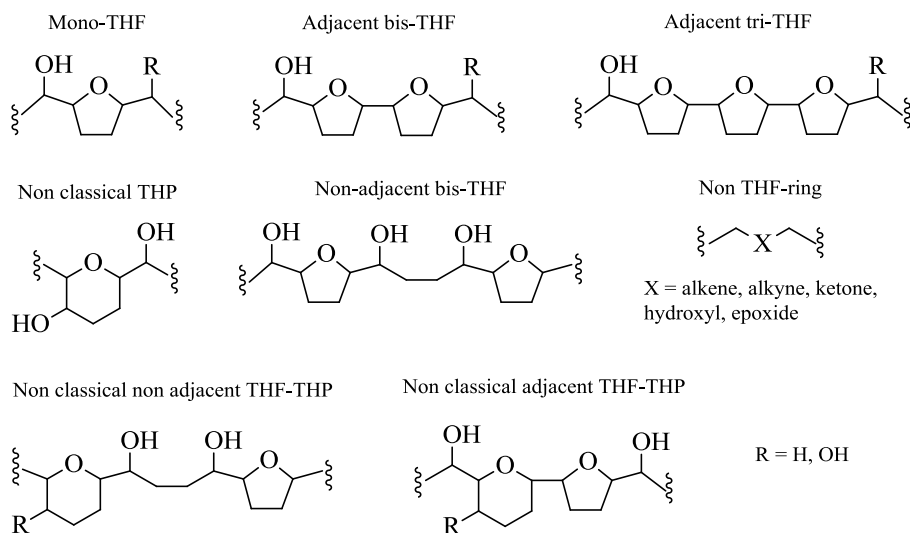


Figure 7. Core units for classification of ACGs.

The core classes can be broken down into sub classes by the nature of the γ -lactones, but commonly a methyl substituted α,β -unsaturated (butenolide) is present with or without hydroxylation in the linking chain.

All ACGs have multiple chiral centers. A number of them share the same skeleton and are differentiated from each other only by their stereochemistries around the THF subunits. In addition, the stereochemistries, in many cases, influence the relative potencies and biological specificities.⁹ The stereochemistry of ring systems leads to subclasses of acetogenins, and these subclasses are subsequently named after the first compound within that subclass to have its relative configuration determined.

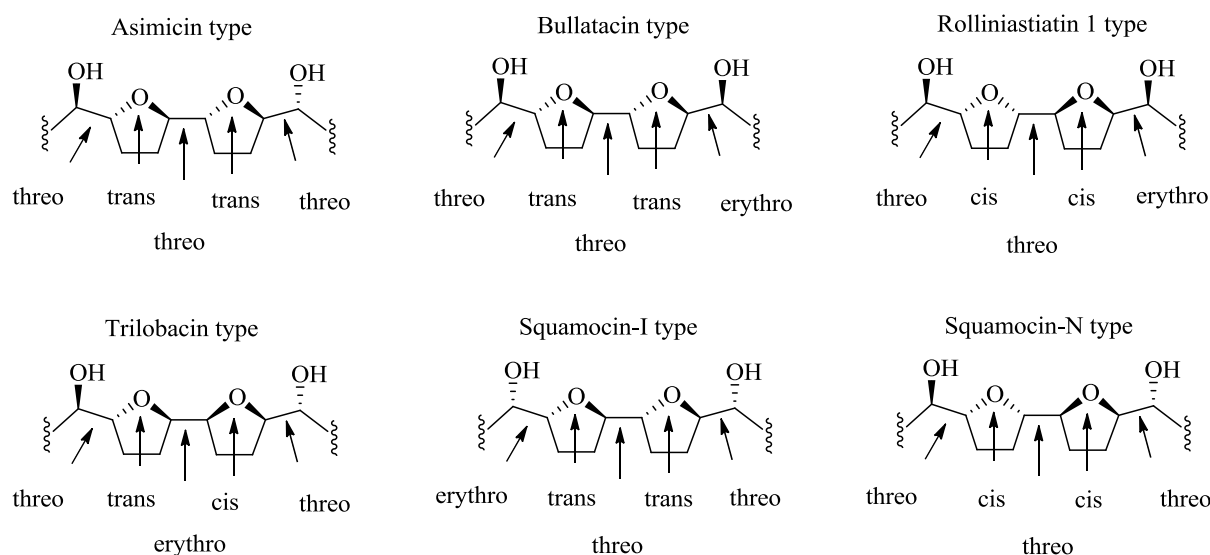


Figure 8. Six types of adjacent bis-THF ring acetogenins.¹⁰

Known synthetic routes to Rolliniastatin I type acetogenins

The core unit of the adjacent bis-THF acetogenins contains six oxygenated stereocenters, and much of the synthetic work on the family has been focused on these stereocenters. Compared to other bis-THF ACGs, there have been very few successful syntheses of Rolliniastatin I type (Figure 9) ACGs reported.

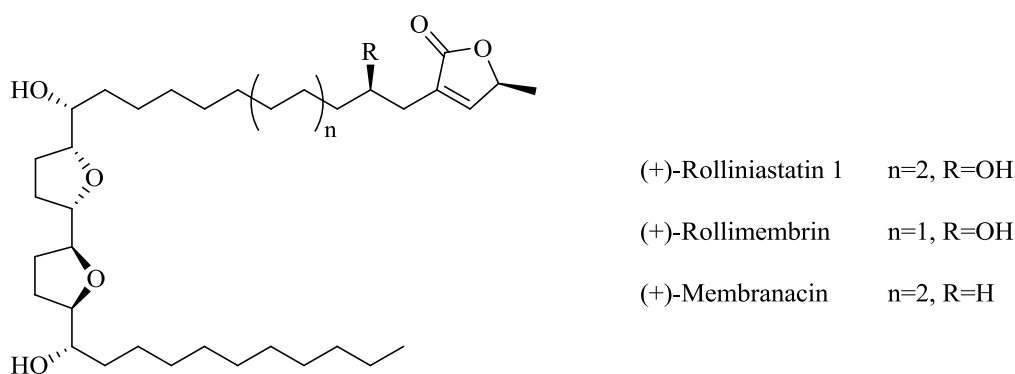
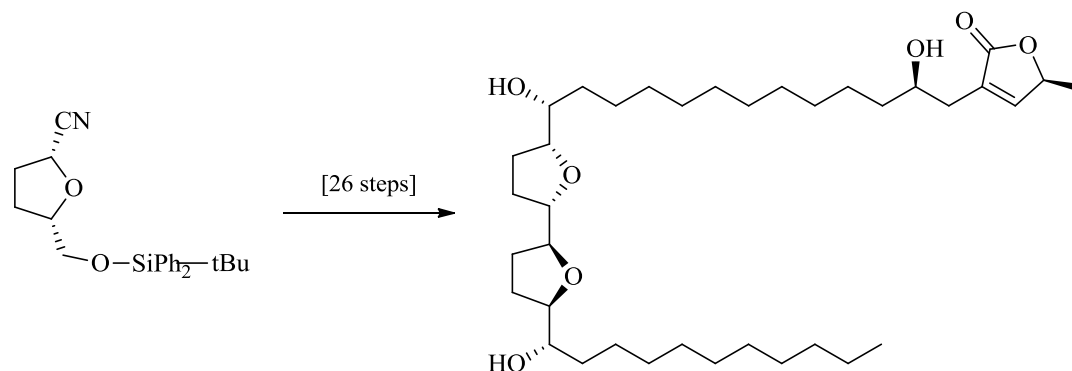


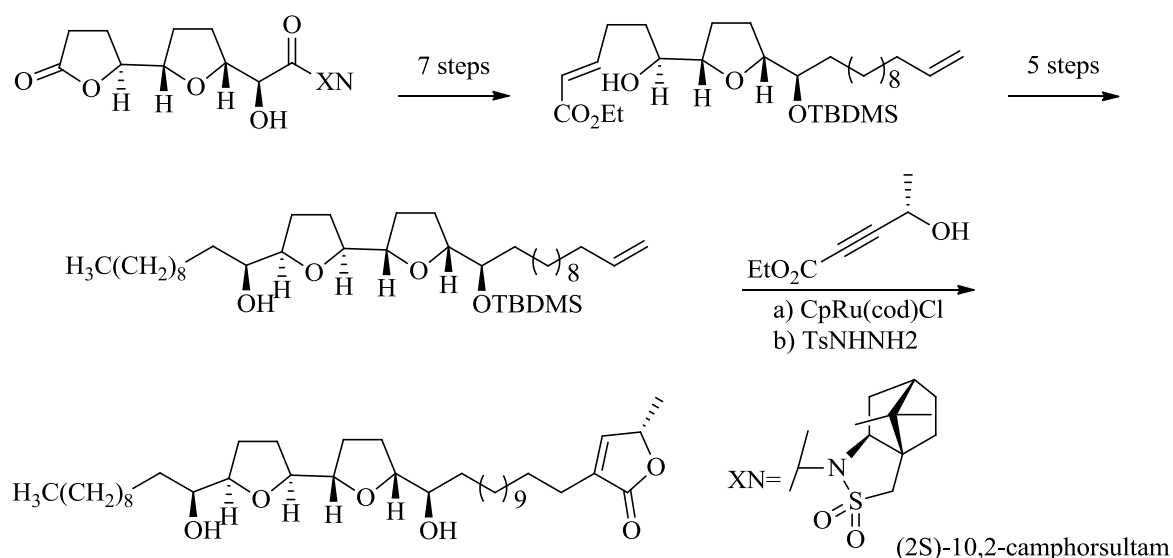
Figure 9. Cytotoxic ACGs from seeds of *Rollinia mucosa* and *R. membranacea*.

First synthesis of rolliniastatin 1 was reported by Koert in 1994 who achieved this in 26 steps, starting with the enantiomerically pure cis-nitril (Scheme 2).¹¹



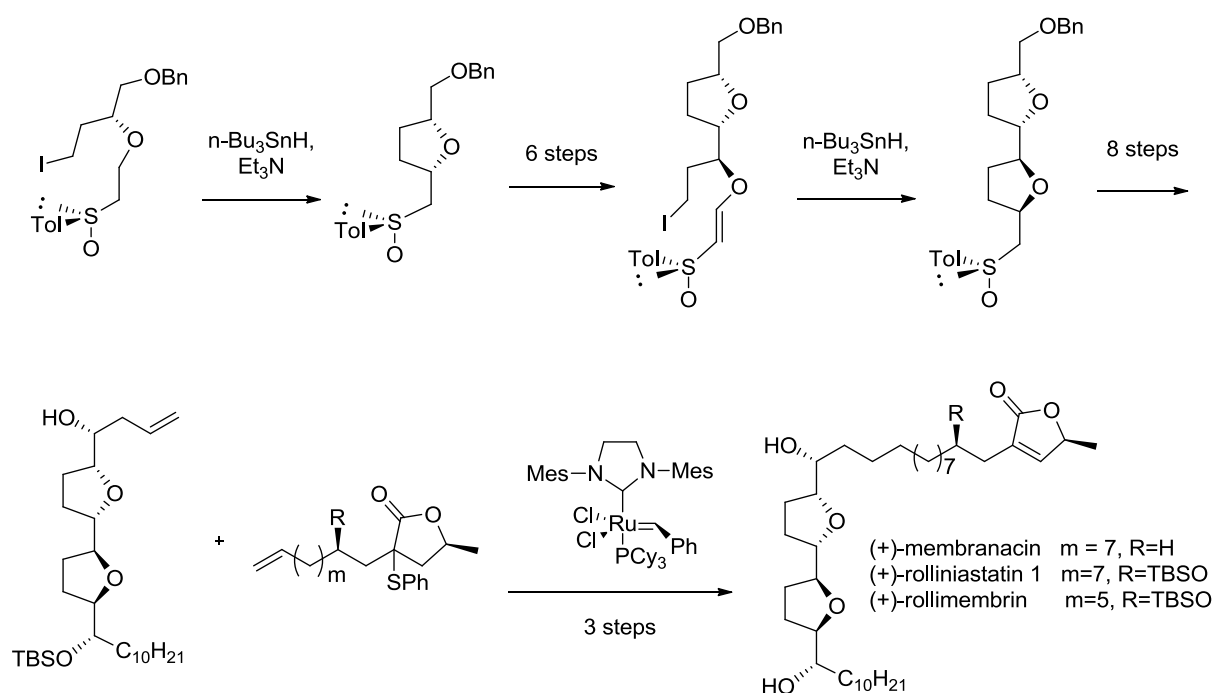
Scheme 2. Synthesis of Rolliniastatin 1.

First synthesis of membranacin was published by Brown's group in 2004 where the bis-THF precursor was constructed from the lactone using metal-oxo and metal-peroxy-mediated oxidative cyclisations as the key steps. The butenolide portion of membranacin was introduced using Trost's ruthenium-catalysed Alder-ene reaction (Scheme 3).¹²



Scheme 3. Total synthesis of membranacin by Brown's group.

In 2005, Lee's group also reported the total synthesis of membranacin, rolliniastatin 1 and rollimembrin (Scheme 4)¹³. First they synthesized bis-oxolane intermediate via radical cyclizations. This pivotal intermediate was used in a cross olefin metathesis reaction followed by the established three step sequence to finish the total synthesis of membranacin, rollimembrin and rolliniastatin.



Scheme 4. Total synthesis of membranacin, rolliniastatin 1 and rollinimembrin by Lee's group.

All of these synthetic routes are very long, in addition, their enantio- and diastereoselectivity is not very good. It is clear that they are not very effective, especially in larger scales, and better synthetic routes are needed.

Literature review about the synthetic steps used in this work

Alkyl-alkyne cross coupling

Alkynes are an important class of organic compounds because they are frequently used as synthetic intermediates and precursors for natural products, biologically active molecules, and organic materials. The alkyl-alkynyl cross-coupling is among the most challenging coupling reactions and as a result, only a few methods are reported. These methods can be classified into four categories (Figure 10).

The four main paths to an alkylated alkyne are: 1) Coupling of alkyl halides with terminal alkynes under Sonogashira-type conditions (path A); 2) Palladium-catalyzed oxidative alkyl-alkynyl coupling (path B); 3) Cross-coupling of alkynyl halides with organometallic alkyl reagents (path C). 4) Coupling of nonactivated alkyl halides with alkynyl organometallic

reagents (path D). Only small number of protocols have been developed based on these reactions.¹⁴

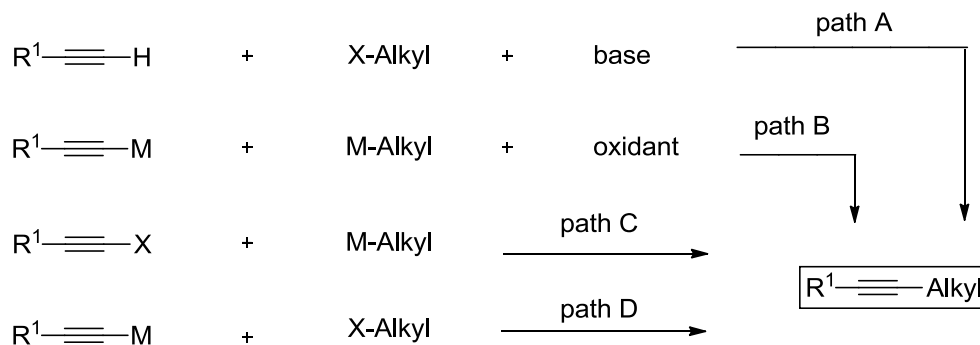
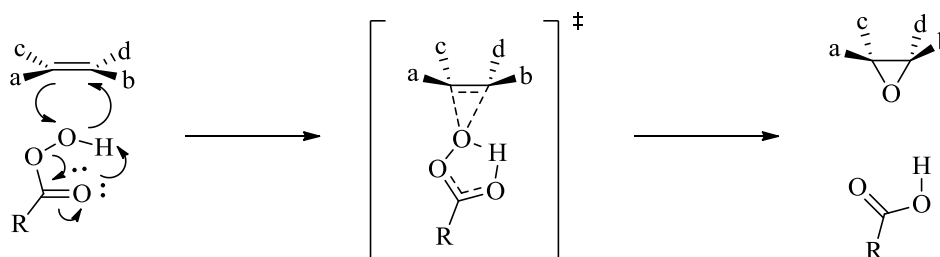


Figure 10. Four types of transition-metal catalyzed cross-coupling methods for the synthesis of alkyl-substituted alkynes. X – halide, M – metal.

Epoxidation

Epoxidation is an extremely valuable transformation in organic synthesis. Epoxides are highly reactive functional groups and their ring-opening allows the formation of a wide variety of substituted alcohol- and amine-containing compounds.

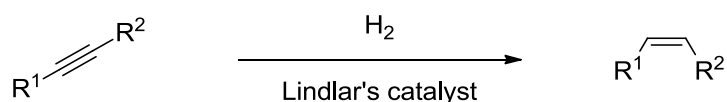
Reaction of an alkene with an oxidizing agent, such as a peroxy-acid, leads to the formation of an epoxide ring. A number of peroxy-acids can be used, although the most common is *meta*-chloroperoxybenzoic acid (mCPBA).¹⁵ Epoxidation of an alkene is a stereospecific reaction, with the geometry of the alkene retained.



Scheme 5. Epoxide formation via five-membered transition state.¹⁶

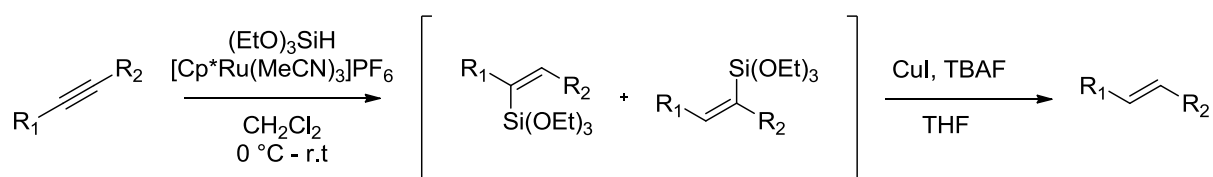
A selective reduction of alkynes

Among alkynes' most important applications is their selective reduction to (Z)-alkenes which is a reliable and highly useful synthetic method (Scheme 6). The catalyst most commonly used for this purpose – Lindlar catalyst - consists of finely powdered palladium metal deposited on solid calcium carbonate that has been specially modified with lead salts.¹⁷ With the use of Lindlar catalyst the reduction slows down once the alkene has been formed, whereas the reaction with typical hydrogenation catalyst, such as Pd/C, the alkene is reduced all the way to the alkane.¹⁸ This reduction is very selective due to hydrogen adding to an alkyne to one side only.



Scheme 6. Cis alkyne reduction by Lindlar catalyst.

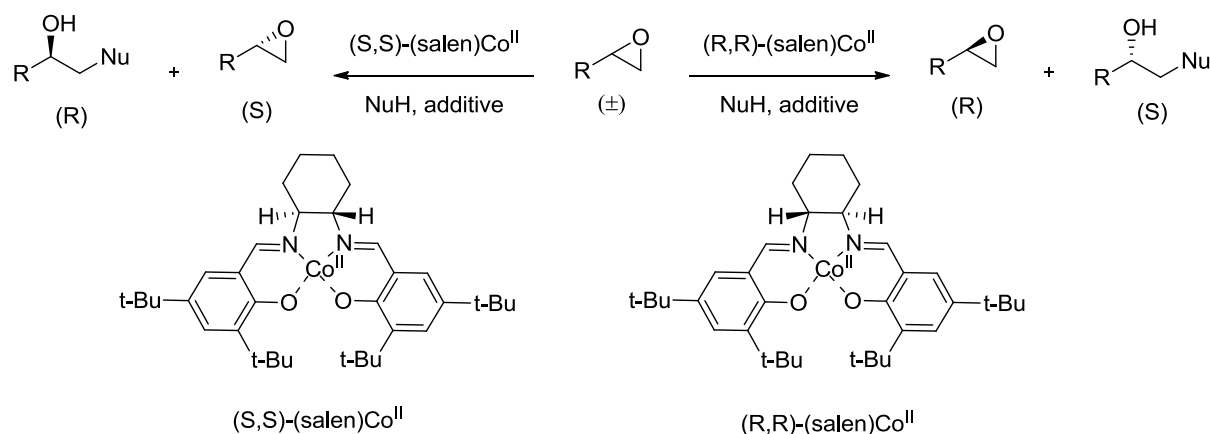
Trans addition of hydrogen to afford (E)-alkenes – the complementary process to cis reduction – remains an elusive goal. One approach is a two-stage trans hydrometalation and subsequent protodemetalation reported by Trost *et al*¹⁹ in 2002. They discovered that the complex $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$ catalyzes the hydrosilylation of a wide variety of alkynes under mild conditions with good functional group tolerance and complete selectivity for the unusual trans addition. They coupled this transformation with a protodesilylation by the action of cuprous iodide and TBAF to achieve a two-step net trans reduction of alkynes (scheme 7).



Scheme 7. Trans alkyne reduction by hydrosilylation-protodesilylation.

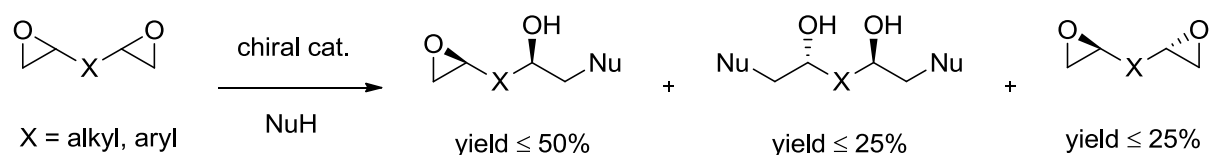
Hydrolytic and aminolytic kinetic resolution of epoxides

The hydrolytic kinetic resolution (HKR) of terminal mono-epoxides is a well-established method originally introduced by Jacobsen and co-workers.²⁰ In the presence of an activated chiral (salen)Co(III) catalyst and a nucleophile, one enantiomer of the racemic epoxide is opened by nucleophile to afford the enantiomerically enriched alcohol and the unreacted epoxide (Scheme 8).



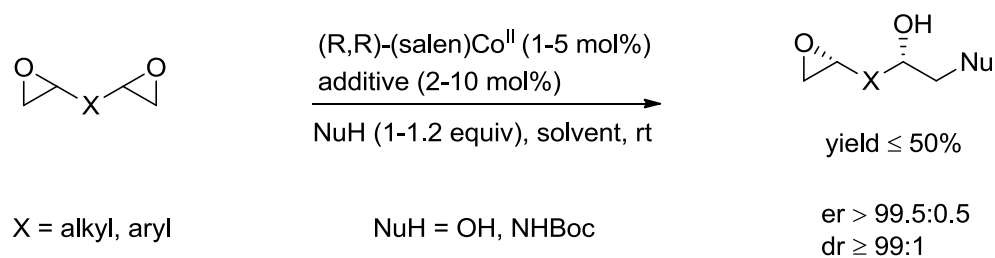
Scheme 8. Kinetic resolution of terminal epoxides

In case of terminal bis-epoxides (Scheme 9) the situation is slightly different, as it consists of three isomers: RS (meso), RR, and SS. The meso isomer is expected to be resolved to afford up to 50% yield, while the other two isomers yield diol and unreacted bis-epoxide, respectively. Few studies have examined bis-epoxides as substrates in kinetic resolution reactions.



Scheme 9. Kinetic resolution of bis-epoxides

In 2013, our research group²¹ reported the first HKR of aromatic bis-epoxides and the aminolytic kinetic resolution (AKR) of bis-epoxides, along with HKR of aliphatic bis-epoxides catalyzed by chiral(salen)-Co^{III} complexes. An efficient use of Jacobsen's catalyst for the highly enantio- and diastereoselective synthesis of epoxy-diols and N-protected epoxy-amino alcohols was reported (Scheme 10).

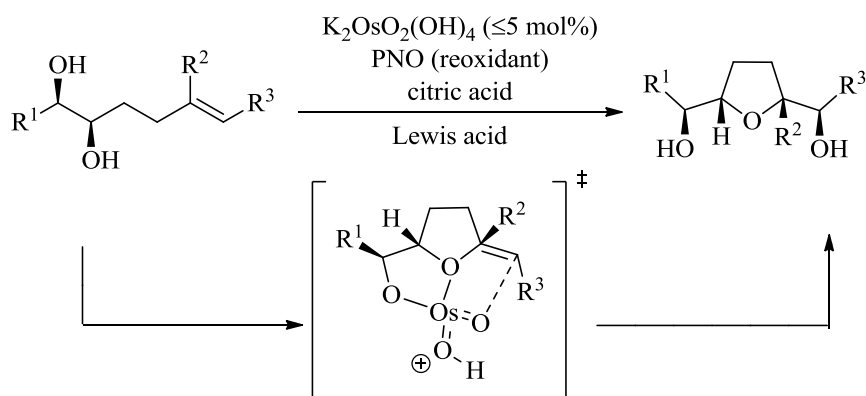


Scheme 10. HKR and AKR of bis-epoxides

Oxidative cyclization in synthesis of enantiomerically pure THFs

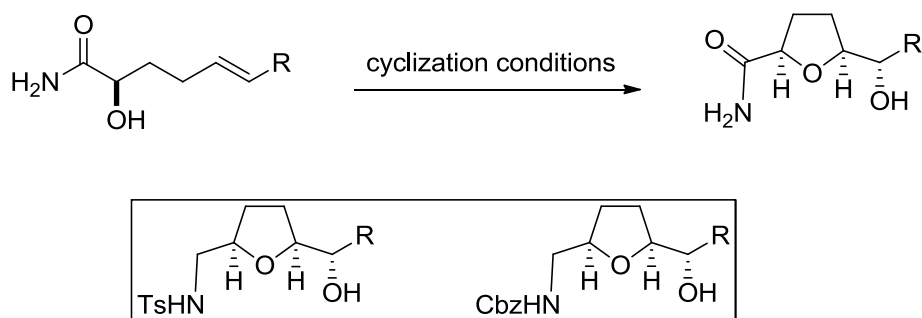
The oxidative cyclization of 1,5-dienes to form the corresponding 2,5-disubstituted THFs has been known for almost 50 years and was first disclosed by Klein and Rojhan in 1965 *via* the use of stoichiometric KMnO_4 .²² Since this initial report a variety of other metal-oxo species have been shown to accomplish this transformation with varying degrees of competency. A significant improvement to the methodology has been made with the realisation that vicinal diols, generated from 1,5-dienes, will form the THF products when subjected to oxidative cyclization conditions with controlled stereoselectivity.

Donohoe and Butterworth developed a novel catalytic process that enables the controlled synthesis of five-membered heterocycles promoted by osmium (Scheme 11). They used PNO as a reoxidant for osmium to oxidize Os(IV) to Os(VI) (this being the more active catalyst for the cyclization process) but not to unwanted Os(VIII) – which can result in the dihydroxylation of the starting material.^{23,24} In addition, Os(VI) species are significantly less toxic than Os(VII) species.



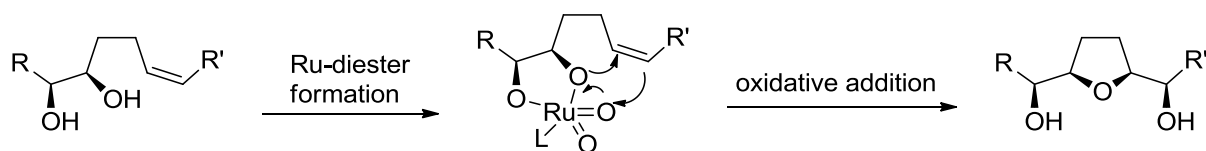
Scheme 11. Osmium-catalyzed oxidative cyclization for the diastereoselective synthesis of cis-THFs.

They also discovered that a greater variety of chelating functionality (other than 1,2-diols) would be able to condense with Os^{VI} and subsequently cyclize to form a wider range of heterocyclic motifs. Exchanging the hydroxyl group at the tris-homoallylic position for a suitable nitrogen-containing substituent allowed the synthesis of a range of THFs flanked with amide, sulfonamide or carbamate functionality in good to excellent yields (Scheme 12).²⁵



Scheme 12. Synthesis of amide, sulfonamide, and carbamate-flanked THFs.

Stark and Cheng presented a new catalytic method for the stereocontrolled oxidative cyclization of 5,6-dihydroxy alkenes to yield THF-diols in high diastereo- and enantiopurity using ruthenium(VII) catalyst (Scheme 13).²⁶

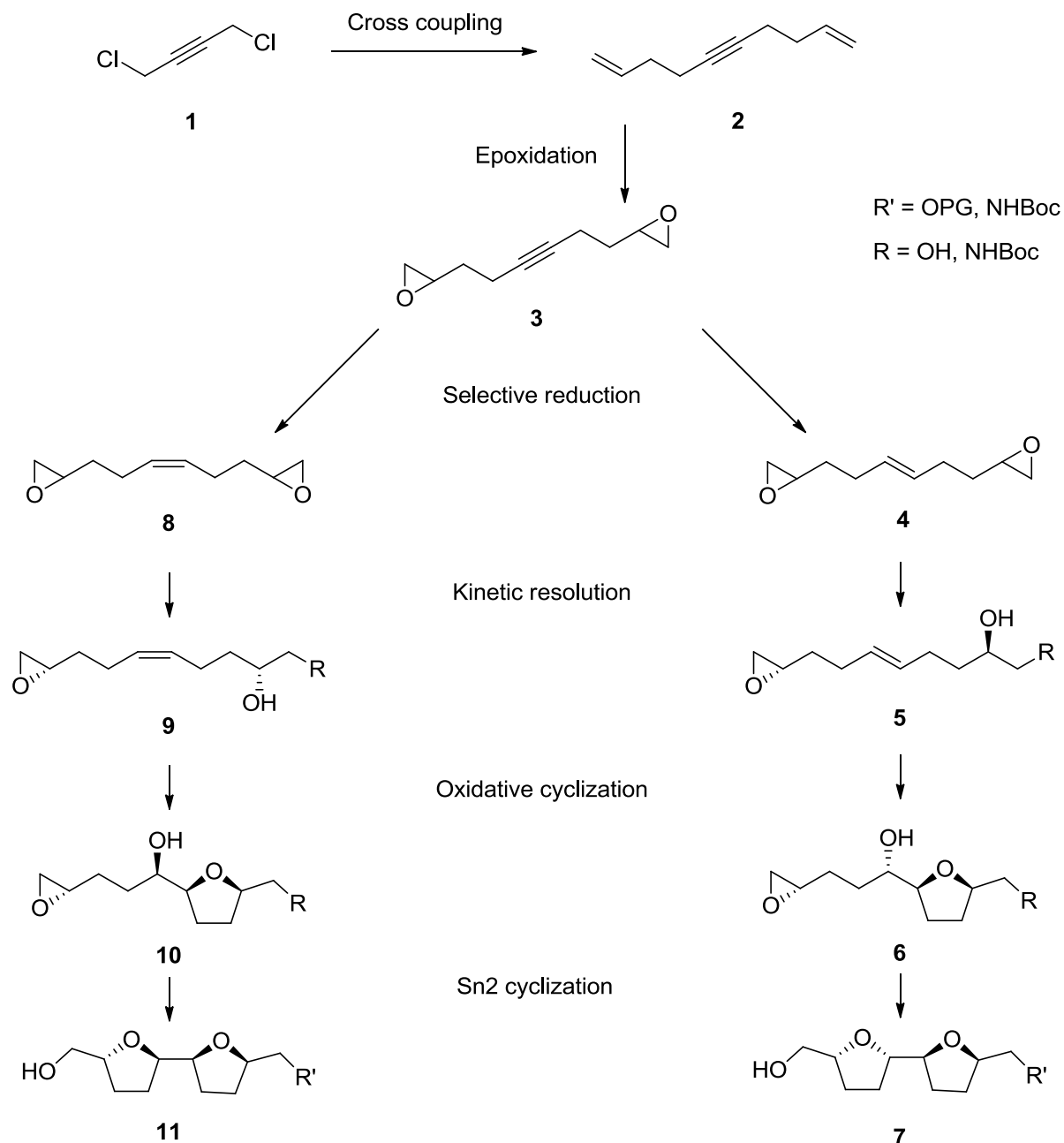


Scheme 13. Ruthenium-catalyzed oxidative cyclization of 5,6-dihydroxy alkenes.

They tested a set of mild ruthenium-based oxidants under different reaction conditions for their ability to promote the selective oxidative cyclization of 5,6-dihydroxy alkenes and found that TPAP (tetrapropylammonium perruthenate), one of the mildest catalysts tested, provided the desired cyclization product in good yield. By using N-methylmorpholine-N-oxide (NMO) as a reoxidant for ruthenium (from Ru(V) back to initial active Ru(VII)) smooth ring formation took place while reaction conditions remained extraordinarily mild.

Results and discussion

The aim of this study was to develop a short, efficient, stereochemically flexible and asymmetric route for the synthesis of bis-THF units (Scheme 14).

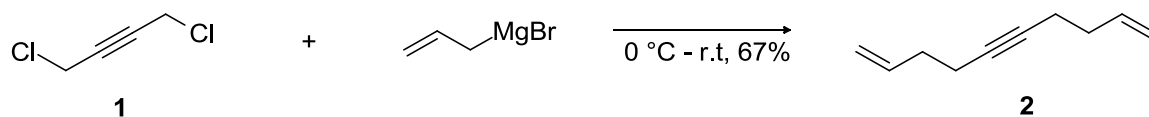


Scheme 14. Devised synthesis route.

The initial plan was focused on the synthesis of core structure **5** as a key motif for bis-THF ring formations. Symmetric alkyne **2** with terminal double bonds was prepared from **1** via alkyne-alkyle cross coupling reaction, followed by epoxidation of double bonds to give bis-epoxide **3**. Compound **3** was then selectively reduced to trans-alkene **4** or cis-alkene **8**. These

alkenes were used in kinetic resolution reactions giving compounds **5** and **9**, respectively. Then oxidative cyclization was used on these compounds to get compounds **6** and **10**, followed by Sn2 cyclization to form bis-THF compounds **7** and **11**.

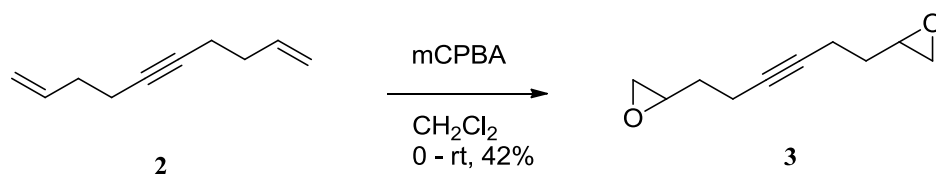
Alkyl-alkyne cross coupling



Scheme 15. Preparation of compound **2**.

No exact method is given in literature for preparing this compound other than a note in a paper by Hopf and Kirsch.²⁷ At first, the experiment was carried out in anhydrous THF as in the literature, but it caused the Grignard reagent to turn grey in color and some precipitation was observed even before addition of alkyne. Because the allylmagnesium bromide was already in ether solution it was decided to leave out THF and carry out the reaction with no additional solvent. Another consideration was reaction time. In test runs it was found out that a few hours was not enough for allyl groups to react completely so the reaction was usually carried out overnight. Byproduct of this reaction has very similar polarity with the product which made purification by column-chromatography problematic. Distillation, as an alternative purification method, did not afford better results. Received yield was 67% (impurity 2%, determined by NMR), which was 16% higher than the Hopf and Kirch had reported and the spectral data was in a good correspondence with the values given in the article.

Epoxidation of terminal alkenes.

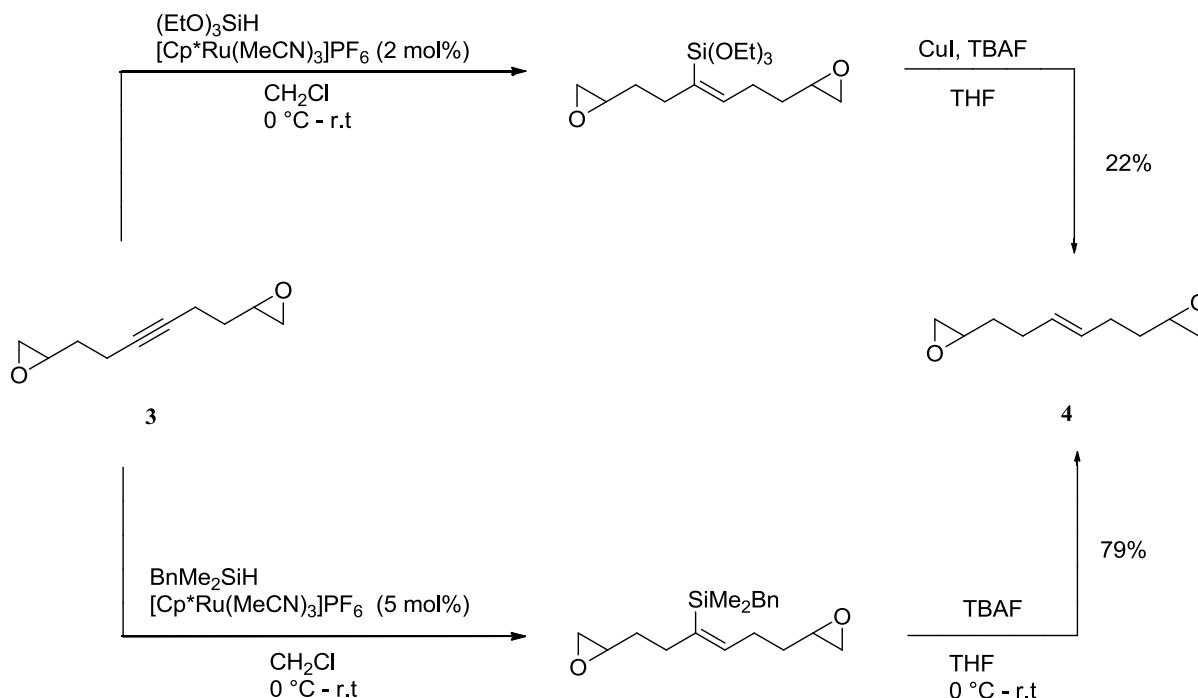


Scheme 16. Epoxidation of diene.

It was anticipated that this reaction would go smoothly because similar reactions, although without a triple bond, had been investigated extensively in our laboratory with no issues. We unexpectedly experienced problems with the low yield, and although we were able to improve

it, the yield remained unsatisfactory. Many different reaction conditions were tested – reaction was carried-out at room temperature and in an ice bath, reaction time was varied from few hours to overnight, and amount of mCPBA was varied from 2 eq to 3,5 eq. One of the proposed reasons for low conversion was that the triple bond could be acid sensitive and decomposes when m-chlorobenzoic acid is produced as byproduct and therefore two phased system should be used;²⁸ that allows the product **3** to stay in organic phase and m-chlorobenzoic acid goes into aqueous bicarbonate phase. This method did not work and gathered yield was even worse than by single solvent system. It was determined by TLC that the starting material was easily converted into intermediate, where one alkene is epoxidized. The problem occurs with the conversion from this intermediate to the desired product. We speculated that this could be due to the lack mCPBA, but increasing the amount of mCPBA to 3.5 eq improved the yield only slightly. After purification process, we treated our unreacted intermediate with an additional amount of mCPBA. However, we could observe that many undesired byproducts formed in this step; and that the reaction had completed and no intermediate was observed by TLC.

Alkyne reduction to (E)-alkene

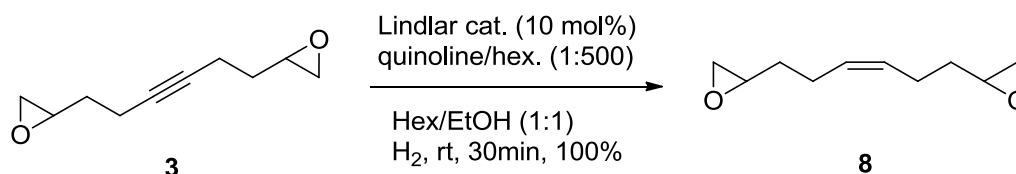


Scheme 17. Trans reduction by different silanes.

There are limited options for trans-alkene reduction in literature with high yields so we were very pleased to find a method by Trost group¹⁹ that promised fairly good yields for compounds similar to ours. This is a two step process (Scheme 17) and for the first step we precisely followed the procedure given in the article and it went rather smoothly; the biggest complication was desilylation step, which was the main reason for very low yield of 22%. We varied the amount of CuI used, reaction times and temperature, however none of these changes resulted in improved yield. In addition, a high amount of CuI probably lead to epoxide ring opening in purification step, which made the handling of crude product very problematic.

Due to the complications and low yields of compound **4** we tested conditions reported by Fürster's²⁹ group. As they also had problems with desilylation step using Trost's original method, they tested different silane and found benzyldimethylsilane to afford faster and smoother conversion in both steps. We tested Fürster's silane and we were pleased that the silylation process improved significantly and we could even reduce the amount of catalyst from 10 mol% to 5 mol%. However, reducing the catalyst loading increased the reaction time from half an hour to 2.5 hours, but there was no reduction in yield. The removal of the silyl group was faster, although not as fast as we had hoped. The desilylation process still had to be carried out overnight, but at room temperature and without the need for CuI at all. With these slight modifications in reaction times and catalyst amount very high yields were obtained. No trace of (Z)-alkene product was observed by ¹H NMR analysis, which can also be expected based on Trost's and Fürster's works.

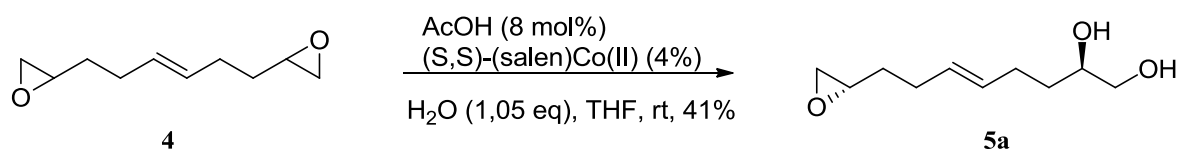
Alkyne reduction to (Z)-alkene



Scheme 18. Alkyne reduction with Lindlar catalyst

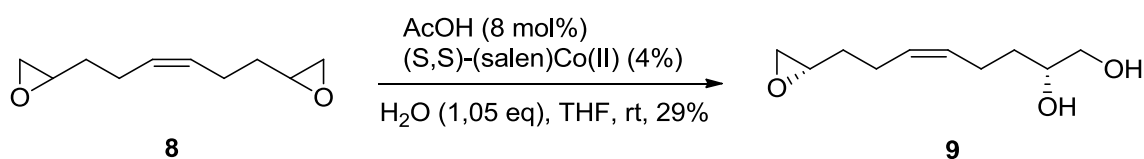
Cis-reduction using Lindlar catalyst was very effective on our alkyne **3**. Reaction went smoothly and according to NMR spectra from crude reaction mixture the conversion to compound **8** was complete and no starting material nor trans-alkene was observed. Lindlar catalyst was filtered out, but no additional purification was done.

Kinetic resolution of bis-epoxide



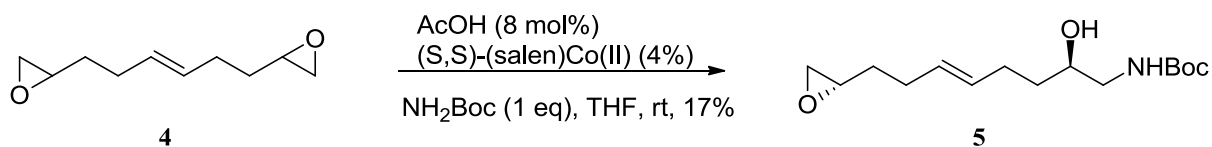
Scheme 19. HKR of (E)-bis-epoxide.

The bis-epoxide **4** used in the synthetic route consists of three isomers: 50% of the meso isomer (R,S), 25% of (S,S)-isomer and 25% of (R,R)-isomer. We subjected this isomeric mixture to HKR with the activated (S,S)-(salen)Co(III)OAc catalyst and used 1.05 eq H₂O as nucleophile. This reaction has been extensively studied in our laboratory and we expected it to go smoothly. Our target product was the epoxy-diol **5a** from the meso isomer (R,S). Fortunately, we had no problems with this conversion and it was also successfully separated on column chromatography after HKR to afford product in 41% yield (maximum yield being 50%).



Scheme 20. HKR of (Z)-bis-epoxide.

We kept the reaction conditions the same as HKR on (E)-bis-epoxide. As expected, this reaction went very well when applied to (Z)-bis-epoxide **8**.



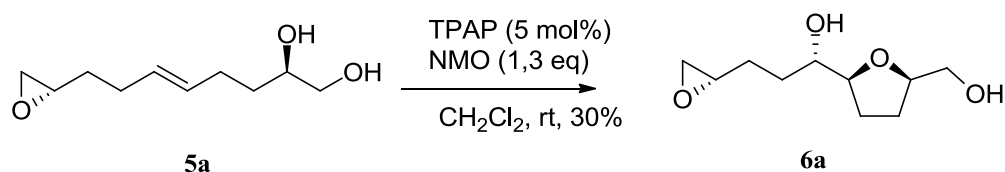
Scheme 21. AKR of (E)-bis-epoxide.

We also tested aminolytic kinetic resolution with our bis-epoxide **4**. Reaction conditions stayed similar as before but instead of H₂O as a nucleophile NH₂Boc was used. According to the TLC analysis the conversion went smoothly. Unfortunately, technical problem occurred in purification step and some of the material was lost. We could isolate the pure product with

only 17% yield (maximum yield being 50%), however, we have reason to believe, that with more careful purification significantly better yields can be achieved.

Enantiomeric and diastereomeric purity of kinetic resolution products was not measured, but based on previous results in our laboratory with related substrates, we could expect high e.r and d.r. It is important to note, that the use of opposite catalyst isomer would result the formation of opposite product enantiomer.

Oxidative cyclization by ruthenium catalyst and addition of protection group



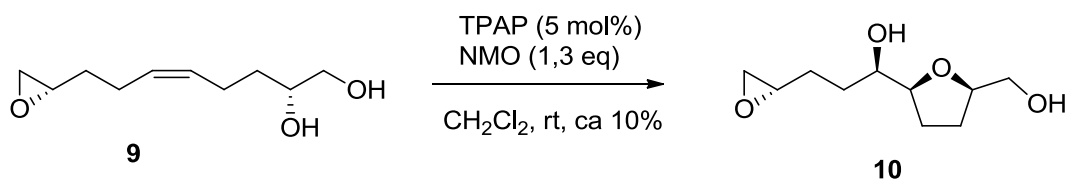
Scheme 22. Cyclization of **5a** with Ru-catalyst.

We then focused on the formation of THF-ring via oxidative cyclization catalyzed by ruthenium. Our first attempts followed protocol reported by Stark²⁵ group. Unfortunately this reaction proved to be inefficient under these reaction conditions. The reaction course was hard to observe by TLC because it was impossible to see product formation as it has very similar polarity as compound **6a**. Because we had difficulties to determine if the reaction had completed, most reactions were carried out for 24 hours at room temperature. Our first test reaction with wet CH₂Cl₂ as a solvent gave at best ca 30% conversion. We were encouraged to see, that the cyclization strategy works, albeit with modest yield. We made several attempts to increase yield with some extra H₂O, as it had helped in some cyclization processes. We also switched solvent to tert-butanol. Unfortunately our efforts did not improve the yield and in most cases no product was observed in crude mixture.

This transformation was then investigated more closely and some test reactions were run in a NMR tube with deuterated chloroform as a solvent. This allowed us to monitor this reaction by taking ¹H spectra hourly and ¹³C spectra every 2-4 hours during the night. We were happy to observe better conversion in which the ration of cyclisized product and starting material was up to 2:1 based on integration of different signals in ¹H NMR spectra. We also noticed that the conversion was in fact fast as opposed to our belief that it is a sluggish reaction; in fact, most of conversion happened in first 10 minutes and then slowly stopped until after 2

hours no further conversion was observed. We were also concerned that a second cyclization might occur in situ but this was not observed. We then added another catalytic amount of TPAP catalyst and NMO in hope it would further improve the conversion, however, this did not have any effect.

We then transferred the conditions developed in NMR tube to the reaction flask and tried to scale up the reaction. Unfortunately though, the conversion was not as good as in the NMR tube and we observed ca 1:1 ration of starting material and product. As it was still better than our initial attempts we went on and tried to purify the crude product. As before, we were unable to efficiently separate starting material from the product. We also observed several byproducts in this reaction that possibly indicate decomposition and/or further cyclization of our product in purification step.



Scheme 23. Cyclization of **9** with Ru-catalyst.

Same NMR tube reaction conditions were applied to cis-compound **9** and monitored over 12 h period. The conversion to compound **10** was only minimal ca 10% based on integration of different signals in ^1H NMR spectra. We noticed that the conversion was happening only in the first minutes and then stopped completely. Addition of TPAP and NMO had no effects on conversion, same as we observed in our reactions with trans-compound **5**.

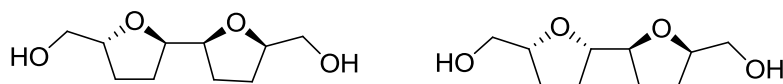


Figure 11. Symmetrical bis-THF units for cis and trans compounds.

Next, we attempted to protect the primary hydroxyl of **6a** since otherwise the second cyclization would lead to a symmetrical bis-THF unit (Figure 11). Suitable protecting strategy was needed, which would not affect other functional groups and would not cause the second cyclization before the protection group was in place. Therefore very mild conditions were

needed as strongly acidic/basic conditions were known to initiate a second cyclization process.

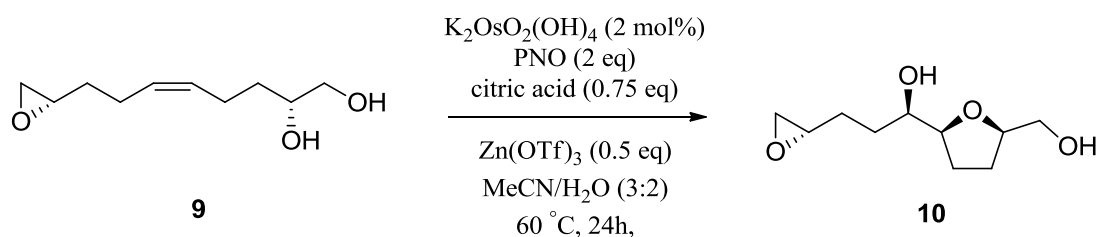
The first protecting group we considered using was tert-butyldiphenylchlorosilane. Unfortunately it initiated the second cyclization process and an undesired symmetric molecule was obtained.

We kept exploring for methods that would suit us and to our delight we found one method that seemed appropriate. This method was based on Copper(I)/TEMPO-catalyzed aerobic oxidation of primary alcohols to aldehydes with ambient air.³⁰ We were very excited about this finding as the method is simple, selective and has mild reaction conditions with fairly high yields. In addition, there is very high selectivity promised for the oxidation of primary alcohols in the presence of secondary alcohols, allowing for the selective oxidation of unprotected diols. This gave us hope that this method would work perfectly for our compound. Unfortunately no oxidation was observed in room temperature using both catalysts suggested in the article.

This method was then applied on more simple alcohols, to make sure the general method works. 1,2-diols were also tested because we considered the possibility of adding protecting group before the first cyclization step. On linear simple primary alcohols this method works very well, but despite our efforts 1,2-diol remained still unreactive.

During our work we discovered that conversions were generally low, and in addition the protection of primary hydroxyl group remained challenging. Due to these reasons we began looking for alternative methods for our synthesis route.

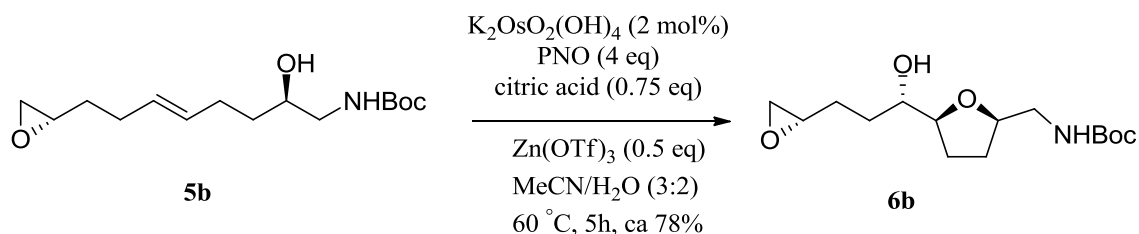
Oxidative cyclization with osmium catalyst



Scheme 24. Cyclization of **9** with Os-catalyst

We first applied this reaction on compound **9**. As this reaction had minimal conversion with ruthenium catalyst we were interested to test if it improved with osmium catalyst. The

reaction was carried out in deuterated solvents to allow us to take NMR. ^1H data was recorded hourly for first few hours and then after 24h. It was immediately observed that the conversion was a lot better this time. We were worried that heating might open our epoxide and second cyclisation would occur, but it did not happen and even after 24h epoxide was intact. The second cyclization did occur on work-up step, but it is clear that this could be avoided.



Scheme 22. Cyclization of **5b** with Os-catalyst.

This reaction was then applied to compound **5b** with deuterated solvents to monitor its course by measuring ^1H spectra hourly. Very good conversion was observed and, after 5 hours of heating at 60 degrees, the ratio of starting material to product was ca 1:4 based on integration of relevant signals in ^1H NMR spectra. As compound **5b** has already NHBoc instead of primary OH, we were not concerned about the second cyclization happening at this point, but none was observed. The second cyclization could likely be initiated in work-up process making it an excellent one-pot reaction.

Conclusion

In this work a stereoselective and effective synthetic route for bis-THF unit has been developed.

Bis-THF units are key motifs for acetogenins that have broad range of bioactivities, most prominent of them being cytotoxic against cancer cells. Considerable effort has been made to synthesize acetogenins and its analogues because the separation of these compounds from plant material is difficult and inefficient. Prior to this work, the synthetic routes for Rolliniastatin I type of acetogenins were long and with poor enantio- and diastereoselectivity, which made them inefficient, particularly in larger scales. In our developed method the synthetic route is significantly shorter, involving only 5 main steps, starting with easily accessible starting material, and offering excellent enantio- and diastereoselectivity. The key steps are selective reduction of alkyne, kinetic resolution of bis-epoxide and oxidative cyclization, making it short, efficient, stereochemically flexible, and highly asymmetric route for bis-THF units.

In the experimental section we proved that this synthesis is indeed possible and the key steps resulted target products in good yields. This is an important breakthrough in the synthesis of bis-THF units and for the synthesis of Rolliniastatin I type acetogenins in general.

Bis-tetrahydrofuraani ühendite stereoselektiivne süntees

Kokkuvõte

Antud töös on välja töötatud stereoselektiivne ja efektiivne sünteesitee bis-THF fragmendi sünteesiks.

Bis-THF fragmendid on tähtsaimaks struktuuriüksuseks atsetogeeniinides, mis on väga huvipakkuvad oma bioloogiliste omaduste poolest. Neist kõige silmapaistvam on atsetogeeniinide tsütotoksiline toime erinevatele vähirakkudele. Märkimisväärseid pingutusi on tehtud atsetogeeniinide ja nende analoogide sünteesis, kuna puhaste atsetogeeniinide eraldamine looduslikest taimeekstraktidest on keeruline ja kulukas. Seni raporteeritud bis-THF fragmendi sünteesiteed, näiteks Rolliniastatin I tüüpi atsetogeeniinideks, on pikad ja kehva enantio- ja diastereoselektiivsusega. See teeb nende sünteesi, eelkõige suures skaalas, ebaefektiivseks. Meie väljatöötatud sünteesitee on oluliselt lühem, koosnedes vaid viiest põhilisest etapist, alustades lihtsalt kättesaadava lähteühendiga ning võimaldab suurepäraselt enantio- ja diastereoselektiivsust. Olulisemad etapid koosnevad alküüni selektiivsest taandamisest, bis-epoksiidi kineetilise lahutamise ja oksüdatiivsest tsükliseerimisest. Sünteesitee on lühike, tõhus, stereokeemiliselt paindlik ja äärmiselt asümmeetriline moodus bis-THF fragmendi sünteesiks.

Eksperimentaalses osas me kinnitasime, et antud sünteesitee toimib ja näitasime, et põhietapid andsid soovitud ühendid väga heade saagistega. Tegemist on olulise läbimurdega bis-THF ühendite sünteesides ja Rolliniastatin I tüüpi atsetogeeniinide sünteesis üldisemalt.

Experimental part

General

All commercially available chemicals were of reagent grade and used without further purification; Flash-column chromatography was performed on silica gel 230-400 mesh or on Isolera One with GraceResolv cartridges. TLC was performed using Macherey-Nagel silica gel plates „Alugram® Sil G/UV 254“. Spots were visualized by UV light at 254 nm or by 3% PMA in ethanolic solution with subsequent heating. NMR spectra were obtained on a Bruker AVANCE II 400 instrument at 400.1 MHz for ^1H and 100.6 MHz for ^{13}C at the Institute of Technology, University of Tartu. The chemical shifts are reported in ppm using CDCl_3 signals (^1H at 7.26 ppm; ^{13}C at 77.0 ppm) as reference unless stated otherwise. Coupling constants (J) are reported in herz (Hz).

Synthesized compounds

1,9-decadiene-5-yne (2)

To allylmagnesium bromide solution 1.0 M in diethyl ether (50 mL, 50 mmol) under an Ar atmosphere was added dropwise 1,4-dichloro-2-butyne (2 mL, 20 mmol) over 20 min. The reaction mixture was stirred and, when necessary, cooled in an ice bath when ether began boiling too rapidly (occured only during the first 30 min after addition of alkyne). After 50 min mixture turned from brown color to dark grey and slowly some precipitation appeared and after another 20 min there was a lot of thick light grey precipitation. The reaction was left to stir overnight, cooled to 0 °C and quenched by addition of NH_4Cl (saturated aqueous). This was followed by filtration and extraction with additional amount of NH_4Cl . Organic layer was then washed with brine, dried over Mg_2SO_4 , filtrated, concentrated (at 150 mbar, 40 °C), and purified by flash chromatography to afford 1.8 g (67%) of the desired compound **2** as colorless liquid. ^1H NMR (400.1 MHz, CDCl_3): δ 5.8-5.9 (m, 2H), 4.99-5.08 (m, 4H), 2.21-2.26 (m, 8H). ^{13}C NMR (100.6 MHz, CDCl_3): δ 137.2, 115.2, 33.3, 18.6.

1,6-di(oxiran-2-yl)hex-3-yne (3)

To 0.3 M solution of 1,9-decadiene-5-yne **2** (1.8 g, 13.4 mmol) in DCM was added mCPBA (9.022 g, 40.25 mmol, 3 eq) in an ice bath. After 1 hour the ice bath was removed and reaction mixture was stirred for another 3 h at rt. The solution was a milky slurry at this point.

Because TLC analysis still showed some incomplete conversion an additional 0.5 g of mCPBA was added. After 1 hour reaction mixture was filtered through the plug of cotton and extracted with Na₂CO₃ (saturated aqueous) and concentrated under reduced pressure. To further remove m-chlorobenzoic acid (byproduct), the impure product was dissolved in EtOAc and extracted twice with aqueous Na₂CO₃. Organic layer was then dried over Mg₂SO₄, filtered, and concentrated to dryness in vacuo. The crude product was purified by flash chromatography to afford 935.8 mg (42%) desired bis-epoxide compound **3** as pale yellow oil. ¹H NMR (400.1 MHz, CDCl₃): δ 2.99-3.08 (dddd, 2H), 2.77-2.82 (dd, 1H), 2.5-2.54 (m, 1H), 2.30-2.37 (m, 1H), 1.73-1.82 (m, 1H), 1.6-1.72 (m, 1H). ¹³C NMR (100.6 MHz, CDCl₃): δ 79.6, 51.3, 47.0, 32.0, 15.5. HRMS (ESI): calcd for C₁₀H₁₄O₂ [M + Na]⁺ 189.0886, found 189.0886.

(E)-1,6-di(oxiran-2-yl)hex-3-ene (4)

To 0.5 M solution of bis-epoxide **3** (353.8 mg, 2.1 mmol) in DCM under an Ar atmosphere was added benzyldimethylsilane (498 μL, 3.15 mmol). Cp*Ru(MeCN)₃]PF₆ (53.7 mg, 0.1 mmol) was added after cooling the flask in an ice bath. After the catalyst was fully dissolved the flask was allowed to warm to ambient temperature, where it was stirred for 2 h. At this point TLC control indicated complete conversion. The solution was diluted in ether (5 mL), filtered through a plug of florisil (1 cm), and washed with additional ether (20 mL). The filtrate was concentrated under reduced pressure (15 mbar, 25 °C) and taken up in THF (2.8 mL) under Ar and cooled in an ice bath. A solution of anhydrous TBAF 1 M in THF (4.9 mL, 4.9 mmol) was then added dropwise and resulting orange mixture was stirred at rt overnight. The dark brown crude product was purified by flash chromatography to afford 278 mg (79%) of product **4**. ¹H NMR (400.1 MHz, CDCl₃): δ 5.51 (s, 1H), 2.93 (bs, 2H), 2.76 (s, 2H), 2.46-2.49 (m, 2H), 2.8 (bs, 3H), 1.55-1.64 (m, 3H). ¹³C NMR (100.6 MHz, CDCl₃): δ. 129.9, 51.8, 47.1, 32.4, 28.9. HRMS (ESI): calcd for C₁₀H₁₆O₂ [M + Na]⁺ 191.1043, found 191.1040.

(R,E)-8-((S)-oxiran-2-yl)oct-5-ene-1,2-diol (5a)

To 0.05 M solution of (S,S)-(salen)Co^{II} complex (16.2 mg, 26.8 μmol) in DCM AcOH (3 μL, 53.6 μmol) was added. The mixture was stirred at room temperature and open to air for 30 min, during which time the color turned from dark red to brown. Then the solution was concentrated to dryness in vacuo. The crude solid was dissolved in 0.3 mL dry THF and added to bis-epoxide **4** (116.4 mg, 0.69 mmol). Then H₂O was added (13.1 μL, 0.72 mmol)

and reaction was stirred over the weekend at room temperature. Solvent was removed in vacuo and the product **5a** was isolated by flash chromatography as a bright yellow oil (53.2 mg, 41%). ¹H NMR (400.1 MHz, CDCl₃): δ 5.46 (m, 2H), 3.56-3.72 (m, 2H), 3.37-3.43 (m, 1H), 2.9 (bs, 2H), 2.73 (dd, 1H), 2.47 (dd, 1H), 2.02-2.21 (m, 4H), 1.4-1.67 (m, 4H). ¹³C NMR (100.6 MHz, CDCl₃): δ. 130.4, 129.8, 71.7, 66.7, 52.0, 47.1, 32.7, 32.4, 29.0, 28.6.

tert-butyl ((R,E)-2-hydroxy-8-((S)-oxiran-2-yl)oct-5-en-1-yl)carbamate (5b)

To 0.05 M solution of (S,S)-(salen)Co^{II} complex (19.7 mg, 32.6 μmol) in DCM was added AcOH (3.7 μL, 65.2 μmol). The mixture was stirred at room temperature open to air for 30 min, during which time the color turned from dark red to brown. Then the solution was concentrated to dryness in vacuo. The crude solid was redissolved in 0.3 mL dry THF and added to bis-epoxide **4** (150 mg, 0.8 mmol). Then NH₂Boc was added (105 mg, 0.9 mmol) and reaction was stirred over night at room temperature. Solvent was removed in vacuo and the product **5b** was isolated by flash chromatography as pale yellow oil (42.1 mg, 17%). ¹H NMR (400.1 MHz, CDCl₃): δ 5.46 (dt, J=5Hz, 2H), 5 (bs, 1H), 3.67 (bs, 1H), 3.23-3.29 (m, 1H), 2.89 (dd, J= 3.3, 1.8, 1H), 2.73 (dd, J= 4.8, 4, 1H), 2.47 (dd, J= 5, 2.8, 1H), 2.04-2.18 (m, 4H), 1.4-1.65 (m, 14H). ¹³C NMR (100.6 MHz, CDCl₃): δ 156.8, 130.4, 129.8, 79.5, 71.0, 52.0, 47.1, 46.6, 34.3, 32.4, 29.0, 28.6, 28.4.

(S)-1-((2S,5R)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3-((S)-oxiran-2-yl)propan-1-ol (6a)

A 0.5 M solution of the diol **5a** (21 mg, 0.113 mmol) in DCM (2.26 ml) was treated with NMO (19.4 mg, 0.143 mmol, 1.2 eq), followed by TPAP (2 mg, 5.64 μmol, 5 mol%). The reaction progress could not be monitored by TLC as the product and starting material had too similar polarities. After 24 h the reaction mixture was concentrated under reduced pressure (25 °C, 0 mbar). Resulting crude product was purified by column chromatography and gave compound **6a** (7 mg, ca 30%) with some impurities. ¹H NMR (400.1 MHz, CDCl₃): δ 4.05-4.17 (m, 2H), 3.82-3.87 (m, 2H), 3.48-3.53 (m, 2H), 2.95-3.0 (m, 1H), 2.77 (m, 1H), 1.65 (m, 6H). ¹³C NMR (100.6 MHz, CDCl₃): δ 82.8, 79.9, 73.7, 65.1, 52.0, 47.3, 30.1, 28.5, 27.2. HRMS (ESI): calcd for C₁₀H₁₈O₄ [M + H]⁺ 203.1277, found 203.1277.

tert-butyl(((2R,5S)-5-((S)-1-hydroxy-3-((S)-oxiran-2-yl)propyl)tetrahydrofuran-2-yl)-methyl)carbamate (6b)

This compound was synthesized by a literature procedure.³¹ To a solution of compound **5b** (24.2 mg, 78.8 μmol) in CD_3CN (958 μL) and D_2O (639 μL) PNO (30.6 mg, 0.16 mmol), citric acid (11.5 mg, 60 μmol), $\text{K}_2\text{OSO}_4 \cdot \text{H}_2\text{O}$ (0.6 mg, 1.6 μmol) and $\text{Zn}(\text{OTf})_3$ (14.5 mg, 40 μmol) were added. The resulting solution was warmed to 60 $^\circ\text{C}$ and the product **6b** formation was monitored by ^1H NMR. ^1H NMR (400.1 MHz, CDCl_3): δ 3.93- 4.02 (m, 2H), 3.73-3.8 (m, 2H), 3.55 (d, J = 3.8, 2H), 2.95-3.0 (m, 1H), 2.77 (m, 1H), 1.65 (m, 2H), 1.37 (s, 17H).

(Z)-1,6-di(oxiran-2-yl)hex-3-ene (8)

Quinoline (2.226 ml of a stock solution [1:500 quinoline/hexane] and alkyne **3** (249 mg, 1.5 mmol) were dissolved in hexane/EtOH (10 mL, 1:1). Lindlar catalyst (304 mg, 0.15 mmol) was added and the resulting suspension was stirred for 30 min under an atmosphere of H_2 (1 atm). The catalyst was filtered off through a pad of Celite, the solvent was evaporated. Product **8** yield was considered to be 100% and was not purified any further. ^1H NMR (400.1 MHz, CDCl_3): δ 5.38-5.46 (m, 2H), 2.93 (bs, 2H), 2.76 (s, 2H), 2.46-2.49 (m, 2H), 2.21 (m, 4H), 1.55-1.64 (m, 3H). ^{13}C NMR (100.6 MHz, CDCl_3): δ . 129.3, 58.3, 51.9, 47.1, 32.4, 23.7, 18.4. HRMS (ESI): calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2$ [$\text{M} + \text{Na}$] $^+$ 191.10425, found 191.1037.

(R,Z)-8-((S)-oxiran-2-yl)oct-5-ene-1,2-diol (9)

To 0.05 M solution of (S,S)-(salen) Co^{II} complex (36.2 mg, 60 μmol) in DCM AcOH (6.8 μL , 120 μmol) was added. The mixture was stirred at room temperature and open to air for 30 min, during which time the color turned from dark red to brown. Then the solution was concentrated to dryness in vacuo. The crude solid was redissolved in 0.7 mL of dry THF and added to bis-epoxide **8** (252 mg, 1.5 mmol). Then H_2O was added (28.3 μL , 1.57 mmol) and reaction was stirred over the weekend at room temperature. Solvent was removed in vacuo and the product **9** was isolated by flash chromatography as pale yellow oil (80.9 mg, 29%). ^1H NMR (400.1 MHz, CDCl_3): δ 5.41 (m, 2H), 3.7-3.75 (m, 1H), 3.38-3.44 (m, 1H), 2.93 (dd, J = 4.3, 2.8, 2H), 2.77 (m, 2H), 2.5 (dd, J = 4.9, 2.9, 1H), 2.13-2.28 (m, 4H). ^{13}C NMR (100.6 MHz, CDCl_3): δ 130.1, 129.1, 71.6, 67.9, 52.0, 47.4, 32.8, 32.3, 25.6, 23.7.

**(R)-1-((2S,5R)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3-((S)-oxiran-2-yl)propan-1-ol
(10)**

A 0.5 M solution of the diol **9** (13.8 mg, 74.2 μmol) in CDCl_3 (1.5 ml) was treated with NMO (12 mg, 89 μmol , 1.2 eq), followed by TPAP (2.6 mg, 7.4 μmol , 10 mol%). The resulting solution was monitored by ^1H NMR.

**(R)-1-((2S,5R)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3-((S)-oxiran-2-yl)propan-1-ol
(10)**

This compound was synthesized by a literature procedure.³² To a solution of compound **9** (10.6 mg, 57 μmol) in CD_3CN (420 μL) and D_2O (280 μL) was added PNO (10.8 mg, 0.11 mmol), citric acid (8.2 mg, 42.7 μmol), $\text{K}_2\text{OSO}_4 \cdot \text{H}_2\text{O}$ (0.4 mg, 1.1 μmol) and $\text{Zn}(\text{OTf})_3$ (10.4 mg, 28.4 μmol). The resulting solution was warmed to 60 $^\circ\text{C}$ and the product **10** formation was monitored by ^1H NMR.

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Appendix

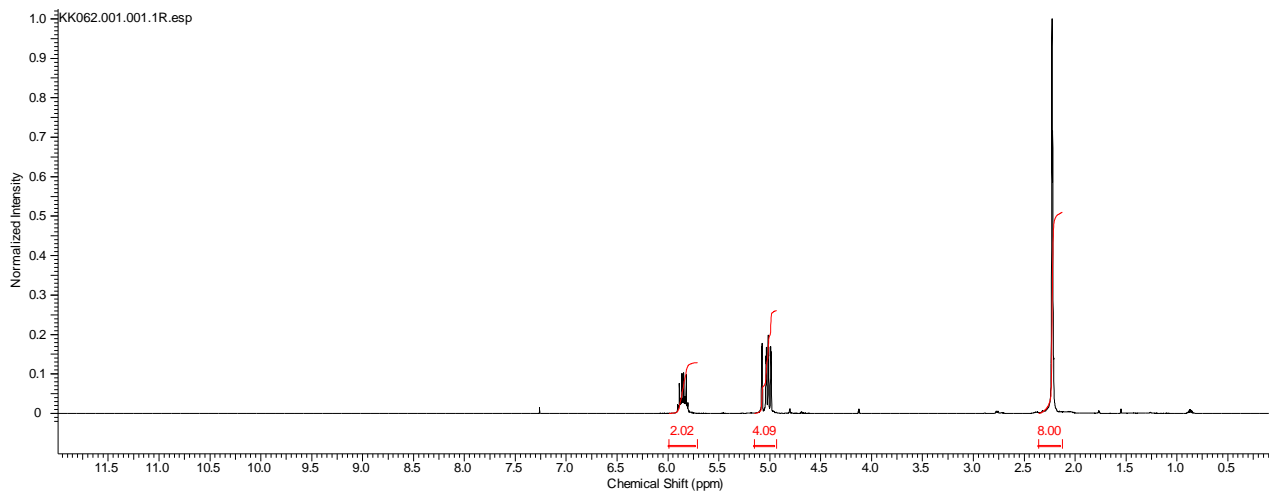


Figure 12. Compound 2 ^1H spectra

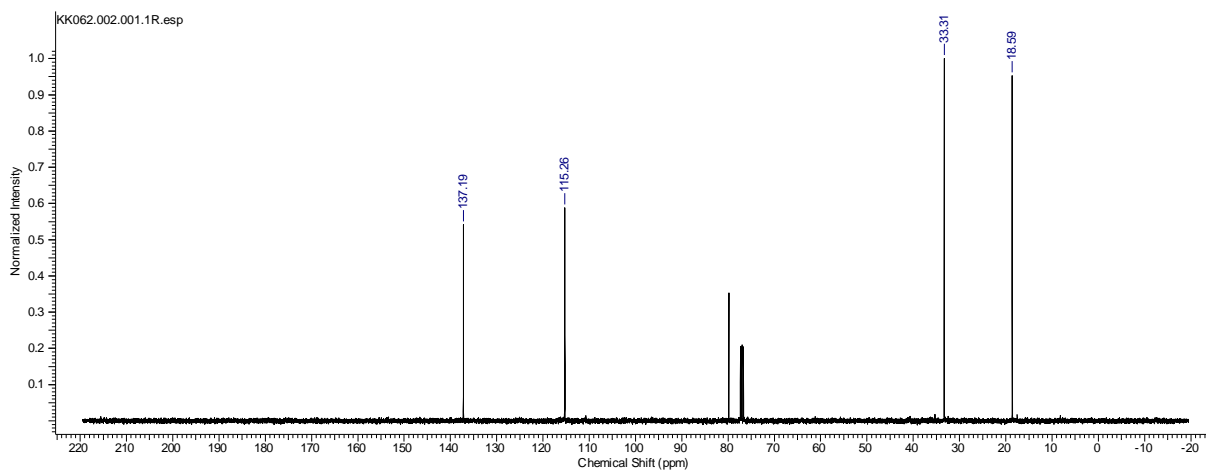


Figure 13. Compound 2 ^{13}C spectra

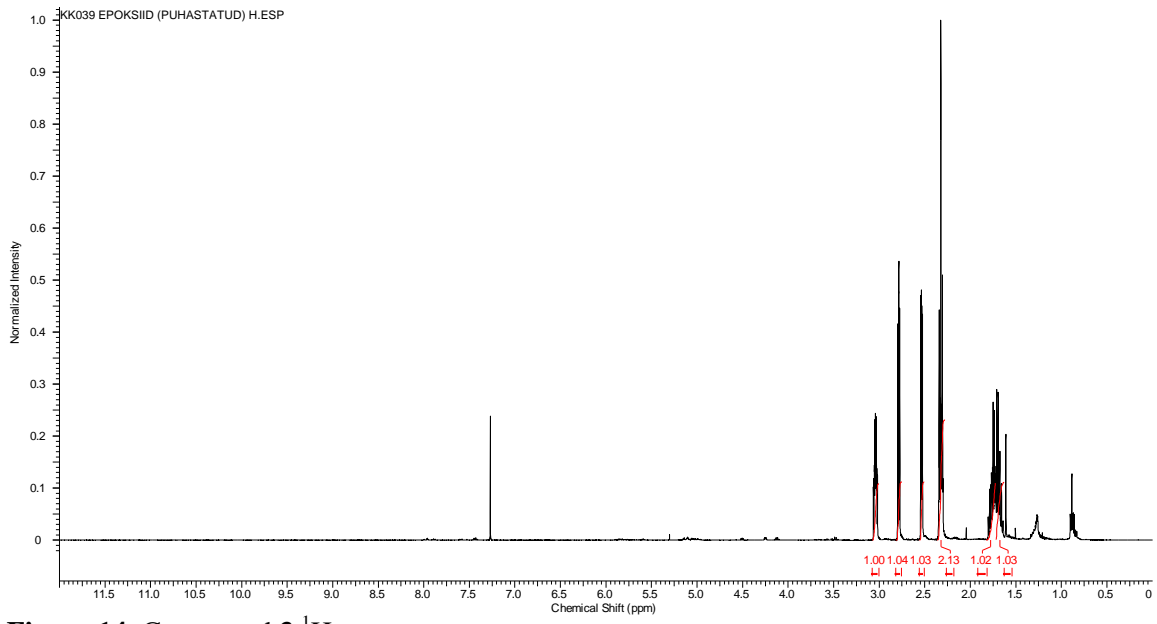


Figure 14. Compound 3 ^1H spectra

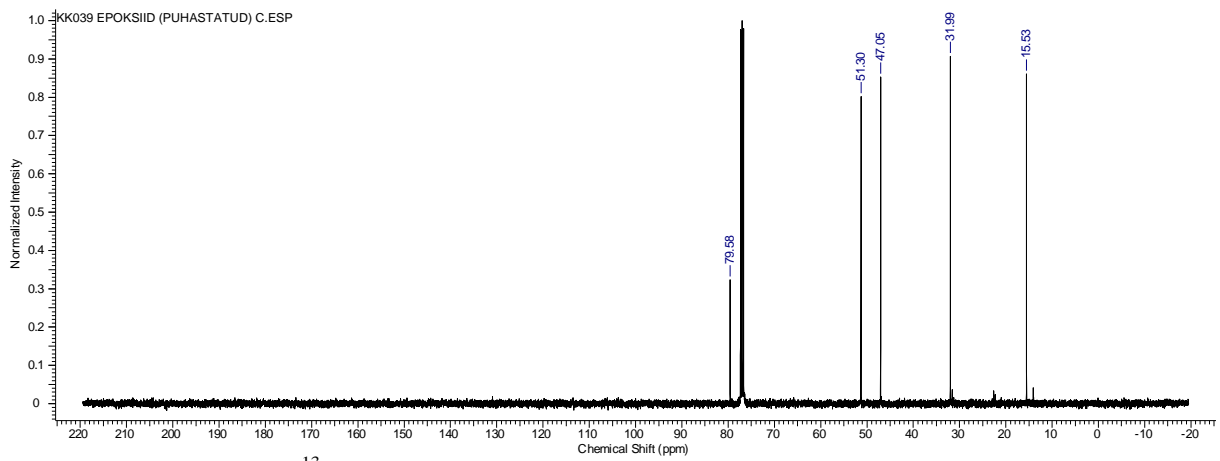


Figure 15. Compound 3 ^{13}C spectra

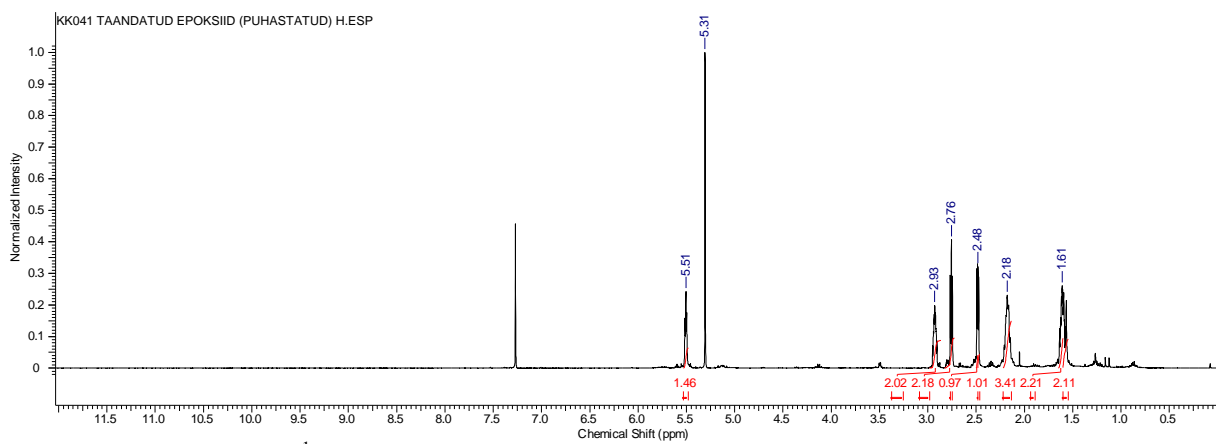


Figure 16. Compound 4 ^1H spectra

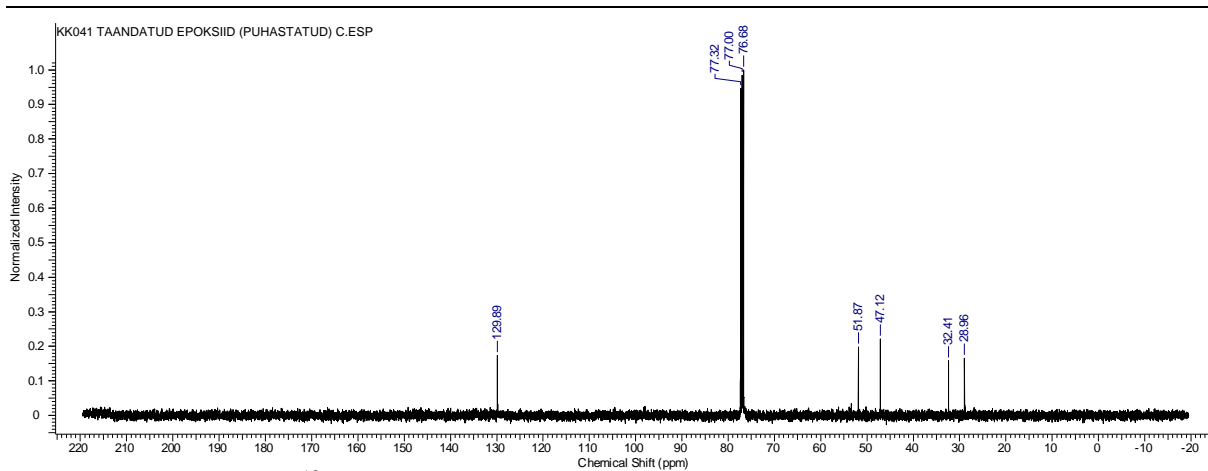


Figure 17. Compound 4 ^{13}C spectra

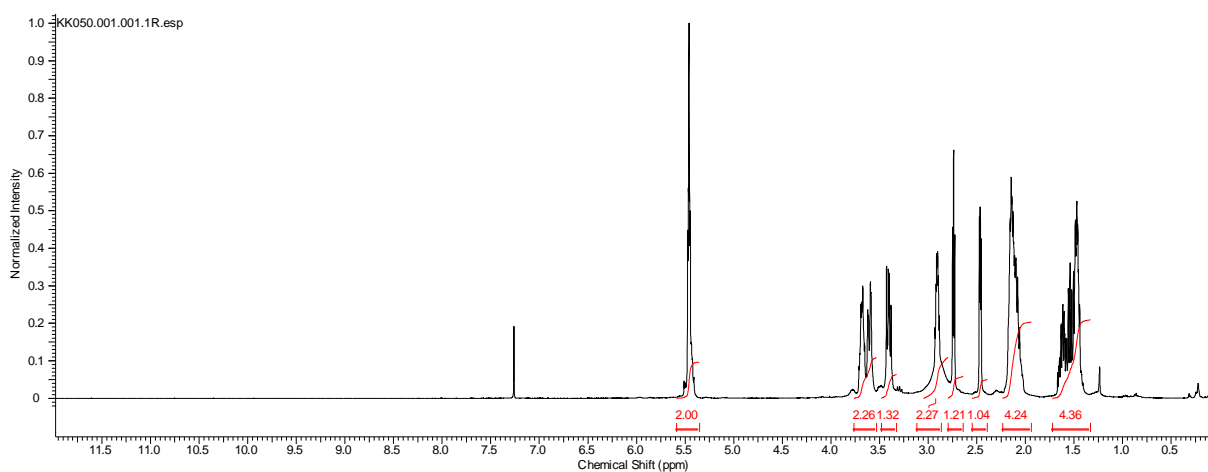


Figure 18. Compound 5a ^1H spectra

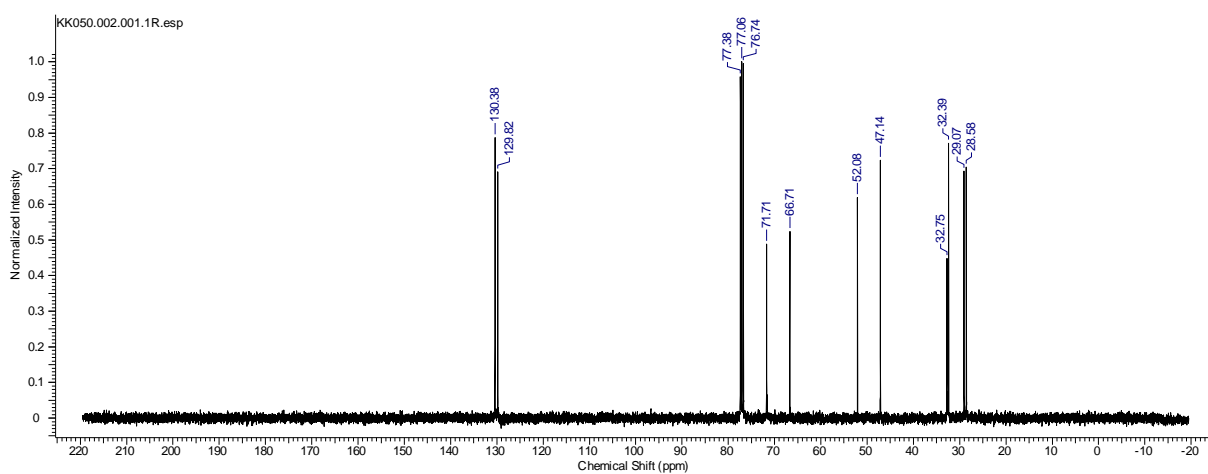


Figure 19. Compound 5a ^{13}C spectra

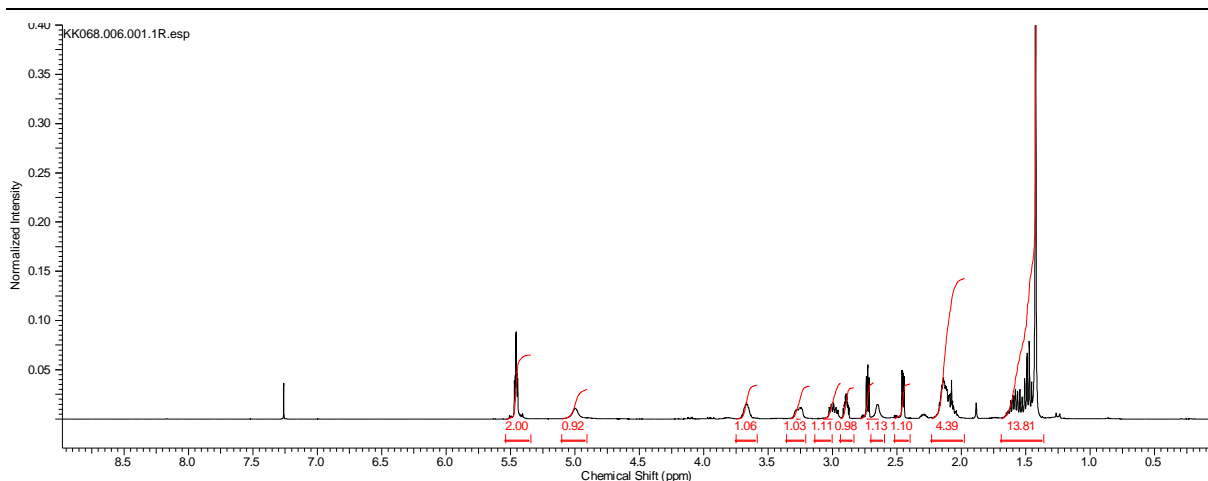


Figure 20. Compound 5b ^1H spectra

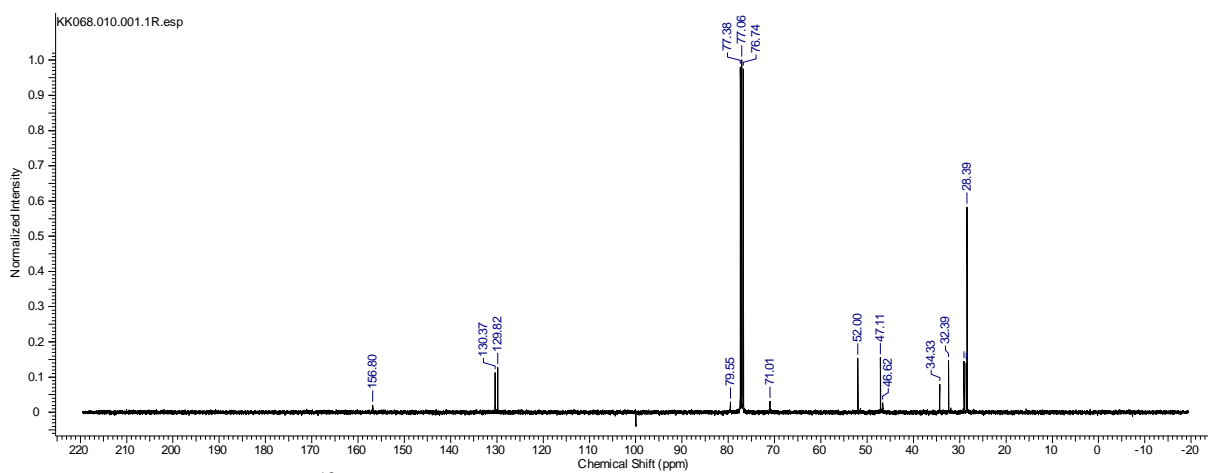


Figure 21. Compound 5b ^{13}C spectra

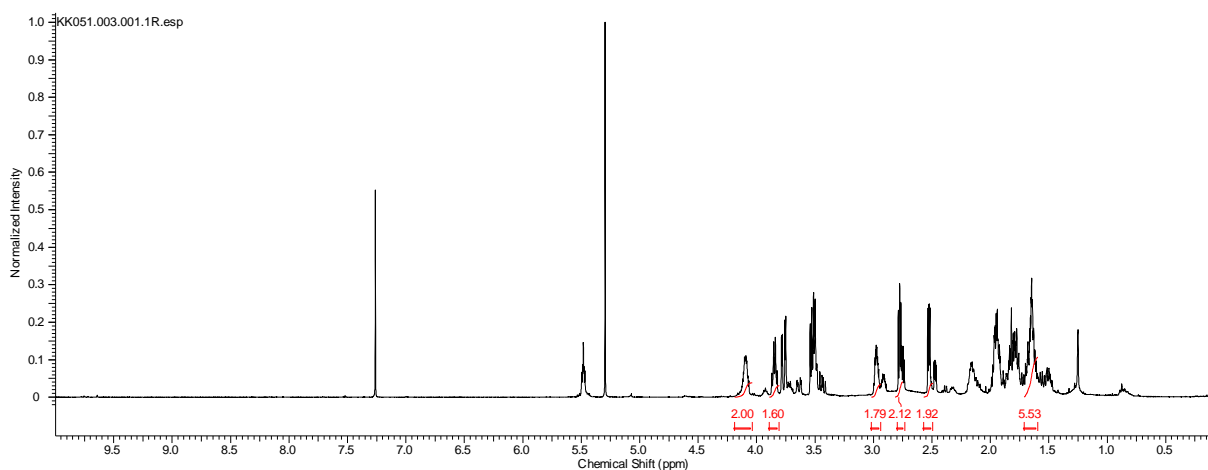


Figure 22. Compound 6a ^1H spectra

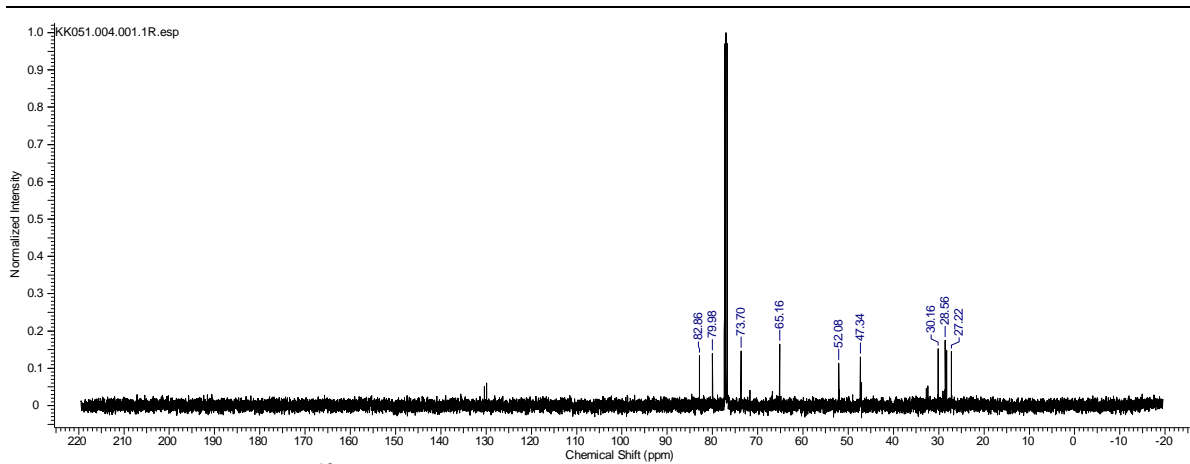


Figure 23. Compound 6a ^{13}C spectra

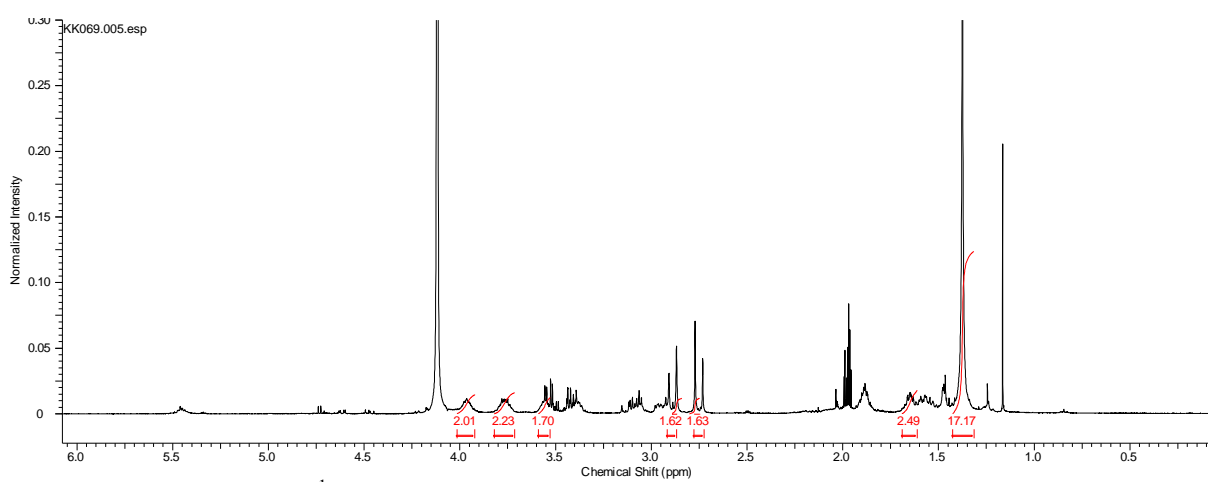


Figure 24. Compound 6b ^1H spectra

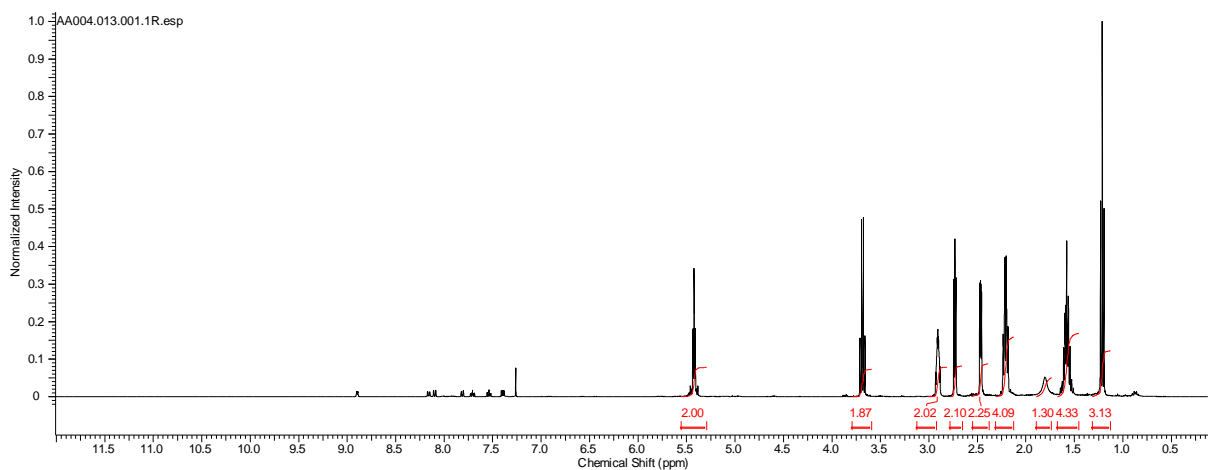


Figure 25. Compound 8 ^1H spectra

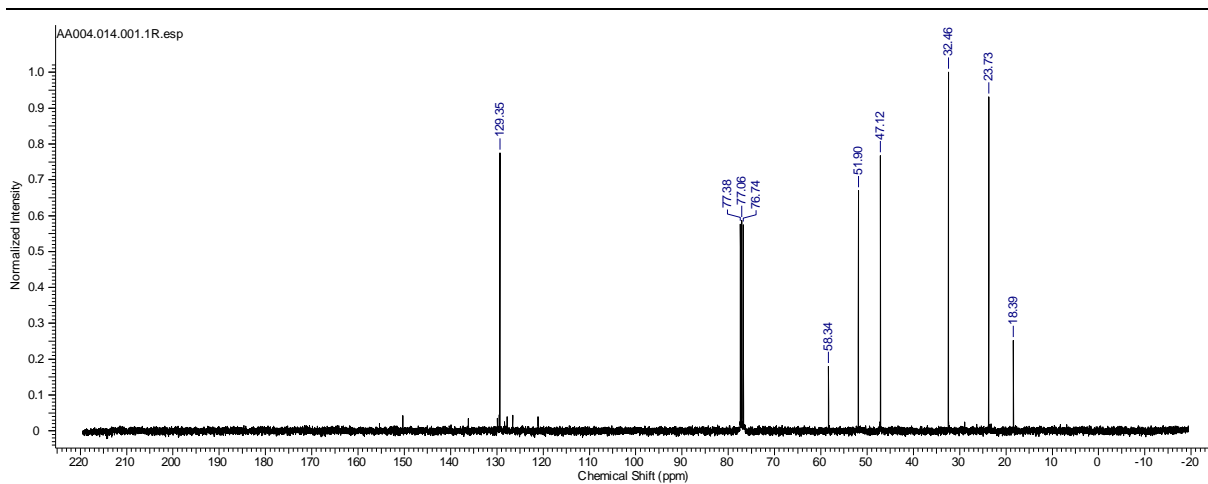


Figure 26. Compound 8 ^{13}C spectra

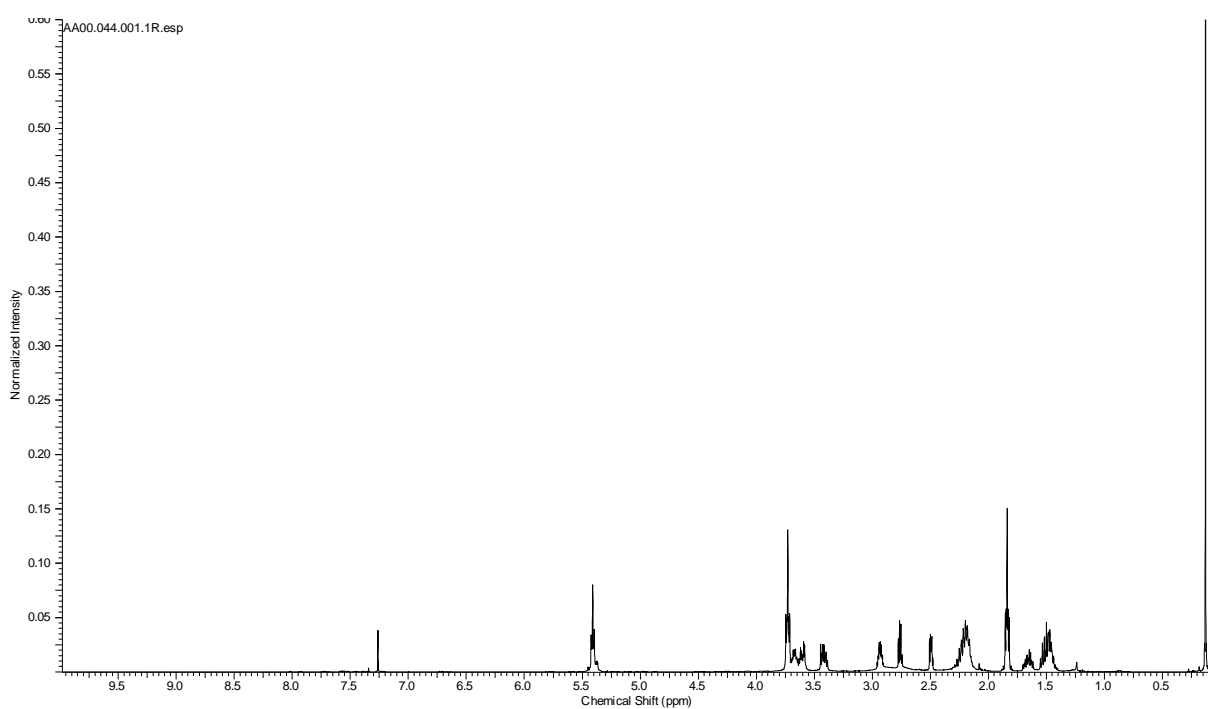


Figure 27. Compound 9 ^1H spectra

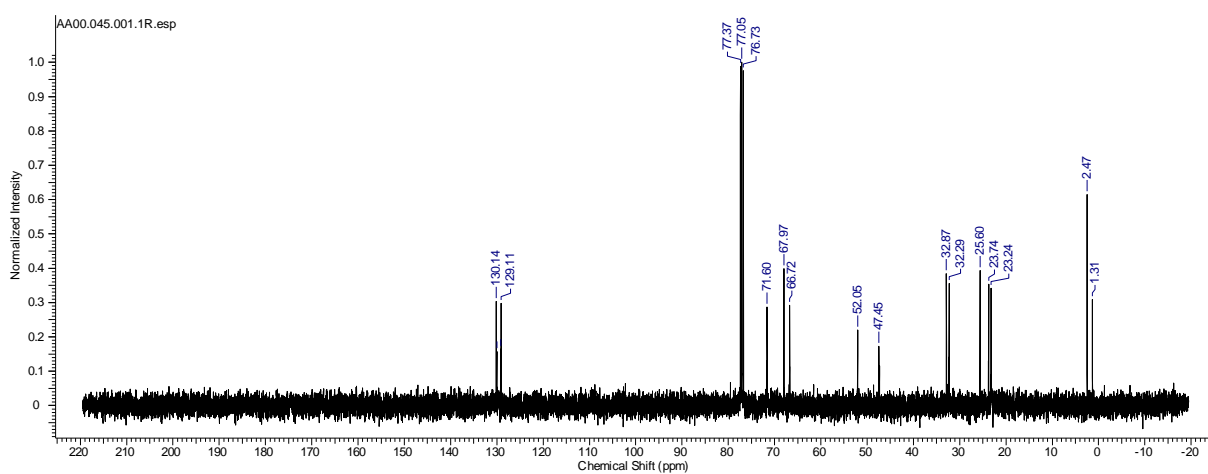


Figure 28. Compound 9 ^{13}C spectra

Lihtlitsents lõputöö reprodutseerimiseks ja lõputöö üldsusele kättesaadavaks tegemiseks

Mina,

Kätlin Korovetski,

(autori nimi)

1. annan Tartu Ülikoolile tasuta loa (lihtlitsentsi) enda loodud teose

Stereoselective synthesis of bis-Tetrahydrofurans

(lõputöö pealkiri)

mille juhendaja on

Lauri Vares,

(juhendaja nimi)

1.1.reprodutseerimiseks säilitamise ja üldsusele kättesaadavaks tegemise eesmärgil, sealhulgas digitaalarhiivi DSpace-is lisamise eesmärgil kuni autoriõiguse kehtivuse tähtaja lõppemiseni;

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Tartus, **29.05.2014**

