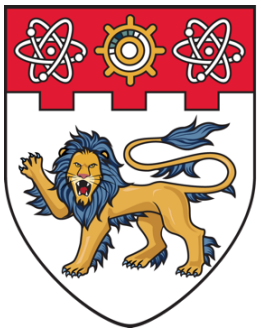

NANYANG TECHNOLOGICAL UNIVERSITY
SINGAPORE

STUDIES ON THE SYNTHESIS OF TETRAHYDROPYRANS VIA OXA-MICHAEL ADDITION LEADING TOWARDS THE TOTAL SYNTHESIS OF MONTANACIN D

ANNABEL HO XUAN YING

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2021

Studies on the Synthesis of Tetrahydropyrans via Oxa-Michael Addition Leading Towards the Total Synthesis of Montanacin D

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School of Physical and Mathematical Sciences

A thesis submitted to the Nanyang Technological University

in partial fulfilment of the requirement for the degree of

Doctor of Philosophy

2021

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research done by me except where otherwise stated in this thesis. The thesis work has not been submitted for a degree or professional qualification to any other university or institution. I declare that this is written by myself and is free of plagiarism and of sufficient grammatical clarity to be examined. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

6th August 2020

Date

Annabel Ho Xuan Ying

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12th August 2020

Date

Assoc. Prof. Roderick W. Bates

Authorship Attribution Statement

This thesis contains material from 1 paper published in the following peer-reviewed journal in which I am listed as an author.

Chapter 1 is published as Csókás, D.; Ho, A. X. Y.; Ramabhadran. R. O.; Bates, R. W., How an early or late transition state impacts the stereoselectivity of tetrahydropyran formation by intramolecular oxa-Michael addition. *Org. Biomol. Chem.* **2019**, *17*, 6293-6304. DOI: 10.1039/c9ob00750d.

The contributions of co-authors are as follows:

- Assoc. Prof. Roderick W. Bates provided the initiation and direction of the project. He has also prepared the manuscript.
- Dr. Raghunath O. Ramabhadran provided guidance for the calculations for the transition states.
- Dr. Dániel Csókás performed the experiments for base catalysis and provided the calculations for the transition states.
- I performed the material synthesis and experiments for acid catalysis.

6th August 2020

Date

Annabel Ho Xuan Ying

Abstract

The first chapter describes a facile stereochemical study and synthetic route towards di-substituted tetrahydropyran rings. The key steps performed in this section involve cross-metathesis and Ozone-Wittig reactions of each alkene substrate, followed by an efficient *oxa*-Michael cyclisation to give the di-substituted tetrahydropyran products in good yields. These tetrahydropyrans adopt chair-like conformations where diequatorial products are exclusively obtained under kinetic control.

The second and third chapters explore an efficient total synthetic route towards Montanacin D. Considered as a unique member of its family, Montanacin D is of great interest as the tetrahydropyran is adjacent to the butenolide moiety, which provides conformational rigidity. The approach to the molecule is done by way of a convergent synthesis, where the key reactions involve high diastereoselectivity in the oxa-Michael step in mild conditions and a more efficient manner of forming the alkene bonds – methods established in the previous chapter. The tetrahydropyran moiety present in this natural product will be generated using a combination of asymmetric dihydroxylation and asymmetric epoxidation.

Acknowledgments

First and foremost, I would like to thank Associate Professor Roderick W. Bates for his immense guidance throughout my studies in NTU. I am deeply appreciative of the patience and the vast amount of knowledge he has generously shown, in Chemistry and of the world. I am sincerely grateful as without whom, there would be no thesis to write, and no molecules to make.

Special thanks go to the Economic Development Board and Pfizer for providing me with the financial support throughout the course of my study. I would also like to express my gratitude towards the faculty and staff of the Division of Chemistry and Biological Chemistry.

Sincerest gratitude goes to the seniors of the lab. If I have seen further, it is only because these giants have allowed me to stand on their shoulders. I would also like to express my fondness for the past and current group members of the lab. Going to work every day is hardly a hardship because of them.

Last but never least, to my friends and family, I am immensely thankful for your continual provision, which never stops even when I have nothing left of my best to give. Thank you for being the people I always come home to.

Table of Contents

List of Abbreviations

Ac	Acetyl
AD	Asymmetric Dihydroxylation
Bu	Butyl
COSY	Correlation Spectroscopy
CO	Carbon monoxide
COD	Cyclooctadiene
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DMF	N,N-dimethylformamide
DHQD	Dihydroquinidine
DEPT	Distortionless Enhancement by Polarization Transfer
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DMSO	Dimethylsulfoxide
Et	ethyl
ee	Enantiomeric excess
HMPA	Hexamethylphosphoramide
Hz	Hertz
IBX	2-iodoxybenzoic acid
IR	Infrared
IND	9-*O*-indolinylcarbamoyl
J	Coupling constant
LDA	lithium diisopropylamide

LiHMDS	lithium bis(trimethylsilyl)amide
Ms	Methanesulfonyl
mcpba	Meta-chloroperoxybenzoic acid
NBS	N-bromosuccinimide
n-Bu	*n*-butyl
NOESY	Nuclear Overhauser Effect Spectroscopy
NMR	Nuclear Magnetic Resonance
Oct	Octyl
ppm	parts per million
PMB	*para*-methoxybenzyl
PHAL	Phthalazine
Red-Al	Sodium bis(2-methoxyethoxy)aluminium hydride
rt	room temperature
THF	tetrahydrofuran
Tf	Trifluoromethanesulfonate
Ts	Toluenesulfonyl
THP	Tetrahydropyran
TLC	Thin Layer Chromatography
TBAF	Tetra-*n*-butylammoniumfluoride
TBAB	Tetra-*n*-butylammoniumbromide
TBAI	Tetra-*n*-butylammoniumiodide
t-Bu	*Tert*-butyl

tet	tetrahedral
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TBS	Tributylsilyl
TES	Triethylsilyl

CHAPTER 1

Studies on the Synthesis of Tetrahydropyrans

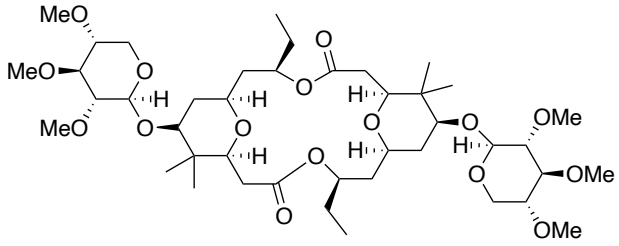
1.1 Introduction

1.1.1 Studies on the Synthesis of Tetrahydropyrans

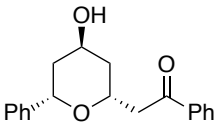
The stereo-controlled synthesis of tetrahydropyrans continues to be a topic worthy to be explored due to the wide range of naturally occurring tetrahydropyrans. Moreover, some of these compounds exhibit biological activity.[1-17] 2,6-*cis*-Substituted tetrahydropyran (THP) rings found in marine and terrestrial natural products are suspected to be the reason for these natural products to show benefits for therapeutic applications.[1-17] The tetrahydropyrans present in these natural products, for example Cyanolide A, which was isolated from the extracts of cyanobacteria; *Lyngbya bouillonii*, have made them popular amongst organic chemists because of the ways they can be synthesized. Of the several common methods used to synthesise 2,6-*cis*-substituted THP ring, oxa-Michael cyclization has been chosen in this project as this method is widely used given its adaptability.[1-17] The specifics of this method will be delved into deeper later.

This project intends to build on previous work[18-23] in the synthesis of THP rings using the combination of cross-metathesis and intramolecular oxa-Michael addition, as described in Scheme **1** below. Some examples of the completed syntheses that have been furnished in this fashion by the laboratory are shown in Scheme **1**.[18-23] This route to various heterocycles have recently garnered considerable attention due to the wide range of naturally occurring THP rings. This approach offers several advantages – the efficiency of cross-metathesis using the commercially available Grubbs' II catalyst which has higher functional group tolerance and higher activity than its predecessor Grubbs I, the simple assembly of the precursors and the main advantage which is the high

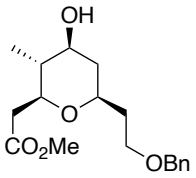
stereoselectivity provided by oxa-Michael cyclisation. The oxa-Michael addition is one of several methods that may be used to construct THP rings shown below in Scheme **2**.



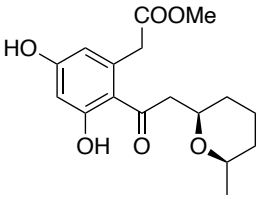
Cyanolide A



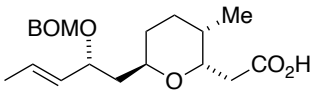
Diospongin A



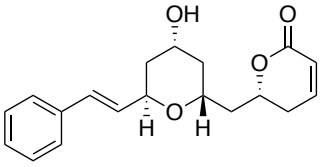
Clavosolide THP Fragment



Curvulone B

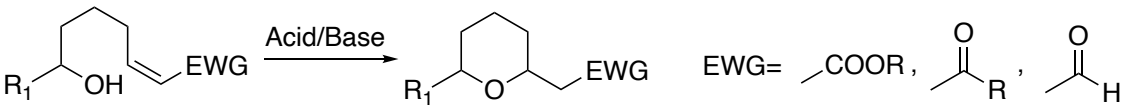


Bistramide D THP Fragment



Cryptoconcatone H

Scheme 1. Completed Natural Products in this lab



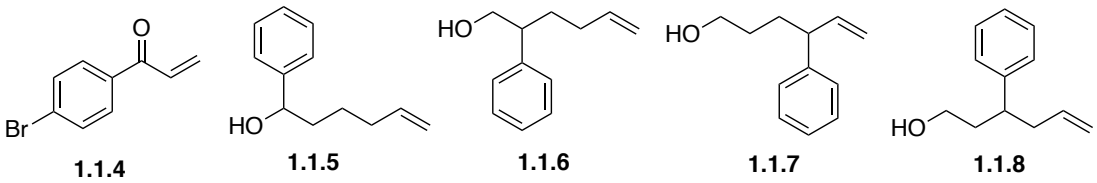
1.1.1 **1.1.2**

Scheme 2. Oxa-Michael reaction

Cross-Metathesis is one of several alkene metathesis reactions and it refers to the metal-catalysed trans-alkylidenation of two terminal alkenes to construct new C=C bonds, driven by the entropically favoured evolution of ethylene or propylene in the process. The first report of double-bond scrambling was published in 1955[22] but the term "*olefin metathesis*" was only introduced by N. Calderon[24] *et al*. in 1968. Other *alkene metathesis* reactions include *ring-opening metathesis* (ROM), *ring-closing metathesis* (RCM), *ring-opening metathesis polymerisation* (ROMP) and *acyclic diene metathesis polymerisation* (ADMET). These metathesis methods allow access to polymers and molecules that would otherwise be difficult to obtain. RCM makes for easy entry into heterocyclic compounds as well as medium and large carbocycles.[25] ROMP allows the preparation of functionalised polymers that was impossible otherwise. The catalyst before the beginning of 1990s had little functional group tolerance and low performances, which explains why the application of *alkene metathesis* for the synthesis of complicated organic molecules only emerged then. Up till now, *alkene metathesis* has proven to be an extensively-used and reliable synthetic method. The catalyst system currently used ($L(L')X_2Ru=CHR$) has adequate functional group tolerance and is highly active. A main advantage of *cross-metathesis* is its inherent atom-efficiency.

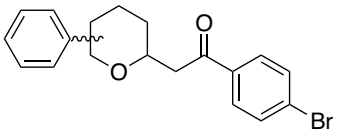
So far, to the best of our knowledge, only a 2,6-disubstituted THP ring is widely studied, thus our project aims to investigate the stereochemistry of other disubstituted THP rings, such as 2,3-, 2,4- 2,5-, as well as 2,6-disubstituted as this moiety is prevalent in many natural products. This project would use phenylhex-5-en-1-ols with a phenyl group attached in different positions (Figure **1**) as precursors. The position of the phenyl group would

affect the stereochemistry of the THP ring in the oxa-Michael addition reaction (Figure **2**).



1.1.4 1-(4-bromophenyl)prop-2-en-1-one **1.1.5** **1.1.6** **1.1.7** phenylhex-5-en-1-ol **1.1.8**

Figure 1. Precursors to THP rings



1.1.3

Figure 2. Stereochemistry of THP to be determined

To prepare the precursors for *cross-metathesis*, 1-(4-bromophenyl)prop-2-en-1-one and phenylhex-5-en-1-ol with the phenyl group present in differing positions were synthesised.

Grubbs' second generation catalyst (Figure **3**) was used for the *cross-metathesis* of 1-(4-bromophenyl)prop-2-en-1-one and phenylhex-5-en-1-ol. This catalyst was chosen because it retains the same uses in organic synthesis as the first generation catalyst but has higher activity. This catalyst also makes for convenient handling in the laboratory because of its stability toward moisture and air. It should also be noted that this catalyst is more effective for cross-metathesis because it is tolerant of a wide range of functional groups in the alkene and is soluble in various solvents.[26-27]

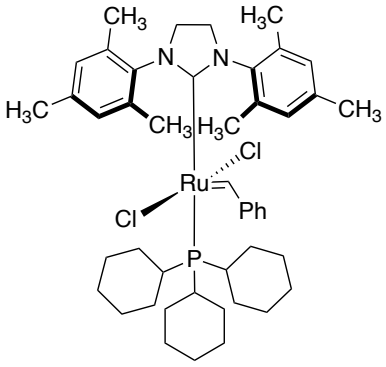
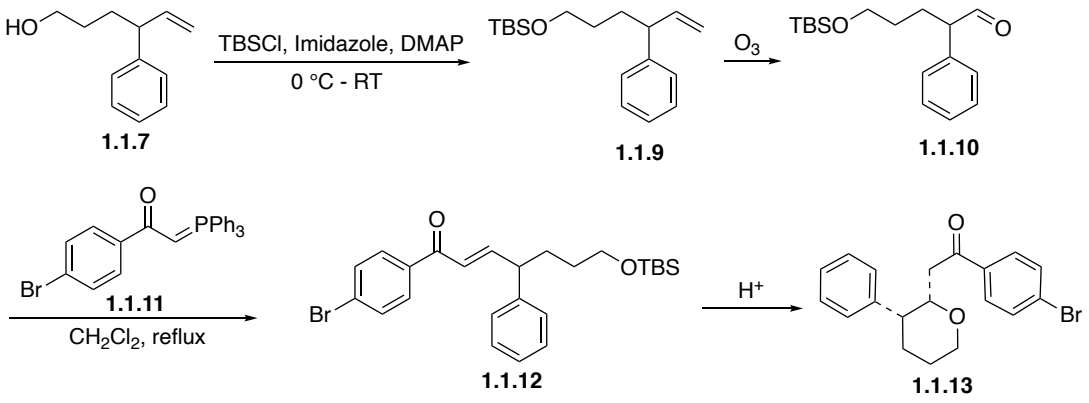


Figure 3 Grubbs' Second Generation Catalyst

A Wittig reaction was also used as an alternative method, which turned out to give more favourable results in terms of yield and purity. This reaction allows the preparation of an alkene by the reaction of an aldehyde or ketone with the ylide generated from a phosphonium salt, which is illustrated below (Scheme **3**) with 4-phenyl-hex-5-en-1-ol as an example.[28-29]

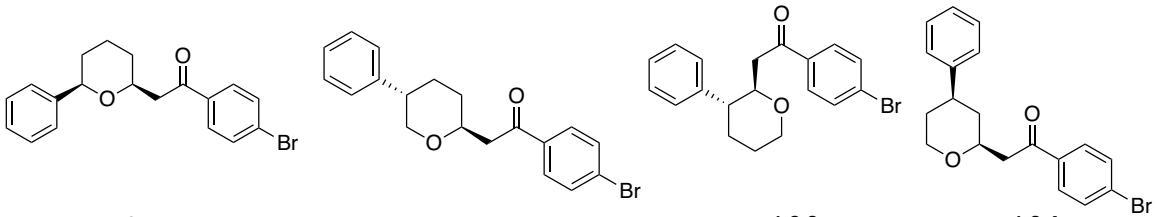


From the information gathered from previous studies done in this laboratory,[18-22] a facile method of building 2,6-THP rings has been crafted and led to desirable results. Dispongin A was isolated from *Dioscorea spongiosa* and shows anti-osteoporotic activity.[18] It contains a 2,6-THP and was synthesized using a combination of cross-metathesis and intramolecular hetero-Michael addition. Another molecule, Bistramide D, belongs to a small family of natural products that are isolated from an ascidian, *Lissoclinum bistratum*. Model studies were done towards the synthesis of the tetrahydropyran moiety via a stereoselective kinetic intramolecular oxa-Michael addition.[19] Clavosolide A and Curvulone B, both marine natural products, also employ the combination of cross-metathesis and intramolecular oxa-Michael addition.[20, 22] With this methodology established from previous studies, a similar one would also be employed for this project.

However, the outcome for other di-substituted THP rings remains unknown, and this project aims to bridge that gap while expanding our knowledge of other di-substituted THP rings.

1.1.2 Synthesis of Tetrahydropyrans

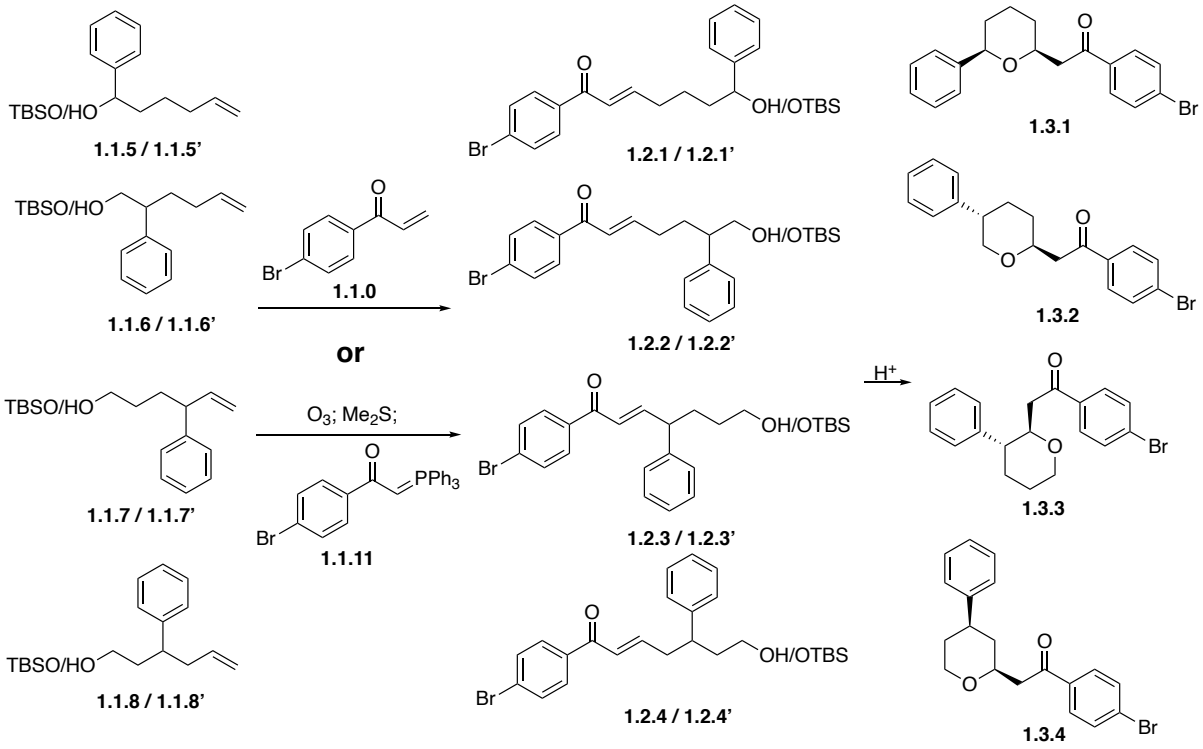
Four variants of tetrahydropyran compounds with phenyl group substituted at different positions of the ring were synthesised (Figure **4**). Their relative stereochemistry has been confirmed by X-ray crystallography, described in Section 1.3.



1.3.1 **1.3.2** **1.3.3** **1.3.4**

Figure 4. THP rings synthesised in this project

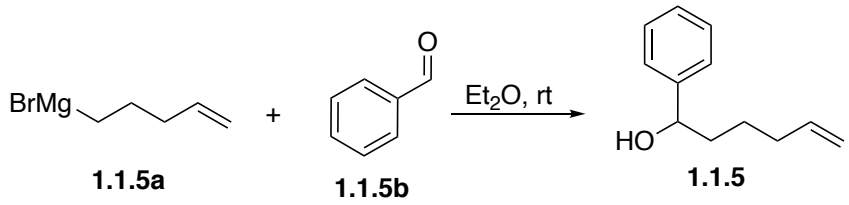
Three key reactions were involved in the synthesis of the THP rings, summarised in Scheme **4** below. To start with, the alcohol was generated with the phenyl group attached at different positions, as shown in **1.1.5** – **1.1.8** and **1.1.5'** – **1.1.8'**. Then, a cross-metathesis or Wittig reaction together with α,β-unsaturated ketone **1.1.0** with the aid of Grubbs' second-generation catalyst or ylide **1.1.11** completes the second reaction, as shown in **1.2.1** – **1.2.4** and **1.2.1'** – **1.2.4'**. Finally, the *oxa*-Michael reaction culminates with a ring closure to form the THP ring, shown in **1.3.1** – **1.3.4**. The respective stereochemistry of THP rings will also be explored in greater detail later in this section.



Scheme 4. THP Synthesis Overview

1.2 Results and Discussion

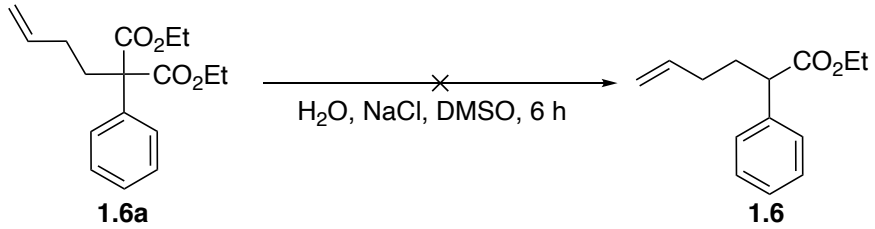
1.2.1 Generation of the alcohol - Phenylhex-5-en-1-ol



Scheme 5. Synthesis of 1-phenylhex-5-en-1-ol

A Grignard addition of pent-4-en-1-ylmagnesium bromide with benzaldehyde, as shown in Scheme **5** above, furnished 1-phenylhex-5-en-1-ol (**1.1.5**) in 83% yield. The structure was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy.

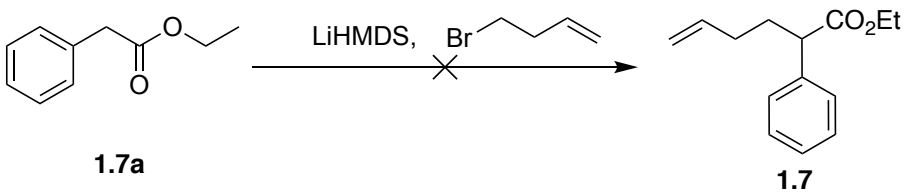
The synthesis of 2-phenylhex-5-en-1-ol (**1.1.6**) posed as a challenge with two unsuccessful synthetic attempts. The first approach was to make a diethyl 2-(but-3-en-1-yl)-2-phenylmalonate, followed by a Krapcho[30] reaction to cleave one ester group. While the malonate was successfully made, the cleavage of the ester group proved to be a problem. The malonate was stirred with H_2O, NaCl and DMSO at 150 °C for 6 hours (Scheme **6**). Even under these harsh conditions, TLC and NMR analyses show no consumption of the starting material.



Scheme 6. First Attempt at Synthesising 2-phenylhex-5-en-1-ol

The second approach (Scheme **7**) involved adding ethyl phenylacetate to LDA dissolved in THF[31] followed by addition of 4-bromo-1-butene. Switching the base

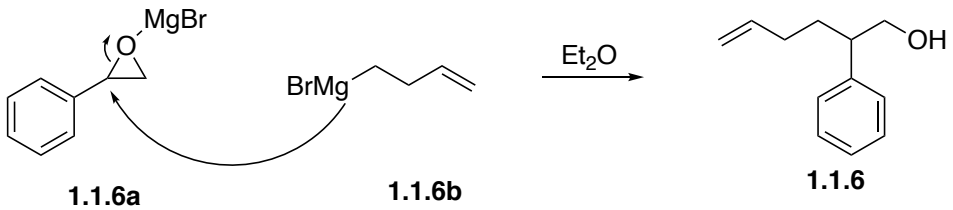
to LiHMDS proved futile. The problem remained even after several tries using two strong bases – Lithium Diisopropylamide (LDA) and Lithium Bis(trimethylsilyl)amide LiHMDS) at 1.1 and 1.2 equivalents respectively. At this point, it was imperative to check if the deprotonation was the cause of the issue. The reaction was quenched with D_2O and NMR analysis showed only starting material with no signs of deprotonation.



1.7a **1.7**

Scheme 7. Second Attempt at Synthesising 2-phenylhex-5-en-1-ol

The third approach involved a Grignard reaction. Gratifyingly, it was successful. The reaction proceeds as a partial S_N1 reaction. Diethyl ether being a non-polar solvent, makes the Grignard reagent a stronger Lewis acid. This could coordinate with the oxygen in the epoxide. The Grignard reagent then attacks the epoxide at the more hindered position. The phenyl group stabilises build up of positive charge on the benzylic carbon. When the Grignard reagent coordinates with the oxygen, it causes a partial positive charge at the hindered carbon. The reaction mechanism is depicted in Scheme **8** below.



1.1.6a **1.1.6b** **1.1.6**

Scheme 8. Mechanism for 2-phenylhex-5-en-1-ol

This reaction resulted in the formation of another isomer because the Grignard reagent can attack at the less hindered site of the epoxide. The

epoxide also rearranged to form another isomer. The three different isomers are displayed in Figure **5**.

The reaction yielded 35% of the desired product and ^{1}H NMR spectroscopic analysis shows a multiplet at 3.74 ppm with an integration number of two, which confirms the synthesis of the targeted isomer. Consideration of the optimisation of this step can be done with the addition of the Grignard reagent at a lower temperature (-20 °C - -78 °C) with the inclusion of a Lewis acid.

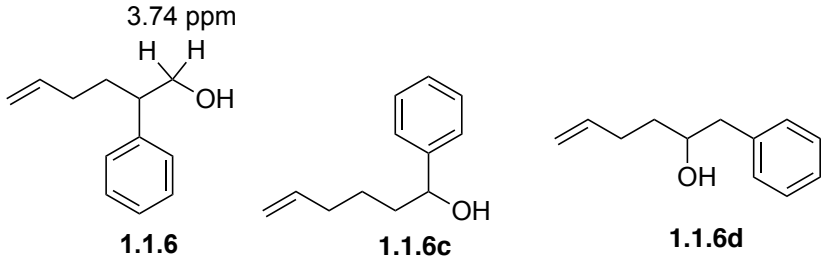
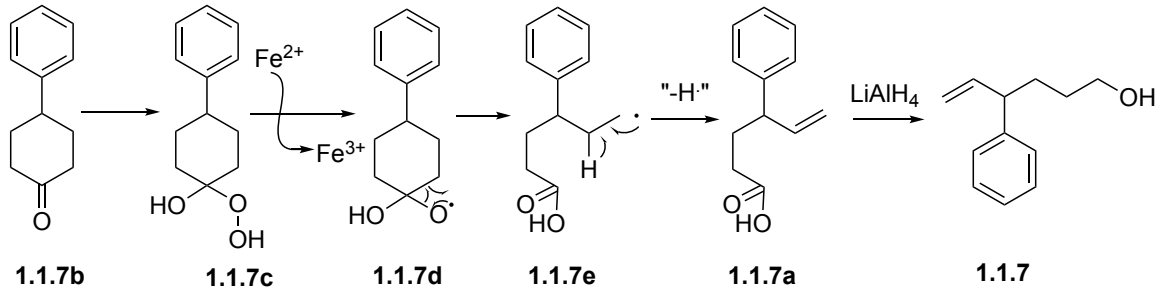


Figure 5. Isomers from the Synthesis of 2-phenylhex-5-en-1-ol

For the synthesis of 4-phenylhex-5-en-1-ol (**1.1.7**), the reaction proceeds via Fenton's reagent[32] where Fe^{2+} ions were oxidised to Fe^{3+} ions by H_2O_2. This redox reaction caused a hydroxide radical and a hydroxyl ion to form in the process. The reduction reaction took place via another molecule of H_2O_2 and formed a hydroperoxyl radical and a proton. H_2O_2 went through disproportionation and formed two different oxygen radical species. Water was formed as a by-product in this process.

These radicals and ions formed in the redox reaction attack the 4-phenylcyclohexanone and finally forms 4-phenylhex-5-en-1-ol after reduction with $LiAlH_4$. The reaction mechanism is proposed in Scheme **9** below.



Scheme 9. Proposed Mechanism for the Synthesis of 4-phenylhex-5-en-1-ol

The yield of the product improved considerably when the concentration of the reaction increased by a hundred fold. H_2O_2 was used to attack the carbonyl group of phenylcyclohexanone. Attempts to optimise the reaction which involved changes in reaction times, equivalents of H_2O_2 added and concentration showed that the concentration of the reaction is crucial. The results are shown in Table **1**.

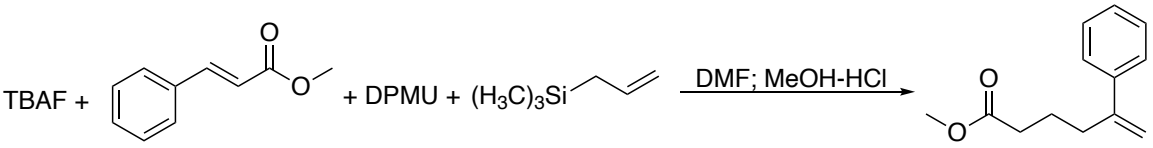
Entry	Reagent	Equiv.	Conc. (mM)	Reaction time	Solvent	Yield[a] (%)
1	H_2O_2	2	0.1	1 minute	Methanol	~1-2
2	H_2O_2	2	0.1	3 hours	Methanol	4
3	H_2O_2	2	0.1	15 minutes	Methanol	22
4	H_2O_2	2	0.1	20 minutes	Methanol	10
5	H_2O_2	2	0.1	20 minutes	Methanol	3
6	H_2O_2	4	10	15 minutes	Methanol	32

[a]% isolated yield

Table 1. Yields of 4-phenylhex-5-en-1-ol

For the synthesis of 3-phenylhex-5-en-1-ol (**1.1.8**), three attempts were made. The desired compound was successfully prepared via [2,3]-Wittig rearrangement.

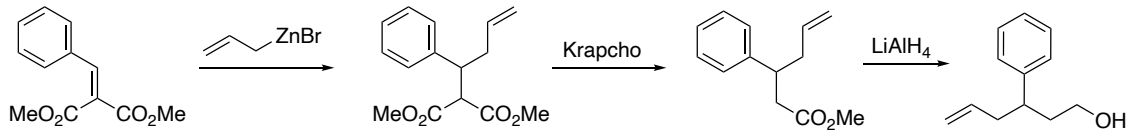
The approach for the first attempt was to synthesise a methyl 3-phenyl-5-hexanoate intermediate, followed by reduction with $LiAlH_4$ to form the alcohol. Methyl cinnamate was stirred with tetra-*n*-butylammonium fluoride (TBAF), *N*,*N*′-Dimethylpropyleneurea (DMPU) and allyltrimethylsilane in dimethylformamide (DMF) for about 10 minutes at room temperature. The reaction was subsequently subjected to methanolysis (MeOH:HCl; 9:1). According to TLC and NMR analyses, the reaction only proceeded with minimal yield. DMPU was chosen as a replacement for hexamethylphosphoramide (HMPA)[33] – the solvent reported in the original literature[34]. The solvent change is a possible reason for the low yield as the reported literature specifically mentioned that the nature of the solvent is crucial. This reaction was attempted twice, and the desired product was only afforded in low yield (Scheme **10**).



Scheme 10. First Attempt at Synthesising 3-phenylhex-5-en-1-ol

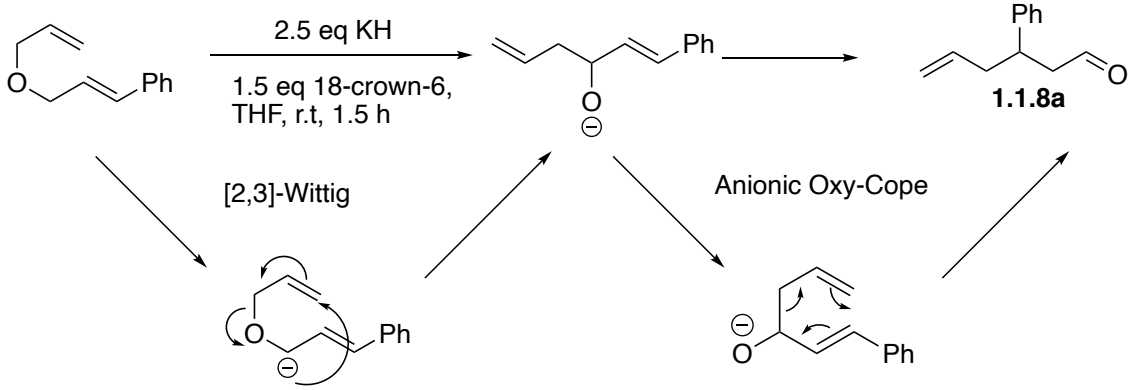
The second approach involves a dimethyl 2-benzylidenemalonate intermediate with allylzinc(II) bromide followed by a Krapcho[30] reaction and finally a reduction with $LiAlH_4$. The dimethyl 2-benzylidenemalonate intermediate has been successfully synthesised, however, the planned synthesis was interrupted as cleavage of the ester using Krapcho did not proceed as expected. The scheme

(Scheme **11**) below illustrates the planned synthesis pathway of the second approach.



Scheme 11. Second Attempt at Synthesising 3-phenylhex-5-en-1-ol

The third approach involved a Williamson-ether synthesis with 3-bromoprop-1-ene, 3-phenylprop-2-en-1-ol, sodium hydroxide (NaOH) and tetra-*n*-butylammonium bromide (TBAB) as a phase transfer catalyst to generate the intermediate. The intermediate was then subjected to KH and 18-crown ether and underwent a [2,3]-Wittig rearrangement with a product yield of 76% (Scheme **12**). Next, the final product was obtained through reduction of the aldehyde to the alcohol with $NaBH_4$. The proposed mechanism[35] of the rearrangement is illustrated below. Previous attempts with other strong bases, i.e., *n*-Butyllithium (*n*-BuLi), *n*-BuLi with tetramethylethylenediamine (TMEDA), sodium hydride (NaH), NaH with 15-crown ether, only yielded starting material.



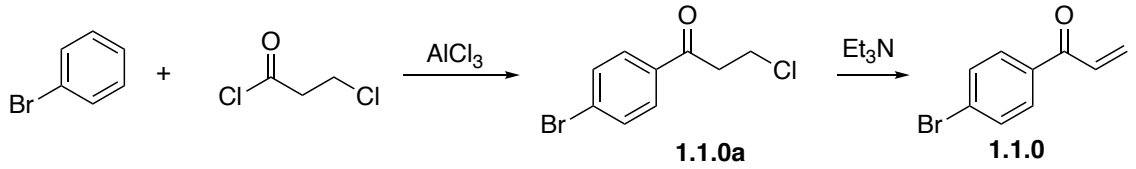
Scheme 12. Proposed synthesis of [2,3]-Wittig Rearrangement

1.2.2 Generation of the α,β-unsaturated ketone - 1-(4-bromophenyl)prop-2-en-1-one

The reason for choosing 1-(4-bromophenyl)prop-2-en-1-one is because the ketone (1.1.0) is a preferred Michael accepter as it is more electrophilic compared to a relatively unreactive corresponding ester. The ketone would also favour the formation of a *cis*-disubstituted THP in acidic conditions. This particular ketone (**1.1.0**) was chosen for its bromophenyl moiety as the molecular weight and polarity would increase the chances of a crystalline structure being formed. To this end, the stereochemical outcomes of the THP rings can be confirmed with x-ray crystallography analysis, which will be discussed in detail later in Section 1.3.

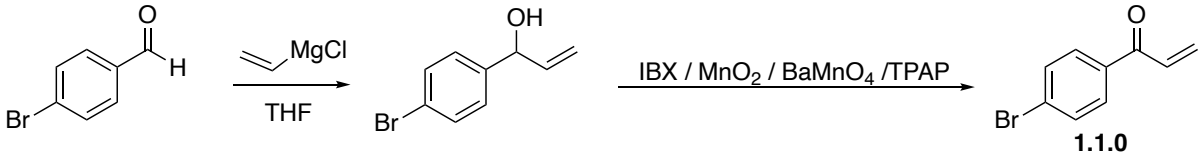
The control experiment done with 1-phenylhex-5-en-1-ol (**1.1.15**) resulted in a 2,6-*cis* THP ring (**1.3.1**), which is consistent with the results of previous work done by this laboratory. [18-22] It is found that in a 2,6-THP ring, the product where both the ketone and phenyl group is in the equatorial position is favoured. This will be discussed in detail later in this section.

Two methods were adopted to synthesise 1-(4-bromophenyl)prop-2-en-1-one (**1.1.0**). The first was performed using Friedel-Crafts reaction with bromobenzene followed by the addition of 3-chloropropionyl chloride with the aid of aluminium chloride to give adduct **1.1.0a**. Subsequently, elimination **of** the terminal chloride using triethylamine formed the alkene. The Friedel-Crafts reaction is also regioselective because only the *para* compound is generated. The reaction is illustrated in Scheme **13** below.



Scheme 13. Friedel-Crafts Approach

The second method involved the oxidation of 1-(4-bromophenyl)prop-2-en-1-ol intermediate with oxidizing agents. Four oxidizing agents were used – IBX, MnO_2, $BaMnO_4$ and TPAP, with IBX giving the best yield at 79%, as shown below in Table **2**.



Scheme 14. Oxidation Approach

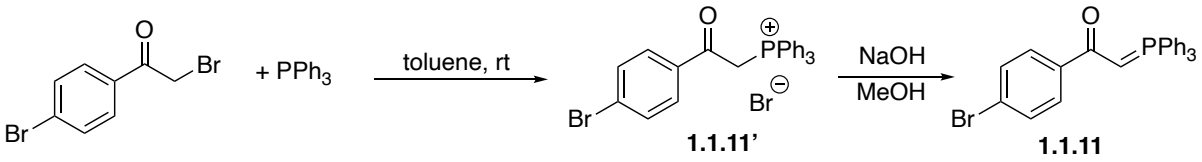
Oxidixing Agents	Yield (%)
IBX	79
MnO_2	7
$BaMnO_4$	49
TPAP	17

Table 2. Product Yields from Oxidising Agents

Generation of the ylide for alternative Ozonolysis-Wittig method

The synthesis of the ylide was relatively straightforward, affording the product in high yield. Triphenylphosphine was added to 2-bromo-1-(4-bromophenyl)ethan-1-one in toluene to obtain the phosphonium salt. The phosphonium salt was then subjected to NaOH in methanol and the final ylide (**1.1.11**) was obtained in 91% yield. The reaction pathway is illustrated below

(Scheme **15**). The Ozonolysis-Wittig method proved to provide better yields than the cross-metathesis method, which will be further discussed at a later section.

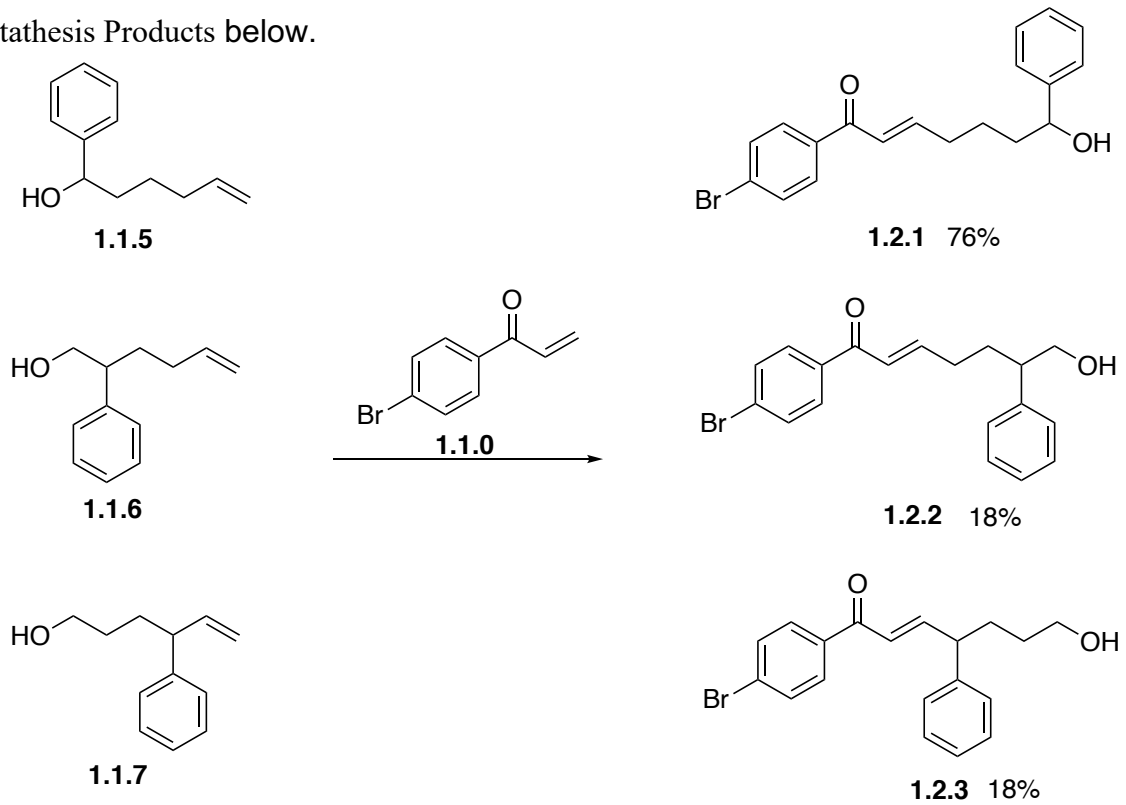


Scheme 15. Synthesis pathway of ylide

1.2.3 Cross-Metathesis And Ozonolysis-Wittig Reaction

The cross-metathesis reaction was the second pathway that led towards the synthesis of the THP rings. This involves the reaction between the synthesised alcohols and 1-(4-bromophenyl)prop-2-en-1-one (**1.1.0**).

The three phenylhex-5-en-1-ols (**1.1.5 – 1.1.7**) each underwent a cross-metathesis reaction with 1-(4-bromophenyl)prop-2-en-1-one (**1.1.0**) giving α,β-unsaturated ketones (**1.2.1 – 1.2.3**) as products shown in Scheme **16.** Cross-metathesis Products below.



Scheme 16. Cross-metathesis Products

α,β-unsaturated ketone **1.2.1** is obtained in 76% yield. A plausible reason for this good yield might be due to the large distance between the bulky phenyl and the alkene, which minimises steric hindrance caused by the phenyl during *cross-metathesis*. In the same manner, the low yield of α,β-unsaturated ketone **1.2.3** (18%) would be caused by the proximity of the bulky phenyl and the alkene, making it more difficult for cross-metathesis to occur. The low yield for α,β-unsaturated ketone **1.2.2** is still unknown. The yields for the various ketones are represented in Scheme **16**.

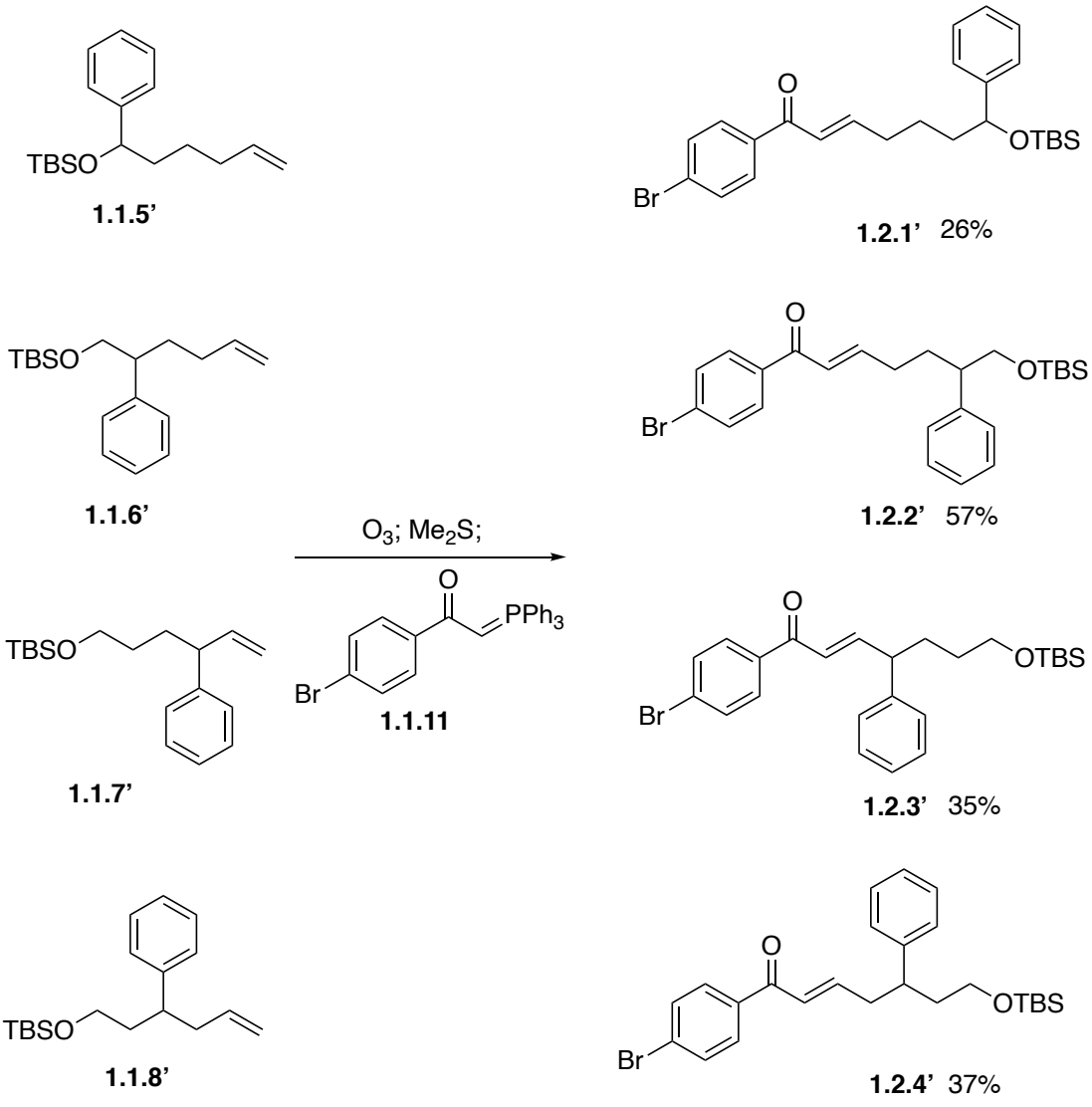
A cross-metathesis reaction was also attempted with 3-phenyl-hex-en-1-ol. However, the characterisation data of the crude product showed inconclusive results.

From the spectroscopic data for **1.2.1 – 1.2.3**, it is known that the α,β-unsaturated ketones that are synthesised are *trans*-alkenes because of the 16 Hz coupling constant at 6.8 ppm for **1.2.1**, 6.74 ppm for **1.2.2** and 6.8 ppm for **1.2.3**.

After multiple attempts with different Grubbs catalysts and solvents, the low yields still persisted. At this point, the decision to explore the alternate route of Wittig was made.

Ozonolysis-Wittig

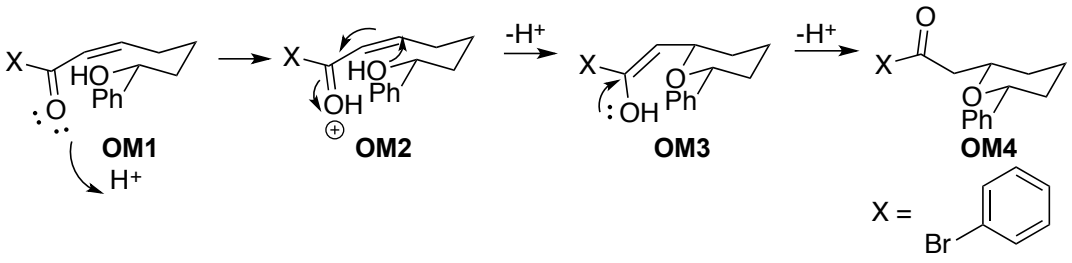
In comparison to cross-metathesis using Grubbs catalysts, this method proved to be greener as it is more atom economical and produced fewer chemical wastes. Moreover, better yields have also been generated as illustrated in Scheme **17** below. The alcohols (**1.1.5 – 1.1.8**) were first protected with the TBS group. The protected alcohols (**1.1.5' – 1.1.8'**) then underwent ozonolysis, followed by a Wittig reaction to generate the desired products (**1.2.1' – 1.2.4'**).



Scheme 17. Ozonolysis-Wittig Products

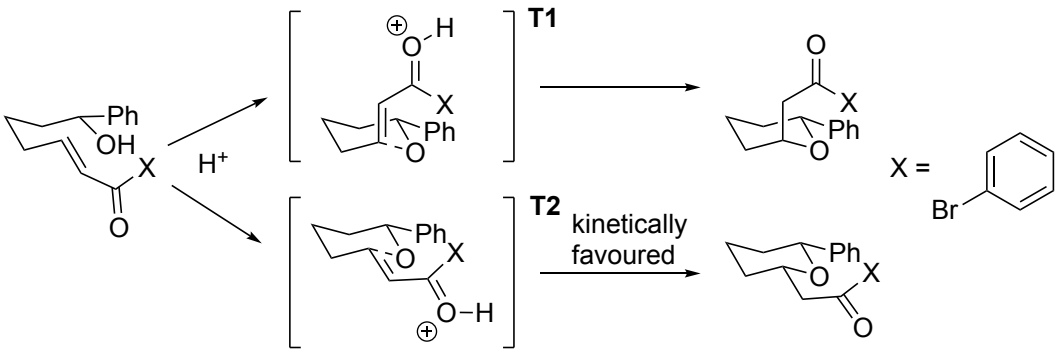
1.2.4 *Oxa*-Michael Cyclisation (Ring Closure)

The *oxa*-Michael cyclisation involves an intramolecular hydroxyl attack on the alkene group through an *exo* cyclisation to give the 2,6-disubstituted (**1.3.1**), 2,5-disubstituted (**1.3.2**), 2,3-disubstituted (**1.3.3**) and 2,4-disubstituted (**1.3.4**) THP derivatives. The reaction mechanism is illustrated in Scheme **18**. The stereochemistry of the THP rings is largely dependent on the conditions that the reactions are subjected to. Herein, the focus was placed on studying the stereochemical outcomes of the synthesised THP rings under acidic conditions.



Scheme 18. Mechanism of Oxa-Michael Reaction

It is postulated that in acidic conditions, the synthesised 2,6-substituted THP ring would adopt a *cis* relationship between the two stereogenic centres (Scheme **19**). The protonation of the C=O group leads to the formation of a chair-like transition state as illustrated in **T1** and **T2** in Scheme **20**. **T2** is favoured over **T1** because of the lack of 1,3-diaxial interaction repulsion, shown in Scheme **19** below. Computationally, calculations done by Dr Dániel Csókás, a PhD graduate who was previously in our laboratory, shows that the acid-catalysed cyclisation proceeds via a late-transition state. It is also worth mentioning that the kinetic favouring of the diequatorial isomer has a steric reasoning.



Scheme 19. Transition state of THP formation in acidic conditions

1.3 Stereochemical Studies on Tetrahydropyrans

It is postulated that the 6-membered THP ring adopts a chair-like conformation and the transition state where the ketone assumes an equatorial position is favoured. The results garnered in this project have evidently proven so.

A control study was done on tetrahydropyran **1.3.1**. According to the proton NMR spectrum, the protons at the position α to C=O shows a doublet of doublet at 3.00 ppm and a doublet of doublet 3.35 ppm, both with coupling constants of 6 Hz and 16 Hz. The H_2 shows a multiplet at 4.10 ppm while the H_6 shows a doublet of doublet peak at 4.40 ppm with a coupling constant of 2 Hz and 10 Hz. In order get a clearer idea of the multiplicity of the H_2 peak, a homo nuclear decoupling NMR was run for the proton at 3.35 ppm. After decoupling, the NMR shows a clear doublet of doublet with a coupling constant of 4 Hz and 11 Hz. H2 couples with the axial proton of H3. This shows that both the H_2 and H_6 protons are in the axial position, making the ketone and phenyl group *cis* to each other. The stereochemistry is illustrated in Figure **6**. The relative stereochemistry is confirmed by data retrieved from NOESY and COSY.

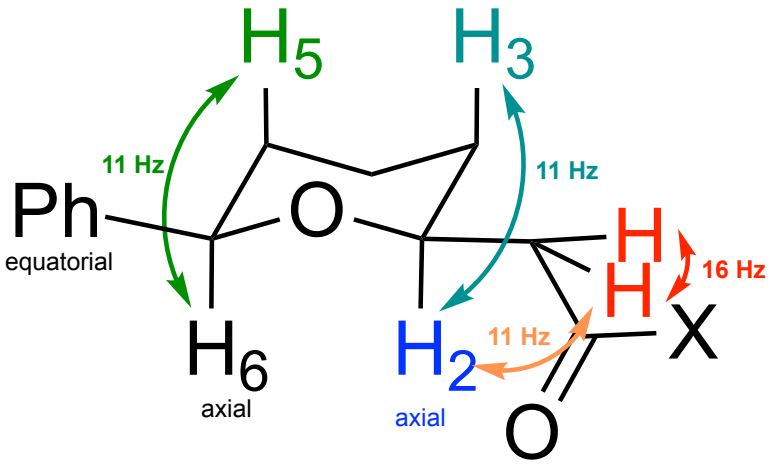


Figure 6. Stereochemistry and Coupling Constants of 1.3.1

According to the COSY spectrum for tetrahydropyran **1.3.2**, the cross peaks show that the peak at 4.00 ppm belongs to H_2, which couples to the peak at 3.50 ppm belonging to H_6 and the peaks at 1.85 ppm and 1.55 ppm belonging to H_3. A hidden peak buried within the signals at 4.0 ppm also belongs to a proton of H_6. The peaks of H_2 also couples to the peaks at 3.30 ppm and 2.95 ppm belonging to the protons at the position α to C=O. H_2 also couples to the peak at 2.80 ppm belonging to H_5. These cross peaks present in the COSY spectrum confirm the relative positions of these protons to one another. Their relative positions are illustrated in Figure **7**.

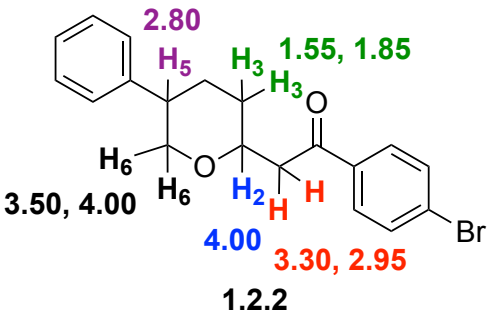


Figure 7. Relative Positions of Protons in 1.3.2

With the knowledge of the relative position of protons H_2, H_3 and H_5, supplementary information from proton NMR will make the coupling constant values known, and these values would confirm the stereochemistry of these protons.

The H_2 peak at 4.00 ppm unfortunately revealed little about its stereochemistry. The H_3 peak at 1.85 ppm has coupling constants of 4 Hz and 13 Hz while the peak at 1.55 ppm shows an apparent doublet of quartet with coupling constants of 4 Hz and 13 Hz. The coupling constant of 4 Hz is consistent with that of $J_{ax,eq}$, showing that the proton at 1.55 ppm is in the axial position while the proton at 1.85 ppm is at the equatorial position. The coupling constant of 13 Hz is

consistent with that of $J_{ax,ax} \approx J_{gem}$. The H_5 peak at 2.80 ppm shows a triplet of triplet with coupling constants of 4 Hz and 10 Hz. The coupling constants of H_5 shows that the proton is in an axial position. The protons at the position α to C=O show one doublet of doublet at 3.30 ppm and another doublet of doublet at 2.95 ppm. The calculated coupling constants of the protons at the position α to C=O at 3.30 ppm are 7 Hz and 16 Hz, while the doublet of doublet at 2.80 ppm have coupling constants at 5 Hz and 16 Hz. The geminal protons at the position α to C=O show a coupling constant of 16 Hz. No decoupling analysis was run because the multiplicity of the necessary signals was adequately clear. The stereochemistry of the proton is displayed in Figure **8** below. Their relative stereochemistry is confirmed by COSY and confirmed with x-ray crystallography (Figure **9**).

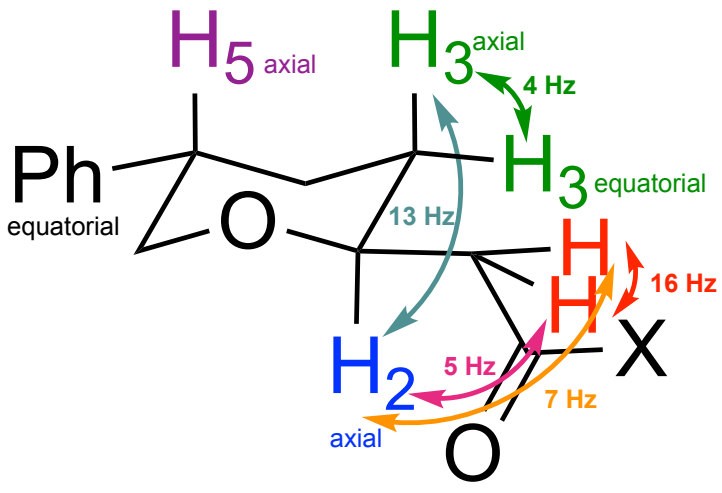
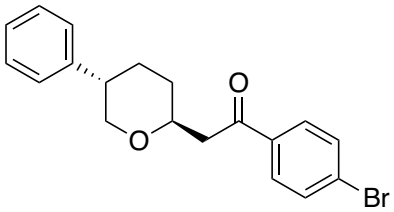


Figure 8. Stereochemistry and Coupling Constants of 1.3.2



1.2.2

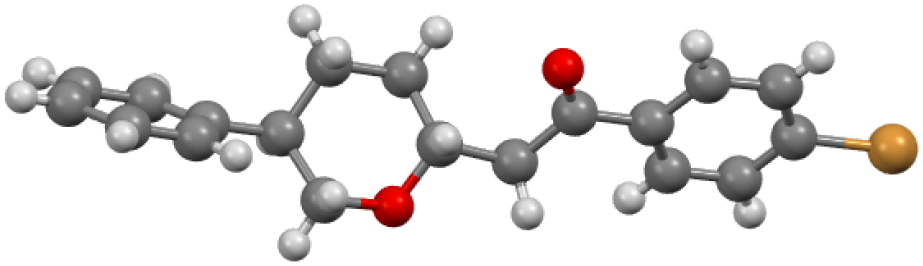
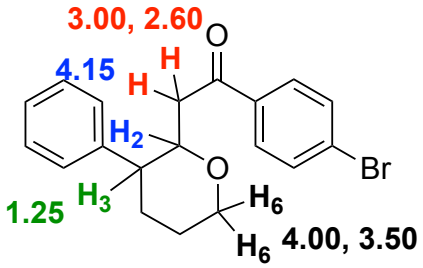


Figure 9. X-ray structure of 2,5-disubstituted THP[a]

We can thus conclude that tetrahydropyran **1.3.2** assumes a chair conformation and that the substituents are *trans* to each other.

The results of the other tetrahydropyran **1.3.3** synthesised were also consistent with our findings above.

According to the COSY spectrum for tetrahydropyran **1.3.3**, the cross peaks show that the peak at 4.15 ppm belongs to H_2, which couples to the peaks at 4.00 ppm and 3.50 ppm belonging to H6 and the peak at 1.25 ppm belonging to H_3. The peaks of H_2 also couples to the peaks at 3.00 ppm and 2.60 ppm belonging to the protons at the position α to C=O. These cross peaks present in the COSY spectrum confirm the relative positions of these protons to one another. Their relative positions are illustrated in Figure **10**.



1.3.3

Figure 10. Relative Positions of Protons in 1.3.3

a: CCDC 1895904

With the knowledge of the relative position of protons H_2, H_3 and H_6, supplementary information from proton NMR will make the coupling constant values known, and these values would confirm the stereochemistry of these protons.

The H_2 peak at 4.15 ppm shows an apparent doublet of triplet, with coupling constants of 2.4 Hz and 10 Hz. It shows a doublet of triplet instead of a doublet of doublet of doublet because the coupling of H_2 with H_3 shares the same coupling constant as that of H_2 and H_6. The protons at the position α to C=O show one doublet of doublet at 3.00 ppm and another doublet of doublet at 2.60 ppm. The calculated coupling constants of the protons at the position α to C=O at 3.00 ppm are 10 Hz and 16 Hz, while the doublet of doublet at 2.60 ppm have coupling constants at 2.4 Hz and 16 Hz. The geminal protons at the position α to C=O show a coupling constant of 16 Hz. The H_2 proton couples with the protons at the position α to C=O, evidence by the coupling constants of 2.4 Hz and 10 Hz. A coupling constant of 10 Hz is consistent with $J_{ax,ax}$ values. This points out that the H_2 proton is in an axial position. A 10 Hz coupling constant also shows that H_3 proton is in an axial position. No decoupling analysis was run because the multiplicity of the necessary signals is adequately clear. The stereochemistry of the proton is displayed in Figure **11** below.

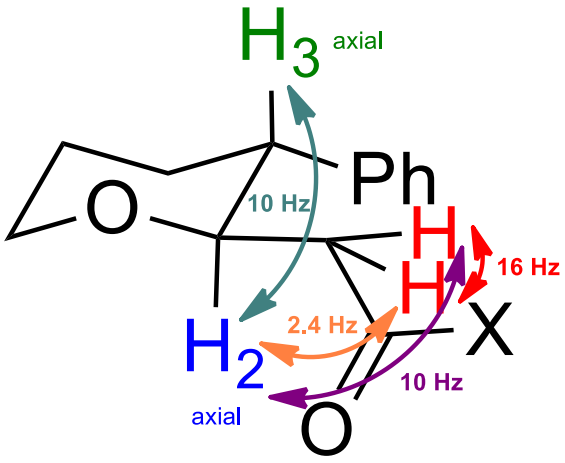
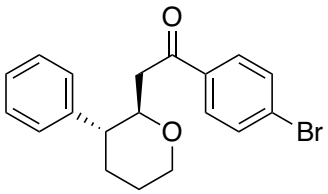


Figure 11. Stereochemistry and Coupling Constants of 1.3.3



1.3.3

We can also thus conclude that tetrahydropyran **1.3.3** assumes a chair conformation and that the substituents are *trans* to each other. The relative stereochemistry of this is confirmed similarly by COSY and confirmed with x-ray crystallography (Figure **12**).

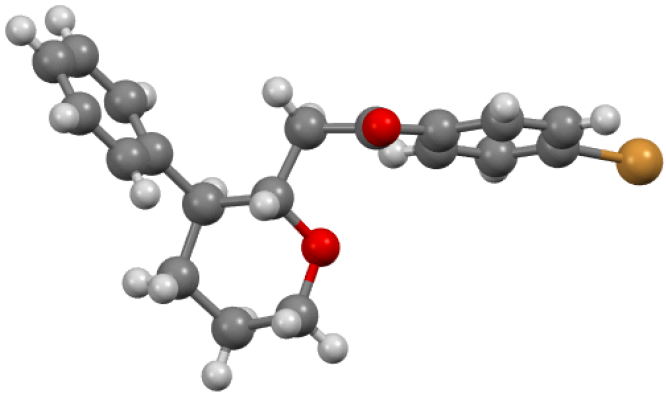


Figure 12. X-ray structure of 2,3-disubstituted THP[b]

The results of the final tetrahydropyran **1.3.4** is also consistent with our findings above.

According to the COSY spectrum for tetrahydropyran **1.3.4**, the cross peaks for H2, H6, Hα, H4 and H5 do not reveal anything conclusive about the stereochemistry of **1.2.4**. Fortunately, the peak at 1.5 ppm belonging to H3 shows a quartet, signifying three identical coupling constants. This shows that it couples to H4, H3' and H2. At a coupling constant of 15 Hz, it points towards an ax/ax coupling. These cross peaks present in the COSY spectrum (Figure **15**) confirm the relative positions of these protons to one another. Their relative positions are illustrated in Figure **13**.

b: CCDC 1895902

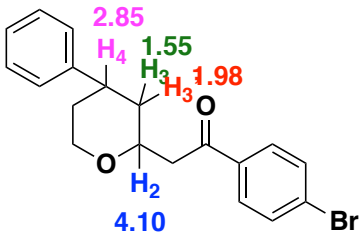


Figure 13. Relative Positions of Protons in 1.3.4

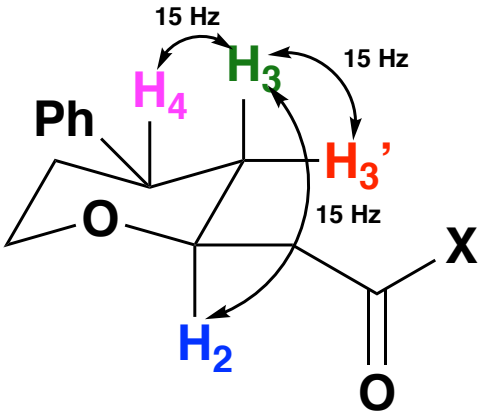
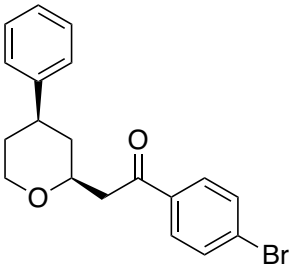


Figure 14. Stereochemistry and Coupling Constants of 1.3.4



1.3.4

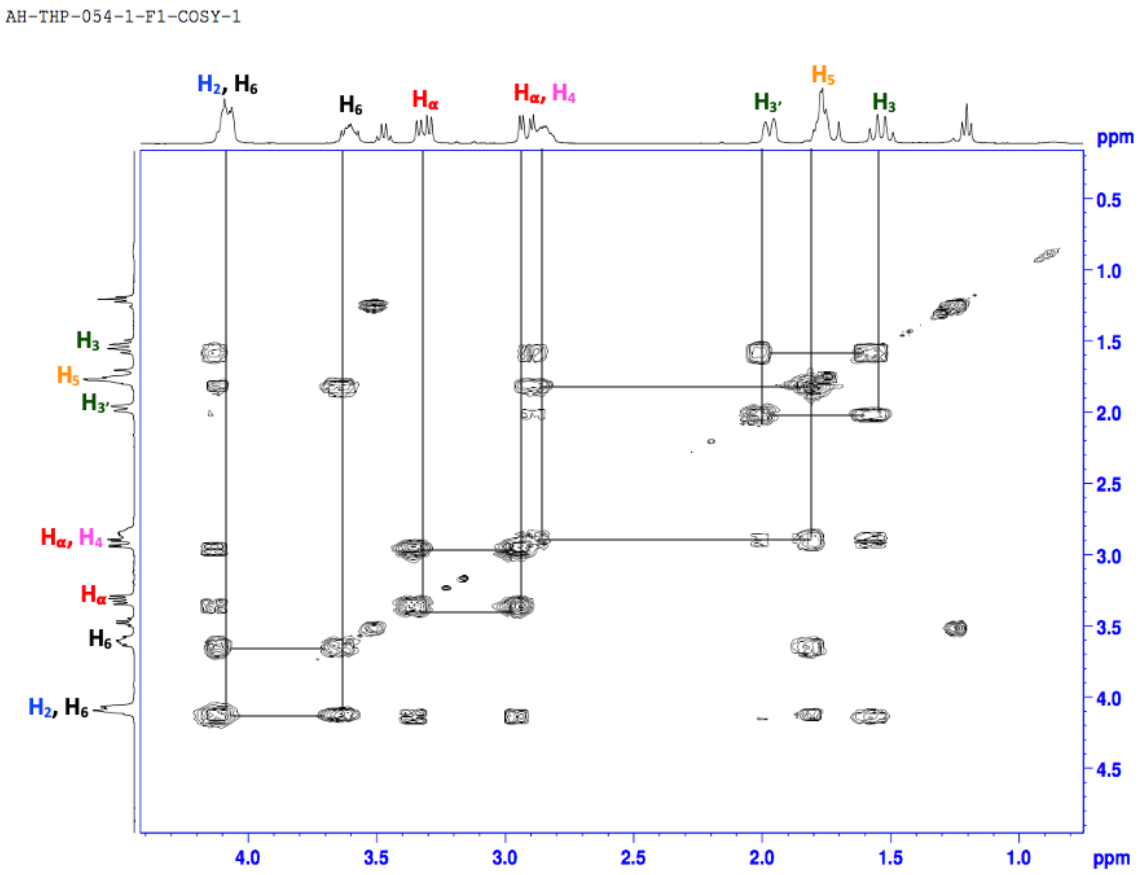


Figure 15. COSY Spectrum of 2,5 disubstituted THP

We can also thus conclude that tetrahydropyran **1.3.4** assumes a chair conformation and that the substituents are *cis* to each other from the calculated coupling constants. The relative stereochemistry of this is similarly confirmed by x-ray crystallography (Figure **16**)

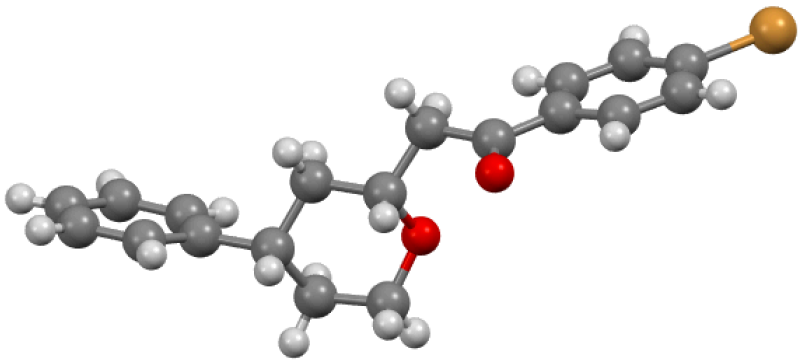


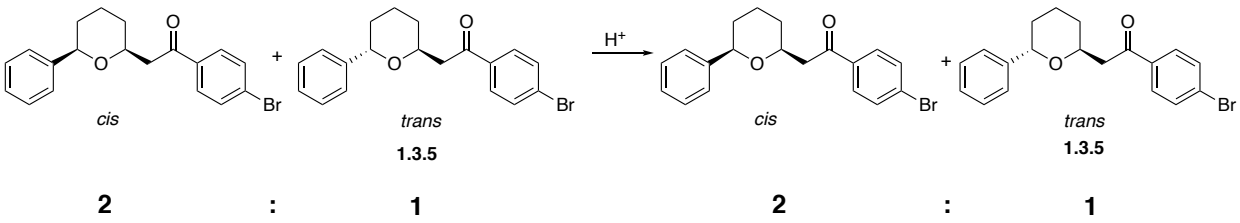
Figure 16. X-ray structure of 2,4-disubstituted THP[c]

c: CCDC 1895903

1.4 Thermodynamic VS Kinetic Control

Even though the diequatorial substituted products are more stable, it does not mean that they are formed for this reason. Kinetic studies have been conducted on the less stable isomer – 2,6-*cis*-disbustituted THP ring (**1.3.5**).

To test this, a 2:1 mixture of the *cis* and *trans* isomer prepared by base catalysed cyclisation was subjected to the same acidic conditions done in this study. It was found that the *cis*:*trans* ratio remained unchanged, signifying that there was no equilibration and that the reaction is kinetically controlled (Scheme **20**).



Scheme **20**. Thermodynamic VS Kinetic Control Experiment

A NOESY experiment was conducted for each isomer, and their relative stereochemistry was confirmed with the spectra below in Figure **17** and Figure **18**.

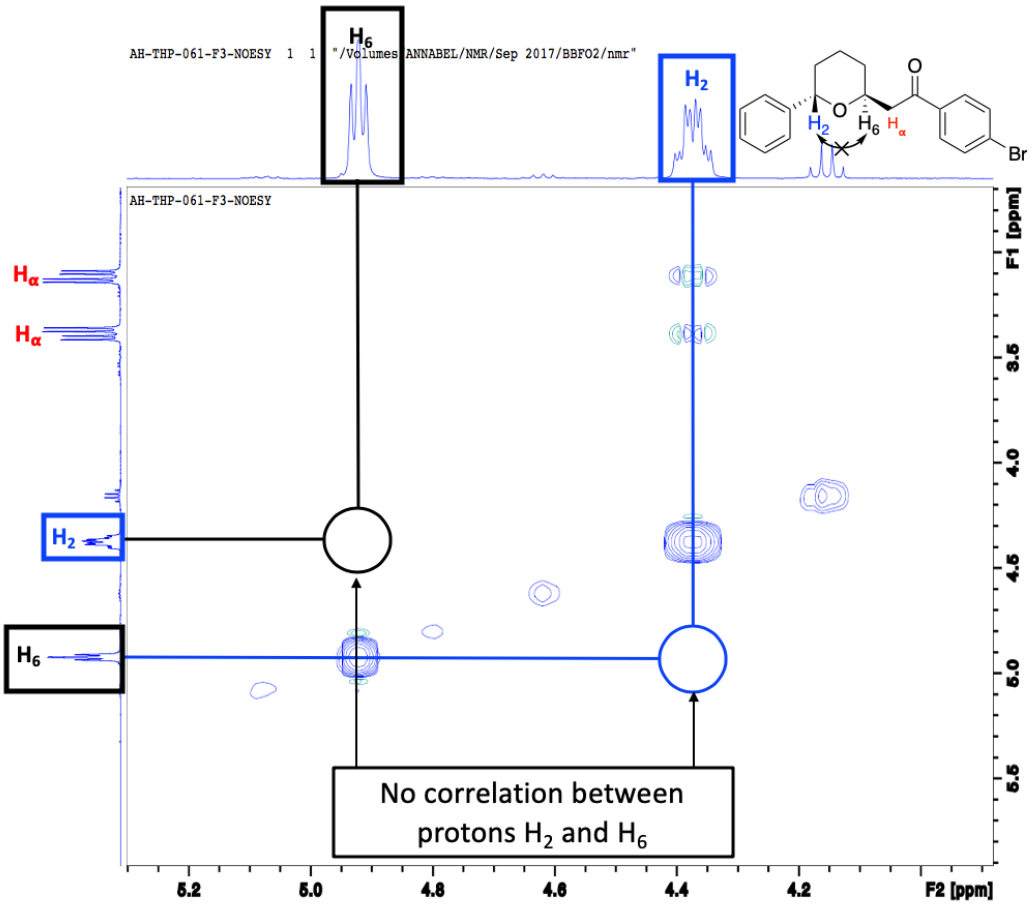


Figure 17. NOESY Spectrum of *trans*-isomer

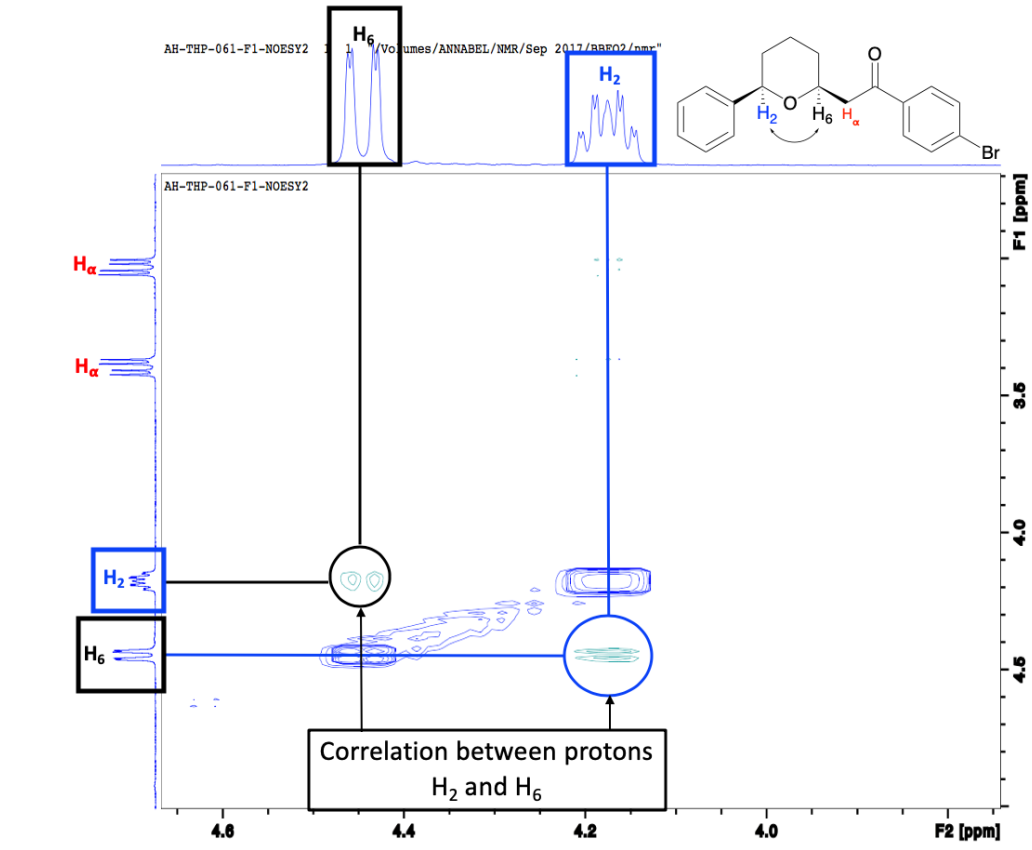


Figure 18. NOESY Spectrum of *cis*-isomer

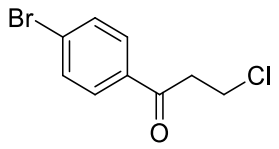
1.5 Conclusion

The key reactions carried out in this project involved cross-metathesis or Ozonolysis-Wittig of alkene substrates followed by a facile oxa-Michael cyclisation to give the di-substituted *bis-equatorial* tetrahydropyran products in good yields. The postulate that these tetrahydropyrans adopt chair-like conformations during transition states is proven true. These tetrahydropyrans adopt chair-like conformations that give stereochemical outcomes where the substituents are *bis-equatorial*. NMR analyses and X-ray crystallography were used to determine the stereochemical outcomes of the tetrahydropyran products. Computationally, it is found that the acid catalysed reaction has a late transition state and the kinetic favouring of the diequatorial isomer has a steric explanation. Further studies have led to the understanding that the cyclisation of the THP rings is kinetically controlled.

1.6 Experimental

All reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware (120 °C), which was cooled under vacuum. Needles and syringes were similarly dried under vacuum before use. Anhydrous tetrahydrofuran was distilled from benzophenone and sodium metal under nitrogen. Anhydrous toluene was distilled over sodium under a nitrogen atmosphere. Anhydrous dichloromethane was dried by distillation from CaH_2 immediately prior to use under nitrogen. Anhydrous methanol was distilled from activated magnesium under nitrogen. All other solvents and reagents were used as received. Flash chromatography was carried out on silica gel, 230-400 mesh.

^{1}H NMR spectra were recorded in deuterated solvent $CDCl_3$, at 300, 400, 500 MHZ, using Bruker AV300, AV400, AV500, BBFO1 400, BBFO2 400, JEOL ECA 400 and ECA 400SL spectrometers. ^{13}C NMR spectra were recorded at the corresponding frequency on the same instruments at 75, 100 or 125 MHz. Chemical shifts are recorded in parts per million and coupling constants are recorded in Hertz. Multiplicity of NMR signals are abbreviated using the following shorthand: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet).

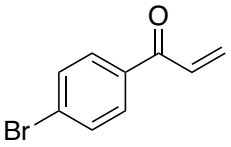


Synthesis of 1-(4-bromophenyl)-3-chloropropan-1-one (1.1.0a)[33]

Bromobenzene (20 mmol, 3.14 g) and $AlCl_3$ (46 mmol, 6.13 g) in anhydrous CH_2Cl_2 were placed in a two-necked flask fitted with a magnetic stirrer. While the mixture was stirring at 40 °C, 3-chloropropanoyl chloride in anhydrous CH_2Cl_2 was added dropwise. After stirring for 2 hours, the reaction was quenched with 5 mL of 2M HCl and extracted with ether. The ethereal extract was washed with water, sodium carbonate solution, with water again and subsequently dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford 1-(4-bromophenyl)-3-chloropropan-1-one (**1.1.0a**, 359 mg, 60 %) as a yellow oil.

Yield: 60 % ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82 (dt, J = 10.5, 2.1 Hz, 2H), 7.63 (dt, J = 10.5, 2.1 Hz, 2H), 3.91 (t, J = 6.9 Hz, 2H), 3.42 (t, J = 6.6 Hz, 2H).

All data is consistent with that reported in literature.

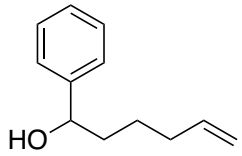


Synthesis of 1-(4-bromophenyl)prop-2-en-1-one (1.1.0)[36]

Triethylamine (12.1 mmol, 1.22 g) was added to a solution of 1-(4-bromophenyl)-3-chloropropan-1-one (**1.1.0a**, 6.05 mmol, 1.50 g) and stirred for 16 hours. On completion, the reaction was quenched by NH_4Cl solution and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with NH_4Cl solution, brine solution, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/Hexane 3:97) to afford 1-(4-bromophenyl)prop-2-en-1one (**1.1.0**, 0.504 g, 83%) as a yellow crystalline solid.

Yield: 83 % ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 (dt, J = 8.7, 2.4 Hz, 2H), 7.63 (dt, J = 8.7, 2.1 Hz, 2H), 7.11 (dd, J = 17.1, 10.8 Hz, 1H), 6.44 (dd, J = 17.1, 1.5 Hz, 1H), 5.96 (dd, J = 10.5, 1.5 Hz, 1H) ; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 189.9, 136.0, 131.9, 130.7, 130.2, 128.2, 125.9.

All data is consistent with that reported in literature.

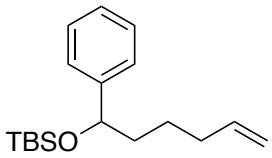


Synthesis of 1-phenylhex-5-en-1-ol (1.1.5)[37]

A crystal of iodine was added to magnesium (8.44 mmol, 205 mg) in anhydrous ether and heated at reflux until the brown colour in the reaction discolours. A solution of 1-bromopentene (4.22 mmol, 629 mg) in anhydrous ether was added dropwise and a gentle reflux was maintained. On completion, benzalydehyde (4.64 mmol, 493 mg) was added to the stirring mixture and allowed to stir at room temperature for 1 hour. The reaction mixture was diluted with water (30 mL) and the aqueous layer was extracted with ether. The combined organic layers were washed with brine solution, dried over anhydrous magnesium sulfate filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford 1-phenylhex-5-en-1-ol (**1.1.5**, 672 mg) as a yellow oil.

Yield: 83 % ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.31-7.25 (m, 5H), 5.80 (ddt, *J* = 13.8, 9.9, 3.3 Hz, 1H), 4.95 (m, 2H), 4.68 (dt, *J* = 7.32, 1.84 Hz, 1H), 2.11-2.04 (m, 2H), 1.83-1.70 (m, 3H), 1.57-1.51 (m, 1H), 1.41-1.39 (m, 1H) ; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.8, 138.6, 128.5, 127.5, 125.9, 114.7, 74.5, 38.5, 33.6, 25.1.

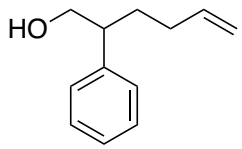
All data is consistent with that reported in literature.



Synthesis of *tert*-butyldimethyl((4-phenylhex-5-en-1-yl)oxy)silane (1.1.5')

To a solution of 1-phenylhex-5-en-1-ol (**1.1.5**, 200 mg, 1.14 mmol) in 1 mL of DCM was added triethyamine (633 µL, 4.54 mmol) and DMAP (2.77 mg, 0.023 mmol). TBSCl (513 mg, 3.40 mmol) in 0.5 mL of DCM was added dropwise at 0 °C. The solution was then stirred overnight. On completion, the reaction was quenched with water. The organic layer was separated and further washed with 10 mL of HCL 2M and brine. The organic layer was then dried with magnesium sulfate and concentrated under vacuo. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford *tert*-butyldimethyl((4-phenylhex-5-en-1-yl)oxy)silane (**1.1.5'**, 208 mg) as a colourless oil.

Yield = 63 % ; **IR** (neat) cm^{-1}: 1605, 1641, 1256, 1213, 993, 910 ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31-7.26 (m, 5H), 5.82-5.74 (m, 1H), 4.99-4.91 (m, 2H), 4.65-4.63 (m, 1H), 2.06-2.02 (m, 2H), 1.69-1.53 (m, 2H), 1.46-1.36 (m, 2H), 0.85 (s, 9H), -0.01 (s, 6H) ; **^{13}C NMR** (125 MHz, CDCl3) δ 145.8, 138.9, 128.0, 126.8, 125.9, 114.4, 75.0, 40.4, 33.7, 25.9, 25.7, 25.7, 24.5, 18.2, 18.1, -2.94, -3.02 ; **MS (ESI)**: [M + H]+ m/z 291; **HRMS**: [M + H]+ calcd. for $C_{18}H_{30}OSi$: 291.2144; found: 291.2101.

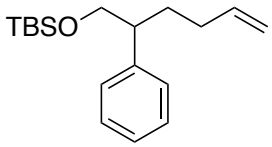


Synthesis of 2-phenylhex-5-en-1-ol (1.1.6)[31]

A crystal of iodine was added to magnesium (8.44 mmol, 205 mg) and anhydrous ether. The mixture was heated at reflux until the iodine colour has disappeared. A solution of 1-bromobutene (4.22 mmol, 629 mg) in anhydrous ether was added dropwise and a gentle reflux was maintained. On completion, styrene oxide was dissolved in anhydrous diethyl ether and 3-Butenylmagnesium bromide was added dropwise. The reaction mixture was stirred at room temperature for 1 h, then quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/Hexane 8:92) to afford 2-phenylhex-5-en-1-ol (**1.1.6**, 963 mg) as a colourless oil.

Yield: 32 % ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.19 (m, 5H), 5.75 (ddt, J = 13.8, 9.9, 3.3 Hz, 1H), 4.99-4.92 (m, 2H), 3.79-3.68 (m, 2H), 2.83-2.76 (m, 1H), 2.00-1.92 (m, 2H), 1.81-1.66 (m, 2H), 1.35 (s, 1H); **DEPT 135 ^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.4, 128.7, 128.3, 128.1, 126.8, 114.8, 60.4, 48.0, 31.4, 31.2.

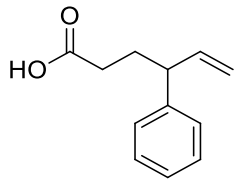
All data is consistent with that reported in literature.



Synthesis of *tert*-butyldimethyl((2-phenylhex-5-en-1-yl)oxy)silane (1.1.6')

To a solution of 2-phenylhex-5-en-1-ol (**1.1.6**, 200 mg, 1.14 mmol) in 1 mL of DCM was added triethylamine (633 μL, 4.54 mmol) and DMAP (2.78 mg, 0.226 mmol). TBSCl (513 mg, 3.40 mmol) in 1 mL of DCM was added dropwise at 0 °C. The solution was then stirred overnight. On completion, the reaction was quenched with water. The organic layer was separated and further washed with 10 mL of HCL 2M and brine. The organic layer was then dried with magnesium sulfate and concentrated under vacuo. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford *tert*-butyldimethyl((2-phenylhex-5-en-1-yl)oxy)silane (**1.1.6'**, 105 mg) as a colourless oil.

Yield = 63 % ; **IR** (neat) cm^{-1}: 1605, 1641, 1495, 1256, 1213, 966, 910 ; **^{1}H NMR** (500 MHz, CDCl3) δ 7.29-7.25 (m, 5H), 5.90-5.82 (m, 1H), 5.04-4.99 (m, 2H), 3.79-3.74 (m, 2H), 2.85-2.80 (m, 1H), 2.06-2.00 (m, 3H), 1.75-1.73 (m, 1H), 0.94 (s, 9H), -0.01 (s, 6H) ; **^{13}C NMR** (125 MHz, CDCl3) δ 143.1, 138.8, 129.1, 128.2, 128.2, 126.3, 125.3, 114.4, 68.1, 48.0, 31.6, 31.0, 25.9, 25.7, 25.7, 18.3, 18.2, -2.91, -2.99, -5.5 ; **MS (ESI)**: [M + H]+ m/z 291 ; **HRMS**: [M + H]+ calcd. for $C_{18}H_{30}OSi$: 291.2144; found: 291.2139.

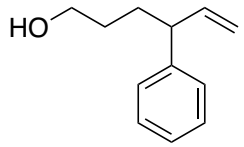


Synthesis of 4-phenylhex-5-enoic acid (1.1.7a)[38]

Aqueous H_2O_2 (5.74 mmol, 195 mg) was added dropwise to a stirred solution of phenylcyclohexanone (2.87 mmol, 500 mg) in MeOH at 25 °C and left to stir for 3 h. The mixture was then added dropwise to a mixture of $FeSO_4.6H_2O$ (5.74 mmol, 1.60 g) and $CuSO_4{\cdot}5H_2O$ (2.74 mmol, 1.43 g) in water (40 mL) then left to stir overnight. On completion, the mixture was extracted with ether (3 x 20 mL). The combined organic extracts were washed with aqueous sodium hydroxide (20%, 2 x 10 mL). The alkaline extract was then brought to pH 2 with aqueous sulfuric acid (20%, 25 mL) and the solution was extracted with ether (3 x 20 mL). The combined organic extracts were washed with water, brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The product was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.18 (m, 5H), 5.94 (ddt, J =13.8, 9.9, 3.3 Hz, 1H), 5.10 (m, 1H), 5.06-5.05 (m, 1H), 2.36-2.31 (m, 1H), 2.30-2.00 (m, 2H), 1.83-1.70 (m, 2H).

All data is consistent with that reported in literature.

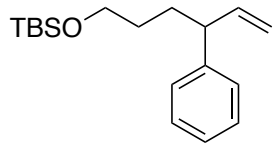


Synthesis of 4-phenylhex-5-en-1-ol (1.1.7)[39]

$LiAlH_4$ (5.74 mmol, 218 mg) was suspended in diethyl ether. A solution of 4-phenylhex-5-enoic acid (**1.1.7a**, 2.87 mmol, 546 mg) in diethyl ether was subsequently added dropwise to the mixture at 0 °C. The reaction mixture was then warmed to room temperature and stirred overnight under nitrogen. The reaction mixture was carefully quenched with water, and the resulting white solution was filtered through Celite, washed with CH_2Cl_2 (3 x 10 mL) and concentrated under reduced pressure to give 4-phenylhex-5-en-1-ol as a brown oil. The crude product was purified by column chromatography (silica gel, eluent EtOAc/Hexane 20:80) to afford 4-phenylhex-5-en-1-ol (**1.1.7**, 475 mg) as a colourless oil.

Yield = 94 % ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32-7.17 (m, 5H), 5.96 (ddt, *J* = 13.8, 9.9, 3.3 Hz, 1H), 5.06 (dt, *J* = 6.0, 1.2 Hz, 1H), 5.01 (d, *J* = 1.2 Hz, 1H), 3.63 (t, *J* = 6.6 Hz, 2H), 3.26 (q, *J* = 7.5 Hz, 1H), 1.82-1.76 (m, 2H), 1.61-1.47 (m, 3H) ; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.2, 142.1, 128.5, 127.6, 126.3, 114.2, 62.9, 49.7, 31.5, 30.8.

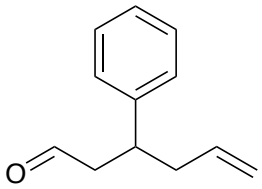
All data is consistent with that reported in literature.



Synthesis of *tert*-butyldimethyl((4-phenylhex-5-en-1-yl)oxy)silane (1.1.7')

To a solution of 4-phenylhex-5-en-1-ol (**1.1.7**, 100 mg, 0.567 mmol) in 1 mL of DCM was added imidazole (155 mg, 2.27 mmol) and DMAP (1.39 mg, 0.113 mmol). TBSCl (257 mg, 1.702 mmol) in 0.5 mL of DCM was added dropwise at 0 °C. The solution was then stirred overnight. On completion, the reaction was quenched with water. The organic layer was separated and further washed with 10 mL of HCL 2M and brine. The organic layer was then dried with magnesium sulfate and concentrated under vacuo. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford *tert*-butyldimethyl((4-phenylhex-5-en-1-yl)oxy)silane (**1.1.7'**, 138 mg, 0.474 mmol) as a colourless oil.

Yield = 83 % ; **IR** (neat) cm^{-1}: 1635, 1601, 1493, 1254, 1186, 972, 912 ; **^{1}H NMR** (400 MHz, CDCl3) δ 7.15-7.28 (m, 5H), 5.88-5.95 (m, 1H), 4.92-5.02 (m, 2H), 3.55-3.58 (m, 2H), 3.22 (app. q, J = 7 Hz, 1H), 1.70-1.77 (m, 2H), 1.38-1.53 (m, 2H), 1.23 (s, 9H), 0.01 (s, 6H) ; **^{13}C NMR** (100 MHz, CDCl3) δ 144.4, 142.4, 128.5, 128.3, 127.6, 126.8, 126.2, 114.0, 63.1, 49.6, 31.6, 30.8, 26.0, 18.4, -5.3 ; **MS (ESI)**: [M + H]+ m/z 291 ; **HRMS**: [M + H]+ calcd. for $C_{18}H_{30}OSi$: 291.2144; found: 291.2158.

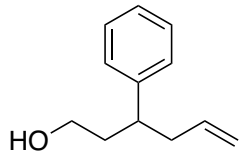


Synthesis of 3-phenylhex-5-enal (1.1.8a)[40]

Anhydrous THF (25 ml) was transferred under inert atmosphere to potassium hydride in oil suspension (95.9 mg, 1.43 mmol, 60%) in a dry round-bottomed flask. 18-crown-6 (227.5 mg, 0.861 mmol) in anhydrous THF (5 ml) was added and the solution was stirred for 15 minutes. (*E*)-(3-(allyloxy)prop-1-en-1-yl)benzene (100 mg, 0.574 mmol) was added in one portion in small volume of anhydrous THF. The mixture was stirred for 1.5 h before the dark brown solution was poured onto a mixture of ice and phosphate buffer (pH 7.0) in a separating funnel. The layers were separated and the aqueous layer was extracted with Et_2O (3x). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, eluent EtOAc/Hexane 10:90) to yield a yellow oil (**1.1.8a**, 75.4 mg).

Yield = 75 % ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.68 (t, J = 5 Hz, 1H), 7.32-7.18 (m, 5H), 5.65 (ddt, J = 13.5, 7, 3.5 Hz, 1H), 4.92-5.00 (m, 2H), 3.57-3.44 (m, 1H), 2.77-2.74 (m, 2H), 2.43-2.37 (m, 2H).

All data is consistent with that reported in literature.

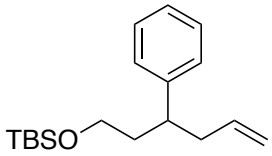


Synthesis of 3-phenylhex-5-en-1-ol (1.1.8)[41]

$LiAlH_4$ (32.8 mg, 0.866 mmol) was suspended in diethyl ether. A solution of 3-phenylhex-5-enal (**1.1.8a**, 75.4 mg, 0.433 mmol) in diethyl ether was subsequently added dropwise to the mixture at 0℃. The reaction mixture was then warmed to room temperature and stirred overnight under nitrogen. The reaction mixture was carefully quenched with water, and the resulting white solution was filtered through celite, washed with DCM (3 x 10 mL) and concentrated under reduced pressure to give 4-phenylhex-5-en-1-ol as a brown oil. The crude product was purified by column chromatography (silica gel, eluent EtOAc/Hexane 15:85) to afford 3-phenylhex-5-en-1-ol (**1.1.8**, 74.1 mg) as a yellow oil.

Yield = 97 % ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.17-7.31 (m, 5H), 5.65 (ddt, *J* = 13.5, 7, 3.5 Hz, 1H), 4.92-5.00 (m, 2H), 3.44-3.57 (m, 2H), 2.77-2.83 (m, 1H), 2.38 (t, *J* = 7 Hz, 2H), 1.96-2.03 (m, 1H), 1.21 (br. s, 1H) ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 144.5, 136.7, 128.5, 127.6, 126.3, 116.2, 61.1, 42.3, 41.4, 38.6.

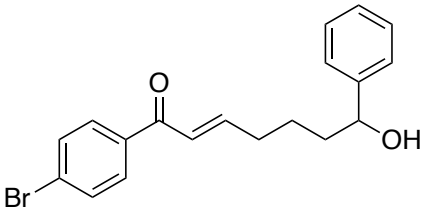
All data is consistent with that reported in literature.



Synthesis of *tert*-butyldimethyl((3-phenylhex-5-en-1-yl)oxy)silane (1.1.8')

To a solution of 3-phenylhex-5-en-1-ol (**1.1.8**, 78.3 mg, 0.444 mmol) in 1 mL of DCM was added imidazole (121 mg, 1.78 mmol) and DMAP (1.1 mg, 0.0089 mmol). TBSCl (201 mg, 1.33 mmol) in 0.5 mL of DCM was added dropwise at 0 °C. The solution was then stirred overnight. On completion, the reaction was quenched with water. The organic layer was separated and further washed with 10 mL of HCL 2M and brine. The organic layer was then dried with magnesium sulfate and concentrated under vacuo. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford *tert*-butyldimethyl((3-phenylhex-5-en-1-yl)oxy)silane (**1.1.8'**, 123 mg) as a colourless oil.

Yield = 96 % ; **IR** (neat) cm^{-1}: 1639, 1603, 1493, 1257, 1217, 995, 912 ; **^{1}H NMR** (500 MHz, CDCl3) δ 7.17-7.32 (m, 5H), 5.65-5.70 (m, 1H), 4.94-5.01 (m, 2H), 3.41-3.55 (m, 2H), 2.84-2.86 (m, 1H), 1.93-2.00 (m, 1H), 1.81 (s, 1H), 0.91 (s, 10H), 0.01 (s, 6H) ; **^{13}C NMR** (100 MHz, CDCl3) δ 144.8, 137.0, 128.2, 127.8, 126.1, 115.9, 61.0, 42.0, 21.2, 38.8, 26.0, 25.7, 18.3, -2.93 ; **MS (ESI)**: [M + H]+ m/z 291 ; **HRMS**: [M + H]+ calcd. for $C_{18}H_{30}OSi$: 291.2144; found: 291.2117.

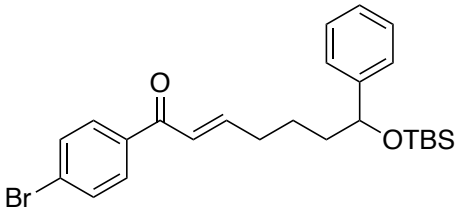


Synthesis of (E)-1-(4-bromophenyl)-7-hydroxy-7-phenylhept-2-en-1-one (1.2.1)

1-phenylhex-5-en-1-ol (**1.1.5**, 0.567 mmol, 100 mg) and 1-(4-bromophenyl)prop-2-en-1-one (**1.1.0**, 1.70 mmol , 359 mg) was dissolved in anhydrous CH_2Cl_2 under nitrogen. Grubbs II catalyst (0.0284 mmol, 24.1 mg) was dissolved in 5 mL of anhydrous CH_2Cl_2 and was added in 0.5 h intervals in portions of 1 mL. The reaction was heated at reflux for 2 h. On completion, the mixture was filtered through Celite and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 20:80) to afford (E)-1-(4-bromophenyl)-7-hydroxy-7-phenylhept-2-en-1-one (**1.2.1**, 154 mg) as a brown oil.

Yield: 76 % ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 (dd, J = 6.6, 2.1 Hz, 2H), 7.59 (dd, J = 6.6, 2.1 Hz, 2H), 7.58-7.07 (m, 5H), 7.07-6.99 (m, 1H), 6.80 (dt, J = 15.6, 1.2 Hz, 1H), 4.73-4.69 (m, 1H), 2.36-2.26 (m, 2H), 1.87-1.24 (m, 5H).

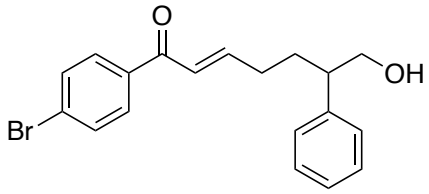
(Only 1H NMR was collected for this)



Synthesis of (*E*)-1-(4-bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-7-phenylhept-2-en-1-one (1.2.1')

To a solution of 5-((*tert*-butyldimethylsilyl)oxy)-5-phenylpentanal (**1.1.5'**, 142.5 mg, 0.487 mmol) in 5 mL DCM was added 1-(4-bromophenyl)-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (**1.1.11**, 268.5 mg, 0.585 mmol). The reaction was fitted with a nitrogen balloon and left to reflux overnight. On completion, the reaction was concentrated under reduced pressure until a bit of DCM is left. It was subsequently filtered with hexane where the ylid will be separated. The filtrate was collected, concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford (*E*)-1-(4-bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-7-phenylhept-2-en-1-one (**6'**, 59.8 mg) as a yellow oil.

Yield = 26 % ; **IR** (neat) cm^{-1}: 1668, 1585, 1566, 1543, 1396, 1360, 1248, 1180, 606; **^{1}H NMR** (500 MHz, CDCl3) δ 7.78-7.83 (m, 2H), 7.61-7.65 (m, 2H), 7.24-7.36 (m, 5H), 7.03-7.10 (m, 1H), 6.81 (d, *J* = 15 Hz, 1H), 4.68-4.71 (m, 1H), 2.32-2.27 (m, 2H), 1.52-1.81 (m, 4H), 0.88 (s, 9H), -0.04 (m, 6H), ; ^{13}C NMR (100 MHz, CDCl3) δ 189.7, 150.34, 145.4, 136.7, 131.8, 130.1, 128.1, 127.7, 127.0, 125.8, 125.5, 74.8, 40.4, 32.8, 25.9, 24.1, 18.2, -4.6, -5.0 ; **MS (ESI)**: m/z 475; **HRMS**: [M + H]+ calcd. for $C_{25}H_{33}BrO_2Si$: 475.1491; found: 475.1499.

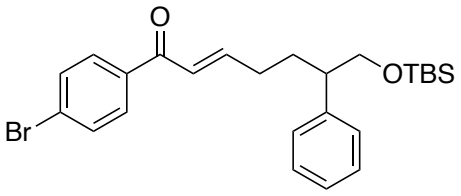


Synthesis of (E)-1-(4-bromophenyl)-7-hydroxy-6-phenylhept-2-en-1-one (1.2.2)

2-phenylhex-5-en-1-ol (**1.1.6**, 0.567 mmol, 100 mg) and 1-(4-bromophenyl)prop-2-en-1-one (**1.1.0**, 1.70 mmol, 359 mg) was dissolved in 5 mL of anhydrous toluene under nitrogen. Grubbs II catalyst (0.0284 mmol, 24.1 mg) was dissolved in 5 mL of anhydrous toluene and was added in 0.5 h intervals in portions of 1 mL. The reaction was heated at 70 °C for 2 h. On completion, the mixture was filtered through Celite and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 20:80) to (E)-1-(4-bromophenyl)-7-hydroxy-6-phenylhept-2-en-1-one (**1.2.2**, 36.6 mg) as a brown oil.

Yield: 18 % ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.7, 2.1 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.37-7.20 (m, 5H), 7.18-6.98 (m, 1H), 6.74 (d, *J* = 15.3 Hz, 1H), 3.78-3.77 (m, 2H), 2.85-2.82 (m, 1H), 2.25-2.21 (m, 2H), 1.99-1.82 (m, 2H), 1.56 (s, 1H).

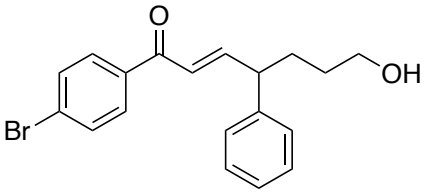
(Only 1H NMR was collected for this)



Synthesis of (*E*)-1-(4-bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-6-phenylhept-2-en-1-one (1.2.2')

To a solution of 5-((*tert*-butyldimethylsilyl)oxy)-4-phenylpentanal (**1.1.6'**, 165.3 mg, 0.524 mmol) in 5 mL DCM was added 1-(4-bromophenyl)-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (**1.1.11**, 311.5 mg, 0.629 mmol). The reaction was fitted with a nitrogen balloon and left to reflux overnight. On completion, the reaction was concentrated under reduced pressure until a bit of DCM is left. It was subsequently filtered with hexane where the ylid will be separated. The filtrate was collected, concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford (*E*)-1-(4-bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-6-phenylhept-2-en-1-one (**1.2.2'**, 153.3 mg) as a yellow oil.

Yield = 57 % ; **IR** (neat) cm^{-1}: 1670, 1585, 1566, 1543, 1396, 1360, 1253, 1220, 606 ; **^{1}H NMR** (400 MHz, CDCl3) δ 7.76-7.74 (m, 2H), 7.61-7.58 (m, 2H), 7.33-7.16 (m, 5H), 7.05-7.01 (m, 1H), 6.74 (d, J = 16 Hz, 1H), 3.75-3.65 (m, 2H), 2.82-2.73 (m, 2H), 2.25-2.19 (m, 2H), 1.85-1.75 (m, 1H), 0.88 (s, 9H), -0.01 (s, 6H) ; **^{13}C NMR** (100 MHz, CDCl3) δ 189.7, 150.4, 142.2, 136.7, 131.8, 130.1, 129.6, 128.4, 128.1, 127.7, 126,6, 125.5, 68.0, 48.2, 30.8, 30.2, 25.9, 18.2, -4.7 ; **MS (ESI)**: m/z 474; **HRMS**: [M + H]+ calcd. for $C_{25}H_{33}BrO_2Si$: 473.1511; found: 473.1524.

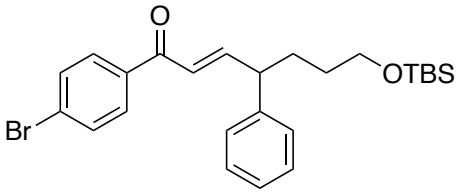


Synthesis of (*E*)-1-(4-bromophenyl)-7-hydroxy-4-phenylhept-2-en-1-one (1.2.3)

4-phenylhex-5-en-1-ol (**1.1.7**, 0.284 mmol, 50 mg) and 1-(4-bromophenyl)prop-2-en-1-one (**1.1.0**, 0.851 mmol, 180 mg) was dissolved in 5 mL of anhydrous CH_2Cl_2 under nitrogen. Grubbs II catalyst (0.0142 mmol, 12.0 mg) was dissolved in 5 mL of anhydrous CH_2Cl_2 and was added in 0.5 h intervals in portions of 1 mL. The reaction was refluxed for 2 h. On completion, the mixture was filtered through Celite and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 20:80) to (*E*)-1-(4-bromophenyl)-7-hydroxy-4-phenylhept-2-en-1-one (**1.2.3**, 18 mg) as a brown oil.

Yield: 18 % ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.60 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.36-7.17 (m, 6H), 6.82 (dd, *J* = 15.3, 1.2 Hz, 1H), 3.70-3.65 (m, 2H), 3.56 (q, *J* = 7.7 Hz, 1H), 2.06 (s, 1H), 1.99-1.94 (m, 2H), 1.31-1.26 (m, 2H).

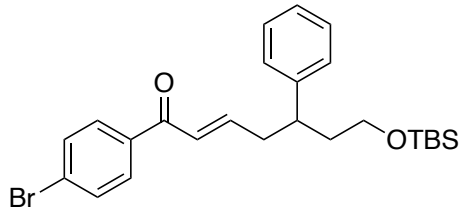
(Only 1H NMR was collected for this)



Synthesis of (*E*)-1-(4-bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-4-phenylhept-2-en-1-one (1.2.3')

To a solution of 5-((*tert*-butyldimethylsilyl)oxy)-2-phenylpentanal (**1.1.7'**, 183.8 mg, 0.628 mmol), prepared using the method written on page 45, in 5 mL CH_2Cl_2 was added 1-(4-bromophenyl)-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (**1.1.11**, 349.2 mg, 0.754 mmol). The reaction was fitted with a nitrogen balloon and left to reflux overnight. On completion, the reaction was concentrated under reduced pressure until a bit of DCM is left. It was subsequently filtered with hexane where the ylid will be separated. The filtrate was collected, concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford (*E*)-1-(4-bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-4-phenylhept-2-en-1-one (**1.2.3'**, 104.5 mg) as a yellow oil.

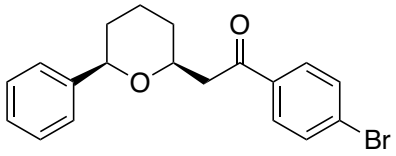
Yield = 35 % ; **IR** (neat) cm^{-1}: 1670, 1585, 1566, 1543, 1396, 1360, 1256, 1220, **661 ; ^{1}H NMR** (500 MHz, CDCl3) δ 7.74 (dd, J = 9, 1.5 Hz, 2H), 7.59 (dd, *J* = 7, 2 Hz, 2H), 7.26-7.15 (m, 6H), 6.78 (dd, *J* = 15.5, 1 Hz, 1H), 3.71 (t, *J* = 6 Hz, 1H), 3.61 (t, *J* = 6.5 Hz, 2H), 3.52 (q, *J* = 7.5 Hz, 1H), 3.07 (t, *J* = 7.5 Hz, 1H) 1.86-1.99 (m, 2H), 0.86 (s, 9H), -0.05 (s, 6H) ; **^{13}C NMR** (100 MHz, CDCl3) δ 200.8, 136.4, 131.8, 130.1, 129.1, 128.8, 128.5, 127.8, 127.6, 126.6, 62.7, 58.9, 31.5, 30.7, 30.2, 26.1, 26.0, 18.3, -4.7 **MS (ESI)**: m/z 474; **HRMS**: [M + H]+ calcd. for $C_{25}H_{33}BrO_2Si$: 473.1511; found: 473.1524.



Synthesis of (*E*)-1-(4-bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-5-phenylhept-2-en-1-one (1.2.4')

To a solution of 5-((*tert*-butyldimethylsilyl)oxy)-3-phenylpentanal (**1.1.8'**, 103.2 mg, 0.353 mmol) in 5 mL DCM was added 1-(4-bromophenyl)-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (**1.1.11**, 194.5 mg, 0.424 mmol). The reaction was fitted with a nitrogen balloon and left to reflux overnight. On completion, the reaction was concentrated under reduced pressure until a bit of DCM is left. It was subsequently filtered with hexane where the ylid will be separated. The filtrate was collected, concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford (*E*)-1-(4-bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-5-phenylhept-2-en-1-one (**1.2.4'**, 60.9 mg) as a yellow oil.

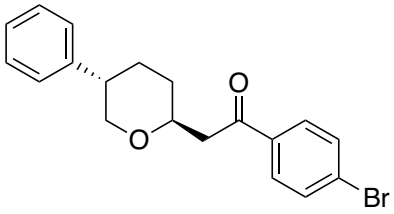
Yield = 37 % ; **IR** (neat) cm^{-1}: 1670, 1585, 1566, 1543, 1396, 1360, 1258, 1223, 663 ; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.69-7.60 (m, 4H), 7.41-7.24 (m, 5H), 6.75-6.99 (m, 1H), 6.72 (m, 1H), 3.66-3.46 (m, 2H), 3.10-3.04, (m, 1H), 2.80-2.60 (m, 2H), 2,12-1.85 (2H), 0.97 (s, 9H), 0.08 (s, 6H) ; **^{13}C NMR** (100 MHz, CDCl3) δ 202.0, 143.4, 128.6, 128.6, 127.7, 127.6, 126.7, 126.6, 102.6, 93.9, 60.6, 60.4, 39.7, 39.3, 38.6, 38.0, 25.9, 18.3, 1.03, -4.7 ; **MS (ESI)**: m/z 474; **HRMS**: [M + H]+ calcd. for $C_{25}H_{33}BrO_2Si$: 473.1511; found: 473.1508.



Synthesis of 1-(4-bromophenyl)-2-((*cis*)-6-phenyltetrahydro-2H-pyran-2-yl)ethanone (1.3.1)

(*E*)-1-(4-bromophenyl)-7-hydroxy-7-phenylhept-2-en-1-one (**1.2.1**, 0.429 mmol, 154.3 mg) was dissolved in methanol, stirred with Amberlyst 15 overnight and checked with TLC. On completion, the reaction mixture was filtered through Celite, washed with CH_2Cl_2 and concentrated under reduced pressure to afford 1-(4-bromophenyl)-2-((*cis*)-6-phenyltetrahydro-2H-pyran-2-yl)ethanone (**1.3.1**, 129.9 mg) as a yellow oil.

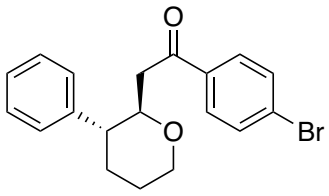
Yield: 84 % ; **IR** (Neat) cm^{-1}: 2932, 2854, 1682, 1582, 702; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86-7.83 (m, 2H), 7.60-7.56 (m, 2H), 7.31-7.19 (m, 5H), 4.41 (dd, *J* = 11.2, 2 Hz, 1H), 4.17-4.11 (m, 1H), 3.36 (dd, *J* = 16, 6.4 Hz,3.0 1H), 3.00 (dd, *J* = 15.6, 6 Hz, 1H), 1.98-1.93 (m, 1H), 1.88-1.69 (m, 3H), 1.34-1.55 (m, 2H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.7, 143.1, 136.3, 131.8, 130.0, 128.2, 127.2, 125.7, 79.8, 75.0, 45.5, 33.3, 31.4, 23.9 ; **MS (ESI)**: m/z 359; **HRMS**: [M + H]+ calcd. for $C_{19}H_{19}BrO_2$: 359.0647; found: 359.0641.



Synthesis of 1-(4-bromophenyl)-2-((*trans*)-5-phenyltetrahydro-2H-pyran-2-yl)ethanone (1.3.2)

(*E*)-1-(4-bromophenyl)-7-hydroxy-6-phenylhept-2-en-1-one (**1.2.2**, 0.324 mmol, 154 mg) was dissolved in methanol, stirred with Amberlyst 15 overnight and checked with TLC. On completion, the reaction mixture was filtered through Celite, washed with CH_2Cl_2 and concentrated under reduced pressure to afford 1-(4-bromophenyl)-2-((*trans*)-5-phenyltetrahydro-2H-pyran-2-yl)ethanone (**1.3.2**, 88.7 mg) as a yellow crystal.

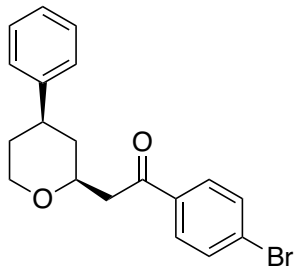
Yield = 77 % ; **IR** (neat) cm^{-1}: 1643, 586 ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.32-7.19 (m, 5H), 4.12 (app q, *J* = 7 Hz, 2H), 3.97-4.05 (m, 2H), 3.44-3.51 (m, 1H), 3.32 (dd, *J* = 16, 7 Hz, 1H), 2.95 (dd, J = 10.5, 5.5 Hz, 1H), 2.79-2.86 (m, 1H), 1.80-1.94 (m, 2H) ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.3, 142.1, 136.0, 132.0, 129.9, 128.6, 127.4, 126.7, 74.1, 73.9, 45.0, 42.6, 31.9, 24.7 ; **MS (ESI)**: $[M + H]^+$ m/z 360; **HRMS**: [M + H]+ calcd. for $C_{19}H_{19}BrO_2$: 359.0647; found: 359.0646 ; **M.P.**: 106.7 ℃



Synthesis of 1-(4-bromophenyl)-2-((*trans*)-3-phenyltetrahydro-2H-pyran-2-yl)ethanone (1.3.3)

(*E*)-1-(4-bromophenyl)-7-hydroxy-7-phenylhept-2-en-1-one (**1.2.3**, 0.0501 mmol, 18 mg) was dissolved in methanol, stirred with Amberlyst 15 overnight and checked with TLC. On completion, the reaction mixture was filtered through Celite, washed with CH_2Cl_2 and concentrated under reduced pressure to afford 1-(4-bromophenyl)-2-((*trans*)-3-phenyltetrahydro-2H-pyran-2-yl)ethanone (**1.3.3**, 18 mg) as a yellow crystal.

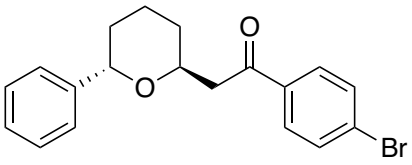
Yield = 100 % ; **IR** (neat) cm^{-1}: 1643, 586; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67-7.65 (m, 2H), 7.54-7.51 (m, 2H), 7.32-7.21 (m, 5H), 4.14 (dt, J = 10, 2 Hz, 1H), 3.99 (dt, *J* = 11.5, 2 Hz, 1H), 3.55 (dt, *J* = 11.5, 2 Hz, 1H), 3.03 (dd, *J* = 15.5, 10 Hz, 1H), 2.63 (dd, *J* = 15.5, 2 Hz, 1H), 2.03-1.99 (m, 1H), 1.85-1.73 (m, 2H), 1.71-1.67 (m, 1H), 1.34-1.24 (m, 1H) ; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.9, 142.8, 136.1, 131.7, 129.8, 128.8, 128.0, 127.8, 127.0, 78.7, 68.5, 48.7, 42.9, 32.4, 29.7, 26.3 ; **MS (ESI)**: m/z 359; **HRMS**: [M + H]+ calcd. for $C_{19}H_{19}BrO_2$: 359.0647; found: 359.0642 ; **M.P.**: 122.9 ℃.



Synthesis of 1-(4-bromophenyl)-2-((*cis*)-4-phenyltetrahydro-2*H*-pyran-2-yl)ethan-1-one (1.3.4)

(*E*)-1-(4-bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-5-phenylhept-2-en-1-one (**1.2.4'**, 153.3 mg, 0.429 mmol) was dissolved in methanol and stirred with Amberlyst® 15 for 60 h. On completion, the reaction mixture was filtered through Celite, washed with DCM and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/Hexane 10:90) to afford 1-(4-bromophenyl)-2-((*cis*)-4-phenyltetrahydro-2*H*-pyran-2-yl)ethan-1-one (**1.3.4**, 78.1 mg) as a yellow crystal.

Yield = 68 % ; **IR** (neat) cm^{-1}: 1676, 1603, 1502, 511; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.19-7.32 (m, 5H), 4.04-4.14 (m, 2H), 3.58-3.63 (m, 1H), 3.32 (dd, *J* = 16, 7 Hz, 1H), 2.82-2.94 (m, 2H), 1.97 (d, *J* = 13 Hz, 1H), 1.75-1.82 (m, 2H), 1.54 (q, *J* = 11.5 Hz, 1H) ; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.2, 145.4, 136.0, 131.9, 129.8, 128.6, 128.4, 126.8, 126.4, 74.3, 68.3, 45.1, 41.6, 39.5, 33.2 ; **MS (ESI)**: $[M + H]^+$ m/z 359; **HRMS**: [M + H]+ calcd. for $C_{19}H_{19}BrO_2$: 359.0647; found: 359.0641; **M.P.**: 84.7 ℃



Synthesis of 1-(4-bromophenyl)-2-((*trans*)-6-phenyltetrahydro-2*H*-pyran-2-yl)ethan-1-one (1.3.5)

(*E*)-1-(4-bromophenyl)-7-((*tert*-butyldimethylsilyl)oxy)-7-phenylhept-2-en-1-one (**1.2.1'**, 114.5 mg, 0.319 mmol) was dissolved in 1 mL of anhydrous THF. KOtBu in 1M THF (63.7 µL, 0.0637 mmol) was added dropwise in -78 °C and warmed to room temperature. On completion after 0.5 h, the reaction mixture was quenched with sat. NH_4Cl solution. The mixture was extracted using diethyl ether (3 x 20 mL) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/Hexane 10:90) to afford 1-(4-bromophenyl)-2-((*trans*)-6-phenyltetrahydro-2*H*-pyran-2-yl)ethan-1-one (**1**, 23.1 mg) as a yellow oil.

Yield = 21 % ; **IR** (neat) cm^{-1}: 2936, 2857, 1682, 1585, 698; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86-7.83 (m, 2H), 7.61-7.57 (m, 2H), 7.32-7.20 (m, 5H), 4.41 (dd, *J* = 11, 2.5Hz, 1H), 4.17-4.11 (m, 1H), 3.36 (dd, *J* = 16, 6 Hz, 1H), 2.99 (dd, *J* = 15.5, 6 Hz, 1H), 1.99-1.94 (m, 1H), 1.88-1.70 (m, 2H), 1.51-1.18 (m, 3H) ; **^{13}C NMR** (125 MHz, CDCl3) δ 195.7, 141.0, 134.2, 129.8, 127.9, 126.2, 125.2, 123.7, 77.8, 73.0, 43.5, 31.2, 29.4, 21.8 ; **MS (ESI)**: $[M + H]^+$ m/z 359; **HRMS**: [M + H]+ calcd. for $C_{19}H_{19}BrO_2$: 359.0647; found: 359.0648.

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CHAPTER 2

Synthesis of Montanacin D:

Right Hand Side (RHS)

2.1 Introduction

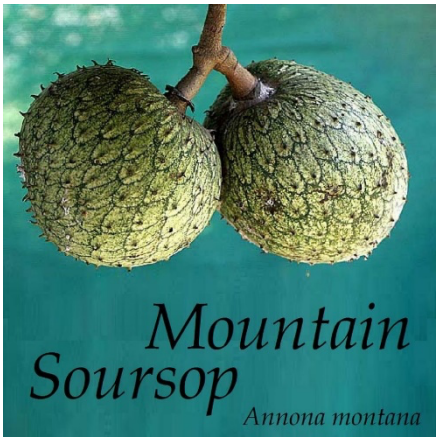
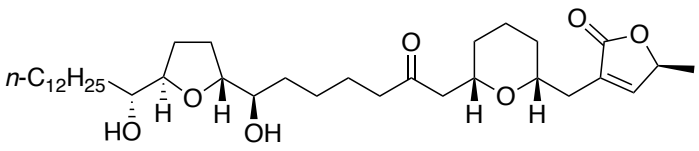


Figure 1. Image of *Annona montana* (Mountain Soursop)[a]



1

Montanacin D

Figure 2. Structure of Montanacin D

Montanacin D is an acetogenin isolated from *Annona montana*, otherwise known as Mountain soursop (Figure **1**). It is an edible, fibrous fruit and medicinal plant in the Annonaceae family native to Central America, the Amazon, and the Caribbean islands. Some native species of the Annonaceae family are considered important economic crops in North and South America and in Asia.[1] Since their initial isolation in 1982 Annonaceous acetogenins (ACGs) have increasingly attracted the interest of medicinal, natural product and synthetic organic chemists. As the name implies, acetogenins are derived biogenetically

from acetates. This class of compounds are a comparatively new class of natural polyketides which show promising biological activities. More than 120 acetogenins have been identified in ethanolic, methanolic or another organic extracts of different organs and tissues of *A. muricata* such as leaves, stems, bark, seeds[2-4], and fruit peel.[5]

The Annonaceous acetogenins from the Annonaceae plants comprise a class of almost 400 natural products that exhibit a remarkably broad spectrum of biological properties such as anti-tumor, anti-infective, pesticidal, anticancer, immunosuppressive and anti-feedant activities.[6-9] Several non-classical acetogenins have been discovered bearing a tetrahydropyran (THP) ring recently.[2, 10-11]

Structurally, three major functional groups can be categorised from these derivatives of long-chained fatty acids. They are mainly split into subclasses - non-adjacent bis-tetrahydrofuran, adjacent bis-tetrahydrofuran and mono-tetrahydrofuran.[2] A new skeletal type of annonaceous acetogenin (Figure **3**) was first discovered in 1995 by McLaughlin[10], where an annonaceous acetogenin bearing both tetrahydrofuran and a hydroxylated tetrahydropyran was found, marking the first of its kind.

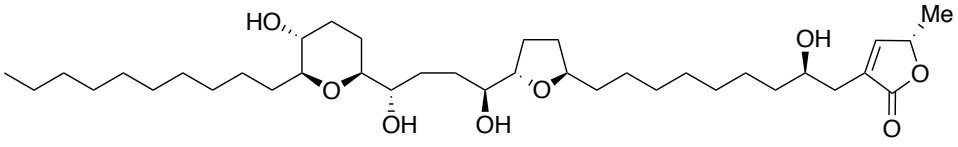


Figure 3[10]. Structure of Mucocin

Acetogenins are characterized by a long aliphatic chain of 35 to 38 carbons bonded to a γ-lactone terminally substituted by a β-unsaturated methyl group. It also has one or two THFs, hydroxyl, acetoxyls, ketones and epoxy groups located across the hydrocarbon chain. Acetogenins have also been reported with two adjacent or nonadjacent THF rings. The structure of Montanacin D in Fig. **2** above shows that it contains the six basic chemical structures of acetogenins reported for *A. muricata*. Some studies suggested that its bioactivity depends on its structure.[12] Annonacin was the most abundant acetogenin reported in both, leaves and fruit of *A. muricata*, but has also been reported in seeds, peel and roots[5, 13-17]. Considered to be main bioactive compounds of the Annonaceae family, the contents (w/w) of acetogenins in leave extracts were measured by ^{1}H NMR through dissolution in deuterated chloroform. The contents range from 3.38 to 15.05 mg/g.[18] Some studies have shown that acetogenins exhibit cytoxicity and are more cytotoxic than alkaloids and rotenone, which is a synthetic cytotoxic compound.[2, 9] As a result, acetogenins and alkaloids are widely studied, due to their therapeutic potential versus neurotoxic activity.

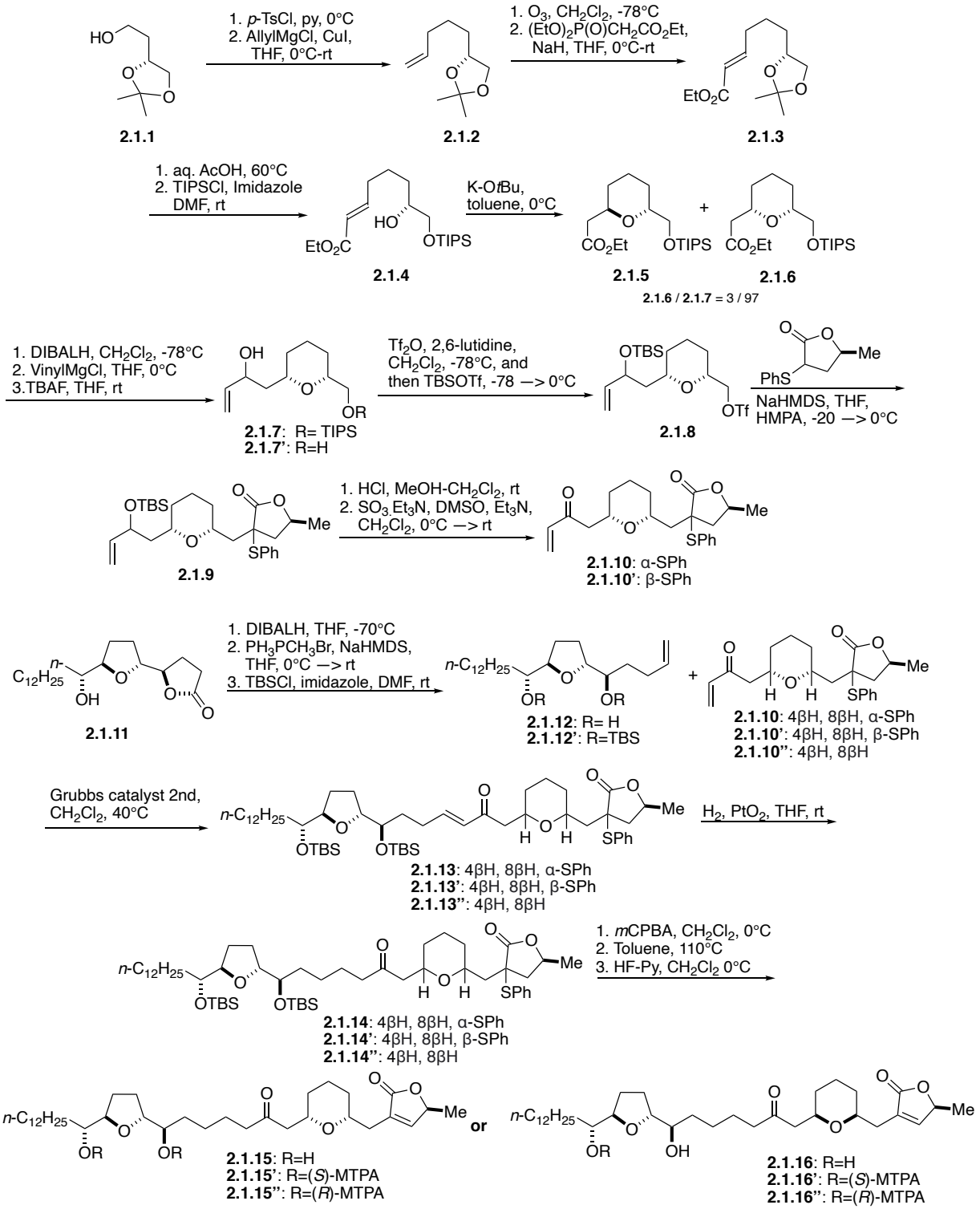
In 1999, Qin and Cheng isolated Montanacin D from the ethanolic extract of the leaves of *Annona montana*.[13-14] The structure was elucidated by NMR spectrometry as well as chemical ionisation mass spectrometry, revealing that the natural product possesses a *cis* THP ring along with a *trans* THF ring (Figure **2**).[19-25,26] Unlike the other approximately 420 acetogenins, the presence of the THP ring adjacent to the butenolide moiety provides a conformational rigidity around the lactone moiety, an essential functionality for several biological activities.[9] Hence, Montanacin D is regarded as a unique member of this family and is expected to have interesting biological activity. The first total synthesis of

Montanacin D was achieved by Takahashi *et al*.[27] However, our proposed longest linear sequence would be shorter with just 11 steps compared to the 16 steps in Takahashi's sequence. The envisioned shorter linear sequence is achievable owing to the more convergent synthetic approach that is proposed towards Montanacin D. The absolute configuration of the THP ring was only proven definitively by Takahashi *et al* through extensive spectroscopic analysis of **2.1.15** and **2.1.16** (Scheme **1**) matched against the ^{1}H NMR data of natural Montanacin D. It is concluded that absolute configuration of Montanacin D is indeed the structure shown in Figure **2**.

Scheme **1** below illustrates Takahashi's synthesis. The synthetic pathway starts with commercially available dioxolane (**2.1.1**) and the subsequent steps led to the formation of a mixture of THPs **2.1.5** and **2.1.6**. The cyclisation to form the THPs is an important difference between our proposed synthesis and Takahashi's. Although the group has been able to optimise the basic cyclisation to generate the targeted isomer **2.1.6** as the major product, the cyclisation still requires the additional step of removing the undesired *trans*-THP via column chromatography. Takahashi's group optimised the cyclisation by subjecting the mixture to prolonged stirring to equilibrate the diastereomic mixture. According to calculations done by a previous member of the laboratory, Dr. Dániel Csókás, on the substrates discussed in Chapter 1 above, there is a positive relationship between the energy difference and the ratio for the *cis*:*trans* isomers obtained – the higher the energy difference, the better the *cis*:*trans* ratio.

The difference between Takahashi's synthesis and our proposed synthesis featured in this Chapter lies in the stereoselective construction of the THP in the final *oxa*-Michael ring-closing step. This would yield Montanacin D

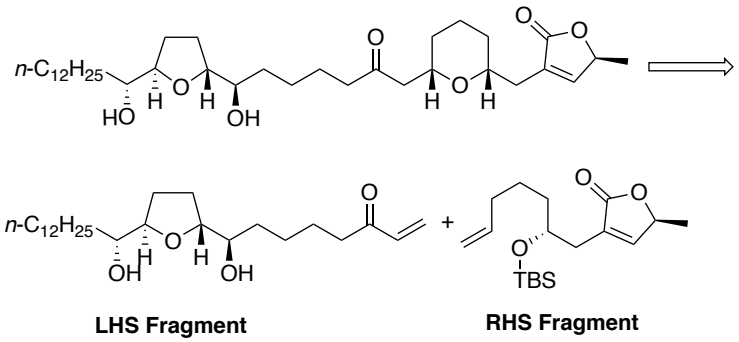
stereoselectively. The generation of the butenolide in Scheme 1 also differs from that of the proposed synthesis, which will be explored further in Section 2.2.1.



Scheme 1. Takahashi's Sequence

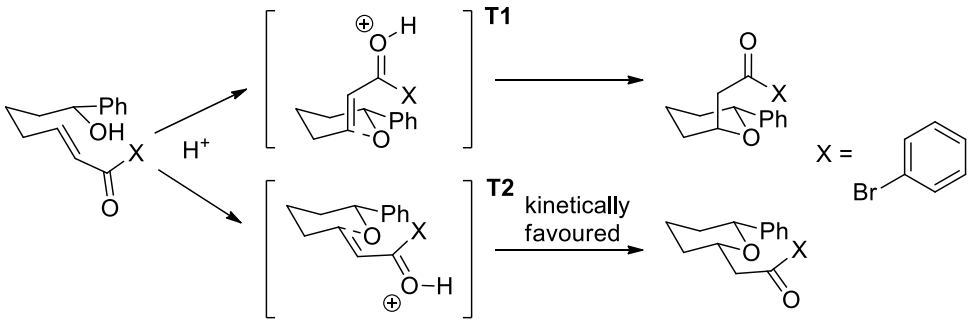
2.1.1 Conceptual Framework

Montanacin D is chosen for its familiar 2,6-disubstituted THP core moiety.[28] Based on stereoselective studies, it is postulated that the *cis* isomer will be generated.[29] The synthesis of Montanacin D will be done convergently with two major fragments, starting from the terminals and subsequently built towards the middle. The final steps culminate in a cross-metathesis and *oxa*-Michael ring closure which joins the two fragments together, as shown in Scheme **2** below.



Scheme **2**. Convergent Synthesis of Montanacin D

In the methods established in the previous project described in Chapter 1, tetrahydropyrans adopt chair-like conformations that give stereochemical outcomes where the substituents are *bis*-equatorial. As shown in Scheme **3** below, the 2,6-disubstituted ring in Montanacin D would also generate similar transition states. With acid catalysis, the diequatorial product is exclusively obtained in a kinetically controlled reaction in all cases.[29]

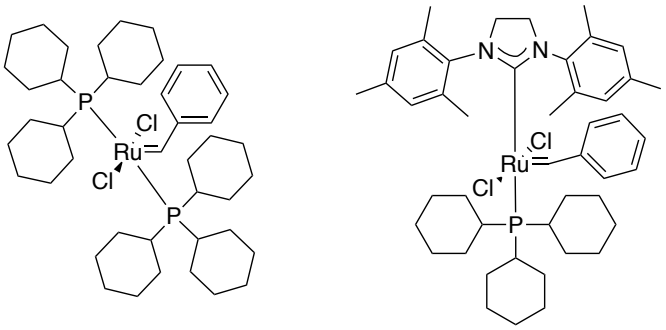


Scheme 3. Transition state of THP formation in acidic conditions

The cross-metathesis reaction is an elegant method for the intermolecular exchange of alkylidene fragments between two alkenes promoted by metal-carbene complexes. Prior to the discovery of cross-metathesis, this particular type of carbon-carbon bond formation was achieved through a Wittig reaction or a Horner-Wadsworth-Emmons reaction, both of which require the preparation of their corresponding phosphorus derivatives. Ever since cross-metathesis' discovery, it has proven to have an array of advantages typical of modern alkene-metathesis reactions.[30]

Cross-metathesis reactions are able to attain a high level of regio-, stereo-, and chemoselectivity. Moreover, as an addition to what was briefly mentioned above, the substrates are generally cheaper and easier to prepare than those associated with other common carbon-carbon bond forming reactions – unsaturated boranes, halides, stannanes and triflates – to name a few. The proposed synthesis plans to use the Grubbs second generation catalyst (Grubbs II catalyst), which is able to tolerate a wider range of functional groups, compared to its predecessor Grubbs second generation catalyst (Grubbs I catalyst). The catalyst structures are displayed in Figure **4** below. The cross-metathesis process is also catalytic and efficient, where a typical amount of only 1-5 mol % of catalyst is required, and high yields can be achieved under short reaction times and mild conditions. The reversible reaction is relatively atom-economic, and usually produces ethylene as the only by-product. The atom economy and by-product make large scale cross-metathesis reactions possible. Since the reaction is reversible, the formation of the desired product can be driven by the removal of ethylene gas using a continuous nitrogen flow through the flask, allowing the reaction to favour the formation of the product.[31-32] The products of cross-

metathesis will be an appropriate precursor for further structural elaboration, e.g. epoxidation, cycloaddition, hydrogenation, halogenation. In our case, Montanacin D will be furnished with an oxa-Michael cyclisation, which is dependent on the alkene as a precursor.



Grubbs I Catalyst

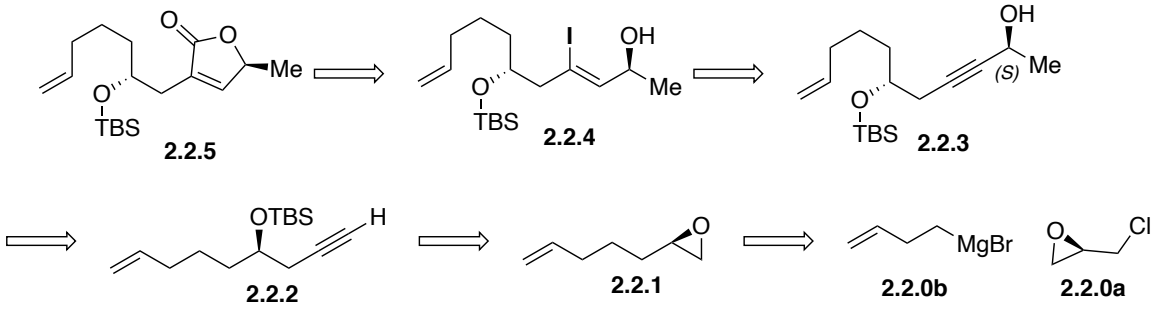
Grubbs II Catalyst

Figure 4. Grubbs Catalysts

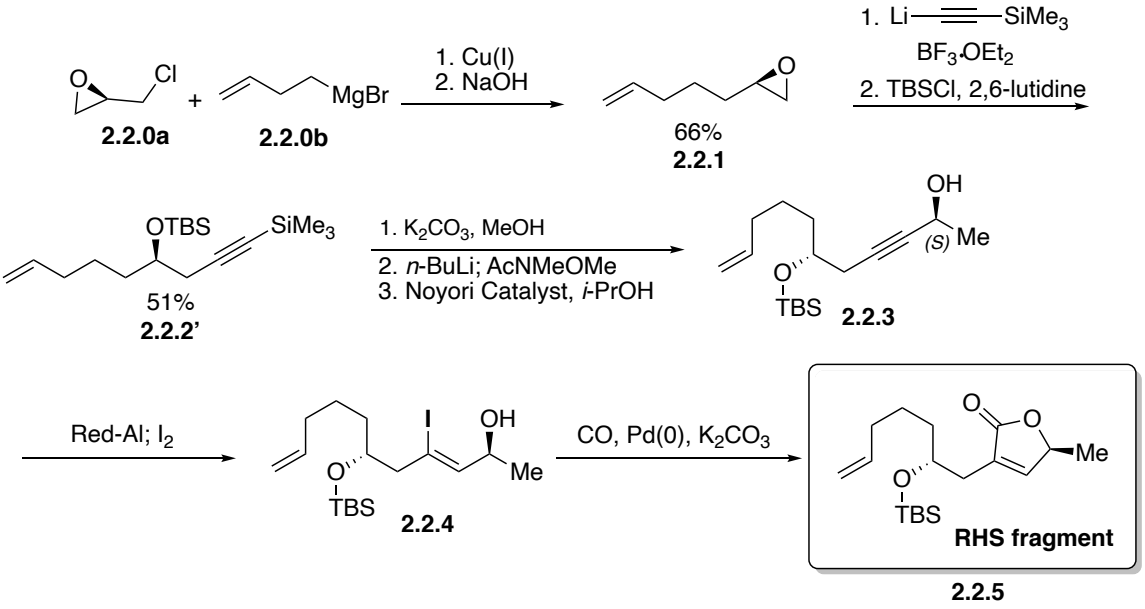
2.2 Results and Discussion

2.2.1 Synthesis of Alkynyl Ketone for Asymmetric Reduction

The initial proposed synthetic route for the right-hand side (RHS) fragment, described below in Scheme **4**, shares a similar synthetic pathway laid out by Marshall et al.[26] The proposed synthesis is highlighted by the approach to which the butenolide is furnished. The synthesis starts from the epoxide (**2.2.0a**) prepared by Jacobsen's kinetic resolution[26] of the racemate, followed by a ring-opening to give epoxide **2.2.1**. Subsequent steps involving Lewis acid-assisted nucleophilic ring-opening and asymmetric reduction would furnish alcohol **2.2.3**. The construction of the butenolide is done using an intramolecular carbonylation from the vinyl iodide (**2.2.4**) following Hoye's method[33], allowing immediate access to **2.2.5.**



Scheme 4. Retrosynthetic Pathway of RHS

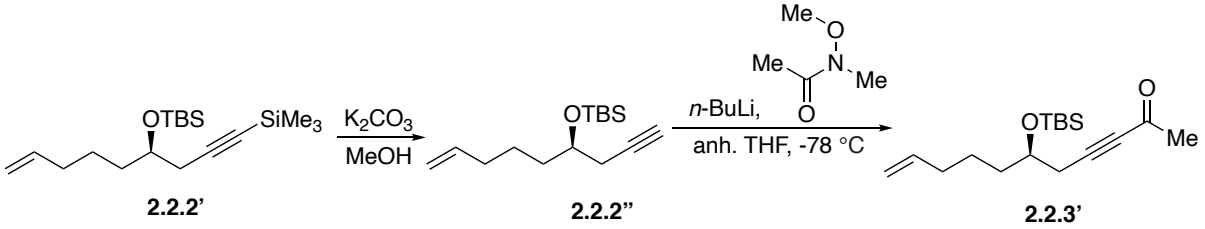


Scheme 5. Proposed Synthesis Pathway of RHS fragment

The synthesis begins with the epoxide (**2.2.1**) afforded in 70% yield over two steps by the ring-opening of (*R*)-epichlorohydrin (**2.2.0a**) using butenyl magnesium bromide (**2.2.0b**). This is followed by re-formation of the epoxide with NaOH. The epoxide (**2.2.1**) was then subjected to a Lewis acid-assisted nucleophilic ring-opening with lithiated TMS acetylide. ^{1}H NMR spectroscopy analysis of the desired ring-opening product shows a multiplet at 3.70 ppm with an integration value of one, which confirms that the nucleophilic ring-opening is successful. Subsequently, protection of the alcohol as the TBS silyl ether gave **2.2.2'** in a modest yield of 51% over both steps. Following which, removal of the TMS group using methanolysis afforded the precursor (**2.2.2**). With **2.2.2** in hand, the next steps involve the formation of the alkynyl ketone that would be eventually subjected to a Noyori asymmetric transfer hydrogenation with the (*S,S*) catalyst[34], giving the secondary alcohol (**2.2.4**). This asymmetric transfer

hydrogenation relies on 2-propanol as the hydrogen source, which is described in detail in Section 2.2.2. It has been noted that attempts to effect a more convergent synthesis of the secondary alcohol (**2.2.4**) through addition of the lithiated TBS or TES acetylide derivative to the epoxide, with or without BF_3 promotion, can cause decomposition of the epoxide.[33] The method of converting the alcohol to the butenolide (**2.2.5**) would follow Hoye's protocol for an analogous intermediate.[35]

The initial idea was to fashion the alkynyl ketone (**2.2.3'**) by the generation of the lithium acetylide species from alkyne **2.2.2'** with a strong base such as *n*-BuLi, followed by the addition of Weinreb amide, giving the desired alkynyl ketone (**2.2.3'**) intermediate prior to asymmetric reduction, as described in Scheme **6** below.



Scheme 6. Proposed Synthesis Pathway of RHS fragment

However, after multiple attempts at the ketone synthesis that involved solvent changes, temperature variance and increases in number of equivalents of *n*-BuLi with respect to the starting material, the yield of the alkynyl ketone remained low at 12%. The majority of starting material was recovered in all attempts as shown in Table **1** below.

Entry[a]	Solvent (anhydrous)	Temperature (°C)	Equiv of *n*-BuLi used	Result
1	Toluene	-78 - -40	1.1	SM Obtained
2	Toluene	-78 - 0	1.5	Product Yield: 10%. The rest of the SM remained unconverted.
3	THF	-78 - -40	1.5	Product Yield: 10%. The rest of the SM remained unconverted.
4	THF	-78 - 0	2	Product Yield: 12%. The rest of the SM remained unconverted.

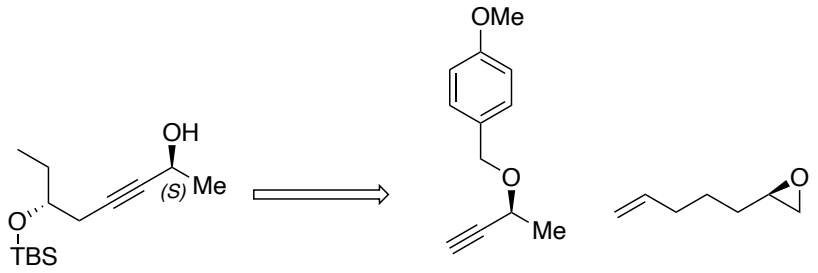
Table **1**. Optimisation of Alkynyl Ketone (**2.3'**)

[a]All reactions were done in 0.25 M concentration of alkyne.

The investigation of the issue behind the low yield began with a D_2O experiment in an attempt to eliminate the possibility of the problem of deprotection. To our surprise, the NMR result showed that only a minute amount of the alkynyl proton was deprotonated by *n*-BuLi, despite prolonged stirring. The result was unexpected as complete deprotonation of TMS acetylene with *n*-BuLi in a previous step allowed for the conversion of the starting material to the product. It was postulated that the TBS group on substrate **2.2.2'** might be too bulky, restricting the access to the alkynyl proton, or that the alkynyl proton was not acidic enough for *n*-BuLi to fully deprotonate. At this point, an alternative strategy to furnishing propargylic alcohol (**2.2.3**) was devised.

2.2.2 Synthesis of Alkynyl Alcohol via Nucleophilic Ring Opening

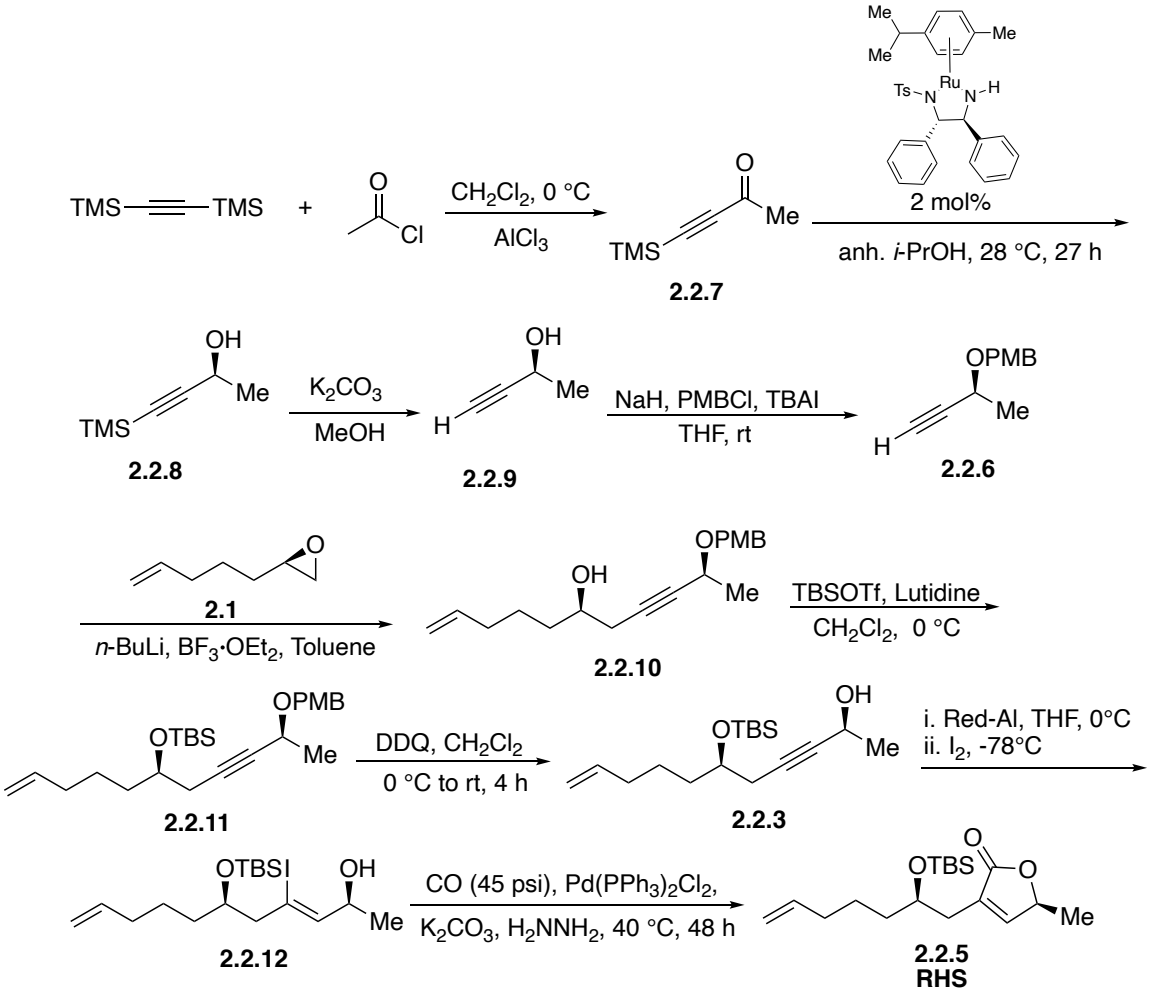
The alternative strategy is in agreement with much of the previous retrosynthesis, differing in the use of an additional protecting group and that the propargylic alcohol (**2.2.3**) was built in a more convergent manner, outlined in Scheme **7** below.



2.2.3 **2.2.6** **2.2.1**

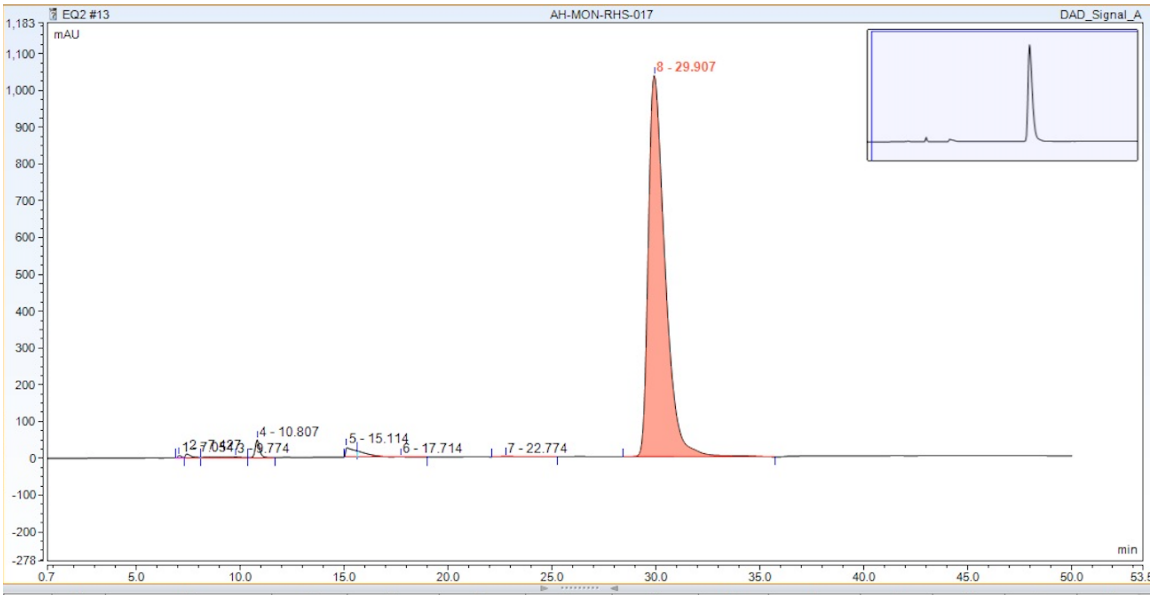
Scheme 7. Second Retrosynthetic Pathway of RHS fragment

The initial steps leading up to the epoxide (**2.2.1**) are the same, as described above. The *p*-methoxybenzyl (PMB) protected propargylic alcohol (**2.2.6**) was prepared as follows in Scheme **8**. The PMB group was selected as the choice protecting group as the methods of removing these two protecting groups - PMB and TBS, are orthogonal to each other under normal conditions, giving us the option of selectively removing one without the other.



Scheme 8. Second Proposed Synthetic Pathway of RHS fragment

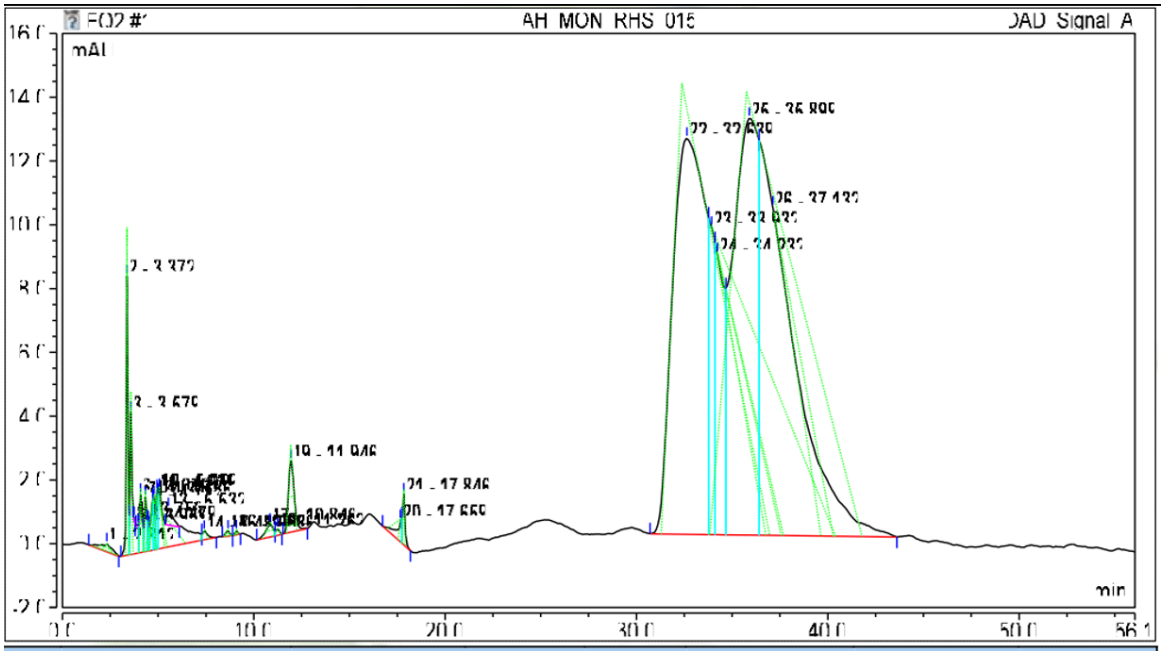
The synthesis (Scheme **8**) began with Friedel-Crafts acylation of bis-(trimethylsilyl)acetylene with acetyl chloride in the presence of Lewis acid[36], followed by an asymmetric reduction of the intermediate ketone (**2.2.7**) using Noyori's (*S*,*S*) catalyst.[34] Both steps gave gratifying yields upwards of 80%. ^{1}H NMR spectroscopic analysis shows a multiplet at 4.50 ppm with an integration value of one, which confirms that the asymmetric reduction was successful. Initial attempts at the asymmetric reduction were met with difficulties as there were no signs of product. The problem was suspected to derive from the presence of residual base that could have been left behind during the formation of the active catalyst. To circumvent this, the active catalyst was washed with water to remove any base that might still be present. Moreover, the catalyst loading was increased from the initial 0.1 mol% to 2 mol%, to ensure efficient and complete conversion of the reaction. The enantiomeric excess (*ee*) of the TMS alcohol (**2.2.8**) was determined at this point by HPLC using the procedure reported[37], which revealed an excellent selectivity of the reduction step with >95% *ee*, as shown in the chromatogram in Figure **5** below.



	A	B	C	D	E	F	G	H	I	J	K	L	M
1	Peak	Peak Name	Ret.Time	Amount	Rel.Area	Area	Height	Type	Width (50%)	Asym.	Resol.	Plates	
2	No.		min	n.a.	%	mAU*min	mAU		min	EP	EP	EP	
4	1		7.054	n.a.	0.11	1.1138	6.26	Ru	n.a.	n.a.	n.a.	n.a.	
5	2		7.427	n.a.	0.32	3.2616	10.52	M	0.258	n.a.	n.a.	4580	
6	3		9.774	n.a.	0.25	2.4856	1.53	M	n.a.	n.a.	n.a.	n.a.	
7	4		10.807	n.a.	1.17	11.7397	48.42	M	0.216	1.23	n.a.	13886	
8	5		15.114	n.a.	1.22	12.2527	26.78	M	n.a.	n.a.	n.a.	n.a.	
9	6		17.714	n.a.	1.09	11.0147	0.78	M	n.a.	n.a.	n.a.	n.a.	
10	7		22.774	n.a.	0.13	1.3154	1.02	M	0.849	2.27	5.02	3988	
11	*8*		*29.907*	*n.a.*	*95.71*	*964.0073*	*1036.71*	*M*	*0.828*	*1.66*	*n.a.*	*7224*	
12	Maximum			0.0000	95.71	964.0073	1036.71		0.849	2.27	5.02	13886	
13	Minimum			0.0000	0.11	1.1138	0.78		0.216	1.23	5.02	3988	
14	Sum			0.0000	100.00	1007.1910	1132.03						
15													

Summary | Peak Results | System Suitability Test | Calibration | Audit Trail

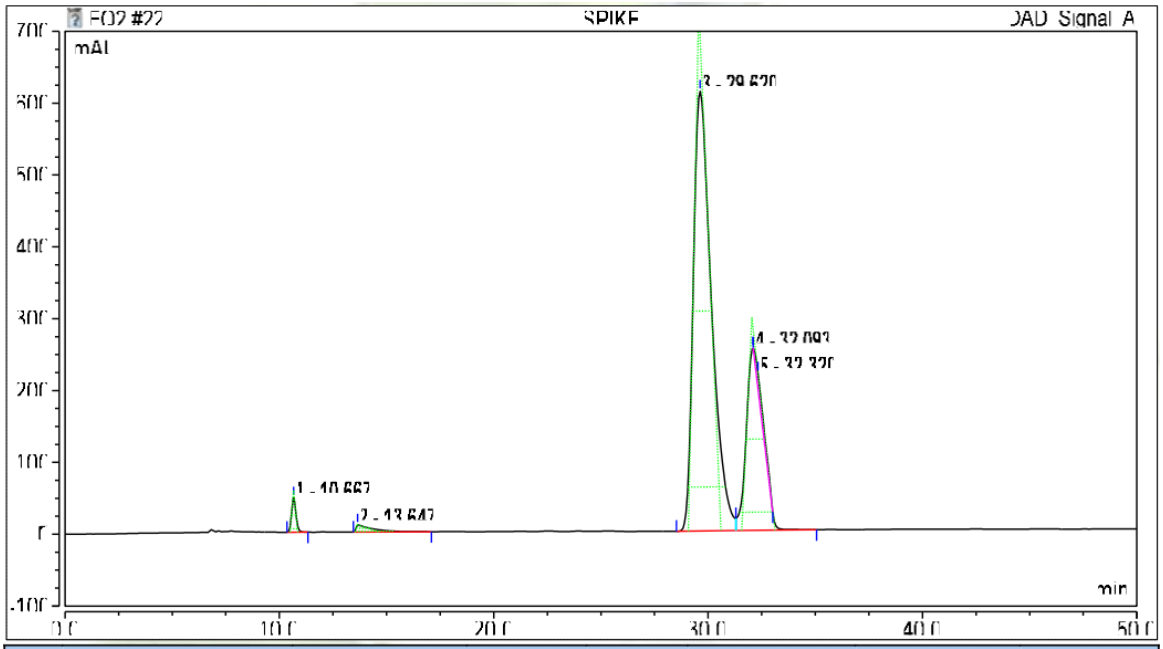
Figure 5. Chromatogram of *ee* of TMS alcohol **2.2.8**



Peak Results

No.	Peak Name	Retention Time min	Width (50%) min	Type	Resolution (EP)	Asymmetry (EP)	Plates (EP)
1		2.312	0.745	BMB	1.50	0.83	53
2		3.372	0.090	BM	1.22	n.a.	7810
3		3.579	0.110	M	2.15	n.a.	5911
4		3.752	n.a.	Rd	n.a.	n.a.	n.a.
5		3.959	n.a.	Rd	n.a.	n.a.	n.a.
6		4.079	0.165	M	n.a.	n.a.	3400
7		4.346	n.a.	M	n.a.	n.a.	n.a.
8		4.479	n.a.	M	n.a.	n.a.	n.a.
9		4.712	n.a.	M	n.a.	n.a.	n.a.
10		4.786	n.a.	M	n.a.	n.a.	n.a.
11		4.939	n.a.	M	n.a.	n.a.	n.a.
12		5.059	n.a.	M	n.a.	n.a.	n.a.
13		5.532	n.a.	Rd	n.a.	n.a.	n.a.
14		7.412	n.a.	MB	n.a.	n.a.	n.a.
15		8.652	0.265	BMB	1.19	0.88	5893
16		9.086	0.163	BMB	3.60	1.12	17172
17		10.846	0.414	BM	n.a.	n.a.	3794
18		11.252	n.a.	MB	n.a.	n.a.	n.a.
19		11.946	0.324	BMB	n.a.	1.24	7554
20		17.659	n.a.	BM	n.a.	n.a.	n.a.
21		17.846	0.150	MB	n.a.	n.a.	78757
22		32.639	n.a.	BM	n.a.	n.a.	n.a.
23		33.932	n.a.	M	n.a.	n.a.	n.a.
24		34.232	n.a.	M	n.a.	n.a.	n.a.
25		35.899	n.a.	M	n.a.	n.a.	n.a.
26		37.132	n.a.	MB	n.a.	n.a.	n.a.

Figure **6**. Chromatogram of racemic mixture of TMS alcohol **2.2.8**

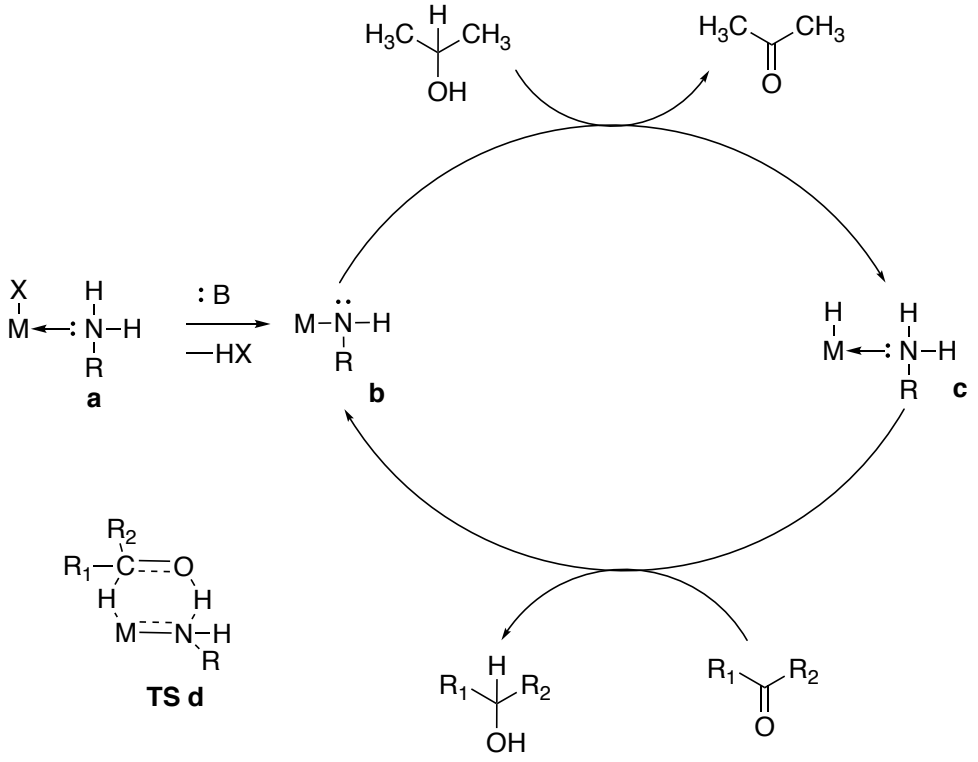


Peak Results

No.	Peak Name	Retention Time min	Width (50%) min	Type	Resolution (EP)	Asymmetry (EP)	Plates (EP)
1		10.667	0.213	M	3.90	1.15	13931
2		13.647	0.689	M	11.93	8.65	2176
3		29.620	0.891	M	1.69	1.62	6124
4		32.093	0.837	M	n.a.	n.a.	8142
5		32.320	n.a.	Rd	n.a.	n.a.	n.a.

Figure **7**. Chromatogram of spike TMS alcohol **2.2.8** with racemic mixture

The Noyori asymmetric hydrogenation relies on 2-propanol as the hydrogen source as it is stable, environmentally friendly, easy to handle, inexpensive, non-toxic and dissolves many organic compounds.[38] Moreover, the acetone bi-product can be easily removed.[39-41] The success of the asymmetric reaction using 2-propanol is dependent on the suitable chiral structures of the Ru complexes, the mechanism-based functional group differentiation, enabling the selective saturation of the C=O group and appropriate thermodynamic and kinetic parameters. In the case of ynone and ynol, the thermodynamic balance favours the formation of the ynol. For this asymmetric reduction, KOH is used as the inorganic base as an essential co-catalyst. The mechanism, supported by calculations[42-43], is outlined below in Scheme **9**.



Scheme 9.[42] Mechanism for Catalytic Asymmetric Reduction

The mechanism starts with **a** as the catalyst precursor. The catalytic cycle involves **b** (16e) and **c** (18 e) as the only two ground-state components. In this metal-ligand bifunctional catalysis, where the metal and surrounding ligand are directly involved in the bond-forming and bond-breaking steps of the dehydrogenative and hydrogenative routes, the amide nitrogen in **b** and the NH proton in **c** are key players. Oxygen atoms from 2-propanol or the substrates do not interact with M in **b** or **c**. The 2-propanol hydroxy proton interacts with the N atom of **b**, while the oxygen of the substrate interacts with the NH proton of **c**. The reaction of the amine-coordinated hydride complex **c** and a ketone substrate gives metal amide **b** and the alcohol as the product via **TS d**.

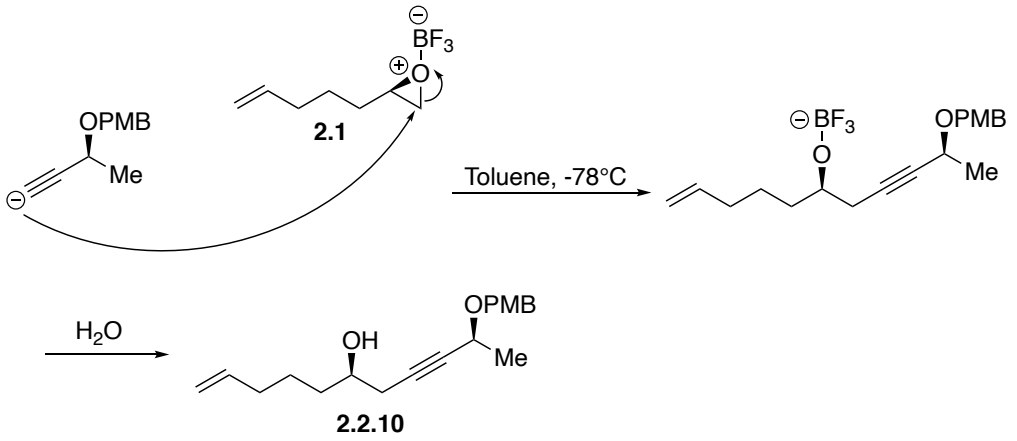
After the Noyori asymmetric treatment to form TMS alcohol (**2.2.8**), the TMS group was then removed, yielding the alkyne adduct in 94%. The alcohol was subsequently protected with freshly prepared PMBCl, giving the desired key propargylic alcohol (**2.2.6**) that defines this synthetic route, with an excellent yield of 77%. ^{1}H NMR spectroscopic analysis shows a doublet at 7.31 ppm and another at 6.89 ppm, both with an integration value of two, which confirms that the installation of the PMB group is accomplished.

The triethylsilyl ether was among the initially selected protecting groups, as the relative resistance of the TBS group in acidic and basic media, compared to TES, is about 300-folds greater.[44] While the initial synthesis of the TES protected propargylic alcohol was successful, the subsequent isolation and volatility of the resultant compound posed issues and inconvenience in its preparation. The careful selection of a protecting group is vital here as this protecting group has to be stable to strong base, and will be selectively removed without the removal of

the TBS protecting group in **2.2.11**. The PMB group was therefore selected as the choice protecting group as the methods of removing these two protecting groups - PMB and TBS, are orthogonal to each other under normal conditions, giving us the option of selectively removing one without the other.

With the desired propargylic alcohol (**2.2.6**) in hand, the synthesis continued with the nucleophilic addition of epoxide (**2.2.1**), giving the alkyl chain with the single free alcohol (**2.2.10**) in an exemplary yield of 81%. ^{1}H NMR spectroscopic analysis shows a multiplet at 3.70 ppm with an integration value of one, which confirms that the nucleophilic ring-opening is successful.

It is well known that the chemistry of BF_3 is characterised by its exceptional Lewis acidity, due to the inherent electron deficiency of the boron atom. $BF_3.OEt_2$ functions as a Lewis acid here to facilitate the epoxide (**2.2.1**) ring opening reaction that was accompanied by a nucleophilic attack by propargylic alcohol (**2.2.6**) on the less sterically hindered carbon. The reaction undergoes an S_N2-like mechanism and is described below in Scheme **10**. Finding the right solvent proved to be crucial in this ring opening step, as previous attempts with THF did not give any product. It was postulated that toluene, being a less polar solvent, would have a solvent effect on the reaction. Toluene would also not contribute to the high solvation of nucleophiles as a result of ion dipole interaction, allowing the reaction to proceed.



Scheme 10. Mechanism of Nucleophilic Addition forming Propargylic Alcohol **2.2.10**

Subsequent protection of the secondary alcohol **2.2.10** with TBSOTf gave the desired silyl ether (**2.2.11**) in a great yield of 90%. ^{1}H NMR spectroscopic analysis shows a singlet at 0.89 ppm with an integration value of nine and a doublet at 0.08 ppm with an integration value of six, which confirms that the installation of the TBS group is a success. TBSOTf was chosen as the source of silylation as it is more reactive than TBSCl, with triflate being a better leaving group than chloride, thus better suited to overcome the steric effect of a secondary alcohol. The silyl ether (**2.2.11**) was then subjected to selective deprotection of PMB with DDQ, where the method of choice is crucial for the deprotection of PMB. At this point, TLC analysis showed that the reaction gave two distinct spots that were inseparable by column chromatography. One of which was the product, while the other was the PMB aldehyde by-product. The aldehyde by-product was subsequently successfully removed with the addition of Girard's Reagent T, shown below in Figure **8**, as the PMB aldehyde reacts to form a Girard T hydrazone that can be easily removed by water[45], giving the desired propargylic alcohol (**2.2.3**) in 76% yield. ^{1}H NMR spectroscopic analysis shows an absence of aromatic protons which shows that the removal of the PMB group is a success.

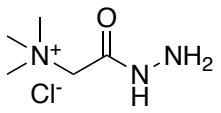
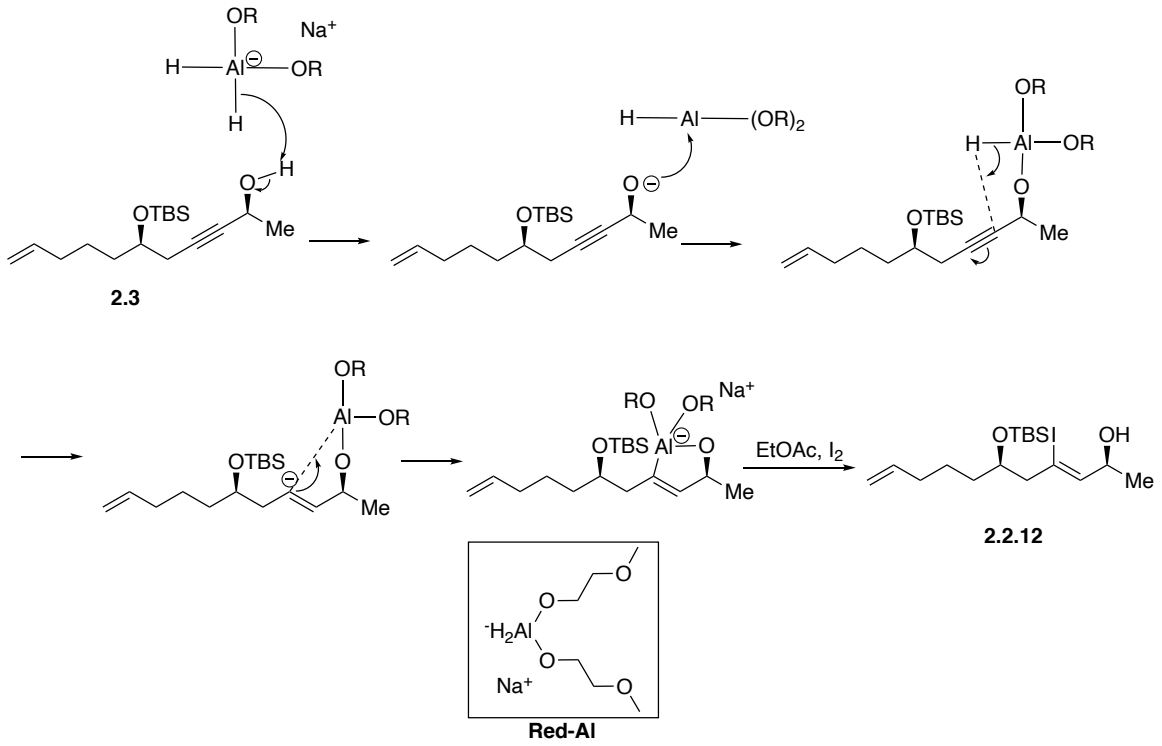


Figure 8. Girard's reagent T

This left us with just two steps short of forming the RHS target. The first being the reduction of the alkyne in the propargylic alcohol (**2.2.3**) with Red-Al and iodine insertion to give **2.2.12**, and the second being CO insertion, which would eventually furnish the targeted butenolide ring of the RHS fragment. The mechanism of the formation of **2.2.12** from propargylic alcohol (**2.2.3**) is described below in Scheme **11**. The mechanism begins with the deprotonation of the alcohol (**2.2.3**) in the presence of Red-Al, forming an oxyanion that coordinates with Al. The removal of another hydride allows the formation of a 5-membered intermediate that is key in this mechanism. The 5-membered intermediate is comparably more stable than the 4-membered one, which undergoes an insertion by iodine during work-up, furnishing *trans*-alkene **2.2.12** in a good yield of 70%. ^{1}H NMR spectroscopic analysis shows one doublet at 5.65 ppm with an integration value of one, which confirms that the reduction of the alkyne and subsequent installation of iodine one the double bond is a success.



Scheme **11**. Mechanism of Red-Al reduction

At this point, the diastereomeric purity of iodide **2.2.12** was determined via ^{13}C NMR spectroscopy, displayed in Figures **9** and **10**. ^{13}C spectra was obtained for both diastereomers and subjected to a direct comparison where the difference in chemical shifts are the same except for a stark difference in the region at 104 – 105 ppm, thus demonstrating the diastereomeric purity of iodide **2.2.12**.

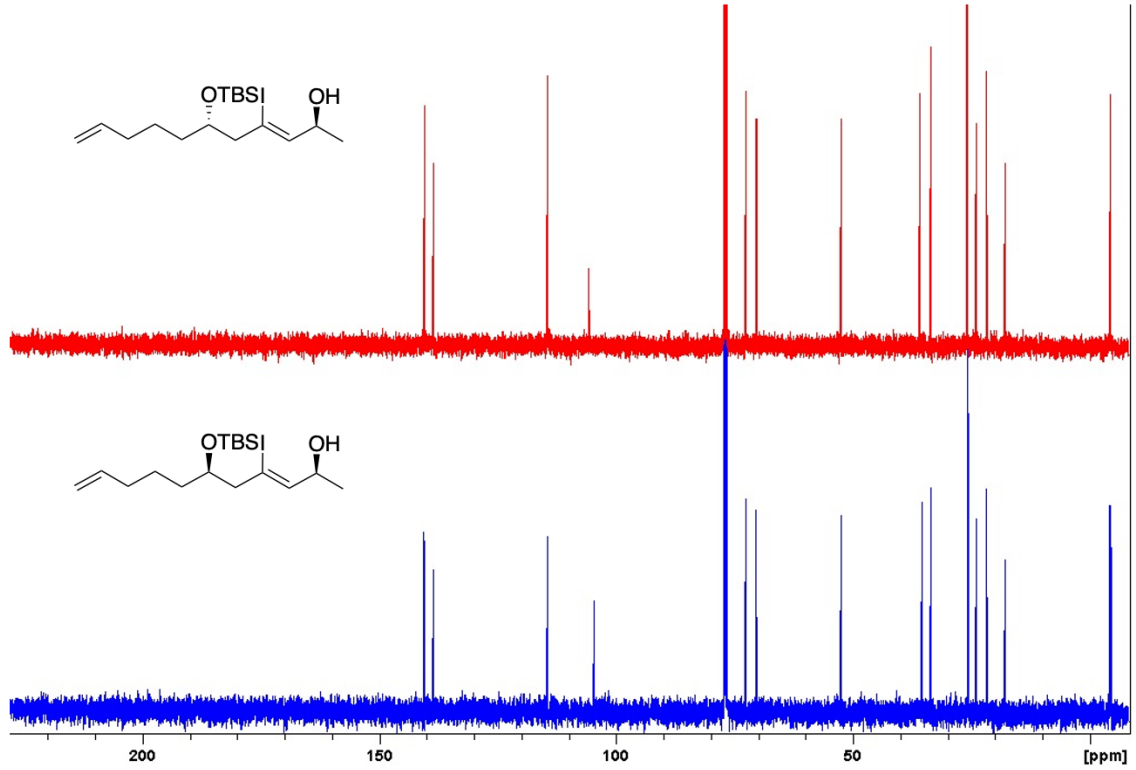


Figure 9. Full ^{13}C Spectra of Iodide Diastereomers

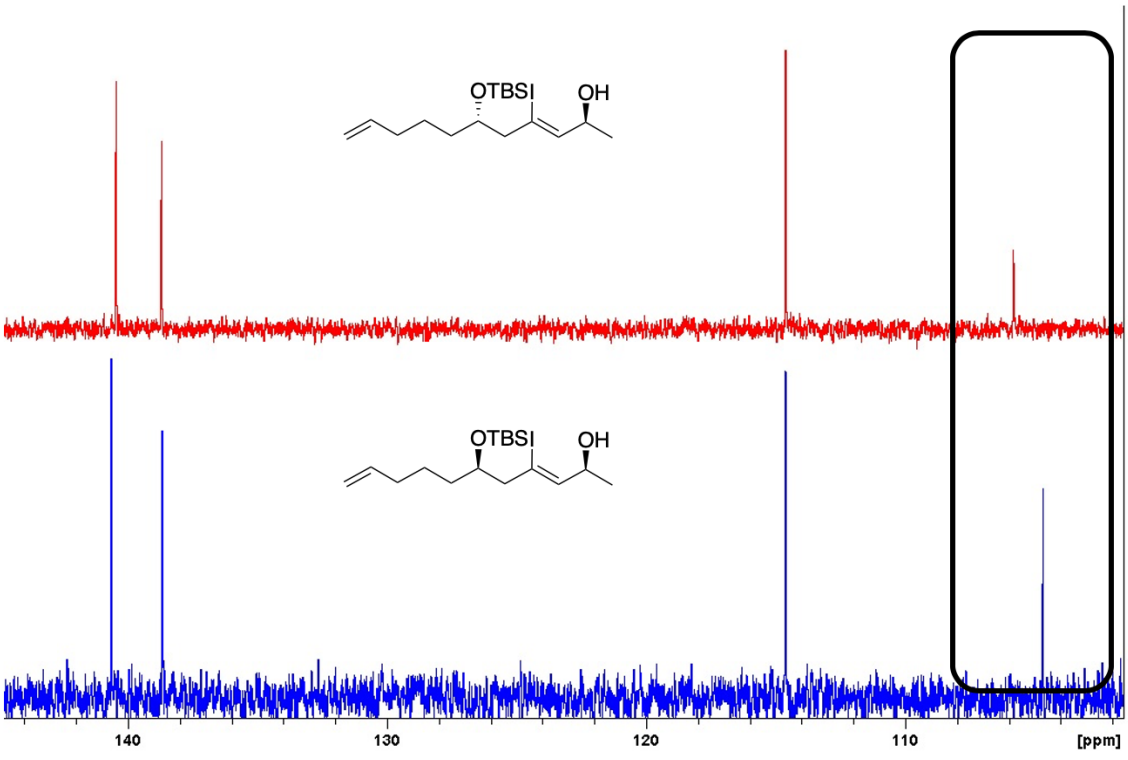
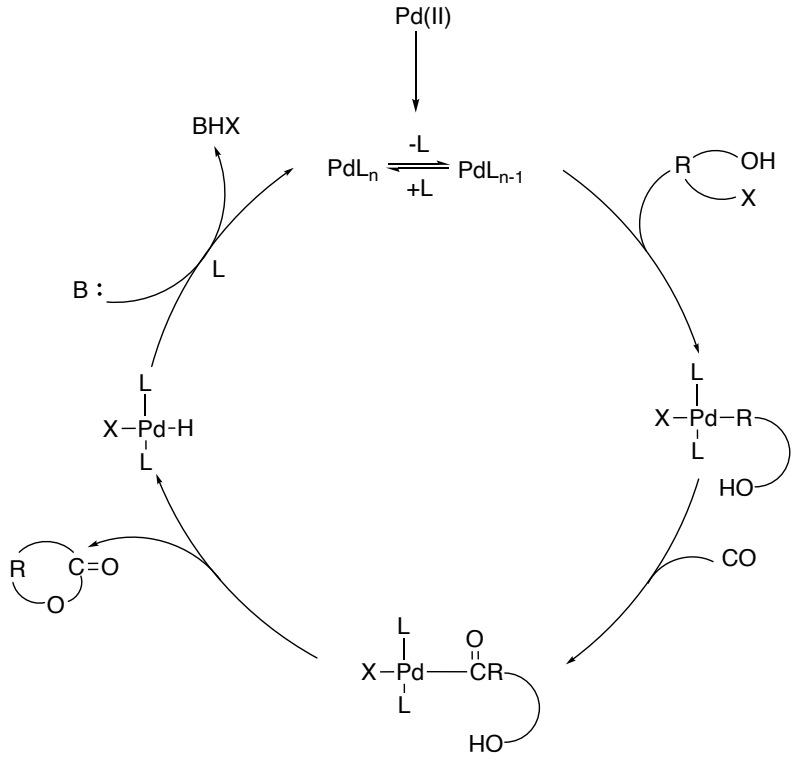


Figure 10. ^{13}C Spectra of Iodide Diastereomers from 145 – 110 ppm

With *trans*-alkene **2.2.12** in hand, the final step can proceed with carbonylation following a method described by Stille[46] (Scheme **12**). The catalytic cycle involves the oxidative addition of the organic halide to Pd(0), followed by the insertion of CO into the Pd-C bond and finally the reductive elimination promoted by the alcohol. The presence of excess base is imperative to keep the catalyst active so that a higher turnover of Pd can be achieved. The base does so by the absorption of the H-X produced during the reaction. Stille notes that the retention of geometry in vinyl halides has been observed and that insertion of CO occurred with a retention of configuration at the carbon. The retention of configuration with vinyl halides is crucial as only the *Z* isomer can be converted to the butenolide. Bis(triphenylphosphine)palladium(II) chloride was the catalyst of choice as it can be conveniently handled in the laboratory. More importantly, it can be readily reduced to Pd(0) in situ. As it is known that free PPh_3 slows the rate of oxidative addition[46], the catalyst is also capable of keeping the concentration of PPh_3 in solution to a minimum. The butenolide was accomplished in a good yield of 77%. ^{1}H NMR spectroscopic analysis shows a doublet at 7.10 ppm with an integration value of one, which confirms that carbonylation is a success.



Scheme **12**. Catalytic Cycle of CO Insertion

2.3 Conclusion

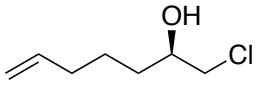
The synthesis of Montanacin D is noteworthy as the class of compounds it belongs to is known to exhibit a remarkably broad spectrum of biological properties such as anti-tumor, anti-infective, pesticidal, anticancer, immunosuppressive and anti-feedant activities. Unlike the other acetogenins, the presence of the THP ring adjacent to the butenolide moiety provides a conformational rigidity around the lactone ring, an essential area for several biological activities. Herein, we report an efficient convergent synthetic route, beginning with the RHS, whose key step involves a nucleophilic ring opening. The RHS was successfully furnished over nine steps, with an overall yield of 17%. The efficient route and good diastereoselectivity makes it an intriguing compound to synthesise.

2.4 Experimental

All reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware (120 °C), which was cooled under vacuum. Needles and syringes were similarly dried under vacuum before use. Anhydrous tetrahydrofuran was distilled from benzophenone and sodium metal under nitrogen. Anhydrous toluene was distilled over sodium under a nitrogen atmosphere. Anhydrous dichloromethane was dried by distillation from CaH_2 immediately prior to use under nitrogen. Anhydrous methanol was distilled from activated magnesium under nitrogen. All other solvents and reagents were used as received. Flash chromatography was carried out on silica gel, 230-400 mesh.

^{1}H NMR spectra were recorded in deuterated solvent $CDCl_3$, at 300, 400, 500 MHZ, using Bruker AV300, AV400, AV500, BBFO1 400, BBFO2 400, JEOL ECA 400 and ECA 400SL spectrometers. ^{13}C NMR spectra were recorded at the corresponding frequency on the same instruments at 75, 100 or 125 MHz. Chemical shifts are recorded in parts per million and coupling constants are recorded in Hertz. Multiplicity of NMR signals are abbreviated using the following shorthand: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet).

Enantiomeric excess was determined by chiral HPLC analysis, using a Diacel Chiracel OJ-H column, eluting with 2-propanol/hexane.

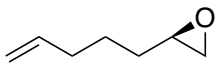


(*R*)-1-chlorohept-6-en-2-ol[47]

A crystal of iodine was added into a mixture of magnesium (711.1 mg, 29.6 mmol) and 15 ml of anhydrous ether. The mixture was heated at reflux until the iodine colour has disappeared. A solution of 1-bromobutene (2 g, 14.8 mmol) in anhydrous ether was added dropwise and a gentle reflux was maintained. After 2 hours, at –78 °C, the Grignard reagent was added dropwise via cannula to a stirred solution of (*R*)-epichlorohydrin (1304.1 g, 14.1 mmol) and CuCN (126.2 mg, 1.41 mmol) in 15 mL of anhydrous THF. The mixture was warmed to -20°C over 3 h and poured into a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined ethereal extracts were dried over $MgSO_4$ and concentrated to afford (*R*)-1-chlorohept-6-en-2-ol as a yellow oil. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford (*R*)-1-chlorohept-6-en-2-ol (1466 mg, 9.86 mmol) as a colourless oil.

Yield: 70%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.85 – 5.77 (m, 1H), 5.04 (d, J = 17.0 Hz, 1H), 4.97 (d, J = 10.1 Hz, 1H), 3.82 (m, 1H), 3.64 (dd, J = 11.1, 3.2 Hz, 1H), 3.48 (dd, J = 11.1, 7.1 Hz, 1H), 2.18 (s, br, 1H), 2.10 (m, 2H), 1.62 – 1.43 (m. 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.22, 114.90, 71.26, 50.45, 33.54, 33.43, 24.70.

All data is consistent with that reported in literature.

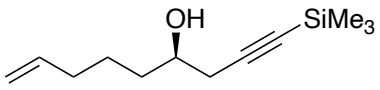


(*R*)-2-(pent-4-en-1-yl)oxirane (2.2.1)[47]

To a solution of (*R*)-1-chlorohept-6-en-2-ol (470.7 mg, 3.17 mmol) in Et_2O (5 mL) was added finely powdered NaOH (697 mg, 17.4 mmol). The mixture was stirred vigorously for 24 h and poured into 20 mL water. After separation of the layers, the aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$. Vacuum distillation (1 torr, 25 °C) afforded the product (**2.2.1**, 332.9 mg, 2.97 mmol) as yellowish oil, which was used without further purification.

Yield: 94%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.88 – 5.72 (m, 1H), 5.09 (d, J = 17.1 Hz, 1H), 4.98 (d, J= 10.2 Hz, 1H), 2.93 – 2.89 (m, 1H), 2.76 – 2.74 (m, 1H), 2.48 – 2.45 (m, 1H), 2.17 – 2.08 (m, 2H), 1.62 – 1.49 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.55, 71.99, 62.46, 14.09.

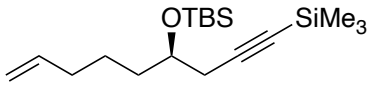
All data is consistent with that reported in literature.



(*R*)-1-(trimethylsilyl)non-8-en-1-yn-4-ol

n-BuLi (3.4 mL, 6.8 mmol, 2.0 M in hexane) was slowly added to a solution of trimethylsilylacetylene (158 µL, 1.41 mmol) in anhydrous THF (10 mL) at -78℃. After stirring for 30 min, a solution of epoxide (**2.2.1**, 644 mg, 5.74 mmol) in anhydrous THF (5 mL) was added via cannula. Further addition of $BF_3.Et_2O$ (708 µL, 5.74 mmol) was added at -78℃ and the reaction was stirred for another 50 minutes. H_2O (2 mL) and concentrated H_2SO_4 (1.8 mL) were added. The cloudy mixture was stirred for 15 min and neutralized with aq. $NaHCO_3$. The mixture was extracted with Et_2O (20 mL x 3). The combined organic solution was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 8:92) to afford the product (636.2 mg, 3 mmol) as a colourless oil.

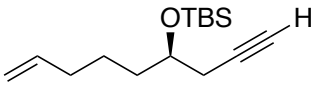
Yield: 53%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.88 – 5.73 (m, 1H), 5.07 – 4.88 (m, 2H), 3.80 – 3.67 (m, 1H), 2.46 (dd, *J* = 16.8, 4.7 Hz, 1H), 2.35 (dd, *J* = 16.8, 4.7 Hz, 1H), 2.15 – 2.00 (m, 2H), 1.93 (dd, *J* = 5.1, 1.3 Hz, 1H), 1.60 – 1.41 (m, 4H), 0.16 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.53, 114.72, 103.17, 87.71, 69.73, 35.63, 33.55, 28.94, 24.83, 0.07.



(*R*)-*tert*-butyldimethyl((1-(trimethylsilyl)non-8-en-1-yn-4-yl)oxy)silane (2.2.2')

To an oven-dried, degassed flask, (*R*)-1-(trimethylsilyl)non-8-en-1-yn-4-ol (261.5 mg, 1.24 mmol) and 2,6-dimethylpyridine (260.6 µL, 2.24 mmol) was stirred with 4 mL of DCM at 0 °C. TBSOTf (342.5 µL, 1.49 mmol) was added dropwise. After stirring for 2 hours, the reaction was quenched with $NaHCO_3$ followed by an addition of water. The reaction mixture was extracted with DCM, dried over $MgSO_4$, filtered and concentrated under vacuo. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford the product (**2.2.2'**, 380.8 mg, 1.17 mmol) as a colourless oil.

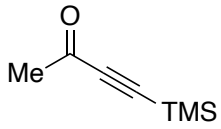
Yield: 96%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.87 – 5.71 (m, 1H), 5.04 – 4.92 (m, 2H), 3.84 – 3.75 (m, 1H), 2.34 (dd, *J* = 6.4, 3.0 Hz, 2H), 2.05 (q, *J* = 7.2 Hz, 2H), 1.69 – 1.35 (m, 5H), 0.93 – 0.84 (m, 11H), 0.14 (d, *J* = 1.2 Hz, 9H); **MS (ESI+)** m/z 325 $[M+H]^+$; **HRMS** calcd for $C_{18}H_{36}OSi_2$ ($[M+H]^+$) 325.2382 found 325.2344



(*R*)-*tert*-butyldimethyl(non-8-en-1-yn-4-yloxy)silane (2.2.2'')

To a stirring solution of TBS ether (**2.2.2'**, 100 mg, 0.308 mmol) in 1 mL of MeOH was added K_2CO_3 (127.7 mg, 0.924 mmol). The reaction mixture was stirred for 1 h and quenched with H_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford the product (**2.2.2''**, 56.5 mg, 0.224 mmol) as a colourless oil.

Yield: 73%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.84 – 5.78 (m, 1H), 5.06 – 4.91 (m, 2H), 3.80 (tt, *J* = 6.6, 4.6 Hz, 1H), 2.34 – 2.29 (m, 1H), 2.13 – 2.00 (m, 2H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.72 – 1.35 (m, 5H), 0.89 (s, 9H), 0.07 (d, *J* = 7.4 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.72, 114.48, 81.68, 70.79, 69.85, 36.04, 33.70, 33.68, 28.81, 27.38, 25.91, 25.88, 25.86, 25.84, 25.70, 24.39, 24.25, 18.12, 18.08, 0.07, -2.95, -4.39, -4.48, -4.62, -4.66; MS (ESI+) m/z 253 $[M+H]^+$; **HRMS** calcd for $C_{15}H_{28}OSi$ ($[M+H]^+$) found

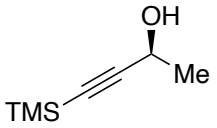


4-Trimethylsilyl-3-butyne-2-one (2.2.7)[36]

A mixture of bis-trimethylsilylacetylene (3.16 mL, 14.7 mmol) and acetyl chloride (0.95 mL, 13.4 mmol) in anhydrous CH_2Cl_2 (27 mL) under nitrogen was cooled to 0 °C and stirred for 5 minutes. Aluminum trichloride (2.14 g, 16 mmol) was added portionwise over 10 minutes. The reaction mixture was stirred at 0 °C under nitrogen for 6 hours. On completion, 10 mL of 0.5 M of aqueous HCl was added dropwise at 0 °C, then warmed slowly to room temperature. The resulting biphasic solution was separated and the aqueous layer was extracted twice with additional CH_2Cl_2 (3 x 20 mL). The organic fractions were combined, dried over $MgSO_4$ and filtered. Evaporation followed by distillation under reduced pressure (aspirator, ~40 torr) (b.p. 55 – 70 °C, oil bath temperature 90 – 100 °C) provided 4-trimethylsilyl-3-butyne-2-one (**2.2.7**, 1.39 g, 9.89 mmol) as a clear colourless oil.

Yield: 75%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 0.24 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.42, 102.35, 99.90, 97.36, 32.47, -0.84.

All data is consistent with that reported in literature.

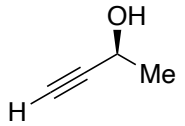


(*S*)-4-trimethylsilyl-3-butyn-2-ol (2.2.8)[37]

A mixture of 4-trimethylsilyl-3- butyn-2-one (**2.2.7**, 500 mg, 3.56 mmol) and catalyst[34] Ru[(1S,2S)-pTsNCH(C_6H_5)CH(C_6H_5)NH] (η^6-cymene) (44 mg, 0.07 mmol) in 2-propanol (35.5 mL) was stirred under nitrogen at 28 °C for 27 h and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 10:90) to afford the product (**2.2.8**, 483 mg, 3.39 mmol) as a colourless oil. Yield: 95%, >95% ee. The ee was determined to be >95% by HPLC analysis for 3,5-dinitrobenzoate derivative, (3S)-2-(3,5-dinitrobenzoyloxy)-4- trimethylsilyl-3-butyne (Daicel Chiralcel OD-H, 5% 2-propanol in hexane, 0.5 mL/min, X = 254 nm, S isomer 30.0 min, R isomer 34.1 min).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.56 – 4.47 (m, 1H), 1.45 (d, *J* = 6.6 Hz, 3H), 0.17 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 107.87, 87.85, 58.26, 24.06, -0.28.

All data is consistent with that reported in literature.

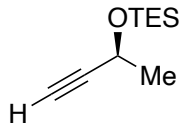


(*S*)-but-3-yn-2-ol (2.2.9)[48]

To a stirring solution of TMS alcohol (**2.2.8**, 178 mg, 1.25 mmol) in 2 mL of MeOH was added K_2CO_3 (518 mg, 3.75 mmol). The reaction mixture was stirred for 1 h, checked by TLC and quenched with H_2O. The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified vacuum distillation (1 torr, 25 °C) to yield the product as a colourless oil (**2.2.9**, 82 mg, 1.18 mmol).

Yield 94%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.57 – 4.47 (m, 1H), 2.45 (d, *J* = 2.0 Hz, 1H), 2.01 (s, br, 1H), 1.47 (dd, *J* = 6.6, 1.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 85.82, 72.03, 58.16, 24.20.

All data is consistent with that reported in literature.

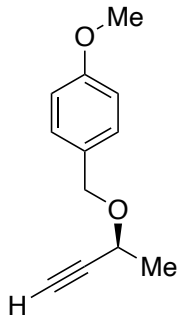


(*S*)-(but-3-yn-2-yloxy)triethylsilane[49]

To an oven-dried, degassed flask, (*S*)-but-3-yn-2-ol (**2.2.9**, 84 mg, 1.19 mmol) and 2,6-dimethylpyridine (249 µL, 2.14 mmol) was stirred with 2 mL of DCM at 0 °C. TESOTf (323 µL, 1.42 mmol) was added dropwise. After stirring for 2 hours, checked by TLC, the reaction was quenched with $NaHCO_3$ followed by an addition of water. The reaction mixture was extracted with DCM, dried over $MgSO_4$, filtered and concentrated under vacuo. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford (*S*)-(but-3-yn-2-yloxy)triethylsilane (124 mg, 0.671 mmol) as a colourless oil.

Yield: 56%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.51 (q, *J* = 6.5 Hz, 1H), 2.37 (s, 1H), 1.47 – 1.41 (m, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.74 – 0.54 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.67, 147.63, 147.32, 147.00, 141.42, 141.39, 128.71, 95.69, 77.00, 74.99.

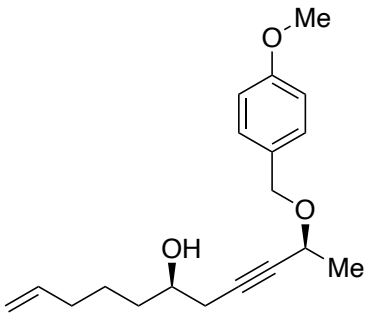
All data is consistent with that reported in literature.



(*S*)-1-((but-3-yn-2-yloxy)methyl)-4-methoxybenzene (2.2.6)

To a stirred suspension of 60% NaH (286 mg, 7.14 mmol) in 4 mL of THF at 0 °C was added (*S*)-but-3-yn-2-ol (**2.2.9**, 357 mg, 5.10 mmol) of. After 30 min, 4-methoxybenzyl chloride (1036 μL, 7.63 mmol) was added followed by a catalytic amount of TBAI. The reaction was allowed to reach r.t. and stirred for 2 days. The mixture was then diluted with H_2O and Et_2O, the organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 10:90) to afford the product (**2.2.6**, 746 mg, 0.671 mmol) as a colourless oil.

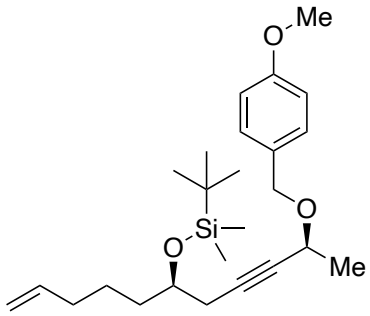
Yield: 77%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 (d, 10.2 Hz, 2H), 6.89 (d, 10.2 Hz, 2H), 4.72 (d, *J* = 11.4 Hz, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 4.18 (dd, *J* = 6.7, 2.1 Hz, 1H), 3.83 – 3.76 (m, 3H), 2.46 (d, *J* = 2.1 Hz, 1H), 1.46 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.32, 130.76, 129.92, 129.63, 113.82, 113.77, 83.83, 72.99, 72.33, 70.11, 55.24, 22.02; **MS (ESI+)** m/z 190 [M]; **HRMS** calcd for $C_{12}H_{14}O_2$ ($[M+H]^+$) 191.1072 found 191.1043.



(6*R*,10*S*)-10-((4-methoxybenzyl)oxy)undec-1-en-8-yn-6-ol (2.2.10)

n-BuLi (0.315 mL, 0.788 mmol, 2.5 M in hexane) was added dropwise to a solution of (*S*)-1-((but-3-yn-2-yloxy)methyl)-4-methoxybenzene (**2.2.6**, 100 mg, 0.526 mmol) in anhydrous toluene (5 mL) at -78 °C. After stirring for 1 hour, the epoxide (**2.2.1**, 118 mg, 1.05 mmol) was added at -78 ℃, followed by $BF_3.Et_2O$ (149 mg, 1.05 mmol). The reaction was stirred for one hour at -78℃ and left to stir overnight at -30 °C. On completion, the mixture was diluted with water and extracted with Et_2O (20 mL x 3). The combined organic solution was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/hexane 10:90) to afford the product (**2.2.10**, 128 mg, 0.260 mmol) as a colourless oil.

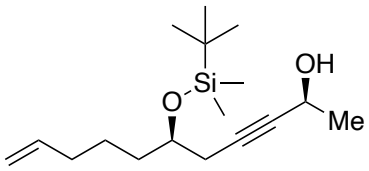
Yield: 81%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.86 – 5.75 (m, 1H), 5.04 – 4.94 (m, 2H), 4.68 (d, *J* = 11.4 Hz, 1H), 4.43 (d, *J* = 11.4 Hz, 1H), 4.19 (qt, *J* = 6.6, 1.9 Hz, 1H), 3.80 (s, 3H), 3.78 – 3.71 (m, 1H), 2.48 (ddd, *J* = 16.6, 4.9, 1.9 Hz, 1H), 2.38 (ddd, *J* = 16.6, 6.7, 1.9 Hz, 1H), 2.16 – 2.03 (m, 3H), 1.63 – 1.52 (m, 3H), 1.43 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.21, 138.45, 130.00, 129.54, 114.71, 114.28, 113.76, 82.77, 81.67, 70.02, 69.90, 64.24, 55.23, 35.62, 33.52, 27.67, 24.79, 22.37; **MS (ESI+)** m/z 303 $[M+H]^+$; **HRMS** calcd for $C_{19}H_{26}O_3$ ($[M+H]^+$) 303.1960 found 303.2009.



***tert*-butyl(((6*R*,10*S*)-10-((4-methoxybenzyl)oxy)undec-1-en-8-yn-6-yl)oxy)dimethylsilane (2.2.11)**

To an oven-dried, degassed flask, (6*R*,10*S*)-10-((4-methoxybenzyl)oxy)undec-1-en-8-yn-6-ol (**2.2.10**, 187 mg, 0.618 mmol) and 2,6-dimethylpyridine (130 µL, 1.11 mmol), DMAP (1.5 mg, 0.012 mmol) was stirred with 2 mL of DCM at 0 °C. TBSOTf (213 µL, 0.928 mmol) was added dropwise. After stirring for 2 hours, checked by TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ solution followed by an addition of water. The reaction mixture was extracted with DCM, dried over $MgSO_4$, filtered and concentrated under vacuo. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford the product (**2.2.11**, 252 mg, 0.604 mmol) as a colourless oil.

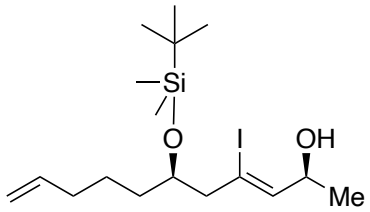
Yield: 98%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.89 – 5.74 (m, 1H), 5.05 – 4.91 (m, 2H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.43 (d, *J* = 11.3 Hz, 1H), 4.23 – 4.12 (m, 1H), 3.88 – 3.76 (m, 4H), 2.39 (dt, *J* = 6.6, 1.9 Hz, 2H), 2.12 – 2.00 (m, 2H), 1.71 – 1.46 (m, 4H), 1.42 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.08 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.20, 138.77, 130.29, 129.61, 123.96, 114.48, 113.76, 82.74, 81.70, 70.96, 69.87, 64.26, 55.27, 36.10, 34.52, 33.73, 30.20, 29.69, 27.66, 25.84, 25.72, 24.40, 22.40, -4.44, -4.63; MS (ESI+) m/z 417 $[M+H]^+$; HRMS calcd for $C_{25}H_{40}OSi$ ($[M+H]^+$) found



(2*S*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)undec-10-en-3-yn-2-ol (2.2.3)

To a stirred solution of PMB ether (**2.2.11**, 83.3 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) and H_2O (0.2 mL) at 0 °C was added 2,3-dicyano-5,6-dichloro-1,4-benzoquinoline (68 mg, 0.3 mmol) in one portion. The reactants were stirred at 0°C for 0.5 h and allowed to warm to r.t. After 3 h 15 min, sat. aq. $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was then dissolved in 1 mL of ethanol, added Girard's reagent T (33.5 mg, 0.2 mmol) and stirred at 45 °C for 2-3 hours, checked by TLC. On completion, the solvent was evaporated, and water was added. The layers were separated and extracted with Et_2O (3 x 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 10:90) to afford the product (**2.2.3**, 59.3 mg, 0.2 mmol) as a colourless oil.

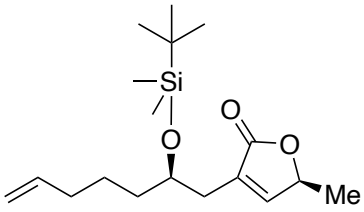
Yield: quantitative. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.83 – 5.78 (m, 1H), 5.05 – 4.90 (m, 2H), 4.52 – 4.50 (m, 1H), 3.82 – 3.73 (m, 1H), 2.34 – 2.31 (m, 2H), 2.11 – 2.00 (m, 2H), 1.64 – 1.46 (m, 4H), 1.42 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.08 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.82, 120.58, 89.90, 87.77, 83.46, 83.14, 82.82, 64.54, 42.18, 39.73, 33.62, 31.97, 31.83, 30.66, 24.14, 1.60, 1.43; **MS (ESI+)** m/z 297 $[M+H]^+$; **HRMS** calcd for $C_{17}H_{32}O_2Si$ ($[M+H]^+$) 297.2250 found 297.2207.



(2*S*,6*R*,*Z*)-6-((*tert*-butyldimethylsilyl)oxy)-4-iodoundeca-3,10-dien-2-ol (2.2.12)

To a solution of alkyne (**2.2.3**, 100 mg, 0.337 mmol) in anhydrous THF (1.25 mL), a 3.3 M Red-Al solution (245 μL, 3.3 M in toluene) was added at 0 °C. The reaction mixture was left to warm to rt and stirred overnight. Anhydrous ethyl acetate (79 μL, 71 mg, 0.809 mmol, 0.99 equiv w.r.t Red-Al) was added and stirred for 20 min. The solution was then cooled to -78 °C and a solution of iodine (128.5 mg, 0.505 mmol in 0.5 mL of THF) was added dropwise. The deep brown/red solution was allowed to warm to room temperature for 15 min, and stirred for 15 min at rt before being quenched with a 1:1 mixture of Na_2SO_3 and Rochelle's salt. The reaction mixture was extracted with EtOAc, washed with aqueous NaCl, dried over $MgSO_4$, filtered and concentrated in chromatography (silica gel, eluent EtOAc/ hexane 10:90) to afford the product (**2.2.12**, 100 mg, 0.236 mmol) as a colourless oil.

Yield: 70%. **FTIR** (CH_2Cl_2, cm^{-1}): ν_{max} 587, 1605, 3684; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.84 – 5.74 (m, 1H), 5.65 (d, *J* = 1.2 Hz, 1H), 5.03 – 4.94 (m, 2H), 4.42 (app quint, *J* = 6.4 Hz, 1H), 3.96 (app quint, *J* = 6 Hz, 1H), 2.62 (dd, *J* = 6.0, 6.4 Hz, 1H), 2.54 (dd, *J* = 6.0, 6.4 Hz, 1H), 1.48 – 1.37 (m, 2H), 1.28 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.08 (d, *J* = 2.8 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.8, 138.8, 114.8, 104.8, 77.2, 73.0, 70.7, 52.8, 35.7, 33.9, 26.1, 24.2, 22.1, 18.2, -4.0, -4.2; **MS** (ESI+) m/z 425 $[M+H]^+$; **HRMS** calcd for $C_{17}H_{33}IO_2Si$ ($[M+H]^+$) 425.1373 found 425.1394.



(*S*)-3-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)hept-6-en-1-yl)-5-methylfuran-2(5*H*)-one (2.2.5, RHS)

The vinyl iodide (**2.2.12**, 100 mg, 0.236 mmol), $Pd(PPh_3)_2Cl_2$ (5 mg, 0.007 mmol), K_2CO_3 (143 mg, 1.04 mmol) and 2 drops of hydrazine (THF solution) were combined in THF (2 mL) sealed into a pressure tube equipped with a magnetic stir bar. The apparatus was charged with 60 psi CO, sealed, and heated to an internal temperature of 60 °C. The solution was stirred for 48 h. The apparatus was allowed to cool, and the CO atmosphere was slowly released in a well-ventilated fumehood. The mixture was filtered through a plug of Celite with EtOAc. The reaction mixture was extracted with EtOAc, washed with aqueous NaCl, dried over $MgSO_4$, filtered and concentrated in chromatography (silica gel, eluent EtOAc/ hexane 10:90) to afford the product (**2.2.5**, **RHS**, 58.8 mg, 0.181 mmol) as a colourless oil.

Yield: 77%. **FTIR** (CH_2Cl_2, cm^{-1}): ν_{max} 1752, 1605, 1319; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 1.2 Hz, 1H), 5.81 – 5.75 (m, 1H), 5.02 – 4.93 (m, 2H), 3.96 (app quint, *J* = 5.6 Hz, 1H), 2.41 (m, 1H), 2.03 (m, 2H), 1.48 – 1.44 (m, 4H), 1.41 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.04 (d, *J* = 2.8 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.9, 151.7, 138.6, 130.8, 114.6, 77.2, 77.0, 76.7, 69.7, 36.4, 33.7, 32.9, 25.9, 25.8, 24.3, 24.2, 19.1, 18.0, -4.5; **MS** (ESI+) m/z 325 $[M+H]^+$; **HRMS** calcd for $C_{18}H_{32}O_3Si$ ($[M+H]^+$) 325.1373 found 325.2189.

2.5 References

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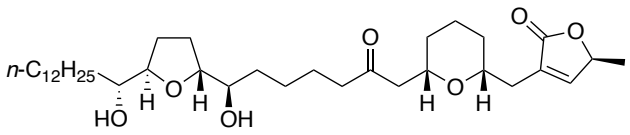
CHAPTER 3

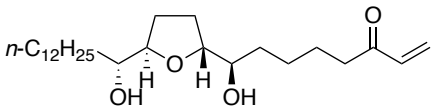
Synthesis of Montanacin D:

Left Hand Side (LHS)

3.1 Introduction



Montanacin D



LHS Fragment

Montanacin D is considered a unique member of its family, and the great interest invested in this molecule is in large part due to the tetrahydrofuran moiety present in the LHS Fragment. Acetogenins are characterized by a long aliphatic chain of 35 to 38 carbons bonded to a γ-lactone terminally substituted by β-unsaturated methyl, with one or two THFs located along the hydrocarbon chain, in this case, one THF. The approach to Montanacin D is done using a convergent synthesis. The final steps involve high diastereoselectivity in the *oxa*-Michael step in mild conditions and cross-metathesis. The tetrahydrofuran present in this natural product will be formed using a combination of asymmetric dihydroxylation and asymmetric epoxidation.

3.2 Discussion of Key Steps

3.2.1 Jacobsen Epoxidation

In 1990, Jacobsen independently reported the first facile, asymmetric epoxidation of unfunctionalized *cis* and *trans* olefins using a manganese-salen catalyst.[1] Despite commendable progress in asymmetric catalysis, only a limited variety of trisubstituted, *cis*-disubstituted and *trans*-disubstituted systems can be converted to epoxides in highly enantioenriched forms. In 1994, the Fluka Prize *Reagent of the Year* was given to Jacobsen for a new compound that has been shown to be a reagent of great importance, as it produced "enantiomerically highly enriched epoxides from unfunctionalized alkenes."

The Jacobsen's catalyst belongs to a large family of *trans*-1,2-diaminocyclohexane based derivatives commonly used for asymmetric reactions.[2] A range of catalysts applicable for asymmetric synthesis were made simply by replacing the metal centre of the Jacobsen catalyst. To name a few, displayed in Figure **1** below, stereogenic alcohols were produced when the catalyst complex was made of a cobalt metal centre that was used for the enantioselective catalytic ring opening of epoxides. When the metal centre was replaced with chromium, enantioselective ring opening of *meso* epoxides gave α-azidoalcohols.[3]

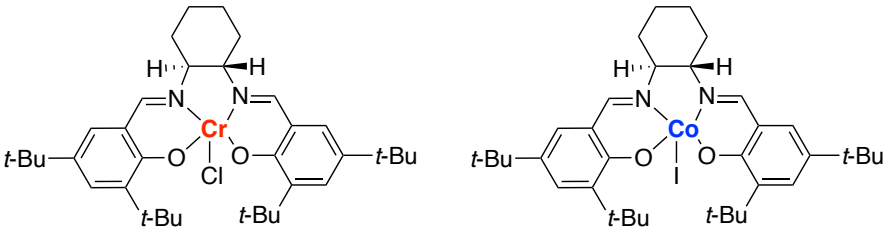


Figure 1. Jacobsen Catalysts with Various Metal Centres

Ever since the introduction of practical asymmetric catalysis methods for the synthesis of epoxides in their highly enantioenriched form, the benefits for utilizing them as useful precursors for the stereo-controlled synthesis of intricate organic compounds increased exponentially. Other than the epoxidation of chiral and prochiral alkenes, asymmetric ring opening of *meso* epoxides and kinetic resolutions of racemic epoxides have also proven valuable in furnishing compounds that were enantiomerically enriched. Considerable progress has been achieved in the advancement of catalytic methods for asymmetric epoxide formation, with ample room available for improvement in extensive use in organic synthesis.

In 1991, Jacobsen[4] and co-workers reported a synthetic catalyst capable of alkene epoxidation with a selectivity higher (>90% ee) than that had been previously recorded[5]. This readily available chiral salen-based Mn(III) complex was able to catalyse the epoxidation of olefins, in good yields, using household bleach – a readily available oxygen atom source compared to iodosylmesitylene[1] which was previously reported.

Previous studies have laid the groundwork for the design of this catalyst.[1, 6-7] To account for the sense and degree of enantioselectivity displayed by the chiral salen and porphyrin-Manganese(III) complexes with *cis*-alkenes, a side-on approach of the alkene to the metal-oxo bond of a high valent intermediate has been invoked. With this in mind, two structural features were what contributed to the catalyst's selectivity. Firstly, bulky groups were responsible in preventing the approach of the substrate and led it away from the diimine bridge. Secondly, the non-symmetrical feature of the diimine bridge allowed access if the attack was made *anti* to the phenyl group but did not favour access if the attack was made

syn to the phenyl group. With three of the four sides of possible approaches towards the complex accounted for, only one approach remains, that was presumably inaccessible owing to the steric bulk of the diimine bridge. While the fundamental basis of the enantioselectivity has been a subject of discussion for many years,[8] the original suggestion by Jacobsen for the epoxidation of *cis*-alkenes that were tested could be explained using this general model illustrated below in Figure **2**.[4]

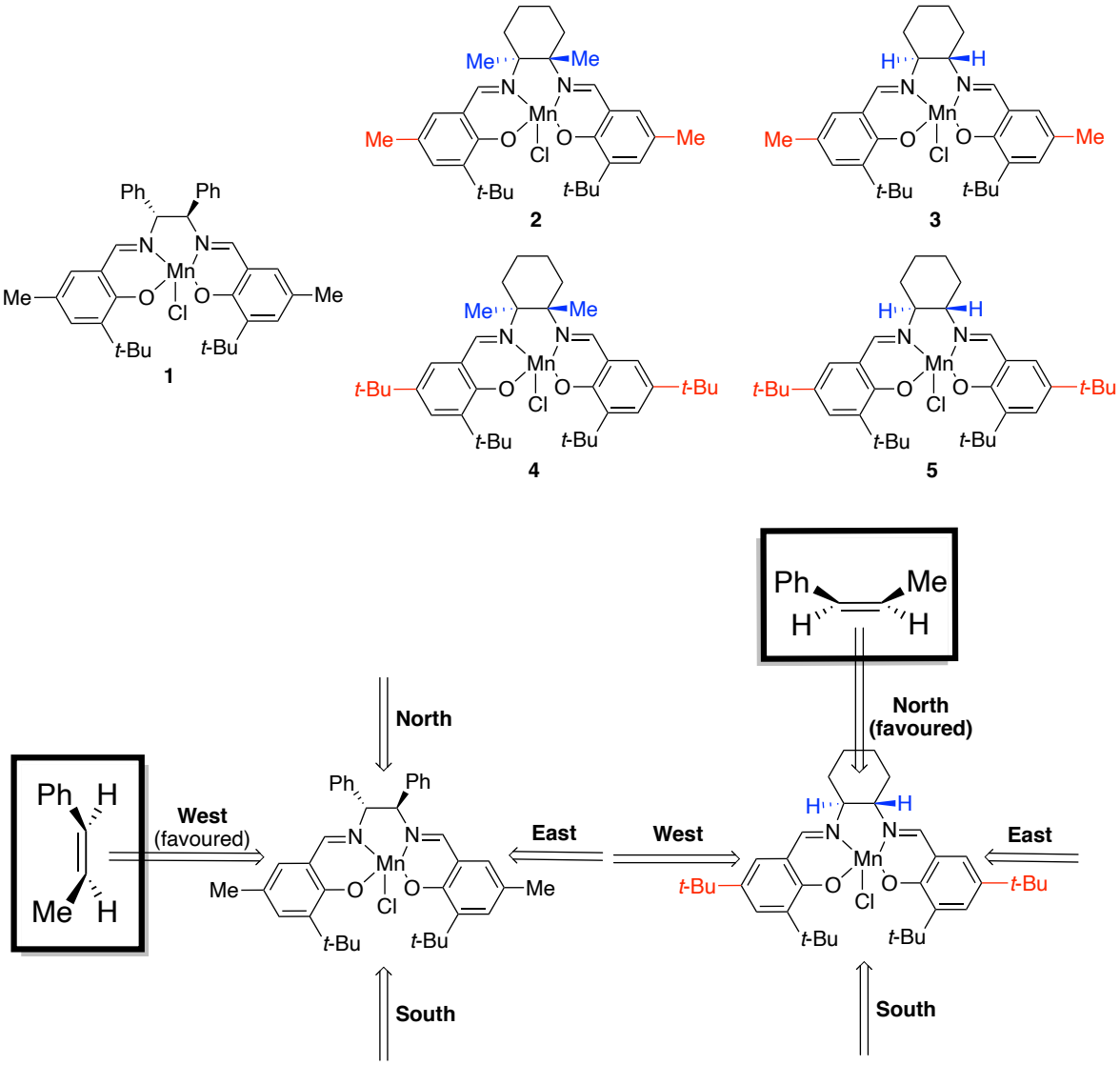


Figure 2[4]. Jacobsen's General Model

Fixing the substituents axially across the diimine bridge could possibly have a greater effect in differentiating approaches from the western and eastern directions of the complex. The catalysts were prepared from *trans*-1,2-diamino-1,2-dimethylcyclohexane with the above prediction in mind. However, the results did not yield as predicted as the corresponding salen derivative **2** only showed average enantioselectivity when the epoxidation was tested with *cis*-β-methylstyrene. In addition, it was also unanticipated that the sense of asymmetric induction happened opposite from what has been postulated from the western approach in Figure **2**. From this observation, it can be gleaned that **2** might have undergone competitive attack from the northern approach as **2** is less sterically hindered than **1** in the diimine bridge region.

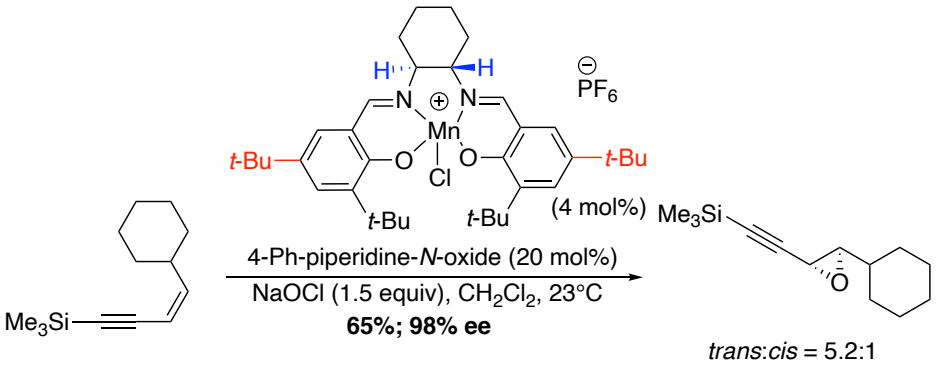
The observation that **3** also gave the unexpected enantiomer with *cis*-β-methylstyrene supported the above suggestion that a less hindered region of the diimine bridge would undergo competitive attack from the northern approach since **3** is less hindered than **2**. These results were complementary with the supported observation as **3** gives a higher ee than **2**. Another pair of *t*-butyl groups were introduced to the positions para to the oxygens in complex **5**. The incorporation of the *t*-butyl groups proved to be beneficial as it resulted in better catalyst selectivity, possibly owing to the fact that apart from the northern approach, it heavily disfavours all side-on approach of the alkene. The selective approach from the northern region can be explained by larger substituents on the substrate, avoiding interaction with the axial hydrogen on the diimine bridge.

From the results gathered by the epoxidation of the range of alkenes, it is evident that catalyst **5** is capable of exhibiting high enantioselectivity with a range of *cis*-disubstituted alkenes. Extreme selectivity was shown in the epoxidation of 2,2-dimethylchromene and its derivatives which in turn allows access to crucial classes of enantiomerically pure biologically active compounds. Subsequently, the epoxides of ketals can subsequently be regioselectively ring-opened to form either α- or β- hydroxyketals, making them flexible chiral building blocks. Optically active erythro-glycidic esters that were known to be difficult to form have now been enabled access with this methodology. The addition of 4-phenyl *N*-oxide to *cis*-methyl cinnamate has shown to result in an improvement in product yield and catalyst selectivity.[9]

One could also harness the Jacobsen methodology for selective asymmetric epoxidation if presented with a diene that had both *cis* and *trans* alkenes. The *cis* C=C would be selectively epoxidized as the rate of reaction for *trans* alkenes is reported to be much slower[4].

Corey[10] and co-workers set out to achieve a more in-depth understanding of the preferred pathway for the epoxidation that could be explained by the key characteristics of the Jacobsen epoxidation and its variables. It has been observed that for alkenes conjugated with a π-system, conjugated cyclic trisubstituted alkenes[9] and conjugated cyclic (*Z*)-1,2-disubstituted alkenes underwent highly enantioselective epoxidation. A postulated two-step pathway[11] with interfering C-C bond rotation was hinted at when an observation with epoxidation of conjugated acyclic (*Z*)-1,2-disubstituted alkenes gave both trans- and *cis*-epoxides (Scheme **1**). The enhancement of the two-step pathway could

be done with 25 mol % of a range of cinchona alkaloid-derived quaternary ammonium salts (Figure **3**) in benzene-type solvents with bleach functioning as the oxidant.[12] The nature of the oxidant would have an effect on the enantioselectivity of the epoxidation.[8] In this case, the oxidants are PhIO and NaOCl. The enantioselectivity of the epoxidation was enhanced when electron-donating groups *para* to the phenolic hydroxyl of the salen ligand were included while the substitution of a nitro group effects the opposite.



Scheme **1**[10]. Epoxidation of a Conjugated Acyclic (Z)-1,2-Disubstituted Olefin

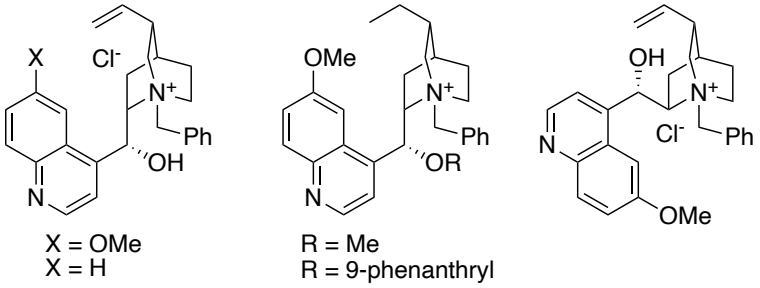


Figure 3[12]. Alkaloid-derived Quaternary Ammonium Salts

Based on the experimental observations summarized above, a mechanistic continuum of pathways for the epoxidation of conjugated alkenes seemed plausible. This mechanism suggested that two of the epoxide bonds were formed at different rates in the transition state. On one end of the continuum, the two bonds between oxygen and the alkene carbons were forming in a synchronous manner while the other end of it was an asynchronous two-step pathway. It seems that since conjugated alkenes were better substrates for enantioselective Jacobsen epoxidation, the asynchronous two-step pathway would appear logical and that a huge positive charge would be formed on the alkene during attack by the oxygen. In the case of styrene, delocalisation of the positive charge suggested that the O-CH_2 bond formation came before that of the O-CH-Ph bond, illustrated in Figure **4**.

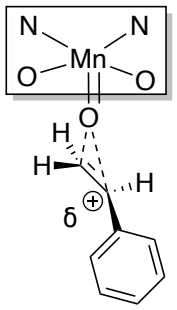


Figure 4. Transition state

It is important to know that the oxygen transfer process was possibly asynchronous with the positive charge being made in the oxidation of the π-group of the double bond. With this in mind, the group began to explore a deeper understanding of the fundamentals of enantioselectivity. The argument was based on two assumptions. The first was that electrophilic attack happened on the π-conjugated double bond to give a non-symmetrical transition state, displayed above in Figure **4**. The second was that both 6-membered chelate

rings in the chiral (salen)Mn(V) were positioned opposite one another, shown in Figure **5** below.

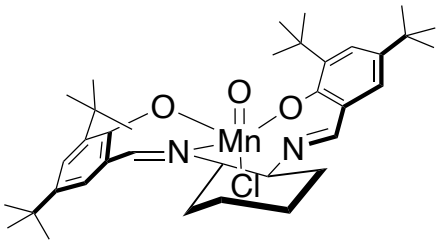


Figure 5. 6-membered chelate rings

When the *t*-butyl groups are placed far apart from each other, it minimizes their chances of clashing. Using indene as an example, it could be seen that these assumptions support that the pretransition-state geometry could be stabilized by the electrostatic interaction between the partially positive charged benzylic carbon and the partially negative charged phenoxy oxygen with indene approaching the oxygen. This is illustrated in Figure **6** below.

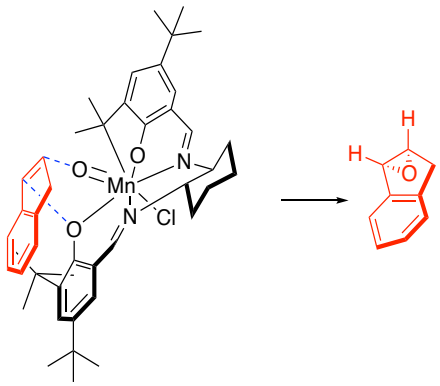


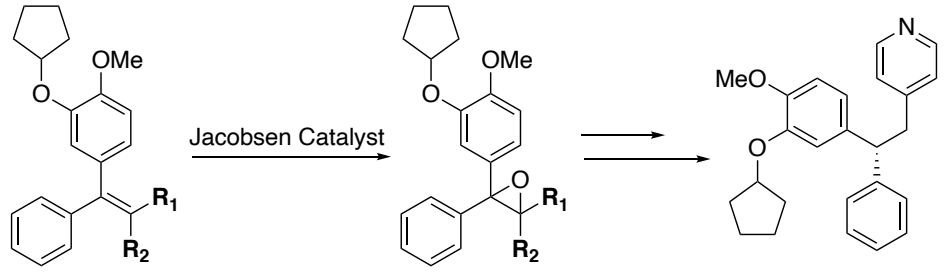
Figure 6. 3D visualization of favoured pathway in epoxidation of indene

The concurrent electrophilic attack by the oxygen of the Mn-oxo group on indene and the electrostatic interaction between the partial opposite charges between

the benzylic carbon and phenoxy oxygen of the indene alkene is shown in the model (Figure **6**). Additionally, this model helped in the understanding that *trans*-1,2-disubstituted alkenes display weak enantioselectivities. Moreover, this model was also able to accurately predict the absolute configuration of the major product of epoxidation of conjugated cyclic (*Z*)-1,2-disubstituted alkenes. This model succinctly specified the preferred relative orientations of the approach by the alkene substrates on (salen)Mn(V)-oxo which engendered a straightforward prediction of the absolute configuration of the products of Jacobsen epoxidation.

The application of the method is prevalent in natural product syntheses over the years.[13-14] The usefulness of the catalyst is highlighted in these two examples found below.

The asymmetric synthesis of CDP840[13], a phosphodiesterase (PDE) IV inihibitor, achieved by Merck Research Laboratories, applied Jacobsen epoxidation to control the absolute stereochemistry of both the *E* and *Z*-triaryl alkene (Scheme **2**). The *ee* obtained was 48% and 89% respectively. Jacobsen[4] mentioned that *trans*-alkenes tend to be a worse substrate for this catalyst, compared to its *cis* counterpart. The difference in stereoselectivity can be attributed to the skewed side-on approach model proposed by Jacobsen. The activation energy of the transition state in the *trans*-alkene is raised due to the added steric hindrance from the interaction of the catalyst ligand and the substrate, which explains the decreased enantioselectivity and rate of conversion, compared to the *cis*-alkene (Scheme **2**).

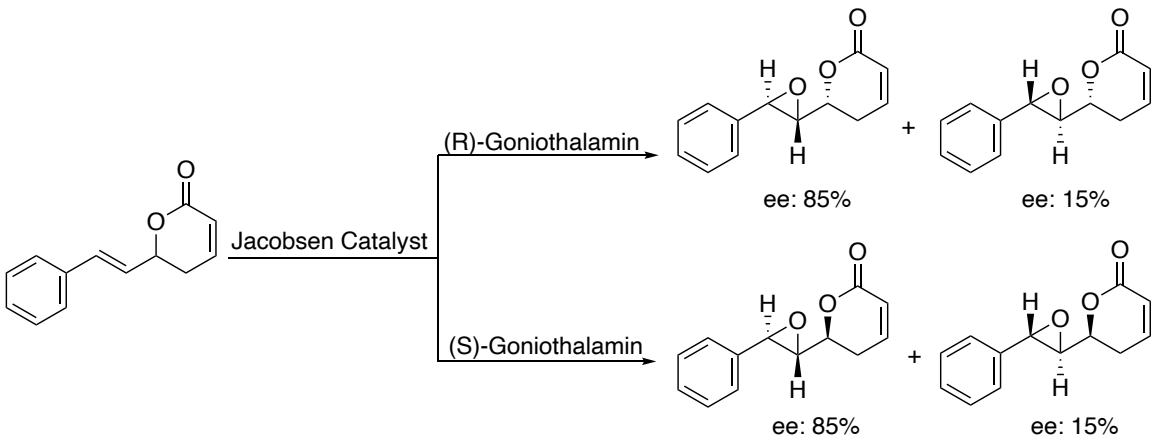


R_1 = 4-pyridyl, R_2 = H
R_1 = H, R_2 = 4-pyridyl

ee	yield
89	58
48	70

Scheme 2.[13] Asymmetric Synthesis of CDP840

Pilli and co-workers achieved the asymmetric total synthesis of Goniothalamin oxide[14] in 52% yield via Jacobsen epoxidation starting from *trans*-cinnamaldehyde (Scheme **3**). Goniothalamin oxide is a styryl lactone isolated from *Goniothalamus* known to show tripanocidal and larvicidal properties (Scheme **3**). The group optimized the stereoselectivity of the epoxidation step from 3:2 with *m*-cpba to 6:1 with Jacobsen's catalyst.



Scheme 3.[14] Asymmetric Synthesis of Goniothalamin Oxide

3.2.2 Berkessel Epoxidation

Developments in the field of organocatalytic epoxidations and metal-based catalytic asymmetric epoxidations have both been made. In spite of these tremendous advancements in catalytic asymmetric epoxidation, terminal alkenes have remained largely overlooked when these methodological developments were made. Apart from Strukul's[15] catalyst (Figure **7**) that uses hydrogen peroxide as an oxidant, the existence of a one-step, relevant method for the catalytic transformation of terminal alkenes to highly enantiomerically enriched epoxides was largely unknown.[16]

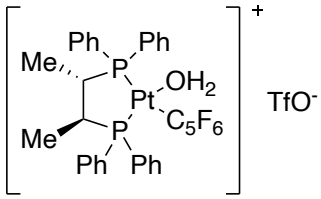
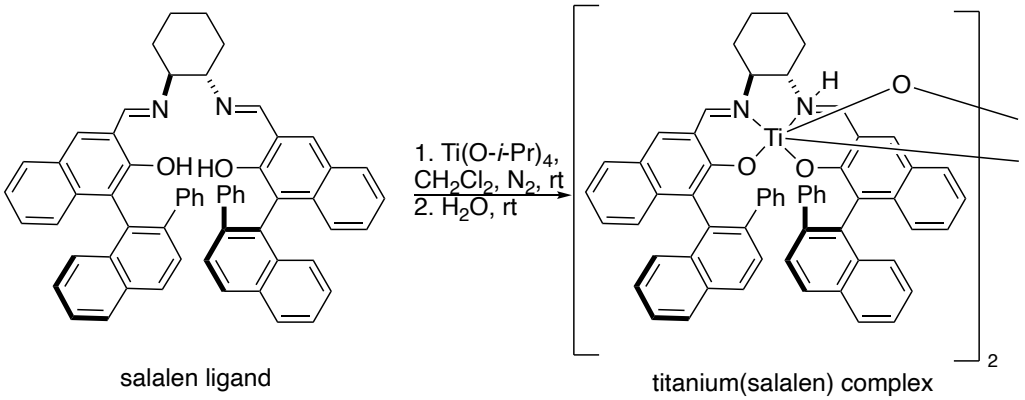


Figure 7.[15] Strukul Catalyst



Salalen Ligands

Scheme 4.[17] Salalen Ligands

The Berkessel group was motivated by the improvement of the methodology of asymmetric epoxidation of inactive, unconjugated alkenes with hydrogen peroxides. This was the motivation behind the development of their titanium complex. Berkessel's previous work had dealt with methodology for the synthesis

of salalen ligands (Scheme **4**) and in 2007, they started experimenting with ligands derived from *trans*-1,2-diaminocyclohexane.[18] When the corresponding titanium complexes were subjected to epoxidation, conjugated alkenes gave good yields and enantioselectivities while unconjugated alkenes gave low conversions. A mass spectroscopy study showed that competing oxidative catalyst degradation was the reason for the low conversions of unconjugated alkenes.[19]

Instead of using *trans*-1,2-diaminocyclohexane as the chiral building block for active and selective salalen ligands, the Berkessel group turned their attention to the use of *cis*-1,2-diaminocyclohexane instead and managed to overcome the oxidative degradation problem.[20-21] Epoxidation of inactivated alkenes using hydrogen peroxide with ligands **3a** and **3b** gave epoxides with high enantioselectivity. The group looked to improve their catalyst further by introducing the 3-(pentafluorophenyl) substituent. The ligand, **3c**, was superior in terms of catalyst stability and activity and allowed the epoxidation of a range of inactivated alkenes to proceed in high enantioselectivity and high yield. The benefits of a CF_3 substitution on the Ti-salan motif contributed to the discovery of **3c**. Thus, the group investigated the general effects of fluorination.[22] After various attempts with fluorinated substituents, the group decided on the pentafluorophenyl substituent as they observed an improvement in enantioselectivity and catalytic activity compared to previously synthesised ligands.

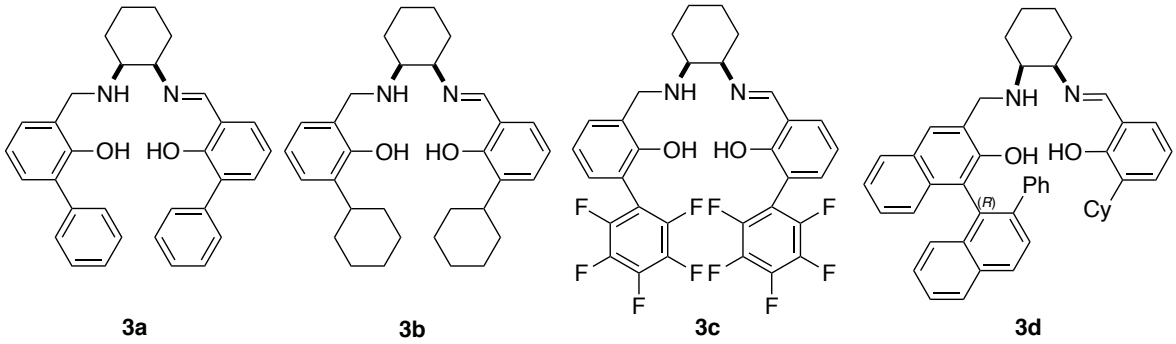
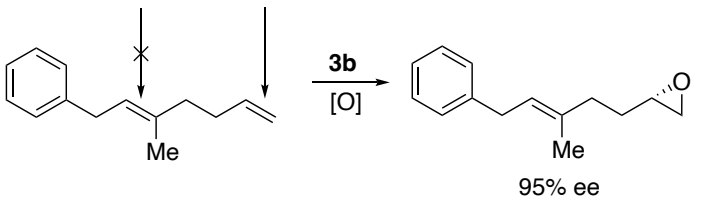
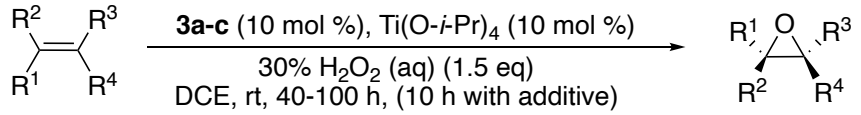


Figure 8. Ligands Showing Most Promising Enantioselectivity

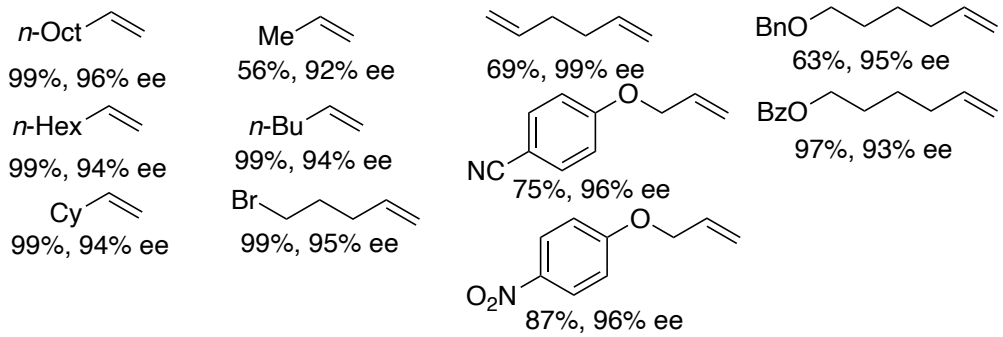
The rate of epoxidation with *cis*-1,2-disubstituted and terminal alkenes is linked to high enantioselectivity. But the same cannot be said for *trans*,1-2,disubstituted, 2,2-disubstituted and trisubstituted alkenes, typically resulting in low yields with low enantioselectivities. As a result, the selective epoxidation of terminal alkenes can happen when presented with a substrate bearing a terminal alkene and a trisubstituted alkene (Scheme **5**). An example is shown below in Scheme **6** together with the various ligands.



Scheme 5. Regioselective Epoxidation



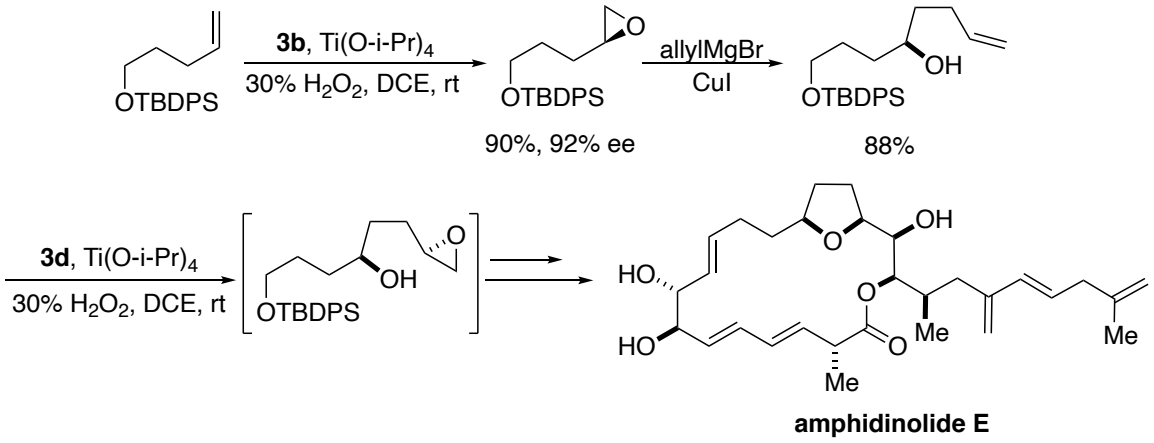
Examples with 3c:



Scheme **6**[23]. Ligands Showing Most Promising Enantioselectivity

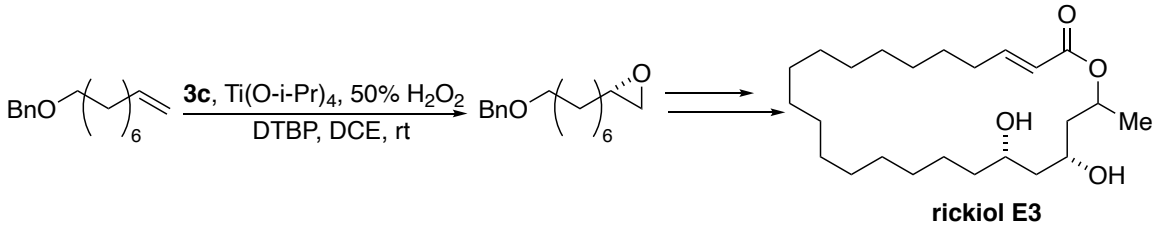
Acidic and basic additives were discovered as co-catalysts that could greatly enhance the rate of the epoxidation.[21] Without the use of the additive, a typical reaction took 40-45 h to complete, while a reaction would only take 10 h if the co-catalyst was employed. Apart from the significant decrease in reaction time, the use of the co-catalyst would also reduce the catalyst loading from 1 to 0.5 mol % while maintaining the enantioselectivity. Three additives proved to be the most beneficial during the screening of acids and bases. They are tetra-*n*-butylammonium hydrogen sulfate, pentafluorobenzoic acid and 2,6-di-*tert*-butylpyridine.

The Berkessel epoxidation has been applied recently in natural product synthesis. Costa, Vilarrasa and co-workers reported the total synthesis of macrolide amphidinolide E[24] (Scheme **7**), using the epoxidation methodology twice to generate their desired building block towards the natural product.



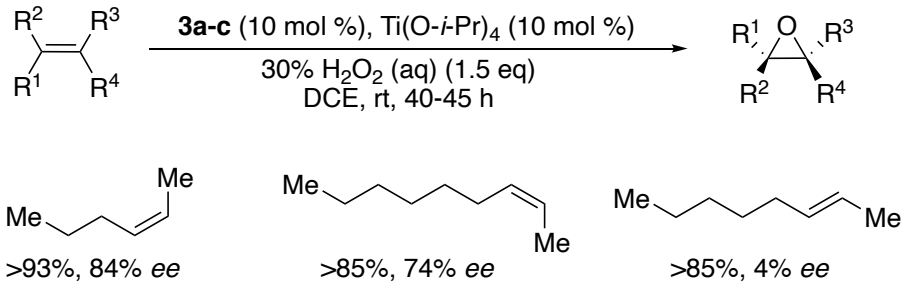
Scheme 7[23]**.** Total Synthesis of amphidinolide E

Stadler and co-workers reported the total synthesis of 24-membered rickiol E3[25] (Scheme **8**), using a similar methodology. The preliminary steps involved the epoxidation of O-benzyl protected 8-nonenol to the corresponding oxirane intermediate.



Scheme 8. Total Synthesis of rickiol E3

Berkessel[21] also noted that an internal *cis*-alkene was obtained in 93% yield during epoxidation, with an ee value of 84%. While the yield was comparable for the *trans*-alkene, the ee reported was only 4%, revealing that there was almost no enantioselectivity shown. The epoxidation of *cis* and *trans* alkenes are summarised below in Scheme **9**.



Scheme **9**[23]. Enantioselectivity of *cis* and *trans* alkenes

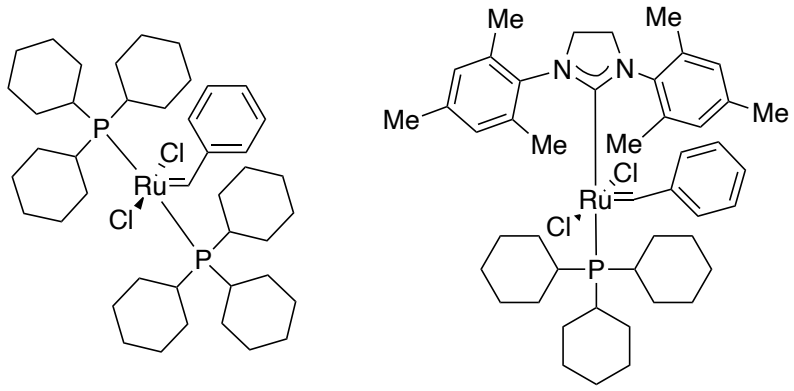
The development of this methodology by Berkessel has enabled a highly yielding, enantioselective one-step epoxidation of inactivated, terminal and unconjugated alkenes. The oxidant, hydrogen peroxide, is also readily available, environmentally harmless and safe, which is an added advantage of this methodology. Berkessel has created a novel class of salalen ligands derived from

cis-1,2-diaminocyclohexane which displayed commendable catalytic activity, stereoselectivity and stability.

This project aims to harness the methodology created by Jacobsen and Berkessel to regioselectively and enantioselectively build an epoxide that is pertinent for the installation of the key 5-membered ring intermediate. The substrate scope of these methodologies would serve as an important basis for the optimisations made to our synthetic strategies. The construction of this 5-membered ring is one of the key-steps that will be explored later in this Chapter.

3.2.3 Cross-Metathesis

The cross-metathesis reaction is the penultimate step of the synthesis of Montanacin D. The commercially available Grubbs' II catalyst (Figure **9**) will be used as it has a higher functional group tolerance and higher activity compared to its predecessor Grubbs' I catalyst. This catalyst also makes for convenient handling in the laboratory because of its stability towards moisture and air. It should also be noted that this catalyst is more effective for cross-metathesis because it is tolerable to a wide range of functional groups in the alkene and are soluble in variable solvents.[26-27]



Grubbs I Catalyst Grubbs II Catalyst

Figure 9. Grubbs' First and Second Generation Catalyst

The first report of double-bond scrambling was published in 1955[22] but the term "olefin metathesis" was only introduced by N. Calderon[28] *et al*. in 1968. The cross-metathesis reaction is an elegant method for the intermolecular exchange of alkylidene fragments between two alkenes promoted by metal-carbene complexes. Prior to the discovery of cross-metathesis, this particular type of carbon-carbon bond formation was achieved through a Wittig reaction or a Horner-Wadsworth-Emmons reaction, both of which require the preparation of their corresponding phosphorus derivatives. Ever since the discovery of cross-metathesis, it has proven to have an array of advantages typical of modern

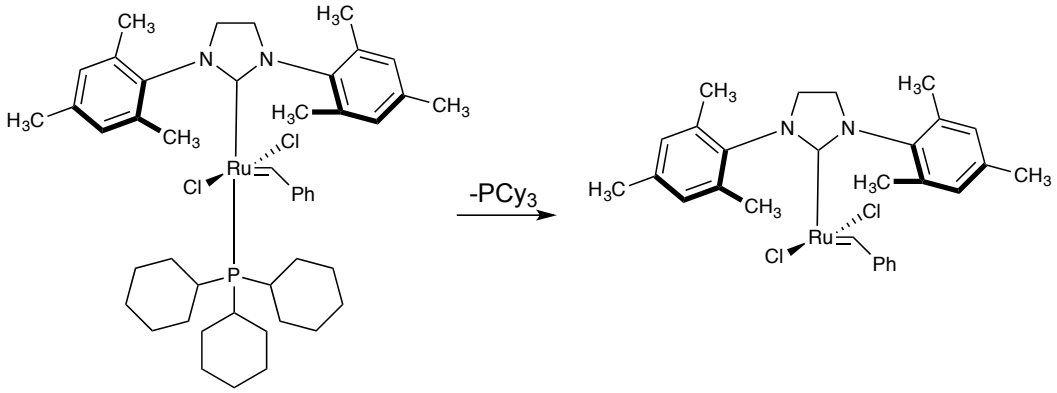
alkene-metathesis reactions.[29] Cross-metathesis is one of several alkene metathesis reactions and it refers to the metal-catalysed trans-alkylidenation of two terminal alkenes to construct new C=C bonds, driven by the entropically favoured evolution of ethylene or propylene in the process. Other alkene metathesis reactions include ring-opening metathesis (ROM), ring-closing metathesis (RCM), ring-opening metathesis polymerisation (ROMP) and acyclic diene metathesis polymerisation (ADMET). These metathesis methods allow access to polymers and molecules that would otherwise be difficult to obtain. RCM makes for easy entry into heterocyclic compounds as well as medium and large carbocycles.[30] ROMP allows the preparation of functionalised polymers that was impossible otherwise. The catalyst before the beginning of 1990s had little functional group tolerance and low performances, which explains why the application of alkene metathesis for the synthesis of complicated organic molecules only emerged then. Up till now, alkene metathesis has proven to be an extensively used and reliable synthetic method. The catalyst system that is currently used ($L(L')X_2Ru=CHR$) has adequate functional group tolerance and is highly active.

Cross-metathesis reactions are able to attain a high level of regio-, stereo-, and chemoselectivity. The process is also catalytic and efficient, where a typical amount of only 1-5 mol % of catalyst is required. High yields can also be achieved under mild conditions and short reaction times. The reversible reaction is relatively atom-economic and usually produces ethylene as the only by-product. The atom economy and by-product make large scale cross-metathesis reactions possible. Since the reaction is reversible, the formation of the desired product can be driven by the removal of ethylene gas using a continuous nitrogen

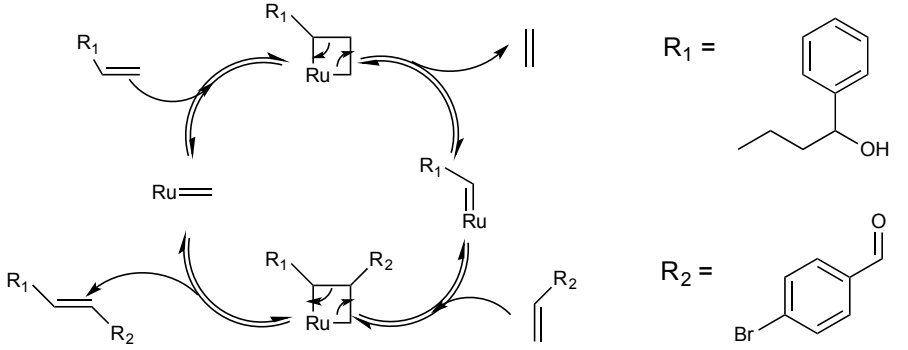
flow through the flask, allowing the reaction to favour the formation of the product.[31-32]

Information gathered from the crystal structures and the extensive kinetic studies conducted on $L_2X_2Ru=CHR$ complexes by Grubbs[33] *et al* can be examined below. The observed activity trends[34] from the cross-metathesis reactions agrees closely with the mechanism that was proposed by Chauvin[35-36]. The proposed mechanistic pathway is illustrated in Scheme **10** below.

Initiation



Catalytic Cycle



Scheme 10.[35-36] Cross-Metathesis Mechanism

The products of cross-metathesis will be an appropriate precursor for further structural elaboration, e.g. epoxidation, cycloaddition, hydrogenation, halogenation. In our case, Montanacin D will be furnished with an oxa-Michael cyclisation, which is dependent on the alkene as a precursor.

3.2.4 Sharpless Dihydroxylation

Another key step in the synthesis of Montanacin D would be the Sharpless asymmetric dihydroxylation. The method combines an alkene with osmium tetroxide in the presence of a chiral quinine or quinidine-derived ligand to form a vicinal diol. Such chiral diols are important in organic synthesis. The introduction of chirality into non-chiral reactants through usage of a chiral catalyst is an important concept, especially for Montanacin D which has 7 chiral centres. High enantioselectivities can be achieved for asymmetric dihydroxylation of alkenes of every substitution pattern. The Sharpless dihydroxylation reaction is also highly regioselective towards electron-rich alkenes, favouring the most electron-rich double bond within the substrate.

The reported *ee* of *cis*-alkenes is much lower compared to those exhibited by *trans*-alkenes. Sharpless[37] reported that *cis*-disubstituted allylic alcohols needed reaction times of 24 – 48 h, compared to the 1 – 4 h needed for *trans*-disubstituted allylic alcohols. The *ee* of the *cis*-substrates reported in Sharpless' article[37] are obtained in ranges from 80 – 86%. As such, in order for complete conversion of the substrate and minimal loss of selectivity, higher temperatures and higher catalyst loadings were required as a workaround.

Katsuki[38] proposed a model that would explain the reason for the sluggish epoxidation for *cis*-disubstituted allylic alcohols. Only the *trans*-alkene substituent (R^1) in Katsuki's Model faces an unrestricted quadrant, providing an explanation to why better enantioselectivities and reaction rates are reflected in *trans*-alkenes. As for *cis*-alkenes, the conformational demand for alleviating the allylic strain due to the small 30° C=C-C-OTi dihedral angle, where H is on the same

plane as the alkene, is energetically preferred than the other two conformations, where R and R' are in the same plane. With alkyl R' being on the bottom of the Transition State, the energy of the Transition State, shown below in Figure **11**, would be raised, resulting in the decrease in reaction rate and enantioselectivity.

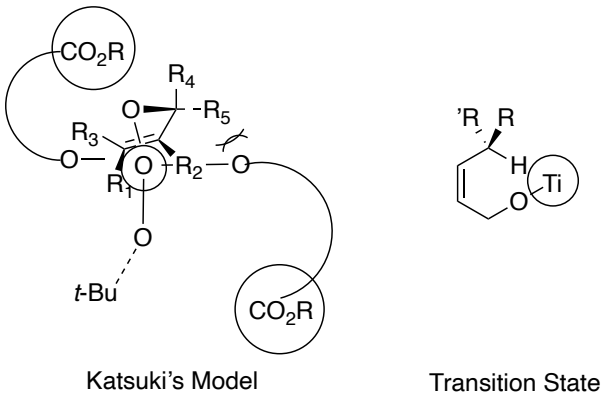


Figure 11[38]. Katsuki's Proposed Model

Sharpless[39] outlined in one of his papers that the PHAL ligands commonly found in AD-mix-α and AD-mix-β did not give good enantioselectivities with *cis*-alkenes. The problem, however, was circumvented with the discovery of Ind ligands, shown below in Figure **12**. The Ind ligand would later prove to be useful in our synthesis.

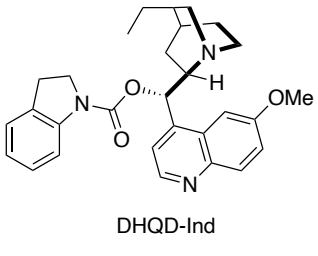
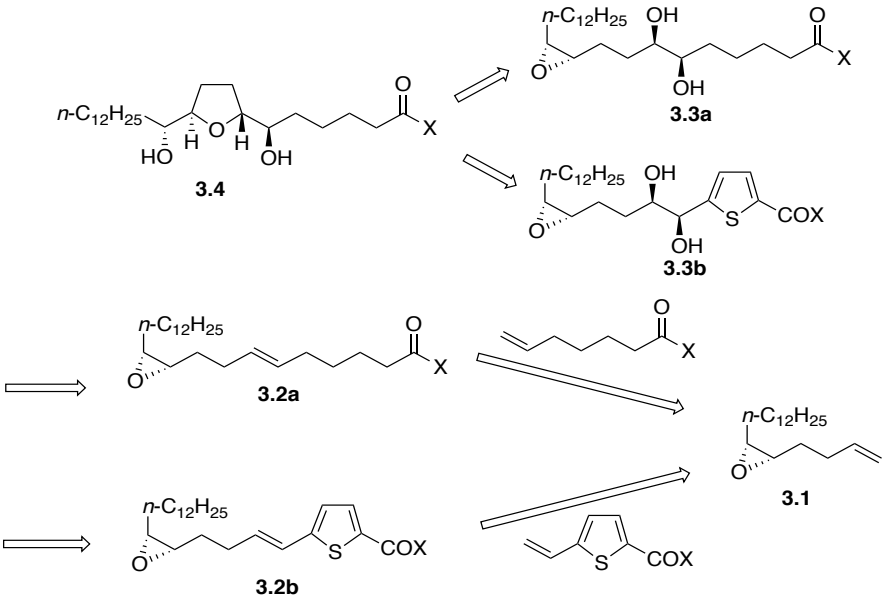


Figure 12. Structure of DHQD-Ind Ligand

3.3 Results and Discussion

3.3.1 Synthetic Approach via Cross-Metathesis

3.3.1.1 Synthetic Plan

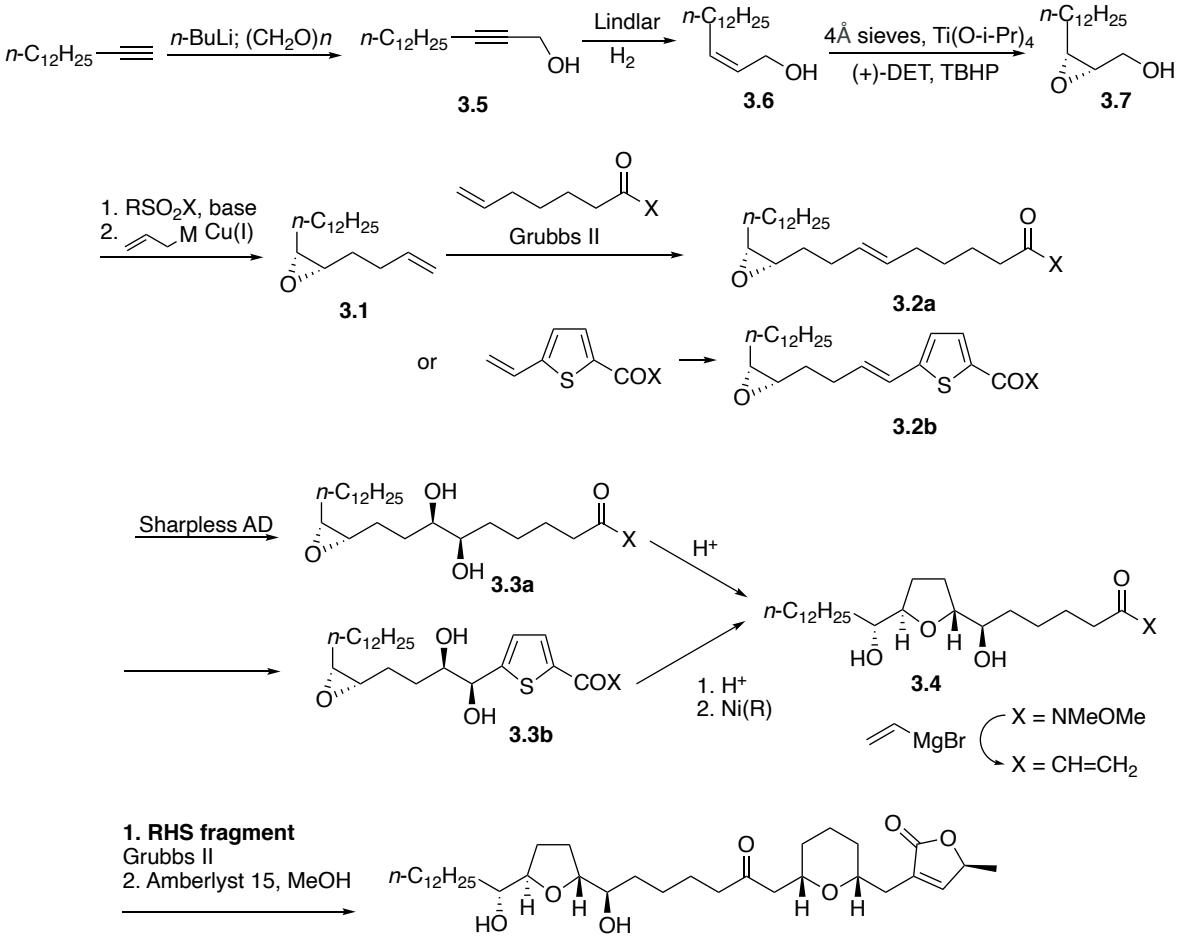


Scheme 10. First Retrosynthetic Pathway of LHS

The initial proposed synthetic route for the LHS fragment (Scheme **10**) is specifically designed to involve a cross-metathesis as one of its key steps, with the reaction mostly favouring the *trans* product (**3.2a or 3.2b**), regardless of the substituent on either carbon of the C=C bond. A thiophene was also introduced as part of the sequence since according to Sharpless' studies on asymmetric dihydroxylation, an aromatic moiety present would lead to better enantioselectivity as the aromatic substituent on the alkene interacts with the quinoline functionality on the ligand.[40] Another advantage for the introduction of a thiophene functional group is that it can be easily reduced with Ra-Ni, which is an important technique for chain extension.[41-45] Moreover, in contrast with benzylic hydrogenation reactions, the α-OH group to the thiophene would survive a Ra-Ni

reduction.[46-50] The synthetic route would then culminate in the formation of a THF moiety (**3.4**), obtained concomitantly from the intramolecular ring opening of the epoxide by the hydroxyl group at the δ-position. (**3.3a or 3.3b**).

3.3.1.2 Synthetic Implementation



Scheme 11. First Proposed Synthesis Pathway of LHS fragment

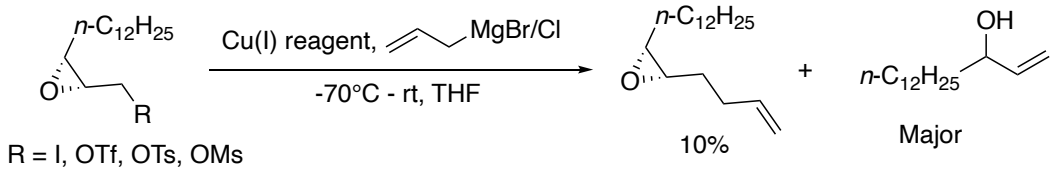
The initial steps leading up to epoxide **3.1** were successful with excellent yields and enantioselectivity (Scheme **11**).

The first step of the synthesis began with an addition reaction of lithiated-tetradecyne and paraformaldehyde, followed by an alkyne reduction using Lindlar's catalyst, giving *Z*-Alkene **3.6** in excellent yields of more than 90%.

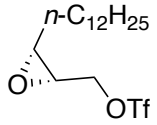
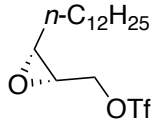
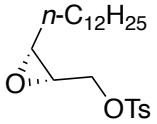
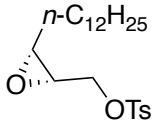
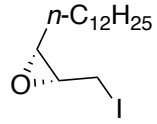
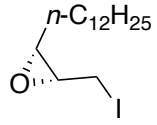
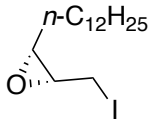
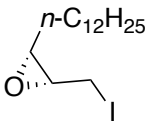
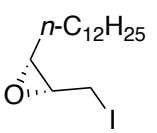
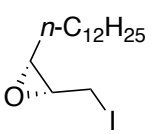
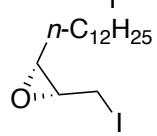
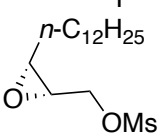
Epoxide **3.7** was then furnished by Sharpless asymmetric epoxidation in good yield and enantioselectivity. The *ee* of the epoxide was determined at this point by HPLC using a reported procedure.[37] This involved the synthesis of the 4-nitrobenzoate derivative of **3.7**. The *ee* was measured using a Daicel-Chiralcel

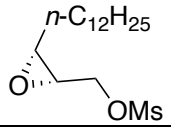
OD-H column and determined as 85%. ^{1}H NMR spectroscopic analysis shows two ddd at 3.86 and 3.68 ppm with an integration value of one each, confirming the successful generation of the desired epoxide.

The subsequent step involved a Cu(I)-catalysed allylation with allylmagnesium bromide derivatives of **3.7** to furnish alkene **3.1**. Although this method has literature precedents,[51-54] multiple attempts involving temperature changes, base variations, modification of leaving groups and alteration of different Cu(I) reagents, the reaction only yielded 10% of the allylated product **3.1**. ^{1}H NMR spectroscopic analysis shows a ddt at 5.86 ppm and a multiplet at 5.00 ppm with an integration value of one and two respectively, which confirms that the allylation is successful. TLC and NMR analyses of the reaction revealed the ring-opening side-product and the unconverted starting material. The reaction outcome is summarised in Table **1** and Scheme **12** below.



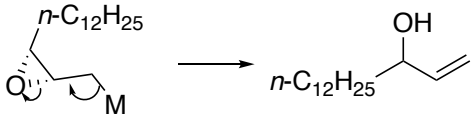
Scheme 12. Alkylation involving Cu(I) reagents

Entry[a]	Substrate	Cu(I) Reagent	T (°C)	Remarks
1		Li_2CuCl_4	-70	Starting material only
2[c]		Li_2CuCl_4	-45 to rt	Starting material observed
3[c]		CuCl	rt	No starting material
4[c, d]		CuI	-23	Starting material observed
5		Li_2CuCl_4	-70	Starting material only
6[c]		CuCl	rt	Starting material observed
7[c]		CuCN	rt	Starting material observed
8[c, d, e]		CuI	-23	**Product yield: 10%** Starting material observed
9[c, d]		CuI	-30	Starting material observed
10[b, d]		CuI	-23	Starting material only
11[c]		$CuBr.SMe_2$	-70 - -60	Starting material observed
12		CuCl	rt	Starting material only

13[c, d]		CuI	-23	Starting material observed

[a]All reactions were run in THF. [b]Iodine added last. [c]Side-product observed as major product. [d]HMPA added with Cu(I) as co-solvent. [e]Isolated yield.

Table 1. Alkylation involving Cu(I) reagents

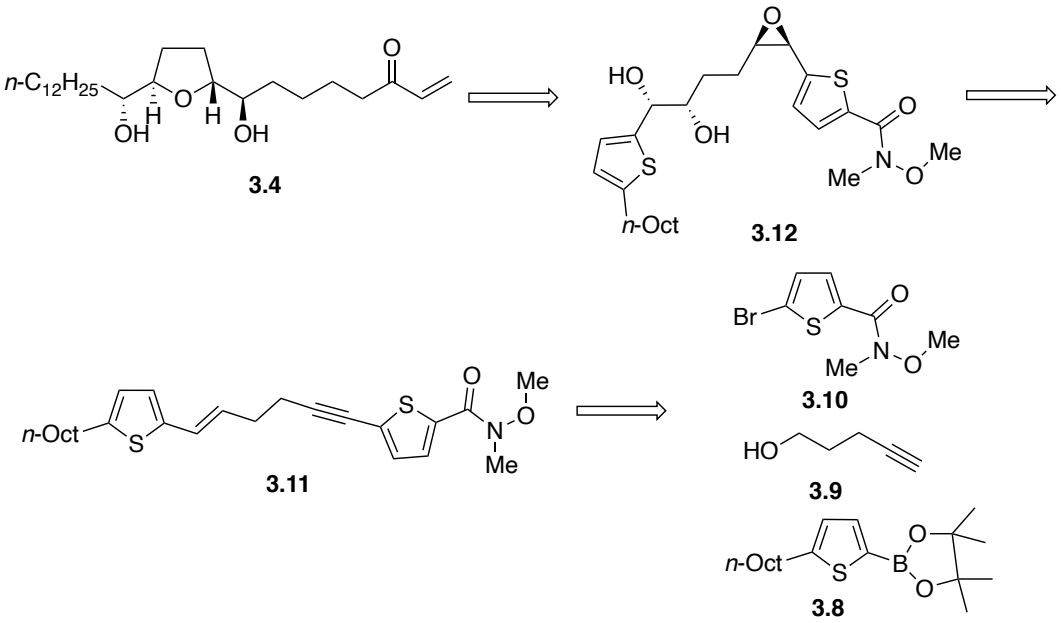


Scheme 13. Proposed Mechanism for Side-Product Formation

The investigation to understand the formation of the side product and subsequent low conversion of the substrate began with an analysis of the reaction mechanism. One possibility was that transmetalation of magnesium to copper was not happening fast enough. However, even after allowing the copper (I) reagent and allylmagnesium bromide to react prior to the addition of the iodide (entry 10), no conversion was observed based on TLC and ^{1}H NMR analysis of the crude reaction. Moreover, there was no alkylation happening on either sides of the epoxide. Judging by the formation of a single side-product, a possible mechanism (Scheme **13**) might explain what could have happened instead. An alternative strategy was devised to synthesise the LHS fragment because the optimisation of **3.1** was not successful.

3.3.2 Synthetic Approach via Suzuki Coupling of Two Thiophene Fragments

3.3.2.1 Synthetic Plan



Scheme 14. Second Retrosynthetic Pathway of LHS fragment

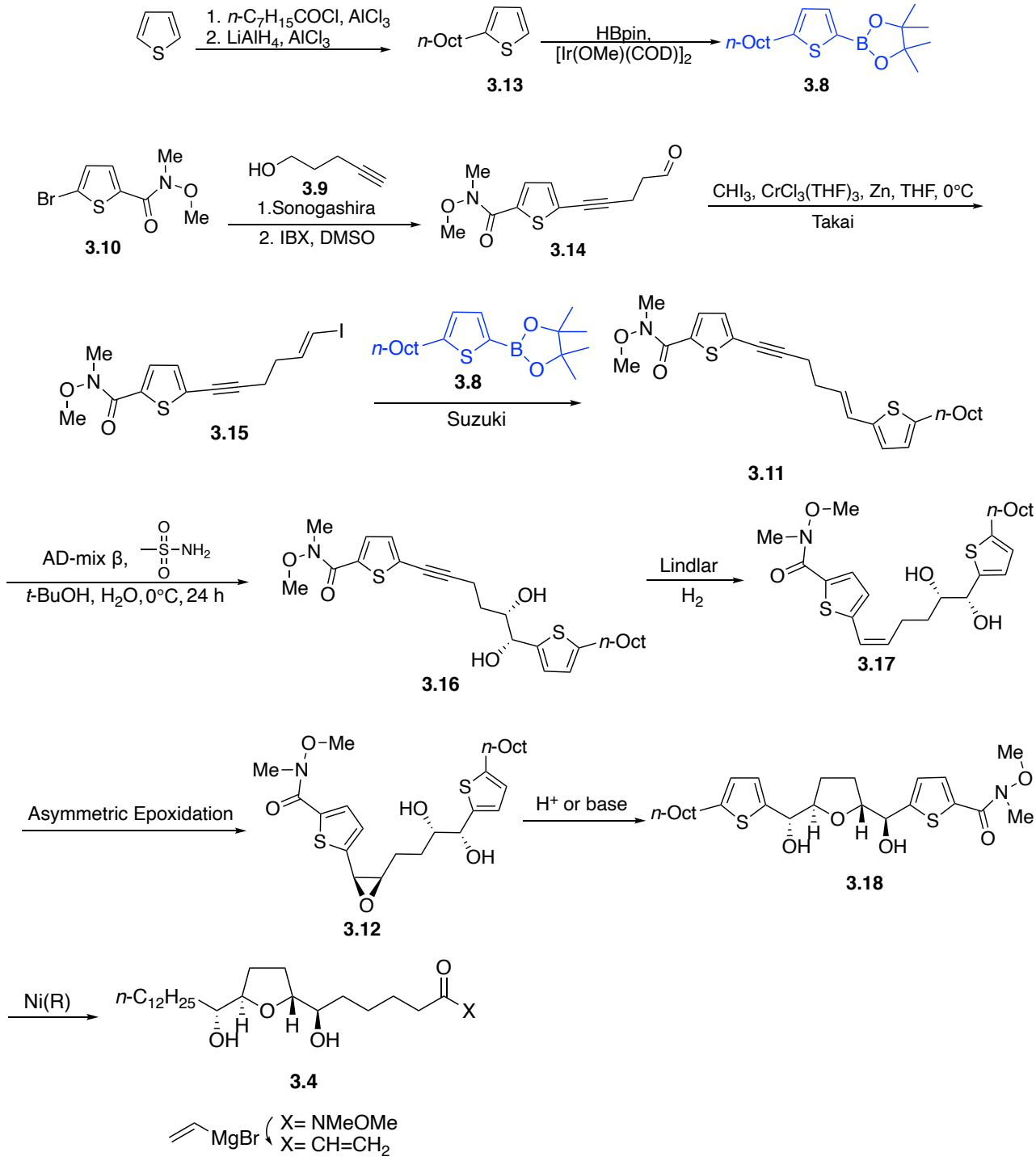
The redesigned synthetic pathway above (Scheme **14**) was envisioned to be more convergent than the previous in Section 3.3.1, allowing more simultaneous constructions to be done.

As mentioned in Section 3.3.1, the reason for including thiophene was the advantage it provides in the enantioselectivity of Sharpless asymmetric dihydroxylation.[40] Moreover, the reduction of thiophene using Ra-Ni is a powerful synthetic method for alkyl chain extension.[55-58]

The reasons for placing the diol and epoxide (**3.12**) in their specific positions are strategic because *trans*-alkenes tend to give higher *ee*s for dihydroxylation compared to *cis* substrates. Although Sharpless[39] has managed to devise a

DHQD-Ind ligand to curb the low *ee* for *cis*-alkenes, the improved *ee* is still lower compared to *trans* substrates.

In this section (Scheme **14**), we discuss one of the key steps that involve the Suzuki coupling[59] of two thiophene fragments (**3.8** and **3.10**) to give adduct **3.11**. The adduct will then be subjected to asymmetric dihydroxylation, alkyne reduction and finally an epoxidation to give the corresponding precursor **3.12** to the THF intermediate. The precursor **3.12** is then subjected to a key 5-*exo*-*tet* ring formation to yield the corresponding THF intermediate before culminating in the reduction with Ra-Ni as the final step to give **3.4**.



Scheme 15. Second Proposed Synthesis Pathway of LHS fragment

The second proposed synthetic pathway above (Scheme **15**) begins with the construction of the precursor **3.8** to the Suzuki coupling. Commercially available thiophene first goes through a Friedel-Crafts acylation with octanoyl chloride, followed by alane reduction, giving adduct **3.13**, which is then subjected to borylation following Hartwig's methodology[60]. The construction of the other Suzuki coupling partner **3.15** starts with a Sonogashira coupling[61] of Weinreb amide **3.10** with 4-pentynol, followed by an oxidation thereby giving the anticipated aldehyde **3.14**. Subsequently, a one-carbon homologation of the aldehyde with an alkenyl halide, furnished iodide **3.15**.[62] The Suzuki coupling of the two thiophene fragments, **3.8** and **3.15**, would generate adduct **3.11**. Sharpless asymmetric dihydroxylation would then yield the corresponding diol **3.16**, which will then undergo a reduction using Lindlar catalyst[63], selectively yielding the *cis*-alkene **3.17** as the reaction is expected to proceed via *syn*-addition. At this point, an asymmetric epoxidation using Jacobsen's methodology explored earlier in Section 3.2.1, would generate enantiomerically pure *cis*-epoxide **3.12**. **3.12** would then give the precursor to the THF, **3.18**, that would be furnished in a *5-exo-tet* fashion via an intramolecular cyclisation under acidic or basic conditions. The calculation studies[64] done supports the envisioned preferential formation of the *5-exo* ring over the *6-endo* product, as predicted by Baldwin's rules[65]. Lerner reasons that the five-membered transition state is less strained because of the nearly ideal attack angle, and that it bears more similarity to the intermolecular reaction transition state, thus contributing to a lower energy compared to the six-membered transition state.[64]

Finally, the LHS fragment 3.4 will then be completed through reduction using Ra-Ni and can then be used for the final step of cross-metathesis with the RHS fragment to form Montanacin D.

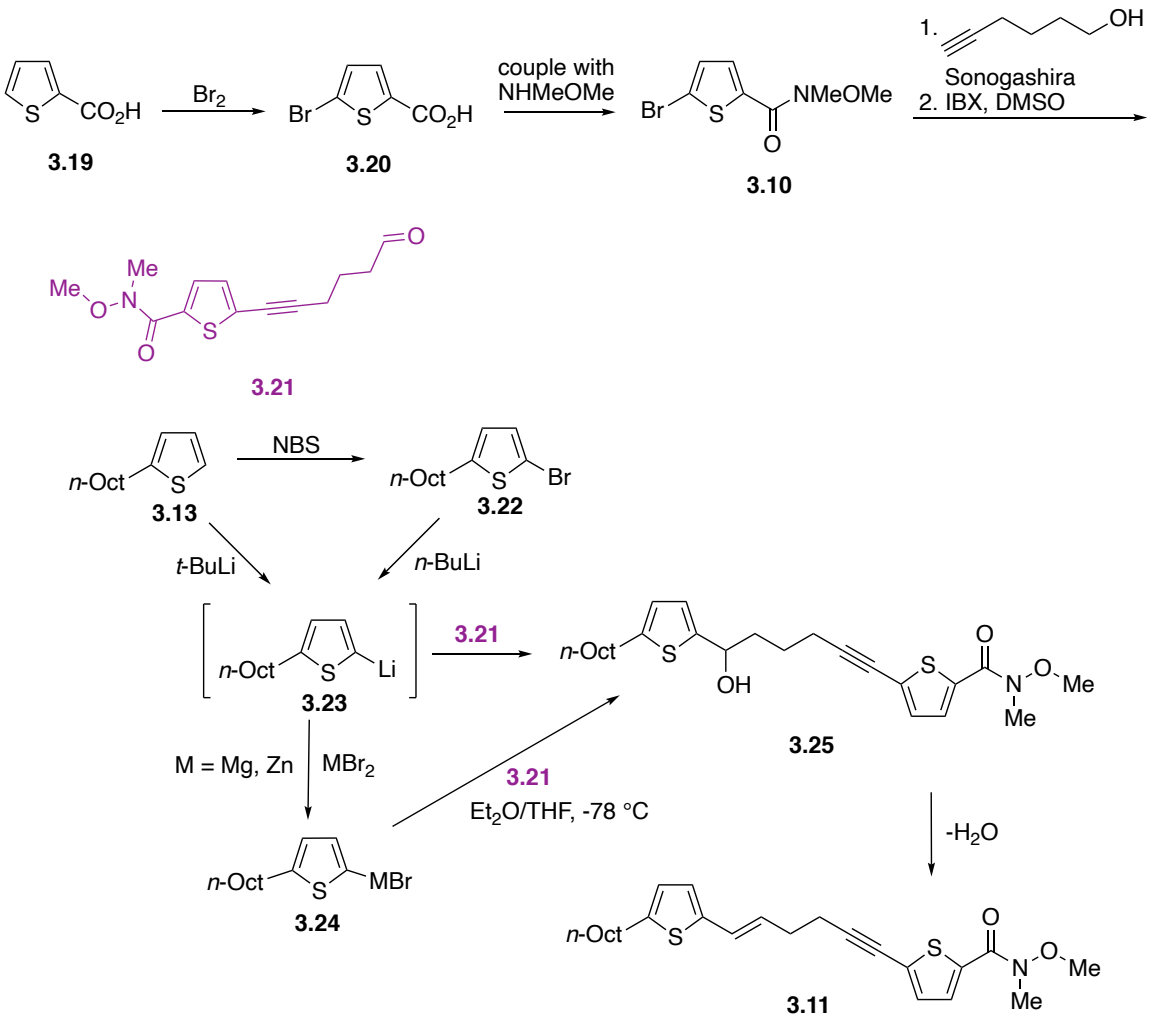
3.3.2.2 Synthetic Implementation

With the synthetic plan in place (Scheme **15**), the synthesis began with a highly facile Friedel-Crafts acylation between commercially available thiophene and octanoyl chloride with aluminium chloride functioning as the Lewis acid. Before deciding to use alane for the reduction of the ketone, attempts were made using Clemmenson reduction, but TLC and NMR analyses showed no sign of product and no ^{1}H NMR signals of the thiophene. The harsh conditions that involve heating the substrate in concentrated hydrochloric acid could be the reason for the disintegration of the thiophene ring. Alane, which was generated *in-situ* with $LiAlH_4$ and $AlCl_3$, proved to be a superior method[66-68] for the reduction of the ketone intermediate, and yielded **3.13** in an excellent yield of 80% over two steps. ^{1}H NMR spectroscopic analysis on page 186 shows a triplet at 2.82 ppm with an integration value of two, which confirms that the reduction of the ketone is successful.

Before the decision to employ Takai's methodology[62] was made, a few considerations were initially done to construct **3.11**, as displayed below in Scheme **16**.

Firstly. lithiated thiophene **3.23** was made from reacting thiophene **3.13** with *t*-BuLi or reacting bromothiophene **3.22** with *n*-BuLi. Bromothiophene **3.22** was furnished via bromination of thiophene **3.13** using NBS. A D_2O quenching experiment revealed that with *t*-BuLi, 80% of the thiophene **3.13** was deprotonated at the C5-position. Therefore, due to the low acidity of thiophene **3.13**'s proton (pK_a 33.0) a lithium-halogen exchange with bromothiophene was necessary. The lithiated thiophene **3.23** was then subjected to a series of coupling methods with aldehyde **3.21**. After lithiated thiophene **3.23** was formed

in-situ, a solution of aldehyde **3.21** in THF was added dropwise at low temperatures (ranging from -78°C to -20°C). Another coupling method involving C5-metalation of thiophene **3.24**, generated *in-situ* using a variety of Zn and Mg salts, i.e. Mg, *i*-PrMgCl.LiCl[69], $MgBr_2$[70], $ZnBr_2$[71] were also attempted. Despite various attempts in doing so, the highest yield achieved for adduct **3.25** was only 11%. The observed low yield was a result of low starting material conversion, suggesting that the C5-substituents for both thiophene moieties, **3.23**/**3.24** and **3.21**, were not sufficiently labile or reactive for the coupling reaction to successfully proceed. With this in mind, the goal was to find the right coupling substituent in order for adduct **3.11** to be successfully furnished.

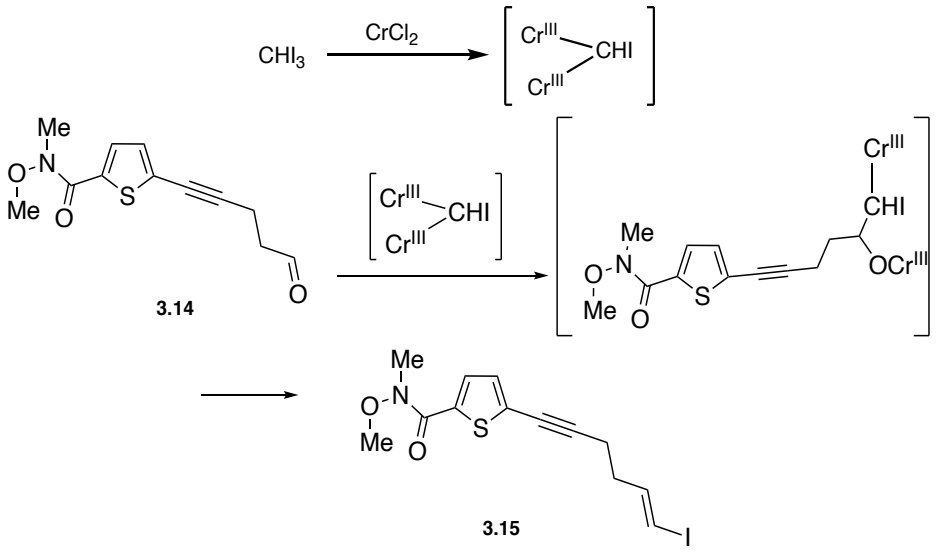


Scheme 16. Coupling considerations to furnish adduct **3.11**

Owing to the more convergent nature of the synthesis, the construction of Weinreb amide **3.10** was done concurrently with finding a suitable coupling method to furnish adduct **3.11**. Weinreb amide **3.10** was built starting with the bromination of commercially available 2-thiophenecarboxylic acid, where the right regioselectivity of the bromination was achieved as anticipated, as confirmed by literature[72]. Subsequently, the installation of the Weinreb amide was accomplished by first changing the 5-bromothiophene-2-carboxylic acid to its corresponding acid chloride, then an immediate addition of *N*,*O*-dimethylhydroxylamine hydrochloride. Weinreb amide **3.10** was obtained in quantitative yields over both steps. ^{1}H NMR spectroscopic analysis showed two singlets at 3.78 and 3.35 ppm with an integration value of three each, which confirmed that the installation of the Weinreb amide is successful. After which, Sonogashira coupling with 4-pentynol gave the coupled product. ^{1}H NMR spectroscopic analysis showed a triplet at 3.71 ppm with an integration value of two, which confirmed that the Sonogashira coupling was effectively accomplished. The alcohol was then oxidised to the aldehyde **3.14** using IBX. Aldehyde **3.14** was obtained in a good yield of 83%, over both steps. ^{1}H NMR spectroscopic analysis showed a singlet at 9.83 ppm with an integration value of one, which confirmed that the aldehyde was successfully furnished. Some yield was lost due to the formation of the Glaser[73] coupling side-product, possibly due to the presence of adventitious air in the flask.

In order to transform aldehyde **3.14** into a suitable coupling partner, the procedure reported by Takai was used. This features a simple and stereoselective method for the conversion of aldehydes to the corresponding (*E*)-alkenyl halides by an organochromium reagent. $CrCl_2$ reacts with iodoform to

give the reactive species, which is a carbodianion intermediate[62]. Thereafter, an insertion by the aldehyde **3.14** to the carbodianion intermediate, followed by elimination, gave iodide **3.15**. Iodoform acts as the synthetic equivalent of the methine trianion synthon and was selected as the choice haloform as it was reported that the *E/Z* ratios of the alkenyl halides would increase in the order of I<Br<Cl. The *E* isomer, iodide **3.15**, was obtained exclusively, as confirmed by the 13.5 Hz coupling constant of the doublet at 6.07 ppm obtained from ^{1}H NMR analysis. The vicinal coupling constant for vinyl iodides would typically be lower than the vicinal coupling constants for similar alkenes attached to other substituents. The reaction is believed to undergo this pathway featured below in Scheme **17**.



Scheme 17[62]**.** Takai Reaction to furnish iodide **3.15**

However, $CrCl_3$ is highly hygroscopic, making it difficult to handle in the laboratory. Therefore, another chromium(III) complex that is less moisture-sensitive, $CrCl_3(THF)_3$[74], was used in replacement of what was originally reported by Takai. The original amount of $CrCl_2$ used, 6 equivalents, would not be

environmentally-friendly, as chromium compounds are known to be toxic.[75] The reaction was thus further optimised with an attempt to halve the amount of chromium(III) used with the aid of activated Zn. This was met with an indistinguishable change in the product yield, from 68% to 65%. An attempt to further reduce the amount of chromium(III) employed, from stoichiometric (3 equivalents) to catalytic amounts (1-15 mol%), resulted in low conversion of the starting material. Fürstner[76-77] was able to achieve a higher turnover rate with Cp_2Cr or $CpCrCl_2$ as the precatalyst after fine-tuning the redox potential using suitable ligands. This alternative precatalyst could improve the low conversion.

With the successful transformation of aldehyde **3.14** into a suitable coupling partner, the transformation for that of thiophene **3.13** was also done simultaneously. Hartwig[60] and co-workers reported a procedure that featured the facile borylation of alkyl-thiophenes, using $[Ir(OMe)(COD)]_2$ as the catalyst, HBpin as the source of the borylation and di-*tert*-butylpyridine as a co-catalyst. The presence of the bulky *t*-butyl groups of the co-catalyst helps to prevent the borylation of the catalyst, allowing the catalyst loading to remain low at 1 mol%. Using this methodology, the construction of boronic ester **3.8** was a success, giving product yields upward of 90%. The desired regioselectivity of the borylation was achieved as anticipated, as confirmed by NMR analysis and supported by literature.[78] ^{1}H NMR spectroscopic analysis showed a multiplet at 1.40 – 1.22 ppm with an increased integration value of twelve, compared to the starting material, which confirms that the borylation is successful. The boronic ester **3.8** and iodide **3.15** were then coupled via the Suzuki method.

The Suzuki coupling of boronic ester **3.8** and iodide **3.15** gave adduct **3.11** in a good yield of 70%. From the screening of Pd(0) sources and bases attempted as shown below in Table 2, $Pd(dppf)Cl_2$ and NaOH produced the highest yield.

Entry[a]	Pd(0) Source	Base	Remarks[d]
1[b]	$Pd(PPh_3)_4$	K_2CO_3	19% yield. Incomplete conversion
2[b]	$Pd(PPh_3)_2Cl_2$	K_2CO_3	35% yield. Incomplete conversion
3[c]	$Pd(PPh_3)_2Cl_2$	NaOH	37% yield. Incomplete conversion
4	$PdCl_2(dppf)$	NaOH	70% yield
5	$PdCl_2(dppf)$	Cs_2CO_3	57% yield. Incomplete conversion

[a]Reactions were run in THF/H_2O at 50°C. [b]Toluene/H_2O, 90°C. [c]90°C. [d]Isolated yield.

Table 2. Screen Test of Pd(0) Sources and Bases

The successful formation of adduct **3.11** allowed the synthesis to move forward with a Sharpless asymmetric dihydroxylation, establishing diol **3.16** in a good yield of 68%. Following which, reduction of the alkyne functional group using Lindlar catalyst[63] selectively gave the *cis*-alkene **3.17** in a good yield of 76%.

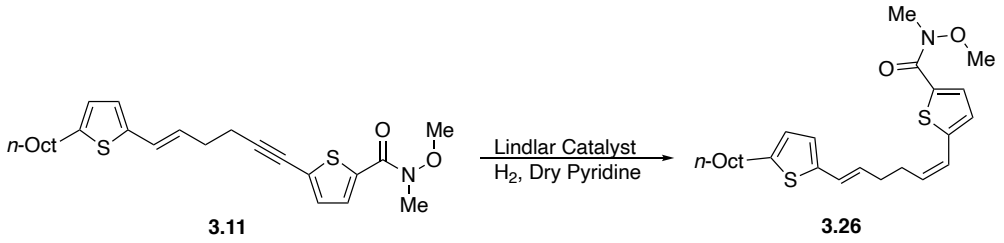
One of the key steps presented in this synthesis is the asymmetric epoxidation that was explored earlier in Section 3.2.1. The Jacobsen epoxidation[1] procedure, featuring NaOCl as the oxidant and the Manganese salen complex as the catalyst, was reported to give enantioenriched epoxides.

The results obtained from the asymmetric epoxidation of *cis*-alkene **3.17** was disappointing. TLC and NMR analyses showed that *cis*-alkene **3.17** was cleaved at the alkene. The TLC analysis showed two spots that were active with 2,4-

DNPH. After isolation of these two spots, ^{1}H NMR findings showed that it complemented the results garnered from TLC analysis Both spots had a distinct singlet at 10 ppm, thus depicting the existence of an aldehyde proton. The isolated spots also bore two clear doublets in the 7-8 ppm region, pointing towards the presence of thiophene. Upon further analysis of the NMR spectra of both isolated spots, the side products were then elucidated as shown in Scheme **19** below.

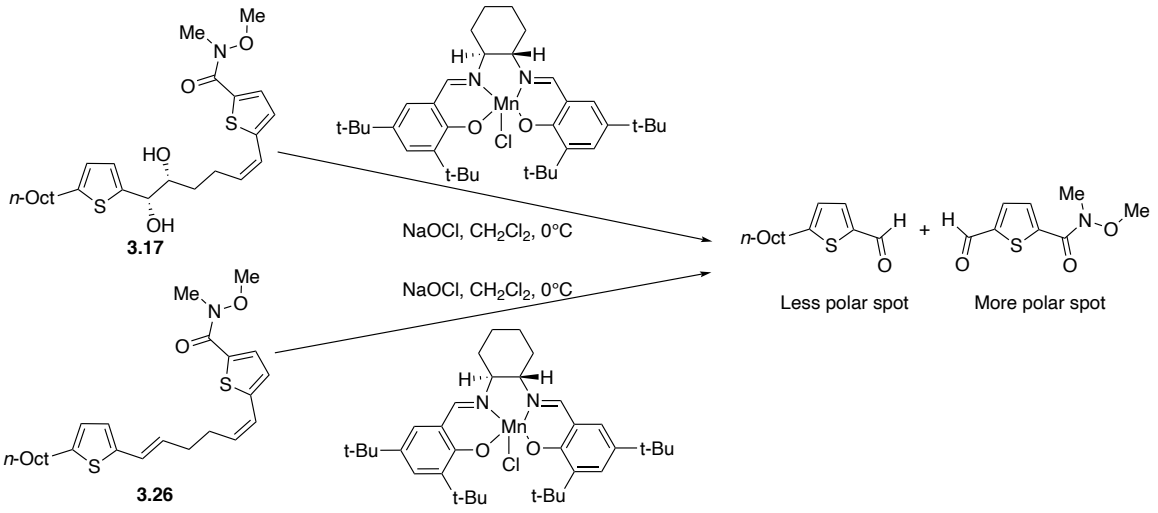
Since unsatisfactory results were obtained from *cis*-alkene **3.17**, an alternative approach using diene **3.26** was constructed as Jacobsen also reported the regioselective nature of the reaction towards *cis*-alkenes.

The construction of diene **3.26** involved the reduction of alkyne **3.11** using Lindlar catalyst, shown below in Scheme **18**. However, diene **3.26** generated similar results as *cis*-alkene **3.17**, illustrated in Scheme **20** below.



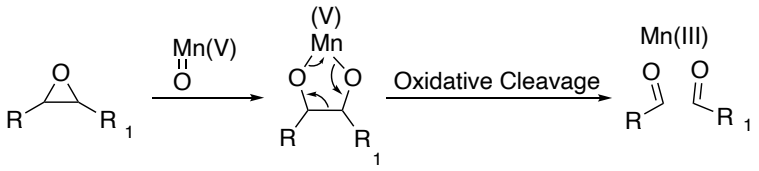
3.11 **3.26**

Scheme 18. Formation of diene **3.26**



Scheme 19. Proposed side-products of Jacobsen Asymmetric Epoxidation

After several attempts with both commercial and homemade catalysts and the employment of an additive, 4-phenylpyridine *N*-oxide, that was reported to be beneficial[9], the problem with the side-products still persisted. This led to the thought that the substrate was unsuitable for an asymmetric epoxidation of this manner. The postulation for the reason behind the formation of these side-products is proposed below (Scheme **20**).



Scheme 20. Postulated Reason for the Formation of Side-Products

A model study was performed using styrene following the original reported procedure[1] and it was found that the reaction was completed under 2 hours. The NMR spectrum of the product also matched what was reported in literature. This confirmed the unsuitability of the substrates using the Jacobsen epoxidation procedure.

As such, epoxidations using other protocols were then considered. An attempt to epoxidize *cis*-alkene **3.17** using *t*-BuOOH and $VO(acac)_2$ following the procedure reported by Sharpless[79], did not succeed. The analysis of the crude NMR spectrum revealed that majority of the starting material remained. Another attempt made with *m*-cpba without the inclusion of a buffer, afforded a major product. However, careful analysis with ^1H and COSY, revealed its identity to be the 6-membered ring intermediate shown in Figure **13** below, instead of the targeted 5-membered ring **3.18**.

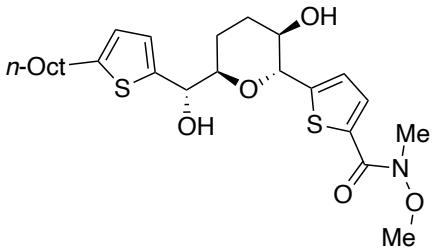
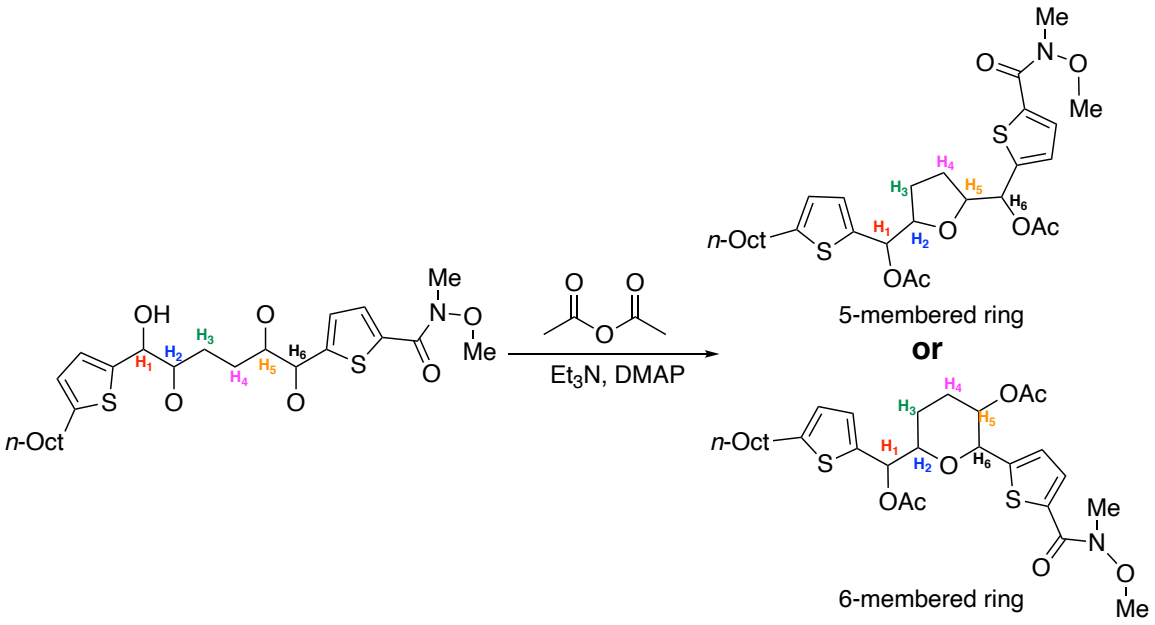


Figure 13. 6-membered ring

To determine whether the 5 or 6-membered ring had been formed, the correlation of the protons of the unknown diol were first established with COSY, shown below in Figure **14**. Special attention was paid to protons H1, H5 and H6, whose chemical shifts are at 4.78 ppm, 3.95 ppm and 3.38 ppm respectively. Upon establishment of the relativity of the protons to one another, the unknown diol was subjected to esterification with acetic anhydride, giving the di-ester. The characteristic of the di-ester was likewise analysed via a COSY experiment. To determine if a 5 or 6-membered ring has been formed, the protons adjacent to the acetoxy groups would have a sizeable difference in chemical shift. The COSY spectrum, shown in Figure **15** below, shows that protons H1 and H5 have shifted the most, to 6.40 ppm and 5.52 ppm respectively, signifying that the 6-membered ring has been formed. Proton H6 remained at 3.35 ppm.



Scheme 21. Determination of Unknown

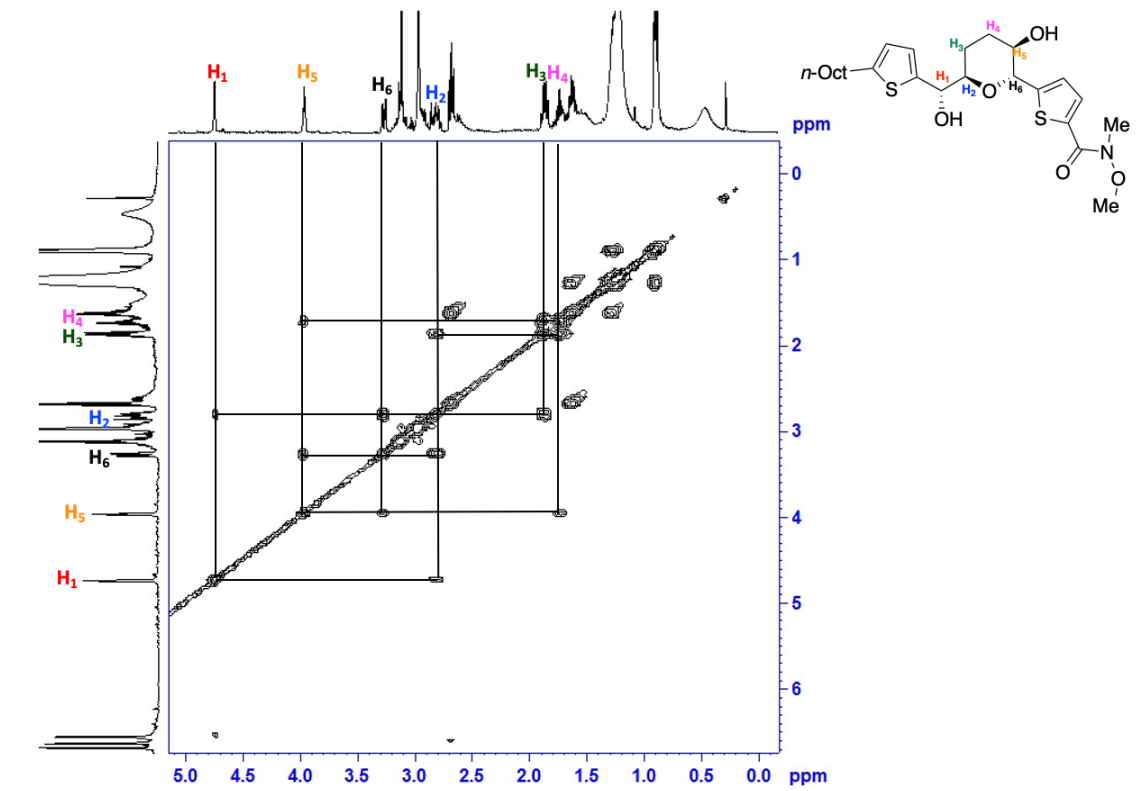


Figure 14. COSY Spectrum of Diol 6-membered ring

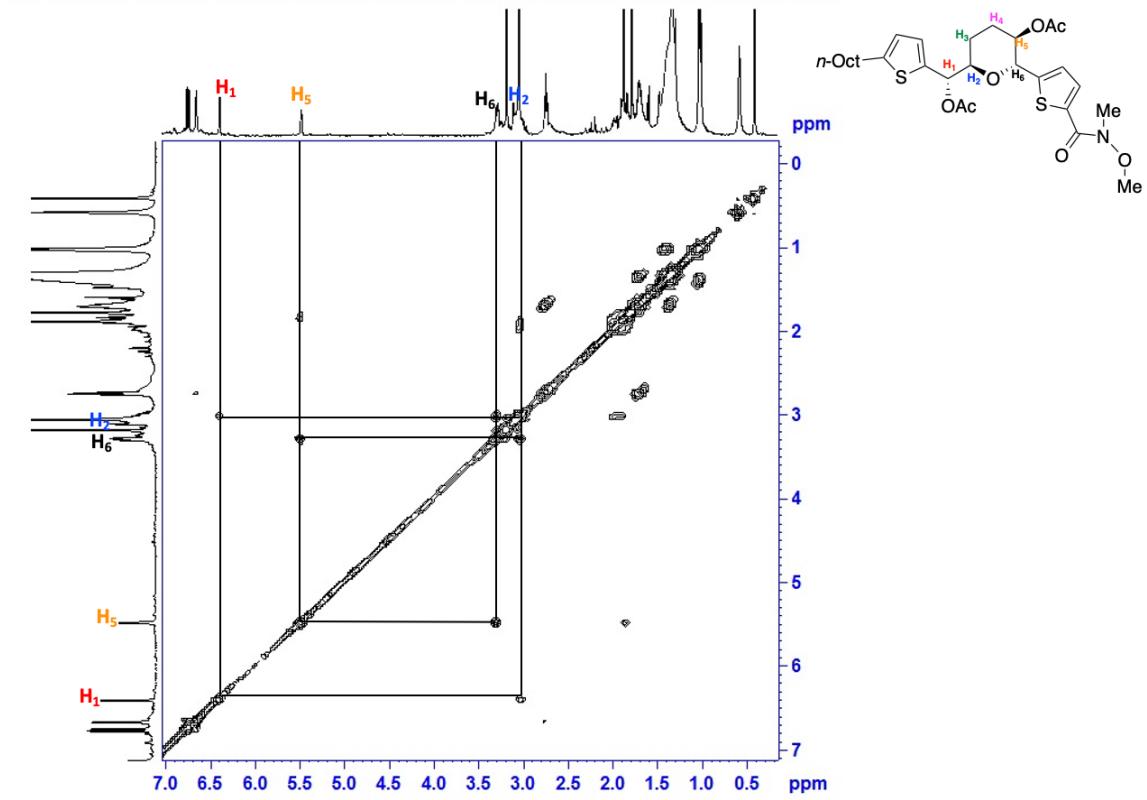
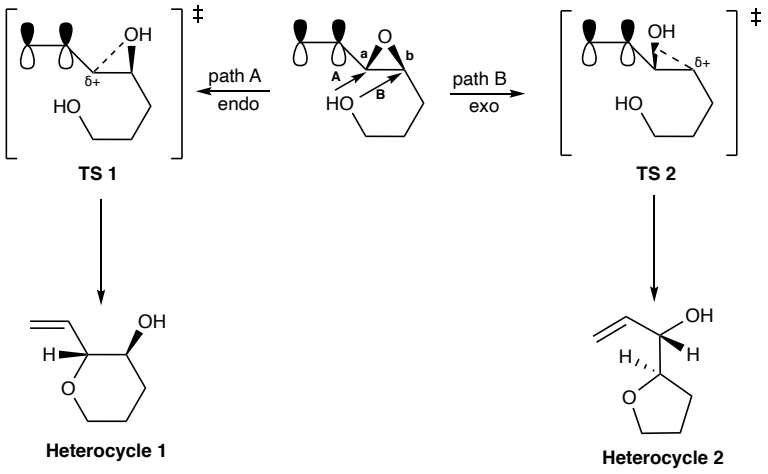


Figure 15. COSY Spectrum of Acetoxy 6-membered ring

The formation of the 6-membered ring can be explained by a concept of selectivity between an *endo* or *exo* mode of attack explained by Nicolaou[80], as displayed in Scheme **22** below. According to this concept, a π-orbital attached next to the epoxide acts as an activator of the C-O bond, before it continues to break selectively. Via **Transition State 1**, an endo cyclisation would occur to give **Heterocycle 1**, as the developing electron-deficient orbital on carbon **a** would be stabilised by electron donation from the adjacent and parallel π-orbital. The less favourable pathway leading to the 5-membered ring **Heterocycle 2**, would occur via exo cyclisation in **Transition State 2**, where the developing positive charge would build up on carbon **b**. It should however also be noted that in the absence of π-orbitals adjacent to the epoxide, the ring closures would be expected to lead to the exo-product **Heterocycle 2**, on the basis of better antiparallel alignment of the developing and breaking bonds.

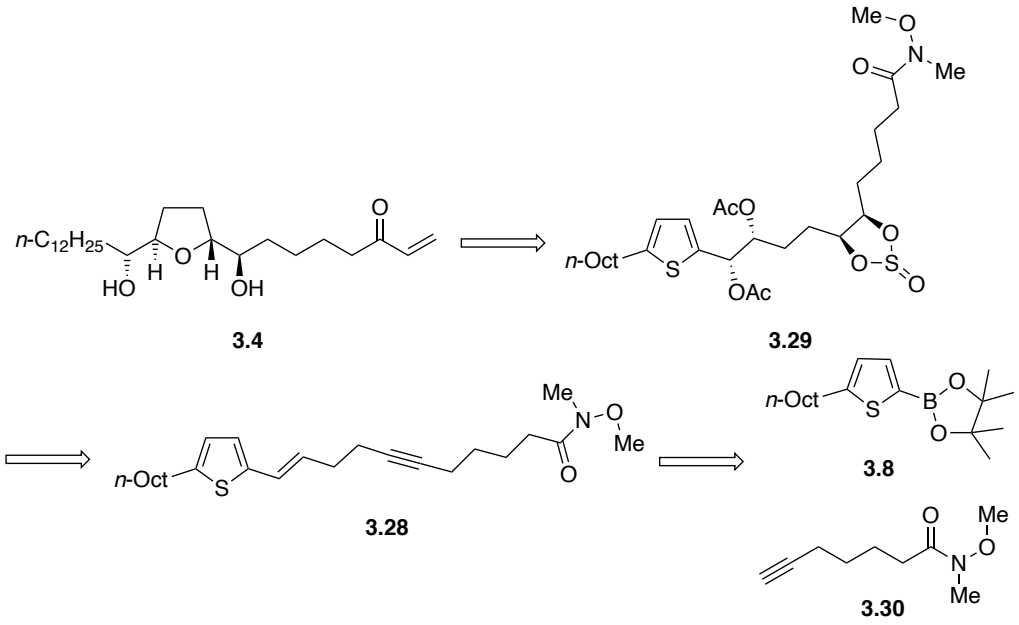


Scheme 22[80]**.** *Endo* and *Exo* Predictions based on Nicolaou's π-orbital concept

As the construction of THF **3.18** did not come to fruition, the synthetic pathway came to a halt and thus another approach needed to be devised.

3.3.3 Synthetic Approach via Suzuki Coupling of One Thiophene and Alkyl Chain

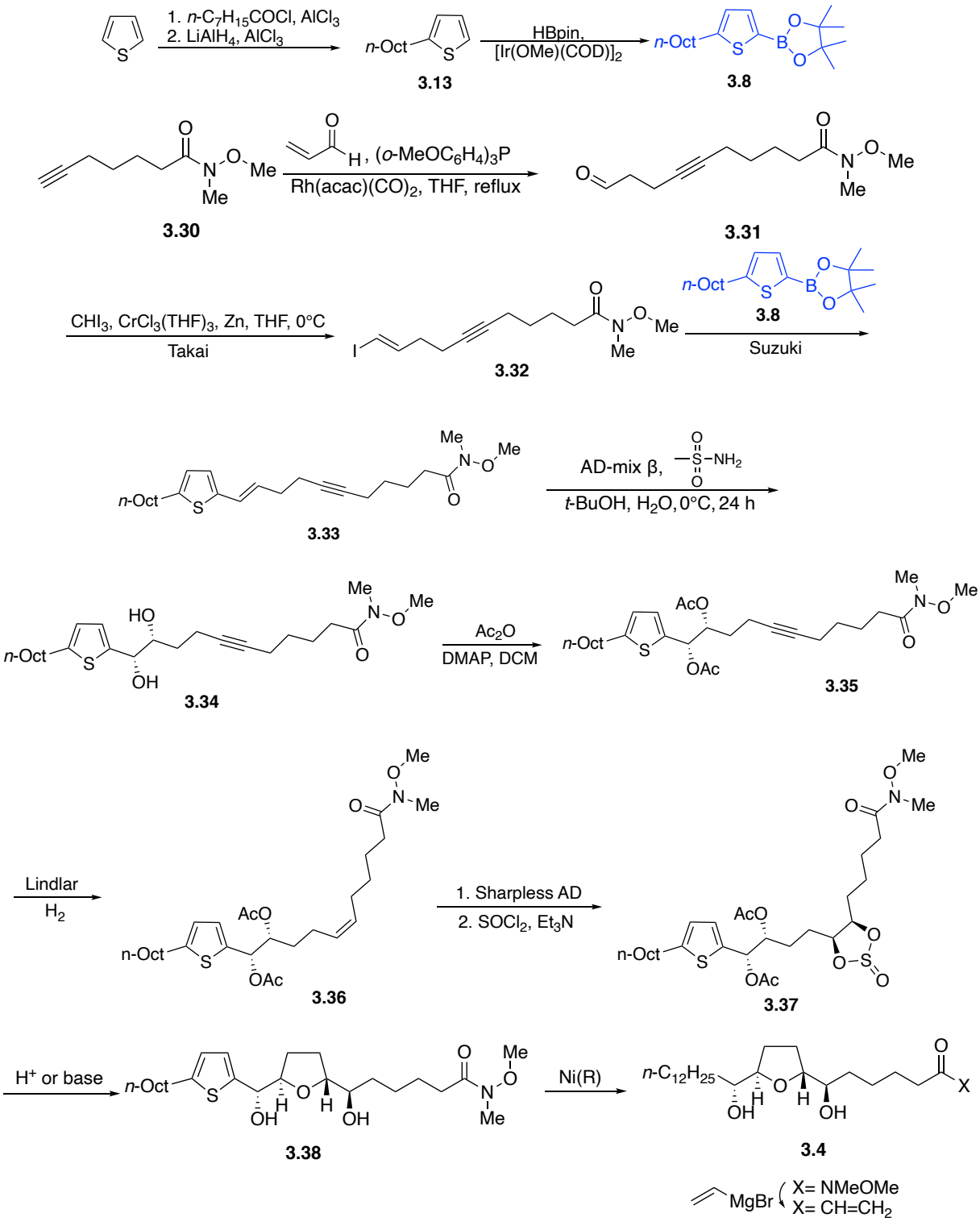
3.3.3.1 Synthetic Plan



Scheme 23. Third Retrosynthetic Pathway of LHS fragment

Although the redevised synthetic pathway (Scheme **23**) shares many similarities with the previous synthesis in Section 3.3.2, it was devised without the presence of the thiophene adjacent to the *cis*-alkene precursor. The decision for the octyl-thiophene to remain was, as mentioned previously, motivated by the thiophene moiety having an added benefit in the enantioselectivity of the Sharpless asymmetric dihydroxylation[40]. Moreover, the easy reduction of thiophene using Ra-Ni is a powerful synthetic method for alkyl chain extension.[55-58] One of the key steps would similarly involve the Suzuki coupling[59] of two fragments (**3.8** and **3.32**) to give adduct **3.28**. The resultant adduct would then be subjected to asymmetric dihydroxylation, alkyne reduction and finally a sulfonylation to give the corresponding precursor **3.29** to the THF. Cyclic sulfite **3.29** would then be

subjected to a key 5-*exo-tet* ring closure to yield the corresponding THF product before culminating in a reduction with Ra-Ni as the final step to give THF **3.4**.



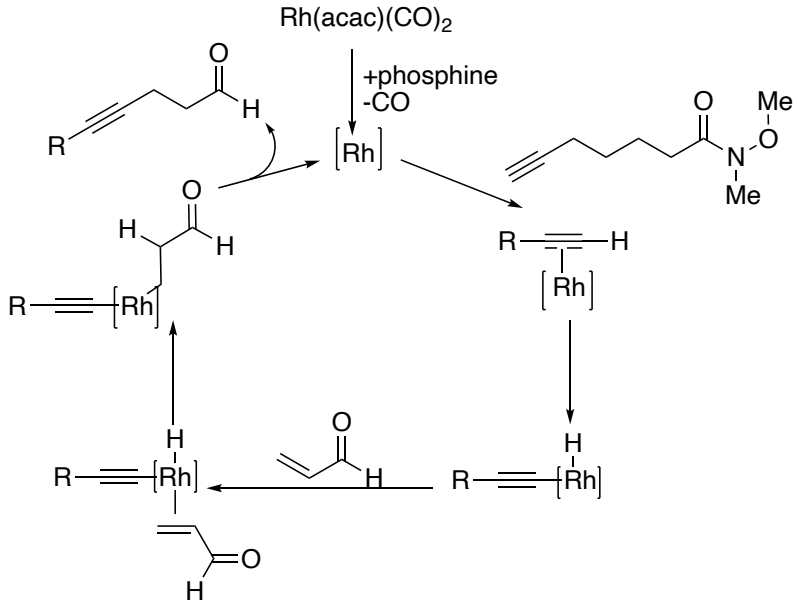
Scheme 24. Third Proposed Synthesis Pathway of LHS fragment

The third proposed synthetic pathway (Scheme **24**) would likewise begin with the construction of the Suzuki precursor **3.8** that was previously detailed in Section 3.3.2. The construction of the other Suzuki coupling partner starts with a Weinreb amide **3.30**, followed by a Rh-catalysed 1,4-addition to give aldehyde **3.31**. Subsequently, a Takai reaction[62] of aldehyde **3.31** would give the corresponding iodide **3.32**. Suzuki coupling of these two fragments, **3.8** and **3.32**, would afford adduct **3.33**, which is followed by the asymmetric dihydroxylation using Sharpless' conditions to yield the corresponding diol **3.34**. Subsequently, the diol **3.34** would be protected with the acetoxy group to give the corresponding ester **3.35**. The purpose for this is such that the cyclic sulfite would be selectively formed at the *cis*-alkene in **3.36**. Moreover, the acetate groups could also be cleaved in a tandem manner during the cyclisation step leading to **3.38**. Through a subsequent reduction using Lindlar's catalyst, *cis*-alkene **3.36** would be formed stereoselectively[63]. A second asymmetric dihydroxylation, followed by the formation of the cyclic sulfite would furnish intermediate **3.37**. At this point, it was envisioned that an asymmetric epoxidation of *cis*-alkene **3.36**, using one of the epoxidation techniques explored earlier in Sections 3.2.1 and 3.2.2 could furnish the corresponding enantiomerically pure *cis*-epoxide, giving the precursor to the THF product **3.38**. THF **3.38** would then be obtained via a *5-exo-tet* cyclisation in the presence of an acid or a base, as predicted from Baldwin's rule[65]. Finally, the LHS fragment **3.4** would be completed with the reduction via Ra-Ni, leaving the final step of cross-metathesis with the RHS fragment to yield Montanacin D.

3.3.3.2 Synthetic Implementation

After constructing thiophene **3.8** in the same manner outlined in Section 3.3.2 (Scheme **24**), the synthesis of Weinreb amide **3.30** started with 6-heptynoic acid that was made from 5-hexynol. Subsequently, the Rh-catalysed 1,4-addition of the alkyne **3.30** to acrolein, outlined by Lerum[81], gave aldehyde **3.31**, that was obtained in a good yield of 74% over both steps. ^{1}H NMR spectroscopic analysis showed a singlet at 9.75 ppm with an integration value of one and two singlets at 3.65 and 3.14 ppm with integration values of three each, confirming that the aldehyde and Weinreb amide are successfully installed.

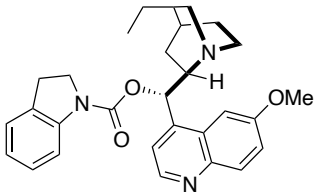
The 1,4-addition of alkyne **3.30** hinges on the benefit of the efficient C-H insertion of alkynes, whereby the acetylide would be obtained and then added to acrolein. This reaction is atom-economic as every atom in the starting materials that are used in stoichiometric amounts end up in the resulting product. Other catalysts used include $Pd(OAc)_2$-PMe_3[82], $[Pd_2(dba)_3]$[83], Ru-bis(oxazolinyl)phenyl[84]. The proposed mechanism of the Rh-catalysed 1,4-addition is illustrated below in Scheme **25**[81, 85-86]. Insertion of the Rh-catalyst into the alkyne was followed by the coordination of the enone. After which, migratory insertion of the alkyne into the alkene resulted in the formation of a new C-C bond. Reductive elimination resulted in the protonation of the oxy-π allyl complex, and finally the 1,4-addition product was obtained and the catalyst regenerated.



Scheme 25[81, 85-86]**.** Proposed Mechanism of Rh-catalysed 1,4-addition

Alkenyl halide **3.32** was then constructed in 92% yield, following the modified Takai's method, allowing the synthesis to proceed subsequently via Suzuki coupling with thiophene **3.8**. The resulting coupling product **3.33** was obtained in an excellent yield of 92%. ^{1}H NMR spectroscopic analysis showed two doublets at 6.66 and 6.58 ppm with integration values of one each and a doublet at 6.45 ppm with a coupling constant of 15.6 Hz having an integration value of one, confirming that the Suzuki coupling was successfully accomplished. Sharpless asymmetric dihydroxylation produced diol product **3.34** which was subsequently esterified to give the di-acetate intermediate **3.35**. Both steps were obtained in good yields. ^{1}H NMR spectroscopic analysis showed a doublet at 6.04 ppm and a multiplet at 5.37 – 5.26 ppm with an integration value of one each, also a multiplet at 2.09 – 2.01 ppm with an integration value of six, which confirmed that the dihydroxylation and subsequent esterification were successful.

Sharpless[39] outlined in one of his papers that the PHAL ligands commonly found in AD-mix-α and AD-mix-β did not give good enantioselectivities with *cis*-alkenes. The problem, however, was circumvented with the discovery of Ind ligands. Upon successful synthesis of the DHQD-Ind ligand, shown below in Figure **16**, the second diol moiety was obtained from the dihydroxylation step and was transformed into a cyclic sulfite intermediate **3.37** in a good yield of 98%.



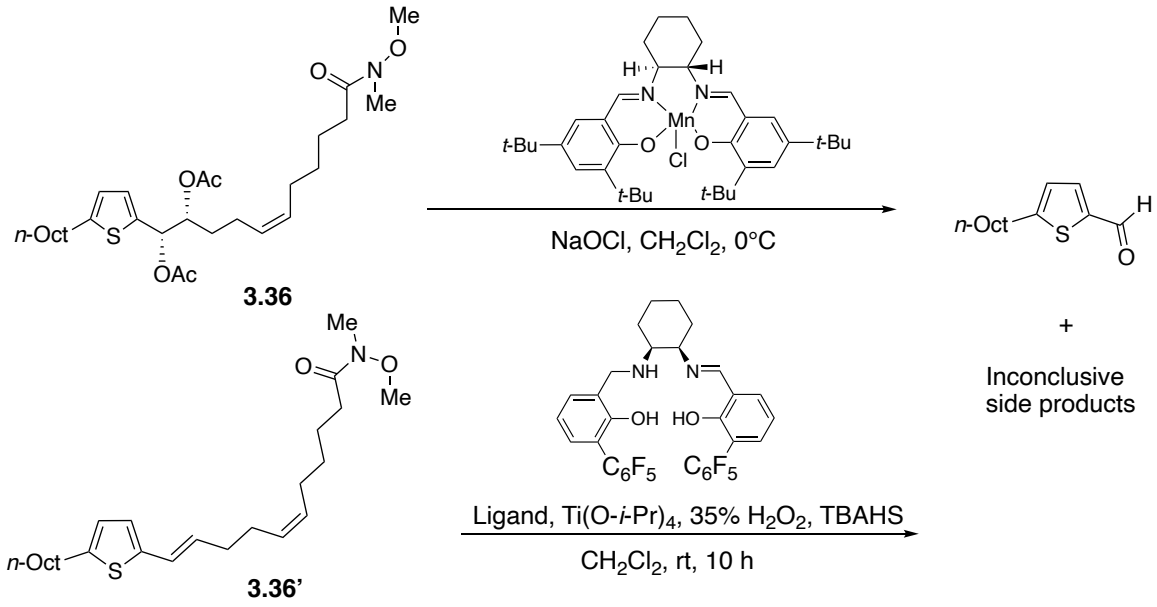
DHQD-Ind

Figure 16. Structure of DHQD-Ind Ligand

At this point, the cyclic sulfite **3.37** was subjected to a tandem reaction involving the deprotection of the di-acetate using methanolysis, followed by a ring closure. However, the synthetic route was halted because NMR analysis showed that while the acetate groups have been successfully cleaved, the ring closure did not proceed as expected. Extensive NMR analyses using ^{1}H, ^{13}C and COSY revealed no signs of either the 5 or 6-membered rings. An attempt to crystallise the unknown product to characterise the unknown molecule via X-ray crystallography did not produce any results either.

Jacobsen and Berkessel epoxidations were performed on alkene **3.36** and diene **3.36'**. After several attempts with both methods and the employment of beneficial additives[9, 21] – tetra-*n*-butylammonium hydrogen sulfate and 2,6-di-*tert*-butylpyridine, NMR analyses revealed the formation of side-products (Scheme

26) similar to what was discussed in Section 3.3.2. It was speculated that the substrate was unsuitable for such methods of asymmetric epoxidation. This was supported by both Jacobsen's and Berkessel's publications that showed that none of their substrates bore a heterocycle.

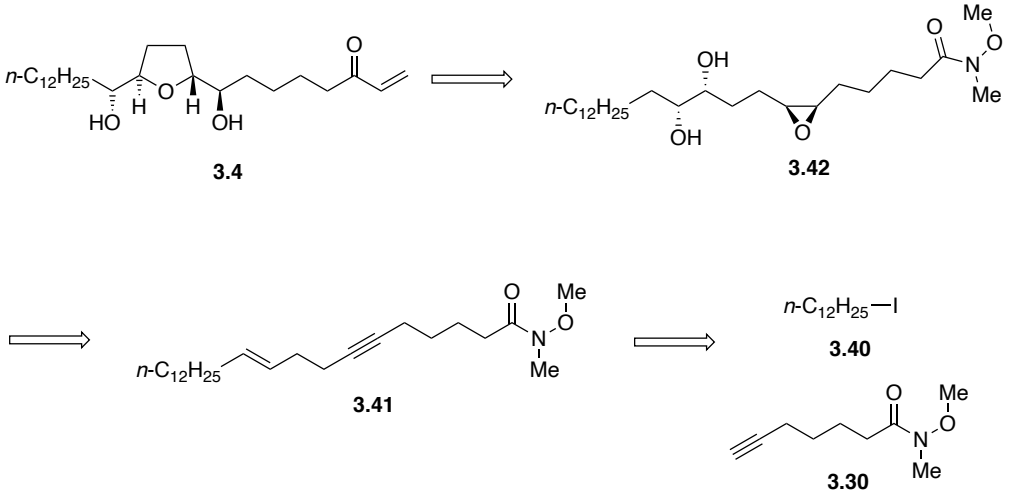


Scheme 26. Side-products of Jacobsen and Berkessel Epoxidation

Since the above strategies did not proceed as expected, another synthetic layout had to be attempted. This layout would exclude the use of thiophene.

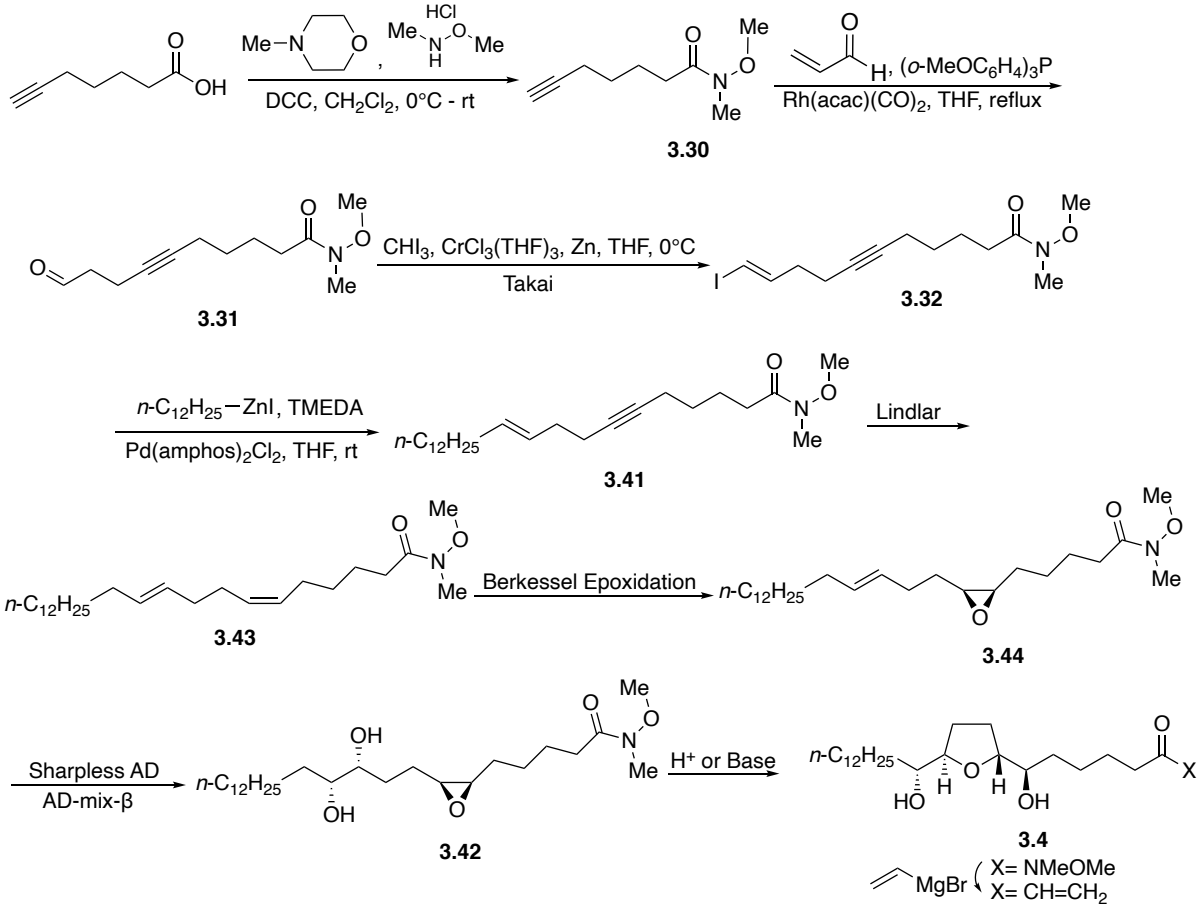
3.3.4 Synthetic Approach via sp^2 – sp^3 Cross-Coupling

3.3.4.1 Synthetic Plan



Scheme 27. Fourth Retrosynthetic Pathway of LHS fragment

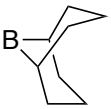
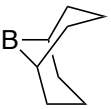
This synthetic outline (Scheme **27**) will focus on coupling two fragments during the early part of the synthesis towards the targeted 5-membered ring **3.4**. One of the key steps involves the formation of adduct **3.41** from an sp^2 – sp^3 Negishi coupling[87] of fragments **3.32** and **3.40**. The rest of the synthesis follows the methods aforementioned, illustrated below in Scheme **28**.



Scheme 28. Fourth Proposed Synthesis Pathway of LHS fragment

3.3.4.2 Synthetic Implementation

Adduct **3.41** was furnished via Negishi coupling (Scheme **28**) in 20% yield using commercially available 1-iododecane **3.40** and previously synthesised iodide **3.32**. Several coupling methods were screened (Table **3**) and Lipshutz's protocol provided the cleanest and highest yielding reaction. ^{1}H NMR spectroscopic analysis showed a multiplet at 5.48 – 5.40 ppm with an integration value of two, representing the presence of the alkene and thus confirming that the cross-coupling reaction was successful.

Entry[a]	Alkyl Species	Catalyst	Temp (°C)	Time (h)	Remarks[b]
1	*n*-$C_{12}H_{25}$—I	Pd(Amphos)Cl_2	rt	12	Starting material retrieved
2	*n*-$C_{12}H_{25}$—I	Pd(Amphos)Cl_2	60	3	No starting material, alkene and Weinreb amide peaks disappeared
3[c]	*n*-$C_{12}H_{25}$—B 	Pd(PPh_3)$_4$	55	12	β-hydride elimination side-product. No starting material
4[c]	*n*-$C_{12}H_{25}$—B 	Pd(dppf)Cl_2	55	12	β-hydride elimination side-product. No starting material
5	*n*-$C_{12}H_{25}$—MgBr	Fe(acac)$_3$	0	0.5	Starting material
6	*n*-$C_{12}H_{25}$—B(OH)(OH)	Pd(dppf)Cl_2	80	10	Side-products, no starting material
7	*n*-$C_{12}H_{25}$—MgBr	Ni(dppp)Cl_2	Reflux	12	10% product. β-hydride elimination side-product. No starting material
8	*n*-$C_{12}H_{25}$—ZnI	Pd(Amphos)Cl_2	rt	24	20% product. Starting material.

[a]All reactions were run in THF. [b]Isolated yield. [c]. NaOH was included as base.

Table 3. Cross-Coupling reactions

In comparison to the cross-coupling of sp^2 – sp^2-hybridised species, the advancement of the sp^2 – sp^3 cross-coupling[88] reaction has been inhibited by side-reactions, namely β-hydride elimination with Pd-catalysis for alkyl halides.[89-90] Research groups have successfully exhibited the effective process involving sp^3 cross-coupling reactions with nickel catalysis,[91-93] organoboranes,[94] organozinc halides[95-96] and Grignard[97] species.

Entries 1 and 2 relied on a Negishi-like cross-coupling that uses micellar technology reported by Lipshutz[98]. This strategy uses water as the replacement for an organic solvent and is also an alternative to the widely-employed multi-step method that requires the synthesis of the organozinc halide. Several attempts were made using Lipshutz micellar strategy at room temperature. However, only starting material was retrieved. Increasing the temperature of the reaction (Entry 2) only led to the disappearance of the alkene and Weinreb amide peaks, with ^{1}H NMR analysis showing the absence of signals at the region from 3 – 6 ppm.

Entry 5 attempted to hinge on the advantages of iron-catalysed cross-coupling[99], using a Grignard reagent as a reaction partner. Iron has the distinctive reactivity of a d-block element while retaining the advantages of a Group I or II metal. Iron salts can also operate as a cheaper and less harmful alternative[100] to Pd or Ni catalysts. In addition, iron-catalysed reactions do not require heat and happen quickly at low temperatures, and are thus suitable for a broad range of functional groups. In our attempt, however, the iron-catalysed cross-coupling did not see any conversion of starting material to product.

One of the most difficult kinds of Negishi couplings is one between alkylzinc halides and alkenyl halides[87]. The simultaneous formation of unwanted by-products associated with these cross-couplings remains a challenge. Several workarounds include a preferential choice for alkenyl iodides[101] as they provide better stability and reactivity than other alkenyl halides. Saturation of the coordination sphere of Pd with bidentate ligands[102-103] would help in overcoming the formation of unwanted products obtained through β-hydride elimination and homocoupling via ligand disorganising. The role of TMEDA in Lipshutz's Negishi coupling strategy is assumed to be a coordinating ligand for Pd[104] and Zn,[105] and

serves the same function by saturating the coordination sphere of Pd in $PdCl_2(Amphos)_2$.

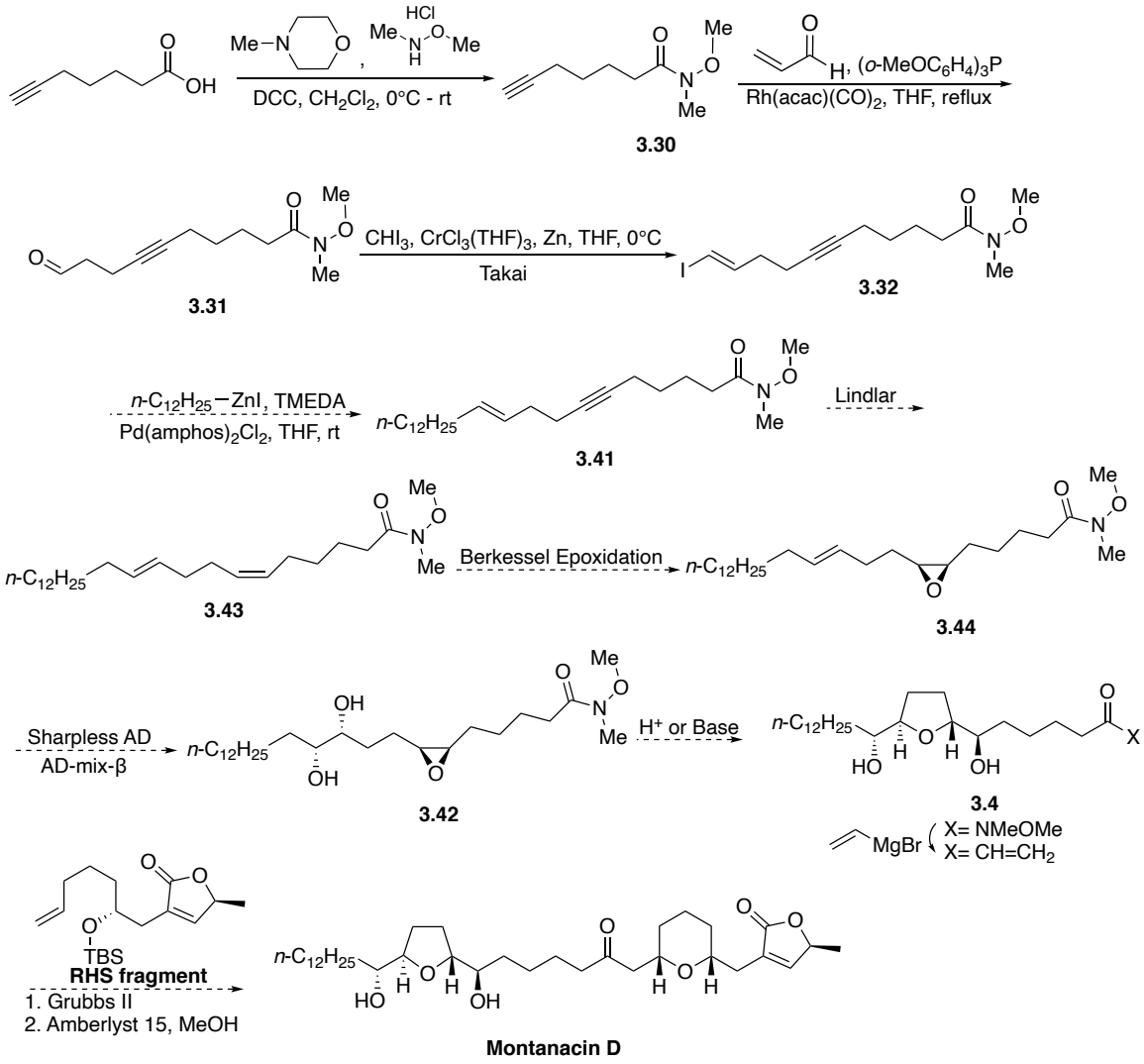
3.4 Conclusion

The completion of the LHS fragment of Montanacin D remains a work in progress. However, the passage towards the synthesis of THF **3.4** has led to the exploration of intriguing chemistry. When successfully achieved, Montanacin D would be synthesised in 11 steps in its longest linear sequence, compared to the 16 steps from the previously reported route, owing to the more convergent nature of the synthetic outline.

3.5 Future Work

The completion of the LHS fragment can begin with the optimisation of the sp^2 – sp^3 cross-coupling reaction, shown below in Scheme **29**. Although the reaction affords a clean product, the conversion of the starting material to the desired product remains low. Workarounds can include the saturation of the coordination sphere of Pd with stronger coordinating bidentate ligands to curb side reactions. A higher ratio of alkylzinc iodide to vinyl iodide can also be employed.

Adduct **3.41** would then be subjected to a Lindlar reduction to produce diene **3.43**, which would subsequently be subjected to Berkessel epoxidation to give epoxide **3.44**. Epoxide **3.44** could then be converted to diol **3.42** via Sharpless asymmetric dihydroxylation, furnishing the precursor ready for the formation of THF intermediate **3.4** through acid or base-induced cyclisation. With that, the LHS fragment would be ready for the final two steps involving firstly its cross-metathesis with the already completed RHS moiety described in Chapter 2, followed by the final step of an *oxa*-Michael reaction to afford Montanacin D.



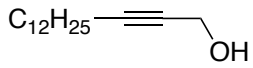
Scheme 29. Proposed Synthetic Pathway of Future Work

3.6 Experimental

All reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware (120 °C), which was cooled under vacuum. Needles and syringes were similarly dried under vacuum before use. Anhydrous tetrahydrofuran was distilled from benzophenone and sodium metal under nitrogen. Anhydrous toluene was distilled over sodium under a nitrogen atmosphere. Anhydrous dichloromethane was dried by distillation from CaH_2 immediately prior to use under nitrogen. Anhydrous methanol was distilled from activated magnesium under nitrogen. All other solvents and reagents were used as received. Flash chromatography was carried out on silica gel, 230-400 mesh.

^{1}H NMR spectra were recorded in deuterated solvent $CDCl_3$, at 300, 400, 500 MHZ, using Bruker AV300, AV400, AV500, BBFO1 400, BBFO2 400, JEOL ECA 400 and ECA 400SL spectrometers. ^{13}C NMR spectra were recorded at the corresponding frequency on the same instruments at 75, 100 or 125 MHz. Chemical shifts are recorded in parts per million and coupling constants are recorded in Hertz. Multiplicity of NMR signals are abbreviated using the following shorthand: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet).

Enantiomeric excess was determined by chiral HPLC analysis, using a Diacel Chiracel OD-H column, eluting with CH_2Cl_2/hexane.

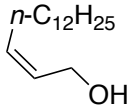


Pentadec-2-yn-1-ol (3.5)[106]

To an oven-dried round-bottomed flask was added a solution of 1-tetradecyne (2 g, 10.3 mmol) in anhydrous THF (75 mL) under stirring at -78 °C. *n*-BuLi (4.5 mL, 11.3 mmol, 2.5 M solution in hexanes) was added dropwise, slowly, to the reaction mixture. The reaction mixture was stirred at -78 °C for 1 h then 0.5 h at rt. After cooling again at -78 °C, a suspension of well-dried paraformaldehyde (1547 mg, 51.5 mmol) in anhydrous THF (25 mL) was added in one portion. The resulting mixture was stirred overnight, and quenched with a solution of sat. NH_4Cl (100 mL). Et_2O (100 mL) was added and the organic layer was washed with brine (2 x 100 mL) and water (2 x 100 mL). The organic layer was dried over $MgSO_4$, and after evaporation of the solvent under reduced pressure, the crude product was purified via column chromatography (silica gel, eluent EtOAc/ hexane 10:90) to give the product as a colourless solid (**3.5**, 1.77 g, 7.9 mmol).

Yield: 77%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.26 – 4.25 (m, 2H), 2.21 (tt, *J* = 7.2, 2.2 Hz, 2H), 1.50 (p, *J* = 7.2 Hz, 2H), 1.40 – 1.33 (m, 2H), 1.27 (s, 16H), 0.88 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 86.8, 78.3, 51.5, 29.7, 29.6, 29.4, 29.2, 29.0, 28.7, 22.8, 18.8, 14.2.

All data is consistent with that reported in literature.

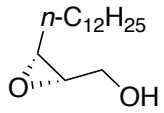


(*Z*)-Pentadec-2-en-1-ol (3.6)[107]

A solution of Pentadec-2-yn-1-ol (**3.5**, 200 g, 0.9 mmol) in anhydrous pyridine (2 mL), and Lindlar catalyst (20 mg) was stirred at rt under a H_2 atmosphere for 24 h. The mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give the pure product as a colourless oil (**3.6**, 197 mg, 0.87 mmol). No further purification was required.

Yield: 97%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.63 – 5.49 (m, 2H), 4.19 (d, *J* = 6.5 Hz, 2H), 2.06 (q, *J* = 7.2 Hz, 2H), 1.34 (q, *J* = 7.0 Hz, 3H), 1.26 (s, 18H), 0.87 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 133.3, 128.3, 58.6, 31.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.3, 29.2, 27.4, 22.7, 14.1.

All data is consistent with that reported in literature.



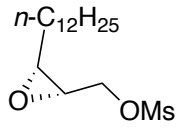
((2*S*,3*R*)-3-dodecyloxiran-2-yl)methanol (3.7)[107]

A mixture of crushed, activated 4 Å molecular sieves (75 mg) and 4.5 mL of anhydrous CH_2Cl_2 was cooled to 0 °C. L-(+)-Diethyl tartrate (28.5 mg, 0.134 mmol, 14 mol%) followed by $Ti(O^iPr)_4$ (27.5 mg, 0.094 mmol, 10 mol%) were added. The reaction mixture was then cooled to -20 °C. After which, TBHP (0.33 mL, 1.88 mmol, 5.8 M in toluene) was added and the resulting mixture was stirred for 20 min. (*Z*)-Pentadec-2-en-1-ol (**3.6**, 212 mg, 0.94 mmol) was then added. After stirring for 0.5 h at -20 °C, the reaction mixture was refrigerated at -10 °C and left to sit for 29 h. On completion, checked by TLC, the reaction was warmed to 0 °C, quenched with water (0.6 mL) and stirred for 45 min, while allowing it to warm to room temperature. 6.0 mL of a 30% solution of NaOH saturated with brine was added and the reaction mixture stirred vigorously for 15 min. The organic phase is separated and the aqueous phase was extracted using CH_2Cl_2 (2 x 10 mL). The organic phase is dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 25:75) to give the product as a white powder (**3.7**, 139 mg, 0.572 mmol). The *ee* was determined by HPLC analysis for 4-nitrobenzoate derivative, ((2*S*,3*R*)-3-dodecyloxiran-2-yl)methyl 4-nitrobenzoate (Daicel Chiralcel OD-H, eluent CH_2Cl_2/ hexane 95:5), 0.5 mL/min, X = 254 nm, S isomer 18.6 min, R isomer 19.7 min).

Yield: 61%. 85% ee. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.86 (ddd, *J* = 11.7, 7.2, 4.1 Hz, 1H), 3.68 (ddd, *J* = 11.8, 6.8, 4.0 Hz, 1H), 3.15 (dt, *J* = 6.9, 4.2 Hz, 1H), 3.03 (dt, *J* = 6.7, 4.9 Hz, 1H), 1.60 – 1.47 (m, 5H), 1.26 (s, 18H), 0.88 (t, *J* = 6.9 Hz,

3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 60.9, 57.3, 56.9, 31.9, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 28.0, 26.6, 22.7, 14.1.

All data is consistent with that reported in literature.

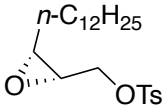


((2*S*,3*R*)-3-dodecyloxiran-2-yl)methyl methanesulfonate

Triethylamine (125.2 mg, 1.24 mmol) was added dropwise, slowly, to a solution of ((2*S*,3*R*)-3-dodecyloxiran-2-yl)methanol (**3.7**, 200 mg, 0.825 mmol) in 1 mL of anhydrous CH_2Cl_2 at 0 °C. Methanesulfonyl chloride (122.9 mg, 1.07 mmol) was then added. The solution was then stirred to room temperature for 1 h. On completion, checked by TLC, the reaction was quenched with saturated aqueous NH_4Cl solution. The organic layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 15:85) to afford ((2*S*,3*R*)-3-dodecyloxiran-2-yl)methyl methanesulfonate as a colourless solid (234 mg, 0.729 mmol).

Yield: 88%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.45 (dd, *J* = 11.6, 3.8 Hz, 1H), 4.23 (dd, *J* = 11.6, 7.4 Hz, 1H), 3.26 (dt, *J* = 7.8, 4.2 Hz, 1H), 3.16 – 3.02 (m, 4H), 1.60 – 1.48 (m, 3H), 1.42 (t, *J* = 6.8 Hz, 3H), 1.26 (s, 16H), 0.88 (t, *J* = 6.8 Hz, 3H); **MS** (ESI+) m/z 321 $[M+H]^+$.

(Only ^{1}H NMR and MS was collected for this)

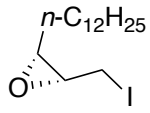


((2*S*,3*R*)-3-dodecyloxiran-2-yl)methyl 4-methylbenzenesulfonate

Triethylamine (125 mg, 1.24 mmol) was added dropwise, slowly, to a solution of ((2*S*,3*R*)-3-dodecyloxiran-2-yl)methanol (**3.7**, 200 mg, 0.825 mmol) in 1 mL of CH_2Cl_2 at 0 °C. Tosyl chloride (204 mg, 1.07 mmol) was then added. The solution was warmed to rt over an hour. On completion, checked by TLC, the reaction was quenched with saturated aqeuous NH_4Cl solution. The organic layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 10:90) to afford ((2*S*,3*R*)-3-dodecyloxiran-2-yl)methyl 4-methylbenzenesulfonate as a colourless solid (272 mg, 0.685 mmol).

Yield: 83%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 4.17 (dd, *J* = 11.1, 5.1 Hz, 1H), 4.09 (dd, *J* = 11.1, 6.3 Hz, 1H), 3.19 – 3.11 (m, 1H), 3.02 – 2.93 (m, 1H), 2.46 (s, 3H), 1.55 (d, *J* = 1.6 Hz, 2H), 1.51 – 1.34 (m, 4H), 1.26 (s, 16H), 0.88 (t, *J* = 6.7 Hz, 3H).

(Only ^{1}H NMR was collected for this)

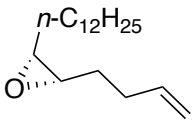


(2*R*,3*R*)-2-dodecyl-3-(iodomethyl)oxirane[107]

To an oven-dried 10 mL flask fitted with a reflux condenser, was charged ((2*S*,3*R*)-3-dodecyloxiran-2-yl)methyl methanesulfonate (150.2 mg, 0.469 mmol) in 0.5 mL of acetone, NaI (119.4 mg, 0.797 mmol) and a catalytic amount of Na_2SO_3. The reaction was stirred at reflux for 6 hours. On completion, checked by TLC, the reaction mixture was quenched with 3 mL of 10 % v/w $Na_2S_2O_3$ solution. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford (2*R*,3*R*)-2-dodecyl-3-(iodomethyl)oxirane as a yellow oil (157 mg, 0.446 mmol).

Yield: 95%. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.38 – 3.20 (m, 2H), 3.06 – 2.92 (m, 2H), 1.64 – 1.44 (m, 4H), 1.26 (s, 18H), 0.87 (t, *J* = 5.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 59.9, 56.8, 31.9, 29.6, 29.60, 29.6, 29.5, 29.5, 29.3, 27.0, 26.5, 22.7, 14.1, 1.3.

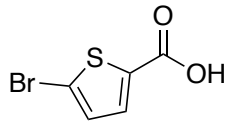
All data is consistent with that reported in literature.



(2*S*,3*R*)-2-(but-3-en-1-yl)-3-dodecyloxirane (3.1)

Allylmagnesiumbromide (1.23 mL, 1.23 mmol, 1 M in solution) was added dropwise, slowly, to a suspension of CuI (9.34 mg, 0.049 mmol) in a solution of (2*R*,3*R*)-2-dodecyl-3-(iodomethyl)oxirane (133 mg, 0.378 mmol) and HMPA (362 mg, 2.02 mmol) in anhydrous THF (0.5 mL) that was previously cooled to -23°C. The resulting mixture was stirred for 20 min at -23°C and then quenched by the addition of sat. NH_4Cl (5 mL) and Et_2O (5 mL). The mixture was extracted with Et_2O (3 x 10 mL) and the combined Et_2O layers were washed with H_2O (10 mL), brine (2 x 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford the product as a colourless oil (10 mg, 0.04 mmol).

Yield: 10%. **FTIR (neat, cm^{-1})**: ν_{max} 1646, 3078; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.86 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.09 – 4.97 (m, 2H), 2.93 (ddt, *J* = 8.7, 6.0, 3.0 Hz, 2H), 2.32 – 2.15 (m, 2H), 1.64 – 1.26 (m, 24H), 0.88 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.7, 115.2, 57.3, 56.7, 31.9, 30.8, 29.7, 29.6, 29.6, 29.4, 27.9, 27.3, 26.6, 22.7, 14.1; **MS (ESI+)** m/z 267 $[M+H]^+$**; HRMS** calcd for $C_{18}H_{34}O$ ($[M+H]^+$) 267.2688 found 267.2624.

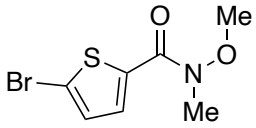


5-bromothiophene-2-carboxylic acid[108]

To a 2-necked, round-bottomed flask fitted with a drying tube was added thiophene-2-carboxylic acid (5 g, 39 mmol) and 37.5 mL of AcOH. The mixture was stirred at room temperature and Br_2 (2 mL, 39 mmol) was added dropwise, slowly, over two hours. The mixture was stirred vigorously overnight. On completion, checked by TLC, the mixture was quenched with water and stirred for 20 min until the mixture decolourised. The mixture was filtered through a Buchner funnel and rinsed with water. The cake was dissolved in ethyl acetate and washed with water. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the product (6.79 g, 32.8 mmol) as a white solid.

Yield: 84%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 4.0 Hz, 1H), 7.12 (d, *J* = 4.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6, 135.4, 133.9, 131.3, 122.3.

All data is consistent with that reported in literature.

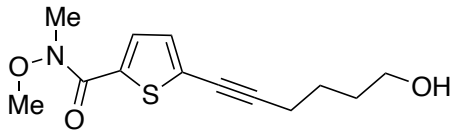


5-bromo-N-methoxy-N-methylthiophene-2-carboxamide (3.10)[109]

A mixture of 5-bromothiophene-2-carboxylic acid (300 mg, 1.45 mmol), thionyl chloride (423 μL, 5.80 mmol) was dissolved in $CHCl_3$ (3 mL) and heated at reflux for 1 hour. After cooling, the reaction mixture was concentrated under reduced pressure to give 5-bromothiophene-2-carbonyl chloride (324 mg, 1.45 mmol) as a pale yellow solid, and immediately subjected to the next step. To a round-bottom flask with 5-bromothiophene-2-carbonyl chloride (324 mg, 1.45 mmol) in CH_2Cl_2 (3 mL), was added *N*-*O*-dimethylhydroxylamine hydrochloride (148 mg, 1.52 mmol). The reaction mixture was cooled to 0 °C. Pyridine (2451 mg, 3.04 mmol) was then added dropwise. The reaction mixture was allowed to warm to rt, upon which a white precipitate formed. The reaction was left to stir overnight. The reaction mixture was then diluted with CH_2Cl_2 (8 mL) and the phases were separated. The organic layer was washed with 1 M HCl (2 x 5 mL), saturated $NaHCO_3$ solution (2 x 10 mL), and brine (1 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated in *vacuo* to yield the product (**3.10**, 323 mg, 1.29 mmol) as a yellow oil without further purification.

Yield: 89% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 4.1 Hz, 1H), 7.09 (d, *J* = 4.1 Hz, 1H), 3.78 (s, 3H), 3.35 (s, 3H).

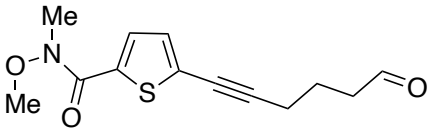
All data is consistent with that reported in literature.



5-(6-hydroxyhex-1-yn-1-yl)-*N*-methoxy-*N*-methylthiophene-2-carboxamide

5-bromo-*N*-methoxy-*N*-methylthiophene-2-carboxamide (**3.10**, 1.8 g, 7.2 mmol), K_2CO_3 (2.49 g, 18 mmol), CuI (54.8 mg, 0.288 mmol), $PdCl_2(PPh_3)_2$ (167 mg, 0.237 mmol) were mixed with distilled 1,2-dimethoxyethane (20 mL) and deoxygenated water (20 mL) at 25 °C under nitrogen atmosphere. This was stirred for 30 minutes and hex-5-yn-1-ol (2025 μL, 18 mmol) was added. The reaction mixture was heated at 80 °C overnight, cooled to rt and filtered through a pad of celite. The reaction mixture was diluted with water, the aqueous phase extracted with EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 40:60) to afford the product (1265 mg, 4.73 mmol) as a yellow oil.

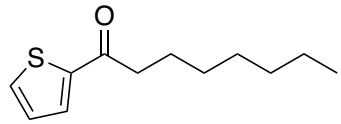
Yield: 66%. **FTIR** (CH_2Cl_2, cm^{-1}): ν_{max} 1412, 2260, 3005; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 4.0 Hz, 1H), 7.08 (d, *J* = 4.0 Hz, 1H), 3.78 (s, 3H), 3.71 (t, *J* = 6.0 Hz, 2H), 3.36 (s, 3H), 2.50 (t, *J* = 6.8 Hz, 2H), 1.80 – 1.65 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.6, 134.4, 131.9, 130.7, 130.5, 96.7, 73.8, 62.3, 61.6, 33.0, 31.8, 24.7, 19.5; **MS** (ESI+) m/z 268 $[M+H]^+$; **HRMS** calcd for $C_{13}H_{17}NO_3S$ ($[M+H]^+$) found 268.1003.



***N*-methoxy-*N*-methyl-5-(6-oxohex-1-yn-1-yl)thiophene-2-carboxamide (3.21)**

5-(6-hydroxyhex-1-yn-1-yl)-*N*-methoxy-*N*-methylthiophene-2-carboxamide (28.3 mg, 0.106 mmol) was added to a solution of 2-iodoxybenzoic acid (44.5 mg, 0.159 mmol) in 1 mL of DMSO and stirred overnight at room temperature. On completion, the reaction was quenched by adding saturated aqueous $NaHCO_3$ solution and filtered over a pad of celite. The organic layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 25:75) to afford *N*-methoxy-*N*-methyl-5-(6-oxohex-1-yn-1-yl)thiophene-2-carboxamide (**3.21**, 25.3 mg, 0.095 mmol) as a yellow oil.

Yield: 90%. **FTIR** (neat, cm^{-1}): ν_{max} 1721, 1615, 3455; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.83 (t, *J* = 1.4 Hz, 1H), 7.80 (d, *J* = 4.0 Hz, 1H), 7.08 (d, *J* = 3.6 Hz, 1H), 3.77 (s, 3H), 3.35 (s, 3H), 2.65 (td, *J* = 7.2, 1.3 Hz, 2H), 2.53 (t, *J* = 6.9 Hz, 2H), 1.94 (app. quint, *J* = 7.1 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.5, 161.6, 134.4, 132.2, 130.7, 130.3, 95.4, 74.5, 61.7, 42.7, 32.9, 20.8, 19.1; **MS** (ESI+) m/z 266 $[M+H]^+$; **HRMS** calcd for $C_{13}H_{15}NO_3S$ ($[M+H]^+$) 266.0851 found 266.0808.

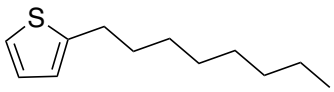


2-octanoylthiophene[110]

$AlCl_3$ (15.9 g, 118.9 mmol, 2 equiv) was added slowly in portions to the solution of octanoyl chloride (4.76 g, 59.5 mmol, 1 equiv) and thiophene (5 g, 59.5 mmol, 1 equiv) in toluene at 0°C. The mixture was stirred at 0°C for 1 h, warmed to rt and left to stir overnight. On completion, checked by TLC, 3% HCl (100 mL) was added and the organic layer was washed with water (4 x 250 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. The product was purified via vacuum distillation (1 torr, 125 °C) to yield 2-octanoylthiophene (10.8 g, 51.2 mmol) as a colourless liquid.

Yield: 86%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.61 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.12 (dd, *J* = 5.0, 3.8 Hz, 1H), 2.89 (t, *J* = 7.4 Hz, 2H), 1.74 (app. quint, *J* = 7.4 Hz, 2H), 1.44 – 1.22 (m, 8H), 0.92 – 0.84 (m, 3H); **^{13}C NMR** (100 MHz $CDCl_3$) δ 193.5, 144.5, 133.3, 131.6, 128.0, 39.4, 31.6, 29.3, 29.0, 24.8, 22.6, 14.0.

All data is consistent with that reported in literature.

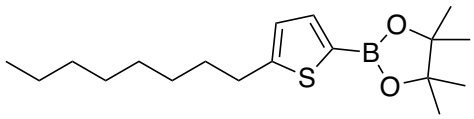


2-octylthiophene (3.13)[111]

To an oven-dried, three-necked, round-bottomed flask fitted with a nitrogen inlet attached to an oil bubbler, septum and solid addition tube, was added $AlCl_3$ (254 mg, 1.90 mmol). The flask was cooled to 0 °C. Anhydrous Et_2O was slowly added to the flask containing $AlCl_3$, with careful stirring. To the same flask, $LiAlH_4$ (289 mg, 7.6 mmol) was added portion-wise slowly, via a solid addition tube. A solution of 2-octanoylthiophene (200 mg, 0.951 mmol) in anhydrous Et_2O at 0 °C was then added. The mixture was warmed to room temperature and then stirred for 3 h. On completion, checked by TLC, the reaction was quenched in an ice-bath by the careful addition of Et_2O and 2 M HCl aqueous solution. The grey precipitate was filtered and washed with Et_2O. The combined filtrate was separated and the aqueous layer extracted with Et_2O (3 x 20 mL), washed with water (2 x 20 mL), dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 5:95) to afford a colourless liquid (**3.13**, 150 mg, 0.765 mmol).

Yield: 80% **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.91 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.78 (dd, *J* = 3.4, 1.1 Hz, 1H), 2.82 (t, *J* = 7.6 Hz, 2H), 1.67 (p, *J* = 7.4 Hz, 2H), 1.41 – 1.14 (m, 10H), 0.88 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.9, 126.6, 123.9, 122.7, 31.9, 31.8, 29.9, 29.3, 29.2, 29.1, 22.7, 14.1.

All data is consistent with that reported in literature.

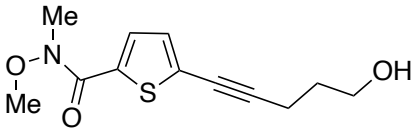


4,4,5,5-tetramethyl-2-(5-octylthiophen-2-yl)-1,3,2-dioxaborolane (3.8)[78]

A two-necked RBF was fitted with a condenser to which a N_2 inlet and an oil bubbler were attached. The flask was charged with bis(1,5-cyclooctadiene)di-μ-methoxydiiridium(I) (6.25 mg, 0.01 mmol), 4,4'ditertbutyl2,2'bipyridine (5.5 mg, 0.02 mmol) and purged with N_2. Anhydrous hexane (4 mL) and pinacolborane (134 μL, 1 mmol) were added by syringe. The mixture was stirred for 5 min to give a dark red solution. 2-octyl-thiophene (**3.13**, 200 mg, 1 mmol) was added dropwise, slowly, and the resulting dark red suspension was left to stir at 50 °C overnight. On completion, checked by TLC, the reaction mixture was allowed to cool to rt. The reaction mixture was loaded directly onto silica gel where the crude product was purified by column chromatography (silica gel, eluent CH_2Cl_2/ hexane 20:80) to afford a colourless liquid **(3.8**, 299 mg, 0.928 mmol).

Yield: 91%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 3.6 Hz, 1H), 6.86 (d, *J* = 2.7 Hz, 1H), 2.89 – 2.78 (m, 2H), 1.68 (t, *J* = 7.6 Hz, 2H), 1.40 – 1.22 (m, 30H), 0.92 – 0.81 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.7, 137.3, 125.8, 83.8, 31.8, 31.7, 30.1, 29.30, 29.2, 29.1, 24.8, 24.8, 22.6, 14.1.

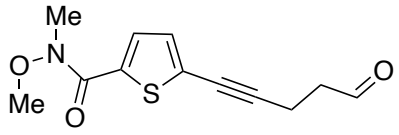
All data is consistent with that reported in literature.



5-(5-hydroxypent-1-yn-1-yl)-*N*-methoxy-*N*-methylthiophene-2-carboxamide

5-bromo-*N*-methoxy-*N*-methylthiophene-2-carboxamide (**3.10**, 200 mg, 0.8 mmol), K_2CO_3 (276 mg, 2 mmol), CuI (6 mg, 0.032 mmol), $PdCl_2(PPh_3)_2$ (46.3 mg, 0.066 mmol) were mixed with distilled 1,2-dimethoxyethane (1 mL) and deoxygenated water (1 mL) at 25 °C under N_2 atmosphere. This was stirred for 0.5 h after which pen-4-yn-1-ol (186 μL, 2 mmol) was added. The mixture was heated at 80 °C overnight, cooled to rt and filtered through a pad of celite. The reaction mixture was diluted with water, extracted with EtOAc, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 35:65) to afford the product (173 mg, 0.682 mmol) as a yellow oil.

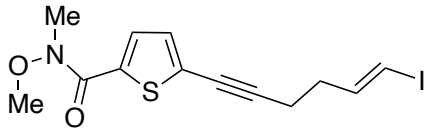
Yield: 85%. **FTIR** (CH_2Cl_2, cm^{-1}): ν_{max} 1412, 1626, 2938; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 4.0 Hz, 1H), 7.08 (d, *J* = 4.0 Hz, 1H), 3.80 (t, *J* = 6.4 Hz, 2H), 3.77 (s, 3H), 3.35 (s, 3H), 2.58 (t, *J* = 6.8 Hz, 2H), 1.87 (app. quint, *J* = 6.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.6, 134.4, 132.0, 130.6, 130.6, 96.1, 73.9, 61.7, 33.0, 31.0, 16.3; **MS** (ESI+) m/z 254 $[M+H]^+$; **HRMS** calcd for $C_{12}H_{15}NO_3S$ ($[M+H]^+$) 254 found 254.0848.



N-methoxy-N-methyl-5-(5-oxopent-1-yn-1-yl)thiophene-2-carboxamide (3.14)

5-(5-hydroxypent-1-yn-1-yl)-N-methoxy-N-methylthiophene-2-carboxamide (158 mg, 0.624 mmol) was added to a solution of 2-iodoxybenzoic acid (262 mg, 0.936 mmol) in 1 mL of DMSO and stirred overnight at rt. On completion, the reaction was quenched by adding water (10 mL) and filtered over a pad of celite. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 25:75) to afford N-methoxy-N-methyl-5-(5-oxopent-1-yn-1-yl)thiophene-2-carboxamide (**3.14**, 125 mg, 0.499 mmol) as a yellow oil.

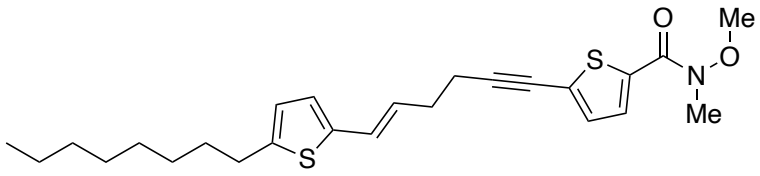
Yield: 80%. **FTIR** (neat, cm^{-1}): ν_{max} 1603, 1637, 1724; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.8 (s, 1H), 7.77 (d, *J* = 4.0 Hz, 1H), 7.06 (d, *J* = 4.0 Hz, 1H), 3.74 (s, 3H), 3.32 (s, 3H), 2.75 (t, *J* = 3.6 Hz, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.8, 161.4, 134.3, 132.2, 130.8, 129.9, 94.4, 74.1, 61.6, 42.1, 32.9, 12.8; **MS (ESI+)** m/z 252 $[M+H]^+$**; HRMS** calcd for $C_{12}H_{13}NO_3S$ ($[M+H]^+$) 252.0694 found 252.0647.



(*E*)-5-(6-iodohex-5-en-1-yn-1-yl)-*N*-methoxy-*N*-methylthiophene-2-carboxamide (3.15)

Freshly activated Zinc powder (132 mg, 2.01 mmol), $CrCl_3(THF)_3$ (440 mg, 1.18 mmol) was suspended in anhydrous THF (2 mL) under a nitrogen atmosphere. A solution of aldehyde (**3.14**, 100 mg, 0.395 mmol) and iodoform (310 mg, 0.789 mmol) in anhydrous THF (2 mL) was added dropwise using a syringe pump to the suspension at 0 °C. On completion, checked by TLC, the reaction mixture is poured into water (25 mL) and extracted with ether (3 x 10 mL). The combined extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 25:75) to afford (*E*)-5-(6-iodohex-5-en-1-yn-1-yl)-*N*-methoxy-*N*-methylthiophene-2-carboxamide (**3.15**, 96 mg, 0.257 mmol) as a yellow oil.

Yield: 65%. **FTIR** (neat, cm^{-1}): ν_{max} 512, 1637, 3300; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 4.0 Hz, 1H), 7.07 (d, *J* = 3.5 Hz, 1H), 6.61 – 6.55 (m, 1H), 6.07 (d, *J* = 13.5 Hz, 1H), 3.76 (s, 3H), 3.34 (s, 3H), 2.52 (t, *J* = 7.0 Hz, 2H), 2.36 – 2.32 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.7, 143.9, 139.1, 134.4, 132.3, 130.8, 95.4, 84.0, 74.7, 61.7, 34.8, 33.6, 19.1; **MS** (ESI+) m/z 375 $[M+H]^+$; **HRMS** calcd for $C_{13}H_{14}INO_2S$ ($[M+H]^+$) 375.9868 found 375.9839.

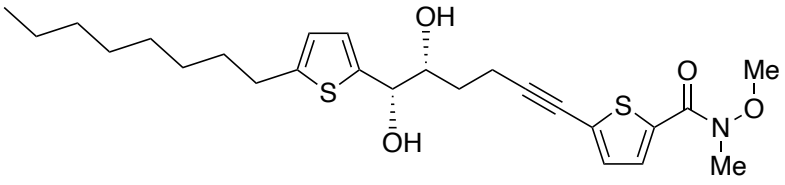


(*E*)-*N*-methoxy-*N*-methyl-5-(6-(5-octylthiophen-2-yl)hex-5-en-1-yn-1-yl)thiophene-2-carboxamide (3.11)

In a two-necked flask was weighed NaOH (33 mg, 0.815 mmol), 4,4,5,5-tetramethyl-2-(5-octylthiophen-2-yl)-1,3,2-dioxaborolane (**3.8**, 96.2 mg, 0.298 mmol), $PdCl_2$(dppf) (9 mg, 0.012 mmol), and (*E*)-5-(6-iodohex-5-en-1-yn-1-yl)-*N*-methoxy-*N*-methylthiophene-2-carboxamide (**3.15**, 101.9 mg, 0.272 mmol). The flask was purged with N_2. THF (1 mL) and deoxygenated H_2O (1 mL) were added and the reaction mixture was heated to 50 °C and left to stir overnight. On completion, checked by TLC, the layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layeres were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 20:80) to afford (*E*)-*N*-methoxy-*N*-methyl-5-(6-(5-octylthiophen-2-yl)hex-5-en-1-yn-1-yl)thiophene-2-carboxamide (**3.11**, 84 mg, 0.190 mmol) as a yellow oil.

Yield: 70%. **FTIR** (CH_2Cl_2, cm^{-1}): ν_{max} 1500, 1670, 2929; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 4.0 Hz, 1H), 7.09 (d, *J* = 4.0 Hz, 1H), 6.70 (d, *J* = 3.4 Hz, 1H), 6.60 (d, *J* = 3.4 Hz, 1H), 6.53 (d, *J* = 15.5 Hz, 1H), 6.02 – 5.96 (m, 1H), 3.77 (s, 3H), 3.36 (s, 3H), 2.74 (t, *J* = 7.6 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 1H), 1.65 (app. quint, *J* = 3.0 Hz, 3H), 1.41 – 1.17 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.7, 144.6, 140.0, 137.89, 130.7, 130.7, 127.5, 126.7,

125.0, 124.8, 124.2, 96.2, 74.2, 61.7, 33.0, 31.9, 31.6, 29.3, 29.1, 29.1, 22.6, 20.1, 14.1; **MS** (ESI+) m/z 443 $[M]^+$; **HRMS** calcd for $C_{25}H_{33}NO_2S_2$ ($[M+H]^+$) 444.2031 found 444.2027.

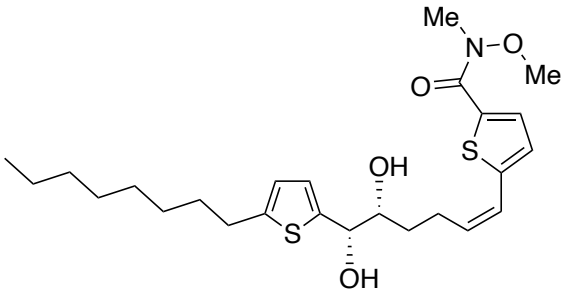


5-((5*R*,6*S*)-5,6-dihydroxy-6-(5-octylthiophen-2-yl)hex-1-yn-1-yl)-*N*-methoxy-*N*-methylthiophene-2-carboxamide (3.16)

To an ice-cold mixture of (*E*)-*N*-methoxy-*N*-methyl-5-(6-(5-octylthiophen-2-yl)hex-5-en-1-yn-1-yl)thiophene-2-carboxamide (**3.15**, 70.2 mg, 0.158 mmol) in *t*-BuOH (1 mL) and H_2O (1 mL) was added $MeSO_2NH_2$ (15 mg, 0.158 mmol), $K_2OsO_2(OH)_4$ (1.16 mg, 0.003 mmol), $K_3Fe(CN)_6$ (156 mg, 0.47 mmol), K_2CO_3 (65 mg, 0.47 mmol), $(DHQD)_2PHAL$ (12 mg, 0.015 mmol). The mixture was stirred for 24 h at 0 °C. On completion, checked by TLC, Na_2SO_3 (100 mg) was added at 0 °C, followed by H_2O (5 mL). Stirring was continued for another 0.5 h then EtOAc (10 mL) was added, followed by saturated aqueous NaCl solution (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 40:60) to afford 5-((5*R*,6*S*)-5,6-dihydroxy-6-(5-octylthiophen-2-yl)hex-1-yn-1-yl)-*N*-methoxy-*N*-methylthiophene-2-carboxamide (**3.16**, 51.4 mg, 0.108 mmol) as a yellow oil.

Yield: 68%. **FTIR** (neat, cm^{-1}): ν_{max} 1521, 1636, 1670, 3449; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 4.0 Hz, 1H), 7.06 (d, *J* = 4.0 Hz, 1H), 6.84 (d, *J* = 3.4 Hz, 1H), 6.64 (d, *J* = 3.4 Hz, 1H), 4.68 – 4.66 (m, 1H), 3.96 – 3.89 (m, 1H), 3.77 (s,

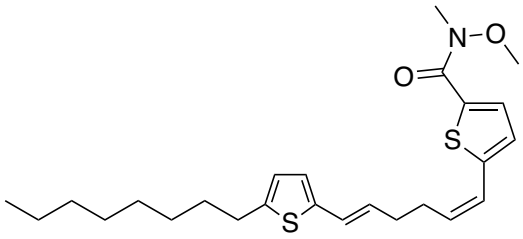
3H), 3.35 (s, 3H), 2.76 – 2.73 (m, 2H), 2.66 – 2.54 (m, 2H), 1.81 (m, 2H), 1.40 – 1.14 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.7, 146.6, 141.2, 134.4, 132.1, 130.7, 125.6, 125.2, 123.6, 96.3, 76.7, 74.7, 74.0, 73.6, 61.7, 33.0, 31.9, 31.6, 31.6, 30.2, 29.3, 29.2, 22.7, 16.3, 14.1; **MS** (ESI+) m/z 478 $[M+H]^+$; **HRMS** calcd for $C_{25}H_{35}NO_4S_2$ ($[M+H]^+$) 478.2086 found 478.2128.



5-((5*R*,6*S*,*Z*)-5,6-dihydroxy-6-(5-octylthiophen-2-yl)hex-1-en-1-yl)-*N*-methoxy-*N*-methylthiophene-2-carboxamide (3.17)

A solution of 5-((5*R*,6*S*)-5,6-dihydroxy-6-(5-octylthiophen-2-yl)hex-1-yn-1-yl)-*N*-methoxy-*N*-methylthiophene-2-carboxamide (**3.16**, 169 mg, 0.354 mmol) in anhydrous pyridine (1 mL) and Lindlar catalyst (20 mg) was stirred at rt under a H_2 atmosphere for 24 h. The mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure to give the product as a colourless oil (**3.17**, 129 mg, 0.269 mmol).

Yield: 76%. **FTIR** (CH_2Cl_2, cm^{-1}): ν_{max}1624, 3608; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 4.0 Hz, 1H), 6.95 (d, *J* = 4.1 Hz, 1H), 6.81 (d, *J* = 5.5 Hz, 1H), 6.63 (d, *J* = 3.4 Hz, 1H), 6.50 (d, *J* = 11.6 Hz, 1H), 5.71 – 5.65 (m, 1H), 4.66 (d, *J* = 6.4 Hz, 1H), 3.80 (m, 1H), 3.70 (s, 3H), 3.35 (s, 3H), 2.76 (t, *J* = 9.5 Hz, 2H), 2.69 – 2.46 (m, 2H), 1.71 – 1.53 (m, 4H), 1.41 – 1.20 (m, 12H), 0.91 – 0.83 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.4, 147.0, 146.3, 141.5, 140.28, 134.2, 133.4, 126.9, 125.1, 123.5, 122.0, 75.4, 73.7, 61.5, 33.1, 32.4, 31.9, 31.6, 30.2, 29.3, 29.2, 29.1, 25.9, 22.6, 14.03; **MS** (ESI+) m/z 480 $[M+H]^+$; **HRMS** calcd for $C_{25}H_{37}NO_4S_2$ ($[M+H]^+$) 480.2242 found 480.2242.



_N_-methoxy-_N_-methyl-5-((1_Z_,5_E_)-6-(5-octylthiophen-2-yl)hexa-1,5-dien-1-yl)thiophene-2-carboxamide (3.26)

A solution of (*E*)-*N*-methoxy-*N*-methyl-5-(6-(5-octylthiophen-2-yl)hex-5-en-1-yn-1-yl)thiophene-2-carboxamide (**3.11**, 120 mg, 0.271 mmol) in anhydrous pyridine (0.5 mL), and Lindlar catalyst (20 mg) was stirred at rt under a H_2 atmosphere for 24 h. The mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure to give the product as a colourless oil (**3.26**, 88.5 mg, 0.198 mmol) without further purification.

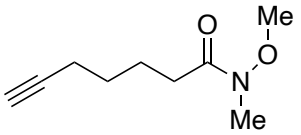
Yield: 73 %. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.86 (d, *J* = 4.0 Hz, 1H), 6.61 (d, *J* = 3.1 Hz, 1H), 6.04 (d, *J* = 6.9 Hz, 1H), 5.40 – 5.32 (m, 1H), 5.30 – 5.20 (m, 2H), 3.67 (s, 3H), 3.16 (s, 3H), 2.75 (t, *J* = 7.6 Hz, 2H), 2.41 (t, *J* = 7.6 Hz, 2H), 2.23 – 1.99 (m, 10H), 1.67 – 1.51 (m, 6H), 1.41 – 1.22 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H).

Jacobsen Epoxidation[4] of 5-((5*R*,6*S*,*Z*)-5,6-dihydroxy-6-(5-octylthiophen-2-yl)hex-1-en-1-yl)-*N*-methoxy-*N*-methylthiophene-2-carboxamide (3.17)

A 0.7 M solution of $NaOCl.5H_2O$ was diluted to approximately 0.55 M in NaOCl with 0.05 M Na_2HPO_4, and the pH of the resulting buffered solution was adjusted to pH = 11.3 by addition of a 1 M NaOH solution. To this solution was added a solution of Jacobsen's Catalyst (3 mg, 5 mol%) and diol (**3.17**, 46 mg, 0.096 mmol) in 0.225 mL of CH_2Cl_2. The two-phase mixture was stirred at 4°C, and the reaction progress was monitored by TLC. After 6 h, 0.225 mL of CH_2Cl_2 was added to the mixture and the brown organic phase was separated, washed twice with 1 mL of H_2O and once with 1 mL of saturated NaCl solution, and then dried (Na_2SO_4). After solvent removal, the residue was purified by flash chromatography on silica gel.

Jacobsen Epoxidation[9] of *N*-methoxy-*N*-methyl-5-((1*Z*,5*E*)-6-(5-octylthiophen-2-yl)hexa-1,5-dien-1-yl)thiophene-2-carboxamide (3.26)

A 0.7 M solution of $NaOCl.5H_2O$ was diluted to approximately 0.55 M in NaOCl with 0.05 M Na_2HPO_4, and the pH of the resulting buffered solution was adjusted to pH = 11.3 by addition of a 1 M NaOH solution. To this solution was added a solution of Jacobsen's Catalyst (12.6 mg, 0.0199 mmol, 10 mol%), diene (**3.26**, 88.5 mg, 0.199 mmol) and 4-phenylpyridine N-oxide (6.8 mg, 0.0397 mmol, 0.0397 mmol) in 0.4 mL of CH_2Cl_2. The two-phase mixture was stirred at 4°C, and the reaction progress was monitored by TLC. After 6 h, 0.4 mL of CH_2Cl_2 was added to the mixture and the brown organic phase was separated, washed twice with 1 mL of H_2O and once with 1 mL of saturated NaCl solution, and then dried (Na_2SO_4). After solvent removal, the residue was purified by flash chromatography on silica gel.

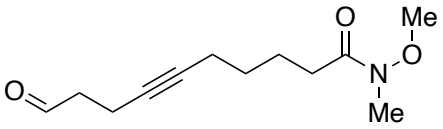


***N*-methoxy-*N*-methylhept-6-ynamide (3.30)**[112]

A solution of hept-6-ynoic acid (600 mg, 4.76 mmol), *N*-methylmorpholine (576 μL, 5.24 mmol), *N,O*-dimethylhydroxylamine hydrochloride (580 mg, 5.23 mmol) in anhydrous CH_2Cl_2 (6 mL) was cooled to 0 °C. *N*,*N*-dicyclohexylcarbodiimide (1.08 g, 5.23 mmol) was added slowly. The reaction mixture was stirred at 0 °C for 3 h and allowed to warm to rt then left to stir overnight. On completion, checked by TLC, the reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 x 50 mL), brine (1 x 50 mL) and dried over Na_2SO_4. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 20:80) to afford *N*-methoxy-*N*-methylhept-6-ynamide (**3.30**, 586 mg, 3.46 mmol) as a yellow oil.

Yield: 73%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.18 (s, 3H), 2.45 (t, *J* = 7.5 Hz, 2H), 2.21 (dt, *J* = 7.2, 2.8 Hz, 2H), 1.94 (t, *J* = 2.4 Hz, 1H), 1.79 – 1.72 (m, 2H), 1.62 – 1.55 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.8, 83.7, 68.2, 60.9, 32.2, 30.9, 27.8, 23.3, 17.9.

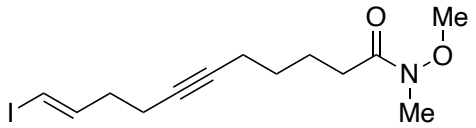
All data is consistent with that reported in literature.[113]



***N*-methoxy-*N*-methyl-10-oxodec-6-ynamide (3.31)**

To a solution of $Rh(acac)(CO)_2$ (15.2 mg, 0.0591 mmol) and tri(*o*-methoxyphenyl)phosphine (31.2 mg, 0.0887 mmol) in 0.6 mL of anhydrous THF, a solution of acrolein (166 mg, 2.96 mmol) and *N*-methoxy-*N*-methylhept-6-ynamide (**3.30**, 100 mg, 0.591 mmol) in 3.5 mL of anhydrous THF was added dropwise via a syringe pump, under nitrogen atmosphere. The reaction mixture was heated at 90 °C overnight. On completion, checked by TLC, the reaction mixture was filtered over a pad of Celite, washed with hexane, EtOAc and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 40:60) to afford *N*-methoxy-*N*-methyl-10-oxodec-6-ynamide (**3.31**, 98.5 mg, 0.437 mmol) as a yellow oil.

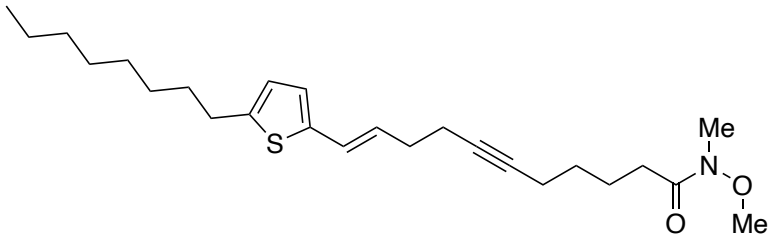
Yield: 74%. **FTIR** (neat, cm^{-1}): ν_{max} 1723, 1648; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.0 Hz, 1H), 3.65 (s, 3H), 3.14 (s, 3H), 2.67 – 2.58 (t, *J* = 7.5 Hz, 2H), 2.53 – 2.37 (m, 4H), 2.22 – 2.10 (m, 2H), 1.69 (p, *J* = 7.5 Hz, 2H), 1.42 – 1.38 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.0, 174.3, 80.9, 78.1, 61.1, 42.9, 31.3, 28.6, 28.5, 23.7, 18.4, 12.1; **MS** (ESI+) m/z 226 $[M+H]^+$; **HRMS** calcd for $C_{12}H_{19}NO_3$ ($[M+H]^+$) 226.1443 found 226.1449.



(*E*)-11-iodo-*N*-methoxy-*N*-methylundec-10-en-6-ynamide (3.32)

Freshly activated Zinc powder (158.4 mg, 2.42 mmol), $CrCl_3(THF)_3$ (530 mg, 1.42 mmol) was suspended in anhydrous THF (2 mL) under a N_2 atmosphere. A solution of aldehyde (**3.31**, 107 mg, 0.475 mmol) and iodoform (374 mg, 0.950 mmol) in anhydrous THF (2 mL) was added dropwise via a syringe pump to the suspension at 0 °C. On completion, checked by TLC, the reaction mixture was poured into water (25 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 25:75) to afford (*E*)-11-iodo-*N*-methoxy-*N*-methylundec-10-en-6-ynamide (**3.32**, 153 mg, 0.437 mmol) as a yellow oil.

Yield: 92%. **FTIR** (neat, cm^{-1}): ν_{max} 508, 1661, 3058; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.63 – 6.46 (m, 1H), 6.09 (d, *J* = 14.1 Hz, 1H), 3.68 (s, 3H), 3.18 (s, 3H), 2.44 (t, *J* = 7.5 Hz, 2H), 2.24 – 2.10 (m, 4H), 1.84 – 1.45 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.4, 144.6, 83.1, 80.9, 80.5, 61.1, 34.2, 31.2, 29.5, 23.6, 23.3, 18.4, 17.49; **MS** (ESI+) m/z 350 $[M+H]^+$; **HRMS** calcd for $C_{13}H_{20}INO_2$ ($[M+H]^+$) 350.0617 found 350.0588.

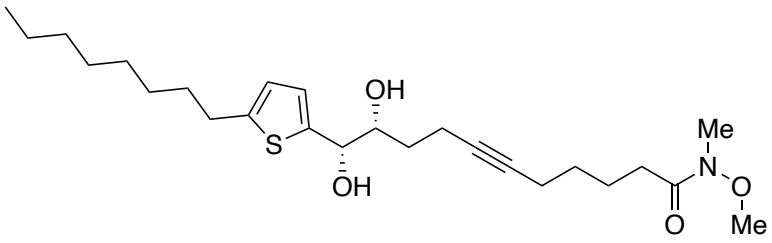


(*E*)-*N*-methoxy-*N*-methyl-11-(5-octylthiophen-2-yl)undec-10-en-6-ynamide (3.33)

In a two-necked flask was weighed NaOH (401 mg, 10 mmol), 4,4,5,5-tetramethyl-2-(5-octylthiophen-2-yl)-1,3,2-dioxaborolane (**3.8**, 1692 mg, 5.03 mmol), $PdCl_2$(dppf) (110 mg, 0.151 mmol), and (*E*)-11-iodo-*N*-methoxy-*N*-methylundec-10-en-6-ynamide (**3.32**, 1.17 g, 3.36 mmol). The flask was purged with N_2. Anhydrous THF (10 mL) and deoxygenated H_2O (10 mL) were added, and the flask was warmed to 50 °C and left to stir overnight. On completion, checked by TLC, the layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 20:80) to afford (*E*)-*N*-methoxy-*N*-methyl-11-(5-octylthiophen-2-yl)undec-10-en-6-ynamide (**3.33**, 1289 mg, 3.09 mmol) as a yellow oil.

Yield: 92%. **FTIR** (neat, cm^{-1}): ν_{max} 1456, 1645, 1666, 3067; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.66 (d, *J* = 3.6 Hz, 1H), 6.58 (d, *J* = 3.5 Hz, 1H), 6.45 (d, *J* = 15.6 Hz, 1H), 5.99 – 5.85 (m, 1H), 3.67 (s, 3H), 3.17 (s, 3H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.43 (t, *J* = 7.6 Hz, 4H), 2.37 – 2.15 (m, 8H), 1.40 – 1.22 (m, 12H), 0.88 (t, *J* = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 182.7, 157.9, 137.0, 125.8, 77.4, 77.3, 61.2, 53.4, 32.2, 31.9, 31.8, 31.6, 31.3, 29.3, 29.2, 29.2, 29.0, 23.9, 22.7, 18.6, 15.3,

14.1; **MS** (ESI+) m/z 418 $[M+H]^+$; **HRMS** calcd for $C_{25}H_{39}NO_2S$ ($[M+H]^+$) 418.2780 found 418.2752.

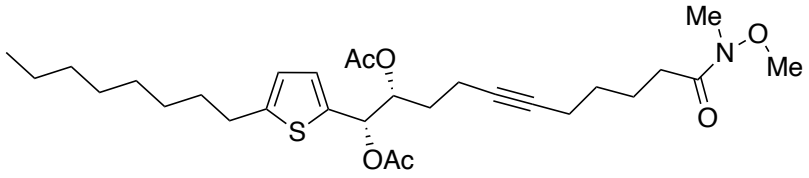


(10*R*,11*S*)-10,11-dihydroxy-*N*-methoxy-*N*-methyl-11-(5-octylthiophen-2-yl)undec-6-ynamide (3.34)

To an ice-cold mixture of (*E*)-*N*-methoxy-*N*-methyl-11-(5-octylthiophen-2-yl)undec-10-en-6-ynamide (**3.33**, 420 mg, 1 mmol) in *t*-BuOH (5 mL) and H_2O (5 mL) was added $MeSO_2NH_2$ (95.6 mg, 1 mmol), $K_2OsO_2(OH)_4$ (7.5 mg, 0.02 mmol), $K_3Fe(CN)_6$ (993 mg, 3.02 mmol), K_2CO_3 (417 mg, 3.02 mmol), $(DHQD)_2PHAL$ (78 mg, 0.1 mmol). The mixture was stirred for 24 h at 0 °C. On completion, checked by TLC, Na_2SO_3 (100 mg) was added at 0 °C, followed by H_2O (20 mL). The reaction mixture was left to stir for 0.5 h then EtOAc (10 mL) was added, followed by saturated aqueous NaCl solution (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 40:60) to afford (10*R*,11*S*)-10,11-dihydroxy-*N*-methoxy-*N*-methyl-11-(5-octylthiophen-2-yl)undec-6-ynamide (**3.34**, 321 mg, 0.71 mmol) as a yellow oil.

Yield: 71%. **FTIR** (neat, cm^{-1}): ν_{max} 1481, 1633, 1654, 3460; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.82 (d, *J* = 3.4 Hz, 1H), 6.62 (d, *J* = 3.4 Hz, 1H), 4.67 (d, *J* = 6.6 Hz,

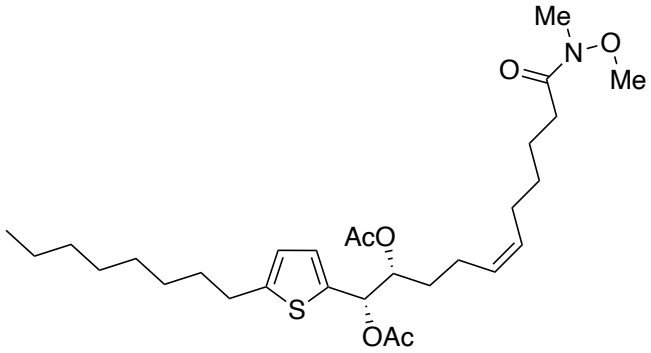
1H), 3.94 (m, 1H), 3.68 (s, 3H), 3.17 (s, 3H), 2.76 (t, *J* = 7.7 Hz, 2H), 2.44 (t, *J* = 7.5 Hz, 2H), 2.38 – 2.23 (m, 2H), 2.18 (tt, *J* = 6.7, 2.3 Hz, 2H), 1.84 – 1.47 (m, 8H), 1.36 – 1.22 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.4, 146.1, 141.5, 124.9, 123.3, 80.5, 74.6, 73.5, 61.2, 31.8, 31.5, 30.8, 29.2, 29.1, 29.1, 28.5, 28.4, 23.6, 22.6, 18.4, 15.1, 14.0; **MS** (ESI+) m/z 451 $[M]^+$; **HRMS** calcd for $C_{25}H_{41}NO_4S$ ($[M+H]^+$) 452.2835 found 452.2772.



(1*S*,2*R*)-11-(methoxy(methyl)amino)-1-(5-octylthiophen-2-yl)-11-oxoundec-5-yne-1,2-diyl diacetate (3.35)

To an oven-dried, degassed round-bottomed flask was added DMAP and (10*R*,11*S*)-10,11-dihydroxy-*N*-methoxy-*N*-methyl-11-(5-octylthiophen-2-yl)undec-6-ynamide (**3.34**, 27.1 mg, 0.06 mmol) in 0.5 mL of DCM. To this mixture, acetic anhydride (14 μL, 0.15 mmol) was added dropwise and the reaction was allowed to stir under N_2 overnight at room temperature. On completion, checked by TLC, the reaction was quenched with sat. $NaHCO_3$ solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 20:80) to afford (1*S*,2*R*)-11-(methoxy(methyl)amino)-1-(5-octylthiophen-2-yl)-11-oxoundec-5-yne-1,2-diyl diacetate (**3.35**, 20.9 mg, 0.039 mmol) as a yellow oil.

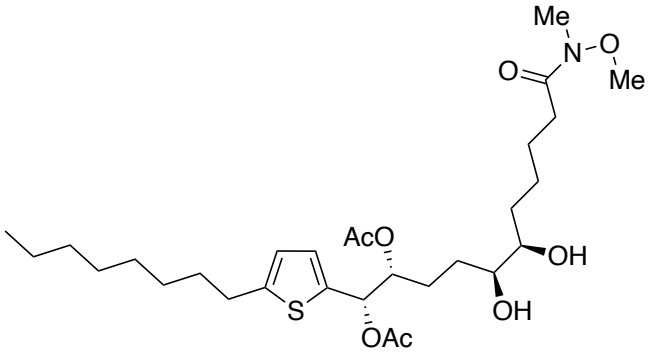
Yield: 75%. **FTIR** (neat, cm^{-1}): ν_{max} 1463, 1653, 1664, 1745; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87 (d, *J* = 4.0 Hz, 1H), 6.62 (d, *J* = 3.4 Hz, 1H), 6.04 (d, *J* = 6.9 Hz, 1H), 5.37 – 5.26 (m, 1H), 3.67 (s, 3H), 3.17 (s, 3H), 2.75 (d, *J* = 7.6 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 2.15 (t, *J* = 7.2 Hz, 4H), 2.09 – 2.01 (m, 6H), 1.76 – 1.57 (m, 4H), 1.56 – 1.46 (m, 2H), 1.40 – 1.17 (m, 12H), 0.92 – 0.84 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.5, 170.2, 169.8, 147.3, 135.9, 127.1, 123.6, 80.7, 78.6, 73.6, 71.9, 61.3, 31.6, 30.2, 29.4, 29.2, 29.2, 29.0, 28.7, 23.9, 22.7, 21.0, 18.6, 15.0, 14.2; **MS** (ESI+) m/z 536 $[M+H]^+$; **HRMS** calcd for $C_{29}H_{45}NO_6S$ ($[M+H]^+$) 536.3046 found 536.3048.



(1*S*,2*R*,*Z*)-11-(methoxy(methyl)amino)-1-(5-octylthiophen-2-yl)-11-oxoundec-5-ene-1,2-diyl diacetate (3.36)

A solution of (1*S*,2*R*)-11-(methoxy(methyl)amino)-1-(5-octylthiophen-2-yl)-11-oxoundec-5-yne-1,2-diyl diacetate (**3.35**, 32.1 mg, 0.06 mmol) in anhydrous pyridine (0.5 mL), and Lindlar catalyst (20 mg) was stirred at rt under a H_2 atmosphere for 24 h. The mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure to give the product as a colourless oil (**3.36**, 32.2 mg, 0.06 mmol) without further purification.

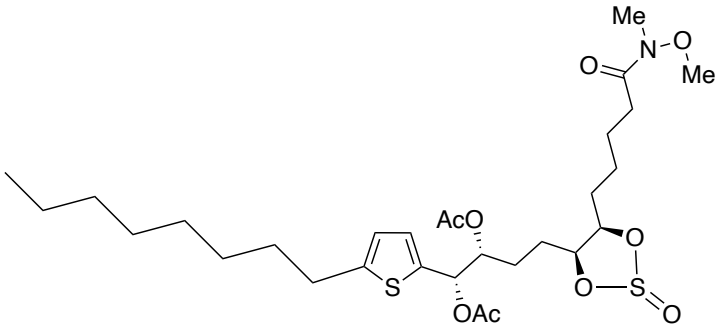
Yield: Quantitative. **FTIR** (neat, cm^{-1}): ν_{max} 1462, 1651, 1661, 1752; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.86 (d, *J* = 4.0 Hz, 1H), 6.61 (d, *J* = 3.1 Hz, 1H), 6.04 (d, *J* = 6.9 Hz, 1H), 5.40 – 5.32 (m, 1H), 5.30 – 5.20 (m, 2H), 3.67 (s, 3H), 3.16 (s, 3H), 2.75 (t, *J* = 7.6 Hz, 2H), 2.41 (t, *J* = 7.6 Hz, 2H), 2.23 – 1.99 (m, 10H), 1.67 – 1.51 (m, 6H), 1.41 – 1.22 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.2, 169.8, 147.1, 135.9, 130.5, 128.2, 126.8, 123.4, 74.1, 71.9, 61.2, 31.8, 31.5, 30.1, 29.3, 29.3, 29.1, 29.1, 29.1, 26.9, 24.2, 22.8, 22.6, 20.9, 20.9, 14.0; **MS** (ESI+) m/z 538 $[M+H]^+$; **HRMS** calcd for $C_{29}H_{47}NO_6S$ ($[M+H]^+$) 538.3202 found 538.3178.



(1*S*,2*R*,5*S*,6*R*)-5,6-dihydroxy-11-(methoxy(methyl)amino)-1-(5-octylthiophen-2-yl)-11-oxoundecane-1,2-diyl diacetate

To a solution of DHQD-Ind (10.7 mg, 0.0227 mmol), $K_3Fe(CN)_6$ (448 mg, 1.36 mmol) and K_2CO_3 (188 mg, 1.36 mmol) in 2 mL of *t*-BuOH and 2 mL of H_2O was added $K_2OsO_2(OH)_4$ (3.34 mg, 0.009 mmol) at room temperature. Methanesulfonamide (43 mg, 0.454 mmol) was then added at 0 °C. The reaction mixture was cooled to 0 °C to give a viscous mixture. At 0 °C, (1*S*,2*R*)-4-((2*S*,3*R*)-3-(5-(methoxy(methyl)amino)-5-oxopentyl)oxiran-2-yl)-1-(5-octylthiophen-2-yl)butane-1,2-diyl diacetate (**3.36**, 244 mg, 0.454 mmol) was added, and the reaction was left to stir overnight. On completion, checked by TLC, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with 2M KOH. Sodium metabisulfite (140 mg, 8 eq) was added to the combined organic phases and stirred with $MgSO_4$ for 1 h. The organic phase was filtered and concentrated under reduced pressure to afford the crude product. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 20:80) to afford (1*S*,2*R*,5*S*,6*R*)-5,6-dihydroxy-11-(methoxy(methyl)amino)-1-(5-octylthiophen-2-yl)-11-oxoundecane-1,2-diyl diacetate (221 mg, 0.386 mmol) as a yellow oil.

Yield: 85%. **FTIR** (neat, cm^{-1}): ν_{max} 1675, 1747, 3509; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.86 (d, *J* = 3.3 Hz, 1H), 6.61 (d, *J* = 3.7 Hz, 1H), 6.05 (dd, *J* = 7.2, 2.4 Hz, 1H), 5.31 – 5.20 (m, 1H), 3.67 (s, 3H), 3.60 – 3.42 (m, 2H), 3.17 (s, 3H), 2.75 (t, *J* = 7.4 Hz, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 2.24 – 2.05 (m, 7H), 1.68 (app. quint, *J* = 7.3 Hz, 4H), 1.84 – 1.10 (m, 17H), 0.87 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.8, 170.3, 169.7, 147.4, 135.5, 127.1, 123.5, 73.4, 71.9, 36.7, 31.8, 31.5, 30.1, 29.7, 29.6, 29.5, 29.3, 29.3, 29.2, 29.1, 25.8, 24.5, 22.6, 20.9, 20.9, 14.1; **MS** (ESI+) m/z 572 $[M+H]^+$; **HRMS** calcd for $C_{29}H_{49}NO_8S$ ($[M+H]^+$) 572.3257 found 572.3254.

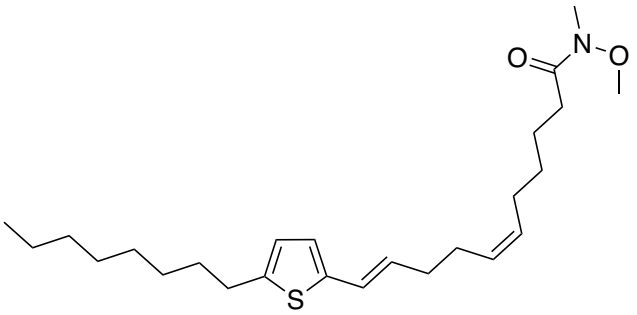


(1*S*,2*R*)-4-((4*S*,5*R*)-5-(5-(methoxy(methyl)amino)-5-oxopentyl)-2-oxido-1,3,2-dioxathiolan-4-yl)-1-(5-octylthiophen-2-yl)butane-1,2-diyl diacetate (3.37)

To a solution of (1*S*,2*R*,5*S*,6*R*)-5,6-dihydroxy-11-(methoxy(methyl)amino)-1-(5-octylthiophen-2-yl)-11-oxoundecane-1,2-diyl diacetate (221 mg, 0.386 mmol) in anhydrous CH_2Cl_2 (2 mL) was added Et_3N (86 mg, 0.85 mmol) followed by a slow addition of $SOCl_2$ (51 mg, 0.425 mmol) at 0 °C. The mixture was allowed to warm to rt and stirred for an additional 0.5 h. On completion, checked by TLC, the reaction mixture was quenched with H_2O. The organic layer was washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent EtOAc/ hexane 20:80) to afford (1*S*,2*R*)-4-((4*S*,5*R*)-5-(5-(methoxy(methyl)amino)-5-oxopentyl)-2-oxido-1,3,2-dioxathiolan-4-yl)-1-(5-octylthiophen-2-yl)butane-1,2-diyl diacetate (**3.37**, 233 mg, 0.377 mmol) as a yellow oil.

Yield: 98%. **FTIR** (neat, cm^{-1}): ν_{max} 1661, 1745; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87 (d, *J* = 3.7 Hz, 1H), 6.63 (d, *J* = 3.7 Hz, 1H), 6.08 – 6.02 (m, 1H), 5.32 – 5.18 (m, 1H), 4.85 – 4.78 (m, 1H), 4.48 – 4.43 (m, 1H), 3.68 (s, 3H), 3.17 (s, 3H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.44 (t, *J* = 6.8 Hz, 2H), 2.13 – 2.01 (m, 6H), 1.75 – 1.41 (m, 10H), 1.40 – 1.18 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.9, 170.5, 147.3, 135.5, 127.0, 84.8, 81.8, 73.9, 71.9, 61.1, 31.7, 31.3, 29.9,

29.6, 29.0, 28.2, 27.3, 26.9, 26.3, 25.6, 24.9, 24.0, 23.8, 22.4, 20.8, 20.8, 13.9; **MS** (ESI+) m/z 618 $[M+H]^+$; **HRMS** calcd for $C_{29}H_{47}NO_9S_2$ ($[M+H]^+$) 618.2770 found 618.2805.



(6*Z*,10*E*)-*N*-methoxy-*N*-methyl-11-(5-octylthiophen-2-yl)undeca-6,10-dienamide (3.36')

A solution of (*E*)-*N*-methoxy-*N*-methyl-11-(5-octylthiophen-2-yl)undec-10-en-6-ynamide (**3.33**, 204 mg, 0.49 mmol) in anhydrous pyridine (0.5 mL), and Lindlar catalyst (20 mg) was stirred at rt under a H_2 atmosphere for 24 h. The mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure to give the product (**3.36'**, 177 mg, 0.42 mmol) as a colourless oil.

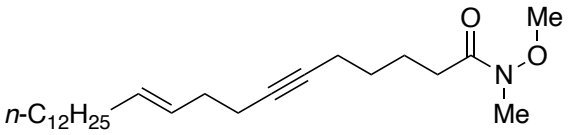
Yield: 86%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.65 (d, *J* = 3.6 Hz, 1H), 6.56 (d, *J* = 3.6 Hz, 1H), 6.44 (d, *J* = 15.6 Hz, 1H), 5.51 – 5.34 (m, 2H), 3.67 (s, 3H), 3.17 (s, 3H), 2.43 (t, *J* = 7.6 Hz, 2H), 2.20 (t, *J* = 6.8 Hz, 2H), 2.07 – 2.01 (m, 2H), 1.74 – 1.59 (m, 4H), 1.46 – 1.18 (m, 16H), 0.88 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.9, 144.0, 140.6, 130.2, 130.1, 129.2, 127.0, 124.8, 61.1, 32.9, 31.9, 31.8, 31.7, 31.6, 30.3, 29.7, 29.4, 29.3, 29.2, 29.1, 27.1, 27.0, 22.6, 14.1; **MS** (ESI+) m/z 420 $[M+H]^+$; **HRMS** calcd for $C_{25}H_{41}NO_2S$ ($[M+H]^+$) 420.2808 found 420.2819.

Jacobsen Epoxidation[9] of (1*S*,2*R*,*Z*)-11-(methoxy(methyl)amino)-1-(5-octylthiophen-2-yl)-11-oxoundec-5-ene-1,2-diyl diacetate (3.36)

A 0.7 M solution of $NaOCl.5H_2O$ was diluted to approximately 0.55 M in NaOCl with 0.05 M Na_2HPO_4, and the pH of the resulting buffered solution was adjusted to pH = 11.3 by addition of a 1 M NaOH solution. To this solution (0.2 mL) was added a solution of Jacobsen's Catalyst (4 mg, 10 mol%) and diol (31.5 mg, 0.059 mmol) in 0.06 mL of CH_2Cl_2. The two-phase mixture was stirred at 4°C, and the reaction progress was monitored by TLC. After 6 h, 0.06 mL of CH_2Cl_2 was added to the mixture and the brown organic phase was separated, washed twice with 1 mL of H_2O and once with 1 mL of saturated NaCl solution, and then dried (Na_2SO_4). After solvent removal, the residue was purified by flash chromatography on silica gel.

Berkessel Epoxidation[21] of (6*Z*,10*E*)-*N*-methoxy-*N*-methyl-11-(5-octylthiophen-2-yl)undeca-6,10-dienamide (3.36')

In a 5 mL vial, the ligand, 2',3',4',5',6'-pentafluoro-3-((*E*)-(((1*R*,2*S*)-2-(((2',3',4',5',6'-pentafluoro-2-hydroxy-[1,1'-biphenyl]-3-yl)methyl)amino)cyclohexyl)imino)methyl)-[1,1'-biphenyl]-2-ol, (1.57 mg, 0.00238 mmol, 1 mol%) and Ti(O-*i*-Pr)$_4$ (0.705 μL, 0.00238 mmol, 1 mol%) were dissolved in anhydrous CH_2Cl_2 (119 μL), and the solution was stirred under an argon atmosphere at rt for 1 h. The solvent was removed under reduced pressure, and the residue was dried in vacuo for 1 h. The diene (100 mg, 0.238 mmol, 1 eq), tetrabutylammonium hydrogen sulfate (0.81 mg, 0.00238 mmol, 1 mol%), 1,2-dichloroethane (11 μL), and 35% H_2O_2 (aq) (24 μL, 0.357 mmol, 1.5 eq) were added, and the mixture was stirred at rt for 10 h (no inert atmosphere necessary). After filtering through a short pad of silica/anhydrous MnO_2 (10:1) (to deactivate the excess amount of H_2O_2), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was then purified by flash chromatography on silica gel.



(*E*)-*N*-methoxy-*N*-methyltricos-10-en-6-ynamide (3.41)

An oven-dried 2-neck flask fitted with a condenser, was added freshly activated Zn (45 mg, 0.684 mmol) and anhydrous THF (1 mL). 2 drops of 1,2-dibromoethane was added to this suspension and the reaction mixture was heated to reflux. The reaction was allowed to cool to room temperature. 2 drops of TMSCl were added and the reaction mixture was once again heated to reflux and allowed to cool to room temperature. Neat 1-iodododecane (134 μL, 0.629 mmol) was added and the reaction mixture was stirred at reflux for 2 hours. The freshly prepared *n*-$C_{12}H_{25}ZnI$ was then added dropwise, via cannula, to a flask containing $Pd(amphos)_2Cl_2$ (8 mg, 2 mol %, 0.011 mmol) in anhydrous THF (1 mL), vinyl halide (**3.32**, 200 mg, 0.572 mmol) and distilled TMEDA (94 μL, 0.629 mmol). The reaction mixture was left to stir for 24 h at rt. On completion, checked by TLC, the reaction mixture was quenched with sat. NH_4Cl solution. The aqueous layer was then extracted with EtOAc (3 x 10 mL) and the combined organic layers concentrated in *vacuo*. The crude product was purified by column chromatography (silica gel, eluent EtOAc/hexane 15:85) to afford the product (**3.41**, 45 mg, 0.114 mmol) as a yellow oil.

Yield: 20%. **FTIR** (neat, cm^{-1}): ν_{max} 1386, 1656, 2927; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.48 – 5.40 (m, 2H), 3.68 (s, 3H), 3.18 (s, 3H), 2.43 (t, *J* = 7.6 Hz, 2H), 2.22 – 2.12 (m, 6H), 2.02 – 1.93 (m, 2H), 1.79 – 1.67 (m, 4H), 1.55 (td, *J* = 10.3, 9.9, 4.8 Hz, 4H), 1.37 – 1.22 (m, 16H), 0.88 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz,

$CDCl_3$) δ 131.7, 128.5, 80.1, 80.0, 61.2, 32.6, 32.4, 31.9, 31.4, 29.7, 29.6, 29.5, 29.4, 29.2, 28.8, 27.1, 23.8, 22.7, 19.3, 18.6, 14.1; **MS** (ESI+) m/z 392 $[M+H]^+$; **HRMS** calcd for $C_{25}H_{45}NO_2$ ($[M+H]^+$) 392.3529 found 392.3537.

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