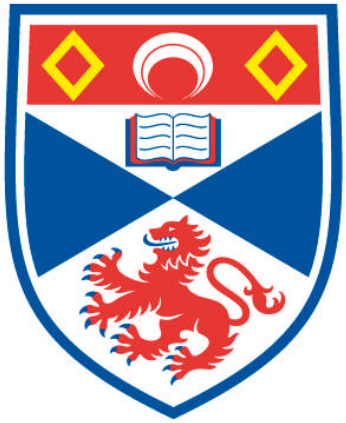
STUDIES IN CYCLIC ETHER SYNTHESIS

Romain Frédéric Cadou

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews

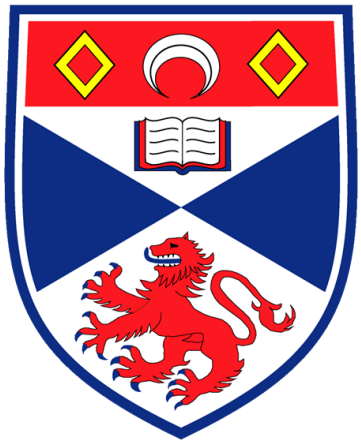


2010

Studies in Cyclic Ether Synthesis:

Part One: Domino Cyclisations to Cyclic Ethers

Part Two: Synthetic Studies Towards Neopeltolide



University
of
St Andrews

School of Chemistry and Centre for Biomolecular Sciences,

St Andrews, Fife, Scotland

Romain Frédéric Cadou

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Thesis submitted to the University of St Andrews in application for the degree of Doctor of Philosophy

Supervisor: Dr Gordon J. Florence

Dedicated to my parents

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I, Romain Frédéric Cadou, hereby certify that this thesis, which is approximately 30000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

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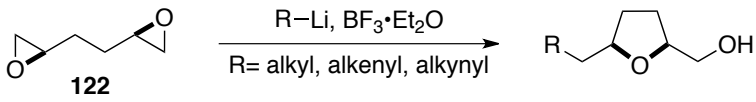
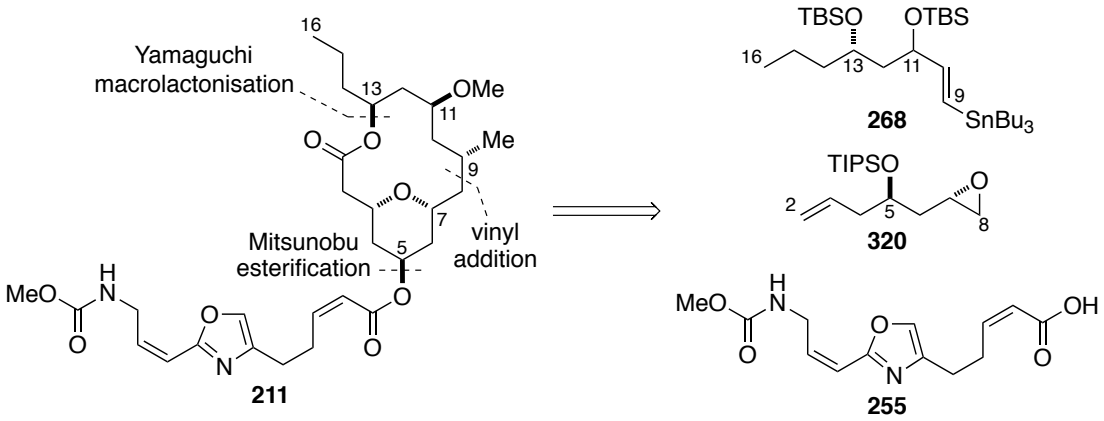
Abstract

Tetrahydrofuran (THF) and tetrahydropyran (THP) rings are commonly found in a wide range of natural products and biologically active compounds. In total synthesis, the formation of THF/THP motifs is often the key step but existing methods often involve numerous steps and low overall efficiencies. Part one of this thesis details the development of a practical method for the synthesis of THF rings by the controlled mono-addition/ cyclisation of organolithium species to C2-symmetric diepoxides (**Scheme A-1**). This method can also be applied to the synthesis of *bis*-THF rings from triepoxides and has potential applications in more complex cascade reactions. A similar cyclisation process providing THF rings from epoxyaldehydes is also described.

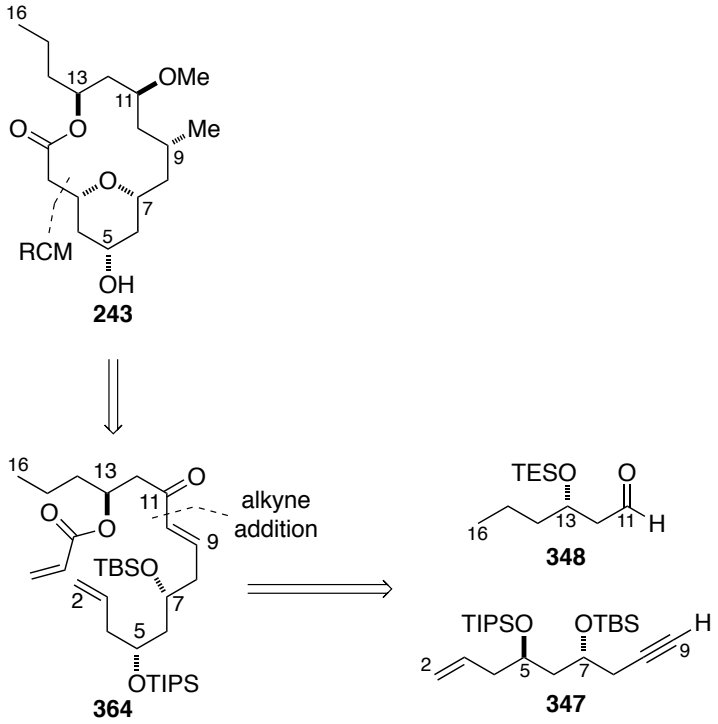


Scheme A-1

Part two of this thesis details our efforts towards the synthesis of the marine macrolide neopeltolide. Wright and co-workers reported the isolation of neopeltolide **211** from a deep-water sponge of the family neopeltidae off the north coast of Jamaica. The structure, which was assigned by NMR and HRMS studies and reassigned by total synthesis, contains a 14-membered macrolactone, a 2,6-*cis* THP ring and an unsaturated oxazole side-chain. Chapter four describes the synthesis of the C2-C8 and C9-C16 fragments (**Scheme A-2**). Chapter five details our initial attempts in the coupling of subunits **268** and **320**, as well as a revised synthetic strategy that allowed us to successfully couple C2-C9 alkyne **347** with C10-C16 aldehyde **348** and the preparation of an advanced intermediate **364** (**Scheme A-3**).



Scheme A-2

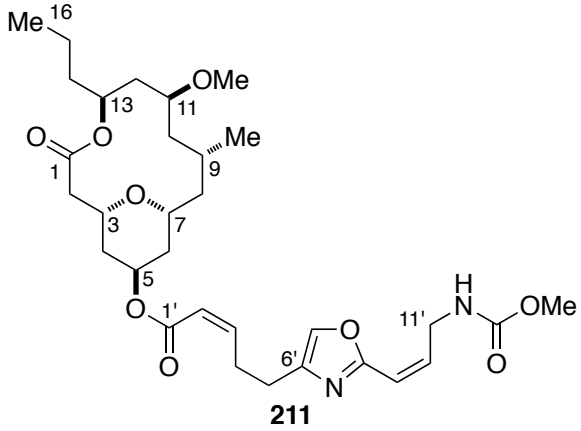


Scheme A-3

Table of Contents

Compound numbering

All compounds intended towards the total synthesis of neopeltolide **211** will be numbered according to the carbon chain of the natural product. This numbering is given on the structure and is used in ^{1}H NMR assignments.



211

The naming of the compounds in the experimental section uses IUPAC convention.

List of Abbreviations

Å	angström
α	alpha
[α]	specific rotation
ABCN	1,1'-azobis(cyclohexanecarbonitrile)
Ac	acetyl
AcOH	acetic acid
AIBN	azobisisobutyronitrile
AMP	adenosine monophosphate
Ar	aryl
ATP	adenosine triphosphate
β	beta
BAIB	[*bis*(acetoxy)iodo]benzene
Bn	benzyl
*n*Bu	normal-butyl
*t*Bu	*tert*-butyl
Bz	benzoyl
°C	degrees Celsius
calc.	calculated
CSA	(+)-10-camphorsulfonic acid
Cp	cyclopentadiene
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DIBAL	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide

DMSO	dimethyl sulfoxide
eq.	equivalent
Et	ethyl
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Ipc	isopinocampheyl
J	^{1}H-^{1}H coupling constant
KHDMS	potassium hexamethyldisilazide
L	litres
m	milli; multiplet
M	concentration in moles L^{-1}
µ	micro
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Mes	mesityl
MHz	megahertz
min	minutes
MOM	methoxymethyl
Ms	mesyl
NBS	*N*-bromosuccinimide
NMO	4-methylmorpholine *N*-oxide
Nu	unspecified nucleophile
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
*i*Pr	*iso*-propyl
Py	pyridine

R	unspecified alkyl group
RT	room temperature
R_f	thin layer chromatography retention factor
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TES	triethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Tris	2,4,6-triisopropylbenzenesulfonyl
Ts	tosyl

Part One:

Domino Cyclisations to Cyclic Ethers

Chapter One

Introduction

Born in 1828 with the synthesis of urea **1** by Wöhler, total synthesis was first limited to the preparation of simple compounds. However, the development of strategy in total synthesis by R. B. Woodward, which was then perfected into retrosynthetic analysis by E. J. Corey, revolutionised total synthesis and made it a respected science. Some important landmarks in total synthesis such as strychnine **2** (Woodward, 1954), vitamin B_{12} **3** (Woodward/ Eschenmoser, 1973), erythronolide B **4** (Corey, 1975) and the endiandric acids family **5** (Nicolaou, 1982) were achieved using these methods (**Figure 1.1**). Nowadays, chemists are able to prepare highly complex molecules such as palytoxin **6**, completed by Kishi *et al.* in 1994.[1,2]

However, it is now no longer a question of what it is possible to synthesise but more how to do it? Indeed, modern total syntheses are trying to obey new criteria including atom economy, improving efficiency in the formation of new bonds, reducing the waste generated and finally, avoiding the use of toxic reagents or solvents.

As such, domino reactions meet many of these criteria and, with careful planning, allow the formation of more complex structures in a reduced number of steps, while minimising waste, time and energy.

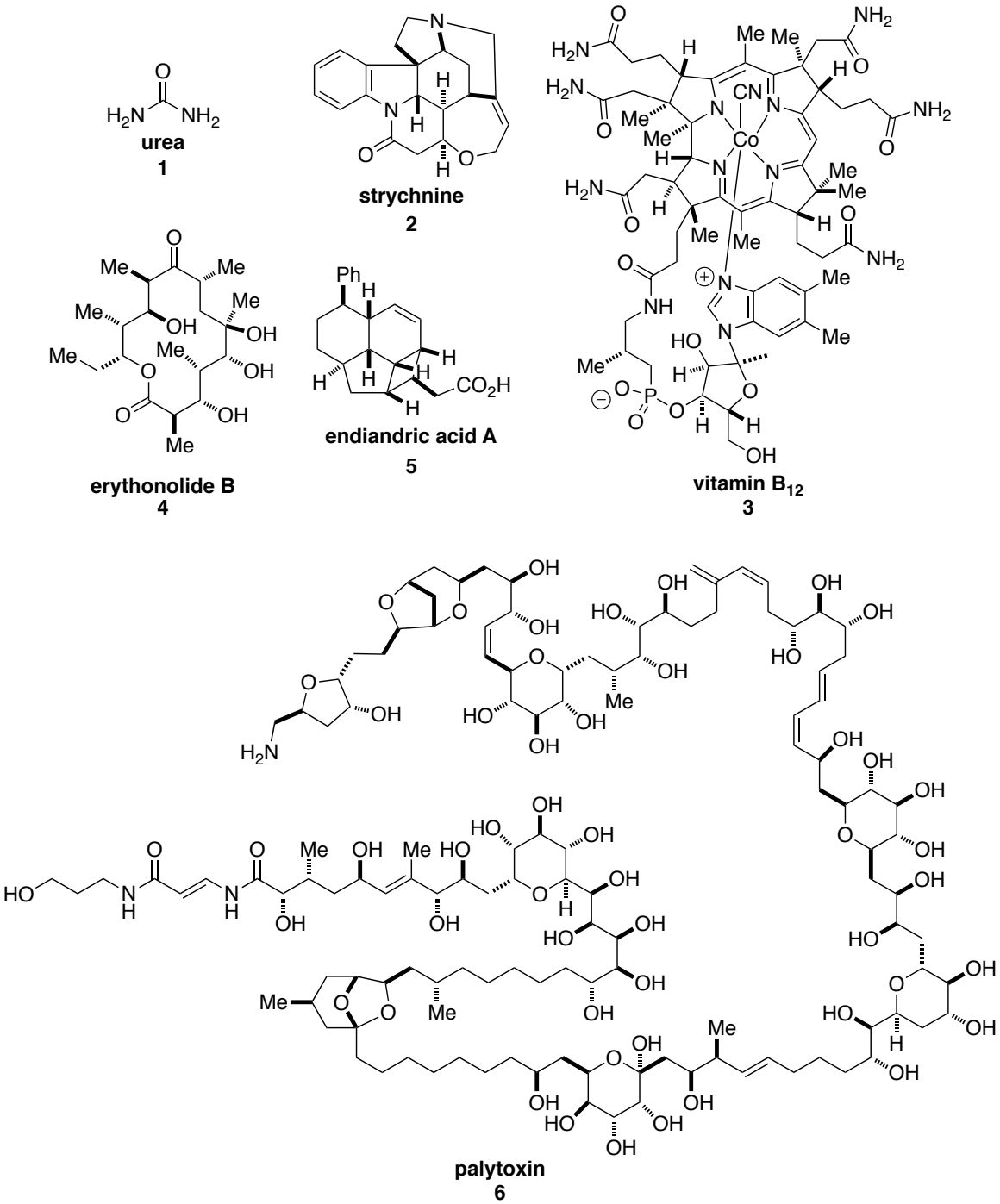
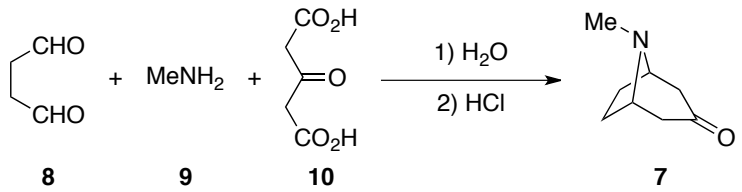


Figure 1.1. Landmarks in total synthesis

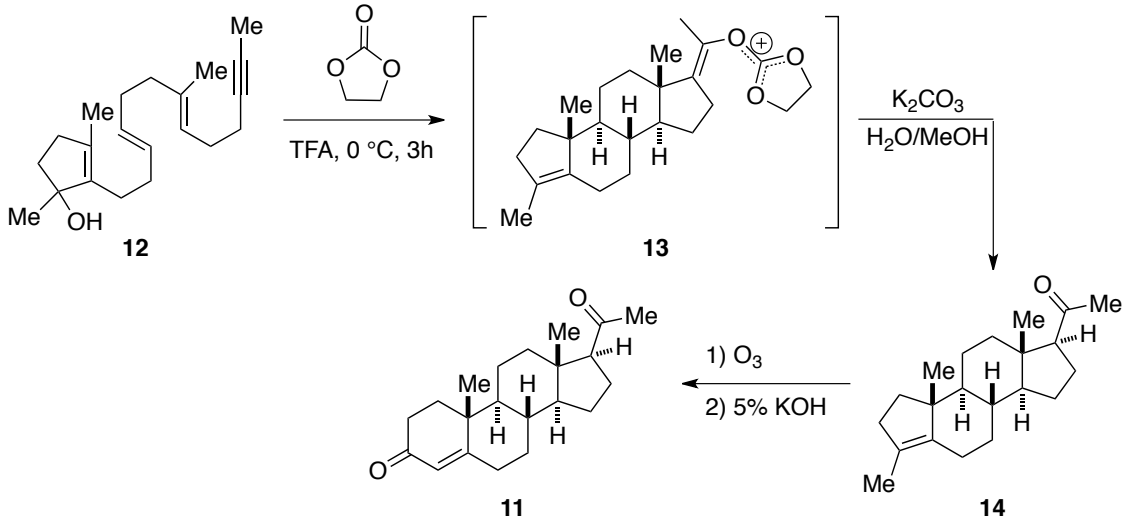
1.1 Historical background

The first use of a domino reaction can be dated back to the early years of total synthesis with Robinson's achievement of the one-pot biomimetic synthesis of tropinone **7** from succindialdehyde **8**, methylamine **9** and acetonedicarboxylic acid **10** (**Scheme 1.1**).[3]



Scheme 1.1. Robinson's biomimetic synthesis of tropinone.[3]

In 1971, Johnson achieved the landmark synthesis of progesterone **11** *via* a series of cationic cyclisations that assembled the entire core of the molecule in a single operation.[4,5] Indeed, treatment of trienynol **12** with trifuoroacetic acid and ethylene carbonate allowed the cyclisation to occur and the formation of carbocation **13**. Addition of potassium carbonate would lead to the formation of methyl ketone **14** which could then be transformed into progesterone **11** by ozonolysis, followed by treatment with 5% aqueous potassium hydroxide (**Scheme 1.2**).



Scheme 1.2. Johnson's biomimetic synthesis of progesterone.[4,5]

1.2 Classification of domino reactions

In recent years, there has been an increase in the development of new domino reactions and several reviews have been dedicated to the subject.[6-13] However, depending on the authors, cascade processes can be given different names. They have been termed "cascade", "domino", "tandem", "consecutive" or "sequential" although attempts have been made to clarify the terminology.

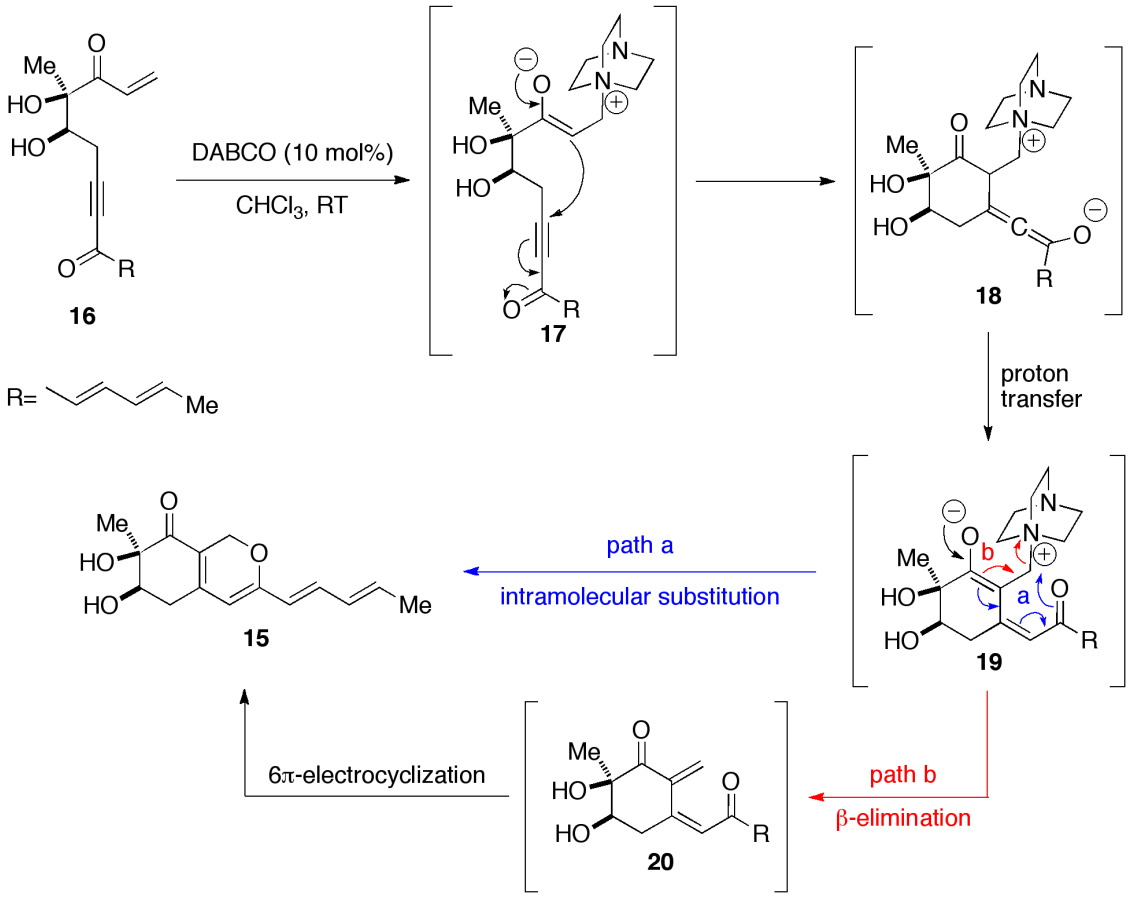
According to Tietze,[6] a domino reaction is "*a process involving two or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step*". This definition is often used but, similarly to the problem encountered in naming those processes, the definition of this concept sometimes varies. For example, in their review on cascade

reactions in total synthesis, Nicolaou *et al.*[10] also include reactions in which the conditions are altered during the process, as well as sequences in which reagents are added at various points.

Although, the classification of cascade reactions can be difficult, as they often involve several distinct steps, it is possible to group them into five main categories: anionic, cationic, radical-mediated, pericyclic and transition-metal induced transformations. Processes that features only one type of mechanism are called homo-domino reactions. However, due to the nature of domino reactions, it is possible to observe steps from different categories in a single process which are then called hetero-domino reactions.

1.2.1 Nucleophilic domino reactions

In nucleophilic domino reactions, the key step of the sequence is a nucleophilic attack. Conjugate additions are often found in these transformations and they can be employed in conjunction with other reactions. For example, Sorensen and co-workers reported a nucleophilic cascade leading to the synthesis of harziphilone **15** (**Scheme 1.3**).[14]



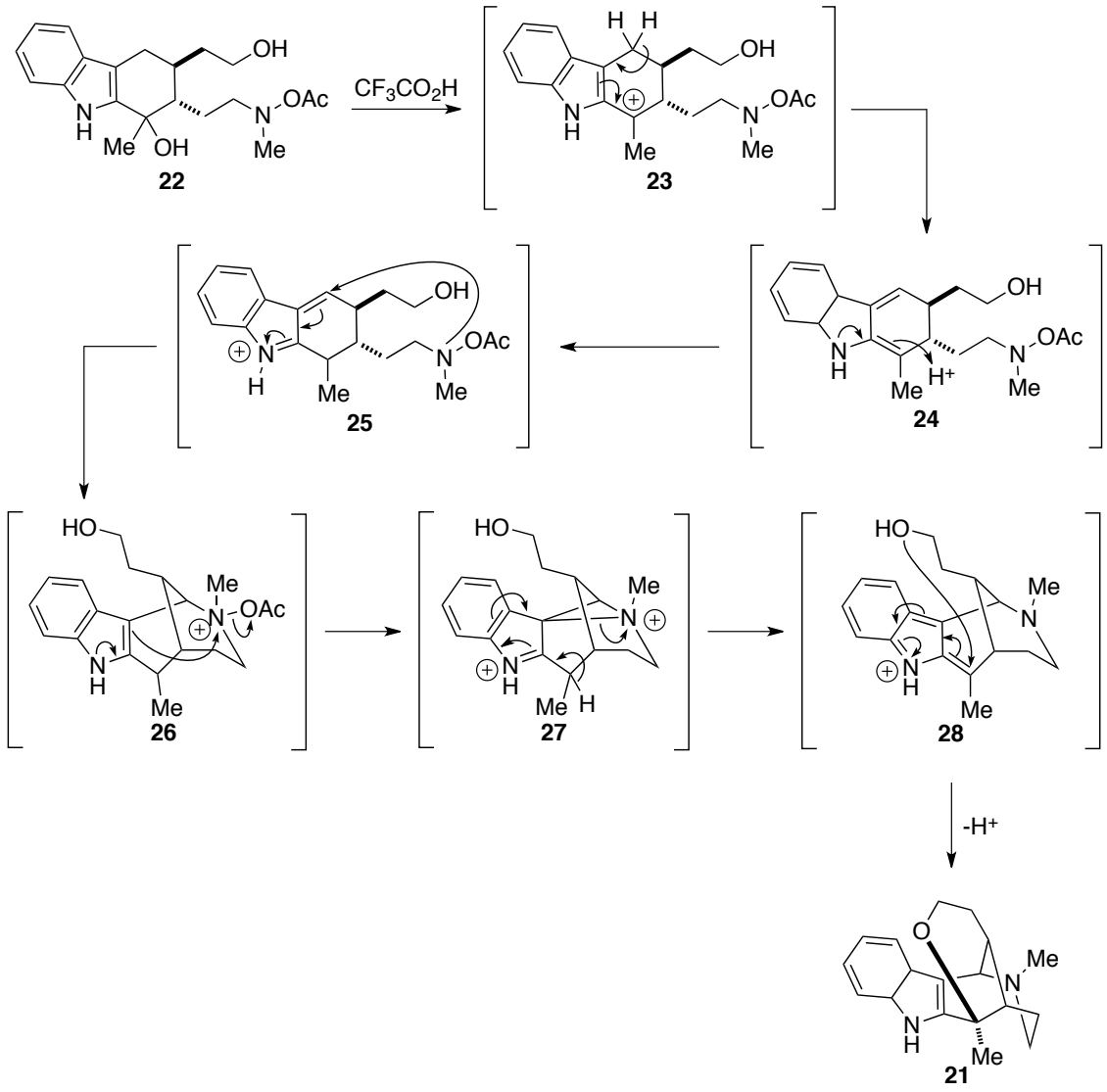
Scheme 1.3. Sorensen's synthesis of harziphilone **15**.[14]

Conjugate addition of DABCO on enone **16** provides enolate **17**, which then undergoes a conjugate addition on the ynone to form the cyclohexane **18**. The putative intermediate **19** can then be obtained *via* a proton transfer that can then follow two possible paths. The first forms harziphilone **15** directly by way of an intramolecular substitution. Alternatively following path b, β-elimination of DABCO gives rise to the product **20** which then undergoes a 6π-electrocyclisation to provide the final product **15**.

1.2.2 Electrophilic domino reactions

Electrophilic domino reactions begin with the formation of a carbocation, either formal or real, by protonation or elimination. Upon reaction with a nucleophile, a new carbocation will be formed and will go through one or more similar events until a stable product is formed.

Blechert and co-workers demonstrated a good example of electrophilic cascade during their synthesis of gilbertine **21** (**Scheme 1.4**).[15] Reaction of tetrahydrocarbazole **22** with trifluoroacetic acid leads to formation of carbocation **23** by loss of the tertiary alcohol. Tautomerization provides intermediate **24** that is transformed to iminium ion **25** by protonation of the double-bond. Conjugate addition on the iminium ion **25** gives ammonium ion **26** which provides aziridinium ion **27** after intramolecular substitution of the acetate group. Fragmentation of the aziridinium ion leads to the formation of iminium ion intermediate **28** which, after tautomerization and intramolecular attack of the hydroxyl group provides (-)-gilbertine **21**.

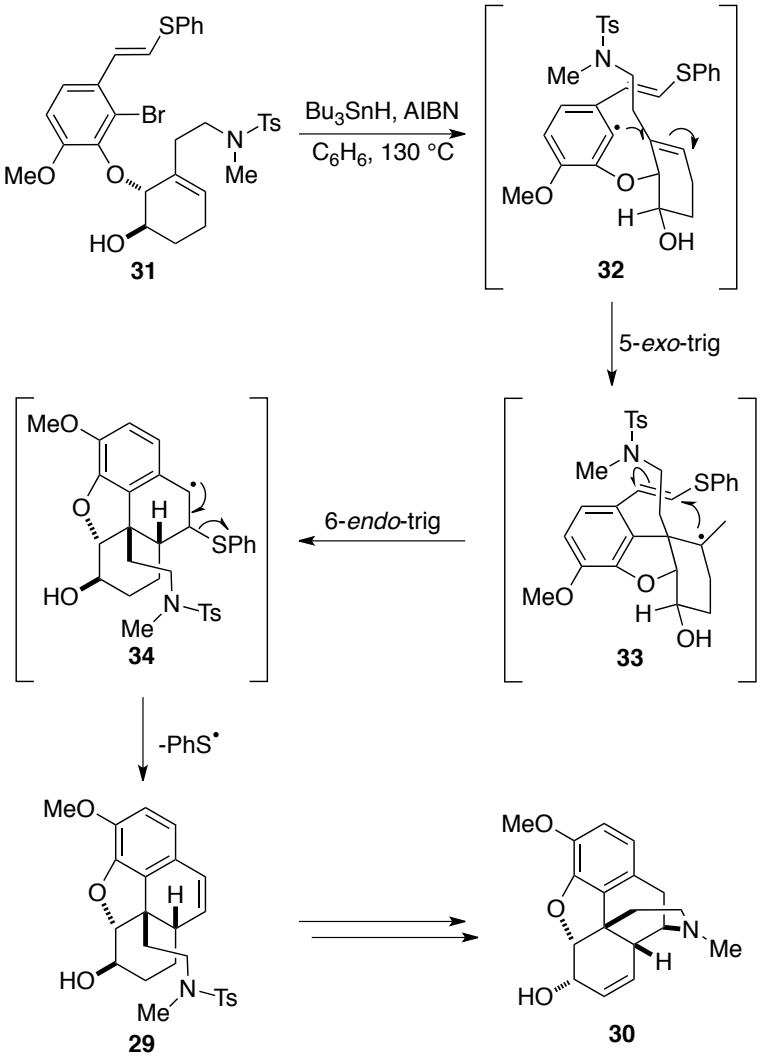


Scheme 1.4. Blechert's cationic domino cyclisation in the synthesis of (-)-gilbertine **21**.[15]

1.2.3 Radical mediated domino reactions

Due to the high reactivity of radicals, they have been widely used in the synthesis of polycyclic compounds and their applications are well documented.[9] Parker and Fokas used a radical domino reaction to construct tetracycle **29** in their total synthesis of (-)-morphine **30** (**Scheme 1.5**).[16,17]

Treatment of bromide **31** with tributyltin hydride and AIBN allows the formation of aryl radical **32**, which undergoes a 5-*exo*-trig cyclisation to form intermediate **33**. The addition of the aryl radical on the lower face of the alkene is controlled by the stereochemistry of the ether bond. Intermediate **33** then goes through a 6-*endo*-trig cyclisation providing radical **34** and completing morphine's core structure. In this case, the kinetically favoured 5-*exo*-trig is less likely to happen due to the geometric constraints enforced by the tricyclic structure. After elimination of phenylsulfinyl radical, product **29** is formed in a remarkable 30% yield, considering the complexity of the transformation.

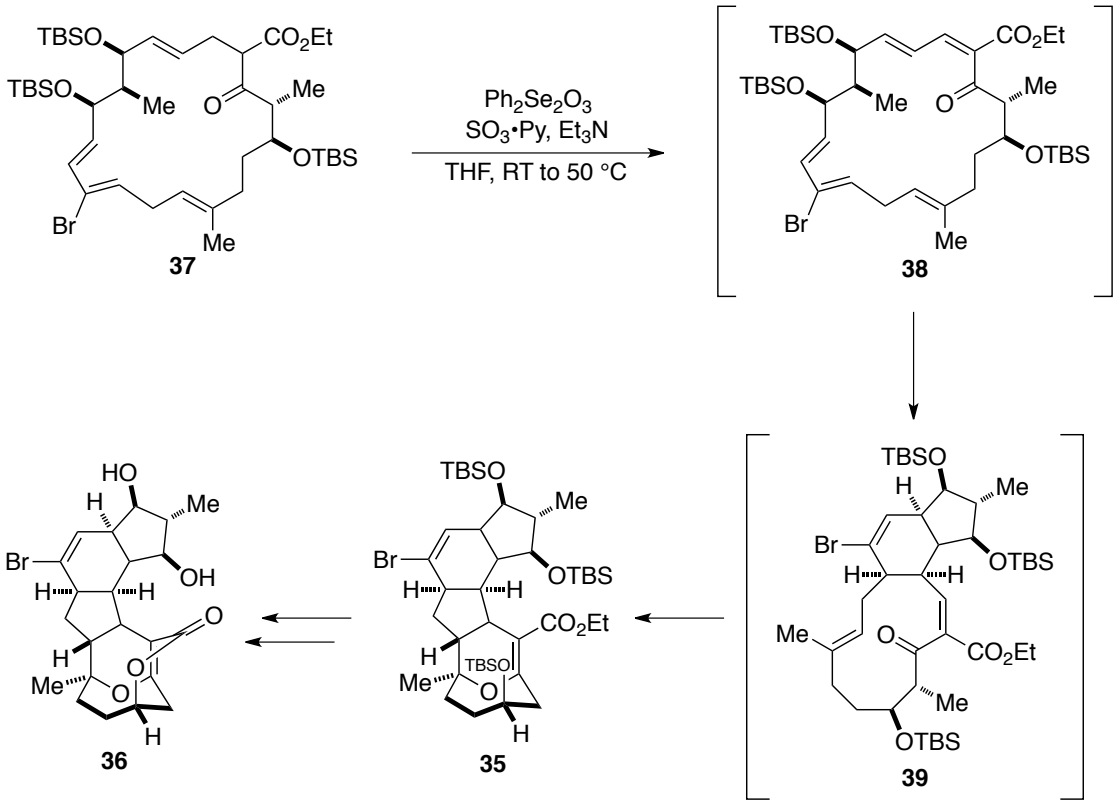


Scheme 1.5. Parker's radical cyclisation towards (-)-morphine.[16,17]

1.2.4 Pericyclic domino reactions

Pericyclic reactions such as Diels-Alder, sigmatropic rearrangements or electrocyclic reactions have been used extensively in domino processes to form complex natural products.

Evans used a domino cycloaddition strategy to form the pentacycle **35** in his synthesis of the secondary metabolite FR-182877 **36** (**Scheme 1.6**).[18,19] Treatment of ketoester **37** with benzeneselenic acid anhydride, sulfur trioxide pyridine complex and triethylamine provided diene **38** that initiated a sequence of transannular cycloadditions. Macrocycle **38** first undergoes a Diels-Alder cycloaddition to form tricycle **39** which was then transformed into the pentacycle **35** *via* an inverse electron-demand hetero-Diels-Alder. The product **35** was obtained as a single diastereoisomer in a 63% yield and was readily converted into FR-182877 **36** in a further three steps.



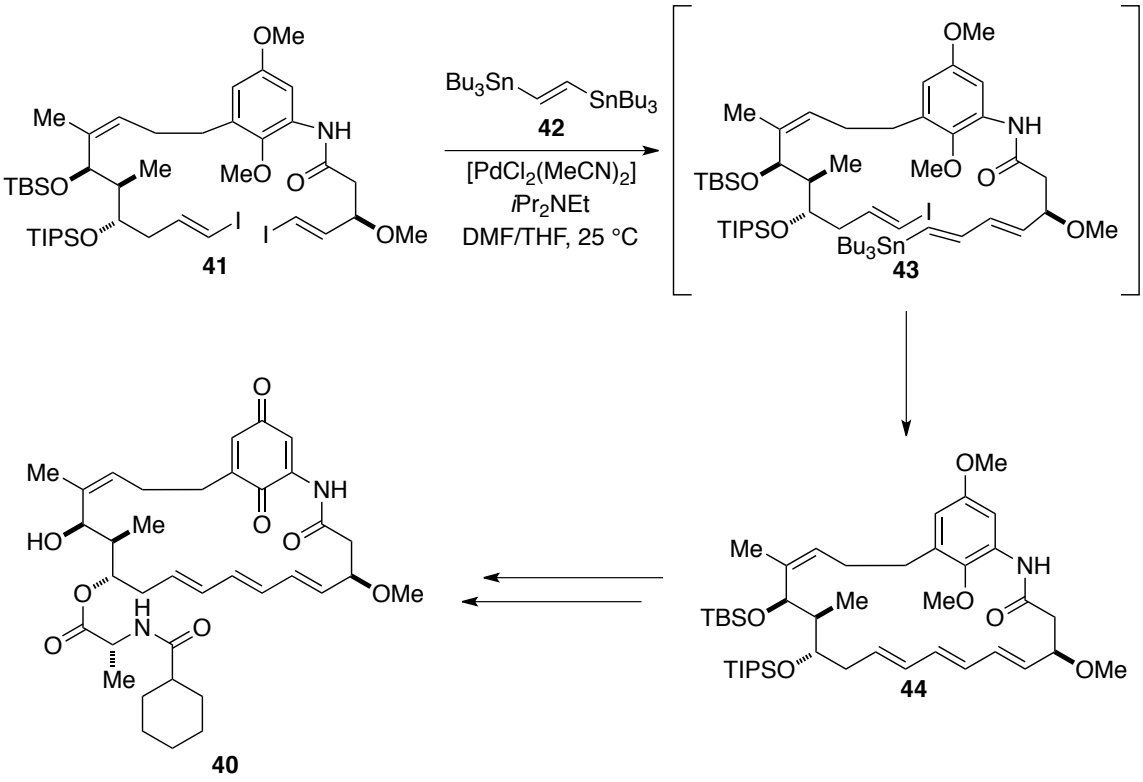
Scheme 1.6. Evans's synthesis of FR-182877.[18,19]

1.2.5 Transition-metal induced domino reactions

The development of transition-metal mediated reactions has been a long-standing research interest and has produced wide variety of methods available for C-C and C-heteroatom bond formation. Palladium-catalysed cross-couplings have played a prominent role in this field and have been used extensively in total synthesis and in the development of domino reaction processes.[20,21] However, other metals such as rhodium or ruthenium have also been used successfully.

The Stille reaction has been exploited in intermolecular cross-couplings, as well as in intramolecular cyclisations. During their total synthesis of (+)-mycotrienin I **40**, Panek and

co-workers used a Stille "stitching cyclisation",[22] to form the macrolactam core of the natural product (**Scheme 1.7**).[23,24] Indeed, treatment of *bis*-vinyl iodide **41** with *bis*-stannyl compound **42** in presence of diisopropylethylamine and 20 mol% of $[PdCl_2(MeCN)_2]$ forms intermediate **43**. After the second, Stille cross-coupling, macrocyclic (*E*,*E*,*E*)-triene **44** is obtained in an excellent 90% yield, an advanced intermediate in the synthesis of mycotrienin I **40**.

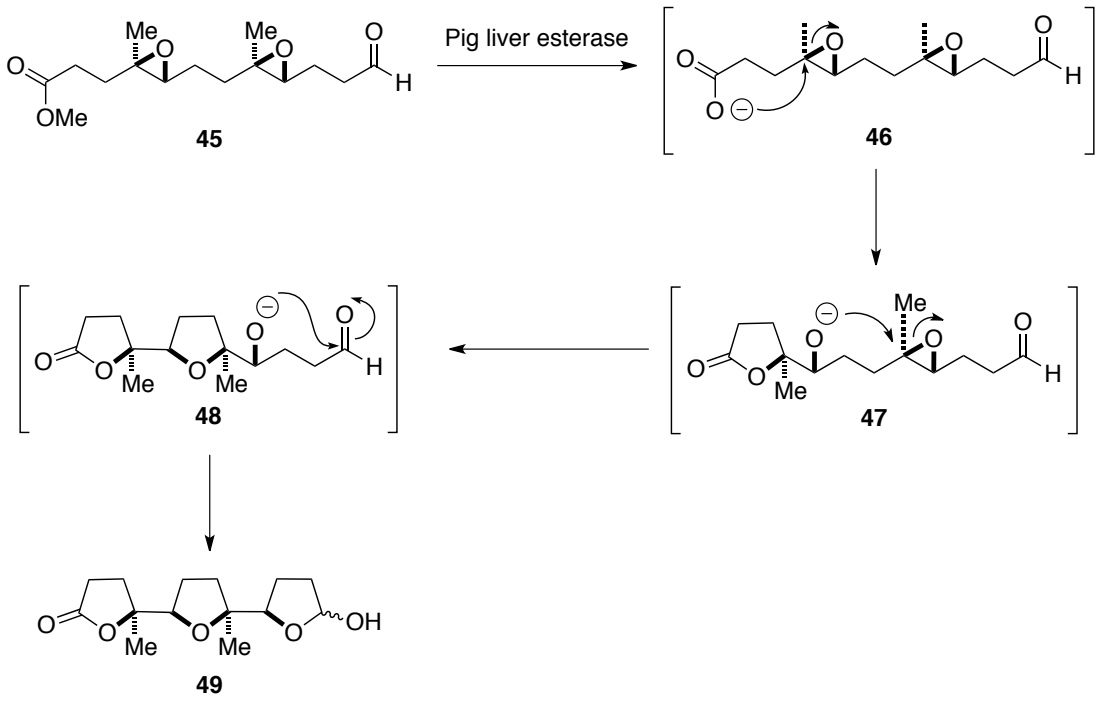


Scheme 1.7. Panek's Stille domino process in (+)-mycotrienin I synthesis.[23,24]

1.2.6 Enzyme-catalysed domino reactions

We have seen that chemists have developed numerous efficient methods to form complex natural products by the way of domino reactions. Very often, the strategy behind these domino processes is guided by biosynthetic considerations. However, despite these successes, chemists are no match to nature's enzyme catalysed reactions. Indeed, after billions of years of evolution, nature's enzymes are capable of catalysing reactions with impressive selectivities coupled with extreme rate acceleration (up to 10^{17} fold). But chemists can now take advantage of nature's toolbox and it is possible to use commercially available enzymes to perform chemical reactions, such as kinetic resolutions, rearrangements and some domino reaction processes.[25]

For example, Robinson and co-workers used ester **45** in an enzyme opening domino reaction, where the enzymatic hydrolysis would form an intermediate nucleophile that would initiate the domino process.[26]



Scheme 1.8. Robinson's enzyme catalysed domino reaction.[26]

Upon treatment with pig liver esterase, the ester **45** is hydrolysed and the carboxylate **46** cyclises on the epoxide in a 5-*exo*-tet manner to provide intermediate **47** (**Scheme 1.8**). A similar cyclisation occurs on the second epoxide to form **48**, which in turn reacts with the aldehyde to provide **49** in an impressive 77% yield.

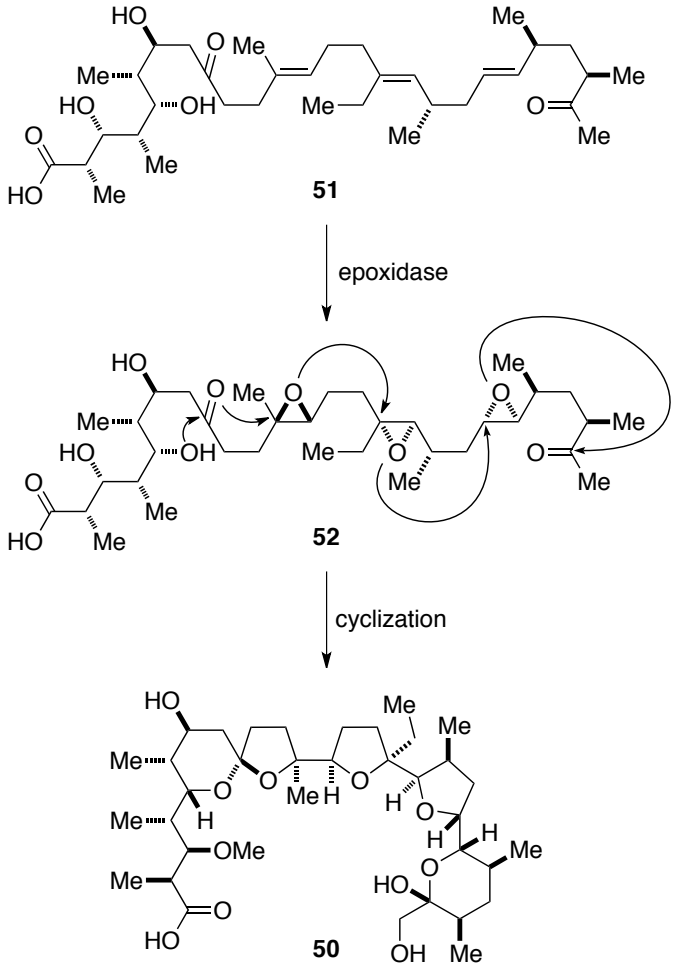
1.3 Domino reactions in polycyclic ether synthesis

Polycyclic ethers are important biologically active compounds that can be divided into three different classes: the polyether ionophores, the annonaceous acetogenins and the marine polyether ladders. The synthesis and biosynthesis of those polycyclic ethers has attracted enormous interest and has been extensively reviewed.[27-31]

1.3.1 Biosynthesis of polyether ionophores

Polyether ionophores are carboxylic acids isolated by fermentation from cultures of *Streptomyces*. They are known to chelate metal ions and display biological activities such as ruminant growth promotion. Two hypotheses to explain the biosynthesis of polyether ionophores are available.

In 1983, Cane, Celmer and Westley (CCW) proposed that monensin **50** is formed from an all-*E*-polyene **51** which is epoxidised stereospecifically to give triepoxide **52**. From **52**, a series of epoxide opening leads to the formation of monensin **50** (**Scheme 1.9**).[32]



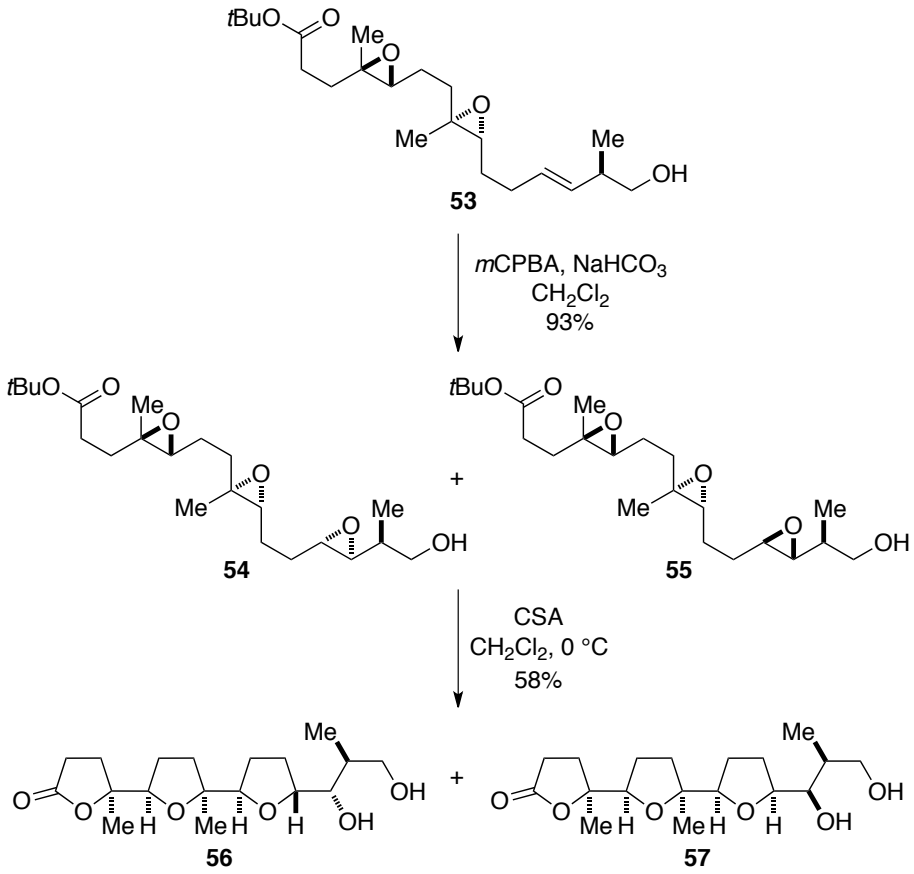
Scheme 1.9. CCW hypothesis for monensin biosynthesis.[32]

Townsend and Basak later proposed an alternative hypothesis in which monensin could be formed through a series of oxidative cyclisations involving an iron-containing monooxygenase.[33] Although synthetic studies supporting this hypothesis have been conducted, recent work in the sequencing of monensin, nachangmycin and other related polyether biosynthetic gene clusters provided strong support to the CCW hypothesis.[34,35]

1.3.2 Synthesis of polyethers by domino reactions

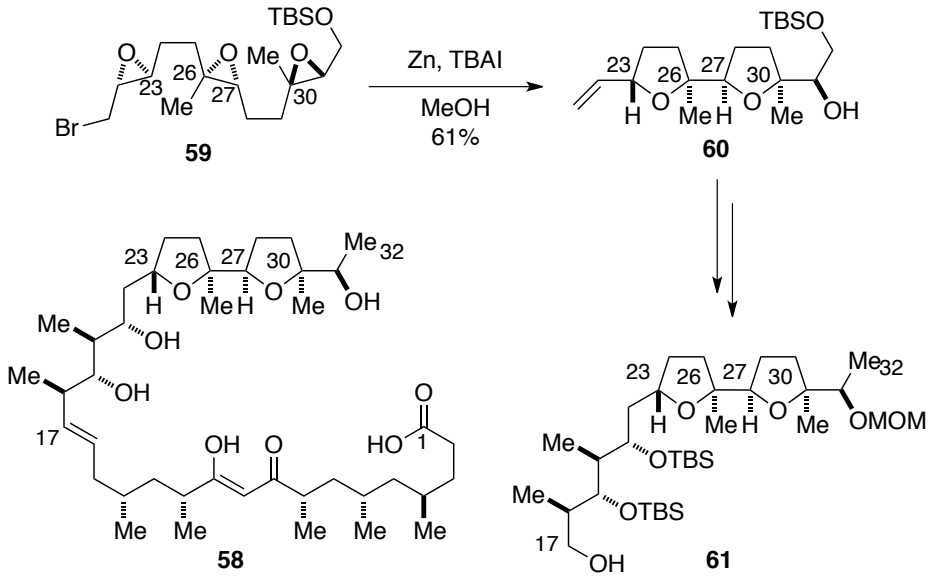
The synthetic community rapidly showed a significant interest in the CCW hypothesis for the biosynthesis of polyethers by way of a domino epoxide opening reaction. Indeed, applications of this biosynthetic pathway would provide rapid access to a plethora of polycyclic ether frameworks.

For example, Paterson and co-workers used a triepoxide domino reaction in their first generation synthesis of etheromycin (**Scheme 1.10**).[36] Epoxidation of alkene **53** using *m*CPBA provided triepoxide **54** and **55** as 1:1 mixture of diastereoisomers. Upon treatment with CSA, the ester is cleaved and triggers the cyclisation to provide a 1:1 mixture of products **56** and **57**.



Scheme 1.10. Paterson domino reaction towards etheromycin.[36]

In their synthesis of the C17-C32 fragment of ionomycin **58**, Marshall and co-workers used a zinc-mediated epoxide opening domino reaction (**Scheme 1.11**).[37] Treatment of bromide **59** with zinc dust and tetrabutylammonium iodide leads to the formation of an intermediate zincate that underwent α-elimination to trigger the cyclisation process and provide the *bis*-THF product **60**, which could then be elaborated into the C17-C32 fragment of ionomycin **61**.



Scheme 1.11. Marshall's synthesis of C17-C32 fragment of ionomycin.[37]

1.4 Domino reactions in cyclic ether synthesis

Substituted tetrahydrofuran (THF) and tetrahydropyran (THP) rings are structural features found in many natural products with important biological activities. Due to the importance of such frameworks, their synthesis has attracted considerable interest and several reviews describing methods towards their formation have been published.[38-41]

1.4.1 Synthesis of THF rings

2,5-Disubstituted THF rings are common structural motifs found in polyether ionophores as described in **section 1.3**, annonaceous acetogenins and amphidinolides. For example, the annonaceous acetogenin *cis*-solamin **62** displays a a 2,5-*cis*-THF-ring (**Figure 1.2**). It is also possible to find 2,5-*trans*-THF rings as in the marine macrolide amphidinolide F **63**.

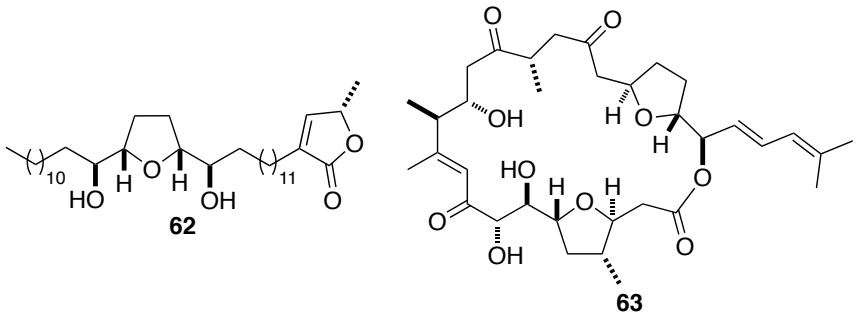
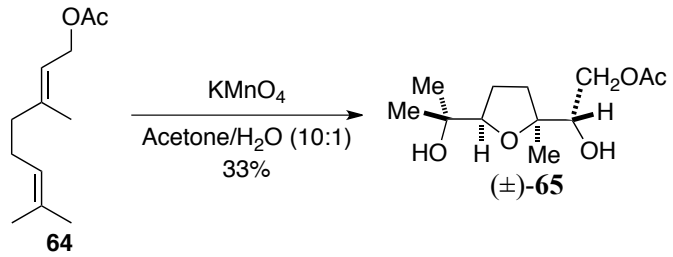


Figure 1.2. 2,5-Disubstituted THF rings in natural products.

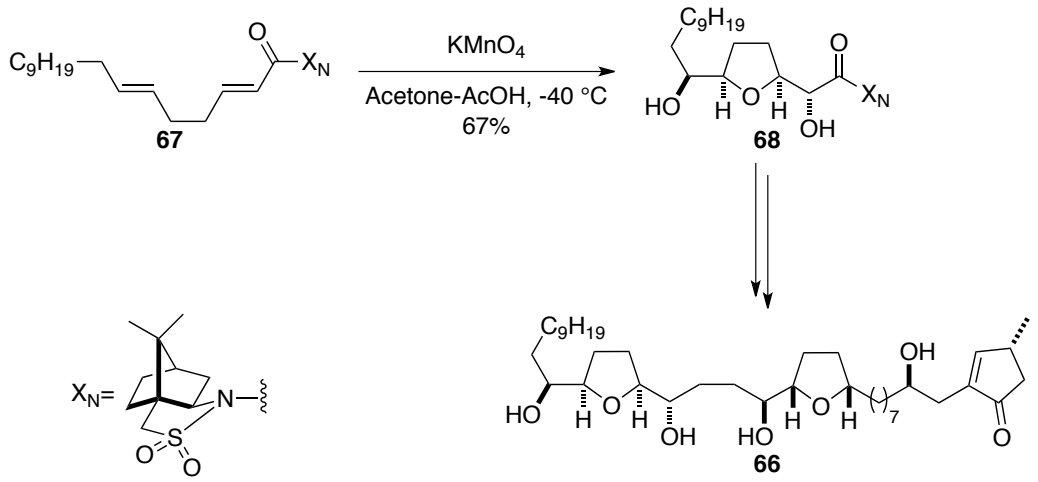
1.4.1.1 Oxidative cyclisation

One of the first methods that have been used in the construction of these motifs is the oxidative cyclisation of polyenes using potassium permanganate. It was pioneered by Klein and Rohjan in 1969, who reported the oxidative cyclisation of geranyl acetate **64**.[42] Treatment of diene **64** with potassium permanganate in an acetone/water mixture provided the *cis*-THF diol **65** in a modest 33% yield (**Scheme 1.12**). Baldwin investigated the cyclisation of deuterated 1,5-dienes in order to deduce the mechanism and stereochemical outcome of this reaction.[43]



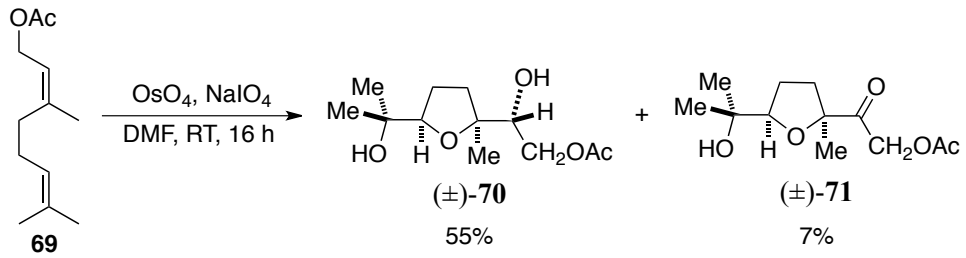
Scheme 1.12. Oxidative cyclisation of geranyl acetate **64**.[42]

Brown used this method in the synthesis of *cis*-sylvaticin **66** (**Scheme 1.13**).[44] Upon treatment with potassium permanganate, triene **67** carrying a camphorsultam chiral auxiliary cyclises to give the 2,5-disubstituted THF ring **68** as 9:1 *trans*:*cis* mixture in 67% yield. This product was then used in the completion of the synthesis of *cis*-sylvaticin **66**.



Scheme 1.13. Brown's synthesis of *cis*-sylvaticin.[44]

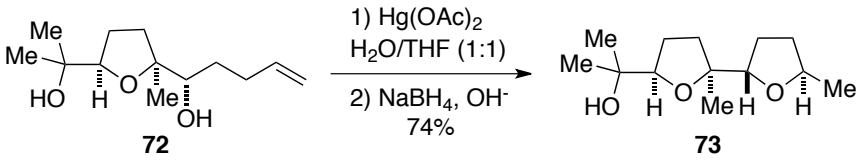
The oxidative cyclisation of polyenes is also possible using catalytic amounts of $RuCl_3$ or osmium tetroxide in the presence of sodium periodate. For example, Piccialli *et al.* reported the synthesis of THF rings by oxidative cyclisation of neryl acetate **69** with osmium tetroxide and sodium periodate. Treatment of neryl acetate **69** with 5 mol% of osmium tetroxide and of sodium periodate provides the 2,5-*cis*-THF ring **70** along with a small amount of the over-oxidation product **71** (**Scheme 1.14**).[45]



Scheme 1.14. Oxidative cyclisation of neryl acetate **69**.[45]

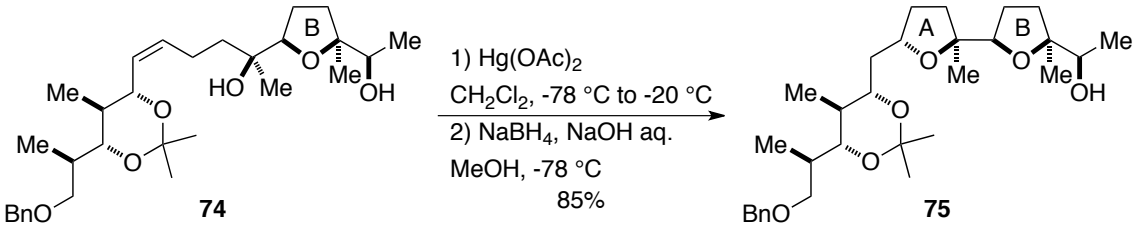
1.4.1.2 Oxymercuration of γ,δ-unsaturated alcohols

Another historic method used in the synthesis of THF rings is the oxymercuration of γ,δ-unsaturated alcohols. This was first investigated by Chastrette and co-workers who reported the cyclisation of compound **72**. Treatment of γ,δ-unsaturated alcohol **72** with mercury acetate, followed by *in situ* reduction of the organomercury species provided the second THF ring of compound **73** as 9:1 *trans*:*cis* mixture (**Scheme 1.15**).[46]



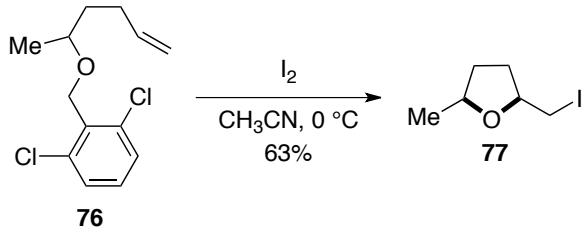
Scheme 1.15. Oxymercuration of γ,δ-unsaturated alcohol.[46]

This method had several successful applications in total synthesis despite its toxicity and the need for stoichiometric amounts of the mercury species. For example, Evans prepared the A ring of ionomycin **58** using mercury acetate (**Scheme 1.16**). Oxymercuration of alkene **74**, followed by cyclisation with the free hydroxyl group provided an intermediate organomercury species which was then reduced with sodium borohydride to provide the THF ring **75** as 97:3 *trans*:*cis* mixture in a 85% yield over two steps.[47]



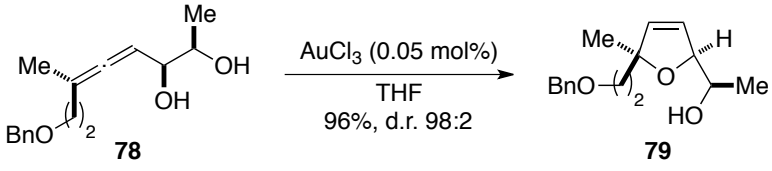
Scheme 1.16. Evan's mercurycyclisation towards ionomycin.[47]

Similar cyclisations of γ,δ-unsaturated alcohols or ethers can be accomplished by halocyclisation or selenocylisation. For example, Bartlett reported that 2,6-dichlorobenzyl ether **76** treated with iodine in acetonitrile at 0 °C provided *cis*-THF ring **77** in 21:1 *cis*:*trans* ratio and 63% yield (**Scheme 1.17**).[48]



Scheme 1.17. Iodocyclization of γ,δ-unsaturated alcohol.[48]

A related cyclisation was reported by Krause who used the gold-catalysed cycloisomerisation of allenes to form dihydrofuran rings.[49] Treatment of allene **78** with gold (III) chloride provided dihydrofuran ring **79** in 96% yield (**Scheme 1.18**).

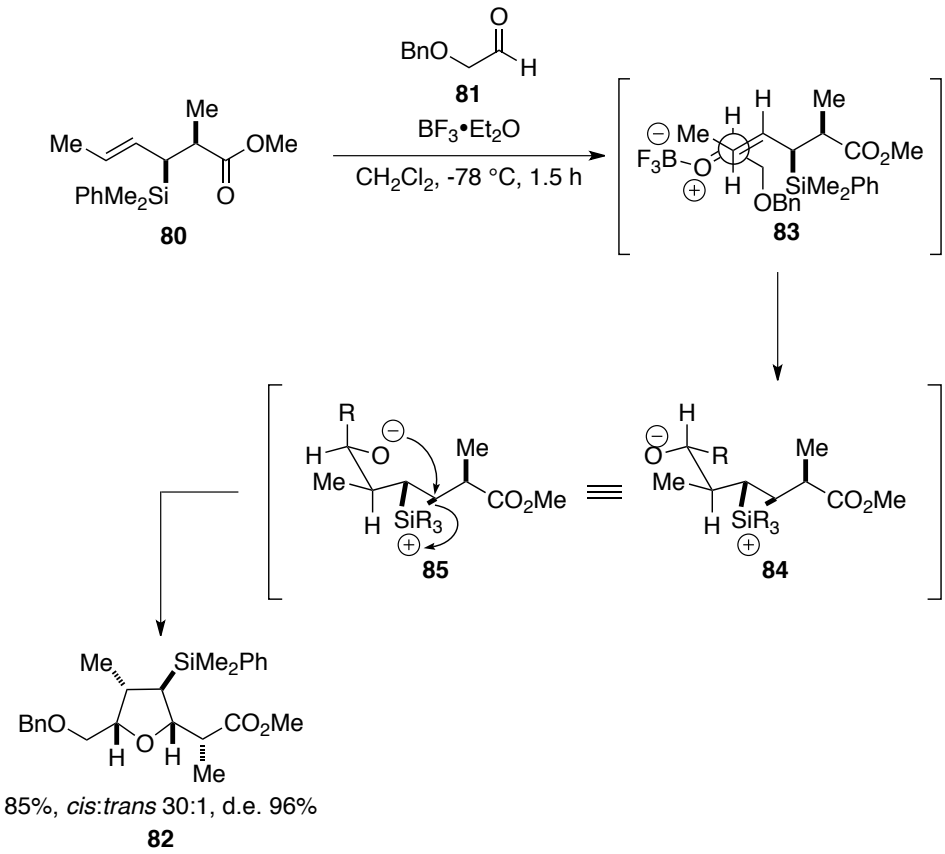


Scheme 1.18. Gold catalysed synthesis of dihydrofuran.[49]

1.4.1.3 [3+2] Cycloadditions

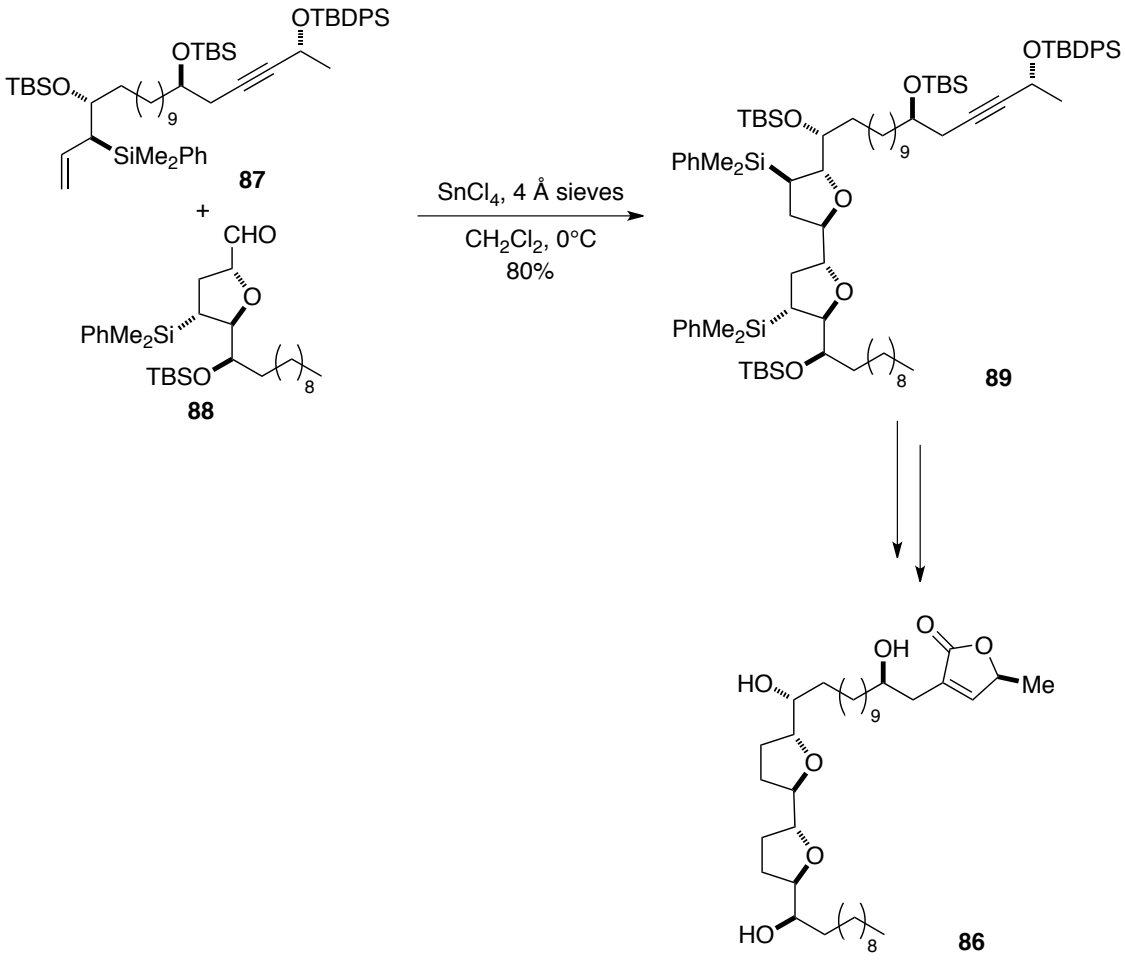
The application of formal [3+2] cycloadditions has proven to be an important method for the formation of THF rings. It usually forms two stereocentres and the ring in a single operation and it is possible to perform those reactions using carbonyl ylides, strained rings or allylsilanes.

Panek pioneered the [3+2] annulation reaction between allylsilanes and aldehydes.[50] For example, reaction of the chiral (*E*)-crotylsilane **80** with benzyl protected aldehyde **81** in the presence of BF_3•Et_2O forms THF ring **82** (**Scheme 1.19**). The proposed mechanism for the reaction proceeds through antiperiplanar transition state **83** to provide intermediate **84**. Rotation along the new C-C bond, followed by a 1,2-silyl shift and cyclisation provides THF ring **82** in 85% yield, 96% d.e. and 30:1 *cis*:*trans* ratio.



Scheme 1.19. Synthesis of THF ring via formal [3+2] annulation.[50]

Since its development, this method has been used extensively to form THF rings and has been applied in several total syntheses.[51] For example, Roush and co-workers reported a [3+2] annulation between a functionalised allylsilane and an advanced aldehyde intermediate in their synthesis of asimicin **86** (**Scheme 1.20**).[52] Treatment of allylsilane **87** with aldehyde **88** in the presence of tin (IV) chloride afforded the *bis*-THF product **89** as a single diastereoisomer in 80% yield. This advanced intermediate was then used to complete the synthesis of the annonaceous acetogenin, asimicin **86**.



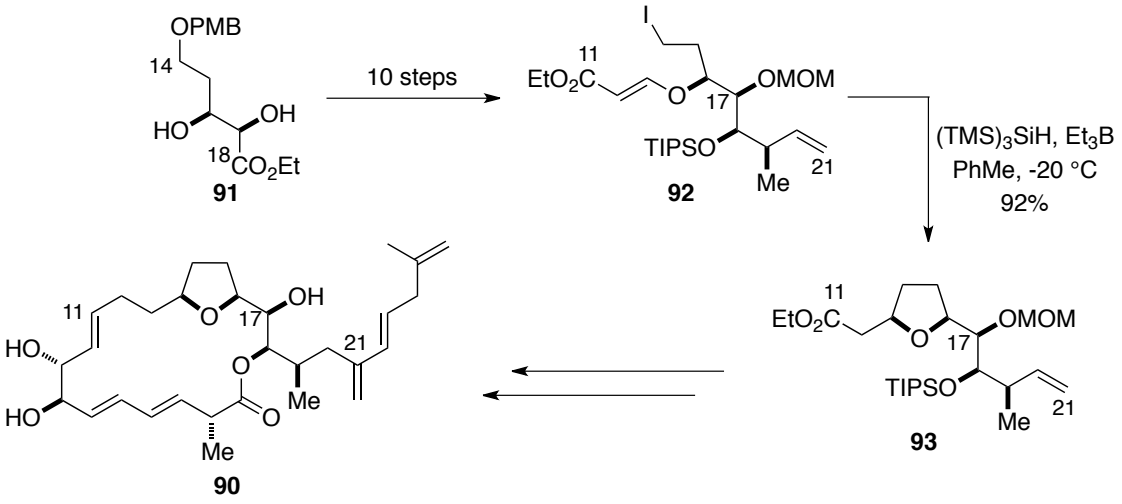
Scheme 1.20. [3+2] annulation in the synthesis of asimicin.[52]

1.4.1.4 Radical cyclisations

Radical cyclisations are very effective and they tolerate a wide variety of functional groups. Unsurprisingly, the use of radical cyclisations has been applied successfully in the synthesis of THF rings. The radical can be trapped using several acceptors such as alkoxyacrylates, alkoxyvinyl ketones and alkoxyvinyl sulfoxides.[53]

In their synthesis of amphidinolide E **90**, Lee and co-workers used a radical cyclisation to construct the *cis*-THF ring (**Scheme 1.21**).[54] Diol **91**, obtained from 1,3-propanediol,[55,56]

was converted into advanced iodide **92** in 10 steps. Treatment of iodide **92** with tris (trimethyl)silane and triethylborane generates a radical, which is trapped with the β-alkoxyacrylate forming the THF ring **93**. The 2,5-*cis*-THF ring is obtained as a single diastereoisomer in 92% yield corresponding to the C11-C21 fragment of amphidinolide E **90**.



Scheme 1.21. Radical cyclisation in Lee's synthesis of amphidinolide E.[54]

1.4.2 Synthesis of tetrahydropyran rings

Tetrahydropyrans are commonly occurring structures found in a large array of natural products with important biological activities such as the macrodiolide SCH-351448 **94** or phorboxazole A **95** (**Figure 1.3**). The importance of these molecules has attracted the interest of many synthetic chemists and this has resulted in numerous elegant methodologies.[40,41]

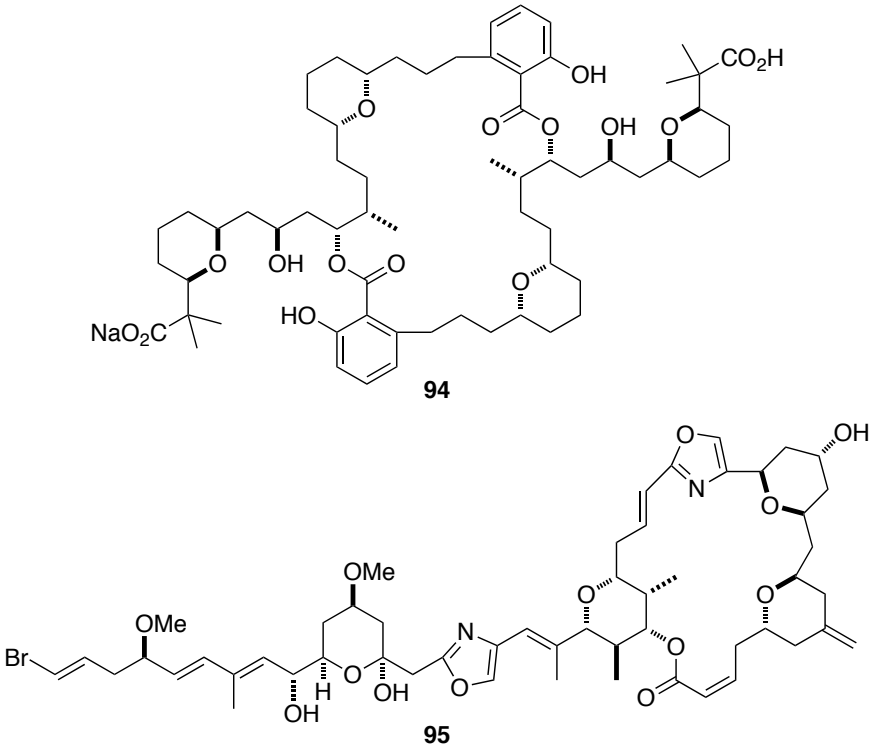


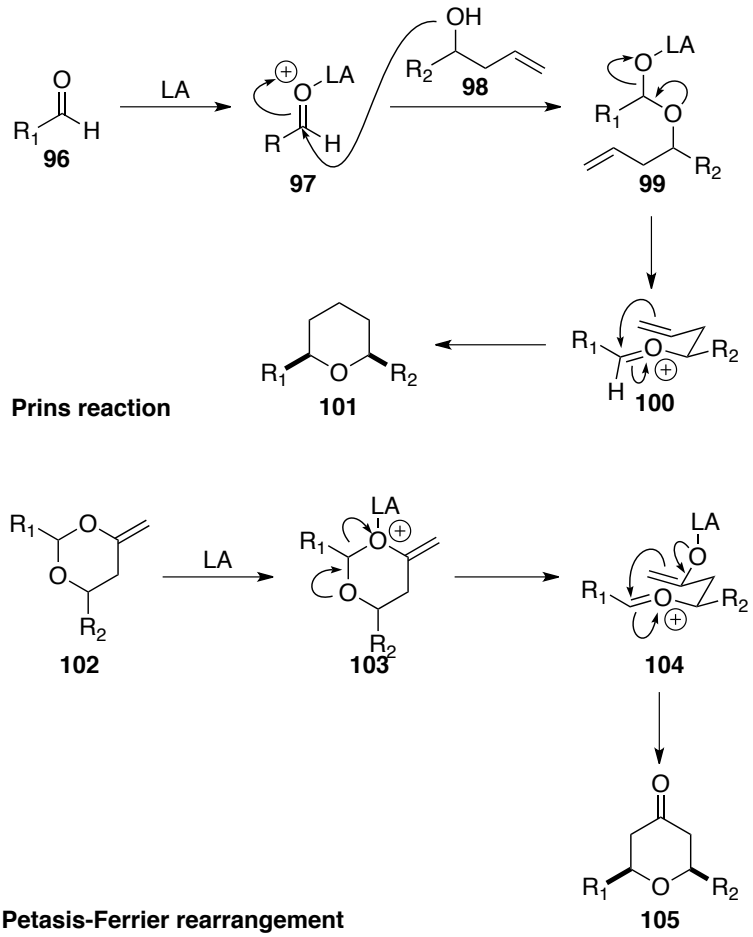
Figure 1.3. THP rings in natural products

1.4.2.1 Prins cyclisation

The formation of THP *via* cyclisation on oxocarbenium ions has been used extensively. Amongst the different approaches that have been used, the Prins reaction is probably the one that made the biggest impact but other related cyclisations such as the Petasis-Ferrier rearrangement have also been applied successfully.

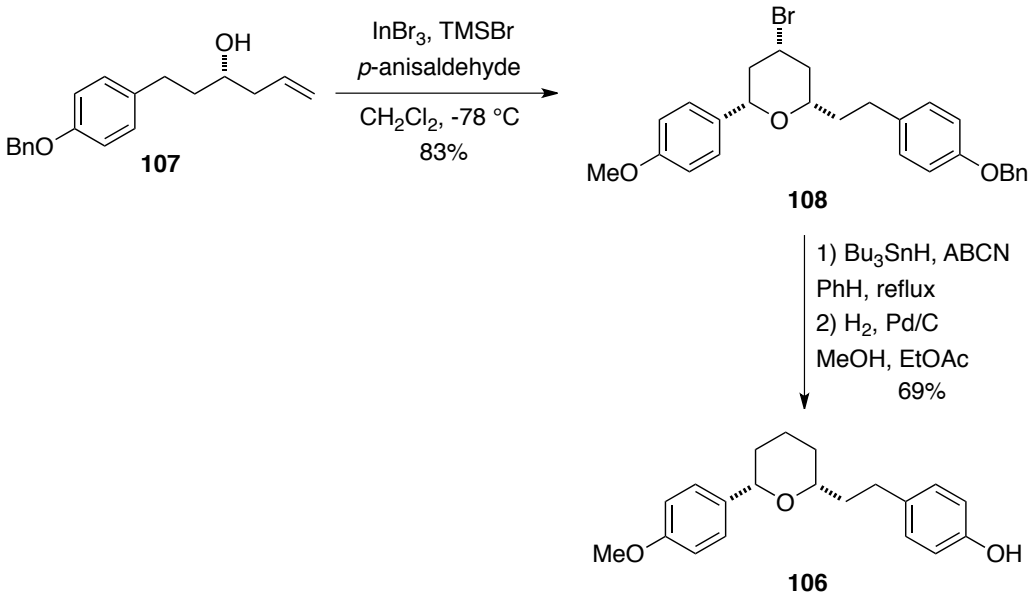
During the Prins reaction, an aldehyde **96** is activated by a Lewis acid. In turn, intermediate **97** is attacked by homo-allylic alcohol **98** to provide hemiacetal **99**, which then leads to the formation of oxonium ion **100** (**Scheme 1.22**). Cyclisation on the oxonium ion then gives *cis*-THP ring **101**. In the case of the Petasis-Ferrier rearrangement, acetal **102** is activated by a Lewis acid. Intermediate **103** is opened under Lewis acidic

conditions and, after bond rotation, forms a six-membered transition **104** state where all substituents occupy equatorial positions. Cyclisation on the oxonium ion provides 2,6-*cis*-pyranone ring **105**.



Scheme 1.22. Prins reaction and Petasis-Ferrier rearrangement mechanisms

The Prins reaction has been reported to suffer from racemisation of the starting homoallylic alcohol. To prevent this, Loh and Chan developed a Prins cyclisation catalysed by indium bromide.[57] Trimethylsilyl bromide was added to the reaction to trap the intermediate carbocation. To demonstrate the utility of this method, they applied it to the synthesis of (-)-centrolobine **106**.



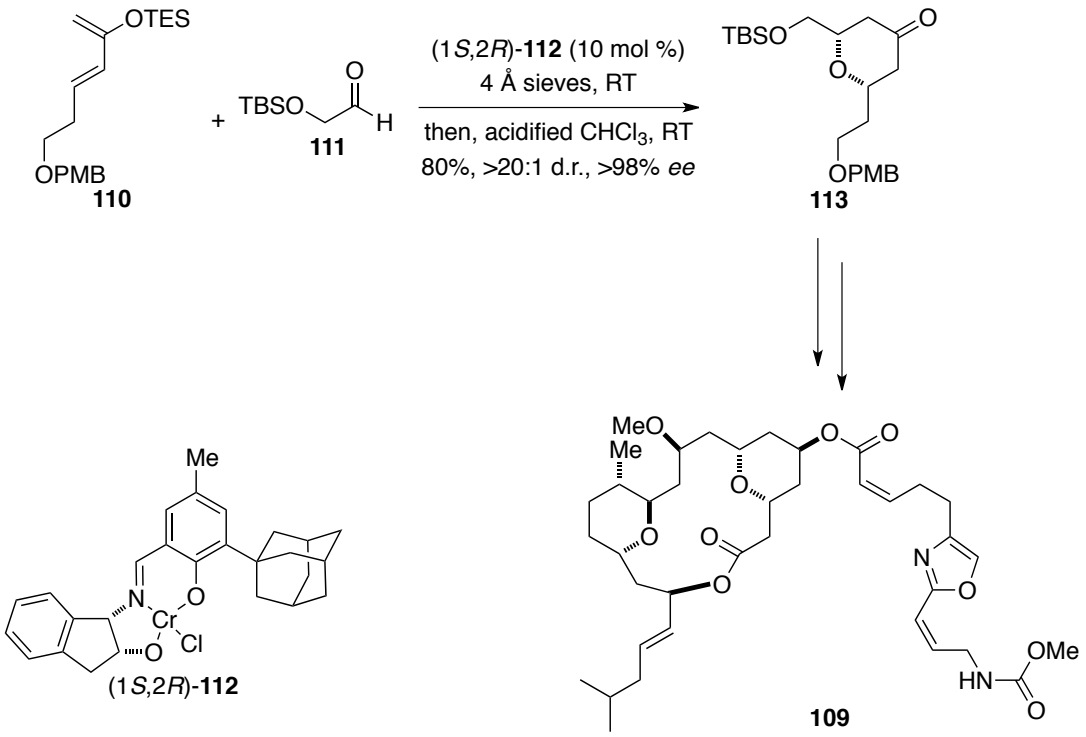
Scheme 1.23. Loh's synthesis of (-)-centrolobine *via* a Prins reaction.[57]

Treatment of allylic alcohol **107** with *p*-anisaldehyde in presence of indium bromide and trimethylsilyl bromide provides the THP ring **108** in a 83% yield without any racemisation (**Scheme 1.23**). A further two steps were then required to finish the synthesis of centrolobine **106** which was obtained in a 57% yield over three steps.

1.4.2.2 Hetero-Diels-Alder cyclisations

Hetero-Diels-Alder (HDA) reactions have been used in the construction of substituted THP rings and have been applied in total synthesis several times.[40] Jacobsen and co-workers reported that HDA cyclisations can be performed using a tridentate chromium (III) catalyst. Paterson and Tudge used this catalyst in their synthesis of leucascandrolide A **109** to form the 2,6-*cis*-THP ring (**Scheme 1.24**).[58]

HDA reaction between aldehyde **110** and diene **111** is promoted by the tridentate catalyst **112**, followed by mild acidic work-up provides the 2,6-*cis*-pyranone **113** in excellent yield, d.r. and ee. This intermediate was then used to complete the synthesis of leucascandrolide A **109**.

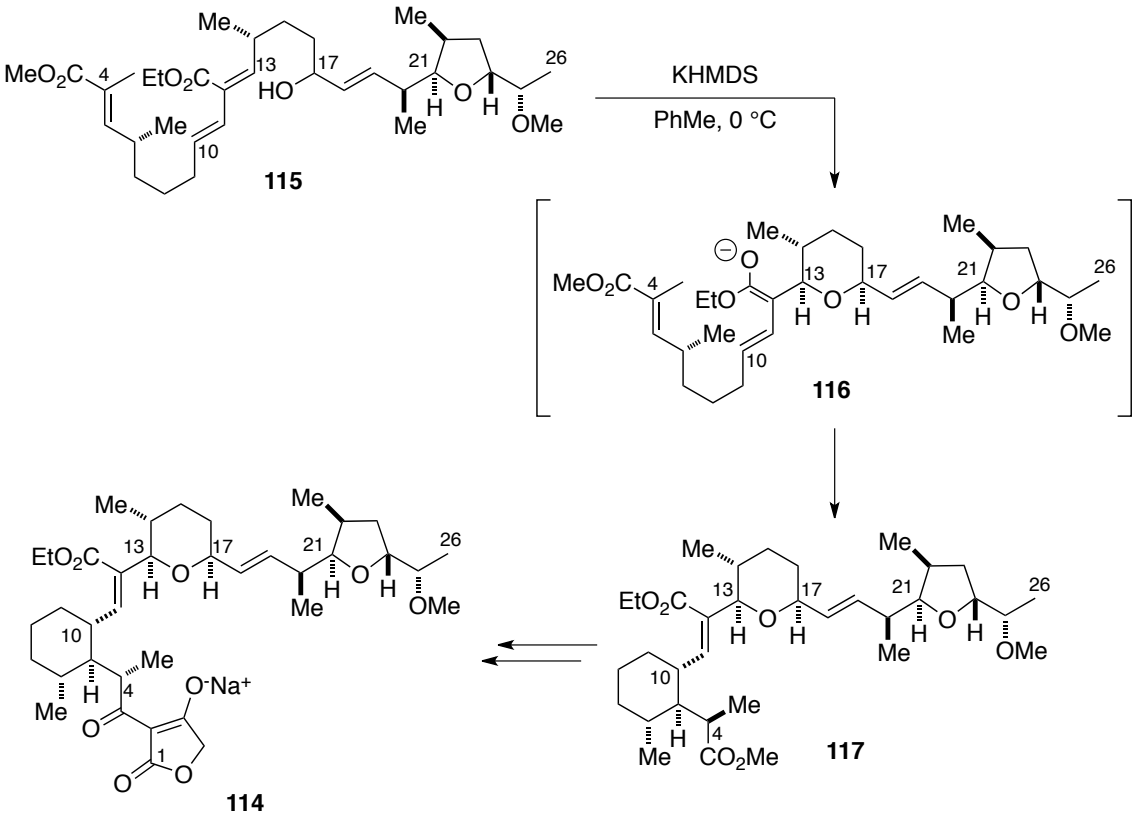


Scheme 1.24. Paterson's synthesis of leucascandrolide A.[58]

1.4.2.3 Conjugate Michael additions

The use of conjugate Michael additions of an alcohol onto α,β-unsaturated compounds is a convenient method to form THP rings and it has been applied in the synthesis of numerous THP-containing natural products.

During their synthesis of tetronasin **114**, Ley and co-workers used an ambitious domino cyclisation of an open chain polyene precursor to form a THP, a cyclohexyl ring and four stereocentres (**Scheme 1.25**).[59] Upon treatment with KHMDS, the secondary alcohol **115** cyclises on the Michael acceptor and the resulting extended enolate **116** undergoes a second cyclisation and forms **117** in 67% yield as a single diastereoisomer. Unfortunately, the C4 methyl was formed with the opposite configuration and had to be epimerized before completion of tetronasin **114**.

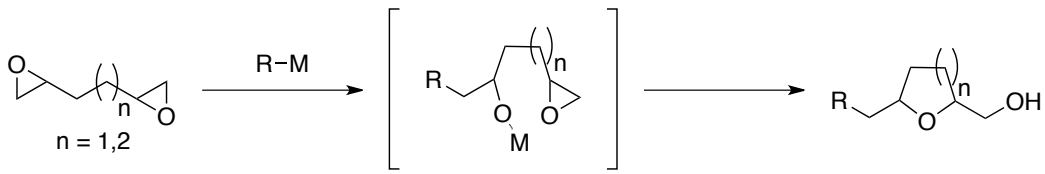


Scheme 1.25. Conjugate addition in the synthesis of tetronasin.[59]

1.4.3 Development of domino reactions in cyclic ether synthesis

The previous section have highlighted that cyclic ethers have been the targets of considerable synthetic studies and that numerous elegant methods are available to form these frameworks with good yields and selectivities. However, the construction of simple cyclic ethers is not trivial as the synthesis of their precursors often involves long synthetic sequences prior to cyclisation.

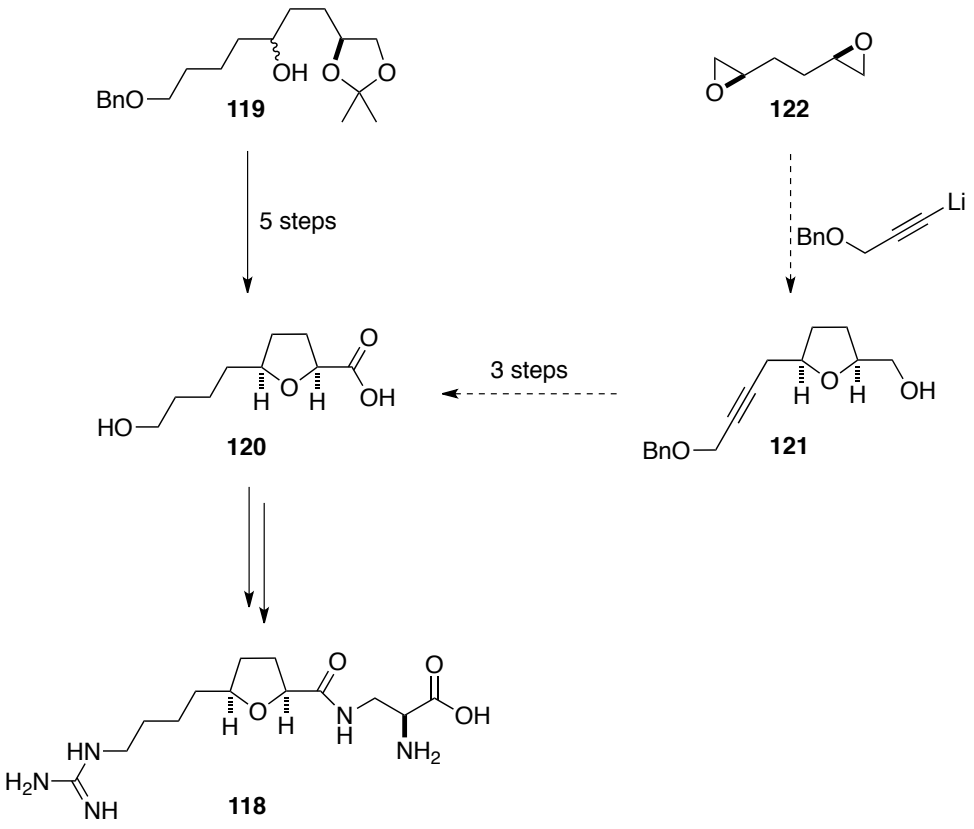
The first aim of this project was to develop a reliable protcol to access cyclic ethers using the domino cyclisation of diepoxides. Indeed, the controlled mono-addition of a metal species to a diepoxide would form an intermediate metalated alkoxide, which would in turn cyclise on the second epoxide to provide the corresponding THF or THP ring (**Scheme 1.26**).



Scheme 1.26. Development of domino reactions in cyclic ether synthesis.

The development of this method would allow the formation of cyclic ethers in a single step from readily accessible starting materials. The thermal and chemical stability of ether rings would allow them to be used in multi-step synthesis without risk of affecting the ring system. The formation of a free alcohol in the product would permit further functionalisation on both sides of the ring independently without having to manipulate protecting groups.

Such a protocol is not only attractive in terms of natural product synthesis but could also serve as a practical method for the drug discovery process. For example, Koert and co-workers have reported the synthesis of integrin antagonist **118** containing a 2,5-*cis*-THF ring motif.[60] Intermediate **119**, prepared from (L)-malic acid in six steps,[61] was transformed into the THF ring fragment **120** in a further five steps, including the chromatographic separation of two diastereoisomers (**Scheme 1.27**). In comparison, THF ring **121** could be accessed in a single transformation using the domino cyclisation of the enantiopure diepoxide **122**. The 2,5-*cis*-THF ring **121** could then be transformed into intermediate **120** in a further three steps.



Scheme 1.27. Synthesis of integrin antagonist **118**.

Chapter Two

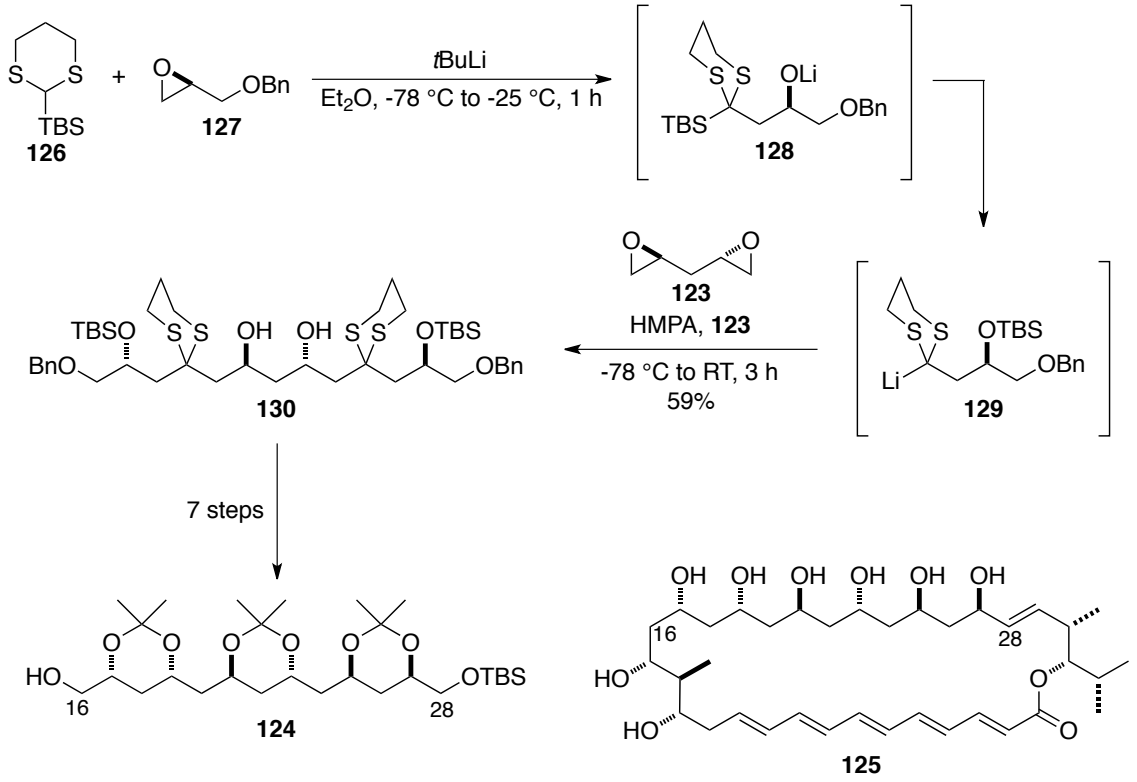
Results and Discussion

Domino cyclisations of diepoxides to cyclic ethers

2.1 Applications of diepoxides in synthesis

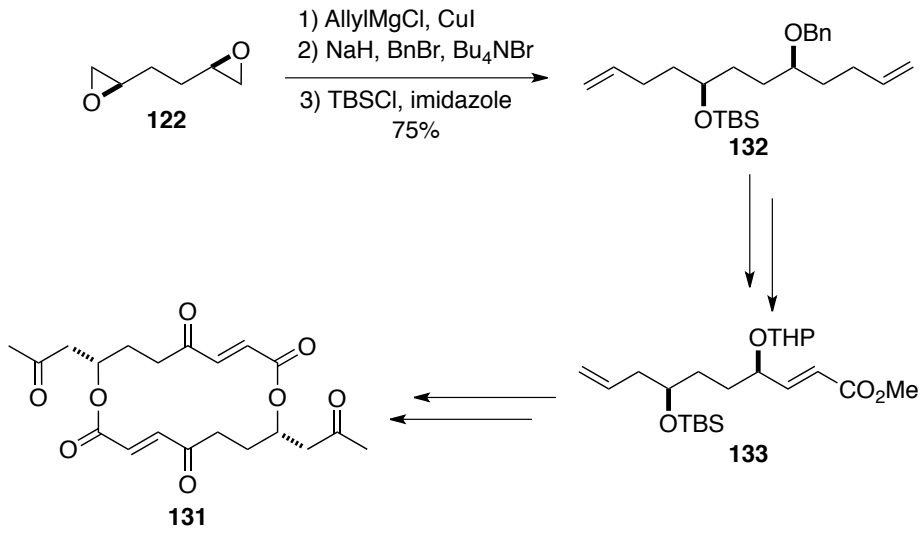
2.1.1 Double-opening reactions

One of the most frequent applications of 1,n-diepoxides is to perform double-opening reactions. This method provides access to 1,n-diols that can be found in numerous natural products. For example, Smith and co-workers used double-addition to (*S*,*S*)-diepoxypentane **123** in the synthesis of the C16-C28 fragment **124** of mycoticin A **125** (**Scheme 2.1**).[62,63] Treatment of dithiane **126** with *tert*-butyllithium generated the intermediate lithium anion that was added to (*S*)-benzylglycidol **127**. Intermediate **128** undergoes a Brook rearrangement to give a second dithiane anion **129**, which was then used in the bidirectional opening of (*S*,*S*)-diepoxypentane **123** to provide diol **130**. The resulting diol was then elaborated into the C16-C28 fragment of mycoticin A, previously reported by Schreiber.[63]



Scheme 2.1. Synthesis of mycoticin A C16-C28 fragment by Smith *et al*.[62]

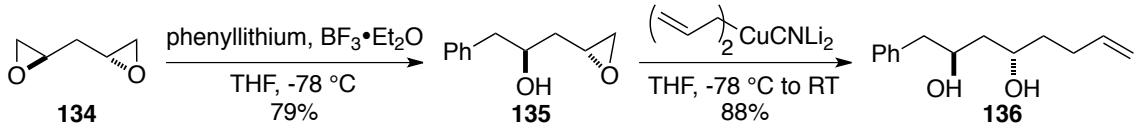
Kibayashi *et al.* was the first to demonstrate the utility of C2-symmetric diepoxides in their synthesis of vermiculine **131** (**Scheme 2.2**).[64] Treatment of (*R*,*R*)-diepoxyhexane **122** with allylmagnesium chloride and copper iodide provided an intermediate diol. The diol was mono-protected with a benzyl group and, following the protection of the second hydroxyl group as its TBS ether, intermediate **132** was obtained. It was then elaborated into ester **133** in a further ten steps, which was used to complete the synthesis of (-)-vermiculine **131**.



Scheme 2.2. Kibayashi's synthesis of (-)-vermiculine.[64]

2.1.2 Mono-opening reactions

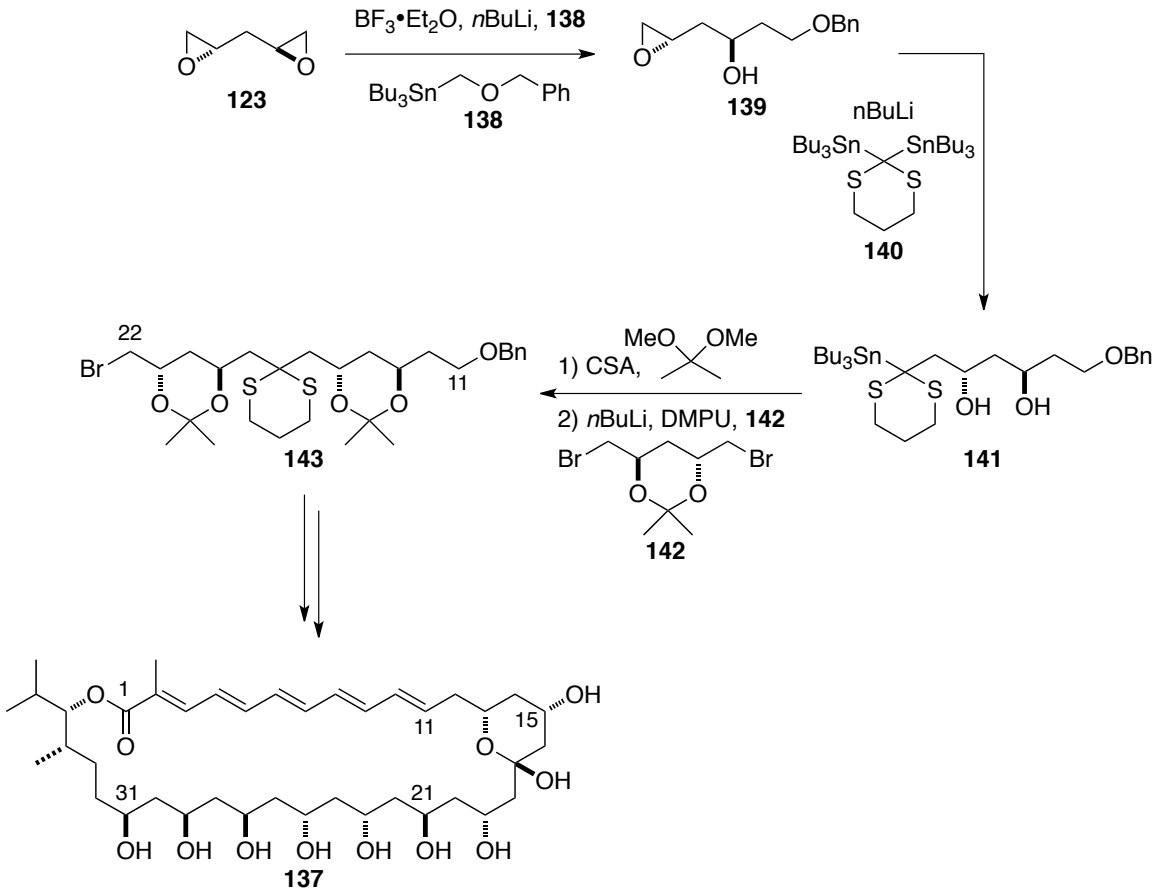
Diepoxides have also been used in mono-opening reactions. Rychnovsky and co-workers demonstrated a selective opening of diepoxide **134**.[65] The second epoxide could be opened to generate asymmetric 1,3-diols that could provide useful synthons in polyol chain synthesis. For example, treatment of (*R*,*R*)-diepoxypentane **134** with phenyllithium in presence of BF_3•Et_2O generates epoxyalcohol **135** in 79% yield (**Scheme 2.3**). Opening of the second epoxide with a high order cuprate provides diol **136** in 81% yield.



Scheme 2.3. Rychnovsky's synthesis of asymmetric 1,3-diols.[65]

Rychnovsky applied this bidirectional tactic in the synthesis of C11-C22 fragment of the polyol roflamycoin **137**.[66] Mono-addition of the lithium species derived from stannane **138**

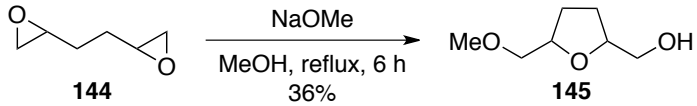
to (*S*,*S*)-diepoxypentane **123** provided intermediate epoxyalcohol **139**. Opening of the second epoxide by addition of the lithium species derived from *bis*-(tributyltin)-dithiane **140** provided diol **141** (**Scheme 2.4**). Protection of the diol as its acetonide was then followed by transmetallation and alkylation with dibromide **142** to afford C11-C22 fragment **143** of roflamycoin **137**.



Scheme 2.4. Rychnovsky's synthesis of roflamycoin.[66]

2.1.3 Cyclisation reactions

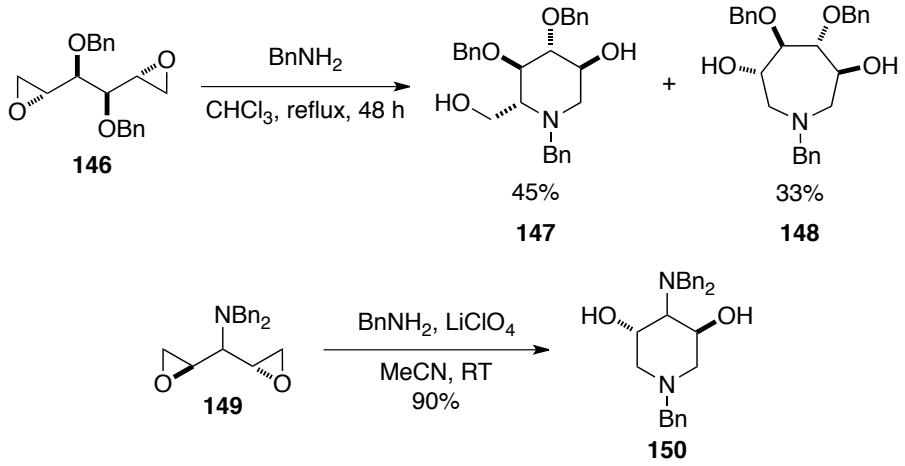
Despite initial studies on the addition/cyclisation of diepoxides, few applications of this tactic have been reported. In 1950, Wiggins and Woods reported the methanolysis of 1,5-diepoxyhexane **144** that provided THF **145** in a 36% yield (**Scheme 2.5**).[67]



Scheme 2.5. Wiggins addition/cyclisation to THF rings.[67]

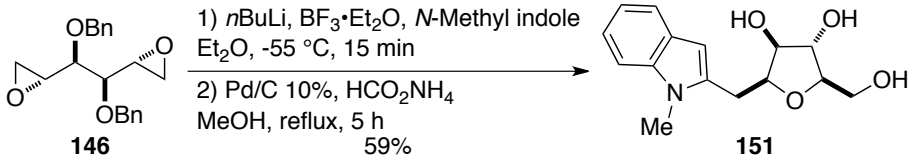
Cassady and co-workers reported a similar reaction using sodium and benzyl alcohol.[68] These methods demonstrated the formation of THF rings from diepoxides. However, the products were formed in low to moderate yields using relatively harsh reaction conditions.

The cyclisations of diepoxides to piperidines and azepanes was reported by Le Merrer *et al*. Treatment of (D)-mannitol derived diepoxide **146** with benzylamine opens a first epoxide which can undergo a 6-*exo*-tet or 7-*endo*-tet cyclisation. This provides piperidine **147** in a 45% yield and azepane **148** in a 33% yield (**Scheme 2.6**).[69,70] Concellón and co-workers also reported a similar cyclisation using a diepoxypentane **149** to form piperidine **150** *via* a 6-*endo*-tet cyclisation.[71]



Scheme 2.6. Addition cyclisation to piperidines and azepanes.[69-71]

In 2002, Le Merrer and co-workers reported the synthesis of ATP mimics from (D)-mannitol derived diepoxide **146** (**Scheme 2.7**).[72] Treatment of diepoxide **146** with α-lithiated methyl indole in the presence of BF_3•Et_2O, followed by hydrogenation provided triol **151** in 59% yield over two steps.



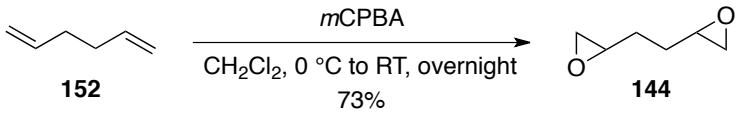
Scheme 2.7. ATP mimic synthesis.[72]

2.2 One-pot cyclisation of racemic diepoxides

In order to investigate the feasibility of the one-pot cyclisation of diepoxides to THF rings, we decided to first examine the cyclisation of readily accessible racemic diepoxides.

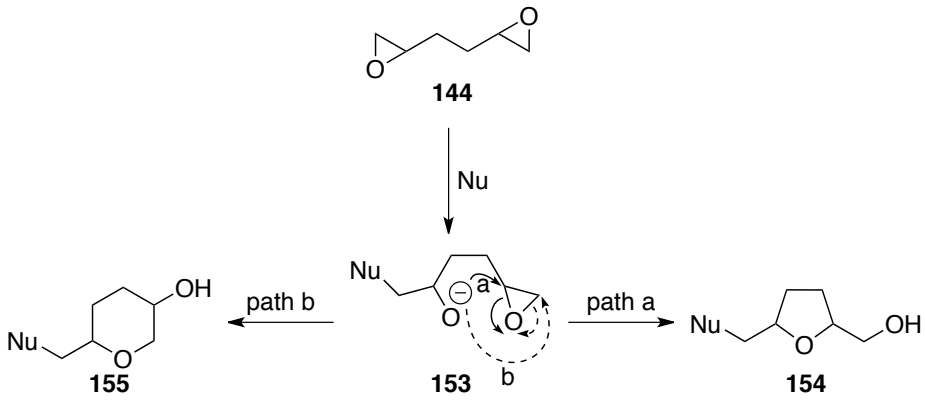
2.2.1 Synthesis of THF rings using organocuprates

1,5-Diepoxyhexane **144** was prepared using conditions reported by Mioskowski.[73] Treatment of 1,5-hexadiene **152** with *m*CPBA provided diepoxide **144** as a racemic/meso mixture in good yield (**Scheme 2.8**). The reaction was carried out on scales up to 0.2 mol of diene and provided convenient access to 1,5-diepoxyhexane **144**.



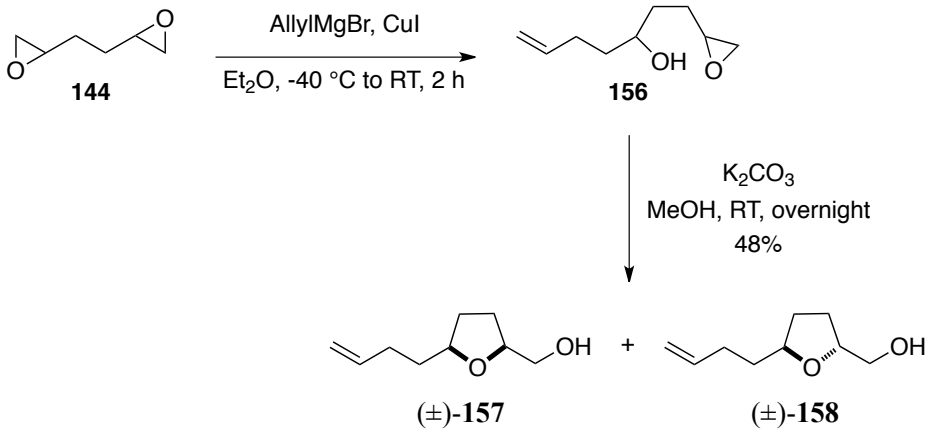
Scheme 2.8. Preparation of 2,5-diepoxyhexane **144**.

With diepoxide **144** in hand, we turned our attention to the development of appropriate reaction conditions for the addition/cyclisation process. It is proposed that the addition of a nucleophile to diepoxyhexane **144**, would lead to the formation of intermediate alkoxide **153** (**Scheme 2.9**). The resulting intermediate could then in turn cyclise on the second epoxide following two competing pathways. Cyclisation following pathway a would form the THF ring **154** while cyclisation following pathway b would give the corresponding THP ring **155**. The use of Baldwin's rules can allow to predict which cyclisation pathway should be favoured over the other.[74] For the cyclisation to occur, the nucleophile and the electrophile must achieve orbital overlap. As a result, a cyclisation will be favoured if the carbon backbone allows the atoms to align with the required trajectory. In this case, the cyclisation can proceed either by a 5-*exo*-tet pathway (path a) or by a 6-*endo*-tet pathway (path b). The 6-*endo*-tet cyclisation requires greater distortion of bond angles and distances and the 5-*exo*-tet cyclisation is therefore more likely to occur.



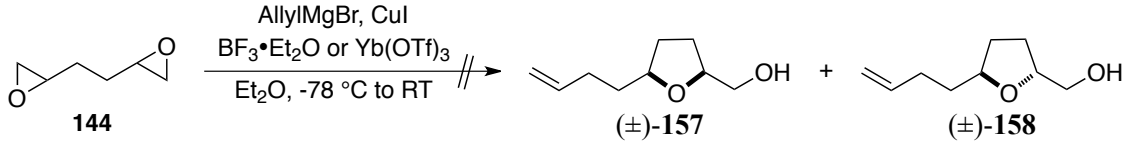
Scheme 2.9. Two possible pathways for the addition/cyclisation of diepoxyhexane **144**.

The addition of allylmagnesium bromide to 1,5-diepoxyhexane **144** in the presence of copper iodide was first investigated (**Scheme 2.10**). Mono-addition on the diepoxide provided the crude epoxyalcohol **156**, which was carried forward without purification. The crude epoxyalcohol **156** was treated with potassium carbonate to facilitate the 5-*exo*-tet cyclisation and provided THF alcohols **157** and **158** as a 50:50 diastereoisomeric mixture in 48% yield.



Scheme 2.10. Addition/cyclisation using allylmagnesium bromide.

We aimed to perform this transformation in a single operation and this initial result proved the viability of our proposed approach, but the THF alcohol was formed over two separate reactions. In an attempt to facilitate the cyclisation, the use of Lewis acids was investigated. Unfortunately, treatment of diepoxide **144** with allylmagnesium, copper iodide and either BF_3•Et_2O or ytterbium (III) trifluoromethanesulfonate led to significant degradation of the starting material (**Scheme 2.11**).



144 (±)-**157** (±)-**158**

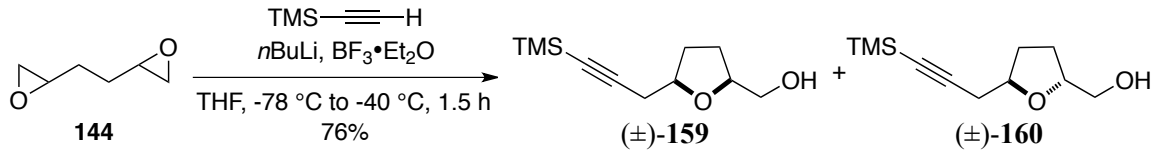
Scheme 2.11. One-pot addition/cyclisation attempts using Lewis acids.

The incompatibility of Lewis acids with the organocuprate system led us to turn our attention toward the use of organolithium species.

2.2.2 Addition/cyclisation using lithium acetylides

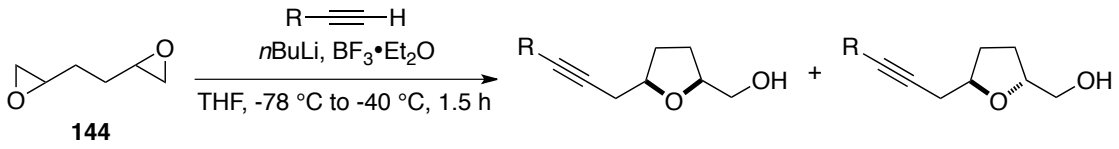
We first decided to attempt the addition/cyclisation in presence of 1.1 equivalents of the lithium anion of TMS acetylene and 2 equivalents of BF_3•Et_2O at -78 °C. Unfortunately, this lead to the degradation of the starting material. This reaction was repeated by adding diepoxide **144** to 1.2 equivalents of the lithium anion of TMS acetylene at -78 °C, followed by addition of 1.5 equivalents of BF_3•Et_2O and warming the reaction mixture to -40 °C to

facilitate the cyclisation. Gratifyingly, those conditions provided a diastereoisomeric mixture of THF alcohols **159** and **160** in 76% yield (**Scheme 2.12**).[75]



Scheme 2.12. One-pot addition/cyclisation using BF_3•Et_2O.

With optimal conditions developed, we turned our attention to the addition of a range of lithium acetylides to 1,5-diepoxyhexane **144**. Addition of the lithium anion of benzyl protected propargyl alcohol proved successful and provided a mixture of THF alcohols **161** and **162** in 73% yield (entry 2, **Table 2.1**). In the case of the acid sensitive TBS-protected propargyl alcohol, careful work-up was required to avoid deprotection of the silyl group (entry 3. **Table 2.1**). The addition of the lithium anions of 1-octyne and phenyl acetylene provided the desired THF alcohols in good yields (entry 4 and 5, **Table 2.1**).



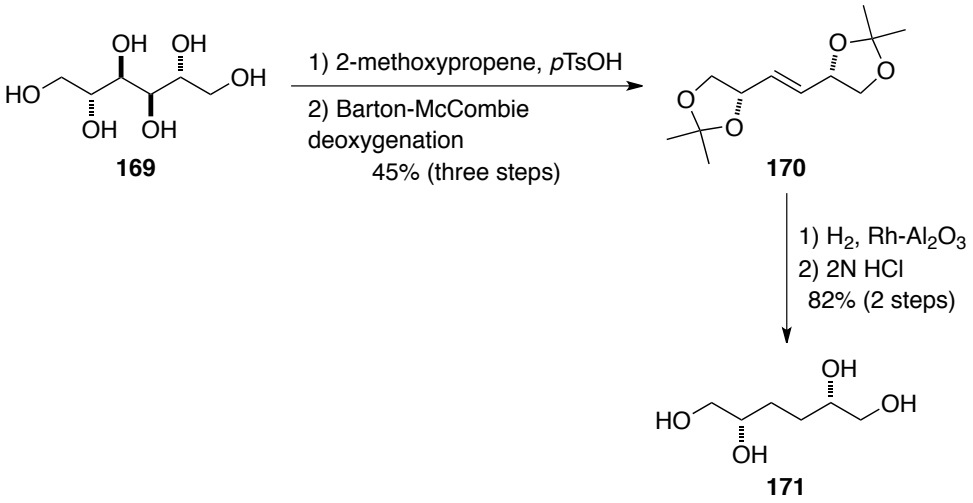
Entry	R	Product	Yield (%)
1	TMS	**159** + **160**	76
2	$BnOCH_2$	**161** + **162**	73
3	$TBSOCH_2$	**163** + **164**	65
4	C_6H_{13}	**165** + **166**	62
5	Ph	**167** + **168**	80

Table 2.1. One-pot addition cyclisation of alkynes using BF_3•Et_2O.

2.3 One-pot cyclisation of enantiopure diepoxides

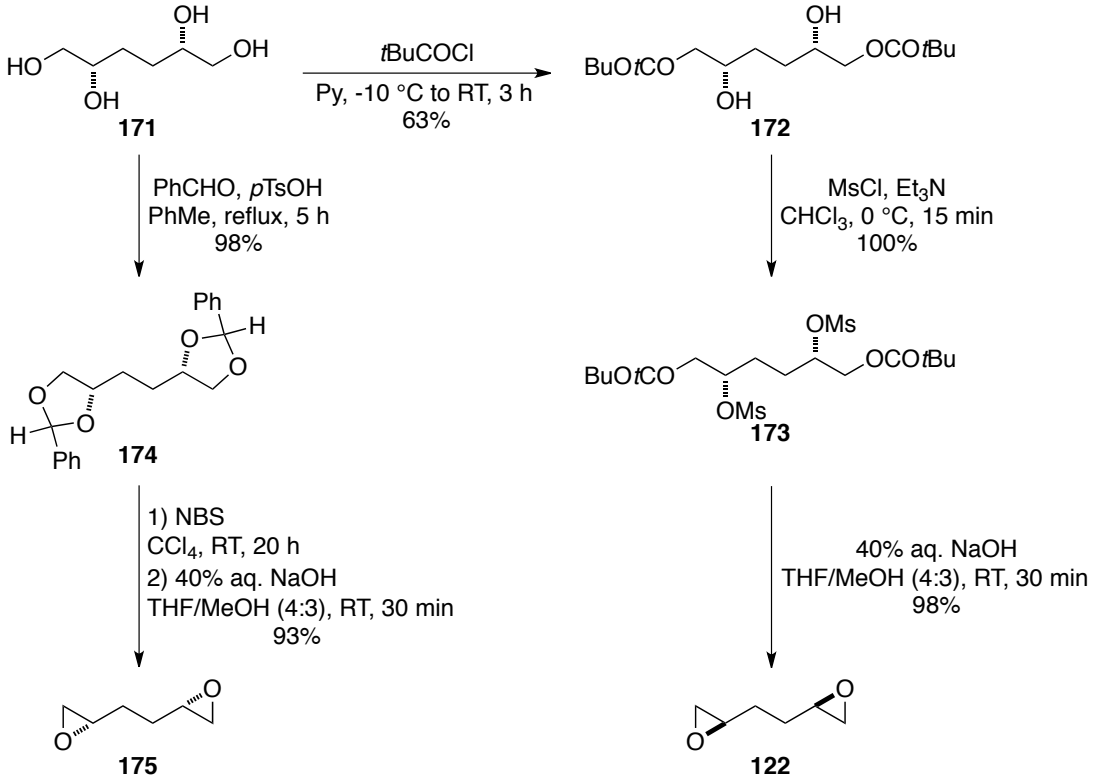
2.3.1 Kibayashi's synthesis of (*R*,*R*) and (*S*,*S*)-diepoxyhexane

For this method to be useful in natural product synthesis, reliable access to both enantiomeric forms of diepoxyhexane was required. The synthesis of these two compounds was first described by Kibayashi and co-workers.[76,77] (D)-Mannitol **169** was first converted to alkene **170** by formation of the diisopropylidene, followed by double Barton-McCombie deoxygenation (**Scheme 2.13**).[78,79] The alkene was then hydrogenated using rhodium on alumina, followed by the deprotection of the acetonide groups using 2N hydrochloric acid to provide tetraol **171** in 82% over the two steps.



Scheme 2.13. Synthesis of tetraol **171**.[76-79]

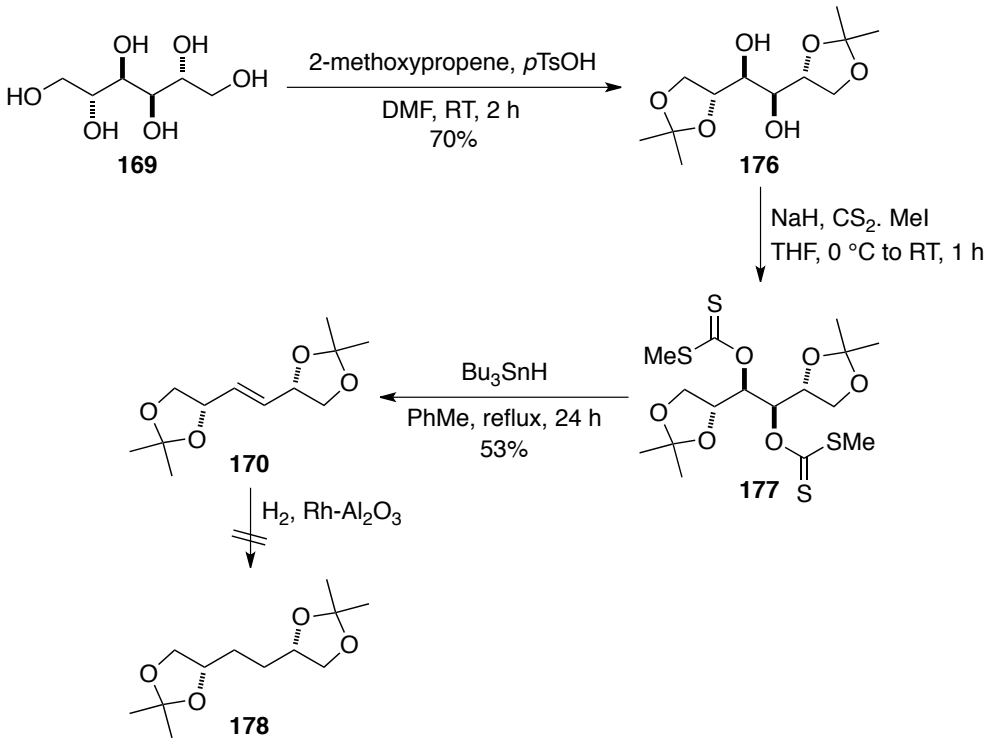
From this common intermediate **171**, both enantiomers of 1,5-diepoxyhexane could be readily prepared. The synthesis of (*R*,*R*)-diepoxyhexane **122** began with the selective protection of the primary alcohols with pivaloyl groups to provide **172** (**Scheme 2.14**). This was followed by the mesylation of the secondary alcohols which formed *bis*-mesylate **173** and upon treatment with a 40% aqueous solution of sodium hydroxide, the desired (*R*,*R*)-diepoxyhexane **122** was formed. The synthesis of the opposite enantiomer began with the formation of the *bis*-benzylidene acetal **174** using benzaldehyde and *p*TsOH. Treatment with NBS, followed by cyclisation using a 40% aqueous solution of sodium hydroxide provided (*S*,*S*)-diepoxyhexane **175**.



Scheme 2.14. Kibayashi's synthesis of (*R*,*R*) and (*S*,*S*)-diepoxyhexane.[76,77]

Attracted by the fact that each step can be performed on multigram scale, we turned our attention to the preparation of enantiopure (*R*,*R*)-diepoxyhexane **122** using the synthesis developed by Kibayashi.

Treatment of (D)-Mannitol **169** with 2-methoxypropene and *p*TsOH afforded diisopropylidene **176** in 70% yield (**Scheme 2.15**). Diol **176** was then used in a double Barton-McCombie deoxygenation. Treatment of diol **176** with sodium hydride, carbon disulfide and methyl iodide provided the crude bisdithiocarbonate **177** that was used without further purification. Refluxing the intermediate **177** with tributyltin hydride provided alkene **170** in a 53% yield over the two steps. Unfortunately, hydrogenation of alkene **170** using the conditions reported by Kibayashi *et al.* was not successful and the starting material was recovered. Using extended reactions times was also unsuccessful and the degradation of the starting material was observed.

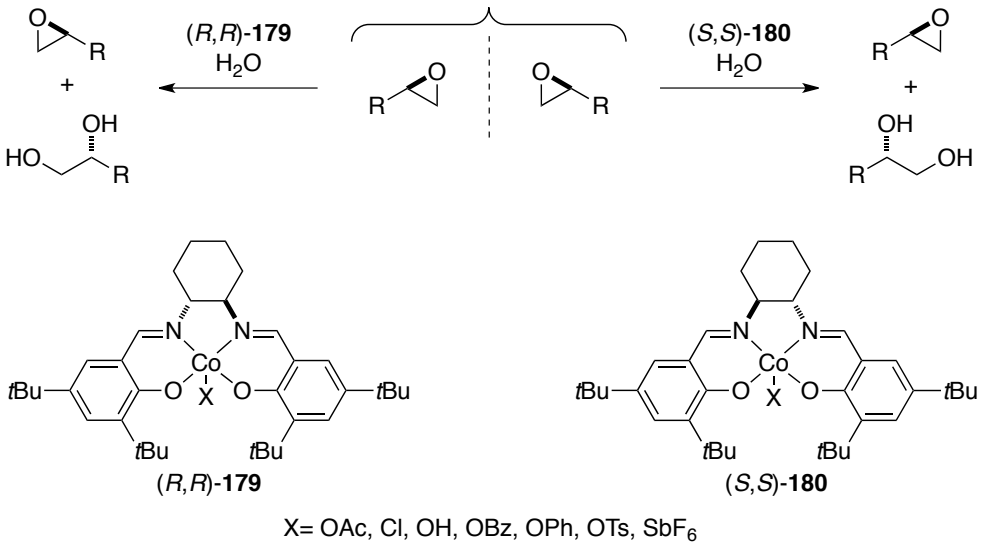


Scheme 2.15. Synthesis of alkane **178**.

Due to the difficulties encountered in the preparation of enantiopure diepoxyhexane using the synthesis reported by Kibayashi, an alternative method for its synthesis was sought.

2.3.2 Hydrolytic kinetic resolution of diepoxides

A convenient and fast way to access enantiopure terminal epoxides is made possible using the ability of chiral salen catalysts to enrich enantiopurity (**Scheme 2.16**). Jacobsen and co-workers first reported the use of salen catalysts in an highly efficient method for the synthesis of enantiopure terminal epoxides and 1,2-diols.[80-83] Jacobsen hydrolytic kinetic resolution (HKR) using either forms of the Co(III)[salen] catalyst **179** or **180** in the presence of water and acetic acid provides the most effective protocol to access enantiopure terminal epoxides and this method has found numerous applications in organic synthesis (**Figure 2.1**).



Scheme 2.16. General scheme for the HKR reaction.

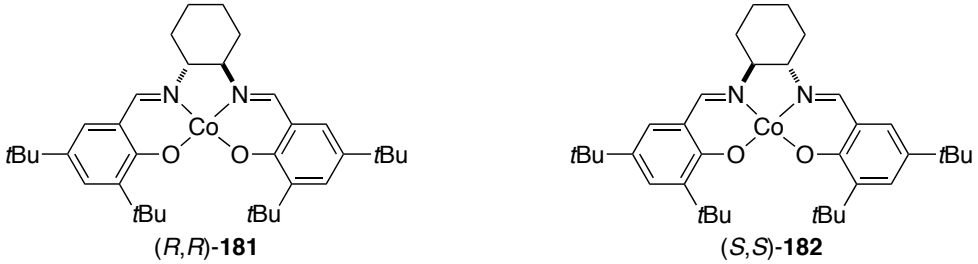
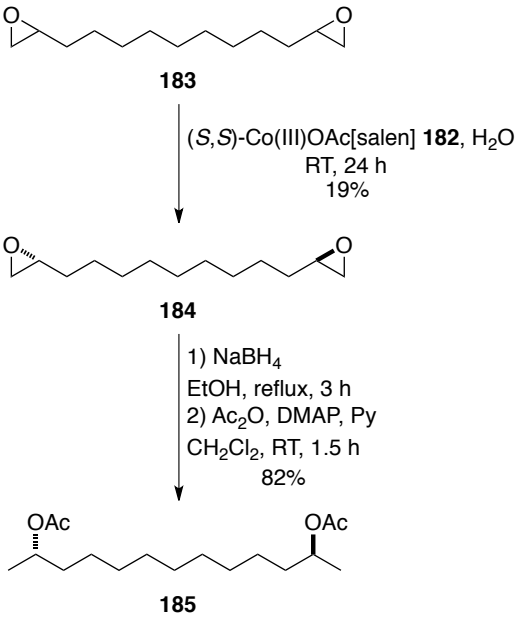


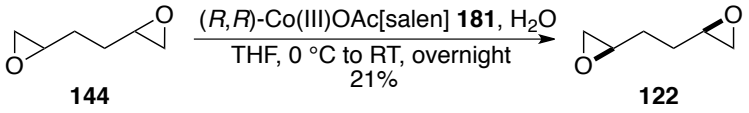
Figure 2.1. Structure of the [(*R*,*R*)-(salen)] and [(*S*,*S*)-(salen)]Co catalysts **181** and **182**.

Although the theoretical yield for the HKR of diepoxides is only 25%, the use of this method could provide access to enantiopure diepoxides in a single step from the corresponding racemic/meso compounds. The use of HKR reaction on diepoxides was first demonstrated by Kitching and co-workers (**Scheme 2.17**).[84,85] In their synthesis, racemic/ meso diepoxide **183** was treated with salen catalyst **182** to provide enantiopure diepoxide **184** in 19% yield. Treatment with sodium borohydride, followed by acetylation provided diacetate **185**, a pheromone from *Contarinia pisi*.



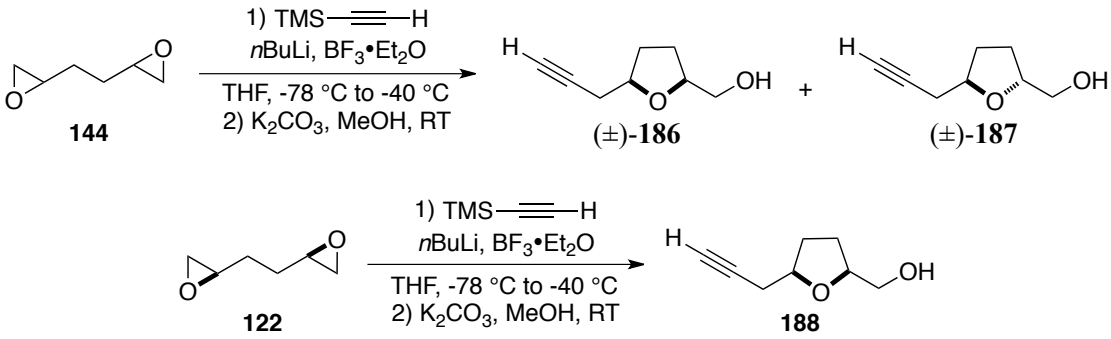
Scheme 2.17. Diepoxide HKR in the synthesis of a pheromone from *Contarinia pisi*.[84]

Racemic/meso diepoxide **144** was treated with (*R*,*R*)-Co(III)salen(OAc) complex, using a modification of conditions developed by Jamison (**Scheme 2.18**).[86] The purification of enantiopure diepoxide **122** proved to be challenging. Indeed, classical purification by column chromatography was not possible due to the low boiling point of the diepoxide. However, it was possible to obtain enantiopure (*R*,*R*)-diepoxyhexane **122** in a 21% yield after vacuum distillation. The diepoxide **122** showed a specific rotation of $[\alpha]_D^{20}$ +20.4 (*c* 1.3, $CHCl_3$), which was consistent with the value of $[\alpha]_D^{20}$ +18.5 (*c* 2.2, $CHCl_3$) reported by Kibayashi.[76] It was not possible to verify the enantiomeric excess of diepoxide by chiral HPLC as diepoxide **122** could not be detected due to its lack of chromophore. As the separation of the racemic/meso diepoxide by chiral GC was also unsuccessful, we decided to verify the enantiopurity of diepoxide **172** after derivatisation.



Scheme 2.18. Synthesis of (*R*,*R*)-diepoxyhexane by HKR reaction.

The method of choice for the derivatisation of racemic/meso diepoxide **144** and (*R*,*R*)-diepoxyhexane **122** is our one-pot addition/cyclisation protocol. Racemic meso diepoxide was treated with the lithium anion from TMS acetylene and the resulting products were treated with potassium carbonate in methanol to provide THF alcohols (±)-**186** and (±)-**187** (**Scheme 2.19**). The same protocol was applied to diepoxide **122** and provided THF alcohol **188**.



Scheme 2.19. Derivatisation of diepoxides **144** and **122**.

The result of the separation of the diastereoisomeric mixture (±)-**186** and (±)-**187** by chiral GC is presented in **Figure 2.2**. As expected, the addition-cyclisation of racemic/meso diepoxide **144** provides four distinct products, with the two *syn* products at 27.3 min and the two *trans*-THF rings at 28.5 min and 28.7 min, respectively. THF alcohol **188** was also analysed by chiral GC and, in this case, only one product is observed (**Figure 2.3**). This result and the fact that THF alcohol **188** showed a specific rotation of $[\alpha]_D^{20}$ +25.5 (*c* 1.7, $CHCl_3$) is consistent with the formation of product **188** as a single diastereoisomer. This confirms that HKR of diepoxide **144** provided (*R*,*R*)-diepoxide **122** with high level of enantioselectivity.

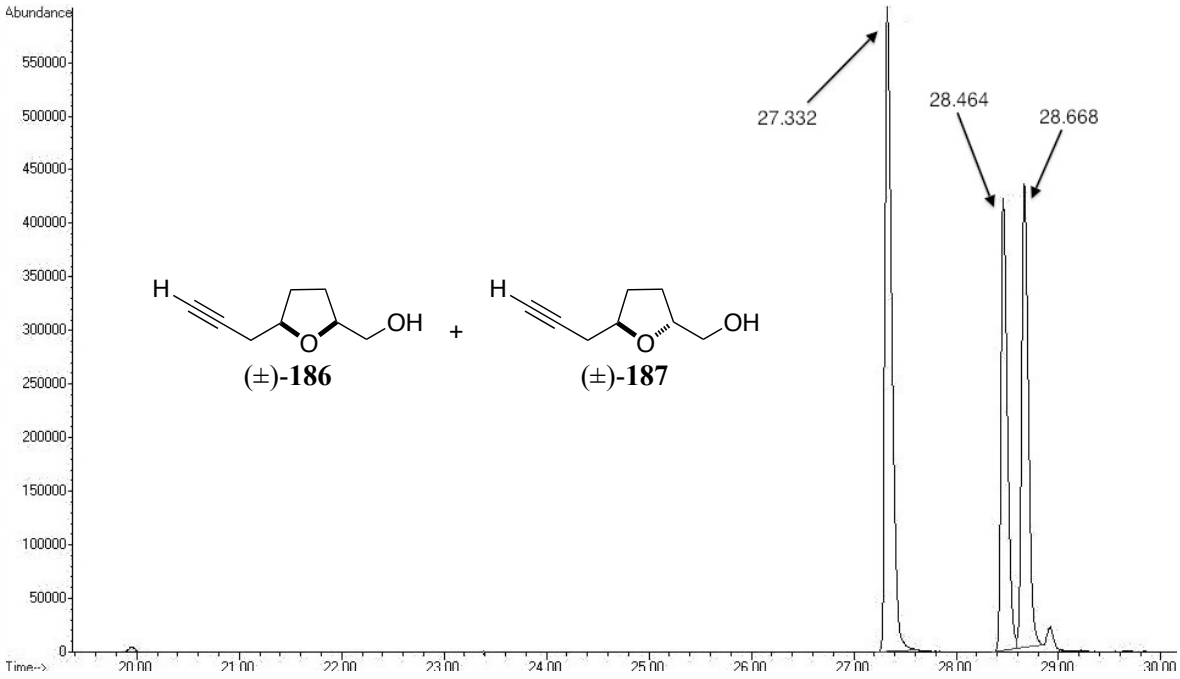


Figure 2.2. Chiral GC of THF alcohols **186** and **187**.

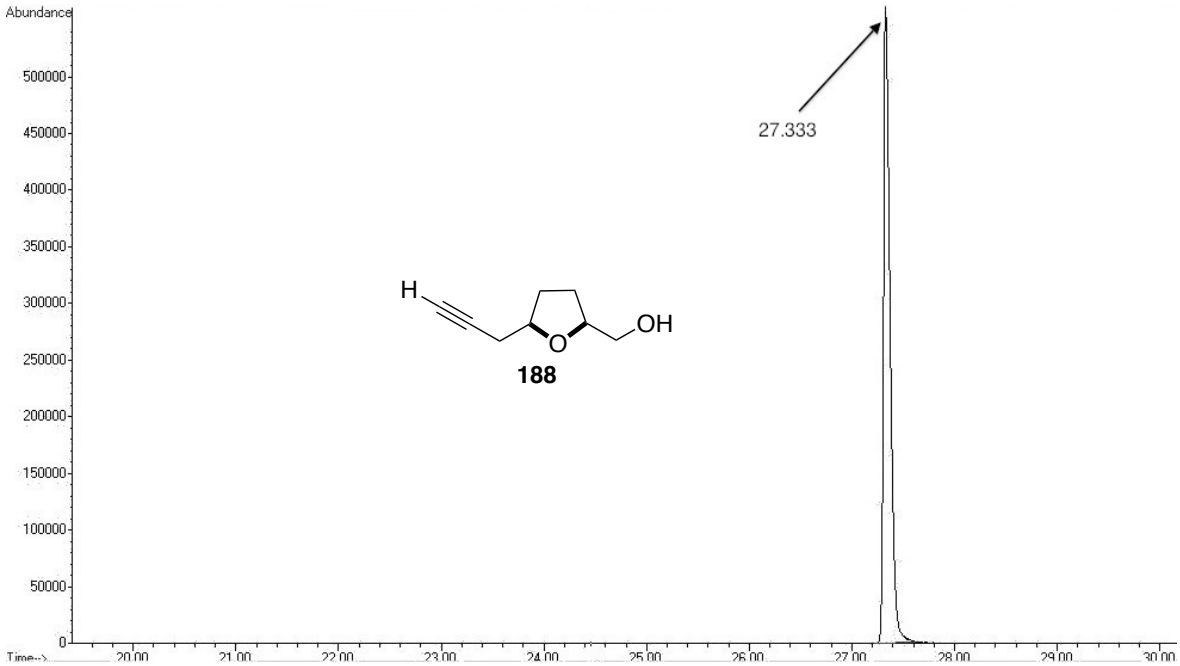
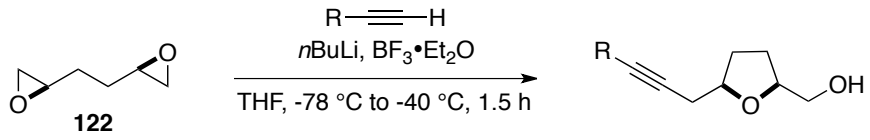


Figure 3.3. Chiral GC of THF alcohol **188**.

2.3.3 Synthesis of enantiomerically pure THF rings

With reliable access to the desired enantiopure diepoxide in hand, we turned our attention to its use in the preparation of enantiomerically pure THF alcohols and extending the scope of the domino cyclisation reaction to include alkyl and vinyllithium species. Applying the optimal conditions developed previously, the addition of the lithium anions of TMS acetylene and 1-octyne provided the 2,5-*syn* THF rings **189** and **190** as single diastereoisomers (entry 1 and 2, **Table 2.2**).



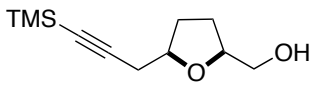
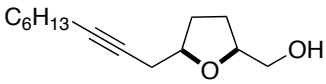
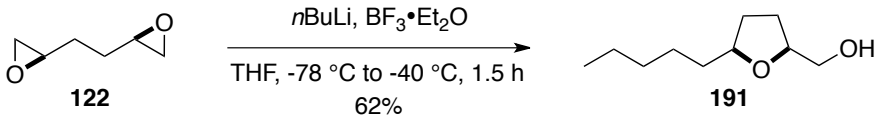
Entry	Reagent	Product	Yield (%)
1	TMS—≡	 **189**	75
2	C_6H_{13}—≡	 **190**	65

Table 2.2. Domino cyclisation of (*R*,*R*)-diepoxyhexane **122**.

In order to extend the scope of the reaction to alkyl species, *n*-butyllithium was used as a reagent in the one-pot addition/cyclisation protocol. Gratifyingly, addition of *n*-butyllithium was successful and provided 2,5-*syn*-THF ring **191** in good yield (**Scheme 2.20**).



Scheme 2.20. One-pot addition cyclisation using *n*-butyllithium.

The 2,5-*syn* relationship of the THF rings was established by NOE analysis of **191**, which showed a diagnostic NOE from H2 to H5 (**Figure 2.2**).

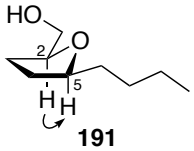
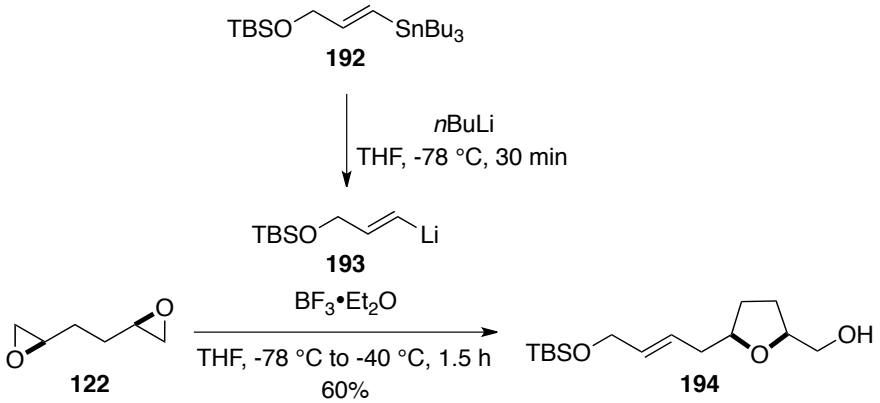


Figure 2.2. NOE analysis of THF alcohol **191**.

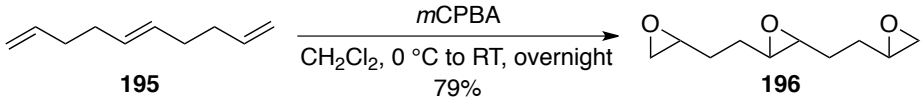
We then turned our attention to the addition of vinyllithium species. Treatment of vinyl stannane **192**[87] with *n*-butyllithium forms an intermediate vinyl lithium species **193** by tin/ lithium exchange (**Scheme 2.20**). Addition of the vinyl lithium species **193** proceeded smoothly and provided the 2,5-*syn*-THF alcohol **194** in good yield.



Scheme 2.20. Domino cyclisation using vinyl stannane **192**.

2.4 Domino cyclisations of triepoxides

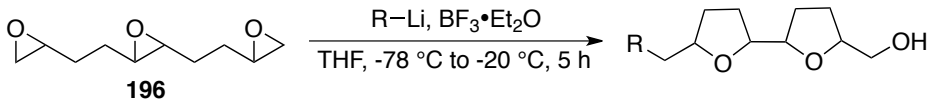
In order to further extend the scope of our domino cyclisation protocol, we turned our attention towards the use of triepoxides. Treatment of such compounds under the conditions developed previously could potentially give access to adjacently linked *bis*-THF rings in a single operation. The required triepoxide can be conveniently accessed by epoxidation of triene **195**.[88] Treatment of commercially available 1,5,9-decatriene **195** with *m*CPBA provided 1,5,9-triepoxydecane **196** as a complex mixture of diastereoisomers in a good 79% yield (**Scheme 2.21**).



Scheme 2.21. Preparation of 1,5,9-triepoxydecane **196**.

Exposure of triepoxide **196** to the optimal conditions developed for the one-pot addition/ cyclisation of diepoxides led to the degradation of the starting material. However, changing the amount of BF_3•Et_2O from 1.5 to 2 equivalents, extending the reaction time to 5 h and warming the reaction mixture to -20 °C allowed the addition/double cyclisation to occur and produced the desired *bis*-THF alcohols as a mixture of diastereoisomers. The results obtained using the addition/double cyclisation protocol are summarised in **Table 2.3**. Addition of n-butyllithium to triepoxide **196** provided *bis*-THF alcohol **197** in excellent yield (entry 1, **Table 2.3**). The addition of the lithium anions of TMS-acetylene and

1-octyne proceeded smoothly and provided the desired products **198** and **199** in yields comparable with the THF cyclisation procedure (entry 2 and 3, **Table 2.3**).



196

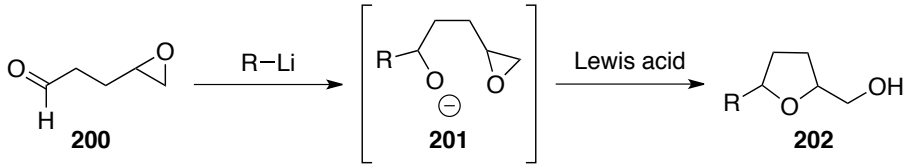
Entry	R−Li	Product	Yield (%)
1	*n*Bu	**197**	70
2	TMS—	**198**	75
3	C_6H_{13}—	**199**	59

Table 2.3. One-pot addition/cyclisation to *bis*-THF rings.

2.5 Synthesis of THF rings from epoxyaldehydes

2.5.1 One-pot addition/cyclisation of epoxyaldehydes

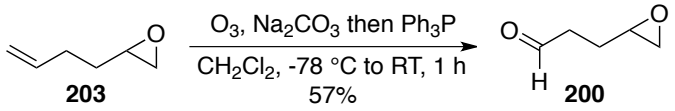
In an attempt to further extend the scope of our studies on the one-pot addition/cyclisation to THF rings, we focused on the use of epoxyaldehydes. Indeed, it can be expected that addition of a lithium species to an epoxyaldehyde **200** would first react with the aldehyde to form an intermediate alkoxide **201** (**Scheme 2.22**). The intermediate could, after addition of a Lewis acid, form the THF ring product **202** *via* a 5-*exo*-tet cyclisation.



200 **201** **202**

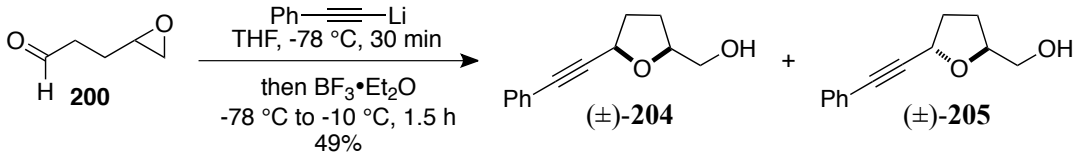
Scheme 2.22. Addition/cyclisation of an epoxyaldehyde.

Epoxyaldehyde **200** is readily accessed from the commercially available 1,2-epoxy-5-hexene **203** by ozonolysis. Treatment of alkene **203** with ozone, followed by reduction of the ozonide with triphenylphosphine provided the required epoxyaldehyde **200** in good yield (**Scheme 2.23**).



Scheme 2.23. Synthesis of epoxyaldehyde **200**.

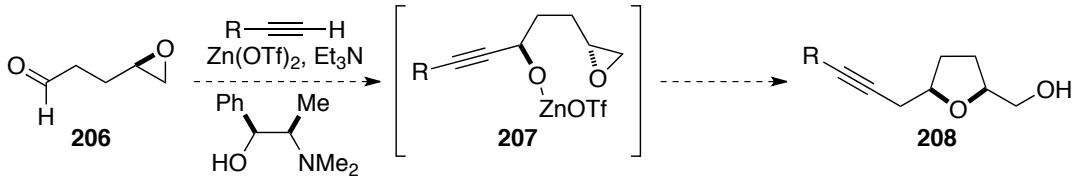
The cyclisation protocol was modified so that nucleophilic addition to epoxide would not compete with addition to the aldehyde. Thus, the lithium anion of phenyl acetylene was added to epoxyaldehyde **200** at -78 °C and after 30 min BF_3•Et_2O was added and the reaction mixture warmed to -10 °C over 1.5 h to facilitate the cyclisation. Gratifyingly, this modified protocol was successful and provided the desired THF alcohol **204** and **205** as a mixture of diastereoisomers in 49% yield (**Scheme 2.24**).



Scheme 2.24. One-pot addition cyclisation of epoxyaldehyde **200**.

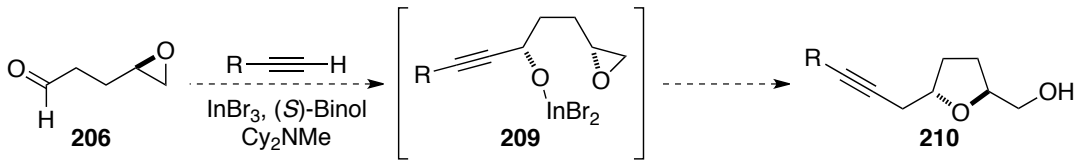
2.5.2 Future work

Extension of the one-pot addition/cyclisation to epoxyaldehydes protocol will provide access to more diverse structures. Indeed, application of a diastereoselective addition to an aldehyde coupled with a one-pot cyclisation on an enantiopure epoxide would allow to access either 2,5-*syn* or 2,5-*anti*-THF rings. The required enantiopure epoxyaldehyde **206**, could be readily accessed by Jacobsen HKR of the commercially available epoxyalkene **203**, followed by ozonolysis. Diastereoselective alkyne addition to epoxyaldehyde **206** using Carreira's conditions would provide intermediate alkoxide **207** (**Scheme 2.25**). The Lewis acidic character of $Zn(OTf)_2$ could then facilitate the 5-*exo*-tet cyclisation and provide 2,5-*syn*-THF ring **208**.[89]



Scheme 2.25. One-pot addition/cyclisation to 2,5-*syn*-THF rings.

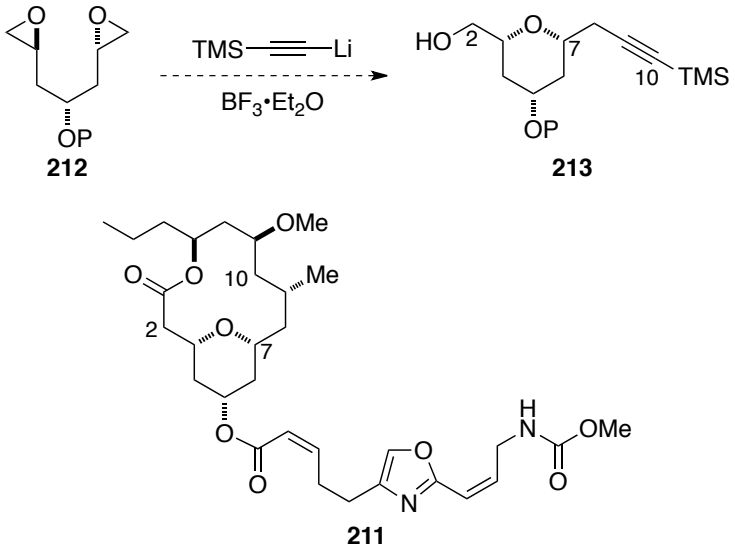
Similarly, a diastereoselective addition using Shibasaki's In(III)/Binol protocol could provide intermediate **209** and the Lewis acidic character of indium(III) bromide should trigger the cyclisation to provide the 2,5-*trans*-THF ring **210** (**Scheme 2.26**).[90]



Scheme 2.26. One-pot addition/cyclisation to 2,5-*anti*-THF rings.

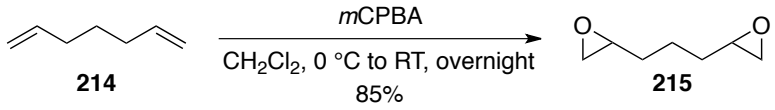
2.6 One-pot addition/cyclisation to THP rings

Having developed a practical method for the one-pot cyclisation of diepoxides to THF alcohols, we turned our attention to the synthesis of THP rings. This method would then be applied to the synthesis of the C2-C10 fragment of neopeltolide **211** (*vide supra*). Alkyne addition on diepoxide **212**, followed by BF_3•Et_2O mediated cyclisation would provide a convenient access to C2-C10 fragment **213** of the marine macrolide neopeltolide (**Scheme 2.27**).



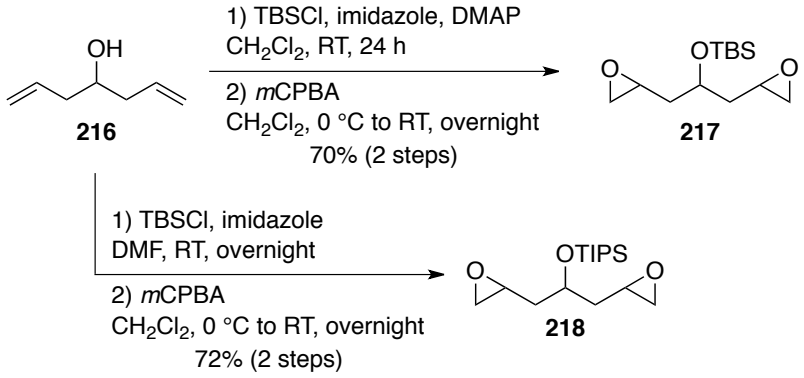
Scheme 2.27. Proposed synthesis of neopeltolide C2-C10 fragment.

In order to investigate the cyclisation of diepoxides to THP rings, we first required a practical access to heptane derived diepoxides. 1,6-Diepoxyheptane can be conveniently accessed by epoxidation of the commercially available diene **214** (**Scheme 2.28**). Treatment of 1,6-heptadiene **214** with *m*CPBA provides the required racemic/meso diepoxide **215** in excellent yield.[91]



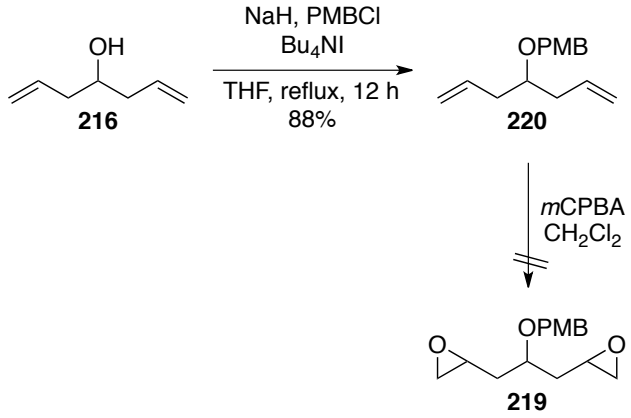
Scheme 2.28. Preparation of 1,6-diepoxyheptane **215**.

In addition to diepoxyheptane **215**, the preparation of diepoxides bearing a protected hydroxyl group was also required. Commercially available 1,6-heptadien-4-ol **216** was protected with a TBS group[92] and was then epoxidised with *m*CPBA to provide racemic/ meso diepoxide **217** in a good yield over the two steps (**Scheme 2.29**). Protection using TIPSCl, followed by epoxidation provided racemic/meso diepoxide **218** in a 72% yield over the two steps.



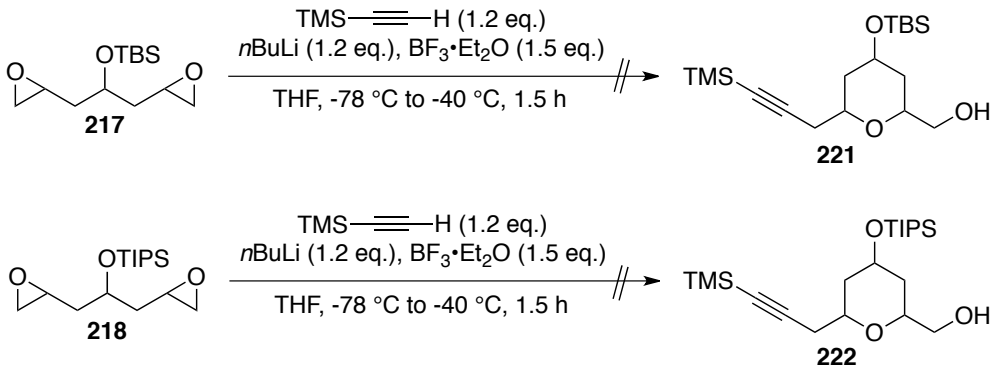
Scheme 2.29. Synthesis of protected diepoxides **217** and **218**.

The synthesis of PMB protected diepoxide **219** was also attempted. 1,6-heptadien-4-ol was first protected using sodium hydride, tetrabutylammonium iodide and PMBCl (**Scheme 2.30**).[93] The PMB protected diene **220** was obtained in excellent yield and was treated with *m*CPBA. Unfortunately, the epoxidation was not successful and the degradation of the starting material was observed.



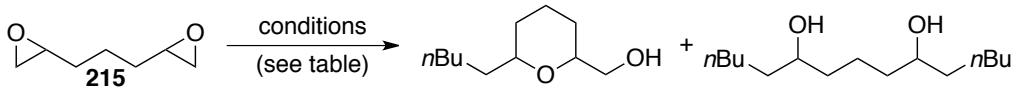
Scheme 2.30. Synthesis of PMB protected diepoxide **219**.

Having prepared the diepoxides, the synthesis of THP rings was attempted. Unfortunately, treatment of diepoxides **217** and **218** with the lithium anion of TMS acetylene under the optimal conditions developed for the addition/cyclisation of THF rings did not lead to the formation of THP alcohols **221** and **222** and the degradation of the starting diepoxides was observed (**Scheme 2.30**).



Scheme 2.31. One-pot addition/cyclisation attempt using diepoxides **217** and **218**.

Facing this unexpected problem, we decided to investigate modifications of the one-pot addition/cyclisation conditions on the more easily accessible 1,6-diepoxyheptane **215**. The results obtained are summarised in **Table 2.4**. Treatment of diepoxide **215** with *n*-butyllithium under our optimal conditions resulted in the degradation of the starting material (entry 1, **Table 2.4**). Degradation of the starting diepoxide **215** was also observed when the solvent was changed to DME (entries 2, **Table 2.4**). Increasing the quantity of both *n*-butyllithium and BF_3•Et_2O to two equivalents resulted in a double-opening reaction (entry 3, **Table 2.4**). Changing the Lewis acid to BH_3•THF also proved unsuccessful and the degradation of the starting material was observed (entry 4, **Table 2.4**). Treatment of diepoxide **215** with *n*-butyllithium, BF_3•Et_2O and HMPA resulted in a double-opening reaction (entry 5, **Table 2.4**). Baldwin's rules predict that 6-*exo*-tet cyclisations are favoured but these processes are slower than the corresponding 5-*exo*-tet cyclisations. The 6-*exo*-tet cyclisation therefore competes with the nucleophilic opening of the second epoxide and with the degradation of the epoxide due to the strong Lewis acidic character of BF_3•Et_2O.



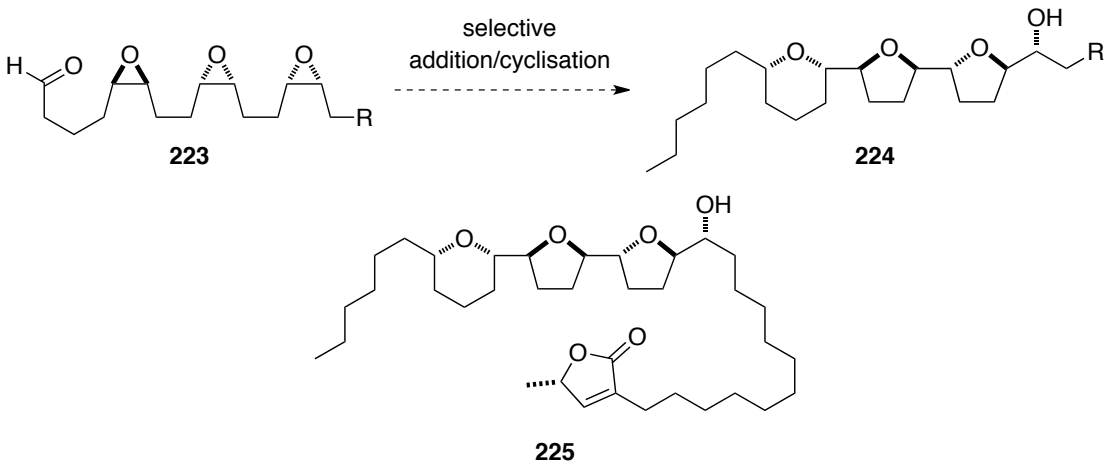
Entry	Conditions	Results
1	*n*BuLi (1.2 eq.), BF_3•Et_2O (1.5 eq.) THF, -78 °C to -40 °C, 1.5 h	degradation
2	*n*BuLi (1.2 eq.), BF_3•Et_2O (1.5 eq.) DME, -78 °C to -20 °C, 2 h	degradation
3	*n*BuLi (2 eq.), BF_3•Et_2O (2 eq.) THF, -78 °C to -40 °C, 1.5 h	double-addition
4	*n*BuLi (1.2 eq.), BF_3•THF (1.5 eq.) THF, -78 °C to -20 °C, 2 h	degradation
5	*n*BuLi (1.2 eq.), BF_3•Et_2O (1.5 eq.), HMPA (1.5 eq.) THF, -78 °C to RT, 3 h	double-addition

Table 2.4. Conditions for the addition/cyclisation attempts on diepoxide **215**.

2.7 Conclusion and future work

In conclusion, a practical one-pot addition/cyclisation method to form THF rings from diepoxyhexane **144** has been developed. Addition of alkyl, alkenyl and alkynyl species to the enantiopure (*R*,*R*)-diepoxyhexane **122** using the optimal conditions developed provided access to 2,5-*syn*-THF alcohols. This protocol was then extended to the one-pot addition/ double cyclisation of triepoxide **196** to *bis*-THF rings. In a further extension of this protocol, we prepared THF alcohols by the one-pot addition/cyclisation of epoxyaldehydes. The synthesis of THP rings from diepoxyheptane **215** was investigated but our efforts were unsuccessful.

As outlined previously, the addition/cyclisation of epoxyaldehydes could be extended to prepare 2,5-*syn* and 2,5-*anti*-THF alcohols from enantiopure epoxyaldehydes (see **section 2.5.2**, **Scheme 2.26 and 2.27**). An ambitious extension of this methodology would be to apply it in complex polyepoxide cyclisations. For example, selective addition on triepoxyaldehyde **223**, followed by *in situ* cyclisation would provide the BCD ring system **224** of the annonaceous acetogenin chamuvarinin **225** (**Scheme 2.31**).



Scheme 2.31. Proposed synthesis of chamuvarinin BCD ring system.

Part Two:

Synthetic Studies Towards Neopeltolide

Chapter Three

Introduction

3.1 Isolation

In 1997, Wright and co-workers reported the isolation of neopeltolide **226** (**Figure 3.1**) from a deep-water sponge of the family neopeltidae off the north coast of Jamaica.[94] The structure, which was established by NMR and HRMS, contains a 14-membered macrolactone, a trisubstituted *cis*-THP ring bearing an unsaturated oxazole side-chain at C5. Careful analysis of coupling constants, as well as COSY, TOCSY and NOESY experiments showed that the protons at H3, H7, H9, H11 and H13 were all on the same side of the macrolide ring. The absolute stereochemistry was not assigned due to lack of material but it was hypothesised that the C9, C11 and C13 substituents would adopt *pseudo*-equatorial positions around the macrolactone. Inspection of the macrocyclic ring reveals several 1,3-hydroxyl motifs consistent with its polyketide origin. However, the C9 methyl displays a variant to the common polyketide biosynthesis pattern. Indeed, the methyl is not found at a propionate position but at a former keto position.

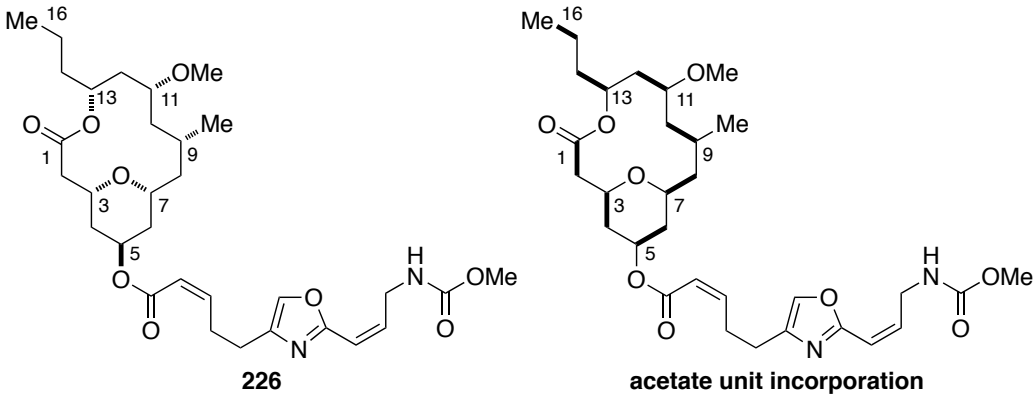


Figure 3.1. Structure of neopeltolide proposed by Wright *et al*.[94]

3.2 Related marine macrolides

Lithistid sponges are a valuable source of a wide range of secondary metabolites with important biological activities. Amongst the different families found in the taxonomic classification, the *Corallistidae* family includes includes sponges of the genera *Callipelta*, from which the macrolide callipeltoside A **227** was isolated (**Figure 3.2**).[95] It displays a 14-membered macrolactone similar to the one found in neopeltolide **226**. An important structural difference between them is the C3 hemiketal functionality in callipeltoside A **227** which is reduced in the case of neopeltolide **226**.

It is believed that the biogenetic origin of callipeltoside A **227** is cyanobacterial. Indeed, the existence of macrolides such as lyngbyaloside B **228** which are produced by cyanobacterias support this hypothesis.[96] Another closely related cyanobacterial macrolide is auriside A **228** that was isolated from the sea hare *Dolabella auricularia*.[97] It features a 14-membered macrolactone with an hemi-ketal functionality. The 18-membered macrolactone of the secondary metabolite leucascandrolide A **109** is also closely related

with neopeltolide.[98] The two marine macrolides share important structural features including a trisubstituted THP ring and an identical oxazole side-chain.

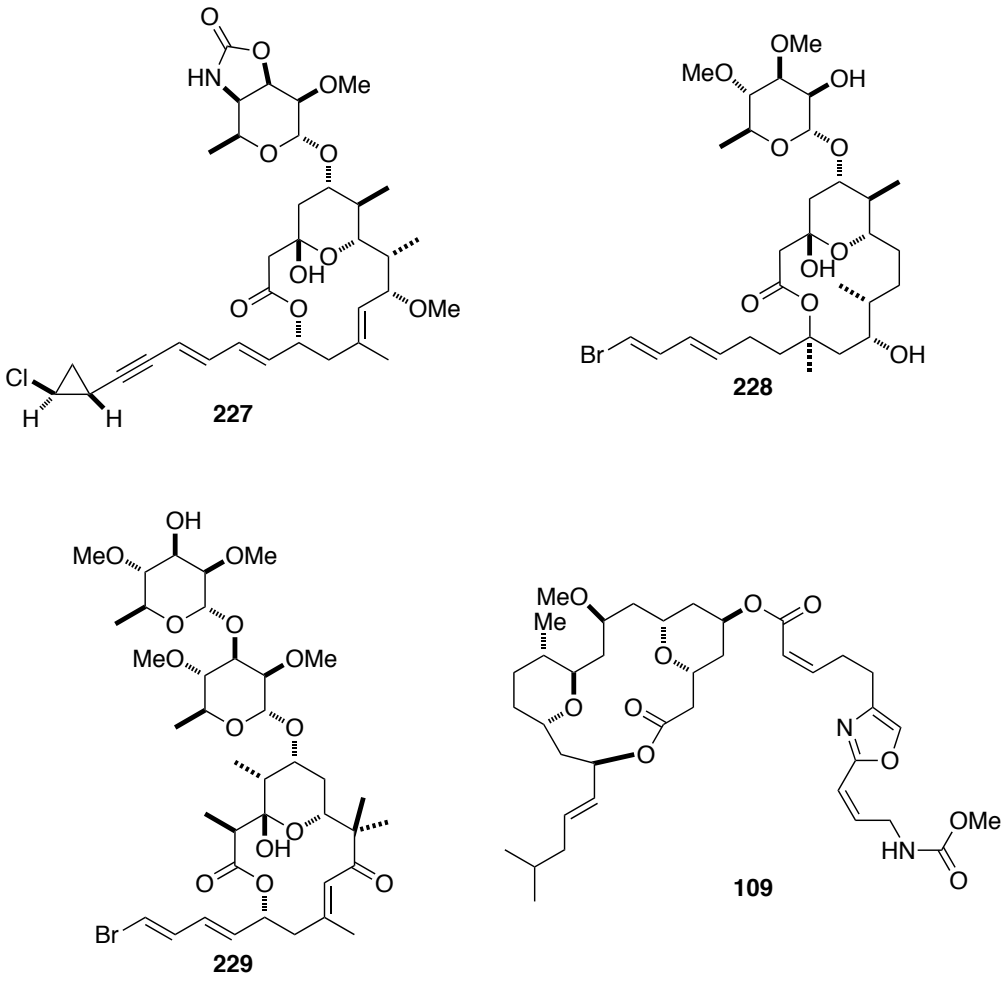


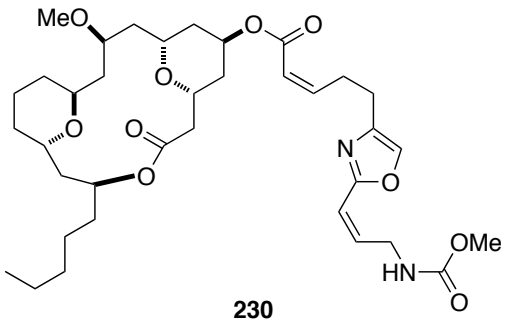
Figure 3.2. Marine macrolides related to neopeltolide.[95-98]

3.3 Biological activity

Wright and co-workers reported that neopeltolide **226** displayed antifungal activity against the pathogen *Candida albicans* at a concentration of 0.625 μg/mL. Neopeltolide also proved to be a potent inhibitor of cancer cell proliferation. Wright and co-workers tested this compound on several cancer cell lines and reported the following IC_{50} values: 1.2 nM

against the A549 human lung adenocarcinoma, 5.1 nM against the NCI/ADR-RES ovarian sarcoma and 0.56 nM against the P388 murine leukemia.[94]

In 2008, Kozmin and co-workers reported their work on the identification of the cellular target of leucascandrolide A **109** and neopeltolide **226**.[99] They hypothesised that the two macrolides inhibit cell proliferation by a similar mechanism, on the basis of their structural resemblance. Their work started with the evaluation of both enantiomers of leucascandrolide A in different cancer cell lines and in *S. cerevisiae*. This showed that the unnatural isomer displays similar potency to the natural (+)-leucascandrolide A and that the oxazole side-chain is probably responsible for the biological activity. Following this observation, they synthesised a simplified analogue of leucascandrolide A **230** (**Figure 3.3**). They used this compound in the screening of 4900 yeast strains with different haploid nonessential gene deletions and they observed the growth inhibition by monitoring the optical density of the culture medium.



230

Figure 3.3. Kozmin *et al.* simplified structure of leucascandrolide A.[99]

One of the most sensitive strains lacked the SNF4 gene, a key regulator of glucose metabolism, that encodes for a subunit that senses the AMP/ATP ratio. Kozmin then hypothesised that the two macrolides interfere with mitochondrial oxidative phosphorylation.[99,100] This was supported by experiments using isolated mitochondria and purified enzyme from bovine heart which established that the cytochrome complex bc_1 is the molecular target of leucascandrolide A **109** and neopeltolide **226**.

3.4 Selected syntheses of neopeltolide

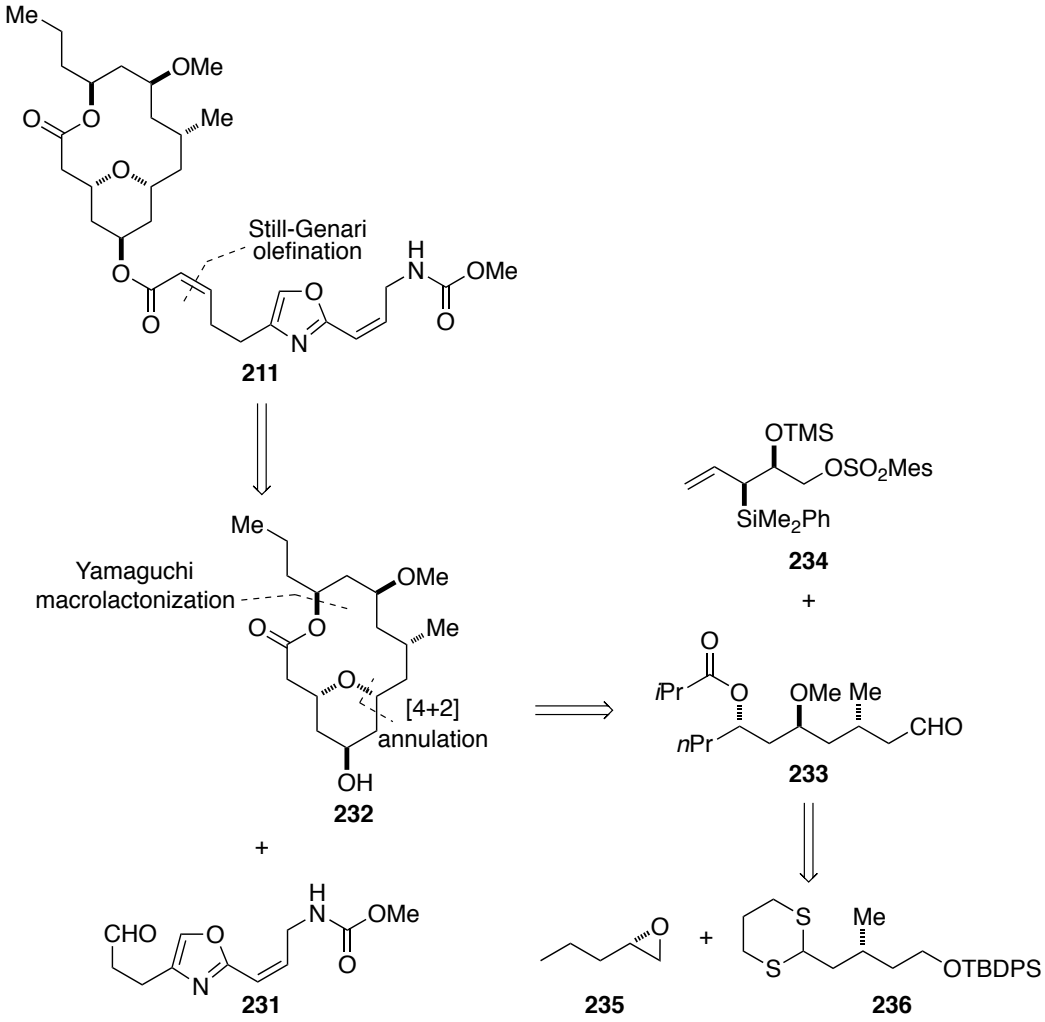
Since its isolation by Wright and co-workers, neopeltolide attracted wide interest from the synthetic community and this resulted in several total synthesis of the macrolide.[99,101-111] This section will describe notable examples of neopeltolide total synthesis.

3.4.1 Panek's synthesis and reassignment

Panek and co-workers first focused on the synthesis of the structure reported in the isolation paper. However, the final compound showed significant differences in both ^{1}H and ^{13}C NMR, which suggested that neopeltolide was possibly miss-assigned. After synthesis of a set of diastereoisomers, they were able to reassign C11 and C13 stereocentres and to establish the absolute stereochemistry of neopeltolide, as shown in **Scheme 3.1**.[101]

Their retrosynthetic strategy relied on the attachment of the oxazole side-chain **231** to the aglycon **232** *via* a Still-Gennari HWE olefination using chemistry developed during their

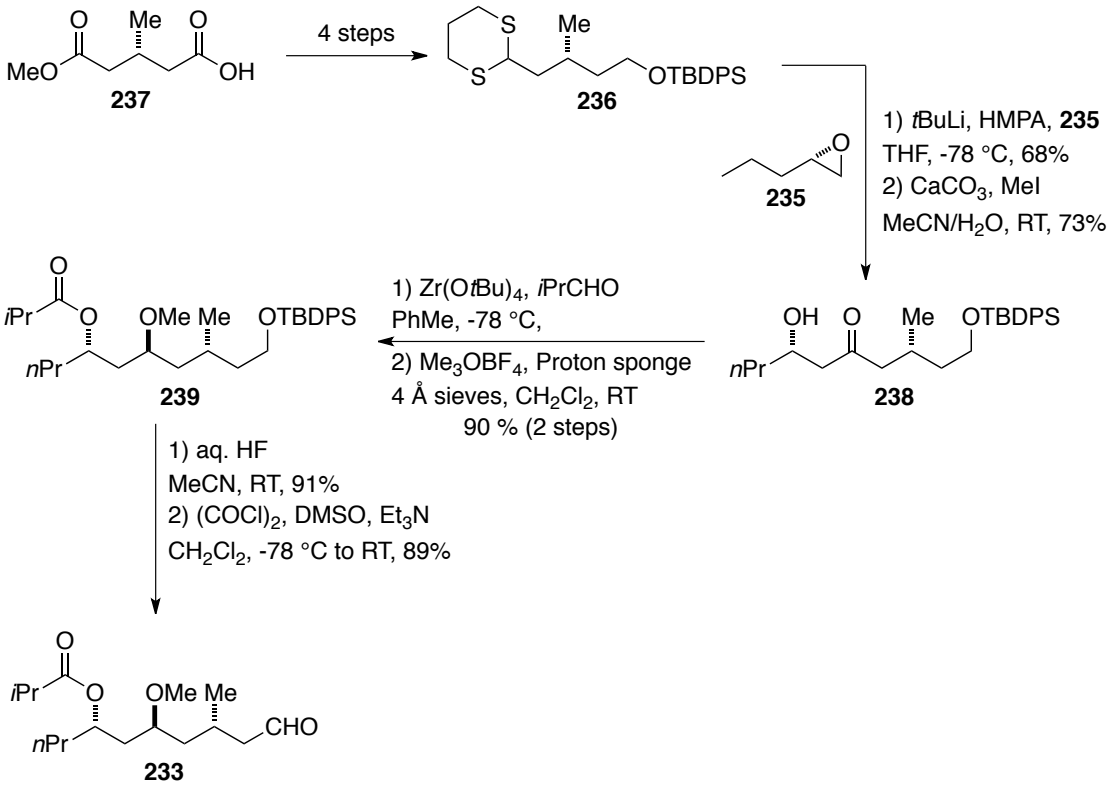
synthesis of leucascandrolide A (**Scheme 3.1**).[112] Yamaguchi macrolactonization[113] would allow the formation of the macrocycle while the THP ring would be formed *via* a [4+2] annulation between aldehyde **233** and allylsilane **234.** The C7-C16 fragment was envisioned to arise from the coupling of **233** and dithiane **234**.



Scheme 3.1. Panek's retrosynthetic strategy.[101]

The synthesis of dithiane **236** required four steps starting from (*R*)-methylglutarate **237** (**Scheme 3.2**). The dithiane **236** was then coupled with epoxide **235** using *t*BuLi and HMPA. The dithioacetal was then deprotected and ketone **238** was obtained in 50% yield

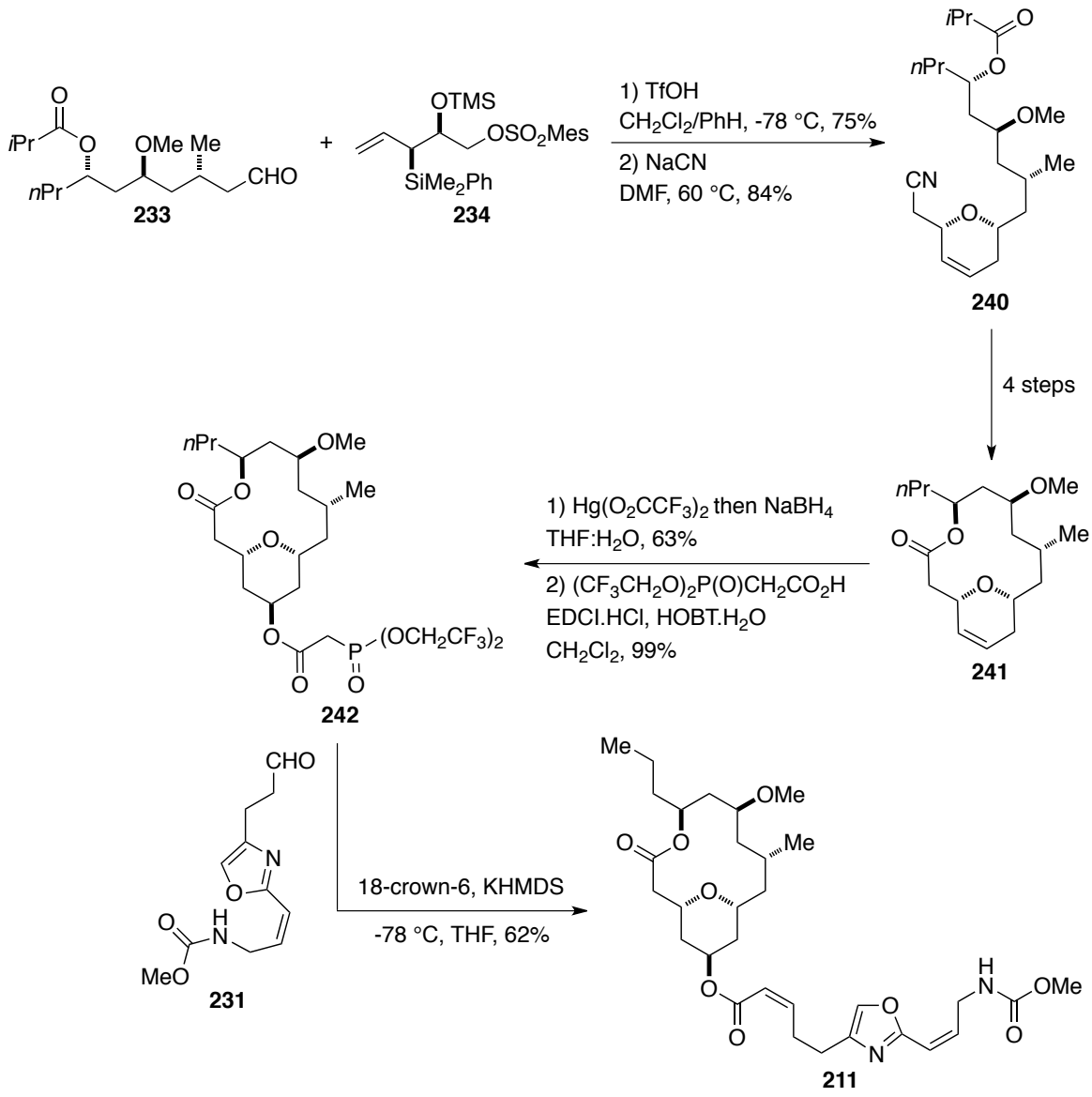
over the two steps. The *anti* relationship between C11 and C13 was installed *via* a modified Evans-Tischenko reduction. During the same step, the C13 alcohol is concomitantly protected as its *iso*butyrate ester, allowing the formation of the C11 methyl ether **237** using Meerwein's salt. After deprotection of the primary silyl ether and Swern oxidation, the C7-C16 fragment **231** was obtained.



Scheme 3.2. C7-C16 fragment synthesis.[101]

Coupling of aldehyde **233** with allylsilane **234** in presence of triflic acid provided dihydropyran with good yield and selectivity (75%, d.r. 10:1) (**Scheme 3.3**). The sulfonate group was then displaced with sodium cyanide to provide intermediate **240** in 84% yield, which was transformed into the macrolactone **241** in a further 4 steps. The C5 stereocentre

was formed by selective oxymercuration. The desired alcohol was obtained as single isomer which was then acylated using bis-(2,2,2-trifluoroethyl)phosphonoacetic acid and provided ketophosphonate **242** in a 99% yield. Treatment of ketophosphonate **242** with KHMDS, followed by addition of the aldehyde **231** provided (*Z*)-olefin in 62% yield and completed the synthesis of neopeltolide **211**.

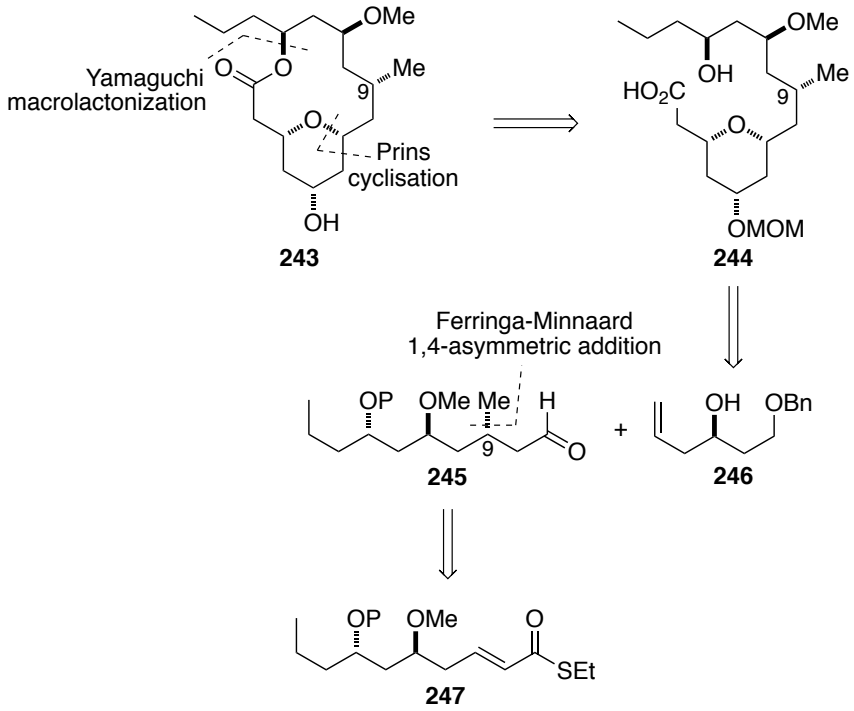


Scheme 3.3. Completion of neopeltolide synthesis.[101]

In summary, Panek and co-workers completed the first total synthesis of neopeltolide in 1.3% overall yield with nineteen steps in its longest linear sequence. During this synthesis, C11 and C13 stereocentres were reassigned and the absolute stereochemistry of neopeltolide was determined.

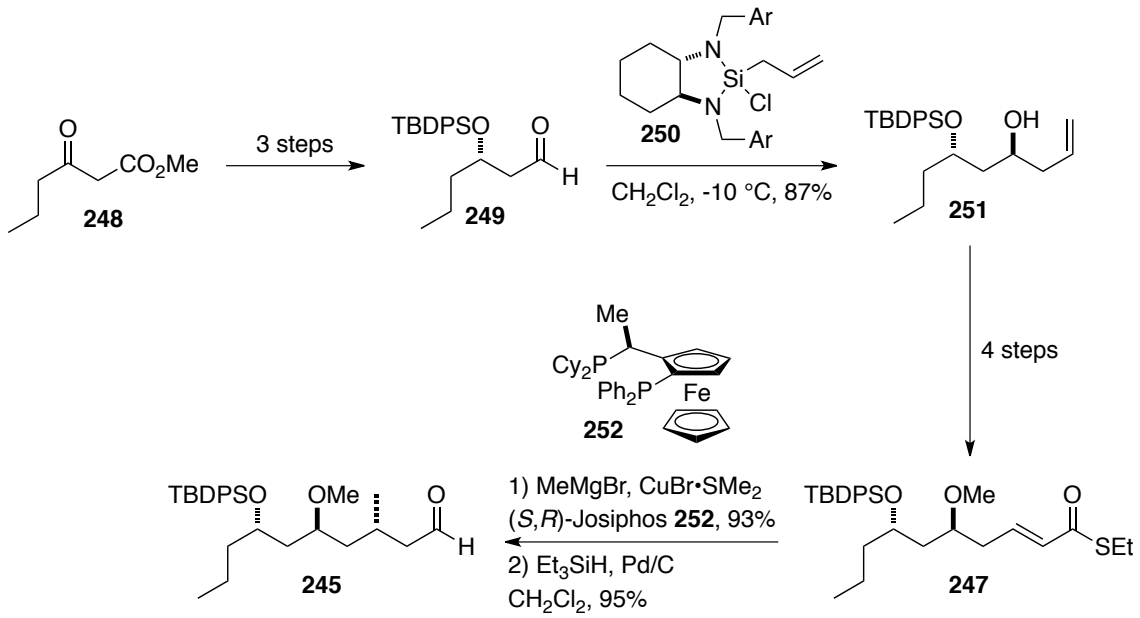
3.4.2 Maier's synthesis

In 2008, Maier and co-workers published a formal total synthesis of neopeltolide.[103] Later that year, they reported the total synthesis of the marine macrolide along with several analogues. Their synthetic strategy uses disconnections that have been employed in several other approaches to neopeltolide. The macrolide **243** would be formed by a Yamaguchi macrolactonisation from carboxylic acid **244**, while the THP ring would be obtained *via* a Prins cyclisation between aldehyde **245** and homoallylic alcohol **246** (**Scheme 3.4**). The C9 stereocentre would be introduced using a Ferringa-Minnaard 1,4-asymmetric methyl addition on α,β-unsaturated thioester **247**.



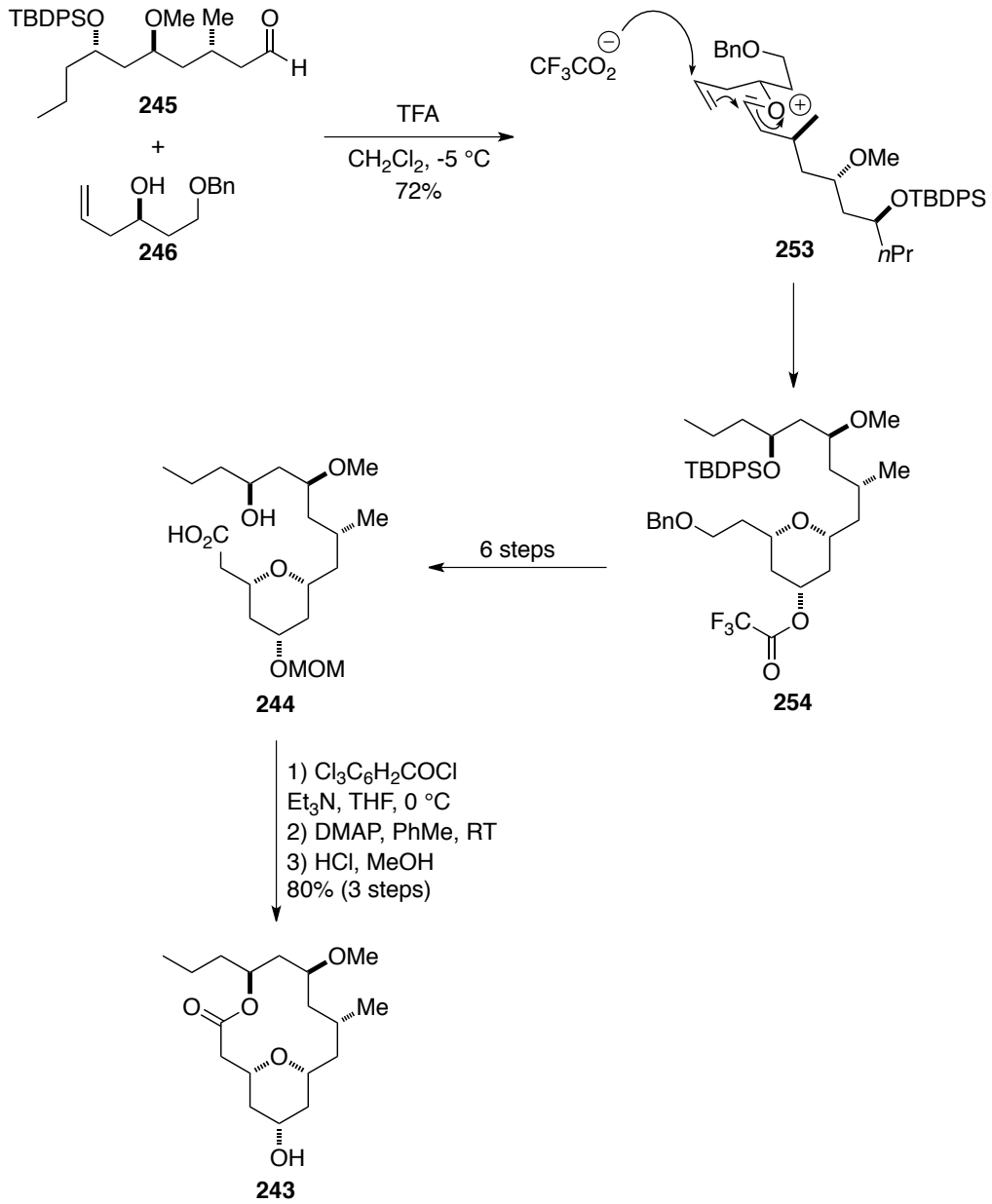
Scheme 3.4. Maier's approach to neopeltolide aglycon.[103]

The synthesis of aldehyde **245** started from ketoester **248**, which was converted to aldehyde **249** in three steps (**Scheme 3.5**). Leighton allylation with allylsilane **250** provided homallylic alcohol **251**, which was transformed into the thioester **247** in four further steps. In the presence of methylmagnesium bromide, copper bromide dimethyl sulphide complex and (*S*,*R*)-Josiphos **252**, conjugate addition took place to introduce the C9 stereocentre selectively. Reduction of the thioester with triethylsilane and Pd/C provided aldehyde **245**.



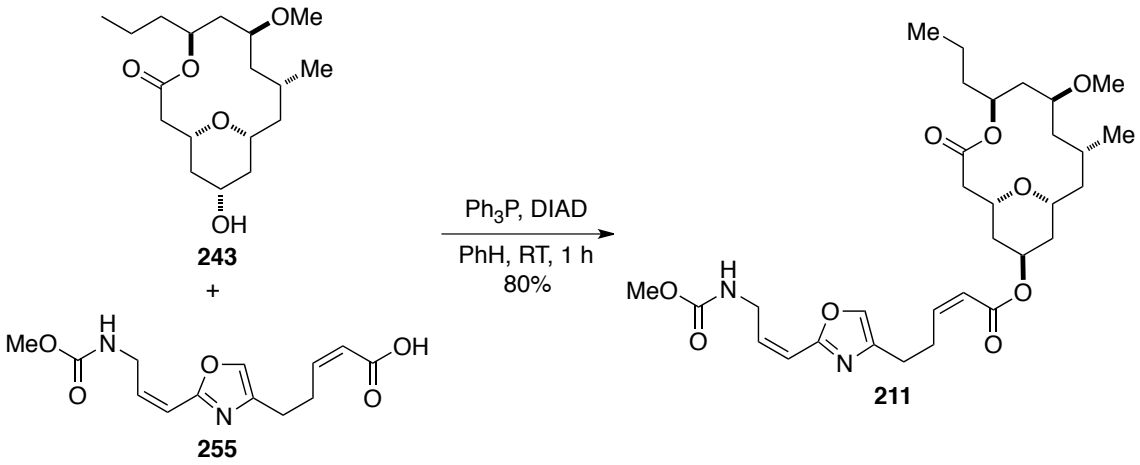
Scheme 3.5. Synthesis of aldehyde **245**.[103]

Prins cyclisation of aldehyde **245** and homoallylic alcohol **246** in the presence of trifluoroacetic acid proceeded *via* transition state **253** to provide THP ring **254** in 72% yield (**Scheme 3.6**). Six steps were then required to transform compound **254** into carboxylic acid **244**. Under the classical Yamaguchi conditions,[113] the macrocycle was formed and after deprotection of the methoxymethyl (MOM) ether group, neopeltolide aglycon **243** was obtained. The longest linear sequence was 17 steps and it provided the final product in 23% overall yield.



Scheme 3.6. Completion of neopeltolide aglycon.[104]

Mitsunobu esterification between aglycon **243** and oxazole sidechain **255** provided neopeltolide **211** in excellent yield (**Scheme 3.7**).[104]



Scheme 3.7. Completion of neopeltolide synthesis.[104]

Maier and co-workers also prepared four analogues of the oxazole sidechain and used the aglycon as a platform to prepare a series of neopeltolide analogues (**Figure 3.4**).

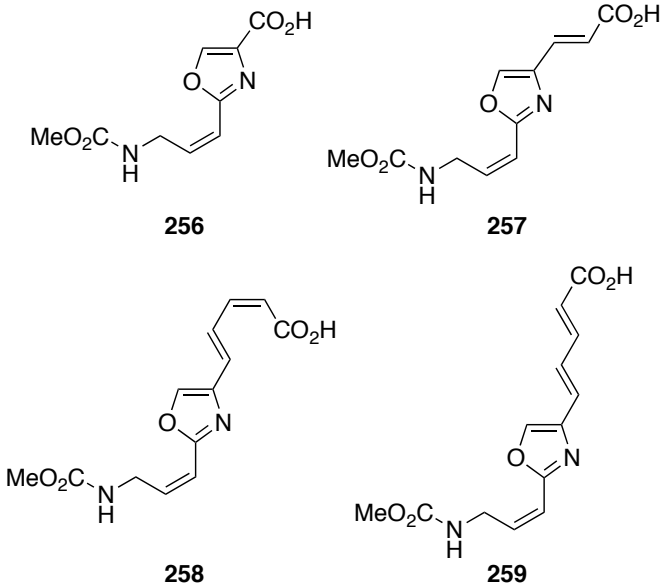
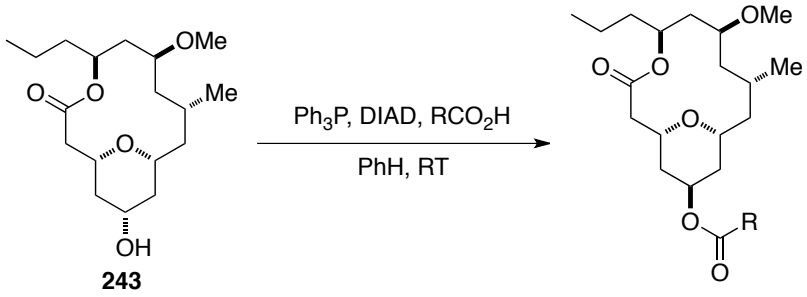


Figure 3.4. Neopeltolide analogues sidechains.[104]

Coupling of the different sidechains with aglycon **243** was achieved under Mitsunobu conditions. This provided compounds **260**-**263** which were tested against L929 mouse fibroblasts and the results are presented in **Table 3.1**. The IC_{50} obtained shows that the distance of the oxazole side-chain to the macrocyclic ring is crucial for biological activity. Indeed, analogue **260** and **261** which both have a very short distance to the macrolactone are almost inactive (entry 2 and 3, **Table 3.1**). However, the analogue **262** containing a *Z*,*E* diene (entry 4, **Table 3.1**) is more active than neopeltolide itself, while the *E*,*E* is eight times less active (entry 5, **Table 3.1**).



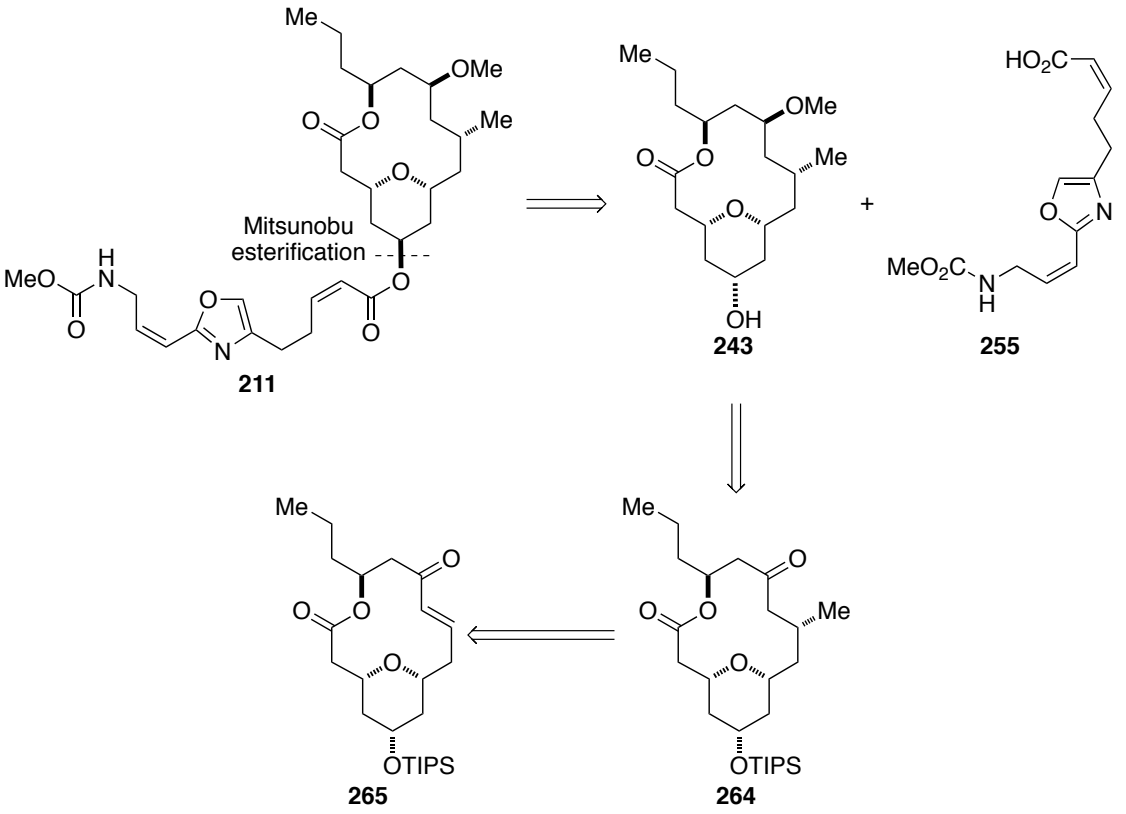
243

Entry	Acid	Product	IC_{50} L929 (nM)
1	**255**	**211**	0.25
2	**256**	**260**	4500
3	**257**	**261**	1120
4	**258**	**262**	0.25
5	**259**	**263**	2.0

Table 3.1. Biological activity of neopeltolide **211** and analogues.[104]

3.5 Synthetic strategy

This section will describe our synthetic strategy toward the total synthesis of neopeltolide **211** (**Scheme 3.8**). The unsaturated oxazole side-chain would be introduced at late stage of the synthesis by Mitsunobu esterification. This logical disconnection has been successfully exploited in several total syntheses, led back to carboxylic acid sidechain **255** and fully elaborated aglycon **243**. As opposed to the previous syntheses of neopeltolide, that relied on the introduction of all the stereocentres before formation of the macrolactone, we envisaged to introduce both C9 and C11 stereocentres using the macrocycle conformation. In the first instance, methyl ether **243** could be obtained by reduction ketone **264**, followed by methylation. Similarly, the methyl at C9 could be introduced by 1,4 addition on enone **265**.



Scheme 3.8. Retrosynthetic strategy for neopeltolide macrolactone **265**.

Molecular modeling was used to obtain the low energy conformations of ketone **264** and enone **265**.[114] This was performed on a structure where the C13 *n*-propyl group was replaced by a methyl and the TIPS ether was replaced by a SiH_3 group. The low energy conformations obtained are presented in **Figure 3.5**. This shows that methyl 1,4-addition should occur from the less hindered *re* face of the enone **265** and that addition of the hydride on ketone **264** should occur from the more accessible *re* face.

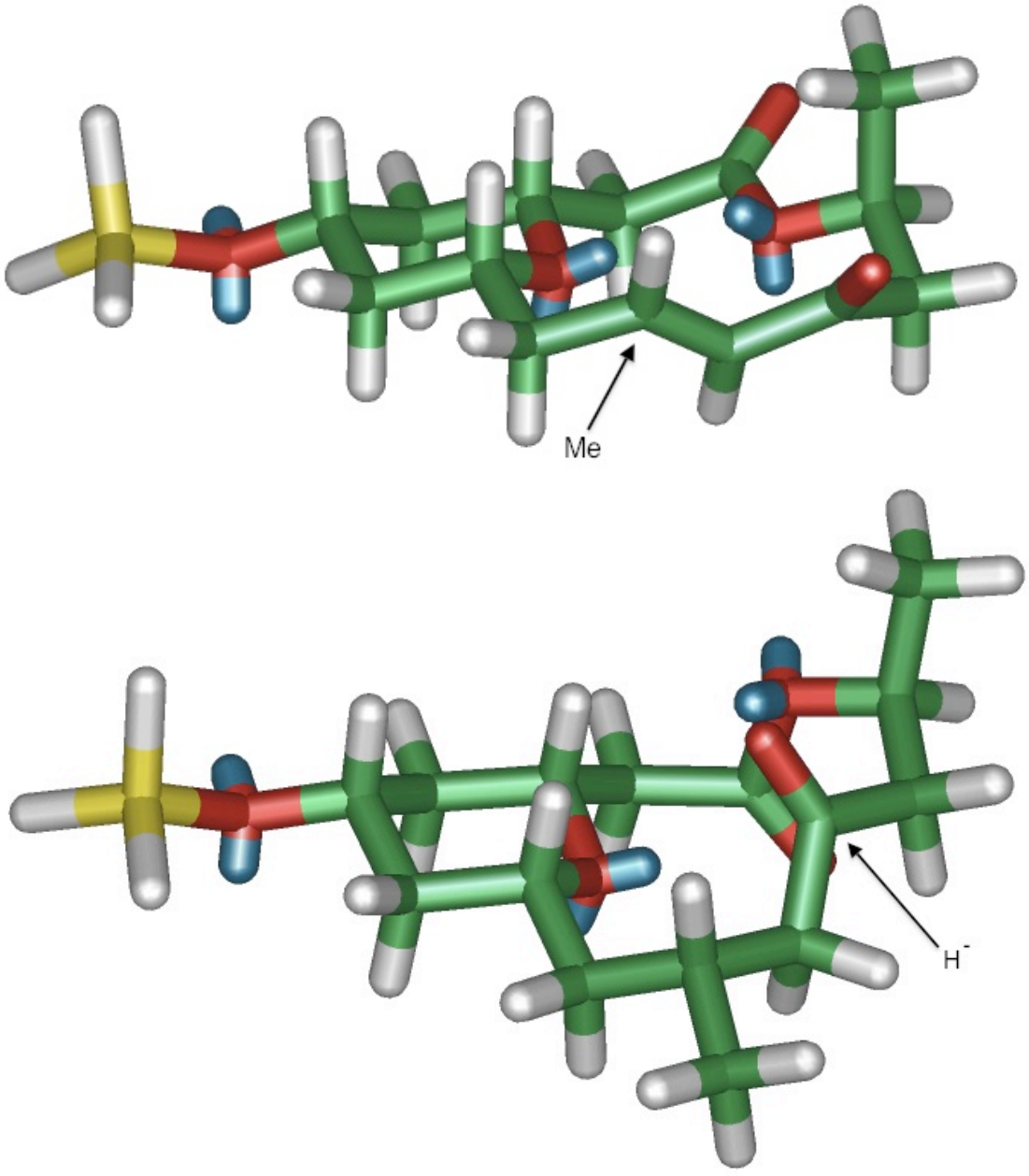
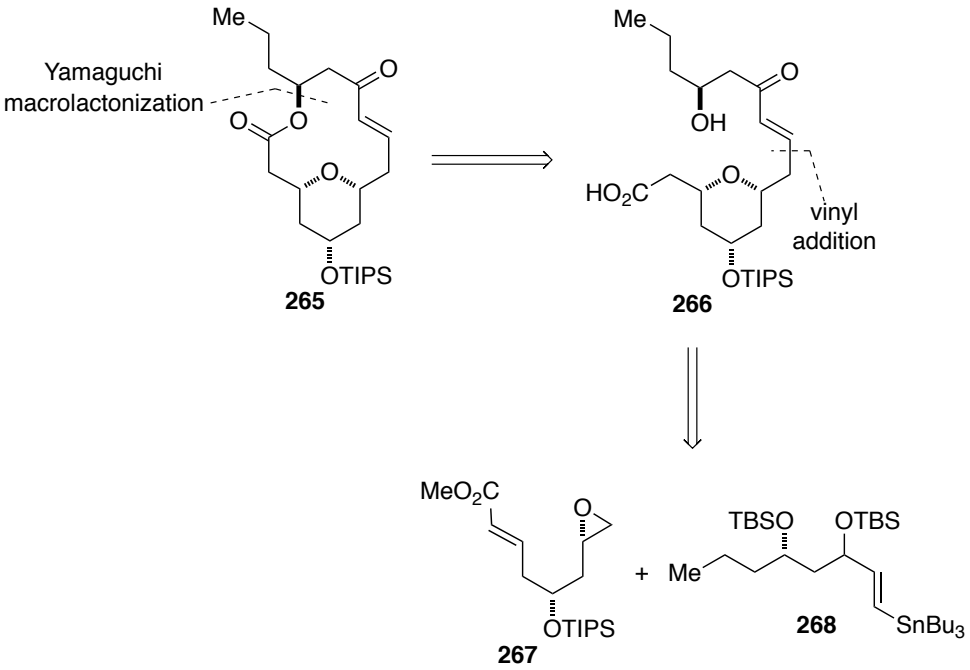


Figure 3.5. Low energy conformations of enone **265** and ketone **264**.

The macrocycle itself would be obtained by Yamaguchi macrolactonisation of seco acid **266** (**Scheme 3.9**). THP ring **266** could be further disconnected in epoxide **267** and vinyl stannane **268**. Vinyl addition on epoxide **267**, followed by cyclisation on the α,β-unsaturated ester would provided an easy access to neopeltolide THP core. The following chapter will describe our progress towards the synthesis of neopeltolide.



Scheme 3.9. Retrosynthetic analysis of enone **260**.

Chapter Four

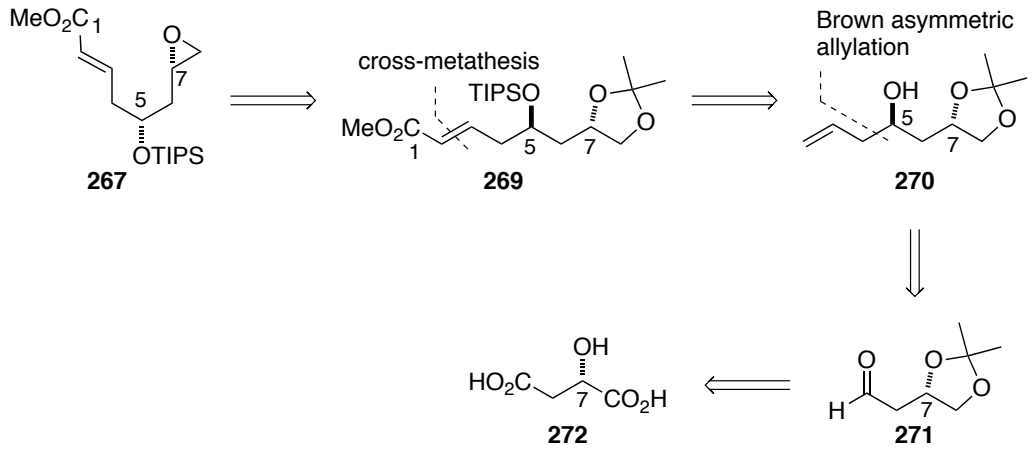
Results and Discussion

Synthesis of C1-C8 and C9-C16 fragments

4.1 Synthesis of C1-C8 fragment

4.1.1 Retrosynthesis

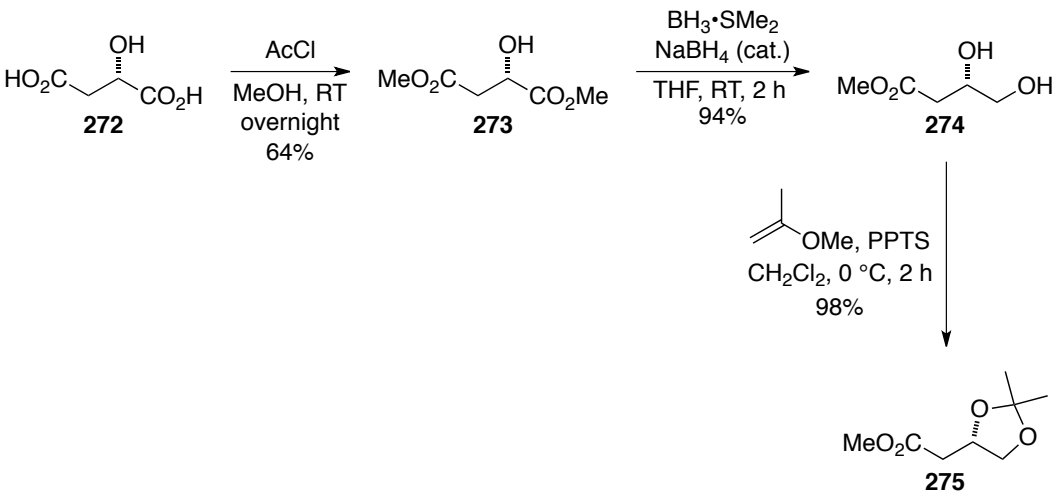
It was envisioned that the epoxide moiety **267** of the C1-C8 fragment could be formed from the protected diol **269**, which would be obtained from alkene **270** by cross-metathesis (**Scheme 4.1**). The homoallylic alcohol **270** would arise from Brown asymmetric allylation of aldehyde **271**, derived from (L)-malic acid **272**.[115]



Scheme 4.1. Retrosynthetic analysis for C1-C8 fragment.

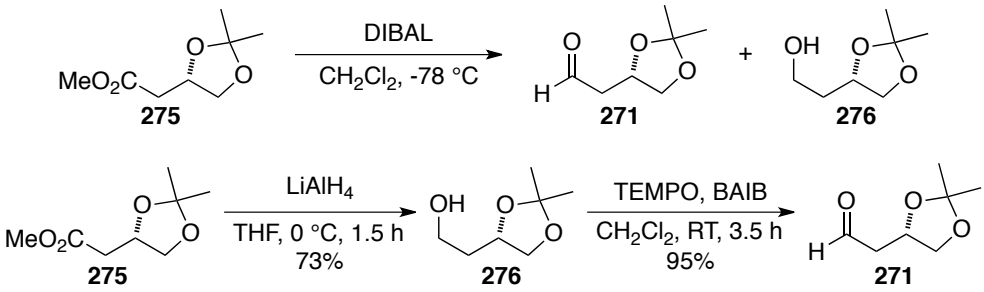
4.1.2 Preparation of aldehyde 271

The synthesis of the C1-C8 fragment began with the preparation of aldehyde **271**. Esterification of (L)-malic acid **272** in acidic methanol provided diester **273** (**Scheme 4.2**). This reaction was performed on scales >50 g and upon distillation, dimethyl malate **273** was isolated in good yield. Using the method developed by Morikawe *et al.*,[116] diester **273** was selectively reduced by borane dimethyl sulfide complex in the presence of catalytic amounts of sodium borohydride to provide diol **274** in excellent yield. Upon treatment with PPTS and 2-methoxypropene, diol **274** was protected as its acetonide. This reaction was performed on multigram scale and after distillation, the desired product **275** was obtained in 98% yield.



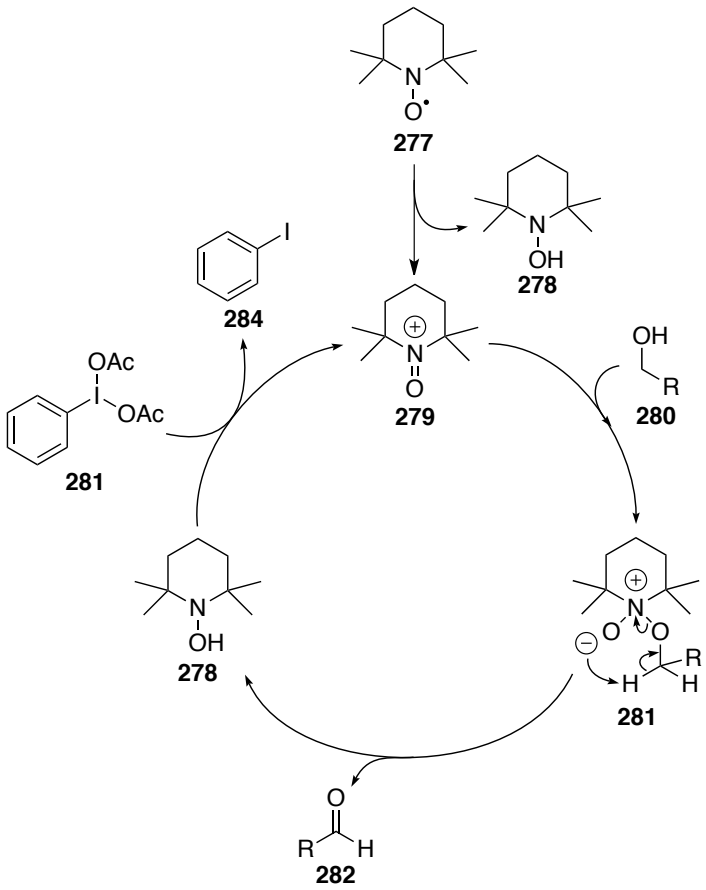
Scheme 4.2. Synthesis of acetonide **275**.

The reduction of ester **275** to aldehyde **271** was then attempted using DIBAL at -78 °C. Unfortunately, this lead to the formation of a mixture of aldehyde **271** and alcohol **276**. To circumvent this problem, ester **275** was reduced to the alcohol **276** using lithium aluminium hydride, which was then oxidized to the aldehyde **271** using TEMPO and BAIB (**Scheme 4.3**).[117] The required aldehyde **271** was obtained in a good yield over the two steps.



Scheme 4.3. Preparation of aldehyde **271**.

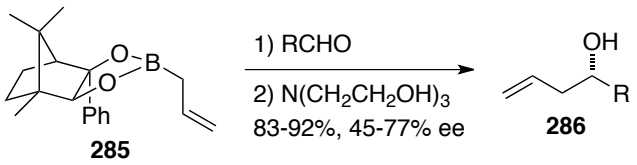
The mechanism for TEMPO oxidation is presented in **Scheme 4.4**. The catalytic cycle starts with the disproportionation of TEMPO **277** to form hydroxylamine **278** and the oxoammonium species **279**. Addition of alcohol **280** to the oxoammonium species forms intermediate **281** which undergoes intramolecular deprotonation to form aldehyde **282** and hydroxylamine **278**. Reaction between *bis*-acetoxyiodobenzene **283** with hydroxylamine **278** regenerates oxoammonium species **279** and forms iodobenzene **284** (**Scheme 4.4**).



Scheme 4.4. Mechanism of TEMPO/BAIB oxidation.

4.1.3 Synthesis of homoallylic alcohol 270

In order to prepare homoallylic alcohol **270**, a stereoselective allylation was required. The stereoselective formation of homoallylic alcohols is of high importance and a large amount of work has been devoted towards this aim. A strategy that has been applied successfully to this end is the use of chiral allylboron reagents. This was first reported by Hoffmann who reacted a (+)-camphor derived allylboronic ester **285** with a series of aliphatic aldehydes (**Scheme 4.5**).[118,119] The corresponding homoallylic alcohols **286** were obtained in excellent yield but with moderate stereoselectivity.



Scheme 4.5. Hoffman's enantioselective synthesis of homoallylic alcohols.[118,119]

This method soon attracted the interest of several research groups who developed alternative chiral allylboranes and allylboronates that could be used for the stereoselective synthesis of homoallylic alcohols (**Figure 4.1**):

- Roush and co-workers described the use of tartrate derived allylboronate **287**[120]
- Brown reported the application of (-)-isopinocampheylallylborane **288**[121,122]
- Corey developed the use of 1,2-diamino-1,2-diphenylethane allylborane **289**[123]
- Masamune *et al.* described a method that uses (*E*)- and (*Z*)- crotyl-2,5-dimethylborolane **290**[124]

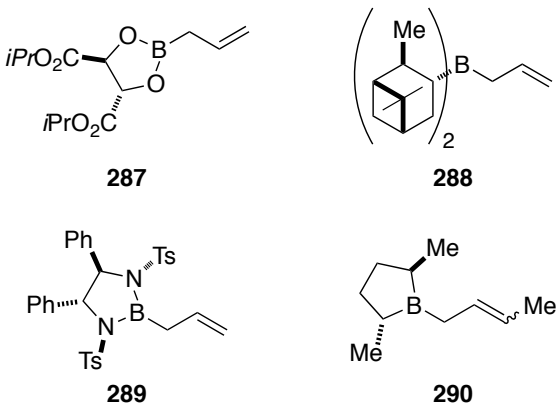
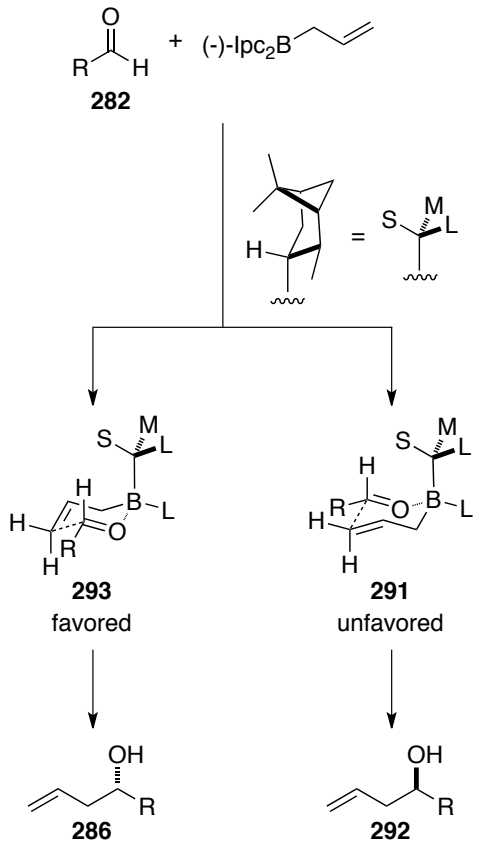


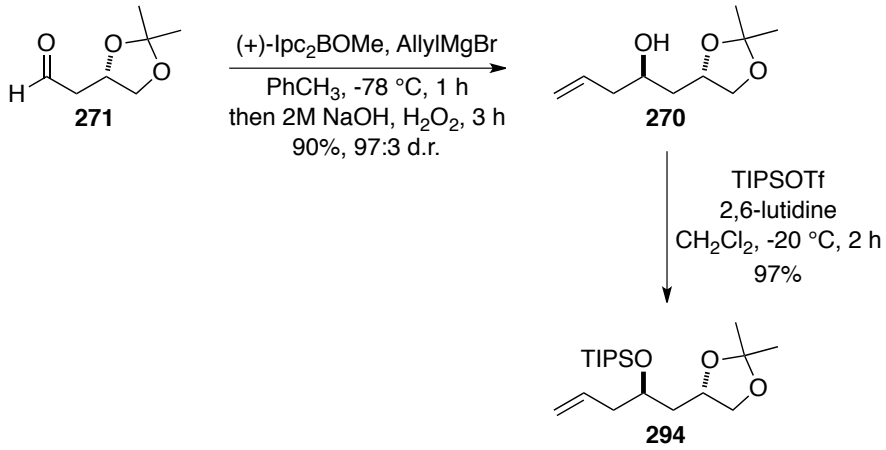
Figure 4.1. Main chiral boranes for the synthesis of homoallylic alcohols.[120-124]

In the case of Brown asymmetric allylation, boron coordinates with the aldehyde and provides a chair transition state where the aldehyde substituent occupies an equatorial position. The π-facial selectivity of the addition to the aldehyde **282** is explained by minimisation of steric interactions between the equatorial methyl of the pinene ligand and the allyl group (**Scheme 4.6**). Indeed when the aldehyde approaches from the opposite face of the methyl from the Ipc ligand, the unfavoured transition state **291** is formed and provides homoallylic alcohol **292**. However, when the aldehyde approaches from the same face as the equatorial methyl group, steric interaction with the allyl group is minimised. The reaction then proceeds through the favoured transition state **293** and provides homoallylic alcohol **286** in excellent yield and impressive enantioselectivity.



Scheme 4.6. Transition states for Brown asymmetric allylation.

Treatment of aldehyde **271** with (+)-allyldiisopinocampheylborane, formed *in situ* by addition of allylmagnesium bromide to (+)-methoxydiisopinocampheylborane, allowed the formation of homoallylic alcohol **270** in excellent yield and d.r. (**Scheme 4.7**). It was then required to protect alcohol **270** as its triisopropylsilyl ether. Thus treatment of homoallylic alcohol **270** with TIPSOTf and 2,6-lutidine afforded silyl ether **294** in excellent yield.



Scheme 4.7. Synthesis of homoallylic alcohol **270**.

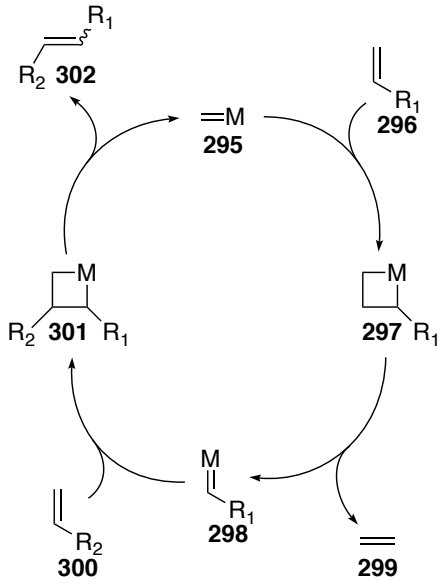
4.1.4 Synthesis of epoxide 267

As planned in our retrosynthetic analysis of the C1-C8 fragment, the ester moiety could be introduced by cross metathesis. The next section will give an overview of olefin metathesis.

4.1.4.1 Olefin metathesis overview

Olefin metathesis was first reported in the mid-1950s but the term itself wasn't coined until 1967.[125] Metathesis has numerous applications such as ring opening metathesis

polymerization (ROMP), ring closing metathesis (RCM), acyclic diene metathesis polymerization (ADMET), ring opening metathesis (ROM) and cross metathesis (CM). In 1971, Chauvin proposed a mechanism for olefin metathesis that is presented in **Scheme 4.8**.[126] The first step of the catalytic cycle consists in the reaction between a metal carbenoid **295** and an alkene **296** to form a metallocyclobutane **297**. This undergoes an intramolecular [2+2] cycloaddition to form intermediate **298** and ethylene **299**. Intermediate **298** reacts with alkene **300** to from a second metallocyclobutane **301**. After [2+2] cycloaddition, the cross-metathesis product **302** is formed and the metal carbenoid **295** is regenerated.



Scheme 4.8. General mechanism for olefin metathesis.[126]

Until the 1980's, the catalysts used were combinations such as $WOCl_4/EtAlCl_2$ or MoO_3/SiO_2. However, they required harsh reactions conditions and were not compatible with most functional groups. In the late 1980's, single component catalysts began to appear with the use of Shrock's molybdenum and tungsten alkylidenes **303** and **304**.[127,128] The main

catalysts used in olefin metathesis are presented in **Figure 4.2**. Molybdenum catalysts are very active but they relatively unstable to air and require to be preparation and use under an inert atmosphere. Grubbs and co-workers developed ruthenium alkylidenes **305**, **306** and **307**.[129,130] Such catalysts are more stable and have proved to be compatible with numerous functional groups, becoming benchmark catalysts for these transformations and providing a model on which numerous catalysts are developed.

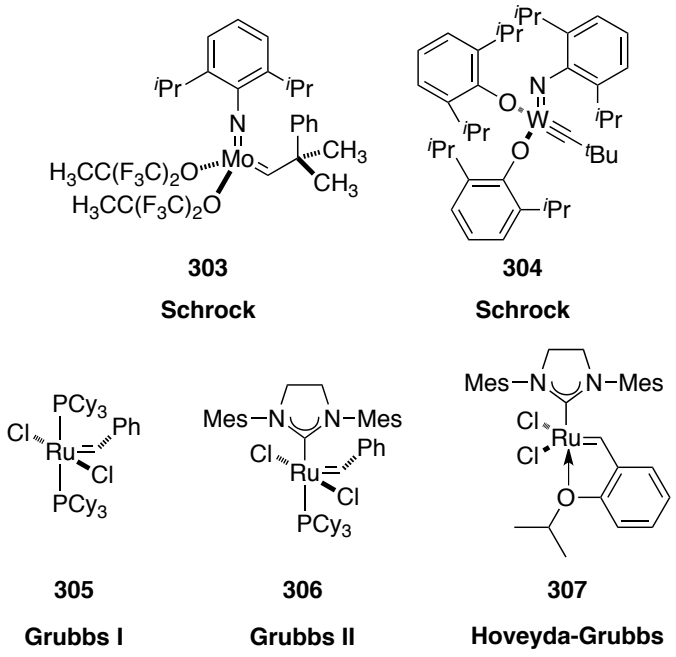
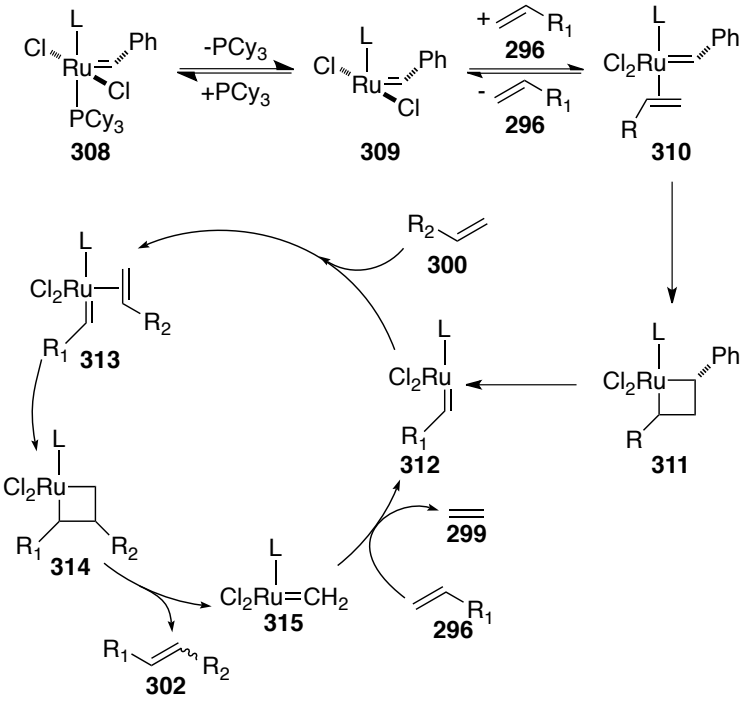


Figure 4.2. Main catalysts for olefin metathesis.[127-130]

With the apparition of well-defined catalysts, the mechanism of the olefin metathesis reaction was investigated thoroughly. After numerous kinetics experiments, Grubbs and co-workers were able to determine that the olefin metathesis reaction proceeds through a dissociative mechanism.[131,132] The first step consists in the release of a phosphine from the catalyst **308** to provide the 14 electron species **309** (**Scheme 4.9**). Ruthenium then coordinates with the olefin **296** to give intermediate **310** and then forms the

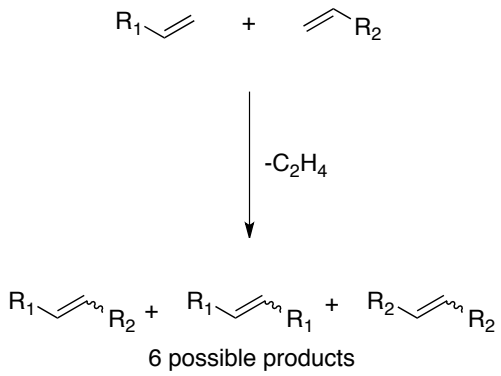
metallocyclobutane **311**. Intramolecular [2+2] cycloaddition provides metal carbenoid **312** and following coordination with the second olefin **300**, intermediate **313** which then forms the second metallocyclobutane **314**. A [2+2] cycloaddition provides the cross-metathesis product **302** as well as the propagating species **315** that can re-coordinate with olefin **296** and re-enter the catalytic cycle.



Scheme 4.9. Dissociative mechanism for olefin cross-metathesis.[131,132]

In its first applications, cross metathesis suffered from the fact that mixtures of products were obtained with low levels of selectivity. Indeed, a cross metathesis reaction can give six possible products including unreacted starting material (**Scheme 4.10**). This lack of selectivity has limited the utility of cross metathesis in synthesis however, significant progress has been made in the recent years. Grubbs and co-workers have investigated cross-metathesis using different classes of olefins and described a general empirical model

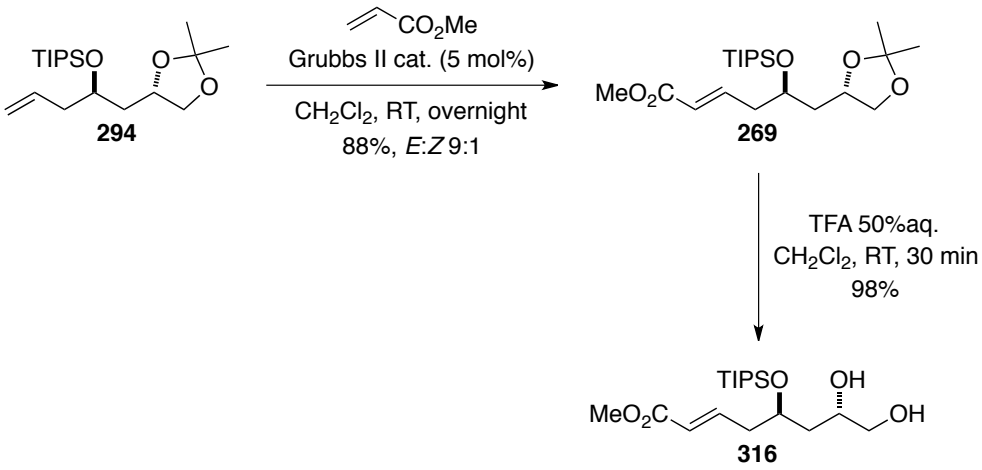
useful to predict product selectivity.[133] By reacting an olefin of high reactivity (electron rich) with an olefin of lower reactivity (electron poor), it is possible to achieve a selective cross-metathesis and to obtain products with excellent *E*:*Z* ratios.



Scheme 4.10. Mixture of products in cross-metathesis.

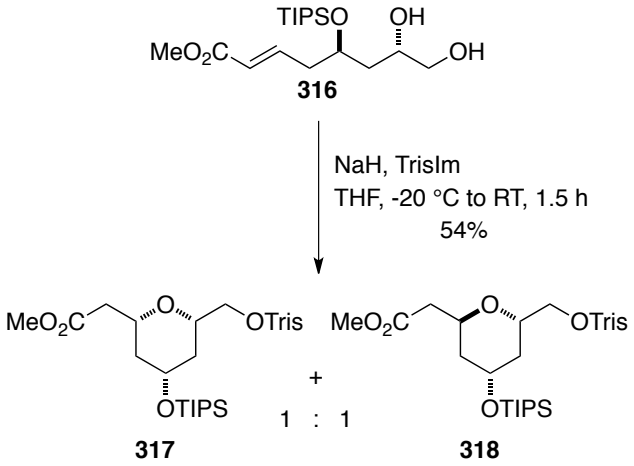
4.1.4.2 First approach to epoxide 267

Cross metathesis between alkene **294** and methyl acrylate catalysed by Grubbs second generation catalyst was accomplished in dichloromethane at room temperature and provided unsaturated ester **269** in 90% yield and 9:1 *E*:*Z* ratio (**Scheme 4.11**). Treatment of the intermediate **269** with a 50% aqueous solution of trifluoroacetic acid at room temperature in dichloromethane effectively cleaved the acetonide group to provide diol **316** in excellent yield.



Scheme 4.11. Synthesis of diol **316**.

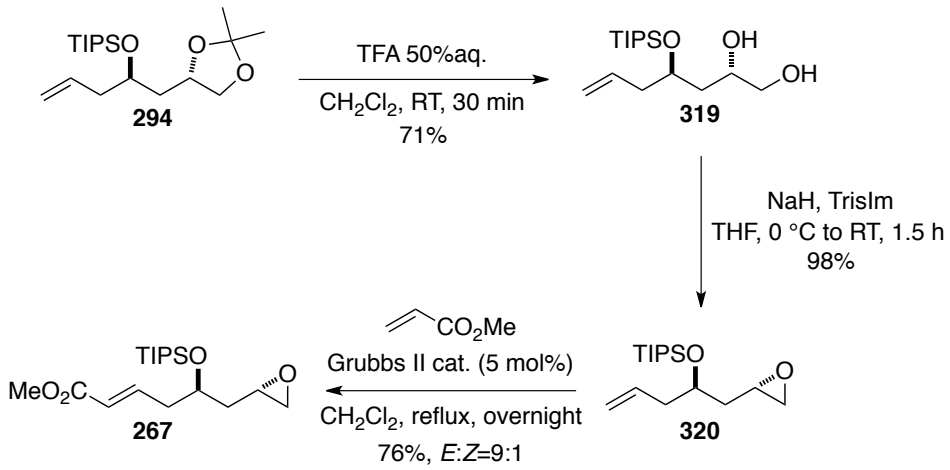
We aimed to form epoxide **267** by treatment of diol **316** with sodium hydride and 2,4,6-triisopropylbenzesulfonyl imidazole (**Scheme 4.12**).[134,135] Unfortunately, under these conditions, the C7 alkoxide undergoes 6-*endo*-trig cyclisation on the α,β-unsaturated ester to give a 1:1 diastereoisomeric mixture of trisylated THP alcohols **317** and **318**. Treatment of the diastereoisomeric mixture with *t*BuOK or sodium methoxide in order to equilibrate the C3 stereocentre towards the required 2,6-*syn*-THP was attempted.[136,137] Unfortunately, this was not successful and an alternative approach to form the C1-C8 epoxide was required.



Scheme 4.12. Cyclisation to THP rings **317** and **318**.

4.1.4.3 Second approach to epoxide 267

In order to access the C1-C8 fragment, we decided to form the epoxide before introducing the acryloyl moiety. Our second approach to epoxide **267** started from acetonide **294**, which was first deprotected using a 50% aqueous trifluoroacetic acid (**Scheme 4.13**). This provided diol **319** in good yield and upon treatment with sodium hydride and trisyl imidazole, epoxide **320** was obtained in 98% yield. Cross metathesis with methyl acrylate and Grubbs second generation catalyst then provided the desired C1-C8 fragment **267** in good yield and *E*:*Z* selectivity.



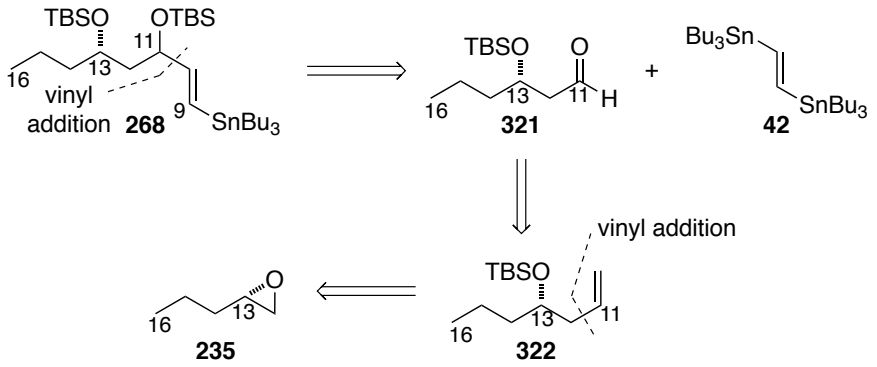
Scheme 4.13. Completion of the C1-C8 fragment **267**.

In conclusion, we have synthesised the C1-C8 fragment **267** in ten steps and 19% overall yield and turned our attention to the synthesis of the C9-C16 fragment.

4.2 Synthesis of C9-C16 fragment

4.2.1 Retrosynthesis

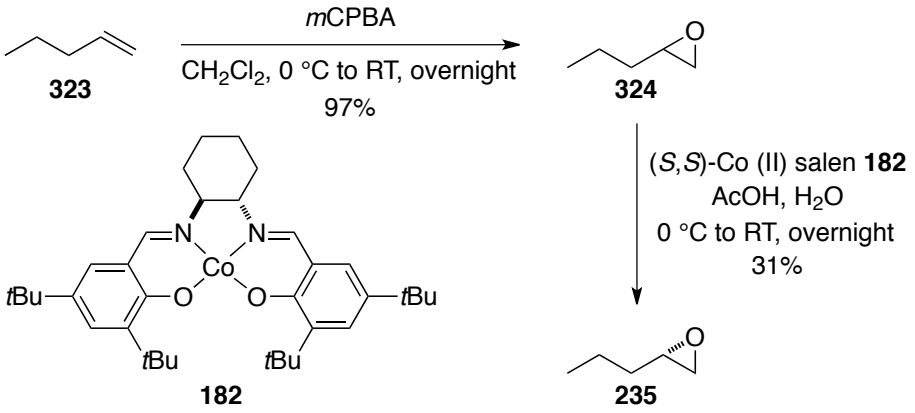
We aimed to form C9-C16 fragment **268** by addition of the *bis*-stannyl compound **42** to aldehyde **321** which can be obtained by ozonolysis of alkene **322** (**Scheme 4.14**). Alkene **322** could in turn be formed by vinyl addition on (*S*)-epoxypentane **235**.



Scheme 4.14. Retrosynthesis of the C9-C16 fragment.

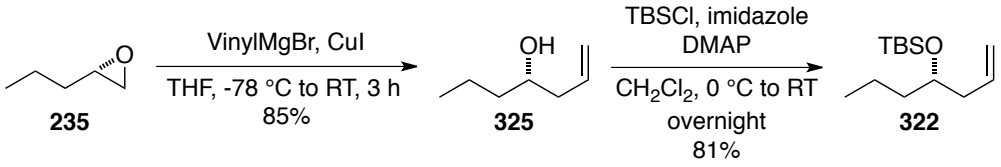
4.2.2 Synthesis of alkene 322

The synthesis of alkene **322** began with the epoxidation of 1-pentene **323**. Treatment of the commercially available alkene **323** with *m*CPBA provided epoxypentane **324** (**Scheme 4.15**). This reaction was performed on multigram scale and after distillation epoxide **324** was obtained in a 97% yield. Jacobsen HKR using (*S*,*S*)-Co (II) salen catalyst **182** provided enantiopure (*S*)-epoxypentane **235**. The epoxide was obtained in a 31% yield after short-path distillation with a specific rotation of $[\alpha]_D^{20}$ -11.1 (*c* 0.9, $CHCl_3$) compared with data reported $[\alpha]_D^{20}$ -8.5 (*c* 2.6, $CHCl_3$).[138]



Scheme 4.15. Preparation of epoxide **235**.

With enantiopure epoxide **233** in hand, reaction with vinylmagnesium bromide provided alcohol **323** in a 85% yield (**Scheme 4.16**). The hydroxyl group was readily protected as its TBS ether *via* treatment TBSCl, DMAP and imidazole, to provide silyl ether **320** in good yield.

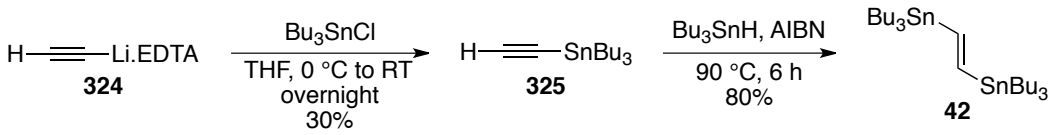


Scheme 4.16. Synthesis of alkene **322**.

4.2.2 Preparation of C9-C16 fragment

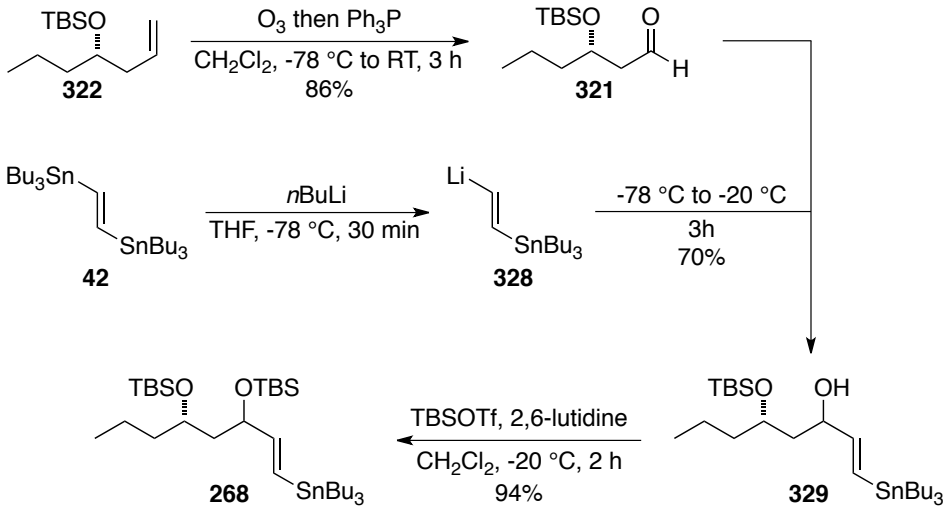
Having accessed alkene **322**, we turned our attention to the preparation of *bis*-stannyl compound **42**. It was synthesised using a method developed by Stille and co-workers.[139] Tributyltin chloride was reacted with lithium acetylide EDTA complex **326** to provide

tributyltin acetylide **327** in a 30% yield (**Scheme 4.17**). This was heated at 90 °C for 6 h in presence of tributyltin hydride and AIBN to form *bis*-stannyl compound **42** in a good yield.



Scheme 4.17. Synthesis of *bis*-stannyl compound **42**.[139]

Ozonolysis of alkene **322**, followed by treatment of the ozonide with triphenylphosphine provided aldehyde **321** in a 86% yield (**Scheme 4.18**). With the key aldehyde in hand we investigated the coupling to form the C9-C16 fragment. Treatment of *bis*-stannyl compound **42** with *n*-butyllithium generated vinyl lithium species **328** *via* tin-lithium exchange. A solution of aldehyde **321** in THF was added and after work-up, allylic alcohol **329** was obtained as a 1:1 mixture of diastereoisomers. The hydroxyl group was protected using TBSOTf and 2,6-lutidine to provide the C9-C16 fragment **268** in 94% yield.



Scheme 4.18. Synthesis of C9-C16 fragment **268**.

With the two fragments in hand, we focused our attention on their coupling and the results will discussed in the next chapter.

Chapter Five

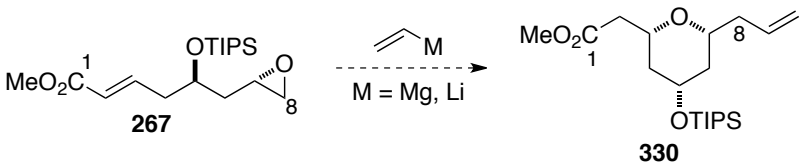
Results and Discussion

Studies towards the synthesis of neopeltolide aglycon

5.1 Coupling of C1-C8 and C9-C16 fragments

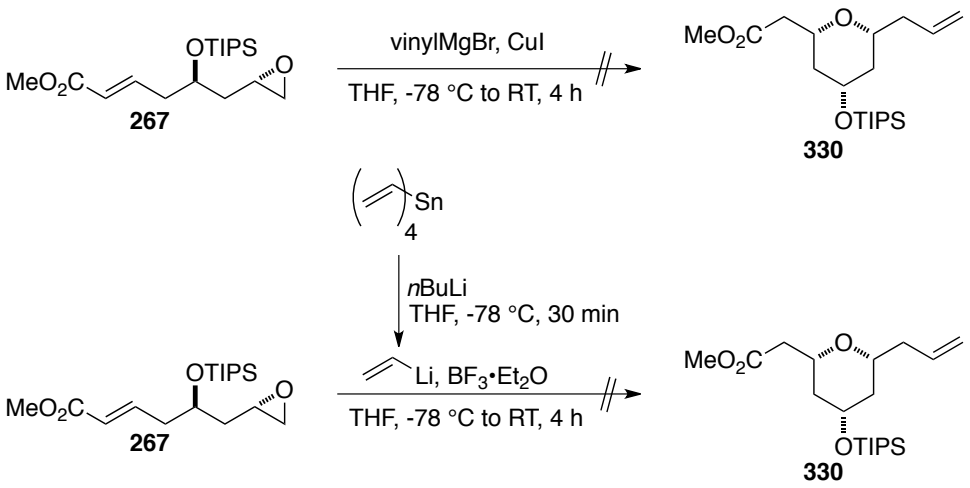
5.1.1 Vinyl addition on C1-C8 fragment

Before attempting the coupling between our two advanced fragments **267** and **268**, a series of model vinyl addition studies were performed. Addition of simple vinyl species would enable the development of optimal conditions for the proposed one-pot addition/conjugate addition cyclisation (**Scheme 5.1**).



Scheme 5.1. Vinyl additions on C1-C8 fragment.

Unfortunately, addition of vinylmagnesium bromide to epoxide **267** was not successful and only starting material was recovered. The addition of vinyllithium, obtained by treatment of tetravinyltin with *n*-butyllithium,[140] was also unsuccessful and led to the degradation of the starting epoxide **267** (**Scheme 5.2**).



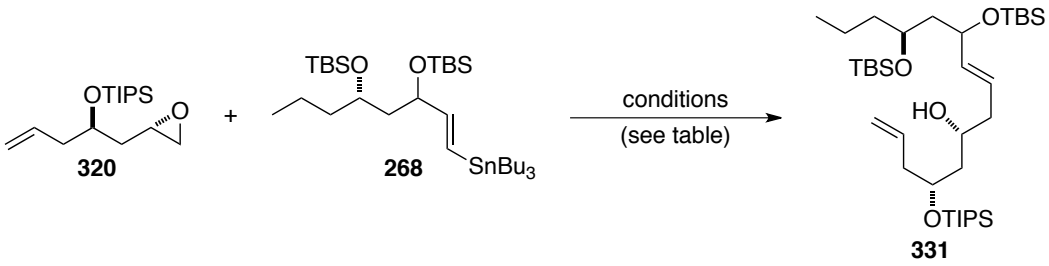
Scheme 5.2. Model vinyl additions on epoxide **267.**

In the light of these disappointing results, we decided to attempt the coupling of a less complex C2-C8 epoxide **320** with the C9-C16 fragment **268**.

5.1.2 Coupling of C2-C8 and C9-C16 fragments

The results of the couplings attempted between epoxide **320** and vinyl stannane **268** are presented in **Table 5.1**. Treatment of vinyl stannane **268** with *n*-butyllithium at -78 °C, followed by addition of epoxide **320** and BF_3•Et_2O (entry 1, **Table 5.1**) did not provide the desired coupling product **331** and the starting vinyl stannane **268** was recovered

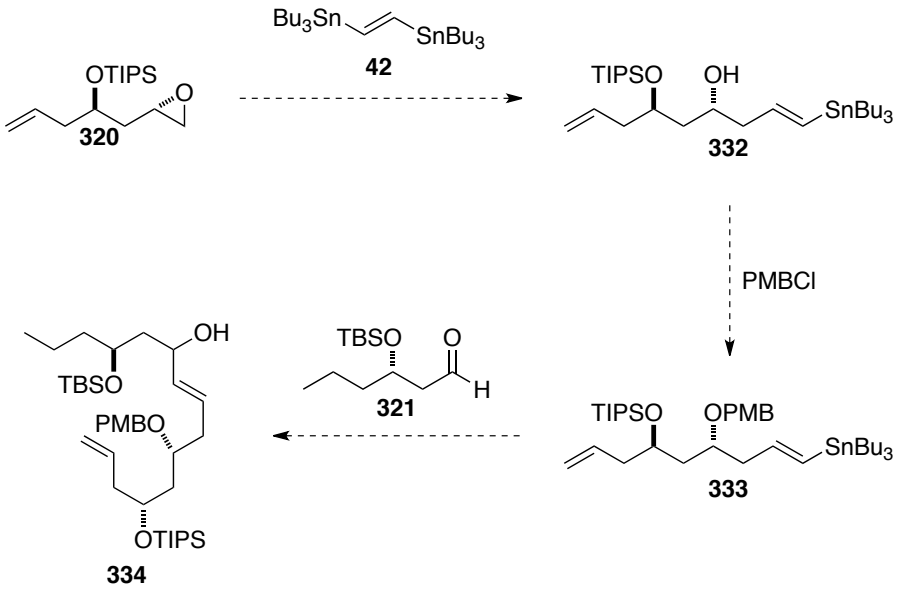
unchanged. Under similar conditions but allowing more time for the tin/lithium exchange to occur (entry 2, **Table 5.1**), no coupling product **331** was formed and degradation of vinyl stannane **268** was observed. Changing from *n*-butyl to *tert*-butyllithium (entry 3, **Table 5.1**) was not successful and led to the degradation of the starting vinyl stannane **268**.



Entry	Conditions	Result
1	**268** (2 eq.), *n*BuLi (2 eq.), THF, -78 °C, 30 min **320** (1 eq.), BF_3•Et_2O (2 eq.), -78 °C to -20 °C, 3 h	vinyl stannane recovered
2	**268** (2 eq.), *n*BuLi (2 eq.), THF, -78 °C to -50 °C, 1 h **320** (1 eq.), BF_3•Et_2O (2 eq.), -78 °C to -20 °C, 3 h	vinyl stannane degradation
3	**268** (2.4 eq.), *t*BuLi (2 eq.), -78 °C, 30 min **320** (1 eq.), BF_3.Et_2O (2 eq.), -78 °C to -10 °C, 5 h	vinyl stannane degradation

Table 5.1. Coupling attempts between epoxide **320** and vinyl stannane **268**.

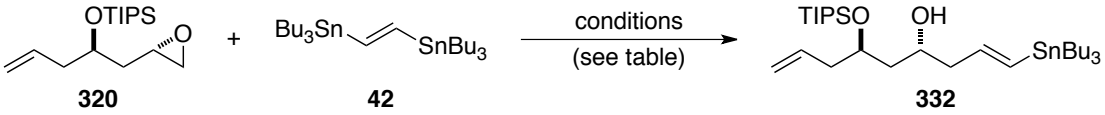
In order to circumvent the difficulties met during the coupling of these two fragments, we decided to reverse our coupling strategy. Addition of *bis*-stannane **42** to the C2-C8 epoxide **320** would provide alcohol **332** which would be protected as its PMB ether to give vinyl stannane **333**. Tin/lithium exchange, followed by addition to aldehyde **321** would then provide the required coupling product **334** (**Scheme 5.3**).



Scheme 5.3. Reverse coupling strategy.

5.1.3 Coupling of C2-C8 epoxide with *bis*-stannane 42

The results of the attempted coupling between epoxide **320** and *bis*-stannane **42** are presented in **Table 5.2**. Treatment of epoxide **320** with two equivalents of *bis*-stannane **42**, *n*-butyllithium and BF_3•Et_2O failed to provide to the desired product **332** and the starting epoxide **320** was recovered in 84% yield (entry 1, **Table 5.2**). Addition of four equivalents of *n*-butyllithium and bis-stannane **42** was not successful and no reaction was observed (entry 2, **Table 5.2**). To increase the reactivity of the lithium anion, three equivalents of HMPA were added but under these conditions, no coupling product was formed and the starting material was recovered in 73% yield (entry 3, **Table 5.2**).



320 **42** **332**

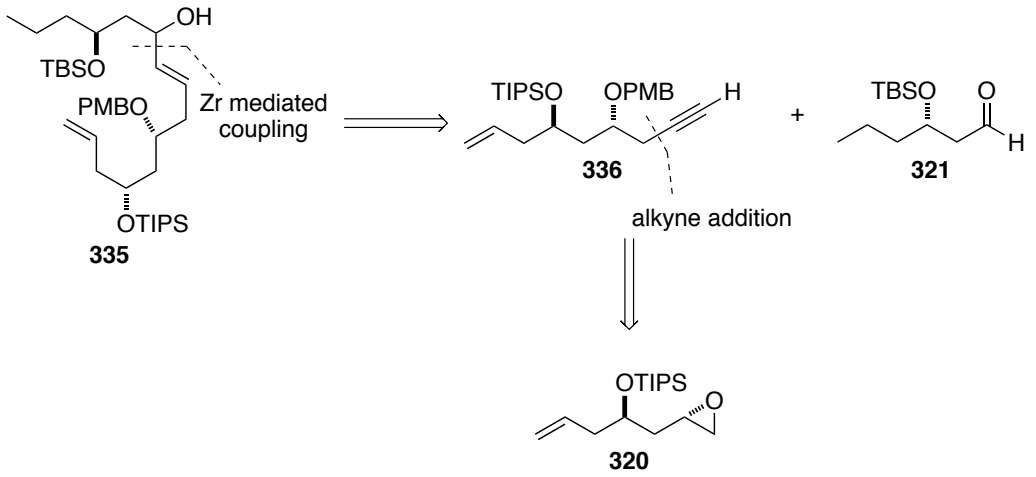
Entry	Conditions	Result
1	**42** (2 eq.), *n*BuLi (2 eq.), THF, -78 °C, 30 min **320** (1 eq.), BF_3•Et_2O (2 eq.), -78 °C to -20 °C, 3 h	epoxide recovered
2	**42** (4 eq.), *n*BuLi (4 eq.), THF, -78 °C, 30 min **320** (1 eq.), BF_3•Et_2O (4 eq.), -78 °C to -20 °C, 3 h	epoxide recovered
3	**42** (3 eq.), *n*BuLi (2 eq.), -78 °C, 30 min **320** (1 eq.), HMPA (3 eq.), BF_3.Et_2O (2 eq.), -78 °C to -10 °C, 5 h	epoxide recovered

Table 5.2. Coupling attempts between epoxide **320** and bis-stannane **42**.

Faced with unexpected difficulties in the addition of a vinyl species to epoxide **320**, we turned our attention towards a different coupling strategy that will be discussed in the next section.

5.2 Revised coupling strategy

Our revised coupling strategy is depicted in **Scheme 5.4**. It was envisaged that alkene **335** could be obtained *via* a zirconium-mediated coupling between alkyne **336** and aldehyde **321**. Alkyne **335** could be formed by alkyne addition to the C2-C8 epoxide **320** (**Scheme 5.4**).

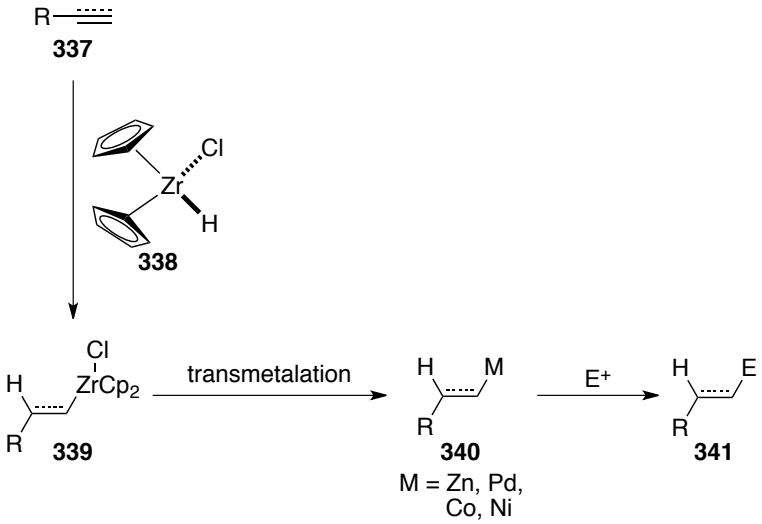


Scheme 5.4. Revised coupling strategy.

5.2.1 Applications of organozirconocenes

Since the synthesis of the first zirconocene, *bis*-cyclopentadienylzirconium(IV) dibromide, in 1953,[141] the chemistry of organozirconocenes has expanded rapidly and their use in carbon-carbon bond formation has become a very useful tool in organic synthesis.[142,143]

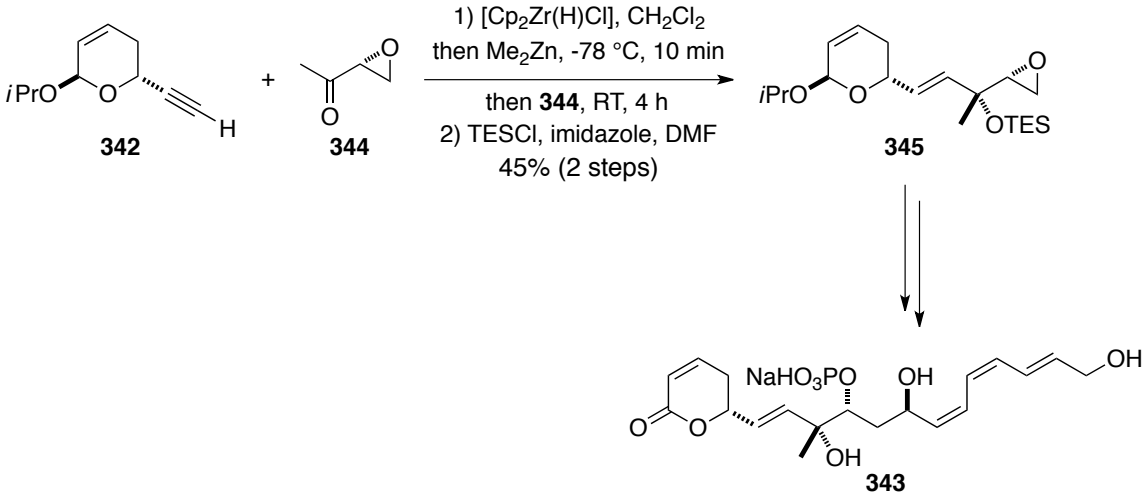
Organozirconocenes can be readily obtained by reaction of an alkyne or an alkene **337** with Schwartz's reagent **338** (**Scheme 5.5**).[144-146] In the case of terminal alkynes, hydrozirconation proceeds with *cis* selectivity and places the metal atom at the terminal carbon atom. Once formed, the organozirconocenes **339** can be transmetalated using different metals such as zinc, palladium, copper or nickel forming the corresponding alkyl or alkenyl metals **340** that can react with various electrophiles and provide disubstituted olefins **341**.



Scheme 5.5. Hydrozirconation of alkynes and alkenes.

Functional group compatibility of the Schwartz reagent **338** is limited by its oxophilic and strong Lewis acid character. Among the compatible functional groups are silyl, *t*-butyl and benzyl esters and ethers. Hydrozirconation of terminal alkynes is also compatible with alkenes as the rate of the reaction was noted to be higher for alkynes.

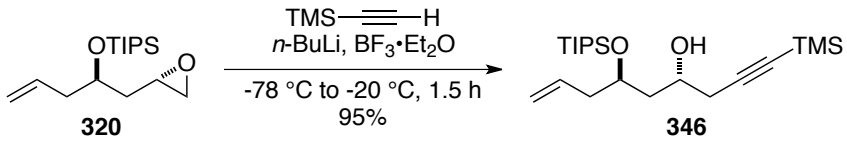
One of the most frequent applications of organozirconocenes is the transmetalation with dialkyl zinc to form alkenylzinc intermediates. This method was applied in numerous total syntheses. For example, Jacobsen and co-workers used the hydrozirconation/ transmetalation of alkyne **342** in their synthesis of fostriecin **343** (**Scheme 5.6**).[147] Alkyne **342** was treated with Schwartz's reagent **338** to form an organozirconocene that was transmetallated with dimethyl zinc. Addition of the alkenyl zinc to ketone **344**, followed by triethylsilyl protection of the resulting hydroxyl group provided epoxide **345** in 45% yield over two steps.



Scheme 5.6. Hydrozirconation in Jacobsen's total synthesis of fostriecin **343**.[147]

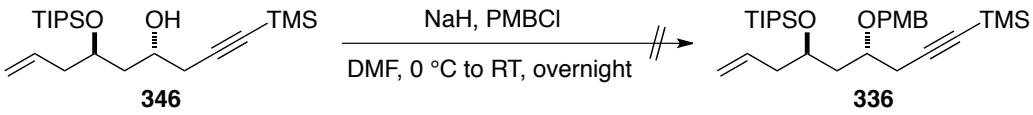
5.2.2 Synthesis of alkyne 336

As outlined in our revised synthetic strategy, the required alkyne coupling partner could be obtained by addition of TMS acetylene to C2-C8 fragment **320**. Gratifyingly, the addition of the lithium anion of TMS acetylene to epoxide **320** in presence of BF_3•Et_2O proceeded smoothly and provided alkyne **346** in an excellent 95% yield (**Scheme 5.7**).



Scheme 5.7. Alkyne addition to epoxide **320**.

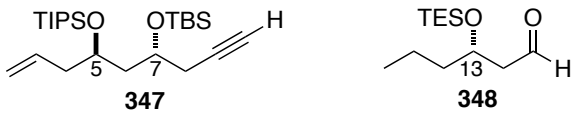
Unfortunately, protection of alcohol **346** using PMBCl and sodium hydride failed to provide the required product **336** and the starting material was recovered (**Scheme 5.8**).



346 **336**

Scheme 5.8. PMB protection of alcohol **346**.

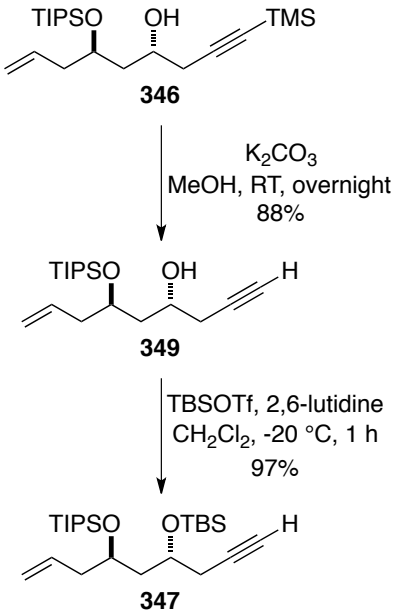
As the PMB protection of the C-7 was not successful, we decided to change the protecting group for a TBS group. As orthogonal protection between the C-7 and the C-13 hydroxyl is required, the protection group of the aldehyde coupling partner **348** was changed to a TES group. The new coupling partners are presented in **Figure 5.1**.



347 **348**

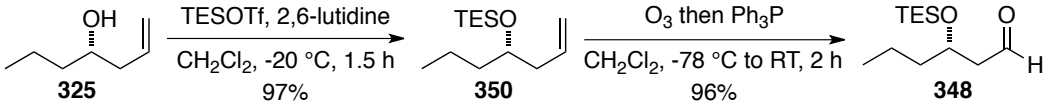
Figure 5.1. Orthogonally protected coupling partners.

In order to prepare alkyne **347**, it was required to remove the TMS group from the alkyne and to protect the C7 hydroxyl group (**Scheme 5.9**). TMS removal was achieved by treatment of alkyne **346** with potassium carbonate in methanol and provided alkyne **347** in 88% yield. Protection of the C7 hydroxyl as its TBS ether was achieved using TBSOTf and 2,6-lutidine, providing the required alkyne coupling partner **347** in excellent yield.



Scheme 5.9. Preparation of alkyne **347**.

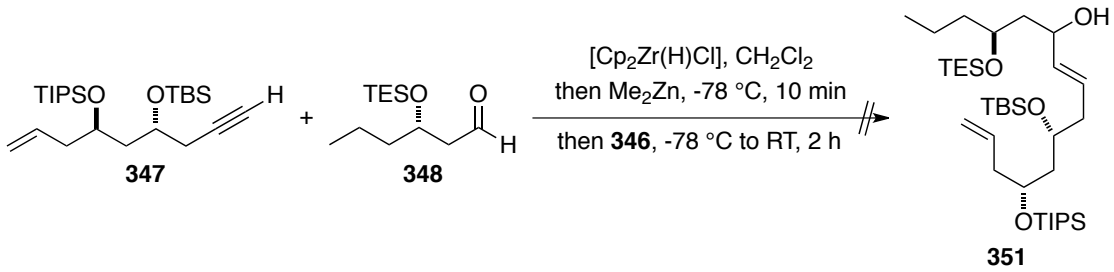
With the alkyne coupling partner **347** in hand, we turned our attention towards the preparation of aldehyde **348**. TES protection of alcohol **325** using TESOTf and 2,6-lutidine provided silyl ether **350** in excellent yield (**Scheme 5.10**). Ozonolysis of alkene **350** provided the aldehyde coupling partner **348** in 96% yield.



Scheme 5.10. Synthesis of aldehyde **348**.

5.2.3 Coupling of alkyne 347 with aldehyde 348

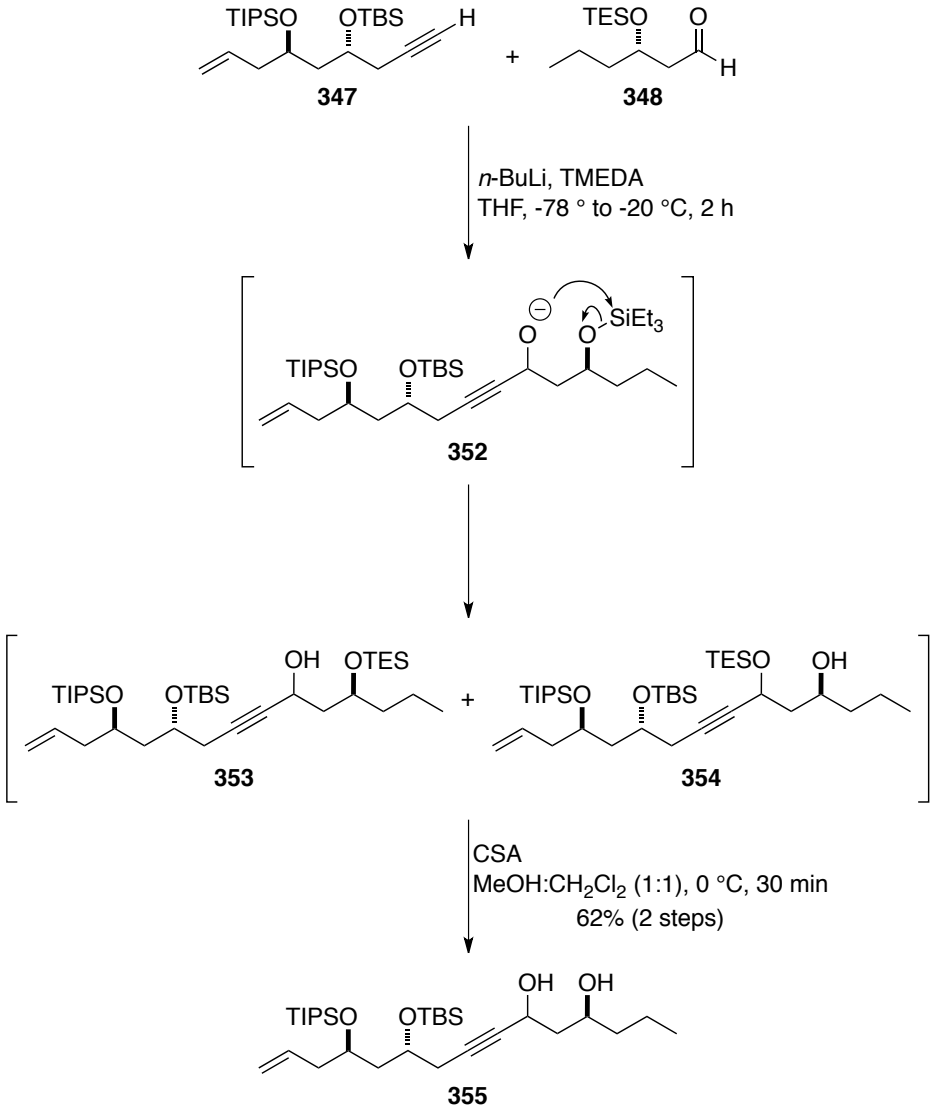
As outlined in our revised coupling strategy, we proceeded to investigate the Zr-mediated coupling between alkyne **347** and aldehyde **348** (**Scheme 5.11**). Unfortunately, treatment of alkyne **347** with Schwartz's reagent and dimethyl zinc, followed by addition of aldehyde **348** did not provide the coupling product **351** and the starting alkyne was recovered in 74% yield.



Scheme 5.11. Attempt at Zr mediated coupling between alkyne **347** and aldehyde **348**.

In order to circumvent this problem, we turned our attention to the addition of the lithium anion of alkyne **347** to aldehyde **348** (**Scheme 5.12**). Treatment of alkyne **347** with *n*-butyllithium and TMEDA, followed by addition of aldehyde **348** provided the intermediate alkoxide **352**. This intermediate is expected to provide the "normal" addition product **353**. However, under basic conditions, silyl groups are known to migrate.[148] In our case, [1,5] Brook rearrangement of intermediate **352** led to the formation of alcohol **354**. The alkyne addition occurs without any selectivity and the C11 hydroxyl group is formed as a 1:1 mixture of diastereoisomers. It was not possible to separate this complex mixture of products by column chromatography. In order to circumvent this problem, alcohols **353**

and **354** were treated with CSA which removed the triethylsilyl group and provided diol **355** as a 1:1 mixture of diastereoisomers in 62% yield over the two steps.



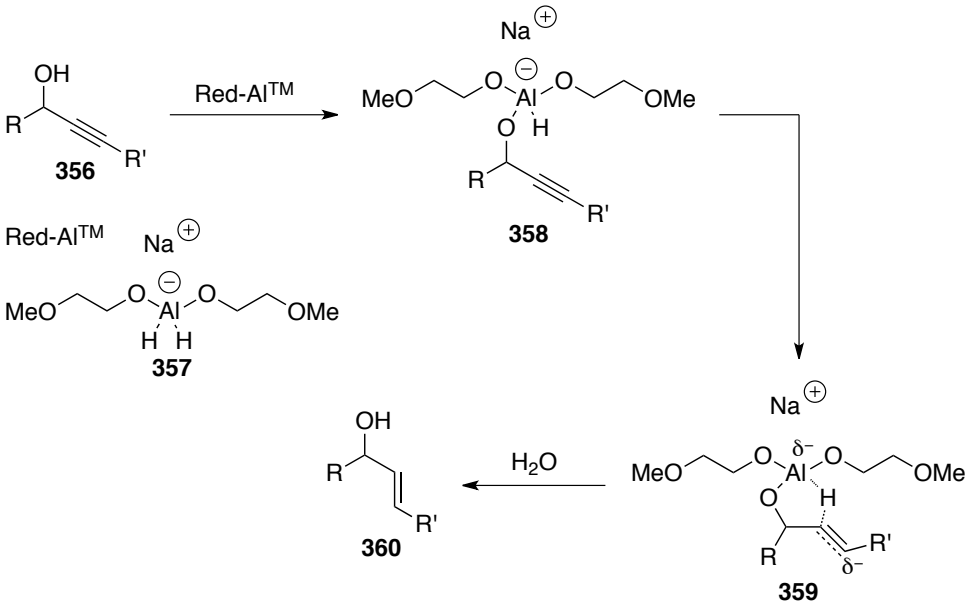
Scheme 5.12. Coupling between alkyne **347** and aldehyde **348**.

5.3 Synthesis of neopeltolide macrolide

5.3.1 Preparation of the macrocycle precursor

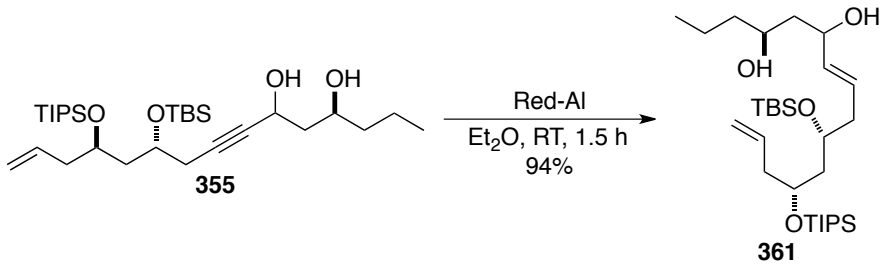
In order to prepare the macrocycle precursor, reduction of alkyne **355** to the *E*-alkene was required, the C-11 hydroxyl group needs to be oxidised selectively and an acryloyl moiety introduced at the C-13 hydroxyl group.

It has been reported that the *E*-selective reduction of propargyl alcohols is possible with lithium aluminium hydride. Earlier studies have shown that the *E*/*Z* selectivity is solvent dependent and that using a cation coordinating solvent leads to high *E*-selectivity.[149] The use of Red-Al™ has been reported to increase both the rate and the *E*-selectivity of this reaction (**Scheme 5.13**).[150] Alcohol **356** first reacts with Red-Al™ **357** to provide intermediate **358** which will then undergo intramolecular hydride addition to the acetylide to form intermediate **359**. In this intermediate, no formal charge is carried by the alkene as the sodium cation is coordinated. Protonation of intermediate **359** during work-up then provided (*E*)-alkene **359**.



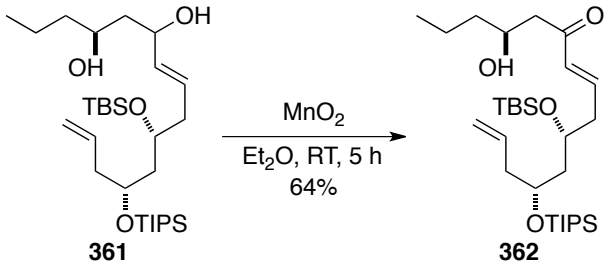
Scheme 5.13. Mechanism of Red-Al™ reduction of alkynes.

Gratifyingly, treatment of alkyne **355** with eight equivalents of Red-Al™ provided the required alkene **361** in excellent yield (**Scheme 5.14**). Unfortunately, it was not possible to determine the *E*/*Z* selectivity of the reaction by *J* coupling analysis due to the 1:1 mixture of diastereoisomers at the neighboring C11 stereocentre. However, it was likely that the selectivity of the reduction could be determined after the required oxidation of the C11 hydroxyl group.



Scheme 5.14. Reduction of alkyne **355** using Red-Al™.

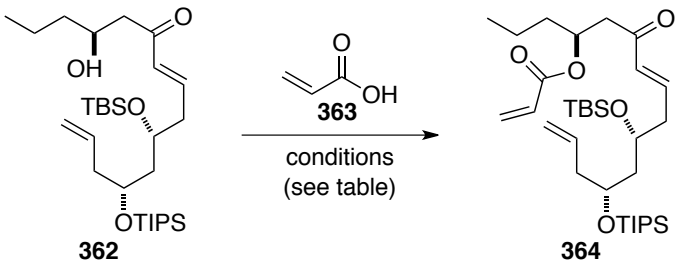
The selective oxidation of allylic alcohol **361** was performed using manganese dioxide and provided the required enone **362** in 64% yield (**Scheme 5.15**). Analysis of the 1H NMR revealed a *J* coupling between H9 and H10 of 15.9 Hz confirming that the reduction of alkyne provided (*E*)-alkene **361** with a 6:1 *E*:*Z* ratio.



361 **362**

Scheme 5.15. Synthesis of enone **362**.

The next step consisted of the introduction of an acryloyl moiety at the C13 hydroxyl group. The conditions used for the coupling between hydroxyl **362** and acrylic acid **363** are summarised in **Table 5.3**. Steglich esterification using four equivalents of DCC and 0.2 equivalents of DMAP was not successful and the starting material was recovered.[151] Gratifyingly, when the esterification was performed under Yamaguchi's conditions using 2,4,6-trichlorobenzoyl chloride, triethylamine and DMAP, the desired product **364** was obtained in a modest 51% yield.[113]



Entry	Conditions	Result
1	**363** (4 eq.), DCC (4 eq.), DMAP (0.2 eq.) CH_2Cl_2, 0 °C to RT, 4 h	starting material recovered
2	**363** (6 eq.), 2,4,6-trichlorobenzoyl chloride (6 eq.) Et_3N (6 eq.), DMAP (4 eq.) $PhCH_3$, RT, 1 h	51%

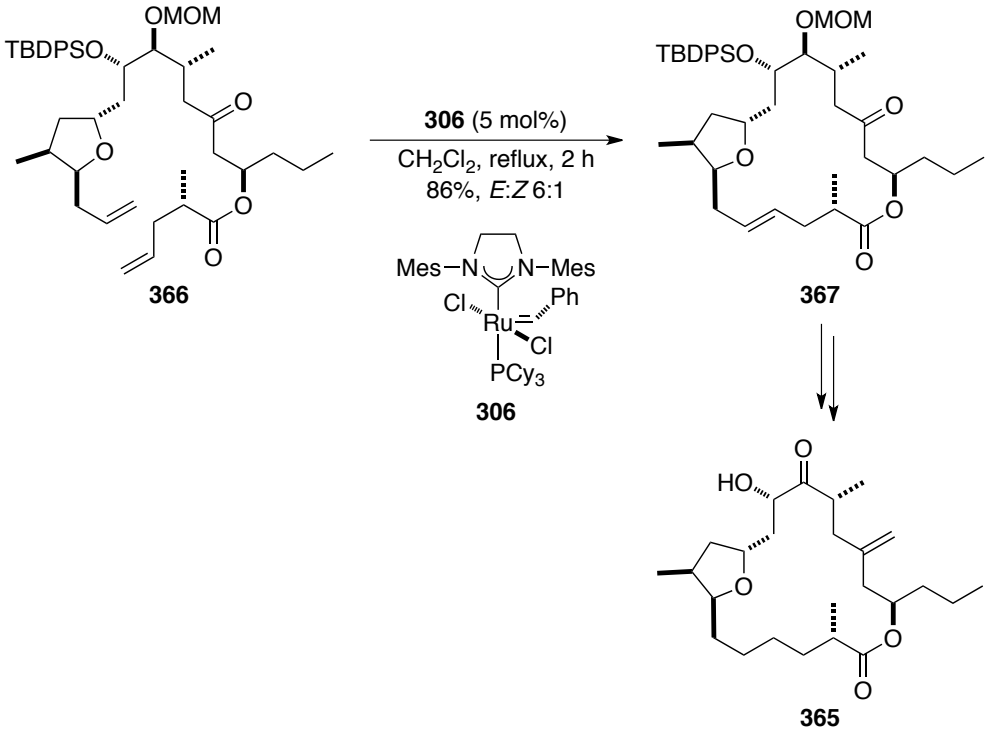
Table 5.3.Synthesis of macrolactone precursor **364**.

With the required macrolide precursor **364** in hand, the next step consisted in the synthesis of the 14-membered macrolactone by ring closing metathesis. The next section will discuss the formation of macrocycles *via* RCM reactions.

5.3.2 Macrocyclisation by ring-closing metathesis

In the synthesis of macrocyclic natural products, the macrocyclisation reaction can be problematic as there is competition between intramolecular and intermolecular processes. The most common strategy to successfully form macrocycles is to use macrolactonization reactions.[152] Other methods such as intra-molecular Horner-Wadsworth-Emmons (HWE) reaction[153,154] or macrocyclisation using a Tsuji-Trost reaction have also been applied.[155] Ring-closing metathesis is a powerful tool for the formation of five or six membered rings[156] but it has also been employed in the synthesis of of macrocyclic rings.[156-158]

For example, Fürstner and co-workers prepared the 19-membered macrocycle from amphidinolide T4 **365** using a ring-closing metathesis reaction.[159,160] Treatment of diene **366** with 5 mol% of Grubbs second generation catalyst **306** provided macrolactone **367** in a 86% yield and a 6:1 *E*:*Z* ratio (**Scheme 5.16**).

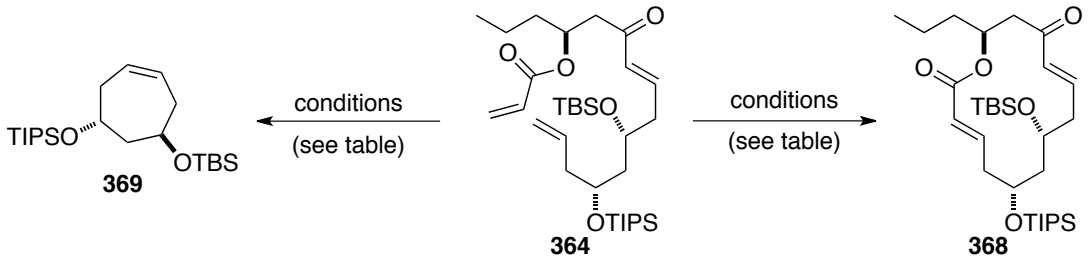


Scheme 5.16. Ring closing metathesis in Fürstner's synthesis of amphidinolide T4.[159,160]

However, macrocyclisation reactions depend on numerous parameters such as the choice of the catalyst, solvent, temperature, concentration and reaction time. As a consequence, no general conditions are available to guarantee the success of such reactions.

5.3.3 Ring-closing metathesis of 364

On the first attempt to form neopeltolide macrocycle *via* ring-closing metathesis, Grubbs second generation catalyst **306** was employed. Unfortunately, refluxing **364** with 5 mol% of **306** overnight did not produce the desired macrocycle **368** but cycloheptene **369** was obtained in a 70% yield (entry 1, **Table 5.4**). This result was unexpected as the formation of seven membered rings is usually difficult due to high ring strain. Treatment of **364** with 10 mol% of Grubbs-Hoveyda catalyst **307** was not successful either and the degradation of the starting material was observed (entry 2, **Table 5.4**). Using Nolan's indenylidene complex **370** was expected to prevent the formation of the cycloheptene **369**.[161] Indeed, this bulky catalyst would make the possibility of ring closing occurring on an internal double-bond less likely. Unfortunately, reacting **364** with catalyst **370** also provided the undesired product **369** in a 65% yield (entry 3, **Table 5.4**). This last result led us to the hypothesis that the formation of the unwanted cycloheptene **369** could be the result of a conformational bias in the macrocyclic precursor **364**. Having lost significant amounts of compound **364**, we decided to turn our attention towards the formation of macrolactone *via* an intramolecular HWE reaction.



Entry	Conditions	Result
1	**306** (5 mol%) CH_2Cl_2, reflux, overnight	70% **369**
2	**307** (10 mol%) CH_2Cl_2, RT, overnight	degradation
3	**370** (20 mol%) CH_2Cl_2, RT, 4 h	65% **369**

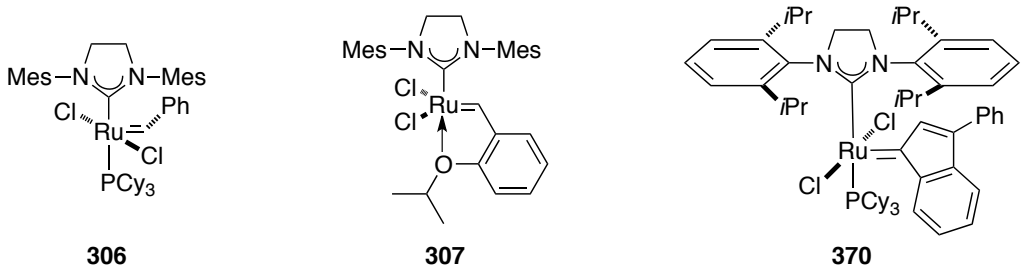
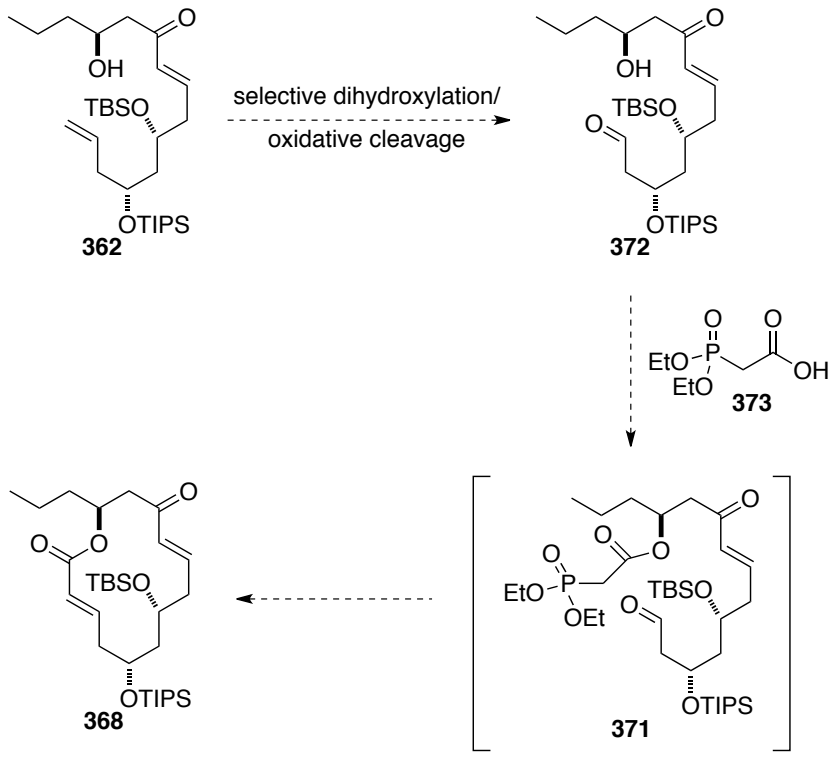


Table 5.4. Attempts at ring closing metathesis of **364**.

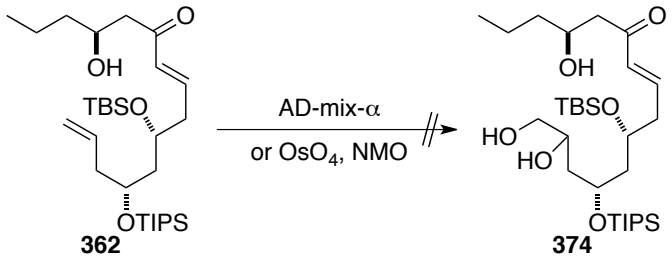
5.3.4 Macrocyclisation *via* an HWE reaction

In order to study the intramolecular HWE reaction, the appropriate intermediate **371** had to be prepared. This could be achieved by selective dihydroxylation of alkene **362**, followed by oxidative cleaved of the intermediate diol to form aldehyde **372** (**Scheme 5.17**).[162,163] From this aldehyde, Yamaguchi esterification with commercially available diethylphosphonacetic acid **373** would provide the required ketophosphonate **371** that would then be used directly in an HWE reaction to form the desired macrolactone **368**.



Scheme 5.17. Revised macrocyclisation strategy.

Unfortunately, selective dihydroxylation of **362** using AD-mix-α did not provide the desired diol **374** and the starting material was recovered (**Scheme 5.18**). Dihydroxylation with osmium tetroxide in presence of NMO was also unsuccessful and led to the degradation of alkene **362**. Unfortunately, further studies of this reaction were not possible due to the lack of advanced alkene **362** and of its precursor, alkyne **355**.



Scheme 5.18. Selective dihydroxylation attempt using AD-mix-α.

5.4 Conclusion

In conclusion, the coupling between vinyl stannane **268** and epoxide **320** was investigated but proved unsuccessful. Addition of *bis*-stannyl compound **42** to epoxide **320** was also attempted but did not provide the desired coupling product.

The C2-C10 alkyne **347** and C11-C16 aldehyde **348** fragments of neopeltolide were prepared and successfully coupled *via* the addition of the lithium anion of **347** to aldehyde **348**. From this coupled product, advanced intermediate **364** in the synthesis of neopeltolide's macrolactone was prepared. The formation of the 14-membered macrocyclic ring was attempted by way of ring closing metathesis but this led to the unexpected formation of cycloheptene **369**. Future work on the completion of neopeltolide **211** will be presented in the next chapter.

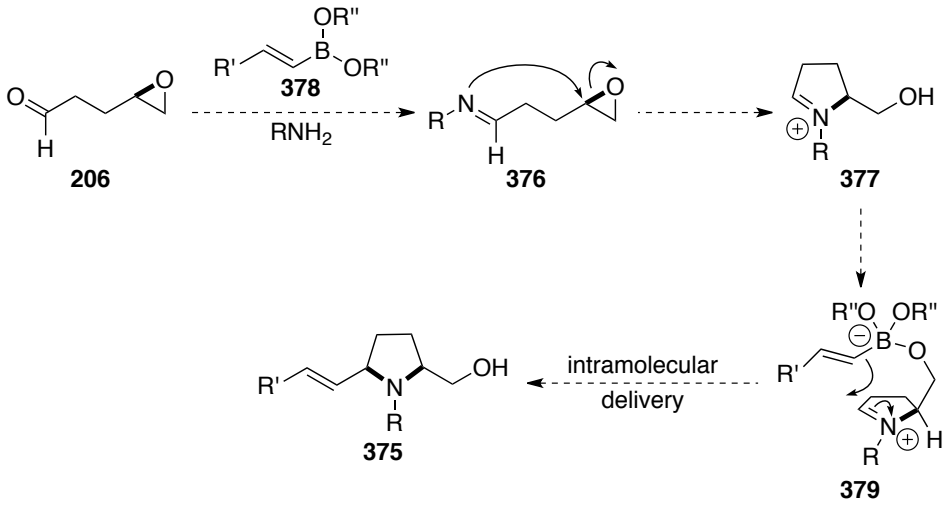
Chapter Six

Summary and Future Work

6.1 Cyclisation of epoxyaldehydes

As it has been outlined previously (see **section 2.5**, **Scheme 2.26**), the addition cyclisation of epoxyaldehydes could be extended to the synthesis of 2,5-*syn* or *anti* THF rings. Application of this method could then be expanded to the ambitious polyepoxide cyclisation to form the BCD ring system of the annonaceous acetogenin chamuvarinin **225** in a single transformation (see **section 2.7**, **Scheme 2.31**).

These applications could also be extended to the synthesis of *N*-heterocycles *via* the development of a multicomponent domino reaction. For instance, reaction of epoxyaldehyde **206** in a substrate-directed Petasis boronic ester-Mannich reaction would provide an easy access to 2,5-*syn*-pyrrolidine **375** (**Scheme 6.1**). Reaction between epoxyaldehyde **206** and a suitable primary amine would lead to the formation of imine **376** that would cyclise on the epoxide to provide the cyclic iminium ion **377**. Reaction between the hydroxyl group and vinyl boronic ester **378** would give intermediate **379**. From this intermediate, intramolecular delivery would provide the 2,5-*syn*-pyrrolidine **375**.

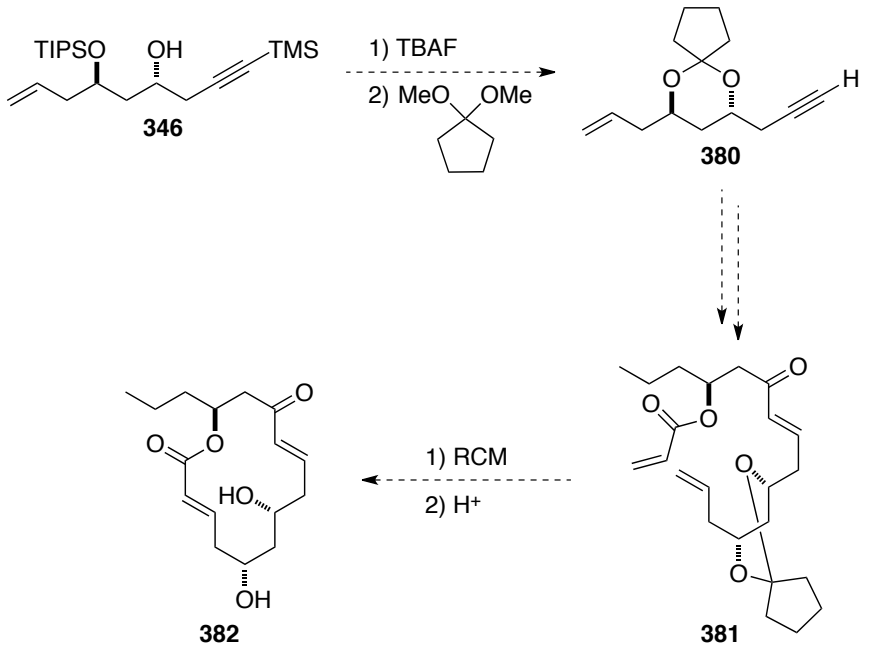


Scheme 6.1. Development of multicomponent domino reaction to pyrrolidines.

6.2 Completion of the formal synthesis of neopeltolide

6.2.1 Proposed synthesis of neopeltolide macrolactone 382

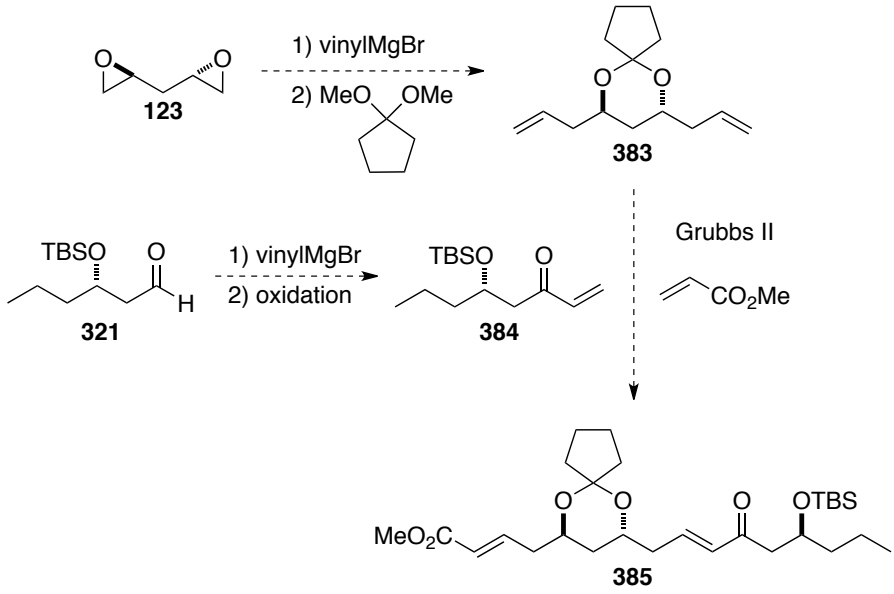
The proposed synthesis of neopeltolide macrolactone is outlined in **Scheme 6.2**. Silyl deprotection of alkyne **346**, followed by protection of C5 and C7 hydroxyl group as a cyclopentylidene acetal would provide intermediate **380**. The alkyne **380** would be transformed into macrolactone precursor **381** using procedures we developed previously (chapter 5, sections **5.2.3** and **5.3.1**). Ring-closing metathesis, followed by diol deprotection would provide macrolactone **382**. It was envisaged that the presence of the cyclopentylidene protecting group at C5 and C7 would restrict flexibility and make the formation of by-product **369** (chapter 5, **section 5.3.2**) more difficult.



Scheme 6.2. Proposed synthesis of macrolactone **382**.

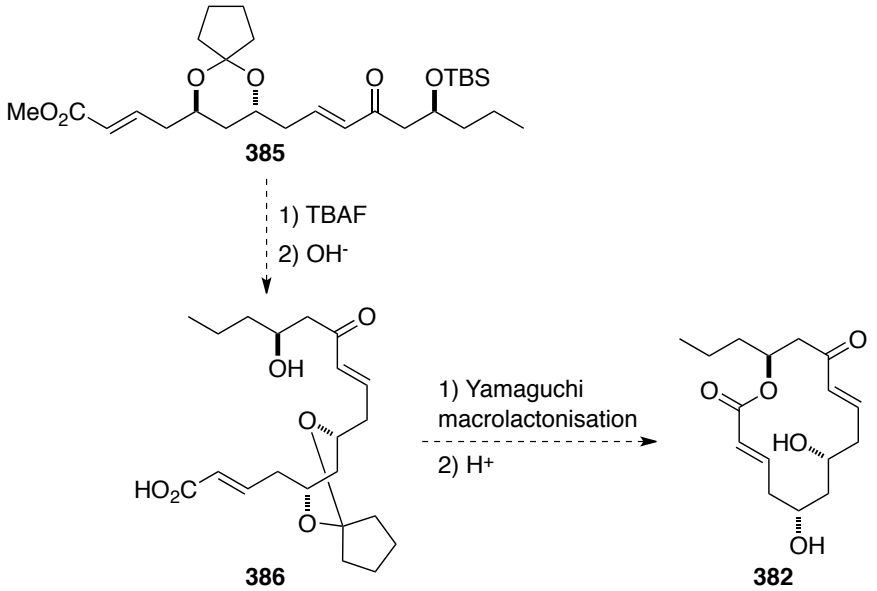
6.2.2 Second generation synthesis of macrolactone 382

A second generation synthesis of macrolactone **382** would require the synthesis of C2-symmetric diene **383**. The synthesis of this diene would start from (*S*,*S*)-diepoxypentane **123**[164] by a double opening using vinylmagnesium bromide, followed by protection of the diol a cyclopentylidene acetal to provide **383** (**Scheme 6.3**). A three component cross-metathesis between diene **383**, methyl acrylate and α,β-unsaturated ketone **384**, prepared from aldehyde **321** by addition of vinyl magnesium bromide, followed by oxidation, would provide macrolactone precursor **385**.[133]



Scheme 6.3. Three component cross-metathesis approach to macrolactone precursor **385**.

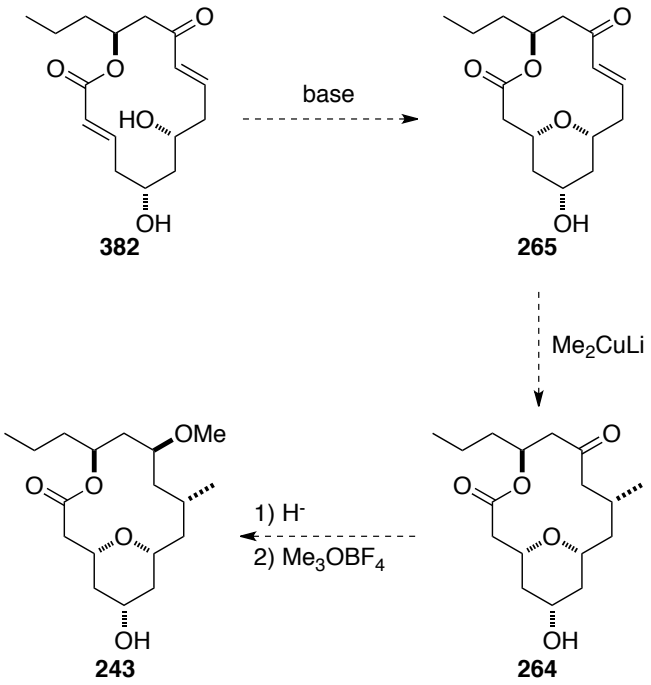
From advanced intermediate **385**, silyl deprotection, followed by ester hydrolysis would provide carboxylic acid **386**. Yamaguchi macrolactonisation and subsequent deprotection of cyclopentylidene acetal would result in the formation of macrolactone **382** (**Scheme 6.4**).



Scheme 6.4. Proposed synthesis of macrolactone **382**.

6.2.3 Completion of the formal synthesis of neopeltolide

Treatment of diol **382** with a base would allow a Michael conjugate to take place and provide the 2,6-*cis*-THP ring **265**. The macrocycle conformation would direct the 1,4-Addition of a methyl on enone **265** and would allow to introduce the C9 methyl with the correct stereochemistry. The macrocycle conformation would also direct the addition of an hydride on the *re* face of ketone **264** and methylation using Meerwein's salt would provide the fully elaborated macrolactone ring **243** and complete neopeltolide's formal synthesis (**Scheme 6.5**).



Scheme 6.5. Completion of neopeltolide formal synthesis.

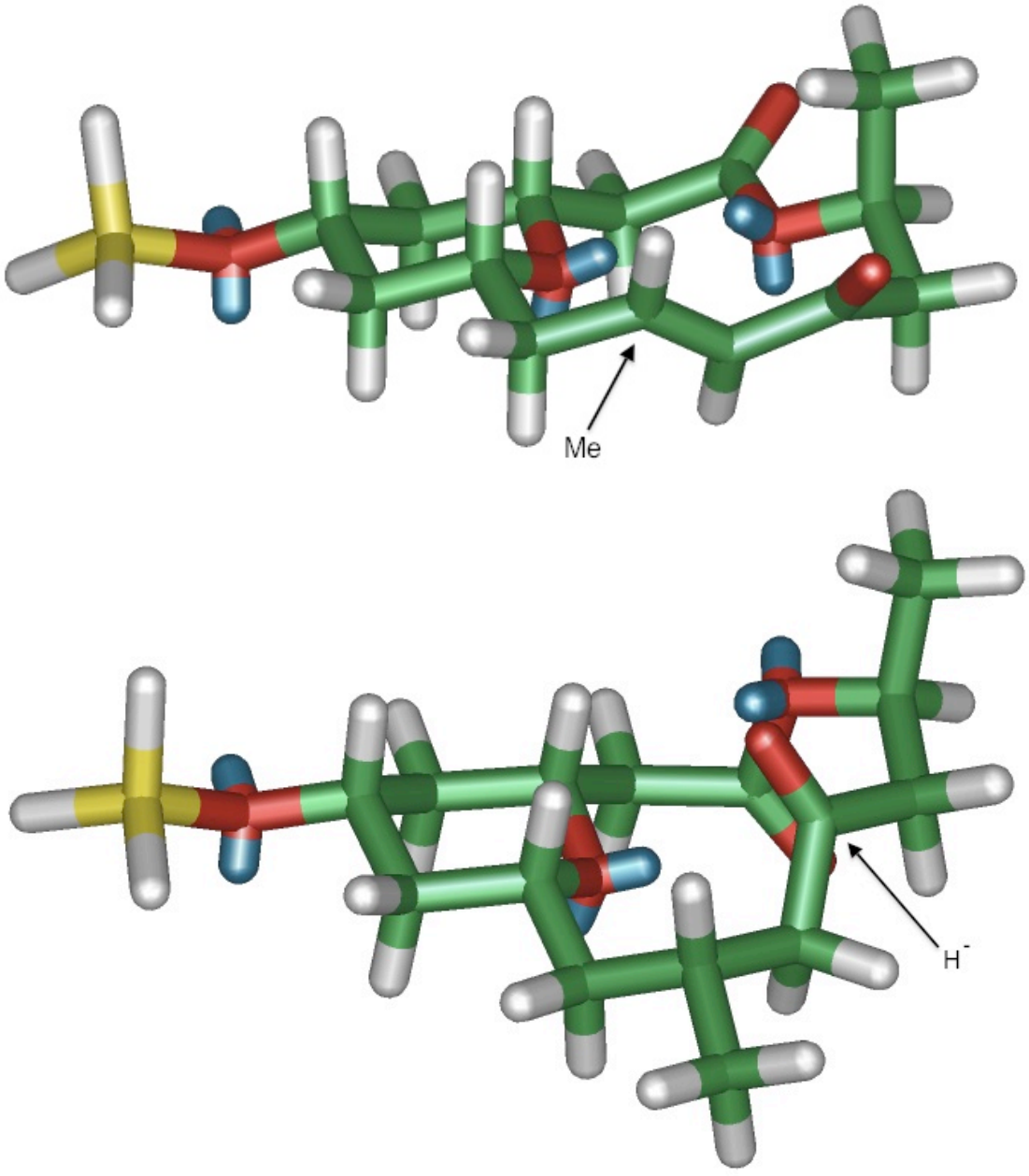


Figure 6.1. Low energy conformations of enone **265** and ketone **264**.

6.3 Summary

Part One:

In conclusion, we have developed a practical protocol to form THF rings by the one-pot addition cyclisation of lithium acetylides to diepoxides. This protocol was applied using (*R*,*R*)-diepoxyhexane **122** and the addition of lithium species was extended to alkyl and alkenyl providing access to 2,5-*syn*-THF rings. The addition/cyclisation of lithium acetylides was also applied to epoxypentanal **200** and provided a second practical access to THF rings. We also developed a protocol for the synthesis of *bis*-THF rings by the one-pot addition cyclisation of lithium species to triepoxides. The extension of the one-pot THF synthesis to the formation of THP rings was also investigated but our efforts were unsuccessful.

Part Two:

In the synthesis of neopeltolide, the coupling of subunits **347** and **348** was achieved and the macrolactone precursor **364** was prepared. However, our attempts in the preparation of the macrocyclic ring were not successful but useful information was gained in the process and will help in the completion of neopeltolide formal synthesis.

In conclusion, although the synthesis of neopeltolide was not achieved, significant progress was made and important information regarding the formation of both the 2,6-*cis*-THP-ring and the macrolactone ring was obtained during these studies.

Chapter Seven

Experimental

7.1 General comments

All reactions were performed in flame-dried glassware under positive pressure of Ar with magnetic stirring unless otherwise stated.

^{1}H NMR (*nuclear magnetic resonance*) spectra were recorded using an internal deuterium lock at ambient probe temperature on the following instruments: Bruker Avance 300 (300.1 MHz), Bruker Avance II 400 (400.1 MHz) instrument or Bruker Avance 500 (499.9 MHz). An internal reference of δ_H 7.27 was used for the residual protons in $CDCl_3$. Date are presented as follows: chemical shift (in ppm on the δ scale relative to $\delta_{TMS} = 0$), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad), coupling constant (*J*/Hz) and interpretation. Coupling constants were taken directly from the spectra and are uncorrected. Assignments were determined either on the basis of unambiguous chemical shift, coupling pattern or by analogy to fully interpreted spectra for related compounds. *^{13}C NMR* spectra were recorded on a Bruker Avance 300 (75 MHz) instrument, Bruker Avance II 400 (100 MHz) or Bruker Avance 500 (125 MHz) at ambient probe temperature using internal deuterium lock, and all chemical shift values are reported in ppm on the δ scale ($\delta_{TMS} = 0$). An internal reference of δ_C 77.0 was used for $CDCl_3$.

IR (*Infrared*) spectra were recorded on a Perkin-Elmer Paragon series 1000 FTIR spectrometer as thin films between potassium bromide discs or neat on a polytetrafluoroethylene (PTFE) card, absorption maxima are reported in wave numbers (cm^{-1}).

Optical rotations were recorded using a Perkin-Elmer Model 341 automatic polarimeter instrument at the sodium D line (589 nm) and are reported as: $[\alpha]_D^{20}$, concentration (*c* in g/ 100mL) and solvent.

Melting points (*mp*) were recorded in glass capillaries using a Gallenkamp Griffin MPA350.BM2.5, and are uncorrected.

Chiral GC was performed on an Agilent 6890 series GC system with a Supelco Betadex 120 column (30 m, 0.25 mm, 0.25 μm).

HRMS and LRMS (High and Low resolution mass spectrometry) were recorded using a Thermofisher LTQ Orbitrap XL mass spectrometer, Finnigan MAT 900 XLT mass spectrometer, Micromass Quattro II mass spectrometer, Waters ZQ4000 mass spectrometer or a Thermofisher DSQ-II mass spectrometer by EPSRC national mass spectrometry service (Swansea, UK) using Electron Impact (EI), Electrospray Ionisation (ES), Chemical Ionisation (CI), Fast Atom Bombardment (FAB) or Atmospheric Pressure Chemical Ionisation (APCI) techniques. Other spectra were recorded on a Micromass LCT mass spectrometer by the University of St Andrews mass spectrometry service (School of Chemistry and Biomolecular Sciences). The parent ion (M^+, $[M+H]^+$, $[M+Na]^+$ or $[M+NH_4]^+$) is quoted, followed by significant fragments with relative intensities (%).

Analytical thin layer chromatography (TLC) was performed on Merck pre-coated (25 μm) silica gel 60F-254 plates. Reagent grade ethyl acetate, diethyl ether and hexanes (commercial mixture) were purchased and used as is for chromatography. Visualisation was by absorption of UV light and/or thermal development after dipping in either an aqueous solution of potassium permanganate, phosphomolybdic acid or anisaldehyde dips.

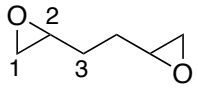
Kugelrohr bulb-to-bulb distillations were carried out using a Büchi Glass Oven B-585 machine. Boiling points are the actual oven temperatures.

Reagents and solvents were purified by standard means.[165] Methanol was distilled from magnesium methoxide in a recycling still under nitrogen. Dichloromethane (DCM), toluene (PhMe), tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by passage through two columns of alumina using a MBRAUN SPS-800 solvent purification system under Ar. Anhydrous *N*,*N'*-dimethylformamide (DMF) was purchased from Aldrich UK and dried by distillation from 4Å molecular sieves under Ar atmosphere. Triethylamine (Et_3N), BF_3•Et_2O and 2,6-lutidine were distilled from CaH_2 under Ar. All other reagents were used as purchased from Aldrich UK, Acros UK, Avocado UK or Molekula. All other chemicals were used as received, except otherwise stated in the experimental procedures.

Aqueous solutions of sodium bicoarbonate ($NaHCO_3$), sodium chloride (brine), potassium sodium tartrate and ammonium chloride (NH_4Cl) were saturated. All experiments were performed under anhydrous conditions and an inert atmosphere of argon, using a vacuum manifold with argon passed through calcium chloride and self-indicating silica gel. Hexane refers to *n*-hexane and petroleum ether (PE) to the fraction boiling between 40 and 60 °C. Room temperature (RT) refers to the temperature of approximately 20 °C.

7.2 Experimental for chapter two

Preparation of (2,5)-diepoxyhexane (**144**)[73]

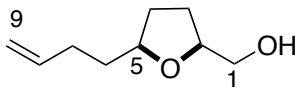


144

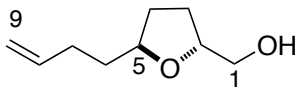
To a solution of 1,5-hexadiene (25.0 mL, 210 mmol) in DCM (350 mL) at 0 ºC was added *m*CPBA (91.0 g, 530 mmol) and the mixture was stirred at RT. After 16 h, H_2O (100 mL) was added and the aqueous layer was extracted with DCM (3 x 125 mL). The combined organic layers were washed with 1M KOH solution (4 x 200 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (70% Et_2O/PE) gave diepoxide **144**, as a colourless oil (17.5 g, 73 %).

R_f 0.52 (40% EtOAc/PE); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.95-2.89 (m, 2H, H_2), 2.73 (2H, app t, J = 4.9 Hz, H_{1a}), 2.45 (2H, app dd, J = 4.9, 2.7 Hz, H_{1b}), 1.70-1.58 (4H, m, H_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 51.8 (0.5C, CH $_{2\ meso}$), 51.5 (0.5C, CH $_{2\ rac}$), 47.0 (1C, $CH_{2\ 1\ rac\ +\ meso}$), 29.2 (0.5C, $CH_{2\ 3\ meso}$), 28.7 (0.5C, $CH_{2\ 3\ rac}$); *m/z* (ES^+) 137 (100, $[M+Na]^+$).

Preparation of 5-allyl-5-(hydroxymethyl)-tetrahydrofuran (**157**,**158**)



(±)-**157**



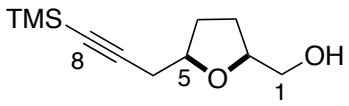
(±)-**158**

To a suspension of CuI (68.0 mg, 0.357 mmol) in Et_2O (5 mL) at -40 ºC was added allylmagnesium bromide (1.30 mL of a 1 M solution in Et_2O, 1.30 mmol). After 30 min, a solution of diepoxide **144** (136 mg, 1.19 mmol) in Et_2O (1 mL) was added dropwise. The mixture was warmed to RT and stirred for 2 h. NH_4Cl (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (4 x 20 mL) and the combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and

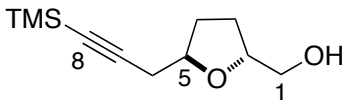
evaporated under reduced pressure. The residue was dissolved in MeOH (10 mL) and K_2CO_3 (330 mg, 2.38 mmol) was added. The suspension was stirred at RT for 16 h. After filtration, the solution was concentrated and purification by flash column chromatography on silica gel (40% EtOAc/PE) afforded a mixture of THF alcohol diastereoisomers **157** and **158**, as a colourless oil (90.0 mg, 48%).

R_f 0.47 (40% EtOAc/PE); **IR** (PTFE) 3299, 2907, 2851, 1278, 1191, 1032, 909 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.89-5.79 (1H, m, H_8), 5.07-5.01 (1H, m, H_{9a}), 4.99-4.95 (1H, m, H_{9b}), 4.15-4.09 (1H, m H_2), 4.04-3.88 (1H, m, H_5), 3.72-3.62 (1H, m, H_{1a}), 3.52-3.47 (1H, m, H_{1b}) 2.18-1.91 (4H, m, H_{3a} + H_{4a} + H_7), 1.74-1.50 (4H, m, H_{3b} + H_{4b} + H_6); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.3, 114.5, 79.5, 79.2, 78.8, 65.2, 65.0, 35.0, 34.8, 31.9, 31.3, 30.4, 27.5, 27.0; *m/z* (ES^+) 170 (100, $[M+Na]^+$); **HRMS** (ES^+) Calc. for $C_9H_{16}O_2Na$ $[M+Na]^+$170.1048; found 179.1043.

Preparation of 2-(hydroxymethyl)-5-(3-(trimethylsilyl)-prop-2-ynyl)-tetrahydrofuran (**159**, **160**)



(±)-**159**

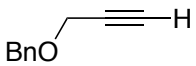


(±)-**160**

To a solution of TMS acetylene (830 µL, 5.89 mmol) in THF (25 mL) at -78ºC was added added *n*-butyllithium (3.68 mL of a 1.6 M solution in hexane, 5.89 mmol) and the mixture was stirred for 30 min. A solution of diepoxide **144** (560 mg, 4.91 mmol) in THF (7 mL) was added, followed by the dropwise addition of BF_3•Et_2O (910 µL, 7.37 mmol). The mixture was warmed to -40 ºC and was stirred for 1.5 h. NH_4Cl (15 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 40 mL) and the combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (25% EtOAc/ PE) gave a mixture of THF alcohol diastereoisomers **159** and **160**, as a colourless oil (800 mg, 77%).

R_f 0.26 (25% EtOAc/PE); **IR** (PTFE) 3423, 2954, 2894, 2873, 1457, 1414, 1366, 1247, 1054, 1027, 841, 758 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.21-4.11 (1H, m, H_2), 4.09-4.04 (1H, m, H_5), 3.77-3.63 (1H, m, H_{1a}), 3.51-3.43 (1H, m, H_{1b}), 2.62-2.37 (2H, m, H_6), 2.12-1.70 (4H, m, H_3 + H_4), 0.14-0.13 (9H, s, Si-(CH_3)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 103.4, 103.3, 86.8, 86.3, 79.9, 79.9, 77.4, 77.1, 65.2, 64.9, 31.2, 30.3, 27.3, 27.2, 26.7, 26.2, 0.03, -0.02; *m/z* (CI^+) 213 (35, $[M+H]^+$), 230 (20, $[M+NH_4]^+$); **HRMS** (ES^+) Calc. for $C_{11}H_{24}O_2NSi$ $[M+NH_4]^+$ 230.1571; found 230.1566.

Preparation of 3-benzyloxy-prop-1-yne (**385**)[166]

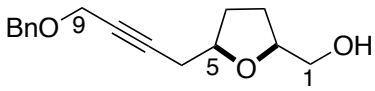


385

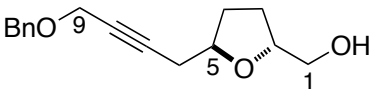
To a solution of propargyl alcohol (2.00 mL, 33.9 mmol) in THF/DMF (1:1, 100 mL) at 0 °C was added NaH (895 mg, 37.3 mmol, 60 wt% dispersion in mineral oil) and the mixture was stirred for 30 min. Benzyl bromide (4.40 mL, 37.3 mmol) was added dropwise and the mixture was stirred at RT for 24 h. NH_4Cl (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (4 x 50 mL) and the combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (20% EtOAc/ PE) gave benzyl ether **385**, as a colourless oil (4.70 g, 95%).

R_f 0.26 (25% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40-7.31 (5H, m, H_{Ar}), 4.62 (2H, s, CH_2-Ph), 4.18 (2H, d, *J* = 2.4 Hz, CH_2OBn), 2.48 (1H, t, *J* = 2.4 Hz, C≡C-H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.2, 128.9, 128.7, 128.3, 128.0, 127.8, 79.5, 74.5, 71.4, 56.9.

Preparation of 5-(4-(benzyloxy)-but-2-ynyl)-2-(hydroxymethyl)-tetrahydrofuran (**161**, **162**)



(±)-**161**

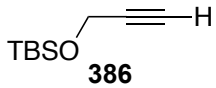


(±)-**162**

To a solution of alkyne **385** (237 mg, 1.62 mmol) in THF (7 mL) at -78 ºC was added *n*-butyllithium (1.01 mL of a 1.6 M solution in hexane, 1.62 mmol) and the mixture was stirred for 30 min. A solution of diepoxide **144** (154 mg, 1.35 mmol) in THF (3 mL) was added, followed by the dropwise addition of BF_3•Et_2O (250 μL, 2.03 mmol). The mixture was warmed to -40 ºC and was stirred for 1.5 h. NH_4Cl (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 15 mL) and the combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (40% EtOAc/PE) provided a mixture of THF alcohol diastereoisomers **161** and **162**, as a colourless oil (256 mg, 73%).

R_f 0.26 (40% EtOAc/PE); **IR** (PTFE) 3277, 2913, 2845, 1191, 1141, 1060, 696 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37-7.30 (5H, m, H_{Ar}), 4.59 (2H, s, C$\underline{H_2}$-Ph), 4.19-4.09 (4H, m, H_2 + H_5 + C$\underline{H_2}$OBn), 3.73-3.61 (1H, m, H_{1a}), 3.55-3.49 (1H, m, H_{1b}), 2.78 (1H, br, OH), 2.55-2.52 (2H, m, H_6), 2.14-1.72 (4H, m, H_3 + H_4); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.3, 128.2, 127.8, 127.6, 83.3, 83.2, 80.0, 79.8, 77.4, 77.2, 71.3, 71.2, 64.8, 64.6, 57.5, 57.4, 31.1, 30.4, 27.2, 26.8, 25.4, 25.3; *m/z* (ES^+) 283 (100, $[M+Na]^+$); **HRMS** (ES^+) Calc. for $C_{16}H_{20}O_3Na$ $[M+Na]^+$ 283.1310; found 283.1316.

Preparation of 3-(*tert*-butyldimethylsilyloxy)-prop-1-yne (**386**)[167]



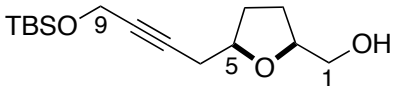
386

To a solution of propargyl alcohol (2.80 g, 49.9 mmol) in DCM (20 mL) at 0 °C was added imidazole (3.61 g, 52.4 mmol) and TBSCl (7.69 g, 50.9 mmol). The mixture was stirred at RT for 16 h, filtered through a plug of silica and washed with H_2O (100 mL). The organic

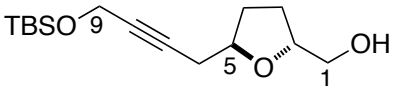
layer was separated, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The TBS ether **386**, was obtained a colourless oil (8.15 g, 96%).

R_f 0.90 (10% EtOAc/PE); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.27 (2H, d, *J* = 2.4 Hz, C$\underline{H}_2$OTBS), 2.36 (1H, t, *J* = 2.4 Hz, C≡C-$\underline{H}$), 0.87 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.08 (6H, s, Si-(C$\underline{H}_3$)$_3$).

Preparation of 5-(4-(*tert*-butyldimethylsilyloxy)-but-2-ynyl)-2-(hydroxymethyl)-tetrahydrofuran (**163**,**164**)



(±)-**163**

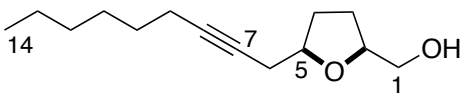


(±)-**164**

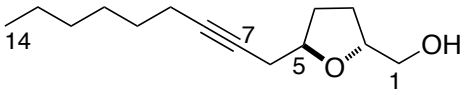
To a solution of alkyne **386** (438 mg, 2.58 mmol) in THF (7 mL) at -78 ºC was added *n*-butyllithium (1.61 mL of a 1.6 M solution in hexane, 2.58 mmol) and the mixture was stirred for 30 min. A solution of diepoxide **144** (245 mg, 2.15 mmol) in THF (3 mL) was added, followed by the dropwise addition of BF_3•Et_2O (400 μL, 3.22 mmol). After 1.5h, NH_4Cl (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (30% EtOAc/PE) gave a mixture of THF alcohol diastereoisomers **163** and **164**, as a colourless oil (400 mg, 65 %).

R_f 0.23 (30% EtOAc/PE); **IR** (PTFE) 3412, 2924, 2851, 2235, 1462, 1367, 1256, 1071, 839, 777 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.21 (2H, t, *J* = 2.1 Hz, H_9), 4.07-3.96 (2H, m, H_2 + H_5) 3.63-3.52 (1H, m, H_{1a}), 3.45-3.38 (1H, m, H_{1b}), 2.43-2.33 (2H, m, H_6), 2.02-1.60 (4H, m, H_3 + H_4), 0.82 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.03 (6H, s, Si-(C$\underline{H}_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 81.4, 81.4, 80.1, 80.0, 80.0, 79.9, 77.4, 77.3, 64.8, 64.6, 51.7, 51.6, 31.0, 30.3, 29.0, 28.5, 27.2, 26.8, 25.6, -5.4; *m/z* (ES^+) 307 (100, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{15}H_{28}O_3NaSi$ $[M+Na]^+$ 307.1705; found 307.1710

Preparation of 2-(hydroxymethyl)-5-(oct-2-ynyl)-tetrahydrofuran (**165**, **166**)



(±)-**165**

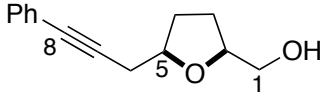


(±)-**166**

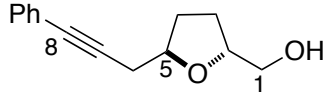
To a solution 1-octyne (235 μL, 1.31 mmol) in THF (15 mL) at -78 ºC was added *n*-butyllithium (990 μL of a 1.6 M solution in hexane, 1.58 mmol) and the mixture was stirred for 30 min. A solution of diepoxide **144** (150 mg, 1.31 mmol) in THF (5 mL) was added at -78 ºC, followed by the dropwise addition of BF_3•Et_2O (240 μL, 1.58 mmol). The mixture was warmed to -40 ºC and stirred for 1.5 h. NH_4Cl (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 15 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (40% EtOAc/ PE) afforded a mixture of THF alcohol diastereoisomers **165** and **166**, as a colourless oil (205 mg, 62%).

R_f 0.3 (30% EtOAc/PE); **IR** (PTFE) 3395, 2924, 2857, 2212, 1457, 1376, 1183, 1046, 875 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.16-3.96 (2H, m, H_2 + H_5), 3.70-3.57 (1H, m, H_{1a}), 3.48-3.42 (1H, m, H_{1b}), 2.67 (1H, br, OH), 2.12-1.66 (2H, m, H_6), 2.12-1.66 (6H, m, 3 x CH_2), 1.46-1.12 (8H, m, 4 x CH_2), 0.84 (3H, t, J = 7.2 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 82.1, 81.8, 80.0, 79.9, 77.9, 77.9, 76.2, 76.1, 65.1, 64.7, 31.3, 31.1, 30.4, 28.9, 28.8, 28.5, 28.4, 27.3, 27.1, 25.3, 25.3, 22.5, 18.7, 18.6, 13.9; *m/z* (ES^+) 242 (80, $[M+NH_4]^+$); **HRMS** (ES+) Calc. for $C_{14}H_{28}O_2N$ $[M+NH_4]^+$ 242.2115; found 242.2113.

Preparation of 2-(hydroxymethyl0-5-(3-phenyl-prop-2-ynyl)-tetrahydrofuran (**167**, **168**)



(±)-**167**



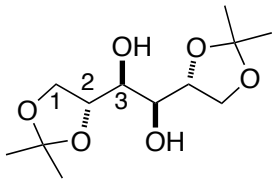
(±)-**168**

To a solution phenylacetylene (240 μL, 2.19 mmol) in THF (7 mL) at -78 ºC was added *n*-butyllithium (1.37 mL of a 1.6 M solution in hexane, 2.19 mmol) and the mixture was

stirred for 30 min. A solution of diepoxide **144** (208 mg, 1.82 mmol) in THF (3 mL) was added, followed by the dropwise addition of BF_3•Et_2O (340 μL, 2.73 mmol). The mixture was warmed to -40 ºC and was stirred for 1.5 h. NH_4Cl (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 15 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (25% EtOAc/PE) provided a mixture of THF alcohol diastereoisomers **167** and **168**, as a colourless oil (315 mg, 80%).

R_f 0.18 (25% EtOAc/PE); **IR** (PTFE) 3412, 2927, 2873, 1489, 1440, 1215, 1059, 755, 691 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42-7.39 (2H, m, H_{Ar}), 7.29-7.26 (3H, m, H_{Ar}), 4.29-4.20 (2H, m, H_2 + H_5), 3.78-3.66 (1H, m, H_{1a}), 3.54-3.49 (1H, m, H_{1b}), 2.75-2.58 (2H, m, H_6), 2.26 (1H, br s, OH), 2.19-1.71 (4H, m, H_3 + H_4); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 131.5, 128.2, 128.1, 127.7, 123.5, 86.4, 81.9, 80.0, 79.9, 77.6, 77.5, 65.1, 64.9, 31.3, 30.5, 27.4, 27.1, 26.2, 26.0; *m/z* (ES^+) 234 (100, $[M+NH_4]^+$), 217 (40 $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{14}H_{20}O_2N$ $[M+NH_4]^+$ 234.1489 found; 234.1486.

Preparation of 1,2,5,6-di-*O*-isopropylidene-D-mannitol (**176**)[78]



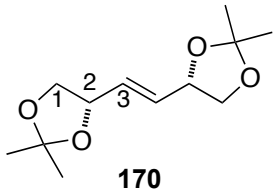
176

To a solution of (D)-mannitol (53.0 g, 291 mmol) in DMF (500 mL) was added 2-methoxypropene (55.7 mL, 582 mmol), *p*TsOH (500 mg, 0.295 mmol) and calcium sulfate (2.50 g). The mixture was stirred at RT for 2 h and 2-methoxypropene (11.1 mL, 116 mmol) was added and the mixture was stirred for 30 min. Sodium carbonate (15.6 g, 147 mmol) was added and stirring was continued for 1 h. The mixture was filtered and the solvent was removed under reduced pressure. The residue was recrystallised from hexane to give diol **176**, as a white solid (56.1 g, 73%).

mp 120-121 °C (Lit.[78] 122 °C; $[\alpha]_D^{20}$ +2.2 (*c* 1.5, MeOH) (Lit.[78] +1.9 (*c* 1.74, MeOH));

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21-4.07 (4H, m), 3.99-3.94 (2H, m), 3.76-3.72 (2H, m), 1.41 (6H, s, 2 x CH_3), 1.35 (6H, s, 2 x CH_3).

Preparation of (2*S*,5*S*,*E*)-1,2,5,6-di-*O*-isopropylidene-tetrahydroxyhex-3-ene (**170**)[79]



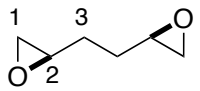
170

To a solution of diol **176** (5.20 g, 22.9 mmol) in THF (40 mL) at RT was added sodium hydride (2.40 g, 60.0 mmol) and the mixture was stirred for 1 h. Carbon disulfide (3.60 mL, 60.0 mmol) was added and the mixture was stirred for 1 h. Iodomethane (7.50 mL, 120 mmol) was added dropwise and the mixture was stirred for 16 h. NH_4Cl (30 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. A portion of the crude dithiocarbonate (3.98, 9.00 mmol) was dissolved in toluene (100 mL). Tributyl tin hydride (6.80 mL, 25.3 mmol) was added and the mixture was refluxed for 24 h. After cooling at RT, the solvent was evaporated under reduced pressure. Purification by flash column chromatography on silica gel (10% EtOAc/PE) provided alkene **170** (1.10, 53%) as a white solid.

mp 75-77 °C (Lit.[79] 75-78 °C; $[\alpha]_D^{20}$ +56.5 (*c* 1.0, $CHCl_3$) (Lit.[79] +57.8 (*c* 1.02, $CHCl_3$));

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (2H, dd, *J* = 3.6, 1.8 Hz, H_3), 4.52-4.46 (2H, m, H_2), 4.05 (2H, dd, *J* = 8.1, 6.0 Hz, H_{1a}), 3.55 (2H, t, *J* = 7.8 Hz, H_{1b}), 1.39 (6H, s, 2 x CH_3), 1.35 (6H, s, 2 x CH_3)

Preparation of (2*R*, 5*R*)-diepoxyhexane (**122**)[76]

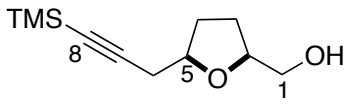


122

To a solution of (*R*,*R*)-*N*,*N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) salen complex (420 mg, 0.69 mmol) in toluene (15 mL) was added acetic acid (85.0 µL, 1.39 mmol) and the mixture was stirred for 30 min. The solvent was removed under reduced pressure and a solution of 1,5-diepoxyhexane **144** (5.30 g, 46.49 mmol) in THF (10 mL) was added. The solution was cooled to 0 ºC and H_2O (670 µL, 37.19 mmol) was added dropwise. The mixture was stirred at RT for 16 h, followed by filtration over a pad of silica. The filter cake was washed with Et_2O and the solvent was removed under reduced pressure. Purification by distillation using a short bend gave diepoxide **122** as a colourless oil (1.11 g, 21%)

R_f 0.52 (40% EtOAc/PE); $[\alpha]_D^{20}$ +20.4 (*c* 1.3, $CHCl_3$) (Lit.[76] $[\alpha]_D^{20}$ +18.5 (*c* 2.2, $CHCl_3$)); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.99-2.97 (2H, m, H_2), 2.77 (2H, app t, *J* = 4.9 Hz, H_{1a}), 2.51-2.49 (2H, dd, *J* = 4.9, 2.7 Hz, H_{1b}), 1.75-1.65 (4H, m, H_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 51.6, 47.1, 28.7.

Preparation of (2*S*)-(hydroxymethyl)-(5*R*)-(3-(trimethylsilyl)-prop-2-ynyl)-tetrahydrofuran (**189**)



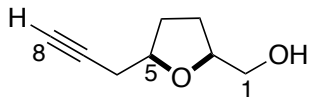
189

To a solution of TMS acetylene (270 µL, 1.89 mmol) in THF (7 mL) at -78 ºC was added *n*-butyllithium (1.18 mL of a 1.6 M solution in hexane, 1.89 mmol) and the mixture was stirred for 30 min. A solution of (*R*,*R*)-1,5-diepoxyhexane **122** (180 mg, 1.58 mmol) in THF (3 mL) was added, followed by the dropwise addition of BF_3•Et_2O (290 µL, 2.37 mmol). After 1.5 h, NH_4Cl (10 mL) was added and the organic layer was separated. The

aqueous layer was extracted with DCM (3 x 15 mL) and the combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (25% EtOAc/PE) gave THF alcohol **189**, as a colourless oil (250 mg, 75%).

R_f 0.26 (25% EtOAc/PE); $[\alpha]_D^{20}$ +47.2 (*c* 1.4, $CHCl_3$); **IR** (PTFE) 3423, 2954, 2900, 2873, 2172, 1459, 1408, 1368, 1247, 1053, 1026, 841, 758 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.11-4.04 (2H, m, H_2 + H_5), 3.76 (1H, dd, *J* = 11.4, 2.7 Hz, H_{1a}), 3.52-3.47 (1H, m, H_{1b}), 2.61 (1H, dd, *J* = 16.8, 5.7 Hz, H_{6a}), 2.50 (1H, dd, *J* = 17.1, 3.9 Hz, H_{6b}), 2.19 (1H, br s, OH), 2.01-1.88 (4H, m, H_3 + H_4), 0.16 (9H, s, Si-($C\underline{H}_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 103.3, 86.8, 79.9, 77.1, 65.3, 30.4, 27.2, 26.2, 0.0; *m/z* (CI^+) 230 (100, $[M+NH_4]^+$); **HRMS** (ES^+) Calc. for $C_{11}H_{24}O_2NSi$ $[M+NH_4]^+$ 230.1571; found 230.1568.

Preparation of (2*S*)-(hydroxymethyl)-(5*R*)-(prop-2-ynyl)-tetrahydrofuran (**188**)

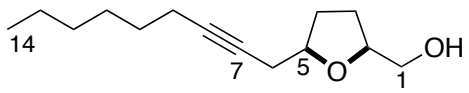


188

To a solution of alkyne **189** (50.0 mg, 0.236 mmol) in MeOH (5 mL) was added K_2CO_3 (65.0 mg, 0.471 mmol) and the mixture was stirred at RT for 16h. Water (5 mL) was added and the aqueous layer was extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatographyon silica gel (50% EtOAc/PE) provided alkyne **188**, as a colourless oil (22 mg, 67%).

R_f 0.30 (50% EtOAc/PE); $[\alpha]_D^{20}$ +25.5 (*c* 1.7, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.15-4.06 (2H, m, H_2 + H_5), 3.77 (1H, dt, *J* = 11.7, 3.3 Hz, H_{1a}), 3.56-3.48 (1H, m, H_{1b}), 2.51 (1H, dd, *J* = 5.1, 2.7 Hz, H_{6a}), 2.49 (1H, dd, *J* = 4.2, 2.7 Hz, H_{6b}), 2.13 (1H, t, *J* = 6.3 Hz, OH), 2.07-1.83 (4H, m, H_3 + H_4); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 80.9, 79.9, 77.2, 70.0, 65.1, 30.5, 27.0, 25.0; *m/z* (ES^+) 163 (100, $[M+Na]^+$); **HRMS** (ES^+) Calc. for $C_8H_{12}O_2Na$ $[M+Na]^+$ 163.0735; found 163.0736.

Preparation of (2*S*)-(hydroxymethyl)-(5*R*)-(oct-2-ynyl)-tetrahydrofuran (**190**)

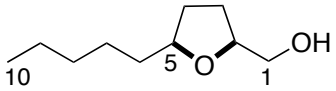


190

To a solution of 1-octyne (235 µL, 1.58 mmol) in THF (7 mL) at -78 ºC was added *n*-butyllithium (990 µL of a 1.6 M solution in hexane, 1.58 mmol) and the mixture was stirred for 30 min. A solution of (*R*,*R*)-1,5-diepoxyhexane **122** (150 mg, 1.31 mmol) in THF (3 mL) was added, followed by the dropwise addition of BF_3•Et_2O (240 µL, 1.97 mmol). The mixture was warmed to -40 ºC over 1.5 h. NH_4Cl (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (30% EtOAc/ PE) provided THF alcohol **190**, as a colourless oil (190 mg, 65%).

R_f 0.3 (30% EtOAc/PE); $[\alpha]_D^{20}$ +20.4 (*c* 1.3, $CHCl_3$); **IR** (PTFE) 3407, 2927, 2857, 2212, 1460, 1376, 1209, 1156, 1051 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.09-4.03 (2H, m, H_2 + H_5), 3.74 (1H, dd, *J* = 11.6, 3.2 Hz, H_{1a}), 3.46-3.40 (1H, dd, *J* = 11.6, 5.0 Hz, H_{1b}), 2.46-2.44 (2H, m, H_6), 2.15 (2H, tt, *J* = 7.1, 2.4 Hz, H_9), 2.01-1.81 (4H, m, H_3 + H_4), 1.48 (1H, d, *J* = 7.3 Hz, H_{10a}), 7.45 (1H, d, *J* = 7.3 Hz, H_{10b}) 1.32-1.19 (6H, m, 3 x CH_2), 0.82 (3H, t, *J* = 7.1 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 82.0, 79.9, 77.8, 76.0, 65.0, 31.2, 30.3, 28.8, 28.4, 27.0, 25.2, 22.4, 18.5, 13.9; *m/z* (CI^+) 242 (100, $[M+NH_4]^+$), 225 (40, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{14}H_{28}O_2N$ $[M+NH_4]^+$ 242.2115; found 242.2114.

Preparation of (2*S*)-(hydroxymethyl)-(5*R*)-(pentyl)-tetrahydrofuran (**191**)



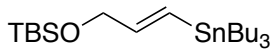
191

A solution of (*R*,*R*)-1,5-diepoxyhexane **122** (160 mg, 1.40 mmol) in THF (3 mL) was added dropwise to a solution of *n*-butyllithium (1.05 mL of a 1.6 M solution in hexane,

1.68 mmol) at -78 ºC in THF (7 mL). BF_3•Et_2O (260 µL, 2.10 mmol) was added dropwise and the mixture was warmed to -40 ºC over 1.5 h. NH_4Cl (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (30% EtOAc/ PE) to gave THF alcohol **191**, as a colourless oil (150 mg, 62%).

R_f 0.53 (25% EtOAc/PE); $[\alpha]_D^{20}$ +9.4 (*c* 1.3, $CHCl_3$); **IR** (PTFE) 3412, 2954, 2927, 2862, 1459, 1376, 1180, 1094, 1040, 884 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.00-3.92 (1H, m, H_2), 3.82 (1H, tt, *J* = 7.8, 6.0 Hz, H_5), 3.63 (1H, dd, *J* = 11.7, 3.6 Hz, H_{1a}), 3.44 (1H, dd, *J* = 11.4, 5.7 Hz, H_{1b}), 2.60 (1H, br s, OH), 1.98-1.80 (2H, m, H_{3a} + H_{4a}), 1.70-1.56 (H_{3b} + H_{4b}), 1.47-1.23 (8H, m, 4 x CH_2), 0.85 (3H, t, *J* = 6.9 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 80.1, 79.2, 35.7, 31.8, 31.2, 27.0, 25.8, 22.5, 13.9; *m/z* (ES^+) 190 (40, $[M+NH_4]^+$), 173 (100, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{10}H_{21}O_2$ $[M+H]^+$ 173.1536; found 173.1537.

Preparation of (3-(*tert*-butyldimethylsilyloxy)-prop-1-enyl)-tri-*n*-butylstannane (**192**)[168]

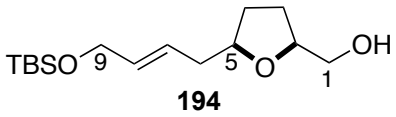


192

To a solution of alkyne **386** (2.00 g, 11.8 mmol) in toluene (50 mL) was added tributyl tin hydride (4.11 mL, 15.3 mmol) and AIBN (77.5 mg, 0.472 mmol). The mixture was refluxed for 16 h and after cooling to RT, the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (hexane) gave vinyl stannane **192**, as a colourless oil (1.10 g, 20%).

R_f 0.32 (hexane); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.16-6.07 (2H, m, H_1 + H_2), 4.21 (2H, dd, *J* = 3.9, 1.2 Hz, H_3), 1.53-1.45 (6H, m, 3 x CH_2), 1.37-1.25 (6H, m, 3 x CH_2), 0.92-0.91 (15H, m, 3 x CH_2 + 3 x CH_3), 0.08 (6H, s, Si-($C\underline{H}_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.3, 126.9, 66.8, 29.1, 27.3, 26.0, 22.7, 13.8, 9.5, -5.1.

Preparation of (5*R*)-(4-(*tert*-butyldimethylsilyloxy)-but-2-enyl)-(2*S*)-(hydroxymethyl)-tetrahydrofuran (**194**)

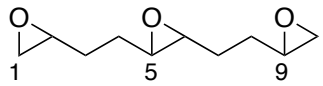


194

To a solution of vinyl stannane **192** (260 mg, 0.562 mmol) in THF (3 mL) at -78 ºC was added added *n*-butyllithium (350 μL of a 1.6 M solution in hexane, 0.562 mmol) and the mixture was stirred for 30 min. A solution of (*R*,*R*)-1,5-diepoxyhexane **122** (53.4 mg, 0.468 mmol) in THF (1 mL) was added at -78 ºC, followed by the dropwise addition of BF_3•Et_2O (86.0 μL, 0.702 mmol). After 1.5 h, NH_4Cl (5 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (25% EtOAc/PE) provided THF ring **194**, as a colourless oil (80 mg, 60%).

R_f 0.47 (30% EtOAc/PE); $[\alpha]_D^{20}$ +9.4 (*c* 1.3, $CHCl_3$); **IR** (PTFE) 3418, 2954, 2927, 2857, 1457, 1247, 1094, 1048, 836 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.67-5.64 (2H, m, H_7 + H_8), 4.16-4.14 (2H, m, H_9), 4.04-3.95 (2H, m, H_2 + H_5), 3.71 (1H, dd, *J* = 11.5, 3.3 Hz, H_{1a}), 3.49 (1H, dd, *J* = 11.5, 5.6 Hz, H_{1b}), 2.41-2.35 (1H, m, H_{6a}), 2.30-2.23 (1H, m, H_{6b}) 1.99-1.72 (4H, m, H_3 + H_{4a}), 0.90 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.07 (6H, s, Si-(C$\underline{H}_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 131.9, 126.7, 79.4, 79.3, 65.2, 63.8, 38.4, 30.7, 26.9, 25.9, 18.4, -5.1; *m/z* (CI^+) 304 (30, $[M+NH_4]^+$); **HRMS** (ES^+) Calc. for $C_{15}H_{34}O_3NSi$ $[M+NH_4]^+$ 304.2302; found 304.2306.

Preparation of (1,5,9)-triepoxydecane (**196**)[88]

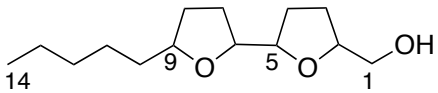


196

To a solution of 1,5,9-decatriene (2.67 mL, 15.0 mmol) in DCM (100 mL) at 0 ºC was added *m*CPBA (11.6 g, 67.5 mmol) and the mixture was stirred at RT for 16 h. H_2O (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (4 x 80 mL) and the combined organic layers were washed with a 1M KOH solution (4 x 80 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (30% Et_2O/PE) gave triepoxide **196**, as a colourless oil (2.18 g, 79 %).

R_f 0.10 (30% Et_2O/PE); **IR** (PTFE) 3547, 2975, 2927, 1446, 1411, 1258, 911, 833 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.97-2.94 (3H, m, H_2 + H_5 + H_9), 2.78-2.74 (3H, m, H_{1a} + H_6 + H_{10a}), 2.51-2.46 (2H, m, H_{1b} + H_{10b}), 1.83-1.58 (8H, m, 4 x CH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 58.3, 58.2, 58.0, 57.9, 56.7, 56.6, 56.5, 56.4, 51.8, 51.5, 51.4, 47.1, 47.0, 59.7, 29.3, 29.3, 29.2, 28.7, 28.2, 24.5, 24.1, 24.1; *m/z* (CI^+) 202 (100, $[M+NH_4]^+$); 185 (80 $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{10}H_{20}O_3N$ $[M+NH_4]^+$ 202.1438; found 202.1441.

Preparation of 2-(hydroxymethyl)-9-(pentyl)-*bis*-tetrahydrofuran (**197**)



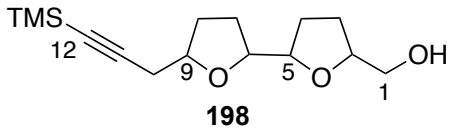
197

A solution of triepoxide **196** (220 mg, 1.19 mmol) in THF (3 mL) was added dropwise to a solution of *n*-butyllithium (890 µL of a 1.6 M in hexane, 1.43 mmol) at -78 ºC in THF (7 mL). BF_3•Et_2O (300 µL, 2.39 mmol) was added dropwise and the mixture was warmed to -20 ºC over 5 h. NH_4Cl (10 mL) was added and the organic layer was separated. The

aqueous layer was extracted with DCM (3 x 15 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (50% EtOAc/PE) afforded a mixture of bis-THF alcohols diastereoisomers **197**, as a colourless oil (210 mg, 70 %).

R_f 0.30 (50% EtOAc/PE); **IR** (PTFE) 3412, 2021, 2857, 1459, 1053 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.19-3.81 (4H, m, H_2 + H_5 + H_6 + H_9), 3.73-3.63 (1H, m, H_{1a}), 3.52-3.44 (1H, m, H_{1b}), 2.23 (1H, br s, OH), 2.04-1.88 (4H, m, 2 x CH_2), 1.76-1.26 (12H, m, 6 x CH_2), 0.89-0.86 (3H, m, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 82.4, 82.3, 82.2, 81.9, 81.8, 81.4, 81.4, 81.3, 81.2, 80.8, 80.8, 80.5, 80.4, 80.3, 80.3, 80.2, 80.2, 80.1, 80.0, 80.0, 79.9, 79.9, 79.9, 79.8, 66.0, 65.9, 65.8, 65.5, 64.9, 64.5, 64.5, 35.8, 35.7, 35.7, 35.7, 35.4, 35.4, 32.1, 31.9, 31.9, 31.9, 31.8, 31.8, 30.9, 30.8, 30.8, 30.7, 29.0, 28.9, 28.7, 28.6, 28.6, 28.5, 28.4, 28.3, 28.0, 27.9, 27.7, 27.6, 27.5, 27.4, 27.3, 27.3, 26.6, 26.4, 25.9, 25.8, 25.8, 25.7, 25.7, 22.6, 22.5; *m/z* (CI^+) 260 (100, $[M+NH_4]^+$), 243 (30, $[M+H]^{\pm}$); **HRMS** (ES^+) Calc. for $C_{14}H_{30}O_3N$ $[M+NH_4]^+$ 260.2220; found 260.2226.

Preparation of 2-(hydroxymethyl)-9-(3-(trimethylsilyl)-prop-2-ynyl)-*bis*-tetrahydrofuran (**198**)

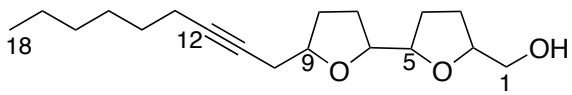


198

To a solution of TMS acetylene (210 μL, 1.49 mmol) in THF (7 mL) at -78 ºC was added *n*-butyllithium (930 μL of a 1.6 M solution in hexane, 1.49 mmol) and the mixture was stirred for 30 min. A solution of triepoxide **196** (228 mg, 1.24 mmol) in THF (3 mL) was added, followed by the dropwise addition of BF_3•Et_2O (310 μL, 2.48 mmol). The mixture was warmed to -20 ºC over 5 h and NH_4Cl (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 15 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (25% EtOAc/PE) provided a mixture of bis-THF alcohol diastereoisomers **198**, as a colourless oil (261 mg, 75 %).

R_f 0.33 (25% EtOAc/PE); **IR** (PTFE) 3428, 2954, 2900, 2873, 2172, 1462, 1411, 1247, 1059, 844, 758 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.17-3.80 (4H, m, H_2 + H_5 + H_6 + H_9), 3.73-3.59 (1H, m, H_{1a}), 3.51-3.44 (1H, m, H_{1b}), 2.57-2.34 (3H, m, H_{10} + OH), 2.16-1.57 (8H, m, 4 x CH_2), 0.12 (9H, s, Si-(C$\underline{H}_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 103.7, 103.6, 103.5, 103.4, 103.3, 103.2, 86.2, 86.1, 86.1, 86.0, 85.9, 82.8, 82.5, 82.3, 82.1, 81.9, 81.9, 81.8, 81.7, 81.5, 81.5, 81.4, 81.2, 81.0, 80.1, 80.0, 80.0, 79.9, 79.8, 77.9, 77.8, 77.7, 77.6, 77.3, 77.2, 65.5, 65.4, 65.3, 65.1, 64.8, 64.7, 64.4, 64.4, 31.1, 31.1, 30.9, 30.8, 30.1, 29.8, 29.7, 28.8, 28.7, 28.6, 28.4, 28.3, 28.2, 28.1, 27.8, 27.8, 27.7, 27.6, 27.4, 27.4, 27.3, 27.2, 27.1, 27.1, 26.8, 26.7, 26.7, 26.6, 26.6, 26.5, 26.4, 26.3, -0.03; *m/z* (CI^+) 300 (100, [M +NH_4]$^+$); **HRMS** (ES^+) Calc. for $C_{15}H_{30}O_3NSi$ [M+NH_4]$^+$ 300.1989; found 300.1987.

Preparation of 2-(hydroxymethyl)-9-(non-2-ynyl)-*bis*-tetrahydrofuran (**199**)



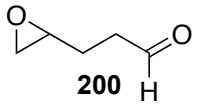
199

To a solution of 1-octyne (215 μL, 1.46 mmol) in THF (7 mL) at -78 ºC was added n-butyllithium (910 μL of a 1.6 M solution in hexane, 1.46 mmol) and the mixture was stirred for 30 min. A solution of triepoxide **196** (224 mg, 1.22 mmol) in THF (3 mL) was added, followed by the dropwise addition of BF_3•Et_2O (300 μL, 2.43 mmol). The mixture was warmed to -20 ºC over 5 h and NH_4Cl (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 15 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (40% EtOAc/PE) afforded a mixture of bis-THF alcohol diastereoisomers **196**, as a colourless oil (210 mg, 59 %).

R_f 0.26 (40% EtOAc/PE); **IR** (PTFE) 3444, 2921, 2857, 1459, 1053 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.16-3.89 (4H, m, H_2 + H_5 + H_6 + H_9), 3.81-3.64 (1H, m, H_{1a}), 3.54-3.46 (1H, m, H_{1b}), 2.57-2.28 (2H, m, H_{10})), 2.17-2.12 (2H, m, H_{13}), 2.06-1.63 (8H, m, 4 x CH_2). 1.51-1.25 (8H, 4 x CH_2), 0.90 (3H, t, *J* = 6.9 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 83.6, 82.8, 82.5, 82.3, 82.1, 82.0, 82.0, 81.8, 81.6, 81.2, 81.1, 80.9, 80.9, 80.3,

80.2, 80.1, 80.0, 80.0, 78.4, 78.3, 73.6, 65.4, 65.2, 64.8, 64.5, 64.5, 64.0, 31.4, 30.3, 30.3, 28.9, 28.8, 28.7, 28.5, 27.8, 27.7, 27.7, 27.4, 27.2, 26.5, 25.7, 25.5, 23.2, 22.6, 22.6, 18.8, 18.7, 14.1; *m/z* (CI^+) 312 (100, $[M+NH_4]^+$), 295 (15, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{18}H_{34}O_3N$ $[M+NH_4]^+$ 312.2533; found 312.2532.

Preparation of 4-epoxypentan-1-al (**200**)[169]

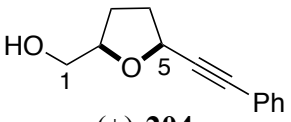


200

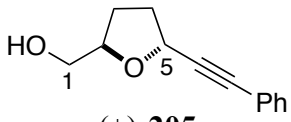
To a solution of 1,2-epoxy-5-hexene (1 mL, 8.86 mmol) in DCM (300 mL) was added solid Na_2CO_3 (2.67 g) and the mixture was cooled at -78 °C. A stream of O_3 was bubbled through for 10 min. The O_3 generator was switched off and O_2 was bubbled through for 5 min. Triphenylphosphine (4.65 g, 17.7 mmol) was added and the mixture was warmed to RT over 1h. The reaction mixture was filtered over a plug of celite and washed with DCM. The residue was suspended in PE and a white precipitate was formed. After filtration, the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (25-50% Et_2O/PE) provided epoxyaldehyde **200**, as a colourless oil (510 mg, 57%).

R_f 0.31 (25% EtOAc/PE); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.84 (1H, t, *J* = 1.2 Hz, CHO), 3.01 (1H, m, H_4), 2.81-2.78 (1H, m, H_{5a}), 2.64 (2H, td, *J* = 7.2, 1.2 Hz, H_2), 2.53 (1H, dd, *J* = 4.8, 2.7 Hz, H_{5b}), 2.12-2.01 (1H, m, H_{3a}), 1.82-1.71 (1H, m, H_{3b}); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.0, 51.1, 47.0, 39.9, 24.7.

Preparation of 2-(hydroxymethyl)-5-(phenylethynyl)-tetrahydrofuran (**204**,**205**)



(±)-**204**

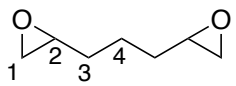


(±)-**205**

To a solution of phenylacetylene (80.4 µL, 0.732 mmol) in THF (5 mL) at -78 ºC was added *n*-butyllithium (293 µL of a 2.5 M solution in hexane, 0.732 mmol) and the mixture was stirred for 30 min. A solution of epoxyaldehyde **200** (61.0 mg, 0.610 mmol) in THF (1 mL) was added and the mixture was stirred for 30 min. BF_3•Et_2O (113 µL, 0.915 mmol) was added dropwise and the mixture was warmed to -10 °C over 1.5 h. NH_4Cl (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (25% EtOAc/PE) provided a mixture of THF alcohol diastereoisomers **204** and **205**, as a colourless oil (60.4 mg, 49%).

R_f 0.19 (25% EtOAc/PE); **IR** (PTFE) 3414, 2953, 2926, 2873, 1598, 1490, 1442, 1338, 1042, 756 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48-7.45 (2H, m, H_{Ar}), 7.34-7.3 (3H, m, H_{Ar}), 4.99-4.87 (1H, m, H_5), 4.39-4.15 (1H, m, H_2), 3.81-3.56 (2H, m, H_1), 2.36-2.01 4H, m, H_3 + H_4); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 131.7, 131.6, 128.4, 128.3, 128.2, 128.2, 122.6, 122.4, 88.9, 88.5, 85.0, 84.8, 80.5, 79.3, 69.1, 69.0, 64.7, 64.6, 33.8, 26.9, 26.7 ; *m/z* (ES^+) 220 (40, $[M+NH_4]^+$); **HRMS** (ES^+) Calc. for $C_{13}H_{18}O_2N$ 220.1333 found 220.1332.

Preparation of (1,6)-diepoxyheptane (**215**)[91]



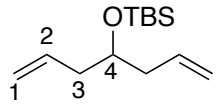
215

To a solution of 1,6-heptadiene (1.00 g, 10.4 mmol) in DCM (50 mL) at 0 °C was added *m*CPBA (4.50 g, 26.0 mmol). The mixture was stirred at RT for 16h and H_2O (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with DCM

(5 x 30 mL). The combined organic layers were washed with KOH 1M (3 x 50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (30% Et_2O/PE) afforded diepoxide **215**, as a colourless oil (1.13 g, 85%).

R_f 0.42 (30% Et_2O/PE); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.90-2.89 (2H, m, H_2), 2.73 (2H, t, J = 4.2 Hz, H_{1a}), 2.48-2.44 (2H, m, H_{1b}), 1.66-1.52 (6H, m, H_3 + H_4); **^{13}C NMR** (75 MHz, $CDCl_3$) 52.2, 52.1, 47.1, 32.3, 32.2, 22.7, 22.6.

Preparation of 4-(*tert*-butyldimethylsilyloxy)-(1,6)-heptadiene (**387**)[92]

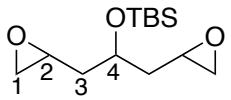


387

To a solution of 1,6-heptadien-4-ol (1.00 g, 8.93 mmol) in DCM (50 mL) at 0 °C was added imidazole (921 mg, 13.4 mmol), DMAP (330 mg, 2.68 mmol). The mixture was stirred at RT for 24 h and NH_4Cl (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (5% EtOAc/PE) afforded the TBS ether **387**, as a colourless oil (1.91 g, 94%).

R_f 0.69 (5% EtOAc/PE); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.83-5.78 (2H, m, H_2), 5.08-5.06 (2H, m, H_{1a}), 5.03 (2H, t, J = 1.3 Hz, H_{1b}), 3.75 (1H, qn, J = 5.8 Hz, H_4), 2.29-2.16 (4H, m, H_3), 0.90 (9H, s, Si-C($C\underline{H}_3$)$_3$), 0.06 (6H, s, Si-($C\underline{H}_3$)$_2$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.2, 116.8, 71.7, 41.5, 25.9, 18.1, -4.5.

Preparation of 4-(*tert*-butyldimethylsilyloxy)-(1,6)-diepoxyheptane (**217**)

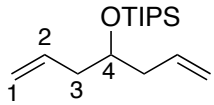


217

To a solution of alkene **387** (1.91 g, 8.43 mmol) in DCM (20 mL) was added *m*CPBA (3.62 g, 21.0 mmol). The mixture was stirred at RT for 24 h and H_2O (15 mL) was added. The organic layer was separated and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with KOH 1M (4 x 20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (20% EtOAc/PE) afforded diepoxide **215**, as a colourless oil (1.63 g, 75%).

R_f 0.55 (25% EtOAc/PE); **IR** (PTFE) 3047, 2956, 2927, 2858, 1473, 1411, 1361, 1257, 1126, 1092, 1073, 1059, 838 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.19 (1H, m, H_4), 3.11-2.99 (2H, m, H_2), 2.85-2.77 (2H, m, H_{1a}), 2.54-2.46 (2H, m, H_{1b}), 1.94-1.62 (4H, m, H_3); 0.93-0.92 (9H, m, Si-C($C\underline{H}_3$)$_3$), 0.13-0.09 (6H, m, Si-($C\underline{H}_3$)$_2$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 68.3, 68.1, 49.7, 49.4, 48.9, 47.7, 47.5, 46.6, 40.9, 40.8, 40.4, 25.7, 17.9, -4.6, -4.7, -4.8; *m/z* (ES^+) 282 (30, $[M+Na]^+$), 276 (100, $[M+NH_4]^+$); **HRMS** (ES^+) Calc. for $C_{13}H_{30}O_3NSi$ $[M+NH_4]^+$ 276.1994; found 276.1989.

Preparation of 4-(triisopropylsilyloxy)-(1,6)-heptadiene (**388**)



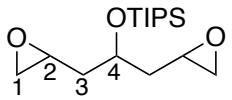
388

To a solution of 1,6-heptadien-4-ol (1.04 g, 9.29 mmol) in DMF (5 mL) at 0 °C was added imidazole (1.58 g, 23.2 mmol) and TIPSCl (2.35 mL, 11.1 mmol). The mixture was stirred at RT for 16 h and NH_4Cl (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (4 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash

column chromatography on silica gel (30% Et_2O/PE) afforded TIPS ether **388**, as a colourless oil (2.24 g, 90%).

R_f 0.94 (10% EtOAc/PE); **IR** (KBr, neat) 2944, 2894, 2868, 1465, 1366, 1358, 1102, 997, 914, 883 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.93 (2H, ddt, *J* = 17.8, 9.5, 7.2 Hz, H_2), 5.11-5.07 (2H, m, H_{1a}), 5.05-5.03 (m, 2H, H_{1b}), 3.93 (1H, tt, *J* = 6.3, 5.1 Hz, H_4), 2.38-2.21 (4H, m, H_3), 1.09 (21H, s, Si-(C<u>H</u>-$(CH_3)_2)_3$ + Si-(CH-(C<u>H</u>$_3)_2)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) 134.9, 116.9, 71.6, 41.0, 18.1, 17.7, 12.5; *m/z* (CI) 269 (100, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{16}H_{33}OSi$ $[M+H]^+$ 269.2295; found 269.2295.

<u>Preparation of 4-(triisopropylsilyloxy)-(1,6)-diepoxyheptane</u> (**218**)

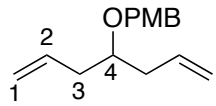


218

To a solution of diene **388** (2.24 g, 8.36 mmol) in DCM (30 mL) at 0 °C was added *m*CPBA (3.60 g, 20.9 mmol) and the mixture was stirred at RT for 16 h. H_2O (15 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 20 mL) and the combined organic layers were washed with KOH 1M (4 x 35 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (20% Et_2O/PE) afforded diepoxide **218**, as a colourless oil (2.03 g, 80%).

R_f 0.45 (20% Et_2O/PE); **IR** (KBr, neat) 2945, 2866, 1466, 1384, 1366, 1256, 1108, 1063, 883 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.33 (1H, m, H_4), 3.13-3.01 (2H, m, H_2), 2.82-2.76 (2H, m, H_{1a}), 2.52-2.45 (2H, m, H_{1b}), 2.11-2.66 (4H, m, H_3), 1.10-1.05 (21H, m, Si-(C<u>H</u>-$(CH_3)_2)_3$ + Si-(CH-(C<u>H</u>$_3)_2)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 69.1, 68.7, 68.5, 49.5, 49.3, 48.9, 48.8, 47.5, 47.3, 46.8, 46.7, 40.8, 40.7, 40.4, 39.5, 18.1, 18.1, 17.7, 12.7, 12.6, 12.4, 12.3; *m/z* (ES^+) 323 (100, $[M+Na]^+$); **HRMS** (ES^+) Calc. for $C_{16}H_{32}O_3NaSi$ $[M+Na]^+$ 323.2007; found 323.2018.

Preparation of 4-(4-methoxybenzyloxy)-(1,6)-diepoxyheptane (**220**)[93]



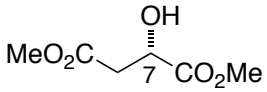
220

To a solution of 1,6-heptadien-4-ol (500 mg, 4.46 mmol) in THF (20 mL) was added NaH (250 mg, 6.25 mmol, 60 wt% dispersion in mineral oil), tetrabutylammonium iodide (165 mg, 0.446 mmol) and PMBCl (660 μL, 4.91 mmol). The mixture was refluxed for 12 h and after cooling at RT, NH_4Cl (20 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 x 20 mL) and the combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (5% EtOAc/PE) provided PMB ether **220**, as a colourless oil (910 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (2H, d, *J* = 8.7 Hz, 2 x H_{Ar}), 6.79 (2H, d, *J* = 9.0 Hz, 2 x H_{Ar}), 5.76 (2H, ddt, *J* = 17.1, 10.2, 7.2 Hz, H_2), 5.05-4.97 (4H, m, H_1), 4.40 (2H, s, OC$\underline{H}_2$-Ar), 3.71 (3H, s, Ar-OC$\underline{H}_3$), 3.41 (1H, qn, *J* = 6.0 Hz, H_4), 1.66-1.52 (4H, m, H_3).

7.3 Experimental for chapter four

Preparation of dimethyl-(*S*)-malate (**273**)[170]

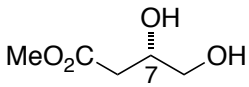


273

Acetyl chloride (17.5 mL, 0.250 mol) was added dropwise to methanol (340 mL) at 0 ºC. (L)-malic acid **272** (53.7 g, 0.400 mol) was added in one portion and the mixture was stirred at RT for 16 h. The solvent was removed under reduced pressure and purification by distillation provided diester **273**, as a colourless oil (41.5 g, 64%).

$[\alpha]_D^{20}$ -6.50 (*c* 1.5, MeOH) (Lit.[170] -7.55 (*c* 3.73, MeOH)); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.49 (1H, dd, *J* = 6.1, 4.5 Hz, H_7), 3.78 (3H, s, CO_2CH_3), 3.69 (3H, s, CO_2CH_3), 3.34 (1H, br s, OH), 2.82 (1H, d, *J* = 4.5 Hz, H_{6a}), 2.79 (1H, d, *J* = 6.0 Hz, H_{6b}) **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.0, 171.3, 67.5, 53.1, 52.3, 38.7.

Preparation of methyl (3*S*)-3,4-dihydroxybutanoate (**274**)[171]

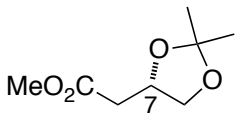


274

To a solution of dimethyl malate **273** (36.0 g, 0.220 mol) in THF (360 mL) was added BH_3•SMe_2 (22.7 mL, 0.230 mol) dropwise over 40 min. After 30 min $NaBH_4$ (420 mg, 11.1 mmol) was added in three portions. The mixture was stirred at RT for 1.5 h. MeOH (150 mL) was carefully added at 0 ºC. The mixture was stirred at RT for 30 min and the solvent was evaporated under reduced pressure. Purification by flash column chromatography on silica gel (EtOAc) gave diol **274**, as a colourless oil (28.0 g, 94%).

R_f 0.42 (EtOAc); $[\alpha]_D^{20}$ -23.6 (*c* 1.1, $CHCl_3$) (Lit.[171] -24.6 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.04-3.97 (1H, m, H_7), 3.59 (3H, s, CO_2CH_3), 3.52 (1H, dd, *J* = 11.4, 3.6 Hz, H_{8a}), 3.39 (1H, dd, *J* = 11.4, 6.3 Hz, H_{8b}), 2.41-2.39 (2H, m, H_6); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.5, 68.4, 65.4, 51.6, 37.6.

Preparation of methyl (3*S*)-3,4-*O*-isopropylidene-dihydroxybutanoate (**275**)[172]



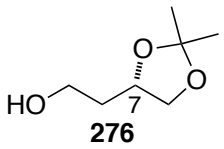
275

To a solution of diol **274** (3.38 g, 25.2 mmol) in DCM (130 mL) at 0 °C was added PPTS (316 mg, 1.26 mmol) and 2-methoxypropene (3.63 mL, 37.8 mmol). After 2 h, $NaHCO_3$ (60 mL) was added and the organic layer was separated. The aqueous layer was extracted

with DCM (2 x 40 mL) and the combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by distillation (80 °C, 8mbar) provided acetonide **275**, as a colourless oil (4.30 g, 98%).

$[\alpha]_D^{20}$ +12.2 (*c* 1.2, $CHCl_3$) (Lit.[172] $[\alpha]_D^{20}$ +17.0 (*c* 2.0, $CHCl_3$)); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.47 (1H, qn, *J* = 6.3 Hz, H_7), 4.15 (1H, dd, *J* = 8.4, 6.0 Hz, H_{8a}), 3.69 (3H, s, CO_2CH_3), 3.64 (1H, dd, *J* = 8.4, 6.4 Hz, H_{8b}), 2.71 (1H, dd, *J* = 15.9, 6.3 Hz, H_{6a}), 2.52 (1H, dd, *J* = 15.9, 6.9 Hz, H_{6b}), 1.41 (3H, d, *J* = 0.6 Hz, CH_3), 1.35 (3H, d, *J* = 0.6 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.0, 109.2, 72.0, 69.1, 51.7, 38.7, 26.8, 25.5.

Preparation of (2S)-1,2-*O*-isopropylidene-1,2,4-butanetriol (**276**)[173]

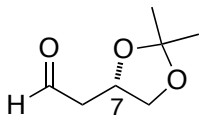


276

To a solution of $LiAlH_4$ (11.0 g 0. 290 mol) in THF (900 mL) at 0 °C was added a solution of ester **275** (16.8 g, 96.5 mmol) in THF (50 mL). After 1.5 h, a saturated solution of Rochelle salt (500 mL) was added with caution and the mixture was stirred for 16 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 300 mL). The combined organic layers were washed with brine (400 mL), dried over $MgSO_4$, filtered and removed under reduced pressure. Purification by flash column chromatography on silica gel (50% Et_2O/PE) provided alcohol **276**, as a colourless oil (10.3 g, 73%).

R_f 0.12 (50% Et_2O/PE); $[\alpha]_D^{20}$ +1.7 (*c* 1.4, $CHCl_3$) (Lit.[173] $[\alpha]_D^{20}$ +1.00 (*c* 2.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.23 (1H, tt, *J* = 7.0, 5.7 Hz, H_7), 4.05 (1H, dd, *J* = 8.1, 6.0 Hz, H_{8a}), 3.74 (2H, dt, 6.0, 1.1 Hz, H_5), 3.55 (dd, *J* = 7.9, 7.2 Hz, H_{8b}), 2.65 (1H, br s, OH), 1.82-1.75 (2H, m, H_6), 1.38 (3H, d, *J* = 0.6 Hz, CH_3), 1.32 (3H, d, *J* = 0.6 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 109.0, 75.1, 69.4, 60.5, 35.6, 26.8, 25.6.

Preparation of (3*S*)-3,4-*O*-isopropylidene-3,4-dihydroxybutanal (**271**)[115]

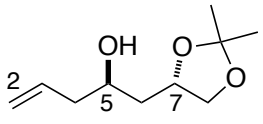


271

To a solution of alcohol **276** (520 mg, 3.56 mmol) in DCM (5 mL) at RT was added TEMPO (55.0 mg, 0.350 mmol) and bisacetoxyiodobenzene (1.26 g, 3.92 mmol) and the mixture was stirred at RT. After 3.5 h, $Na_2S_2O_4$ (5 mL) was added and the reaction was diluted with Et_2O (20 mL). The organic layer was separated and washed with $NaHCO_3$ (10 mL) and H_2O (10 mL), dried over $MgSO_4$, filtered and removed under reduced pressure. Purification by flash column chromatography on silica gel (30% Et_2O/PE) provided aldehyde **271**, as a pale yellow oil (490 mg, 95%).

R_f 0.38 (30% Et_2O/PE); $[\alpha]_D^{20}$ +12.0 (*c* 1.1, $CHCl_3$) (Lit.[115] $[\alpha]_D^{20}$ +16.5 (*c* 5.32, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.81 (1H, t, *J* = 1.5 Hz, CHO), 4.54 (1H, qn, *J* = 6.3 Hz, H_7), 4.19 (1H, dd, *J* = 8.4, 6.0 Hz, H_{8a}), 3.60 (1H, dd, *J* = 8.1, 6.6 Hz, H_{8b}), 2. 85 (1H, ddd, *J* = 17.1, 6.6, 1.8 Hz, H_{6a}), 2.65 (1H, ddd, *J* = 17.1, 6.0, 1.2 Hz, H_{6b}), 1.42 (3H, d, *J* = 0.6 Hz, CH_3), 1.37 (3H, d, *J* = 0.6 Hz, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.9, 109.2, 70.6, 69.1, 47.8, 26.8, 25.4.

Preparation of (2*S*,4*R*)- 1,2-*O*-isopropylidene-hept-6-ene-4-ol (**270**)[174]



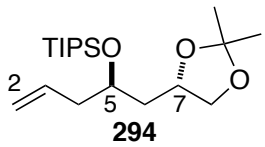
270

Allylmagnesium bromide (9.08 mL of a 1.0 M solution in Et_2O, 9.08 mmol) was added dropwise to a solution of (+)-Ipc_2BOMe (3.10 g, 9.84 mmol) in toluene (20 mL) at -78 °C. The mixture was stirred for 15 min and was warmed to RT After 3 h, the mixture was cooled to -78 °C and a solution of aldehyde **271** (1.09 g, 7.57 mmol) in toluene (10 mL) was added dropwise. After 1 h, NaOH 2M (8 mL) and H_2O_2 (14 mL, 30% v/v) and the

mixture was stirred at RT for 3 h. The organic layer was separated and the aqueous layer was extracted with Et_2O (30 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (25% EtOAc/PE) provided alcohol **270**, as a colourless oil (1.26 g, 90%, 97:3 d.r.).

R_f 0.45 (25% EtOAc/PE); $[\alpha]_D^{20}$ -7.8 (*c* 1.5, $CHCl_3$) (Lit.[174] -8.5 (*c* 2.6, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.89-5.75 (1H, m, H_3), 5.18-5.15 (1H, m, H_{2a}), 5.13-5.11 (1H, m, H_{2b}), 4.35 (1H, tdd, *J* = 7.5, 6.0, 4.8 Hz, H_7), 4.09 (1H, dd, *J* = 8.1, 6.0 Hz, H_{8a}), 3.94-3.86 (1H, m, H_5), 3.58 (1H, dd, *J* = 8.1, 7.8 Hz, H_{8b}), 2.32-2.20 (2H, m, H_4), 1.82-1.64 (2H, m, H_6), 1.42 (3H, d, ^4J = 0.6 Hz, CH_3), 1.37 (3H, d, ^4J = 0.6, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.4, 118.2, 108.7, 73.6, 69.5, 67.9, 42.3, 39.5, 26.9, 25.6; *m/z* (ES^+) 209 (40, $[M+Na]^+$), 187 (100, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{10}H_{18}O_3$ $[M+H]^+$ 187.1329; found 187.1328.

Preparation of (2*S*,4*R*)-1,2-*O*-isopropylidene-4-triisopropylsilyloxy-hept-6-ene (**294**)



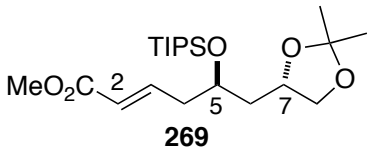
294

To a solution of alcohol **270** (1.30 g, 6.99 mmol) in DCM (80 mL) at -20 °C was added 2,6-lutidine (1.60 mL, 14.0 mmol) and TIPSOTf (2.45 mL, 9.09 mmol). After 2 h, $NaHCO_3$ (40 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 80 mL) and the combined organic layers were washed with brine (80 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (2% EtOAc/PE) gave silyl ether **294**, as a colourless oil (2.31 g, 97%).

R_f 0.37 (PE); $[\alpha]_D^{20}$ -14.0 (*c* 1.4, $CHCl_3$); **IR** (KBr, neat) 2925, 2864, 1464, 1379, 1368, 1060, 882 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5,83 (1H, ddt, *J* = 17.7, 9.6, 6.9 Hz, H_3), 5.11-5.08 (1H, m, H_{2a}), 5.06-5.04 (1H, m, H_{2b}), 4.27 (1H, tdd, *J* = 8.1, 5.7, 4.2 Hz, H_7),

4.12-4.02 (2H, m, H_5 + H_{8a}), 3.48 (1H, t, J = 8.1 Hz, H_{8b}), 2.36-2.28 (2H, m, H_4), 1.77 (1H, ddd, J = 14.1, 8.1, 3.9 Hz, H_{6a}), 1.58 (1H, ddd, J = 13.8, 8.4, 4.5, H_{6b}), 1.39 (3H, d, ^4J = 0.6 Hz, CH_3), 1.34 (3H, d, ^4J = 0.6 Hz, CH_3), 1.10-1.06 (21H, m, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-(CH(C<u>H</u>$_3)_2)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.5, 117.4, 108.6, 73.1, 70.0, 69.5, 42.9, 40.6, 27.1, 25.9, 18.3, 12.9; *m/z* (ES^+) 343 (100, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{19}H_{39}O_3Si$ $[M+H]^+$ 343.2663; found 343.2667.

<u>Preparation of methyl-(5*R*,7S,*E*)-7,8-*O*-isopropylidene-5-triisopropylsilyloxy-oct-2-enoate</u> (**269**)

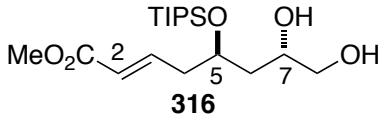


269

To a solution of alkene **294** (550 mg, 1.44 mmol) in DCM (15 mL) was added methyl acrylate (435 μL, 4.33 mmol) and Grubbs second generation catalyst (61.0 mg, 71.8 μmol). The mixture was stirred at RT for 16 h. The volatiles were removed under reduced pressure and purification by flash column chromatography on silica gel (10% EtOAc/PE) provided ester **269**, as a (9:1) mixture of *E*:*Z* as a brown oil (575 mg, 90 %).

R_f 0.51 (10% EtOAc/PE); $[\alpha]_D^{20}$ -14.0 (*c* 1.4, $CHCl_3$); **IR** (KBr, neat) 2947, 2867, 1725, 1464, 1435, 1272, 1171, 1108, 1063, 883 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.91 (1H, dt, J = 15.6, 7.2 Hz, H_3), 5.87 (1H, dt, J = 15.9, 1.5 Hz, H_2), 4.27-4.16 (2H, m, H_5 + H_7), 4.02 (1H, dd, J = 7.8, 5.7 Hz, H_{8a}), 3.72 (3H, s, CO_2CH_3), 3.45 (1H, t, J = 7.8 Hz, H_{8b}), 2.49-2.45 (2H, m, H_4), 1.67-1.60 (2H, m, H_6), 1.37 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.07-1.04 (21H, m, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-(CH(C<u>H</u>$_3)_2)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.6, 145.0, 123.4, 108.7, 72.7, 69.7, 68.9, 40.8, 26.9, 25.7, 18.1, 17.6, 12.7, 12.3; *m/z* (ES^+) 401 (100, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{21}H_{40}O_5Si$ $[M+H]^+$ 401.2713; found 401.2718.

Preparation of methyl-(5*R*,7*S*,*E*)-7,8-dihydroxy-5-triisopropylsilyloxy-oct-2-enoate (**316**)

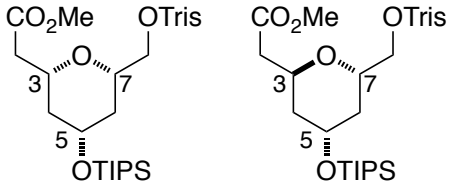


316

To a solution of acetonide **269** (115 mg, 0.260 mmol) in DCM (4 mL) was added TFA 50% aq. solution (0.290 mL, 1.38 mmol). After 30 min at RT, DCM (20 mL) and H_2O (10 mL) were added. The organic layer was separated and washed with $NaHCO_3$ (10 mL) and brine (10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (50% EtOAc/PE) provided diol **316**, as a colourless oil (90.0 mg, 97%).

R_f 0.23 (50% EtOAc/PE); $[\alpha]_D^{20}$ -20.4 (*c* 1.2, $CHCl_3$); **IR** (KBr, neat) 3417, 2941, 2863, 1726, 1463, 1435, 1267, 1197, 1166, 1096, 881 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.88 (1H, dt, *J* = 15.3, 7.5 Hz, H_3), 5.89 (1H, dt, *J* = 15.9, 1.5 Hz, H_2), 4.33-4.26 (1H, m, H_5), 4.09-4.01 (1H, m, H_7), 3.73 (3H, s, CO_2CH_3), 3.61 (1H, dd, *J* = 11.1, 3.3 Hz, H_{8a}), 3.42 (1H, dd, *J* = 11.1, 6.3 Hz, H_{8b}), 2.64-2.57 (2H, m, H_4), 1.80 (1H, ddd, *J* = 14.7, 10.5, 3.9 Hz, H_{6a}), 1.51 (1H, ddd, *J* = 14.7, 4.8, 2.4 Hz, H_{6b}), 1.07 (21H, s, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-(CH(C<u>H</u>$_3)_2)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6, 144.4, 123.5, 70.3, 68.6, 67.0, 51.5, 39.4, 37.2, 18.0, 18.0, 12.6, 12.4; *m/z* (ES^+) 743 (80, $[2M+Na]^+$), 378 (100, $[M+NH_4]^+$), 361 (75, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{18}H_{40}O_5NSi$ $[M+NH_4]^+$ 378.2670; found 378.2675.

Preparation of (5*R*,7*S*)-3-methylacetyl-5-triisopropylsilyloxy-7-triisopropylphenylsulfonyloxymethyl-tetrahydropyran (**317**,**318**)

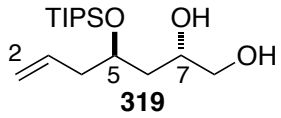


317 **318**

To a solution of diol **316** (30 mg, 83.3 μmol) in THF (3 mL) at -20 °C was added NaH (8.0 mg, 0.220 mmol, 60 wt% dispersion in mineral oil). The mixture was stirred for 30 min and *N*-(2,4,6-triisopropylbenzensulfonyl) imidazole (26.0 mg, 77.7 μmol) was added and the mixture was warmed to RT over 1.5 h. H_2O (7 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (10% EtOAc/PE) provided a mixture of THP ring diastereoisomers **317** and **318**, as a colourless oil (25.0 mg, 54%).

R_f 0.62 (10% EtOAc/PE); $[\alpha]_D^{20}$ -0.70 (*c* 1.4, $CHCl_3$); **IR** (KBr, neat) 2855, 1717, 1464, 1377, 1263, 1179, 745 cm^{-1} ;**^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.18 (2H, s, 2 x H_{Ar}), 4.14 (2H, qn, *J* = 6.7 Hz, 2 x *o*-(C<u>H</u>$(CH_3)_2$), 4.03-4.01 (2H, m, H_8), 3.92-3.86 (1H, m, H_5), 3.76-3.74 (2H, m, H_3 + H_7), 3.65 (3H, s, $CO_2C\underline{H}_3$), 2.91 (1H, qn, *J* = 6.9 Hz, *p*-(C<u>H</u>$(CH_3)_2$), 2.53 (1H, dd, *J* = 15.6, 7.1 Hz, H_{2a}), 2.37 (1H, dd, 15.6, 5.9 Hz, H_{2b}), 1.97-1.88 (2H, m, H_{4a} + H_{6a}), 1.27-1.25 (20H, m, H_{4b} + H_{6b} + 3 x Ph(CH(C<u>H</u>$_3)_2$), 1.06-1.04 (21H, m, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-(CH(C<u>H</u>$_3)_2)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.2, 153.6, 150.8, 129.3, 123.7, 73.2, 72.2, 70.8, 67.9, 51.6, 41.1, 40.6, 37.4, 34.2, 29.6, 24.7, 23.5, 18.0, 17.7, 12.2; *m/z* (ES^+) 644 (100, $[M+NH_4]^+$); **HRMS** (ES^+) Calc. for $C_{33}H_{62}O_7NSSi$ $[M+NH_4]^+$ 644.3999; found 644.4011.

Preparation of (2*S*,4*R*)-4-triisopropylsilyloxy-hept-6-ene-1,2-diol (**319**)

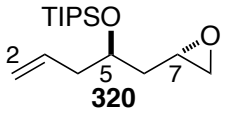


319

To a solution of acetonide **294** (1.05 g, 3.07 mmol) in DCM (30 mL) at RT was added a TFA 50% aq. solution (3.90 mL, 18.4 mmol) and the mixture was stirred at RT for 45 min. $NaHCO_3$ aq. (25 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 30 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (25% EtOAc/PE) provided diol **319**, as a colourless oil (664 mg, 71%).

R_f 0.28 (25% EtOAc/PE); $[\alpha]_D^{20}$ -4.3 (*c* 1.2, $CHCl_3$); **IR** (KBr, neat) 3408, 2926, 2854, 1463, 1377, 1258, 1109, 1033, 744 cm^{-1} ;**^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.73 (1H, ddt, *J* = 17.1, 10.2, 7.2 Hz, H_3), 5.15-5.07 (2H, m, H_2), 4.21-4.14 (1H, m, H_5), 4.10-4.02 (1H, m, H_7), 3.63 (1H, dd, *J* = 11.1, 3.6 Hz, H_{8a}), 3.45 (1H, dd, 11.1, 6.0 Hz, H_{8b}), 2.53-2.48 (2H, m, H_4), 1.87 (1H, ddd, *J* = 14.4, 10.5, 3.9 Hz, H_{6a}), 1.57 (1H, ddd, *J* = 14.4, 4.8, 2.4 Hz, H_{6b}), 1.12-1.10 (21H, m, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-(CH(C<u>H</u>$_3)_2)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.0, 117.8, 71.5, 68.7, 67.1, 40.7, 36.1, 18.1, 18.0, 12.4; *m/z* (ES^+) 627 (65, $[2M+Na]^+$), 325 (40, $[M+Na]^+$), 303 (100, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{16}H_{35}O_3Si$ $[M+H]^+$ 303.2350; found 303.2353.

Preparation of (2*S*,4*R*)-1-epoxy-4-triisopropylsilyloxy-hept-6-ene (**320**)



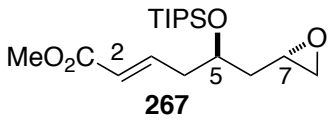
320

To a solution of diol **319** (458 mg, 1.52 mmol) in THF (150 mL) at 0°C was added NaH (175 mg, 4.55 mmol, 60 wt% dispersion in mineral oil). After 30 min, *N*-(2,4,6-triisopropylbenzensulfonyl) imidazole (557 mg, 1.67 mmol) was added and the mixture

was warmed to RT over 1.5 h. NH_4Cl (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and removed under reduced pressure. Purification by flash column chromatography on silica gel (5% EtOAc/PE) gave epoxide **320**, as a colourless oil (424 mg, 98%).

R_f 0.29 (5% EtOAc/PE); $[\alpha]_D^{20}$ -16.2 (*c* 1.1, $CHCl_3$); **IR** (KBr, neat) 2941, 2918, 2862, 1462, 1096, 1062, 884, 667 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.80(1H, ddt, *J* = 18.0, 11.1, 7.2 Hz, H_3), 5.10-5.06 (1H, m, H_{2a}), 5.03 (1H, t, *J* = 1.2 Hz, H_{2b}), 4.12 (1H, ddd, *J* = 11.7, 6.3, 5.4 Hz, H_5), 3.10-3.04 (1H, m, H_7), 2.79 (1H, dd, *J* = 5.1, 4.2 Hz, H_{8a}), 2.47 (1H, dd, *J* = 5.1, 3.0 Hz, H_{8b}), 2.38-2.32 (2H, m, H_4), 1.67 (2H, dt, *J* = 6.6, 1.2 Hz, H_6), 1.08-1.07 (21H, m, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-(CH(C<u>H</u>$_3)_2)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.3, 117.4, 70.1, 49.6, 47.7, 42.4, 39.7, 18.1, 12.6; *m/z* (ES^+) 285 (100, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{16}H_{33}O_2Si$ $[M+H]^+$ 285.2244; found 285.2250.

<u>Preparation of methyl-(5*R*,7*S*,*E*)-7-epoxy-5-triisopropylsilyloxy-oct-2-enoate</u> (**267**)



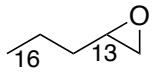
267

To a solution of alkene **320** (59.0 mg, 0.210 mmol) in DCM (5 mL) was added Grubbs second generation catalyst (9.0 mg, 10.6 μmol) and methyl acrylate (104 μL, 1.04 mmol). The mixture was refluxed for 16 h and cooled to RT. After concentration under reduced pressure, purification by flash column chromatography on silica gel (5% EtOAc/PE) afforded ester **267**, as a colourless oil (54.6 mg, 76 %).

R_f 0.22 (5% EtOAc/PE); **IR** (KBr, neat) 2943, 2868, 1726, 1462, 1435, 1271, 1172, 1107, 1064, 881 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.98 (1H, dt, *J* = 15.6, 7.5 Hz, H_3), 5.87 (1H, dt, *J* = 15.9, 1.5 Hz, H_2), 4.25-4.17 (1H, m, H_5), 3.72 (3H, s, CO_2CH_3), 3.04 (1H, m, H_7), 2.79 (1H, dd, *J* = 5.1, 4.2 Hz, H_{8a}), 2.53-2.46 (3H, m, H_{8b} + H_4), 1.76 (1H, ddd, *J* = 14.1, 6.6, 4.5 Hz, H_{6a}), 1.58 (1H, ddd, *J* = 14.1, 6.9, 5.4 Hz, H_{6b}), 1.10-1.06 (21H, m, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-(CH(C<u>H</u>$_3)_2)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.6, 144.9,

123.4, 69.6, 51.4, 49.3, 47.4, 40.6, 40.1, 18.1, 12.5; *m/z* (ES^+) 360 (100, $[M+NH_4]^+$), 343 (15, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{18}H_{38}O_4NSi$ $[M+NH_4]^+$ 360.2565; found 360.2565.

Preparation of 1-epoxypentane (**324**)[175]

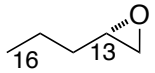


324

To a solution of 1-pentene **323** (10.9 mL, 0.100 mol) in DCM (300 mL) at 0 °C was added mCPBA (29.1 g, 0.130 mol) and the mixture was stirred at RT for 16 h. H_2O (150 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 100 mL) and the combined organic layers were washed with KOH 1M (4 x 100 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Kugelrhor distillation (90 °C) gave 1-epoxypentane **324**, (8.35 g, 97%) as a colourless oil (8.35 g, 97%).

R_f 0.72 (20% EtOAc/PE); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.93-2.90 (1H, m, H_{13}), 2.75 (1H, dd, *J* = 5.1, 4.0 Hz, H_{12a}), 2.47 (1H, dd, *J* = 5.1, 2.7 Hz, H_{12b}), 1.51-1.50 (4H, m, H_{14} + H_{15}), 0.97 (1H, t, *J* = 7.2 Hz, H_{16}).

Preparation of (2*S*)-epoxypentane (**235**)[138]

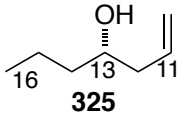


235

To a stirred solution of epoxyoctane **324** (10.3 g, 0.120 mol) and (*S*,*S*)-Co (II) salen catalyst **182** (363 mg, 0.601 mmol) was added AcOH (144 µL, 2.40 mmol). The solution was stirred at RT for 15 min and cooled at 0 °C. H_2O (975 µL, 54.1 mmol) was added dropwise and the mixture was stirred at RT for 16 h. Distillation under reduced pressure (110 mbar) *via* short path distillation, followed by filtration on silica to remove residual water provided (2*S*)-epoxypentane **235**, as a pale yellow oil (3.20 g, 31%).

R_f 0.72 (20% EtOAc/PE); $[\alpha]_D^{20}$ -11.1 (*c* 0.9, $CHCl_3$) (Lit.[138] $[\alpha]_D^{20}$ -8.5 (*c* 2.6, $CHCl_3$)); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.93-2.90 (1H, m, H_{13}), 2.75 (1H, dd, *J* = 4.8, 3.9 Hz, H_{12a}), 2.47 (1H, dd, *J* = 5.1, 2.7 Hz, H_{12b}), 1.53-1.50 (4H, m, H_{14} + H_{15}), 0.97 (1H, t, *J* = 7.2 Hz, H_{16}).

Preparation of (4*S*)-hept-1-en-4-ol (**325**)[176]

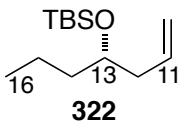


325

To a solution of (2*S*)-epoxypentane **235** (845 mg, 9.82 mmol) in THF (40 mL) at -78 °C was added CuI (560 mg, 2.95 mmol) and vinylmagnesium bromide (16.8 mL of a 0.7 M solution in THF, 11.8 mmol). The solution was warmed to RT over 3 h and NH_4Cl (40 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with brine (45 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (20% Et_2O/PE) afforded alcohol **325**, as a pale yellow oil (955 mg, 85%).

R_f 0.30 (20% Et_2O/PE); $[\alpha]_D^{20}$ -7.6 (*c* 1.4, $CHCl_3$) (Lit.[176] $[\alpha]_D^{20}$ -12.7 (*c* 0.54, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.91-5.78 (1H, m, H_{11}), 5.19-5.15 (1H, m, H_{10a}), 5.14-5.11 (1H, m, H_{10b}), 3.78-3.64 (1H, m H_{13}), 2.36-2.27 (1H, m, H_{12a}), 2.20-2.01 (1H, m, H_{12b}), 1.52-1.41 (4H, m, H_{14} + H_{15}), 0.94 (3H, t, *J* = 7.2 Hz, H_{16}).

Preparation of (4*S*)-4-(tert-butyldimethylsilyloxy)-hept-1-ene (**322**)



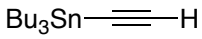
322

To a solution of alcohol **323** (354 mg, 3.10 mmol) in DCM (30 mL) at 0 °C was added imidazole (465 mg, 6.83 mmol), DMAP (95.3 mg, 0.780 mmol) and TBSCl (561 mg, 3.72

mmol). The mixture was stirred at RT for 16 h. NH_4Cl (30 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 30 mL) and the combined organic layers were washed with brine (45 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (PE) provided TBS ether **320**, as a colourless oil (575 mg, 81%).

R_f 0.55 (PE); $[\alpha]_D^{20}$ -14.9 (*c* 1.3, $CHCl_3$); **IR** (KBr, neat) 3080, 2960, 2932, 2869, 1473, 1463, 1362, 1255, 1127, 1098, 1079, 1042, 913, 836, 774 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.92-5.78 (1H, m, H_{11}), 5.01-5.06 (1H, m, H_{10a}), 5.03 (1H, t, *J* = 1.5 Hz, H_{10b}), 3.72 (1H, qn, *J* = 5.7 Hz, H_{13}), 2.26-2.21 (2H, m, H_{12}), 1.45-1.30 (4H, m, H_{14} + H_{15}), 0.93 (12H, m, Si-C(CH_3)$_3$ + H_{16}), 0.08 (3H, s, Si-CH_3), 0.07 (3H, s, Si-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.5, 116.5, 71.8, 42.0, 39.1, 25.9, 18.6, 18.1, 14.2, -4.4, -4.5; *m/z* (ES^+) 229 (100, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{13}H_{29}OSi$ $[M+H]^+$ 229.1979; found 229.1982.

Preparation of tributylethynylstannane (**327**)[139]

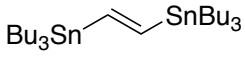


327

To a solution of lithium acetylide-ethylenediamine complex **326** (4.81 g, 52.2 mmol) in THF (160 mL) at 0 °C was added tributyltin chloride (11.8 mL, 43.5 mmol) dropwise over 45 min. The reaction is then stirred at room temperature for 16 h. The mixture is then cooled at 0 °C and H_2O (5 mL) is added. The reaction mixture is concentrated under reduced pressure and extracted with hexane (3 x 10mL). The combined organic layers are washed with $MgSO_4$, filtered and evaporated under reduced pressure. Purification by distillation afforded tributyltin acetylide **327**, as a colourless oil (5.03 g, 30%).

^{1}H NMR (300 MHz, $CDCl_3$) 2.21 (1H, s, C≡C-H), 1.58-1.53 (6H, m, 3 x CH_2), 1.41-1.29 (6H, m ,3 x CH_2), 0.92 (9H, t, *J* = 7.2 Hz, 3 x CH_3)

Preparation (*E*)-1,2-bis(tributylstannyl)ethylene (**42**)[139]

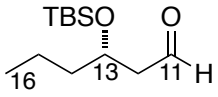


42

To tributyltin acetylide **327** (5.01 g, 15.8 mmol) was added AIBN (64.0 mg, 0.390 mmol) and tributyltin hydride (5.12 mL, 19.0 mmol) and the mixture was heated at 90 °C for 6 h. The mixture was then cooled at RT and purification by flash column chromatography on silica gel (PE) afforded alkene **42**, as a colourless oil (7.70 g, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) 6.88 (2H, s, C<u>H</u>=C<u>H</u>), 1.63-1.45 (12H, m, 6 x CH_2), 1.37-1.25 (12H, m, 6 x CH_2), 0.92-0.86 (30H, m, 6 x CH_2 + 6 x CH_3)

Preparation of (3*S*)-3-(tert-butyldimethylsilyloxy)-hexanal (**321**)



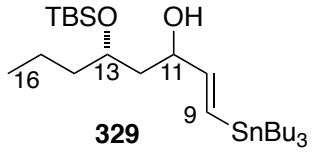
321

To a solution of alkene **322** (297 mg, 1.30 mmol) in DCM (50 mL) was added solid Na_2CO_3 (400 mg) and the mixture was cooled at -78 °C. A stream of O_3 was bubbled through for 5 min. The O_3 generator was switched off and O_2 was bubbled for 5 min. Triphenylphosphine (580 mg, 3.77 mmol) was added and the mixture was warmed to RT over 3 h. The reaction mixture was filtered on a plug of celite and washed with DCM. The residue was suspended in PE and a white precipitate was formed. After filtration, the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (5% Et_2O/PE) provided aldehyde **321**, as a colourless oil (259 mg, 86%).

R_f 0.59 (10% EtOAc/PE); $[\alpha]_D^{20}$ +2.3 (*c* 1.2, $CHCl_3$); **IR** (KBr, neat) 2960, 2858, 1728, 1473, 1362, 1255, 1123, 1098, 1040, 837, 776 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.83 (1H, t, *J* = 2.7 Hz, CHO), 4.20 (1H, qn, *J* = 5.7 Hz, H_{13}), 2.53 (2H, dd, *J* = 5.7, 2.7 Hz, H_{12a+b}), 1.59-1.32 (4H, m, 2 x CH_2), 0.93 (3H, t, *J* = 7.5 Hz, CH_3), 0.89 (9H, s, Si-C(C<u>H</u>$_3$)$_3$),

0.09 (3H, s, Si-C$\underline{H}_3$), 0.07 (3H, s, Si-C$\underline{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.5, 68.0, 50.8, 40.0, 25.7, 18.4, 18.0, 14.1, -4.4, -4.7; *m/z* (ES^+) 231 (100, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{12}H_{26}O_2Si$ $[M+H]^+$ 231.1775; found 231.1775.

Preparation of (5*S*,*E*)-5-(*tert*-butyldimethylsilyloxy)-1-tributylstannyl-oct-1-en-5-ol (**329**)

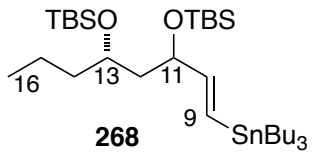


329

To a solution (*E*)-1,2-bis(tributylstannyl)ethylene **42** (2.06 g, 3.39 mmol) in THF (25 mL) at -78 °C was added *n*-butyllithium (2.12 mL, 3.39 mmol, 1.6 M solution in hexane). After 30 min, a solution of aldehyde **321** (557 mg, 2.42 mmol) in THF (5 mL) and the mixture was warmed to -20 °C over 3 h. NH_4Cl (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 25 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (2-5% EtOAc/PE) afforded a mixture of alcohol diastereoisomers **329**, as a colourless oil (930 mg, 70%).

R_f 0.45 (5% EtOAc/PE); **IR** (KBr, neat) 3448, 2958, 2929, 2856, 1465, 1378, 1255, 1071, 1039, 837, 775 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.23-5.98 (1H, m, H_9), 6.05-5.98 (1H, m, H_{10}), 4.42-4.23 (1H, m, H_{11}), 4.04-3.92 (1H, m, H_{13}), 3.22 (0.5H, d, *J* = 3.2 Hz, OH), 3.12 (0.5H, d, *J* = 2.0 Hz, OH), 1.68-1.47 (12H, m, H_{12} + H_{14} + H_{15}+ (C$\underline{H}_2$CH$_2$CH$_2$CH$_3$)$_3$), 1.37-1.28 (12H, m, 6 x (CH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_3$)$_3$), 0.94-0.91 (21H, m, CH_3 + Si-C(C$\underline{H}_3$)$_3$ + (CH$_2$CH$_2$CH$_2$C$\underline{H}_3$)$_3$), 0.13-0.11 (6H, m, Si-(C$\underline{H}_3$)$_2$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.0, 150.5, 127.2, 126.7, 74.3, 72.6, 72.1, 71.0, 43.1, 41.9, 40.2, 38.8, 29.1, 27.3, 25.8, 18.8, 17.9, 14.3, 14.2, 13.7, 9.4, -4.6; *m/z* (ES^+) 571 (100, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{26}H_{56}O_2NaSi^{120}Sn$ $[M+H]^+$ 571.2969; found 571.2963.

Preparation of (5*S*,*E*)-3,5-bis(*tert*-butyldimethylsilyloxy)-1-tributylstannyl-oct-1-ene (**268**)



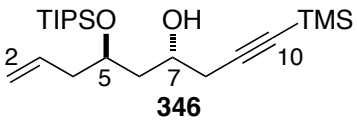
268

To a solution of alcohol **329** (930 mg, 1.70 mmol) in DCM (75 mL) at -20 °C was added 2,6-lutidine (395 μL, 3.39 mmol) and TBSOTf (390 μL, 2.20 mmol). After 2 h, NH_4Cl (75 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 75 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (2% EtOAc/PE) afforded TBS ether **268**, as a colourless oil (1.05 g, 94%).

R_f 0.47 (2% EtOAc/PE); **IR** (KBr, neat) 2958, 2929, 2858, 1463, 1377, 1361, 1255, 1071, 1041, 836, 774 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.09-6.00 (1H, m, H_9) 5.95-5.89 (1H, m, H_{10}), 4.17-4.09 (1H, m, H_{11}), 3.78-3.70 (1H, m, H_{13}), 1.74-1.25 (18H, m, H_{12} + H_{14} + H_{15} + ($C\underline{H}_2C\underline{H}_2CH_2CH_3)_3$), 0.92-0.87 (36H, m, CH_3 + 2 x Si-C($C\underline{H}_3)_3$ + ($CH_2CH_2C\underline{H}_2C\underline{H}_3)_3$), 0.07-0.04 (12H, m, 2 x Si-($C\underline{H}_3)_2$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.0, 151.7, 127.4, 127.1, 74.9, 74.3, 69.5, 69.3, 46.3, 45.8, 39.8, 39.6, 29.1, 27.3, 26.0, 25.9, 18.3, 14.3, 13.4, 9.5, 9.4, -4.2, -4.3, -4.6, -4.8; *m/z* (ES^+) 685 (100, $[M+Na]^+$); **HRMS** (ES^+) Calc. for $C_{32}H_{70}O_2NaSi_2{}^{120}Sn$ $[M+Na]^+$ 685.3834; found 685.3830.

7.3 Experimental for Chapter five

Preparation of (4*R*,6*R*)-6-triisopropylsilyloxy-1-trimethylsilyl-non-8-en-1-yn-4-ol (**346**)



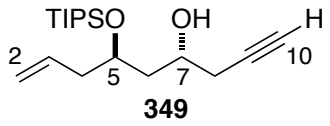
346

To a solution of TMS-acetylene (290 μL, 2.93 mmol) in THF (20 mL) at -78 °C was added *n*-butyllithium (1.83 mL, 2.93 mmol, 1.6 M solution in hexane). After 30 min, epoxide **320** (277 mg, 0.970 mmol) in THF (4 mL) was added dropwise at -78 °C, followed by the

dropwise addition of BF_3•Et_2O (240 μL, 1.95 mmol). The mixture was warmed to -20 °C over 1.5 h and quenched with NH_4Cl (20 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with NaCl (30 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (5% EtOAc/PE) afforded alkyne **346**, as a pale yellow oil (352 mg, 95%).

R_f 0.43 (5% EtOAc/PE); $[\alpha]_D^{20}$ -11.0 (*c* 1.5, $CHCl_3$); **IR** (KBr, neat) 3445, 2938, 2868, 2178, 1462, 1381, 1247, 1080, 1064, 882, 841, 758 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.73 (1H, ddt, *J* = 17.1, 10.2, 7.2 Hz, H_3); 5.15-5.05 (2H, m H_2); 4.25-4.13 (2H, m, H_5 + H_7), 3.79 (1H, dd, *J* = 1.8 Hz, OH), 2.51-2.31 (4H, m, H_4 + H_8), 1.92-1.73 (2H, m, H_6), 1.11-1.10 (21H, m, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-$(CH(C\underline{H}_3)_2)_3$), 0.15 (9H, s, Si-$(C\underline{H}_3)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.1, 133.9, 117.7, 117.5, 103.5, 86.7, 71.8, 67.0, 40.6, 39.1, 28.9, 18.1, 18.0, 12.8, 12.3, 0.03; *m/z* (ES^+) 405 (10, $[M+Na]^+$), 383 (100, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{21}H_{43}O_2Si_2$ $[M+H]^+$ 383.2796; found 383.2798.

<u>Preparation of (4*R*,6*R*)-6-triisopropylsilyloxy-non-8-en-1-yn-4-ol</u> (**349**)



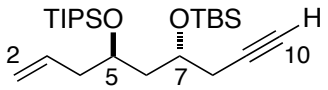
349

To a solution of alkyne **346** (308 mg, 0.810 mmol) in MeOH (10 mL) was added K_2CO_3 (223 mg, 1.61 mmol) and the mixture was stirred at RT for 16 h. Water (5 mL) was added and the aqueous layer was extracted with EtOAc (3 x 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (5% EtOAc/PE) gave alkyne **349**, as a colourless oil (219 mg, 88%).

R_f 0.33 (5% EtOAc/PE); $[\alpha]_D^{20}$ -7.7 (*c* 1.2, $CHCl_3$); **IR** (KBr, neat) 3482, 2944, 2868, 1465, 1385, 1087, 999, 917, 884, 737 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.72 (1H, ddt, *J* = 17.1, 10.2, 7.2 Hz, H_3); 5.15-5.06 (2H, m, H_2), 4.25-4.16 (2H, m, H_5 + H_7), 2.52-2.43 (2H, m, H_4), 2.38 (1H, dd, *J* = 5.7, 2.7 Hz, H_{8a}), 2.35 (1H, dd, *J* = 6.6, 2.7 Hz, H_{8b}), 2.02 (1H, t,

J = 2.7 Hz, H_{10}), 1.82 (1H, d, *J* = 7.0 Hz, H_{6a}), 1.79 (1H, d, *J* = 3.3, H_{6b}), 1.11-1.09 (21H, m, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-(CH(C<u>H</u>$_3)_2)_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 133.9, 117.8, 81.0, 71.7, 70.2, 66.9, 40.6, 39.3, 27.5, 18.1, 12.4; *m/z* (ES^+) 311 (100, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{18}H_{35}O_2Si$ $[M+H]^+$ 311.2401; found 311.2402.

<u>Preparation of (4*R*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-6-triisopropylsilyloxy-non-8-1-yne</u> (**347**)

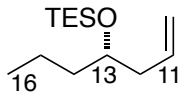


347

To a solution of alcohol **349** (226 mg, 0.730 mmol) in DCM (15 mL) at -20 °C was added 2,6-lutidine (170 μL, 1.46 mmol), followed by the addition of TBSOTf (220 μL, 0.950 mmol). The mixture was stirred at -20 °C for 1 h and quenched with NH_4Cl (15 mL). The aqueous layer was extracted with DCM (3 x 15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (0-2% EtOAc/PE) afforded silyl ether **347**, as a colourless oil (300 mg, 97%).

R_f 0.93 (10% EtOAc/PE); $[\alpha]_D^{20}$ -15.5 (*c* 1.2, $CHCl_3$); **IR** (KBr, neat) 2945, 2866, 1463, 1383, 1255, 1101, 837, 776 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.94-5.81 (1H, m, H_3), 5.12-5.05 (2H, m, H_2), 4.01-3.92 (2H, m, H_5 + H_7), 2.40-2.29 (4H, m, H_4 + H_8), 1.97 (1H, t, *J* = 2.7 Hz, H_{10}), 1.79 (2H, td, *J* = 6.0, 2.7 Hz, H_6), 1.08 (21H, s, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-(CH(C<u>H</u>$_3)_2)_3$), 0.89 (9H, s, Si-C(C<u>H</u>$_3)_3$), 0.10 (3H, s, Si-C<u>H</u>$_3$), 0.08 (3H, s, Si-C<u>H</u>$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.6, 117.1, 81.4, 70.2, 69.7, 68.8, 44.6, 42.2, 27.9, 25.8, 18.2, 18.0, 12.7, -4.1, -4.4; *m/z* (ES^+) 425 (20, $[M+H]^+$); **HRMS** (ES^+) Calc. for $C_{24}H_{49}O_2Si_2$ $[M+H]^+$ 425.3266; found 425.3266.

Preparation of (4*S*)-4-triethylsilyloxy-hept-1-ene (**350**)

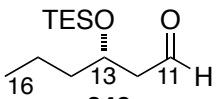


350

To a solution of alcohol **325** (360 mg, 3.16 mmol) in DCM (35 mL) at -60 °C was added 2,6-lutidine (735 μL, 6.32 mmol) and TESOTf (930 μL, 4.10 mmol). The mixture was warmed to -20 °C over 1.5 h and quenched with NH_4Cl (30 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (PE) gave silyl ether **350**, as a colourless oil (700 mg, 97%).

R_f 0.21 (PE); $[\alpha]_D^{20}$ -14.1 (*c* 1.3, $CHCl_3$); **IR** (KBr, neat) 3078, 2959, 2876, 1460, 1416, 1239, 1127, 1072, 1005, 911, 735 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.86 (1H, ddt, *J* = 16.8, 10.5, 7.2 Hz, H_{11}), 5.09 (1H, ddt, *J* = 8.7, 2.1, 1.2 Hz, H_{10a}), 5.03 (1H, t, *J* = 1.2 Hz, H_{10b}), 3.74 (1H, qn, *J* = 6.0 Hz, H_{13}), 2.25 (2H, ddq, *J* = 7.1, 6.0, 1.2 Hz, H_{12}), 1.50-1.29 (4H, m, H_{14} + H_{15}), 0.98 (9H, t, *J* = 7.8 Hz, Si-($CH_2C\underline{H}_3$)$_3$), 0.94-0.89 (3H, m, H_{16}), 0.66-0.57 (6H, m, Si-($C\underline{H}_2CH_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.4, 116.5, 71.8, 42.1, 39.2, 18.6, 14.2, 6.9, 5.0; *m/z* (ES^-) 227 (100, $[M-H]^+$); **HRMS** (ES^-) Calc. for $C_{13}H_{27}OSi$ $[M-H]^+$ 227.1827; found 227.1826.

Preparation of (3*S*)-3-triethylsilyloxy-hexanal (**348**)



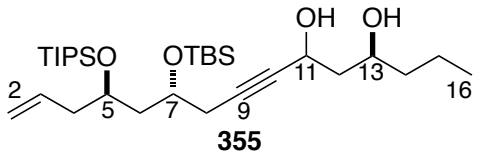
348

To a solution of alkene **350** (271 mg, 1.19 mmol) in DCM (30 mL) was added solid Na_2CO_3 (360 mg) and the mixture was cooled at -78 °C. A stream of O_3 was bubbled through for 5 min. The O_3 generator was switched off and O_2 was bubbled through for 5 min. Triphenylphosphine (545 mg, 2.08 mmol) was added and the mixture was warmed to

RT over 2 h. The reaction mixture was filtered on a plug of celite and washed with DCM. Solvent was removed under reduced pressure and purification by flash column chromatography on silica gel (5% Et_2O/PE) provided aldehyde **348**, as a colourless oil (262 mg, 96%).

R_f 0.57 (5% Et_2O/PE); $[\alpha]_D^{20}$ +2.8 (*c* 1.4, $CHCl_3$); **IR** (KBr, neat) 2959, 2877, 1727, 1458, 1415, 1379, 1240, 1101, 1042, 1008, 735 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.83 (1H, t, *J* = 2.4 Hz, CHO), 4.21 (1H, qn, *J* = 5.7 Hz, H_{13}), 2.52 (2H, dd, *J* = 6.0, 2.7 Hz, H_{12}), 1.55-1.48 (2H, m, H_{14}), 1.39-1.34 (2H, m, H_{15}), 0.99-0.93 (12H, m, Si-($CH_2C\underline{H}_3$)$_3$+H_{16}), 0.65-0.60 (6H, m, Si-($C\underline{H}_2CH_3$)$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.4, 68.0, 50.9, 40.2, 18.4, 14.1, 6.8, 5.0.

Preparation of (4*R*, 6*R*, 12*S*)-6-(*tert*-butyldimethylsilyloxy)-4-triisopropylsilyloxy-1-ene-8-yn-10,12-diol (**355**)



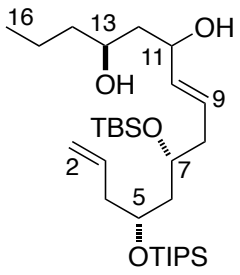
355

To a solution of alkyne **347** (174 mg, 0.410 mmol) in THF (10 mL) at -78 °C was added *n*-butyllithium (260 μL, 0.410 mmol, 1.6 M solution in hexane) and TMEDA (63.1 μL, 0.410 mmol). After 30 min, a solution of aldehyde **348** (47.1 mg, 0.205 mmol) in THF (2 mL) was added dropwise. The mixture was warmed to -20 °C over 2 h and quenched with NH_4Cl (10 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (3% EtOAc/PE) afforded intermediate TES ether (109 mg, 81%) as a colourless oil. To a solution of TES ether (112 mg, 0.171 mmol) in MeOH/DCM (1:1, 4 mL) at 0 °C was added CSA (7.9 mg, 34.2 μmol). The mixture was stirred for 30 min and quenched with $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and

evaporated under reduced pressure. Purification by flash column chromatography on silica gel (20% EtOAc/PE) afforded diol **355**, as a colourless oil (71.1 mg, 77%).

R_f 0.43 (20% EtOAc/PE); $[\alpha]_D^{20}$ -6.9 (*c* 2.2, $CHCl_3$); **IR** (KBr, neat) 3374, 2927, 2855, 1464, 1375, 1265, 1109, 1030, 743 cm^{-1};**^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.92-5.78 (1H, m, H_3), 5.10-5.08 (1H, m, H_{2a}), 5.06-5.04 (1H, m, H_{2b}), 4.66-4.57 (1H, m, H_{11}), 4.17-3.84 (3H, m, H_5 + H_7 + H_{13}), 2.69 (2H, br s, 2 x OH), 2.39-2.30 (4H, m H_4 + H_8), 1.83-1.73 (4H, m, H_6 + H_{12}), 1.47-1.38 (4H, m, H_{14} + H_{15}), 1.07 (21H, m, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-(CH($C\underline{H}_3)_2)_3$), 0.97-0.91 (3H, m, H_{16}), 0.89-0.87 (9H, m, Si-C($C\underline{H}_3)_3$), 0.08 (3H, s, Si-$C\underline{H}_3$), 0.07 (3H, s, Si-$C\underline{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.6, 117.1, 117.1, 82.7, 82.6, 71.2, 69.6, 69.3, 68.8, 62.7, 61.2, 44.6, 44.5, 44.3, 42.9, 42.2, 39.9, 39.7, 28.1, 25.8, 18.6, 18.5, 18.2, 18.0, 14.0, 14.0, 12.7, 12.6, -4.1, -4.4; *m/z* (ES^+) 1098 (10, $[2M+NH_4]^+$), 558 (100, $[M+NH_4]^+$); **HRMS** (ES^+) Calc. for $C_{30}H_{64}O_4NSi_2$ 558.4368 found 558.4358.

<u>Preparation of (4*R*,6*R*,12*S*,*E*)-6-(*tert*-butyldimethylsilyloxy)-4-triisopropylsilyloxy-pentadec-1,8-dien-10,12-diol</u> (**361**)

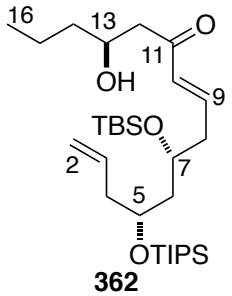


361

To a solution of alkyne **355** (66.0 mg, 0.122 mmol) in Et_2O (6 mL) at RT was added Red-Al™ (280 μL, 0.980 mmol). The mixture was stirred for 1.5 h and quenched with a saturated solution of Rochelle's salt (6 mL), diluted with EtOAc (10 mL) and stirred for 2 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (20% EtOAc/PE) provided alkene **361**, as a colourless oil (62.2 mg, 94%).

R_f 0.22 (10% EtOAc/PE); $[\alpha]_D^{20}$ -10.9 (*c* 1.4, $CHCl_3$); **IR** (KBr, neat) 3364, 2927, 2862, 1462, 1382, 1252, 1097, 881, 771 cm^{-1};**^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.87 (1H, ddt, *J* = 17.4, 9.6, 7.2, H_3), 5.73 (2H, m, H_9 + H_{10}), 3.95-3.80 (3H, m, H_5 + H_7 + H_{13}), 2.45 (2H, br s, 2 x OH), 2.37-2.17 (4H, m, H_4 + H_8), 1.69-1.54 (4H, m, H_6 + H_{12}), 1.48-1.40 (4H, m, H_{14} + H_{15}), 1.06 (21H, s, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-$(CH(C\underline{H}_3)_2)_3$), 0.94 (3H, t, *J* = 6.9 Hz, H_{16}), 0.88 (9H, s, Si-C(C<u>H</u>$_3)_3$), 0.05 (6H, s, Si-$(C\underline{H}_3)_2$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.0, 134.9, 134.7, 134.6, 127.8, 117.0, 73.9, 72.1, 70.6, 69.9, 69.8, 69.7, 69.7, 68.9, 44.5, 43.2, 42.6, 42.1, 42.0, 40.5, 40.3, 40.2, 39.6, 25.9, 18.8, 18.5, 18.2, 18.0, 14.0, 12.7, -4.0, -4.3; *m/z* (ES^+) 565 (100, $[M+Na]^+$); **HRMS** (ES^+) Calc. for $C_{30}H_{62}O_4NaSi_2$ $[M+Na]^+$ 565.4084; found 565.4092.

<u>(4*R*,6*R*,12*S*,*E*)-6-(*tert*-butyldimethylsilyloxy)-12-hydroxy-4-triisopropylsilyloxy-pentadec-1,8-dien-10-one</u> (**362**)



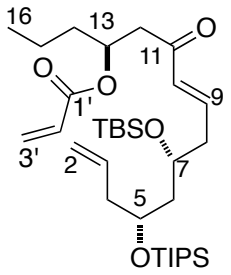
362

To a solution of alcohol **361** (62.2 mg, 0.115 mmol) in Et_2O (8 mL) at RT was added MnO_2 (100 mg, 1.15 mmol). After 2 h, MnO_2 (100 mg, 1.15 mmol) was added and the reaction was stirred for a further 3 h. Solids were filtered over a plug of silica and washed with EtOAc. Volatiles were removed under reduced pressure and purification by flash column chromatography on silica gel (10% EtOAc/PE) afforded enone **362**, as a colourless oil (39.7 mg, 64%).

R_f 0.36 (10% EtOAc/PE); $[\alpha]_D^{20}$ +5.2 (*c* 1.4, $CHCl_3$); **IR** (KBr, neat) 3483, 2938, 2862, 1668, 1462, 1383, 1254, 1103, 1065, 835 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.88 (1H, dt, *J* = 15.9, 7.2 Hz, H_9), 6.11 (1H, dt, *J* = 15.9, 1.2 Hz, H_{10}), 5.92-5.79 (1H, m, H_3), 5.11-5.05 (2H, m, H_{2a+b}), 4.12-4.04 (1H, m, H_{13}), 3.95 -3.91 (2H, m, H_5 + H_7), 2.75 (1H,

dd, J = 17.4, 2.7 Hz, H_{12a}), 2.60 (1H, dd, J = 17.4, 9.0 Hz, H_{12a}), 2.44-2.26 (4H, m, H_4 + H_8), 1.64-1.37 (6H, m, H_6 + H_{14} +H_{15}), 1.08-1.06 (21H, m, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-(CH(C<u>H</u>$_3$)$_2)_3$), 0.94 (3H, t, J = 6.9 Hz, CH_3), 0.88 (9H, s, Si-C(C<u>H</u>$_3)_3$), 0.06 (3H, s, Si-C<u>H</u>$_3$), 0.05 (3H, s, Si-C<u>H</u>$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.9, 145.1, 134.3, 132.7, 117.3, 69.5, 67.4, 45.7, 44.8, 41.9, 40.7, 38.6, 25.8, 18.7, 18.2, 18.0, 14.0, 12.7, -4.3; *m/z* (ES^+) 563 (100, $[M+Na]^+$); **HRMS** (ES^+) Calc. for $C_{30}H_{60}O_4NaSi_2$ $[M+Na]^+$ 563.3928; found 563.3930.

<u>Preparation of (4*R*,6*R*,12*S*,*E*)-13-acryloyloxy-6-(*tert*-butyldimethylsilyloxy)-4-triisopropylsilyloxy-pentadec-1,8-dien-10-one</u> (**364**)



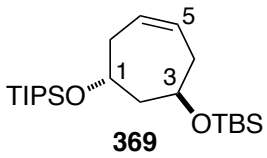
364

To a solution of acrylic acid **363** in toluene (2 mL) was added trichlorobenzoyl chloride (52.0 μL, 0.333 mmol) and Et_3N (46.4 μL, 0.333 mmol). The mixture was stirred for 10 min and a solution of alcohol **362** (30.0 mg, 55.5 μmol) in toluene (2 mL) was added, followed by the addition of DMAP (27.1 mg, 0.222 mmol). The reaction was stirred for 1 h at RT and quenched with pH 7 buffer (4 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (5% EtOAc/PE) gave ester **364**, as a colourless oil (16.8 mg, 51%).

R_f 0.36 (5% EtOAc/PE); $[\alpha]_D^{20}$ -17.7 (*c* 1.7, $CHCl_3$); **IR** (KBr, neat) 2946, 2865, 1727, 1674, 1463, 1406, 1258, 1192, 1085, 985, 836 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.88 (1H, dt, J = 15.9, 7.2 Hz, H_9), 6.39 (1H, dd, J = 17.4, 1.8 Hz, $H_{3'a}$), 6.16-6.05 (2H, m, $H_{2'}$ + H_{10}), 5.91-5.79 (2H, m, H_3 + $H_{3'b}$), 5.38 (1H, qn, J = 6.3 Hz, H_{13}), 5.11-5.05 (2H, m, H_2),

3.96-3.91 (2H, m, H_5 + H_7), 2.94 (1H, dd, *J* = 15.9, 6.6 Hz, H_{12a}), 2.73 (1H, dd, *J* = 15.9, 6.3 Hz, H_{12a}), 2.44-2.26 (4H, m, H_4 + H_8), 1.79-1.38 (6H, m, H_6 + H_{14} +H_{15}), 1.07 (21H, m, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-$(CH(C\underline{H}_3)_2)_3$), 0.94 (3H, t, *J* = 7.2 Hz, H_{16}), 0.89 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.07 (3H, s, Si-C<u>H</u>$_3$), 0.06 (3H, s, Si-C<u>H</u>$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 196.7, 165.5, 144.6, 134.4, 132.5, 130.5, 128.6, 117.3, 70.6, 69.6, 69.1, 44.8, 44.1, 41.9, 40.7, 36.2, 25.8, 18.5, 18.2, 18.0, 13.8, 12.7, -4.2, -4.3; *m/z* (ES^+) 617 (100, $[M+Na]^+$); **HRMS** (ES^+) Calc. for $C_{33}H_{62}O_5NaSi_2$ $[M+Na]^+$ 617.4034; found 617.4015.

<u>Preparation of (1*R*,3*R*,*Z*)-3(*tert*-butyldimethylsilyloxy)-1-triisopropylsilyloxy-cyclohept-5-ene</u> (**369**)



369

To a solution of alkene **364** (16.8 mg, 28.3 μmol) in DCM (5 mL) was added Grubbs second generation catalyst (1.2 mg, 5 mol %) and the mixture was refluxed for 16 h. After cooling at RT, the solvent was removed under reduced pressure. Purification by column chromatography on silica gel (5% EtOAc/PE) afforded cyclic alkene **369**, as a colourless oil (7.9 mg, 70%).

R_f 0.86 (5% EtOAc/PE); $[\alpha]_D^{20}$ -119.2 (*c* 1.8, $CHCl_3$); **IR** (KBr, neat) 2957, 2927, 2856, 1462, 1377, 1256, 1199, 1065, 743 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.69-5.67 (2H, m, H_5 + H_6), 4.16-4.03 (2H, m, H_1 + H_3), 2.41-2.26 (4H, m, H_4 + H_7), 2.03 (2H, t, *J* = 5.6 Hz, H_2), 1.07 (21H, s, Si-(C<u>H</u>$(CH_3)_2)_3$ + Si-$(CH(C\underline{H}_3)_2)_3$), 0.89 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.06 (3H, s, Si-C<u>H</u>$_3$), 0.05 (3H, s, Si-C<u>H</u>$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 128.0, 127.9, 66.9, 66.8, 37.2, 37.1, 25.8, 18.1, 18.1, 12.3, -4.8, -4.9; *m/z* (ES^+) 397 (65, $[M-H]^+$); **HRMS** (ES^+) Calc. for $C_{22}H_{45}O_2Si_2$ $[M-H]^+$ 397.2953; found 397.2946.

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Appendix: Selected ^{1}H and ^{13}C NMR spectra

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PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             4194.631 Hz
FIDRES          0.128010 Hz
AQ              3.9059956 sec
RG                   128
DW                119.200 usec
DE                  6.00 usec
TE                297.1 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 =======
NUC1                  1H
P1                 6.80 usec
PL1                0.00 dB
SFO1         300.1318008 MHz
SI                 32768
SF           300.1300530 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 1.00
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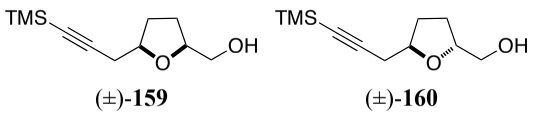
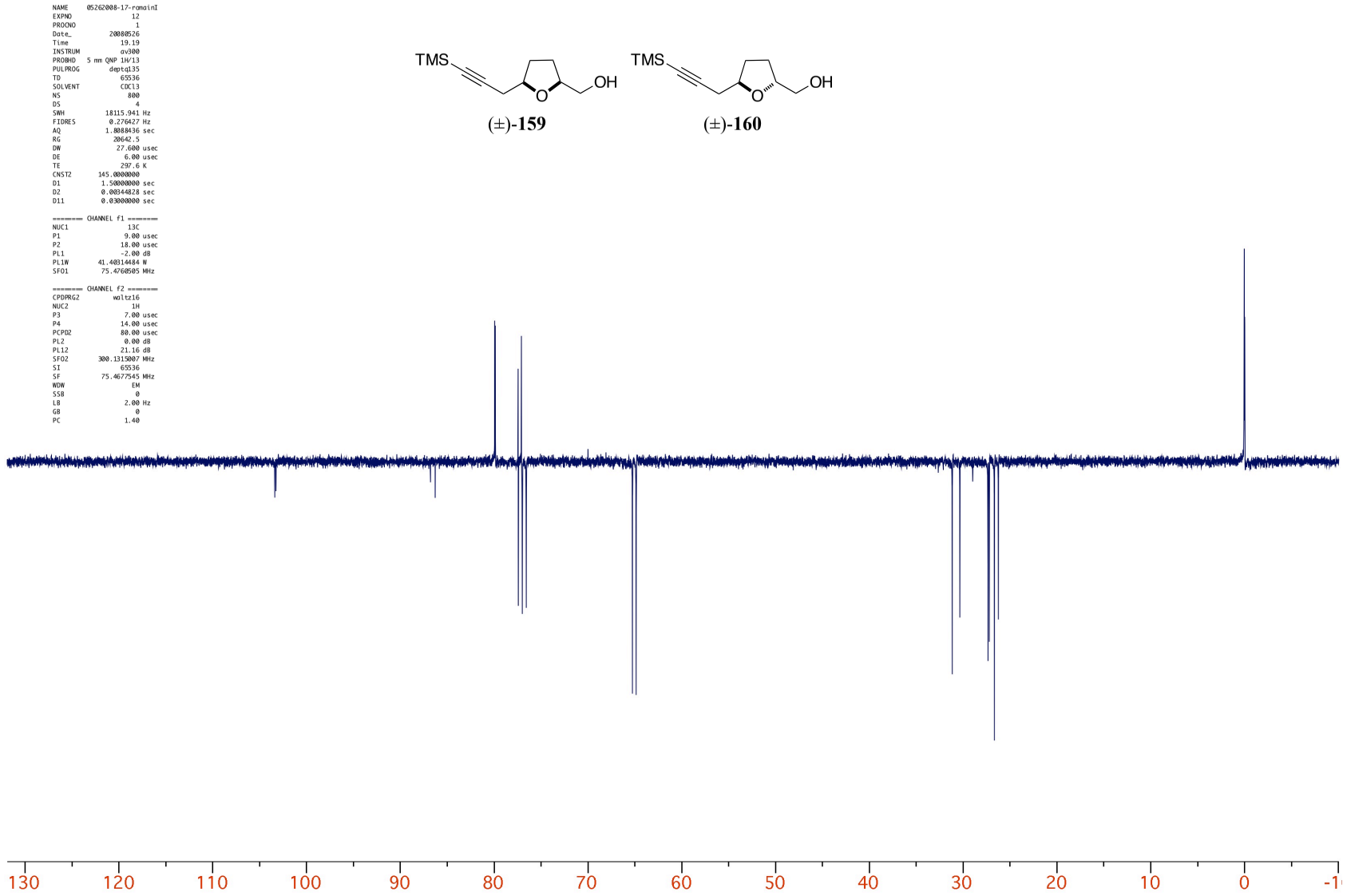


(±)-**159**

(±)-**160**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PULPROG deptq135
TD 65536
SOLVENT CDCl3
NS 800
DS 4
SWH 18115.941 Hz
FIDRES 0.276427 Hz
AQ 1.8088436 sec
RG 20642.5
DW 27.600 usec
DE 6.00 usec
TE 297.6 K
CNST2 145.0000000
D1 1.50000000 sec
D2 0.00344828 sec
D11 0.03000000 sec
====== CHANNEL f1 ======
NUC1 13C
P1 9.00 usec
P2 18.00 usec
PL1 -2.00 dB
PL1W 41.40314484 W
SFO1 75.4760505 MHz
====== CHANNEL f2 ======
CPDPRG2 waltz16
NUC2 1H
P3 7.00 usec
P4 14.00 usec
PCPD2 80.00 usec
PL2 0.00 dB
PL12 21.16 dB
SFO2 300.1315007 MHz
SI 65536
SF 75.4677545 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40
TMS
OH
O
(±)-159
TMS
OH
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130
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110
100
90
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70
60
50
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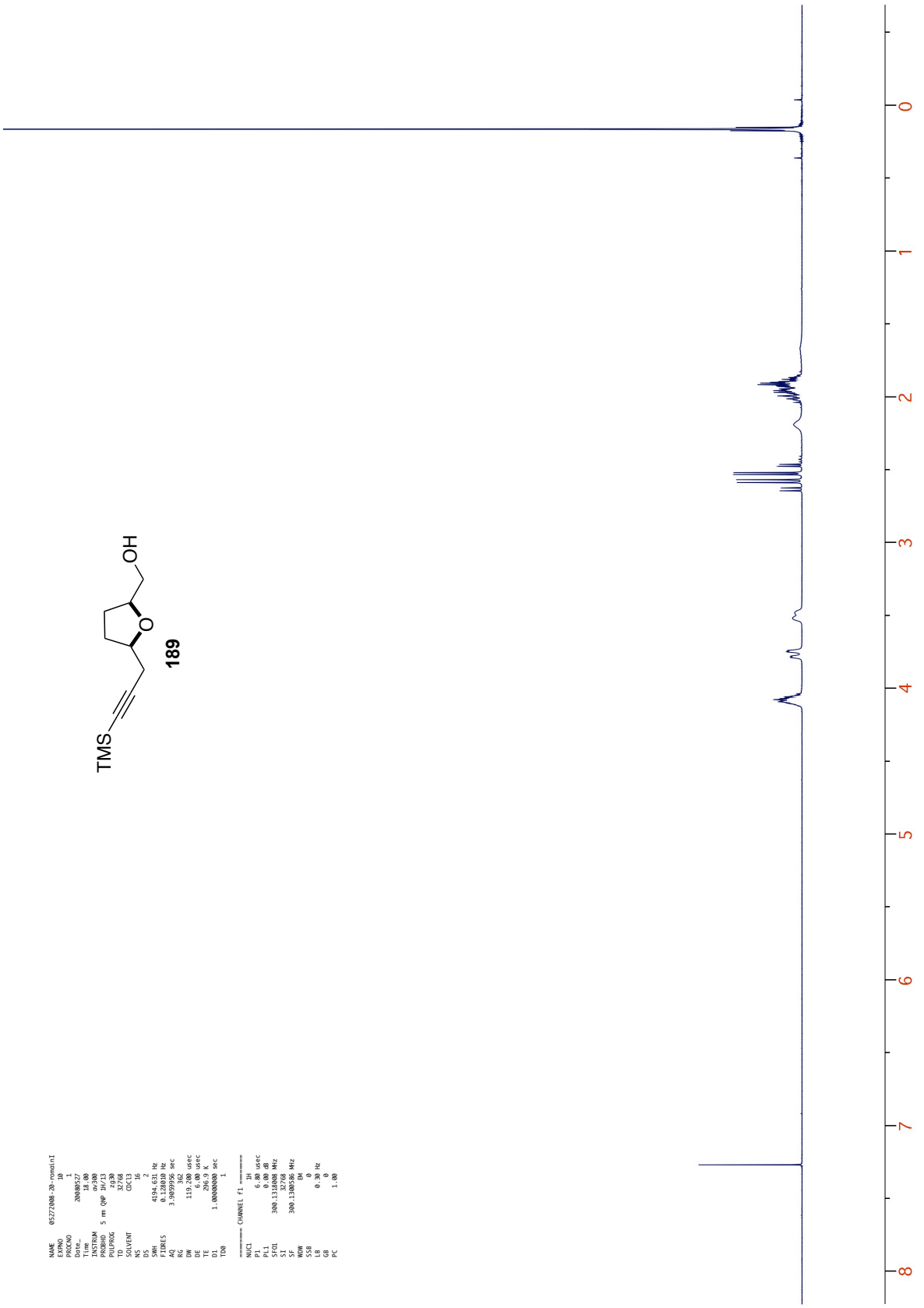
30
20
10
0
-1

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PULPROG             zg30
TD                 32768
SOLVENT             CDCl3
NS                    16
DS                     2
SWH              4194.631 Hz
FIDRES           0.128010 Hz
AQ               3.9059956 sec
RG                   362
DW                119.200 usec
DE                  6.00 usec
TE                296.9 K
D1               1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                1H
P1                6.80 usec
PL1               0.00 dB
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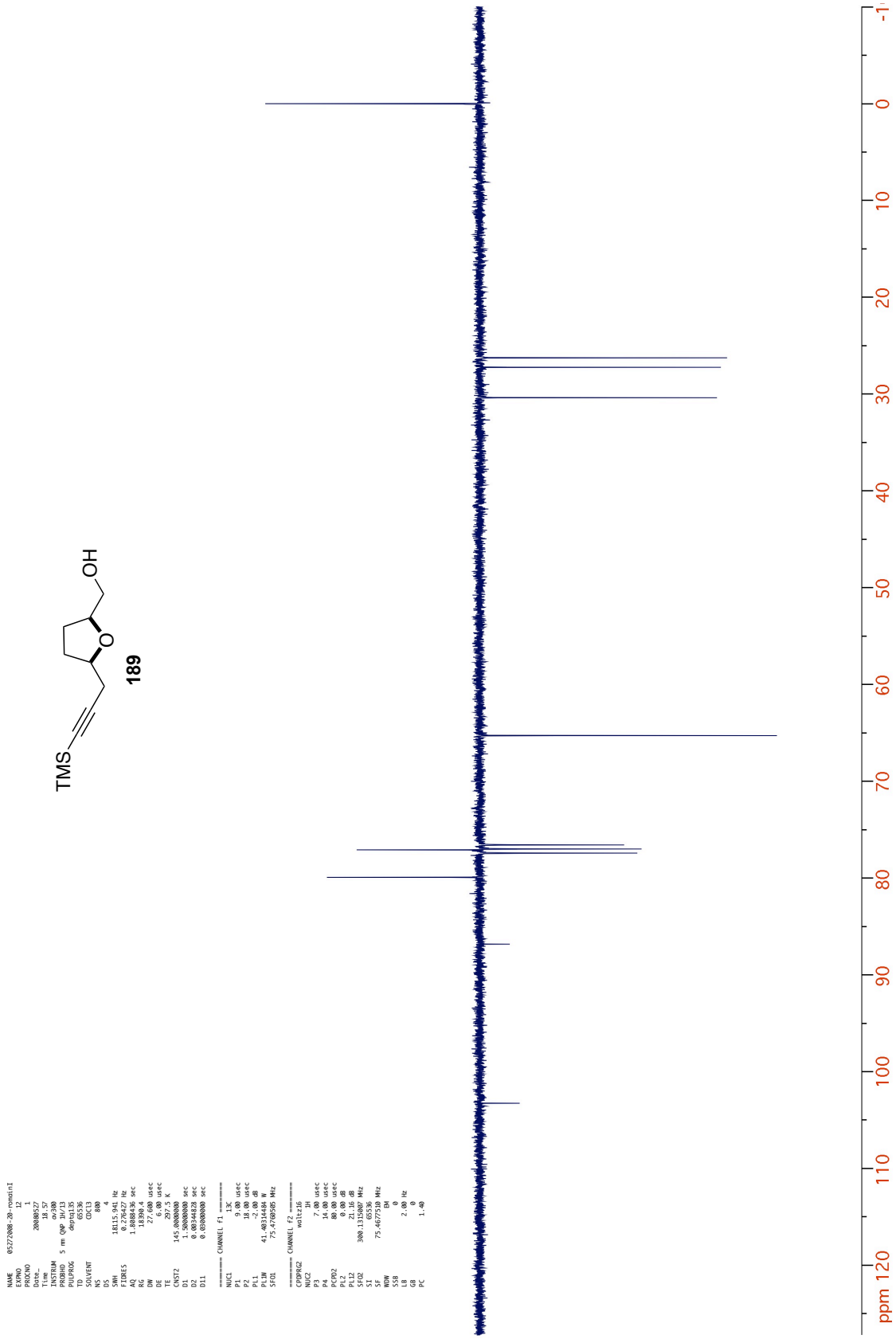
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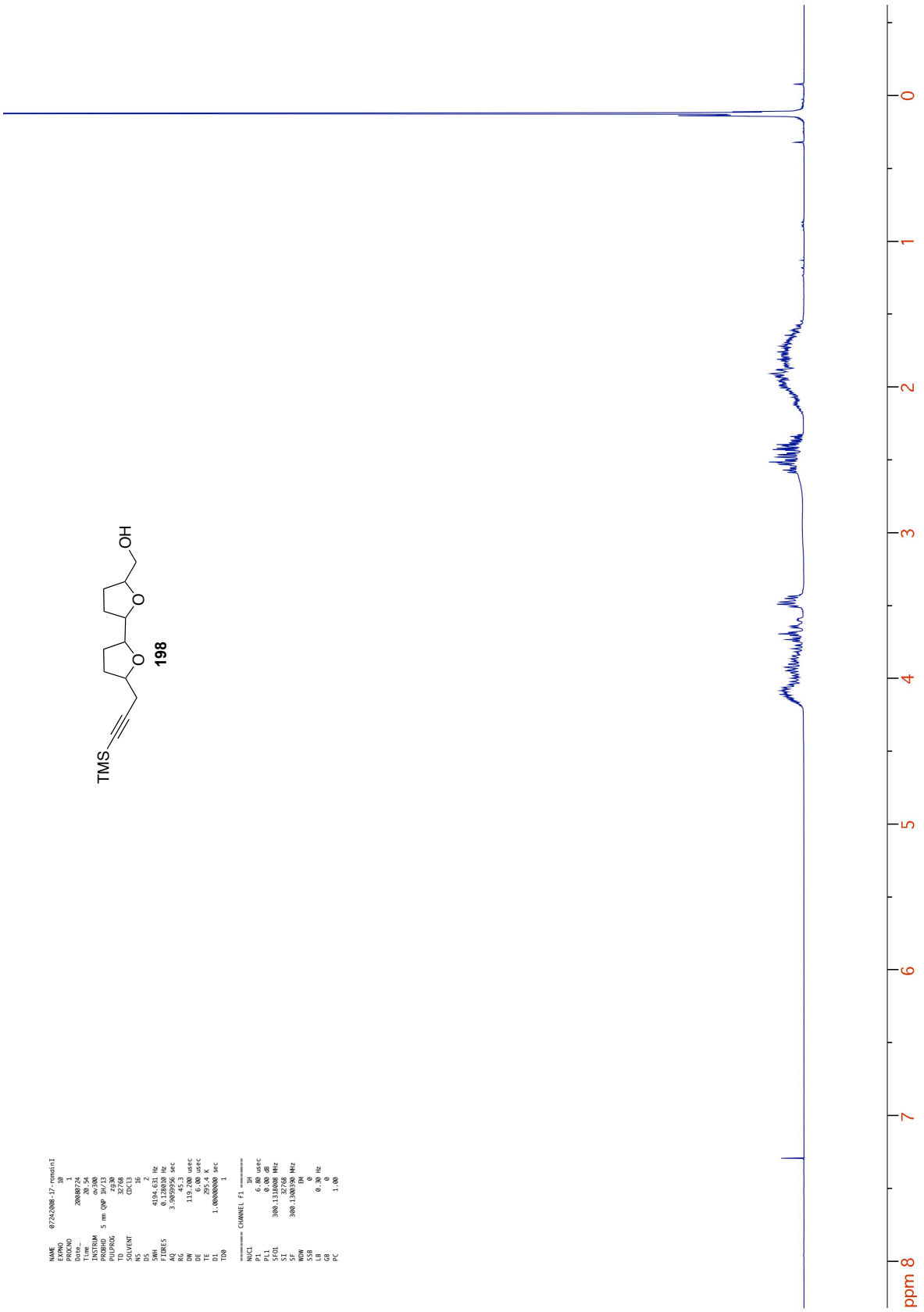


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PULPROG         zg30
TD             32768
SOLVENT        CDCl3
NS                16
DS                 2
SWH          4194.631 Hz
FIDRES       0.128010 Hz
AQ           3.9059956 sec
RG              45.3
DW             119.200 usec
DE               6.00 usec
TE             295.4 K
D1          1.00000000 sec
TD0                1

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P1               6.80 usec
PL1             0.00 dB
SFO1     300.1318008 MHz
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PC             1.00
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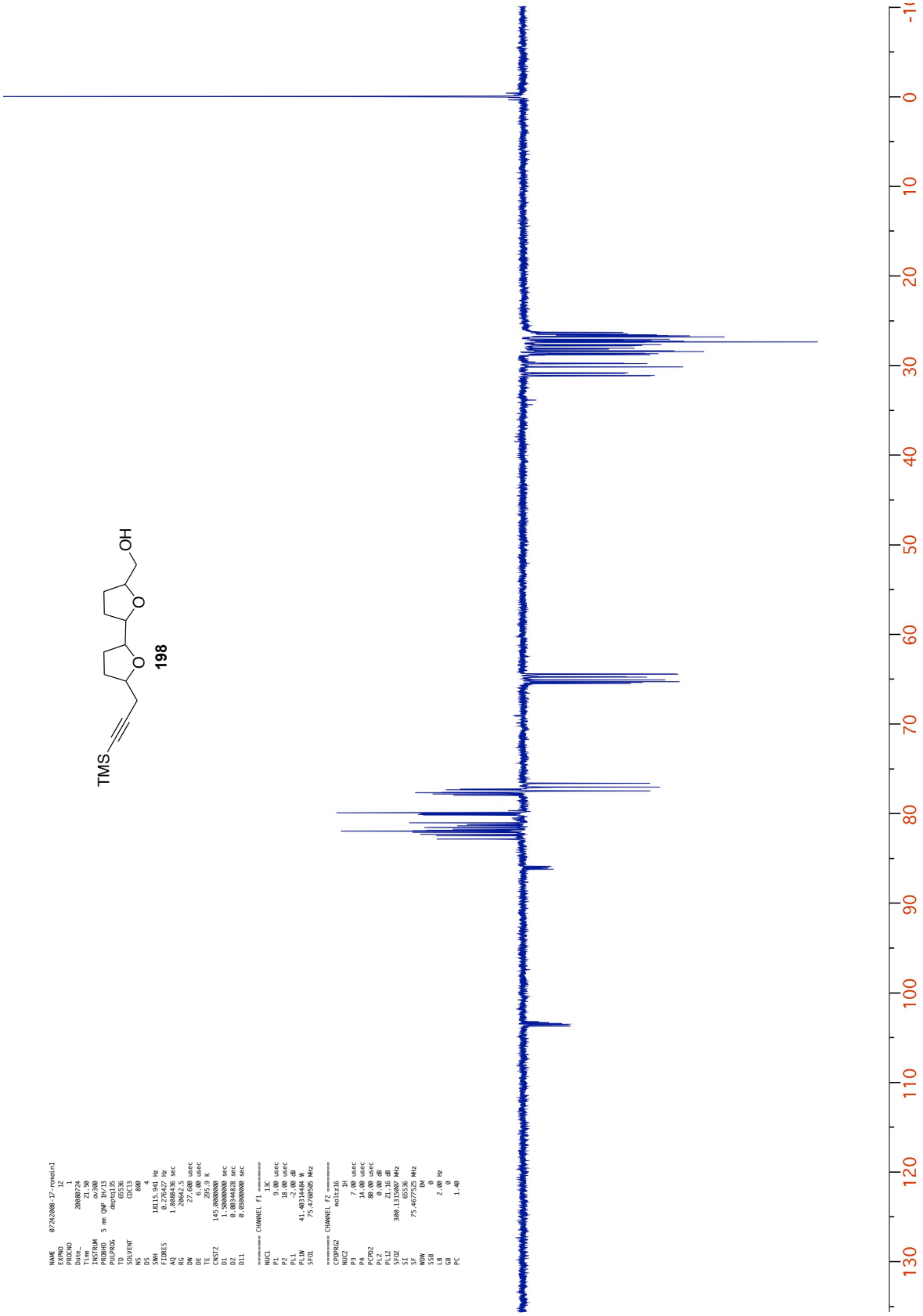
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PULPROG dept135
TD 65536
SOLVENT CDCl3
NS 800
DS 4
SWH 18115.941 Hz
FIDRES 0.276427 Hz
AQ 1.8088436 sec
RG 20642.5
DW 27.600 usec
DE 6.00 usec
TE 295.9 K
CNST2 145.0000000
D1 1.5000000 sec
D2 0.0034428 sec
D11 0.0300000 sec
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P1 9.00 usec
P2 18.00 usec
PL1 2.00 dB
PL1W 41.4071044 W
SFO1 75.4760005 MHz
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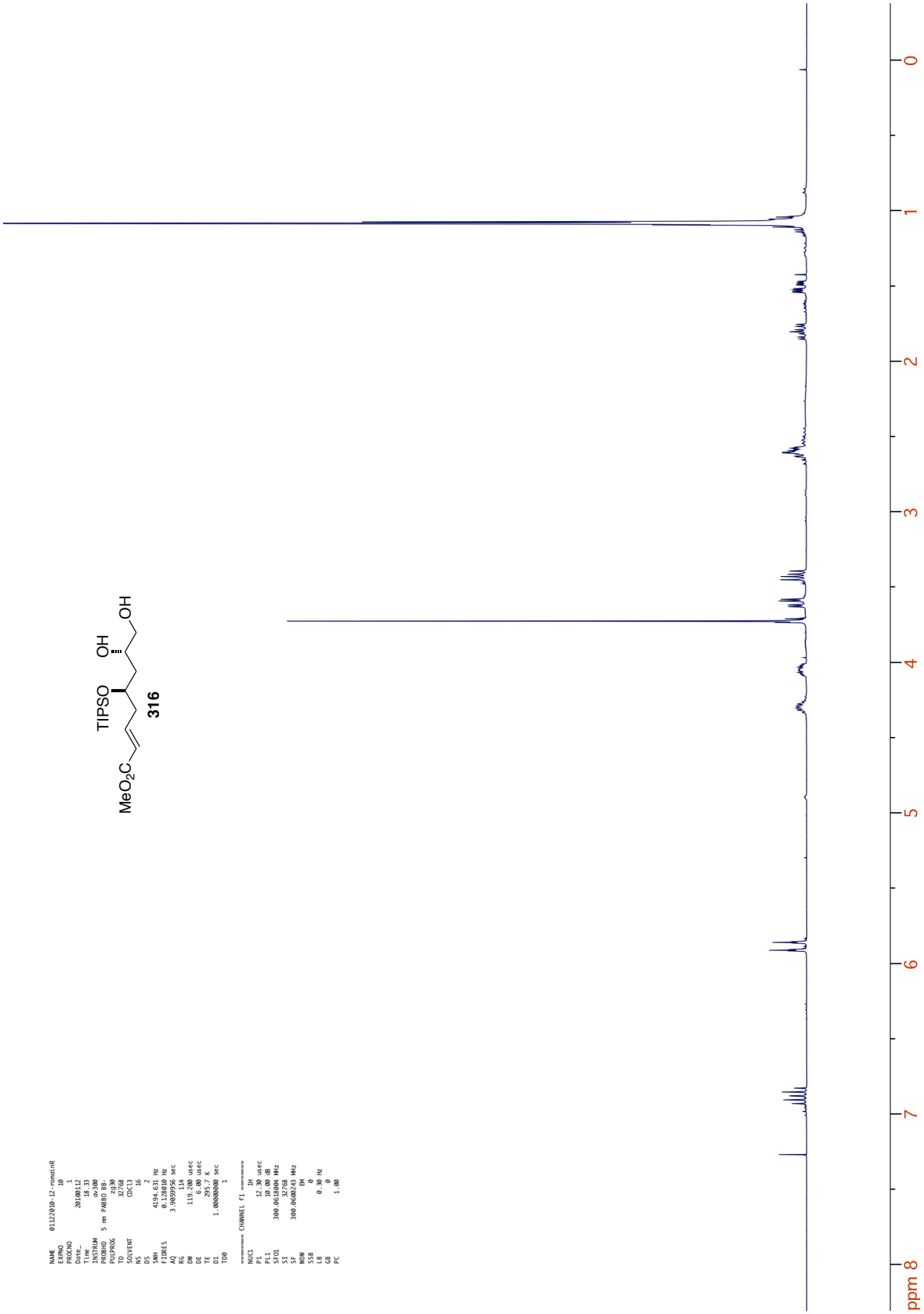
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 21.15 dB
SFO2 300.1315007 MHz
SI 65536
SF 75.4677525 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40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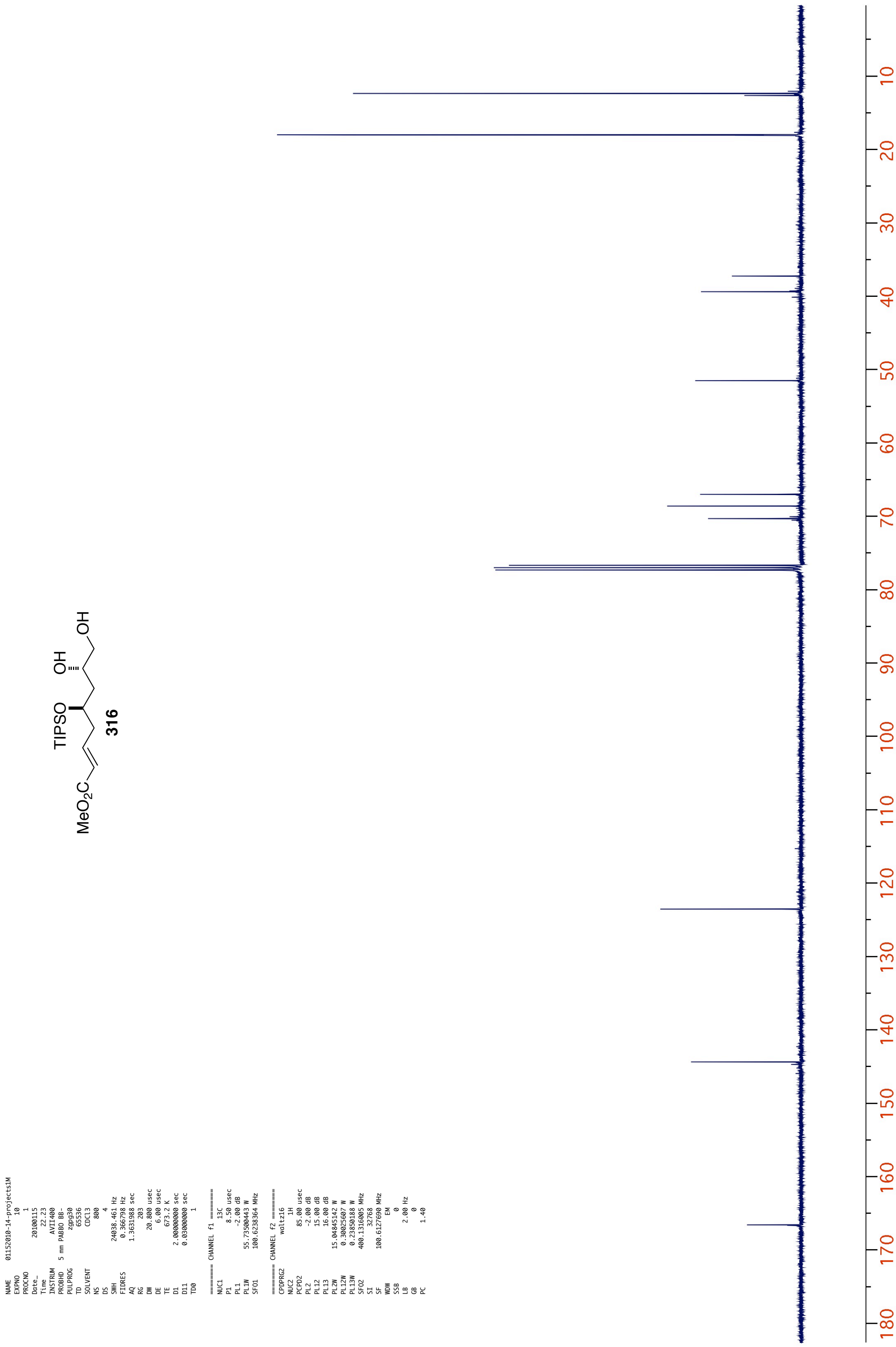

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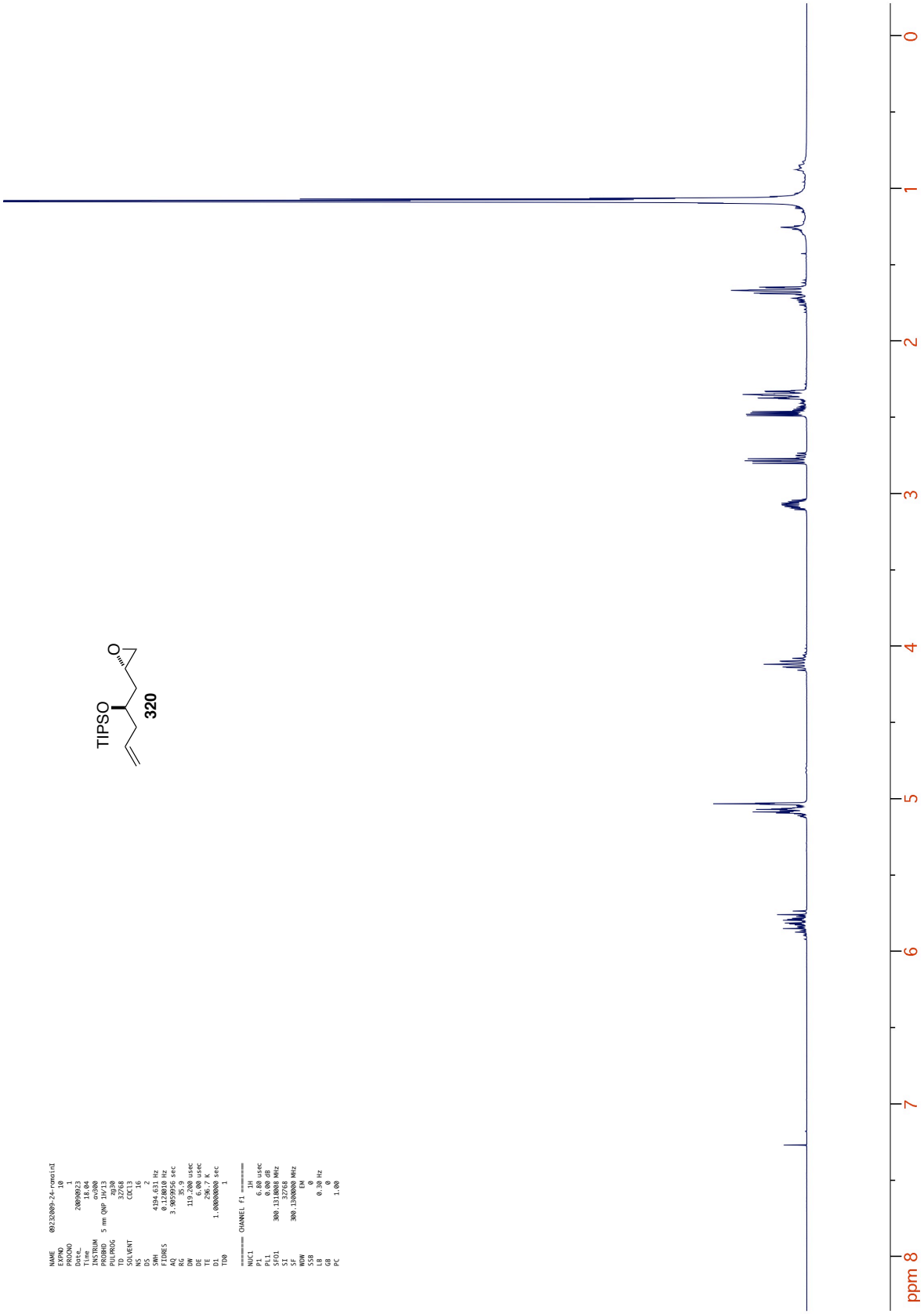


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PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                    16
DS                     2
SWH              4194.631 Hz
FIDRES           0.128010 Hz
AQ               3.9059956 sec
RG                  57.09
DW                 119.200 usec
DE                   6.00 usec
TE                 296.7 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 6.80 usec
PL1               0.00 dBW
SFO1         300.1318088 MHz
SI                 32768
SF           300.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

```
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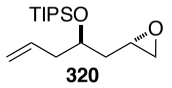
PROCNO                    1
Date_           20090923
Time                 18.50
INSTRUM              av300
PROBHD   5 mm QNP 1H/13
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   800
DS                     4
SWH           18115.941 Hz
FIDRES        0.276427 Hz
AQ            1.8088436 sec
RG               7298.2
DW               27.600 usec
DE                6.00 usec
TE                297.7 K
D1           1.50000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.00 usec
PL1                 -2.00 dB
PL1W        41.40314484 W
SFO1         75.4760505 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                  0.00 dB
PL12                21.16 dB
PL13                23.00 dB
SFO2        300.1315007 MHz
SI                 65536
SF           75.4677490 MHz
WDW                   EM
SSB                    0
LB                  2.00 Hz
GB                     0
PC                  1.40
```



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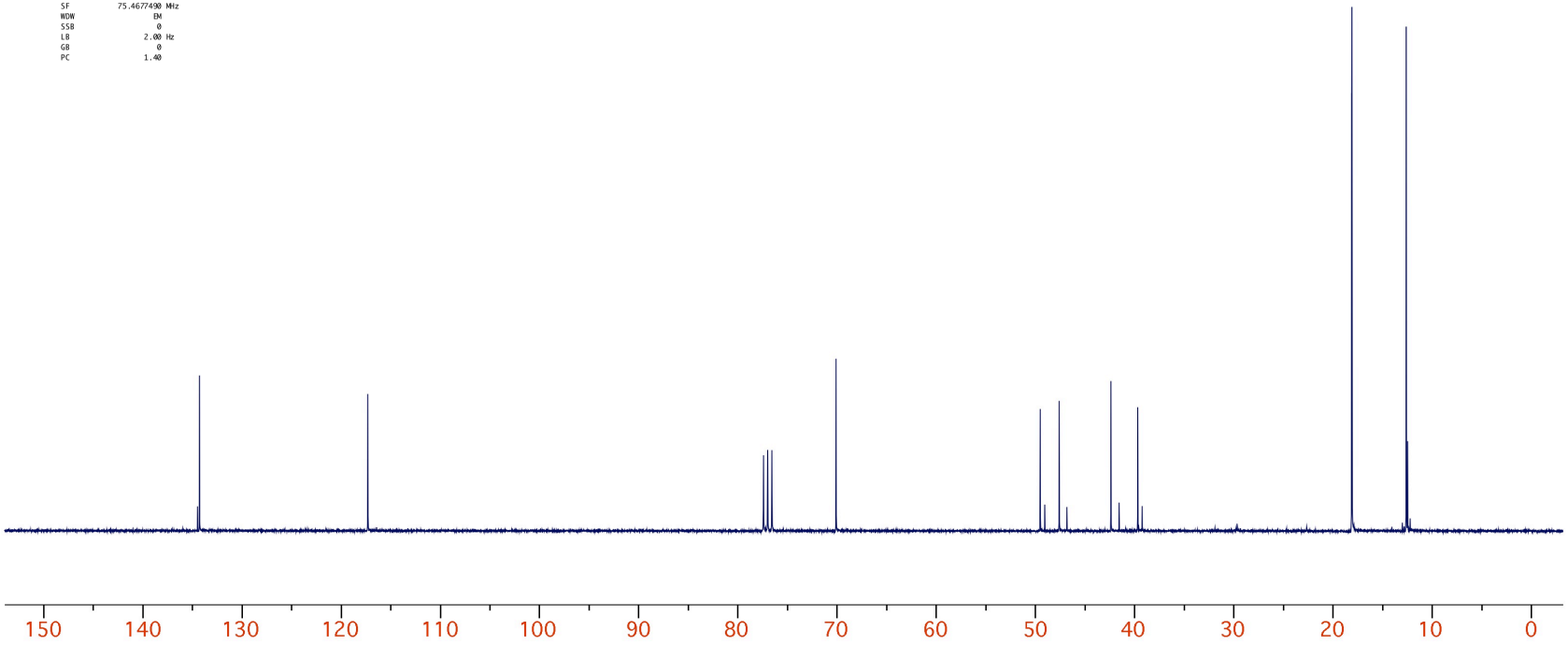

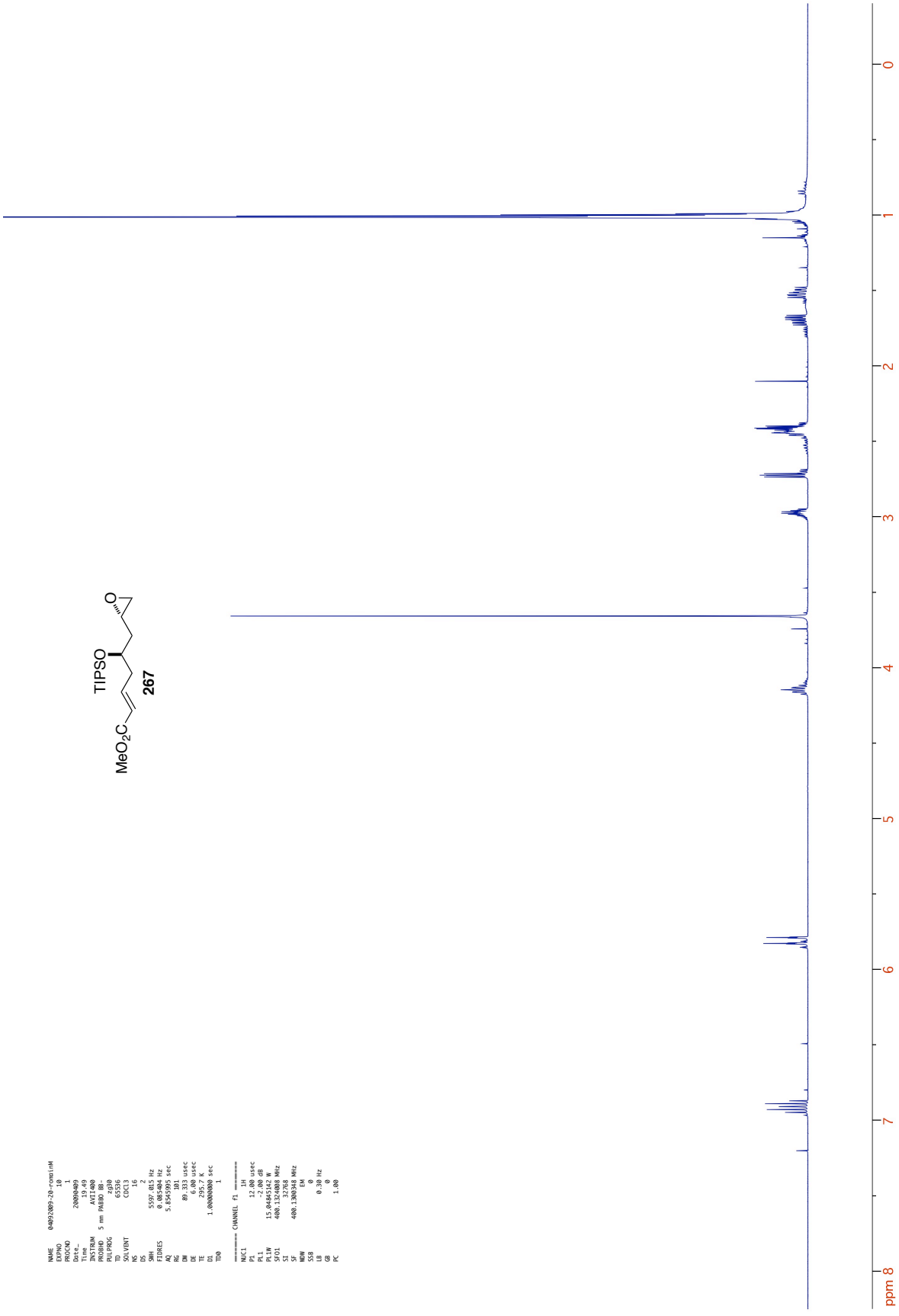


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TD                       65536
SOLVENT                 CDCl3
NS                          16
DS                           2
SWH                 5597.015 Hz
FIDRES              0.085404 Hz
AQ                  5.8545995 sec
RG                         101
DW                      89.331 usec
DE                      6.00 usec
TE                     295.7 K
D1                  1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                       1H
P1                      12.00 usec
PL1                     2.00 dB
PL1W                15.04845142 W
SFO1               400.1324008 MHz
SI                       32768
SF                 400.1300344 MHz
WDW                        EM
SSB                         0
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PC                       1.00
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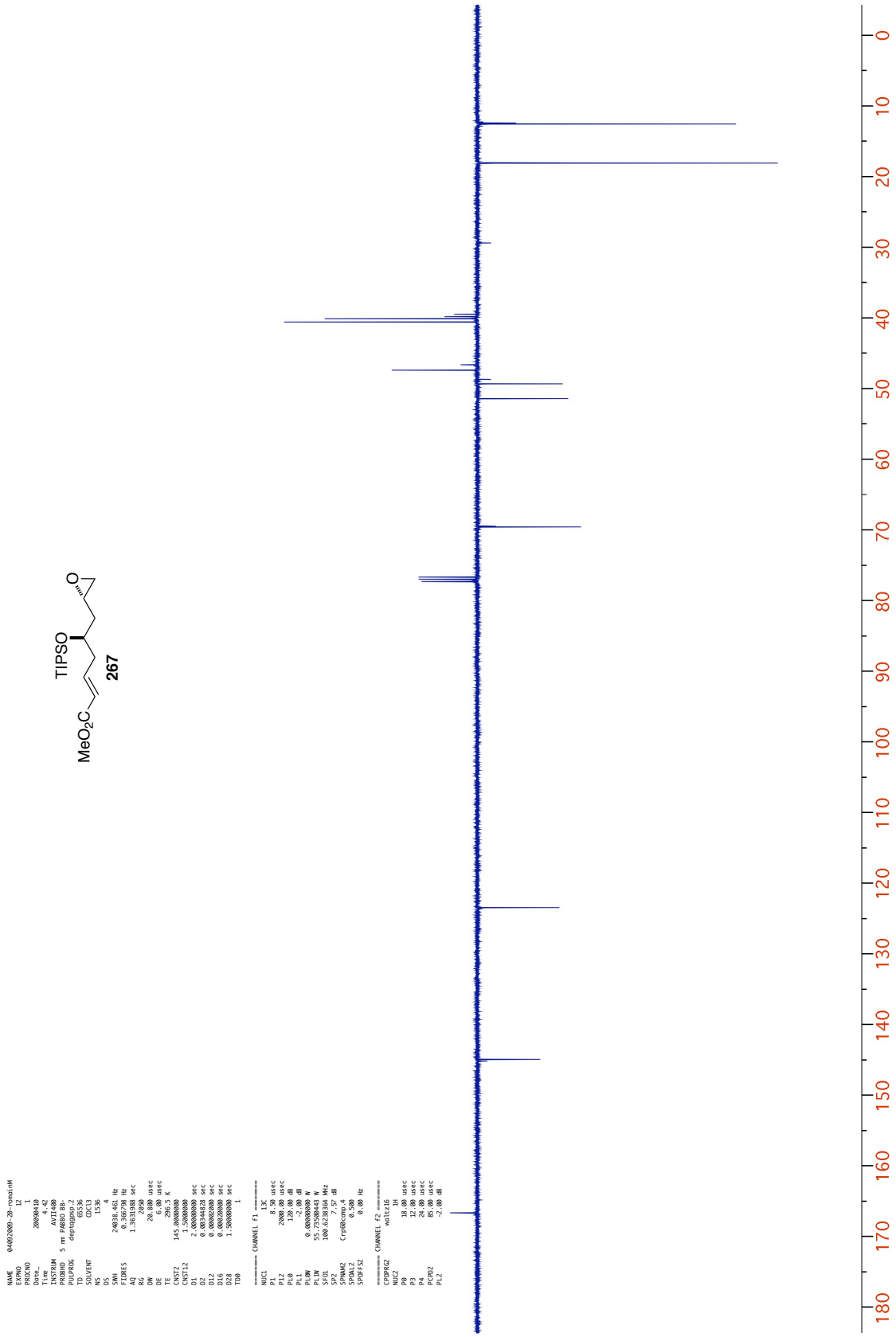
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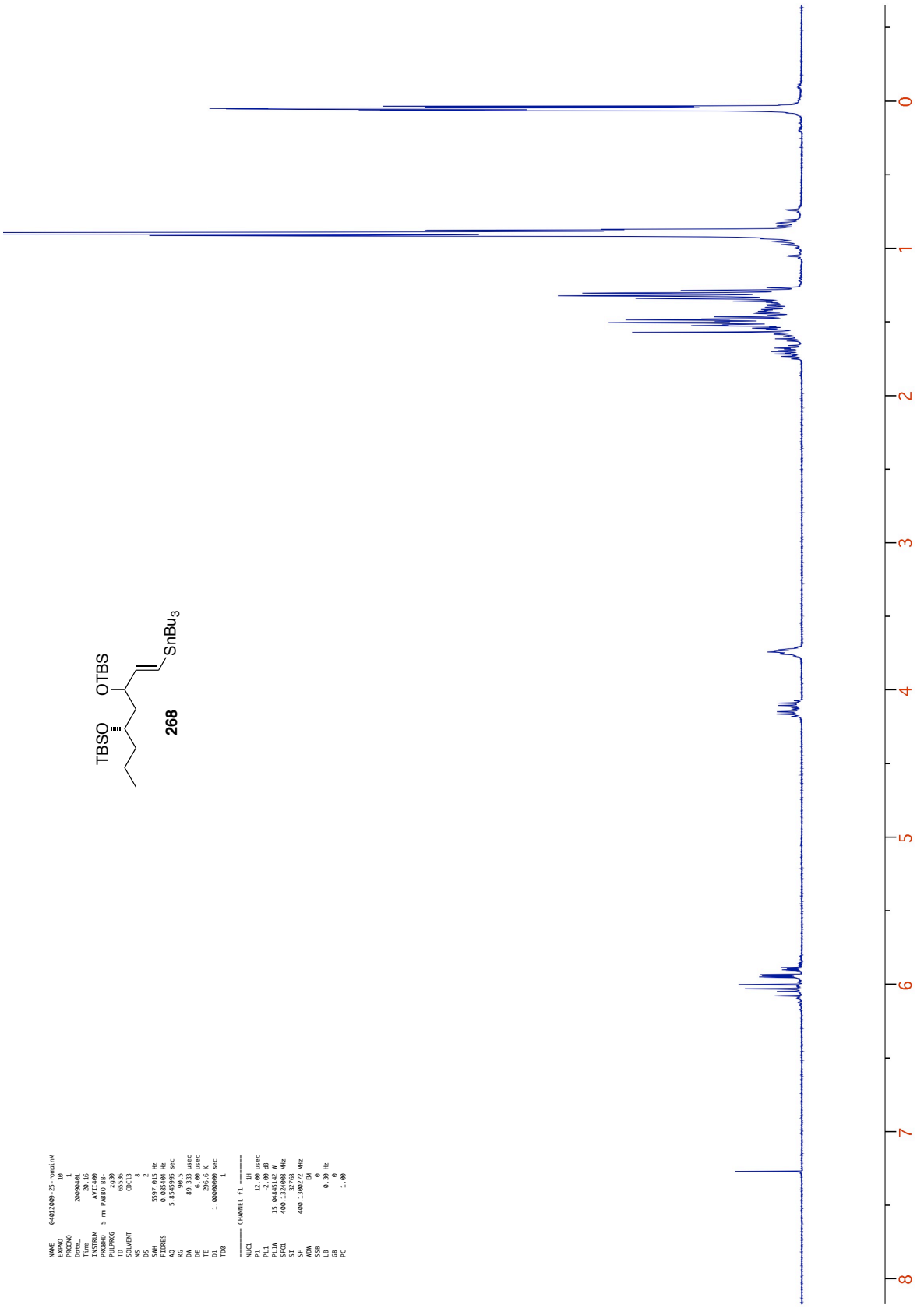


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PULPROG                 zg30
TD                      65536
SOLVENT                 CDCl3
NS                          8
DS                          2
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FIDRES              0.085404 Hz
AQ                  5.8545995 sec
RG                      90.5
DW                      89.313 usec
DE                       6.00 usec
TE                      296.6 K
D1                  1.00000000 sec
TD0                         1

======== CHANNEL f1 ========
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P1                     12.00 usec
PL1                    -2.00 dB
PL1W                15.0484512 W
SFO1               400.1324008 MHz
SI                      32768
SF                 400.1300272 MHz
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SSB                         0
LB                      0.30 Hz
GB                          0
PC                       1.00
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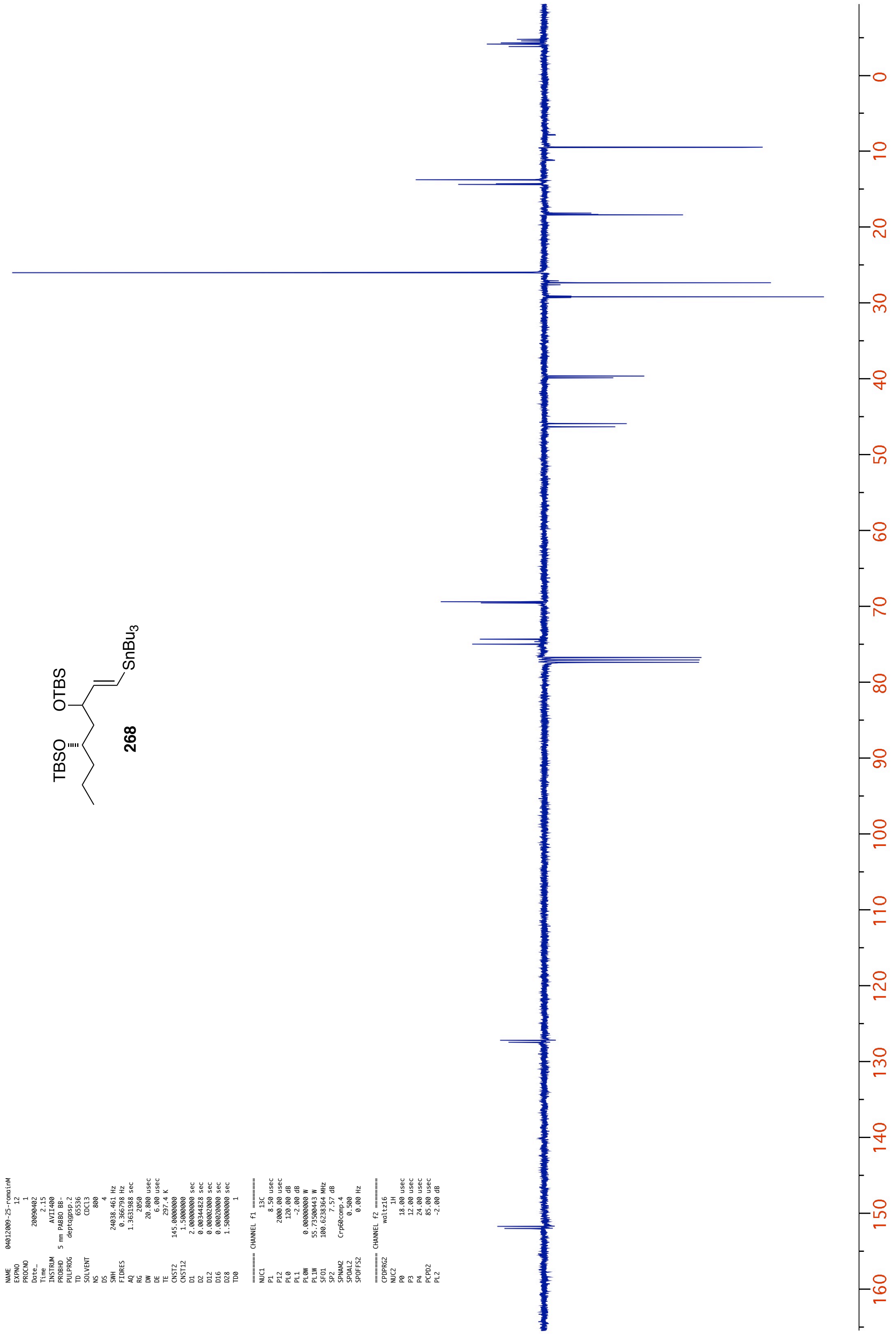
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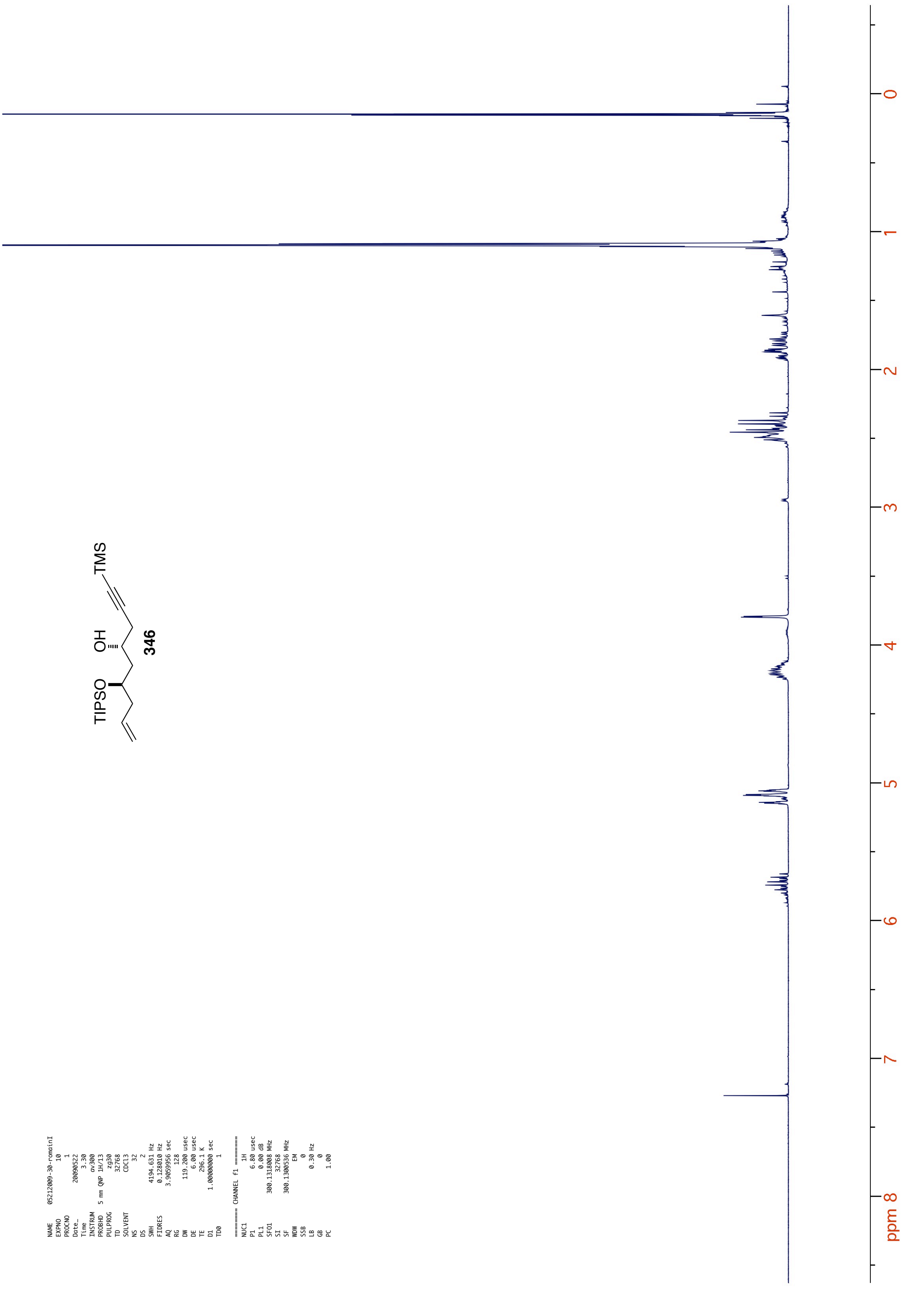

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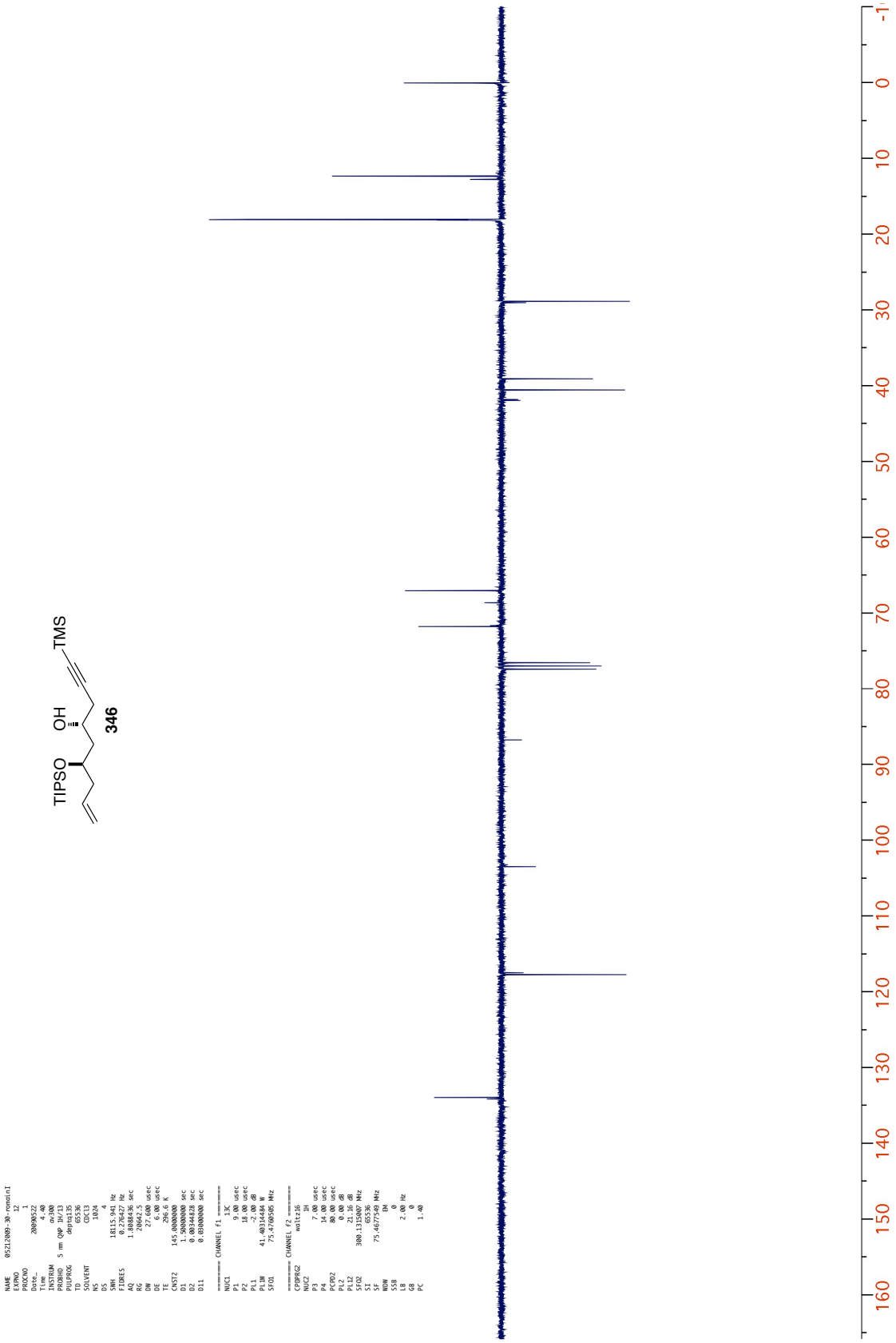
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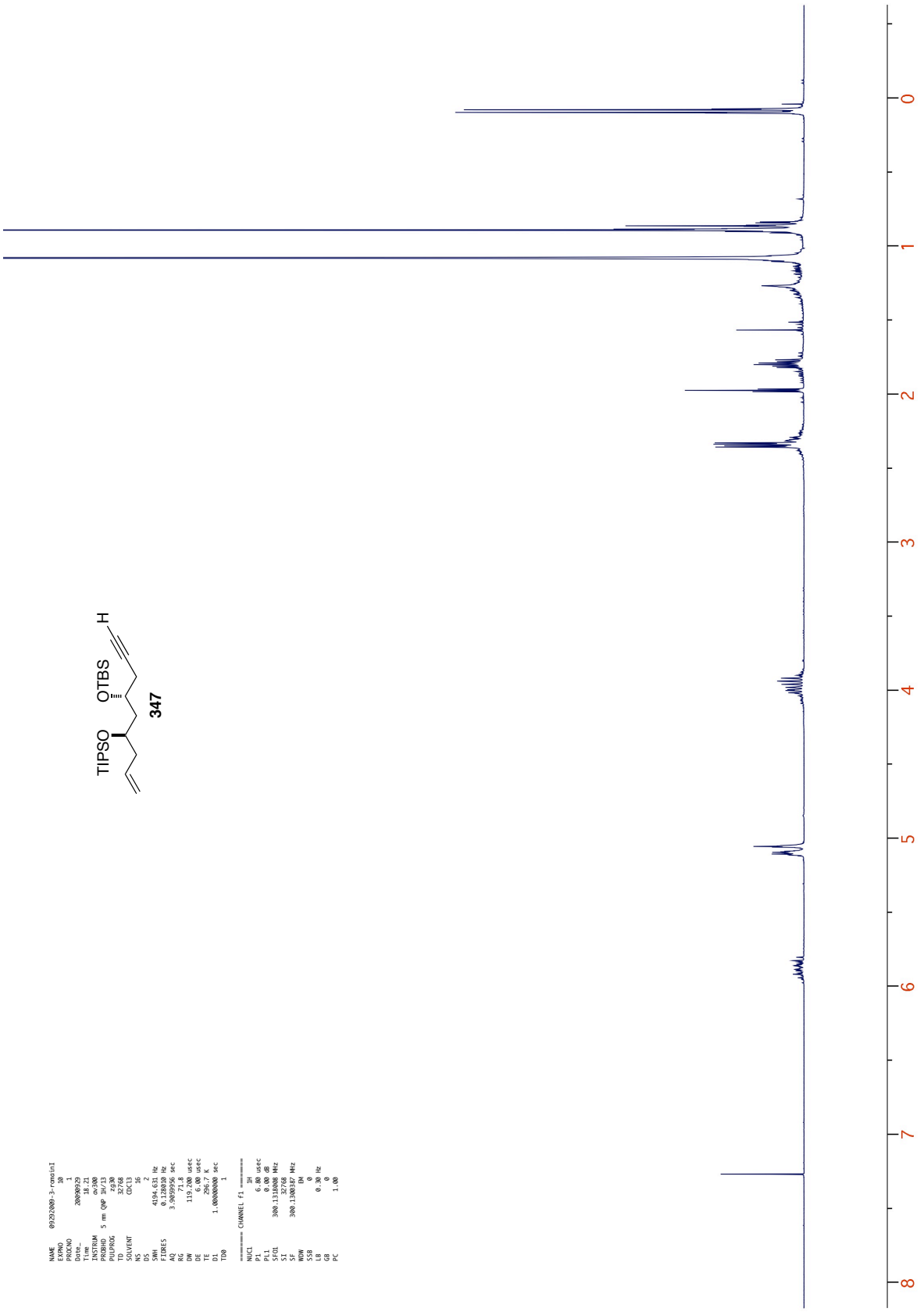


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PULPROG                zg30
TD                        32768
SOLVENT                CDCl3
NS                           16
DS                            2
SWH                  4194.631 Hz
FIDRES               0.128010 Hz
AQ                   3.9059956 sec
RG                        71.18
DW                   119.200 usec
DE                      6.00 usec
TE                     296.7 K
D1                   1.00000000 sec
TD0                          1

======== CHANNEL f1 ========
NUC1                       1H
P1                      6.80 usec
PL1                     0.00 dB
SFO1                300.1318008 MHz
SI                        32768
SF                  300.1300387 MHz
WDW                        EM
SSB                         0
LB                       0.30 Hz
GB                          0
PC                       1.00
```

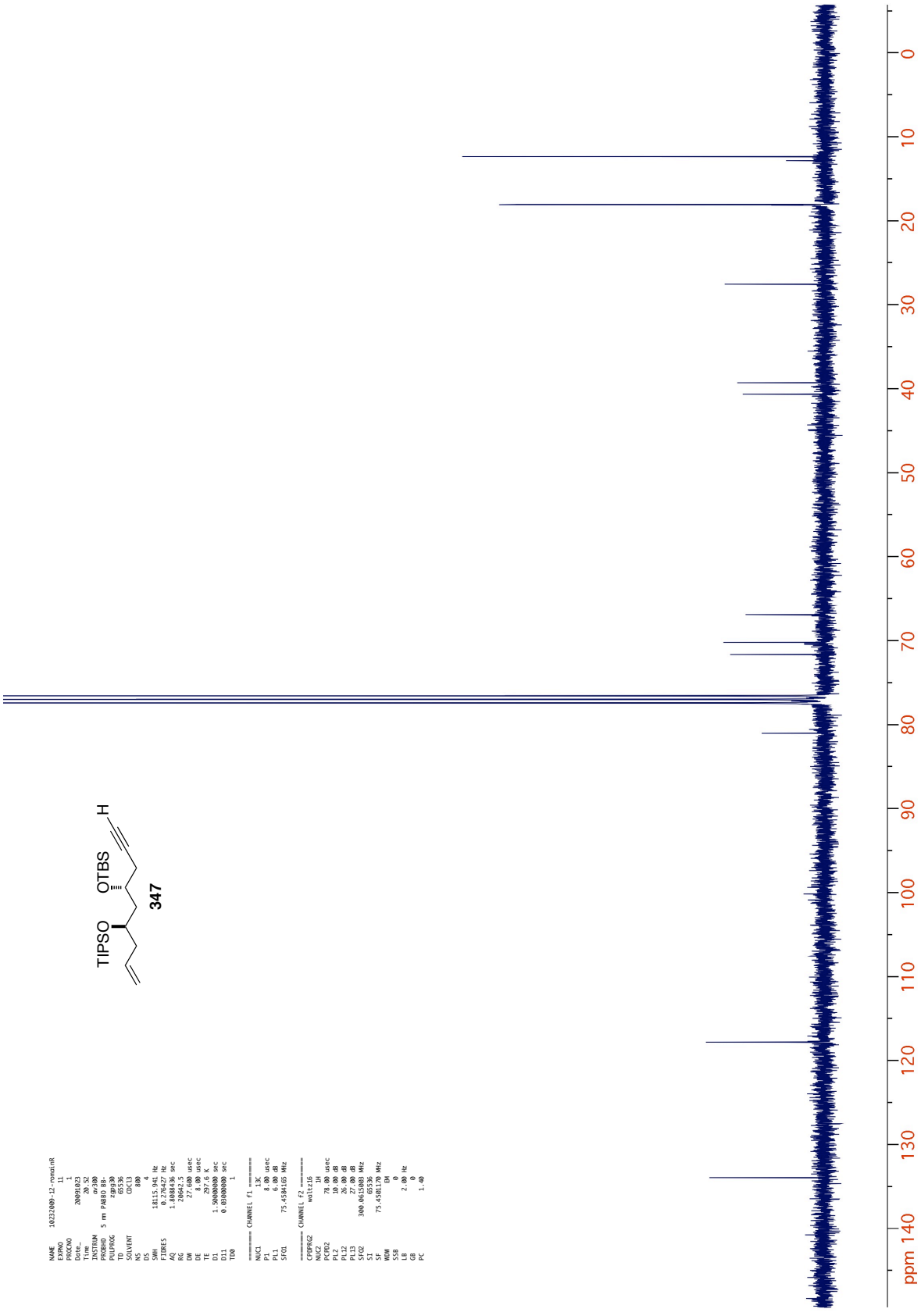
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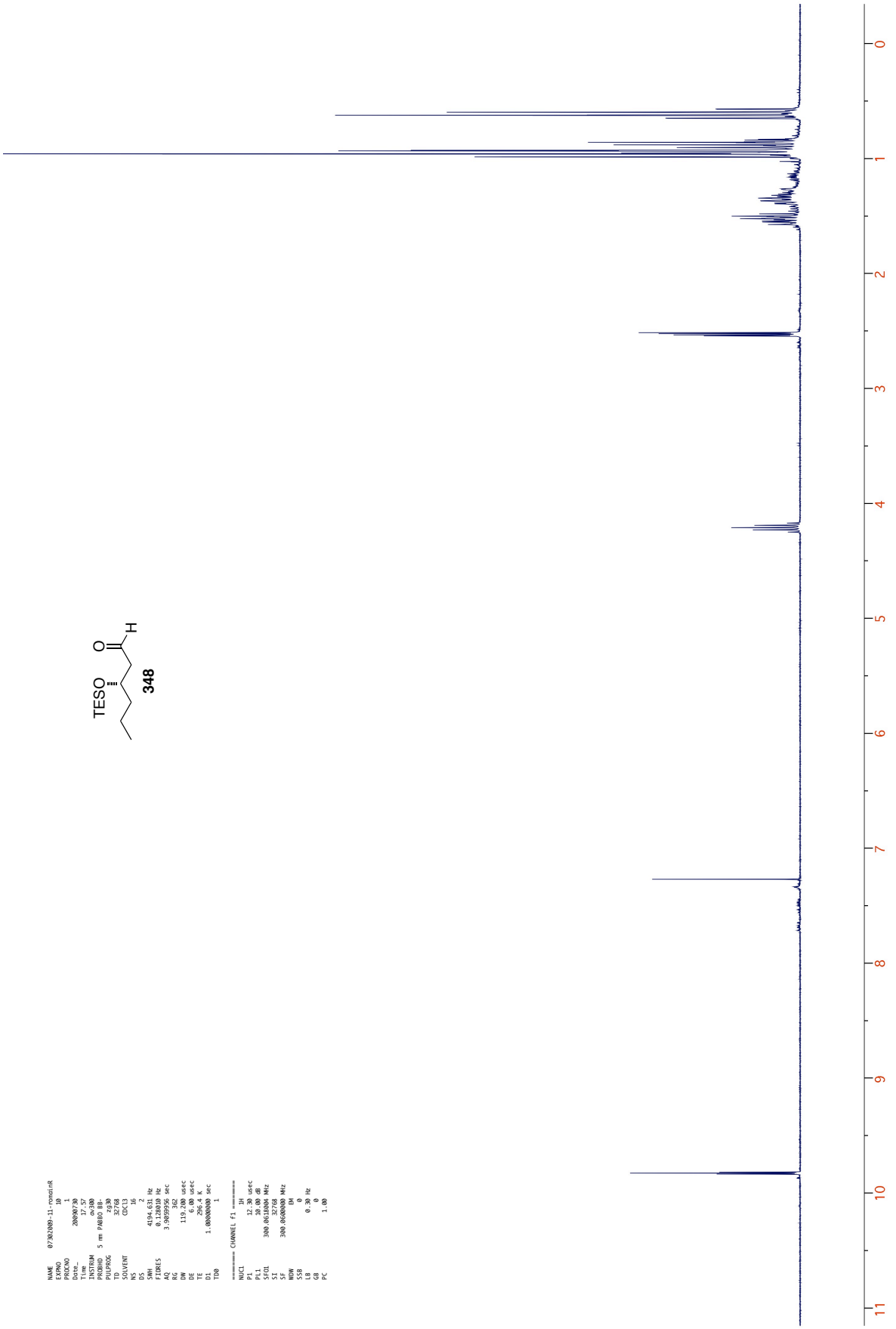
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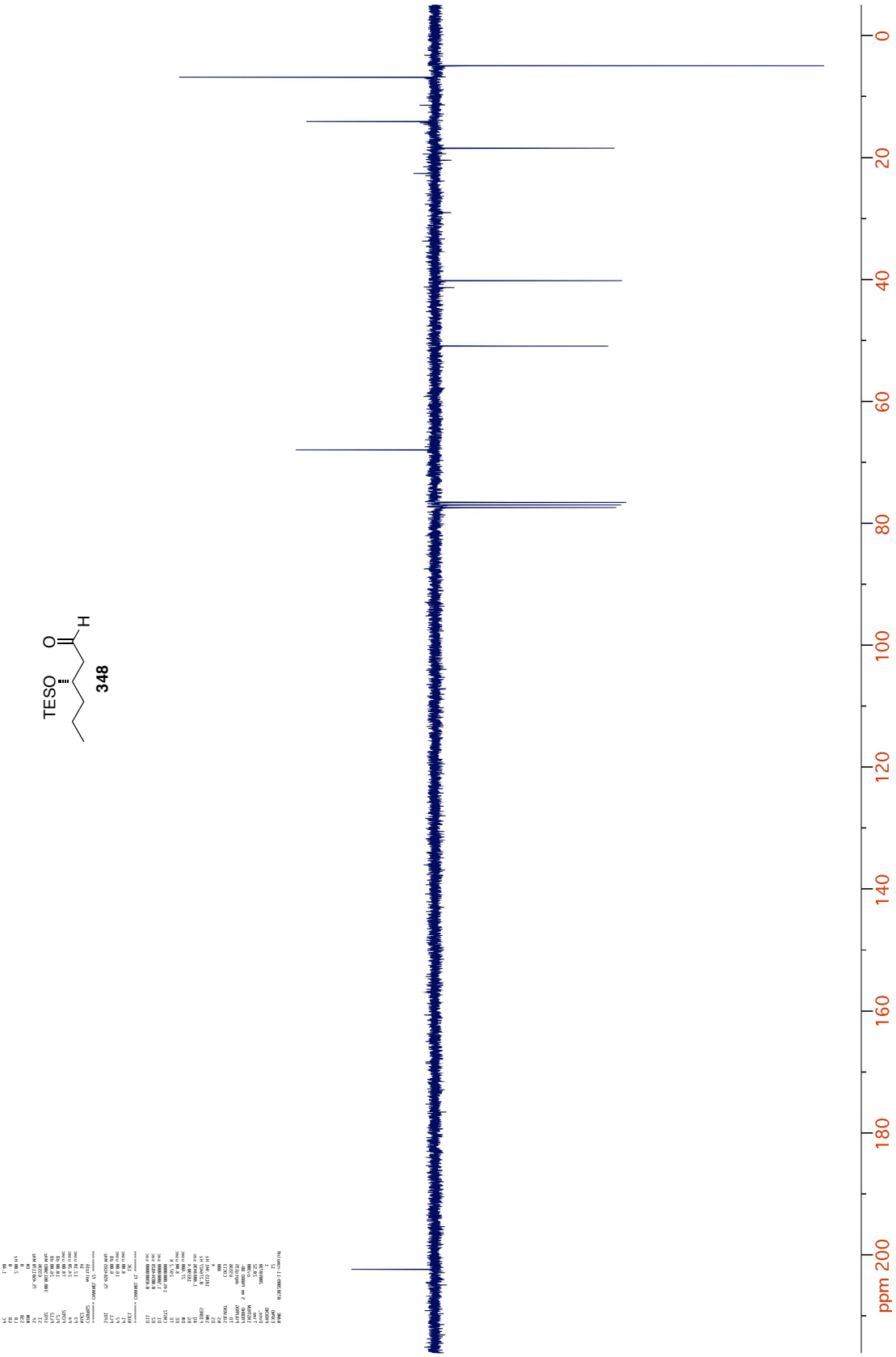
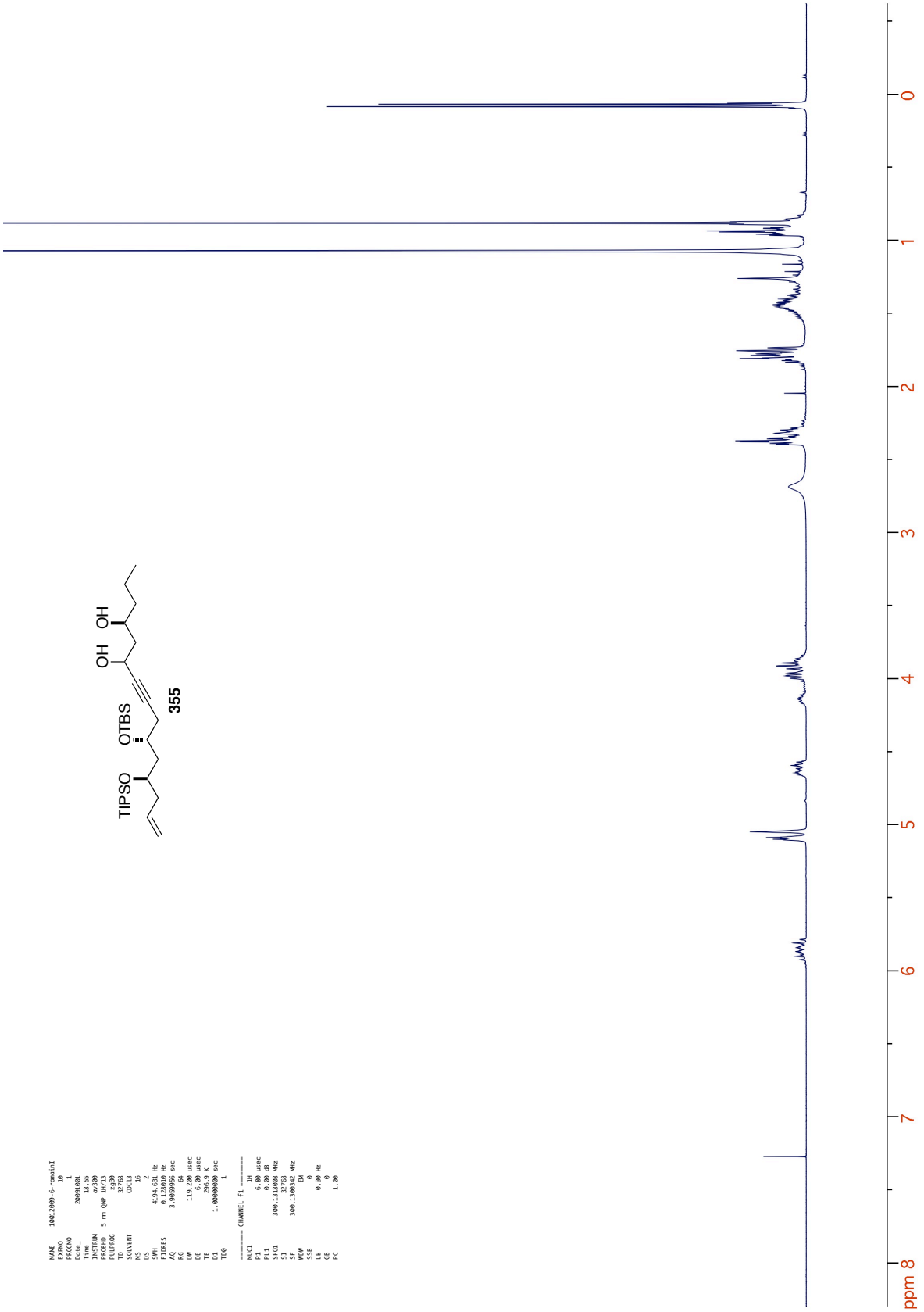
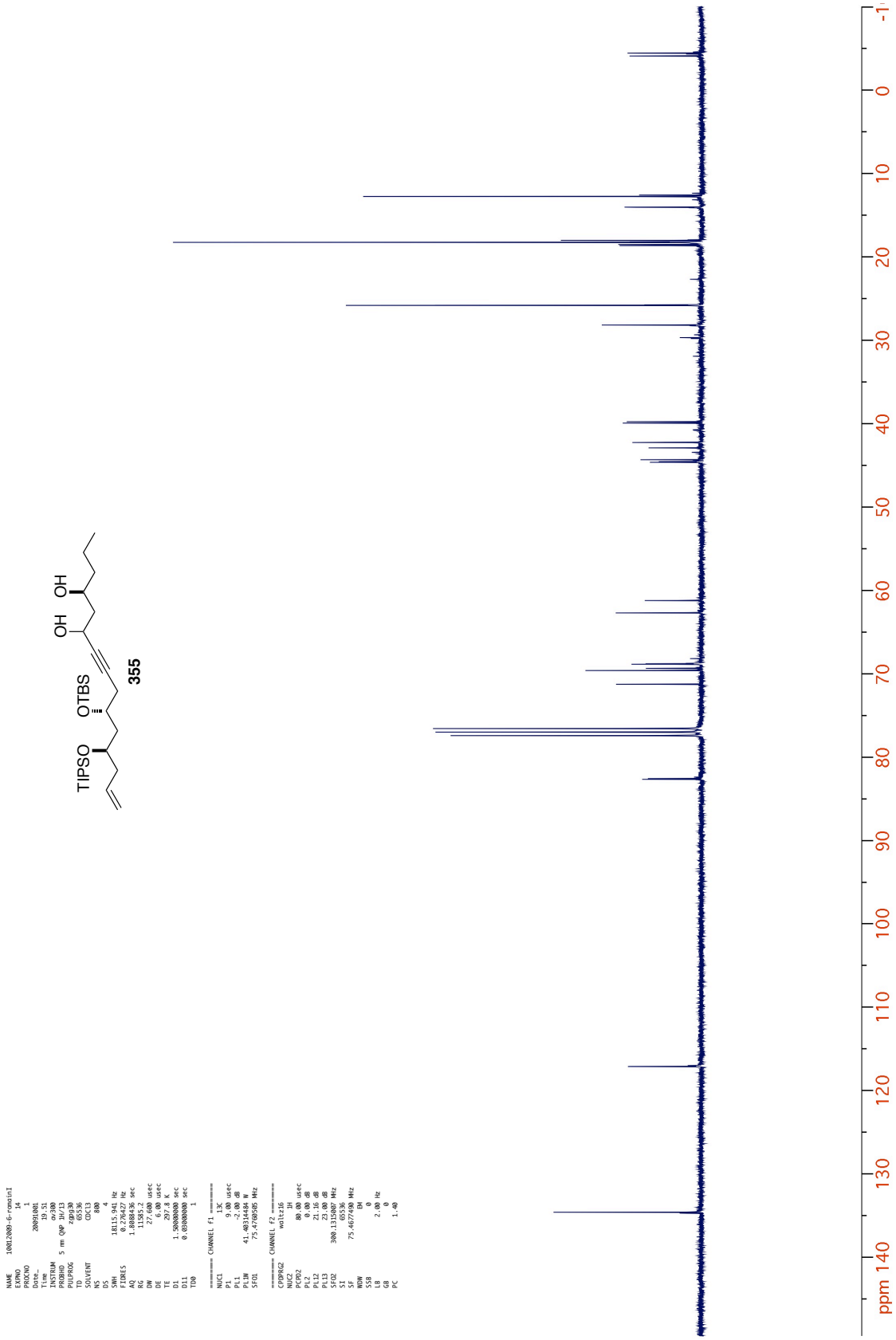
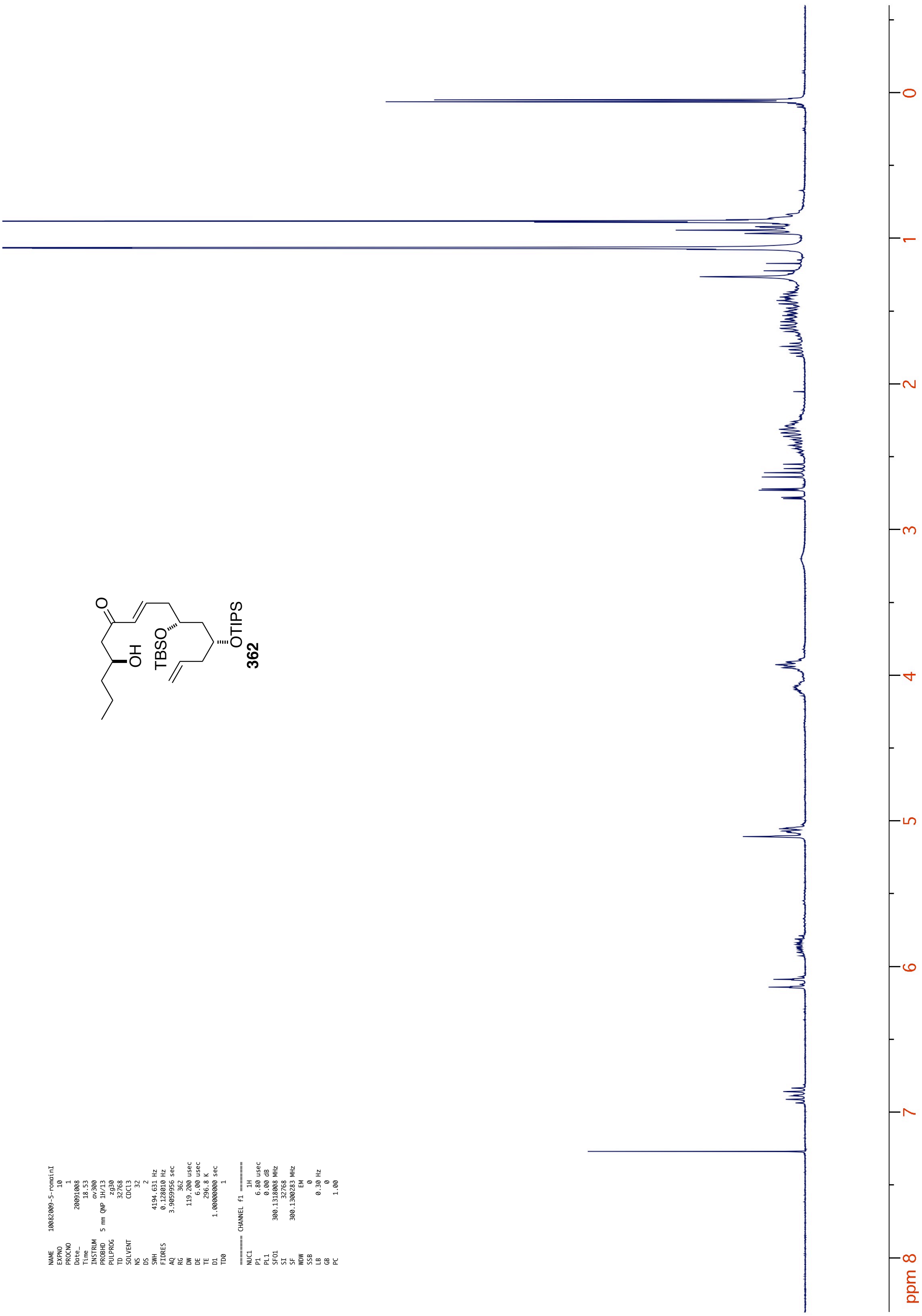
RG 362
DW 119.200 usec
DE 6.00 usec
TE 296.4 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.30 usec
PL1 0.00 dB
SFO1 300.0618004 MHz
SI 32768
SF 300.0600000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0
1
2
3
4
5
6
7
8
9
10
11


TESO
O
H
348
0
20
40
60
80
100
120
140
160
180
200
ppm



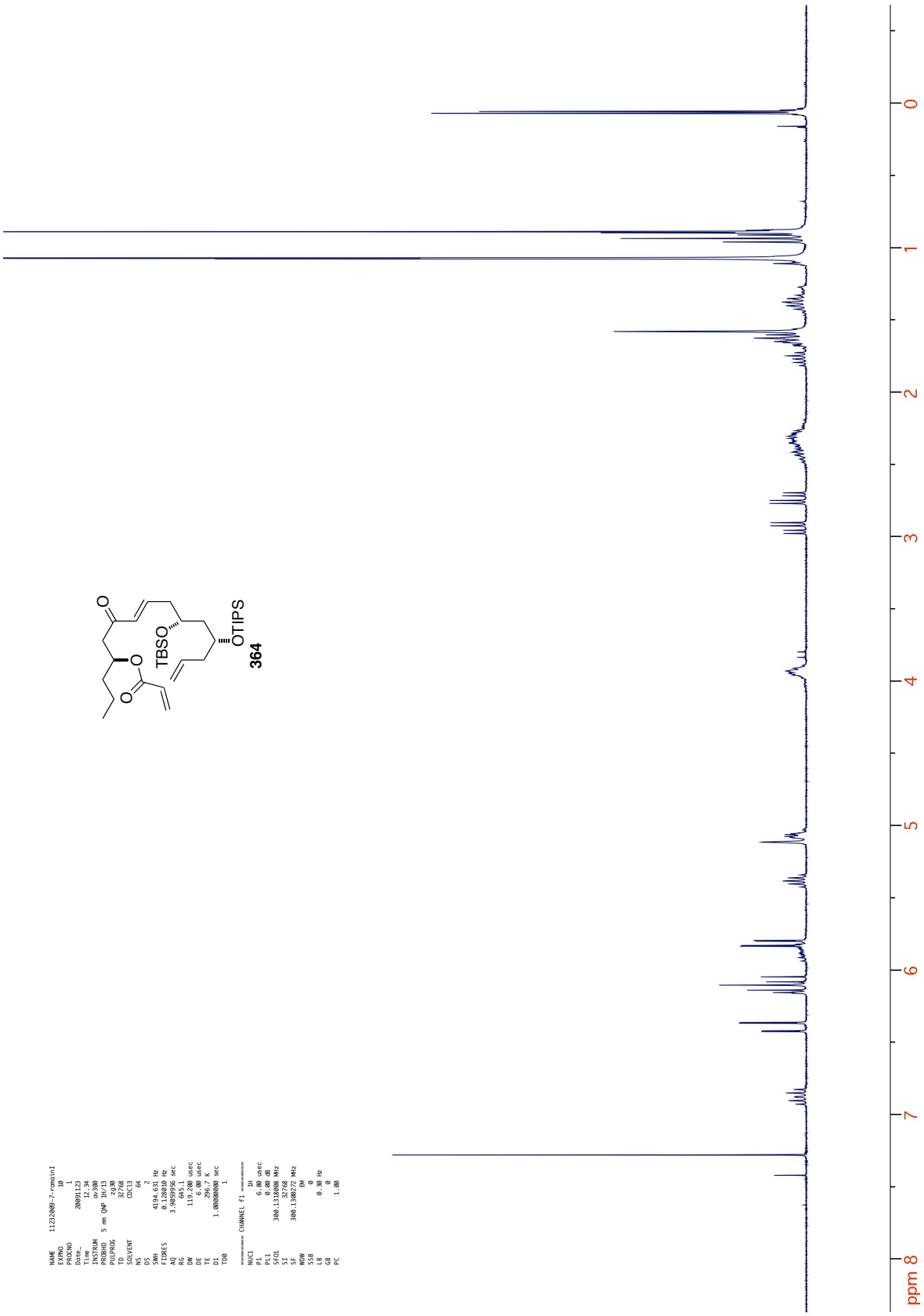

```
NAME                 1001200D-E-ronnin1
EXPNO                      10
PROCNO                      1
Date_              20091001
Time                   18.55
INSTRUM                av360
PROBHD     5 mm QNP 1H/13
PULPROG                zg30
TD                     32768
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                4194.631 Hz
FIDRES             0.128010 Hz
AQ                 3.9059956 sec
RG                        64
DW                 119.200 usec
DE                   6.00 usec
TE                   296.9 K
D1                 1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                    6.80 usec
PL1                   0.00 dB
SFO1           300.1318008 MHz
SI                     32768
SF             300.1300342 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```


OH
OH
OTBS
TIPSO
355
ppm 140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1

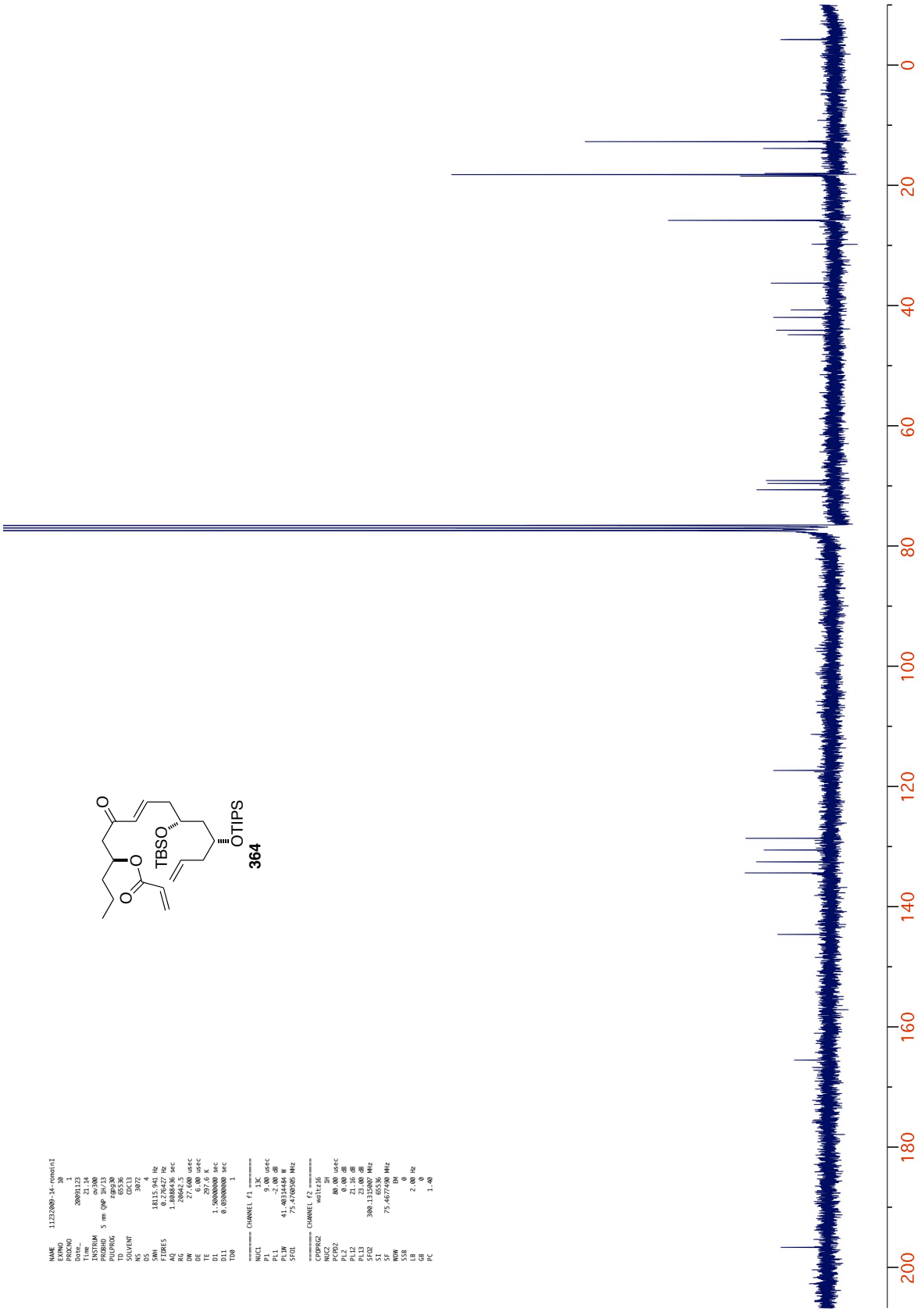


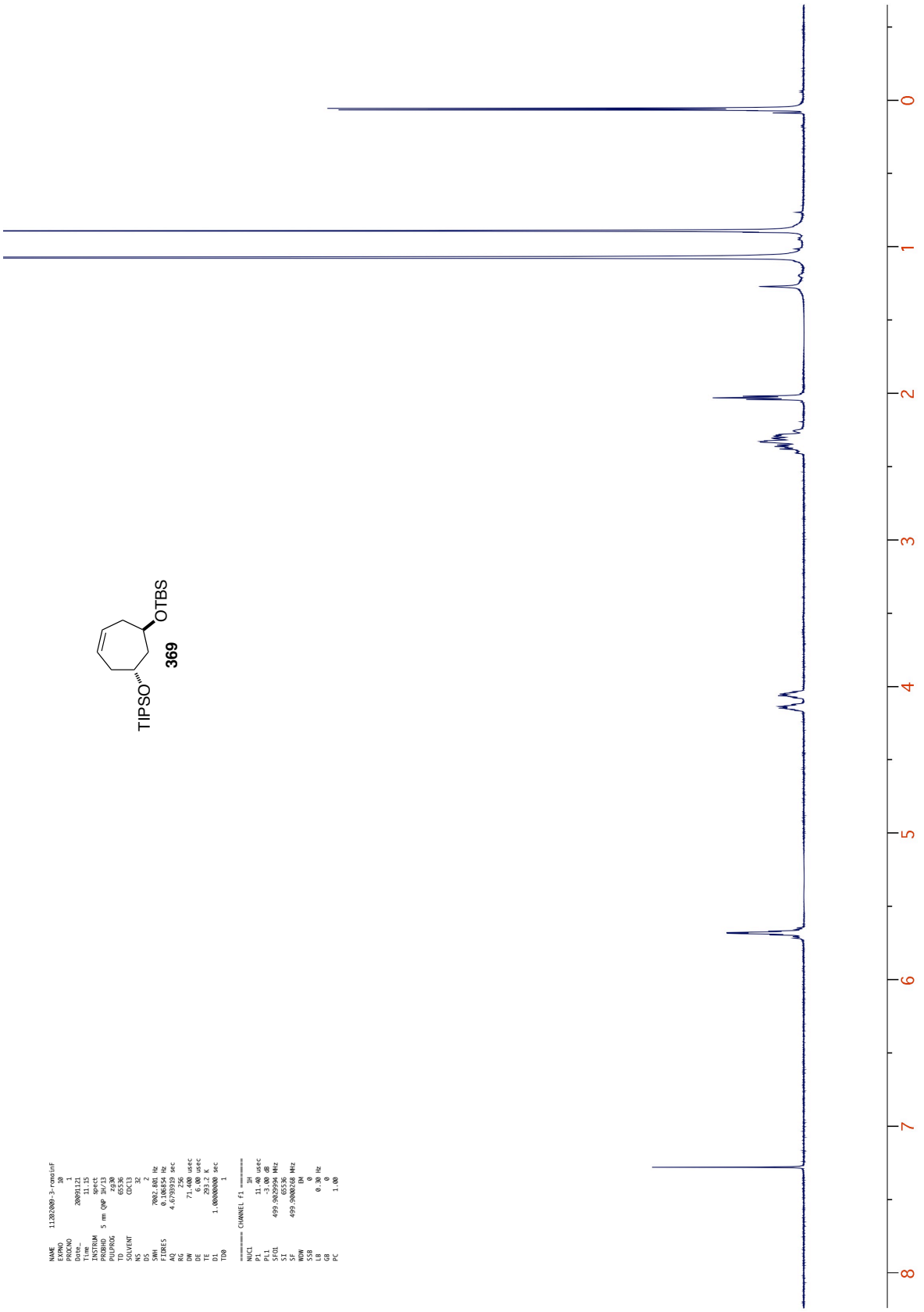
TBSO
OH
O
OTIPS
362
ppm

NAME 11032009-6-romain1
EXPNO 14
PROCNO 1
Date_ 20091103
Time 20.08
INSTRUM av300
PROBHD 5 mm QNP ¹H/¹³
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 800
DS 4
SWH 18115.941 Hz
FIDRES 0.276427 Hz
AQ 1.8088436 sec
RG 4597.6
DW 27.600 usec
DE 6.00 usec
TE 297.8 K
D1 1.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 -2.00 dB
PL1W 41.40314484 W
SFO1 75.4760905 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 21.16 dB
PL13 23.00 dB
SFO2 300.1315007 MHz
SI 65536
SF 75.4677000 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40
O
OH
TBSO
OTIPS
362

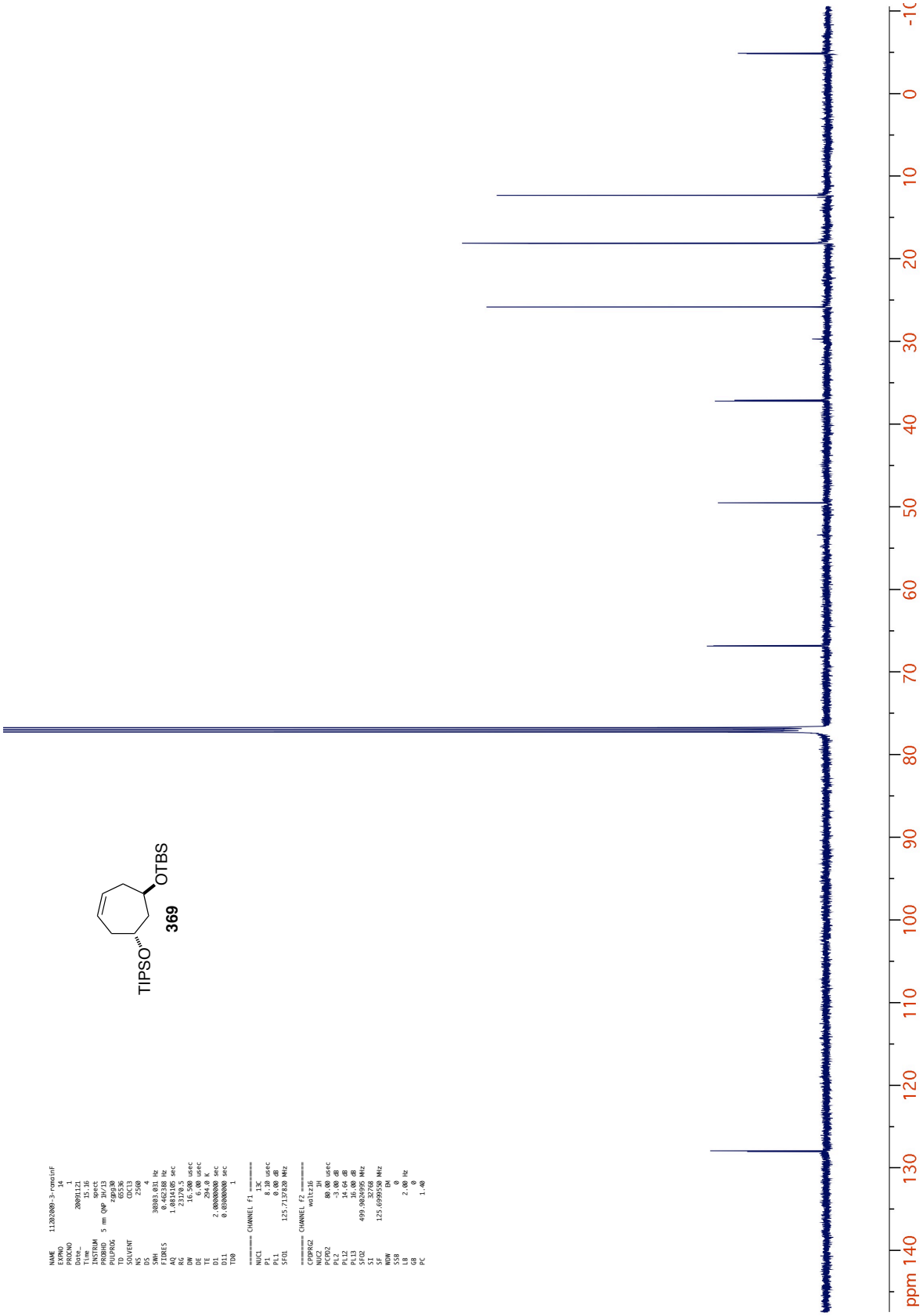



```
NAME                 11232008-7-romain1
EXPNO                      10
PROCNO                      1
Date_              20091123
Time                   12.34
INSTRUM                spect
PROBHD     5 mm QNP 1H/13
PULPROG                zg30
TD                     32768
SOLVENT                CDCl3
NS                        64
DS                         2
SWH                4194.631 Hz
FIDRES             0.128010 Hz
AQ                 3.9059956 sec
RG                    645.51
DW                 119.200 usec
DE                   6.00 usec
TE                   296.7 K
D1                 1.00000000 sec
TD0                        1
======== CHANNEL f1 ========
NUC1                     1H
P1                    6.80 usec
PL1                   0.00 dB
SFO1           300.1318008 MHz
SI                     32768
SF             300.1300272 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```


OTIPS
TBSO
O
O
O
364
0
20
40
60
80
100
120
140
160
180
200




```
NAME                 11202009-3-rotatinf
EXPNO                        10
PROCNO                        1
Date_              20091121
Time                      11.15
INSTRUM                   spect
PROBHD     5 mm QNP 1H/13
PULPROG                  zg30
TD                      65536
SOLVENT                 CDCl3
NS                           32
DS                            2
SWH                  7002.801 Hz
FIDRES               0.106854 Hz
AQ                   4.6793919 sec
RG                         285
DW                   71.400 usec
DE                     6.00 usec
TE                     293.2 K
D1                   1.00000000 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                       1H
P1                      11.40 usec
PL1                     -2.00 dB
SFO1             499.3029994 MHz
SI                      65536
SF               499.3000268 MHz
WDW                        EM
SSB                         0
LB                       0.30 Hz
GB                          0
PC                       1.00
```


TIPSO
OTBS
369
ppm 140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1(