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Towards the Total Synthesis of Amphidinolide F

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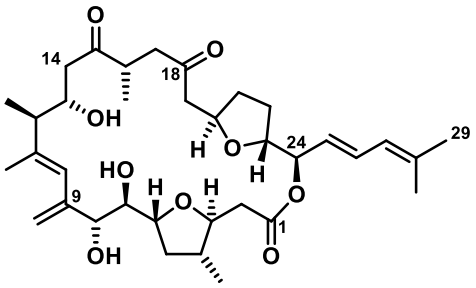
Abstract

Amphidinolide natural products are a family of marine macrolides, isolated from *Amphidinium* dinoflagellates located in the coral reefs around the Okinawa islands of Japan. Over 30 members of this family of natural products have been isolated to date, with many exhibiting potent cytotoxicities against human epidermoid carcinoma and murine lymphoma cancer cell lines. Amphidinolide F is a member of this family and is the principal subject of this body of work.



Amphidinolide F

Previously, a divergent approach for the synthesis of amphidinolide F has been attempted within the Clark group (2009–2013). However, due to a number of issues associated with this strategy a new approach, more convergent in nature, is reported here. Efforts towards both southern (C-1 to C-9) and northern (C-18 to C-29, and C-14 to C-24) fragments of amphidinolide F are documented. Whilst the natural product is not quite at completion, this project has successfully resolved several previous synthetic issues.

Relevant publications surrounding the synthesis of amphidinolide F, and other closely related amphidinolides, are discussed at length with the mechanistic details of key reactions being highlighted. Some of the insights gleaned from these publications has been influential in the development and application of the new synthetic strategy.

Declaration

The work contained within this thesis, submitted for the degree of Doctor of Philosophy, is the result of my own original work, except where explicit reference is made to the contribution of others, and has not been submitted for a degree at the University of Glasgow or any other institution.

***Printed Name*:** Daniel A. Mills

***Signature*:**

Acknowledgements

Firstly, I would like to thank my supervisor, Prof. J. Stephen Clark, for the opportunity to work on this project. I would like to thank him also for his help, guidance, and support over the years, and also for providing me the freedom to try and find my own solutions to problems. I have thoroughly enjoyed my time in your research group.

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And finally. I would like to thank the analytical technicians and the Stores team (Karen and Finlay) for always being there to help with friendly faces.

Abbreviations

acac	acetylacetonate
AIBN	azobisisobutyronitrile
Bz	benzoate
aq	aqueous
CBS	Corey-Bakshi-Shibata
COD	1,5-cyclooctadiene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DET	diethyl tartarate
DiBAl-H	diisobutyl aluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N,N*'-dimethylproylene urea
DMSO	dimethyl sulfoxide
DNA	deoxyribose nucleic acid
dppf	1,1′-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
EE	ethoxy ethyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital

HWE	Horner-Wadsworth-Emmons
IBX	2-iodobenzoic acid
IC50	half maximal inhibitory concentration
imid	imidazole
IPC	diisopinocampheylborane
IR	infrared
LDA	lithium diisopropyl amide
LHMDS	lithium bis(trimethylsilyl)amide
L-selectride®	lithium tri-*sec*-butylborohydride
LUMO	lowest unoccupied molecular orbital
MOM	methoxy methyl
NBS	*N*-bromosuccinimide
NHK	Nozaki-Hiyama-Kishi
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine N-oxide
NMP	*N*-methyl piperazine
Nuc.	Nucleophile
PCC	pyridinium chlorochromate
pin	pinacol
Piv	pivaloyl
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
pyr	pyridine
quant.	quantitative
RCAM	ring-closing alkyne metathesis
RCM	ring-closing metathesis

Red-Al®	sodium bis(2-methoxyethoxy)aluminium dihydride
Rf	retention factor
rt	room temperature
SE	electrophilic substitution
SN	nucleophilic substitution
TBAF	tetra-*N*-butylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBS	t-butyldimethylsilyl
TC	thiophene-2-carboxylate
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
TSA	toluenesulfonic acid
WHO	World Health Organisation

Table of Contents

1. Introduction

1.1 Natural Products

The simplest definition of a natural product is any molecule produced by an organism. In the broadest interpretation, this includes a plethora of molecules ranging in size and complexity from carbon dioxide to deoxyribonucleic acid (DNA). As a consequence of this vast range of molecules, the label is more commonly applied to secondary metabolites, compounds produced by organisms which are not directly related to their growth and survival.[1,2] Many natural products have potent biological activities with some, such as paclitaxel (**1**), pilocarpine (**2**), and quinine (**3**), finding use as therapeutic agents (**Figure 1**). The compounds **1**–**3** are included in the World Health Organisation (WHO) Model List of Essential Medicines and are used as a chemotherapeutic agent, a component of eyedrops, and an antimalarial agent respectively.[3,4,5,6] Alongside their medicinal relevance, the complex structures of natural products have rendered them enticing synthetic targets for organic chemists.

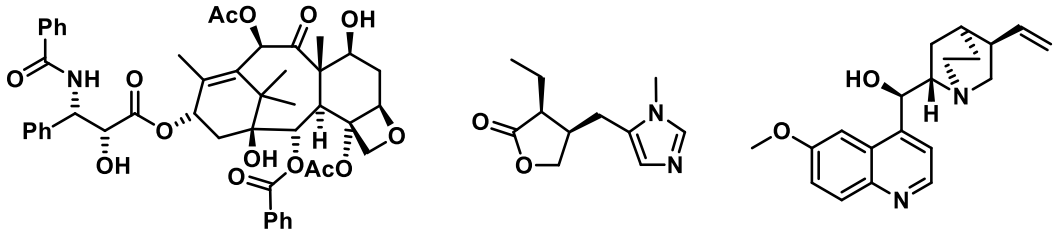


Figure 1. Examples of Medicinally Relevant Natural Products

Natural products are often divided into two further sub-categories (marine and terrestrial) depending upon the location of their isolation. Terrestrial natural products have long been explored and used therapeutically, even before the advent of modern medicine, as evidenced by the Ebers Papyrus and other historical texts.[7,8] However, it is only relatively recently that marine natural products have been explored extensively as drugs. Consequently, a wealth of novel marine natural products, with potential new modes of biological activity, remain to be discovered in marine ecosystems. Furthermore, marine natural products tend to have an increased molecular weight when compared to their

terrestrial counterparts, often corresponding to an increase in molecular complexity. These marine natural products cover a wide range of chemical structures from alkaloids and macrolides [e.g. rhizovarin F (**4**) and cyclothiocurvularin B (**5**)], to polycyclic ethers and terpenoids [e.g. brevenal (**6**) and anvilone A (**7**)] (**Figure 2**).[9,10,11,12]

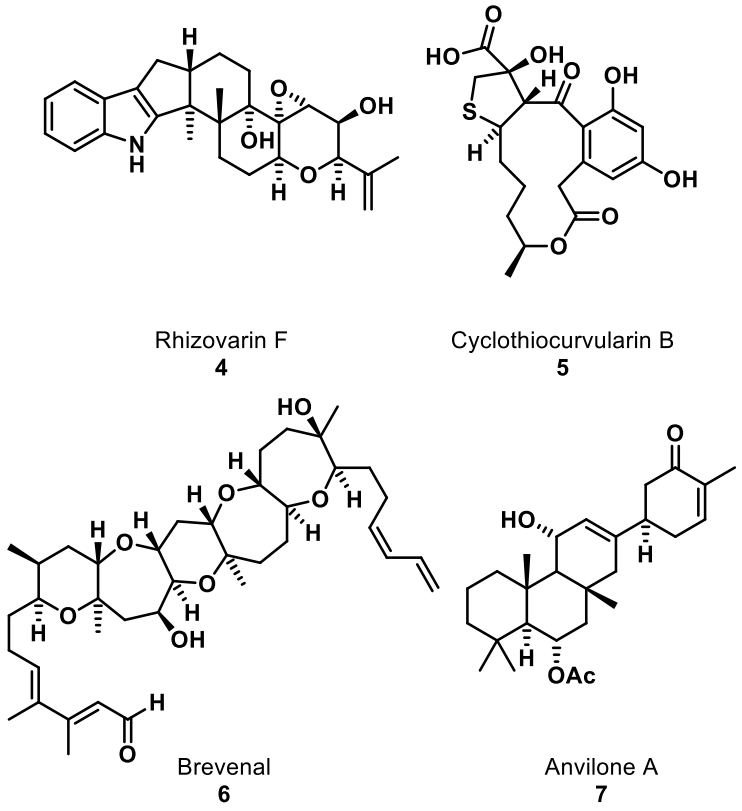


Figure 2. Examples of Marine Natural Products

Given the often-complex structures of marine natural products and their potentially novel modes of biological activity, it is essential to be able to confidently assign structures to these molecules. It is important to note that the quantity of natural products isolated from biological sources is usually limited, making it challenging to acquire the data necessary to assign the chemical structure with a high level of certainty or to fully assess biological activities. To this end, the total synthesis of natural products remains an invaluable tool. Furthermore, the total synthesis of biologically active natural products provides synthetic organic chemists with challenging targets to which novel methodology may be applied. Often, the wider synthetic application of novel synthetic methods can be demonstrated in the process.

A relevant example is the total synthesis of antheliolide A (**8**), reported by Corey *et. al.* in 2006, which enabled confirmation of the absolute configuration of the molecule that had previously only been isolated from natural sources (**Figure 3**).[13] Caution must, however, be exercised even when X-ray crystallographic techniques have been employed to determine the structure of the natural product.[14] Although X-ray crystallography is a powerful analytical tool, it can be fallible and there are many examples of misassignment arising due to the inability of this technique to definitively reveal the position of hydrogen atoms. A further issue associated with X-ray crystallography is a difficulty in differentiating between heteroatoms and associated functionalities. The initially proposed structure of (−)-spiroleucettadine (**9**), assigned by the use of X-ray crystallography alongside other analytical techniques, was called into question primarily due to the failed synthetic efforts of Danishefsky *et. al.*, Ciufolini *et. al.*, and Smith *et. al.* which were reported in 2006 and 2007.[15,16,17] The structure was revised in 2008 as the consequence of density functional theory calculations and was confirmed in 2017 after the successful total synthesis of the natural product by Hawkins and co-workers (**10**).[18,19]

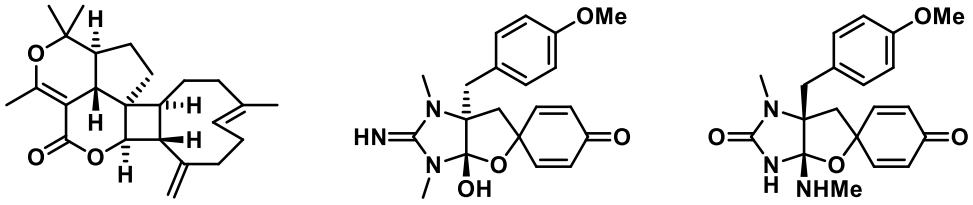


Figure 3. Examples of Structures of Natural Products Confirmed by Total Synthesis

1.2 Amphidinolide Natural Products

The amphidinolides are a family of macrolide natural products, which were originally isolated from dinoflagellates of the genus *Amphidinium*.[20] While macrolide natural products typically have attached deoxy-sugars these are notably absent from the amphidinolides and may therefore be more aptly lumped together with the broader polyketide classification of natural products. These dinoflagellates are symbionts of the acoel flatworms *Amphiscolops* sp., which are found in coral reefs off the coast of the Japanese Okinawa archipelago. Recently, three novel amphidinolides, B8 (**11**), B9 (**12**), and C4 (**13**), and two known amphidinolides, P (**14**) and T1 (**15**), have also been isolated from Brazilian octocoral *Stragulum bicolor* (**Figure 4**).[21] It is proposed that *Amphidinium* sp. is also a symbiont of this octocoral, but this has yet to be confirmed.

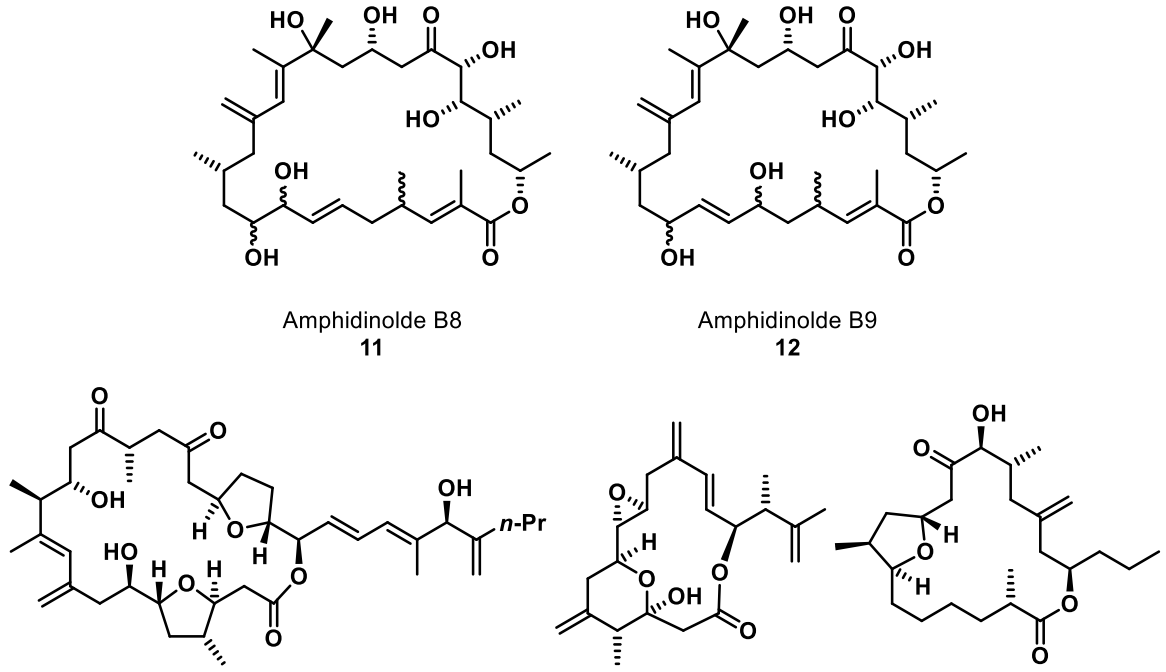
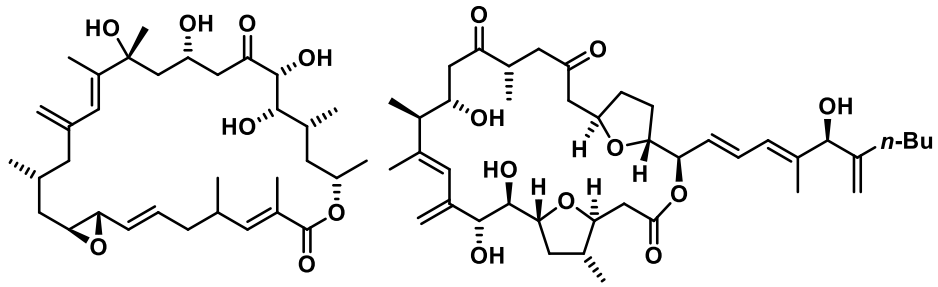


Figure 4. Amphidinolide Natural Products Isolated from Brazilian Octocoral

As illustrated by the amphidinolide natural products isolated from Brazilian octocoral shown in **Figure 4**, this family of natural products contains compounds that have a broad range of structures. There are, however, structural similarities between the members of the family. For example, all amphidinolides are macrolides with multiple sites of unsaturation and have a minimum ring size of 12

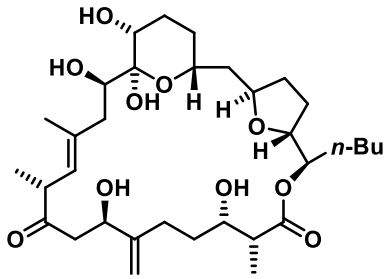
atoms. In addition, these macrocyclic lactones commonly contain oxa-cycles ranging from 3-membered epoxides up to 6-membered tetrahydropyrans.

The amphidinolides have also been shown to possess a range of anti-cancer activities against murine lymphoma (L1210) and human epidermoid carcinoma (KB12) cell lines (**Table 1**).[20] Several members of this family of natural products have IC_{50} values in the low to sub nano-gram range against these cell lines.



Amphidinolde B
16

Amphidinolide C
17



Amphidinolide N
18

Table 1. Cytotoxicity of Selected Amphidinolides

Amphidinolide	**Cytotoxicity** (IC_{50}, $ngmL^{-1}$ (nM))	
	KB12	L1210
B (**16**)	4.2 (7.7)	0.14 (0.26)
C (**17**)	4.6 (6.4)	5.8 (8.1)
N (**18**)	0.06 (0.09)	0.05 (0.08)

1.2.1 Amphidinolides C and F

Amphidinolides C (**17**), C2 (**19**), C3 (**20**), and F (**21**) all have a common 25-membered lactone that contains two 2,5-*trans* tetrahydrofurans, two 1,3-diene systems, a 1,4-diketone, and either 11 or 12 stereogenic centres (**Figure** 5). They vary only in the structure of the side chain at the C-29 position. Amphidinolide F possesses the simplest structure in this family, having only a methyl group at this position. In contrast, amphidinolides C, C2, and C3 have a longer oxygen-containing chain. It is worth noting that amphidinolide C4 differs from amphidinolide C only by the lack of a hydroxyl group in the C-8 position and the presence of an *n*-propyl in the terminal position of the side chain instead of the *n*-butyl group found in the other members of the amphidinolide C-family.

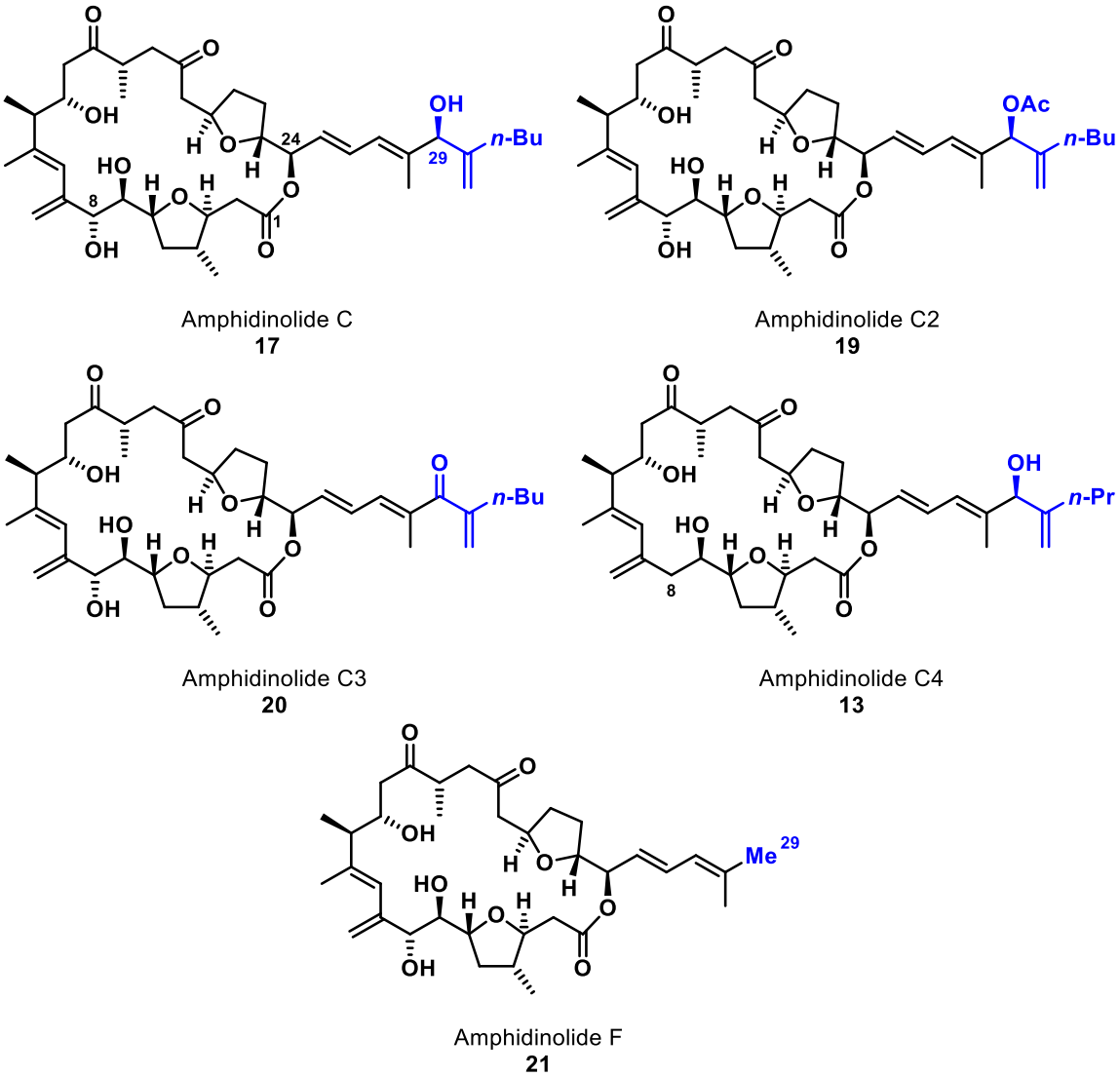


Figure 5. Structure of the C and F Family of Amphidinolides

Amphidinolide C was the first member of this amphidinolide family to be isolated.[22] This was achieved in 1988 by Kobayashi and co-workers; interestingly, it was the first 25-membered lactone to be isolated from a natural source. The gross structure of amphidinolide C was principally assigned by 2D NMR experiments. The absolute configuration was later revealed by further NMR analysis. This work included Mosher ester analysis as well as comparisons to synthetic fragments and degradation products. The unique structure of this natural product, alongside its potent cytotoxicity to cancer cell lines, rendered it a target of immediate synthetic interest.

Following the isolation of amphidinolide C, other members of this family were isolated by the Kobayashi group: amphidinolide F in 1991, amphidinolide C2 in 2004, and amphidinolide C3 in 2010.[23,24,25] While the group was able to confirm the absolute structures of amphidinolide C, C2, and C3, the low quantity of amphidinolide F obtained from the isolation process (0.1 mg from 1 kg of dried cell matter) prevented structure confirmation with certainty.

Biological tests conducted on this group of natural products revealed that all members possessed at least some cytotoxicity against L1210 and KB12 cancer cell lines (**Table 2**).[20] As a result of these tests amphidinolide C was found to be two to three orders of magnitude more potent against the tested cell lines than the other members of this family. This large difference in cytotoxic activity, when compared to the relatively small changes in structure, is likely to highlight the key mode of activity in the natural product. When the C-29 hydroxyl group in amphidinolide C is acetylated, as is observed in amphidinolide C2, the natural product is over 100 times less potent. This suggests that the hydrogen bond donor group at the C-29 position is key to the cytotoxic activity of the natural product. If additional studies into the activity of these natural products were to be undertaken it might be possible to further understand the relationship between the structure and activity of these molecules.

Table 2. Cytotoxicity of the C and F Family of Amphidinolides

Amphidinolide	**Isolation Yield** (%)	**Cytotoxicity** - IC_{50}, $ngmL^{-1}$ (nM)- KB12	L12109
C	0.0015	4.6 (6.4)	5.8 (8.1)
C2	0.00015	3000 (3900)	800 (1100)
C3	0.00006	10000 (14000)	7600 (11000)
F	0.00001	3200 (5200)	1500 (2400)

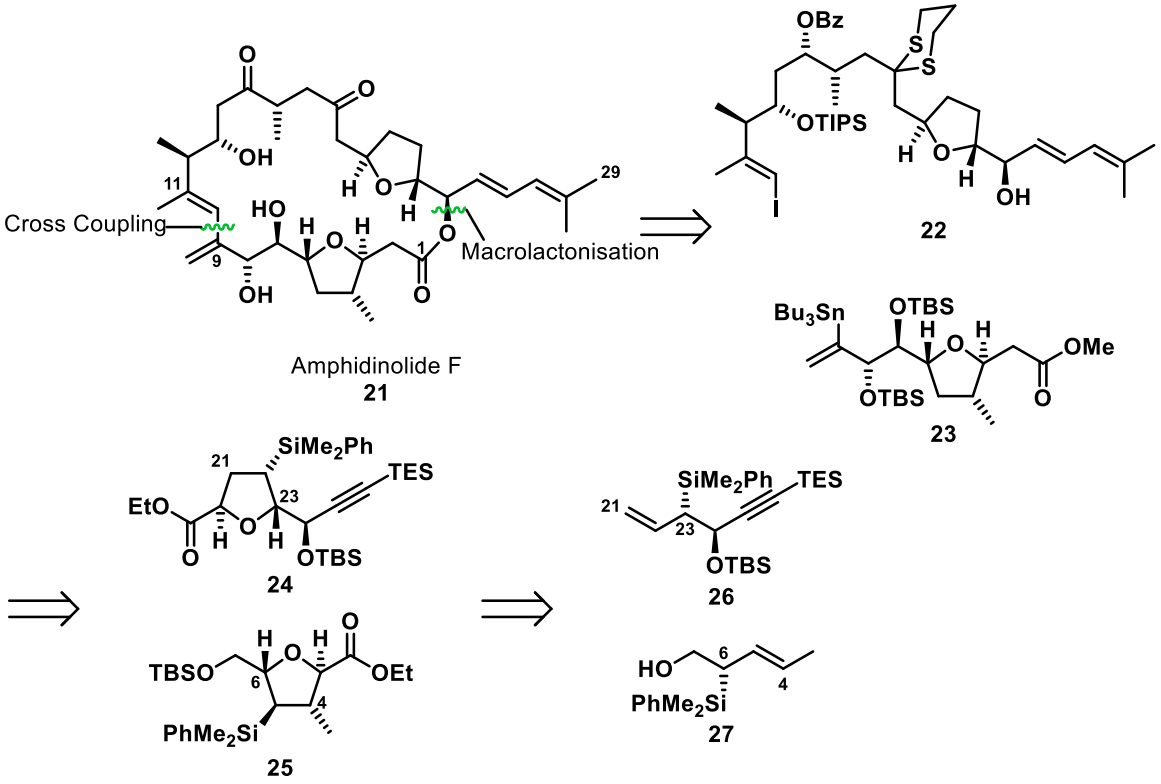
2 Previously Reported Synthetic Approaches Towards Amphidinolides C and F

The complex structures of this family of amphidinolide natural products, and their potent biological activities, have inspired several groups to perform synthetic studies. To date, there have been three total syntheses of amphidinolide F, which have been published by the groups of Carter (2012), Fürstner (2013), and Ferrié (2018).[26,27,28] Modification of the approaches employed by the groups of Carter and Fürstner additionally led to syntheses of amphidinolide C in 2013 and 2015, respectively.[29,30] There have also been numerous fragment syntheses relating to amphidinolides C and F, all of which will be discussed in the following section.

2.1 Fragment Syntheses

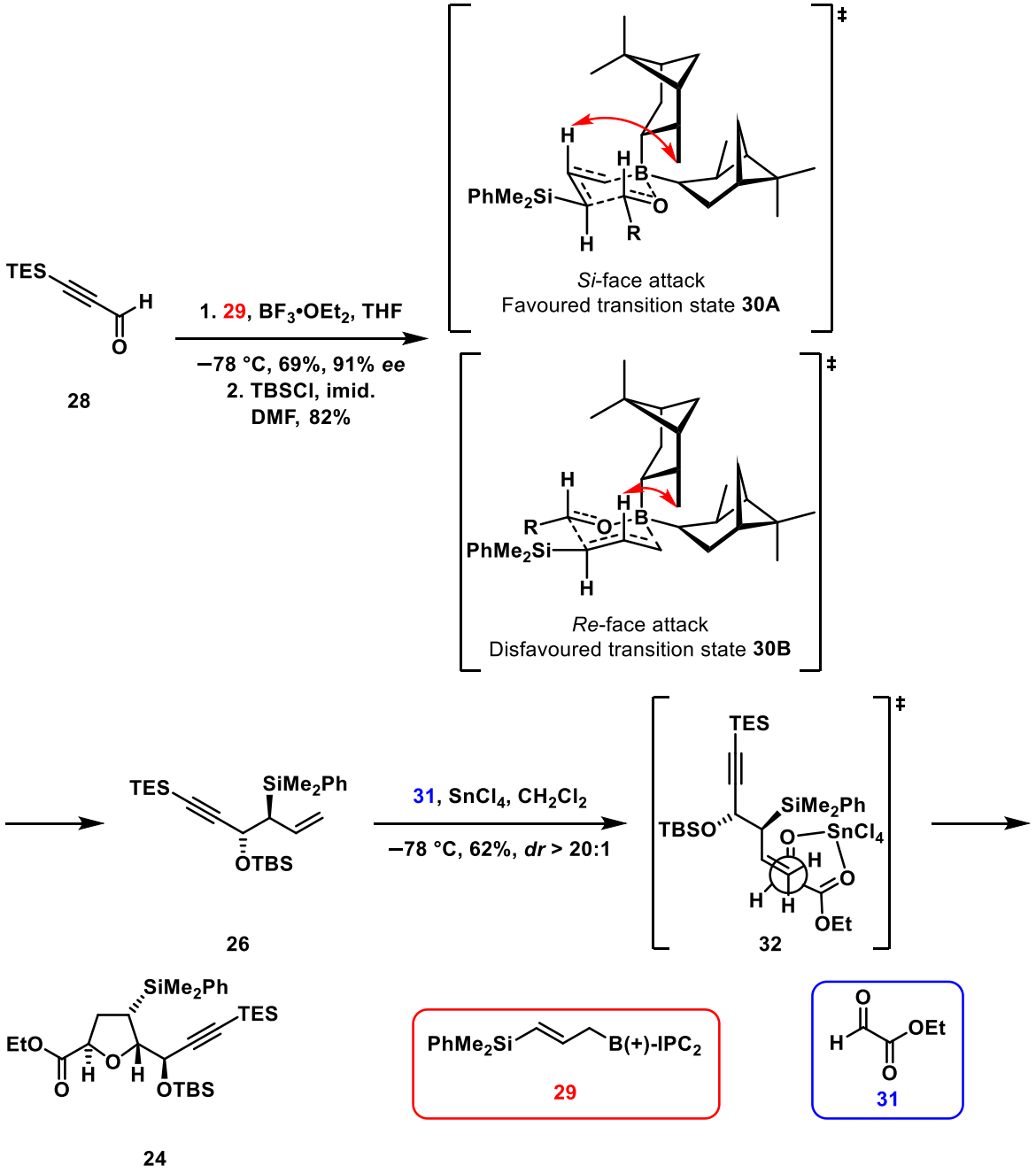
2.1.1 Roush: Stereocontrolled [3+2] Annulation Approach

In 2004 Roush and co-workers published a strategy for the synthesis of the C-11 to C-29 fragment of amphidinolide F, with a further publication in 2008 that detailed the synthesis of the C-1 to C-9 fragment.[31,32] The retrosynthetic analysis breaks the natural product into two fragments: a northern fragment (**22**) and a southern fragment (**23**), that each contains a 2,5-*trans* THF ring (**Scheme 1**). Roush proposed that a stereocontrolled [3+2]-annulation reaction between an aldehyde and an allylic silane, **26** and **27** for the northern and southern fragments respectively, could be used to access these THF-containing fragments.



Scheme 1. Retrosynthetic Analysis of the Roush Group

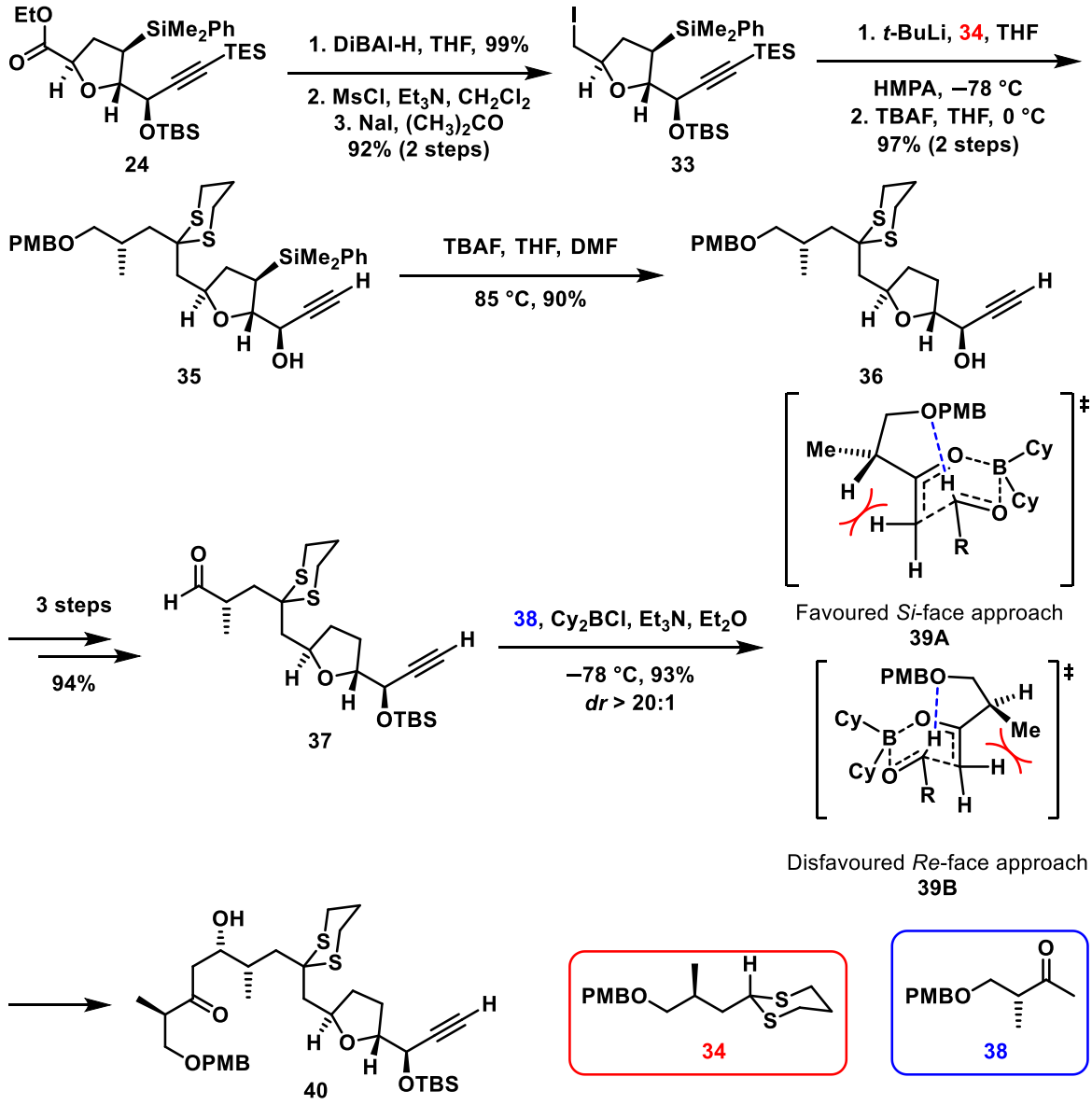
For the northern C-11 to C-29 fragment (**22**), the synthesis began with silylallylboration of the known propargylic aldehyde **28** with the (+)-pinene-derived allylborane **29** (**Scheme 2**).[33] The selectivity in this initial silylallylboration reaction is proposed to arise from the lower energy transition state minimising the steric interaction between the alkenyl hydrogen atom and the pinene-derived borane ligand.[34] This lower energy transition state (**30A**) leads to formation of the required 1,2-*anti* hydroxy silane. The resultant homo-allylic alcohol was then protected as the silyl ether **26**. Allylic silane **26** was used in a [3+2]-annulation reaction with ethyl glyoxylate **31** and this produced the 2,5-*trans* THF **24** in 62% yield with a *dr* > 20:1. The observed selectivity arises from the *syn*-synclinal transition state **32** being the lowest energy transition state.[35] This is due to the minimisation of steric interactions alongside a strong HOMO-LUMO interaction between the allylic silane and the aldehyde respectively which provides further stabilisation of the transition state.



Scheme 2. Synthesis of Northern trans-THF Ring

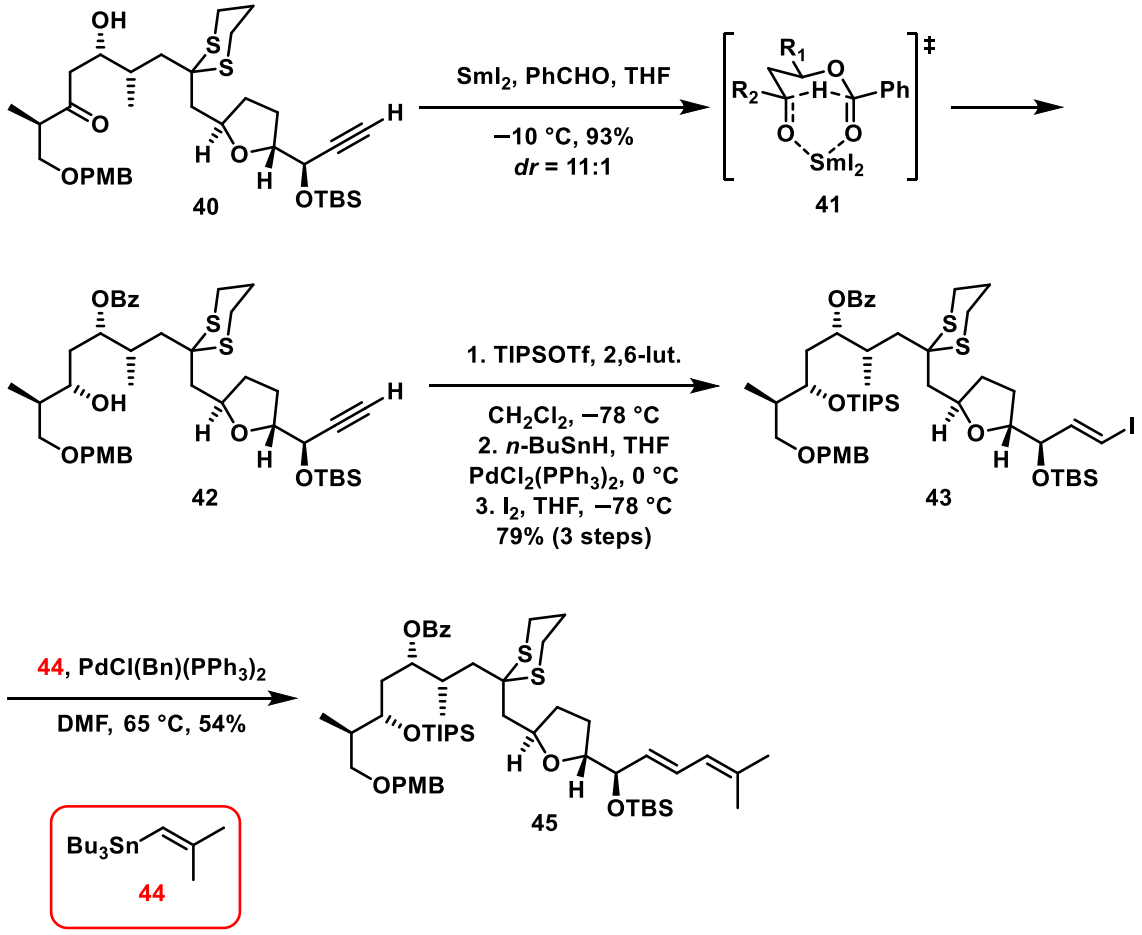
DiBAl-H was then used to reduce ester **24** to the corresponding alcohol (**Scheme** 3). The alcohol was converted into a mesylate and subsequently into iodide **33** using a Finkelstein reaction.[36] The resultant iodide **33** was coupled to 1,3-dithiane **34**; partial removal of the alkynyl TES group occurred concurrently and affected one fifth of the product. To remove the silyl groups completely, progressively more forcing desilylating conditions, employing TBAF, were used; initially the dithiane **35** was obtained and then the fully desilated product **36** was generated. A further three steps were needed to transform the PMB-protected alcohol into

the corresponding aldehyde **37**. An aldol reaction between aldehyde **37** and the boron enolate of ketone **38** gave alcohol **40** with the desired stereochemistry (*S*, *dr* > 20:1). Hydrogen bonding between the PMB ether oxygen and the aldehyde hydrogen result in the formation of two potential boat transition states, arising from the *si*- and *re*- face approaches of the aldehyde, **39A** and **39B** respectively. Although two approaches are possible, it is the *si*-face approach of the aldehyde that is favoured. This preference arises because of the reduction of (1,3)-allylic strain caused by interaction between the methyl group with the vinylic hydrogen.



Scheme 3. Synthesis of Terminal Alkyne 40

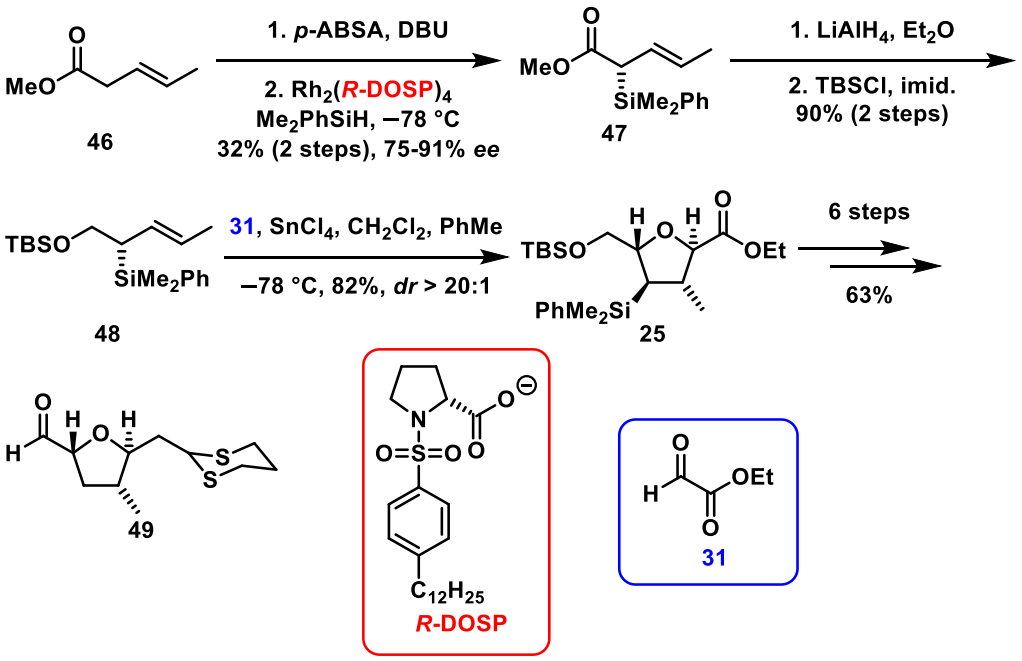
An Evans-Tishchenko reduction reaction was used to convert the ß-hydroxyketone **40** into the *anti*-1,3-diol **42** with a *dr* = 11:1 (**Scheme 4**).[37] TIPS protection of the hydroxyl group, followed by a two-step hydrostannylation-iododestannylation sequence gave vinylic iodide **43**. Stille cross coupling with vinylic stannane **44** was used to give the 1,3-diene (**45**) and complete the northern (C-11 to C-29) fragment of amphidinolide F in 13 steps with an overall yield of 24%.[38] To add a degree of versatility to this approach the authors proposed that alteration of the stannane fragment could provide access to both natural and unnatural, potentially pharmacologically relevant, congeners.



Scheme 4. Completion of Northern Fragment

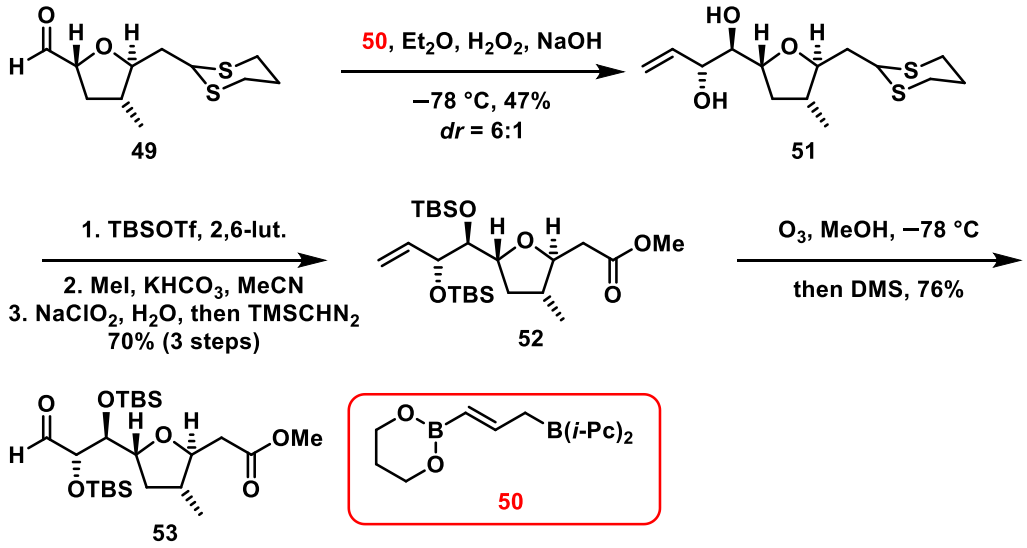
Two routes to the C-1 to C-9 southern fragment were published by Roush and co-workers in 2008. The routes differ primarily in the synthetic approach used to construct the 2,5-*trans* THF that is at the heart of the fragment. The first approach utilised an enantioselective rhodium(II)-catalysed insertion reaction of a diazoester into a Si-H bond to give the allylic silane **47** with 75-91% *ee* (**Scheme 5**). Reduction of the ester with $LiAlH_4$, followed by formation of the TBS ether,

gave the protected allylsilane **48**. Efforts to use this allylic silane to perform a [3+2]-annulation reaction with a variety of aldehydes proved unsuccessful, preferentially forming the 2,5-*cis* THF with only trace quantities of the 2,5-*trans* THF being isolated. The annulation reaction did, however, proceed smoothly when the reactive aldehyde ethyl glyoxylate **31** was used as the reaction partner. This gave the desired 2,5-*trans* THF (**25**) in 82% yield with a *dr* > 20:1. A further six steps were then required to obtain the aldehyde **49**.



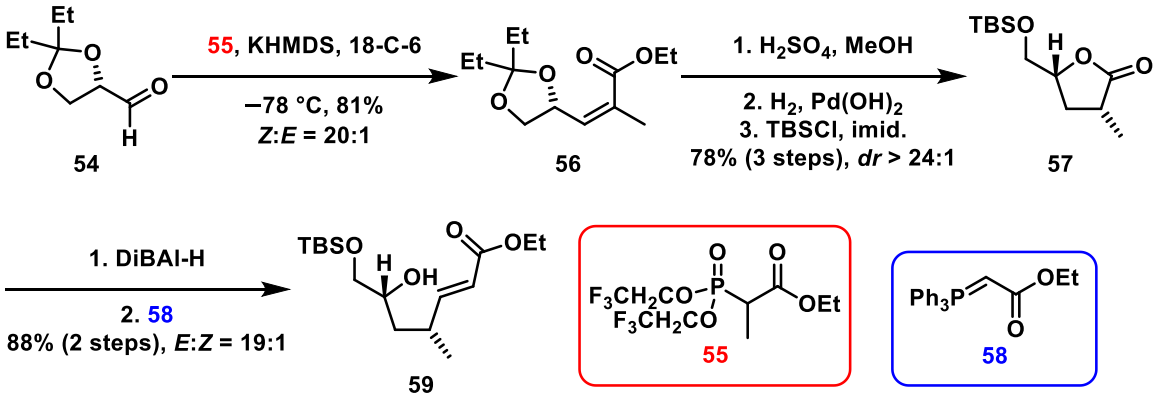
Scheme 5. Synthesis of the Southern THF Ring

Aldehyde **49** was converted to *anti*-1,2-diol **51** (*dr* = 6:1) by reacting it with Browns' γ-borylallylborane (**50**) and the methyl ester **52** was produced in a further three steps (**Scheme 6**).[39] Subsequent ozonolysis of the alkene gave the aldehyde **53** and the desired C-1 to C-9 fragment was completed in a total of 17 steps with an overall yield of 4%.



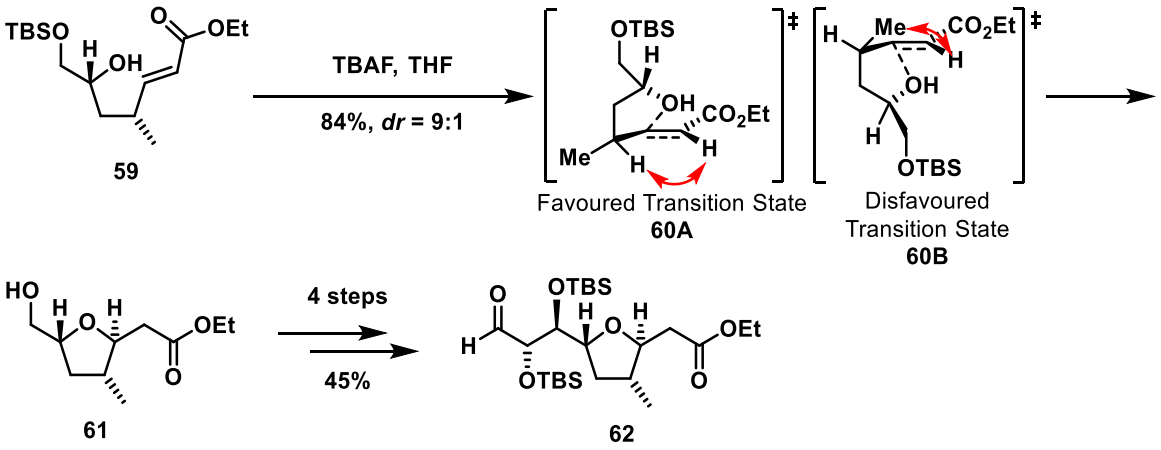
Scheme 6. Completion of the First-Generation Synthesis of the Southern Fragment

Roush and co-workers revised their original strategy with the aim of reducing the step count and improving the overall yield. The alternative strategy commenced with a Horner-Wadsworth-Emmons (HWE) olefination reaction between ketal **54** and the electron-deficient Still-Gennari reagent **55** to produce the *Z*-enoate **56** with a *Z*:*E* ratio of 20:1 (**Scheme 7**).[40] Treatment of the enoate **56** with sulfuric acid resulted in removal of the ketal group and spontaneous cyclisation of the γ-hydroxy ester to form the corresponding butenolide. After diastereoselective reduction of the butenolide and subsequent TBS protection of the primary alcohol, the lactone **57** was produced with a *dr* > 96:4. Lactone **57** was reduced with DiBAl-H to give the corresponding lactol and Wittig olefination with the stabilised phosphonium ylide **58** then delivered the *E*-olefin **59**.[41]



Scheme 7. Second Generation Route Towards the Southern Fragment

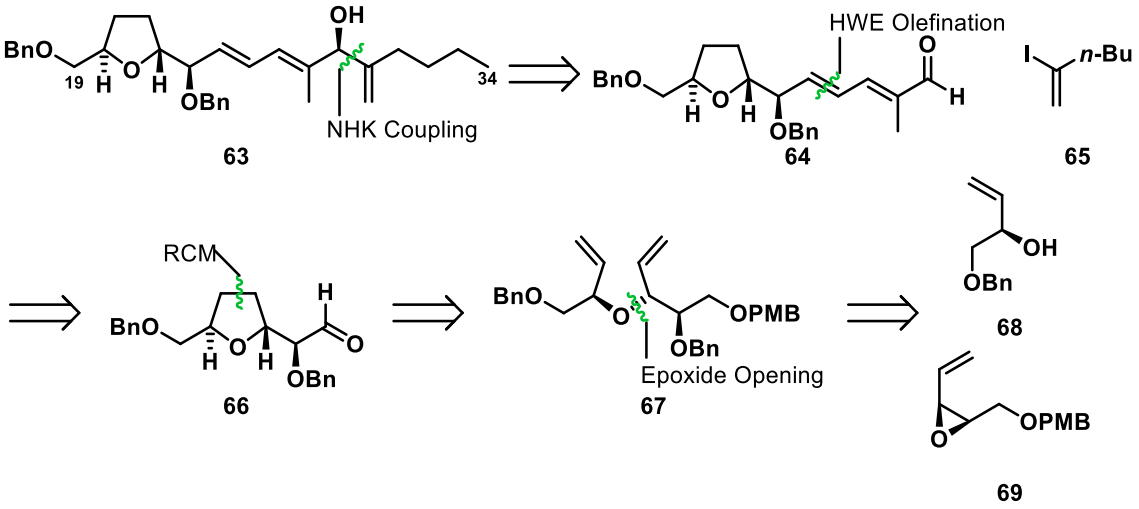
Treatment of the enoate **59** with TBAF resulted in an intra-molecular Michael reaction with preferential formation of the 2,5-*trans* THF through transition state **60A** rather than transition state **60B** due to the minimisation of 1,3-allylic strain in the former (**Scheme 8**). The desired alcohol (**61**) was produced in 84% yield with *dr* = 9:1. A further four steps, analogous to those employed in the initial route, were now required to furnish aldehyde **62**. This revised route resulted in the synthesis of the C-1 to C-9 fragment in 12 steps with an overall yield of 21%, a marked improvement on the initial method.



Scheme 8. Completion of the Second-Generation Route Towards the Southern Fragment

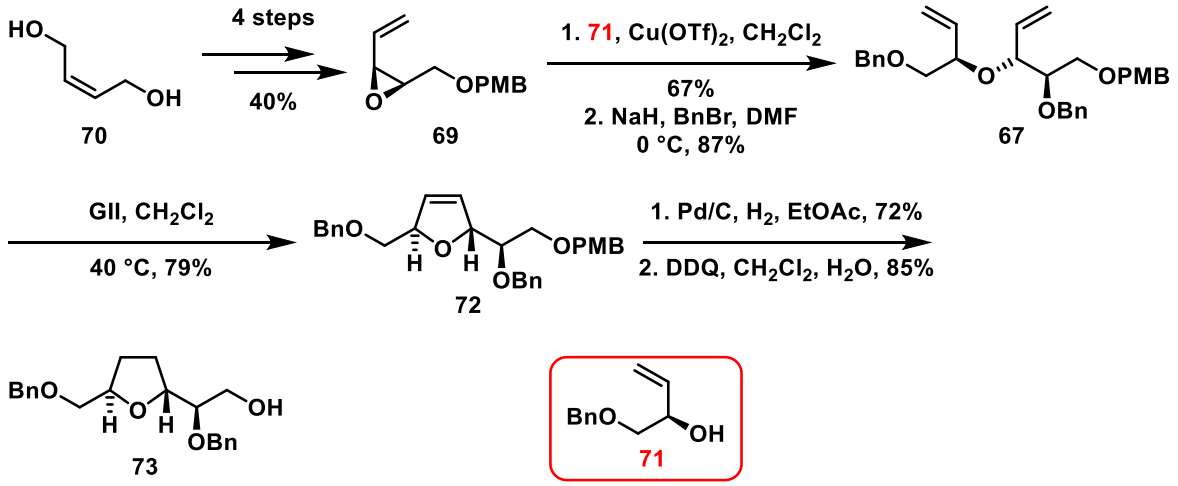
2.1.2 Mohapatra: Ring-Closing Metathesis Approach

In 2007, Mohapatra and co-workers reported the synthesis of the C-19 to C-34 fragment of amphidinolide C.[42] Their strategy involved the synthesis of the diene precursor by opening epoxide **69** with chiral alcohol **68** (**Scheme 9**). This would be followed by a ring-closing metathesis reaction to furnish the THF ring; sequential HWE olefination and Nozaki-Hiyama-Kishi (NHK) coupling would then be used to install the desired C-24 side chain.



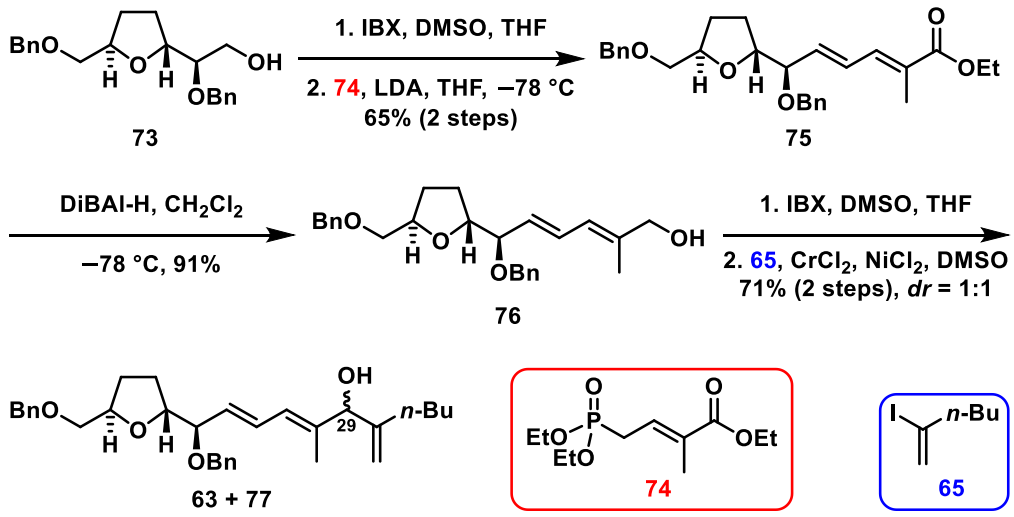
Scheme 9. Retrosynthetic Analysis of the C-19 to C-34 Fragment of Amphidinolide C

Diol **70** was first converted into epoxide **69** in four steps (**Scheme 10**). Lewis acid-catalysed opening of epoxide **69** with alcohol **71**, followed by benzyl protection of the secondary alcohol, gave metathesis precursor **67**. Ring-closing metathesis of the diene produced the 2,5-*trans* dihydrofuran **72**. Sequential hydrogenation and PMB deprotection gave alcohol **73**.



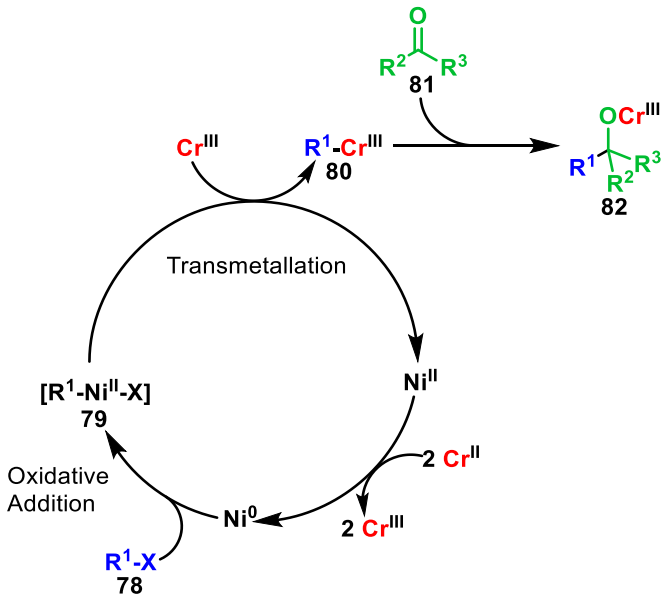
Scheme 10. Synthesis of Primary Alcohol 73

Oxidation of alcohol **73** and subsequent HWE olefination gave dienoate **75** in 65% yield over the two steps (**Scheme 11**).[43,44] Reduction of ester **75** gave the corresponding alcohol, **76.** Subsequent oxidation of alcohol **76** with IBX gave the aldehyde, which then underwent a NHK coupling reaction with iodide **65.**[45] This sequence resulted in the isolation of the C-19 to C-34 fragment **77** as a mixture of epimers at the C-29 position with a *dr* = 1:1.



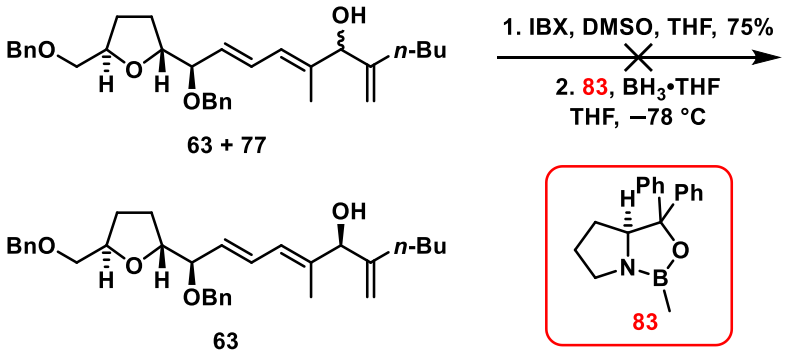
Scheme 11. Completion of C-19 to C-34 Fragment as a Mixture of C-29 Epimers

The nickel-catalysed NHK coupling reaction to afford alcohol **77** first requires the nickel(II) to be reduced to nickel(0) (**Scheme 12**). The reduction is achieved by the oxidation of chromium(II) to chromium(III). The active nickel(0) species then undergoes oxidative addition with an alkenyl halide or alkenyl triflate. Transmetallation of the alkyl nickel species with chromium(III) generates an organochromium species which reacts with the carbonyl compound and furnished the alcohol upon work-up.



Scheme 12. Catalytic Cycle for Nickel-Catalysed Nozaki-Hiyama-Kishi Coupling

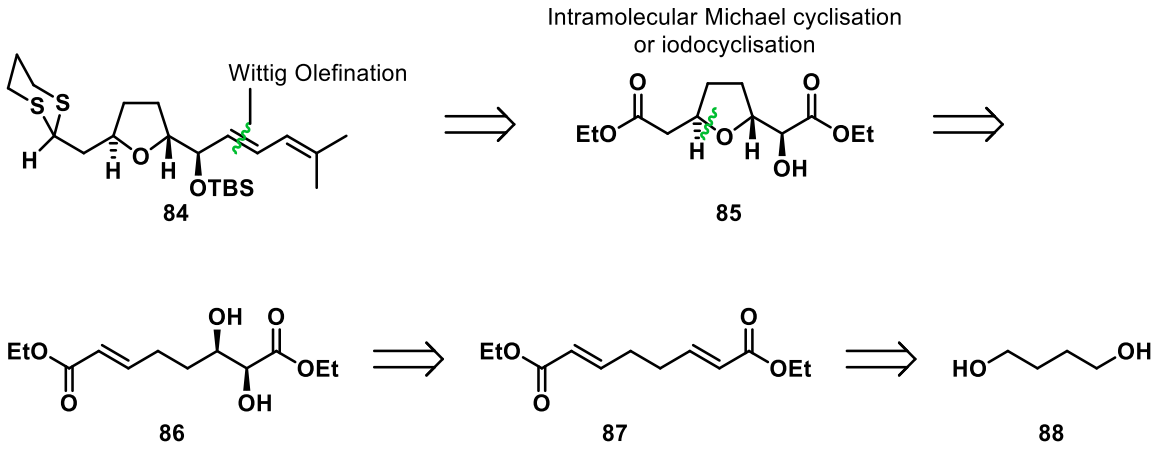
Unfortunately, the diastereoselectivity for the required alcohol **63** was poor. Though ultimately unsuccessful, an attempt to improve the diastereoselectivity was made. Both alcohol diastereoisomers were oxidised to the ketone before undergoing a Corey-Bakshi-Shibata (CBS) reduction reaction, also known as a Corey-Itsuno reduction reaction (**Scheme 13**).[46,47] Due to the highly conjugated nature of the substrate an inseparable mixture of products was obtained. Thus, Mohapatra and co-workers reported the synthesis of the C-19 to C-34 fragment and its corresponding C-29 epimer.



Scheme 13. Unsuccessful Attempt to Correct the C-29 Stereochemistry

2.1.3 Armstrong: Desymmetrisation and Michael Cyclisation Approach

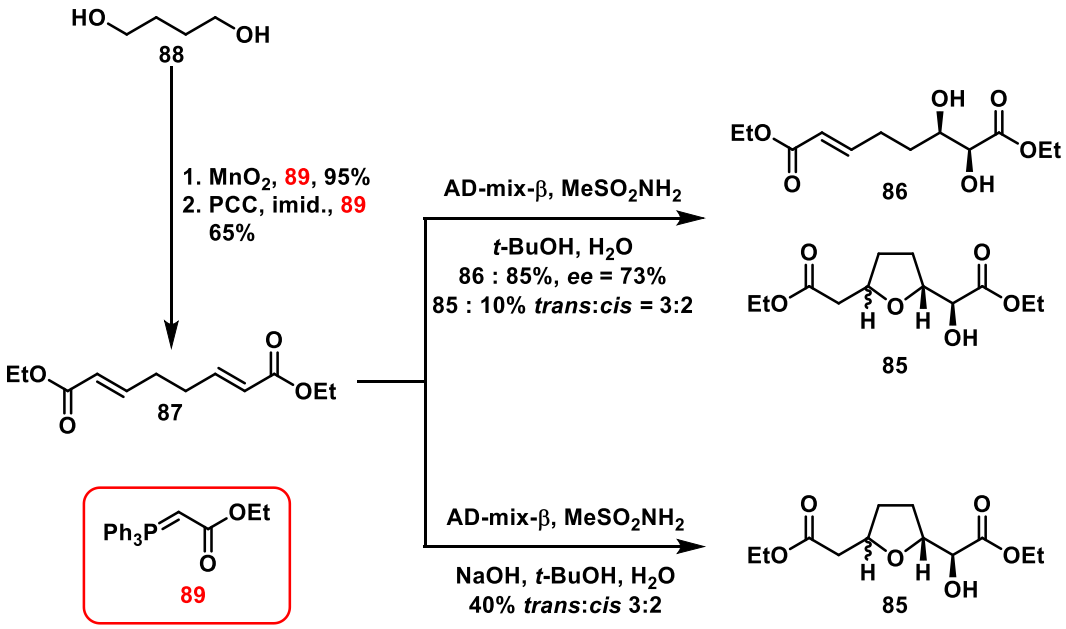
In 2009, Armstrong and co-workers reported the synthesis of the C-18 to C-29 fragment of amphidinolide F.[48] Armstrong proposed that the fragment could be accessed by an intramolecular Michael-type reaction of *syn*-diol **86** (**Scheme 14**). Diol **86** could be formed by the desymmetrisation of dienoate **87**. With the dienoate being accessed from diol **88**.



Scheme 14. Armstrong's Retrosynthetic Analysis of the Northern C-18 to C-29 Fragment

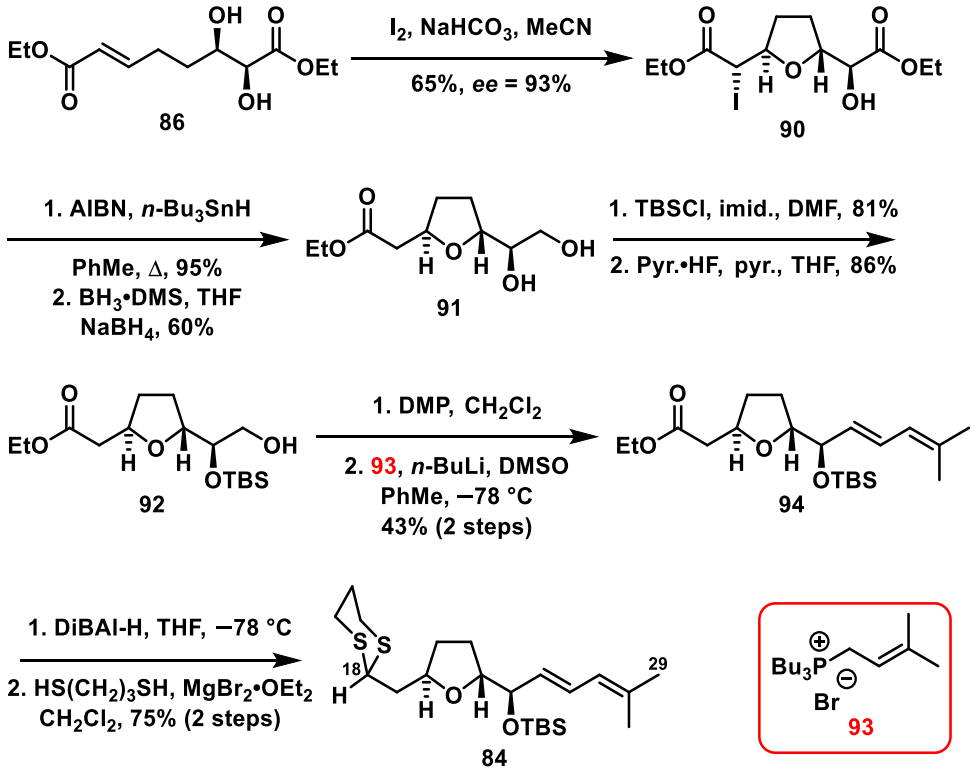
The synthesis started with mono-oxidation of diol **88** using MnO_2 with *in situ* Wittig olefination using stabilised ylide **89** to give the corresponding *E*-alkene (**Scheme 15**). Pyridinium chlorochromate (PCC) was then used to oxidise the remaining alcohol before *in situ* olefination with stabilised ylide **89** delivered the diene **87** in a 65% yield, with an *E*,*E*:*E*,*Z* ratio of 92:8. Dienoate **87** was subjected to Sharpless asymmetric dihydroxylation conditions with AD-mix β and this reaction

resulted in formation of diol **86** in 85% yield with an *ee* of 73%.[49] Concurrent intramolecular Michael cyclisation afforded some of desired THF **85**. However, both the yield (10%) and the diastereoselectivity (*trans*:*cis* = 3:2) for the required THF were poor. The yield of the THF product was increased by inclusion of a base additive; NaOH proved to be the most successful and afforded THF **85** in a yield of 40%. Despite the improved yield, the diastereomeric ratio was unchanged and continuation of this approach could not be justified. Consequently, an alternative method to deliver THF **85** with improved diastereoselectivity was required.



Scheme 15. Intramolecular Michael Cyclisation Reaction to Afford THF Ring 85

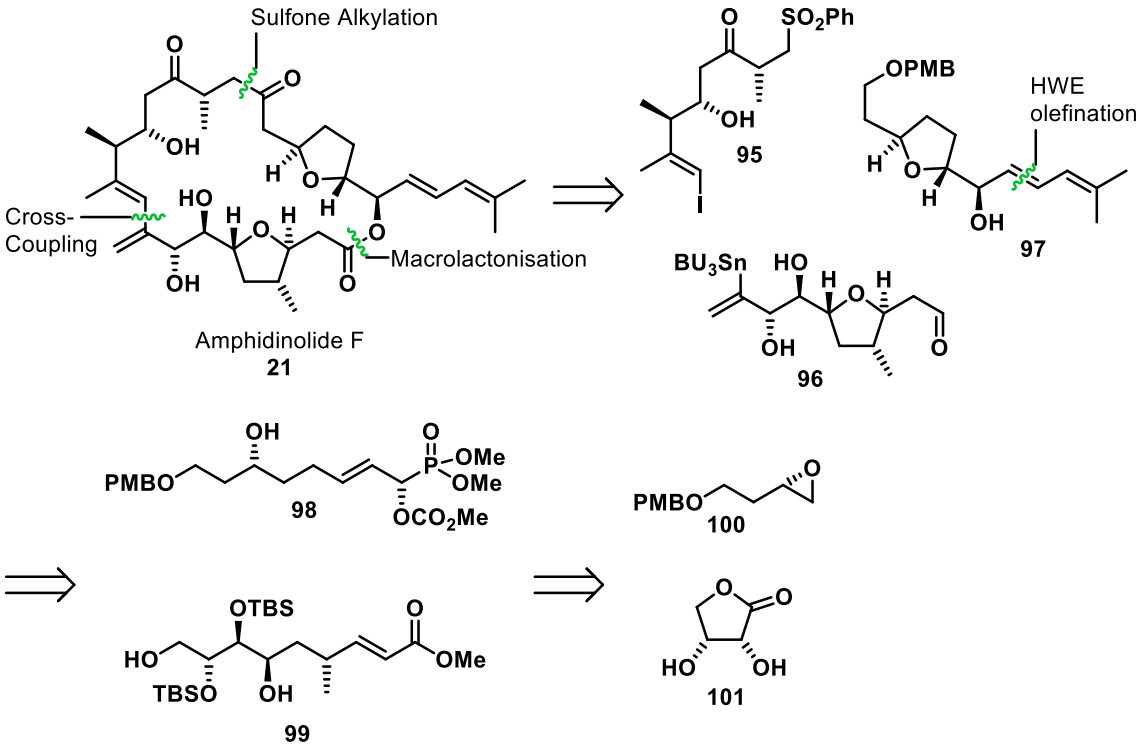
As an alternative to the Michael reaction, an iodocyclisation reaction was employed to form the desired *trans*-THF in a 65% yield (**Scheme 16**). The *cis*-THF accounted for a further 21% of the product mixture, and so the *trans*:*cis* ratio had improved from 3:2 to 3:1. After recrystallisation, the *ee* of α-iodo-THF **90** was 93%. Deiodination of α-iodo-THF **90** under free radical conditions followed by reduction of the α-hydroxyester gave 1,2-diol **91**. The primary alcohol **92** was obtained thereafter by manipulation of the protecting groups and oxidation of the primary hydroxyl group with Dess-Martin periodinane (DMP). The resulting aldehyde was subjected to Wittig olefination with a Vedejs-type phosphonium salt to give the diene **94** with an *E*:*Z* ratio of 87:13 .[50] The remaining ester was reduced to the aldehyde and this was converted into the 1,3-dithiane **84** to complete the C-18 to C-29 fragment.



Scheme 16. Iodocyclisation Approach to the Northern C-18 to C-29 Fragment

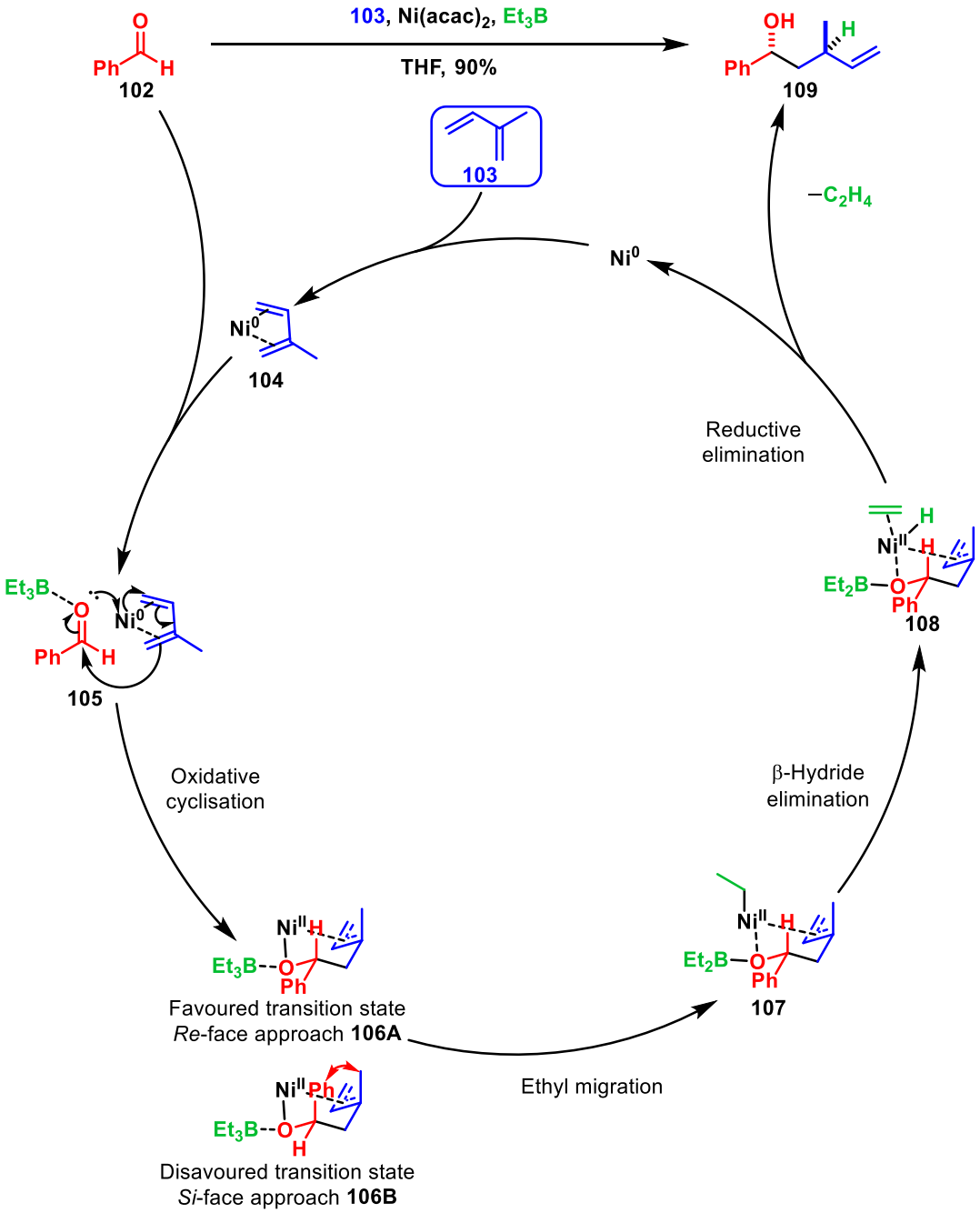
2.1.4 Spilling: Nickel-Catalysed Homoallylation Approach

In 2010, Spilling and co-workers published approaches to the synthesis of both the northern and southern *trans*-THF-containing fragments of amphidinolides C and F.[51,52] It was proposed that the macrocycle could be completed by sequential Stille cross coupling, sulfone alkylation, and macrolactonisation (**Scheme 17**). The northern fragment **97** would arise from a Tsuji-Trost reaction of carbonate **98** and the southern fragment would come from cyclisation of enoate **99**.



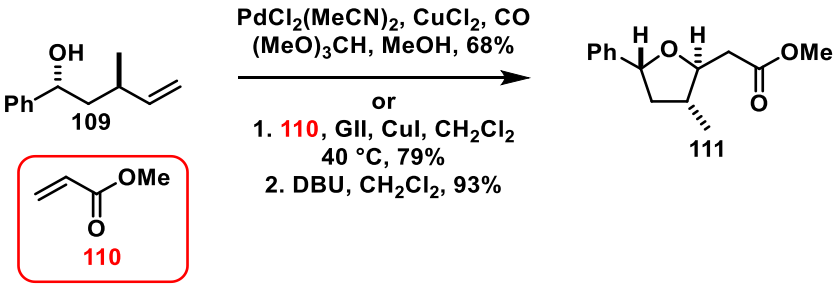
Scheme 17. Spilling's Retrosynthetic Analysis of Amphidinolide F

The group first published their approach to the synthesis of the southern fragment and began by designing a model system to test the synthesis of the 2,5-*trans* THF. This comprised the nickel-catalysed homoallylation of benzaldehyde (**102**) with 1,3-diene **103** which gave 1,3-*anti* alcohol **109** with a *dr* = 15:1 (**Scheme 18**). An extensive study into the regio- and stereoselectivity of this homoallylation reaction had been conducted by Tamaru and co-workers in 2006.[53] Ultimately, Tamaru and co-workers observed that regioselectivity is controlled by electron density and the most electron-rich alkene is favoured to undergo reaction with the aldehyde. Oxidative cyclisation, accelerated by the presence of a Lewis acid (e.g. BEt_3), of the nickel(0) complex (**104**) through the nucleophilic isoprene and electrophilic aldehyde gives the diastereomeric intermediates **106A** and **106B**. These diastereoisomers arise from *Re*- and *Si*- face approaches of the aldehyde respectively. Sterics dictate that the lower energy transition state is **106A** because there is minimisation of the diaxial interaction between the methyl and phenyl substituents. Transfer of an ethyl group from boron to nickel with concurrent cleavage of the nickel-oxygen bond produces intermediate **107**. Subsequent ß-hydride elimination and reductive elimination gives the observed 1,3-*anti* product **109**.



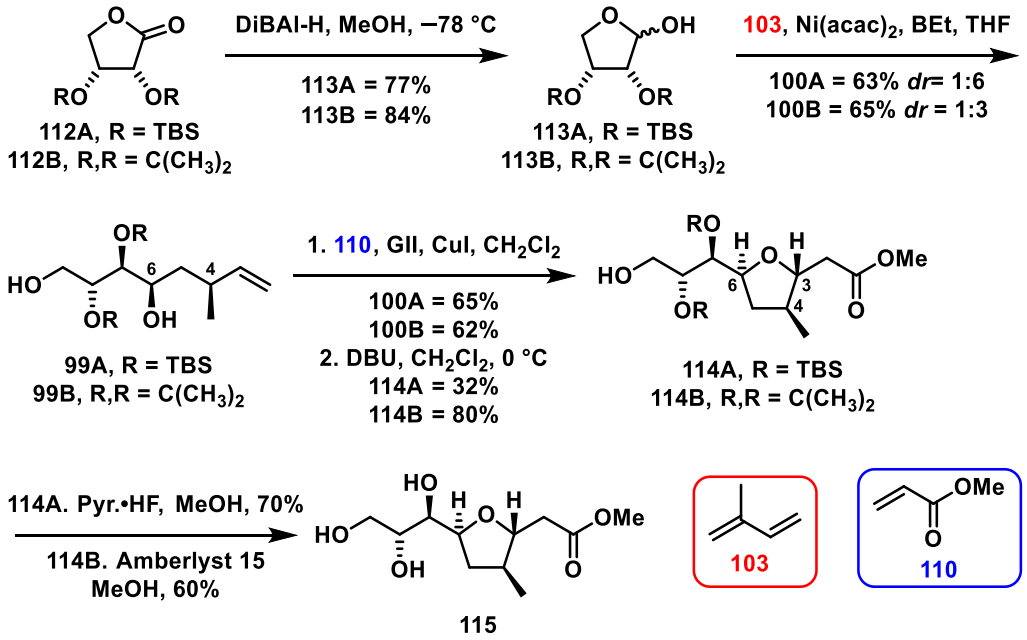
Scheme 18. Mechanism of the Nickel-Catalysed Formation of 1,3-Anti Alcohols

Spilling and co-workers tested various cyclisation conditions to produce the 2,5-*trans* THF. Initially, a palladium-catalysed cyclisation and alkoxycarbonylation reaction was investigated and the methyl ester **111** was obtained in a yield of 68% (**Scheme 19**). The yield of methyl ester **111** was higher when it was prepared by sequential cross metathesis of alkene **109** with methyl acrylate (**110**) and DBU mediated intramolecular oxa-Michael addition. The yield over two steps was 73% and so the two-step protocol was used in the synthesis of the southern *trans*-THF.



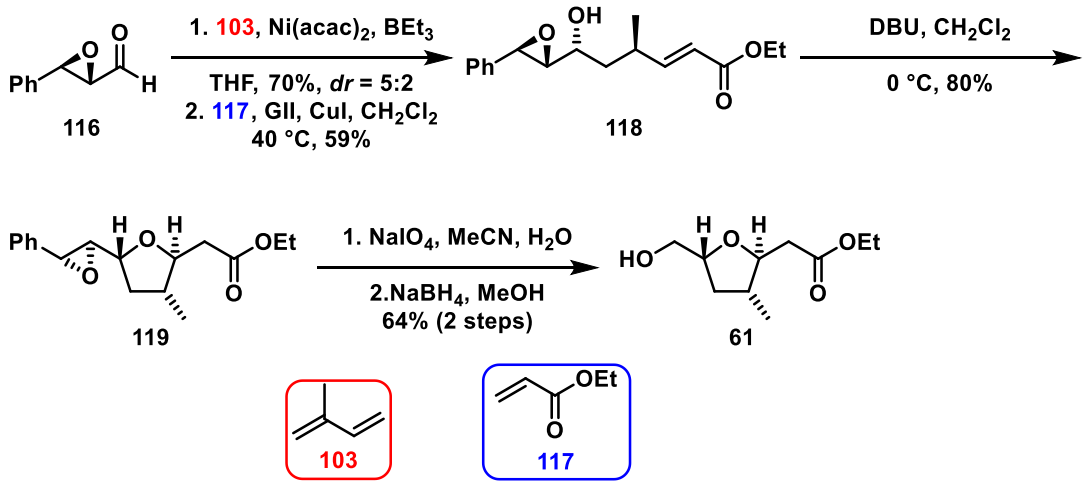
Scheme 19. Two Strategies Towards the Trans-THF Ring 111

After the key reactions had been tested on the model systems, synthesis of the southern fragment commenced. The di-TBS silyl ether of erythrolactone **112A** was first reduced with DiBAl-H to afford the lactol **113A** (**Scheme 20**)**.** Lactol **113A** was used in the nickel-catalysed homo-allylation reaction to give alcohol **99A** with a *dr* = 1:6 in favour of the undesired C-4 and C-6 *ent*-diastereoisomer. Although the reaction favoured the undesired diastereoisomer, the diastereoisomers were separable by column chromatography. Spilling and co-workers proceeded with the synthesis using the C-4 and C-6 *ent*-isomer because it was the major product from nickel-catalysed homoallylation reaction. Cross metathesis followed by the DBU mediated cyclisation resulted in formation of the *trans*-THF as the expected C-3, C-4, and C-6 *ent*-diastereoisomer **114A**. Partial migration of a TBS group to the primary alcohol was also observed accounting for 63% of the product mixture. Removal of the silyl groups from *trans*-THF **114A** afforded the desired C-1 to C-9 fragment. When the substrate **112B**, in which the TBS protecting groups were replaced with an acetonide, was employed in the homoallylation reaction, the undesired diastereoisomer was the major product but the *dr* was improved from 1:6 to 1:3. Furthermore, use of an acetonide protecting group meant that migration of the protecting groups during oxa-Michael cyclisation was avoided, thus improving the overall selectivity of the reaction.



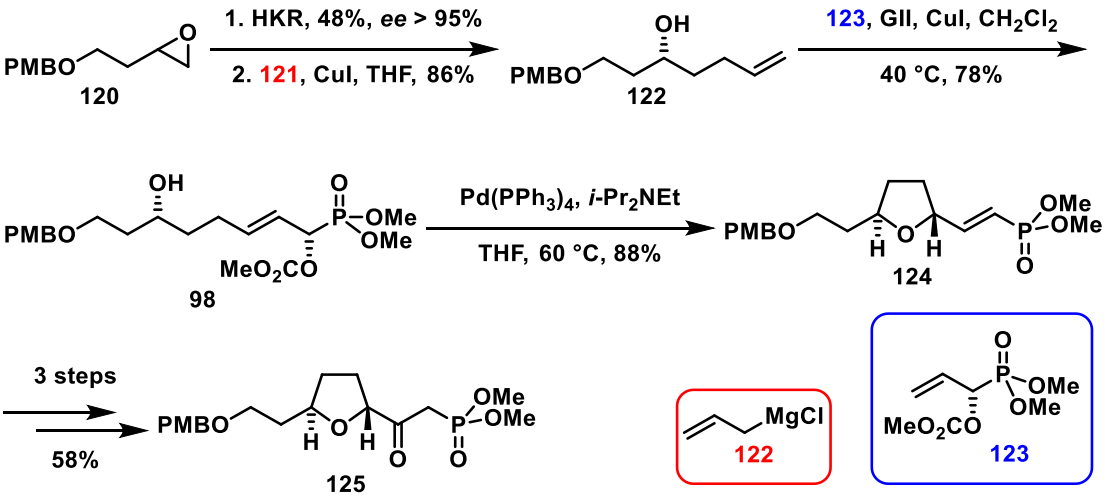
Scheme 20. First Generation Synthesis of the C-1 to C-9 Fragment

To improve the levels of diastereocontrol during the synthesis, Spilling and co-workers investigated the use of the enantiomerically pure epoxy-aldehyde **116** instead of erythrolactone. Homo-allylation of aldehyde **116** favoured the formation of desired diastereoisomer with a *dr* = 5:2 (*cf*. *dr* of the acetonide protected homo-allylation of erythrolactone derivative **113B** was 1:3) (**Scheme** 21). This approach therefore resulted in a vast improvement in diastereoselectivity when compared to that involving the use of erythrolactone. Subsequent cross metathesis and oxa-Michael cyclisation reactions gave *trans*-THF **119**. Periodate cleavage of the epoxide, followed by reduction to give alcohol **61**, completed the C-1 to C-7 fragment. This fragment had been employed by Roush and co-workers as an intermediate in their synthesis of the larger C-1 to C-9 fragment (**Section 2.1.1**).



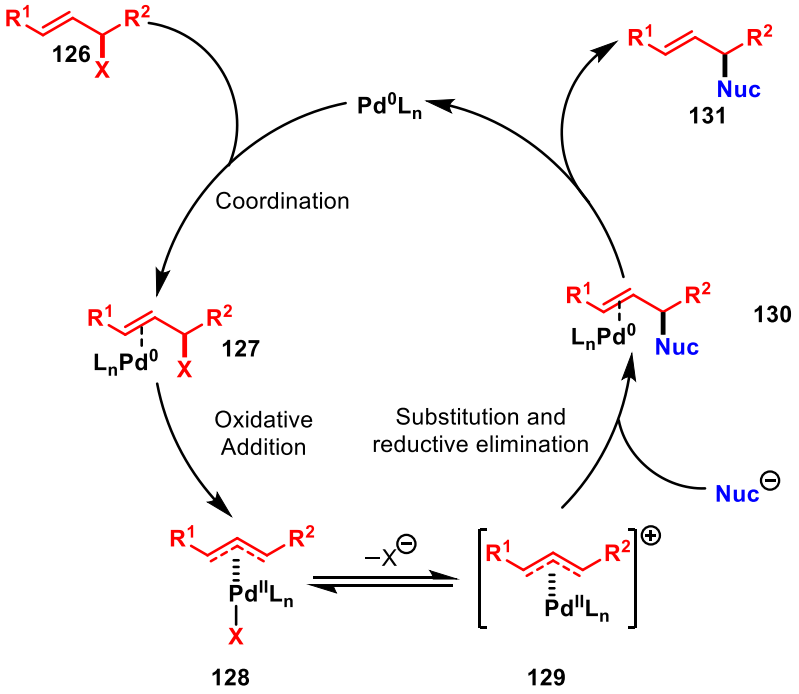
Scheme 21. Second Generation Route Towards the C-1 to C-7 Fragment

For the synthesis of the northern *trans*-THF, Spilling and co-workers used Jacobsen's method to perform hydrolytic kinetic resolution of the epoxide **120** (**Scheme 22**).[54] The enantioenriched epoxide was then reacted with allyl magnesium chloride **121** and copper iodide to give alcohol **122**. Cross metathesis of alcohol **122** with (*S*)-carbonate **123** gave Tsuji-Trost precursor **98**. The Tsuji-Trost allylation then afforded *trans*-THF **124** in 88% yield, with the *cis*-THF diastereoisomer accounting for a further 8% yield.[55,56] Vinyl-phosphonate **124** was converted into keto-phosphonate **125** in a further three steps with an overall yield of 58%.



Scheme 22. Synthesis of the Northern THF Ring

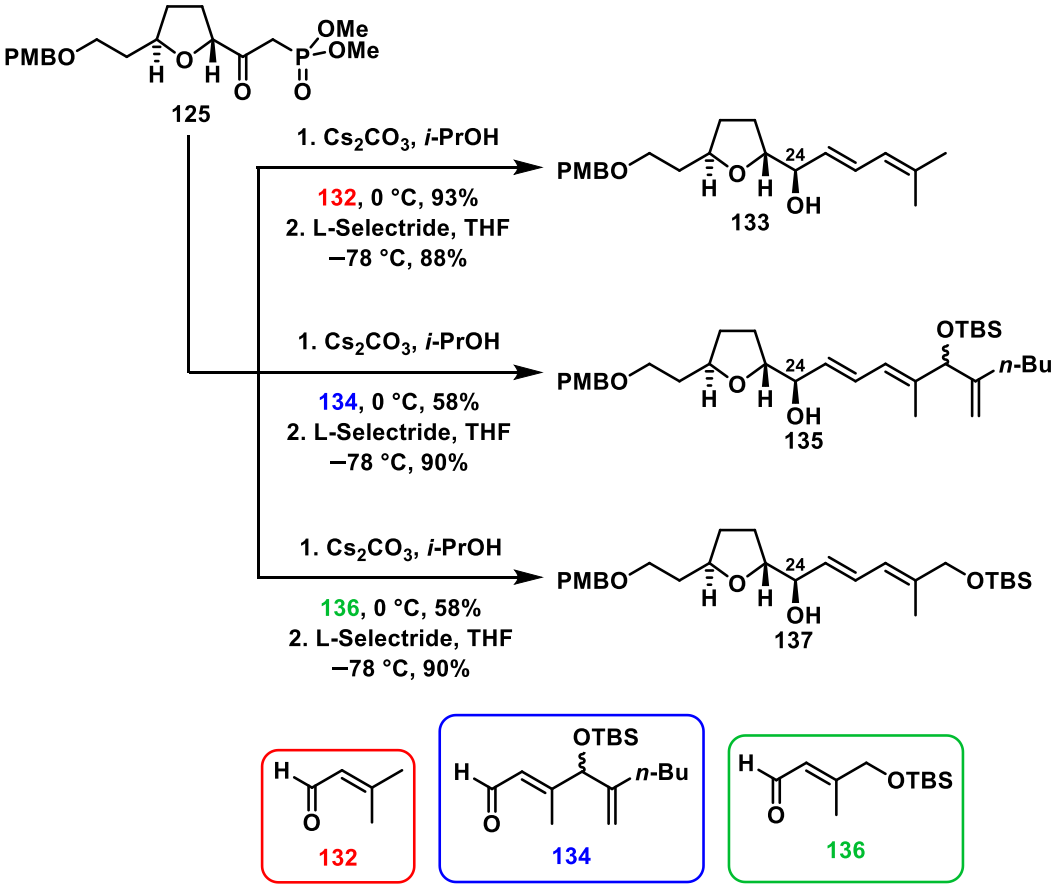
The Tsuji-Trost allylation reaction commences with coordination of the palladium(0) catalyst to the alkene to form the complex **127** where R^1 is a bulkier group than R^2 (**Scheme 23**). Oxidative addition then occurs, inverting the stereochemistry of the starting material, to give organopalladium complex **128**. Following this, substitution and reductive elimination occur forming complex **130**, again causing a stereochemical inversion and resulting in an overall retention of configuration when forming the desired alkene product **131**, in cases where a softer nucleophile with a $pK_{A(H)}$ < 25 is used. For nucleophiles with $pK_{A(H)}$ > 25, however, transmetallation of the palladium with reductive elimination results in overall inversion of stereochemistry. The final step, reductive elimination, determines the regioselectivity of the reaction with the nucleophile preferentially 'attacking' the less hindered carbon.



Scheme 23. Mechanism for the Tsuji-Trost Reaction with a Soft Nucleophile

Spilling and co-workers used a range of aldehydes, corresponding to both natural and non-natural products, in the final step of the sequence in order to highlight the versatility of this approach (**Scheme 24**). A HWE reaction gave the desired dienones. Subsequent reduction of the dienones using lithium tri-*sec*-butylborohydride (L-selectride®) gave the required C-24 (*R*)-diastereoisomer. This outcome can be explained by invoking a Felkin-Ahn transition state for each of the substrates **133**, **135**, and **147**. Thus, the C-18 to

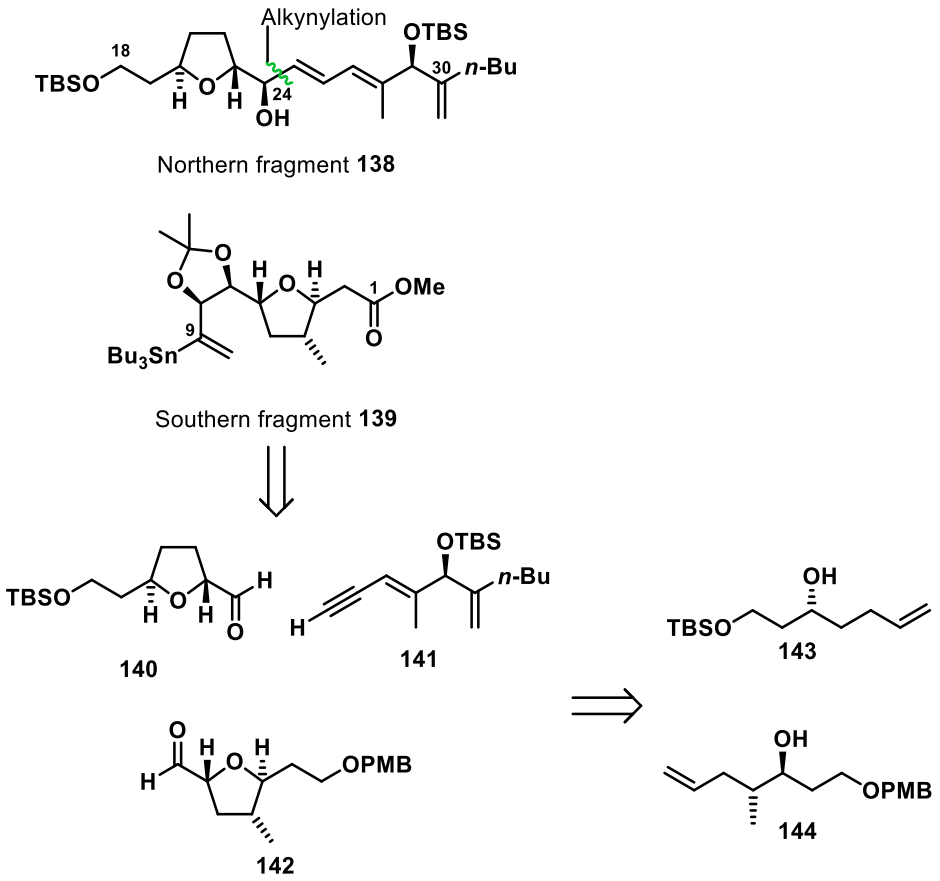
C-29 fragment of amphidinolide F and the C-18 to C-34 fragment of amphidinolide C were synthesised in good yield.



Scheme 24. Synthesis of Three Northern Fragment Variants

2.1.5 Pagenkopf: Oxidative Mukaiyama Cyclisation Approach

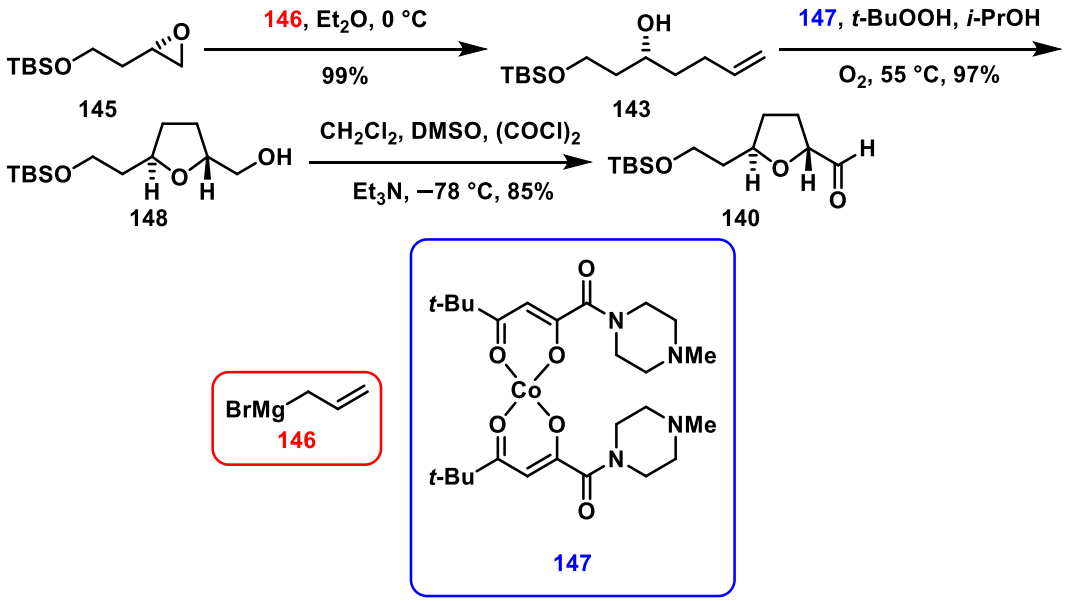
In 2011 Pagenkopf and co-workers reported a synthesis of the northern fragment (C-10 to C-34, **138**) of amphidinolide C; a synthesis of the C-1 to C-9 fragment (**139**) was reported in 2013.[57,58] The group used a cobalt-catalysed oxidative Mukaiyama cyclisation of alcohols **143** and **144** to afford *trans*-THF rings **140** and **142** respectively (**Scheme 25**).



Scheme 25. Pagenkopfs' Retrosynthetic Analysis of the Northern and Southern Fragments

For the northern *trans*-THF fragment the synthesis began with addition of allyl magnesium bromide to the enantiomerically enriched epoxide **145** (**Scheme 26**). The resultant alcohol (**143**) was used in the pivotal oxidative Mukaiyama cyclisation reaction mediated by $Co(NMP)_2$ (**147**), a catalyst developed within the Pagenkopf group, [59] to give *trans*-THF ring **148**. A key aspect of the catalyst design is the presence of the *N*-methyl piperazine (NMP) functionality in the ligand. Under mildly acidic conditions the NMP group is protonated which increases its aqueous

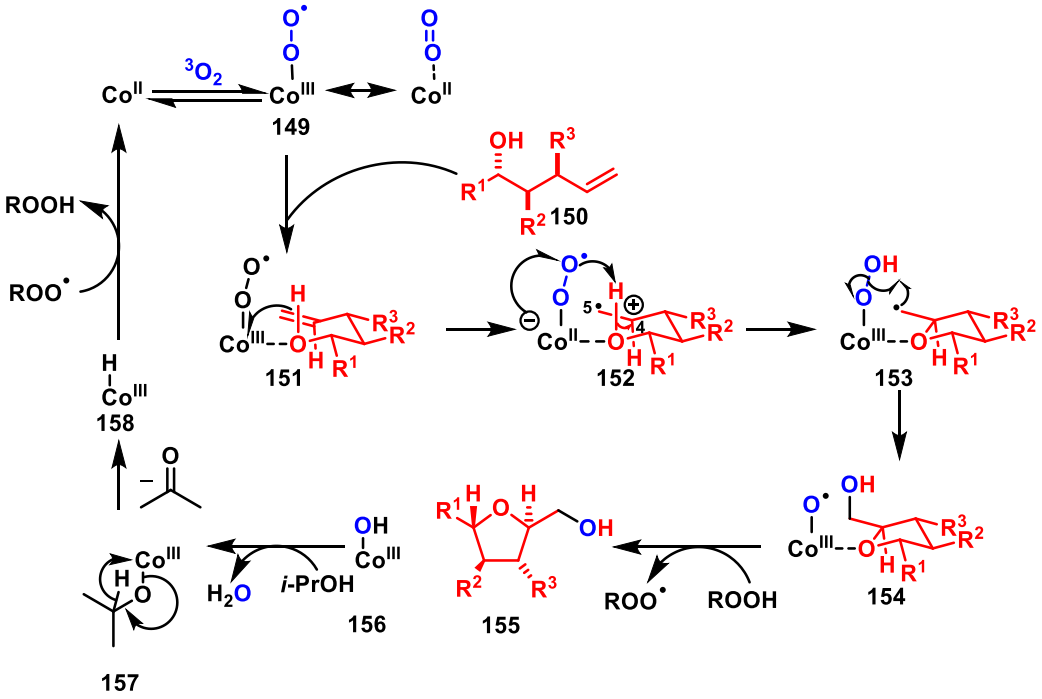
solubility and thereby aids removal of the catalyst and related impurities during work-up. Subsequent Swern oxidation of the alcohol **148** gave aldehyde **140**.[60]



Scheme 26. Synthesis of the Northern THF Ring

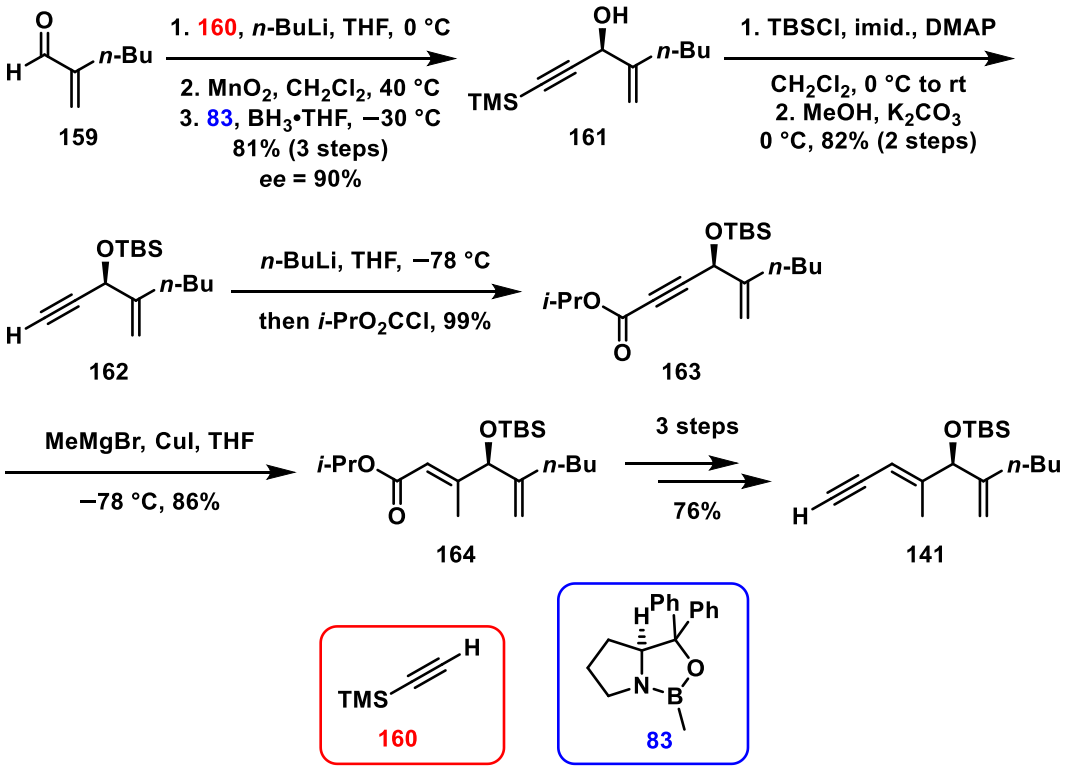
A mechanism to explain the 2,5-*trans* selectivity of the cyclisation reaction was proposed, by Hartung and co-workers in 2008 (**Scheme 27**).[61] It was proposed here that the oxygen is activated by first binding to cobalt(II) to give the superoxo-cobalt species **149**, which acts as a strong Lewis acid and forms the complex **151** with alcohol **150**. The resulting cobalt(III) complex oxidises the alkene to give a cobalt(II) radical cation species **152**. This alkene to alkane transformation, resulting in a reduction in bond order, is evidenced by a 1:1 diastereomer distribution at this position implying free rotation around C-4 to C-5 bond. If the reaction proceeds through a chair-like transition state, where the bulkier substituents are preferentially in pseudo-equatorial positions, and C-O bond formation occurs from this conformation, then the observed 2,5-*trans* selectivity of the cyclisation can be explained. This cyclisation reaction affords cobalt radical species **153** and migration of a hydroxyl radical then occurs to give the alcohol cobalt complex **154**. In the presence of a hydrogen atom donor, such as *t*-BuOOH, the radical quenches to furnish the 2,5-*trans* THF **155** and the hydroxy cobalt(III) species **156**. Exchange of the hydroxyl ligand for an isopropoxyl ligand on the cobalt(III) centre gives cobalt complex **157**. ß-Hydride elimination

produces acetone and a cobalt(III) hydride species **158**. This hydridocobalt species can be oxidised, either by O_2 or a peroxyl radical, to regenerate the cobalt(II) species.



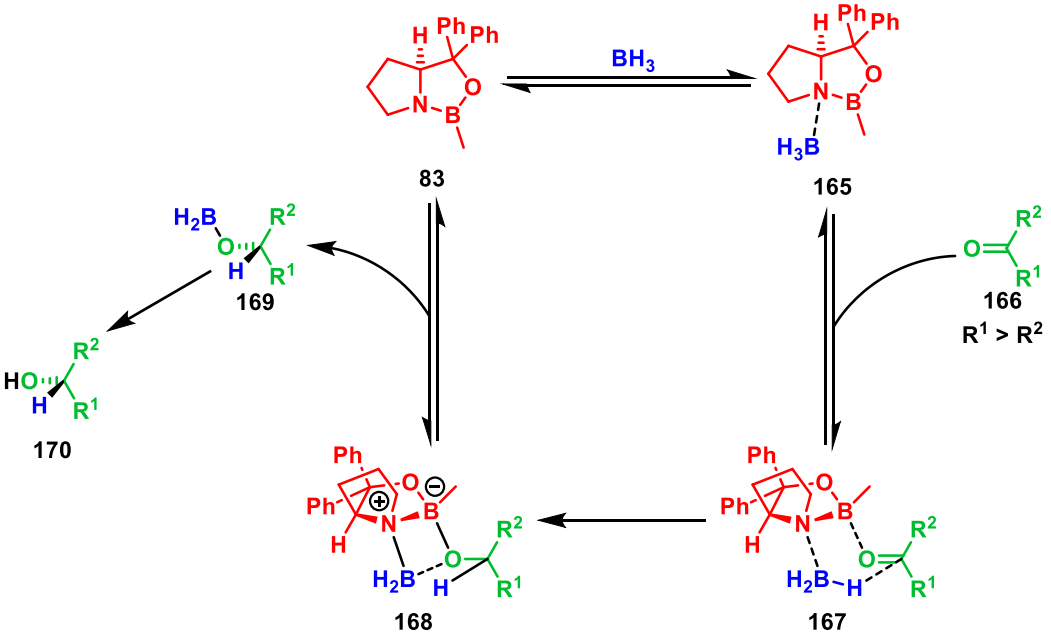
Scheme 27. Proposed Mechanism for the Oxidative Mukaiyama Cyclisation

To synthesise the required C-24 side chain, Pagenkopf and co-workers began by performing an asymmetric synthesis of the alcohol **161** from 2-methylene hexanal **159** (**Scheme 28**). This was achieved in three steps, with the stereochemical component arising from a CBS reduction of a ketone. Subsequent protecting group manipulation afforded the terminal alkyne **162** which was converted into the propargylic ester **163** and then subjected to a copper-mediated Grignard reaction to give (*E*)-alkene **164**. A further three steps were required to give the terminal alkyne **141** required for attachment to the *trans*-THF.



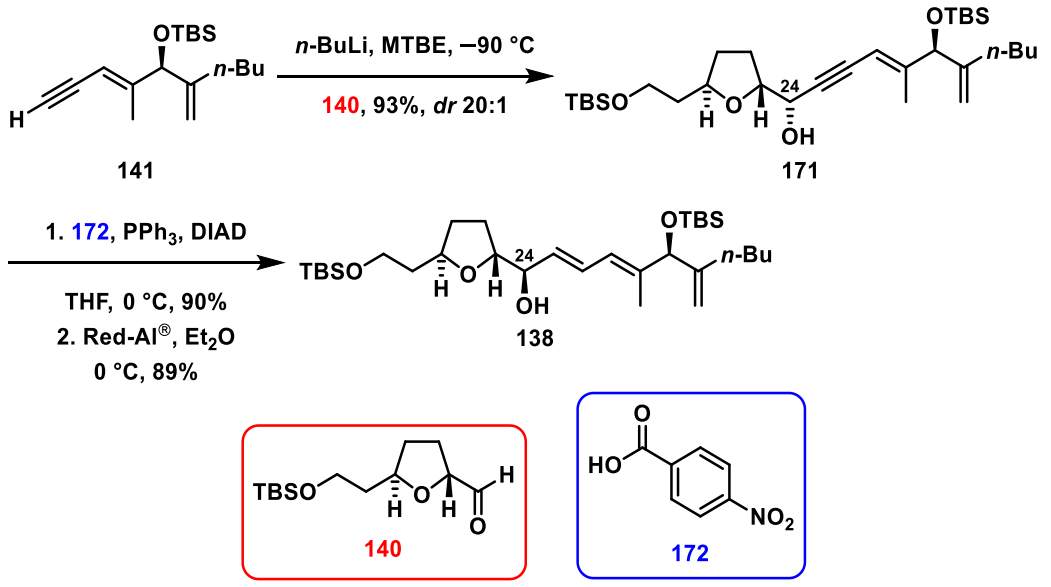
Scheme 28. Synthesis of the Amphidinolide C C-29 Side Chain Fragment

The stereochemical outcome of the CBS reduction reaction arises from the use of chiral oxazaborolidine catalysts, such as oxazaborolidine **83** (**Scheme 29**).[62] The reaction commences with coordination of borane to the tertiary amine, giving complex **165**. This coordination results in the borane being a stronger hydride donor and the endocyclic boron becoming more Lewis acidic. The ketone then binds to the CBS catalyst-borane complex in such a way that steric interactions are minimised. The face selective hydride transfer occurs *via* a 6-membered chair transition state (**167**). Decomplexation of the oxo-borane species **168** regenerates the CBS catalyst **83**, and upon work-up, the chiral alcohol product **170** is obtained.



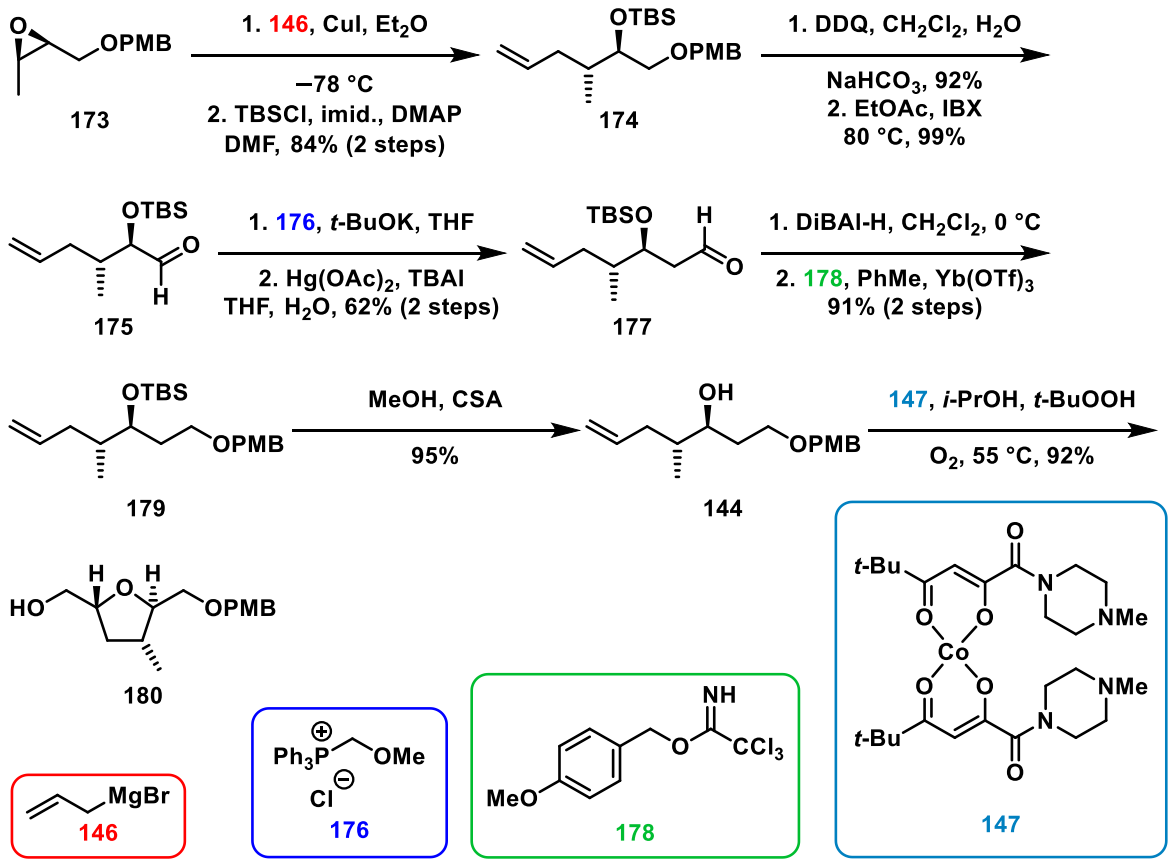
Scheme 29. Mechanism of the Corey-Bakshi-Shibata (Corey-Itsuno) Reduction

To complete the northern fragment of the natural product, alkyne **141** was coupled to aldehyde **140** to give the C-24 epimer of the desired fragment with a *dr* of 20:1 (**Scheme 30**). A Mitsunobu reaction was used to invert the stereochemistry at C-24 of the propargylic alcohol **171** and the resulting ester was reduced along with the alkyne to give *trans* alkene **138**, which corresponds to the northern fragment of the natural product.[63]



Scheme 30. Completion of the Northern C-18 to C-34 Fragment

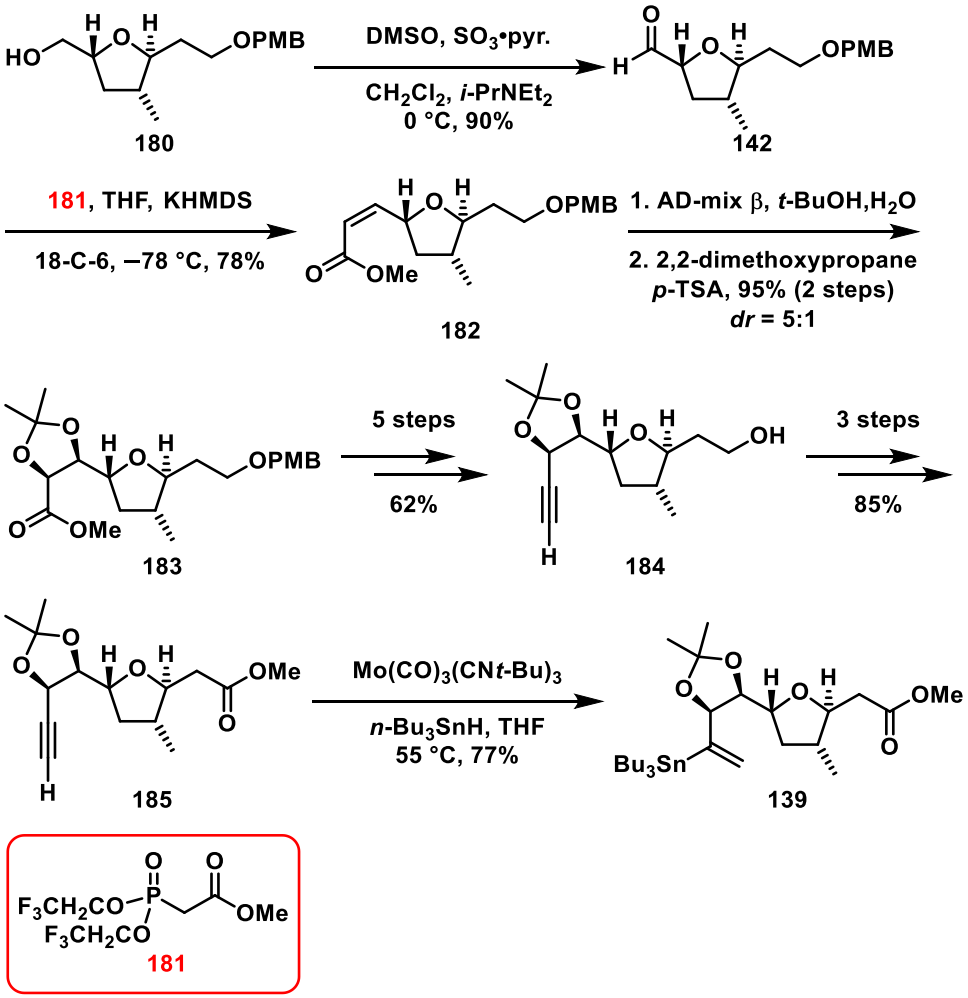
In the first step of the synthesis of the southern fragment, Pagenkopf and co-workers opened the epoxide **173** with allyl magnesium bromide (**146**) (**Scheme 31**). TBS protection of the secondary alcohol then gave silyl ether **174**. The PMB group was removed using DDQ and the corresponding primary alcohol was oxidised to give the aldehyde **175** using IBX. Aldehyde **175** underwent one-carbon homologation by sequential Wittig olefination and mercury mediated hydrolysis of the intermediate enol ether to give aldehyde **177**. DiBAl-H was used to reduce the aldehyde to the alcohol, which was then PMB protected, to give the ether **179**. The silyl ether was hydrolysed to give Mukiyama cyclisation precursor **144**, which upon cyclisation produced the 2,5-*trans* THF **180** in 92% yield.



Scheme 31. Synthesis of the Southern THF Ring

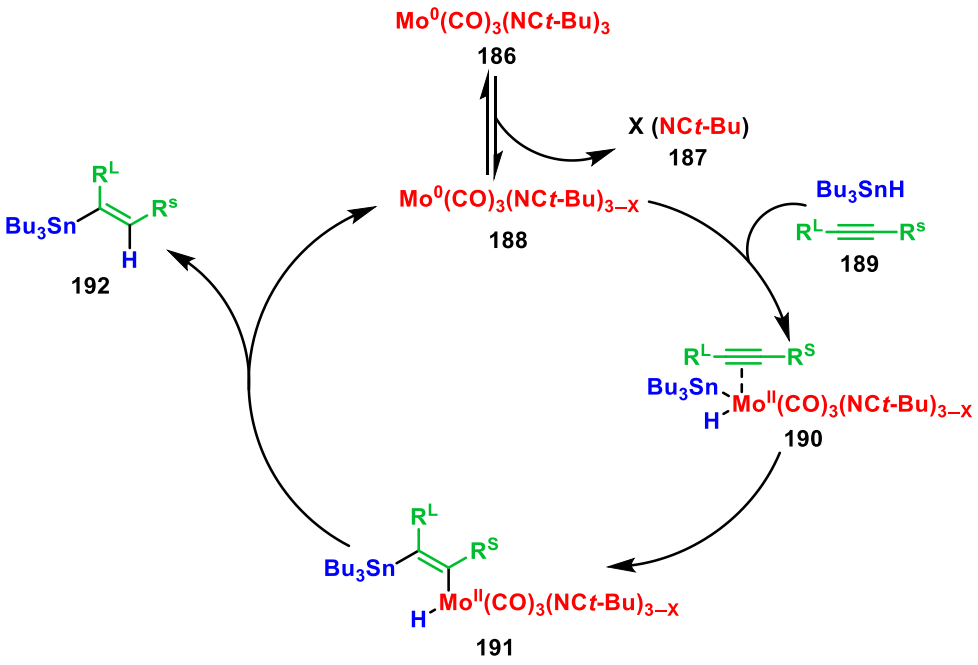
Parikh-Doering oxidation gave aldehyde **142** which was used in a Still-Gennari modified HWE olefination to give the *Z*-substituted alkene **182** (**Scheme 32**).[64] Sharpless asymmetric dihydroxylation, followed by protection of the 1,2-diol, gave acetonide **183** with a *dr* = 5:1. A further five steps were required to produce the alcohol **184**, which was then oxidised to the acid over two steps and methylated to give methyl ester **185**. A molybdenum-catalysed hydrostannylation reaction,

originally developed by Kazmaier, gave the vinylic stannane **139** and thereby completed the C-1 to C-9 southern fragment of the natural product.[65]



Scheme 32. Completion of the Southern C-1 to C-9 Fragment

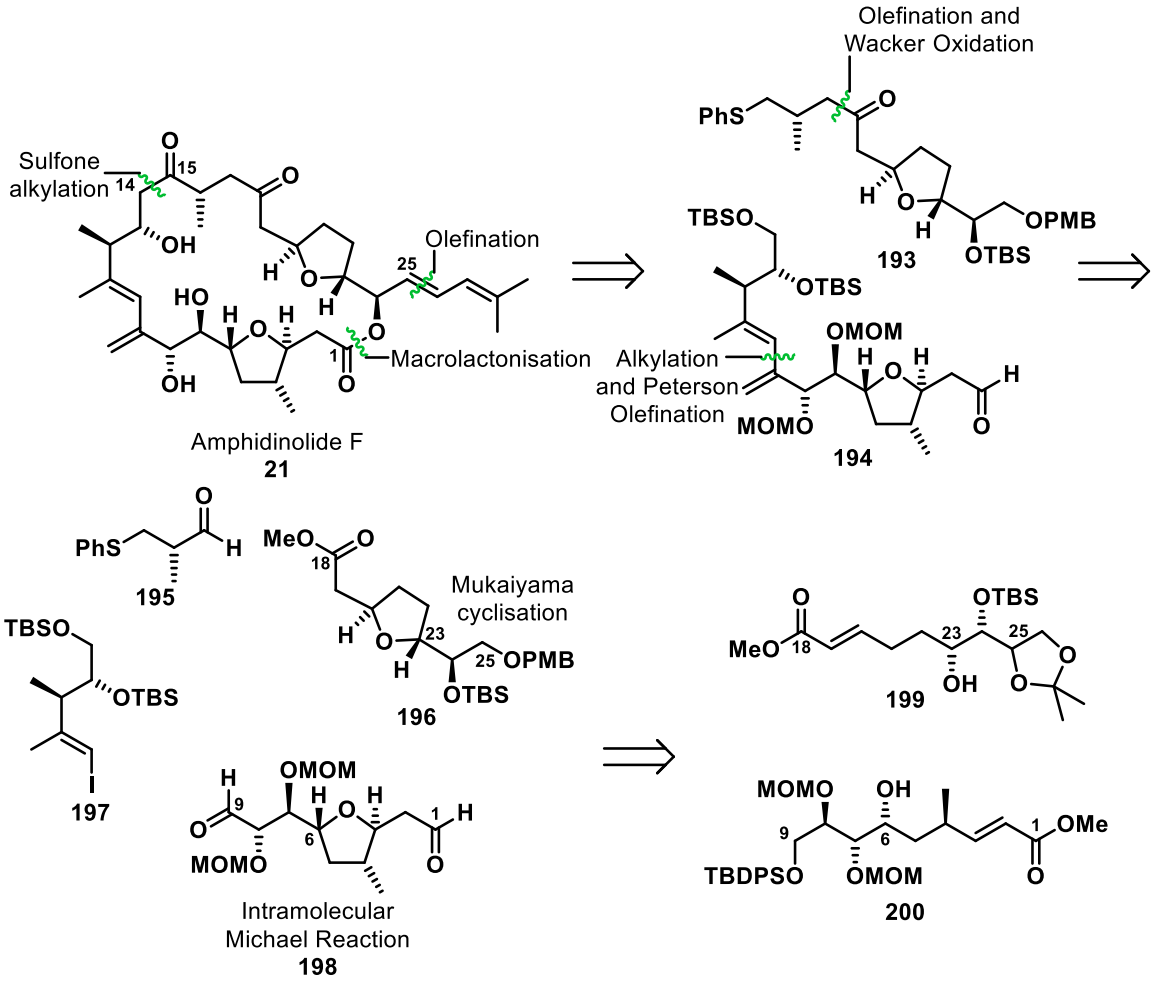
The selectivity of the hydrostannylation reaction can be rationalised by consideration of the steric demands of the catalyst. Initially, the molybdenum complex (**186**) loses one or more isocyanide ligands thereby creating one or more sites on the metal centre that then allows oxidative insertion of molybdenum into the tin-hydrogen bond and complexation of the alkyne to give the complex **190** (**Scheme 33**). The alkyne then inserts across the molybdenum-tin bond in such a way that the more sterically congested molybdenum centre is positioned at the less hindered site of the alkyne. Reductive elimination regenerates the molybdenum(0) catalyst and gives vinylic stannane **192**.



Scheme 33. Mechanism for the Molybdenum-Catalysed Hydrostannylation Reaction

2.1.6 Forsyth: Mukaiyama Alkenol Cyclisation and Intramolecular Michael Approach

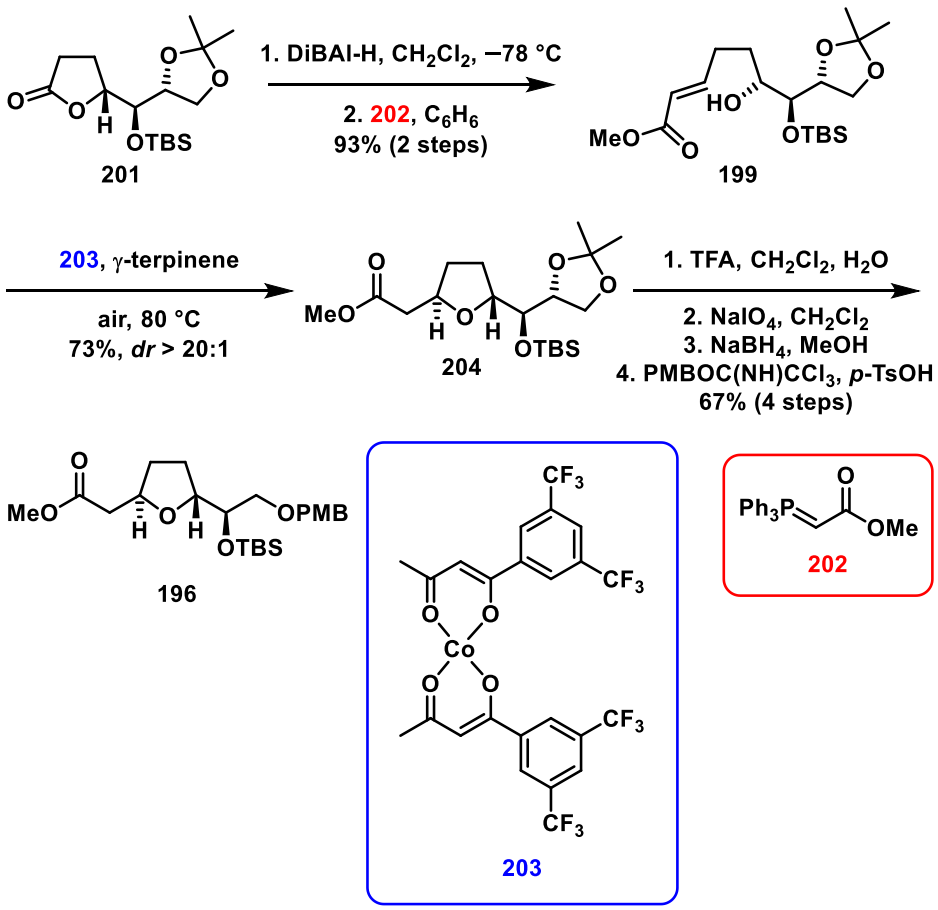
In 2013 Forsyth and co-workers published the synthesis of the C-1 to C-14 and the C-15 to C-25 fragments of amphidinolides C and F.[66] The group envisaged the use of macrolactonisation and sulfone alkylation reactions to couple the fragments **193** and **194**, with the desired side chain being installed through an appropriate olefination reaction (**Scheme 34**). The northern *trans*-THF was to be synthesised by Mukaiyama alkenol cyclisation of enoate **199** and the southern *trans*-THF synthesised from an intramolecular Michael reaction of enoate **200**.



Scheme 34. Forsyths' Retrosynthetic Analysis of Amphidinolide F

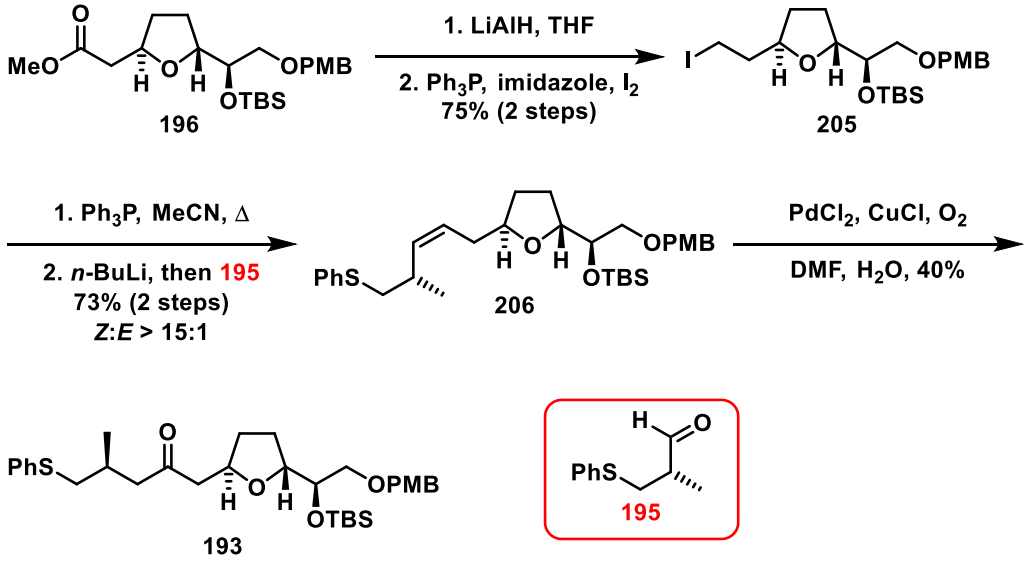
The synthesis of the northern C-15 to C-25 fragment commenced with partial reduction and Wittig olefination of the resulting lactol to produce the enoate **199** (**Scheme 35**). A Mukiyama alkenol cyclisation reaction was then used to give the 2,5-*trans* THF (**204**) in 73% yield. Formation of an α-hydroxy THF that arises from

a competing oxidative Mukiyama cyclisation reaction, similar to that reported by Pagenkopf (**147**, **Scheme 26**), was retarded by the presence of γ-terpinene. Forsyth *et. al.* were , however, unable to suppress this side reaction completely and the α-hydroxy THF accounted for 18% of the product mixture. A further four steps were required to the give PMB-protected alcohol **196** in a 67% yield.



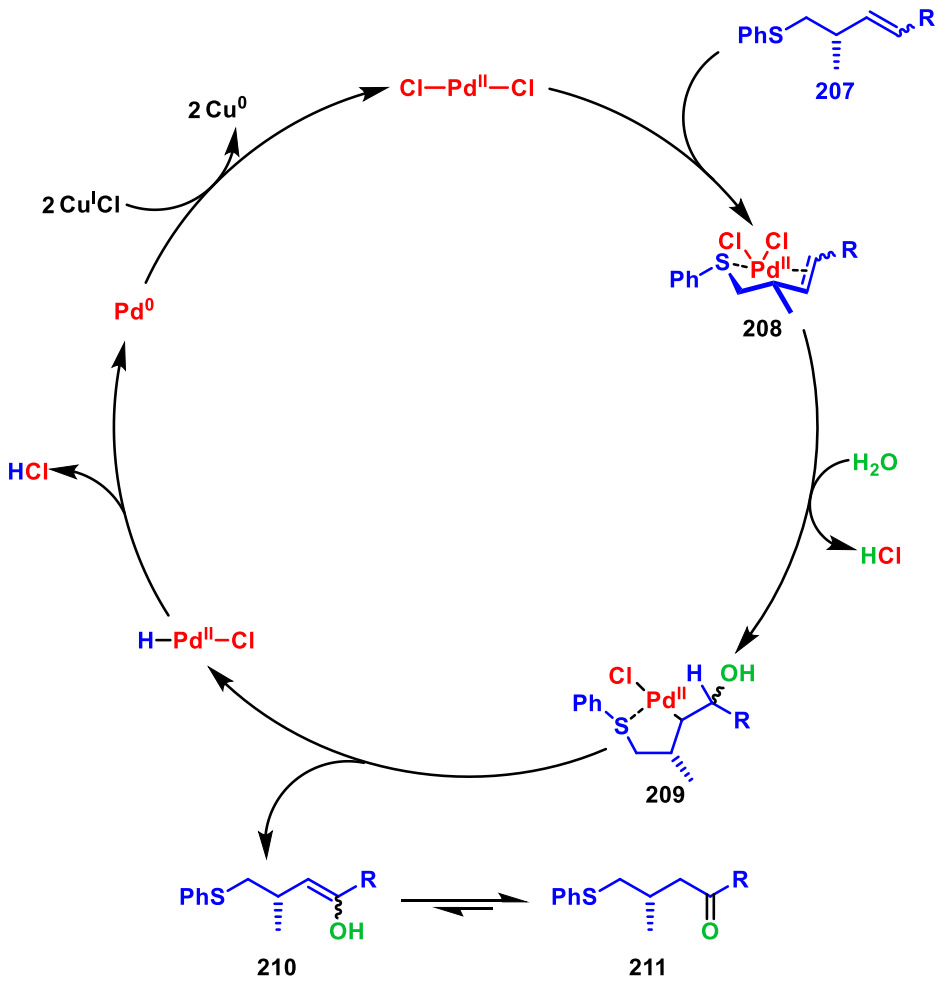
Scheme 35. Mukaiyama Alkenol Cyclisation Towards the Northern THF Ring

Ester **196** was first reduced with $LiAlH_4$ before an Appel reaction was employed to convert the resultant alcohol into iodide **205** (**Scheme 36**). A phosphonium salt was generated by reaction of the iodide with PPh_3 and this was used in a Wittig olefination reaction with aldehyde **195** to give *Z*-alkene **206**. A thioether-directed Wacker oxidation reaction was employed to produce the ketone **193** and thereby complete the northern fragment of the natural product.[67]



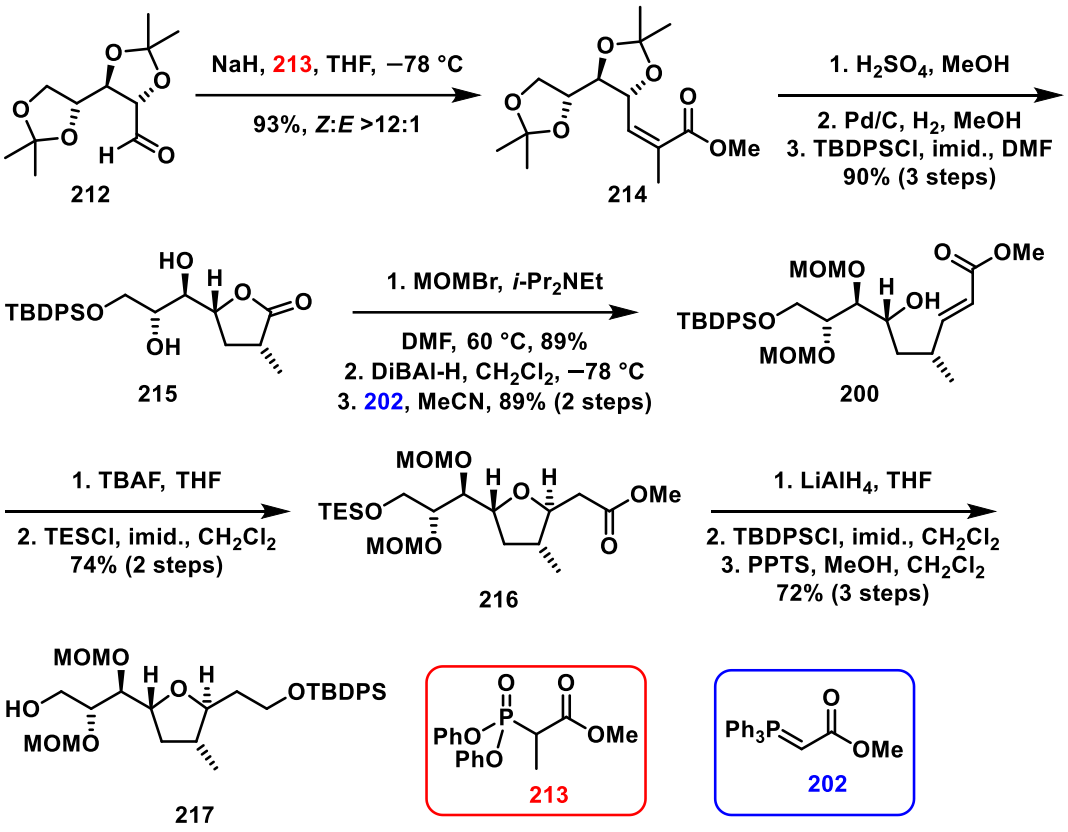
Scheme 36. Synthesis of the Northern Fragment

For the directed Wacker oxidation, $Pd^{II}Cl_2$ co-ordinates to thioalkene **207** to form the complex **208** (**Scheme 37**). Water then attacks the distal carbon because the thioether directs the palladium towards the proximal carbon of the alkene to give the hydroxy-palladium species **209**. ß-Hydride elimination results in elimination of enol **210**, which tautomerises to give ketone product **211** and $HPd^{II}Cl$. Reductive elimination results in net loss of HCl and generation of palladium(0). To regenerate the palladium(II) catalyst, two equivalents of $Cu^{I}Cl$ are reduced to copper(0) giving the $Pd^{II}Cl_2$.



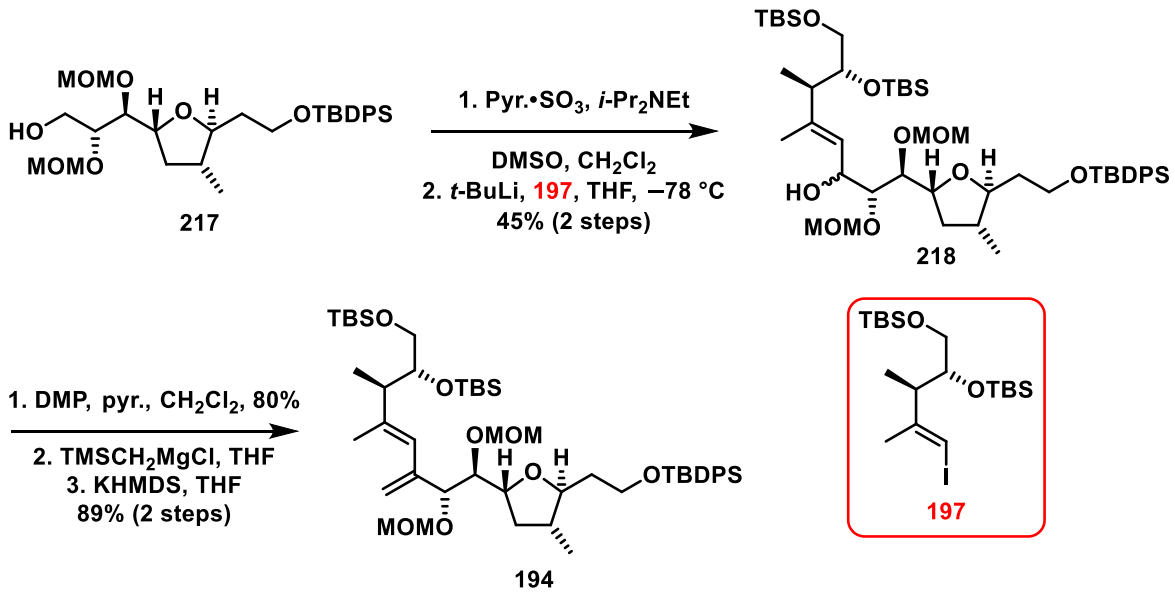
Scheme 37. Mechanism for the Thioether directed Wacker Oxidation

Synthesis of the C-1 to C-14 fragment began with an Ando modification to the HWE olefination of known aldehyde **212** to give *Z*-alkene **214** (**Scheme 38**). Acetonide deprotection with a concurrent intramolecular cyclisation, followed by palladium-catalysed reduction and silyl protection of the primary alcohol gave lactone **215**. Protection of the remaining hydroxyl was achieved using methoxymethyl (MOM) bromide. From here, the lactone was reduced using DiBAl-H and Wittig olefination was then performed to give *E*-enoate **200**. Subsequent cyclisation of enoate **200** was accomplished using TBAF and was accompanied by loss of the primary silyl protecting group to yield 2,5-*trans* THF. It was necessary for the primary alcohol to be re-protected with a silyl protecting group to furnish the TES ether **216**. A further three steps, involving sequential ester reduction, silyl protection of the free hydroxyl group and removal of the TES group were required to furnish primary alcohol **217** in a 72% yield.



Scheme 38. Synthesis of the Southern THF Ring

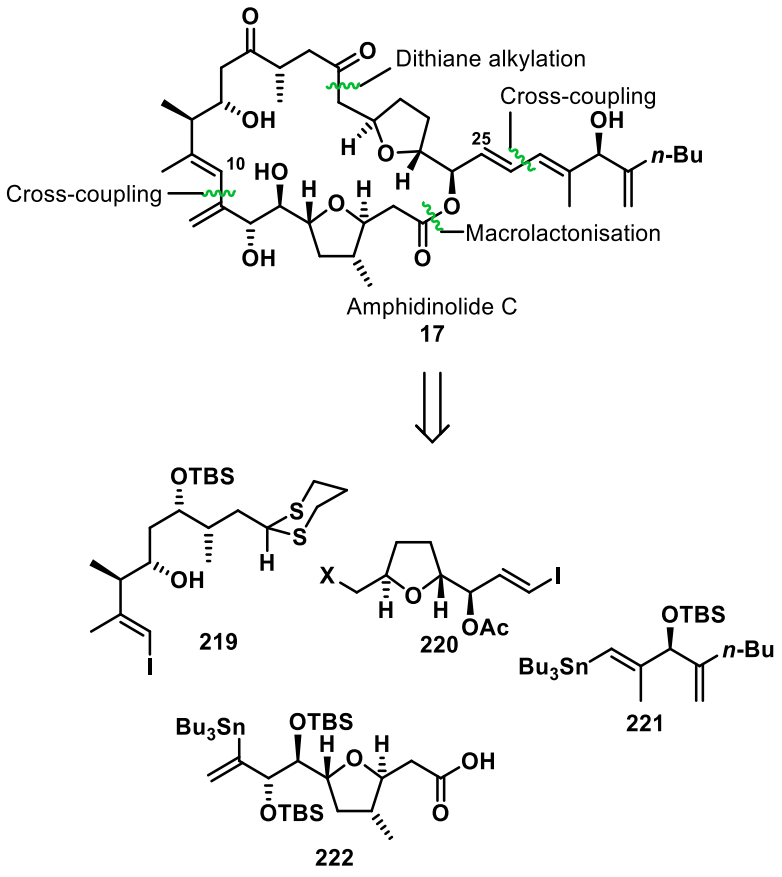
Alcohol **217** was oxidised using a Parikh-Doering oxidation reaction and the resulting aldehyde was reacted with the lithiated intermediate generated from the vinylic iodide **197** (**Scheme 39**). The vinylic iodide was the same as that used by Carter during his total synthesis of amphidinolide F *vide infra* (**Section 2.2.1**). A mixture of diastereomeric secondary alcohols (**218**) was produced from this coupling process and this mixture was oxidised to give the corresponding enone. Peterson olefination of the ketone produced the diene **194** and thus completed the C-1 to C-14 fragment of the natural product.[68]



Scheme 39. Synthesis of the Southern Fragment

2.1.7 Williams: Epoxide Opening *trans*-THF Formation

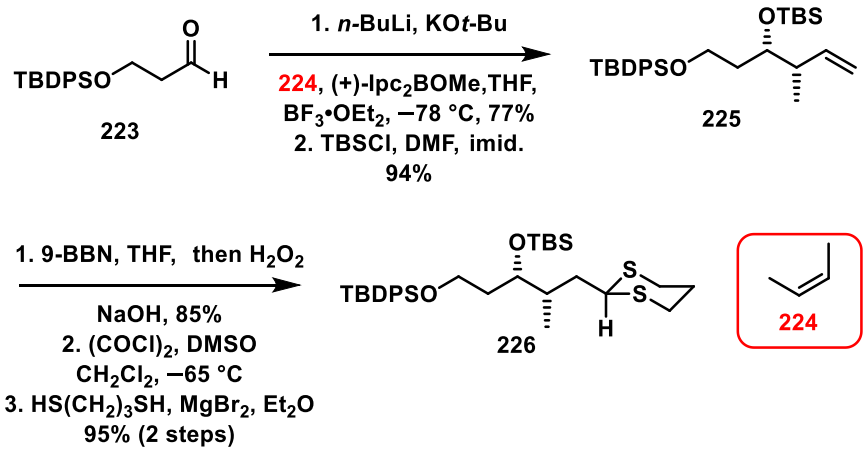
Williams and co-workers reported a synthesis of the C-10 to C-25 fragment of amphidinolides C and F in 2020.[69] Williams' retrosynthetic analysis of the natural product implied key bond construction by use of the commonly seen macrolactonisation and two cross coupling events with a further acyl anion coupling reaction (**Scheme 40**). This analysis resulted in disconnection of the natural product into four smaller fragments whilst allowing the group the flexibility to prepare interesting congeners of the natural product from a late-stage intermediate and then use these for biological studies.



Scheme 40. Williams' Retrosynthetic Analysis Breaking the Natural Product into Four Fragments

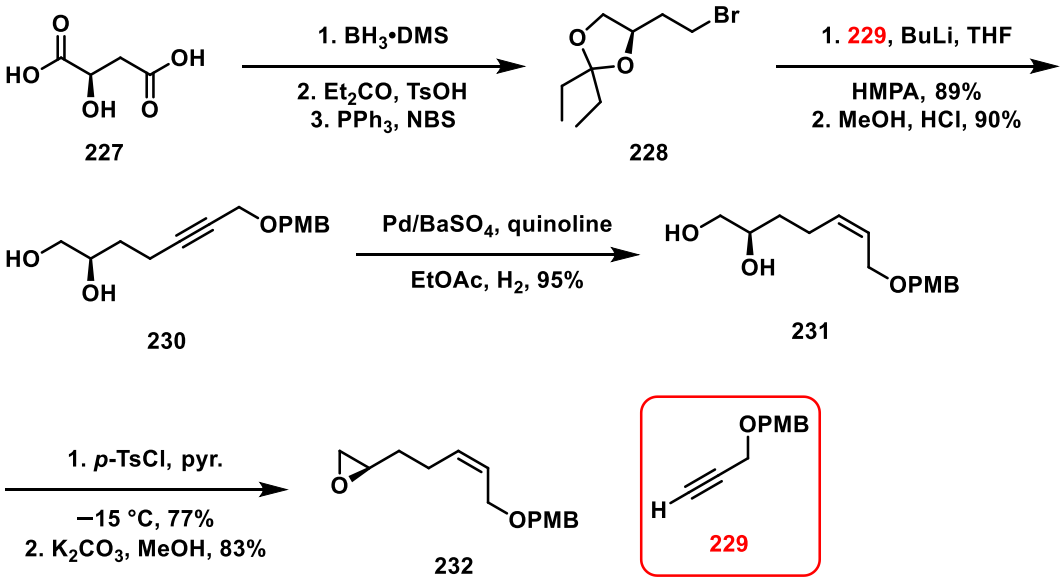
The primary route developed by the group for the synthesis of the C-10 to C-25 fragment of the natural product commenced with the enantioselective synthesis of the dithiane **226**. This was achieved by performing an asymmetric Brown crotylation reaction on the aldehyde **223**, with a subsequent TBS protection to

afford (*S*,*S*)-alkene **225** (**Scheme 41**).[70] Hydroboration of the alkene, followed by Swern oxidation, and dithiane formation gave desired dithiane **226** with high *ee*.



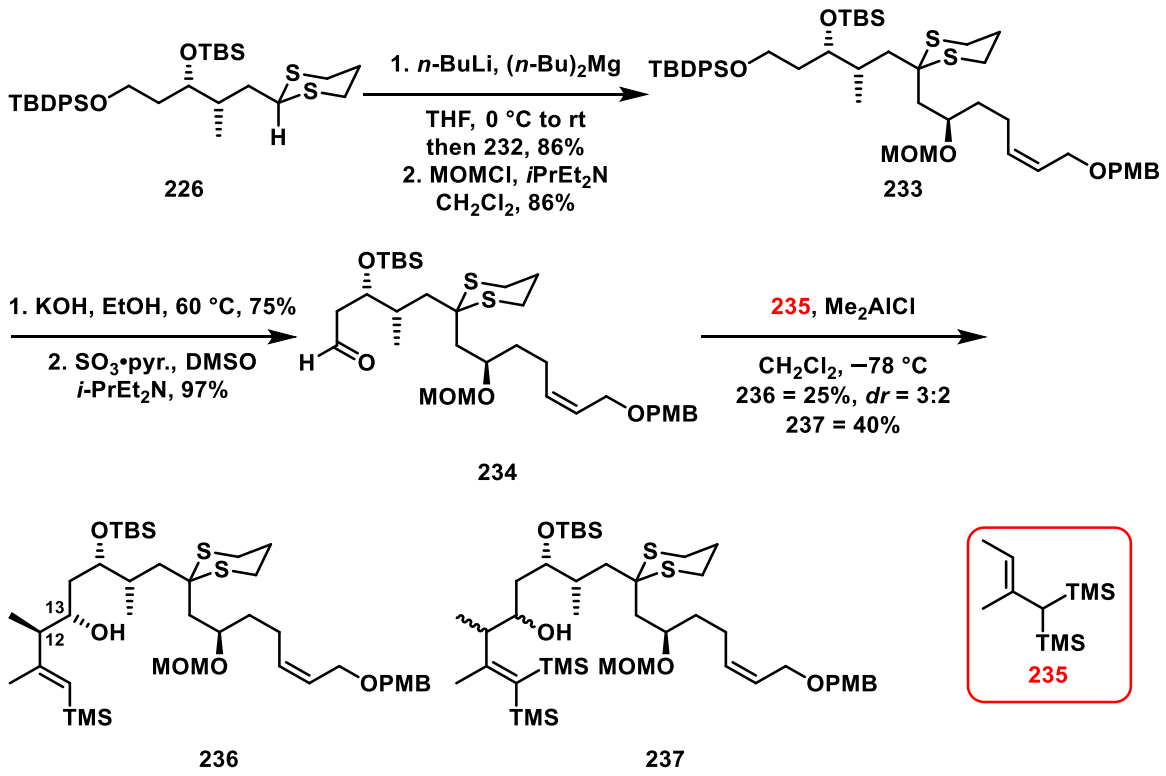
Scheme 41. Synthesis of Chiral Dithiane 226

The epoxide required as a coupling partner for the dithiane **226** was synthesised from D-malic acid (**227**). D-Malic acid was reduced to the triol and the 1,2-diol which was protected as a ketal (**Scheme 42**). The remaining primary hydroxyl group was then converted into the corresponding bromide **228**. Lithiated alkyne **229** was used to displace the bromide and complete the carbon framework. The ketal was hydrolysed to produce the 1,2-diol **230**, the alkyne was partially reduced using Lindlar's catalyst to give the *Z*-alkene **231**. Formation of the epoxide **232** was accomplished by conversion of the primary alcohol into the tosylate, which was then displaced by the secondary alcohol in a 3-*exo*-*tet* cyclisation reaction.



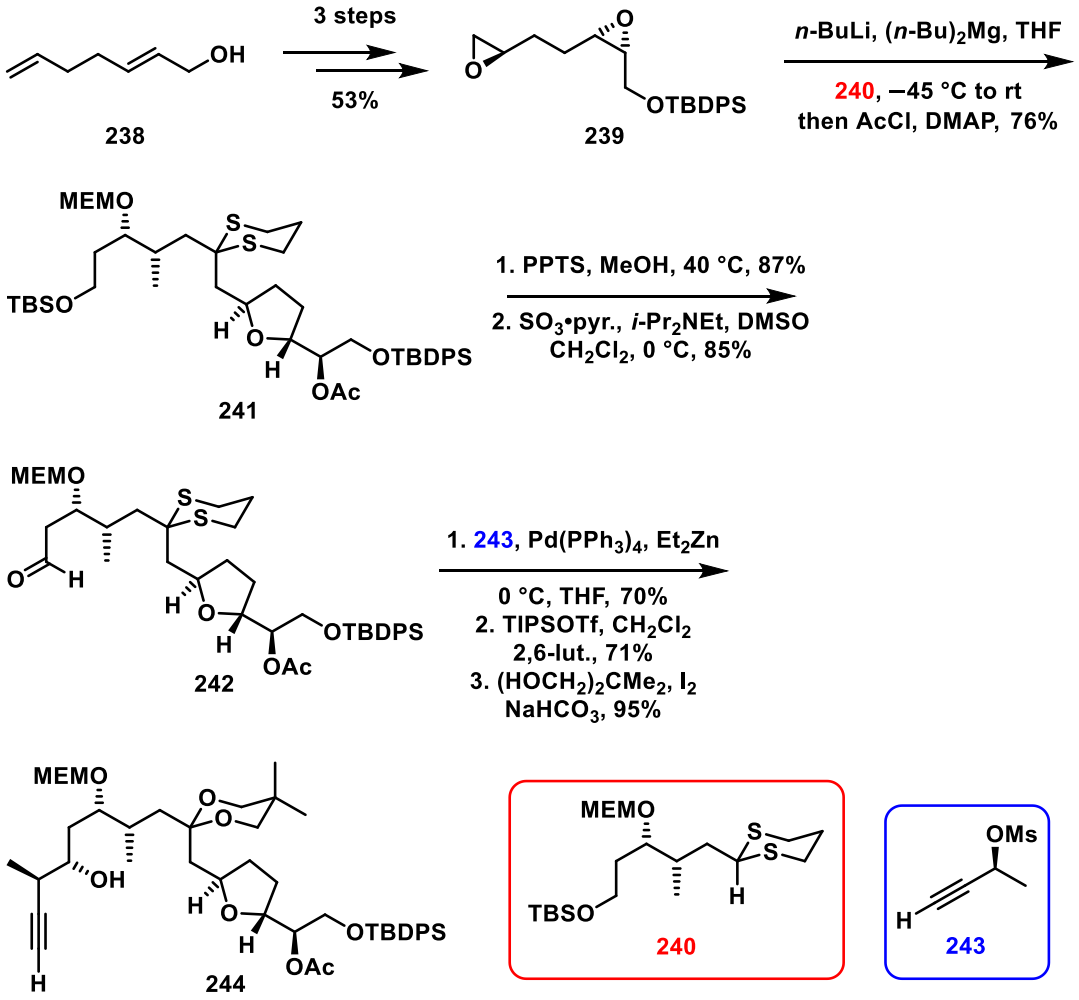
Scheme 42. Synthesis of Epoxide 232 for Dithiane Alkylation

Dithiane **226** was deprotonated using *n*-BuLi and (*n*-Bu)$_2$Mg, a combination of bases reported by Ide and Nakata that results in reduced decomposition of the substrate when compared to the outcome using alternative strong bases.[71] The resulting anion was then used to open epoxide **232** (**Scheme 43**). After protection of the resulting secondary hydroxyl group as a MOM ether, the fully protected fragment **233** was obtained. The primary TBDPS group was removed and the resulting alcohol oxidised to give the corresponding aldehyde (**234**). The group then completed the C-10 to C-25 fragment of the natural product by attempting a Lewis acid-catalysed S_E' reaction with 1,1-bis-silylated alkene **235**. However, this reaction did not proceed smoothly and produced a mixture of mono-silylated alkenes, with a *dr* = 3:2 in favour of the required *E*-alkene (**236**), which comprised 25% of the product mixture, along with bis-silylated alkene **237**, which accounted for a further 40% of the material. As a result of this unsatisfactory product mixture, an alternative route to the fragment was devised.



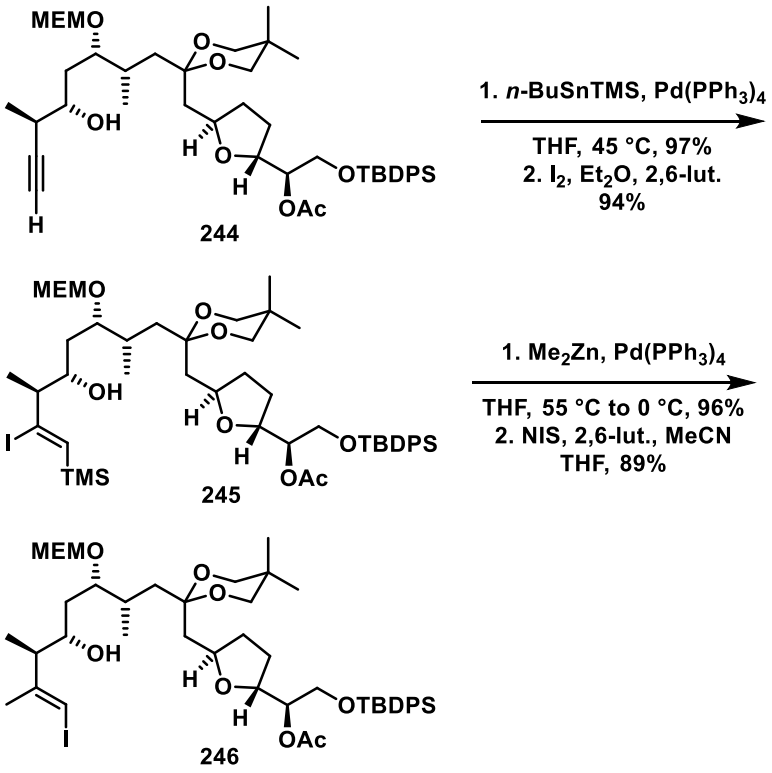
Scheme 43. Initial Coupling of the Dithiane and the Epoxide

The second route started from 1,5-diene **238**, which was converted into the bis-epoxide **239** in three steps (**Scheme 44**). The terminal epoxide was opened with lithiated dithiane **240**, which is analogous to **226**. However, the choice of functionality in dithiane **240** meant that the alkoxide, generated by opening of the first epoxide, then attacked the second epoxide in a 5-*exo*-*tet* reaction to produce the 2,5-*trans* THF. Quenching of the reaction with AcCl produced the acetate **241**. The primary TBS group was removed under acidic conditions and the resulting alcohol was oxidised to give the aldehyde **242**. A Marshall propargylation reaction was then used to install carbons C-10 to C-12 of the natural product and the ketal **244** was obtained after manipulation of the protecting group.[72]



Scheme 44. Alternative Synthesis of the THF Ring

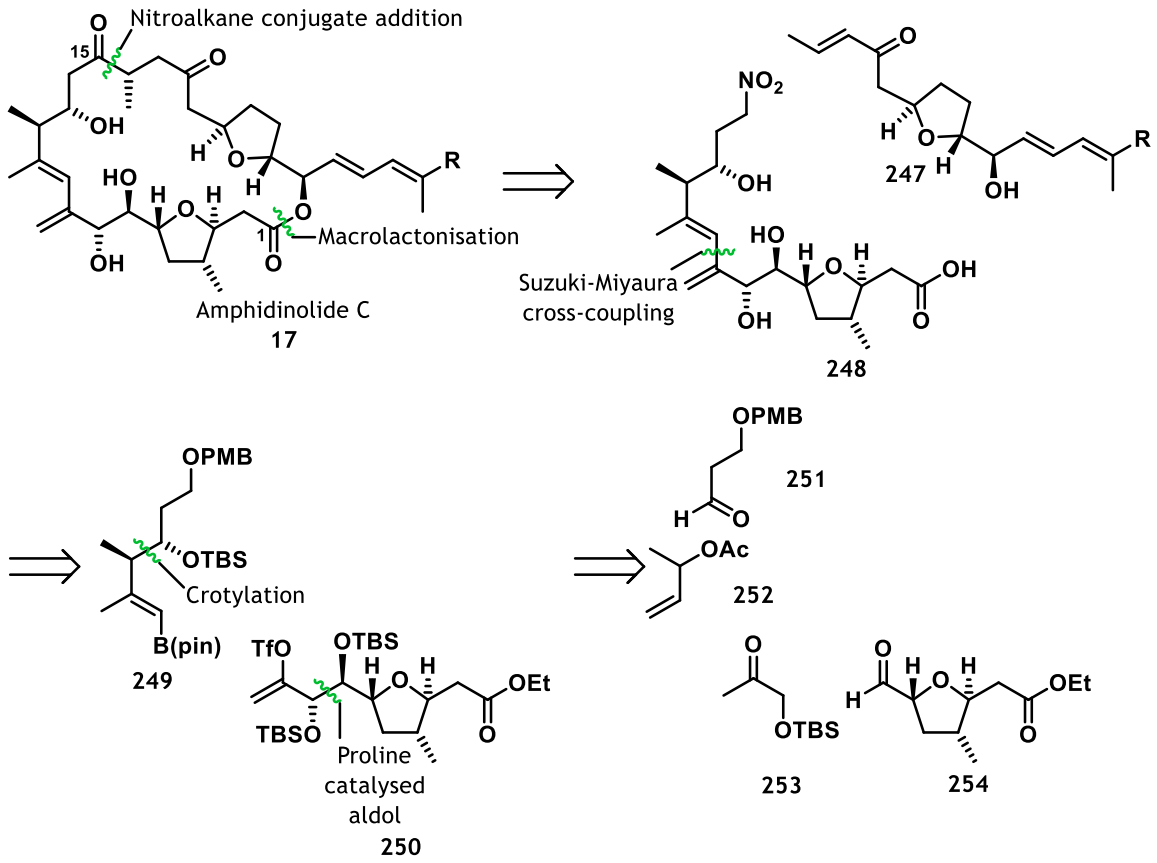
Alkyne **244** underwent a palladium-catalysed *syn*-silylstannation reaction to give a vinylic stannane, which was converted into the vinylic iodide **245** by reaction with I_2 (**Scheme 45**). A Negishi cross coupling reaction was then used to install the methyl group.[73] To complete the C-10 to C-25 fragment, the TMS group was replaced with iodine to give the complete the C-10 to C-25 fragment **246**. The vinylic iodide would serve as a versatile functional handle to couple this fragment to the C-1 to C-9 fragment of the natural product or to various sp^2-sp^2 coupling partners to give unnatural congeners of the natural product.



Scheme 45. Completion of the C-10 to C-25 Fragment of the Natural Product

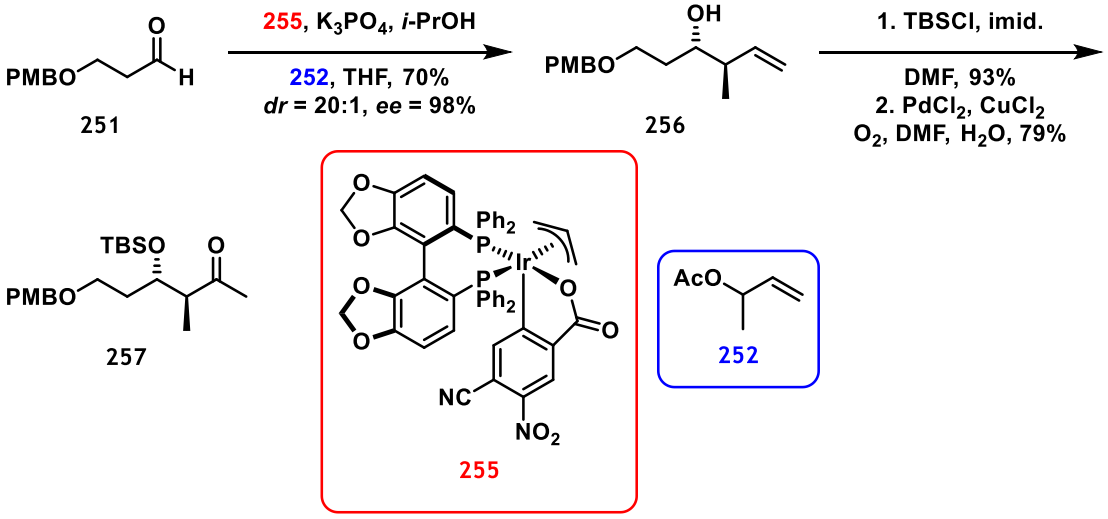
2.1.8 Morken: Boron-based Wittig Reaction and Suzuki-Miyaura Cross Coupling Reaction

Morken and co-workers reported a synthesis for the C-1 to C-15 fragment of amphidinolide C and F in 2020. The retrosynthetic analysis of Morken involved disconnection of the natural product to give a northern fragment **247** and southern fragment **248** which suggests the use of macrolactonisation and nitroalkane conjugate addition reactions in the forward direction (**Scheme 46**). Disconnection of the southern fragment into a vinylic boronate **249** and vinylic triflate **250** suggests the use of Suzuki-Miyaura cross coupling reaction for bond formation.



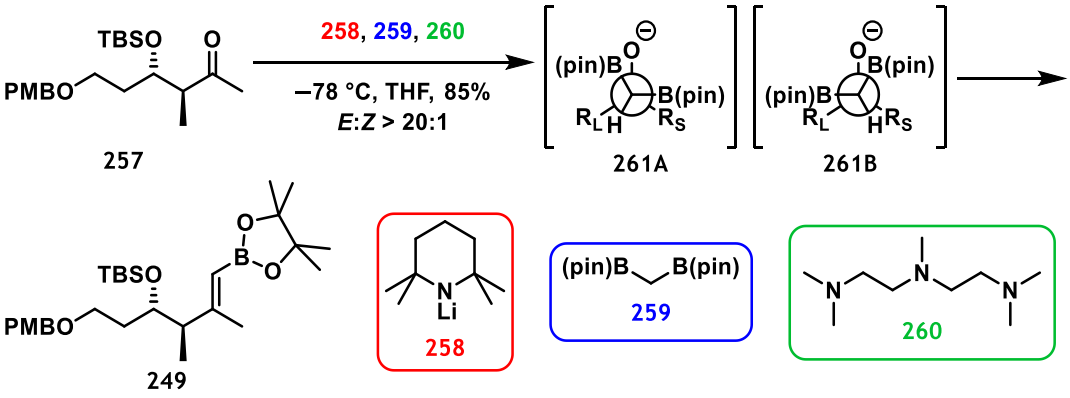
Scheme 46. Morkens' Retrosynthetic Analysis

The synthesis of vinylic boronate **249** commenced with Krische *anti*-crotylation reaction of aldehyde **251** to give chiral alcohol **256** in 70% yield with a *dr* = 20:1 and an *ee* = 98% (**Scheme 47**). Protection of the hydroxyl group as a TBS ether was followed by Wacker oxidation of the terminal alkene to give the methyl ketone **257**.



Scheme 47. Kirsche Anti-Crotylation Introduces Stereocentres

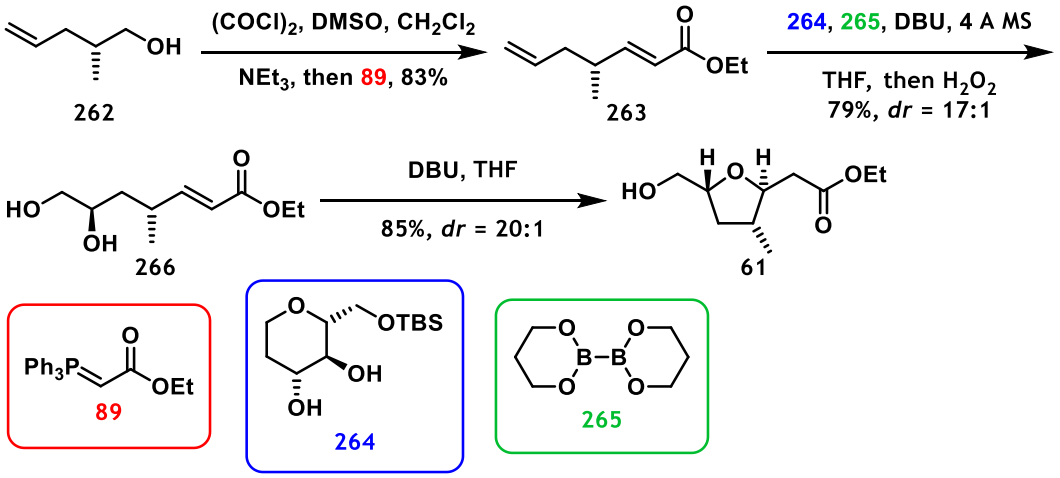
Finally, a boron-Wittig reaction was performed on the ketone **257** to give the required *E*-vinylic boronate **249** in 85% yield (**Scheme 48**). The selectivity of this reaction can be explained by considering the steric interactions arising from transition states **261A** and **261B** where R_L represents the bulkier substituent of the ketone. Favouring the transition state which minimises the steric interaction between the B(pin) group and the bulkier substituent (R_L) of the ketone resulting in the formation of the required boronate **249**.



Scheme 48. Synthesis of Vinylic Boronate 249

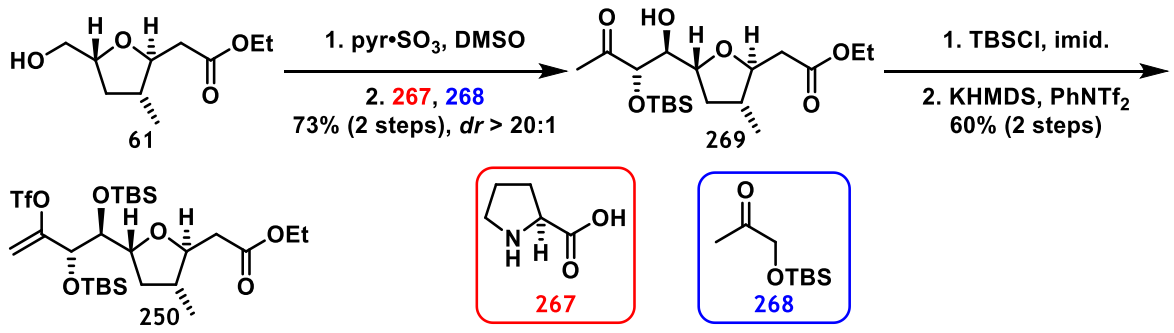
The synthesis of vinylic triflate **250** began from the known alcohol **262** (**Scheme 49**). Oxidation of the alcohol to the aldehyde was accomplished under Swern conditions and the resulting aldehyde was subjected to a Wittig olefination reaction utilising the stabilised ylide **89** to give *E*-alkene **263**. Diastereoselective diboration of the terminal double bond was effected using the D-glucal-derived catalyst **264** alongside propanediol diboron **265**; subsequent oxidation with

hydrogen peroxide delivered the diol **266** in 79% yield with a *dr* = 17:1. Use of an approach similar to that employed by Roush and co-workers resulted in intramolecular Michael reaction to form the *trans*-THF **61** in 85% yield with a *dr* = 20:1.



Scheme 49. Synthesis of the C-1 to C-7 Fragment of Amphidinolide C

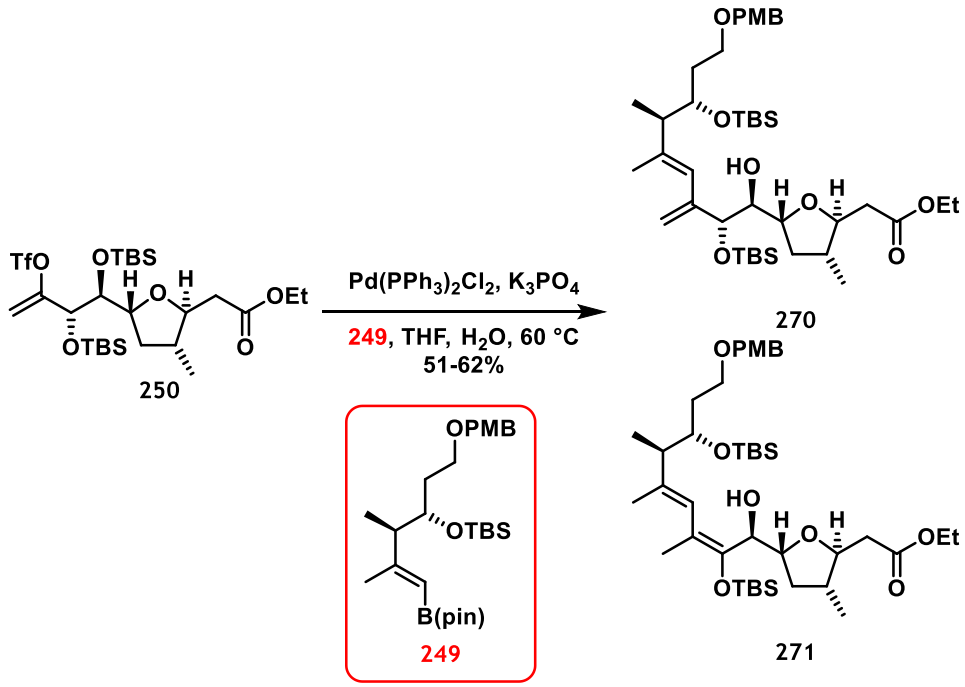
Parikh-Doering oxidation of the hydroxyl group gave an unstable aldehyde which was immediately subjected to an L-proline (**267**) catalysed aldol reaction with 22 equivalents of TBS protected α-ketol **268** to give the required *S*-alcohol **269** in 73% yield with a dr > 20:1 (**Scheme 50**). The hydroxyl group was protected as the TBS ether and the ketone was transformed into the vinylic triflate **250**, using KHMDS and bis(trifluoromethanesulfonyl)aniline, in 60% yield over two steps.



Scheme 50. Synthesis of Vinylic Triflate 250

To complete the C-1 to C-15 fragment of amphidinolide C1, vinylic triflate **250** was used in a Suzuki-Miyaura cross coupling reaction (**Scheme 51**). Careful choice of base was required to avoid protodeboronation of the vinylic borane **249**. Furthermore, to avoid isomerisation of the terminal alkene to give the tri-

substituted isomer **271**, the reaction necessitated the exclusion of light. The cross coupling reaction proceeded best using $Pd(dppf)Cl_2$, with K_3PO_4, to give the required diene **270**, with loss of the C-7 hydroxyl protecting group, in up to 62% yield. Overall, the C-1 to C-15 fragment was synthesised in 9 steps (longest linear sequence) with an overall yield of 15% from chiral alcohol **262**.

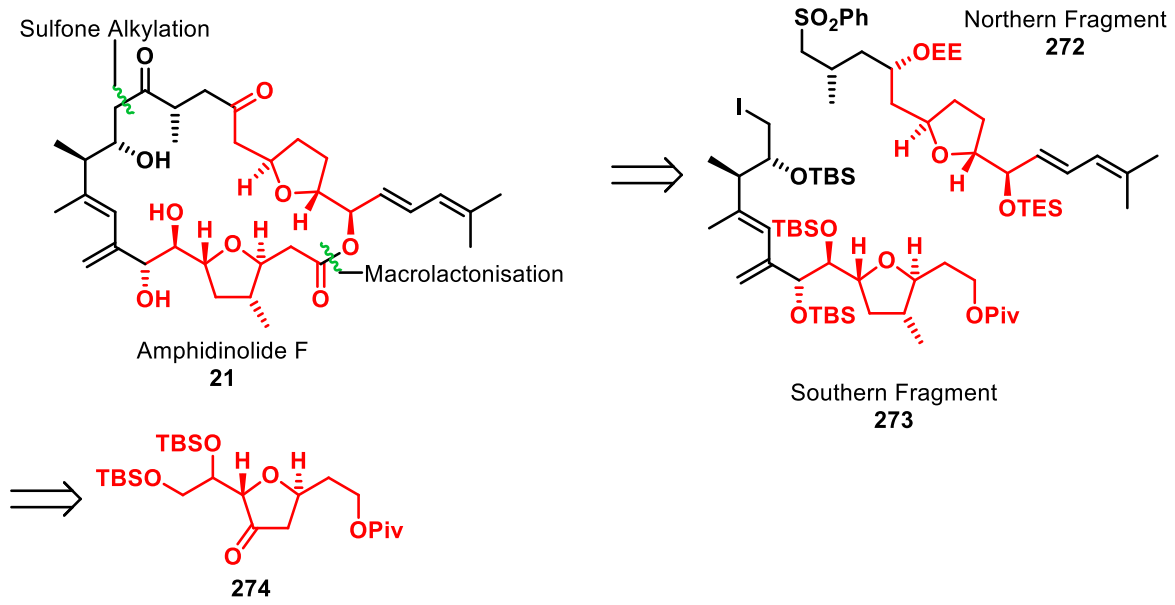


Scheme 51. Suzuki-Miyaura Cross Coupling to Complete the C-1 to C-15 Fragment of Amphidinolide C, C2, C3, and F

2.2 Total Synthesis of Amphidinolides C and F

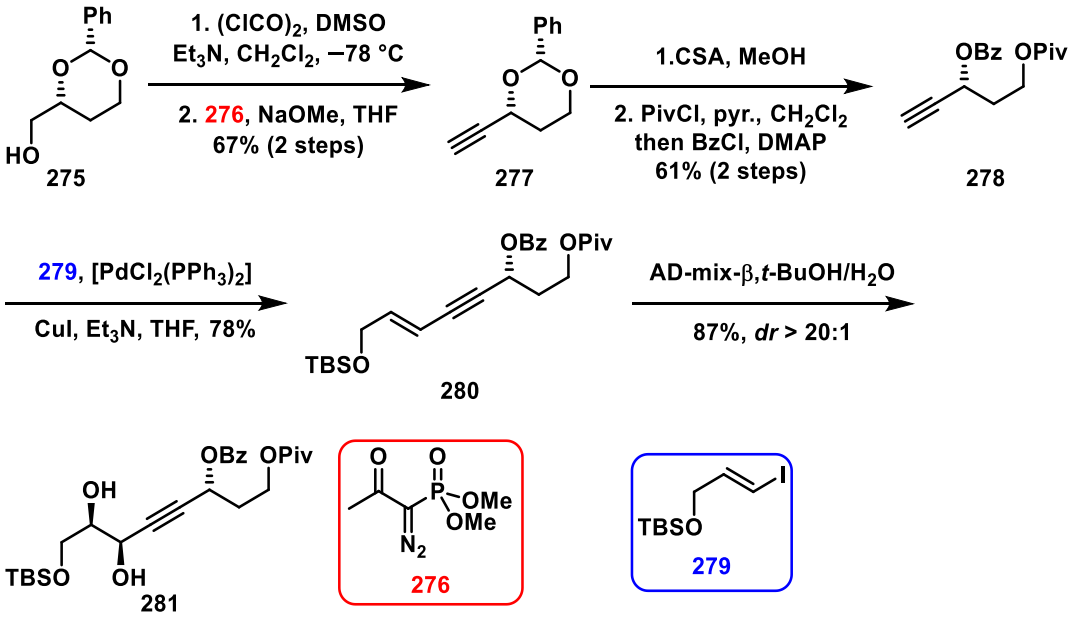
2.2.1 Carter: Silver-Catalysed Cyclisation Approach for Amphidinolides C and F

Carter and co-workers reported the first total synthesis of amphidinolide F in 2012. Their synthetic strategy took advantage of the hidden symmetry present in the natural product (**Scheme 52**).[26] In his retrosynthesis, Carter broke the natural product into a northern fragment (**272**) and a southern fragment (**273**), which both originate from a common 2,5-*trans* dihydrofuranone intermediate (**274**). The fragments were to be coupled *via* a sulfone alkylation reaction and the macrocycle was to be completed by macrolactonisation.



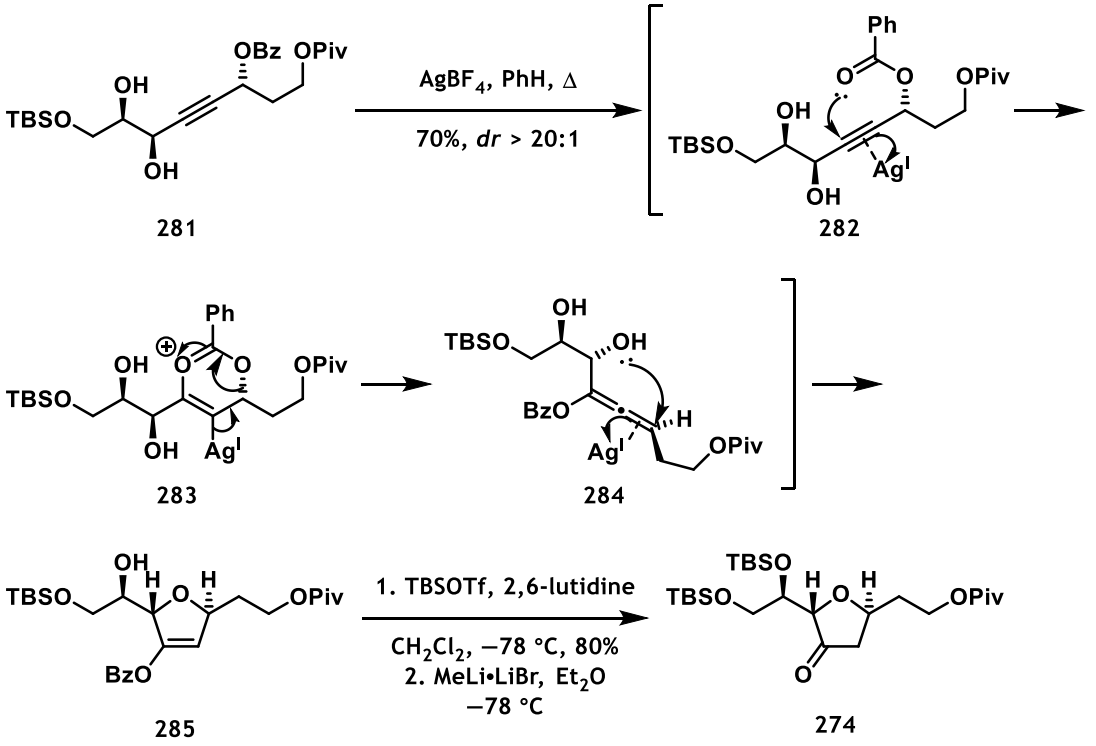
Scheme 52. Retrosynthesis of Amphidinolde F Exploiting Hidden Symmetry

The common 2,5-*trans* dihydrofunanone fragment (**274**) was accessed from D-malic acid. The known alcohol **275** was prepared from D-malic acid in two steps and Swern oxidation followed by a Seyferth-Gilbert homologation reaction using the Ohira-Bestmann reagent (**276**) gave alkyne **277** in 67% yield over two steps (**Scheme 53**).[74] Subsequent protecting group manipulation gave the differentially diprotected acyclic 1,3-diol **278**. Alkyne **278** was then used in a Sonogashira cross coupling reaction with vinylic iodide **279** to give the enyne **280** in 78% yield.[75] Sharpless asymmetric dihydroxylation of the alkene, using AD-mix-β, produced the diol **281** in 87% yield with a *dr* > 20:1.



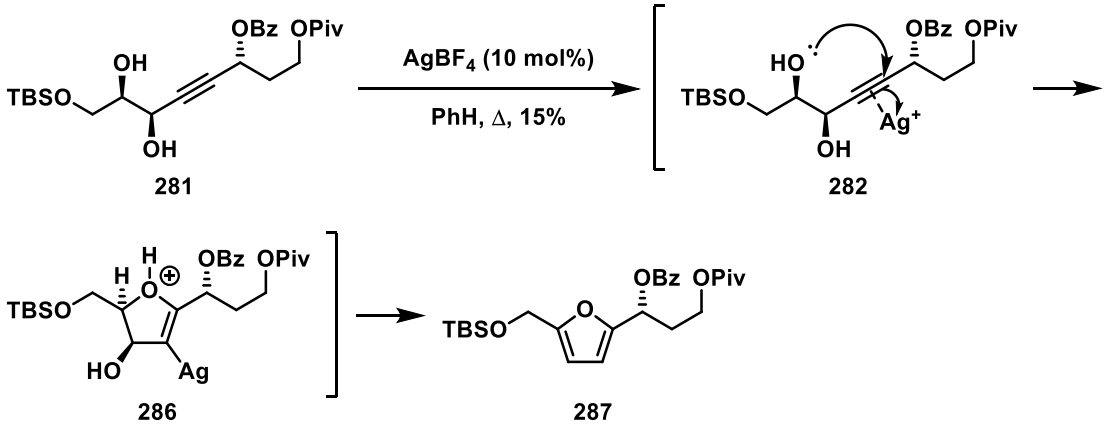
Scheme 53. Synthesis of the Cyclisation Precursor

The diol **281** was then used in a silver(I)-catalysed cyclisation to form the common 2,5-*trans* 2,5-dihydrofuran. In this reaction, the silver(I) catalyst first activates the alkyne (**281**) by π-complexation, allowing migration of the benzoate ester to form the allene **284** (**Scheme 54**).[29] Activation of the allene, by coordination of the silver(I) catalyst, promotes 5-*endo*-*trig* cyclisation and upon work-up the dihydrofuran **285** was obtained. Finally, protecting group manipulation afforded the 2,5-*trans* dihydrofuranone fragment **274** in 70% yield.



Scheme 54. Completion of the Common 2,5-trans Dihydrofuranone Intermediate

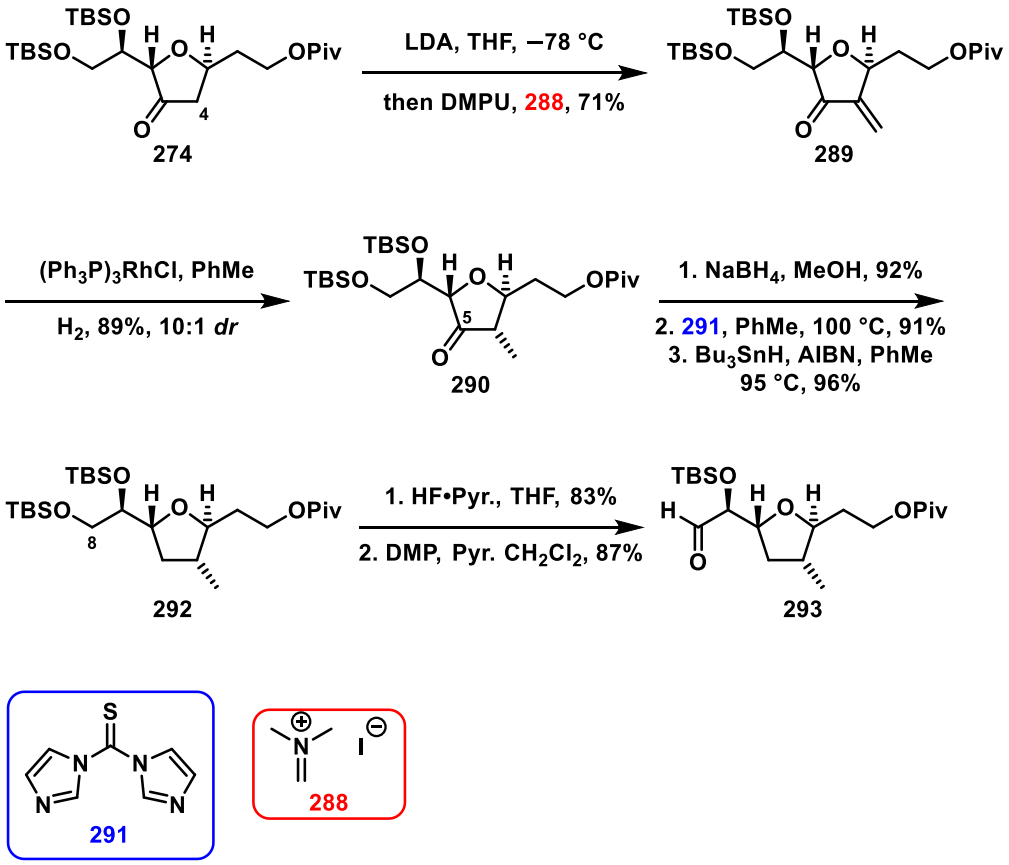
The furan by-product **287** was obtained alongside the dihydrofuranone **274** during the silver-mediated cyclisation reaction.[29] It was proposed that, once the silver(I) catalyst activates the alkyne **281**, direct attack of the homo-propargylic alcohol competes with the desired migration reaction to give alkenyl silver intermediate **286** (**Scheme 55**). Proto-demetallation, followed by acid catalysed dehydration, results in the observed furan by-product **287**.



Scheme 55. Mechanism Explaining the Formation of a Furan By-product

From this point the synthesis of the routes to the two fragments diverged. For the southern fragment, a methylene group was first introduced into the C-4 position

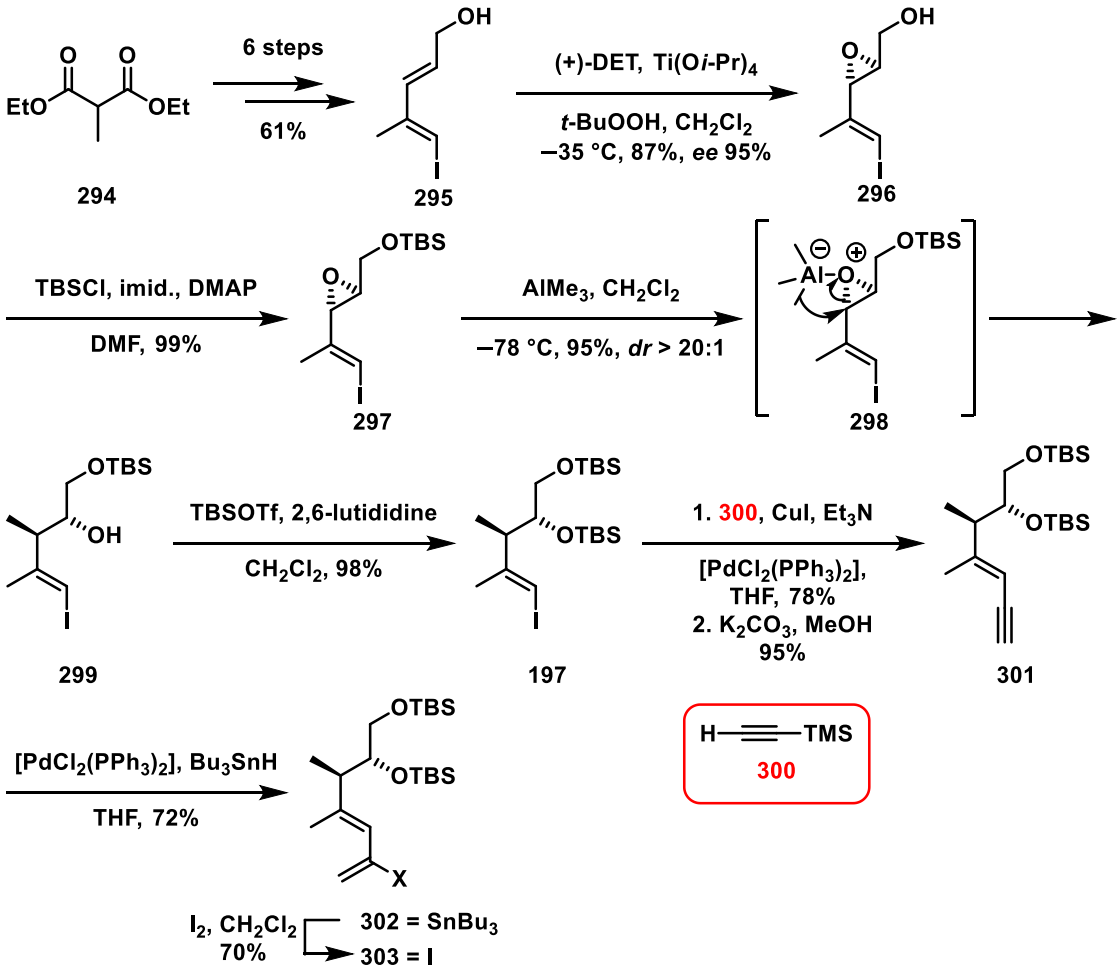
by alkylation with Eschenmoser's salt (**288**) and subsequent elimination (**Scheme 56**).[76] This methylene group was reduced stereoselectively (*dr* = 10:1) to give the required methyl substituent with the desired (*S*)-configuration at the methyl-bearing stereogenic centre using Wilkinson's catalyst; the required product (**290**) was obtained in a 63% yield over two steps. The ketone was then reduced with $NaBH_4$ to give the corresponding alcohol. The hydroxyl group was then excised using the Barton-McCombie deoxygenation procedure to give the 2,5-*trans* fused tetrahydrofuran (**292**) in 80% yield over three steps. The primary *tert*-butyl dimethyl silyl (TBS) group at the C-8 position was first removed and the resulting alcohol was oxidised to give the corresponding aldehyde (**293**) using DMP.



Scheme 56. Completion of the C-1 to C-8 Fragment

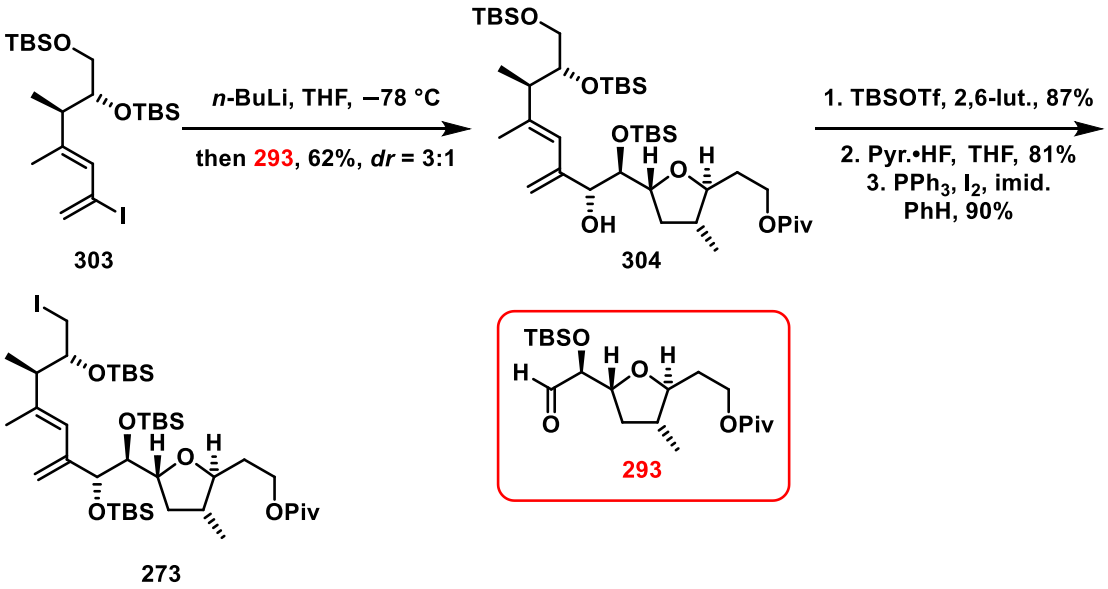
To complete the southern fragment of amphidinolide F it was necessary to couple the previously discussed 2,5-*trans* tetrahydrofuran **293** to the C-9 to C-14 fragment (**303**). The latter fragment was synthesised in thirteen steps starting from diethyl methylmalonate (**294**) (**Scheme 57**) The allylic alcohol **295**, synthesised from diethyl methylmalonate in six steps by following a known procedure, was subjected to Sharpless asymmetric epoxidation with

(+)-diethyl tartrate (DET) to give the required epoxide **296**.[77,78] The primary hydroxyl group of epoxide **296** was then TBS-protected and the epoxide was opened using Me_3Al giving the secondary alcohol **299** in 95% yield and with a *dr* > 20:1. Temperature control was found to be critical in this reaction: an increase in temperature (−78 °C to −50 °C) resulted in significant erosion of diastereoselectivity, giving a *dr* = 7:2. After protection of the secondary hydroxyl group of **299** as the corresponding TBS ether, a Sonogashira cross coupling reaction with TMS-acetylene (**300**) was performed to give the corresponding TMS-alkyne in 78% yield. Treatment of the TMS-alkyne with K_2CO_3 in MeOH gave enyne **301** in 95% yield and subsequent regioselective palladium-catalysed hydrostannylation gave the vinylic stannane **302** in 72% yield. The final step to complete the C-9 to C-14 fragment of the natural product was conversion of vinylic stannane **302** into vinylic iodide **303** by treatment with I_2.



Scheme 57. Synthesis of the C-9 to C-14 Fragment

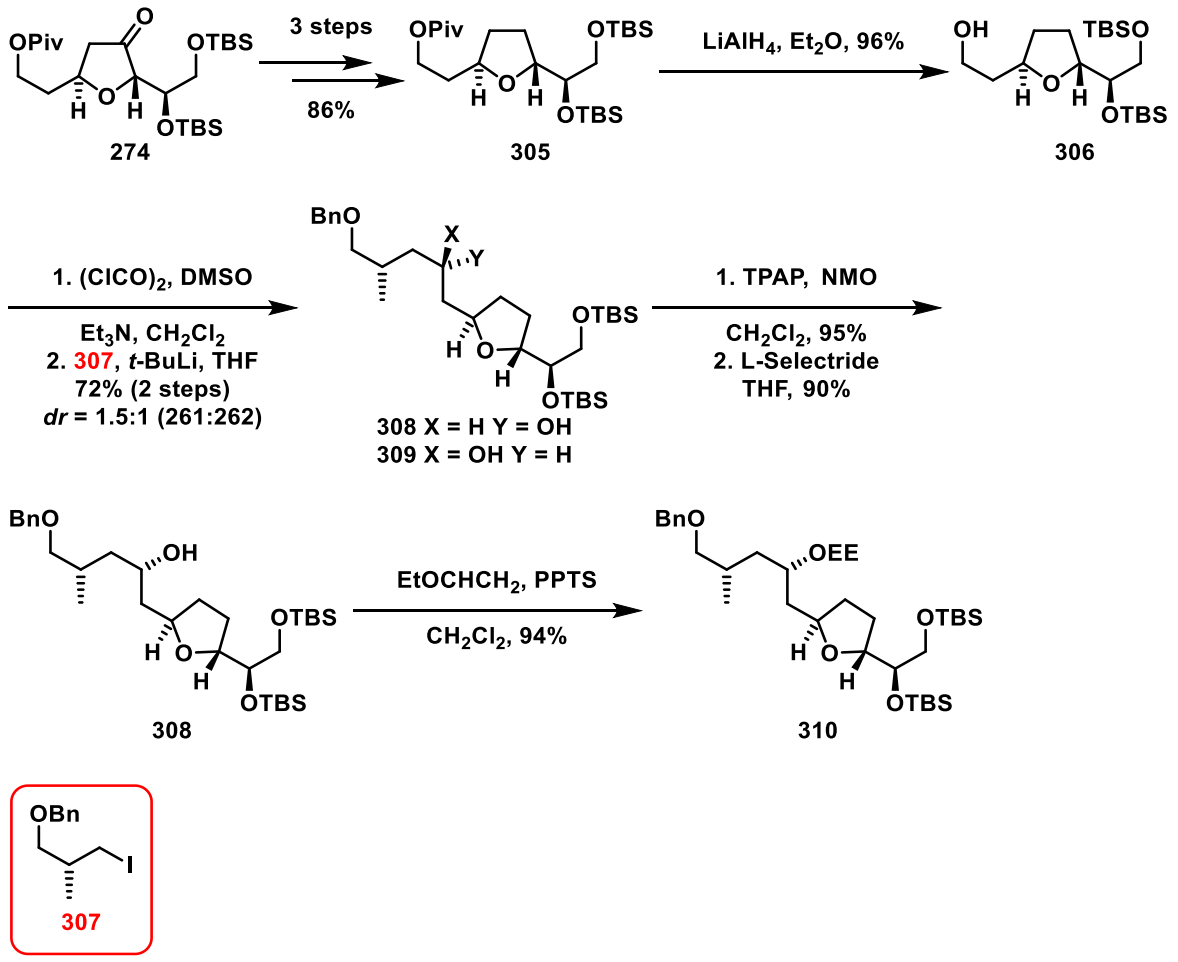
To synthesise the southern C-1 to C-14 fragment of the natural product it was necessary to couple vinylic iodide **303** to aldehyde **293**. This was achieved by treatment of vinylic iodide **303** with *n*-BuLi to form the corresponding vinyl lithium species and then reaction with aldehyde **293** (**Scheme 58**). This reaction resulted in formation of the desired C-1 to C-14 fragment **304** in 62% yield but the *dr* was modest (3:1). Carter and co-workers had concerns about a potential 1,3-metallotropic shift to give a lithiated allene species that would result in scrambling of the geometry of the C-10–C-11 double bond, but this reaction was not observed. The secondary alcohol was protected as a silyl ether before selective cleavage of the primary silyl ether. An Appel reaction was then employed to convert the intermediate primary alcohol into the alkyl iodide **273** in 90% yield and thereby complete the C-1 to C-14 fragment of the natural product.[79]



Scheme 58. Completion of the Southern Fragment

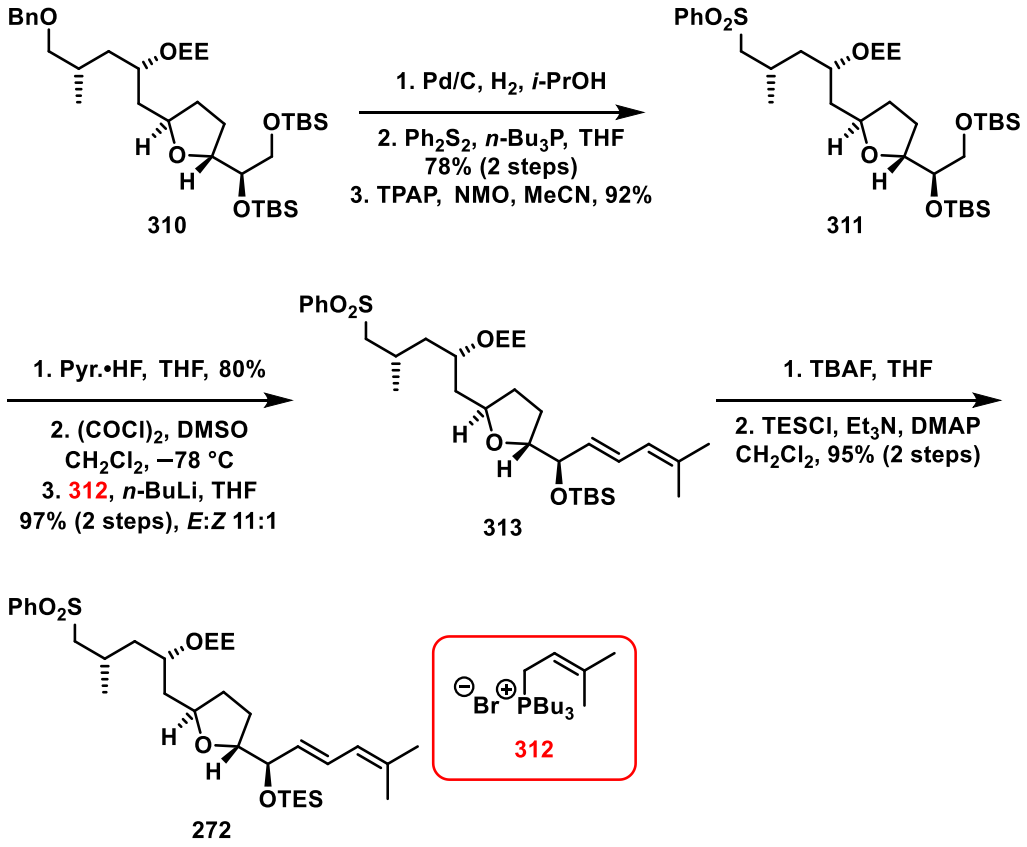
In order to synthesise the northern fragment from dihydrofuranone **274**, it was first necessary to remove the carbonyl functionality from the dihydrofuranone. As with the southern fragment (**Scheme 56**), tetrahydrofuran **305** was obtained in 86% yield by reduction of the ketone to the corresponding alcohol followed by Barton-McCombie deoxygenation (**Scheme 59**).[80] Following removal of the pivaloyl (Piv) group, alcohol **306** was subjected to Swern oxidation reaction and the resulting aldehyde was then coupled to the C-14 to C-17 unit using an organolithium reagent derived from vinylic iodide **307**. This reaction produced an inseparable diastereomeric mixture of the secondary alcohols **308** and **309**

(*dr* = 1.5:1). Initially, it was assumed that this mixture of alcohols could be oxidised to give the ketone which could then converted into the dimethyl ketal directly under Noyori conditions because this methodology had proven successful in model systems. However, attempts to accomplish ketalisation proved unfruitful and an alternative approach, using ethoxyethyl (EE) protected alcohols, was pursued. Although it was believed that both isomers would be viable going forward, Carter and co-workers choose to proceed with the major C-18-(*S*) isomer. A single isomer was employed in order to simplify the synthetic strategy and facilitate compound characterisation by NMR spectroscopy. In order to obtain *only* the (*S*) isomer, the C-18 isomer mixture was subjected to Ley-Griffith oxidation and the resulting ketone was reduced stereoselectively (*dr* = 15:1) with L-selectride® which gave C-18-(*S*) isomer **308** in 86% yield.[81] This alcohol was then converted into the corresponding EE protected alcohol **310**.



Scheme 59. Synthesis of the C-18 to C-25 Fragment

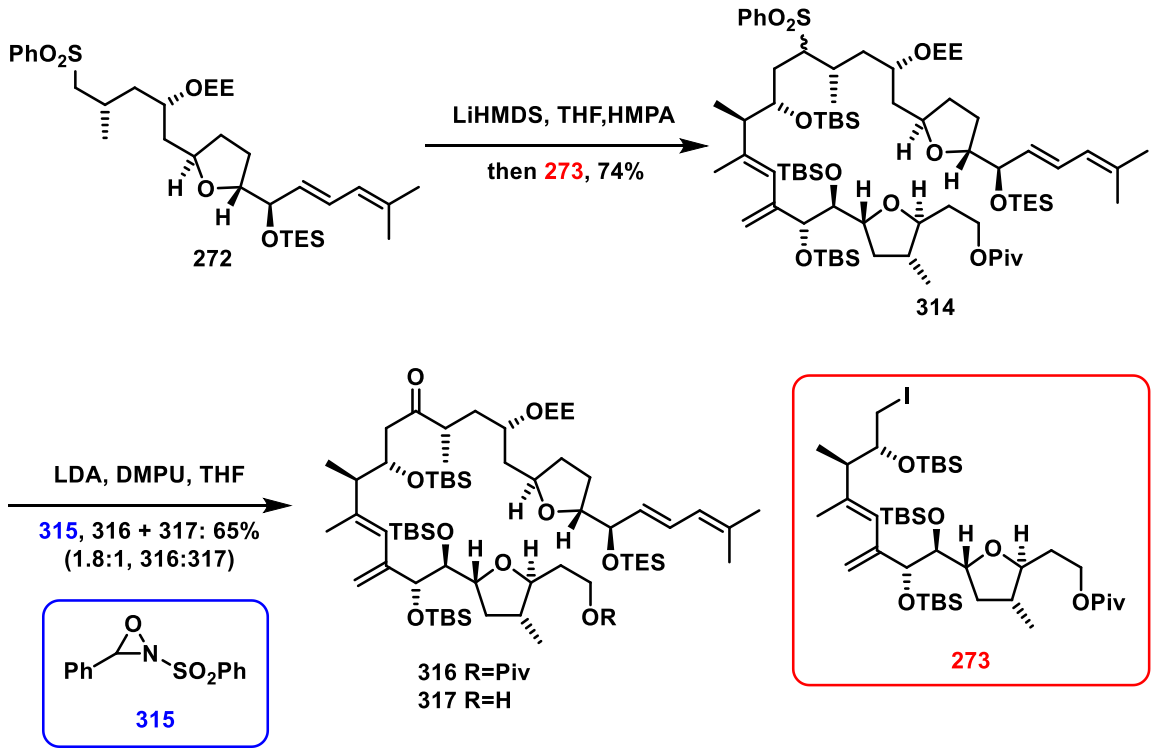
Benzyl ether **310** underwent palladium-catalysed hydrogenolysis to give the corresponding primary alcohol, which was converted into the phenyl sulphone **311** in two steps (**Scheme 60**). Following selective TBS deprotection to reveal the primary hydroxyl group, Swern oxidation was used to form an aldehyde, which was then subjected to Wittig olefination. In this case, a Vedejs-type tributyl phosphonium salt **312** was used to install the desired C-25 side chain in a stereoselective fashion and the 1,3-diene **313** was obtained in 97% yield with an isomer ratio of 11:1 (*E*:*Z*). To complete the northern C-15 to C-29 fragment the TBS protecting group was exchanged for a TES group and the sulfone **272** was formed. This would allow selective deprotection at this hydroxyl group to be accomplished without cleavage of the TBS ethers that would be present at a later stage in the synthesis.



Scheme 60. Completion of the Northern Fragment

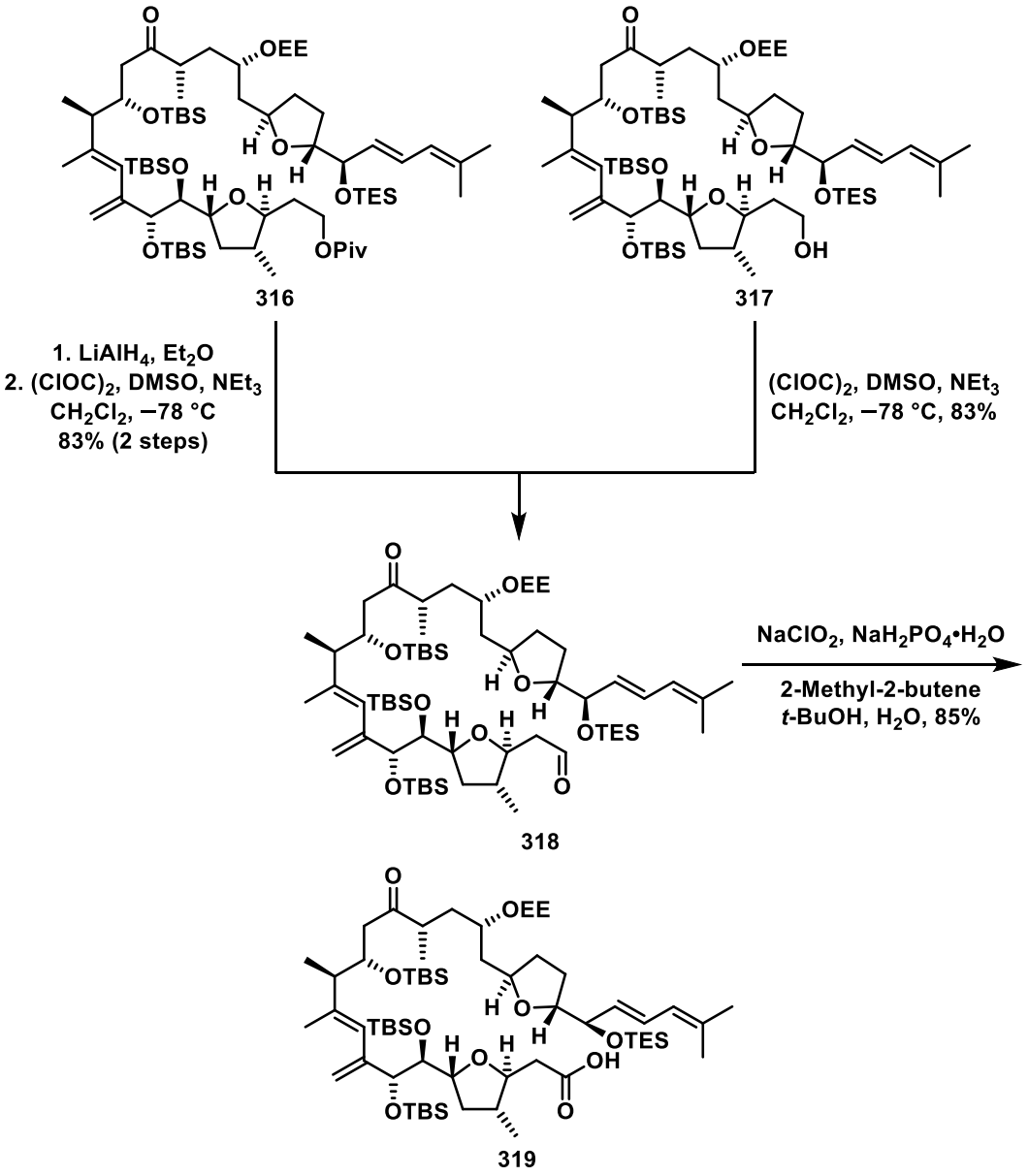
The northern and southern fragments were coupled by a standard alkylation reaction (**Scheme 61**). Deprotonation of the sulfone **272** with lithium bis(trimethylsilyl)amide (LHMDS) followed by addition of alkyl iodide **273** gave the bis-2,5-*trans* THF **314** in 74% yield and thereby completed the carbon framework

of the natural product. Oxidative desulfurisation was accomplished thereafter using lithium diisopropylamide (LDA) and the Davis oxaziridine (**315**).[82] These conditions also resulted in the concurrent partial removal of the Piv group to give the ketones **316** and **317** in a ratio of 1.8:1 and in a combined yield of 65%.



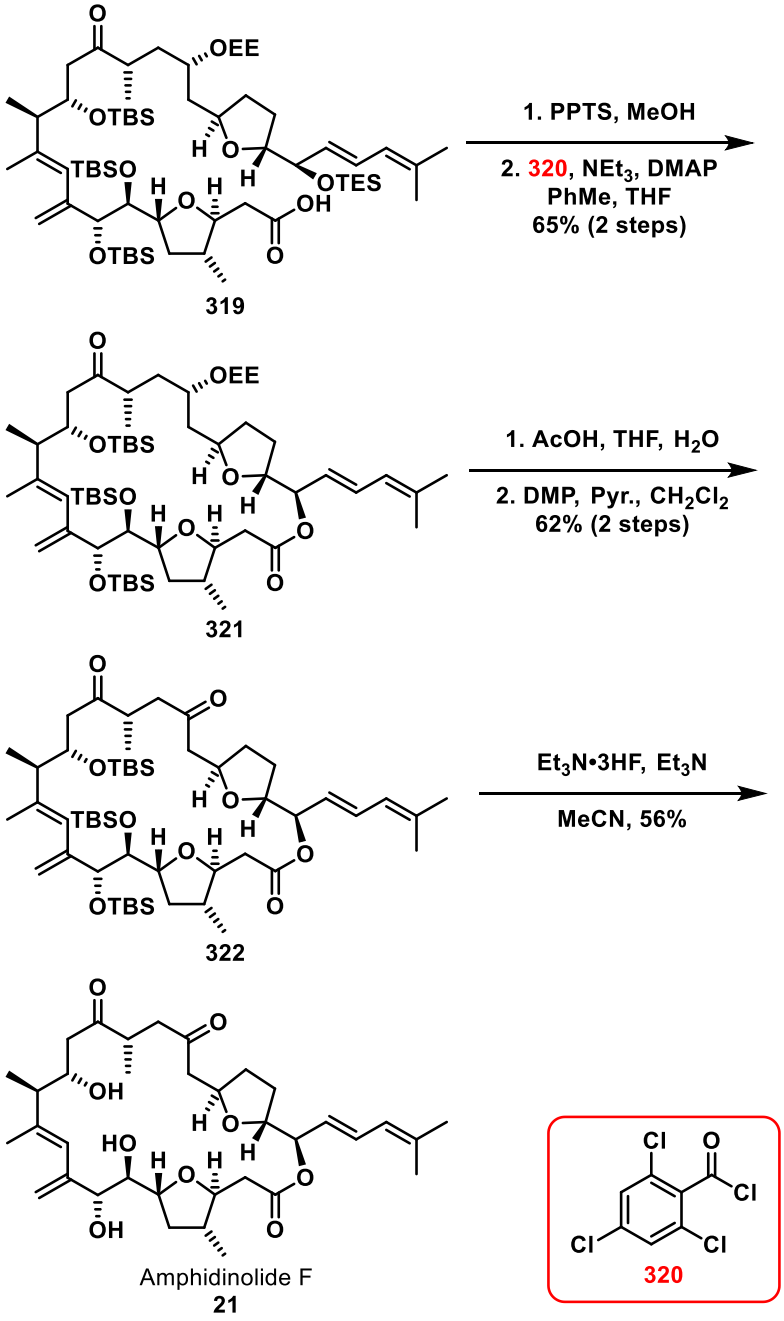
Scheme 61. Coupling of the Northern and Southern Fragments

The next steps involved conversion of the ketones **316** and **317** into the aldehyde **318** (**Scheme 62**). For alcohol **317**, Swern oxidation afforded aldehyde **318** directly. However, in the case of the Piv-protected alcohol **316** reductive removal of the Piv group was required before the Swern oxidation could be conducted to produce the aldehyde **318**. Pinnick oxidation of the aldehyde **318** then delivered the corresponding carboxylic acid **319**.[83]



Scheme 62. Synthesis of the Carboxylic Acid Lactonisation Precursor

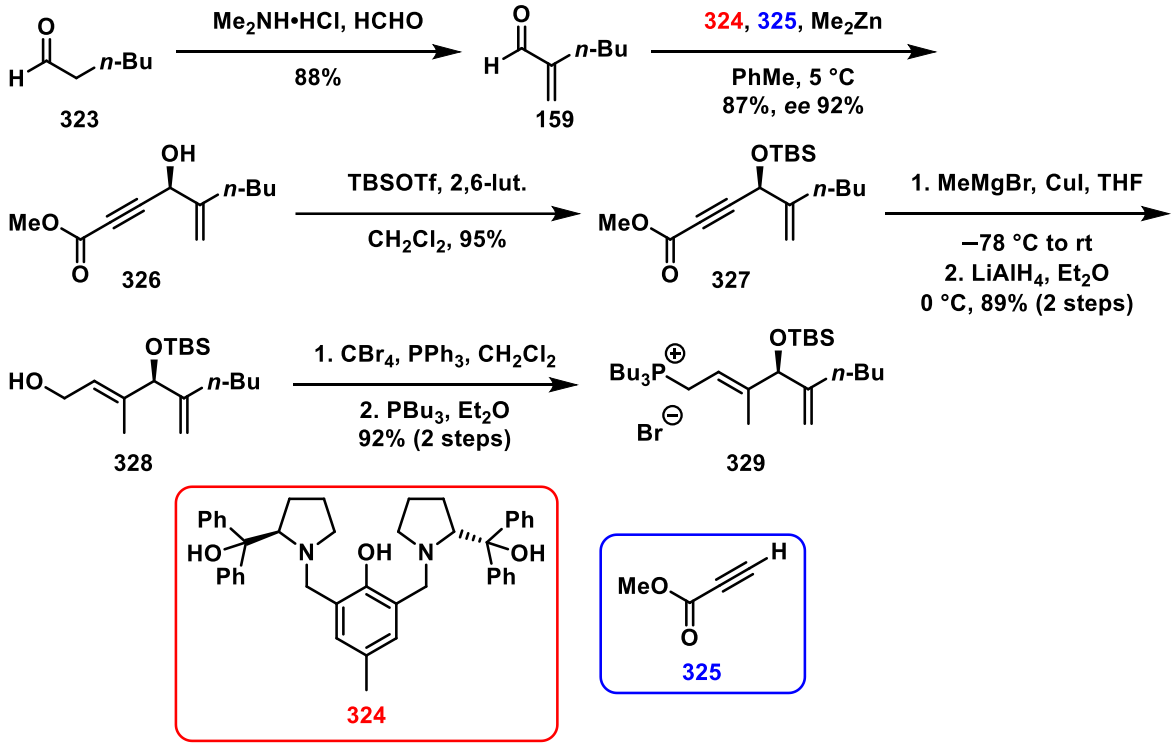
Subsequent acidic cleavage of the labile TES-ether of carboxylic acid **319** gave a seco-acid which was used in a Yamaguchi macrolactonisation reaction to afford macrolactone **321** (**Scheme 63**).[84] The EE group was then removed under acidic conditions, and the resulting alcohol was oxidised to give ketone **322** using DMP. Treatment of ketone **322** with $NEt_3 \cdot HF$ removed the remaining TBS groups and furnished amphidinolide F in a longest linear sequence of 36 steps and with an overall yield of 0.03%.



Scheme 63. Completion of Amphidinolide F

In 2013 the Carter group reported modifications to the route that allowed it to be used for the synthesis of amphidinolide C. The revised synthetic strategy required a modified Vedejs-type reagent **329** to install the more elaborate side chain. This reagent was synthesised from hexanal **323**, starting with an Eschenmoser methylenation reaction to give enal **159** (**Scheme 64**). A Trost asymmetric alkynation reaction using enal **159** gave (*S*)-alcohol **326** in 87% yield and with an *ee* of 92%. The resultant secondary alcohol (**326**) was TBS protected to furnish silyl ether **327**. Copper-mediated conjugate addition to the alkynoate with

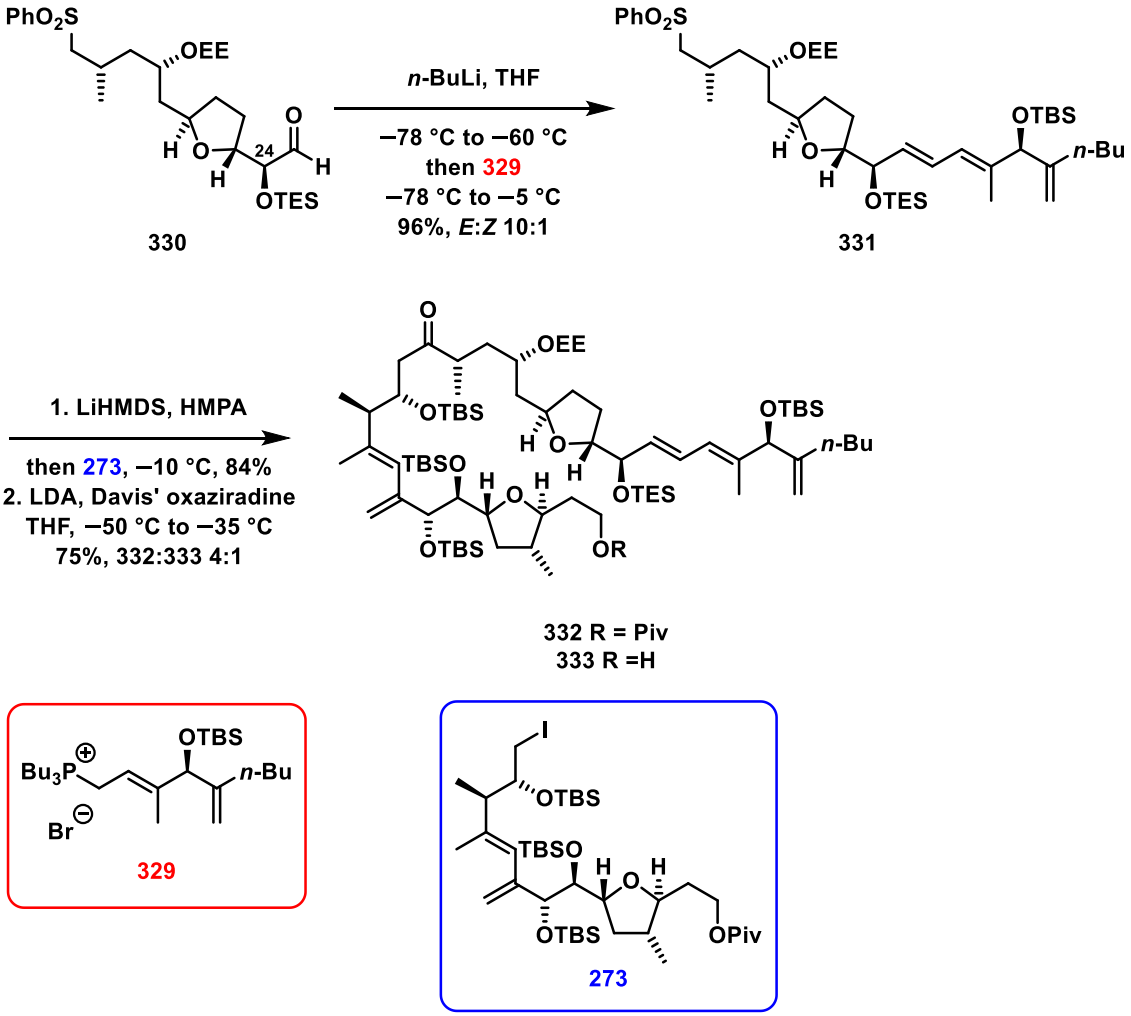
MeMgBr gave the desired *E*-alkene and subsequent reduction of the ester using $LiAlH_4$ yielded allylic alcohol **328**, which was then converted into the corresponding bromide using Appel conditions. The bromide was then displaced with PBu_3 to give the required Vedejs-type reagent (**329**) in a total of 7 steps and with an overall yield of 60%.



Scheme 64. Synthesis of the Amphidinolide C: C-29 Side Chain

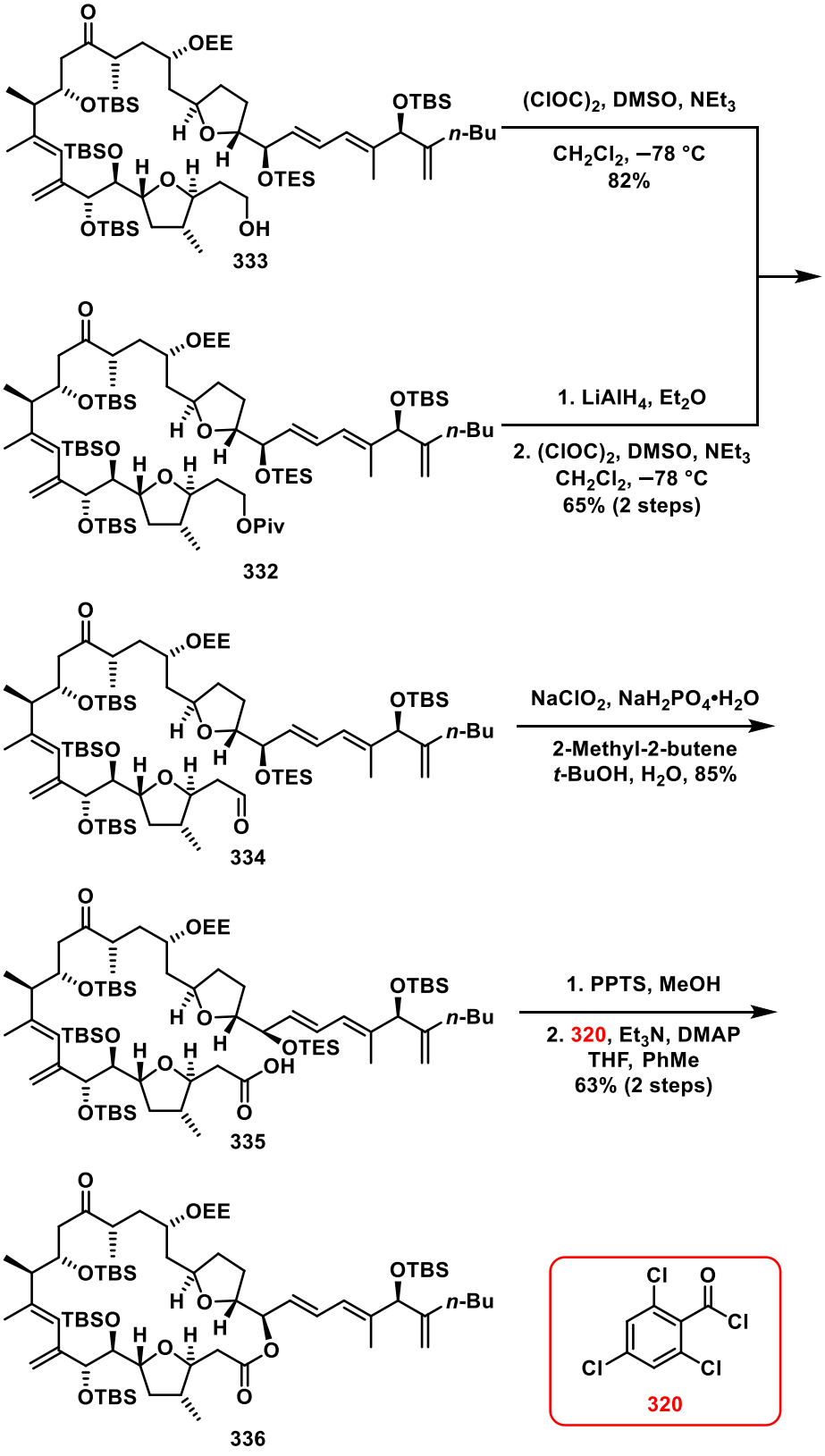
The use of previously described Wittig olefination conditions (**Scheme 60**) resulted in complete decomposition of the ylide. Fortunately, increasing the number of equivalents of the salt, from 1.5 equivalents to 2.2 equivalents, and reducing the reaction temperature, from −40 °C to −60 °C, minimised the effect of ylide decomposition such that the required 1,3,6-triene (**331**) was produced (96% yield) almost exclusively (**Scheme 65**). Formation of the 1,3,6-triene completed the northern fragment of amphidinolide C. However, it is worth noting that the inclusion of the TBS-silyl ether in the side chain meant that the protecting group strategy had to be revised. Consequently, the hydroxyl group at the C-24 position was masked as a TES-ether prior to the Wittig olefination. Lithiation of sulfone **331** followed by the addition of previously discussed alkyl iodide **273** resulted in smooth coupling of the northern and southern fragments in 84% yield. Oxidative

desulfurisation using LDA and Davis' oxaziridine gave a 4:1 mixture of ketones **332** and **333**.



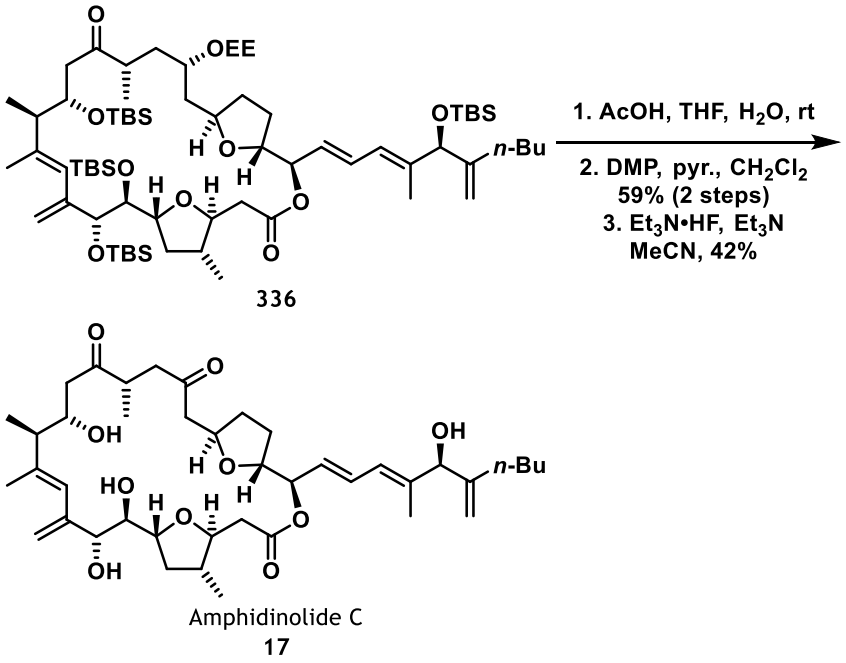
Scheme 65. Completion of the Carbon Framework of Amphidinolide C

Ketones **332** and **333** were converted into aldehyde **334** and Pinnick oxidation was employed to give the corresponding carboxylic acid (**335**) in 95% yield (**Scheme 66**). The TES-ether was cleaved using PPTS to afford a seco-acid and subsequent Yamaguchi macrolactonisation furnished the macrocycle **336** in 63% yield.[84]



Scheme 66. Synthesis of the Macrolactone Core of Amphidinolide C

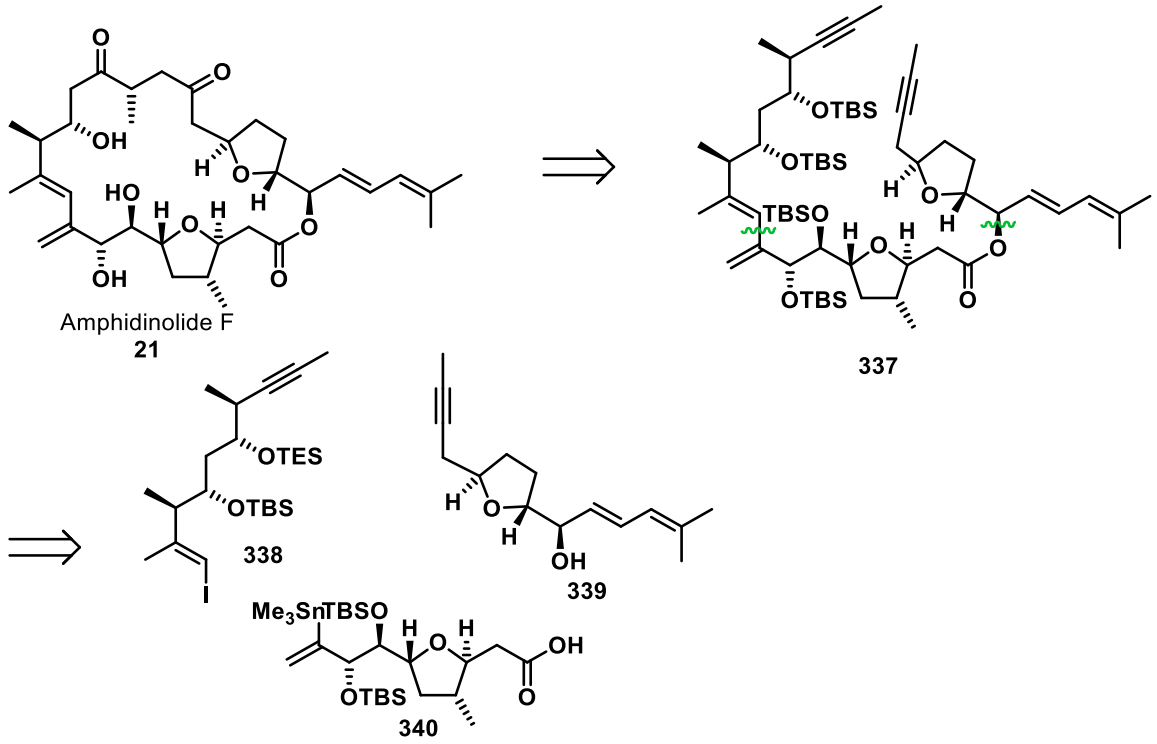
Treatment of the macrocycle **336** with acetic acid resulted in removal of the EE protecting group and the resultant alcohol was then oxidised to the ketone using DMP (**Scheme 67**). Finally, global deprotection by cleavage of the TBS ethers was accomplished using $Et_3N{\cdot}HF$ to afford amphidinolide C in 33 steps (longest linear sequence) and with a 0.2% overall yield.



Scheme 67. Completion of Amphidinolide C

2.2.2 Fürstner: Ring-Closing Alkyne Metathesis for Amphidinolides C and F

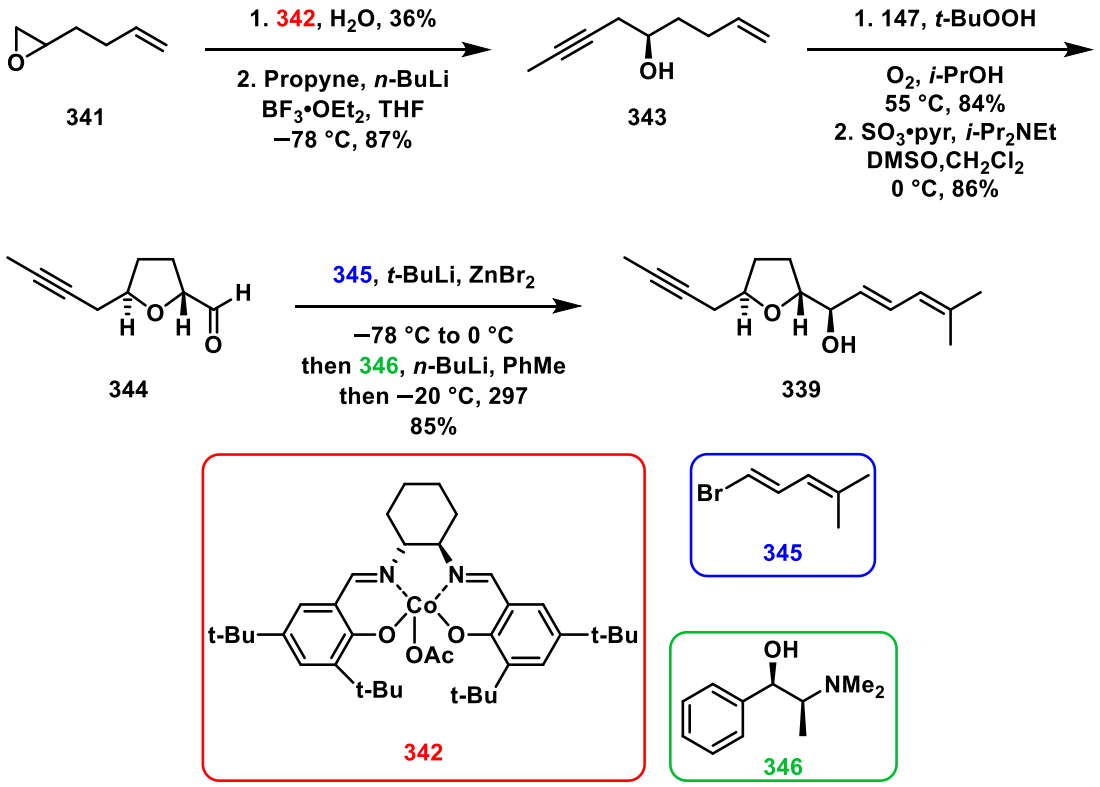
In 2013 Fürstner and co-workers reported the second total synthesis of amphidinolide F.[27] In contrast to the approach reported by Carter, the synthesis did not take advantage of the latent symmetry of the molecule. Instead, a molybdenum-based ring-closing diyne metathesis reaction was employed, in an approach which was considerably more concise, ultimately affording amphidinolide F in 13 fewer steps than Carter (**Scheme 68**). The Fürstner group proposed that a ring closing alkyne metathesis (RCAM) of the diyne **337** could be used to close the macrolactone. The required diyne was to be accessed by a Yamaguchi esterification reaction between the carboxylic acid **340** and the alcohol **339** followed by Stille cross coupling with vinylic iodide **338**.



Scheme 68. Retrosynthetic Analysis of Amphidinolide F Invoking a Ring-Closing Alkyne Metathesis

The synthesis of allylic alcohol **339** commenced with (±)-epoxide **341** which was initially subjected to a Jacobsen hydrolytic kinetic resolution reaction to afford the desired *R*-epoxide in 36% yield and with an *ee* > 99% (**Scheme 69**). The enantio-enriched epoxide was then opened using lithiated propyne, to furnish the precursor required for an oxidative Mukaiyama cyclisation reaction (**343**). The

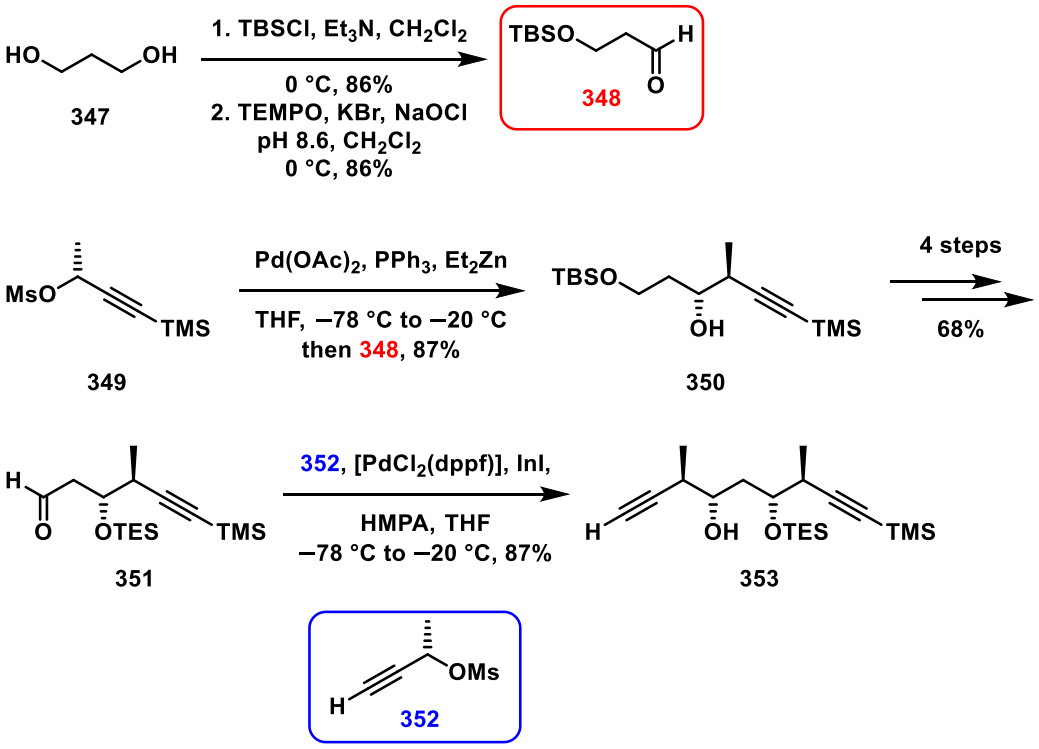
group was apprehensive about the proposed cyclisation reaction because two potential locations for cyclisation (the alkene or the alkyne) were present in the substrate and so the chemoselectivity of the reaction was potentially problematic. Pleasingly for the group, the reaction proceeded in a chemoselective fashion when the oxidative cyclisation reaction was performed using the $Co(NMP)_2$ catalyst (**147**) that had been developed by Pagenkopf (**Section 2.1.5**). The desired 2,5-*trans*-THF was obtained from the reaction in 84% yield. Aldehyde **344** was produced in 86% yield following a Parikh-Doering oxidation of the alcohol and a subsequent chelation-controlled Barbier reaction gave northern *trans*-THF fragment **339** in five steps with an overall yield of 19%.[85]



Scheme 69. Synthesis of the Northern THF Fragment

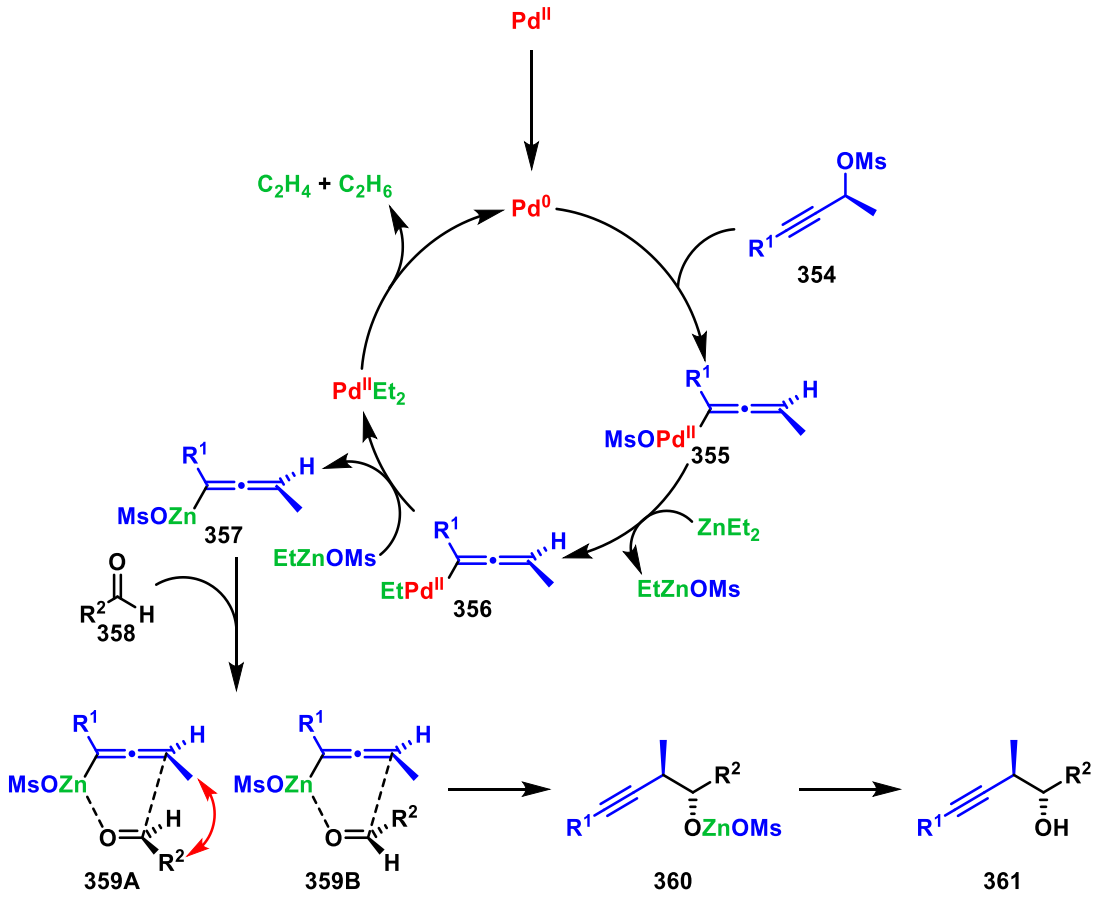
The synthesis of the western fragment commenced with mono TBS protection of 1,3-propanediol. Subsequent oxidation mediated by (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) afforded the aldehyde **348** in 74% yield over two steps (**Scheme 70**). Aldehyde **348** was then used in an enantioselective Marshall propargylation reaction to give homopropargylic alcohol **350** in 87% yield.[72] Following manipulation of the protecting groups and a Parikh-Doering oxidation reaction, the aldehyde **351** was obtained in a 68% yield

over four steps. A second Marshall propargylation reaction then produced the homopropargylic alcohol **353** in 73% yield. In this case, an organoindium intermediate was employed instead of an organozinc intermediate.



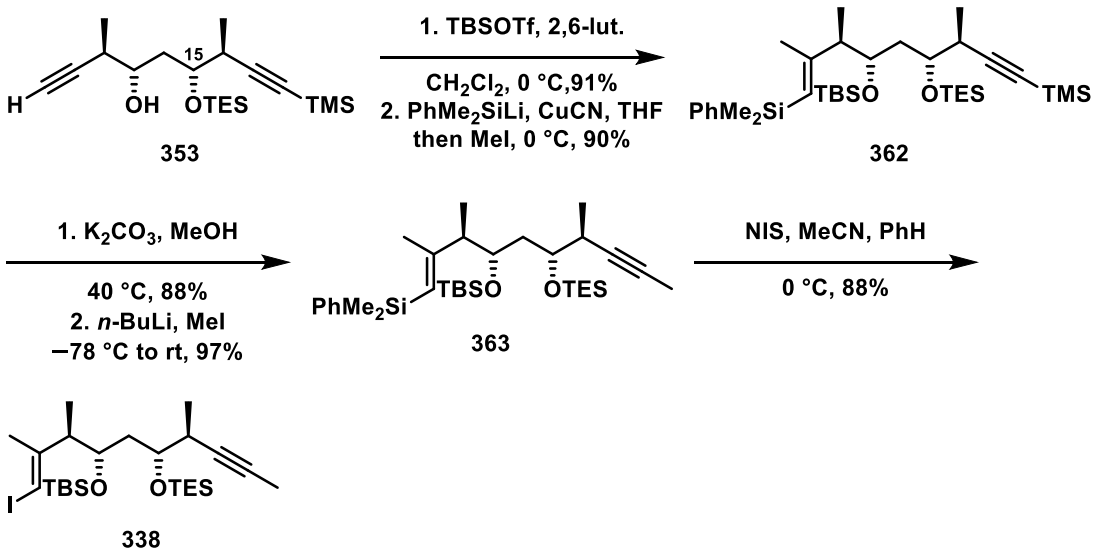
Scheme 70. Synthesis of Diyne 353

The Marshall propargylation reaction begins with reduction of the palladium(II) pre-catalyst to the active palladium(0) species (**Scheme 71**). The palladium(0) species reacts with alkenyl mesylate **354**, in an S_N2' reaction, to produce the allenylic palladium species **355** with inversion of configuration. Reaction with Et_2Zn gives organopalladium species **356** and EtZnOMs and transmetallation produces the organozinc species **357** and $Pd^{II}Et_2$. The palladium(0) catalyst is regenerated following loss of ethylene and ethane. Organozinc species **357** forms a complex with aldehyde **358** to produce **359A** or **359B** by *Si*- or *Re*- face approach of the aldehyde respectively. The favoured transition state is determined by the minimisation of steric interactions between the aldehyde and the allene, leading to formation of the *anti*-alkoxide **360**. The *anti*-alcohol **361** is produced after work-up.



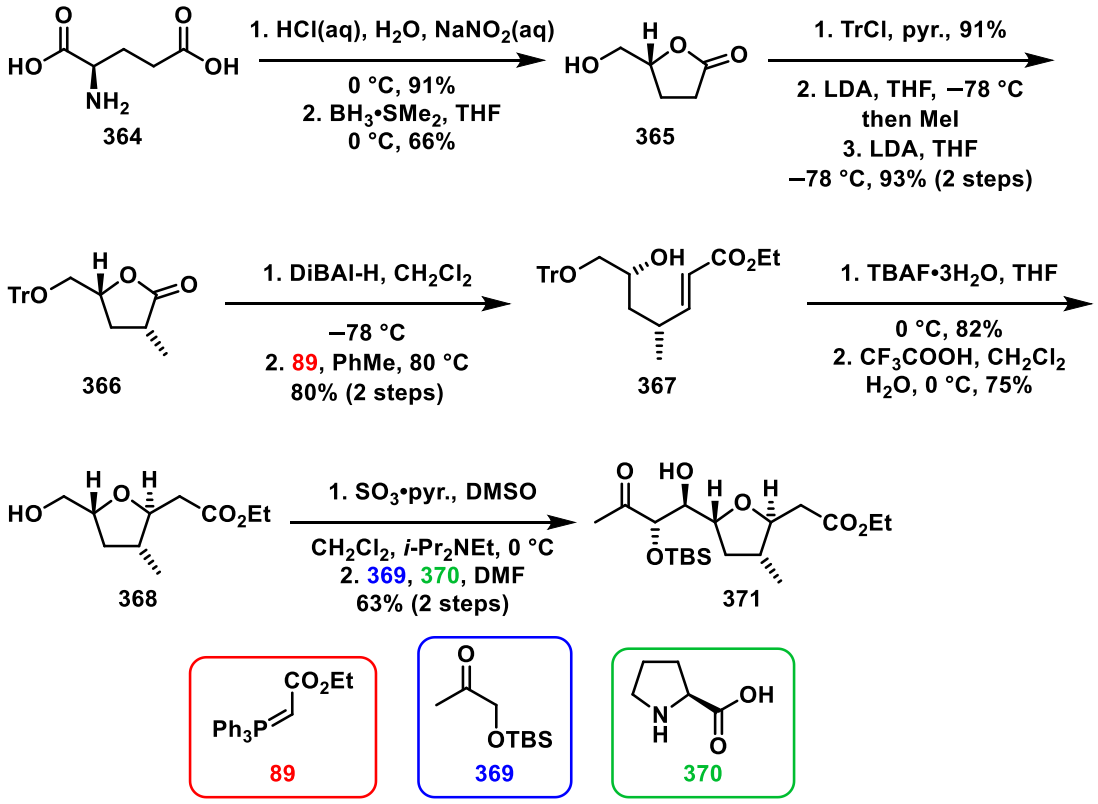
Scheme 71. Mechanism of the Marshall Propargylation

The free homopropargylic alcohol **353** was protected as a TBS-ether (**Scheme 72**). This step was crucial to enable the selective removal of the TES group at the C-15 hydroxyl position at a later stage of the synthesis. The primary alkyne was then used in a silyl-cupration reaction in which the intermediate organocopper species was quenched with MeI. The resulting enyne **362** was subsequently converted into the alkyne **363** in 85% overall yield by a two-step procedure. To complete the western iodide **338**, *N*-iodo succinimide (NIS) was employed to convert the alkenyl silane to the corresponding alkenyl iodide. The western fragment **338** was completed from diol **347** in 13 steps and with an overall yield of 27%.



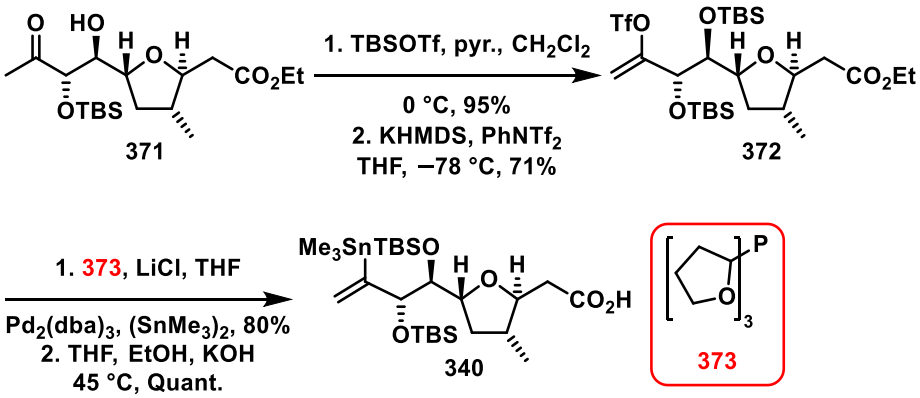
Scheme 72. Completion of the Western Fragment

To commence the synthesis of the southern fragment, the lactone **365** was prepared from D-glutamic acid (**364**) in two steps (**Scheme 73**). The lactone **365** was then transformed into enoate **367** in five steps. Following this, enoate **367** was used in an oxa-Michael cyclisation reaction to produce the required *trans*-THF as a single diastereoisomer. At this point the trityl group was removed to give the hydroxyester **368** and the primary alcohol was subjected to a Parikh-Doering oxidation to give the corresponding aldehyde. The aldehyde then underwent a stereoselective aldol reaction catalysed by (L)-proline to give the anti-aldol product (**371**).



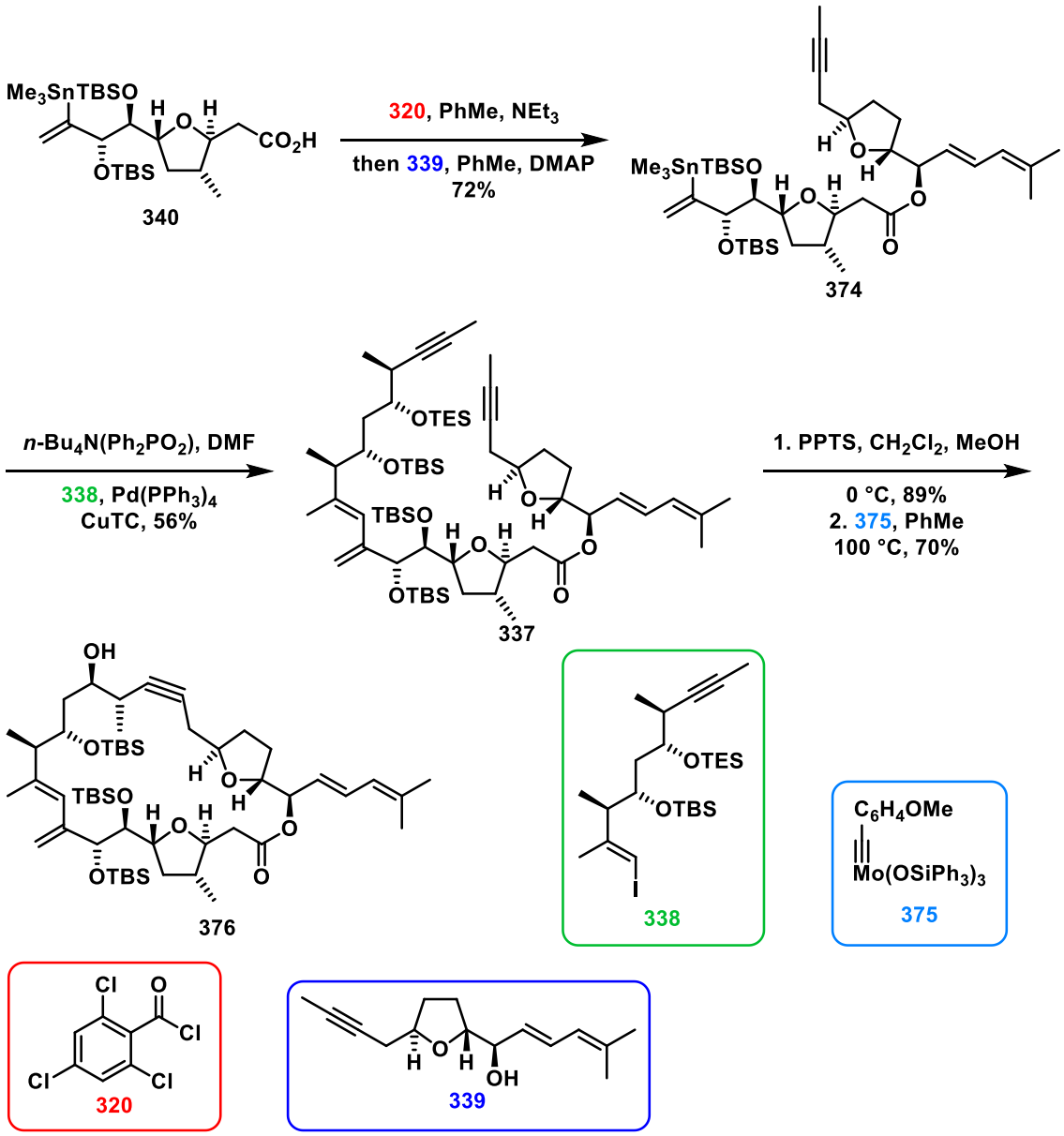
Scheme 73. Synthesis of the Southern THF Ring

At this stage it was necessary to protect the free hydroxyl group as a TBS-ether (**Scheme 74**). Under the reaction conditions employed for protection of the hydroxyl group, the ketone was also converted into the silyl enol ether. Consequently, an acidic work-up with ethanolic HCl was required to convert the silyl enol ether back into the ketone. The ketone was subsequently transformed into the vinylic triflate **372** and this compound was then converted into the corresponding vinylic stannane. Completion of the southern fragment was accomplished by saponification of the ethyl ester, which delivered the carboxylic acid **340** in 12 steps and with an overall yield of 19%.



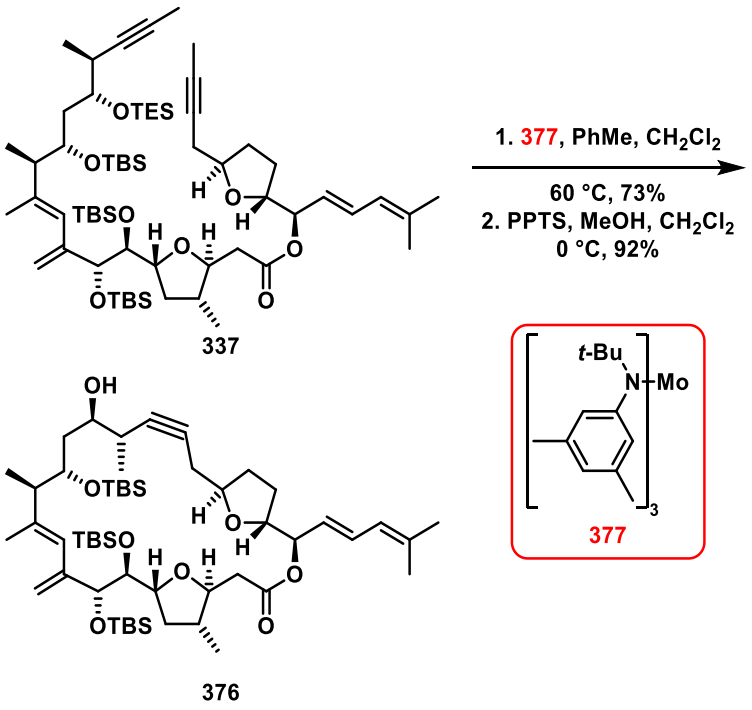
Scheme 74. Synthesis of the Southern Coupling Partner

Completion of all three fragments meant that the coupling process could commence. Firstly, Yamaguchi esterification was utilised to couple the carboxylic acid **340** with the allylic alcohol **339** (**Scheme 75**). A Stille cross coupling reaction under mild conditions, developed during Fürstner's initial foray into the synthesis of other members of the amphidinolide family, was used to couple the vinylic stannane **374** to the vinylic iodide **338**.[86] This completed the carbon framework of amphidinolide F. Selective removal of the TES group, to yield the propargylic alcohol, enabled macrocycle formation. A molybdenum-mediated alkyne metathesis reaction then delivered the macrolactone **376** in 62% yield over the two steps.



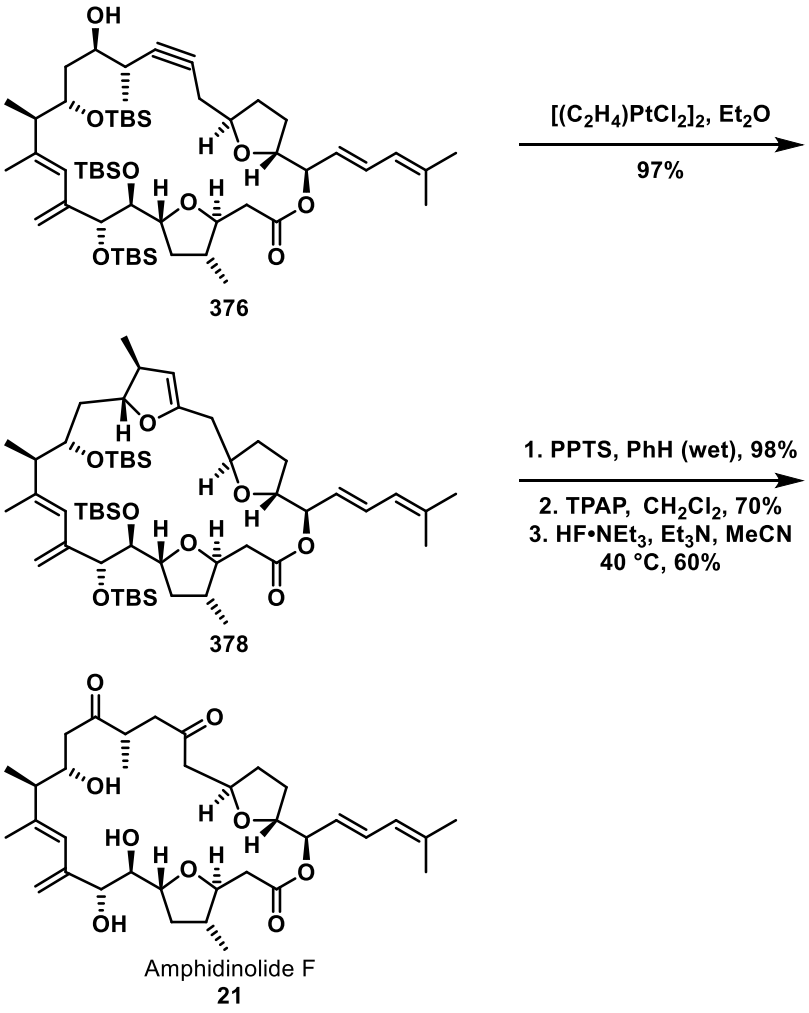
Scheme 75. Completion of the Macrocyclic Core of the Natural Product

During the process of refining the synthetic methodology, the order of the alkyne metathesis and the TES deprotection steps was reversed by the Fürstner group (**Scheme 76**). Although the reversal of steps was successful, the extra bulk associated with the TES group β to the alkyne (C-15) combined with the bulky nature of the siloxane molybdenum catalyst (**375**) resulted in competitive alkyne dimerization. However, the RCAM proceeded smoothly when the less sterically hindered molybdenum catalyst **377**, pioneered previously by the group, was used.[87] Ultimately, the use of this sequence of reactions and catalyst resulted in a slightly improved overall yield of 67%.



Scheme 76. Use of an Alternative Metathesis Catalyst

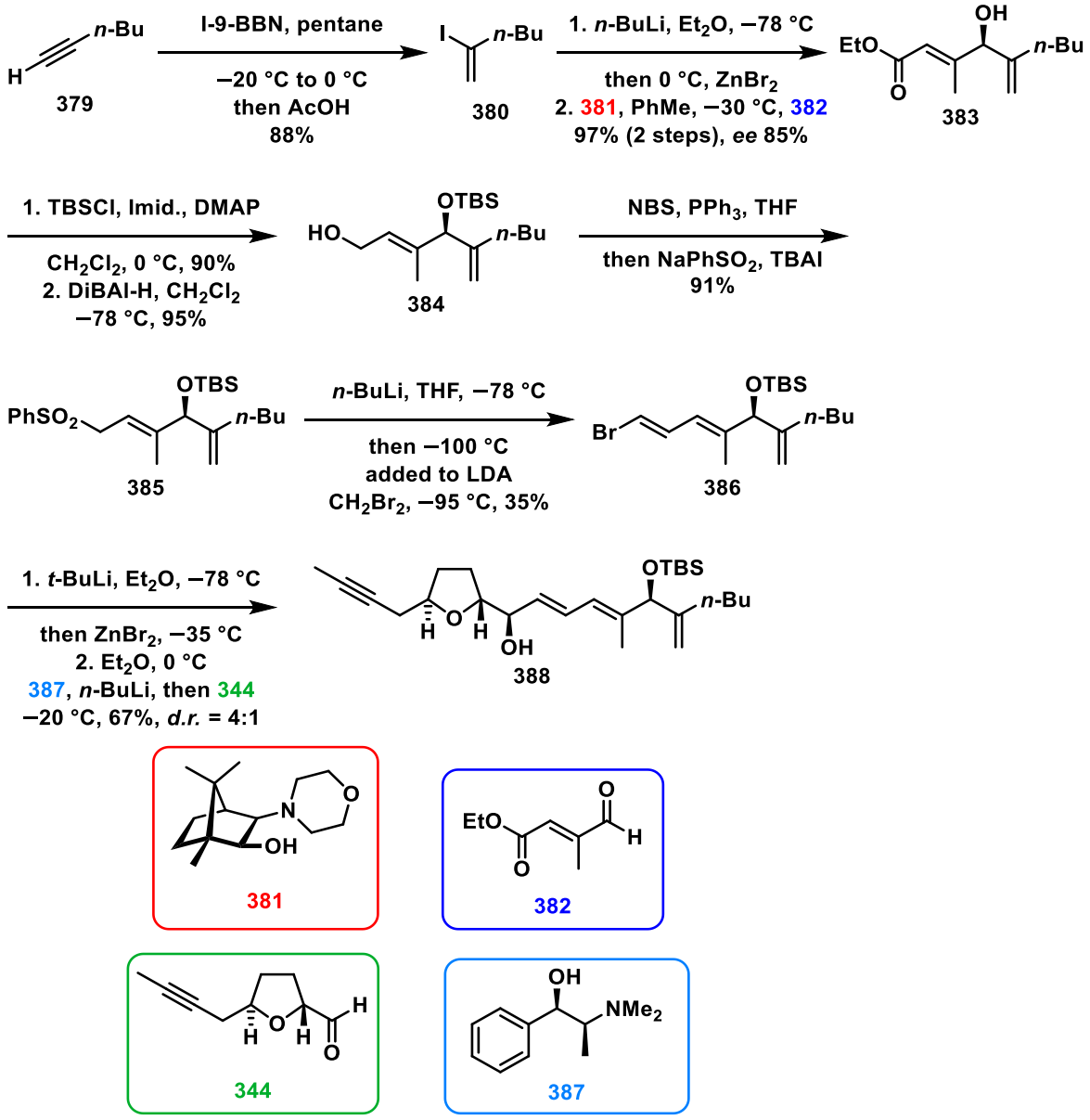
The final stages of the synthesis began with a platinum-catalysed 5-*endo*-*dig* cyclisation of alkyne **376** which gave cyclic enol-ether **378** in a 97% yield (**Scheme** 77). The subsequent acid-catalysed hydration of the enol-ether **378** gave an equilibrium mixture, comprising two lactols and the corresponding hydroxy-ketone. The product mixture was oxidised using TPAP to yield the 1,4-diketone exclusively. Removal of the protecting groups, by treatment with $Et_3N{\cdot}HF$, gave amphidinolide F in 23 steps (longest linear sequence) and with an overall yield of 0.8%.



Scheme 77. Completion of Amphidinolide F

In 2015, the Fürstner group reported a modification to the route that enabled the synthesis of amphidinolide C.[30] The synthesis of the vinylic iodide **338** and the vinylic stannane **340** remained unchanged. However, an alternative side chain was required on the third fragment. Formation of the side chain commenced with haloboration of 1-hexyne (**379**) to give vinylic iodide **380** in 88% yield (**Scheme** 78). The organozinc reagent generated from this vinylic iodide was then used in an enantioselective addition reaction to the commercially available aldehyde **382**, giving enoate **383**. TBS protection of the hydroxyl group followed by DiBAl-H mediated reduction of the ethyl ester gave the allylic alcohol **384**, which was then transformed into the phenyl sulfone **385**. Reaction of the sulfone **385** with the carbene generated by treating dibromomethane with *n*-BuLi, gave the vinylic bromide **386** in a 90% yield with an *E*:*Z* isomer ratio of 4:1. Unfortunately, the isolated yield of the *E*-alkene was only 35% after HPLC purification. Vinylic bromide **386** was converted into a vinylzinc reagent, that underwent chelation-

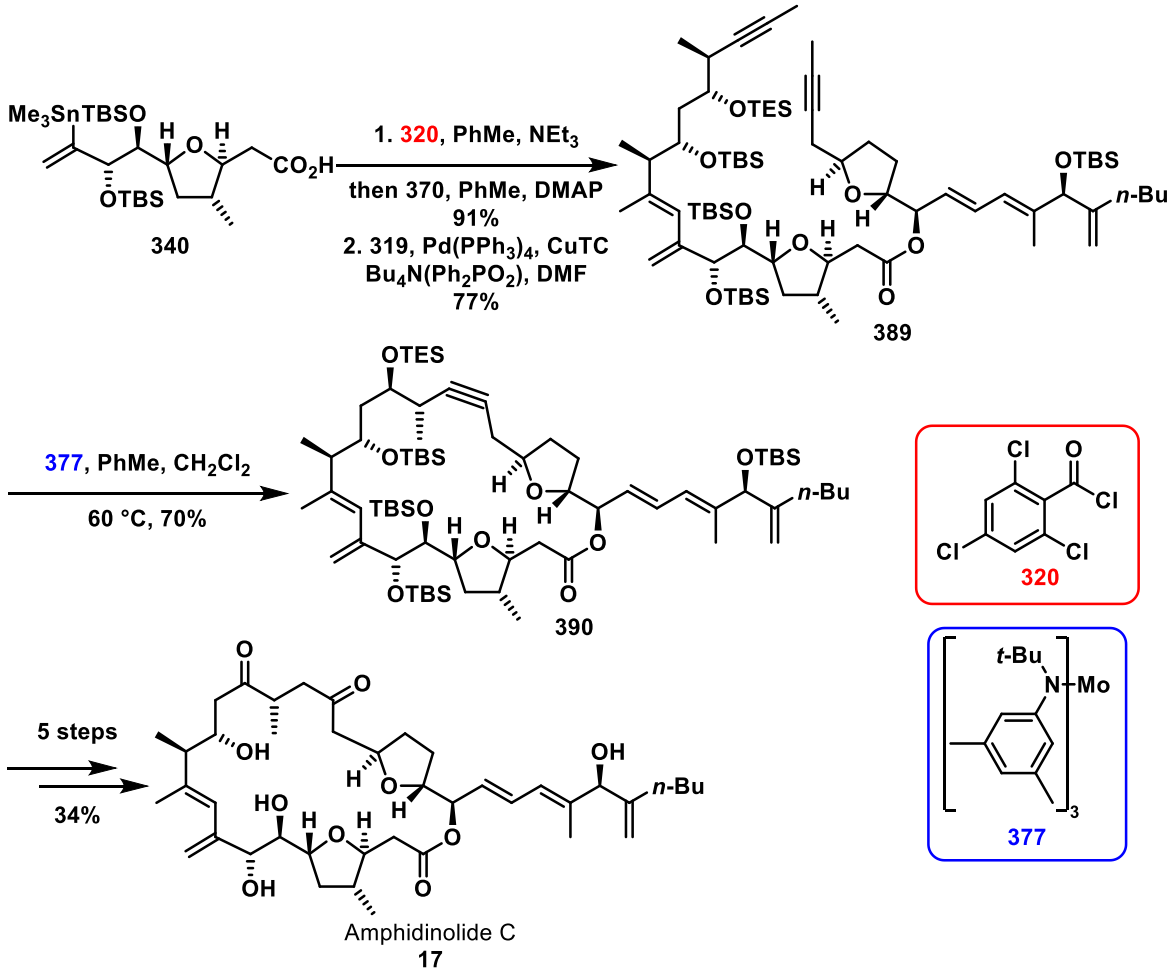
controlled addition to aldehyde **344** to give the alcohol **388** required for synthesis of amphidinolide C in 67% yield.



Scheme 78. Synthesis of the Northern Fragment of Amphidinolide C

Completion of amphidinolide C was achieved by use of a sequence analogous to that used to synthesise amphidinolide F. Specifically, Yamaguchi esterification and Stille cross coupling reactions were employed to complete the carbon framework of the natural product and RCAM was then used to close the macrocyclic lactone (**Scheme 79**). Amphidinolide C was completed in a further five steps marking the second reported synthesis of this natural product. The natural product was prepared in 23 steps (longest linear sequence), which is

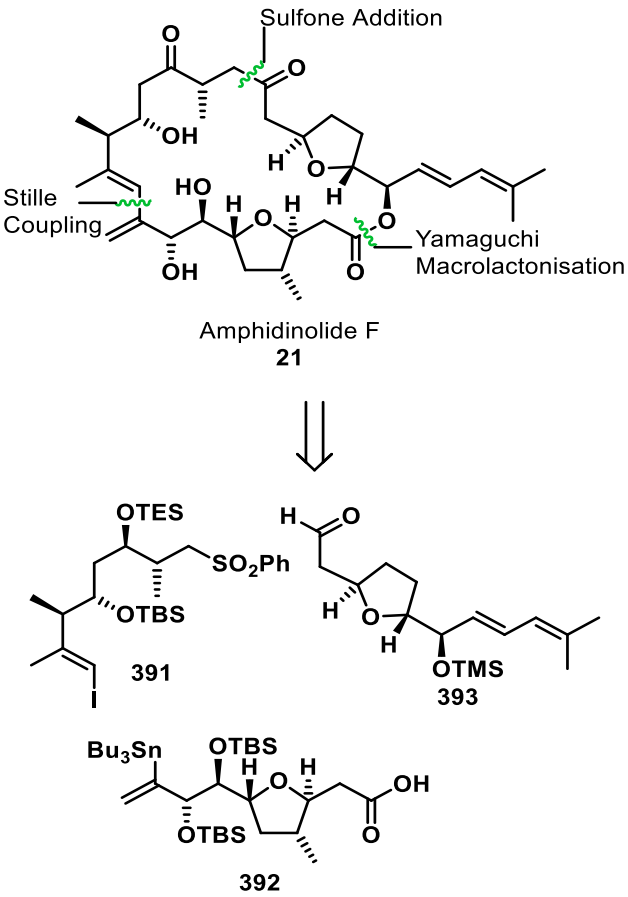
significantly fewer steps than the earlier synthesis reported by Carter, and with an overall yield of 1.6%



Scheme 79. Completion of Amphidinolide C

2.2.3 Ferrié: C-Glycosylation Approach for Amphidinolide F

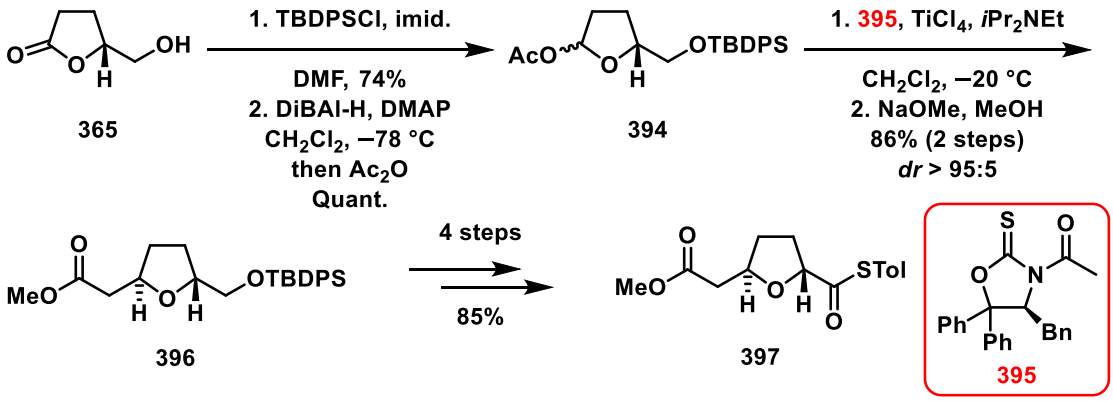
The most recent synthesis of amphidinolide F was reported by the group of Ferrié in 2018.[30] The synthetic strategy again involves both Stille cross coupling and Yamaguchi macrolactonisation reactions (**Scheme 80**). In common with the approaches employed by Carter and Fürstner, three fragments (**391**, **392**, and **393**) were synthesised and then coupled to produce amphidinolide F. The group initially proposed the use of glycosylation reactions to access both 2,5-*trans* THF fragments. While this approach worked well for the southern fragment (**392**), model studies showed that the 1,3-diene system in the northern fragment (**393**) would be incompatible with this approach.



Scheme 80. Retrosynthetic Analysis Breaking Amphidinolide F into Three Fragments

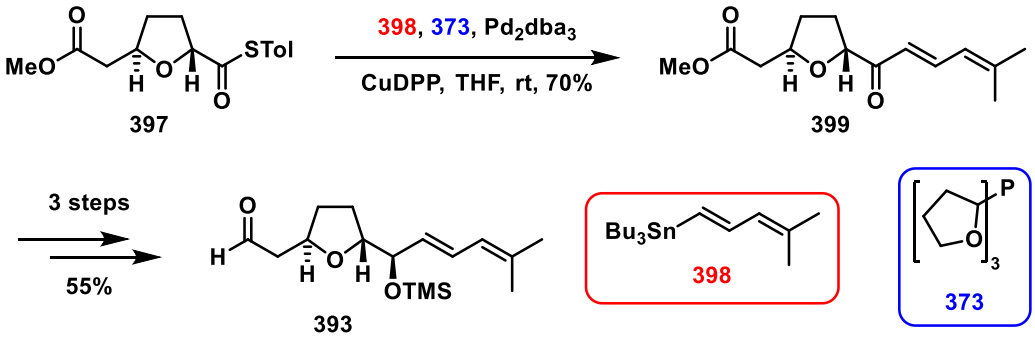
The synthesis of the northern *trans*-THF fragment **393** commenced with protection of the hydroxyl group in lactone **365** followed by reduction of the lactone to the lactol with subsequent acetylation to give activated acetal **394** (**Scheme 81**).

Typically, γ-substituted lactols display poor or unpredictable diastereoselectivity between *cis*- and *trans*- substituted products; substitution at the α- and ß-positions usually has a much greater impact on diastereoselectivity. Despite this, nucleophilic addition of the titanium enolate generated from the bulky chiral oxazolidinethione **395** to the acetal **394** was highly diastereoselective. Methanolysis to remove the chiral auxiliary produced the methyl ester **396** in 86% yield with a *dr* ≥ 95:5. A further four steps were required to synthesise the thioester **397** in 85% yield.



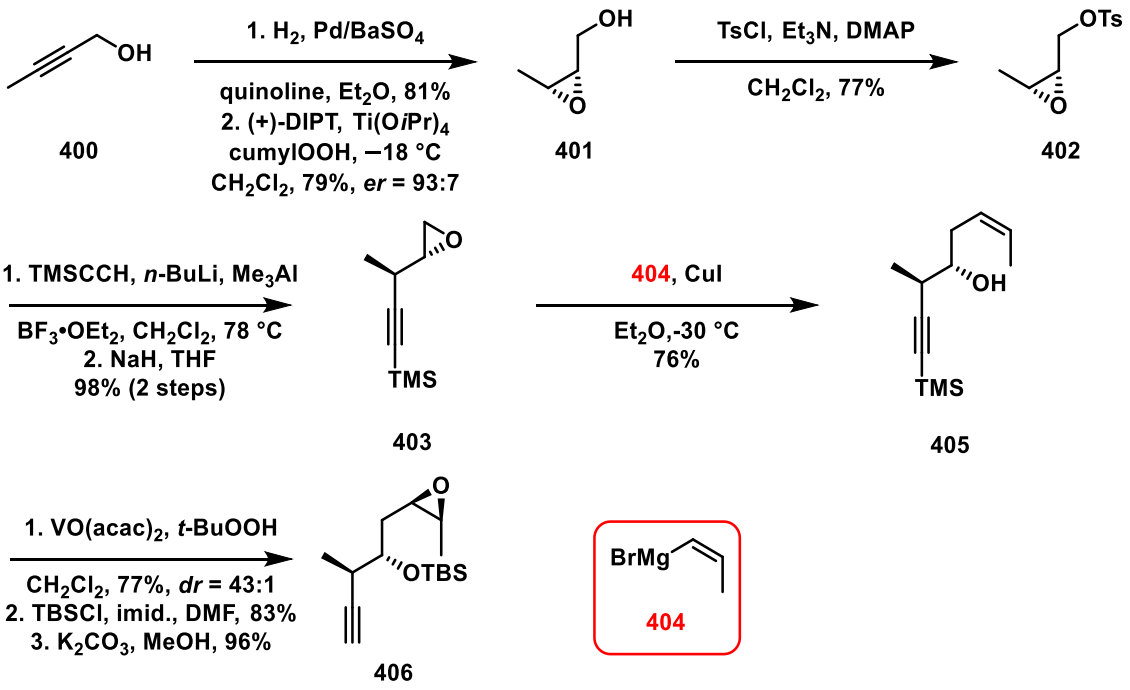
Scheme 81. Synthesis of the Northern THF Ring

A Liebeskind-Srogl cross coupling, using thioester **397**, was used to install the required side chain (**Scheme 82**).[88] Initially a boronic acid analogue of vinylic stannane **398** was used by the group to deliver the required framework. However, yields were unreproducible due to the instability of the boronic acid. As an alternative, the stannane **398** was employed as the coupling partner and completion of the carbon backbone of the northern *trans*-THF fragment was accomplished in 70% yield. A further three steps were required to access the aldehyde **393**, which possessed the functionality required to couple the fragments.



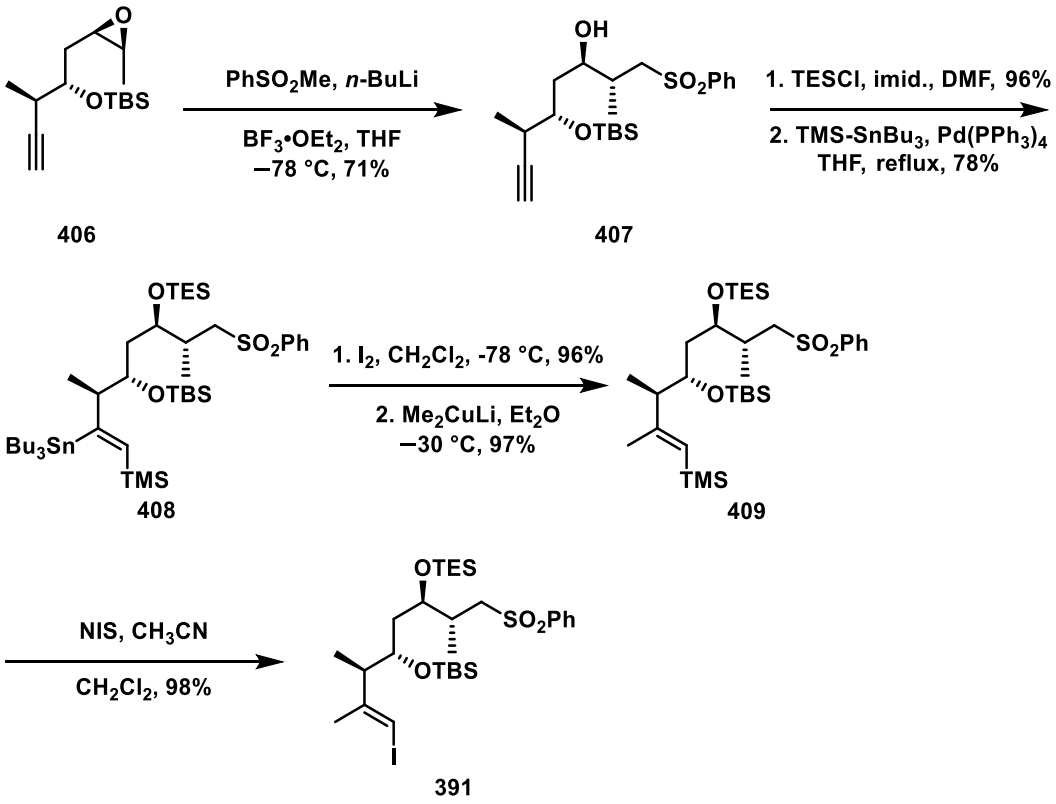
Scheme 82. Completion of the Northern THF Fragment

The synthesis of western fragment (**391**) began from 2-butyn-1-ol (**400**), which after sequential hydrogenation over palladium based Rosenmund's catalyst (in this instance, alkyne reduction was performed and so the name Lindlar's catalyst may be more appropriate) to the *Z*-alkene, Sharpless asymmetric epoxidation and tosylation of the hydroxyl group, gave epoxy-tosylate **402** (**Scheme 83**). Opening of epoxide **402**, at the less hindered site, was achieved by reaction with lithiated TMS-alkyne; subsequent displacement of the tosylate by an internal alkoxide afforded the terminal epoxide **403**. Opening of epoxide **403**, again at the less hindered site, using Grignard reagent **404** in the presence of CuI produced the *Z*-homo allylic alcohol **405**. Directed vanadium-mediated epoxidation of the alkene, followed by TBS protection of the hydroxyl group and removal of the terminal TMS group gave epoxide **406**.



Scheme 83. Synthesis of the Western Fragment

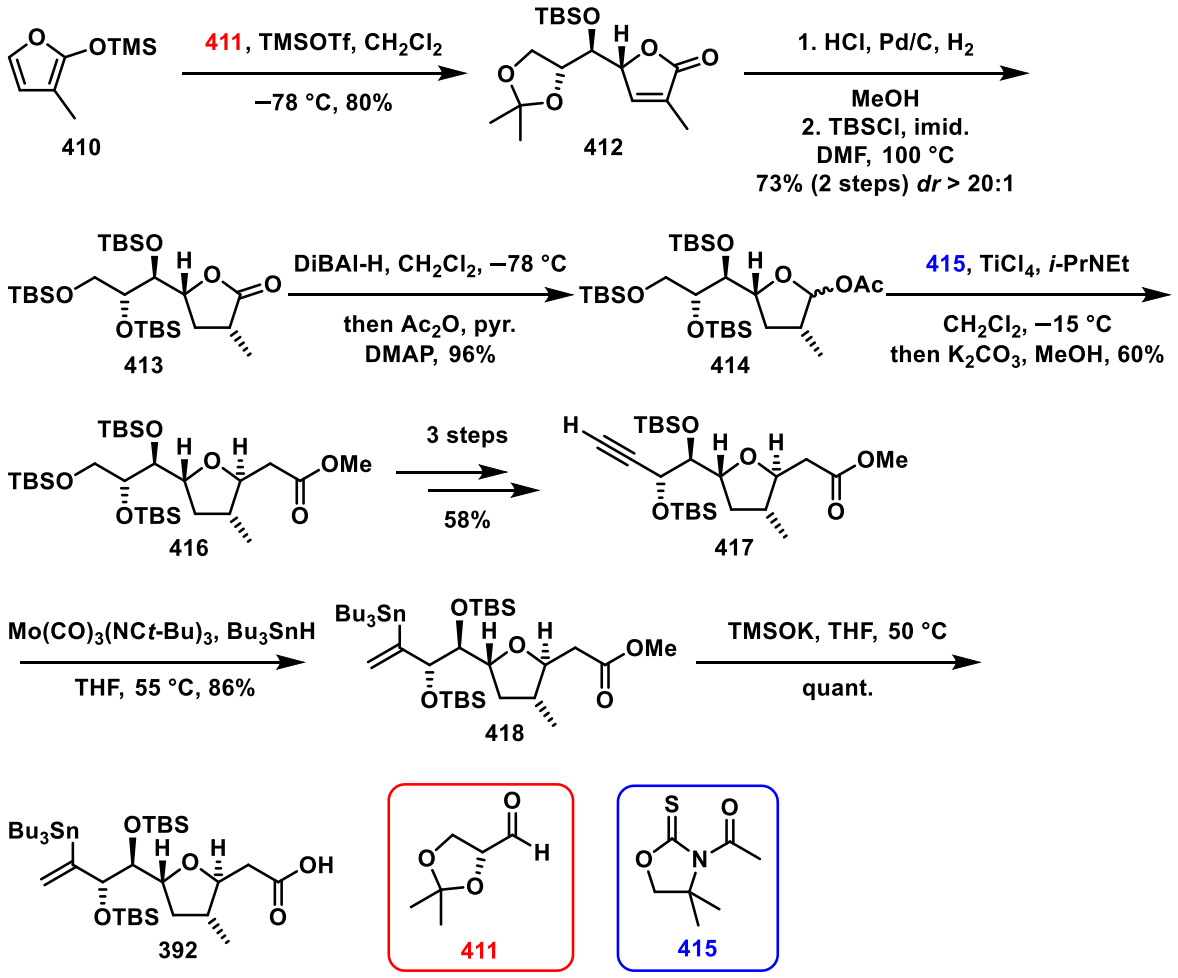
The final epoxide opening reaction was undertaken using the anion generated by deprotonation of methylphenylsulphone with *n*-BuLi. The reaction delivered a mixture of separable regioisomers (71:29) favouring the product obtained by attack at the less hindered carbon (**Scheme 84**). Protection of the free hydroxyl group as the TES-ether followed by palladium-mediated stannylation gave vinyl stannane **408**. A tin-iodine exchange reaction followed by displacement of the iodide substituent with a methyl group, gave alkenyl silane **409**. To complete the western fragment, NIS was used to replace the TMS group with iodine and deliver the iodide **391**.



Scheme 84. Completion of the Western Vinyl Iodide

The synthesis of the southern fragment started with TMSOTf-mediated coupling of the furan **410** with aldehyde **411** to give the lactone **412** as a diastereomeric mixture (*dr* = 3:1), with the required diastereoisomer (**412**) as the predominant product (**Scheme 85**). Hydrogenation of furanone **412** under acidic conditions, followed by TBS protection of the free hydroxyl groups, gave the lactone **413** with a *dr* > 20:1. One-pot reduction of the lactone and acetylation of resultant lactol produced the acetate **414**. As in the synthesis of the northern fragment, a titanium enolate generated from an oxazolidinethione (**415**), this time achiral, was used to install the side chain and produce the 2,5-*trans* THF. Subsequent removal of the auxiliary by methanolysis afforded the methyl ester **416**. Alkyne **417** was accessed in a further three steps with an overall yield of 58%. Following a protocol pioneered by Kazmaier, the researchers performed a molybdenum-catalysed hydrostannylation reaction (mechanism outlined in **Scheme 33**) of the alkyne **417**, which gave a mixture of vinylic stannanes in 86% yield. Unfortunately, the required vinylic stannane (**418**) accounted for only 69% of the product with the terminal (*E*)-stannane accounting for a further 17%. Completion of the southern fragment

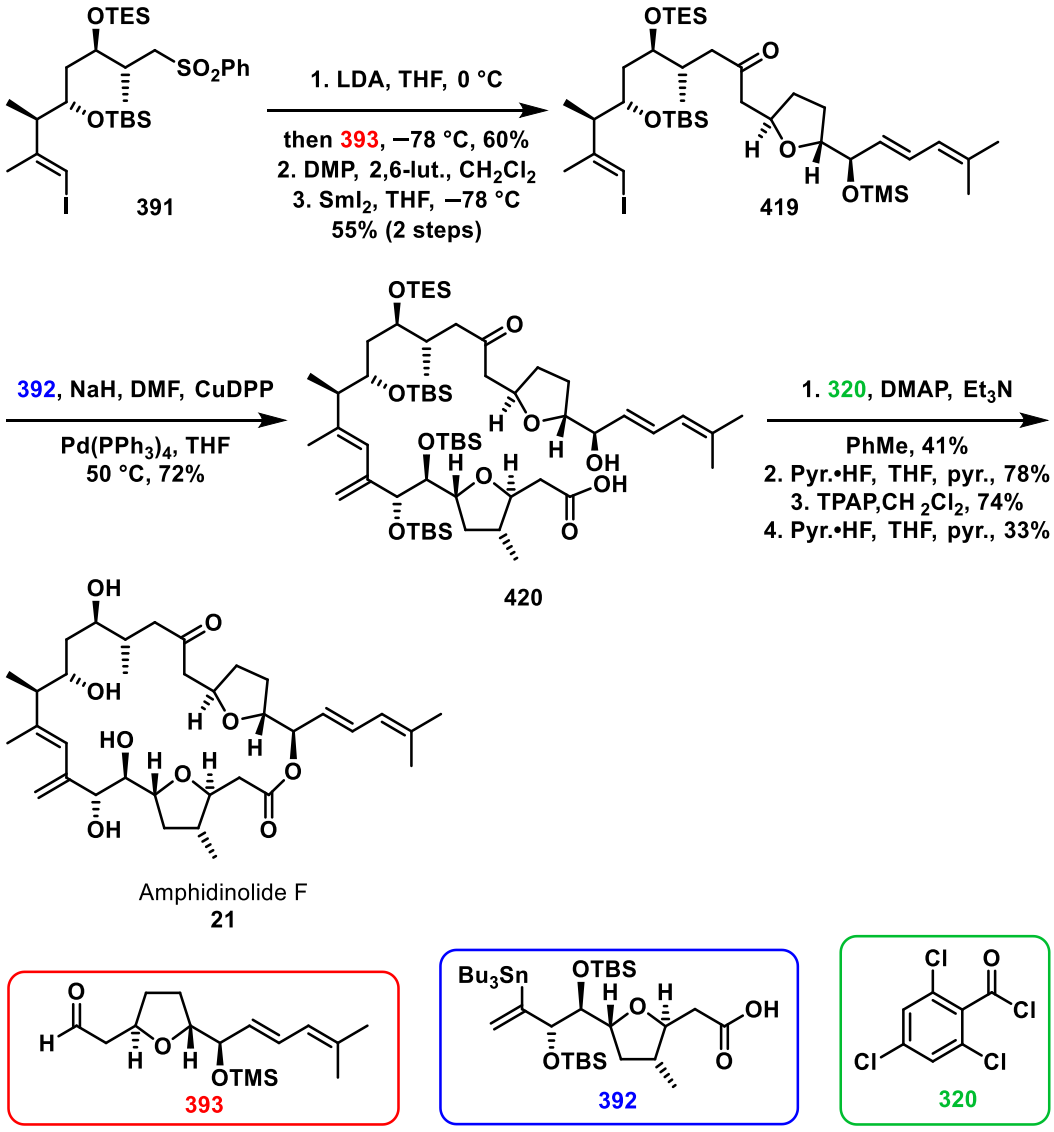
was achieved by saponification of the methyl ester using TMSOK and then aqueous work-up to give the carboxylic acid **392**.



Scheme 85. Synthesis of the Southern THF Fragment

Coupling the western and northern fragments was achieved by deprotonation of the sulfone **391** with LDA and addition of the resulting anion to the aldehyde **393** (**Scheme 86**). Ketone **419** was obtained after oxidation and samarium mediated desulfonylation. Stille cross coupling was then used to couple vinylic iodide **419** with vinylic stannane **392**. To avoid potential proto-demetallation of the vinylic cuprate generated *in situ*, the carboxylic acid fragment was first treated with NaH to generate the sodium carboxylate. Loss of the TMS group occured concurrently with the coupling reaction and the seco-acid **420** was obtained. Under standard reaction conditions, deprotection was found to be incomplete and so an acidic work-up with dilute acid (0.1 M $HCl_{(aq)}$) was used to ensure complete hydrolysis. The seco-acid **420** was then subjected to a Yamaguchi macrolactonisation reaction to form the macrocycle. Completion of the natural product was achieved in a

further three steps, with the final global TBS deprotection reaction resulting in significant degradation of material and a yield of just 33%. The natural product was obtained with an overall yield of 0.2%. At 23 steps, the synthesis (longest linear sequence) reported by Ferrié was significantly shorter than the original synthesis reported by Carter and comparable in length to that documented by Fürstner. Moreover, whist this strategy does not utilise any novel chemistry, it implements well-known reliable reactions that deliver a robust synthesis.

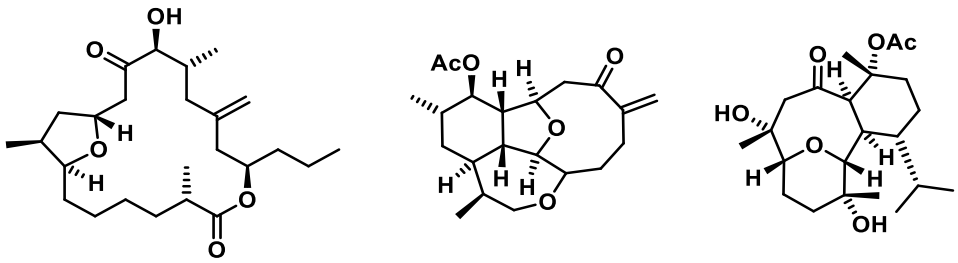


Scheme 86. Completion of the Natural Product

3 Previous Synthetic Strategy Employed Within the Clark Group Towards Amphidinolides C and F

3.1 Oxacycle Synthesis *via* Oxonium Ylide Formation and [2,3]-Sigmatropic Rearrangement

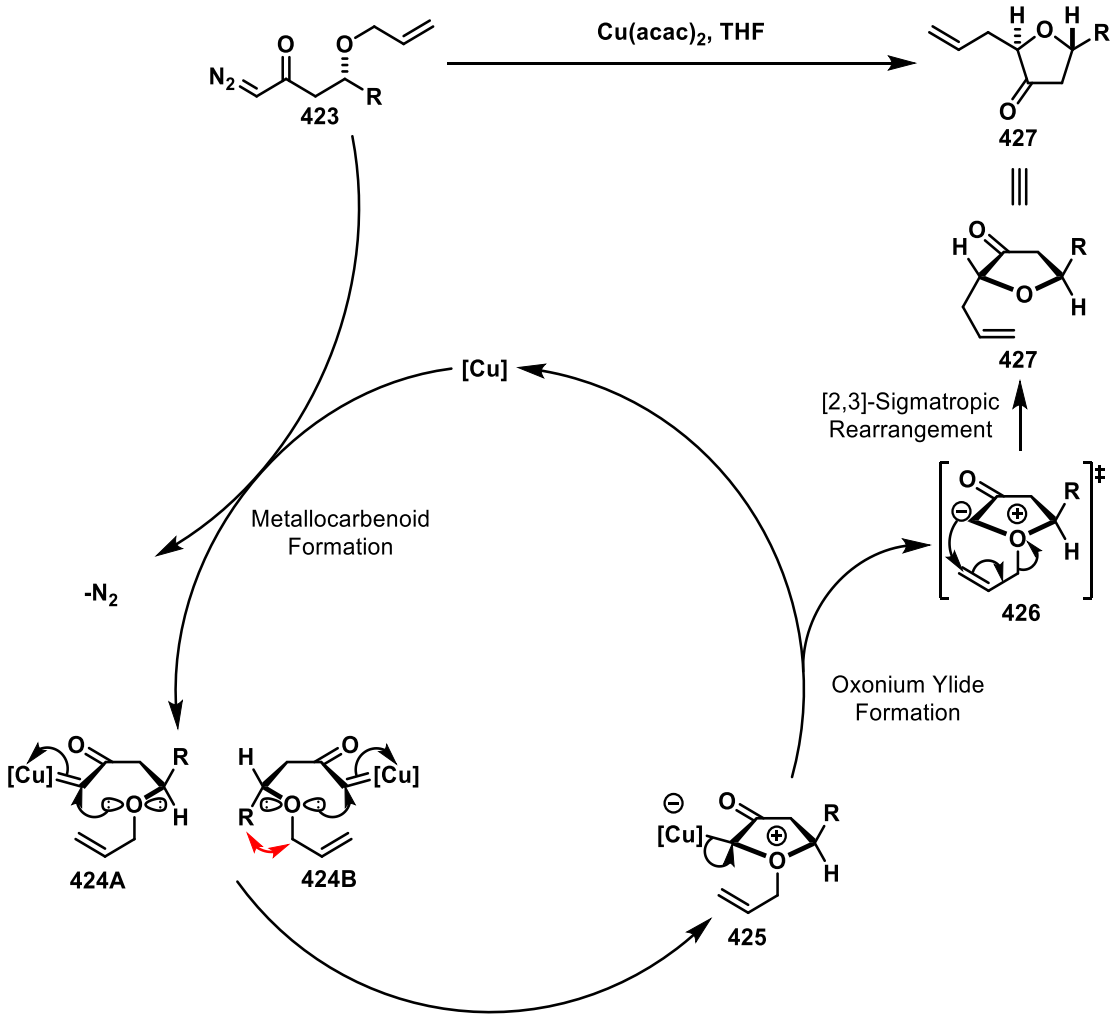
The Clark group have previously conducted thorough studies into tandem copper-catalysed oxonium ylide formation and [2,3]-sigmatropic rearrangement reactions of diazoketones to give cyclic ethers.[89,90,91] This methodology been applied to the synthesis of several natural products including the amphidinolides of the T-series, the cladiellins, asbetinins, as well as the core structure of other natural products such as australin A (**Figure 6**).[92,93,94]



Amphidinolide T1 **15** | Asbestinin 10 **421** | Australin A **422**

Figure 6. Natural Products Synthesised within the Clark Group Utilising Diazoketone Methodology

The oxonium ylide formation and [2,3]-sigmatropic rearrangement reaction progresses through a metallocarbenoid (**424**) which arises from the loss of dinitrogen from diazoketone **423** (**Scheme 87**). The ethereal oxygen has two diastereotopic lone pairs of electrons, with the reaction passing through one of two transition states, arising after following the arrows in either **424A** or **424B**. The pathway which incurs the least steric hindrance between the allyl group and the R group is favoured and so the reaction proceeds through oxonium ylide **426**. Following [2,3]-sigmatropic rearrangement of the oxonium ylide it is *trans*-oxacycle **427** that is formed.



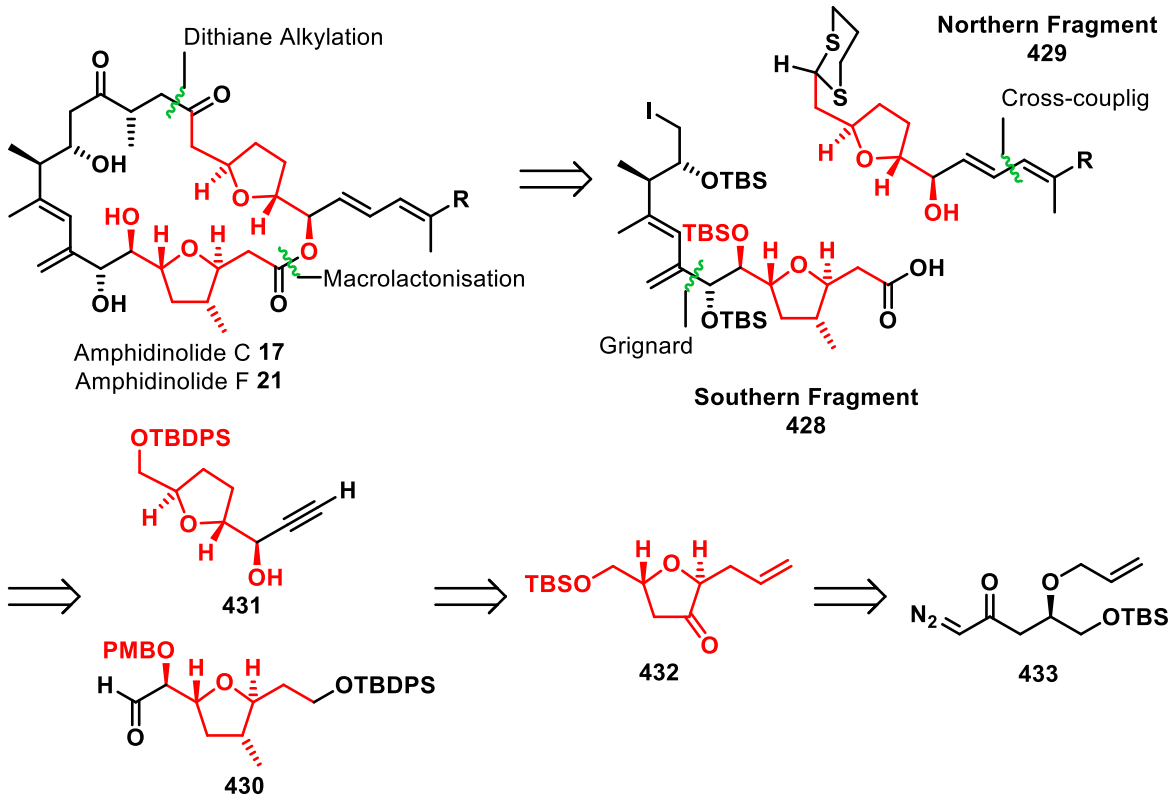
Scheme 87. Proposed Mechanism of Oxonium Ylide Formation and [2,3]-sigmatropic Rearrangement

Oxacycles are common structural motifs in the amphidinolide series of natural products. Consequently, it was proposed that this methodology could be applied to the synthesis of many members of the family, and in particular for the synthesis of the 2,5-*trans* THF units present in the C and F families of amphidinolides.

3.2 Application of the Oxonium Ylide Formation and [2,3]-Sigmatropic Rearrangement Towards Amphidinolides C and F

The syntheses of several amphidinolides using the aforementioned methodology have been undertaken previously within the Clark group. These studies have resulted in the publication of the total syntheses of amphidinolide T1, T3, and T4, as well as construction of substantial fragments (C-1 to C-17 and C-18 to C-29 or onwards) of the amphidinolides C and F.[95,96]

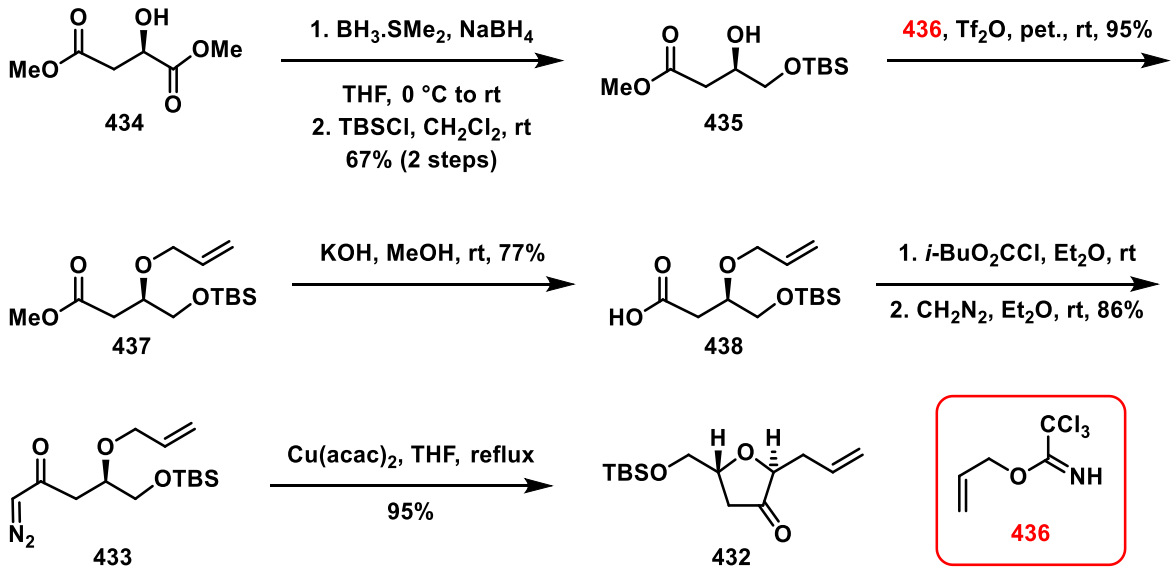
For amphidinolides C and F, the Clark group strategy involved Yamaguchi macrolactonisation and dithiane alkylation reactions to couple the northern fragment **429** and southern fragment **428** (**Scheme 88**). It was proposed that the *trans*-THF units present in both fragments could be synthesised from a common dihydrofuranone intermediate **432**, thereby taking advantage of latent symmetry in the natural product, a feature of the targets that was discussed in **Section 2.2.1**. The dihydrofuranone could be accessed from diazoketone **433** by the use of the tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement reaction.



Scheme 88. Clark Group Retrosynthetic Strategy

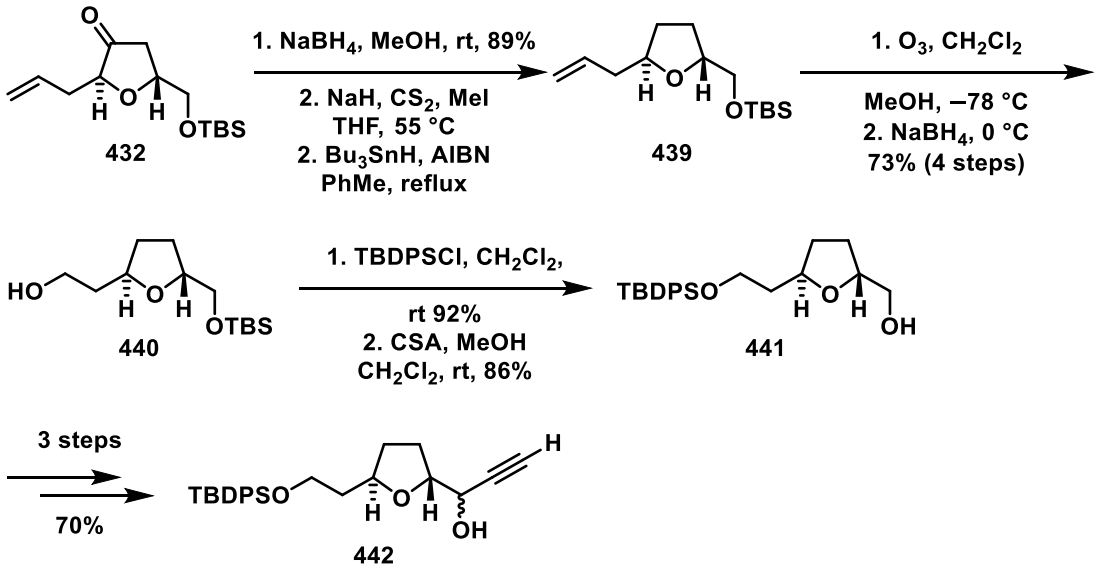
Intermediates in the synthesis of both fragments can be accessed from a common dihydrofuranone core, the synthesis of which commences from the dimethyl ester of D-malic acid (**434**) (**Scheme 89**). Borane reduction of the diester produced the 1,2-diol, and TBS protection of the primary hydroxyl group afforded the secondary alcohol **435** in 62% yield over two steps. Acid-catalysed allylation of the secondary alcohol, using allyl trichloroacetimidate **436**, followed by saponification of the methyl ester gave the carboxylic acid **438**. The carboxylic acid **438** was transformed into a mixed anhydride, which upon treatment with an ethereal

solution of diazomethane gave the corresponding diazoketone (**433**) required for the subsequent copper-catalysed reaction. Tandem carbenoid generation, oxonium ylide formation, and [2,3]-sigmatropic rearrangement ultimately afforded the 2,5-*trans* dihydrofuranone **432** required for the synthesis of both fragments.



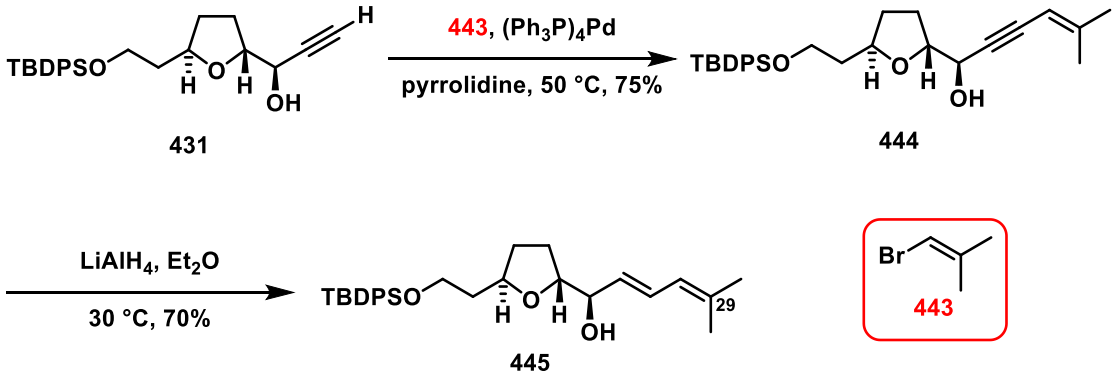
Scheme 89. Synthesis of the Common Dihydrofuranone Intermediate

At this point the synthesis of the northern and southern fragments diverged. For the northern *trans* THF of both amphidinolide C and amphidinolide F, the furanone (**432**) was reduced to give the corresponding alcohol and a Barton-McCombie deoxygenation reaction was performed to remove the oxygen substituent and deliver the 2,5-*trans* THF **439** (**Scheme 90**). Ozonolysis of the allyl group, followed by a reductive work-up, gave primary alcohol **440**. A further five steps were required to access the propargylic alcohol **442** as an inseparable mixture of diastereoisomers (*dr* = 1.5:1). Oxidation and immediate reduction of propargylic alcohol **442** failed to provide the required diastereoisomer in a highly selective manner. However, the diastereomers were separated by forming a cobalt complex with the corresponding TMS alkyne and then performing column chromatography. Subsequent oxidative removal of cobalt and desilylation of the alkyne afforded **431**.



Scheme 90. Synthesis of the Common Northern Fragment

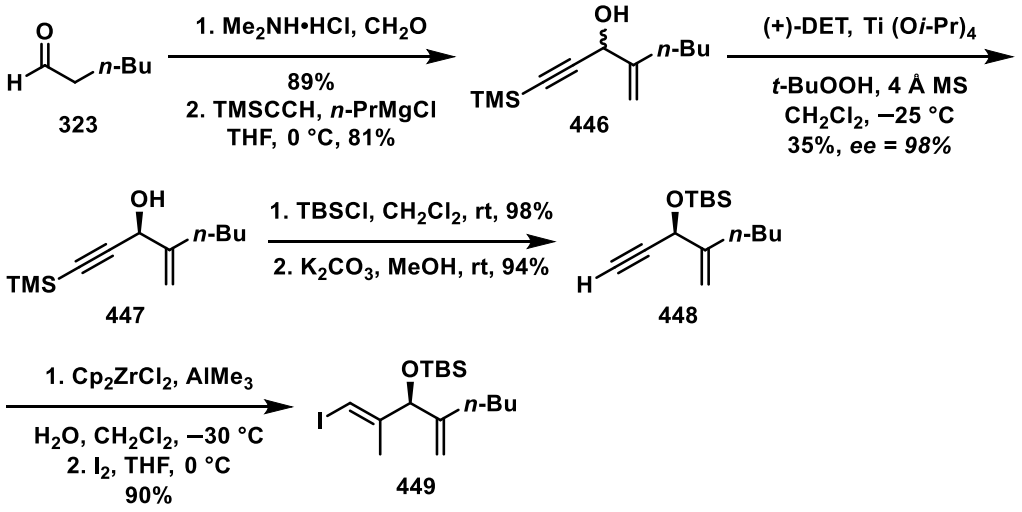
Following the successful formation of alkyne **431**, a copper-free Sonogashira cross coupling reaction was employed to synthesise enyne **444** using the bromide **443** (**Scheme 91**). $LiAlH_4$ was then used to reduce the alkyne to give the *trans*-alkene and complete the northern fragment of amphidinolide F (**445**). Due to the differences in the side chains of between amphidinolides C and F, an alternative coupling partner was required to obtain the northern fragment of amphidinolide C.



Scheme 91. Completion of the Northern Fragment of Amphidinolide F

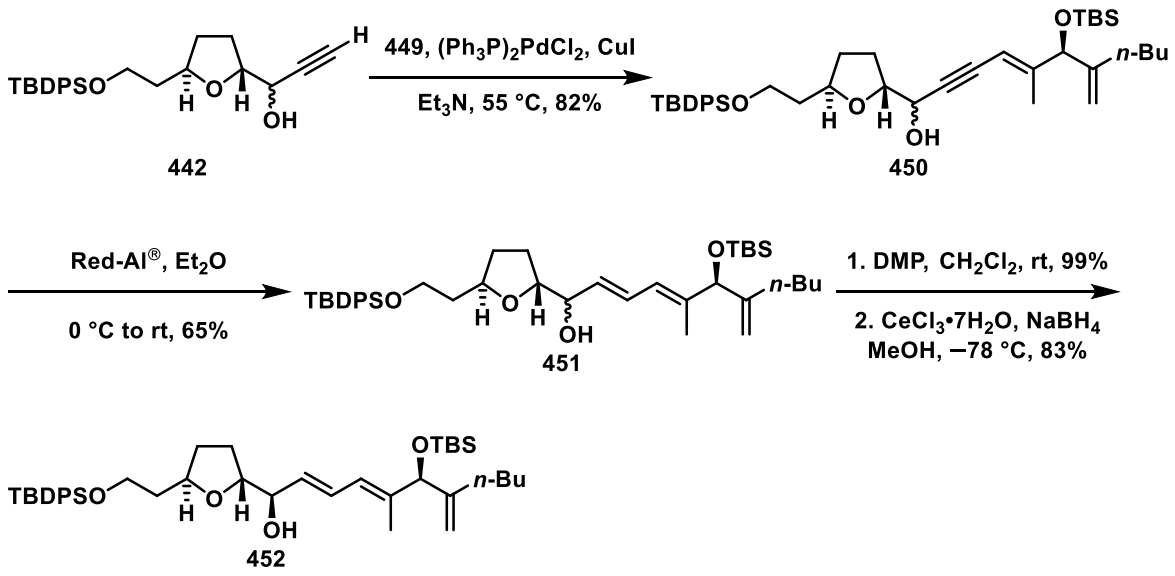
Synthesis of the coupling partner required for the construction of the northern fragment of amphidinolide C commenced with hexenal (**323**). An α-methylenation reaction followed by Grignard addition of TMS-acetylene to the intermediate enal afforded a racemic mixture of allylic alcohols **446** (**Scheme 92**). A Sharpless asymmetric kinetic resolution reaction was performed using (+)-DET to give the

(*S*)-allylic alcohol **447** with an *ee* = 98%. The secondary hydroxyl group was then TBS protected and the TMS group was removed to produce the terminal alkyne **448**. Finally, the *E*-alkenyl iodide **449** was obtained following the Negishi carboalumination and iodination protocol.



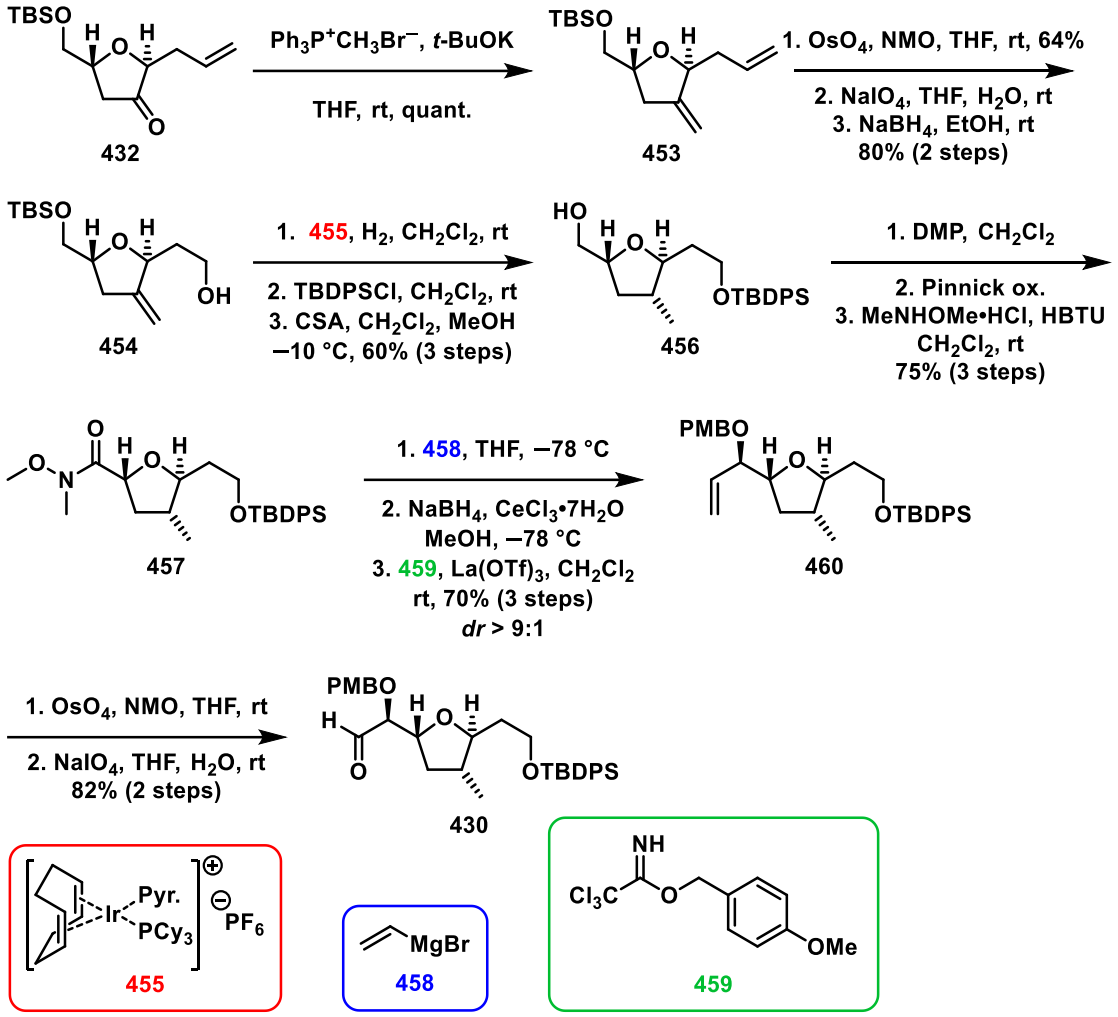
Scheme 92. Synthesis of the C-25 Side Chain of amphidinolide C

The iodide **449** was coupled to a diastereomeric mixture of the propargylic alcohols **442** using a Sonogashira cross coupling reaction (**Scheme 93**). Reduction of the alkyne was achieved using sodium bis(2-methoxyethoxy)aluminium dihydride (Red-Al®) and the *E*-alkene **451** was obtained in 65% yield. The stereochemistry at the C-24 position was corrected by an oxidation-reduction sequence. Reduction of the intermediate ketone under Luche conditions gave allylic alcohol **452** as a single diastereoisomer and thereby completed the northern fragment of amphidinolide C.[97]



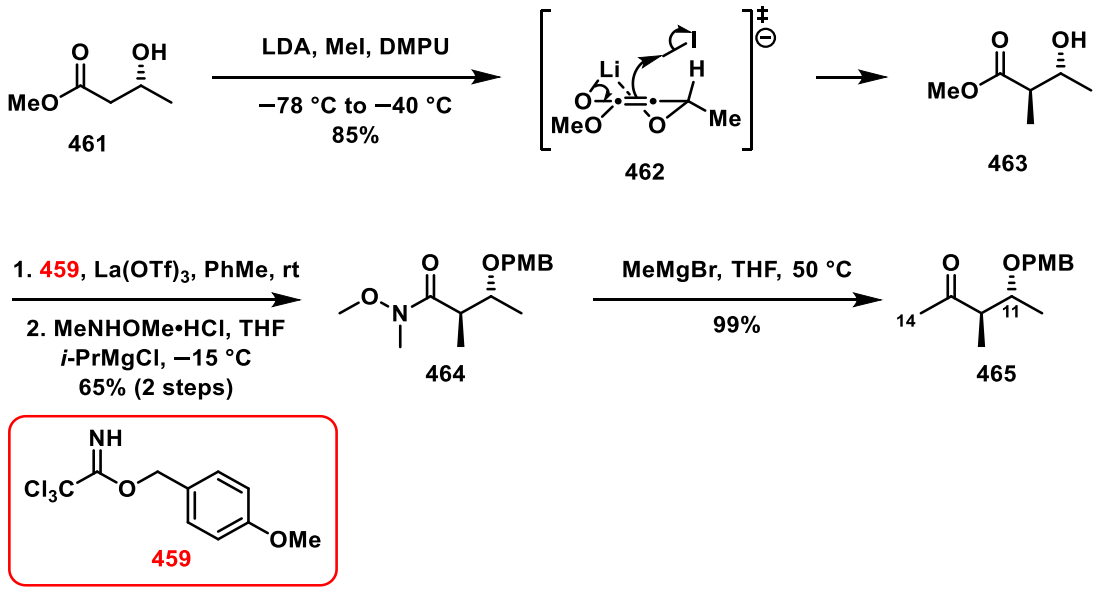
Scheme 93. Completion of the Northern Fragment of Amphidinolide C

Synthesis of the southern fragment from dihydrofuranone **432** commenced with Wittig olefination to convert the carbonyl group into a methylene group and produce the diene **453** (**Scheme 94**). The terminal alkene of **453** was transformed into a primary alcohol (**454**) by sequential Upjohn dihydroxylation, oxidative cleavage, and carbonyl reduction. Stereoselective reduction of the methylene group was achieved using Crabtree's catalyst which reversibly coordinates to the hydroxyl group, delivering the hydrogen to the required face and giving THF **456**. A further three steps were required to convert the alcohol **456** into the Weinreb amide **457**.[98] Amide **457** was then reacted with vinylmagnesium bromide and the resulting enone was subjected Luche reduction. PMB protection of the newly formed hydroxyl group gave alkene **460** in 70% yield. The alkene **460** was then converted into the aldehyde **430** by sequential Upjohn dihydroxylation and periodate cleavage of the resulting 1,2-diol.



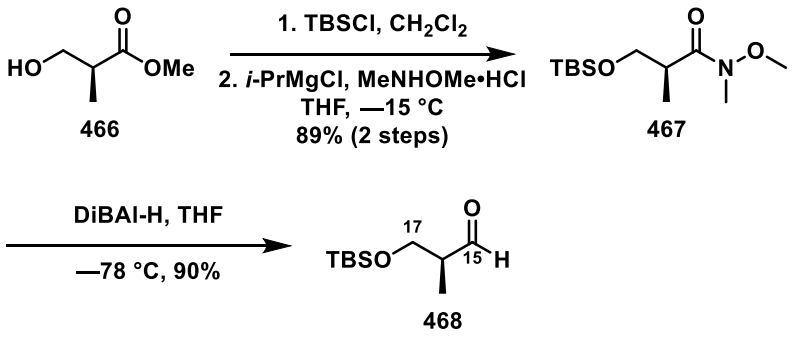
Scheme 94. Synthesis of the Southern THF Fragment

The synthesis for the western fragment began from (*R*)-ß-hydroxy methyl ester **461** which underwent a stereoselective Fráter-Seebach alkylation reaction (**Scheme 95**). Weinreb amide formation and subsequent PMB protection of the hydroxyl group gave amide **464**.[99] Grignard addition to amide **464** afforded ketone **465**, thereby completing the first part of the western fragment.



Scheme 95. Synthesis of the C-11 to C-14 Fragment

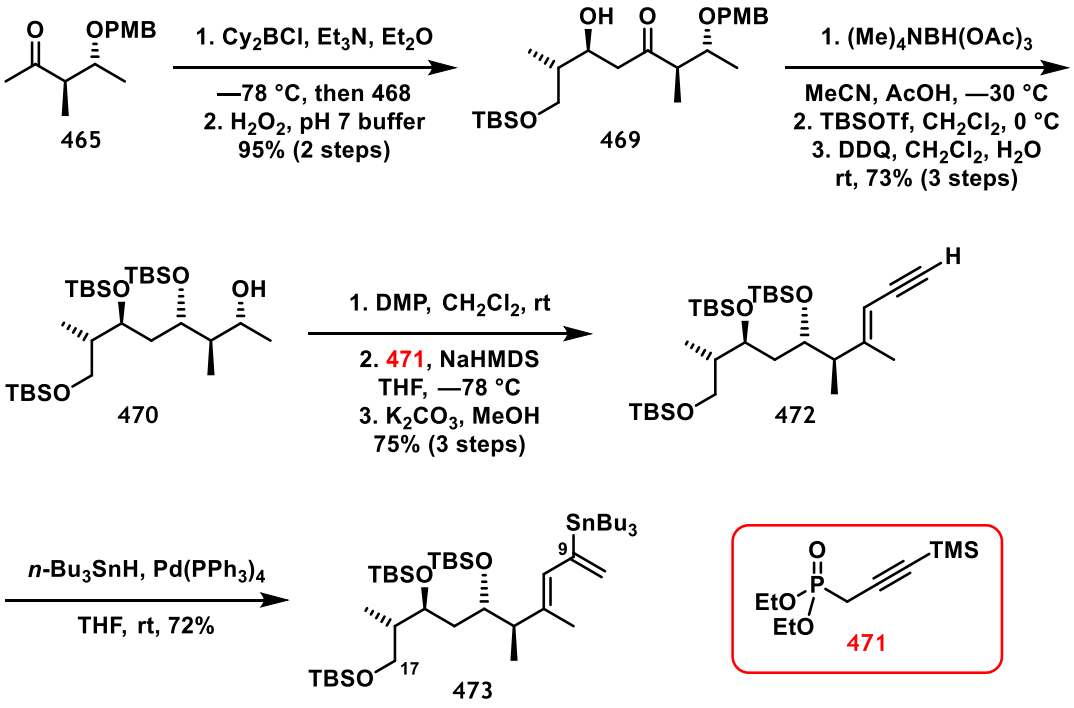
The synthesis of the remainder of the western fragment commenced with protection of Roche ester **466** followed by formation of Weinreb amide **467** (**Scheme 96**). DiBAl-H was then used to reduce the resultant amide **467** to give the aldehyde **468.**



Scheme 96. Synthesis of C-15 to C-17 Fragment

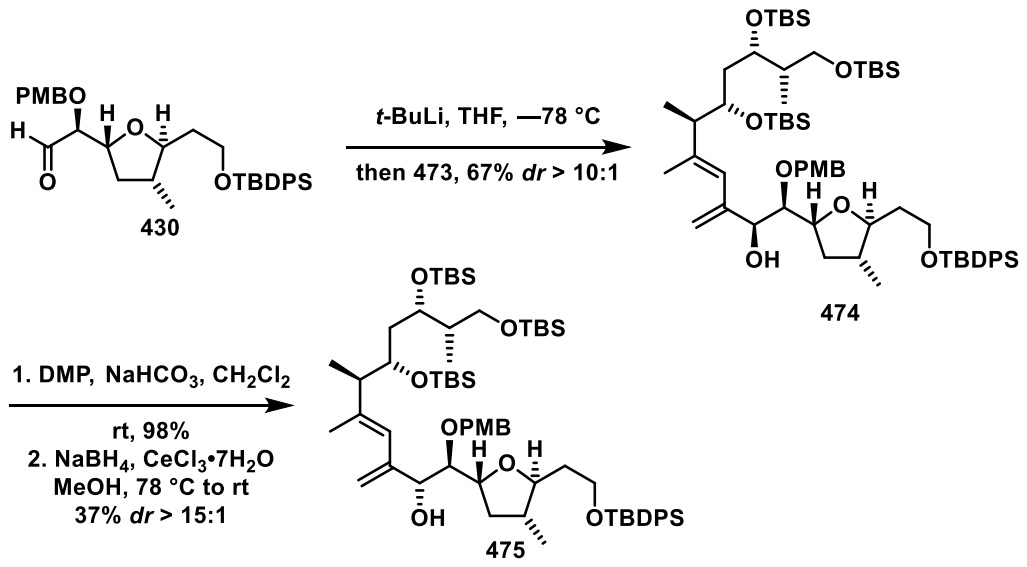
A Paterson aldol reaction was employed to couple the ketone **465** and aldehyde **468** fragments (**Scheme 97**). The stereochemical outcome of this reaction can be rationalised by invoking transition states that are similar to those discussed in **Section 2.1.1** (**Scheme 3**). Stereoselective reduction of the ketone (**469**) followed by protecting group manipulation gave secondary alcohol **470**. DMP was used to oxidise the secondary alcohol and HWE olefination of the resulting ketone followed by removal of the TMS group, gave the (*E*)-enyne **472.** Hydrostanylation of the

alkyne **472** produced the stannane (**473**) required to couple the western fragment to the southern fragment.



Scheme 97. Completion of the C-9 to C-17 Western Fragment

To couple the western and southern fragments together *t*-BuLi was used to convert the stannane (**473**) into the lithiated analogue and this was then added to the aldehyde **430** (**Scheme 98**). The undesired (*S*)-C-8 epimer (**474**) was the major product (*dr* > 10:1). To obtain the required diastereoisomer, the alcohol was oxidised using DMP and the resulting ketone was subjected to a Luche reduction reaction to give the C-8 (*R*) diastereoisomer (**475**) (*dr* > 15:1). Despite the favourable diastereoselective outcome, the yield for alcohol **475** was only 37%.

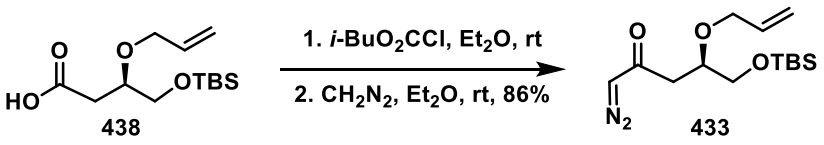


Scheme 98. Completion of the Southern Fragment

3.3 Drawbacks Associated with the Divergent Oxonium Ylide Formation and [2,3]-Sigmatropic Rearrangement Approach

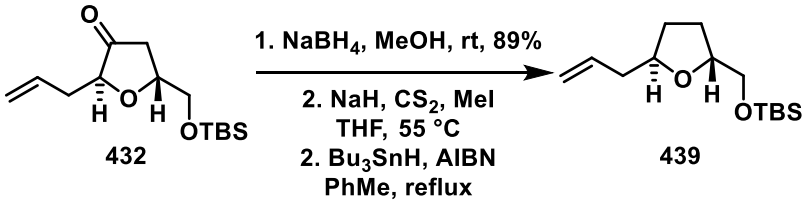
Although the first-generation approach to the synthesis of amphidinolides C and F did result in formation of the carbon framework of the northern and southern fragments, there were a few drawbacks to this approach. One of the drawbacks was the need to correct the stereochemistry at the C-8 position at a late stage in the synthesis, which resulted in a low yield (37%) of the required diastereoisomer (**Scheme 98**). Furthermore, at a future point in the synthesis it would be necessary to cleave the C-15 TBS-ether in the presence of the C-13 TBS-ether. Thus, the protecting group strategy would need to be revised to allow for the selective removal of one of these protecting groups in the presence of the other.

Although the tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement reaction is a very powerful tool for accessing cyclic ethers, such as those seen in the amphidinolides, there are a few disadvantages associated with this approach. Specifically, the use of diazomethane at an early stage of the synthesis is problematic because the scale of diazoketone formation was limited to 2.5 g batches as a result of the equipment available and safety considerations as a consequence of the hazards associated with diazomethane (**Scheme 99**). Such a scale limitation at an early stage in the synthetic route is not ideal.



Scheme 99. Formation of the Diazoketone Limits Scales of Reactions at an Early Stage of the Synthesis

Furthermore, although the carbonyl group in the dihydrofuranone was useful for the incorporation of the methyl substituent required for the THF of the southern fragment, a three-step deoxygenation procedure was required to remove this carbonyl group during the preparation of the THF in the northern fragment (**Scheme 100**). This increased the step count and decreased the overall yield of the route. It should also be noted that the use of a divergent strategy for the synthesis of these natural products has been reported by Carter and co-workers and consequently this initial strategy had lost an aspect of novelty (**Section 2.2.1**). As a result of these observations it was decided to revise the synthetic strategy for the synthesis of these natural products. In the new strategy a divergent approach would not be used so that the syntheses of each fragment could be tailored more specifically and thereby reduced in length.



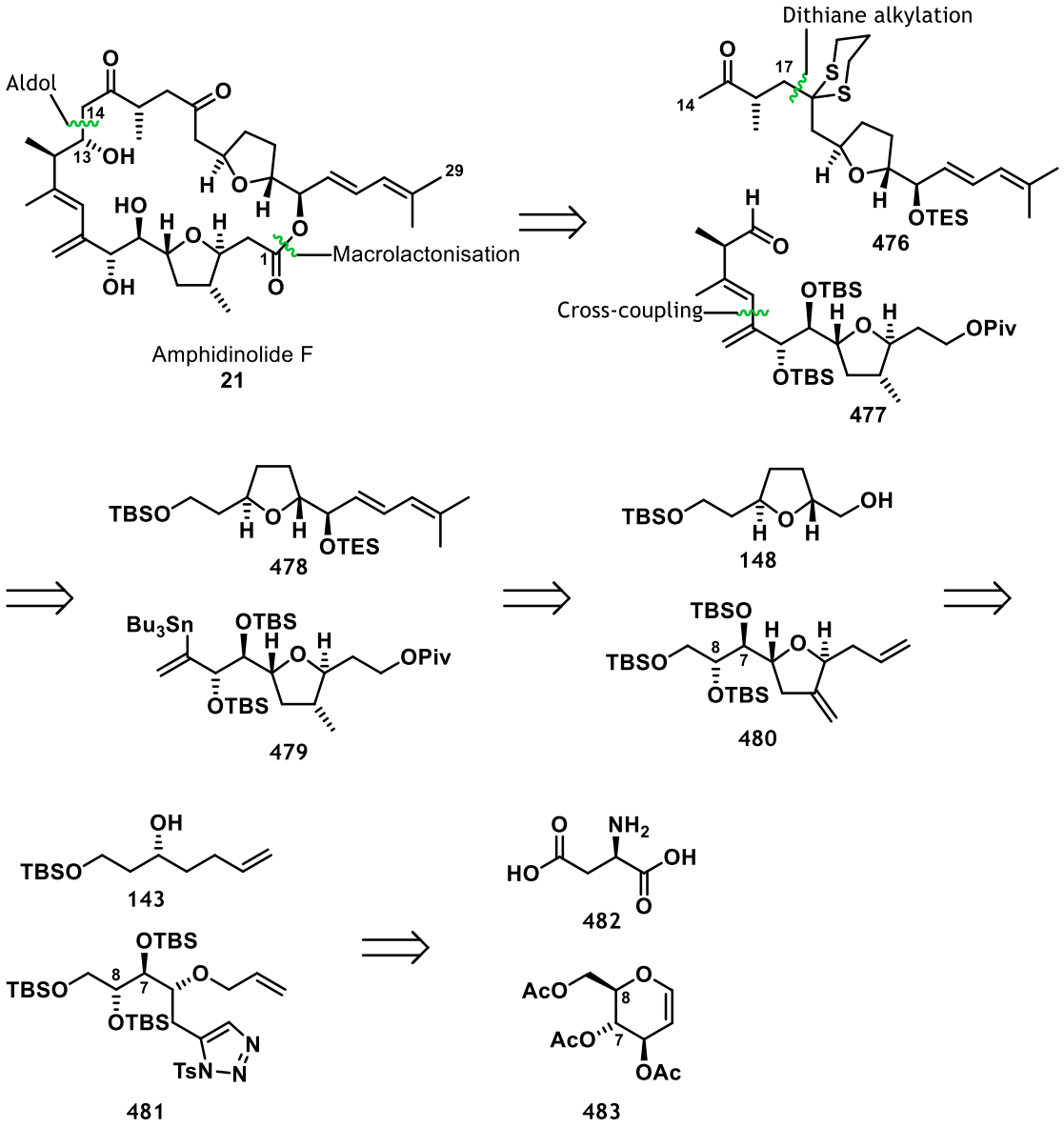
Scheme 100. Three Step Deoxygenation Procedure Increases Step Count for the Synthesis of the Northern Fragment

4 Results and Discussion

4.1 Background to the Revised Retrosynthetic Approach Towards Amphidinolides C and F

As described in **Section 3.2**, the previous Clark group strategy utilised diazo-carbonyl chemistry to access a common dihydrofuranone intermediate that was then used to prepare the northern and southern fragments of amphidinolides C and F. Whilst this strategy was successful in synthesising the two component fragments, the divergent strategy had several issues which resulted in low yielding steps alongside a high step count. Consequently, the synthetic approach was revised, allowing a route more tailored to each fragment to be developed.

Two previous PhD projects conducted simultaneously by L. Decultot (northern fragment, C-14 to C-29) and F. Romiti (southern fragment, C-1 to C-13) within the Clark group (2011–2016) have been devoted to the revised route.[100,101] The strategy employed by Decultot and Romiti focussed on a macrolactonisation reaction and an aldol reaction approach to form the macrocyclic core (**Scheme** 101). Dithiane alkylation reaction was employed to install the C-14 to C-17 fragment of the natural product (**476**), with the THF portion of the aforementioned fragment accessible through an oxidative Mukaiyama cyclisation reaction on the alcohol **143**, which is readily accessible from D-aspartic acid (**482**). The southern fragment (**477**) was accessed from a Stille cross coupling reaction with vinylic stannane **479** and a rhodium-catalysed triazole rearrangement reaction of the triazole **481** to give the required THF intermediate. It was identified that, if a D-glucal derivative (**483**) was used to access the triazole, the configurations of the C-7 and C-8 stereogenic centres correlates with those in the commercially available starting material. This work differs from that of F. Romiti with regards to the synthesis of the southern fragment through the investigation of alternative protecting groups at early stages of the synthesis. For the synthesis of the northern fragment this work differs from that of L. Decultot in the pursuit of a cationic furan generation approach as well as pursuing an alternative synthetic route to synthesise the oxidative Mukaiyama cyclisation precursor. It should be noted that the current synthetic strategy employed by the Clark group has been influenced by the successes and failures of approaches reported in the literature, as described in detail previously (**Sections 2.1–3.2**).



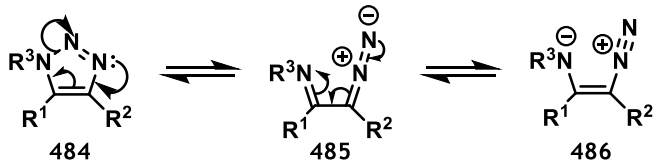
Scheme 101. Current Clark Group Retrosynthetic Analysis

4.2 Southern Fragment Synthesis

4.2.1 Key Features of the Revised Southern Fragment Synthetic Route

D-Glucal was chosen as the starting material for the synthesis of the southern fragment because the configuration of its stereogenic centres correlates with those required in the target fragment. In the previous divergent approach (**Section 3.2**), the desired configuration at the C-8 stereocentre had to be set by employing an oxidation reduction sequence. The use of D-glucal as a starting material removes the necessity for this low yielding sequence.

Another major modification made to the synthetic approach was the use of a tosyl triazole as opposed to a diazoketone for the synthesis of the 2,5-*trans* THF. A Dimroth-type equilibrium exists between a closed triazole (**484**) and an open diazo tosyl iminium (**485**) meaning the this type of intermediate can serve as an analogue of a diazoketone (**Scheme 102**).[102]

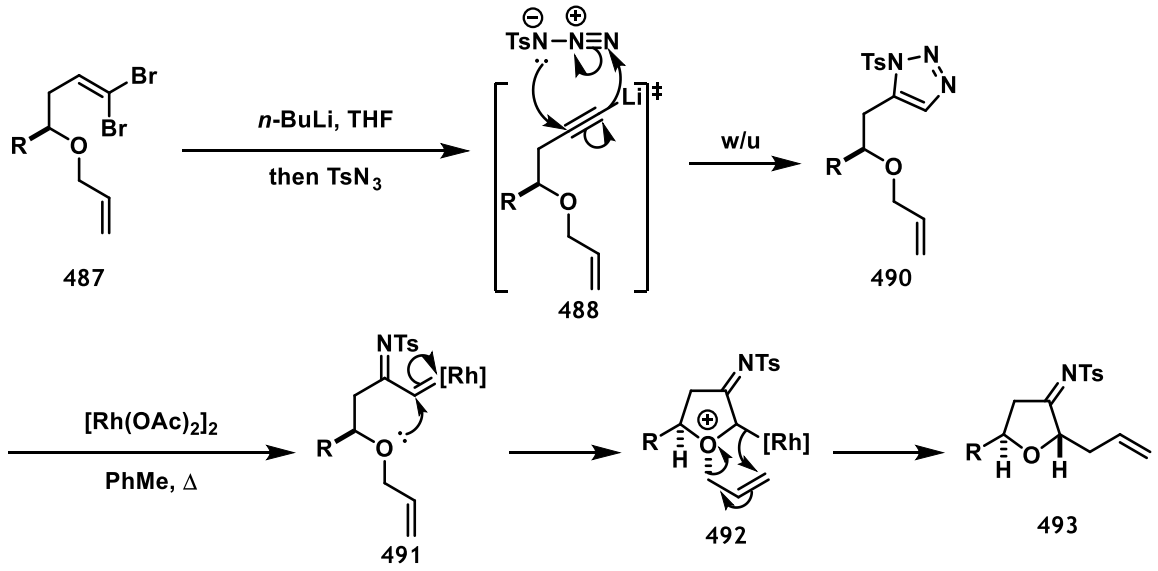


Scheme 102. Dimroth-type Equilibrium Between Triazoles and Diazoimines

The existence of such an equilibrium suggests that triazoles may undergo many of the reactions observed for diazoketones while not suffering from the scale limitations associated with the use of diazomethane for the formation of diazoketones. Changing the substitution on the triazole by adding electron withdrawing groups, such as a sulfonyl group, enables the system to be tuned such that the open diazo form is favoured. This further increases the reactivity of the triazole towards diazoketone type reactivity.

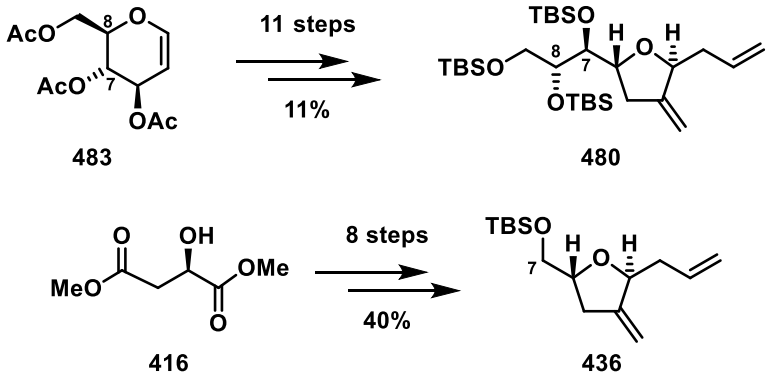
Work performed by Boyer in 2014 indicated that 1,5-sulfonyl triazoles (**490**) could undergo a reaction analogous to the oxonium ylide formation and [2,3]-sigmatropic rearrangement reaction previously employed within the Clark group to access 2,5-*trans* THF rings.[103] This work also established a convenient

route to access appropriate sulfonyl triazoles from di-bromo olefins (**487**) and sulfonyl azides (**489**) (**Scheme 103**).



Scheme 103. Synthesis of Dihydrofuranyl Imines from Di-bromo Olefins

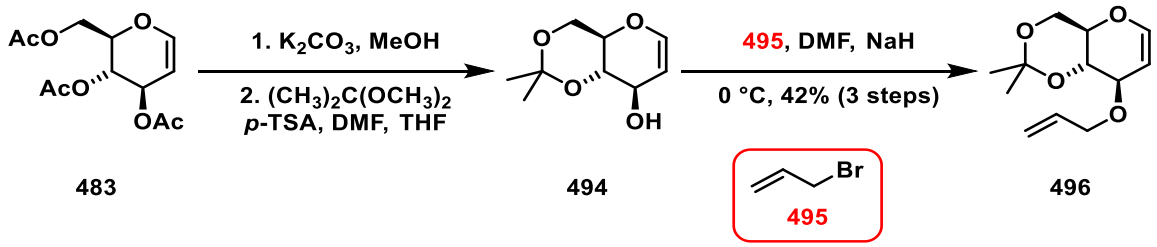
As a result of this work, the use of a D-glucal-derived triazole as an alternative to the previously used diazoketone **433** was proposed. The use of this approach would give access to a 2,5-trans THF with the stereochemistry required for the southern fragment in place from the outset of the synthesis, specifically the stereochemistry at the C-7 and C-8 positions which had previously proven challenging to install (**Scheme 104**). When applying this methodology to the synthesis of amphidinolides C and F it was necessary to devise a concise and scalable route to access the required triazole. To achieve this several protecting group strategies were investigated, with the findings discussed in detail in **Sections 4.2.2–4.2.4**.



Scheme 104. Comparison Between Stereochemical Outcomes and Starting Material

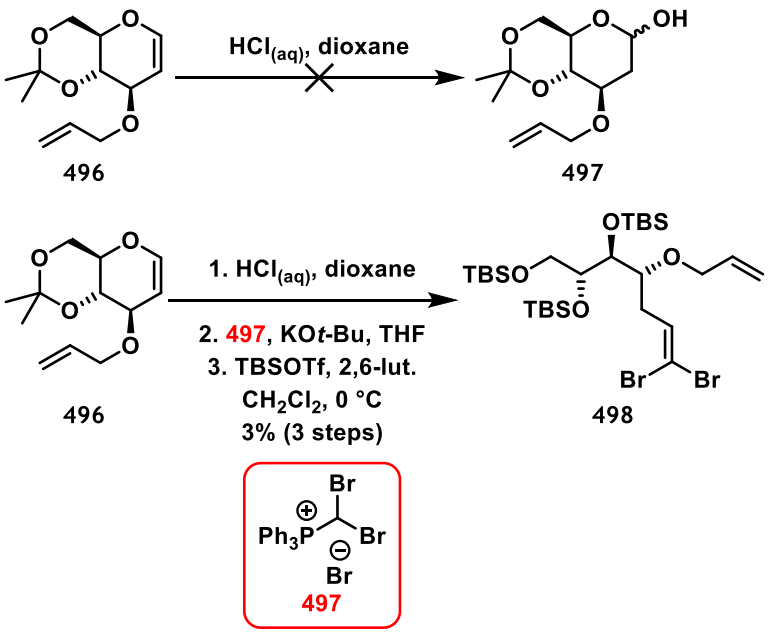
4.2.2 Acetonide Protection

As discussed previously, an appropriate protecting group strategy had to be developed and successfully implemented in order to access the desired triazole. In the first instance an acetonide protecting group was investigated (**Scheme** 105). Starting from tri-*O*-acetyl D-glucal (**483**) the acetate groups were removed using K_2CO_3 in MeOH. Subsequent 1,3-acetonide formation using 2,2-dimethoxypropane gave acetonide **494**. The allylic alcohol was transformed into the allyl ether **496** using a Williamson ether synthesis with allyl bromide (**495**).[104] Unfortunately, this sequence was found to be low yielding (42%) due to the initial acetonide formation.



Scheme 105. Synthetic Route Towards Acetonide Protected D-Glucal

Following acetonide protection, hydration of the dihydropyran double bond was required to give proposed lactol **497** which would be transformed into the required triazole **481** subsequently. To achieve this transformation, the dihydropyran **496** was treated under acidic conditions (**Scheme 106**). This had the unfortunate, but predictable, side effect of removing the acetonide protecting group. The resulting product mixture was not amenable to purification by column chromatography in a wide range of eluent systems because a mixture of several highly polar products with similar R_f values had been obtained. Following hydration of the double bond the crude product mixture was used directly in a Ramirez olefination reaction and the resulting di-bromo olefin was converted to tri-TBS silyl ether **498** in a 3% yield over three steps.[105]



Scheme 106. Efforts to Hydrate Vinyl Ether of Acetonide Protected D-Glucal

The low yield of the hydration-Ramirez olefination reaction sequence meant that alternative strategies were necessary to produce the desired lactol **497** in an acceptable yield. Acid sources other than aqueous HCl that would allow for precise control over the quantity of water added, were investigated (**Table 3**). It was found that the most promising outcome was observed when $HBr{\cdot}PPh_3$ in THF was used as the acid source. In this case there was consistent evidence for formation of the lactol. A similar outcome was reported by Mioskowski *et. al.* in 1990.[106] It was proposed that limiting the quantity of water present might retard the hydrolysis of the acetonide protecting group sufficiently to enable isolation of the desired lactol with the acetonide group remaining in place. Unfortunately, alteration of the volume of water added to the reaction mixture failed to change the outcome of the reaction. Despite evidence in the ^1H NMR spectrum of the crude material that indicated hydration of the double bond, specifically the absence of the distinctive alkene protons at C-4 and C-5 as well as the appearance of a small peak at ~9 ppm presumably corresponding to the aldose form of **497**,these conditions were still incompatible with the acetonide because they also led to hydrolysis of the protecting group. Isolation and purification of the lactol product, therefore, remained challenging.

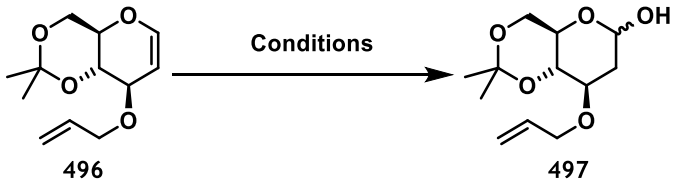
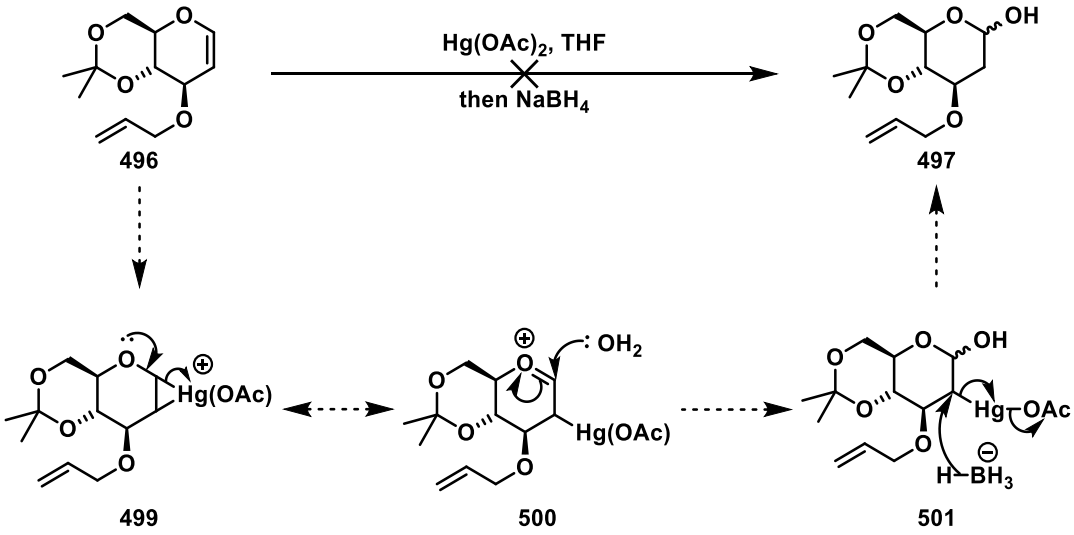


Table 3. Conditons Investigated to Avoid Acetonide Hydrolysis

Acid Source	Equivalents	Water / mL	Solvent (1 mL)	Evidence of lactol in ^{1}H NMR
$HBr•PPh_3$	0.2	0.05	THF	Yes
$HBr•PPh_3$	1	0.05	THF	Yes
$HBr•PPh_3$	0.2	0.05	CH_2Cl_2	No
$HBr•PPh_3$	1	0.05	CH_2Cl_2	No
$HCl•Et_2O$	1	0.05	CH_2Cl_2	Yes
$HCl•Et_2O$	1	0.05	THF	No

As shown in **Table 3**, acidic hydration of the double bond was found to be unfruitful and consequently an alternative hydration methodology was considered. It was envisaged that an oxymercuration-demercuration sequence would deliver the required lactol **497** (**Scheme 107**). In theory this reaction would progress by the formation of merconium ion **499**, with water quenching the cation at the more electrophilic carbon (α to the pyran oxygen) to give the lactol intermediate **501**. Demercuration using $NaBH_4$ would then result in formation of the required lactol **497**. Nevertheless, when this was attempted only quantitative recovery of starting material was observed with no evidence of lactol formation.

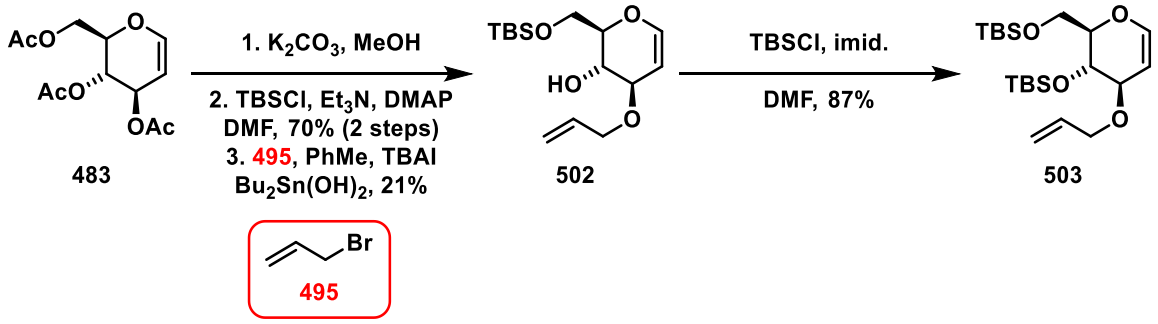


Scheme 107. Proposed Oxymercuration-Demercuration Strategy to Hydrate the Vinyl Ether

4.2.3 Silyl Protection

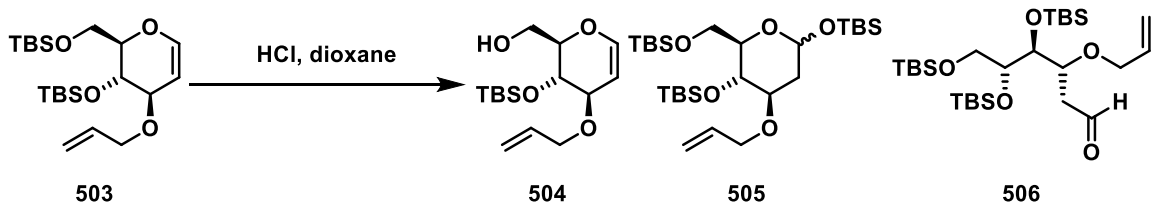
From the results of the acetonide protecting group approach, it was evident that stability under acidic conditions was key to the development of a successful protecting group strategy. Given the diverse range of readily available silyl protecting groups with a variety of stabilities it was decided to investigate a silyl protecting group strategy. Initially a 1,3-di-TBS protection strategy was proposed. Although TBS groups are not notably acid stable, they do withstand acidic conditions better than acetonide protecting groups. In the synthetic sequence the primary alcohol was TBS protected and then a tin-mediated ether synthesis was employed to form allyl ether **502** (**Scheme 108**). While the yield for this tin

mediated ether synthesis appears much less effective than the corresponding reaction using the TBDPS protected D-glucal derivative, the reaction was performed only once. As the reaction provided sufficient material to determine that the hydration of **503** would not be feasible moving forward it was not repeated to optimise yields. Finally, the remaining allylic alcohol was TBS-protected to give D-glucal derivative **503**.



Scheme 108. Synthetic Route Towards Di-TBS Ether D-Glucal Derivative

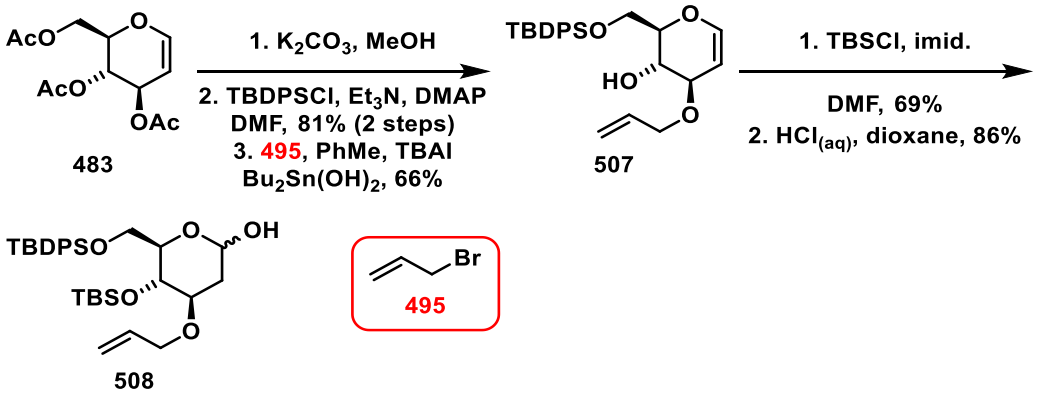
A wide range of products were formed when the di-TBS protected glucal derivative **503** was subjected to acidic hydration (**Scheme 109**). Principally, loss of the primary TBS group resulted in formation of alcohol **504**. The tri-TBS protected product **505** was also observed suggesting that TBS migration to the newly formed lactol hydroxyl group was occurring. An alternative product, **506**, generated by TBS migration on to the aldose form of the lactol was also identified.



Scheme 109. Observed Products from Attempted Hydration of Di-TBS D-Glucal Derivative

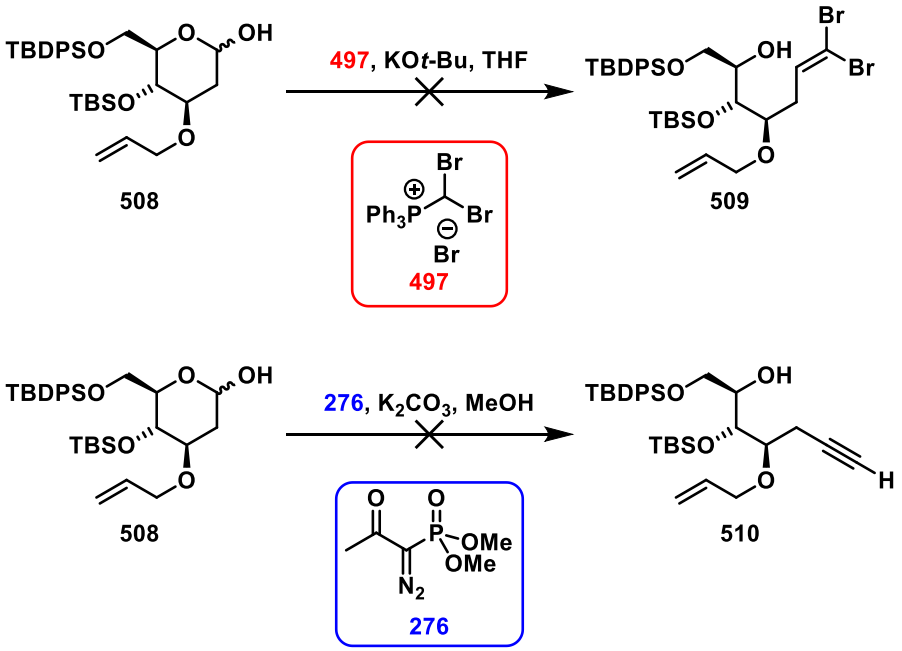
To avoid the acid sensitivity issue associated with the primary TBS ether, the more acid stable TBDPS group was introduced instead (**Scheme 110**). An analogous synthetic approach was utilised to prepare this di-silyl ether whereby the primary alcohol was TBDPS protected and then a tin mediated ether synthesis was employed to form allyl ether **507**. Finally, the remaining alcohol was TBS

protected, with subsequent hydration of the internal double bond proceeding smoothly to produce the lactol **508** in 86% yield.



Scheme 110. Synthesis of the Primary TBDPS Ether D-Glucal derivative

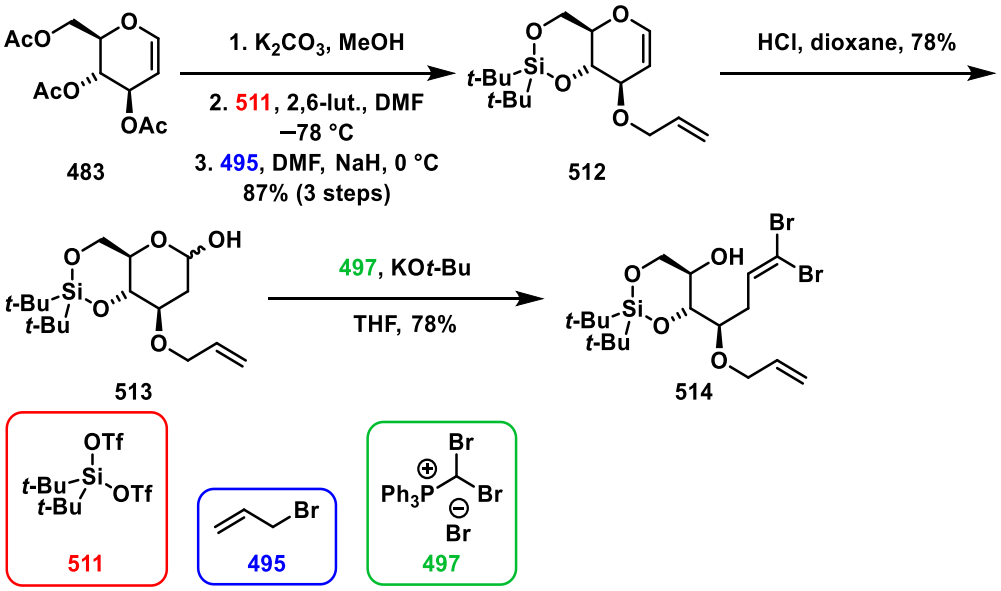
Ramirez olefination has been successfully applied to similar lactol substrates within the Clark group and was therefore the initial proposal for the synthesis of the required alkyne or alkyne precursor.[100] Unfortunately, attempts to access dibromo-olefin **509** using a Ramirez olefination on lactol **508** were unfruitful (**Scheme 111**). As an alternative, direct synthesis of the alkyne **510** by Seyferth-Gilbert homologation with the Bestmann-Ohira reagent **276** was also investigated.[107] However, this too was unsuccessful and merely resulted in quantitative re-isolation of the starting material. Although it is not clear why neither the Ramirez olefination and Seyferth-Gilbert homologation were successful on lactol **508** it is possible that the increased steric bulk associated with the use of a TBS and TBDPS protecting groups, when compared to the use of the single bis *tert*-butyl silyl protecting group which was employed successfully (**Section 4.2.4**), meant that the reactants could not get close enough together to react.



Scheme 111. Attempts to Form the Dibromo Olefin and Alkyne from Lactol 508

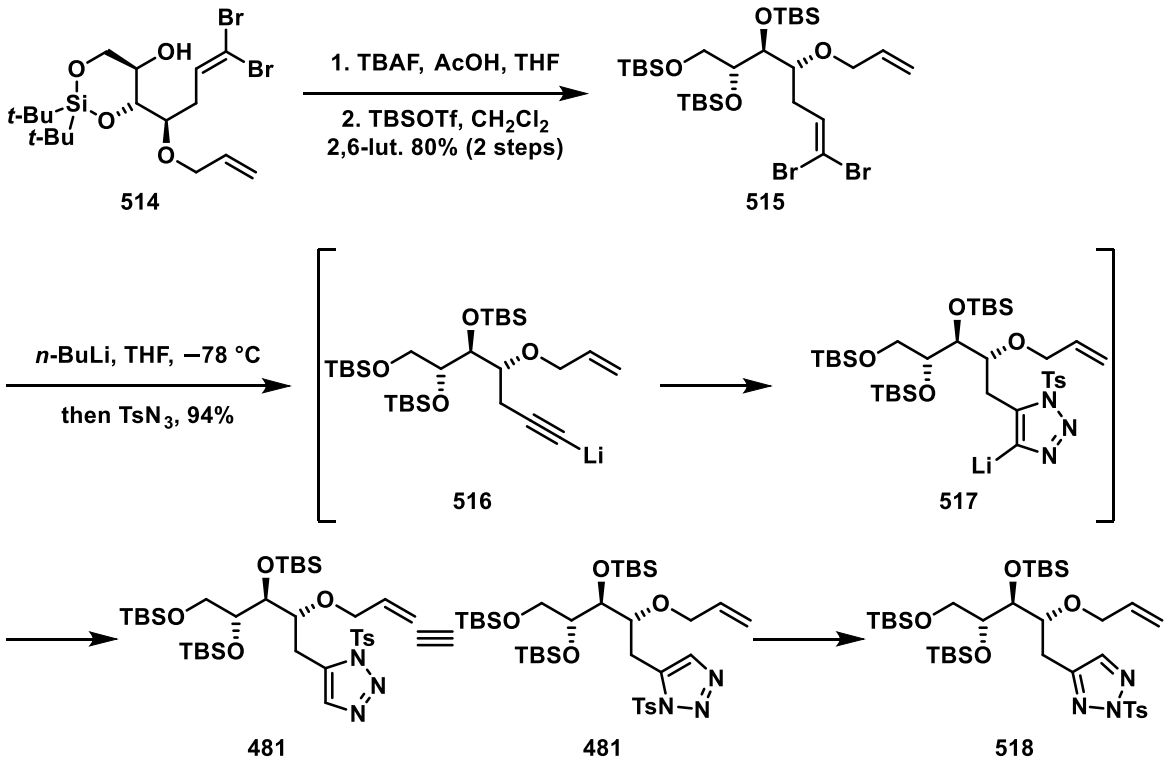
4.2.4 Di-*tert*-Bu Silyl Protecting Groups

Following the unsuccessful use of TBS and TBDPS silyl ethers a more niche silyl protecting group was investigated. The di-*tert*-butyl silyl group has been employed to protect 1,3-diols previously within the Clark group with great success.[100] This protecting group is very stable under acidic conditions and favours 1,3-diol protection over competing 1,2-diol protection. This feature meant that an increased yield of the desired protection product **512** was observed in comparison to the acetonide-protected D-glucal derivative **496** (**Scheme 112**). This increase in yield could also be attributed to the irreversible nature of this protection reaction. The synthesis began, again, from tri-*O*-acetyl D-glucal with the removal of the acetyl groups and formation of the di-*tert*-butyl silylene derivative and subsequent Williamson ether synthesis to give the allyl ether **512**.[104] Hydration of the cyclic enol ether proceeded smoothly to produce the lactol **513**. Ramirez olefination of lactol **513** gave di-bromo olefin **514**.[105]



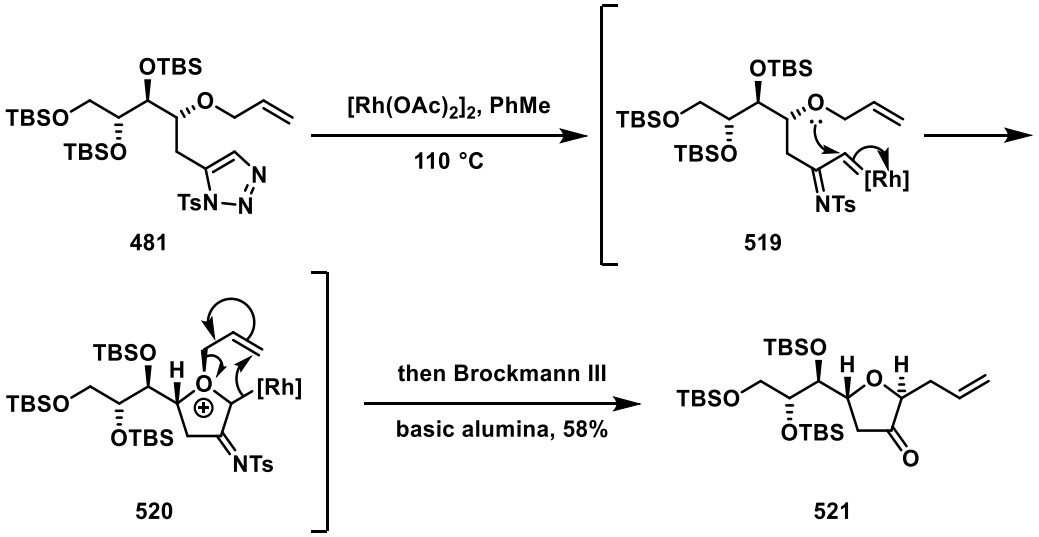
Scheme 112. Synthesis of the Di-tert-Bu Silyl Protected D-Glucal Derivative

Cleavage of the di-*tert*-butyl silylene was effected using TBAF and an acetic acid buffer which had been shown to be necessary to prevent decomposition of the starting material **514** (**Scheme 113**). The resulting triol was then directly converted into the tri-TBS ether **515**. Treatment of di-bromo olefin with two equivalents of *n*-BuLi resulted in the formation of lithiated alkyne **516** which, when treated with tosyl azide, resulted in formation of lithiated triazole **517**. After aqueous work-up the 1,5-disubstitued 1,2,3-triazole **481** was isolated in a yield of 94%. Due to the propensity of the 1,5-disubstitued 1,2,3-triazole **481** to isomerise to give the less sterically encumbered 1,4-disubstituted 1,2,3-triazole **518** when concentrated, as well as on silica gel, it was imperative to perform rapid chromatographic purification of the desired triazole and store it as a 1 M solution in toluene.



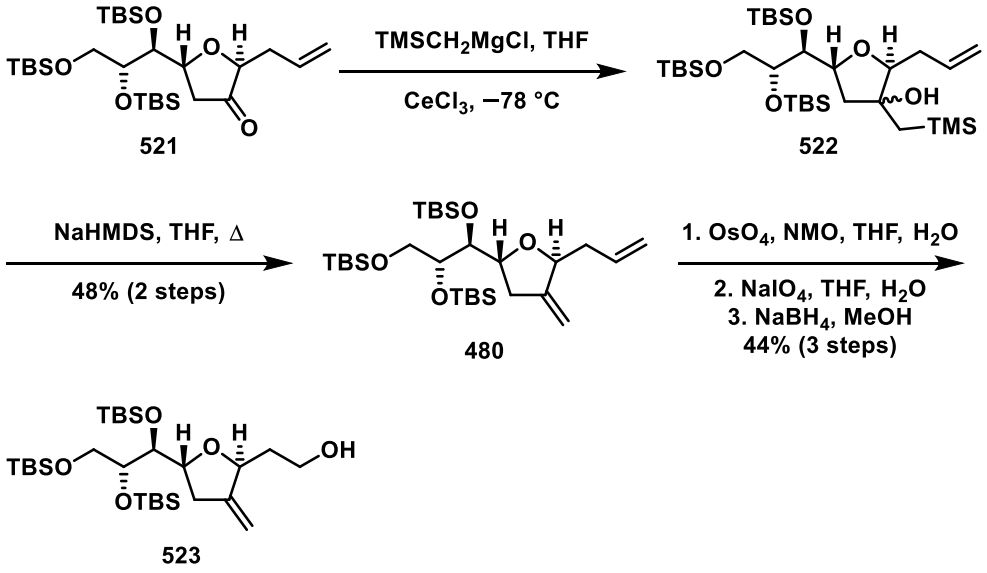
Scheme 113. Synthesis of Tosyl-Triazole 481

Rhodium-catalysed de-nitrogenation of tosyl triazole **481** gave metallocarbenoid intermediate **519**, where a subsequent intramolecular cyclisation gave the metal-bound oxonium ylide **520** (**Scheme 114**). An apparent [2,3]-sigmatropic rearrangement reaction then produced the desired 2,5-*trans* ring system and subsequent addition of basic alumina (Brockmann III) to the reaction mixture resulted in hydrolysis of the initially formed N-tosyl imine to give the 2,5-*trans* dihydrofuranone **521**.



Scheme 114. De-nitrogenation and [2,3]-Sigmatropic Rearrangement to give Dihydrofuranone 521

A Peterson olefination sequence was used to convert dihydrofuranone **521** to *exo*-cyclic alkene **480** (**Scheme 115**).[68] Previous work within the group had shown that this substrate was prone to epimerisation under Wittig olefination conditions.[100] To avoid epimerisation, freshly prepared TMS-methyl magnesium chloride was added to anhydrous cerium trichloride to give the corresponding organocerium reagent. Addition of dihydrofuranone **521** to the solution of organocerium reagent resulted in the formation of sterically hindered tertiary alcohol **522**. The Peterson elimination to give the diene **480** was effected by heating the crude tertiary alcohol with NaHMDS in THF under reflux. Upjohn dihydroxylation of the alkene followed by periodate cleavage of the resulting diol and then $NaBH_4$ reduction gave alcohol **523**.[108] During the dihydroxylation step it was imperative to use no more than 1.2 equivalents of NMO, the stoichiometric re-oxidant, to ensure it was only the less sterically hindered primary alkene which underwent dihydroxylation.



Scheme 115. Synthesis of Alcohol 523

In the synthesis of the T series of amphidinolides, within the group, Crabtree's catalyst had been employed to promote the hydrogenation of a similar *exo*-cyclic alkene.[92] In this case, the iridium catalyst displayed high activity and delivered excellent diastereoselectivity arising from co-ordination between the primary hydroxyl group and the catalyst to form the complex **524.** Previous work within the group found that even equimolar quantities of Crabtree's catalyst gave a yield of only 24% of the desired (*R*) alkane **525** (**Table 4**).[100] Raising the reaction temperature was not deemed to be a viable option for improving the reaction outcome because of the thermal instability of Crabtree's catalyst, which has a propensity to irreversibly form inactive clusters at higher temperatures in the presence of hydrogen and so alternative catalysts were investigated.[109] Work by Kerr had shown that an iridium catalyst possessing an *N*-heterocyclic carbene, along with a bulky phosphine ligand, exhibited increased reactivity as well as an increased thermal stability.[110] Use of these alternative catalysts gave pleasing yields with catalyst loadings as low as 1 mol%.

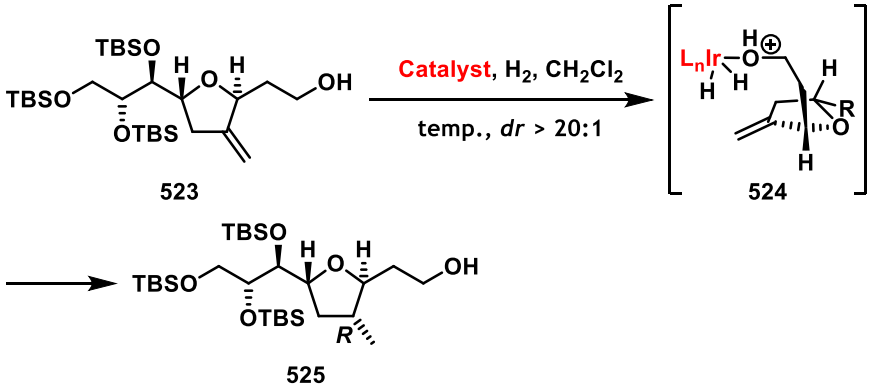
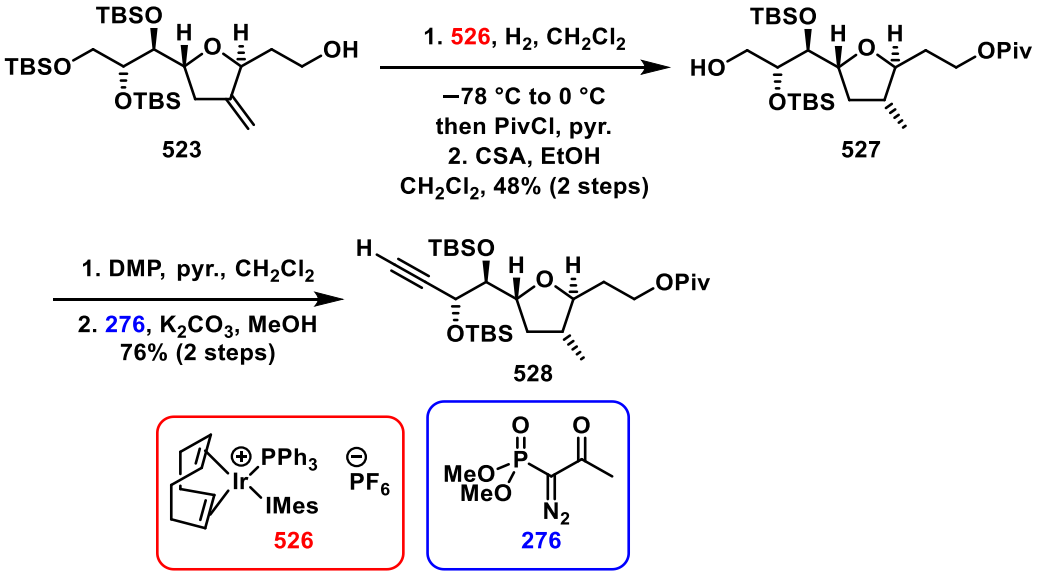


Table 4. Iridium Catalysts Investigated to Stereoselectively Reduce exo-Cyclic Alkene

Catalyst	Equivalents of Catalyst	Temp.	Time/h	Yield/%
$[Ir(cod)(pyr)(PCy_3)]PF_6$	0.1	rt	24	0 (0)[a]
$[Ir(cod)(pyr)(PCy_3)]PF_6$	0.2	rt	24	0
$[Ir(cod)(pyr)(PCy_3)]PF_6$	0.5	rt	24	14 (0)
$[Ir(cod)(pyr)(PCy_3)]PF_6$	1	rt	24	24
$[Ir(cod)(IMes)(PPh_3)]PF_6$	0.1	−78 °C to rt	0.5	97 (67)[a]
$[Ir(cod)(IMes)(PPh_3)]PF_6$	0.05	−78 °C to rt	0.5	96 (68)[a]
$[Ir(cod)(IMes)(PPh_3)]PF_6$	0.01	−78 °C to rt	1	96 (64)[a]

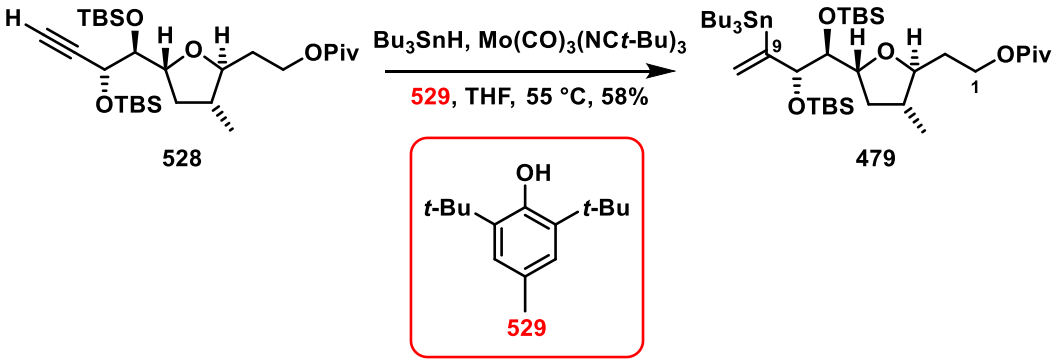
[a] Presented yields reported by F. Romiti except yields in brackets which were reported by D. Mills.

Following directed hydrogenation of the *exo*-cyclic alkene **523** with catalyst **526** the primary hydroxyl group was protected as pivalate ester in a one-pot process and the primary TBS protecting group was removed under acidic conditions, to furnish alcohol **527** in 48% over two steps (**Scheme 116**). The alkyne **528** was obtained by oxidation of the alcohol with DMP followed by Seyferth-Gilbert homologation, with Bestmann-Ohira reagent.[107,111]



Scheme 116. Stereoselective Reduction and Seyferth-Gilbert Homologation to Synthesise Alkyne 528

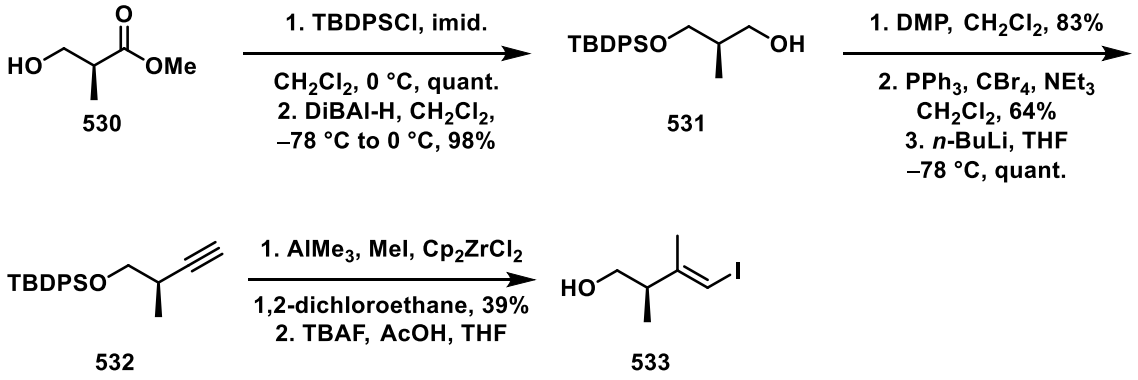
Regio-selective hydrostannylation of the alkyne was employed to furnish the C-1 to C-9 fragment of the natural product (**Scheme 117**). A protocol developed by Kazmaier, in which a sterically encumbered molybdenum catalyst is employed, was used to give predominantly the α-vinylic stannane **479**.[65] Use of $Pd(PPh_3)_4$ to catalyse the hydrostannylation reaction resulted in a reversal of the regioselectivity and produced a 4:1 ratio of isomers in favour of the undesired *E*-olefin.[100]



Scheme 117. Synthesis of Vinylic Stannane 479

Stille cross coupling was to be employed to couple vinylic stannane **479** with vinylic iodide **533** and thereby complete the southern fragment of the natural product.[112] The synthesis of vinylic iodide began with the protection of (*S*)-Roche ester as a TBDPS ether and subsequent reduction of the ester affording alcohol **531** (**Scheme 118**). Oxidation of the alcohol using DMP followed by a

Seyferth-Gilbert homologation using Bestmann-Ohira reagent gave alkyne **532.**[107,111] An iodomethylation reaction was employed to synthesise the requisite vinylic iodide and upon cleavage of the TBDPS ether using TBAF and AcOH vinylic iodide **533** was produced. Regrettably, the coupling of vinylic iodide **533** with vinylic stannane **479** was never successfully carried out due to time constraints.



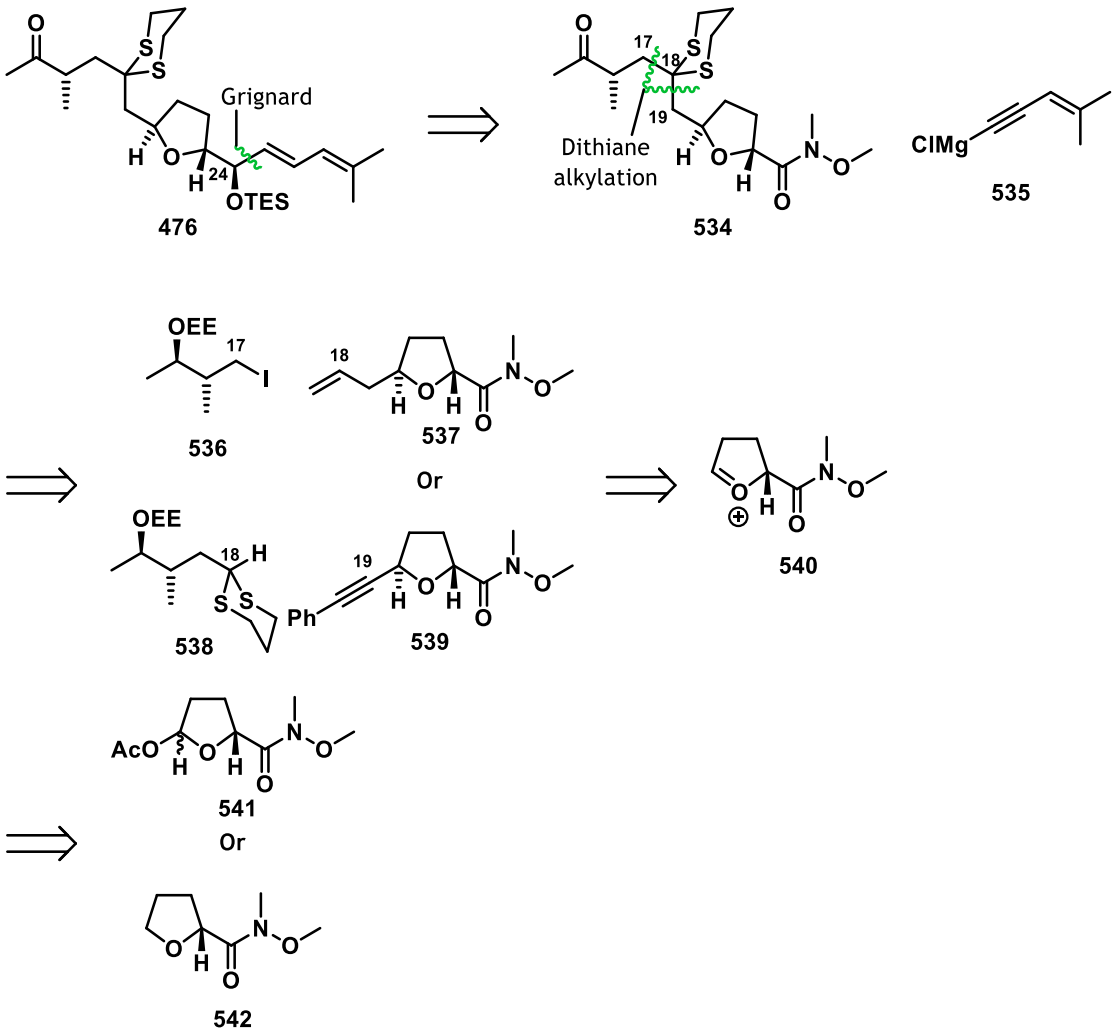
Scheme 118. Synthesis of Vinylic Iodide 533

4.3 Northern Fragment

For the synthesis of the northern fragment, it would be beneficial to avoid a dihydrofuranone intermediate so that deoxygenation would not be necessary. Two synthetic approaches were investigated to achieve this goal: cationic furan generation, and an oxidative Mukaiyama cyclisation reaction. Both will be discussed in detail in the following sections.

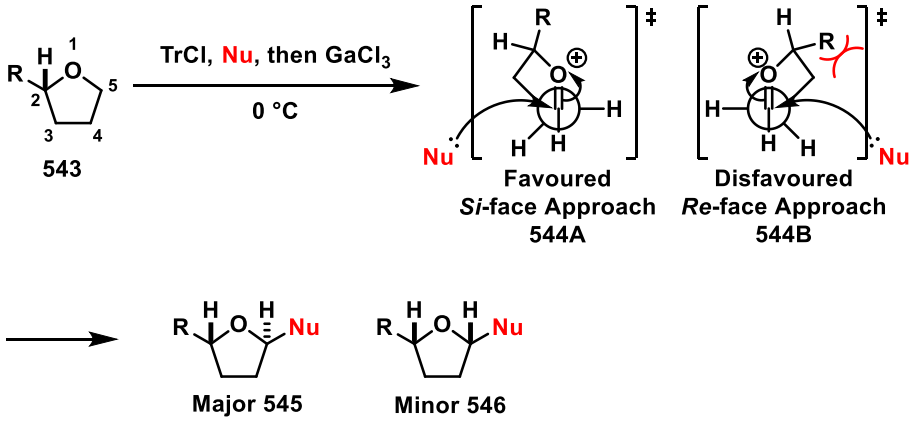
4.3.1 Cationic Furan Generation

In the retrosynthetic analysis for the northern fragment of the natural product a Grignard reaction to install the required C-24 side chain by use of the Weinreb amide **534** was proposed (**Scheme 119**). A dithiane alkylation reaction was proposed to install the C-14 to C-17 (**536**) or C-14 to C-18 (**538**) fragment. This approach appeared to be beneficial because it afforded a degree of flexibility to the synthesis by allowing the alkylation reaction to be altered by choice of nucleophile being used to quench the furan cation. Either an allyl or alkynyl group could be used to quench the cationic species and so deliver **537** or **539** respectively. Generation of the cationic species was also proposed to be achieved in two fashions; by use of trityl chloride to abstract a hydride from a furan ring **542**, or by use of an appropriate leaving group (such as an acetate) in **541**.



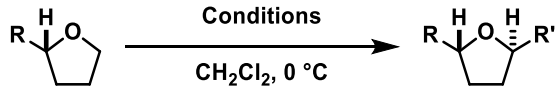
Scheme 119. Retrosynthetic Analysis for the Northern Fragment of Amphidinolide F

Recent work by Liu and co-workers has shown that trityl cations can be used as hydride abstractors to effect C-H functionalisation on cyclic ethers. Liu and co-workers showed that a trityl cation can be used to abstract a hydride α to a hetero-atom, for example in THF (**Scheme 120**).[113] While this work reports examples with *dr* ≥ 20:1 in favour of the *trans*-THF these examples had substitution at the C-3 position either exclusively or alongside substitution at the C-2 position. The selectivity observed on substrates with only C-2 substitution, as would be the case in the proposed synthesis reported here, was significantly more modest and a *dr* = 3:1 in favour of the *trans*-THF **545** was obtained in most cases.



Scheme 120. Trityl Mediated Cation Formation

Although a test reaction using THF as the substrate was successful, yielding a similar result to that reported by Liu *et. al.*, reactions performed using substituted furans **547**, **548**, and **549** did not deliver the expected products (**Table 5**).[113] Initially racemic Weinreb amides and protected alcohols were synthesised to investigate the possibility of applying an analogous reaction to the synthesis of the northern fragment of the natural product. Unfortunately, the use of both trifluoroborates and Grignard reagents alongside a variety of Lewis acid promoters failed to elicit any reaction. Whilst the study conducted by Liu *et. al.* showcased promising outcomes, simple alkyl substituted cyclic ethers were used as substrates in most cases, with the only heteroatom being the ethereal oxygen of the cyclic ether.[113] The presence of multiple heteroatoms may have attenuated the electrophilicity of the trityl cation, and thus its ability to abstract hydride. This would prevent the formation of the reactive cationic furan intermediate and therefore prohibit formation of the desired product.



542: R = CO(N(OMe)Me)

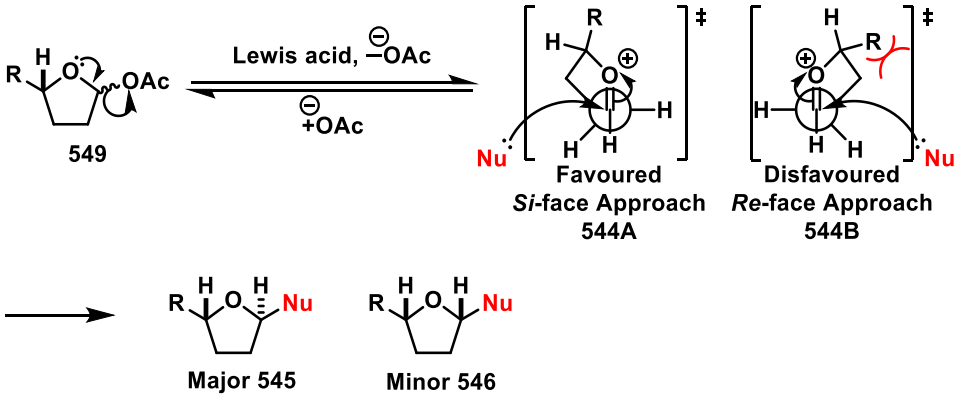
547: R = CH_2OTBS

548: R = CH_2OTr

Table 5. Conditions Explored to Mediate Hydride Abstraction

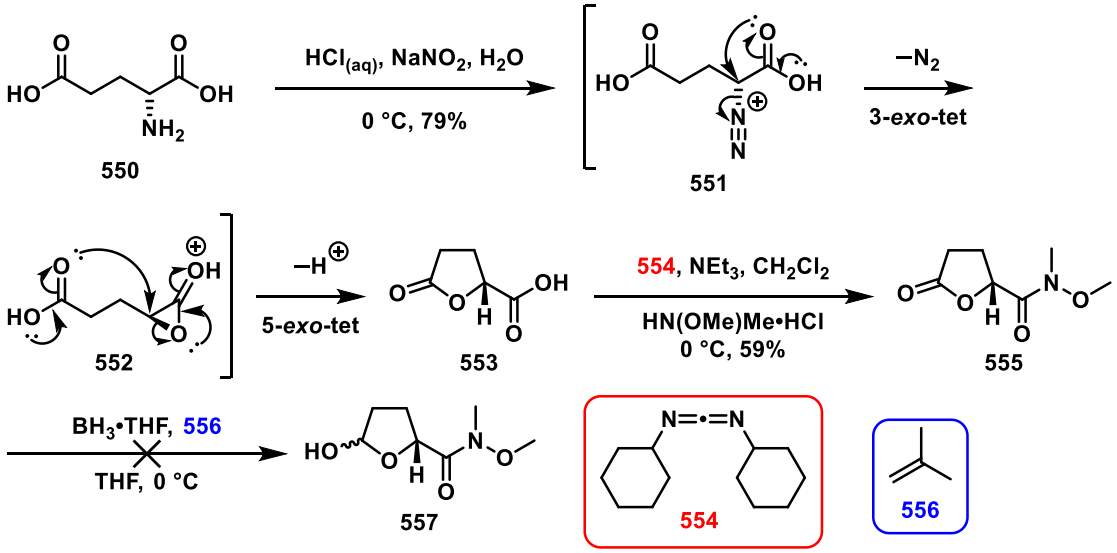
Substrate	Trityl source	Nucleophile	Yield / %
THF	$FeCl_3$, TrCl	K[F_3BCCPh]	20
542	$GaCl_3$, TrCl	K[F_3BCCPh]	0
542	$FeCl_3$, TrCl	K[F_3BCCPh]	0
542	$TrBF_4$	K[F_3BCCPh]	0
542	$TrBF_4$	CH_2CHCH_2TMS	0
547	$FeCl_3$, TrCl	K[F_3BCCPh]	0
547	$TrBF_4$	K[F_3BCCPh]	0
547	$TrBF_4$	CH_2CHCH_2TMS	0
548	$TrBF_4$	CH_2CHCH_2TMS	0

As shown above (**Table 5**), hydride abstraction using a trityl cation was not an effective method for generating the desired 2,5-*trans* THF. The general concept of using a furan cation remained appealing due to the inexpensive nature of the proposed starting materials as well as the potential for improved scalability as a result of the absence of diazomethane as a reagent. An alternative method which may be employed to form a cationic species involves the elimination of a leaving group from the starting material (**Scheme 121**). The leaving group is commonly an alkoxide, generated from the corresponding lactol, or a carboxylate which can leave under comparatively mild conditions.



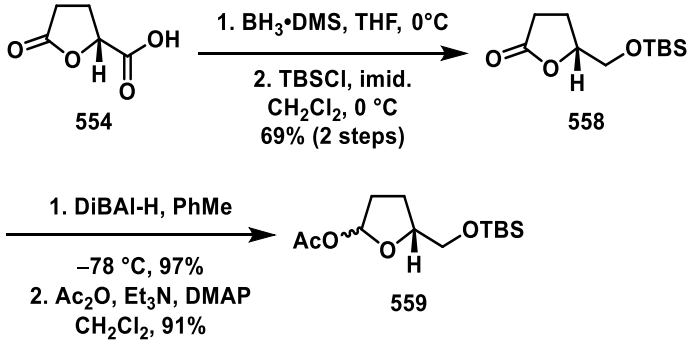
Scheme 121. Cation Formation Following Eviction of a Leaving Group

Investigation of this route began with the formation of the acetate, which was prepared from D-glutamic acid (**550**) following a procedure reported by Akita *et. al*. for accessing (*R*)-γ-lactones (**Scheme 122**).[114] Deamination of D-glutamic acid using a nitrosonium ion, generated *in situ* from sodium nitrite and HCl, results in formation of (*R*)-γ-lactone **553** with net retention of configuration at the stereogenic centre. The retention of configuration arises through a double Walden inversion process. Initially the nitrous acid reacts with the amine moiety to form diazonium intermediate **551**, the α-carboxylic acid then displaces dinitrogen in a 3-*exo*-tet cyclisation reaction to form the strained α-lactone **552** accounting for the initial Walden inversion. The γ-carboxylic acid then opens the α-lactone, to relieve the strain of the three-membered lactone and form the γ-lactone **553**. This reaction accounts for the second Walden inversion and observed net retention of configuration. The carboxylic acid **553** was converted into the corresponding Weinreb amide **555** by use of *N,N'*-dicyclohexylcarbodiimide (DCC) (**554**) as a dehydrating reagent. Unfortunately, efforts to reduce the lactone to the corresponding lactol resulted in complex mixtures of products from which the required lactol **557** was not isolable.



Scheme 122. Attempted Synthesis of Lactol with Wienreb Amide Present

It is proposed that the observed complex mixture of products was arising due to the Weinreb amide being incompatible with the reductive conditions. To circumvent this issue an alternative route was used. In this case, the carboxylic acid was selectively reduced in the presence of the lactone to give the primary alcohol and the free hydroxyl group was protected as the TBS ether **558** (**Scheme** 123). Carboxylic acids have been reduced to their corresponding alcohols using BH_3 complexes extensively in the literature and the selectivity for carboxylic acids in the presence of other carbonyl species is usually good.[115] Reduction of lactone **558** using DiBAl-H gave the corresponding lactol which was subsequently converted into the acetate **559**.



Scheme 123. Selective Reduction of Carboxylic Acid in the Presence Lactone Functionalities

To investigate the interception of the cation generated by loss of the acetate group a range of nucleophiles were tested. The initial nucleophile employed was

the allylmagnesium chloride which reacted to give a mixture of products from which the desired product was not isolable (**Table 6**). Changing the nucleophile to allyl TMS resulted in 57% yield of 2,5-substituted THF with a *dr* = 1.3:1 in favour of the *trans* diastereoisomer **560**. While changing the nucleophile to the allyl tin reagent resulted in a moderate improvement of the diastereoselectivity of the reaction and gave a *dr* = 1.6:1 in favour of the required *trans* diastereoisomer. However, the compromised yield of this reaction was not acceptable. As a consequence of the low diastereoselectivities and yields observed using the cationic furan approach, this route was abandoned.

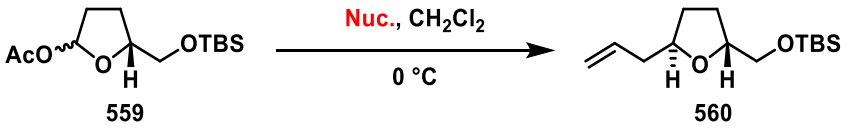


Table 6. Investigation of a Range of Nucleophiles to Quench Cationic Furan

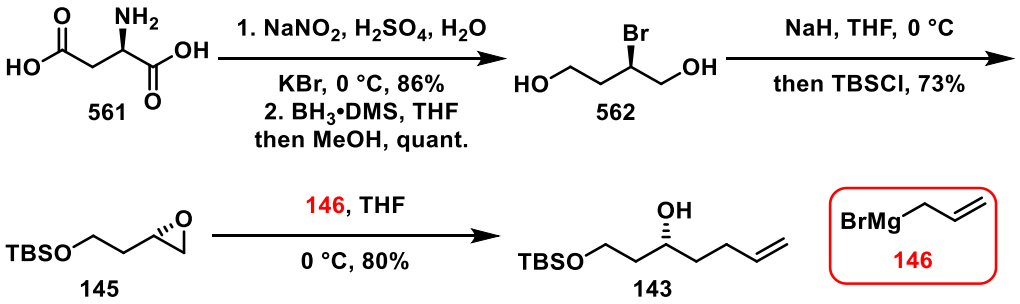
Nucleophile (Nuc.)	Yield	Diastereoselectivity
AllylMgCl	0	N/A
Allyl TMS	57	1.3:1
$AllylSnBu_3$	12	1.6:1

4.3.2 Oxidative Mukaiyama Cyclisation

An alternative route, using an oxidative Mukaiyama cyclisation, to form 2,5-*trans* THFs was used. The reaction had been shown to be an efficient approach by Pagenkopf *et. al.*[59] The application of this methodology had previously proved powerful for the preparation of fragments and in total syntheses of amphidinolides C and F published by other groups.[57,58] Consequently, the decision was made to apply this methodology to the synthesis of the northern fragment of the natural product.

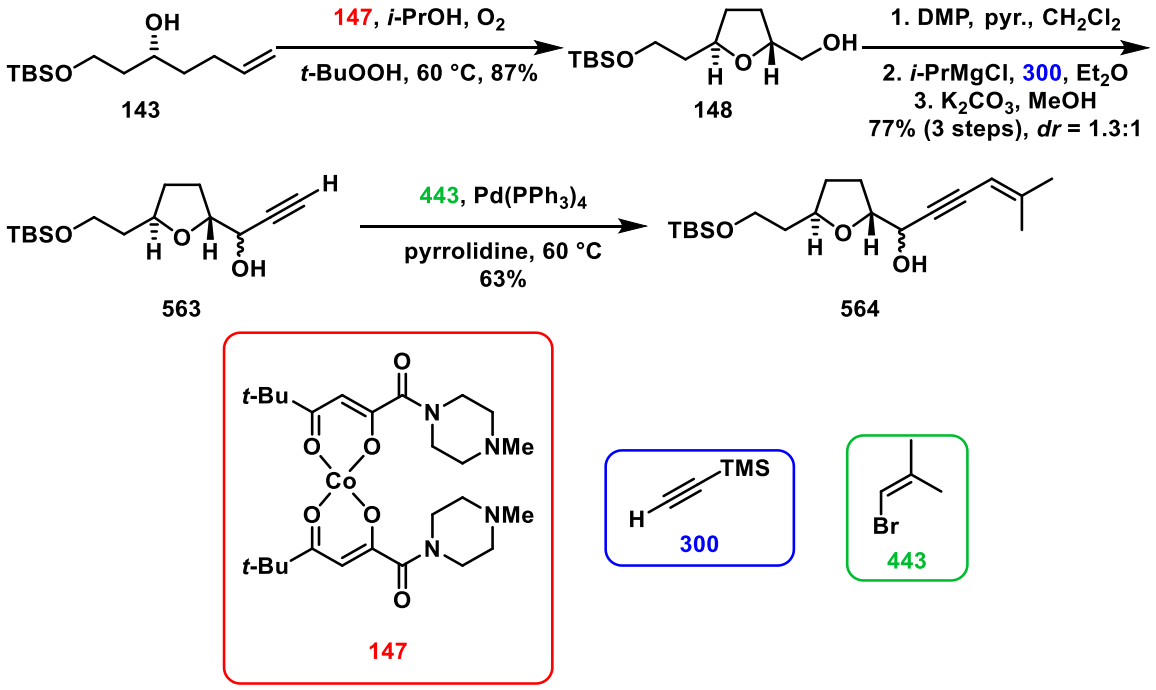
To begin this route, D-aspartic acid (**561**) was first converted to the bromo diacid and subsequent borane reduction was used to produce the corresponding diol **562** (**Scheme 124**). Treatment of the diol with NaH followed by addition of TBSCl

afforded epoxide **145**. Opening of epoxide **145** was achieved by reaction with allylmagnesium bromide **146**, which gave chiral alcohol **143**.



Scheme 124. Synthesis of the Oxidative Mukaiyama Cyclisation Precursor from D-Aspartic Acid

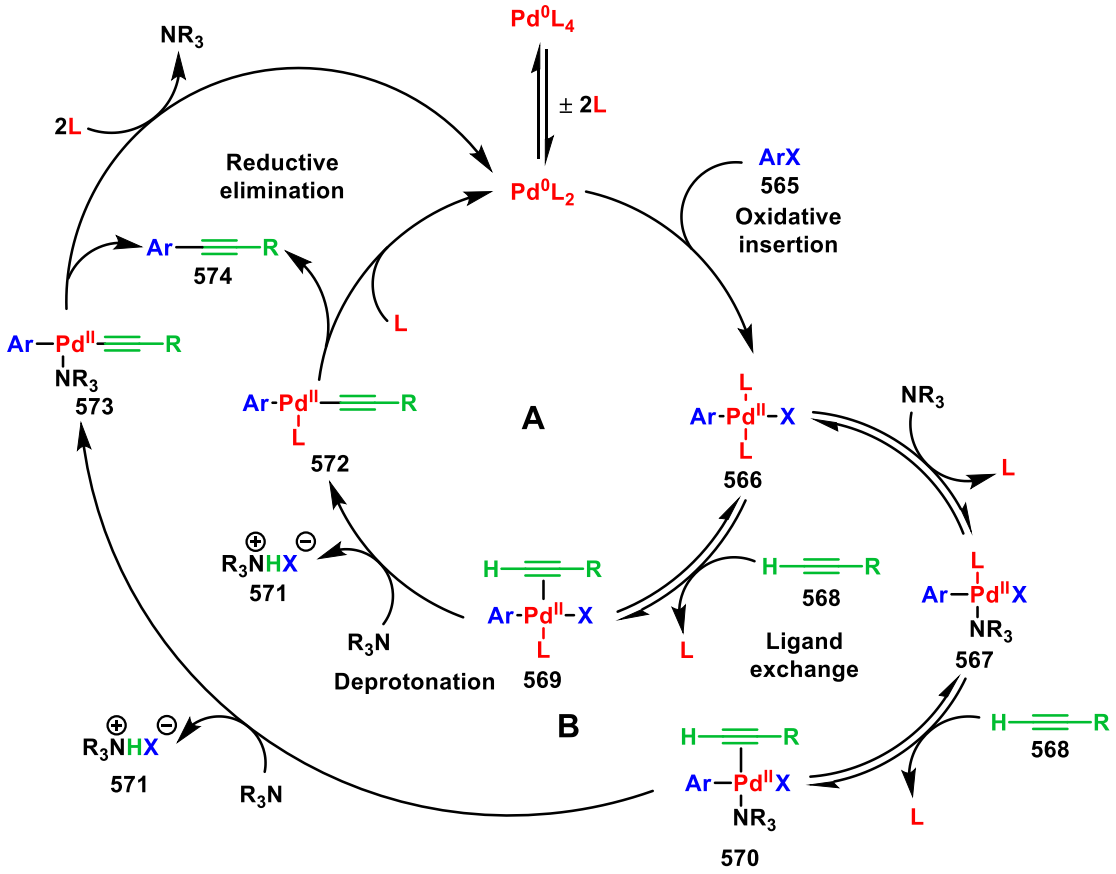
Treatment of the alcohol **143** with the cobalt(II) catalyst **147** developed by Pagenkopf and co-workers effected the desired oxidative Mukaiyama cyclisation reaction and delivered the 2,5-*trans* THF **148** with a *dr* > 20:1 (**Scheme 125**).[59] DMP oxidation of the alcohol to give the corresponding aldehyde followed by a Grignard addition produced the TMS-alkyne.[111] Treatment of the TMS-alkyne with K_2CO_3 in MeOH afforded the propargylic alcohol **563** as a mixture of diastereoisomers (*dr* = 1.3:1) in 77% yield over three steps. A copper-free Sonogashira cross coupling reaction was employed to couple the diastereomeric mixture of propargylic alcohols **563** with vinylic bromide **443** to give eneyne **564**.[75]



Scheme 125. Oxidative Mukaiyama Cyclisation to give the 2,5-trans THF Ring

Previous work within the Clark group had shown that the use of a copper co-catalyst resulted in complete consumption of alkyne **563** to produce the homocoupled Glaser product.[96] Fortunately, the Sonogashira cross coupling has been studied extensively and a wide range of alternative conditions are available to overcome such issues. It was found that omitting the copper co-catalyst allowed for consistent yields of the desired ene-yne. The mechanism of the reaction in the absence of copper is clearly different, although not fully elucidated, with many proposed catalytic cycles **A**, **B**, and **C** (**Scheme 126**, **Scheme 127**).[116,117] The cycle which is favoured depends on the ligands present on the catalyst and the rate of substitution of the ligand with the alkyne compared to substitution of the ligand with the amine. Cycle **A** is favoured when, after oxidative insertion, ligand exchange favours exchange with the alkyne **568**, which leads to formation of complex **569**. The alkyne, which is activated towards deprotonation when compared to the free alkyne by ligation to the palladium(II) centre, is then deprotonated by the amine present which gives intermediate **572**. Finally, reductive elimination gives the coupled product **574** and regenerates the palladium(0) catalyst. Pathway **B**, on the other hand, is favoured when substitution with the amine occurs preferentially over substitution with the alkyne. The initial ligand exchange process results in formation of complex **567**

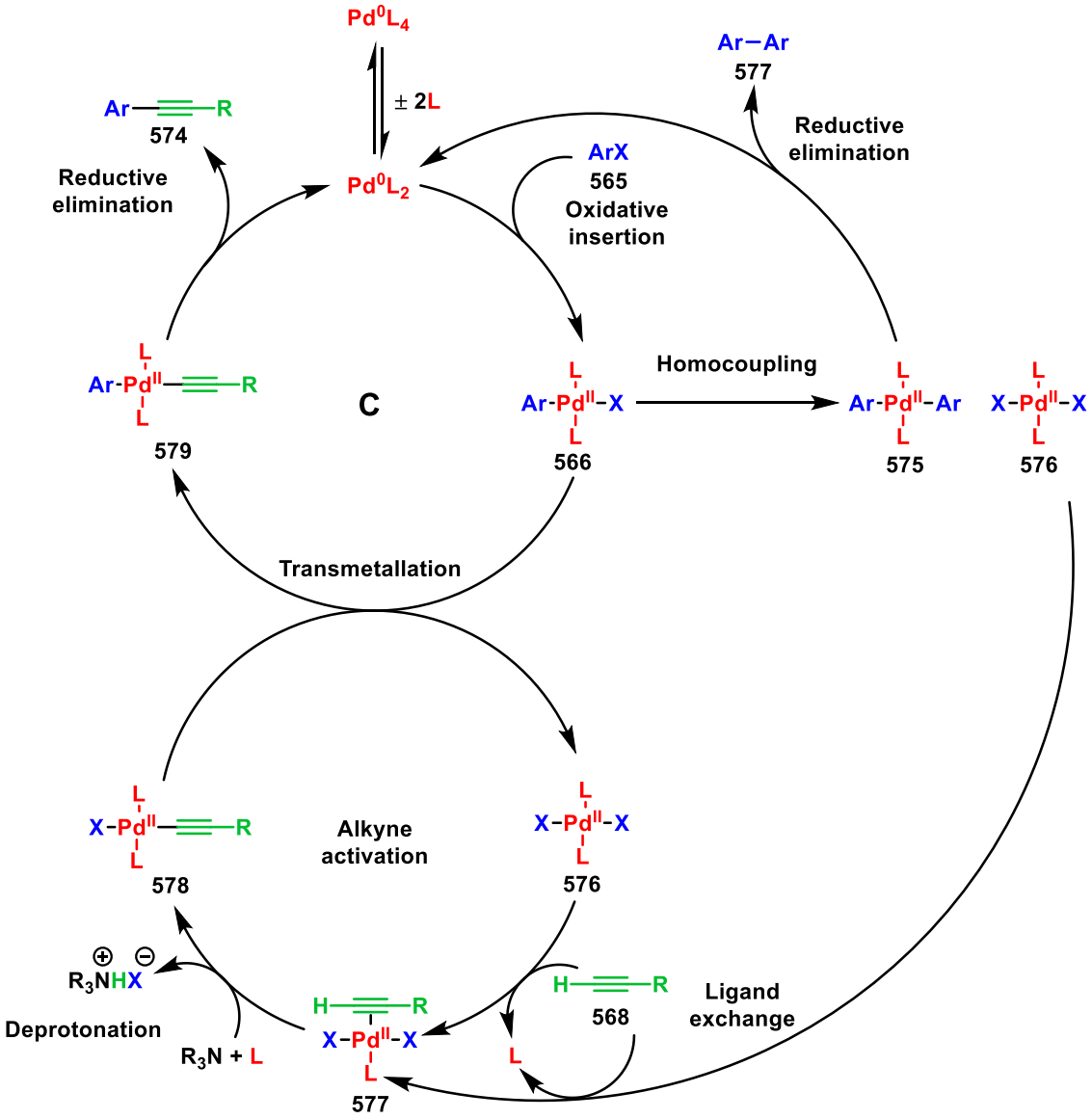
with an amine ligand, subsequent ligand exchange with the alkyne produces complex **570**. Again, the ligated alkyne is deprotonated by a free amine to produce complex **573**, which upon reductive elimination gives the desired product **574** and regenerates the palladium(0) catalyst.



Scheme 126. Proposed Catalytic Cycles for the Copper-free Sonogashira Cross-Coupling Reaction

Pathway **C** is distinct from the two pathways discussed previously because it involves two palladium catalytic cycles within the one mechanism and more closely resembles the mechanism of the classic copper-mediated Sonogashira cross coupling. The first cycle accounts for the activation of the alkyne, while the second cycle involves oxidative insertion into the aryl halide bond followed by a transmetallation event to afford the palladium species required for the reductive elimination. As seen in the previously discussed reaction mechanisms, the initial steps of this catalytic cycle are catalyst activation followed by oxidative insertion to give the palladium(II) species **566**. In the initial cycle there is no palladium(II) species **578** to undergo the required transmetallation step, instead homocoupling occurs to produce the palladium(II) species **575** and **576**. Reductive elimination

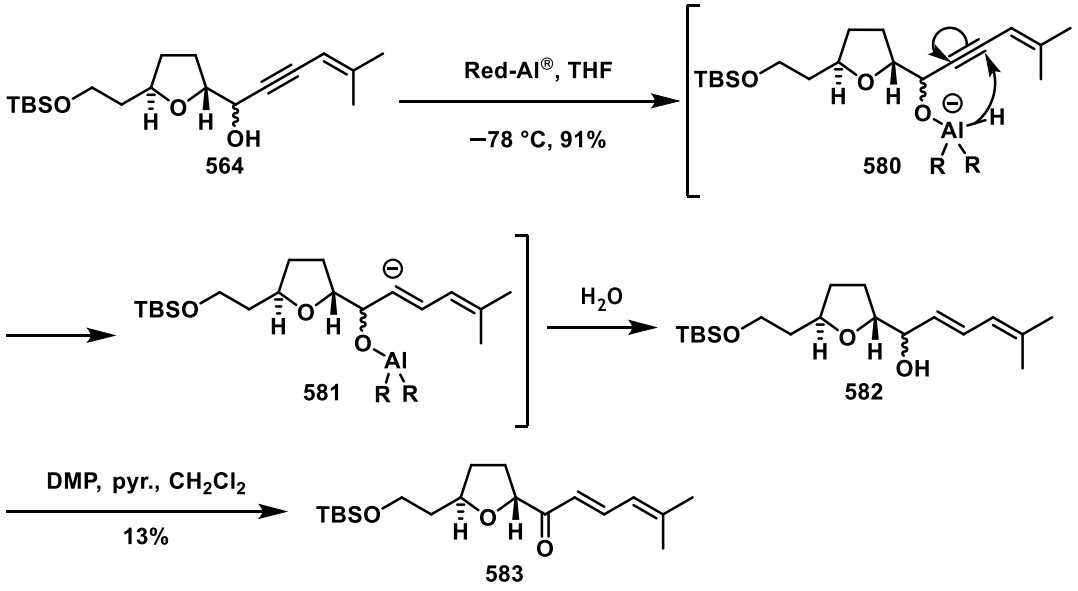
of species **575** regenerates the palladium(0) catalyst as well as giving a bis-aryl by-product **577**. Meanwhile, palladium(II) species **576** co-ordinates to the alkyne **568** and activates it towards deprotonation, which allows the alkyne activation cycle to begin. Once palladium(II) species **578** is present, transmetallation begins resulting in formation of the palladium(II) species **579** and regeneration of the palladium(II) species **576**; the rates between transmetallation and homocoupling determine which route is favoured. Reductive elimination delivers the product **574** and regenerates palladium(0) catalyst, thereby completing the catalytic cycle.



Scheme 127. Alternative Mechanism for the Copper-free Sonogashira Cross Coupling Reaction with two Dependant Palladium Cycles

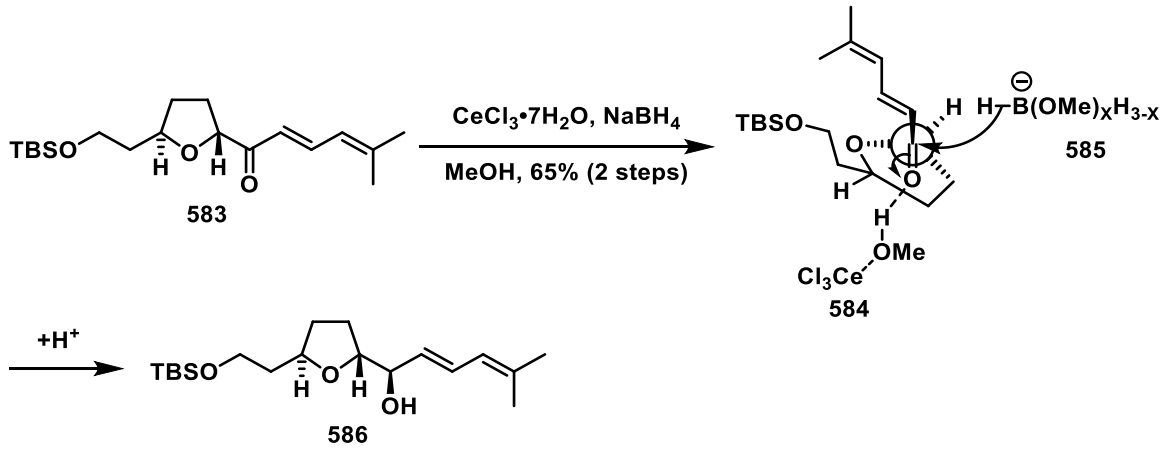
While catalytic cycles **A** and **B** result in the same outcome catalytic cycle **B** results in formation of the homo-coupled by-product **577**. This may not have a noticeable impact on the outcome of the reaction on scales performed here but it is important to be mindful of what is happening mechanistically in reactions. For example, scaling up these reactions to industrial levels build-up of the by-product **577** could be problematic with regards to extra purification requirements.

Reduction of propargyl alcohol **564** was effected using Red-Al® by use of a Chan alkyne reduction reaction to afford the *E*-alkene **582** (**Scheme 128**).[118] Despite the fact that differentiation between alkynes and alkenes under reductive conditions is often challenging, the Chan alkyne reduction achieves remarkable selectivity for reducing alkynes over alkenes. Reduction of the alkyne to the *E*-alkene demonstrates complimentary selectivity to that obtained by use of a poisoned catalyst, such as Lindlar catalyst, hydrogenation reactions. The reaction does, however, have stricter substrate requirements in that it relies on the presence of an α-hydroxyl group to direct reduction of the alkyne. Firstly, the complex **580** is formed in which the alcohol coordinates to the aluminium centre, which results in the irreversible loss of dihydrogen. Coordination is key to the chemoselectivity of the reaction and hydride is then transferred to the carbon proximal to the hydroxyl group in this complex. This hydride migration process generates the anionic intermediate **581** which persists until aqueous work-up. Aqueous work-up causes hydrolysis of the carbon aluminium bond, resulting in formation of the *E*-alkene **582**. Following this key reaction the C-24 hydroxyl group was oxidised using DMP to give the ketone **583** as a sole diastereoisomer. Purification of ketone **583** resulted in poor yields, however, when the ketone was used directly in the subsequent Luche reduction yields were greatly improved.[97] Possibly indicating an instability to the acidic silica of the conjugated ketone.



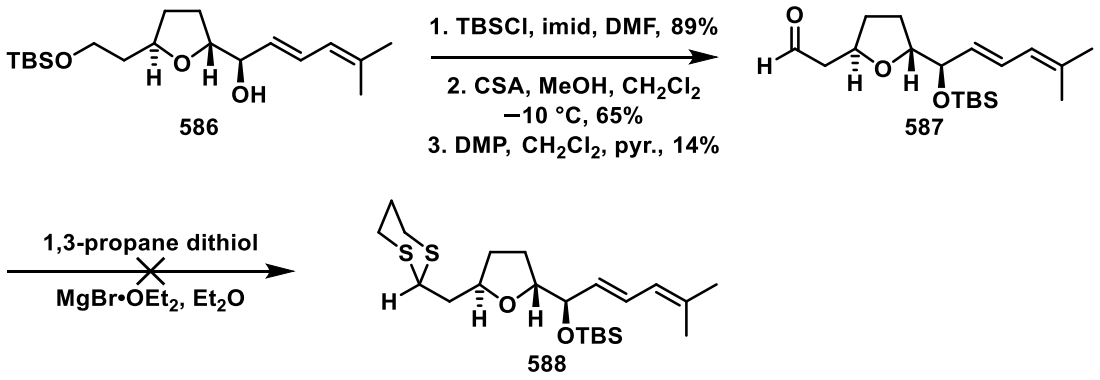
Scheme 128. Formation of the Dienone and Correction of C-24 Stereochemistry

The reduction of the conjugated carbonyl group using just $NaBH_4$, a soft reducing agent, would risk reduction at the softer carbon-carbon double bonds, as in a 1,4- or 1,6-reduction. To avoid this side reaction Luche reduction was employed (**Scheme 129**).[97] The conditions of the Luche reduction reaction minimise competing reduction at the undesired locations and vastly favour the 1,2-reduction, through two mechanisms. Firstly, the $CeCl_3$ acts as a catalyst to aid in the methanolysis of $NaBH_4$ to form a $NaBH_{(4-n)}(OMe)_{(n)}$ species **585**. This newly formed sodium methoxyborohydride is a harder reducing agent, and as a result reduction at the harder carbonyl carbon is favoured leading to 1,2-reduction. The second mechanism by which competing conjugate reduction is suppressed is by increasing the electrophilicity of the carbonyl carbon. This results from the coordination of $CeCl_3$ to the solvent, which increases the acidity of the reaction mixture, and results in formation of complex **584**. The stereoselectivity of the of the Luche reduction can be explained by considering the transition state through which the reaction progresses. A Felkin-Ahn transition state is adopted where the polar, oxygen containing, side chain is oriented to maximise orbital interaction between the σ* orbital of the carbon oxygen bond and the π and π* orbitals of the carbonyl group. This interaction stabilises the incoming nucleophile, resulting in preferential nucleophilic attack on the *Si*-face of the molecule giving the desired *R*-allylic alcohol **586**.



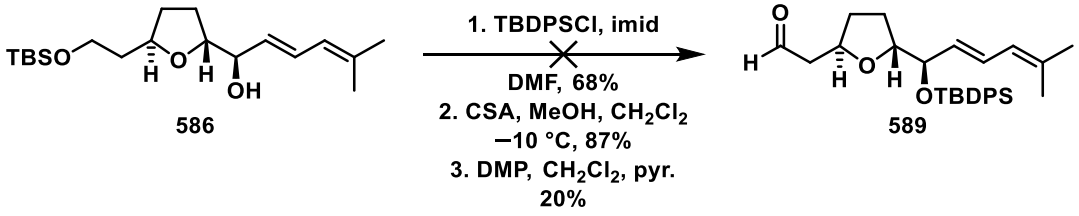
Scheme 129. Formation of the Required Stereogenic C-24 Centre

After manipulation of the protecting group, the intermediate primary alcohol was oxidised to give the corresponding aldehyde **587** (**Scheme 130**). Attempts to convert the aldehyde **587** into the corresponding dithiane **588** were unsuccessful. Furthermore, poor yields were observed when attempting to oxidise the primary alcohol to the corresponding aldehyde **587**.



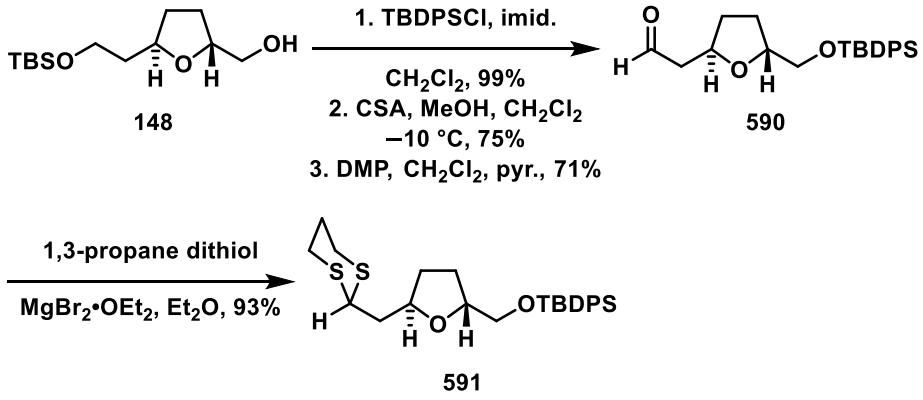
Scheme 130. Attempts to form the 1,3-Dithiane were Unsuccessful

To remedy this poor yield the allylic alcohol **586** was converted to the TBDPS ether instead and subsequent deprotection proved to be significantly more selective (**Scheme 131**). The resulting primary alcohol was oxidised to give the corresponding aldehyde **589**, again using DMP. This oxidation reaction remained relatively low yielding, possibly due to issues with the 1,3-diene under the oxidising conditions.



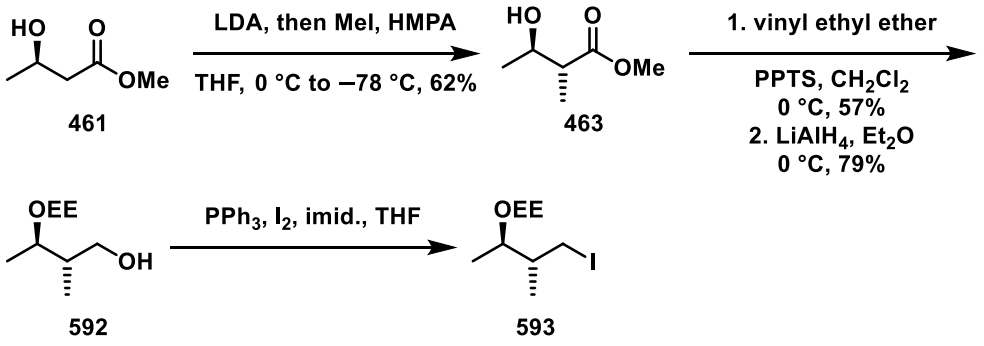
Scheme 131. Formation of the 1,3-Dithiane Remained Unsuccessful with an Alternative Hydroxyl Protecting Group

To overcome issues associated with oxidation and reduction sequences in the presence of a 1,3-diene system the order of the steps in the synthesis of the northern fragment was revised. From 2,5-*trans* THF **148** the primary alcohol was protected as a TBDPS ether and the primary TBS group was removed using TBAF and AcOH (**Scheme 132**). The resulting primary alcohol was converted into the corresponding aldehyde **590** and then the 1,3-dithiane **591**. This sequence of reactions proceeded much more smoothly and ultimately allowed the synthesis of the 1,3-dithiane, which had previously proved problematic, to be completed.



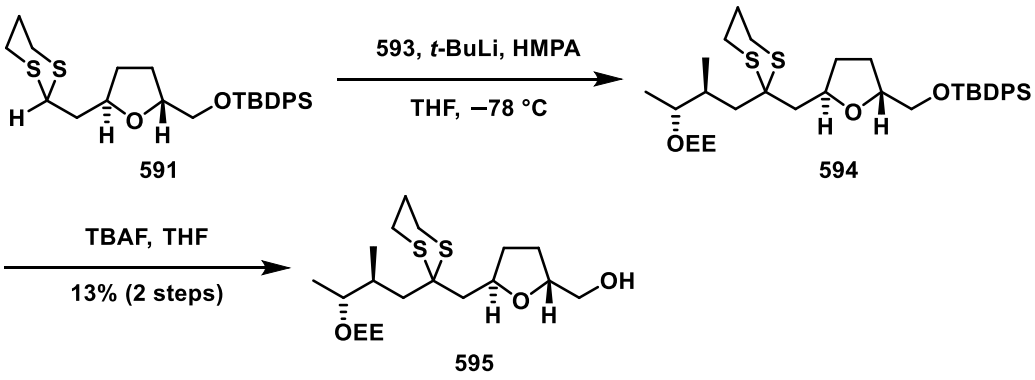
Scheme 132. Synthesis of 1,3-Dithiane Before Inclusion of 1,3-Diene System

The synthesis of the C-14 to C-17 fragment began from (*R*)-hydroxy ester **461** with a Fráter-Seebach alkylation reaction to install the required methyl group diastereoselectively and deliver the alcohol **463** in a 62% yield (**Scheme 133**). The reaction involves a pseudo chair transition state in which methyl iodide preferentially approaches from the less sterically congested face of the pseudo chair as seen previously in **Section 3.2.1**. Protection of the alcohol as an ethoxy-ethyl ether was followed by reduction of the ester with $LiAlH_4$ to give the alcohol **592**. Finally, an Appel reaction was used to prepare the alkyl iodide **593** required for coupling to the dithiane which was used directly in the next step.



Scheme 133. Synthesis of Alkyl Iodide 593

Alkylation of the dithiane was effected by treating the dithiane **591** with *t*-BuLi followed by addition of alkyl iodide **593** to deliver the coupled product **594** (**Scheme 134**). Cleavage of the silyl ether using TBAF delivered primary alcohol **595** in 13% yield over two steps. While the alkylated product was not fully purified, meaning the step that resulted in the poor yield can't be proven, previous work within the group had found that similar dithiane alkylation steps were also poor yielding so it seems likely that it was the alkylation step which was responsible for the poor yield.[101]

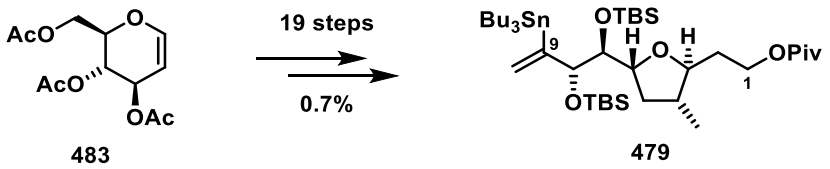


Scheme 134. Coupling of 1,3-Dithiane with Alkyl Iodide

4.4 Conclusions and Future Work

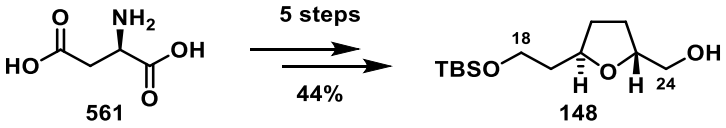
Significant progress towards the synthesis of amphidinolide F has been made. The synthetic strategy discussed differed from the original Clark group approach which had been divergent in nature. In an effort to tailor the synthesis of each fragment to its' specific needs the more convergent approach reported here was proposed. For the southern fragment the use of tri-*O*-acetyl D-glucal allowed the geometry required for the natural product to be easily achieved as this was present in the starting material. This avoided the low yielding oxidation-reduction reaction sequence to set the stereochemistry at the C-8 position which had been a major drawback of the previous divergent approach. For the northern fragment, the use of dihydrofuranone intermediates, which necessitate awkward deoxygenation procedures, were avoided.

Investigations into protecting group strategies for the synthesis of the southern fragment of the natural product were conducted. Ultimately, it was found that the most expeditious and productive route for the synthesis of this fragment was using di-*tert*-butyl silylene as a protecting group. When this group was employed the C-1 to C-9 fragment was synthesised in a total of 19 steps from tri-*O*-acetyl D-glucal (**483**) with an overall yield of 0.7% (**Scheme 135**). Vinylic iodide **532** was also synthesised but to date attempts to couple these two fragments to form the complete southern fragment have been unsuccessful.



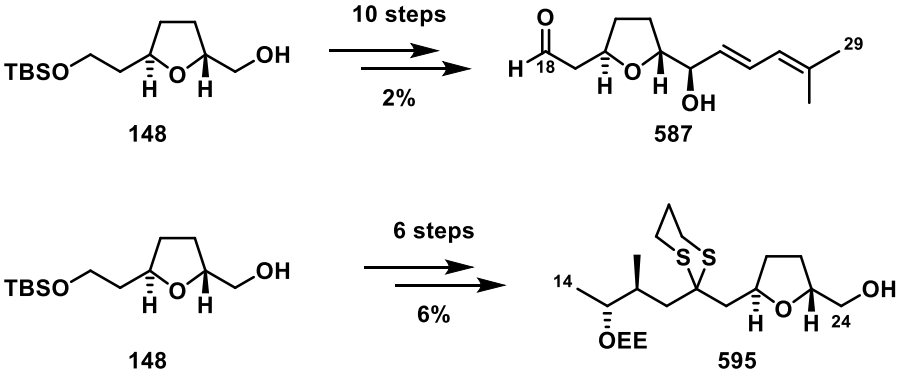
Scheme 135. Synthesis of the C-1 to C-9 Fragment of Amphidinolide F from tri-O-Acetyl D-Glucal

While various strategies were explored for the synthesis of the northern fragment the approaches which utilised a cationic furanyl intermediate were universally underwhelming in both yields and stereoselectivities. Conversely, when an oxidative Mukaiyama cyclisation reaction was used to access the 2,5-*trans* THF, multiple grams of the C-18 to C-24 section of the natural product were accessed (**Scheme 136**).



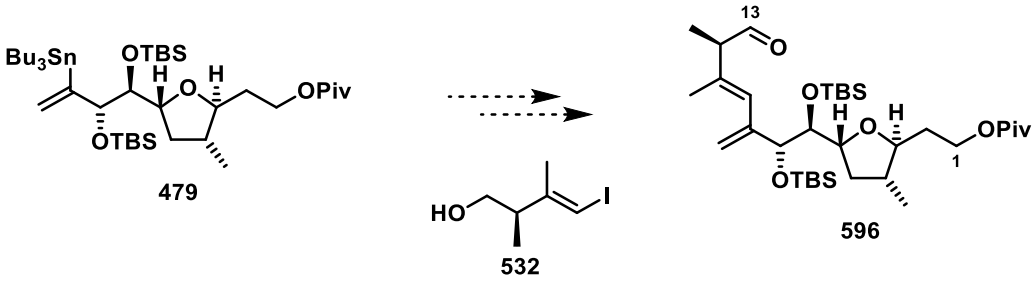
Scheme 136. Synthesis of the C-18 to C-24 Fragment of Amphidinolide F using an Oxidative Mukaiyama Cyclisation Reaction

This oxidative Mukaiyama approach allowed for the synthesis of the C-18 to C-29 fragment of the natural product. Whilst this compound was not initially compatible with formation of the required dithiane (**Scheme 137**, top) it was fortuitous that altering the order of reactions in the synthesis allowed for formation of the dithiane, as well as the subsequent dithiane alkylation to take place (**Scheme 137**, bottom).



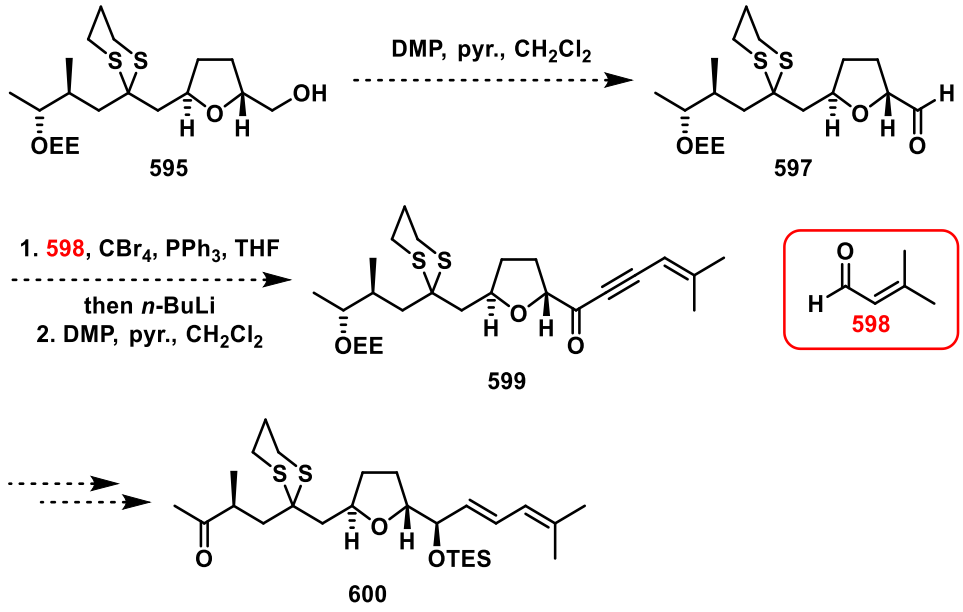
Scheme 137. Overview of the Synthesis of the C-18 to C-29 and C-14 to C-24 Fragments of Amphidinolide F

Looking to the future, completion of both southern and northern fragments would be essential for production of the natural product. For the southern fragment this would involve development of the Stille cross coupling reaction with vinylic iodide **532**. Based on the outcomes of previous attempts at this reaction and insight provided for similar reactions reported in the literature, the use of diphenyl phosphite to sequester the tin may be sufficient to drive this reaction. From here an oxidation of the hydroxyl group would give the aldehyde (**596**) which would then be ready for the aldol reaction to complete the carbon framework of the natural product (**Scheme 138**).



Scheme 138. Proposed Route to Complete the Synthesis of the Southern Fragment of Amphidinolide F

Completion of the northern fragment of amphidinolide F would be more involved (**Scheme 139**). Starting with oxidation of the primary hydroxyl group and subsequent reaction with an organolithium reagent, accessible from commercially available aldehyde **598**. At this juncture it would be presumed that an oxidation-reduction reaction sequence would be required to set the configuration at the C-24 position with the required diastereoisomer. Subsequent reduction of the alkyne and protection of the free hydroxyl group as the TES ether would give a diene. Finally, removal of the EE protecting group would be required and oxidation of the free hydroxyl group to the corresponding ketone would complete the northern fragment of the natural product. This ketone (**600**) would then be used in an aldol reaction to couple the southern and northern fragments together, thus completing the carbon framework of the natural product.



Scheme 139. Proposed Route to Complete the Synthesis of the Northern Fragment of Amphidinolide F

5. Experimental Details

General Experimental

Air and/or moisture sensitive reactions were performed under an atmosphere of argon in flame dried apparatus. Tetrahydrofuran (THF), toluene (PhMe), acetonitrile (MeCN), dichloromethane (CH_2Cl_2), and diethyl ether (Et_2O) were purified using a Pure-Solve™ 500 Solvent Purification System. Other dry organic solvents and starting materials were obtained from commercial sources and used as received unless specified otherwise. Petroleum ether (pet. ether) used for reactions and flash chromatography was the 40-60 °C fraction.

Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 covered aluminium backed plates F_{254}. TLC plates were visualised under UV light and stained using either a potassium permanganate solution or an acidic ethanolic anisaldehyde solution. Flash chromatography was performed with silica gel (Fluorochem 60A 40–63 μm or Geduran Si 60 35–70 μm) as a solid support.

IR spectra were recorded as thin films at ambient temperature using a Shimadzu FTIR-8400S spectrometer equipped with Pike Technologies MIRacle ATR accessory.

^{1}H NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer at ambient temperature using the deuterated solvent as the internal deuterium lock. ^{1}H NMR data are reported as follows: chemical shift relative to $CHCl_3$ (7.26) or MeOH (3.35) on the δ scale, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, app = apparent, or a combination of these), coupling constant(s) *J* (Hz), and assignment. ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer at 101 MHz and ambient temperature and multiplicities were obtained using a DEPT sequence. ^{13}C NMR data are reported as follows: chemical shift relative to $CDCl_3$ (77.16) on the δ scale and assignment.

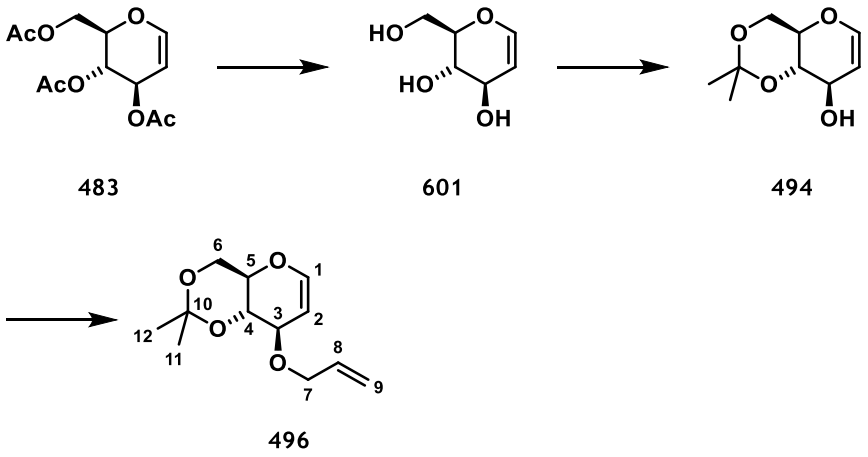
Optical rotations were recorded using an automatic polarimeter Rudolph Research Analytical Autopol V or Rudolph Research Analytical Autopol III.

High resolution mass spectra (HRMS) were recorded using positive ion electrospray (ESI+) on Bruker microOTOF-Q instrument operated by University of Glasgow staff.

Elemental analyses were carried out on an Exeter Analytical Elemental Analyser EA 440 operated by University of Glasgow staff.

Melting points were recorded with a Barnstead Electrothemal IA 9100 melting point apparatus.

3-*O*-allyl-4,6-*O*-isopropylidene-D-glucal 496



To a stirred solution of tri-*O*-acetyl-D-glucal **483** (10.1 g, 37.1 mmol) in MeOH (50 mL) at rt was added K_2CO_3 (45 mg, 0.33 mmol) and stirred for 16 h. The reaction mixture was concentrated under reduced pressure to afford crude D-glucal (**601**) which was used in the next step without further purification.

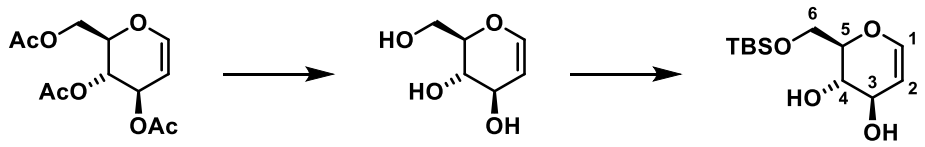
To a stirred solution of crude D-glucal (**601**) in THF (150 mL) at 0 °C was added 2,2-dimethoxypropane (25 mL, 200 mmol) followed by *p*-TSA until pH ~ 3 was reached and the reaction mixture was stirred at 0 °C for 4 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (50 mL) and diluted with EtOAc (50 mL). The phases were separated and the aqueous phase was washed with EtOAc (2 × 50 mL). The combined organic fractions were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude acetonide **494** which was used in the next step without further purification.

To a stirred solution of crude acetonide **494** in DMF (100 mL) at 0 °C was added NaH (2.23 g, 55.8 mmol) and stirred at 0 °C until 10 min after evolution of gas ceased. To the reaction mixture at 0 °C was added allyl bromide (9.7 mL, 110 mmol) and TBAI (1.37 g, 3.71 mmol) and the reaction mixture was stirred at 0 °C for a further 2 h. The reaction was quenched by the addition of NH_4Cl (100 mL) and diluted with EtOAc (100 mL). The phases were separated and the aqueous phase was washed with EtOAc (3 × 100 mL). The combined organic fractions were washed with brine (250 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash

chromatography (pet. ether:EtOAc, 99:1) affording allyl ether **496** (3.54 g, 42%) as a colourless oil.

R_f = 0.43 (pet. ether:EtOAc, 19:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (1H, dd, *J* = 6.2, 1.7 Hz, CH-C1), 5.92 (1H, dddd, *J* = 17.2, 10.4, 5.7, 5.4 Hz, CH-C8), 5.29 (1H, dddd, *J* = 17.2, 1.6, 1.5, 1.4 Hz, CH_2-C9), 5.17 (1H, dddd, *J* = 10.4, 1.5, 1.4, 1.3 Hz, CH_2-C9), 4.75 (1H, dd, *J* = 6.2, 1.9 Hz, CH-C2), 4.21 (1H, ddd, *J* = 13.4, 5.4, 1.6, 1.4 Hz, CH_2-C7), 4.13 (1H, ddd, *J* = 7.2, 1.9, 1.7 Hz, CH-C3), 4.12 (1H, dddd, *J* = 13.4, 5.7, 1.4, 1.3 Hz, CH_2-C7), 3.97 (1H, dd, *J* = 10.3, 7.2 Hz, CH-C4), 3.94 (1H, dd, *J* = 10.6, 5.7 Hz, CH_2-C6), 3.83 (1H, dd, *J* = 10.6, 10.4 Hz, CH_2-C6), 3.72 (1H, ddd, *J* = 10.4, 10.3, 5.7 Hz, CH-C5), 1.54 (3H, s, CH_3-C11), 1.43 (3H, s, CH_3-C12); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5 (CH-C1), 135.2 (CH-C8), 116.9 (CH_2-C9), 102.5 (CH-C2), 99.7 (C-C10), 73.7 (CH-C4), 72.6 (CH-C3), 70.7 (CH-C5), 69.7 (CH_2-C7), 61.9 (CH_2-C6), 29.2 (CH_3-C11), 19.3 (CH_3-C12); ν_{max} 2994, 2895, 1641, 1383, 1373, 1268, 1232, 1201, 1168, 1116, 1093, 1070, 868, 756 cm^{-1}; HRMS calculated for $C_{12}H_{18}NaO_4$ $[M+Na]^+$ 249.1097, found 249.1097, Δ = 0.2 ppm.

6-*O*-[(*tert*-Butyl)bis(methyl)silyl]-D-glucal 602



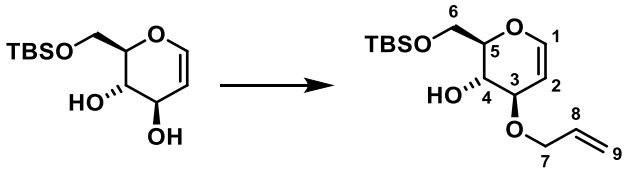
483 601 602

To a stirred solution of tri-*O*-acetyl-D-glucal **483** (1.03 g, 3.78 mmol) in MeOH (10 mL) at rt was added K_2CO_3 (7 mg, 0.05 mmol) and stirred for 16 h. The reaction mixture was concentrated under reduced pressure to afford crude D-glucal (**601**) which was used in the next step without further purification.

To a stirred solution of D-glucal (**601**) in CH_2Cl_2 (50 mL) at 0 °C was added TBSCl (613mg, 4.07 mmol) followed by Et_3N (1.0 mL, 7.2 mmol) and DMAP (112 mg, 0.917 mmol). The reaction mixture was warmed to rt and stirred for a further 16 h. The reaction was then quenched by the addition of HCl (1 M in H_2O, 10 mL). The phases were separated, and the aqueous phase was washed with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was then purified by flash chromatography (pet. ether:EtOAc, 7:3) affording TBS ether **602** (694 mg, 70%) as a colourless oil.

R_f = 0.31 (pet. ether:EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (1H, dd, *J* = 6.1, 1.7 Hz, CH-C1), 4.73 (1H, dd, *J* = 6.1, 2.3 Hz, CH-C2), 4.28–4.22 (1H, m, CH-C5), 3.99 (1H, ddd, *J* = 11.1, 2.1, 1.3 CH_2-C6), 3.93–3.88 (1H, m, CH_2–C6), 3.81–3.78 (2H, m, CH-C3, CH-C4), 3.14 (1H, d, *J* = 2.6 Hz, OH-C3), 2.47 (1H, d, *J* = 5.7 Hz, OH-C4), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.10 (6H, s, CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3 (CH-C1), 102.6 (CH-C2), 76.8 (CH-C5), 72.4 (CH-C4), 69.4 (CH-C3), 63.9 (CH_2-C6), 26.0 (CH_3-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), –5.2 (CH_3-Me-TBS); ν_{max} 3387, 2953, 2930, 2886, 2857, 1647 cm^{-1}; HRMS calculated for $C_{12}H_{24}NaO_4Si$ $[M+Na]^+$ 283.1336, found 283.1333, Δ = 1.2 ppm.

3-*O*-Allyl-6-*O*-[(*tert*-butyl)bis(methyl)silyl]-D-glucal 502

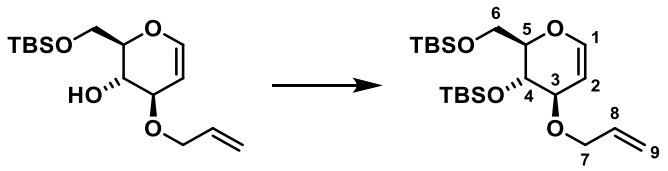


602 502

To a stirred solution of TBS ether **602** (280 mg, 1.08 mmol) in PhMe (40 mL) at rt was added Bu_2SnO (590 mg, 2.37 mmol), the reaction mixture was heated to reflux and stirred at this temperature for 2.5 h. The reaction mixture was then cooled to 80 °C and allyl bromide (0.10 mL, 1. mmol) and TBAI (466 mg, 1.26 mmol) were added. The reaction mixture was stirred at this temperature for 30 h. After which time the reaction was cooled to rt and the reaction mixture was washed with H_2O (40 mL). The aqueous phase was washed with EtOAc (2 × 40 mL). The combined organic fractions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) affording allyl ether **502** (69 mg, 21%) as a colourless oil.

R_f = 0.21 (pet. ether:EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.32 (1H, dd, *J* = 6.0, 1.6 Hz, CH-C1), 5.95 (1H, dddd, *J* = 17.2, 10.4, 5.9, 5.7 Hz, CH-C8), 5.30 (1H, dddd, *J* = 17.2, 1.9, 1.6, 1.5 Hz, CH_2-C9), 5.18 (1H, dddd *J* = 10.4, 1.6, 1.4, 1.3 Hz, CH_2-C9), 4.78 (1H, dddd, *J* = 6.0, 1.9, Hz, CH-C2), 4.14 (1H, dddd, 6.4, 5.7, 1.5, 1.4 Hz, CH_2-C6), 4.11–4.05 (1H, m, CH_2-C6), 4.03 (1H, ddd, *J* = 6.9, 2.5, 2.0 Hz, CH-C4), 3.99–3.77 (4H, m, 2 × CH_2-C7, CH-C5, CH-C3), 2.94 (1H, d, *J* = 2.5 Hz, OH-C4) 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.09 (6H, s, CH_3-Me-TBS); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 144.6 (CH-C1), 135.2 (CH-C8), 117.2 (CH_2-C9), 100.3 (CH-C2), 77.4 (CH-C4), 76.4 (CH-C3), 70.1 (CH-C5), 69.9 (CH_2-C7), 63.5 (CH_2-C6), 26.0 (CH_3-*t*-Bu-TBS), 22.8 (C-*t*-Bu-TBS), −5.3 (CH_3-Me-TBS).

3-*O*-Allyl-4,6-*O*-{bis[(*tert*-butyl)bis(methyl)silyl]}-D-glucal 503

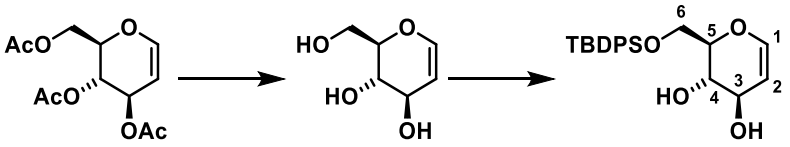


502 503

To a stirred solution of TBS ether **502** (69 mg, 0.23 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C was added TBSOTf (0.07 mL, 0.3 mmol) and 2,6-lutidine (0.05 mL, 0.5 mmol). The reaction mixture was warmed to rt and stirred for 16 h, after which time the reaction mixture was quenched by the addition of HCl (1 M in H_2O, 5.0 mL), CH_2Cl_2 (5.0 mL) was added and the phases were separated. The aqueous phase was washed with CH_2Cl_2 (2 × 5.0 mL). The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 99:1) affording bis-TBS ether **503** (83 mg, 87%) as a colourless oil.

R_f = 0.32 (pet. ether:EtOAc, 19:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.36 (1H, d, *J* = 6.1 Hz, CH-C1), 5.94 (1H, dddd, *J* = 16.7, 10.6, 5.7, 5.5 Hz, CH-C8), 5.28 (1H, ddd, *J* = 16.7, 1.8, 1.6, 1.1 Hz, CH_2-C9), 5.16 (1H, dddd, *J* = 10.6, 1.6, 1.2, 1.1 Hz, CH_2-C9), 4.79 (1H, dd, *J* = 6.1, 2.2 Hz, CH-C2), 4.09 (1H, dddd, *J* = 11.7, 5.7, 1.8, 1.6 Hz, CH_2-C7), 3.94 (1H, dddd, *J* = 11.7, 5.5, 1.6, 1.2 Hz, CH_2-C7), 3.91–3.84 (4H, m, CH-C3, CH-C4, 2 × CH_2-C6), 3.73 (1H, ddd, *J* = 7.8, 3.6, 3.6 Hz, CH-C5), 0.89 (18H, CH_3-*t*-Bu-TBS), 0.12 (6H, CH_3-Me-TBS), 0.06 (6H, CH_3-Me-TBS).

6-*O*-[(*tert*-Butyl)bis(phenyl)silyl]-D-glucal 603



483 601 603

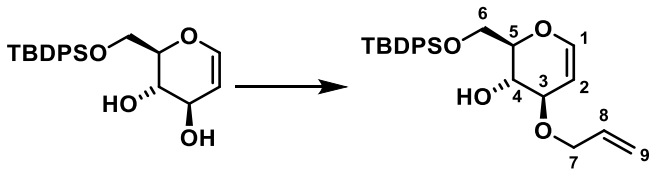
To a stirred solution of tri-*O*-acetyl D-glucal **483** (5.02 g, 18.4 mmol) in MeOH (50 mL) at rt was added K_2CO_3 (35 mg, 0.25 mmol) and stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure to afford crude D-glucal (**601**) which was used in the next step without further purification.

To a stirred solution of crude D-glucal (**601**) in THF (80 mL) at 0 °C was added imidazole (1.37 g, 20.1 mmol) followed by dropwise addition of TBDPSCl (5.0 mL, 19.3 mmol). The reaction mixture was then stirred at 0 °C for a further 1 h before being warmed to rt and stirred for a further 3.5 h. After which time the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (100 mL). The phases were separated and the aqueous phase was washed with EtOAc (3 × 50 mL). The combined organic fractions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1 to 1:1) affording TBDPS ether **603** (5.75 g, 81%) as a colourless oil.

R_f = 0.16 (pet. ether:EtOAc, 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71–7.67 (4H, m, Ph-TBDPS), 7.48–7.37 (6H, m, Ph-TBDPS), 6.32 (1H, dd, *J* = 6.0, 1.9 Hz, CH-C1), 4.73 (1H, dd, *J* = 6.0, 2.2 Hz, CH-C2), 4.28 (1H, dddd, *J* = 6.1, 5.3, 2.2, 1.9 Hz, CH-C3), 4.01 (1H, dd, *J* = 11.5, 4.2 Hz, CH_2-C6), 3.97 (1H, dd, *J* = 11.5, 4.1 Hz, CH_2-C6), 3.90 (1H, ddd, *J* = 9.8, 6.1, 3.2 Hz, CH-C4), 3.82 (1H, ddd, *J* = 9.8, 4.2, 4.1 Hz, CH-C5), 2.95 (1H, br. s, OH-C4), 2.39 (1H, br. s, OH-C3), 1.08 (9H, s, CH_3-*t*-Bu-TBDPS); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 144.5 (CH-C1), 135.8 (CH-Ph-TBDPS), 135.7 (CH-Ph-TBDPS), 133.0 (C-Ph-TBDPS), 132.8 (C-Ph-TBDPS), 130.1(CH-Ph-TBDPS), 130.1 (CH-Ph-TBDPS), 128.0 (CH-Ph-TBDPS), 128.0 (CH-Ph-TBDPS), 102.5 (CH-C2), 77.1 (CH-C5), 72.0 (CH-C4), 69.8 (CH-C3), 64.0 (CH_2-C6), 27.0 (CH_3-*t*-Bu-TBDPS), 19.4 (C-*t*-Bu-TBDPS); ν_{max} 3387, 3071, 2955,

2932, 2884, 2857, 1647, 1427, 1234, 1053, 702 cm^{-1}; HRMS (ESI+) $[M+Na]^+$ calculated for $C_{22}H_{28}NaO_4Si$ 407.1649, found 407.1636, Δ = 3.2 ppm.

3-*O*-Allyl-6-*O*-[(*tert*-butyl)bis(phenyl)silyl]-D-glucal 507



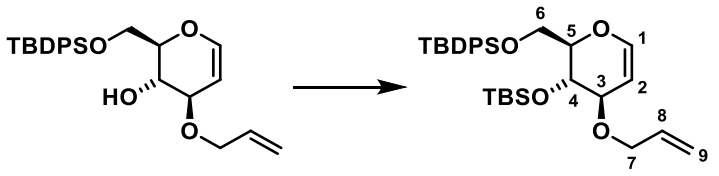
603 507

To a stirred solution of TBDPS ether **603** (3.95 g, 10.3 mmol) in PhMe (250 mL) was added Bu_2SnO (4.18 g, 16.8 mmol) and heated to reflux for 16 h under Dean-Stark conditions. The reaction mixture was concentrated under reduced pressure. The resulting crude material was diluted with PhMe (100 mL), allyl bromide (7.5 mL, 87 mmol) and TBAI (5.26 g, 14.2 mmol) were added sequentially. The reaction mixture was heated to 60 °C and stirred for 54 h. The reaction mixture was then cooled to rt and H_2O (250 mL) was added. The phases were separated and the aqueous phase was washed with EtOAc (3 × 100 mL). The combined organic fractions were washed with brine (250 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) affording allyl ether **507** (2.86 g, 66%) as a colourless oil.

R_f = 0.58 (pet. ether:EtOAc, 4:1); $[\alpha]_D^{20}$ −4.7 (c = 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73–7.68 (4H, m, Ph-TBDPS), 7.47–7.37 (6H, m, Ph-TBDPS), 6.34 (1H, dd, *J* = 6.2, 1.2 Hz, CH-C1), 5.96 (1H, dddd, *J* = 17.3, 10.3, 5.7, 5.6 Hz, CH-C8), 5.32 (1H, dddd, *J* = 17.3, 1.7, 1.6, 1.5 Hz, CH_2-C9), 5.20 (1H, dddd, *J* = 10.3, 1.7, 1.4, 1.3 Hz, CH_2-C9), 4.80 (1H, dd, *J* = 6.2, 1.8 Hz, CH-C2), 4.18 (1H, dddd, *J* = 12.7, 5.6, 1.6, 1.4 Hz, CH_2-C7), 4.12 (1H, dddd, *J* = 12.7, 5.7, 1.5, 1.3 Hz, CH_2-C7), 4.05–4.03 (2H, m, CH-C3, CH-C4), 4.01 (1H, dd, *J* = 11.1, 4.2 Hz, CH_2-C6), 3.96 (1H, dd, *J* = 11.1, 4.0 Hz, CH_2-C6), 3.86 (1H, dddd, *J* = 10.0, 4.2, 4.0 Hz, CH-C5), 2.71 (1H, d, *J* = 3.2 Hz, OH-C4), 1.07 (9H, s, CH_3-*t*-Bu-TBDPS); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 144.7 (CH-C1), 135.8 (CH-Ph-TBDPS), 135.7 (CH-C8), 135.1 (CH-Ph-TBDPS), 133.3 (C-Ph-TBDPS), 133.1 (C-Ph-TBDPS), 130.0 (CH-Ph-TBDPS), 129.9 (CH-Ph-TBDPS), 127.9 (CH-Ph-TBDPS), 127.8 (CH-Ph-TBDPS), 117.2 (CH_2-C9), 100.1 (CH-C2), 77.7 (CH-C4), 76.4 (CH-C3), 70.0 (CH_2-C7), 69.3 (CH-C5), 63.7 (CH_2-C6), 27.0 (CH_3-*t*-Bu-TBDPS), 19.4 (C-*t*-Bu-TBDPS); ν_{max} 3451, 3071, 2959,

2930, 2857, 1645, 1471, 1427, 1238, 1113, 824, 741, 702 cm^{-1}; HRMS (ESI+) $[M+Na]^+$ calculated for $C_{25}H_{32}NaO_4Si$ 447.1962, found 447.1952, Δ = 2.3 ppm.

3-*O*-Allyl-4-*O*-[(*tert*-butyl)bis(methyl)silyl]-6-*O*-[(*tert*-butyl)bis(phenyl)silyl]-D-glucal 604

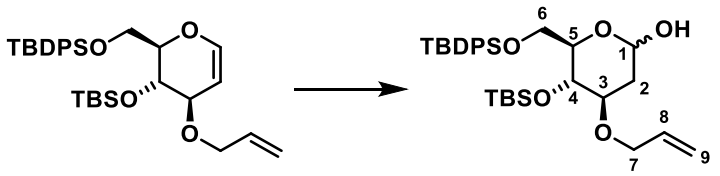


507 604

To a stirred solution of alcohol **507** (2.86 g, 6.74 mmol) in CH_2Cl_2 (100 mL) at rt was added TBSOTf (1.5 mL, 8.6 mmol) and 2,6-lutidine (1.6 mL, 14 mmol) and the reaction mixture was stirred for 4 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (100 mL), the phases were separated and the aqueous phase was washed with CH_2Cl_2 (3 × 75 mL). The combined organic fractions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 200:1 to 100:1) affording disilyl ether **604** (2.89 g, 80%) as a colourless oil.

R_f = 0.28 (pet. ether:EtOAc, 99:1); $[\alpha]_D^{23}$ −7.86 (c = 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71–7.67 (4H, m, Ph-TBDPS), 7.44–7.33 (6H, m, Ph-TBDPS), 6.36 (1H, dd, *J* = 6.1, 1.2 Hz, CH-C1), 5.92 (1H, dddd, *J* = 17.2, 10.4, 5.6, 5.6 Hz, CH-C8), 5.26 (1H, ddd, *J* = 17.2, 3.2, 1.5 Hz, CH_2-C9), 5.15 (1H, ddd, *J* = 10.4, 3.2, 1.4 Hz, CH_2-C9), 4.80 (1H, dd, *J* = 6.1, 2.6 Hz, CH-C2), 4.08 (1H, dddd, *J* = 12.3, 5.6, 1.5, 1.4 Hz, CH_2-C7), 4.00–3.91 (3H, m,CH-C5, CH_2-C6, CH_2-C7), 3.91–3.82 (3H, m, CH-C3, CH-C4, CH_2-C6), 1.07 (9H, s, *t*-Bu-TBDPS), 0.82 (9H, s, *t*-Bu-TBS), 0.10 (3H, s, Me-TBS), 0.03 (3H, s, Me-TBS); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 144.8 (CH-C1), 136.0 (CH-Ph-TBDPS), 135.9 (CH-Ph-TBDPS), 135.0 (CH-C8), 133.9 (C-Ph-TBDPS), 133.7 (C-Ph-TBDPS), 129.7 (CH-Ph-TBDPS), 127.7 (CH-Ph-TBDPS), 127.7 (CH-Ph-TBDPS), 117.0 (CH_2-C9), 98.9 (CH-C2), 79.6 (CH-C4), 76.8 (CH-C3), 69.3 (CH_2-C7), 68.2 (CH-C5), 62.9 (CH_2-C6), 27.1 (CH_3-*t*-Bu-TBDPS), 26.0 (CH_3-*t*-Bu-TBS), 19.5 (C-*t*-Bu-TBS), 18.3 (C-*t*-Bu-TBDPS), −4.0 (CH_3-Me-TBS), −4.8 (CH_3-Me-TBS); ν_{max} 2955, 2857, 1647, 1472, 1427,1248, 1113, 837, 700 cm^{-1}; HRMS (ESI+) $[M+Na]^+$ calculated for $C_{31}H_{46}NaO_4Si_2$ 561.2827, found 561.2810, Δ = 3.0 ppm.

3-*O*-Allyl-4-*O*-[(*tert*-butyl)bis(methyl)silyl]-6-*O*-[(*tert*-butyl)bis(phenyl)silyl]-2-deoxy-D-glucose 508



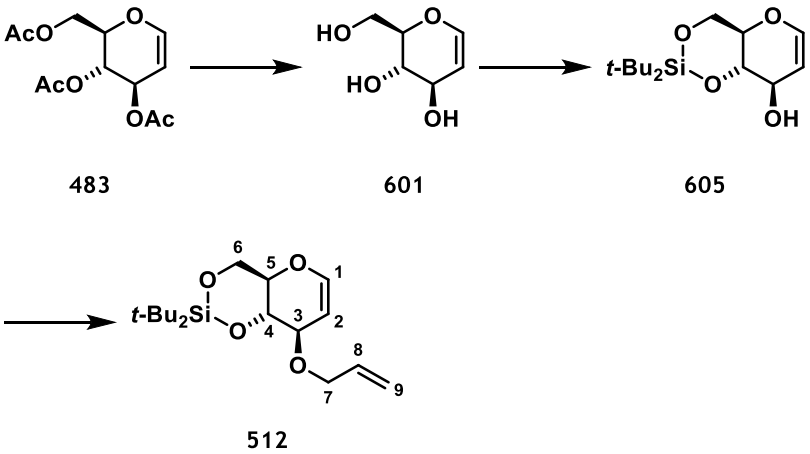
604 508

To a stirred solution of disilyl ether **604** (1.01 g, 1.87 mmol) in 1,4-dioxane (25 mL) at rt was added HCl (8 M in H_2O, 4.5 mL, 36 mmol) and the reaction mixture was stirred for 4 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (30 mL) and diluted with CH_2Cl_2 (30 mL). The phases were separated and the aqueous phase was washed with CH_2Cl_2 (2 × 30 mL). The combined organic fractions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) affording lactol **508** (3:1 mixture of anomers, 771 mg, 74%) as a colourless oil.

R_f = 0.67 (pet. ether:EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (8H, m, Ph-TBDPS, two anomers), 7.43–7.32 (12H, m, Ph-TBDPS, two anomers), 5.93 (1H, ddt, *J* = 11.1, 5.5, 3.2 Hz, CH-C8, major anomer), 5.91 (1H, app. ddt, *J* = 11.2, 10.5, 3.2 Hz, CH-C8, minor anomer), 5.34-5.31 (1H, m, CH-C1, major anomer), 5.29-5.22 (2H, m, CH_2-C9, two anomers), 5.16 (1H, app. dq, *J* = 10.2, 1.5 Hz, CH_2-C9, minor anomer), 5.15 (1H, app. dq, *J* = 10.4, 1.4 Hz, CH_2-C9, major anomer), 4.70 (1H, ddd, *J* = 9.3, 6.3, 2.1 Hz, CH-C1, minor anomer), 4.07 (1H, ddd, *J* = 5.8, 2.8, 1.4 Hz, CH_2-C6, minor anomer), 4.04 (1H, ddd, *J* = 5.8, 2.9, 1.5 Hz, CH_2-C6, major anomer), 3.99-3.91 (2H, m, CH-C4, two anomers), 3.90-3.78 (4H, m, CH-C3, major anomer, CH-C5, major anomer, CH_2-C6, two anomers), 3.66 (1H, ddd, *J* = 10.9, 8.5, 4.7 Hz, CH-C3, major anomer), 3.62-3.52 (2H, m, CH-C4 two anomers), 3.30 (1H, ddd, *J* = 9.1, 6.9, 3.9 Hz, CH-C5, minor anomer), 2.63 (1H, dd, *J* = 14.4, 5.7 Hz, OH-C4, major anomer), 2.35 (1H, ddd, *J* = 12.5, 4.7, 2.0 Hz, CH_2-C2, minor anomer), 2.27 (1H, app. t, *J* = 2.4 Hz, major anomer), 2.26 (1H, ddd, *J* = 13.0, 4.8, 1.4 Hz, CH_2-C2, major anomer), 1.56-1.45 (2H, m, major anomer, major anomer), 1.41-1.31 (1H, m, major anomer), 1.07 (9H, s, CH_3-*t*-Bu-TBDPS, minor anomer), 1.06 (9H, s, CH_3-*t*-Bu-TBDPS, major anomer),

0.80 (9H, s, CH_3-*t*-Bu-TBS, minor anomer), 0.80 (9H, s, CH_3-*t*-Bu-TBS, major anomer), 0.09 (3H, s, CH_3-Me-TBS, minor anomer), 0.07 (3H, s, CH_3-Me-TBS, major anomer), 0.05 (3H, s, CH_3-Me-TBS, major anomer), −0.04 (3H, s, CH_3-Me-TBS, minor anomer); ν_{max} 3430, 2957, 2930, 2857, 1471, 1111, 837, 779, 702 cm^{-1}; HRMS (ESI+) $[M+Na]^+$ calculated for $C_{31}H_{48}NaO_5Si_2$ 579.2938, found 579.2924, Δ = 2.4 ppm.

3-*O*-Allyl-4,6-*O*-[di(*tert*-butyl)silanediyl]-D-glucal 512



483 601 605

512

To a stirred solution of tri-*O*-acetyl-D-glucal **483** (7.06 g, 25.9 mmol) in MeOH (55 mL) at rt was added K_2CO_3 (36 mg, 0.26 mmol) and stirred for 16 h. The reaction mixture was concentrated under reduced pressure to afford crude D-glucal (**601**) which was used in the next step without further purification.

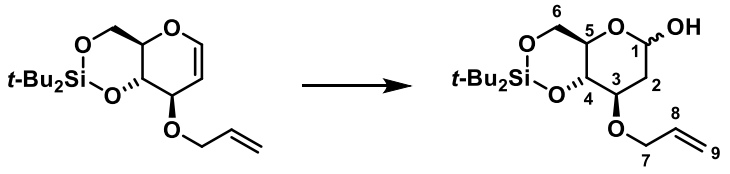
To a stirred solution of D-glucal (**601**) in DMF (64 mL) at −40 °C was added di-*tert*-butylsilyl-bis(trifluoromethanesulfonate) (9.1 mL, 28 mmol) *via* syringe pump over 1 h. After complete addition the reaction was stirred at −40 °C for a further 2 h after which time the reaction was quenched by the addition of pyridine (8 mL). The reaction mixture was diluted with Et_2O (100 mL) and H_2O (100 mL), the phases were separated and the aqueous phase was washed with Et_2O (2 × 100 mL). The combined organic fractions were washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford allylic alcohol **605** which was used in the next step without further purification.

To a stirred solution of allylic alcohol **605** in DMF (64 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 1.65 g, 41.3 mmol) in 8 portions and stirred for 10 min after gas evolution ceased. To the reaction mixture at 0 °C was added allyl bromide (11.3 mL, 131 mmol) followed by TBAI (823 mg, 2.55 mmol). The reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was cooled to 0 °C and the reaction quenched by the addition of sat. aq. NH_4Cl (100 mL) and diluted with Et_2O (200 mL). The phases were separated and the aqueous phase was washed with Et_2O (3 × 200 mL). The combined organic fractions

were washed with sat. aq. LiCl (100 mL) dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:Et_2O, 100:1) affording allyl ether **512** (7.38 g, 87%) as a colourless oil.

R_f = 0.26 (pet. ether:Et_2O, 50:1); $[\alpha]_D^{17}$ −27.4 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (1H, ddd, *J* = 6.1, 1.7, 0.5 Hz, CH-C1), 5.94 (1H, dddd, *J* = 17.2, 10.4, 5.7, 5.3 Hz, CH-C8), 5.31 (1H, app. dq, *J* = 17.2, 1.7 Hz, CH_2-C9), 5.17 (1H, app. dq, *J* 10.4, 1.5 Hz, CH_2-C9), 4.72 (1H, dd, *J* = 6.1, 1.9 Hz, CH-C2), 4.37 (1H, app. ddt, *J* = 13.1, 5.5, 1.5 Hz, CH_2-C7), 4.23 (1H, ddt, *J* = 13.1, 5.5, 1.4 Hz, CH_2-C7), 4.16 (1H, dd, *J* = 10.0, 4.9 Hz, CH_2-C6), 4.13 (1H, dd, *J* = 10.0, 7.0 Hz, CH-C4), 4.08 (1H, dtd, *J* = 7.0, 1.9, 0.5 Hz, CH-C3), 3.97 (1H, t, *J* = 10.4 Hz, CH_2-C6), 3.81 (1H, ddd, *J* = 17.3, 8.4, 3.7 Hz, CH-C5), 1.07 (9H, s, CH_3-*t*-Bu-Si), 1.00 (9H, s, CH_3-*t*-Bu-Si); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (CH-C1), 135.5 (CH-C8), 116.7 (CH_2-C9), 102.7 (CH-C2), 77.0 (CH-C4), 76.6 (CH-C3), 72.8 (CH-C5), 71.4 (CH_2-C7), 66.1 (CH_2-C6), 27.6 (3 × C, CH_3-*t*-Bu-Si), 27.1 (3 × C, CH_3-*t*-Bu-Si), 22.8 (C-*t*-Bu-Si), 20.0 (C-*t*-Bu-Si); ν_{max} 2963, 2934, 2889, 2859, 1647, 1472, 1233, 1158, 1119, 922 cm^{-1}; HRMS calculated for $C_{17}H_{30}NaO_4Si$ $[M+Na]^+$ 349.1806, found 349.1795, Δ = 3.0 ppm; elemental analysis calculated for $C_{17}H_{30}O_4Si$: C 62.54%, H 9.26%, found C 62.73%, H 9.41%.

3-*O*-Allyl-4,6-*O*-[di(*tert*-butyl)silanediyl]-2-deoxy-D-glucose 513



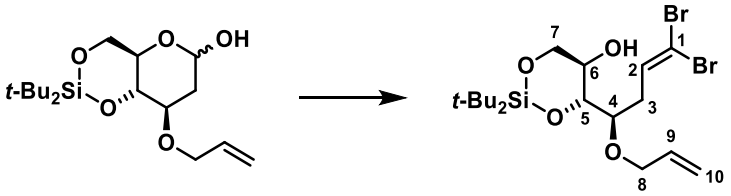
512 513

To a stirred solution of allyl ether **512** (7.38 g, 22.6 mmol) in 1,4-dioxane (270 mL) at rt was added HCl (8 M in H_2O, 56 mL, 450 mmol) and the reaction mixture was stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 (500 mL) and sat. aq. $NaHCO_3$ (500 mL), the phases were separated and the aqueous phase was washed with CH_2Cl_2 (2 × 500 mL). The combined organic fractions were washed with brine (500 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) to give lactol **513** (3:1 mixture of diastereoisomers, 6.13 g, 78%) as a colourless solid.

R_f = 0.11 (pet. ether:EtOAc, 9:1); $[\alpha]_D^{18}$ +32 (c = 0.70, $CHCl_3$); mp = 85–86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (1H, ddt, *J* = 16.0, 10.4, 5.5 Hz, CH-C8, major anomer), 5.93 (1H, dtd, *J* = 15.3, 10.4, 5.5 Hz, CH-C8, minor anomer), 5.33–5.26 (3H, m, CH-C1, major anomer, CH_2-C9 two anomers), 5.17 (1H, ddt, *J* = 10.4, 1.9, 1.3 Hz, CH_2-C9, minor anomer), 5.15 (1H, ddt, *J* = 10.4, 1.8, 1.3 Hz, CH_2-C9 major anomer), 4.87 (1H, ddd, *J* = 9.2, 6.9, 2.1 Hz, CH-C1 minor anomer), 4.42 (1H, ddt, *J* = 13.0, 5.4, 1.5 Hz, CH_2-C7, major anomer), 4.39 (1H, ddt, *J* = 13.0, 5.3, 1.5 Hz, CH_2-C7, minor anomer), 4.23 (1H, ddt, *J* = 13.0, 5.8, 1.4 Hz, CH_2-C7, two anomers), 4.14 (1H, dd, *J* = 10.2, 5.0 Hz, CH_2-C6, minor anomer), 4.05 (1H, dd, *J* = 9.5, 4.5 Hz, CH_2-C6, major anomer), 3.99–3.90 (2H, m, CH-C4, two anomers), 3.90-3.72 (4H, m, CH-C3, major anomer, CH-C5, major anomer, CH_2-C6 two anomers), 3.44 (1H, ddd, *J* = 11.6, 8.4, 5.0 Hz, CH-C3, minor anomer), 3.36 (1H, ddd, *J* = 10.1, 9.5, 5.0 Hz, CH-C5, minor anomer), 3.05 (1H, d, *J* = 6.9 Hz, OH-C1, minor anomer), 2.59 (1H, dd, *J* = 2.9, 2.4 Hz, OH-C1, major anomer), 2.29 (1H, ddd, *J* = 12.9, 5.0, 2.1 Hz, CH_2-C2, minor anomer), 2.15 (1H, ddd, *J* = 13.3, 4.7, 1.2 Hz, CH_2-C2, major anomer), 1.67 (1H, dddd, *J* = 13.5, 11.3, 3.7, 2.3 Hz, CH_2-C2, major anomer), 1.54 (1H, ddd, *J* = 12.9, 11.6, 9.8 Hz, CH_2-C2, minor anomer), 1.07 (9H, CH_3-*t*-Bu-Si, major anomer), 1.06 (9H, CH_3-*t*-Bu-Si, minor

anomer), 1.01 (9H, CH_3-*t*-Bu-Si, major anomer), 1.00 (9H, CH_3-*t*-Bu-Si, minor anomer); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7 (CH-C8, major anomer), 135.5 (CH-C8, minor anomer), 116.8 (CH_2-C9, minor anomer), 116.6 (CH_2-C9, major anomer), 94.7 (CH-C1, minor anomer), 92.7 (CH-C1, major anomer), 80.4 (CH-C3, major anomer), 79.3 (CH-C3, minor anomer), 75.1 (CH-C5, major anomer), 72.8 (CH_2-C7, major anomer), 72.4 (CH_2-C7, minor anomer), 71.1 (CH-C5, minor anomer), 67.2 (CH-C4, two anomer), 67.1 (CH_2-C6, major anomer), 66.7 (CH_2-C6, minor anomer), 39.3 (CH_2-C2, minor anomer), 36.5 (CH_2-C2, major anomer), 27.6 (3 × C, CH_3-*t*Bu-Si, major anomer), 27.6 (3 × C, CH_3-*t*Bu-Si, minor anomer), 27.2 (3 × C, CH_3-*t*Bu-Si, major anomer), 27.2 (3 × C, CH_3-*t*Bu-Si, minor anomer), 22.9 (C-*t*Bu-Si, major anomer), 22.8 (C-*t*Bu-Si, minor anomer), 20.1 (C-*t*Bu-Si, major anomer), 20.1 (C-*t*Bu-Si, minor anomer); ν_{max} 3404, 2963, 2934, 2886, 2859, 1472, 1387, 1387, 1364, 1159, 1096 cm^{-1}; HRMS calculated for $C_{17}H_{32}NaO_5Si$ $[M+Na]^+$ 367.1911, found 367.1897, Δ = 3.9 ppm; elemental analysis calculated for $C_{17}H_{32}O_5Si$: C 59.27%, H 9.36%, found C 58.95%, H 9.69%.

(2*R*,3*R*,4*R*)-1,1-Dibromo-4-allyloxy-5,7-*O*-[di(*tert*-butyl)silanediyl]-1-hepten-6-ol 514

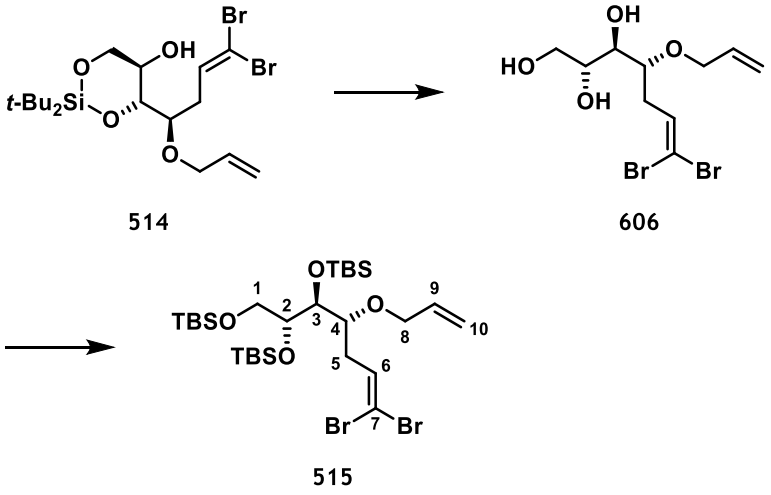


513 514

To a stirred solution of $[Ph_3PCHBr_2]Br$ **497** (27.6 g, 53.7 mmol) in THF (200 mL) at rt was added a solution of KO*t*-Bu (5.56 g, 49.6 mmol) in THF (300 mL) and stirred for 30 min. A solution of lactol **513** (6.13 g, 17.8 mmol) in THF (100 mL) was added and the reaction mixture was stirred at rt for 16 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (500 mL) and diluted with Et_2O (500 mL), the phases were separated and the aqueous phase was washed with Et_2O (2 × 500 mL). The combined organic fractions were washed with brine (500 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 19:1) to give di-bromo olefin **514** (6.98 g, 78%) as a colourless oil.

R_f = 0.31 (pet. ether:EtOAc, 9:1); $[\alpha]_D^{18}$ −12.0 (c = 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (1H, t, *J* = 7.2 Hz, CH-C2), 5.90 (1H, ddt, *J* = 17.2, 10.4, 5.7 Hz, CH-C9), 5.30 (1H, app. dq, *J* = 17.2, 1.6 Hz, CH_2-C10), 5.22 (1H, app. dq, *J* = 10.4, 1.3 Hz, CH_2-C10), 4.14 (1H, ddt, *J* = 12.7, 5.5, 1.4 Hz, CH_2-C8), 4.11 (1H, dd, *J* = 10.5, 4.2 Hz, CH_2-C7), 4.08 (1H, ddt, *J* = 12.7, 5.8, 1.3 Hz, CH_2-C8), 3.99–3.90 (2H, m, CH-C5, CH-C6), 3.79 (1H, t, *J* = 10.0 Hz, CH_2-C7), 3.73 (1H, ddd, *J* = 7.7, 4.9, 2.5 Hz, CH-C4), 2.09 (1H, s, OH-C6), 2.62 (1H, ddd, *J* = 15.0, 7.5, 5.0 Hz, CH_2-C3), 2.43 (1H, ddd, *J* = 14.9, 7.9, 6.9 Hz, CH_2-C3), 1.05 (9H, s, CH_3-*t*-Bu-Si), 1.00 (9H, s, CH_3-*t*-Bu-Si); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.4 (CH-C2), 134.3 (CH-C9), 117.9 (CH_2-C10), 90.3 (C-C1), 78.9 (CH-C4), 76.8 (CH-C5), 71.9 (CH_2-C8), 68.7 (CH_2-C7), 67.1 (CH-C6), 33.4 (CH_2-C3), 27.7 (3 × C, CH_3-*t*-Bu-Si), 27.2 (3 × C, CH_3-*t*-Bu-Si), 23.0 (C-*t*-Bu-Si), 20.3 (C-*t*-Bu-Si); ν_{max} 3439, 2963, 2934, 2891, 2861, 1474, 1146, 1134, 856, 826, 773, 652 cm^{-1}; HRMS calculated for $Br_2C_{18}H_{32}NaO_4Si$ $[M+Na]^+$ 521.0329, found 521.0317, Δ = 2.3 ppm; elemental analysis calculated for $Br_2C_{18}H_{32}O_4Si$: C 43.21%, H 6.45%, found C 42.67%, H 6.25%.

(2*S*,3*S*,4*R*)-4-(Allyloxy)-7,7-dibromo-1,2,3-tris[(*tert*-butyl)bis(methyl)siloxy]-6-heptene 515



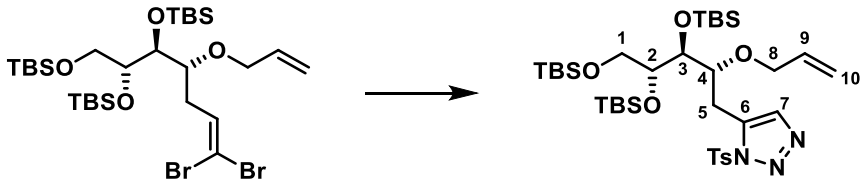
To a stirred solution silyl ether **514** (6.97 g, 134 mmol) in THF (170 mL) at rt was added AcOH (1.6 mL, 28 mmol) followed by TBAF (1 M in THF, 56 mL, 56 mmol). The reaction mixture was stirred at this temperature for 16 h, then concentrated under reduced pressure. The crude material was filtered through a short pad of silica (pet. ether:EtOAc, 1:2) to afford crude triol **606** as a pale yellow solid.

To a stirred solution of crude triol **606** in CH_2Cl_2 (190 mL) at rt was added TBSOTf (16 mL, 70 mmol) followed by 2,6-lutidine (13 mL, 110 mmol). The reaction mixture was stirred at this temperature for 3 h then quenched by the addition of sat. aq. $NaHCO_3$ (200 mL) The phases were separated and the aqueous phase was washed with Et_2O (3 × 100 mL). The combined organic fractions were washed with sat. aq. $CuSO_4$ (200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 19:1) to give silyl ether **515** (7.84 g, 80%) as a colourless oil.

R_f = 0.92 (pet. ether:EtOAc, 19:1); $[\alpha]_D^{20}$ −2.07 (c = 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (1H, dd, *J* = 7.2, 6.4 Hz, CH-C6), 5.89 (1H, ddt, *J* = 17.1, 10.4, 5.7 Hz, CH-C9), 5.25 (1H, dq, *J* = 17.2, 1.5 Hz, CH_2-C10), 5.16 (1H, dq, *J* = 10.4, 1.4 Hz, CH_2-C10), 4.07 (1H, ddt, *J* = 12.5, 5.6, 1.5 Hz, CH_2-C8), 3.96 (1H, ddt, *J* = 12.6, 5.9, 1.4 Hz, CH_2-C8), 3.82–3.76 (3H, m, CH-C3, CH-C2, CH_2-C1), 3.49–3.41 (2H, m, CH-C4, CH_2-C1), 2.46 (1H, ddd, *J* = 16.0, 6.2, 4.2 Hz, CH_2-C5), 2.37 (1H, dt, *J* = 16.0, 7.1 Hz, CH_2-C5), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.89 (9H, s,

CH_3-*t*-Bu-TBS), 0.89 (9H, s, CH_3-*t*-Bu-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0 (CH-C6), 135.2 (CH-C9), 117.1 (CH_2-C10), 79.4 (CH-C4), 76.5 (CH-C3), 75.3 (CH-C2), 71.6 (CH_2-C8), 64.6 (CH_2-C1), 34.8 (CH_2-C5), 26.2 (3 × C, CH_3-*t*-TBS), 26.2 (3 × C, CH_3-*t*-TBS), 26.2 (3 × C, CH_3-*t*-TBS), 18.5 (C-*t*-Bu-TBS), 18.5 (C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), −4.3 (CH_3-Me-TBS), −4.4 (CH_3-Me-TBS), −4.5 (CH_3-Me-TBS), −4.5 (CH_3-Me-TBS), −5.3 (CH_3-Me-TBS), −5.3 (CH_3-Me-TBS); ν_{max} 2953, 2930, 2886, 2857, 1474, 1254, 1076, 837, 779, 660 cm^{-1}.

(2*R*,3*S*,4*R*)-4-(Allyloxy)-1,2,3-tris[(*tert*-butyl)bis(methyl)siloxy]-5-[3-tosyl-3*H*-1,2,3-triazol-4-yl]pentane 481



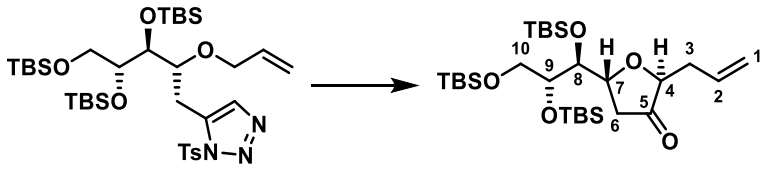
515 481

To a stirred solution of di-bromo olefin **515** (5.50 g, 7.83 mmol) in THF (50 mL) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 6.3 mL, 16 mmol) and stirred at this temperature for 20 min. TsN_3 (1.3 mL, 8.5 mmol) was added and the resulting solution was stirred for a further 30 min at −78 °C. The reaction was quenched by the addition of sat. aq. NH_4Cl (100 mL). The mixture was warmed to rt and diluted with Et_2O (100 mL), the phases were separated and the aqueous fraction was washed with Et_2O (3 × 100 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) to give tosyl triazole **481** (5.48 g, 95%) as a colourless oil.

R_f = 0.28 (pet. ether:EtOAc, 9:1); $[\alpha]_D^{20}$ +20 (c = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, d, *J* = 8.2 Hz, Ar-Ts), 7.54 (1H, s, CH-C7), 7.35 (2H, d, *J* = 8.2 Hz, Ar-Ts), 5.56 (1H, ddt, *J* = 16.0, 10.4, 5.7 Hz, CH-C9), 5.09 (1H, dq, *J* = 17.3, 1.5 Hz, CH_2-C10), 5.03 (1H, dq, *J* = 10.4, 1.5 Hz, CH_2-C10), 4.01 (1H, dd, *J* = 5.8, 1.3 Hz, CH-C3), 3.98 (1H, ddt, *J* = 12.5, 5.5, 1.3 Hz, CH_2-C8), 3.87 (1H, td, *J* = 6.3, 1.3 Hz, CH-C2), 3.82 (1H, dd, *J* = 9.8, 6.3 Hz, CH_2-C1), 3.73 (1H, ddt, *J* = 12.5, 5.7, 1.5 Hz, CH_2-C8), 3.68 (1H, dt, *J* = 7.2, 5.8 Hz, CH-C4), 3.51 (1H, dd, *J* = 9.8, 5.8 Hz, CH_2-C1), 3.38–3.30 (2H, m, CH_2-C5), 2.45 (3H, s, CH_3-Ts), 0.92 (9H, CH_3-*t*-Bu-TBS), 0.91 (9H, CH_3-*t*-Bu-TBS), 0.87 (9H, CH_3-*t*-Bu-TBS), 0.12 (3H, CH_3-Me-TBS), 0.10 (3H, CH_3-Me-TBS), 0.06 (6H, 2 × CH_3-Me-TBS), 0.05 (3H, CH_3-Me-TBS), 0.05 (3H, CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0 (C-C6), 138.2 (C-Ts), 134.4 (CH-C9), 134.2 (C-Ts), 134.0 (CH-C7), 130.4 (2 × C, CH-Ts), 130.4 (CH-Ts), 128.8 (2 × C, CH-Ts), 117.4 (CH_2-C10), 79.7 (CH-C4), 76.2 (CH-C2), 74.7 (CH-C3), 71.8 (CH_2-C8), 65.0 (CH_2-C1), 26.2 (3 × C, CH_3-*t*-Bu-TBS), 26.2 (3 × C, CH_3-*t*-Bu-TBS), 26.1 (3 × C, CH_3-*t*-Bu-TBS), 25.8 (CH_2-C5), 22.0 (CH_3-Ts), 18.5

(C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), 18.3 (C-*t*-Bu-TBS), −4.2 (CH_3-Me-TBS), −4.5 (CH_3-Me-TBS), −4.6 (CH_3-Me-TBS), −4.6 (CH_3-Me-TBS), −5.3 (CH_3-Me-TBS), −5.3 (CH_3-Me-TBS); ν_{max} 2928, 2886, 2857, 2126 1595, 1472, 1389, 1252, 1196, 1087, 835, 779, 669, 586 cm^{-1}; HRMS calculated for $C_{35}H_{65}N_3NaO_6SSi_3$ $[M+Na]^+$ 762.3794, found 762.3780, Δ = 1.9 ppm.

(2*S*,5*R*)-5-{(1*S*,2*R*)-1,2,3-Tris[(*tert*-butyl)bis(methyl)siloxy]propyl}-2-allyl-4,5-dihydro-2*H*-furan-3-one 521



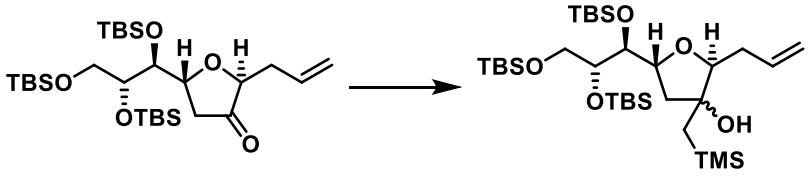
481 521

To a stirred solution of triazole **481** (2.00 g, 2.70 mmol) in PhMe (85 mL) at rt was added $[Rh(OAc)_2]_2$ (13 mg, 0.027 mmol). The reaction mixture was heated to reflux and stirred for 1 h. The reaction mixture was cooled to rt, basic alumina (Brockmann activity III, 20 g, prepared from Brockmann activity I basic alumina, 18.8 g, and H_2O, 1.2 g) was added, and stirred for a further 30 min. After removing the solids by filtration, the filtrate was concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 50:1) affording dihydrofuranone **521** (881 mg, 58%) as a colourless oil.

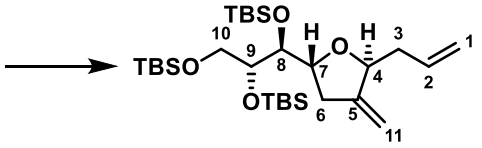
R_f = 0.76 (pet. ether:EtOAc, 9:1); $[\alpha]_D^{21}$ −32.7 (c =1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (1H, dddd, *J* = 17.1, 10.2, 7.0, 7.0 Hz, CH-C2), 5.12 (1H, ddd, *J* = 18.1, 3.6, 1.9 Hz, CH_2-C1), 5.08 (1H, dddd, *J* = 10.2, 1.8, 0.9, 0.9 Hz, CH_2-C1), 4.49 (1H, ddd, *J*= 7.5, 6.5, 5.6 Hz, CH-C7), 4.03 (1H, dd, *J* = 7.5, 4.6 Hz, CH-C4), 3.83 (1H, dd, *J* = 9.5, 5.6 Hz, CH_2-C10), 3.79 (1H, ddd, *J* = 5.5, 5.5, 2.0 Hz, CH-C9), 3.75 (1H, *J* = 5.4, 2.0 Hz, CH-C8), 3.47 (1H, dd, *J* = 9.5, 5.5 Hz, CH_2-C10), 2.48 (1H, dd, *J* = 18.1, 7.7 Hz, CH_2-C6), 2.45–2.38 (1H, m, CH_2-C3), 2.35 (1H, ddd, *J* = 18.2, 6.5, 0.5 Hz, CH_2-C6), 2.27 (1H, app. dtdd, *J* = 14.6, 7.3, 1.1, 1.0 Hz, CH_2-C3), 0.89 (9H, s, *t*-Bu, TBS), 0.88 (9H, s, *t*-Bu, TBS), 0.88 (9H, s, *t*-Bu, TBS), 0.10 (3H, s, Me, TBS), 0.09 (3H, s, Me, TBS), 0.08 (6H, s, Me, TBS), 0.05 (3H, s, Me, TBS), 0.05 (3H, s, Me, TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.9 (C-C5), 133.5 (CH-C2), 118.2 (CH_2-C1), 79.5 (CH-C8), 78.9 (CH-C7), 76.8 (CH-C9), 76.2 (CH-C4), 64.6 (CH_2-C10), 39.5 (CH_2-C6), 35.9 (CH_2-C3), 26.2 (CH_3-*t*-Bu-TBS), 26.2 (CH_3-*t*-Bu-TBS), 26.1 (CH_3-*t*-Bu-TBS), 18.6 (C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), −4.1 (CH_3-Me-TBS), −4.3 (CH_3-Me-TBS), −4.4 (CH_3-Me-TBS), −4.6 (CH_3-Me-TBS), −5.2 (CH_3-Me-TBS), −5.2 (CH_3-Me-TBS); ν_{max} cm^{-1} 2951, 2928, 2887, 2857, 1759, 1472,

1361, 1254, 1076 Hz; HRMS calculated for $C_{28}H_{58}NaO_5Si_3$ $[M+Na]^+$ 581.3484, found 581.3482, Δ = 0.4 ppm.

(1*S*,2*R*)-1-[(2*R*,5*S*)-5-Allyl-4-methylene-3,5-dihydro-2*H*-fur-2-yl]-1,2,3-tris[(*tert*-butyl)bis(methyl)siloxy]propane 480



521 522



480

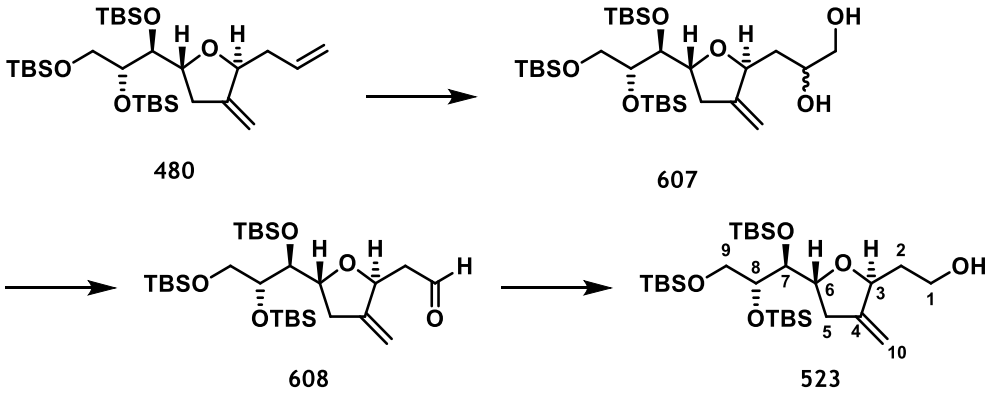
$CeCl_3 \cdot 7H_2O$ (9.70 g, 39.4 mmol) was added to a 100 mL round-bottom flask and dried following a known procedure.[119] To the dried $CeCl_3$ was added THF (40 mL) and stirred under argon for 2 h to give $CeCl_3$-THF complex as a colourless precipitate.

To a stirred suspension of Mg turnings (869 mg, 35.7 mmol) and 1,2-dibromoethane (2 drops) in THF (10 mL) was added a solution of $TMSCH_2Cl$ (4.6 mL, 33 mmol) in THF (20 mL). Formation of the Grignard reagent was achieved by heating the mixture to reflux, followed by slow addition of the halide to maintain reflux. The Grignard reagent was stirred at rt for 2 h then added to the $CeCl_3$-THF complex at −78 °C. The resulting mixture was stirred at −78 °C for a further 30 min. After which time a solution of ketone **521** (5.00 g, 8.94 mmol) in THF (10 mL) was added. The reaction mixture was stirred at −78 °C for 1 h then warmed to rt and stirred for a further 16 h. The reaction mixture was cooled to 0 °C and quenched by the addition of sat. aq. NH_4Cl (100 mL), the mixture was stirred for 30 min then diluted with H_2O (100 mL) and Et_2O (200 mL). The phases were separated and the aqueous phase was washed with Et_2O (2 × 200 mL). The combined organic fractions were washed with brine (400 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude alcohol as a yellow oil and used in the next step without further purification.

To a stirred solution of the crude alcohol in THF (60 mL) at rt was added NaHMDS (1 M in THF, 11 mL, 11 mmol). The reaction mixture was stirred for 5 min then heated to reflux for a further 1.5 h. The reaction mixture was cooled to rt and quenched by the addition of sat. aq. NH_4Cl (50 mL) and diluted with Et_2O (50 mL) and H_2O (50 mL). The phases were separated and the aqueous phase was washed with Et_2O (3 × 50 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 40:1) affording diene **480** (3.12 g, 63%) as a colourless oil.

R_f = 0.82 (pet. ether:EtOAc, 40:1); $[\alpha]_D^{22}$ −24 (c = 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (1H, ddt, *J* = 17.2, 10.2, 6.9 Hz, CH-C2), 5.08 (1H, dq, *J* = 17.2, 1.6 Hz, CH_2-C1), 5.04 (1H, ddt, *J* = 10.2, 2.2, 1.2 Hz, CH_2-C1), 4.97 (1H, q, *J* = 2.1 Hz, CH_2-C11), 4.83 (1H, q, *J* = 2.1 Hz, CH_2-C11), 4.41 (1H, t, *J* = 4.6 Hz, CH-C4), 4.06 (1h, q, *J* = 7.2 Hz, CH-C7), 3.81 (1H, dd, *J* = 9.9, 6.0 Hz, CH_2-C10), 3.68 (1H, td, *J* = 5.9, 1.4 Hz, CH-C9), 3.62 (1H, dd, *J* = 7.2, 1.4 Hz, CH-C8), 3.44 (1H, dd, *J* = 9.9, 5.8 Hz, CH_2-C10), 2.60 (1H, ddq, *J* = 11.2, 4.9, 1.5 Hz, CH_2-C6), 2.36 (1H, ddd, *J* = 9.2, 5.7, 2.1 Hz, CH_2-C6), 2.30 (1H, ddd, *J* = 6.9, 3.6, 1.1 Hz, CH_2-C3), 2.26(1H, ddt, *J* = 14.4, 6.8, 1.3 Hz, CH_2-C3), 0.88 (18H, 2 × CH_3-*t*-Bu-TBS), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.08 (3H, CH_3-Me-TBS), 0.07 (3H, CH_3-Me-TBS), 0.07 (3H, CH_3-Me-TBS), 0.06 (3H, CH_3-Me-TBS), 0.04 (6H, 2 × CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5 (C-C5), 135.3 (CH-C2), 116.9 (CH_2-C1), 104.8 (CH_2-C11), 79.4 (CH-C8), 79.3 (CH-C4), 79.0 (CH-C7), 75.7 (CH-C9), 64.3 (CH_2-C10), 40.0 (CH_2-C3), 36.0 (CH_2-C6), 26.2 (3 × C, CH_3-*t*-Bu-TBS), 26.2 (3 × C, CH_3-*t*-Bu-TBS), 26.2 (3 × C, CH_3-*t*-Bu-TBS), 18.6 (C-*t*-Bu-TBS), 18.5 (C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), −4.3 (CH_3-Me-TBS), −4.4 (CH_3-Me-TBS), −4.5 (CH_3-Me-TBS), −4.5 (CH_3-Me-TBS), −5.3 (CH_3-Me-TBS), −5.3 (CH_3-Me-TBS); ν_{max} 2951, 2932, 2889, 2859, 1254, 1068, 829, 775, 660 cm^{-1}; HRMS calculated for $C_{29}H_{60}NaO_4Si_3$ $[M+Na]^+$ 579.3692, found 579.3679, Δ = 2.2 ppm.

2-[(2*S*,5*R*)-5-{(1*S*,2*R*)-1,2,3-Tris[(*tert*-butyl)bis(methyl)siloxy]propyl}-3-methylene-4,5-dihydro-2*H*-fur-2-yl]ethanol 523



To a stirred solution of diene **480** (732 mg, 1.31 mmol) in THF (16 mL) and H_2O (1.6 mL) at rt was added NMO (176 mg, 1.31 mmol) followed by OsO_4 (4% in H_2O, 0.10 mL, 16 μmol). The reaction mixture was stirred for 16 h after which time the reaction was quenched by the addition of solid NaS_2O_3 (658 mg, 5.22 mmol). The mixture was stirred for 30 min before CH_2Cl_2 (25 mL) and H_2O (30 mL) were added, the phases were separated and the aqueous phase was washed with CH_2Cl_2 (3 × 25 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give crude diol **607** which was used in the next step without further purification.

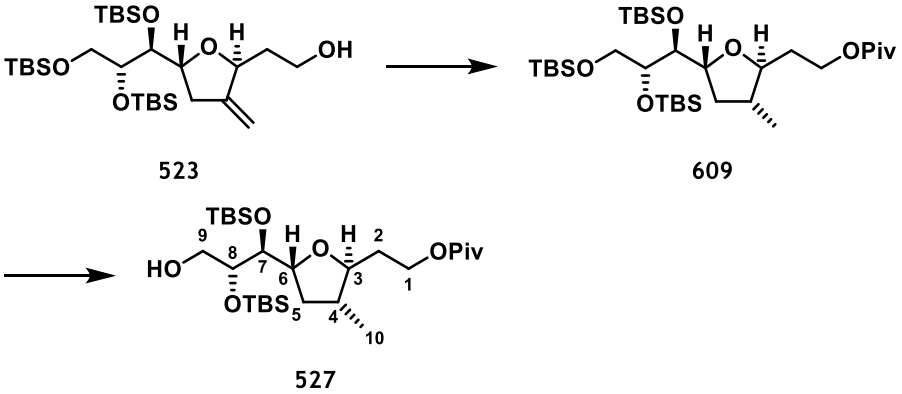
To a stirred solution of the crude diol **607** in THF (18 mL) and H_2O (3.6 mL) was added $NaIO_4$ (526 mg, 2.46 mmol) at rt and stirred at this temperature for 1.5 h, after which time the reaction mixture was diluted with H_2O (30 mL) and Et_2O (30 mL). The phases were separated and the aqueous phase was washed with Et_2O (2 × 30 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give crude aldehyde **608** which was used in the next step without further purification.

To a stirred solution of crude aldehyde **608** in EtOH (14 mL) at rt was added $NaBH_4$ (55 mg, 1.5 mmol) and stirred for 1 h. The reaction mixture was concentrated under reduced pressure and CH_2Cl_2 (15 mL) and H_2O (15 mL) were added. The phases were separated and the aqueous phase was washed with CH_2Cl_2 (2 × 15 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography

(pet. ether:EtOAc, 19:1) to give primary alcohol **523** (320 mg, 44%) as a colourless oil.

R_f = 0.14 (pet. ether:EtOAc, 19:1); $[\alpha]_D^{19}$ −14 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (1H, app q, *J* = 2.1 Hz, CH_2-C10), 4.82 (1H, app q, *J* = 2.1 Hz, CH_2-C10), 4.59 (dd, 6.2, 2.0 Hz, CH-C3), 4.14 (1H, dt, *J* = 14.3, 7.6 Hz, CH-C6), 3.86–3.78 (2H, m, CH_2-C1), 3.78 (1H, dd, *J* = 9.9, 6.6 Hz, CH_2-C9), 3.70 (1H, ddd, *J* = 6.3, 6.3, 1.1 Hz, CH-C8) 3.66 (1H, dd, *J* = 7.4, 1.1 Hz, CH-C7), 3.44 (1H, dd, *J* = 9.8, 5.5 Hz, CH_2-C9), 2.88–2.68 (1H, m, OH-C1), 2.64 (1H, ddq, *J* = 15.4, 6.4, 2.0 Hz, CH_2-C5), 2.38 (1H, ddt, *J* = 15.4, 8.1, 2.3 Hz, CH_2-C5), 1.86–1.72 (2H, m, CH_2-C2), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.88 (18H, s, 2 × CH_3-*t*-Bu-TBS), 0.08 (3H, s, CH_3-Me-TBS), 0.08 (3H, s, CH_3-Me-TBS), 0.08 (3H, s, CH_3-Me-TBS), 0.07 (3H, s, CH_3-Me-TBS), 0.05 (3H, s, CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (C-C4), 104.9 (CH_2-C10), 79.9 (CH-C3), 79.0 (CH-C6), 78.9 (CH-C7), 75.9 (CH-C8), 64.3 (CH_2-C9), 61.5 (CH_2-C1), 37.0 (CH_2-C2), 35.9 (CH_2-C5), 26.2 (3 × C, CH_3-*t*-Bu-TBS), 26.2 (3 × C, CH_3-*t*-Bu-TBS), 26.1 (3 × C, CH_3-*t*-Bu-TBS), 18.5 (C-*t*-Bu), 18.5 (C-*t*-Bu), 18.4 (C-*t*-Bu), −4.2 (CH_3-Me-TBS), −4.4 (CH_3-Me-TBS), −4.4 (CH_3-Me-TBS), −4.4 (CH_3-Me-TBS), −5.3 (CH_3-Me-TBS), −5.3 (CH_3-Me-TBS); ν_{max} 337, 2953, 29228, 2857, 1472, 1252, 1084, 1005, 831, 775, 669 cm^{-1}; HRMS calculated for $C_{28}H_{60}NaO_5Si_3$ $[M+Na]^+$ 583.3641, found 583.3648, Δ = 1.2 ppm.

2-[(2*S*,3*R*,5*R*)-5-{(1*S*,2*R*)-1,2-Bis[(*tert*-butyl)bis(methyl)siloxy]-3-hydroxypropyl}-3-methyltetrahydro-2-furyl]ethyl pivalate 527

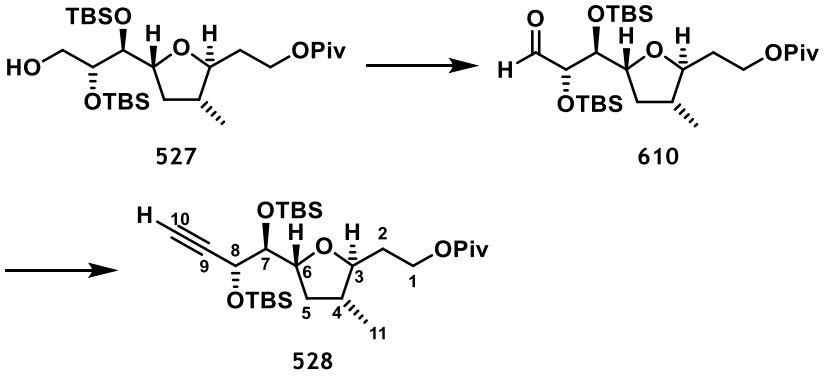


A solution of alcohol **523** (322 mg, 0.574 mmol) and [Ir(cod)(IMes)(PPh_3)]PF_6 (21 mg, 0.021 mmol) in CH_2Cl_2 (5 mL) was cooled to −78 °C and the flask was purged three time with H_2 before the cooling bath was removed. The solution was stirred under an atmosphere of H_2 for 1 h at rt and then the atmosphere of H_2 was replaced with argon. Pyridine (0.30 mL, 3.7 mmol) and PivCl (0.34 mL, 2.8 mmol) were added to the reaction mixture and the resulting solution was stirred at rt for 16 h. The reaction was quenched by the addition of HCl (1 M in H_2O, 10 mL) and the mixture was diluted with Et_2O (10 mL). The phases were separated and the aqueous phase was washed with Et_2O (3 × 10 mL). The combined organic fractions were washed with NaOH (1 M in H_2O, 15 mL) and sat. aq. $CuSO_4$ (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude piv-protected alcohol **609** which was used in the next step without further purification.

To a stirred solution of piv-protected alcohol **609** in MeOH (2.5 mL) and CH_2Cl_2 (2.5 mL) at 0 °C was added CSA (14 mg, 0.060 mmol) and stirred for 3 h. After which time the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5 mL) and the mixture was diluted with CH_2Cl_2 (10 mL). The phases were separated and the aqueous phase was washed with CH_2Cl_2 (2 × 10 mL). The combined organic fractions were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 19:1) affording alcohol **527** (147 mg, 48%) as a colourless oil.

R_f = 0.30 (pet. ether:EtOAc, 9:1); $[\alpha]_D^{16}$ −10.9 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (1H, ddd, *J* = 11.0, 6.4, 5.6 Hz, CH_2-C1), 4.12 (1H, ddd, *J* = 11.0, 5.4, 2.2 Hz, CH_2-C1), 4.07 (1H, ddd, *J* = 7.6, 5.6, 2.7 Hz, CH-C6), 4.02 (1H, app. dt, *J* = 8.3, 5.2 Hz, CH-C3), 3.80–3.73 (2H, m, CH-C8, CH_2-C9), 3.63 (1H, dd, *J* = 3.6, 1.8 Hz, CH-C7), 3.51 (1H, app. td, *J* = 8.8, 2.7 Hz, CH_2-C9), 3.32–3.24 (1H, br. s, OH-C9), 2.32–2.22 (1H, m, CH-C4), 2.08 (1H, ddd, *J* = 12.4, 9.0, 7.1 Hz, CH_2-C5), 1.78 (1H, dddd, *J* = 8.3, 6.4, 5.6, 3.4 Hz, CH_2-C2), 1.73 (1H, dddd, *J* = 8.3, 4.1, 2.5, 2.2 Hz, CH_2-C2), 1.64 (1H, ddd, *J* = 12.4, 7.0, 2.0 Hz, CH_2-C5), 1.18 (9H, s, CH_3-*t*-Bu-Piv), 0.90 (3H, d, *J* = 6.6 Hz, CH_3-C10), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.90 (9H, s, CH_3-*t*Bu-TBS), 0.12 (3H, s, CH_3-Me-TBS), 0.09 (3H, s, CH_3-Me-TBS), 0.08 (3H, s, CH_3-Me-TBS), 0.07 (3H, s, CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6 (C-Piv), 79.1 (CH-C3), 79.0 (CH-C7), 78.2 (CH-C6), 75.7 (CH-C8), 63.0 (CH_2-C9), 62.3 (CH_2-C1), 38.9 (C-*t*-Bu-Piv), 36.5 (CH_2-C5), 36.3 (CH-C4), 30.2 (CH_2-C2), 27.3 (3 × C, CH_3-*t*-Bu-Piv), 26.2 (3 × C, CH_3-*t*-Bu-TBS), 26.1 (3 × C, CH_3-*t*-Bu-TBS), 18.6 (C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), 14.3 (CH_3-C10), −4.0 (CH_3-Me-TBS), −4.5 (CH_3-Me-TBS), −4.5 (CH_3-Me-TBS), −4.8 (CH_3-Me-TBS); ν_{max} 3441, 2955, 2932, 2884, 2857, 1732, 1470, 1285, 1254, 1153, 1092, 1057, 1007, 833, 775 cm^{-1}; HRMS calculated for $C_{27}H_{56}NaO_6Si_2$ $[M+Na]^+$ 555.3508, found 555.3502, Δ = 1.0 ppm.

2-[(2*S*,3*R*,5*R*)-5-{(1*S*,2*R*)-1,2-Bis[(*tert*-butyl)bis(methyl)siloxy]-3-butynyl}-3-methyltetrahydro-2-furyl]ethyl pivalate 528

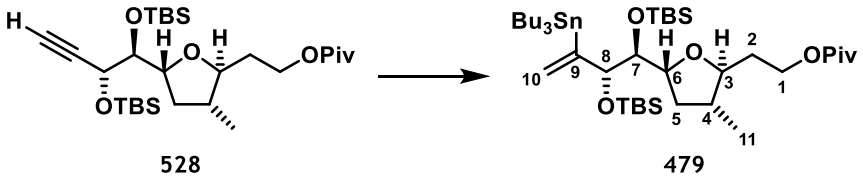


To a stirred solution of alcohol **527** (80 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) at rt was added pyridine (0.15 mL, 1.9 mmol) and Dess-Martin periodinane (255 mg, 4.38 mmol). The reaction mixture was stirred at rt for 3 h after which time the reaction was quenched by the addition of sat. aq. NaS_2O_3 (2.5 mL) and sat. aq. $NaHCO_3$ (2.5 mL). The mixture was diluted with Et_2O (5 mL) and the phases were separated, the aqueous phase was washed with Et_2O (2 × 5 mL). The combined organic fractions were washed with sat. aq. $NaHCO_3$ (10 mL), sat. aq. $CuSO_4$ (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude aldehyde **610** which was used in the next step without further purification.

To a stirred solution of Ohira-Bestmann reagent (115 mg, 0.599 mmol) in MeOH (5 mL) at 0 °C was added K_2CO_3 (62 mg, 0.45 mmol). The mixture was stirred at this temperature for 1 h, after which time a solution of crude aldehyde **610** in THF (1 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, then the reaction mixture was warmed to rt and stirred for a further 15 min. The reaction was quenched by the addition sat. aq. NH_4Cl (10 mL) and diluted with Et_2O (10 mL). The phases were separated and the aqueous phase was washed with Et_2O (3 × 10 mL). The combined organic fractions were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 50:1) to give alkyne **528** (60 mg, 76%) as a colourless oil.

R_f = 0.47 (pet. ether:EtOAc, 20:1); $[\alpha]_D^{16}$ −29 (c = 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (1H, dd, *J* = 4.3, 2.2 Hz, CH-C8), 4.20 (1H, ddd, *J* = 11.2, 7.0, 5.7 Hz, CH_2-C1), 4.15 (1H, ddd, *J* = 8.2, 7.1, 5.5 Hz, CH-6), 4.11 (1H, ddd, *J* = 11.2, 7.7, 6.8 Hz, CH_2-C1), 3.96 (1H, app. dt, *J* = 8.2, 5.1 Hz, CH-C3), 3.57 (1H, dd, *J* = 5.5, 4.3 Hz, CH-C7), 2.37 (1H, d, *J* = 2.2 Hz, CH-C10), 2.30–2.21 (1H, m, CH-C4), 2.11 (1H, ddd, *J* = 12.4, 8.2, 7.0 Hz, CH_2-C5), 1.77–1.69 (2H, m, 2 × CH_2C2), 1.63 (1H, ddd, *J* = 12.4, 7.1, 2.6 Hz, CH_2-C5), 1.19 (9H, s, CH_3-*t*-Bu-Piv), 0.90 (3H, d, *J* = 7.8 Hz, CH_3-C11), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.13 (3H, s, CH_3-Me-TBS), 0.12 (3H, s, CH_3-Me-TBS), 0.12 (3H, s, CH_3-Me-TBS), 0.09 (3H, s, CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7 (C-Piv), 84.4 (C-C9), 79.0 (CH-C7), 78.0 (CH-C3), 77.3 (CH-C6), 74.0 (CH-C10), 65.7 (CH-C8), 62.7 (CH_2-C1), 38.9 (C-*t*-Bu-Piv), 36.4 (CH-C4), 36.0 (CH_2-C5), 30.3 (CH_2-C2), 27.4 (3 × C, CH_3-*t*-Bu-Piv), 26.3 (3 × C, CH_3-*t*-Bu-TBS), 26.0 (3 × C, CH_3-*t*-Bu-TBS), 18.6 (C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), 14.3 (CH_3-C11), −3.9 (CH_3-Me-TBS), −4.0 (CH_3-Me-TBS), −4.5 (CH_3-Me-TBS), −5.0 (CH_3-Me-TBS); ν_{max} 2957, 2928, 2857, 1730, 1472, 1252, 1155, 1084, 833, 777 cm^{-1}; HRMS calculated for $C_{28}H_{54}NaO_5Si$ $[M+Na]^+$ 549.3402, found 549.3405, Δ = 0.5 ppm.

2-[(2*S*,3*R*,5*R*)-5-{(1*S*,2*S*)-1,2-Bis[(*tert*-butyl)bis(methyl)siloxy]-3-(tributylstannanyl)-3-butenyl}-3-methyltetrahydro-2-furyl]ethyl pivalate 479



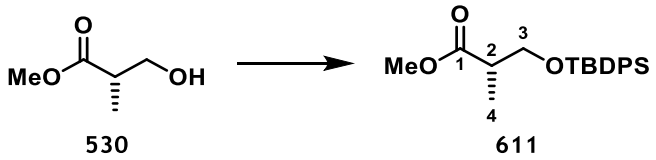
528 479

To a stirred solution of alkyne **528** (44 mg, 0.084 mmol), 2,6-*tert*-butyl-4-methylphenol (3.5 mg, 0.016 mmol), and $Mo(CO)_3(CN$*t*$-Bu)_3$ (7.0 mg, 0.032 mmol) in THF (2.0 mL) at rt was added *n*-Bu_3-SnH (0.2 mL). The reaction mixture was heated to 55 °C for 24 h, after which time a further portion of $Mo(CO)_3(CN$*t*$-Bu)_3$ (3.5 mg, 0.016 mmol) was added and stirred at 55 °C for a further 48 h. The reaction mixture was concentrated under reduced pressure and the crude material was purified by flash chromatography (pet. ether:EtOAc, 200:1) affording 1,1-di-substituted vinyl stannane **479** (21 mg, 31%) as a colourless oil.

R_f = 0.87 (pet. ether:EtOAc, 20:1); $[\alpha]_D^{15}$ −19 (c = 0.43, $CHCl_3$); ν_{max} 2956, 2928, 2856, 1733, 1463, 1251, 1155, 1089, 1071, 832 cm^{-1}; HRMS calculated for $C_{40}H_{82}NaO_5Si_2Sn$ $[M+Na]^+$ 841.4615, found 841.4618, Δ = 0.4 ppm.

^1H NMR and ^{13}C NMR matched that recorded by Dr. Filippo Romiti.[100]

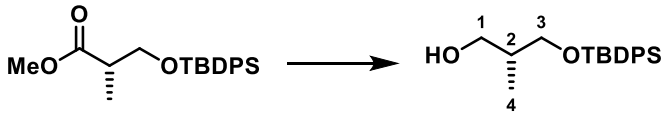
Methyl (*S*)-3-[(*tert*-butyl)bis(phenyl)siloxy]-2-methylpropionate 611



To a stirred solution of (*S*)-Roche ester **530** (1.00 mL, 9.06 mmol) in CH_2Cl_2 (11 mL) at 0 °C was added imidazole (802 mg, 11.8 mmol) and TBDPSCl (2.3 ml, 8.9 mmol). The reaction mixture was warmed to rt and stirred for 16 h. The reaction was quenched by the addition of H_2O (20 mL). The phases were separated and the aqueous phase was washed with EtOAc (3 × 20 mL). The combined organic fractions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure affording silyl ether **611** (3.23 g, quant.) as a colourless oil.

R_f = 0.23 (pet. ether:EtOAc,49:1); $[\alpha]_D^{31}$ +16.8 (c = 1.39, $CHCl_3$) [lit[120] $[\alpha]_D^{20}$ +17.1 (c = 1.05, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (4H, m, Ph-TBDPS), 7.46–7.35 (6H, m, Ph-TBDPS), 3.84 (1H, dd, *J* = 9.8, 6.9 Hz, CH_2-C3), 3.73 (1H, dd, *J* = 9.8, 5.7 Hz, CH_2-C3), 3.69 (3H, s, CH_3-OMe), 2.72 (1H, qdd, *J* = 7.0, 6.9, 5.7 Hz, CH-C2), 1.16 (3H, d, *J* = 7.0 Hz, CH_3-C4), 1.04 (9H, s, CH_3-*t*-Bu-TBDPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5 (C-C1), 135.7 (CH-Ph-TBDPS), 135.0 (CH-Ph-TBDPS), 133.7 (C-Ph-TBDPS), 133.6 (C-Ph-TBDPS), 129.8 (CH-Ph-TBDPS), 127.8 (CH-TBDPS), 66.1 (CH_2-C3), 51.7 (CH_3-OMe), 42.6 (CH-C2), 26.9 (3 × CH_3-*t*-Bu-TBDPS), 19.4 (C-*t*-Bu-TBDPS), 13.6 (CH_3-C4); HRMS calculated for $C_{21}H_{28}NaO_3Si$ $[M+Na]^+$ 379.1700, found 379.1689, Δ = 3.0 ppm.

(*R*)-3-[(*tert*-Butyl)bis(phenyl)siloxy]-2-methyl-1-propanol 531

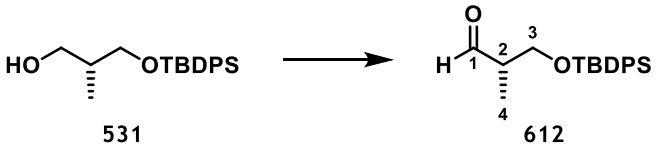


611 531

To a stirred solution of methyl ester **611** (3.09 g, 8.66 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added DiBAl-H (1 M in hexanes, 19.0 mL, 19.0 mmol) dropwise and stirred for 5 min. After which time the reaction mixture was warmed to rt and stirred for a further 6 h. The reaction mixture was cooled to 0 °C and the reaction quenched by the addition of MeOH (20 mL) then a sat. aq. solution of Rochelle salt (20 mL) was added and the mixture was stirred for a further 10 h. The phases were separated and the aqueous phase was washed with Et_2O (2 × 30 mL). The combined organic fractions were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure affording alcohol **531** (2.71 g, 95%) as a colourless oil.

R_f = 0.28 (pet. ether:EtOAc, 9:1); $[\alpha]_D^{28}$ +5.16 (c = 1.64, $CHCl_3$) [lit[121] $[\alpha]_D^{23}$ +6.0 (c = 1.15, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.65 (4H, m, Ph-TBDPS), 7.47–7.37 (6H, m, Ph-TBDPS), 3.73 (1H, dd, *J* = 10.0, 4.5 Hz, CH_2-C3), 3.68 (2H, dd, *J* = 5.5, 5.2 Hz, CH_2-C1), 3.60 (1H, dd, *J* = 10.0, 7.7 Hz, CH_2-C3) 2.53 (1H, d, *J* = 5.5 Hz, OH-C1), 2.00 (1H, dqtd, *J* = 7.7, 7.0, 5.2, 4.5 Hz, CH-C2), 1.07 (9H, s, CH_3-*t*-Bu-TBDPS), 0.84 (3H, d, *J* = 7.0 Hz, CH_3-C4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6 (CH-Ph-TBDPS), 134.8 (CH-Ph-TBDPS), 133.2 (C-Ph-TBDPS), 129.8 (CH-Ph-TBDPS), 127.8 (CH-TBDPS), 68.7 (CH_2-C1), 67.6 (CH_2-C3), 37.3 (CH-C2), 26.9 (3 × CH_3-*t*-Bu-TBDPS), 19.2 (C-*t*-Bu-TBDPS), 13.2 (CH_3-C4); HRMS calculated for $C_{20}H_{28}NaO_2Si$ $[M+Na]^+$ 351.1751, found 351.1753, Δ = 0.7 ppm.

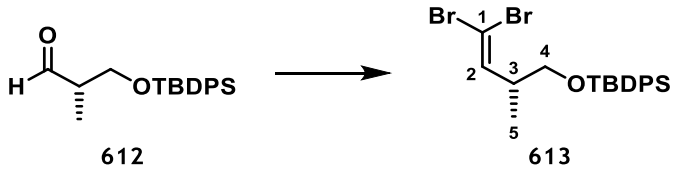
(*S*)-3-[(*tert*-Butyl)bis(phenyl)siloxy]-2-methylpropanal 612



To a stirred solution of alcohol **531** (2.60 g, 7.91 mmol) in CH_2Cl_2 (40 mL) at rt was added Dess-Martin periodinane (3.51 g, 8.28 mmol) in five portions. The reaction mixture was stirred for 1.5 h after which time the reaction was quenched by the addition of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ (1:1, 30 mL). The phases were separated and the aqueous phase was washed with Et_2O (3 × 50 mL). The combined organic fractions were washed with sat. aq. $NaHCO_3$ (50 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 19:1) affording aldehyde **612** (2.14 g, 83%) as a colourless oil.

R_f = 0.41 (pet. ether:EtOAc, 9:1); $[\alpha]_D^{28}$ +6.75 (c = 1.02, $CHCl_3$) [lit[120] $[\alpha]_D^{20}$ +8.5 (c = 0.65, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, d, *J* = 1.6 Hz, CH-C1), 7.67–7.63 (4H, m, Ph-TBDPS), 7.47–7.37 (6H, m, Ph-TBDPS), 3.91 (1H, dd, *J* = 10.3, 5.0 Hz, CH_2-C3), 3.85 (1H, dd, *J* = 10.3, 6.4 Hz, CH_2-C3), 2.57 (1H, qddd, *J* = 7.0, 6.4, 5.0, 1.6 Hz, CH-C2), 1.11 (3H, d, *J* = 7.0 Hz, CH_3-C4), 1.05 (9H, s, CH_3-*t*-Bu-TBDPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5 (CH-C1), 135.7 (CH-Ph-TBDPS), 133.4 (C-Ph-TBDPS), 130.0 (CH-Ph-TBDPS), 127.9 (CH-Ph-TBDPS), 64.3 (CH_2-C3), 49.0 (CH-C2), 26.9 (CH_3-*t*-Bu-TBDPS), 19.4 (C-*t*-Bu-TBDPS), 10.5 (CH_3-C4); HRMS calculated for $C_{20}H_{26}NaO_2Si$ $[M+Na]^+$ 349.1594, found 349.1590, Δ = 1.2 ppm.

(*R*)-4-[(*tert*-Butyl)bis(phenyl)siloxy]-1,1-dibromo-3-methyl-1-butene 613

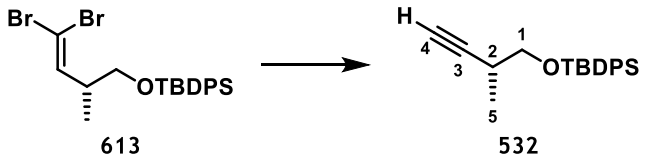


612 613

To a stirred solution of PPh_3 (6.90 g, 26.3 mmol) in CH_2Cl_2 (40 mL) at rt was added CBr_4 (4.35 g, 13.1 mmol) in four portions and stirred for 10 min. The reaction mixture was cooled to −78 °C and a solution of aldehyde **612** (2.13 g, 6.52 mmol) and Et_3N (0.90 mL, 6.5 mmol) in CH_2Cl_2 (15 mL) was added. The reaction mixture was stirred at this temperature for 30 min then warmed to rt and stirred for a further 1 h. After which time pet. ether (150 mL) was added and the reaction mixture stirred for a further 10 min. The resulting suspension was filtered through Celite® and the filtrate was concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 100:1) affording dibromo olefin **613** (2.01 g, 64%) as a colourless oil.

R_f = 0.20 (pet. ether:EtOAc, 19:1); $[\alpha]_D^{33}$ −15.3 (c = 1.47, $CHCl_3$) [lit[122] $[\alpha]_D^{25}$ −14.3 (c = 0.53, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.72 (4H, m, Ph-TBDPS), 7.52–7.41 (6H, m, Ph-TBDPS), 6.35 (1H, d, *J* = 9.3 Hz, CH-C2), 3.65 (1H, dd, *J* = 9.9, 5.9 Hz, CH_2-C4), 3.61 (1H, dd, *J* = 9.9, 6.1 Hz, CH_2-C4), 2.78 (1H, dqdd, *J* = 9.3, 6.8, 6.1, 5.9 Hz, CH-C3), 1.15 (9H, s, CH_3-*t*-Bu-TBDPS), 1.11 (1H, d, *J* = 6.8 Hz, CH_3-C5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5 (CH-C2), 135.7 (CH-Ph-TBDPS), 133.6 (C-Ph-TBDPS), 129.8 (CH-Ph-TBDPS), 127.8 (CH-Ph-TBDPS), 88.8 (C-C1), 62.0 (CH_2-C4), 41.1 (CH-C3), 26.9 (3 × C, CH_3-*t*-Bu-TBDPS), 19.4 (C-*t*-Bu-TBDPS), 15.6 (CH_3-C5); HRMS calculated for $Br_2C_{21}H_{26}NaOSi$ $[M+Na]^+$ 503.0012, found 502.9996, Δ = 3.2 ppm.

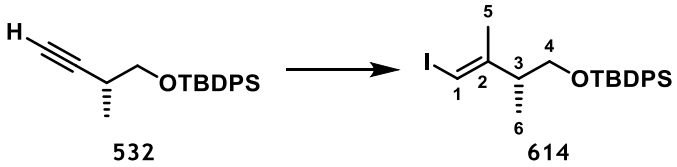
(*R*)-1-[(*tert*-Butyl)bis(phenyl)siloxy]-2-methyl-3-butyne 532



To a stirred solution of dibromo olefin **613** (2.01 g, 4.17 mmol) in THF (40 mL) at −78°C was added *n*-BuLi (2.3 M in hexane, 5.0 mL, 11 mmol) dropwise and stirred for 2 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (30 mL) and the resulting solution allowed to warm to rt. The phases were separated and the aqueous phase was washed with Et_2O (3 × 20 mL). The combined organic fractions were washed with brine (70 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure affording alkyne **532** (1.35 g, quant.) as a colourless oil.

R_f = 0.26 (pet. ether); $[\alpha]_D^{33}$ +4.61 (c = 1.02, $CHCl_3$) [lit[123] $[\alpha]_D^{25}$ +5.6 (c = 1.00, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.52 (4H, m, Ph-TBDPS), 7.33–7.22 (6H, m, Ph-TBDPS), 3.61 (1H, dd, *J* = 9.6, 5.7 Hz, CH_2-C1), 3.42 (1H, dd, *J* = 9.6, 7.6 Hz, CH_2-C1), 2.53 (1H, dqdd, *J* = 7.6, 6.9, 5.7, 2.4 Hz, CH-C2), 1.89 (1H, d, *J* = 2.4 Hz, CH-C4), 1.10 (3H, d, *J* = 6.9 Hz, CH_3-C5), 0.93 (9H, s, CH_3-*t*-Bu-TBDPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8 (CH-Ph-TBDPS), 133.8 (C-Ph-TBDPS), 129.8 (CH-Ph-TBDPS), 127.8 (CH-Ph-TBDPS), 86.7 (C-C3), 69.2 (CH-C4), 67.7 (CH_2-C1), 29.0 (CH-C2), 27.0 (CH_3-*t*-Bu-TBDPS), 19.5 (C-*t*-Bu-TBDPS), 17.5 (CH_3-C5).

(*R*,*E*)-4-[(*tert*-Butyl)bis(phenyl)siloxy]-1-iodo-2,3-dimethyl-1-butene 614

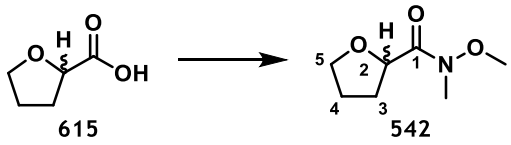


532 614

To a stirred solution of Cp_2ZrCl_2 (141 mg, 0.482 mmol) in 1,2-dichloroethane (2 mL) at rt was added $AlMe_3$ (2 M in hexane, 0.60 mL, 1.2 mmol) dropwise. The reaction mixture was stirred at rt for 30 min, before the dropwise addition of a solution of alkyne **532** (97 mg, 0.30 mmol) in 1,2-dichloroethane (1 mL). The reaction mixture was stirred at rt for 24 h, before being cooled to −30 °C. A solution of I_2 (155 mg, 0.611 mmol) in THF (1 mL) was added dropwise until the red-brown colour persisted. The reaction mixture was stirred for a further 30 min at −30 °C. The reaction mixture was quenched by the dropwise addition of a sat. aq. potassium sodium tartrate solution (5 mL). Et_2O (5 mL) was added, the phases were separated and the aqueous phase was washed with Et_2O (3 × 10 mL). The combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 19:1) affording vinylic iodide **614** (55 mg, 39%) as a colourless oil.

R_f = 0.32 (pet. ether); $[\alpha]_D^{27}$ +9.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.62 (4H, m, CH-Ph-TBDPS), 7.46–7.36 (6H, m, CH-Ph-TBDPS), 5.97 (1H, dq, *J* = 1.4, 1.0 Hz, CH-C1), 3.57 (1H, dd, *J* = 10.0, 6.9 Hz, CH_2-C4), 3.54 (1H, dd, *J* = 10.0, 6.2 Hz, CH_2-C4), 2.60 (1H, qddd, *J* = 7.0, 6.9, 6.2, 1.4 Hz, CH-C3), 1.71 (3H, d, *J* = 1.0 Hz, CH_3-C5), 1.05 (9H, s, CH_3-*t*-Bu-TBDPS), 1.02 (3H, d, *J* = 7.0 Hz, CH_3-C6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7 (C-C2), 135.8 (CH-Ph-TBDPS), 135.8 (CH-Ph-TBDPS), 133.9 (C-Ph-TBDPS), 133.7 (C-Ph-TBDPS), 129.8 (CH-Ph-TBDPS), 129.8 (CH-Ph-TBDPS), 127.8 (CH-Ph-TBDPS), 127.8 (CH-Ph-TBDPS), 76.6 (CH-C1), 66.8 (CH_2-C4), 45.7 (CH-C3), 27.0 (CH_3-*t*-Bu-TBDPS), 21.7 (CH_3-C5), 19.4 (C-*t*-Bu-TBDPS), 15.7 (CH_3-C6); ν_{max} 2953, 2930, 2859, 1471, 1427, 1112, 822, 739; HRMS calculated for $C_{22}H_{23}INaOSi$ $[M+Na]^+$ 487.0925, found 487.0926, Δ = 0.2 ppm.

***N*-Methoxy-*N*-methyl-tetrahydro-2-furamide 542**

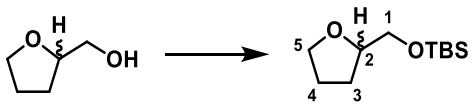


615 542

To a stirred solution of (±)-tetrahydrofuran-2-carboxylic acid (**615**) (4.0 mL, 40 mmol) in CH_2Cl_2 (50 mL) at rt was added $SOCl_2$ (3.6 mL, 50 mmol). The reaction mixture was stirred at rt for 2 h, then cooled to 0 °C, K_2CO_3 (2.68 g, 19.4 mmol) was added and stirred at 0 °C for a further 10 min. After which time Et_3N (13.4 mL, 100 mmol) was added dropwise to the reaction mixture followed by the addition of CH_2Cl_2 (20 mL) and *N*,*O*-dimethylhydroxylamine (4.56 g, 46.8 mmol). The resulting mixture was stirred at 0 °C for 1 h, then rt for 16 h. The reaction was quenched by the addition of HCl (1 M in H_2O, 20 mL), the phases were separated, and the aqueous phase was washed with CH_2Cl_2 (30 mL). The combined organic fractions were washed with NaOH (1 M in H_2O, 10 mL), H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) affording Weinreb amide **542** (4.04 g, 63%) as an amber oil.

R_f = 0.31 (pet. ether:EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (1H, dd, *J* = 6.8, 4.9 Hz, CH-C2), 4.02 (1H, ddd, *J* = 5.8, 5.8, 5.1 Hz, CH_2-C5), 3.91 (1H, ddd, *J* = 7.7, 7.7, 5.1 Hz, CH_2-5), 3.71 (3H, s, CH_3-OCH_3), 3.19 (3H, s, CH_3-NCH_3), 2.19 (1H, ddd, *J* = 8.4, 8.4, 6.8 Hz, CH_2-C3), 2.08–1.95 (2H, m, CH_2-C3, CH_2-C4), 1.94-1.83 (1H, m, CH_2-C4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9 (C-C1), 75.1 (CH-C2), 69.4 (CH_2-C5), 61.3 (CH_3-OCH_3), 32.3 (CH_3-NCH_3), 29.5 (CH_2-C3), 25.6 (CH_2-C4); ν_{max} 2970, 2941, 2876, 1669, 1179, 1071 cm^{-1}; HRMS calculated for $C_7H_{13}NNaO_3$ $[M+Na]^+$ 182.0788, found 182.0787, Δ = 0.2 ppm.

2-{[(*tert*-Butyl)bis(methyl)siloxy]methyl}tetrahydrofuran 547

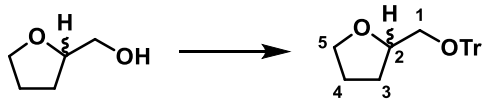


616 547

To a stirred solution of (±)-tetrahydrofurfuryl alcohol (**616**) (1.95 mL, 20.1 mmol) in CH_2Cl_2 (20 mL) at rt was added TBSCl (1.90 g, 12.6 mmol) and Et_3N (3.00 mL, 21.6 mmol). The reaction mixture was stirred at rt for 16 h and was then quenched by the addition of sat. aq. NH_4Cl (20 mL), the phases were separated and the aqueous phase was washed with CH_2Cl_2 (2 × 20 mL). The combined organic fractions were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) affording TBS ether **547** (1.61 g, 60%) as a colourless oil.

R_f = 0.83 (pet. ether:EtOAc, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (1H, app. dtd, *J* = 6.7, 5.1, 5.0 Hz, CH-C2), 3.84 (1H, ddd, *J* = 11.8, 7.3, 6.4 Hz, CH_2-C5), 3.76 (1H, ddd, *J* = 13.6, 7.3, 3.4 Hz, CH_2-C5), 3.62 (1H, dd, *J* = 10.5, 5.0 Hz, CH_2-C1), 3.56 (1H, dd, *J* = 10.5, 5.1 Hz, CH_2-C1), 1.96–1.78 (3H, m, CH_2-C3, 2 × CH_2-C4), 1.68 (1H, app. tdd, *J* = 9.2, 7.2, 6.7 Hz, CH_2-C3), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.06 (6H, s, CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) 79.6 (CH-C2), 68.6 (CH_2-C5), 66.0 (CH_2-C1), 28.0 (C-*t*-Bu-TBS), 26.1 (3 × CH_3-*t*-Bu-TBS), 25.9 (CH_2-C3), 18.5 (CH_2-C4), −5.2 (CH_3-Me-TBS); ν_{max} 2955, 2928, 2857, 1472, 1462, 1254, 1086, 835 cm^{-1}; HRMS calculated for $C_{11}H_{24}NaO_2Si$ $[M+Na]^+$ 239.1438, found 239.1432, Δ = 2.2 ppm.

2-[(Trityloxy)methyl]tetrahydrofuran 548

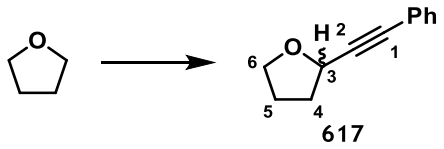


616 548

To a stirred solution of tetrahydrofurfuryl alcohol (**616**) (0.20 mL, 2.1 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (0.42 mL, 3.0 mmol), TrCl (632 mg, 2.27 mmol) and DMAP (55 mg, 0.45 mmol). The reaction mixture was stirred at rt for 16 h after which time the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (10 mL), the phases were separated and the aqueous phase was washed with EtOAc (3 × 10 mL). The combined organic fractions were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) affording trityl ether **548** (313 mg, 45%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.20 (5H, m, Ch-Ph Tr), 7.29–7.16 (10H, m, CH-Ph-Tr), 4.09 (1H, dddd, *J* = 6.5, 6.0 5.5, 4.5 Hz, CH-C2), 3.87–3.74 (2H, m, 2 × CH_2-C5), 3.11 (1H, dd *J* = 9.5, 5.5 Hz, CH_2-C1), 3.01 (1H, dd, *J* = 9.5, 4.5 Hz, CH_2-C1) 1.91-1.69 (3H, m, CH_2-C4, 2 × CH_2-C3), 1.61 (1H, dddd, *J* = 11.6, 8.0, 7.0, 6.5 Hz, CH_2-C4).

2-(2-Phenylethynyl)tetrahydrofuran 617

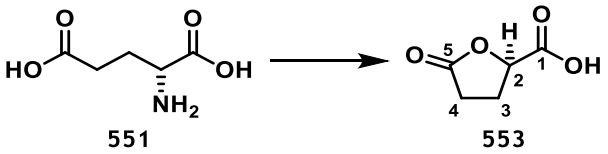


617

To a stirred solution of THF (0.33 mL, 4.1 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added K[F_3BCCPh] (460 mg, 2.2 mmol) and the resulting solution was stirred at 0 °C for 20 min. TrCl (454 mg, 2.18 mmol) and $FeCl_3$ (337 mg, 2.05 mmol) were added and the reaction mixture was stirred at 0 °C for a further 2 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (10 mL), the phases were separated and the aqueous phase was washed with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 49:1) affording phenyl alkyne **617** (76 mg, 20%) as a colourless oil.

R_f = 0.52 (pet. ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.37 (2H, m, CH-Ph), 7.28–7.21 (3H, m, CH-Ph), 4.77 (1H, dd, *J* = 7.1, 5.1 Hz, CH-C3), 3.97 (1H, ddd, *J* = 8.4, 7.7, 7.7 Hz, CH_2-C6), 3.82 (1H, ddd, *J* = 7.7 , 7.7, 5.6 Hz, CH_2-C6), 2.23 (1H, m, CH_2-C5), 2.11–1.98 (2H, m, CH_2-C5, CH_2-C4), 1.95–1.85 (1H, m, CH_2-C4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.7 (C-Ph), 128.2 (CH-Ph), 127.9 (CH-Ph), 89.1 (C-C1), 84.5 (C-C2), 68.6 (CH_2-C6), 68.0 (CH-C3), 33.4 (CH_2-C4), 25.5 (CH_2-C5); ν_{max} 3057, 2951, 2872, 1489, 1445, 1335, 1051, 916, 756, 692 cm^{-1}; HRMS calculated for $C_{12}H_{12}NaO$ $[M+Na]^+$ 195.0780, found 195.0777, Δ = 1.5 ppm.

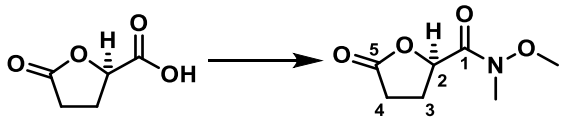
(*R*)-5-Oxo-3,4-dihydro-2*H*-furan-2-carboxylic acid 553



To a stirred solution of D-glutamic acid (**551**) (10.1 g, 68.8 mmol) in H_2O (50 mL) at 0 °C was added a solution of $NaNO_2$ (7.04 g, 102 mmol) in H_2O (20 mL), followed by the dropwise addition of HCl (2 M in H_2O, 48 mL, 96 mmol). The resulting solution was stirred at 0 °C for 2 h, then warmed to rt and stirred for a further 3 h. The solvent was removed under reduced pressure and the crude material was dried azeotropically with toluene (2 × 25 mL). Na_2SO_4 was then added, and the product was extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure affording lactone **553** (7.00 g, 79%) as a colourless solid which was used without further purification.

R_f = 0.26 (CH_2Cl_2:MeOH, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (1H, br s, COOH), 5.03–4.97 (1H, m, CH-C2), 2.73–2.51 (3H, m, 2 × CH_2-C3, CH_2-C4), 2.46−2.36 (1H, m, CH_2-C4); ν_{max} 2949, 2361, 2342, 1751, 1420, 1179, 1150, 1067, 893 cm^{-1}; HRMS calculated for $C_5H_6NaO_4$ $[M+Na]^+$ 153.0158, found 153.0160, Δ = 0.9 ppm; M. P. = 67–69 °C [lit[124] M. P. = 67−70 °C].

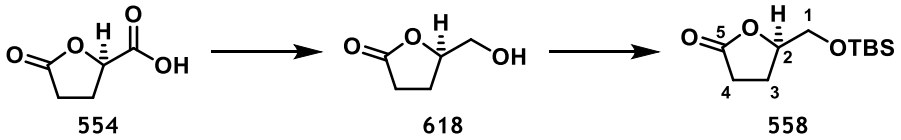
***N*-Methoxy-*N*-methyl-(*R*)-5-oxo-3,4-dihydro-2*H*-furan-2-carboxamide 555**



To a stirred solution of carboxylic acid **554** (3.08 g, 23.7 mmol) in CH_2Cl_2 (200 mL) at 0 °C Et_3N (4.0 mL, 29 mmol) followed by the slow addition of *N,O*-dimethoxyhydroxylamine hydrochloride (2.90 g, 29.8 mmol). DCC (6.05 g, 29.3 mmol) was added at 0 °C over the course of 45 min and the reaction mixture was stirred for a further 10 min before warming to rt and stirred for 3 h. The reaction mixture was cooled to 0 °C and HCl (1 M in H_2O, 50 mL) was added and the phases were separated, the aqueous phase was washed with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), the solids were removed by filtration and the filtrate was concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) affording Weinreb amide **555** (2.41 g, 59%) as a colourless solid.

R_f = 0.38 (pet. ether:EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (1H, dd, *J* = 7.7, 4.1 Hz, CH-C2), 3.75 (3H, s, CH_3-OCH_3), 3.21 (3H, s, CH_3-NCH_3), 2.70–2.27 (4H, m, 2 × CH_2-C3, 2 × CH_2-C4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8 (C-C5), 169.8 (C-C1), 74.5 (CH-C2), 61.9 (CH_3-OCH_3), 31.0 (CH_3-NCH_3), 27.0 (CH_2-C3), 25.2 (CH_2-C4); ν_{max} 2972, 2943, 1775, 1670, 1460, 1420, 1393, 1148, 1055, 986 cm^{-1}; HRMS calculated for $C_7H_{11}NNaO_4$ $[M+Na]^+$ 196.0580, found 196.0582, Δ = 0.2 ppm; M. P. = 49–51 °C.

(*R*)-5-{[(*tert*-Butyl)bis(methyl)siloxy]methyl}-4,5-dihydro-3*H*-furan-2-one 558

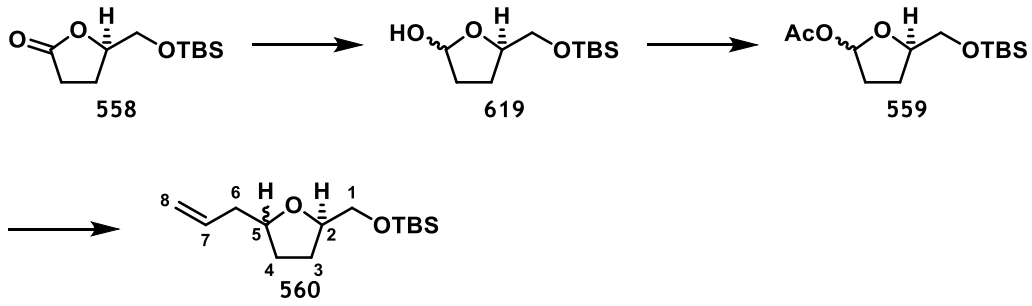


To a stirred solution of carboxylic acid **554** (6.50 g, 49.9 mmol) in THF (100 mL) at 0 °C was added BH_3·DMS (2 M, 28.0 mL, 56.0 mmol) dropwise. The reaction mixture was stirred at 0 °C for 2 h and then the reaction quenched by the addition of MeOH (50 mL). The solvent was removed under reduced pressure, the crude material was dissolved and concentrated from MeOH (2 × 75 mL) and PhMe (2 × 50 mL) affording alcohol **618** as a yellow oil which was used in the next step without further purification.

To a stirred solution of alcohol **618** in CH_2Cl_2 (100 mL) at 0 °C was added TBSCl (10.25 g, 68.01 mmol), followed by imidazole (4.25 g, 62.4 mmol). The reaction mixture was stirred at 0 °C for 3 h before the reaction was quenched by the addition of HCl (1 M in H_2O, 30 mL). The phases were separated and the aqueous phase was washed with EtOAc (2 × 50 mL). The combined organic fractions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. Ether:EtOAc, 4:1) affording TBS ether **558** (8.84 g, 77%) as a yellow oil.

R_f = 0.83 (pet. ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (1H, dddd, *J* = 8.1, 5.0, 3.1, 3.1 Hz, CH-C2), 3.79 (1H, dd, *J* = 11.3, 3.1 Hz, CH_2-C1), 3.61 (1H, dd, *J* = 11.3, 3.1 Hz, CH_2-C1), 2.54 (1H, ddd, *J* = 17.6, 10.2, 7.3 Hz, CH_2-C4), 2.39 (1H, ddd, *J* = 17.6, 10.1, 6.2 Hz CH_2-C4), 2.20 (1H, dddd, *J* = 12.8, 10.1, 8.1, 7.3 Hz, CH_2-C3), 2.10 (1H, dddd, *J* = 12.8, 10.2, 6.2, 5.0 Hz, CH_2-C3), 0.81 (9H, s, CH_3-*t*-Bu-TBS), 0.00 (3H, s, CH_3-Me-TBS), −0.01 (3H, s, CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6 (C-C5), 80.1 (CH-C2), 64.9 (CH_2-C1), 28.6 (CH_2-C4), 25.8 (CH_3-*t*-Bu-TBS), 23.6 (CH_2-C3), 18.2 (C-*t*-Bu-TBS), −5.5 (CH_3-Me-TBS), −5.6 (CH_3-Me-TBS); ν_{max} 2955, 2930, 2857, 1777, 1254, 1173, 1121, 835 cm^{-1}; HRMS calculated for $C_{11}H_{22}NaO_3Si$ $[M+Na]^+$ 253.120, found 253.1224, Δ = 2.7 ppm.

{[(2*R*)-5-Allyltetrahydro-2-furyl]methoxy}(*tert*-butyl)bis(methyl)silane 560



To a stirred solution of lactone **558** (337 mg, 1.46 mmol) in PhMe (5 mL) at −78 °C was added DiBAl-H (1 M in hexane, 1.60 mL, 1.60 mmol). The reaction mixture was stirred at −78 °C for 1.5 h before the reaction was quenched by the addition of MeOH (5 mL). To the mixture a solution of sat. aq. potassium sodium tartarate (10 mL) was added and stirred until two clear phases formed. The phases were separated and the aqueous phase was washed with EtOAc (3 × 10 mL). The combined organic fractions were washed with H_2O (20 mL), brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure affording crude lactol **619** which was used in the next step without further purification.

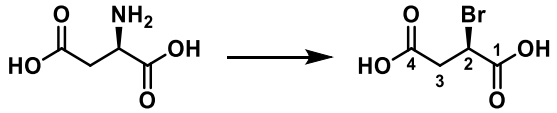
To a stirred solution of lactol **619** in CH_2Cl_2 (30 mL) at 0 °C was sequentially added Ac_2O (2.30 mL, 24.3 mmol), Et_3N (3.35 mL, 24.2 mmol), and DMAP (218 mg, 1.78 mmol). The reaction mixture was stirred at 0 °C for 3 h before the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (20 mL). The phases were separated and the aqueous phase was washed with CH_2Cl_2 (2 × 30 mL). The combined organic fractions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure affording acetate **559** as a yellow oil which was used in the next step without further purification.

To a stirred solution of acetate **559** in CH_2Cl_2 (200 mL) at −78 °C was added $BF_3{\cdot}OEt_2$ (2.50 mL, 20.3 mmol) followed by allyl TMS (11.6 mL, 73.1 mmol). The reaction mixture was stirred at −78 °C for 1 h, then slowly warmed to rt before the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (100 mL). The phases were separated and the aqueous phase was washed with CH_2Cl_2 (2 × 100 mL). The combined organic fractions were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude

material was purified by flash chromatography (pet. ether:EtOAc, 99:1) affording allyl THF **560** (2.66 g, 51%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (1H, ddtd, *J* = 17.3, 10.5, 7.0, 3.4 Hz, CH-C7), 5.02 (1H, ddt, *J* = 17.3, 3.1, 1.8 Hz, CH_2-C8), 4.98 (1H, ddt, *J* = 10.5, 3.1, 1.1 Hz, CH_2-C8), 3.99 (1H, dtt, *J* = 21.4, 6.9, 5.0 Hz, CH_2-C1), 3.92–3.83 (1H, m, CH_2-C1) 3.58 (1H, ddd, *J* = 10.5, 4.6, 2.6 Hz, CH-C2), 3.49 (1H, dt, *J* = 10.5, 5.6 Hz, CH-C5), 2.34–2.25 (1H, m, CH-C3), 2.21–2.12 (1H, m, CH-C3), 1.99–1.80 (2H, m, CH-C4), 1.75–1.62 (1H, m, CH_2-C6), 1.48 (1H, tddd, *J* = 11.1, 7.2, 5.4, 3.6 Hz CH_2-C6), 0.84 (9H, s, *t*-Bu-TBS), 0.01 (3H, s, CH_3-Me-TBS), 0.00 (3H, s, CH_3-Me-TBS)

(*R*)-2-Bromosuccinic acid 620

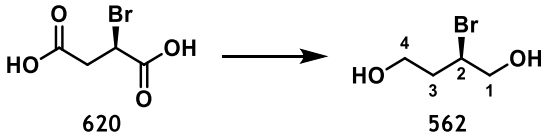


561 620

To a stirred solution of D-aspartic acid (**561**) (5.03 g, 37.8 mmol), KBr (19.9 g, 167 mmol), and H_2SO_4 (24.0 mL, 263 mmol) in H_2O (100 mL) at 0 °C was added a solution of $NaNO_2$ (4.73 g, 68.6 mmol) in H_2O (14 mL) over the course of 3 h then stirred at rt for 16 h. EtOAc (100 mL) was added and the phases were separated, the aqueous phase was washed with EtOAc (2 × 100 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was dissolved in EtOAc (100 mL) and concentrated under reduced pressure, this process was repeated three times affording bromo diacid **620** (6.39 g, 86%) as a colourless solid.

$[\alpha]_D^{27}$ +51.1 (c = 0.98, MeOH) [lit[125] $[\alpha]_D^{24}$ +60.8 (c = 0.9, MeOH)]; ^{1}H NMR (400 MHz, D_3-MeOD) δ 4.56 (1H, dd, *J* = 8.7, 6.2 Hz, CH-C2), 3.19 (1H, dd, *J* = 17.2, 8.7 Hz, CH_2-C3), 2.95 (1H, dd, *J* = 17.2, 6.2 Hz, CH_2-C3); ^{13}C NMR (101 MHz, D_3-MeOD) δ 173.2 (C-C1), 172.3 (C-C4), 40.8 (CH_2-C3), 40.1 (CH-C2); ν_{max} 3152, 1717, 1288, 1227, 1173, 1084 cm^{-1}; HRMS calculated for $BrC_4H_5NaO_4$ $[M+Na]^+$ 220.9248, found 220.9176, Δ = 33; M. P. = 165–166 °C [lit[125] = 166–167 °C].

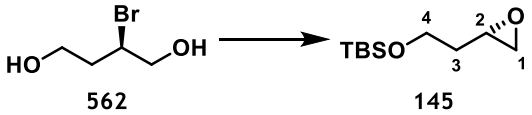
(*R*)-2-Bromo-1,4-butanediol 562



To a stirred solution of bromo diacid **620** (10.8 g, 54.8 mmol) in THF (200 mL) at 0 °C was added BH_3·DMS (13.7 mL, 153 mmol) dropwise. The reaction mixture was warmed to rt and stirred for 16 h. The reaction mixture was then cooled to 0 °C and the reaction quenched cautiously by the addition of MeOH (200 mL). This crude mixture was concentrated under reduced pressure, and the crude material was diluted with MeOH (150 mL) then concentrated under reduced pressure. This process was repeated four times affording bromo diol **562** (9.39 g, Quant.) as a colourless oil.

$[\alpha]_D^{18}$ +23.3 (c = 1.49, $CHCl_3$) [lit[125] $[\alpha]_D^{24}$ +33.3 (c = 15.2, MeOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (1H, dddd, *J* = 8.0, 5.4, 5.3, 5.2 Hz, CH-C2), 3.89 (1H, dd, *J* = 11.0, 5.4, 5.0 Hz, CH_2-C4), 3.87 (1H, dd, *J* = 12.2, 5.3 Hz, CH_2-C1), 3.83 (1H, dd, *J* = 12.2, 5.4 Hz, CH_2-C1) 3.80 (1H, ddd, *J* = 11.0, 7.6, 4.6 Hz, CH_2-C4), 2.15 (1H, dddd, *J* = 15.1, 7.6, 5.2, 5.0 Hz, CH_2-C3), 2.09 (1H, dddd, *J* = 15.1, 8.0, 5.4, 4.6 Hz, CH_2-C3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.3 (CH_2-C1), 60.2 (CH_2-C4), 55.2 (CH-C2), 37.9 (CH_2-C3); ν_{max} 3312, 2930, 2882, 1420, 1375, 1051, 1022, 638 cm^{-1}; HRMS calculated for $BrC_4H_9NaO_2$ $[M+Na]^+$ 190.9678, found 190.9686, Δ = 3.9 ppm.

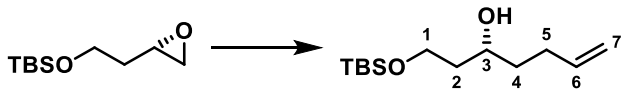
{2-[(*S*)-2-Oxiranyl]ethoxy}(*tert*-butyl)bis(methyl)silane 145



To a suspension of NaH (60% dispersion in mineral oil, 9.14 g, 229 mmol) in THF (250 mL) at 0 °C was slowly added a solution of bromo diol **562** (10.7 g, 63.3 mmol) in THF (100 mL). The reaction mixture was stirred at 0 °C for 30 min after the cessation of gas evolution, after which time TBSCl (12.8 g, 84.9 mmol) was added in three portions. The reaction mixture was warmed to rt and stirred for a further 9 h, after which time the reaction was quenched by the addition of H_2O (150 mL). The phases were separated, and the aqueous phase acidified to pH ~ 2 with HCl (1 M in H_2O) and washed with EtOAc (4 × 50 mL). The combined organic fractions were washed with brine (2 × 75 mL), dried over $MgSO_4$, filtered, and then concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) affording epoxide **145** (9.32 g, 73%) as a colourless oil.

$[\alpha]_D^{18}$ −12.2 (c = 1.19, $CHCl_3$) [lit[126] $[\alpha]_D^{27}$ −13.7 (c = 2.31, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (1H, dd, *J* = 5.7, 2.2 Hz, CH_2-C1), 3.77 (1H, d, *J* = 5.7 Hz, CH_2-C1), 3.04 (1H, dddd, *J* = 6.6, 4.9, 4.1, 2.2 Hz, CH-C2), 2.78 (1H, dd, *J* = 4.8, 4.2 Hz, CH_2-C4), 2.51 (1H, dd, *J* = 5.1, 2.7 Hz, CH_2-C4), 1.78 (1H, dddd, *J* = 13.9, 7.2, 6.5, 5.0 Hz, CH_2-C3), 1.69 (1H, ddd, *J* = 13.9, 11.7, 5.6 Hz, CH_2-C3), 0.90 (9H, s, *t*-Bu-TBS), 0.06 (3H, Me, TBS), 0.06 (3H, Me, TBS);^{13}C NMR (101 MHz, $CDCl_3$) δ 60.16 (CH_2-C1), 50.17 (CH-C2), 47.32 (CH_2-C4), 36.05 (CH_2-C3), 26.03 (CH_3-*t*-Bu-TBS), 18.42 (C-*t*-Bu-TBS), −5.25 (CH_3-Me-TBS), −5.26 (CH_3-Me-TBS); ν_{max}, 2955, 2928, 2859, 1254, 1099 cm^{-1}; HRMS calculated for $C_{10}H_{22}NaO_2Si$ $[M+Na]^+$ 225.1287, found 225.1318, Δ = 13.8 ppm.

(*R*)-1-[(*tert*-Butyl)bis(methyl)siloxy]-6-hepten-3-ol 143

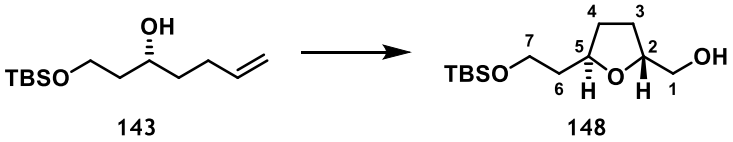


145 143

To a stirred solution of epoxide **145** (5.39 g, 26.6 mmol) in THF (200 mL) at 0 °C was added allyl magnesium chloride (1.7 M in THF, 19.5 mL, 33.2. mmol) dropwise and stirred for 4.5 h. The reaction was quenched by the addition of saturated NH_4Cl (100 mL), the phases were separated, and the aqueous phase washed with EtOAc (3 × 50 mL). The combined organic fractions were washed with brine (50 mL) and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 100:1 to 1:1) affording alcohol **143** (5.21 g, 80%) as a colourless oil.

R_f = 0.43 (pet. ether:EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (1H, dddd, *J* = 17.0, 10.2, 6.6, 6.6 Hz, CH-C6), 5.04 (1H, dddd, *J* = 17.0, 3.6, 1.6, 1.4 Hz, CH_2-C7), 4.96 (1H, dddd, *J* = 10.2, 2.1, 1.4, 1.2 Hz, CH_2-C7), 3.91 (1H, ddd, *J* = 9.5, 4.7, 4.7 Hz, CH_2-C1),3.88–3.80 (1H, m, CH-C3), 3.83 (1H, ddd, *J* = 12.7, 9.5, 9.5 Hz, CH_2-C1), 3.40 (1H, d, *J* = 2.5 Hz, OH-C3), 2.27–2.07 (2H, m, CH_2-C2), 1.69–1.46 (4H, m, 2×CH_2-C4, 2×CH_2-C5), 0.90 (9H, s, *t*-Bu-TBS), 0.08 (6H, s, Me, CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8 (CH-C6), 114.7 (CH_2-C7), 71.8 (CH-C3), 63.0 (CH_2-C1), 38.4 (CH_2-C4), 36.8 (CH_2-C2), 30.0 (CH_2-C5), 26.0 (CH_3-*t*-Bu-TBS), 18.3 (C-*t*-Bu-TBS), −5.4 (CH_3-Me-TBS), −5.4 (CH_3-Me-TBS); ν_{max} 3450, 2953, 2930, 2859, 2361, 1256, 1089 cm^{-1}; HRMS calculated for $C_{13}H_{28}NaO_2Si$ $[M+Na]^+$ 267.1751, found 267.1743, Δ = 3.1 ppm; elemental analysis calculated for $C_{13}H_{28}O_2Si$: C 63.88%, H 11.55%, found C 63.76%, H 11.49%.

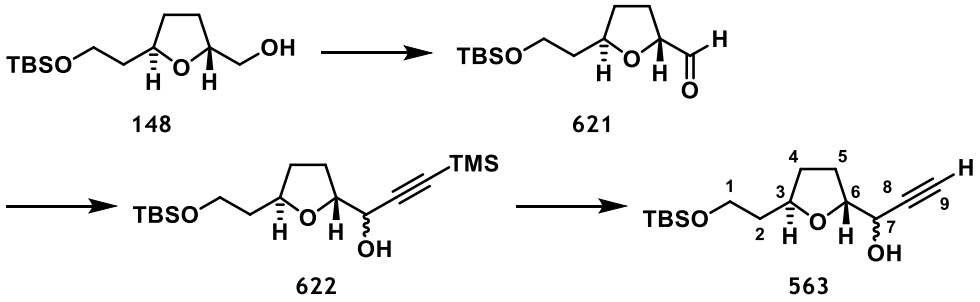
[(2*R*,5*R*)-5-{2-[(*tert*-Butyl)bis(methyl)siloxy]ethyl}tetrahydro-2-furyl]methanol 148



A stirred solution of alcohol **143** (511 mg, 2.09 mmol) in *i*-PrOH (15 mL) and $Co^{II}(NMP)_2$ (**147**) (122 mg, 0.211 mmol) was purged with O_2 for 30 min. To this solution was added *t*-BuOOH (5 M in decane, 0.05 mL, 0.3 mmol) and stirred at 55 °C for 16 h under an atmosphere of O_2. The reaction mixture was cooled to rt, purged with Ar, and concentrated to half volume under reduced pressure. The resulting crude material was diluted with EtOAc (25 mL) and washed with HCl (1 M in H_2O, 25 mL), the aqueous phase was washed with EtOAc (2 × 20 mL). The combined organic fractions were washed with H_2O (20 mL) and brine (25 mL). Then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 8:2) affording *trans*-THF **148** (298 mg, 55%) as a colourless oil.

R_f = 0.38 (pet. ether:EtOAc, 7:3); $[\alpha]_D^{23}$ −23 (c = 0.85, $CHCl_3$) [lit[126] $[\alpha]_D^{20}$ −14.4 (c = 1.00, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (1H, tdd, *J* = 6.5, 5.6, 4.8 Hz, CH-C5), 4.07 (1H, tt, *J* = 7.5, 4.0 Hz, CH-C2), 3.72 (1H, d, *J* = 7.0 Hz, CH_2-C1), 3.70 (1H, d, *J* = 7.0 Hz, CH_2-C1), 3.62 (1H, dd, *J* = 11.5, 3.2 Hz, CH_2-C7), 3.48 (1H, dd, *J* = 11.5, 6.4 Hz, CH_2-C7), 2.08-1.61 (7H, m, CH_2-C6, CH_2-C4, CH_2-C3, OH-C1), 0.89 (9H, s, *t*-Bu-TBS), 0.05 (3H, s, Me, TBS), 0.05 (3H, s, Me, TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 79.0 (CH-C5), 76.6 (CH-C2), 65.2 (CH_2-C1), 60.6 (CH_2-C7), 38.9 (CH_2-C6), 32.4 (CH_2-C4), 27.6 (CH_2-C3), 26.1 (CH_3-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), −5.2 (CH_3-Me-TBS), −5.2 (CH_3-Me-TBS); ν_{max} 3437, 2955, 2930, 2859, 1471, 1389, 1096 cm^{-1}; HRMS calculated for $C_{13}H_{28}NaO_3Si$ $[M+Na]^+$ 283.1700, found 283.1694, Δ = 1.9 ppm; elemental analysis calculated for $C_{13}H_{28}O_3Si$: C 59.95%, H 10.84%, found C 59.95%, H 10.93%.

1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyl)bis(methyl)siloxy]ethyl}tetrahydro-2-furyl]-2-propyn-1-ol 563



To a stirred solution of *trans*-THF **148** (1.89 g, 7.22 mmol) in CH_2Cl_2 (100 mL) at rt was added pyridine (2.50 mL,31.0 mmol), and Dess-Martin periodinane (5.16 g, 12.2 mmol) in two portions and stirred at rt for 2 h. After which time the reaction was quenched by the addition of a 1:1 mixture of sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ (110 mL) and stirred vigorously for a further 10 min. The phases were separated, and the aqueous phase was washed with EtOAc (3 × 100 mL), the combined organic fractions were washed with brine (250 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude aldehyde **621** was used without further purification in the next step.

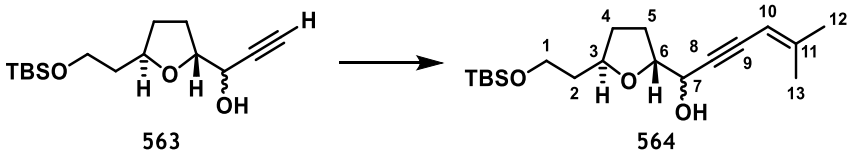
To a stirred solution of trimethylsilylacetylene (5.30 mL, 38.3 mmol) in Et_2O (40 mL) was added *i*-PrMgCl (1.6 M in THF, 20.0 mL, 32.0 mmol) and stirred at 0 °C for 1 h. After which time the brown suspension was transferred dropwise to a stirred solution of crude aldehyde **621** in Et_2O (150 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for a further 2.5 h, after which time the reaction was cooled to 0 °C and quenched by the addition of a mixture of 3:1 mix of sat. aq. NH_4Cl and H_2O (250 mL). The phases were separated, and the aqueous phase was washed with EtOAc (2 × 75 mL). The combined organic fractions were washed with brine (200 mL) and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude TMS-alkyne **622** was used without further purification in the next step.

To a stirred solution of the TMS-alkyne **622** in MeOH (55 mL) at rt was added K_2CO_3 (2.11 g, 15.3 mmol) and stirred at rt for 2 h. After which time the solution was concentrated under reduced pressure and the crude material was purified by flash

chromatography (pet. ether:EtOAc, 9:1) affording propargyl alcohol **563** (1.05 g, 51%, 3:1 mixture of diastereoisomers) as a yellow oil.

R_f = 0.23 (pet. ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (1H, ddd, *J* = 5.8, 3.3, 2.3 Hz, CH-C7, minor diastereoisomer), 4.19 (1H, ddd, *J* = 6.5, 4.0, 2.2 Hz CH-C7, major diastereoisomer), 4.16–4.04 (4H, m, CH-C3, CH-C6, both diastereoisomer), 3.71 (4H, dd, *J* = 7.0, 5.6, CH_2-C1, both diastereoisomers), 2.51 (1H, d, *J* = 4.7 Hz, OH-C7, major diastereoisomer), 2.43 (1H, d, *J* = 2.2 Hz, CH-C9, major diastereoisomer), 2.42 (1H, d, *J* = 2.3 Hz, CH-C9, minor diastereoisomer), 2.39 (1H, d, *J* = 6.2 Hz, OH-C7, minor diastereoisomer), 2.16-2.00 (4H, m, CH_2-C5, CH_2-C4, both diastereoisomers), 1.87–1.75 (4H, m, 2 × CH_2-C2, both diastereoisomers), 1.73–1.64 (2H, m, CH_2-C4, both diastereoisomers), 1.62–1.54 (2H, m, CH_2-C5, both diastereoisomers), 0.89 (18H, s, CH_3-*t*-Bu-TBS, both diastereoisomers), 0.05 (6H, s, CH_3-Me-TBS), 0.05 (3H, s, CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 82.2 (C-C8, major diastereoisomer), 82.2 (C-C8, minor diastereoisomer), 81.5 (CH-C6, major diastereoisomer), 80.7 (CH-C6, minor diastereoisomer), 78.2 (CH_2-C9, minor diastereoisomer), 77.3 (CH_2-C9, major diastereoisomer), 74.1 (CH-C3, minor diastereoisomer), 73.8 (CH-C3, major diastereoisomer), 65.4 (CH-C7, major diastereoisomer), 64.7 (CH-C7, minor diastereoisomer), 60.5 (CH_2-C1, minor diastereoisomer), 60.4 (CH_2-C1, major diastereoisomer), 38.9 (CH_2-C2, minor diastereoisomer), 38.7 (CH_2-C2, major diastereoisomer), 32.4 (CH_2-C5, minor diastereoisomer), 32.2 (CH_2-C5, major diastereoisomer), 28.2 (CH_2-C4, major diastereoisomer), 26.8 (CH_2-C4, minor diastereoisomer), 26.1 (CH_3-*t*–Bu–TBS, both diastereoisomers), 18.5 (C-*t*–Bu–TBS, both diastereoisomers), −5.2 (CH_3-Me-TBS, minor diastereoisomer), −5.2 (CH_3-Me-TBS, major diastereoisomer); ν_{max} 3408, 3312, 2955, 2930, 2886, 2859, 1472 cm^{-1}; HRMS calculated for $C_{15}H_{28}NaO_3Si$ $[M+Na]^+$ 307.1700, found 307.1701, Δ = 0.4 ppm; elemental analysis calculated for $C_{15}H_{28}O_3Si$: C 63.33%, H 9.92%, found C 63.07%, H 10.01%.

1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyl)bis(methyl)siloxy]ethyl}tetrahydro-2-furyl]-5-methyl-4-hexen-2-yn-1-ol 564

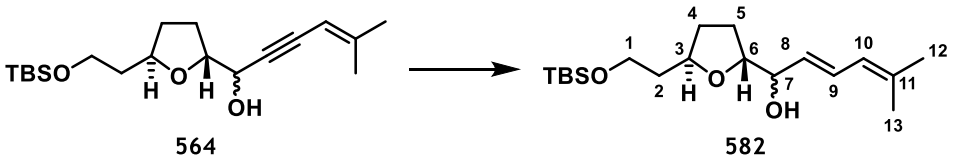


To a stirred solution of $Pd(PPh_3)_4$ (113 mg, 0.0978 mmol) in pyrrolidine (2.0 mL) at rt was added isocrotyl bromide (0.55 mL, 5.4 mmol) and stirred for 5 min. After which time a solution of alkyne **563** (506 mg, 1.78 mmol) in pyrrolidine (2.0 mL) was added. The reaction mixture was heated to 50 °C and stirred at this temperature for 18 h. The reaction mixture was cooled to rt diluted with Et_2O (20 mL) and sat. aq. NH_4Cl (25 mL). The phases were separated and the aqueous phase was washed with Et_2O (2 × 25 mL). The combined organic fractions were washed with brine (60 mL) dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) to afford en-yne **564** (433 mg, 72%, 2:1 mixture of diastereoisomers) as a yellow oil.

R_f = (pet. ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28–5.25 (2H, m, CH-C10, both diastereoisomers), 4.58 (1H, ddd, *J* = 5.6, 3.1, 1.9 Hz, CH-C7, minor diastereoisomer), 4.33 (1H, ddd, *J* = 7.0, 3.8, 1.6 Hz, CH-C7, major diastereoisomer), 4.21 (1H, ddd, *J* = 15.5, 7.4, 5.5 Hz, CH_2-C1, minor diastereoisomer), 4.15 (1H, ddd, *J* = 7.4, 7.3, 3.4 Hz, CH_2-C1, minor diastereoisomer), 4.12–4.03 (2H, m, CH-C3, CH-C6, major diastereoisomer), 3.71 (4H, m, 2 × CH_2-C1, major diastereoisomers, CH-C3, CH-C6, minor diastereoisomer), 2.49 (1H, d, *J* = 3.8 Hz, OH-C7, major diastereoisomer), 2.33 (1H, d, *J* = 5.6 Hz, OH-C7, minor diastereoisomer), 2.16–1.99 (3H, m, CH_2-C4, both diastereoisomers), 1.88 (6H, s, CH_3-C13, both diastereoisomers), 1.86–1.75 (2H, m), 1.80 (6H, s, CH_3-C12, both diastereoisomers), 1.73–1.65 (2H, m, CH_2-C4, both diastereoisomers), 1.65–1.51 (3H, m, CH_2-C5, both diastereoisomers), 0.89 (18H, s, CH_3-*t*-Bu-TBS), 0.50 (12H, s, CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6 (C-C11, major diastereoisomer), 149.8 (C-C11, minor diastereoisomer), 104.8 (CH-C10, minor diastereoisomer), 104.7 (CH-C10, major diastereoisomer), 89.1 (C-C8, major diastereoisomer), 89.1 (C-C8, minor diastereoisomer), 83.8 (C-C9,

both diastereoisomer), 82.0 (CH-C6, major diastereoisomer), 81.0 (CH-C6, minor diastereoisomer), 78.2 (CH-C3, minor diastereoisomer), 77.1 (CH-C3, major diastereoisomer), 66.3 (CH-C7, major diastereoisomer), 65.4 (CH-C7, minor diastereoisomer), 60.6 (CH_2-C1, minor diastereoisomer), 60.5 (CH_2-C1, major diastereoisomer), 39.0 (CH_2-C2, minor diastereoisomer), 38.7 (CH_2-C2, major diastereoisomer), 32.4 (CH_2-C4, minor diastereoisomer), 32.2 (CH_2-C4, major diastereoisomer), 28.4 (CH_2-C5, major diastereoisomer), 26.8 (CH_2-C5, minor diastereoisomer), 26.1 (CH_3-*t*-Bu-TBS, both diastereoisomers), 24.9 (CH_3-C13, both diastereoisomers), 21.2 (CH_3-C12, both diastereoisomers), 18.5 (C-*t*-Bu-TBS, both diastereoisomers), −5.2 (CH_3-Me-TBS, both diastereoisomers); ν_{max} 3402, 2928, 2857, 1472, 1381, 1256, 1093, 837, 777 cm^{-1}; HRMS calculated for $C_{19}H_{34}NaO_3Si$ $[M+Na]^+$ 361.2169, found 361.2162, Δ = 2.1 ppm.

(2*E*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyl)bis(methyl)siloxy]ethyl}tetrahydro-2-furyl]-5-methyl-2,4-hexadien-1-ol 582

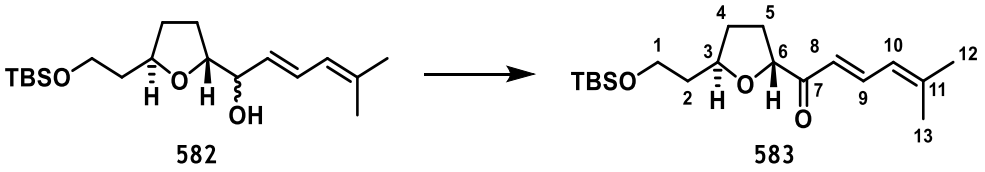


To a stirred solution of en-yne **564** (3.07 g, 9.07 mmol) in THF (90 mL) at 0 °C was added Red-Al® (65% by weight in PhMe, 5.8 mL, 16 mmol) dropwise. The reaction mixture was then warmed to rt and stirred for a further 16 h. The reaction mixture was then cooled to 0 °C and the reaction was quenched by the slow addition of sat. aq. potassium sodium tartrate (100 mL) and stirred until two clear phases formed. The resultant biphasic mixture was diluted with Et_2O (100 mL). The phases were separated and the aqueous phase was washed with Et_2O (2 × 100 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 10:1) affording 1,3-diene **582** (2.88 g, 93% as a 2: 1 mixture of diastereoisomers) as a colourless oil.

R_f = (pet. ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (1H, td, *J* = 10.8, 0.9 Hz, CH-C9, major diastereoisomer), 6.49 (1H, td, *J* = 10.8, 0.9 Hz, CH-C9, minor diastereoisomer), 5.82 (1H, d, *J* = 10.8 Hz, CH-C10, both diastereoisomers), 5.48 (1H, dd, *J* = 15.4, 6.9 Hz, CH-C8 minor diastereoisomer), 5.46 (1H, dd, *J* = 15.2, 6.9 Hz, CH-C8, major diastereoisomer), 4.33 (1H, dt, *J* = 6.0, 2.8 Hz, CH-C7, minor diastereoisomer), 4.15–4.04 (2H, m, both diastereoisomers), 3.99 (1H, td, *J* = 7.7, 3.6 Hz, minor diastereoisomer), 3.94 (1H, td, *J* = 7.1, 2.0 Hz, major diastereoisomer), 3.84 (1H, q, *J* = 7.0 Hz, major diastereoisomer), 3.71 (2H, dd, *J* = 7.0, 5.7 Hz, both diastereoisomers), 3.71 (2H, dd, *J* = 7.0, 5.8 Hz, both diastereoisomers), 2.57 (1H, d, *J* = 2.6 Hz, major diastereoisomer), 2.12 (1H, d, *J* = 3.1 Hz, minor diastereoisomer), 2.09–2.01 (2H, m, both diastereoisomers), 1.99-1.90 (1H, m, major diastereoisomer), 1.89–1.78 (3H, m, both diastereoisomers, minor diastereoisomer), 1.78 (6H, s, CH_3-35, both diastereoisomers), 1.76 (6H, s, CH_3-12, both diastereoisomers), 1.75–1.49 (6H, s), 0.89 (18H, s, CH_3-*t*-Bu-TBS), 0.06 (6H, s, CH_3-Me-TBS, both diastereoisomers), 0.05 (6H, s, CH_3-Me-TBS, both diastereoisomers); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5,

196.3, 129.4, 128.8, 128.4, 128.3, 124.6, 124.6, 82.0, 81.5, 77.6, 76.5, 75.7, 73.8, 60.6, 60.6, 39.2, 38.8, 32.5, 32.5, 28.2, 26.2, 26.1, 25.8, 18.5, −5.2; ν_{max} 3402, 2953, 2928, 2827, 1472, 1445, 1383, 1362, 1256, 1096, 959, 837, 777 cm^{-1}; HRMS calculated for $C_{19}H_{36}NaO_3Si$ $[M+Na]^+$ 363.2326, found 363.2310, Δ = 4.5 ppm.

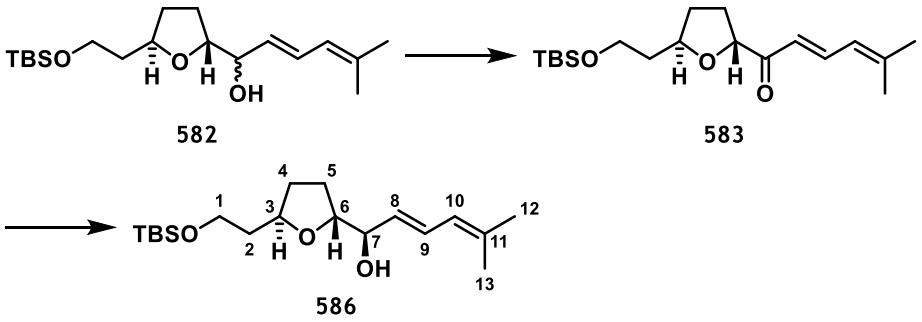
(2*E*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyl)bis(methyl)siloxy]ethyl}tetrahydro-2-furyl]-5-methyl-2,4-hexadien-1-one 583



To a stirred solution of allylic alcohol **582** (881 mg, 2.59 mmol) at rt in CH_2Cl_2 (70 mL) was added pyridine (0.8 mL) followed by Dess-Martin periodinane (1.91 g, 4.50 mmol) and stirred for 16 h, after which time a further portion of Dess-Martin periodinane (664 mg, 1.57 mmol) was added and stirred for a further 3 h. The reaction was quenched by the addition of sat. aq $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ (1:1, 60 mL) and stirred until two clear layers formed. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 × 50 mL). The combined organic fractions were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) affording dienone **583** (641 mg, 73%) as a yellow oil.

R_f = 0.44 (pet. ether:EtOAc, 9:1); $[\alpha]_D^{19}$ +24.6 (c = 0.344, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, dd, *J* = 15.2, 11.7 Hz, CH-C9), 6.43 (1H, d, *J* = 15.2 Hz, CH-C10), 6.03 (1H, d, 11.7 Hz, CH-C8), 4.51 (1H, dd, *J* = 7.8, 7.2 Hz, CH-C6), 4.18 (1H, ddd, *J* = 13.3, 7.2, 5.6 Hz, CH-C3), 3.76 (1H, d, *J* = 5.8 Hz, CH_2-C1), 3.74 (1H, d, *J* = 5.7 Hz, CH_2-C1), 2.25 (1H, tdd, *J* = 11.8, 7.8, 3.6 Hz, CH_2-C5), 2.08–1.81 (3H, m, CH_2-C19, CH_2-C21, CH_2-C5), 1.92 (3H, s, CH_3-C12), 1.90 (3H, s, CH_3-C13), 1.77-1.65 (1H, m, CH_2-C2), 1.59 (1H, ddd, *J* = 11.8, 8.3, 7.2 Hz, CH_2-C4), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.07 (3H, s, CH_3-Me-TBS), 0.06 (3H, s, CH_3-Me-TBS); ^{13}C NMR δ 202.0 (C-C7), 148.8 (C-C11), 140.4 (CH-C9), 124.8 (CH-C10), 122.2 (CH-C8), 82.7 (CH-C6), 78.1 (CH-C3), 60.5 (CH_2-C1), 38.9 (CH_2-C2), 31.8 (CH_2-C5), 29.9 (CH_2-C4), 29.8 (CH_3-*t*-Bu-TBS), 26.1(C-*t*-Bu-TBS), −5.2 (CH_3-Me-TBS); ν_{max} 2953, 2920, 2851, 1682, 1628, 1585, 1462, 1088, 995, 837 cm^{-1}; HRMS calculated for $C_{19}H_{34}NaO_3Si$ $[M+Na]^+$ 361.2169, found 361.2152, Δ = 4.8 ppm.

(*R*,2*E*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyl)bis(methyl)siloxy]ethyl}tetrahydro-2-furyl]-5-methyl-2,4-hexadien-1-ol 586



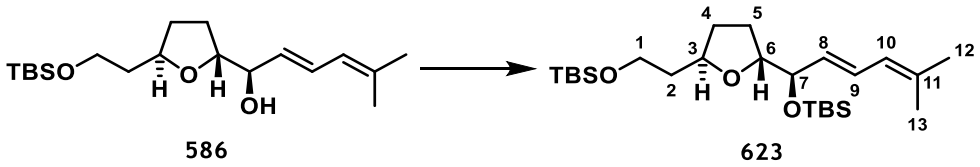
To a stirred solution of allylic alcohol **582** (555 mg, 1.63 mmol) in CH_2Cl_2 (30 mL) at rt was added pyridine (0.52 mL, 3.1 mmol) and Dess-Martin periodinane (1.17 g, 2.76 mmol). The reaction mixture was stirred at this temperature for 2 h before being quenched by the addition of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ (1:1, 50 mL). The phases were separated, and the aqueous phase was washed with CH_2Cl_2 (2 × 50 mL). The combined organic fractions were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude enone **583** was used in the next step without further purification.

To a stirred solution of crude enone **583** in MeOH (50 mL) and CH_2Cl_2 (10 mL) at rt was added $CeCl_3{\cdot}7H_2O$ (1.24 g, 3.33 mmol). The solution was cooled to −78 °C and stirred for 30 min. $NaBH_4$ (120 mg, 3.17 mmol) was added and the reaction mixture stirred for 16 h, slowly warming to rt. The reaction was quenched by the addition of sat. aq. NH_4Cl (100 mL). The phases were separated, and the aqueous phase was washed with EtOAc (4 × 50 mL). The combined organic fractions were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 4:1) affording allylic alcohol **586** (369 mg, 66% over two steps) as a colourless oil.

R_f = 0.21 (pet. ether:EtOAc, 9:1); $[\alpha]_D^{18}$ +2.01 (c = 0.77, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (1H, ddd, *J* = 15.1, 11.0, 0.6 Hz, CH-C9), 5.82 (1H, d, *J* = 11.0 Hz, CH-C10), 5.46 (1H, dd, *J* = 15.1, 6.9 Hz, CH-C8), 4.07 (1H, ddd, *J* = 11.1, 7.6, 5.7 Hz, CH-C3), 3.94 (1H, ddd, *J* = 7.6, 7.3, 2.5 Hz, CH-C7), 3.84 (1H, app. dt, *J* = 7.3, 7.0 Hz, CH-C6), 3.71 (2H, dd, *J* = 7.0, 5.7 Hz, CH_2-C1), 2.58 (1H, d,

J = 2.5 Hz, OH-C7), 2.05 (1H, dddd *J* = 9.7, 5.7, 4.6, 2.9 Hz, CH_2-C4), 1.94 (1H, dddd, *J* = 9.3, 7.0, 3.3, 2.9 Hz, CH_2-C5), 1.88–1.51 (4H, m, 2 ×CH_2-C2, CH_2-C4, CH_2-C5) 1.77 (3H, s, CH_3-C13), 1.76 (3H, s, CH_3-C12), 0.89 (9H, s, *t*-Bu, TBS), 0.05 (3H, s, Me, TBS), 0.05 (3H, s, Me, TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5 (C-C11), 129.4 (CH-C9), 128.4 (CH-C8), 124.6 (CH-C10), 82.0 (CH-C6), 76.5 (CH-C3), 75.7 (CH-C7), 60.6 (CH_2-C1), 38.8 (CH_2-C2), 32.5 (CH_2-C4), 28.2 (CH_2-C5), 26.1 (CH_3-C13), 26.1 (CH_3-*t*-Bu-TBS), 18.5 (CH_3-C12), 18.5 (C-*t*-Bu-TBS), −5.2 (CH_3-Me-TBS), −5.2(CH_3-Me-TBS); ν_{max} 3441, 2928, 2857, 1622, 1360, 1076, 957 cm^{-1}; HRMS calculated for $C_{19}H_{36}NaO_3Si$ $[M+Na]^+$ 363.2326, found 363.2312, Δ = 3.9 ppm.

[(*R*,2*E*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyl)bis(methyl)siloxy]ethyl}tetrahydro-2-furyl]-5-methyl-2,4-hexadienyloxy](*tert*-butyl)bis(methyl)silane 623

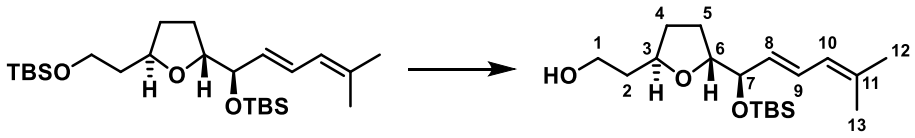


586 623

To a stirred solution of allylic alcohol **586** (364 mg, 1.07 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added 2,6-lutidine (0.32 mL, 2.7 mmol) and TBSOTf (0.32 mL, 1.4 mmol). The reaction mixture was stirred at this temperature for 1 h and then quenched by the addition of H_2O (10 mL). The reaction mixture was diluted with CH_2Cl_2 (15 mL), the phases were separated and the aqueous phase was washed with CH_2Cl_2 (2 × 15 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 98:2) affording di-TBS-protected **623** (519 mg, quant.) as a colourless oil.

R_f = 0.68 (pet. ether:EtOAc, 19:1); $[\alpha]_D^{20}$ +14 (c = 0.93, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (1H, ddd, *J* = 15.1, 11.0, 1.3 Hz, CH-C9), 5.83 (1H, d, *J* = 10.5 Hz, CH-C10), 5.54 (1H, dd, *J* = 15.2, 5.5 Hz, CH-C8), 4.20 (1H, app t, *J* = 5.5 Hz, CH-C7), 3.98 (1H, ddd, *J* = 7.8, 6.7, 3.6 Hz, CH-C3), 3.94 (1H, ddd, *J* = 13.2, 7.4, 5.5 Hz, CH-C6), 3.71 (1H, dd, *J* = 6.8, 3.9 Hz, CH_2-C1), 3.69 (1H, dd, *J* = 6.8, 5.0 Hz, CH_2-C1), 1.95 (1H, dddd, *J* = 11.5, 8.3, 5.5, 3.1 Hz, CH_2-C4), 1.91–1.77 (1H, m, CH_2-C5), 1.77 (3H, s, CH_3-C13), 1.75 (3H, s, CH_3-C12), 1.75–1.61 (3H, m, CH_2-C2, CH_2-C4, CH_2-C5), 1.46 (1H, ddt, *J* = 11.8, 9.6, 8.3 Hz, CH_2-C4), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.07 (3H, s, CH_3-Me-TBS), 0.05 (3H, s, CH_3-Me-TBS), 0.05 (6H, s, 2 × CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.9 (C-C11), 130.1 (CH-C9), 127.5 (CH-C8), 125.0 (CH-C10), 82.1 (CH-C6), 76.7 (CH-C3), 75.5 (CH-C7), 60.9 (CH_2-C1), 39.2 (CH_2-C2), 32.5 (CH_2-C4), 27.3 (CH_2-C5), 26.1 (CH_3-*t*-Bu-TBS), 26.1 (CH_3-*t*-Bu-TBS), 18.5 (C-*t*-Bu-TBS, CH_3-C12), 18.4 (C-*t*-Bu-TBS), −4.4 (CH_3-Me-TBS), −4.6 (CH_3-Me-TBS), −5.2 (CH_3-Me-TBS), −5.2 (CH_3-Me-TBS); ν_{max} 2955, 2928, 2886, 2857, 1472, 14622, 1385, 1086, 837, 777 cm^{-1}; HRMS calculated for $C_{25}H_{50}NaO_3Si_2$ $[M+Na]^+$ 477.3191, found 477.3177, Δ = 2.9 ppm.

2-[(2*R*,5*R*)-5-{(*R*,2*E*)-1-[(*tert*-Butyl)bis(methyl)siloxy]-5-methyl-2,4-hexadienyl}tetrahydro-2-furyl]ethanol 624

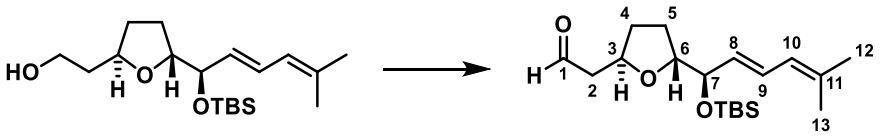


623 624

To a stirred solution of di-TBS protected **623** (200 mg, 0.440 mmol) in MeOH (10 mL) and CH_2Cl_2 (10 mL) at −10 °C was added CSA (16 mg, 0.069 mmol) and stirred for 5 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (20 mL), the phases were separated and aqueous phase was washed with CH_2Cl_2 (3 × 25 mL). The combined organic fractions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) affording primary alcohol **624** (95 mg, 63%) as a colourless oil.

R_f = 0.30 (pet. ether:EtOAc, 4:1); $[\alpha]_D^{22}$ +13.8 (c = 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (1H, ddd, *J* = 15.1, 11.0, 1.2 Hz, CH-C9), 5.82 (1H, d, *J* = 10.9 Hz, CH-C10), 5.51 (1H, dd, *J* = 15.2, 5.9 Hz, CH-C8), 4.14 (1H, t, *J* = 6.2 Hz, CH-C7), 4.10 (1H,ddd, *J* = 10.9, 8.4, 4.6 Hz, CH-3), 3.96 (1H, app. dt, *J* = 7.8, 6.4 Hz, CH-C6), 3.81-3.74 (2H, m, 2 × CH_2-C1), 3.00 (1H, dd, *J* = 5.2, 4.8 Hz, OH-C1), 2.00 (1H, tdd, *J* = 8.2, 6.1, 3.4 Hz, CH_2-C4), 1.88 (1H, dddd, *J* = 12.3, 8.2, 6.8, 2.8 Hz, CH-C5), 1.77 (3H, s, CH_3-C13), 1.75 (3H, s, CH_3-C12), 1.76–1.62 (3H, m, 2 × CH_2-C2, CH-C5), 1.53 (1H, ddt, *J* = 11.9, 10.0, 8.3 Hz, CH_2-C4), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.07 (3H, s, CH_3-Me-TBS), 0.04 (3H, s, CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.4 (C-C11), 129.8 (CH-C9), 127.9 (CH-C8), 124.7 (CH-C10), 82.7 (CH-C6), 80.1 (CH-C3), 75.7 (CH-C7), 62.0 (CH_2-C1), 37.4 (CH_2-C2), 32.6 (CH_2-C4), 27.3 (CH_2-C5), 26.1 (CH_3-C12), 26.0 (3 × CH_3-*t*-Bu-TBS),18.4 (CH_3-C13, C-*t*-Bu-TBS), −4.3 (CH_3-Me-TBS), −4.6 (CH_3-Me-TBS); ν_{max} 3414, 2928, 2857, 1471, 1377, 1067, 961, 835 cm^{-1}; HRMS calculated for $C_{19}H_{36}NaO_3Si$ $[M+Na]^+$ 363.2326, found 363.2317, Δ = 2.5 ppm.

[(2*R*,5*R*)-5-{(*R*,2*E*)-1-[(*tert*-Butyl)bis(methyl)siloxy]-5-methyl-2,4-hexadienyl}tetrahydro-2-furyl]acetaldehyde 587

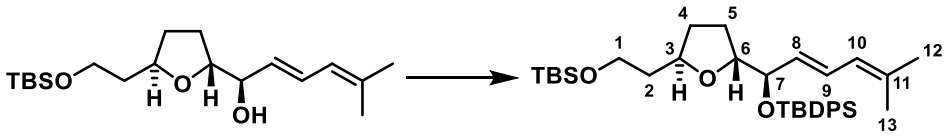


624 587

To a stirred solution of primary alcohol **624** (120 mg, 0.352 mmol) in CH_2Cl_2 (14 mL) at rt was added pyridine (0.20 mL, 2.5 mmol) and Dess-Martin periodinane (310 mg, 0.731 mmol) and stirred for 4 h after which time the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (1:1, 10 mL) and stirred until two clear phases formed. The phases were separated, and the aqueous phase was washed with CH_2Cl_2 (3 × 10 mL). The combined organic fractions dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) affording aldehyde **587** (64 mg, 54%) as a colourless oil.

R_f = 0.43 (pet. ether:EtOAc, 9:1); $[\alpha]_D^{22}$ +14 (c = 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (1H, t, *J* = 2.2 Hz, CH-C1), 6.47 (1H, ddd, *J* = 15.2, 11.0, 1.3 Hz, CH-C9), 5.83 (1H, d, *J* = 11.0 Hz, CH-10), 5.53 (1H, dd, *J* = 15.1, 5.7 Hz, CH-C8), 4.35 (1H, ddt, *J* = 8.2, 7.5, 5.5 Hz, CH-C3), 4.20 (1H, t, *J* = 5.5 Hz, CH-C7), 3.99 (1H, td, *J* = 7.2, 5.9 Hz, CH-C6), 2.65 (1H, ddd, *J* = 16.1, 7.4, 2.6 Hz, CH_2-C2), 2.54 (1H, ddd, *J* = 16.1, 5.3, 2.0 Hz, CH_2-C2), 2.09 (1H, dddd, *J* = 8.6, 8.1, 5.7, 3.3 Hz, CH_2-C4), 1.91 (1H, dddd, *J* = 13.5, 11.4, 6.8, 3.3 Hz, CH_2-C5), 1.82–1.72 (1H, m, CH_2-C5), 1.77 (3H, s, CH_3-C13), 1.75 (3H, s, CH_3-C12), 1.52 (1H, ddt, *J* = 12.1, 9.5, 8.3 Hz, CH_2-C4), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.05 (3H, s, CH_3-Me-TBS), 0.04 (3H, s, CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.6 (CH-C1), 135.4 (C-C1), 129.6 (CH-C8), 127.9 (CH-C9), 124.8 (CH-C10), 82.7 (CH-C6), 75.4 (CH-C7), 74.5 (CH-C3), 49.7 (CH_2-C2), 32.4 (CH_2-C4), 27.2 (CH_2-C5), 26.1 (CH_3-C13), 26.0 (3 × CH_3-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), 18.4 (CH_3-C12), −4.4 (CH_3-Me-TBS), −4.6 (CH_3-Me-TBS); ν_{max} 2956, 2926, 2855, 2735, 1726, 1462, 1377, 1362, 1076, 986, 961, 835 cm^{-1}; HRMS calculated for $C_{19}H_{34}NaO_3Si$ $[M+Na]^+$ 361.2169, found 361.2153, Δ = 4.6 ppm.

[(*R*,2*E*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyl)bis(methyl)siloxy]ethyl}tetrahydro-2-furyl]-5-methyl-2,4-hexadienyloxy](*tert*-butyl)bis(phenyl)silane 625

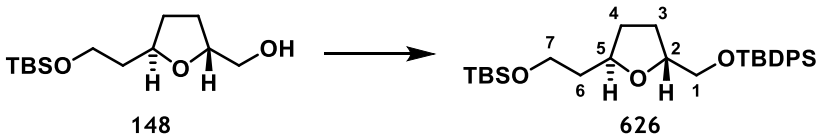


586 625

To a stirred solution of allylic alcohol **586** (70 mg, 0.21 mmol) in CH_2Cl_2 (2.0 mL) at rt was added TBDPSCl (0.06 mL, 0.2 mmol) and imidazole (20 mg, 0.29 mmol). The reaction mixture was stirred for 16 h after which time the reaction was quenched by the addition of sat. aq. NH_4Cl (5 mL). The phases were separated and the aqueous phase was washed with Et_2O (3 × 5 mL). The combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 99:1) affording allyl TBDPS ether **625** (54 mg, 44%) as a colourless oil.

R_f = 0.40 (pet. ether:EtOAc, 19:1); $[\alpha]_D^{16}$ −13.8 (c = 0.91, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.63 (4H, m, TBDPS-Ph), 7.41–7.30 (6H, m, TBDPS-Ph), 6.17 (1H, ddd, *J* = 15.2, 11.0, 0.9 Hz, CH-C9), 5.71 (1H, dd, *J* = 11.0, 0.5 Hz, CH-C10), 5.47 (1H, dd, *J* = 15.2, 6.2 Hz, CH-C8), 4.25 (1H, dd, *J* = 6.2, 6.0 Hz, CH-C7), 3.97 (1H, td, *J* = 7.1, 6.0 Hz, CH-C6), 3.86 (1H, ddt, *J* = 8.2, 7.3, 5.6 Hz, CH-C3), 3.66 (1H, ddd, *J* = 7.7, 5.5, 4.4 Hz, CH_2-C1), 3.61 (1H, dt, *J* = 10.2, 5.4 Hz, CH_2-C1), 1.95-1.82 (2H, m, CH_2-C5, CH_2-C4), 1.79–1.67 (1H, m, CH_2-C5), 1.73 (3H, s, CH_3-12), 1.63–1.58 (2H, m, CH_2-C4, CH_2-C2), 1.60 (3H, s, CH_3-13), 1.43 (1H, tt, *J* = 10.0, 7.7 Hz, CH_2-C2), 1.07 (9H, s, CH_3-*t*-Bu-TBDPS), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.03 (6H, s, CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2 (CH-Ph-TBDPS), 136.2 (CH-Ph-TBDPS), 135.0 (C-C11), 134.5 (C-Ph-TBDPS), 134.5 (CH-Ph-TBDPS), 129.6 (CH-C9), 129.5 (CH-Ph-TBDPS), 129.2 (CH-Ph-TBDPS), 128.6 (CH-Ph-TBDPS), 127.5 (CH-C8), 127.4 (CH-C10), 124.9 (CH-C7), 81.6 (CH-C6), 76.4 (CH-C3), 60.9 (CH_2-C1), 39.1 (CH_2-C2), 32.4 (CH_2-C4), 27.2 (CH_2-C5), 27.2 (CH_3-*t*-Bu-TBDPS), 26.1 (CH_3-*t*-Bu-TBS), 19.6 (CH_3-C12), 18.4 (C-*t*-Bu-TBDPS), 18.3 (C-*t*-Bu-TBDPS), −5.2 (CH_3-Me-TBS), −5.2 (CH_3-Me-TBS).

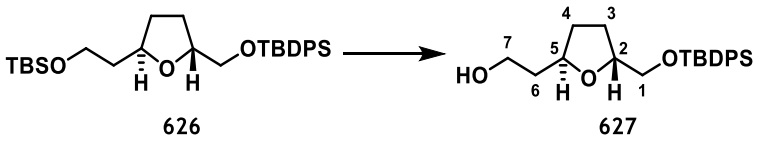
{2-[(2*R*,5*R*)-5-{[(*tert*-Butyl)bis(phenyl)siloxy]methyl}tetrahydro-2-furyl]ethoxy}(*tert*-butyl)bis(methyl)silane 626



To a stirred solution of alcohol **148** (591 mg, 2.27 mmol) in CH_2Cl_2 (10 mL) at rt was added TBDPSCl (0.82 mL, 3.2 mmol) followed by imidazole (191 mg, 2.81 mmol) and stirred for 16 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (20 mL). CH_2Cl_2 (20 mL) was added and the phases were separated, the aqueous phase was washed with CH_2Cl_2 (2 × 20 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 19:1) affording TBDPS ether **626** (1.12 g, quant.) as a colourless oil.

R_f = 0.42 (pet. ether:EtOAc, 19:1); $[\alpha]_D^{16}$ −11.0 (c = 0.950, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.66 (4H, m, Ar-TBDPS), 7.45–7.34 (6H, m, Ar-TBDPS), 4.12 (1H, dddd, *J* = 6.9, 6.9, 5.0, 4.8 Hz, CH-C2), 4.04 (1H, dddd, *J* = 8.0, 7.5, 5.6, 5.6 Hz, CH-C5), 3.78–3.68 (2H, m, 2 × CH_2-C7), 3.66 (1H, dd, *J* = 10.5, 4.8 Hz, CH_2-C1), 3.61 (1H, dd, *J* = 10.5, 5.0 Hz, CH_2-C1), 2.08–1.96 (2H, m, CH_2-C4, CH_2-C3), 1.87–1.76 (2H, m, CH_2-C6, CH_2-C3), 1.67 (1H, dddd, *J* = 12.5, 7.1, 7.1, 5.6 Hz, CH_2-C6), 1.53 (dddd, *J* = 12.5, 9.9, 8.6, 8.0 Hz, CH_2-C4), 1.05 (9H, s, CH_3-*t*-Bu-TBDPS), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.05 (6H, s, CH_3-Me-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8 (4 × CH-Ph-TBDPS), 133.9 (2 × C-Ph-TBDPS), 129.7 (CH-Ph-TBDPS), 129.7 (CH-Ph-TBDPS), 127.7 (4 × CH-Ph-TBDPS), 78.9 (CH-C2), 77.4 (CH-C5), 66.7 (CH_2-C1), 60.9 (CH_2-C7), 39.2 (CH_2-C6), 32.3 (CH_2-C4), 28.3 (CH_2-C3), 27.0 (3 × CH_3-*t*-Bu-TBDPS), 26.1 (3 × CH_3-*t*-Bu-TBS), 19.4 (C-*t*-Bu-TBDPS), 18.5 (C-*t*-Bu-TBDPS), −5.2 (CH_3-Me-TBS), −5.2 (CH_3-Me-TBS); ν_{max} 2929, 2856, 1472, 1428, 1254, 1105, 1084, 834 cm^{-1}; HRMS calculated for $C_{29}H_{46}NaO_2Si_2$ $[M+Na]^+$ 521.2878, found 521.2877, Δ = 0.2 ppm.

2-[(2*R*,5*R*)-5-{[(*tert*-Butyl)bis(phenyl)siloxy]methyl}tetrahydro-2-furyl]ethanol 627

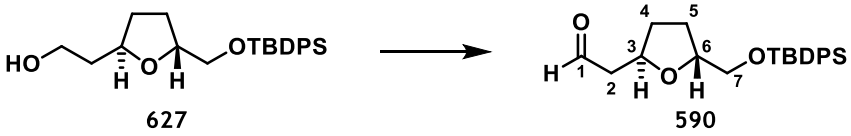


626 627

To a stirred solution of TBS ether **626** (2.30 g, 4.61 mmol) in MeOH (40 mL) and CH_2Cl_2 (40 mL) at −10 °C was added CSA (210 mg, 0.904 mmol). The reaction mixture was stirred for 3 h before the reaction was quenched by the addition of Et_3N (0.50 mL, 3.6 mmol). The resulting solution was concentrated under reduced pressure and the crude material was purified by flash chromatography (pet. ether:EtOAc, 4:1) affording alcohol **627** (1.40 g, 79%) as a colourless oil.

R_f = 0.25 (pet. ether:EtOAc, 4:1); $[\alpha]_D^{13}$ −8.1 (c = 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.60 (4H, m, CH-Ph-TBDPS), 7.40–7.30 (6H, m, CH-Ph-TBDPS), 4.12 (1H, dddd, *J* = 6.8, 6.8, 4.8, 4.6 Hz, CH-C2), 4.09 (1H, dddd, *J* = 10.5, 8.5, 4.4, 3.6 Hz, CH-C5), 3.80–3.67 (2H, m, 2 × CH_2-C7), 3.60 (1H, dd, *J* = 10.7, 4.6 Hz, CH_2-C1), 3.56 (1H, dd, *J* = 10.7, 4.8 Hz, CH-C1), 2.95 (1H, dd, *J* = 6.7, 3.8 Hz, OH-C7), 2.11–1.95 (2H, m, CH_2-C3, CH_2-C4), 1.86–1.72(4H, m, 2 × CH_2-C6, CH_2-C4, CH_2-C3), 1.06 (9H, s, CH_3-*t*-Bu-TBDPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8 (CH-Ph-TBDPS), 133.7 (C-Ph-TBDPS), 129.8 (CH-Ph-TBDPS), 127.8 (CH-Ph-TBDPS), 80.2 (CH-C2), 79.6 (CH-C5), 66.5 (CH_2-C1), 62.1(CH_2-C7), 37.4 (CH_2-C6), 32.6 (CH_2-C3), 27.6 (CH_2–4), 26.9 (CH_3-*t*-Bu), 19.4 (C-*t*-Bu-TBDPS); ν_{max} 3355, 2930, 2857, 1472, 1427, 1112, 1077, 823 cm^{-1}; HRMS calculated for $C_{23}H_{32}NaO_2Si$ $[M+Na]^+$ 407.2013, found 407.2004, Δ = 2.1 ppm.

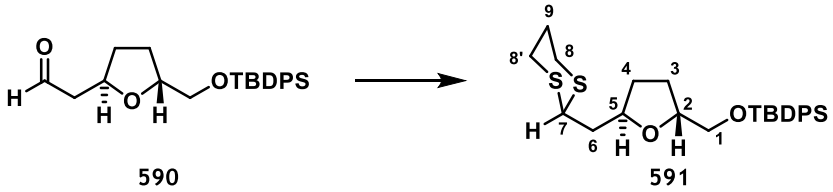
[(2*R*,5*R*)-5-{[(*tert*-Butyl)bis(phenyl)siloxy]methyl}tetrahydro-2-furyl]acetaldehyde 590



To a stirred solution of alcohol **627** (295 mg, 0.767 mmol) in CH_2Cl_2 (20 mL) at rt was added pyridine (0.25 mL, 2.3 mmol) and Dess-Martin periodinane (574 mg, 1.35 mmol) sequentially. The reaction mixture was stirred for 3 h after which time the reaction was quenched by the addition of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ (1:1, 20 mL) and stirred until two clear phases formed. The phases were separated and the aqueous phase was washed with Et_2O (3 × 20 mL). The combined organic fractions were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) affording aldehyde **590** (209 mg, 71%) as a colourless oil.

R_f = 0.53 (pet. ether:EtOAc, 4:1); $[\alpha]_D^{13}$ −11.0 (c = 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (1H, dd, *J* = 2.6, 2.0 Hz, CH-C1), 7.70–7.65 (4H, m, Ar-TBDPS), 7.43-7.35 (6H, m, Ar-TBDPS), 4.41 (1H, dddd, *J* = 8.1, 7.6, 5.7, 5.5 Hz, CH-C3), 4.17 (1H, dddd, *J* = 7.1, 7.0, 4.0, 3.9 Hz, CH-C6), 3.67 (1H, dd, *J* = 9.3, 4.0 Hz, CH_2-C7), 3.64 (1H, dd, *J* = 9.3, 3.9 Hz, CH_2-C7), 2.66 (1H, ddd, *J* = 16.1, 7.4, 2.6 Hz, CH_2-C2), 2.56 (1H, ddd, *J* = 16.1, 5.3, 2.0 Hz, CH_2-C2), 2.17 (1H, dddd, *J* = 11.9, 8.1, 5.8, 3.8 Hz, CH_2-C4), 2.03 (1H, dddd, *J* = 10.8, 8.3, 7.1, 3.7 Hz, CH_2-C5), 1.90 (1H, dddd, *J* = 12.5, 9.1, 8.0, 7.0 Hz, CH_2-C5), 1.57 (1H, dtd, *J* = 10.9, 8.9, 8.4 Hz, CH_2-C4), 1.05 (9H, s, CH_3-*t*-Bu-TBDPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5 (CH-C1), 135.8 (CH-Ph-TBDPS), 133.8 (C-Ph-TBDPS), 129.8 (CH-Ph-TBDPS), 127.8 (CH-Ph-TBDPS), 79.6 (CH-C6), 74.4 (CH-C3), 66.5 (CH_2-C7), 49.8 (CH_2-C2), 32.3 (CH_2-C4), 27.9 (CH_2-C5), 27.0 (CH_3-*t*-Bu-TBDPS), 19.4 (C-*t*-Bu-TBDPS); ν_{max} 2955, 2932, 2857, 2728, 1727, 1472, 1428, 1390, 1112, 1083 cm^{-1}; HRMS calculated for $C_{23}H_{30}NaO_3Si$ $[M+Na]^+$ 405.1862, found 405.1883, Δ = 5.2 ppm.

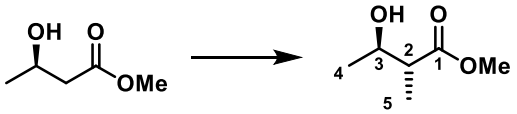
({(2*R*,5*R*)-5-[(1,3-Dithian-2-yl)methyl]tetrahydro-2-furyl}methoxy)(*tert*-butyl)bis(phenyl)silane 591



To a stirred solution of $MgBr_2 \cdot OEt_2$ (96 mg, 0.37 mmol) in Et_2O (10 mL) at rt was added 1,3-propanedithiol (0.03 mL, 0.3 mmol) and the reaction mixture stirred for 10 min, after which time a solution of aldehyde **590** (109 mg, 0.285 mmol) in Et_2O (1 mL). The reaction mixture was stirred at rt for 16 h the reaction was then quenched by the addition of sat. aq. $NaHCO_3$ (15 mL). The phases were separated and the aqueous phase was washed with Et_2O (2 × 20 mL). The combined organic fractions were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAC, 19:1) affording dithiane **591** (125 mg, 93%) as a colourless solid.

R_f = 0.48 (pet. ether:EtOAc, 9:1); $[\alpha]_D^{13}$ −6.17 (c = 0.645, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.67 (4H, m, CH-Ph-TBDPS), 7.45–7.36 (6H, m, CH-Ph-TBDPS),4.27 (1H, dddd, *J* = 8.5, 7.8, 6.0, 4.5 Hz, CH-C5) 4.20 (1H, dd, *J* = 9.3, 5.0 Hz, CH-C7), 4.13, (1H, ddd, *J* = 11.8, 6.8, 4.9 Hz, CH-C2), 3.67 (1H, dd, *J* = 10.5, 4.9 Hz, CH_2-C1), 3.61 (1H, dd, *J* = 10.5, 5.3 Hz, CH_2-C1), ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9 (CH-Ph-TBDPS), 135.8 (CH-Ph-TBDPS), 133.9 (C-Ph-TBDPS), 129.7(CH-Ph-TBDPS), 127.8 (CH-Ph-TBDPS), 79.2 (CH-C2), 75.7 (CH-C5), 66.7 (CH_2-C1), 44.7 (CH-C7), 42.0 (CH_2-C6), 32.0 (CH_2-C4), 30.7 (CH_2-C8), 30.3 (CH_2-C8'), 28.2 (CH_2-C3), 27.0 (C-*t*-Bu-TBDPS), 26.2 (CH_2-C9), 19.4 (CH_3-*t*-Bu-TBDPS); ν_{max} 2927, 2856, 1472, 1427, 1086, 1079 cm^{-1}; HRMS calculated for $C_{26}H_{36}NaO_2S_2Si$ $[M+Na]^+$ 495.1818, found 495.1821, Δ = 0.5 ppm; M. P. = 69-70 °C.

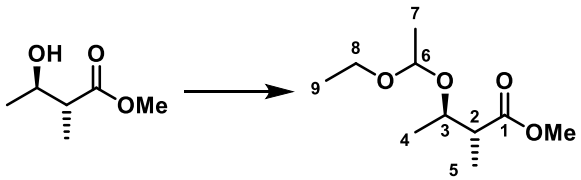
Methyl (2*R*,3*R*)-3-hydroxy-2-methylbutyrate 463



To a stirred solution of *i*-Pr_2NH (2.8 mL, 20 mmol) in THF (20 mL) at 0 °C was added *n*-BuLi (2.2 M in hexane, 8.7 mL, 19 mmol) dropwise. The reaction mixture was stirred at 0 °C for 10 min before being cooled to −78 °C, then (*R*)-methyl-3-hydroxybutanoate (**461**) (1.1 mL, 10 mmol) was added dropwise over 5 min. The reaction mixture was stirred at −78 °C for 30 min, then a solution of MeI (0.68 mL, 11 mmol) in HMPA (3.3 mL) was added dropwise over 15 min. The reaction mixture was stirred at −78 °C for a further 15 min then warmed to 0 °C and stirred for 30 min. The reaction was quenched by the addition of 0 °C sat. aq. NH_4Cl (35 mL), the phases were separated and the aqueous phase was washed with Et_2O (2 × 30 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 3:1) affording alcohol **463** (817 mg, 62%) as a colourless oil.

R_f = 0.37 (pet. ether:EtOAc, 3:2); $[\alpha]_D^{16}$ −18.2 (c = 0.685, $CHCl_3$) [lit[127] $[\alpha]_D^{24}$ −28.3 (c = 0.42, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (1H, dqd, *J* = 7.1, 6.4, 5.6 Hz, CH-C3), 3.70 (3H, s, CH_3-OCH_3), 2.69 (1H, d, *J* = 5.6 Hz, OH-C3), 2.45 (1H, dq, *J* = 7.2, 7.1 Hz, CH-C2), 1.21 (3H, d, *J* = 6.4 Hz, CH_3-C4), 1.17 (3H, d, *J* = 7.2 Hz, CH_3-C5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5 (C-C1), 69.6 (CH-C3), 51.9 (CH_3-OCH_3), 47.0 (CH-C2), 10.9 (CH_3-C4), 14.2 (CH_3-C5); ν_{max} 3354, 2959, 2924, 2851, 1715, 1464, 1377, 1261, 1198, 1173, 1111, 1045 cm^{-1}; HRMS calculated for $C_6H_{12}NaO_3$ $[M+Na]^+$ 155.0679, found 155.0682, Δ = 1.9 ppm.

Methyl (2*R*,3*R*)-3-(1-ethoxyethoxy)-2-methylbutyrate 628

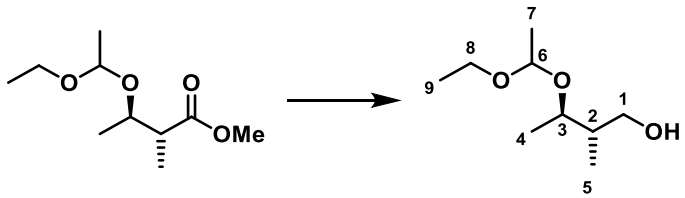


463 628

To a stirred solution of alcohol **463** (817 mg, 6.18 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added ethyl vinyl ether (1.8 mL, 19 mmol) and PPTS (149 mg, 0.593 mmol) The reaction mixture was stirred for 4 h then warmed to rt and stirred for a further 17 h. The reaction mixture was diluted by the addition of Et_2O (180 mL) and washed with brine (140 mL). The organic fraction was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 19:1) affording ethoxy-ethyl ether **628** (716 mg, 57%) as a 1.1:1 mixture of diastereoisomers as a colourless oil.

R_f = 0.38 (pet. ether:EtOAc, 9:1), $[\alpha]_D^{12}$ −25.1 (c = 0.240, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (1H, q, *J* = 5.3 Hz, CH-C6), 4.69 (1.1H, q, *J* = 5.3 Hz, CH-C6), 3.96 (1H, dq, *J* = 12.5, 6.2 Hz, CH_2-C3), 3.87 (1.1H, dq, *J* = 12.6, 6.3 Hz, CH_2-C3), 3.68 (6.3H, s, CH_3-OMe), 3.62 (1H, dq, *J* = 9.2, 7.1 Hz, CH_2-C8), 3.61 (1.1H, dq, *J* = 9.0, 7.1 Hz, CH_2-C8), 3.48 (1.1H, dq, *J* = 9.0, 7.1 Hz, CH_2-C8), 3.41 (1H, dq, *J* = 9.2, 7.1 Hz, CH_2-C8), 2.64 (1H, app p *J* = 7.1 Hz, CH-C2), 2.60 (1.1H, app p, *J* = 7.1 Hz, CH-C2), 1.29 (3H, d, *J* = 5.3 Hz, 3 × CH_3-C7), 1.24 (3.3H, d, *J* = 5.3 Hz, 3.3 × CH_3-C7), 1.22-1.65 (9.6H, m, 3.3 × CH_3-C4, 3.3 × CH_3-C9, 3 × CH_3-C9), 1.13 (3H, d, *J* = 6.8 Hz, 3 × CH_3-C5), 1.13 (3H, d, *J* = 6.3 Hz, 3 × CH_3-C4), 1.11 (3.3H, d, *J* = 7.1 Hz, CH_3-C5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7 (C-C1), 175.6 (C-C1), 100.5 (CH-C6), 98.3 (CH-C6), 75.3 (CH-C3), 72.5 (CH-C3), 60.3 (CH_2-C8), 60.1 (CH_2-C8), 51.7 (2 × CH_3-OCH_3), 46.0 (2 × CH-C2), 20.8 (CH_3-C7), 20.6 (CH_3-C7), 18.2 (CH_3-C4), 17.1 (CH_3-C4), 15.5 (CH_3-C9), 15.4 (CH_3-C9), 12.6 (CH_3-C5), 12.6 (CH_3-C5); HRMS calculated for $C_{10}H_{20}NaO_4$ $[M+Na]^+$ 227.1254, found 227.1255, Δ = 0.7 ppm.

(2*S*,3*R*)-3-(1-Ethoxyethoxy)-2-methyl-1-butanol 592

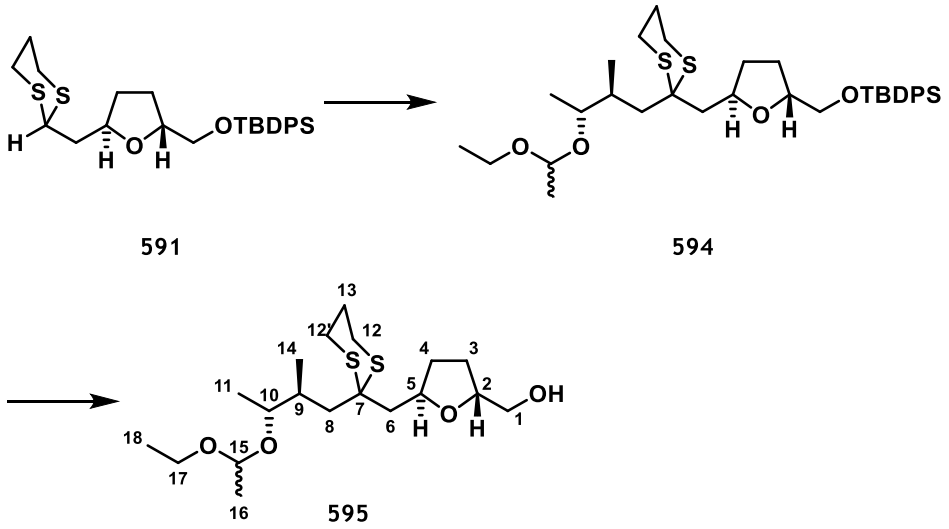


628 592

To a stirred solution of $LiAlH_4$ (330 mg, 8.70 mmol) in Et_2O (30 mL) at 0 °C was added a solution of ester **628** (715 mg, 3.50 mmol) in Et_2O (5 mL) dropwise over 5 min. The reaction mixture was stirred for 2 h after which time the reaction was quenched by the slow addition of H_2O (0.3 mL), NaOH (15% w/w in H_2O, 0.3 mL), and H_2O (1.0 mL). The mixture was stirred vigorously at rt for 30 min after which time the solids were removed by filtration. The filtrate was concentrated under reduced pressure and the alcohol **592** (485 mg, 79%) was used directly in the next step without further purification.

R_f = 0.44 (pet. ether:EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (1.1H, q, *J* = 5.2 Hz, CH-C6), 4.68 (1H, q, *J* = 5.1 Hz, CH-C6), 3.83 (1H, ddd, *J* = 11.1, 6.3, 3.3 Hz, CH_2-C1), 3.70–3.44 (9.5H, m, 3 × CH_2-C1, 2 × CH-C3, 4 × CH_2-C8), 3.21 (1H, app. t, *J* = 6.3 Hz, OH-C1), 2.63 (1.1H, app. t, *J* = 5.6 Hz, OH-C1), 1.77-1.59 (2.1H, m, 2 × CH-C2), 1.32 (3.3H, d, *J* = 5.2 Hz, CH_3-C7), 1.30 (3H, d, *J* = 5.1 Hz, CH_3-C7), 1.23 (3.3H, d, *J* = 6.3 Hz, CH_3-C4), 1.21 (3H, t, *J* = 7.1 Hz, CH_3-C9), 1.19 (3.3H, t, *J* = 7.1 Hz, CH_3-C9), 1.16 (3H, d, *J* = 6.2 Hz, CH_3-C4), 0.93 (3H, d, *J* = 7.0 Hz, CH_3-C5), 0.92 (3.3H, d, *J* = 7.0 Hz, CH_3-C5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 100.2 (CH-C6), 98.4 (CH-C6), 78.0 (CH-C3), 75.7 (CH-C3), 66.3 (CH_2-C1), 65.9 (CH_2-C1), 61.3 (CH_2-C8), 60.6 (CH_2-C8), 41.5 (CH-C2), 41.2 (CH-C2), 20.8 (CH_3-C7), 20.6 (CH_3-C7), 19.0 (CH_3-C4), 18.3 (CH_3-C4), 15.4 (2 × CH_3-C9), 14.5 (CH_3-C5), 13.9 (CH_3-C5).

[(2*R*,5*R*)-5-({2-[(2*S*,3*R*)-3-(1-Ethoxyethoxy)-2-methylbutyl]-1,3-dithian-2-yl}methyl)tetrahydro-2-furyl]methanol 595



To a stirred solution of alcohol **592** (485 mg, 2.75 mmol) in THF (20 mL) at 0 °C was added PPh_3 (1.45 g, 5.51 mmol) and imidazole (750 mg, 11.0 mmol) sequentially. The reaction mixture was stirred at for 10 min before I_2 (1.40 g, 5.51 mmol) was added in small portions until a red colour persisted. The red solution was stirred at 0 °C for 10 min then warmed to rt and stirred for a further 1 h. The reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$ (20 mL), the phases were separated, and the aqueous phase was washed with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was filtered through a short pad of silica gel (pet. ether:EtOAc, 19:1) to give crude alkyl iodide **593** which was used directly in the next step without further purification.

To a solution of dithiane **591** (506 mg, 1.07 mmol) in THF (4.0 mL) and HMPA (0.4 mL) at −78 °C was added *t*-BuLi (1.3 M in hexanes, 1.2 mL, 1.6 mmol) dropwise giving a red solution. The red solution was stirred at −78 °C for 10 min after which time a solution of alkyl iodide **593** in THF (6 mL) was added slowly. The reaction mixture was stirred at −78 °C for 1 h before being quenched by the addition of phosphate buffer (pH = 7, 10 mL). The reaction mixture was warmed to rt, diluted with Et_2O (10 mL), the phases were separated and the aqueous phase was washed with Et_2O (2 × 10 mL). The combined organic fractions were washed with brine

(20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 19:1) affording dithiane **594** (218 mg, 32%) as a colourless oil.

To a stirred solution of TBDPS ether **594** (109 mg, 0.173 mmol) in THF (2.0 mL) at rt was added TBAF (1 M in THF, 0.34 mL, 0.34 mmol). The reaction mixture was stirred for 3 h after which time H_2O (2.0 mL) was added, the phases were separated and the aqueous phase was washed with Et_2O (2 × 5 mL). The combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (pet. ether:EtOAc, 9:1) affording alcohol **595** (57 mg, 88%) as a colourless oil.

R_f = 0.56 (pet. ether:EtOAc, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (1H, q, *J* = 5.4 Hz), 4.73 (1H, q, *J* = 5.3 Hz), 4.25–4.17 (2H, m), 4.16–4.08 (2H, m), 3.70-3.52 (6H, m), 3.55–3.43 (4H, m) 2.92–2.71 (8H, m), 2.27–2.11 (8H, m), 2.11-1.89 (2H, m), 1.72–1.55 (6H, m), 1.31 (3H, d, *J* = 5.3 Hz), 1.30 (3H, d, *J* = 5.4 Hz), 1.20 (3H, t, *J* = 7.1 Hz), 1.19 (3H, t, *J* = 7.0 Hz), 1.10 (3H, d, *J* = 6.4 Hz), 1.07 (3H, d, *J* = 6.4 Hz), 1.05 (3H, d, *J* = 5.8 Hz), 1.02 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 99.1, 98.2, 78.9, 78.9, 76.1, 76.1, 75.5, 65.1, 60.4, 53.5, 44.9, 34.9, 34.0, 33.7, 27.5, 27.5, 26.5, 26.5, 25.1, 21.1, 21.0, 17.5, 16.4, 16.1, 15.8, 15.5; ν_{max} 3438, 2974, 2927, 2874, 1442, 1377, 1336, 1076, 1052, 958 cm^{-1}; HRMS calculated for $C_{19}H_{36}NaO_4S_2$ $[M+Na]^+$ 415.1947, found 415.1949, Δ = 0.5 ppm.

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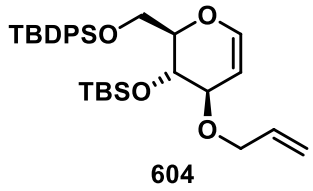
Appendix



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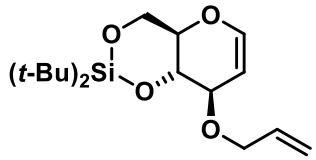
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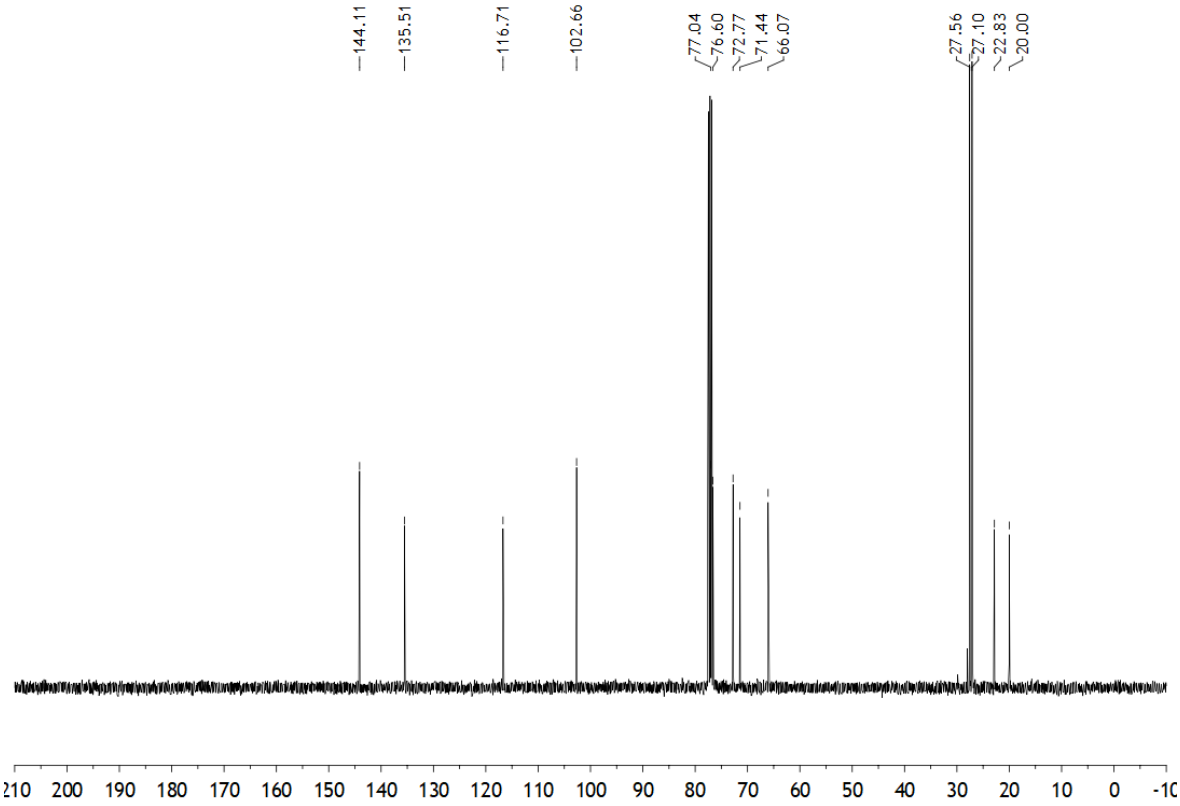
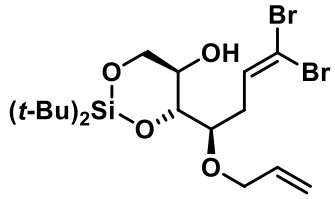
8.61
8.54
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


144.11
135.51
116.71
102.66
77.04
76.60
72.77
71.44
66.07
27.56
27.10
22.83
20.00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


Br
OH
Br
O
(t-Bu)2Si
O
O

514

0.96
1.07
1.09
1.00
3.58
1.97
1.11
1.08
0.92
1.00
1.03
9.00
9.07
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
145.06
134.67
117.46
98.04
78.93
72.66
69.28
68.42
61.50
52.82
28.00
27.91
21.62
21.40
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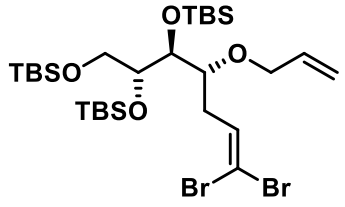
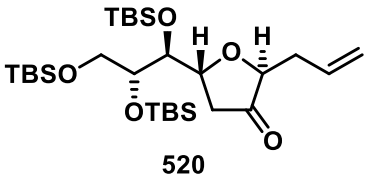

OTBS
TBSO
TBSO
O
Br
Br

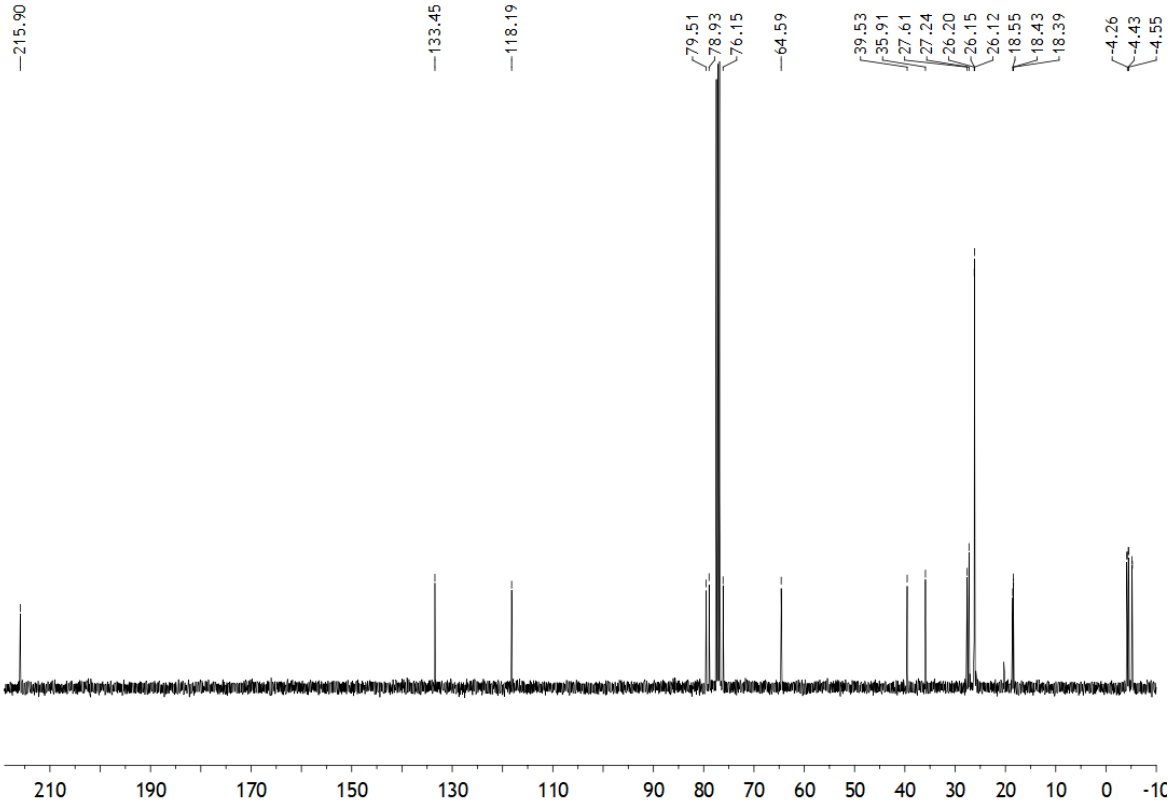
515

0.94
1.01
1.00
1.02
1.03
1.01
2.99
1.97
1.00
0.97
9.46
10.47
9.07
2.98
3.14
3.31
3.13
6.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
136.00
135.21
117.10
89.50
79.37
76.51
75.34
71.57
64.64
34.78
26.19
26.17
26.16
18.49
18.45
18.36
-4.42
-4.45
-4.47
-5.31
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


TBSO
H
O
H
TBSO
OTBS
O

520

1.00
2.07
0.98
1.03
1.06
1.09
1.06
0.99
0.96
0.98
1.08
1.02
9.44
9.02
8.98
3.00
3.10
6.06
3.13
2.95
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


215.90
133.45
118.19
79.51
78.93
76.15
64.59
39.53
35.91
27.61
27.24
26.20
26.15
26.12
18.55
18.43
18.39
-4.26
-4.43
-4.55
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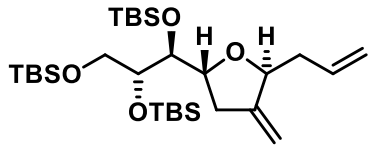
TBSO
H
O
H
TBSO
OTBS

480

1.00
1.02
1.06
1.00
0.99
0.93
0.95
0.96
1.00
0.97
0.95
0.90
0.92
2.06
17.74
9.60
3.06
3.08
2.94
3.17
5.93
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
151.48
135.34
116.85
104.78
79.35
79.26
78.97
75.70
64.27
39.99
36.02
27.60
27.23
26.19
26.18
26.15
18.60
18.52
18.38
-4.34
-4.37
-4.46
-4.48
-5.26
-5.30
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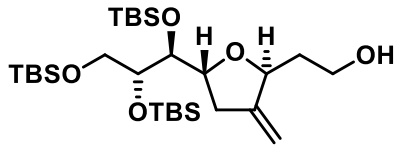
TBSO
H
O
H
OH
TBSO
OTBS

522

0.99
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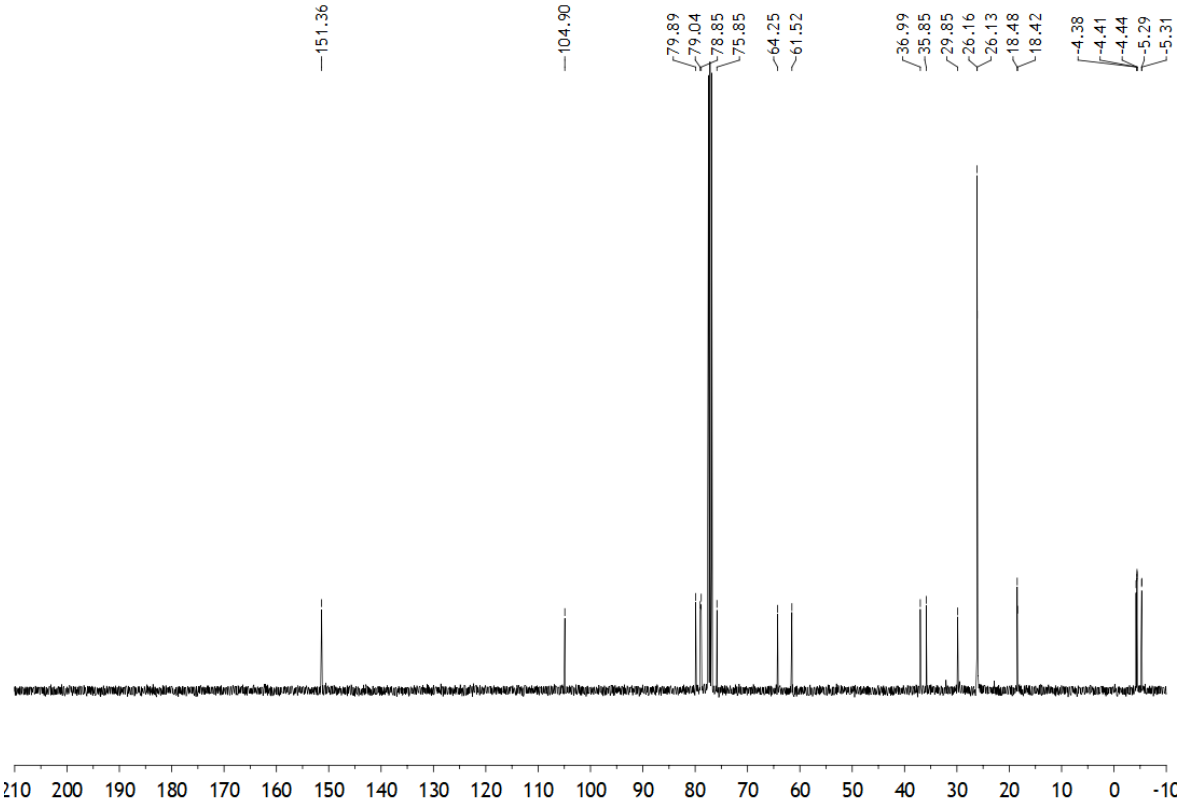
0.98
0.97
1.03
1.91
1.12
0.98
1.04
1.10
1.07
1.99
8.98
17.92
3.00
3.07
3.07
3.01
5.99
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5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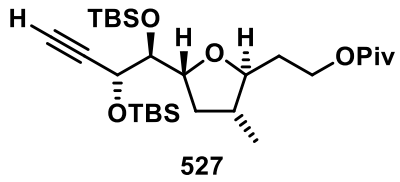
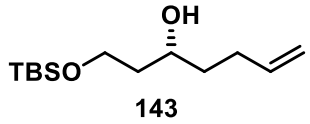
79.89
79.04
78.85
75.85
64.25
61.52
36.99
35.85
29.85
26.16
26.13
18.48
18.42
-4.38
-4.41
-4.44
-5.29
-5.31
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


H
TBSO
H
O
H
OPiv
OTBS

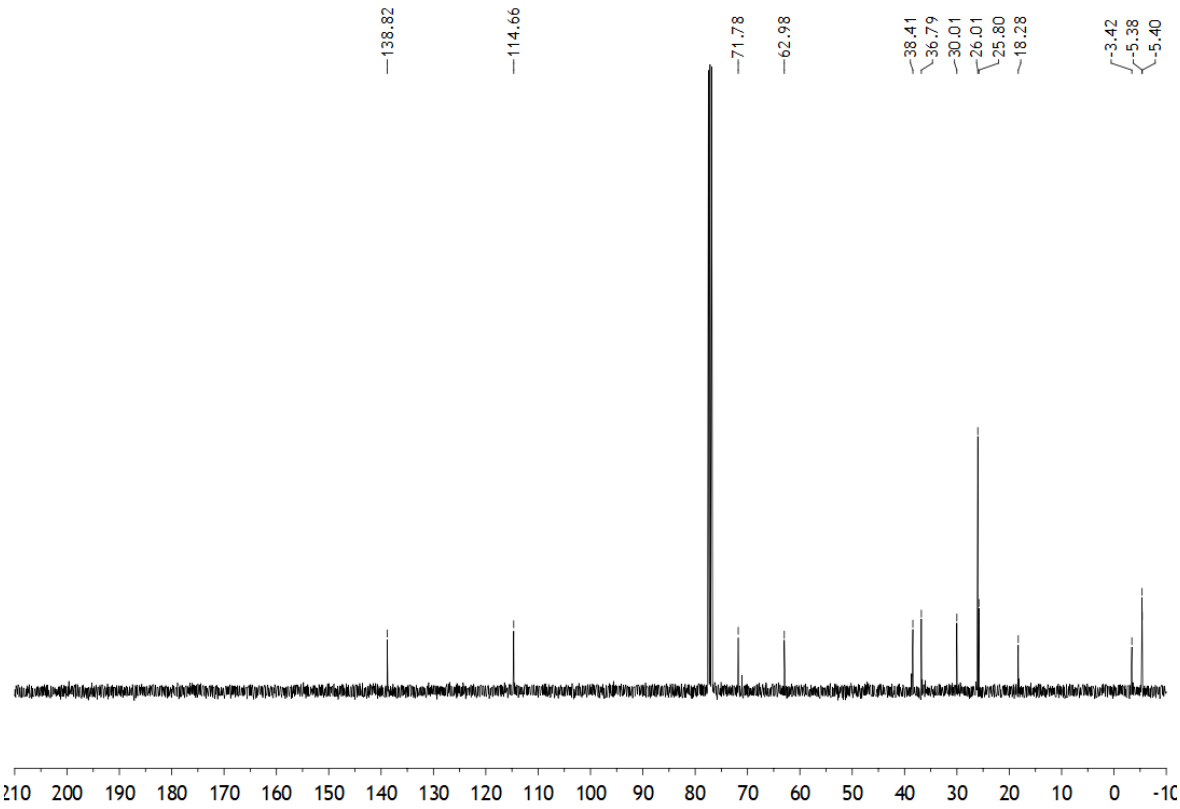
527

1.00
3.13
0.91
0.94
0.97
0.93
0.95
1.04
1.08
9.03
9.02
9.19
2.67
3.02
2.93
3.06
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
178.69
84.41
78.95
77.34
74.00
65.71
62.67
38.86
36.41
36.01
30.25
29.85
27.37
26.26
25.95
18.58
18.38
14.35
-3.93
-4.51
-5.02
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


OH
TBSO

143

1.00
1.01
0.98
1.03
1.98
0.96
2.09
3.00
1.08
8.99
6.04
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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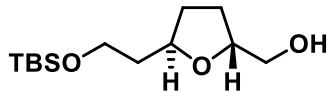
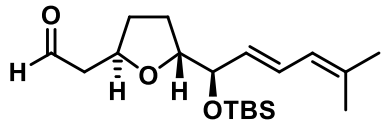
114.66
71.78
62.98
38.41
36.79
30.01
26.01
25.80
18.28
-3.42
-5.38
-5.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


TBSO
OH
H
O
H

148

1.00
1.05
1.04
1.03
1.96
1.08
2.15
2.20
1.06
1.13
9.14
6.24
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
78.95
76.64
65.20
60.57
38.90
32.38
27.63
26.09
18.48
-5.19
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


O
H
O
H
H
OTBS

587

0.92
1.00
1.00
0.99
0.98
1.02
0.98
0.93
1.02
0.92
1.05
7.11
1.11
9.02
3.04
3.04
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
201.57
135.38
129.64
127.86
124.79
82.68
75.43
74.46
49.66
32.44
29.86
27.15
26.13
26.01
18.44
18.40
-4.38
-4.62
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10