Towards the Total Synthesis of Amphidinolide C

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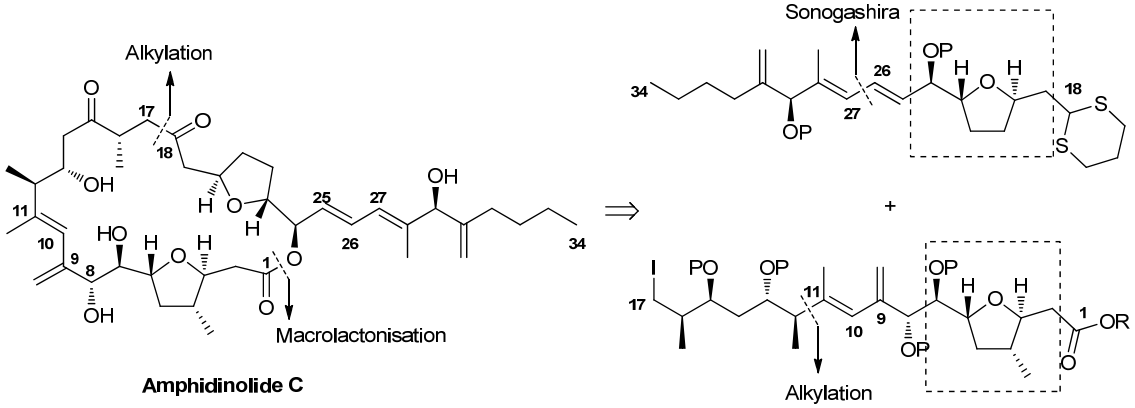
Abstract

Amphidinolide C is a macrolactone possessing two *trans*-2,5 substituted tetrahydrofurans embedded in the ring, isolated from the inner cells of acoel flatworms that live on algae and seaweed in the coral reefs of Okinawa. Amphidinolide C possesses complex molecular architecture and this combined with its potent biological activity make it an alluring target for synthesis.



Herein, is presented the convergent synthetic route towards the total synthesis of amphidinolide C, including the enantioselective total synthesis of two key intermediates C1–C17 and C18–C34 fragments.

The key transformations in the synthetic route of C1–C17 fragment include intramolecular conjugate addition of an oxygen nucleophile to obtain the *trans*-2,5 tetrahydrofuran (C1–C8 subunit), stereoselective boron-mediated aldol condensation, *E*-selective HWE olefination of a ketone followed by regioselective hydrostannylation of an enyne to give the desired diene system. Lastly, C1–C17 fragment was complete by nucleophilic addition of aldehyde with a vinylic anion.

Important features of the synthesesis of the C18–C34 fragment include kinetic resolution under Sharpless asymmetric epoxidation conditions to furnish the enantionmericly pure alcohol, Sonogashira coupling followed by Red-Al reduction of the enyne system to obtain the *E*,*E*-diene system.

Declaration

I declare that, except where explicit reference is made to the contribution of others, the substance of this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Selected portions of the work described herein have been published elsewhere as listed below:

Synthesis of the C1–C17 Fragment of Amphidinolides C, C2, C3 and F. J. Stephen Clark, Guang Yang, and Andrew P. Osnowski *Org. Lett.* **2013**, *15*, 1460. DOI: 10.1021/ol400482j

Synthesis of the C18–C34 Fragment of Amphidinolides C, C2, and C3. J. Stephen Clark, Guang Yang, and Andrew P. Osnowski *Org. Lett.* **2013**, *15*, 1464. DOI: 10.1021/ol4004838

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Guang Yang

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Prof. J. Stephen Clark

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最后我要感谢我的爸爸妈妈，我的亲戚朋友对我四年来学习和生活的鼓励和支持。

Abbreviations

Ac	Acetate
acac	Acetylacetonate
AIBN	Azobisisobutyronitrile
Bu	Butyl
Bz	Benzoyl
CI	Chemical ionization
COD	1,5-Cyclooctadiene
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
DBU	1,8-Diazabicycloundec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DET	*N*,*N*-Diethyltryptamine
DIBAL	Diisobutylaluminium hydride
DIAD	Diisopropyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DOSP	(*R*)-(+)-*N*-(*p*-dodecylphenylsulfonyl)prolinato
DPEPhos	*Bis*[(2-diphenylphosphino)phenyl] ether
dppp	1,3-*Bis*(diphenylphosphino)propane
dr	Diastereomeric ratio
EDCl	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
Et	Ethyl
ESI	Electrospray ionization
FAB	Fast Atom Bombardment
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide

HRMS	High resolution mass spectrometry
IBX	2-Iodoxybenzoic acid
IC_{50}	Half maximal inhibitory concentration
Im	Imidazole
KR	Kinetic resolution
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
LiDBB	Lithium 4,4'-di(tert-butyl)biphenylide
LRMS	Low resolution mass spectrometry
Me	Methyl
mp	Melting point
Ms	Methanesulfonyl
MTBE	Methyl *tert*-butyl ether
MTPA	α-Methoxy-α-trifluoromethylphenylacetic acid
NMO	*N*-Methylmorpholine-*N*-oxide
OTf	Triflate
p-ABSA	*p*-Acetamidobenzenesulfonyl azide
Piv	Pivaloyl
PMB	*p*-Methoxybenzyl
PMBTCA	*p*-Methoxybenzyl trichroloacetimidate
PMP	Methoxyphenyl
PNB	*p*-Nitrobenzyl
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
Py	Pyridine
TBAF	*tert*-Butyl ammonium fluoride
TBHP	*tert*-Butyl hydroperoxide
TBDPS	*Tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl

TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate

Table of Contants

1. Introduction

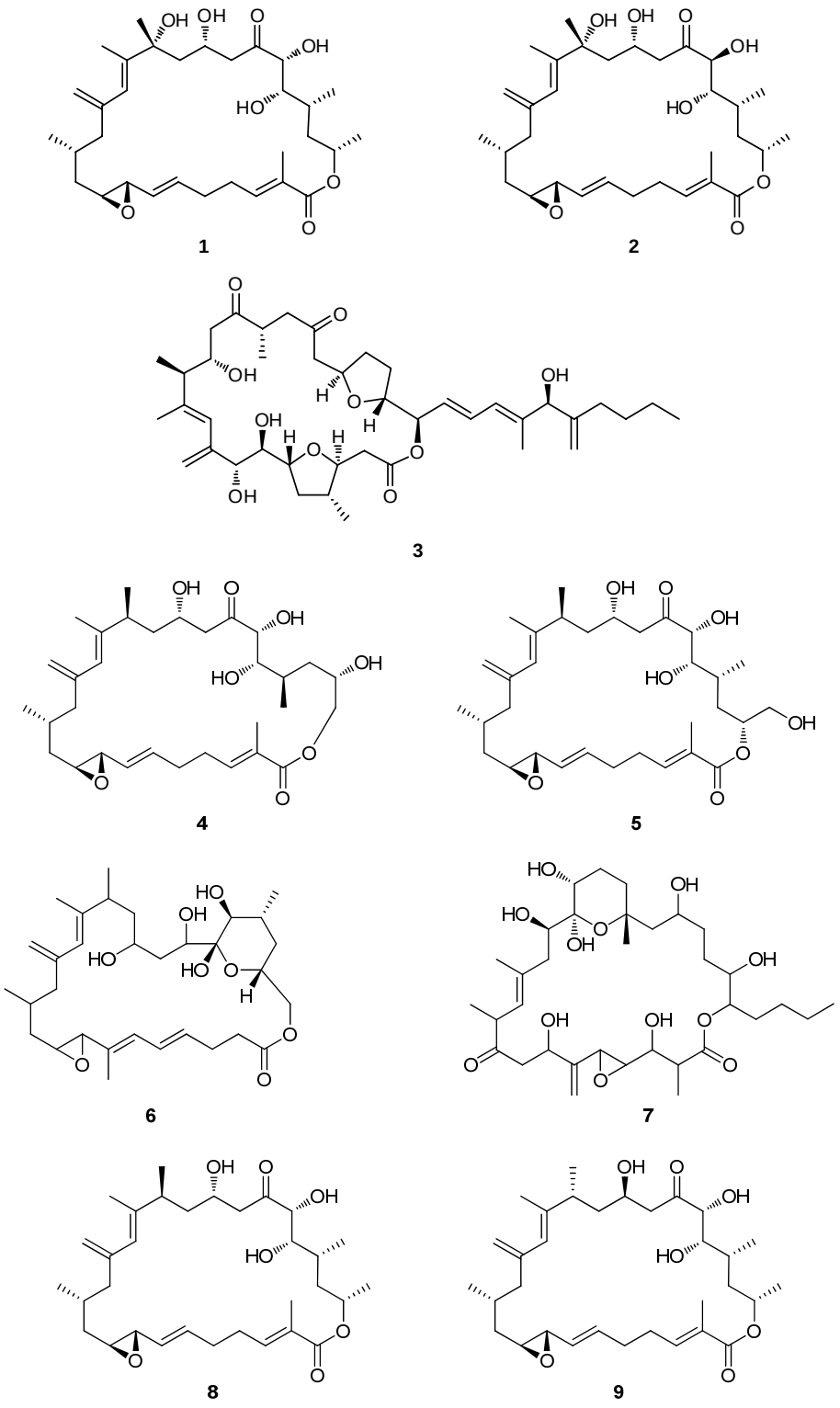
1.1 Overview of the Dinoflagellates *Amphidinium* sp.

Marine microorganisms such as bacteria, cyanobacteria, dinoflagellates, *etc.* are the producers of marine toxins that can act as fish and algal poisons. Bioactive substances isolated from marine invertebrates such as sponges and tunicates, which have attracted many natural product chemists. Among marine microorganisms, dinoflagellates have been important sources of marine toxins, and have been investigated worldwide by natural product chemists.[1a]

Symbiotic dinoflagellates of the genus *Amphidinium*, were first isolated from the inner cells of acoel flatworms, *Amphiscolops* sp., living on algae or seaweeds in Okinawan coral reefs.[1] Since 1980, *Amphidinium* sp. has been widely investigated by Kobayashi and co-workers, and several chemically interesting and biologically significant secondary metabolites have been isolated from this source.

1.2 Amphidinolide Family and Bioactivity

The amphidinolides are a large family of cytotoxic macrolides and polyketides. Numerous amphidinolide compounds have been isolated from *Amphidinium* sp. by Kobayashi.[1b] Some stuctures of biologically important amphidinolides are shown in Scheme 1. Specifically, most of these compounds were found to exhibit potent cytotoxic activity against murine lymphoma L1210 cells and human epidermoid carcinoma KB cells (Table 1).



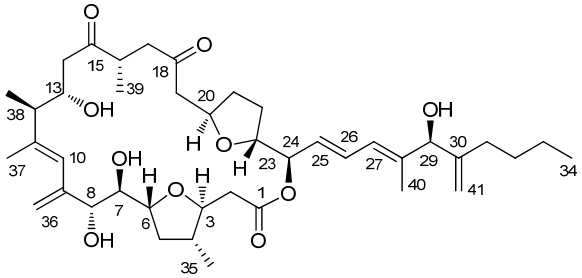
Scheme 1. Stuctures of the Various Amphidinolide Compounds

Table 1. Bioactivities of Amphidinolide Compounds

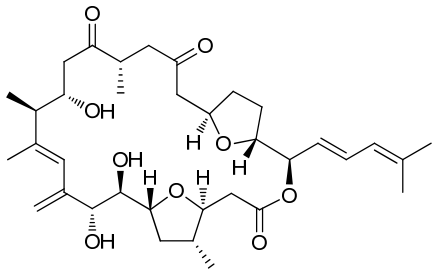
			Cytotoxicity (IC_{50}, $\mu g \cdot mL^{-1}$)	
Compound	Amiphidinolide	Lactone size	L1210	KB
1	B	26	0.00014	0.0042
2	D	26	0.019	0.08
3	C	25	0.0058	0.0046
4	G	27	0.0054	0.0059
5	H	26	0.00048	0.00052
6	L	27	0.092	0.1
7	N	26	0.00005	0.00006
8	B4	26	0.00012	0.001
9	B5	26	0.0014	0.004

1.3 Amphidinolides C and F

Amphidinolide C **3** was isolated from *Amphidinium* sp. by Kobayashi and coworkers in 1988.[1a] This compound is unique amongst 25-membered macrolides, having two tetrahydrofuran rings and vicinally located methyl groups (C37 and C38). Amphidinolide F, which was also isolated at the same time, differs only in structure of side chain at C24 (Scheme 2).



3 Amphidinolide C



10 Amphidinolide F

Scheme 2. Stucture of Amphidinolide C and F

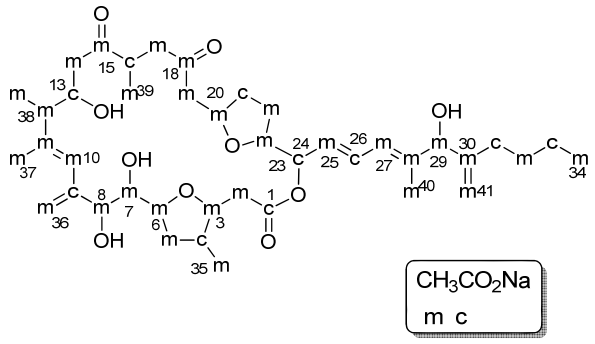
1.3.1 Isolation and Characterization

The dinoflagellate *Amphidinium* sp. was isolated from the inside of the cells of the Okinawan flatworm *amphisclops* sp. and cultured in the laboratory.[1b] The harvested cells were extracted with methanol/toluene, and the extract was subjected to repeated chromatography on silica gel with methanol/chloroform and hexane/acetone, followed by reversed-phase HPLC to give amphdinolide C in 0.0015% yield (wet weight) as a colorless amorphous solid.

The structure of the majority of amphidinolide C has determined by NMR analyses alone. Specifically, the gross structure of **3** was elucidated by 2D NMR data, and the relative stereochemistry of the C1 to C8 and C20 to C23 portions were assigned tentatively by NOESY observed for **3** and its 7,8-*O*-iso-propylidene derivative (for the assignment for amphidinolide C, see Scheme 2). Subsequent development of the modified Mosher method[16] enabled the absolute configuration of the stereocentres at C7, C8, C13, C29 to be assigned.[1d]

1.3.2 Proposed Biosynthesis of Amphidinolide C

A possible biosynthetic pathway of amphidinolide C was postulated by Kobayashi and co-workers. Feeding experiments performed by culturing the dinoflagellate *Amphidinium* sp. in the pure source of labeled sodium acetate (1-^{13}C, 2-^{13}C and 1,2-^{13}C, respectively) resulted in significant enrichment of the whole compound (Scheme 3).[2] The result suggested that four parts from C7 to C10, C16 to C19, C24 to C27 and C31 to C34 were likely to be diketide chains. Two irregular labeling patterns derived only from C2 of acetates were observed for C11 to C12 (m-m) and C28 to C30 (m-m-m). The remaining fragments were all derived from acetates or from acetates in which the carbonyl carbons were lost. This indicated that amphidinolide C is a unique non-successive mixed polyketide.



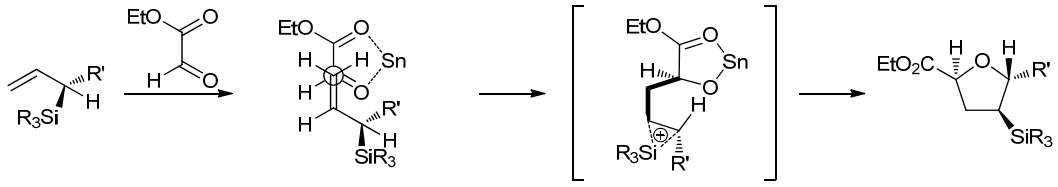
Scheme 3. Biosynthetic Study Using Labeled Sodium Acetate

1.4 Previous Synthetic Studies Concerning Amphidinolide C (& F)

Amphidinolide C possesses complex molecular architecture combined with potent biological activity, making it a challenging and interesting target for synthesis. Several internationally-leading synthetic groups are currently exploring its synthesis. The groups of Roush,[3] Armstrong,[4] Spilling,[5] Mohapatra,[6] Pagenkopf,[7] Figadère[8] and Carter[9] have reported the synthesis of significant fragments of amphidinolide C or F.

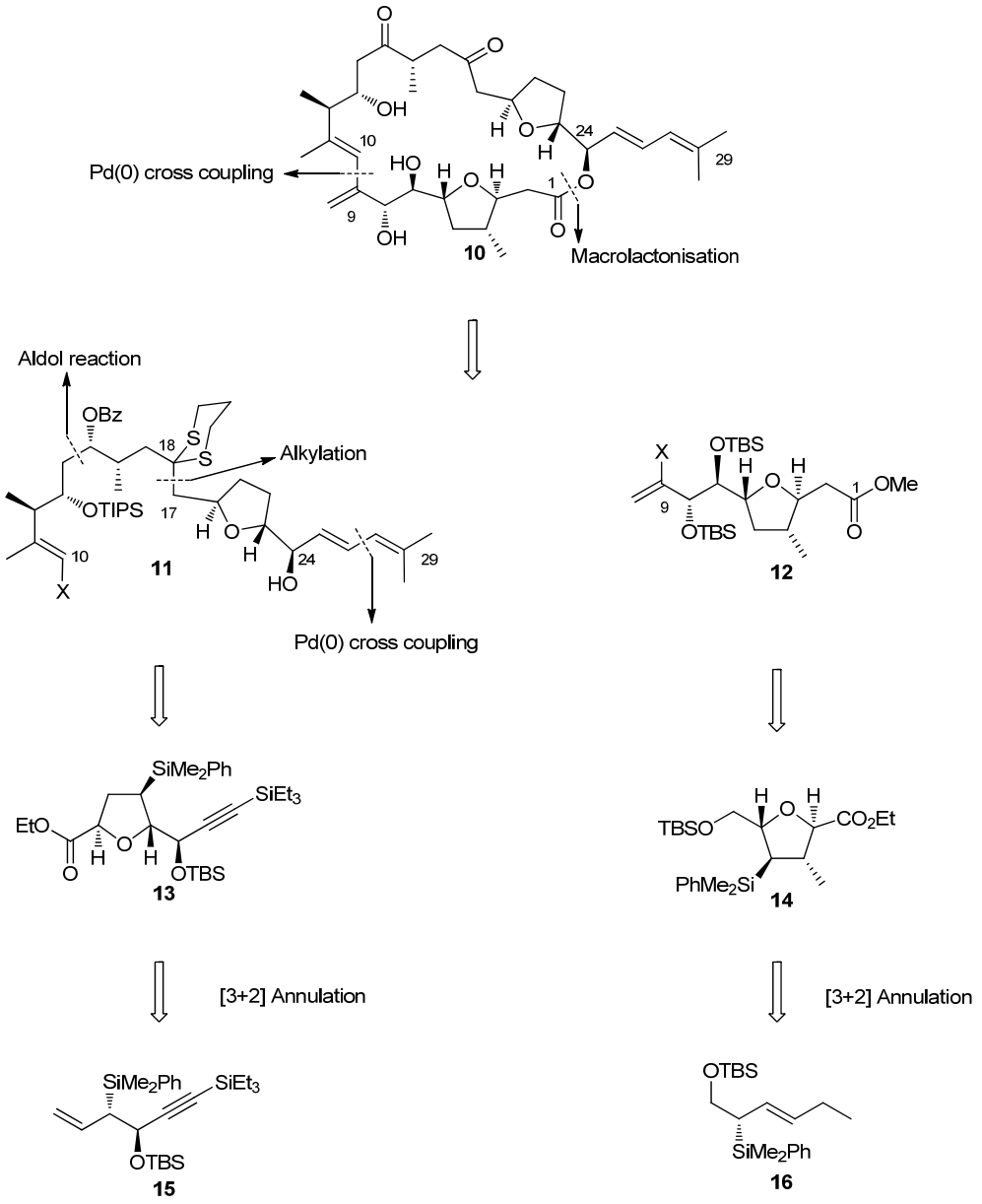
1.4.1 Roush Group Approach

Roush and co-workers have reported the synthesis of fragment C1-C9 and C11-C29 of amphidinolide F. They reported some efficient methodologies for the *trans*-tetrahydrofurans formation, the key reaction being a diastereoselective [3 + 2] annulation between a functionalised allyl silane and ethyl glyoxylate (Scheme 4).[10]



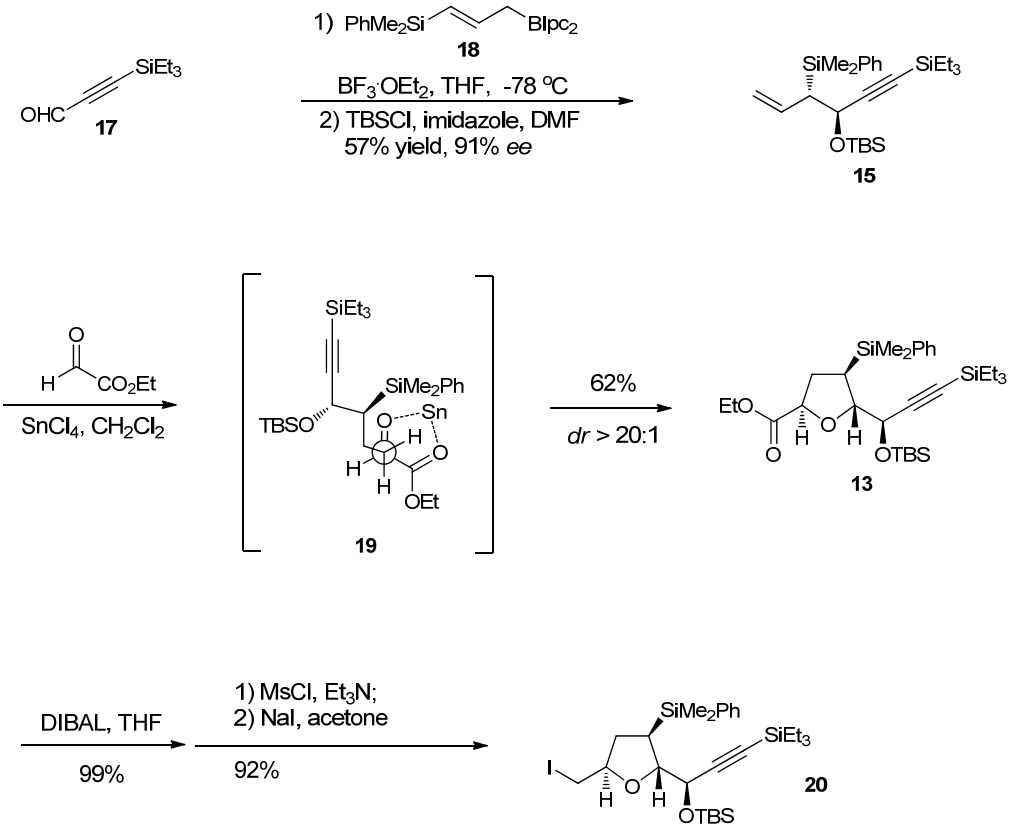
Scheme 4. Roush's Diastereoselective [3 + 2] Annulation

The retrosynthetic analysis is based on the disconnections between C9 and C10, which suggest a metal-mediated cross coupling in the forward direction, and at the lactone C-O bond, leading to C1-C9 fragment **12** and C10-C29 fragment **11** (Scheme 5). Fragments **11** and **12** were synthesised from tetrahydrofurans **13** and **14**, which were obtained by [3 + 2] annulation of ethyl glyoxylate with allylsilanes **15** and **16**, respectively.[3]



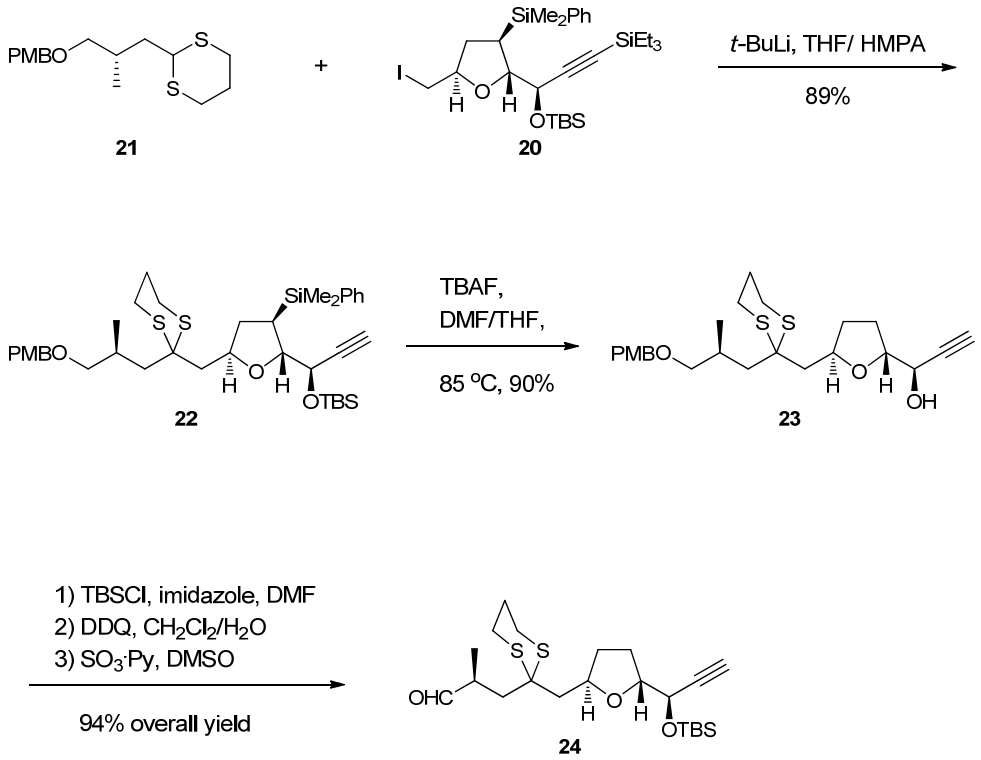
Scheme 5. Roush's Retrosynthetic Analysis of Amphidinolide F

The synthesis of the C20-C23 tetrahydrofuran utilised aldehyde **17** as a starting material (Scheme 6). Silylallyboration of **17** with (+)-pinene-derived silylallyborane **18** followed by TBS-protection afforded allylsilane **15** in 57% overall yield (91% *ee*).[3a] Treatment of **15** with ethyl glyoxylate in the presence of $SnCl_4$ delivered [3 + 2]-annulation adduct **13** (consistent with transition state **19**) in 62% yield as a single diastereoisomer,[3a] which was further converted to iodide **20** in 3 steps with 91% overall yield.



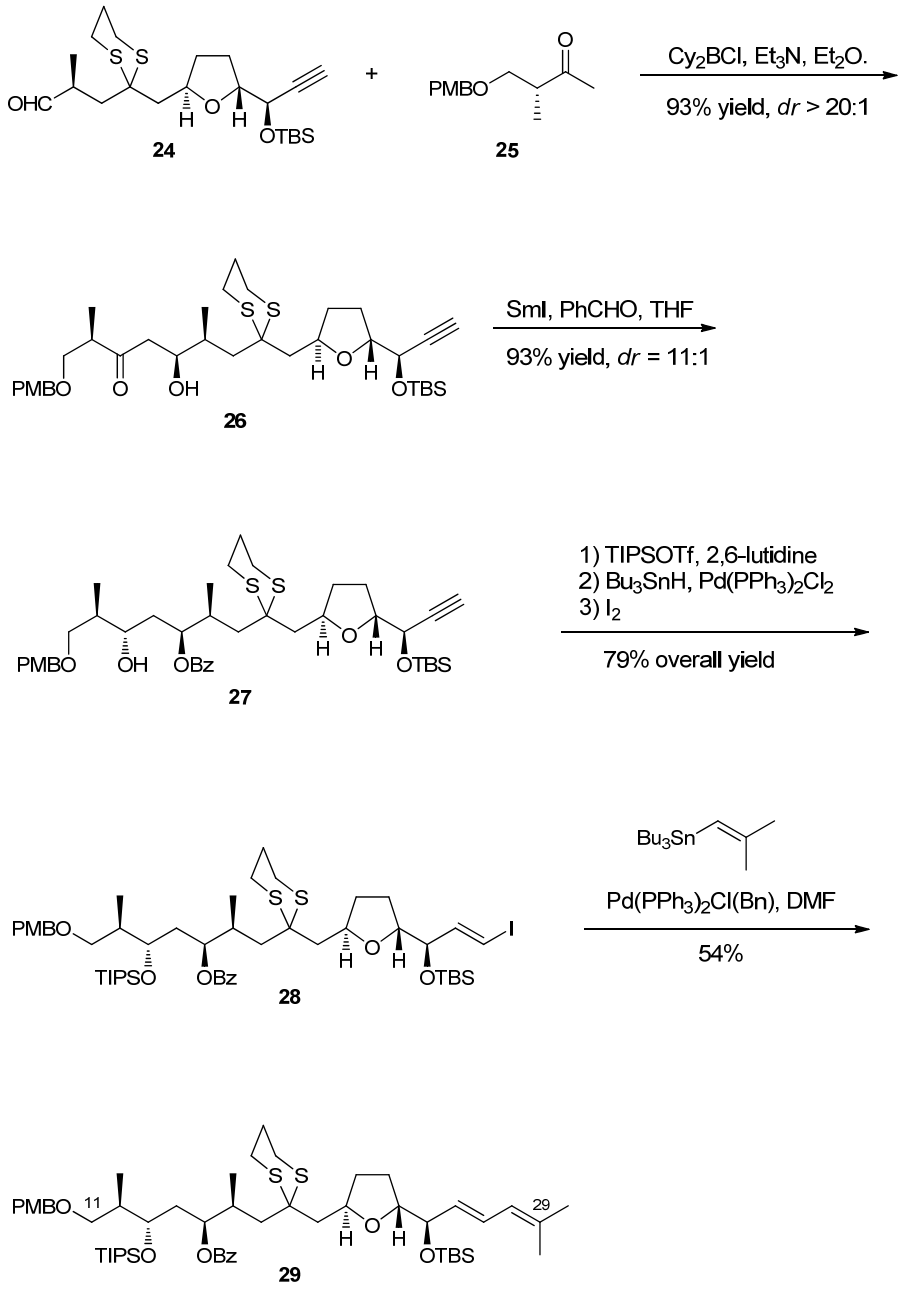
Scheme 6. Roush's Synthesis of THF Compound **20**

Following this, compound **22** was prepared by umpolung coupling between dithiane **21** and iodide **20** using *t*-BuLi as a base (Scheme 7). PMB ether **22** was then transformed into aldehyde **24** in 4 steps and with high yield.



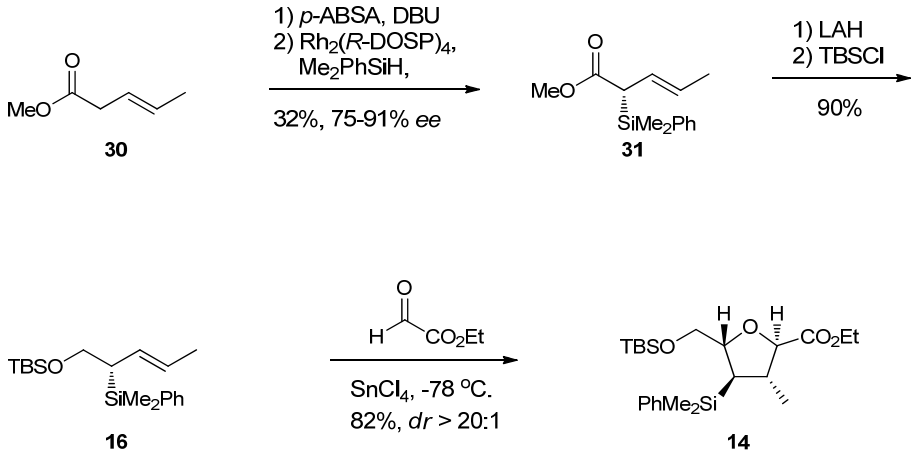
Scheme 7. Synthesis of Aldehyde **24**

Treatment of the aldehyde **24** with the dicyclohexylboron enolate derived from methyl ketone **25,** afforded aldol product **26** as a single diastereoisomer in excellent yield (93%, Scheme 8). Evans-Tishchenko reduction of β-hydroxy ketone **26** afforded an 11:1 mixture of diastereoisomers, with the desired *anti*-1,3-benzoate **27** as the major product. Vinylic iodide **28** was then prepared in 3 steps. The C11-C29 fragment **29** was completed by Stille coupling.



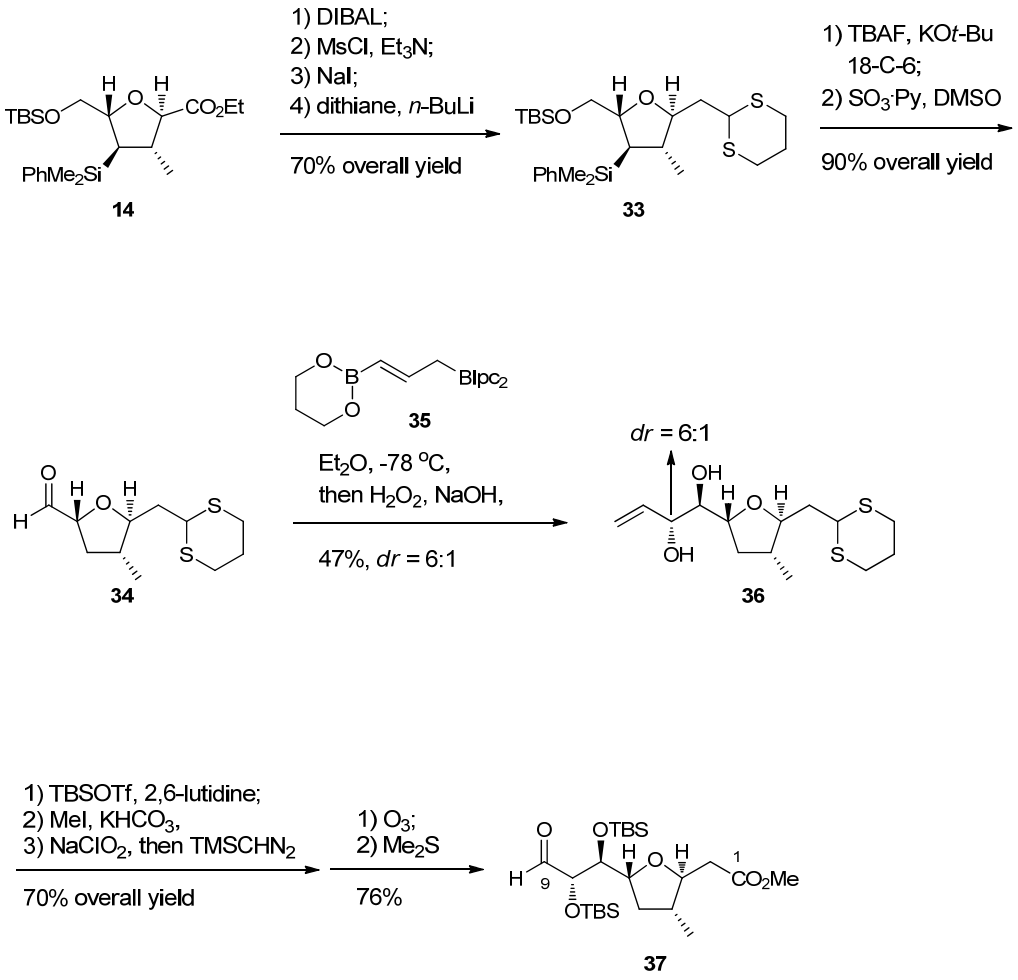
Scheme 8. Roush's Synthesis of the C11-C29 Fragment **29**

Following the success of the synthesis of the C11-C29 fragment, the synthesis of the C1-C9 fragment[3b] started from compound **30**, which was converted into the allylic silane **31** in 75-91% *ee* by enantioselective Rh(II)-catalysed insertion into the Si-H bond of phenyldimethylsilane (Scheme 9).[12] Subsequently, compound **31** was reduced and protected as the corresponding TBS ether to deliver compound **16**. With this intermediate in hand, the same methodology (see scheme 6)[10] was used to construct the required 2,5-*trans*-tetrahydrofuran **14** *via* a $SnCl_4$-promoted [3 + 2] annulation reaction of crotylsilane **16** and ethyl glyoxalate. The reaction provided **14** in 82% yield as a single diastereoisomer.



Scheme 9. Roush's Synthesis of *trans*-Tetrahedrofuran **14**

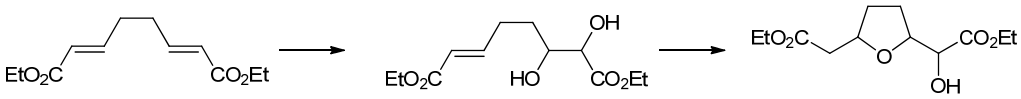
Tetrahydrofuran **14** was converted into *tri*-substituted tetrahydrofuran **34** in 6 steps (Scheme 10). Treatment of this compound with Brown's γ-borylallylborane **35** afforded *anti*-diol **36** in 47% yield with 6:1 diastereoselectivity,[13] which was then converted into aldehyde **37** in 5 steps.



Scheme 10. Roush's Synthesis of the C1-C9 Fragment **37**

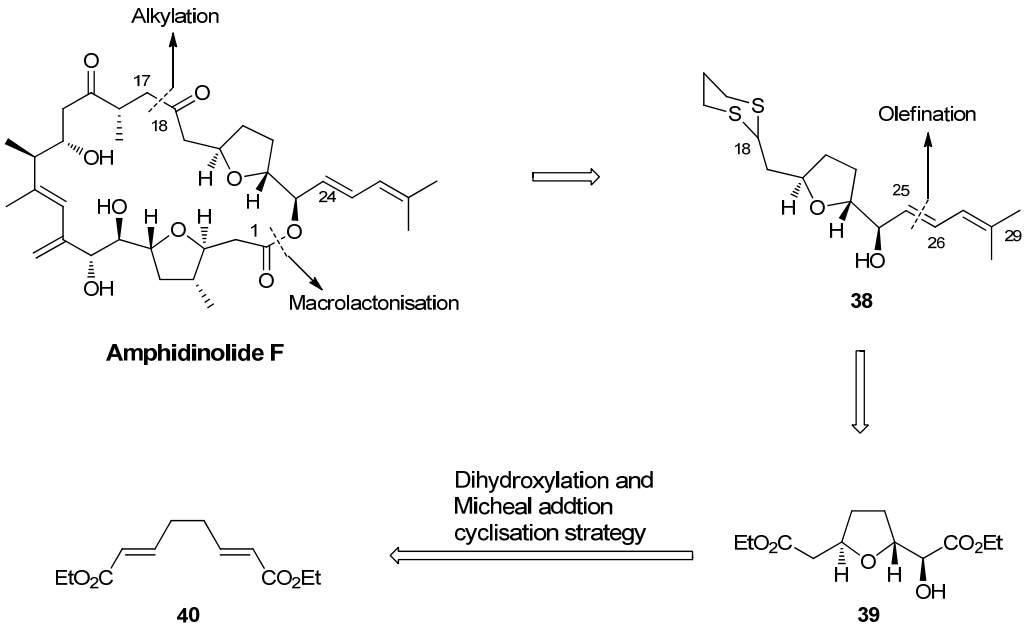
1.4.2 Armstrong Group Approach

Armstrong and co-workers reported the synthesis of the C18-C29 fragment of amphidinolide F.[4] Key featuers of the route included Sharpless dihydroxylation of just one of the alkenes in the dienoate, followed by an oxo-Michael addition to construct the *trans*-THF system (Scheme 11).



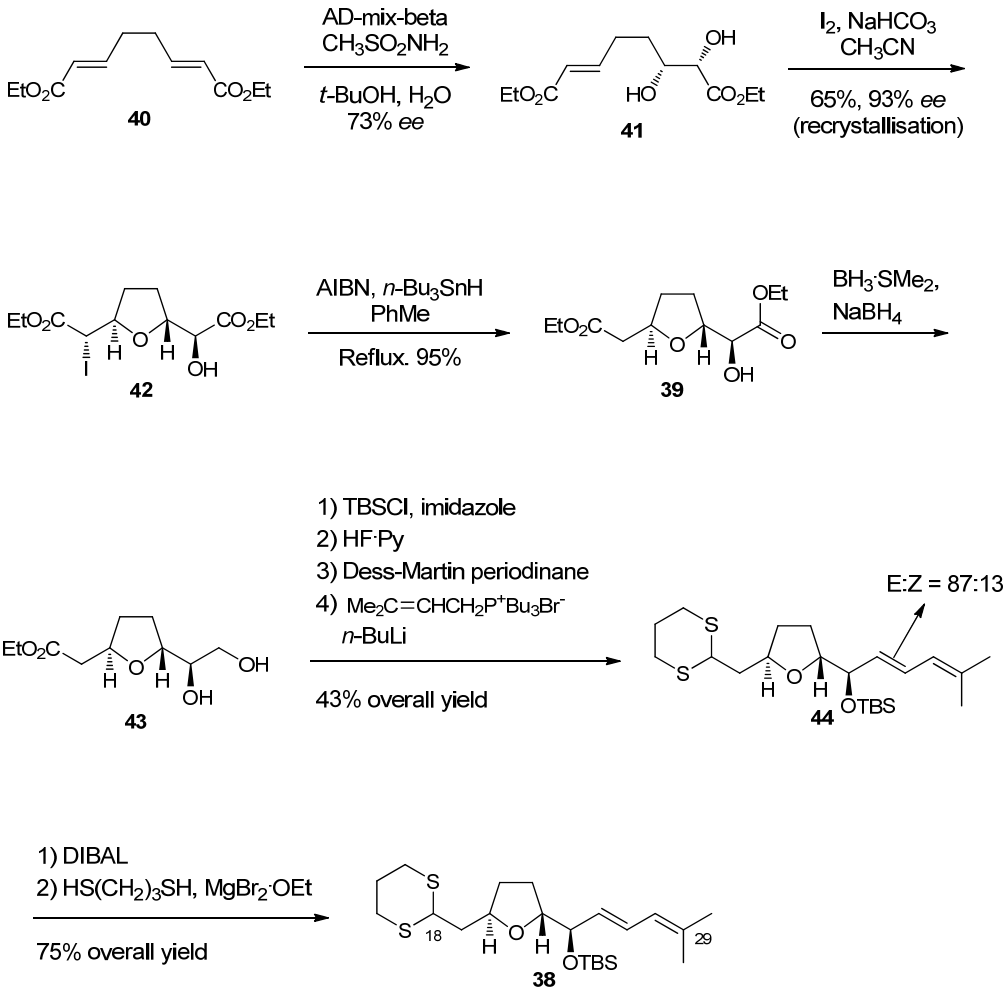
Scheme 11. Armstrong's Strategy for the THF formation

Disconnection at C17-C18 suggested umpolung coupling of the dithiane acetal **38** (Scheme 12). Further disconnection between C25 and C26 led to compound **39**, containing a substituted tetrahydrofuran, which could be synthesised from diene dionate **40** by Sharpless asymmetric dihydroxylation (Sharpless AD reaction) at one of the alkenes followed by oxo-Michael addition.[14]



Scheme 12. Armstrong's Retrosynthetic Analysis of Amphidinolide F

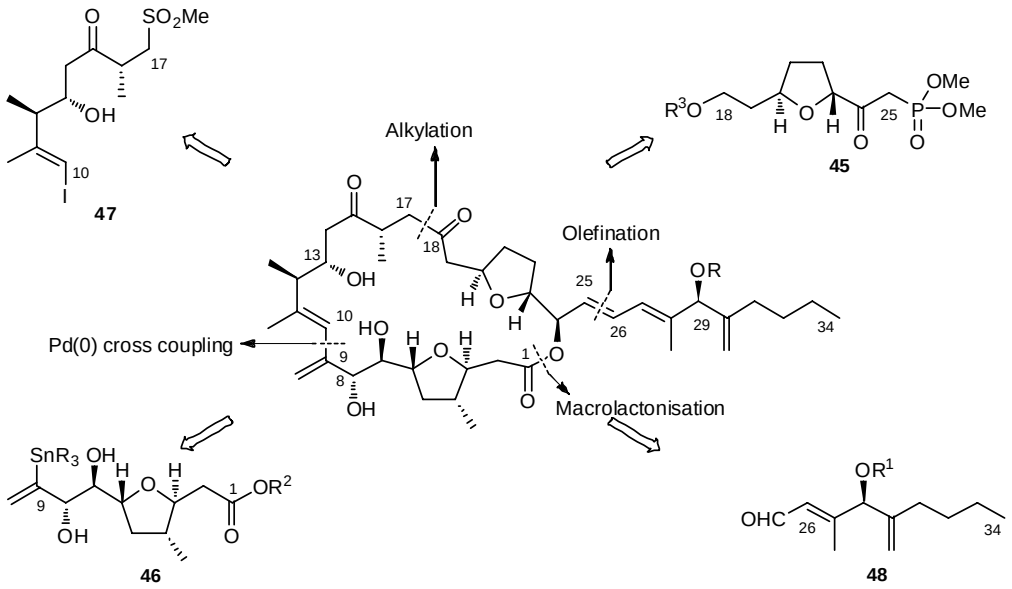
Application of standard Sharpless AD conditions to compound **40** in the presence of AD-mix β and methanesulfonamide afforded the diol **41** in 85% yield. The enantiomeric excess of compound **41** was determined by chrial HPLC and found to be 73%. Following this, intramolecular iodocyclisation was used to construct the THF **42** from **41** with 65% yield and 93% *ee* along with 20% of the cis tetrahydrofuran(Scheme 14).[15] Deiodonation of **42**, by treatment with AIBN in the presence of *n*-BuSnH in toluene, gave diester **39**. Selective reduction of the ester group adjacent to the hydroxyl group was accomplished using $BH_3{\cdot}SMe_2$ and catalytic $NaBH_4$.[16] Finally, the C18-C29 fragment **38** was synthesised from diol **43** in a further 5 steps and in 22% overall yield.



Scheme 14. Armstrong's Synthesis of the C18-C29 fragment **38**

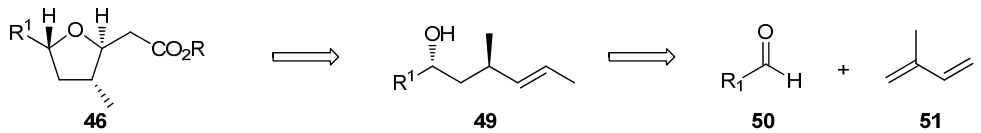
1.4.3 Spilling Group Approach

The strategy of the Spilling group was to divide amphidinolide C into four different subunits: the northern **45** (C18-25),[5a] southern **46** (C1-C9),[5b] and western **47** (C10-C17) subunits, and the side chain **48** (C26-C34, Scheme 15).



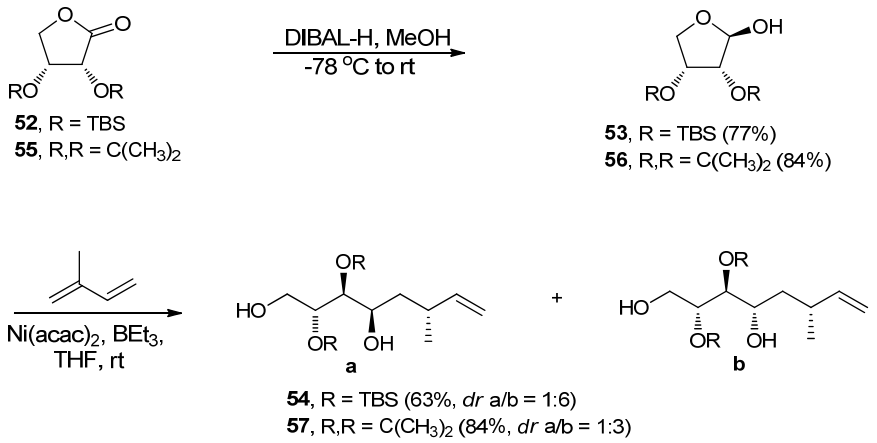
Scheme 15. Spilling's Retrosynthesis Analysis of Amphidinolide C

Spilling proposed that the formation of fragment **46** could be achieved by cyclisation of the alcohol **49**, which could in turn be synthesised from aldehyde **50** and diene **51** using a homoallylation reaction promoted by Ni catalyst.[17]



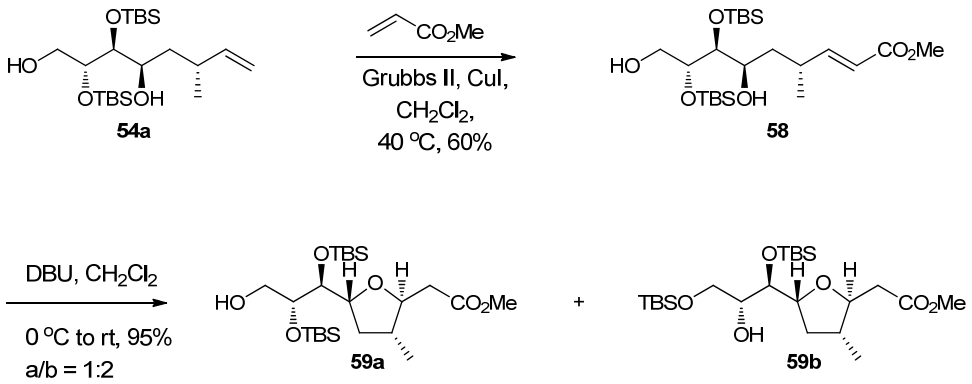
Scheme 16. Spilling's Retrosynthesis Analysis for the Northern Fragment **46**

In a forward sense, the synthesis commenced from lactones **52** and **55**, which differed only in diol protecting group. DIBAL reduction gave lactols **53** and **56** which were subjected to Ni mediated homoallylation[17] to provided the diastereoisomeric alcohols **a** and **b** (the combined yield was 63% and ratio was 1:6 ratio for **54**, an 84% yield and a 1:3 ratio was obtained for **57**). Unfortunately, the minor isomer **54a** and **57a** were the desired compounds (Scheme 17).



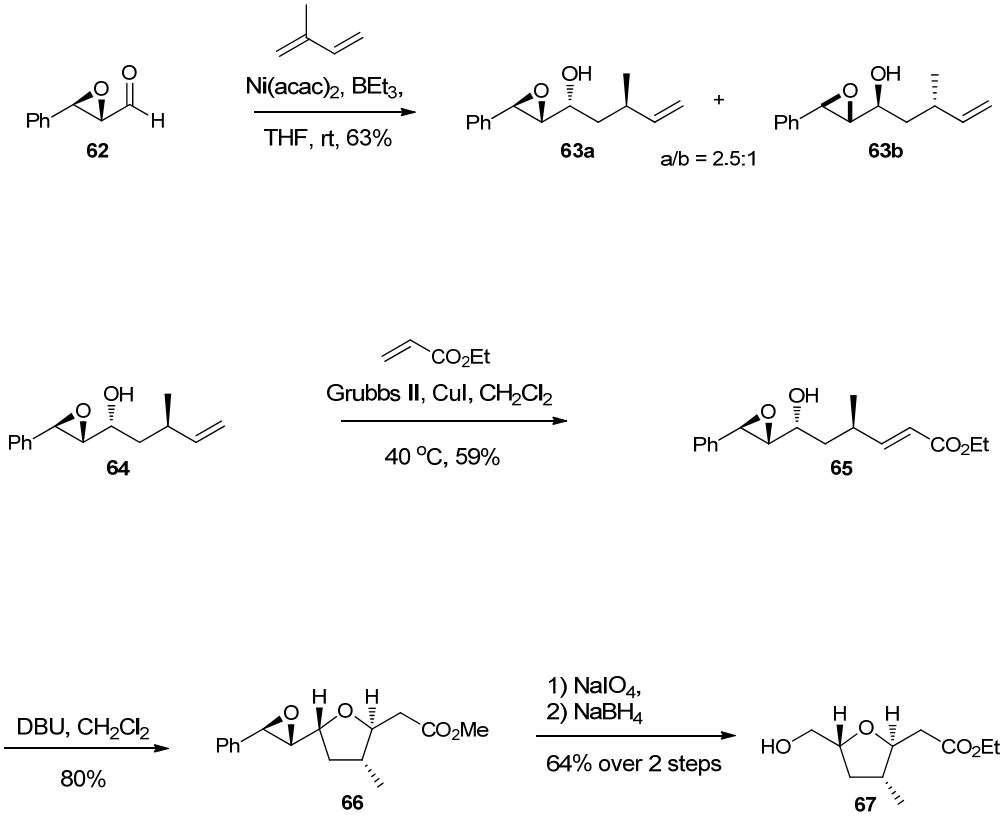
Scheme 17. Homoallylation of Erythrolactol

The minor product **54a**, that with the correct stereochemistry, was transformed into the α,β-unsaturated methyl ester **58** by cross-metathesis. Cyclization in the presence of DBU led to the 2,5-*trans*-tetrahydrofuran **59a** (Scheme 18). However, during the cyclization process, concomitant migration of the secondary silyl group to the primary alcohol to give **59b** was observed (**59a**/**59b** = 1:2).



Scheme 18. Cross Metathesis and Cyclization from a Homoallylation.

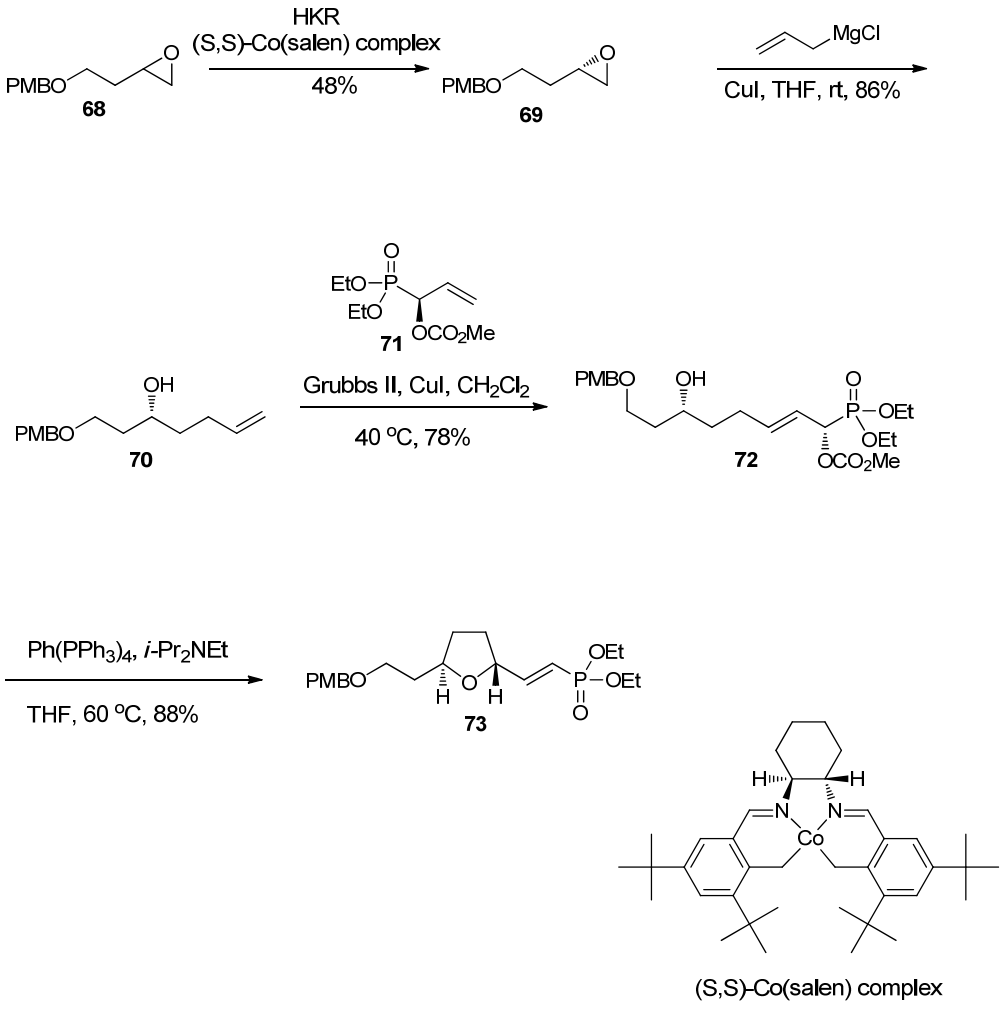
As a consequence of the limitations of the above route, an alternative approach was sought. With the epoxyaldehyde **62** in hand, homoallylation furnished a separable mixture of diastereoiosmers **63a** and **63b** in a 2.5:1 ratio and in 63% combined yield (Scheme 19). Cross metathesis of **64** with ethyl acrylate gave α,β-unsaturated methyl ester **65** which was cyclised by treatment with DBU to give **66** as a single diastereoisomer. Cleavage of the epoxide **66,** by treatment with $NaIO_4$ in acetonitrile/water (2:1), afforded the aldehyde, which was reduced *in situ* with $NaBH_4$ in MeOH to afford the desired alcohol **67**.



Scheme 19. An Alternative Synthetic Pathway to **67**

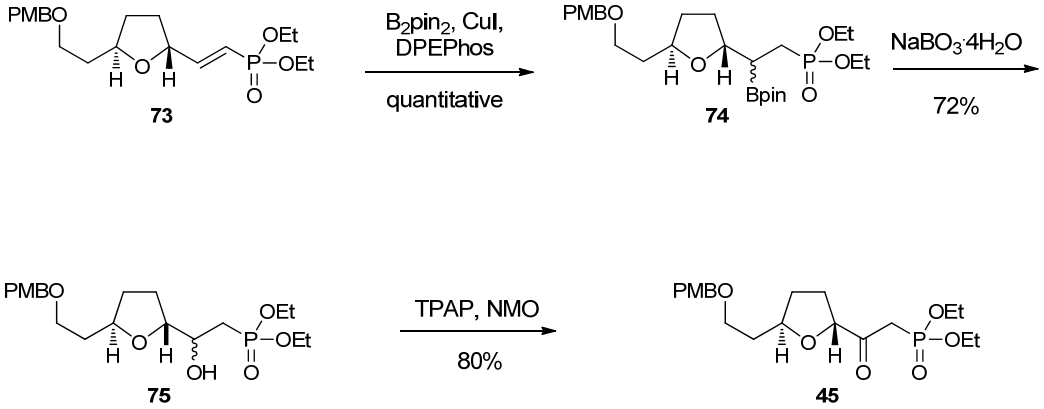
In the subsequent publications,[5b] the group reported the synthesis of the northern C18-C25 fragment **45**, and coupling to three side chain aldehydes to form the C18-C34 unit of amphidinolide C, the C18-C29 unit of amphidinolide F, and an additional synthetic analogue.

The known (*S*)-epoxide **69**[18] was obtained by hydrolytic kinetic resolution[19] of the racemic epoxide **68** in 48% yield and greater than 95% *ee* (Scheme 20). Grignard addition of allyl magnesium chloride to **69** afforded olefin **70**. After cross metathesis of **70** and phosphonate **71**, alkenol **72** was obtained as a 9:1 mixture of *E*- and *Z*-isomers. The palladium(0)-catalysed cyclisation of **72** gave the *trans*-THF compound **73** as major product (88%) along with 5-8% of undesired *cis* diastereoisomer.



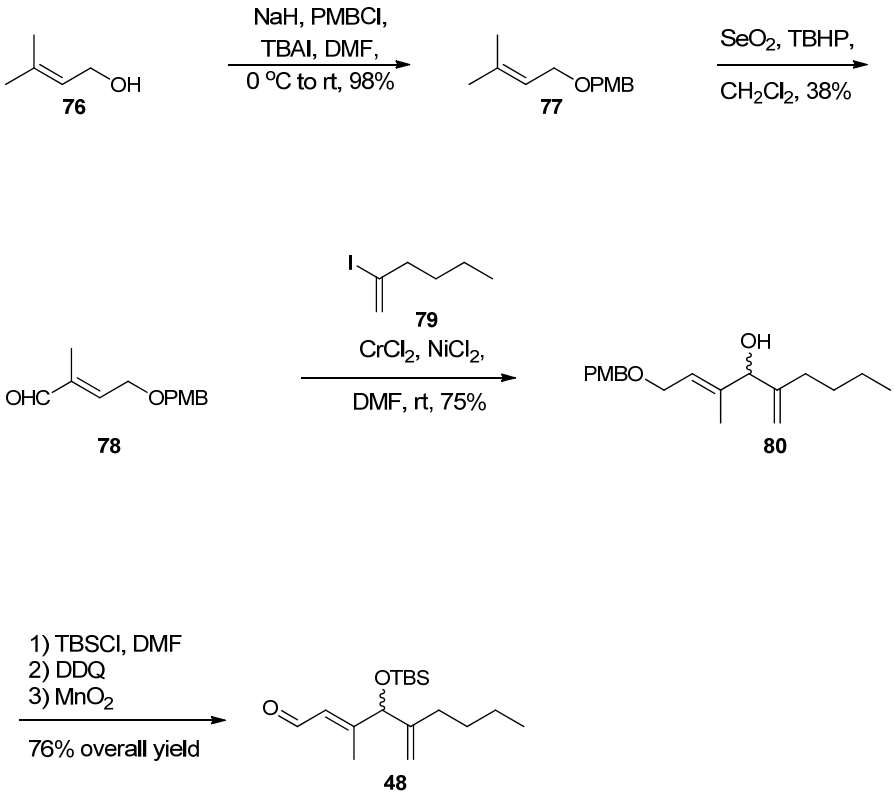
Scheme 20. Spilling's Synthesis of the 2,5-*trans*-tetrahydrofuran **73**

With the key THF fragment in hand, borylation,[20] using *bis*(pinacolato)diboron (B_2pin_2) in the presence of copper(I) iodide and *bis*(2-diphenylphosphinophenyl)ether (DPEPhos), furnished the desired β-borylated product **74** in quantitative yield (Scheme 21). The β-borylated product **74** was then oxidised by $NaBO_3$ to afford the β-hydroxy phosphonate **75**. Oxidation of **75** was achieved using tetrapropylammonium perruthenate (TPAP)[21] and NMO to give β-ketophosphonate **45**, thus completing the synthesis of the northern C18-C25 fragment.



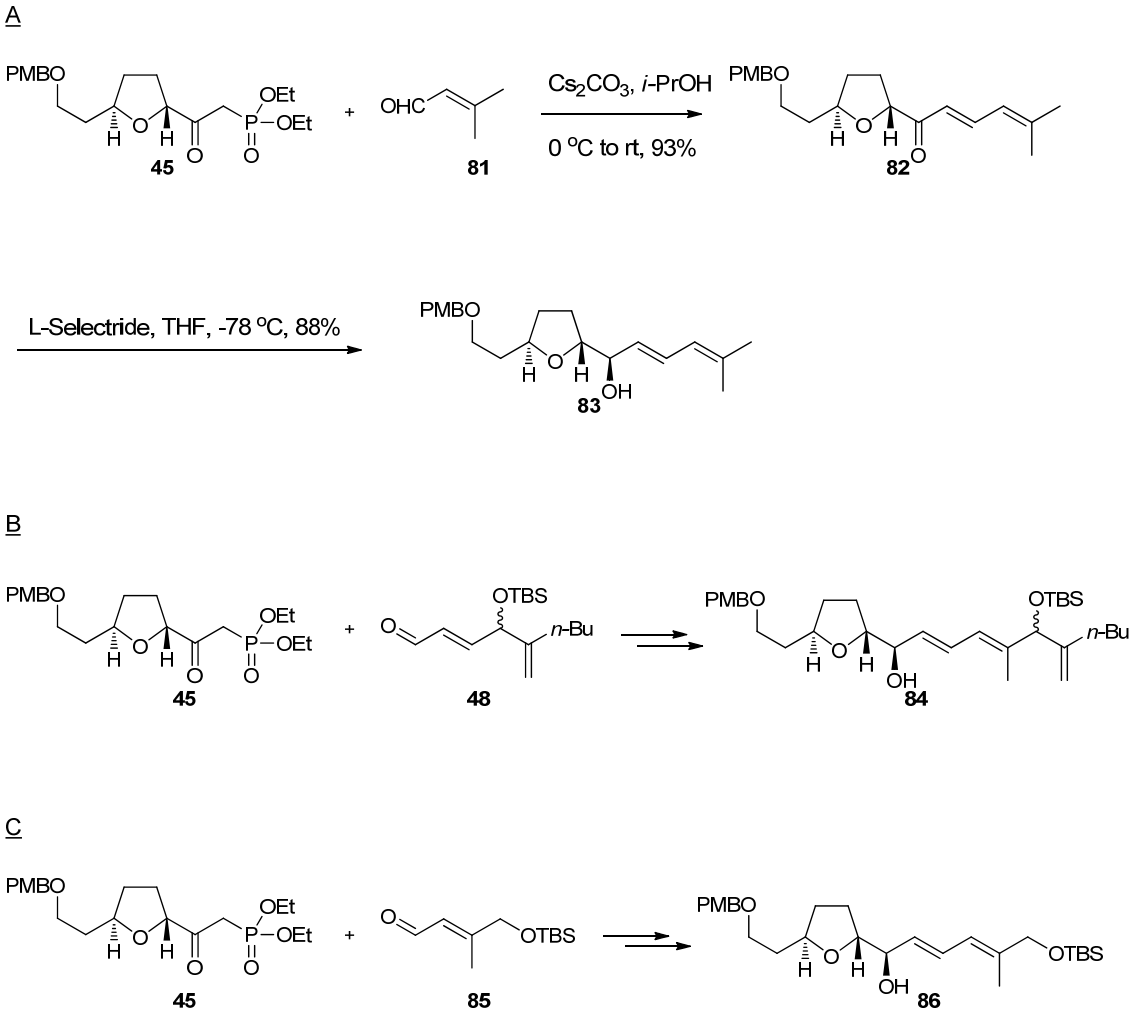
Scheme 21. Synthesis of Northern Fragment **45**

The synthesis of the sidechain **48** started from the commercially available allylic alcohol **76** (scheme 22). PMB protection of the alcohol, followed by SeO_2 allylic oxidation of **77** gave the aldehyde **78**. Nozaki-Hiyama-Kishi (NHK) reaction coupled with aldehyde **78** and vinylic iodide **79** to yield allylic alcohol **80** as a racemic mixture. The alcohol **80** was then converted into the enal **48** using a three-step sequence.



Scheme 22. Spilling's Synthesis of the Racemic Sidechain **48**

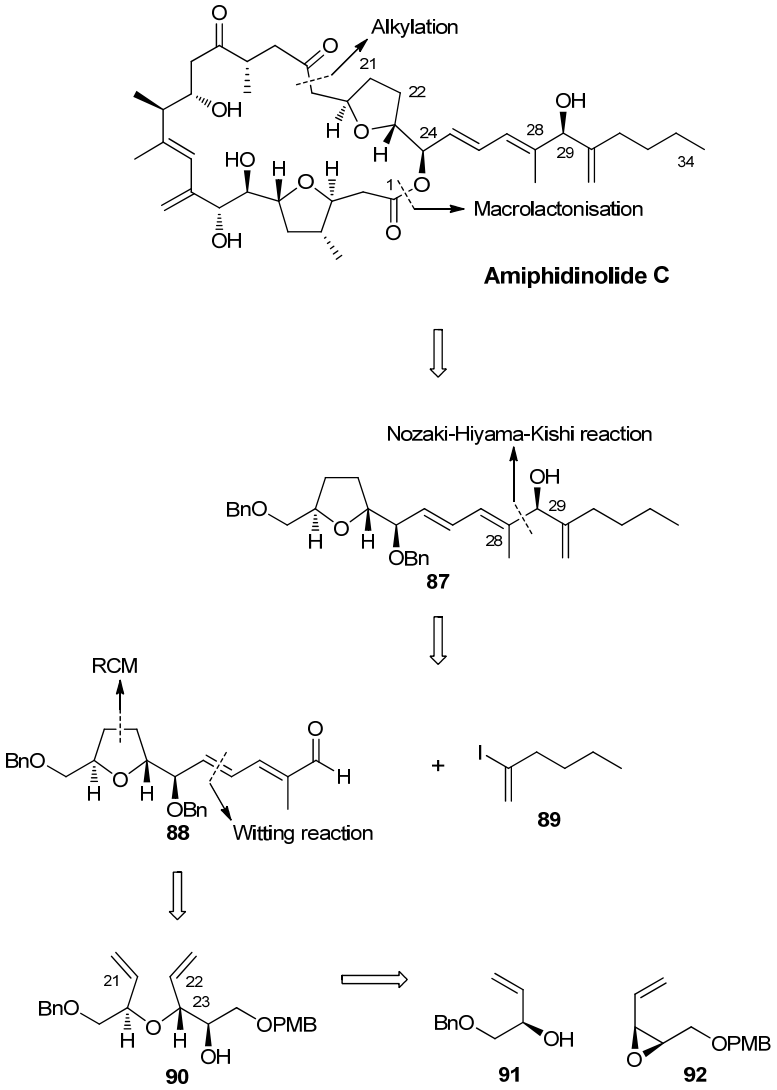
Finally, a Horner-Wadsworth-Emmons (HWE) reaction was used to couple northern fragment **45** with a variety of aldehyde side chains (**81**, **48** and **85)**, in the presence of Cs_2CO_3 in *i*-PrOH. Subsequent ketone reduction with L-selectride gave the conjugated dienes **83**, **84** and **86** diastereoselectively (Scheme 23).



Scheme 23. Spilling's Synthesis of the Northern Fragments

1.4.4 Mohapatra Group Approach

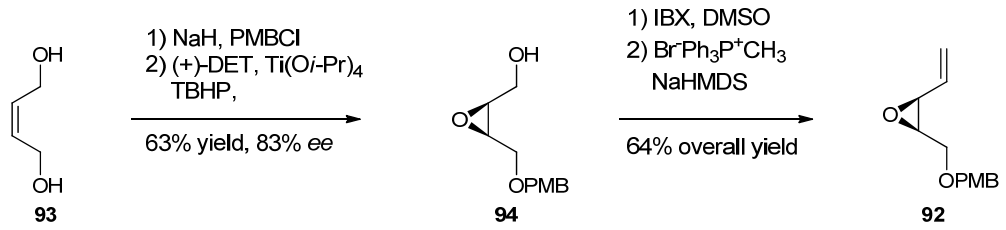
In Mohapatra's work,[6] the synthesis of the C19–C34 segment of amphidinolide C is described. The key steps include *trans*-THF system formation by Lewis acid catalysed epoxide **92** opening with the alcohol **91** followed by ring-closing metathesis of diene **90**, and Nozaki–Hiyama–Kishi coupling reaction between aldehyde **88** and vinylic iodide **89**.



Scheme 24. Mohapatra's Retrosynthetic Analysis of Amphidinolide C

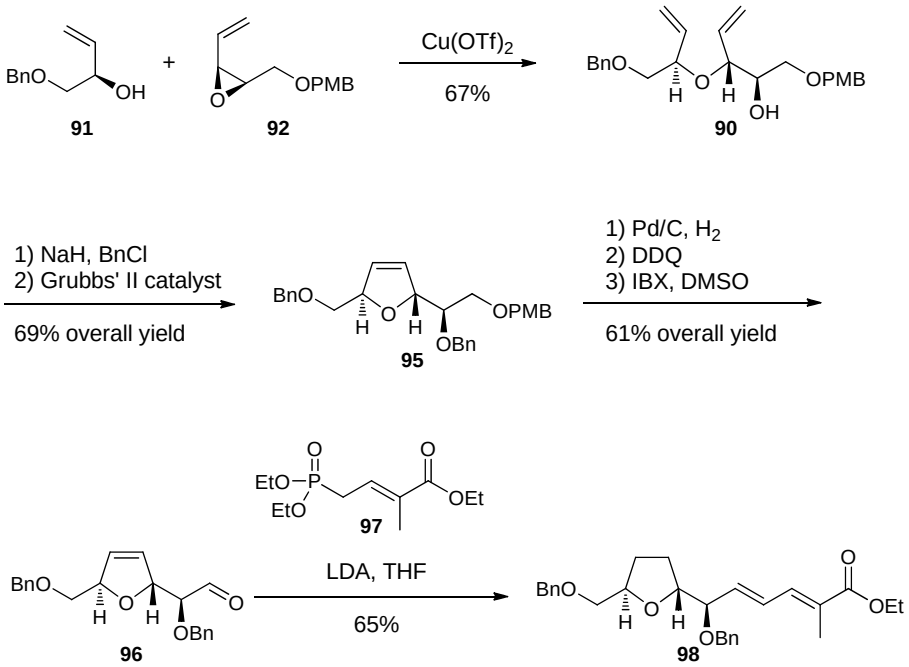
The synthesis of **92** began with *cis*-2-butene-1,4-diol **93** which was converted into **94** employing the Sharpless asymmetric epoxidation (Scheme 24). Subsequent oxidation of **94** using 2-iodoxybenzoicacid (IBX) in DMSO followed by Wittig reaction produced the vinylic epoxide **92** in good yield

.



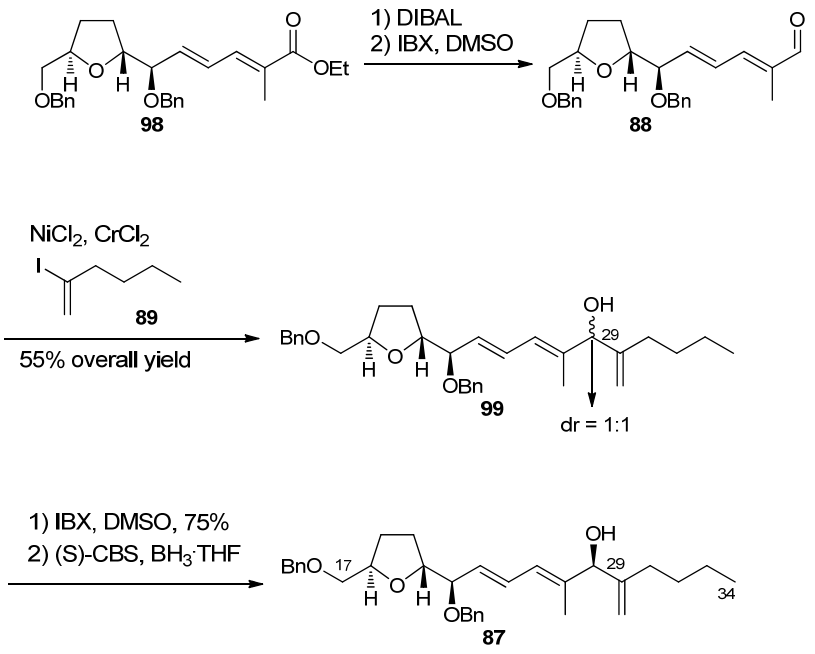
Scheme 24. Mohapatra's Synthesis of Epoxide **92**

The coupling reaction between **91** and **92** was carried out in the presence of catalytic amount of $Cu(OTf)_2$ to afford the diene moiety **90** in 67% yield (Scheme 25).[22] Sequence of ring-closing metathesis catalysed by Grubbs II catalysis delivered the compound **95**. Wittig reaction between **97** and the aldehyde **96**, which was derived from **95** in 3 steps, furnished the diene **98** in good yield and regioselectivity.



Scheme 25. Diastereoselective Synthesis of Diene **98**

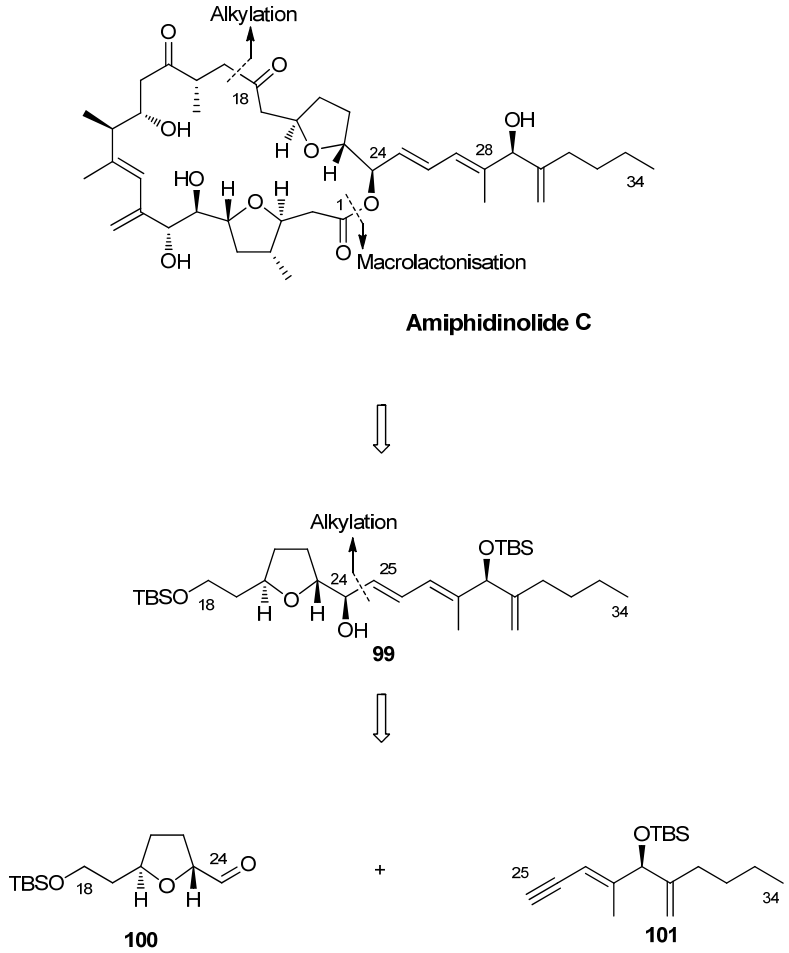
With the intermediate **98** in hand, a two steps transformation from **98** produced aldehyde **88** (Scheme 26). The Nozaki-Hiyama-Kishi (NHK) coupling reaction between **88** and **89** was effected in the presence of $CrCl_2$ and a catalytic amount of $NiCl_2$ to give a diastereomeric mixture **99** in a 1:1 ratio. To improve the diastereoselectivity at C29, the diastereomeric mixture was oxidized to the corresponding enone and reduced with Corey–Bakshi–Shibata (CBS) reagent. The desired diastereoisomer was separated by preparative liquid chromatography. At this stage, the C17-C24 fragment of amphidinolide C was completed.



Scheme 26. Mohapatra's Synthesis of the C17-C34 Fragment **87** of Amphidinolide C

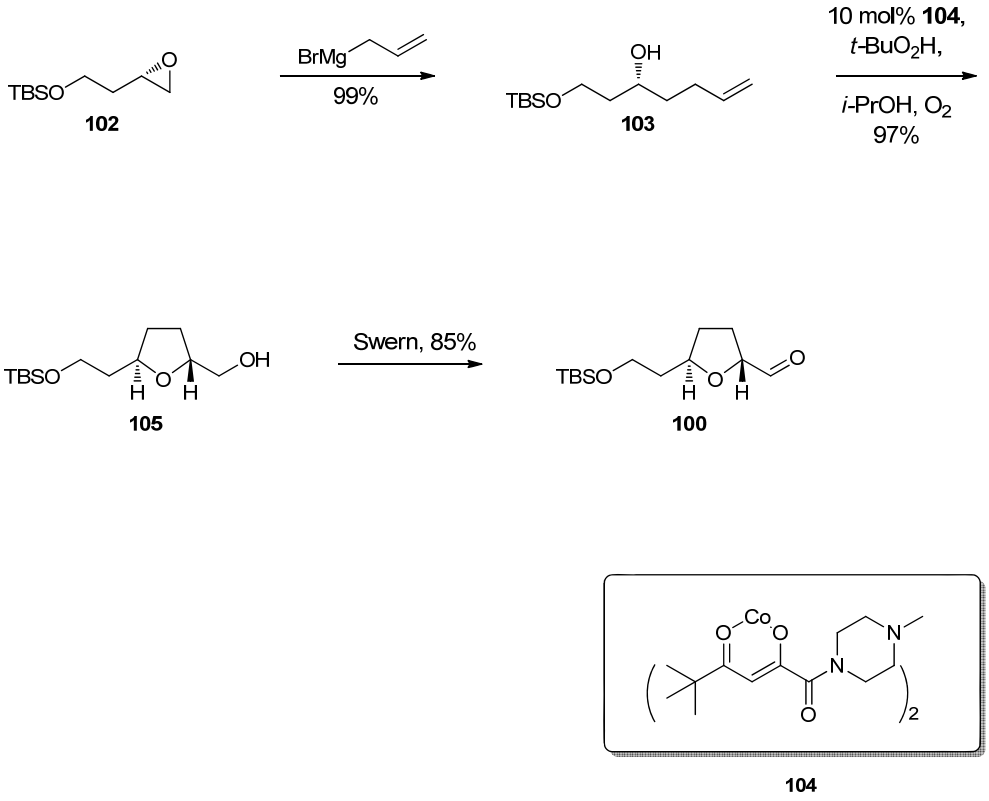
1.4.5 Pagenkopf Group Approach

In Pagenkopf's work,[7] the C18-C34 fragment of amphidinolide C was accessed via two routes (Scheme 27). In a retrosynthetic sense, Pagenkopf and coworkers proposed that the C18-C34 fragment **99** could be obtained by stereoselective alkynylation of THF-aldehyde **100** by alkyne **101**, followed by stereoselective alkyne reduction.



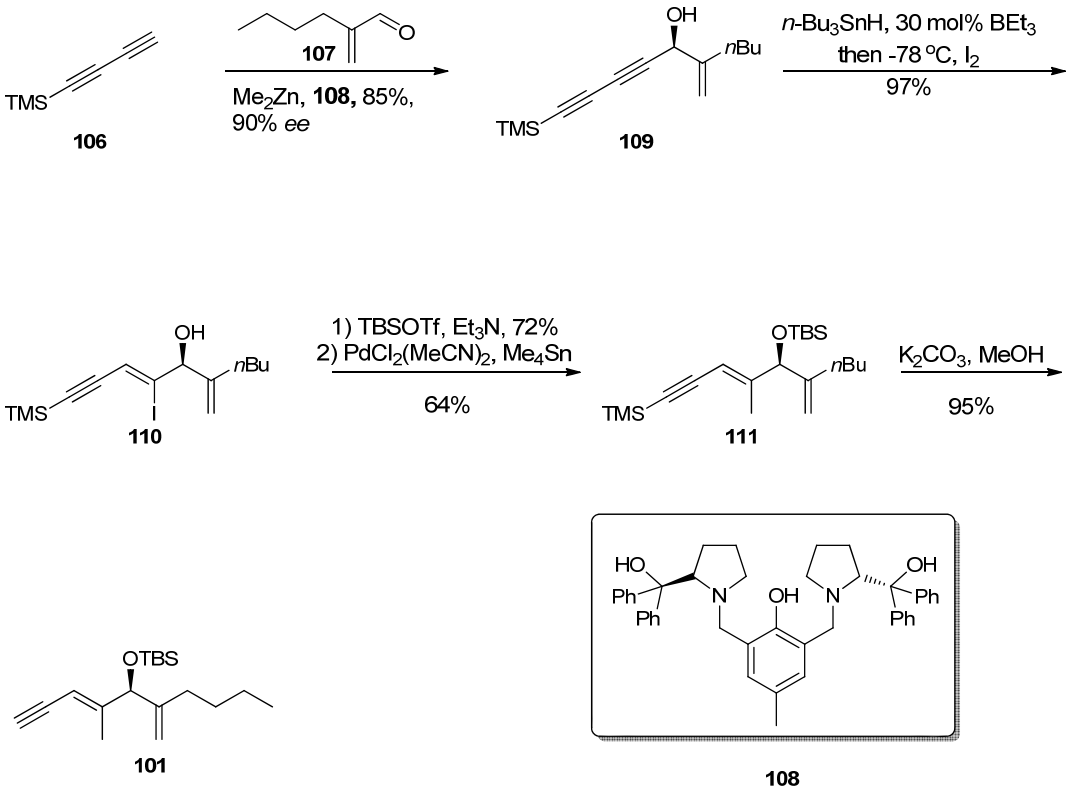
Scheme 27. Pagenkopf's Retrosynthetic Analysis of Amphidinolide C

In a forward sense, the synthesis of the tetrahydrofuran started with the opening of known epoxide **102** by allyl magnesium bromide, to provide cyclization precursor **103**. By using methodology already developed within the Pagenkopf group,[23a] the THF compound **105** was constructed in the presence of $Co(nmp)_2$ (Catalyst **104**).[23] Swern oxidation of **91** then delivered the desired aldehyde **86** (Scheme 28).



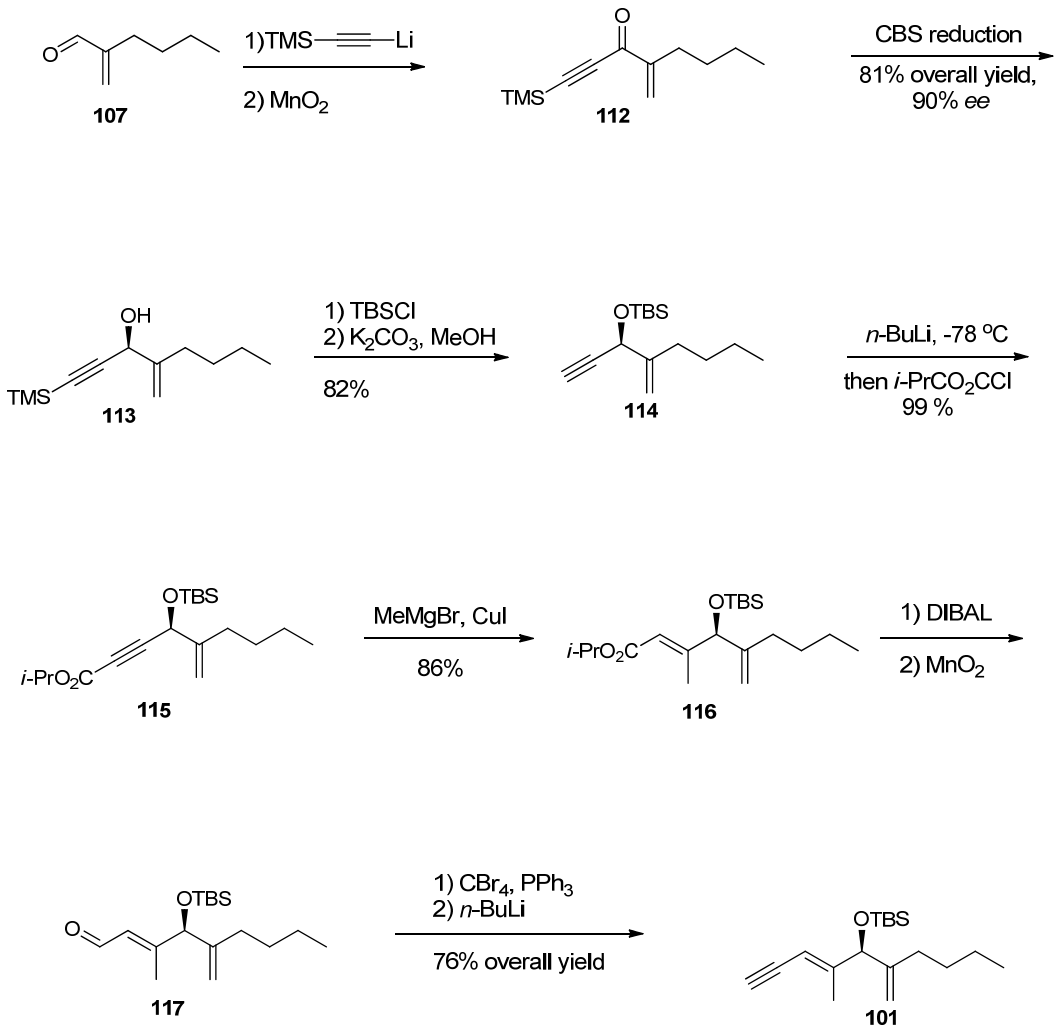
Scheme 28. Pagenkopf's Synthesis of Aldehyde **100**

With the aldehyde **100** in hand, Pagenkopf turned to the synthesis of alkyne **101**. The first generation synthesis started from an asymmetric alkynylation of 2-methylenehexanal **106** (Scheme 29). The Trost protocol[24] proved to be the most effective for this transformation, providing propargylic alcohol **109** in 90% *ee*. Regioselective hydrostannation of the alkyne of **109**, followed by substitution of the tributyltin group with iodine gave vinylic iodide **110**. Protection of the secondary alcohol as the TBS ether, methylation using the Stille coupling reaction and deprotection gave the desired fragment **101**.



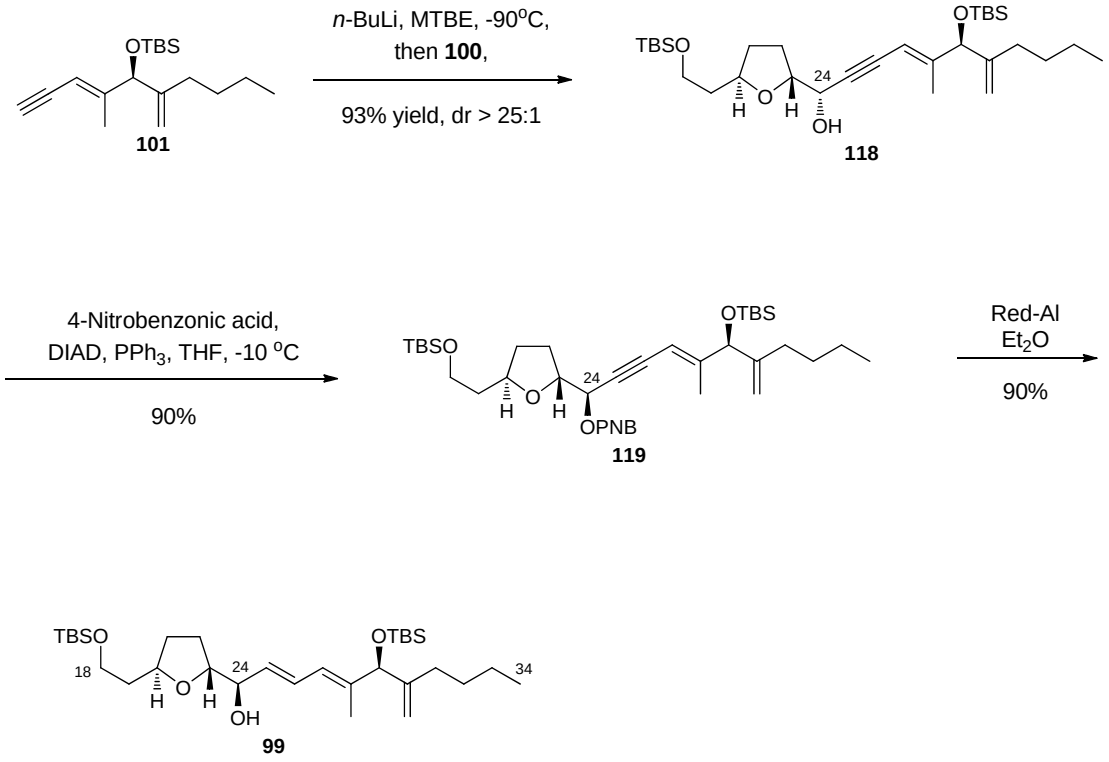
Scheme 29. Pagenkopf's First Generation Synthesis of **101**

The second generation synthesis used the same aldehyde **107** as starting material (Scheme 30). Transformation to ketone **112** and subsequent CBS reduction yielded propargyl alcohol **113** in 90% *ee*. Protection of the alcohol **113**, alkyne deprotection followed by treatment with *n*-BuLi generated the alkynyl anion, which was treated with *i*-$PrCO_2CCl$ to give alkynoate ester **115**. Installation of the required methyl group by a copper(I)-catalyzed conjugate addition delivered **116**. Reduction with DIBAL and oxidation by MnO_2 gave aldehyde **117**, which was transformed into the terminal alkyne **101** in good yield by Corey-Fuchs homologation.



Scheme 30. Second Generation Synthesis of Alkyne **101**

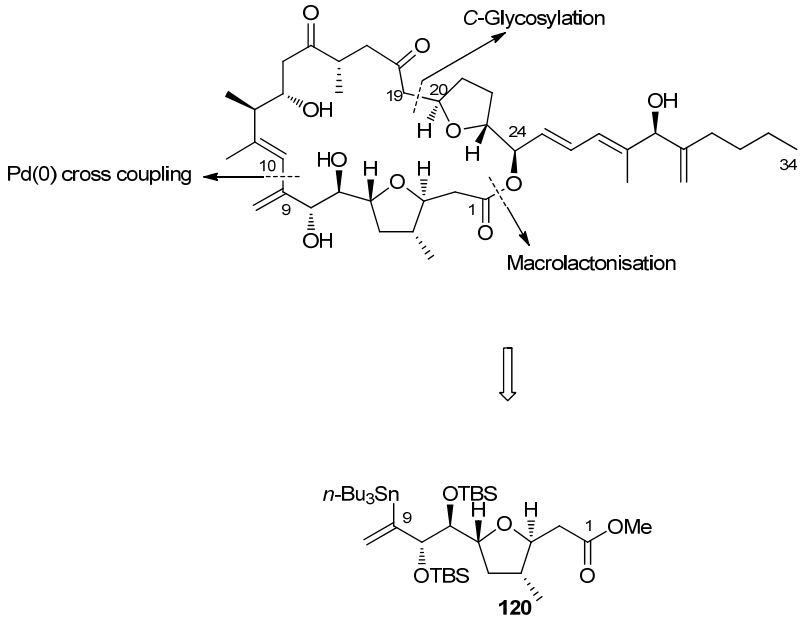
With both aldehyde **100** and alkyne **101** in hand, great efforts were made by the Pagenkopf group to accomplish diastereoselective coupling. Finally, they found that treatment of **101** with *n*-BuLi in MTBE at –90 °C then addition of aldehyde **100** led to **118** in excellent yield (93%) as a single diastereoisomer (Scheme 31). However, the newly formed chiral centre at C24 had incorrect stereochemistry. Converting the hydroxyl of **118** into the desired configuration using the Mitsunobu protocol gave **101**. Finally, reduction of the propargylic alcohol with Red-Al produced the C18-C34 fragment **99**.



Scheme 31. Pagenkopf's Completion of the Synthesis of the C18-C34 Fragment **99**

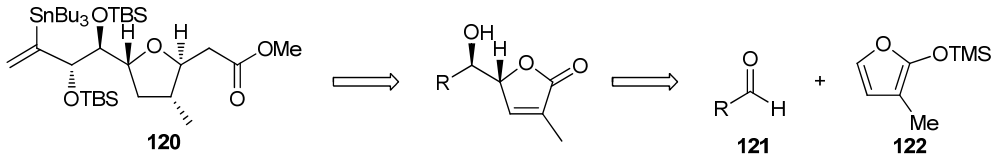
1.4.6 Figadère Group Approach

In the report from Figadère et al, the retrosynthetic approach for amphidinolides C, C2 and F was to divide the molecule into three fragments (Scheme 32).[8] However, only the synthesis of C1-C9 fragment **120** was reported.



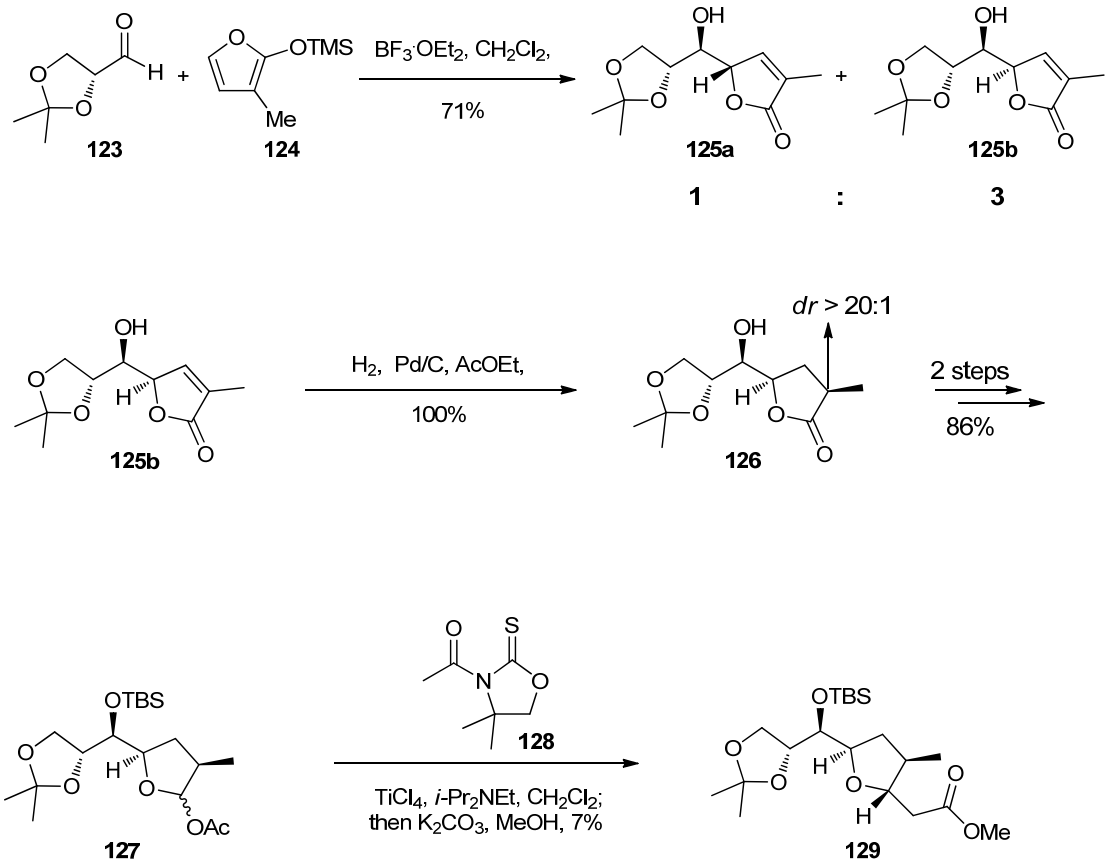
Scheme 32. Figadère's Retrosynthetic Approach to Amphidinolide C

The key step in the synthesis of the C1-C9 fragment **120** was a vinyloguous Mukaiyama aldol reaction of aldehyde **121** with the silyloxyfuran **122** (Scheme 33).



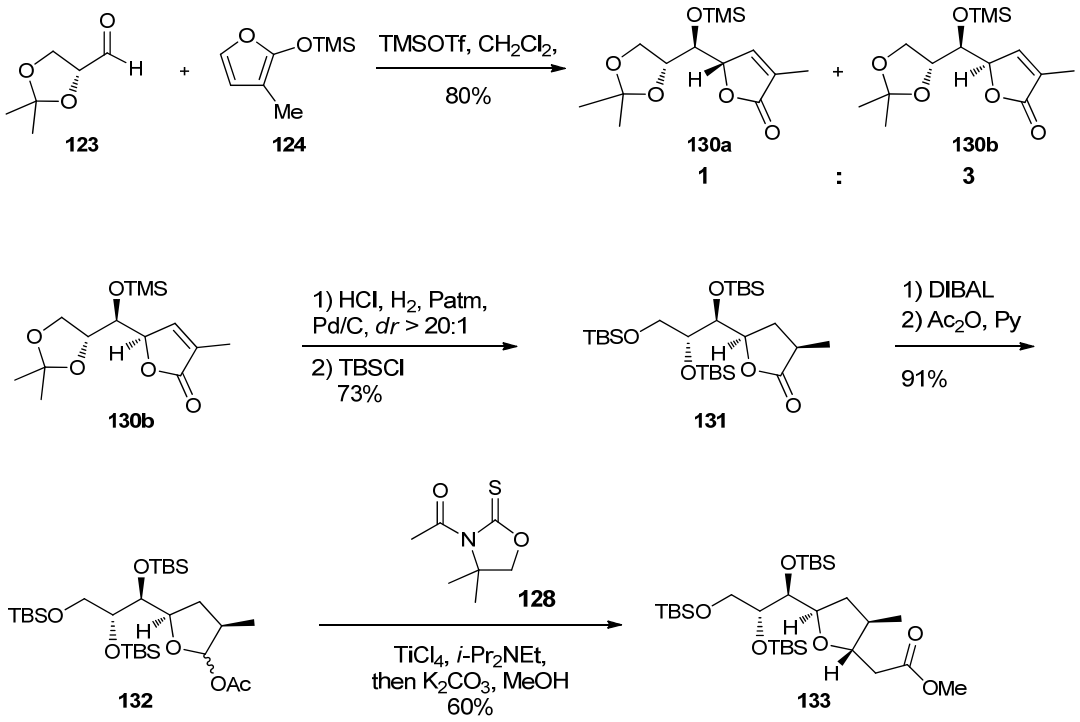
Scheme 33. Key Aldol Rection of **121** and **122**

The synthetic studies began with the vinylogous addition of furan **124** to the known aldehyde **123** in the presence of $BF_3 \cdot OEt_2$ at –78 °C (Scheme 34). The combined yield of the addition products **125a** and **125b** was 71%, with a 1:3 diastereometric ratio. Hydrogenation of lactone **125b** at atmospheric pressure proceeded in quantitative yield with exclusive reduction from the less hindered face of the double bond to give **126** as single diastereoisomer. Compound **127** was then obtained in 4 steps from **126**. The key step in the synthesis was the *C*-glycosylation of **127** with an acetyloxazolidinethione **128**. Unfortunately, the desired product **129** was obtained as single diastereoisomer but in very poor yield (7%).[25]



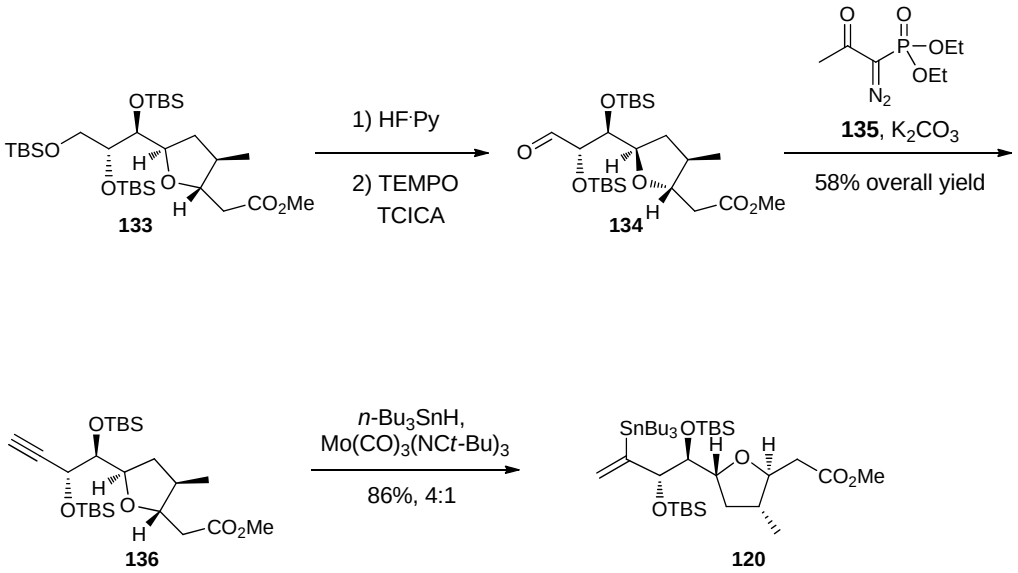
Scheme 34. Figadère's First Synthetic Approach to Fragment **129**

To solve the problem, the authors used different protecting groups. Using the same starting materials **123** and **124** in the presence of a different Lewis acid, TMSOTf at – 78 °C, two diastereoisomeric adducts **130a** and **130b** were obtained in the same ratio the TMS protecting group was introduced (Scheme 35). Hydrogenation of the desired product **130b** under acidic conditions in MeOH gave the triol, which was converted directly into *tri*-TBS protected compound **131** without any further purification. After two further steps, the compound **132** was reacted with Ti enolate generated from the same oxazolidinethione **128** to give compound **133** as a single diastereoisomer in reasonable yield (60%).



Scheme 35. Figadère's Second Synthetic Approach to Fragment **133**

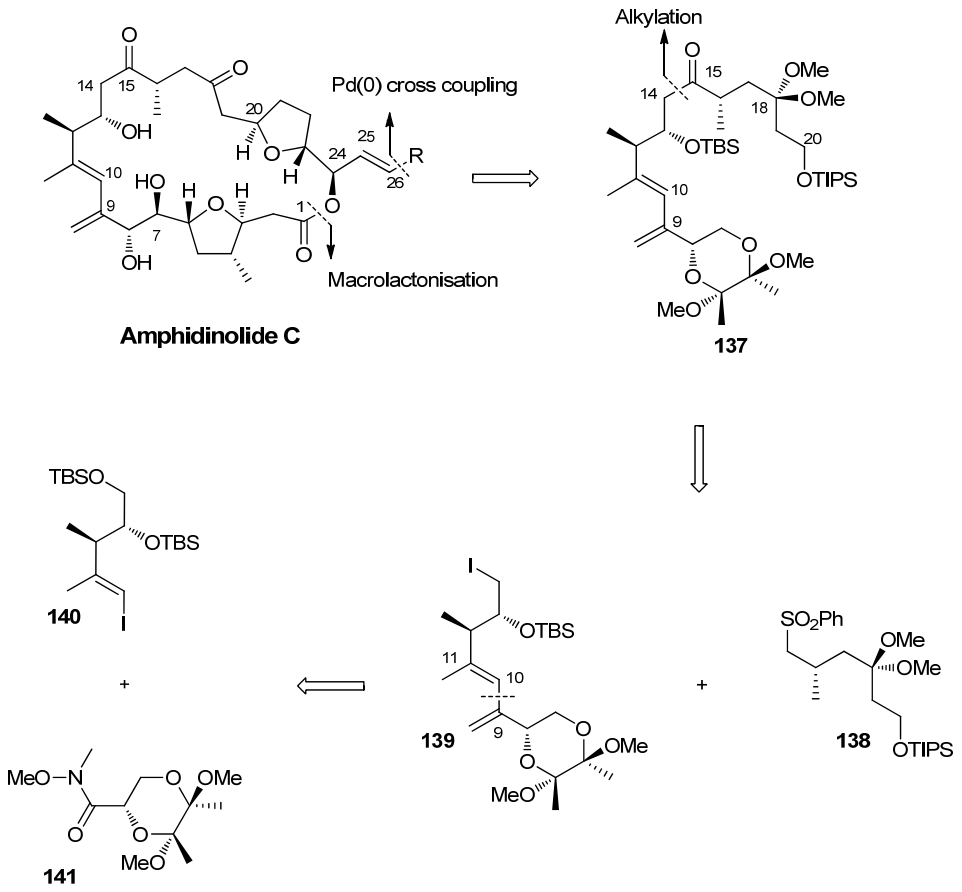
Following construction of ester **133**, two steps transformed it into aldehyde **134** (Scheme 36), which was then transformed into the terminal alkyne **136** using the Bestmann-Ohira protocol. Next, a molybdenum [$Mo(CO)_3(NC\textit{t}\text{-}Bu)_3$] catalyzed hydrostannation[26] of **136** produced the desired C1-C9 fragment **120** in 86% yield (4:1 regioisometric mixture). Fortunately, the mixture of regioisomers was separable by chromatography.



Scheme 36. Figadère's Synthesis of the C1-C9 Fragment **105**

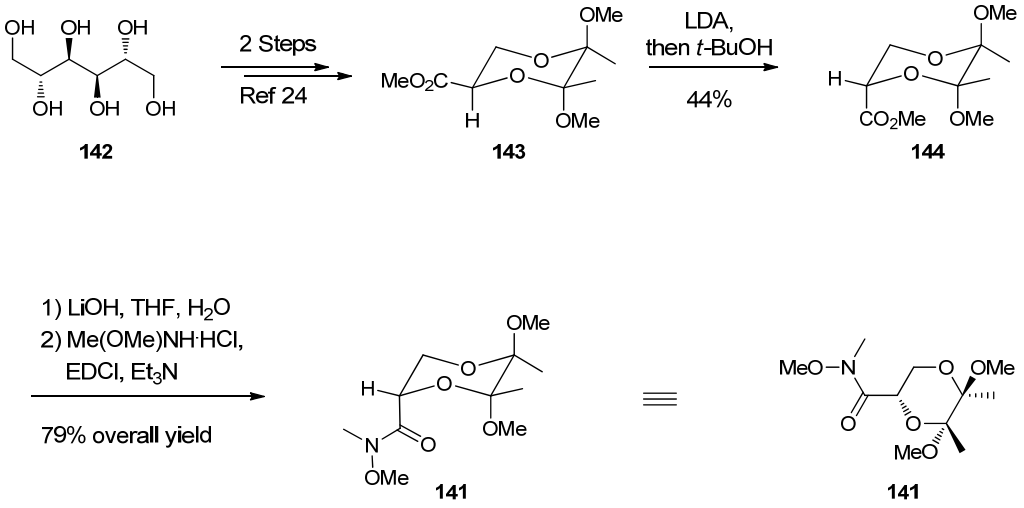
1.4.7 Carter Group Approach

Carter and coworkers were the first to complete the total synthesis of amphidinolide F.[9b] In 2009, Carter and co-workers reported the synthesis of the C7-C20 fragment of amphidinolides C and F.[9a] Carter's original retrosynthetic analysis of amiphidinolide C (Scheme 37) involved disconnection across C-O bond of the macrolactone by macrolactonisation as well as at C25-C26, suggesting an organometallic coupling to give fragment **137**. Disconnection across C14-C15 gave the fragments **138** and **139**. Diene **140** could be synthesized *via* an addition reaction between the Weinreb amide **141** and an organolithium species derived from vinylic iodine **140**, followed by functional group transformations.



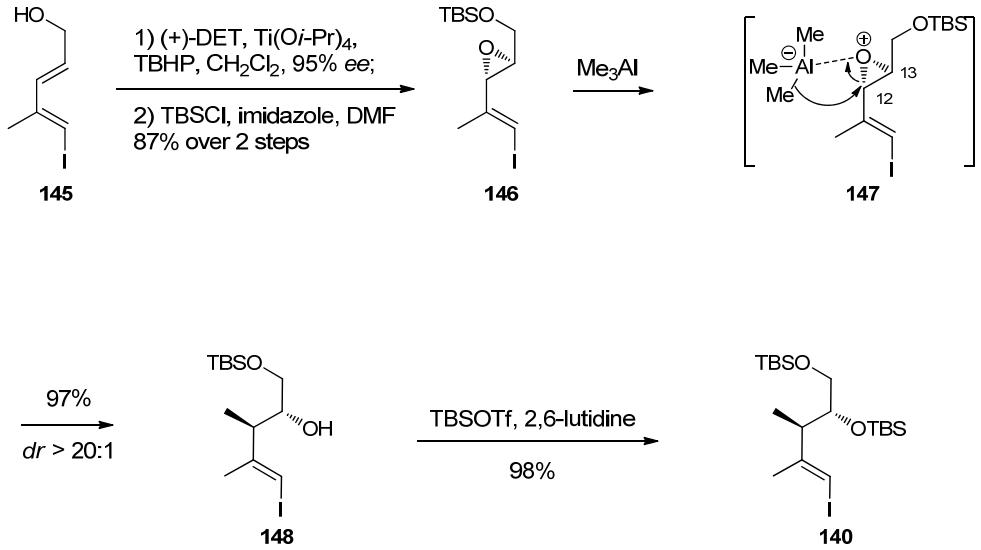
Scheme 37. Carter's First Generation of Retrosynthetic Analysis of Amphidinolide C

The forward synthesis began from D-mannitol **142** to obtain compound **143** in two steps.[27] Equatorial ester **143** was epimerised to afford axial ester **144** by treatment with LDA in THF, followed by a diastereoselective protonation with *t*-BuOH in 44% yield. Ester **144** was then further transformed into Weinreb amide **141** (Scheme 38).



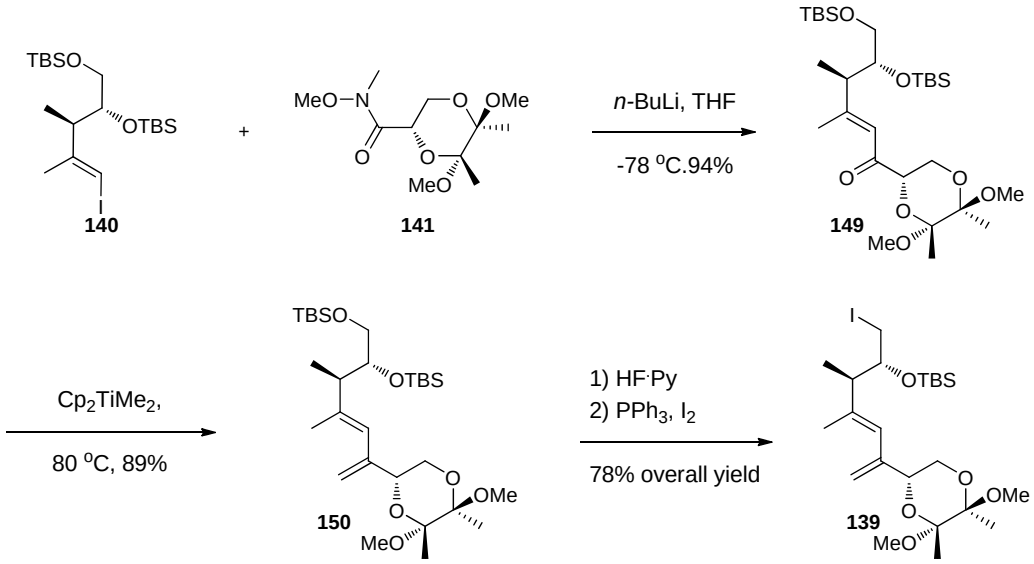
Scheme 38. Synthesis of Weinreb amide **141** by Epimerisation

With **141** in hand, Carter and co-workers sought to prepare iodide coupling partner **140**. Sharpless epoxidation of the known vinylic iodide **145**[28] proceeded cleanly to provide epoxide **146** in 87% yield with 95% *ee* (Scheme 36). $AlMe_3$-Mediated epoxide ring-opening at −78 ºC provided product **148**, through intermediate **147**, as a single diastereoisomer (*dr* > 20:1) with excellent regioselectivity. The author noted that the temperature was critical to the success of this transformation (*dr* at C12 droped to 3.5:1 when the reaction carried out at −50 ºC). Finally protection of the secondary alcohol as a TBS ether afforded desired iodide subunit **140**.



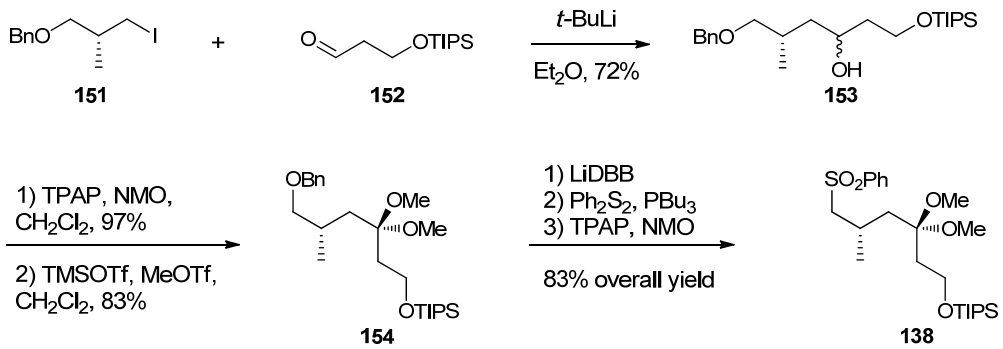
Scheme 39. Synthesis of Vinylic Iodide **140**

The enone **149** was obtained through lithium-halogen exchange, accomplished by treatment of **123** with *n*-BuLi, followed by addition to the Weinreb amide **124** (Scheme 40). Olefination of **132** using the Petasis reagent produced diene **133** and the iodide **122** was then obtained in further two steps.



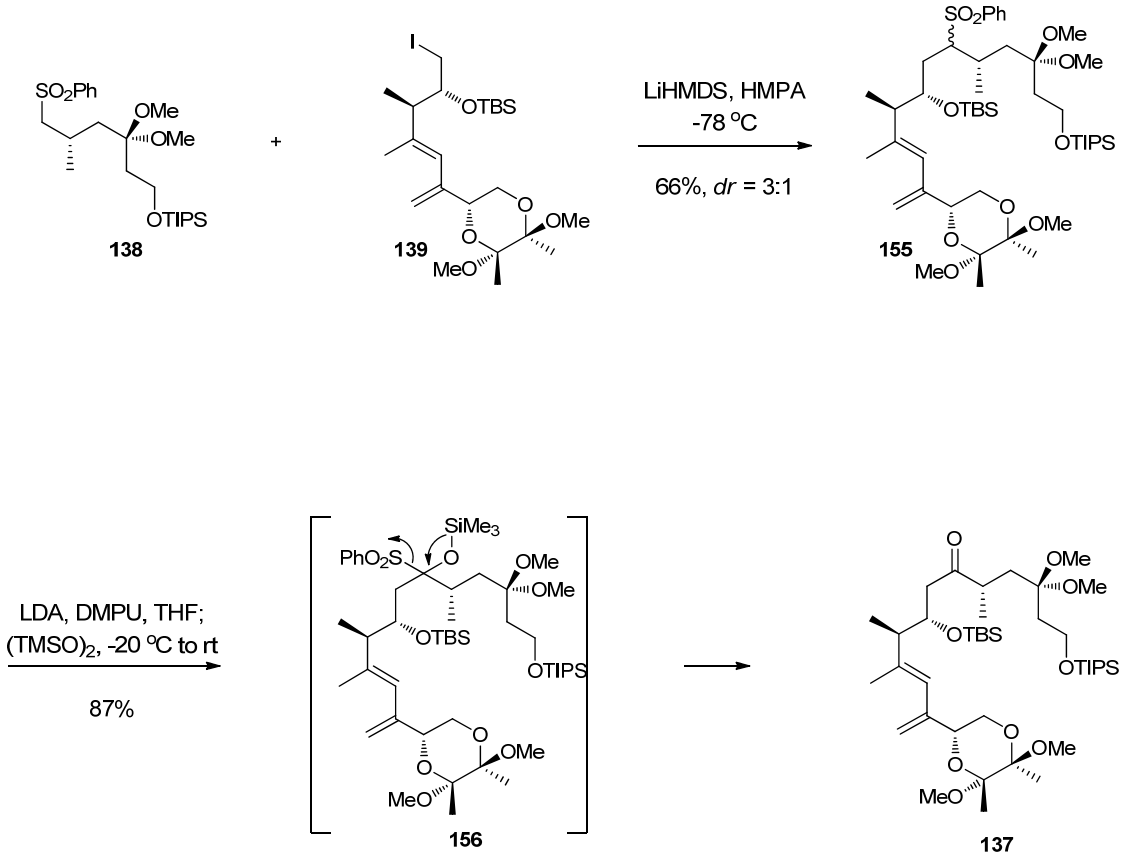
Scheme 40. Synthesis of Iodide Subunit **139**

The synthesis of the sulfone coupling partner **138** started from the iodide **151**. Metal-halogen exchange, followed by addition of the lithiated compound to the aldehyde **151**, generated alcohol **152** as a mixture of diastereoisomers (Scheme 41). TPAP oxidation[21] followed by Noyori ketalisation[29] generated the dimethyl ketal **154**. Selective deprotection of the benzyl group, sulfide formation and oxidation afforded phenyl sulfone **138**.



Scheme 41. Synthesis of Sulfone **138**

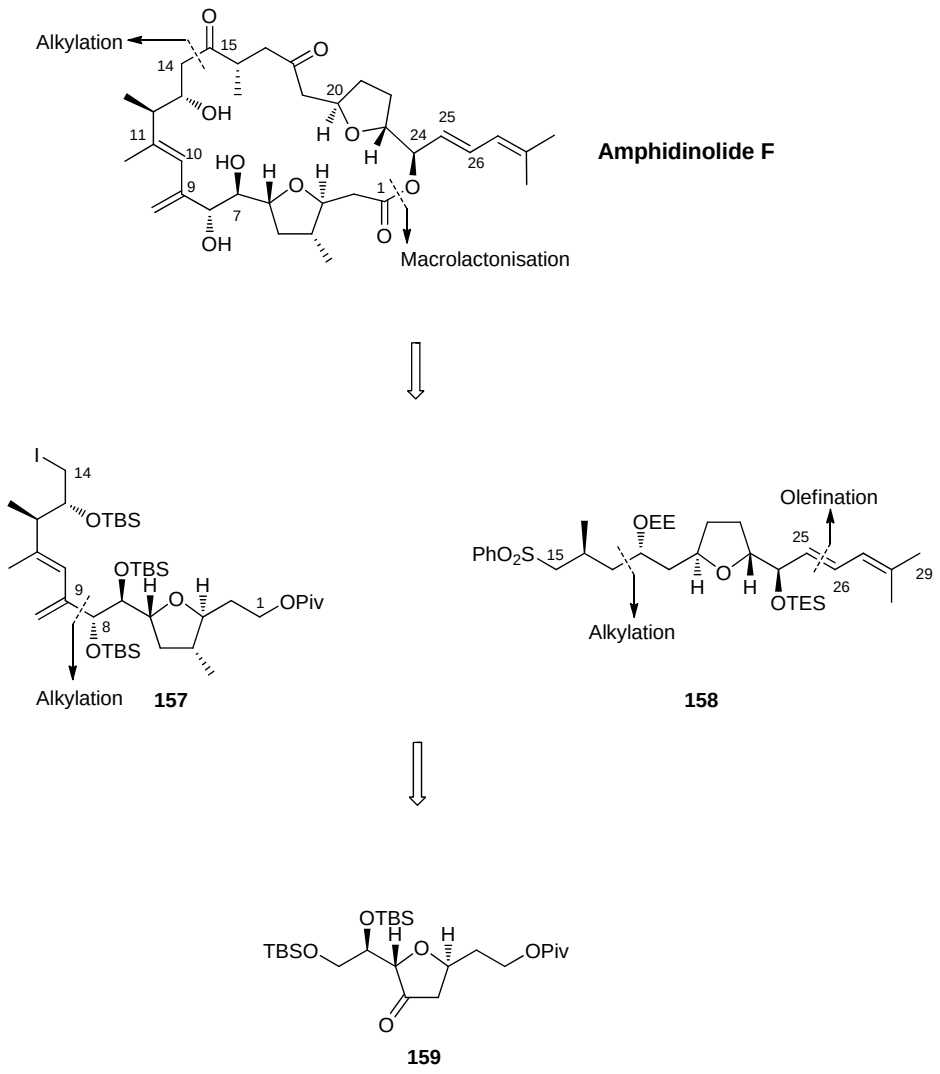
With both subunits **138** and **139** in hand, treatment of phenylsulfone **138** with LiHMDS followed by the addition of iodide **139** provided the coupled compound **155** in 66% yield (Scheme 42). The procedure previously developed by Carter and co-workers for the hydroxylation of sulfones was then deployed.[30] Compound **155** was treated with $(TMSO)_2$ in the presence of LDA and DMPU leading to proposed intermediate **156**, which then collapsed to afford ketone **137**, corresponding to the C7-C20 fragment.



Scheme 42. Carter's Synthesis of the C7-C20 Fragment **137**

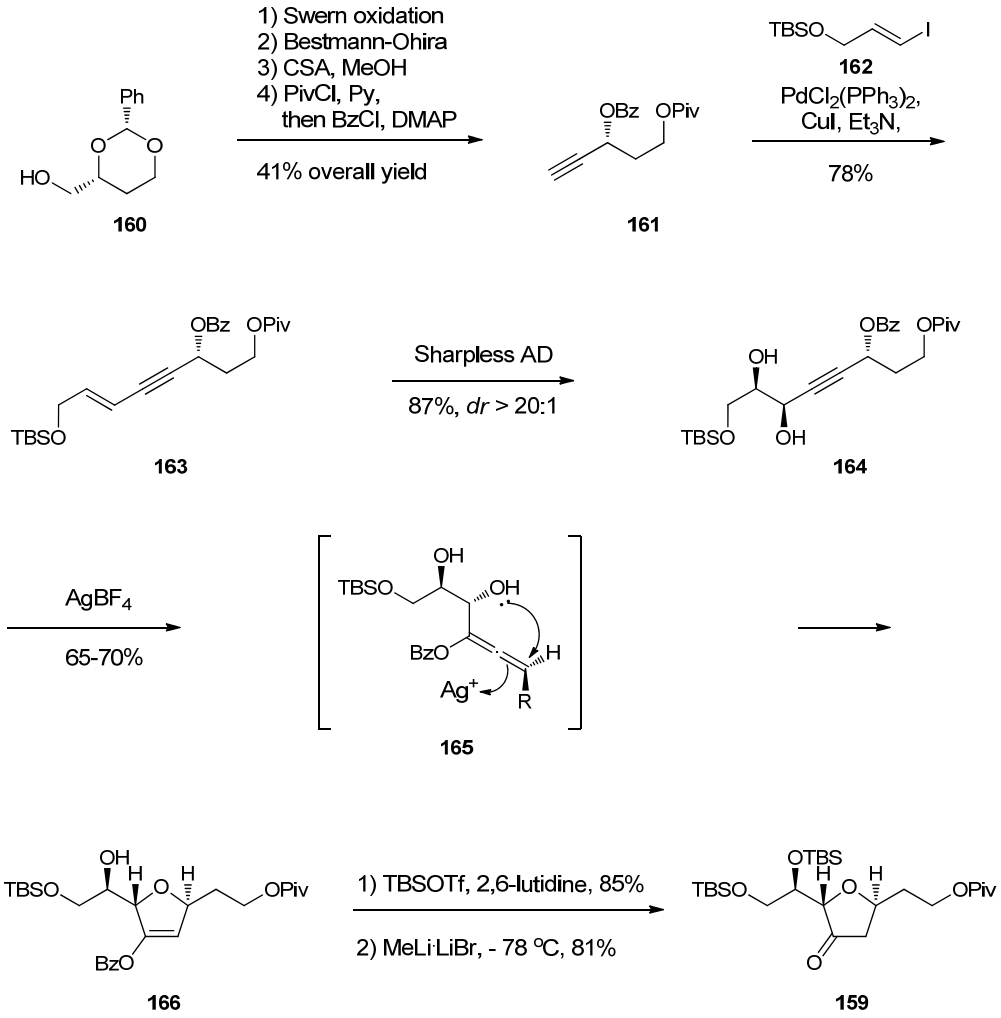
This paper was the first in which formation of C9-C10 bond (See Scheme 40) of amphidinolide C (or F) was reported. However, this alkylation-metathesis strategy may not be suitable for more complex systems and so Carter and co-workers presented an alternative alkylation (disconnection from C8-C9) to furnish the conjugated diene system (C9-C11) in their second paper.[9b]

In 2012 the first total synthesis of amphidinolide F was reported by Carter.[9b] The retrosynthetic strategy is shown in Scheme 43. In this approach, the initial disconnection involved the macrolactonisation at C-O band followed by umpolung disconnection at C14-C15. This gave two coupling partners, iodide **157** and sulfone **158**. The considerable symmetry of both of the C1-C14 and C15-C29 fragments **157** and **158** within the *trans*-tetrahydrofuran structure suggested that both of the two fragments could be derived from the same tetrahydrofuran building-block **159**.



Scheme 43. Carter's Second Generation Retrosynthetic Analysis of Amphidinolide F

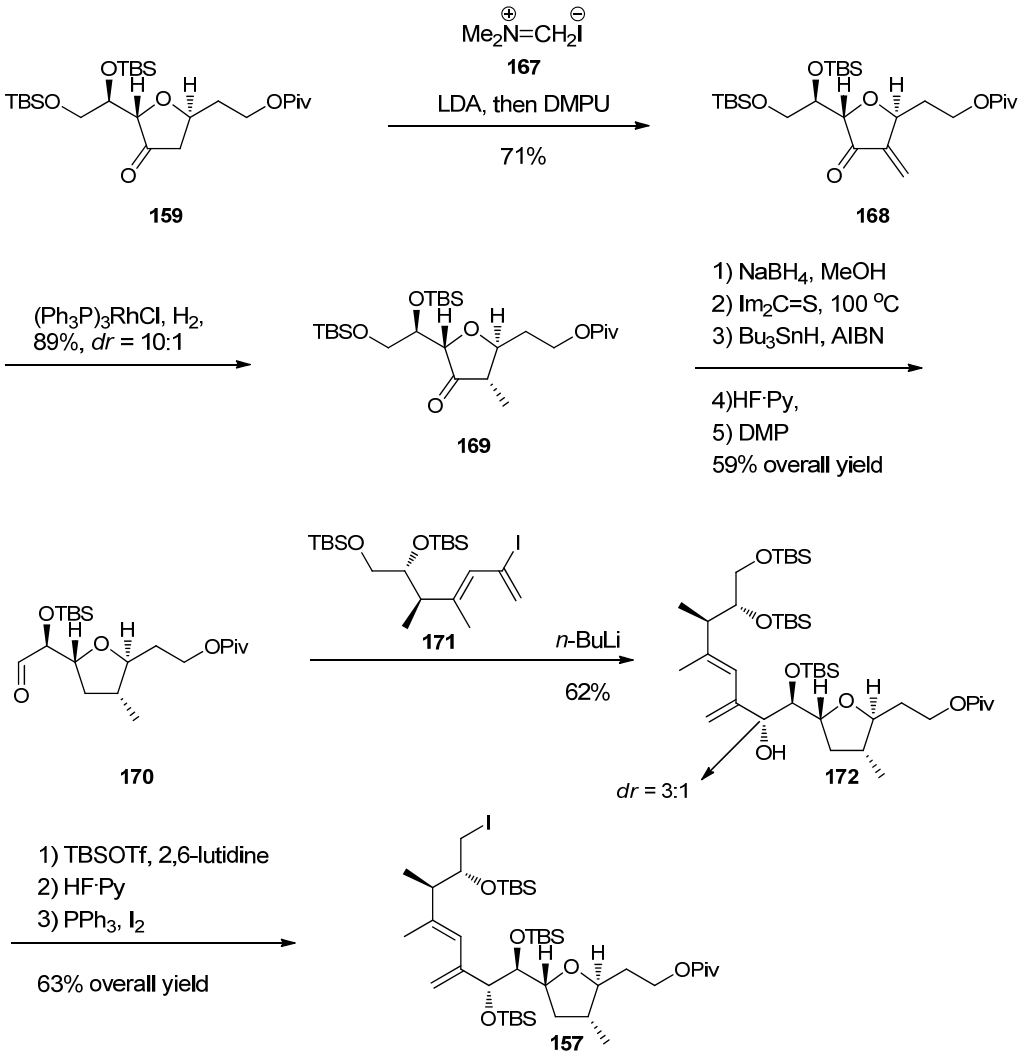
In the forward sense, the first challenge was to synthesise the *trans*-tetrahydrofuran **159** in an efficient manner (Scheme 44). The synthesis started from the known alcohol **160**.[31] After 4 steps, alkyne **161** was obtained in 41% overall yield. Sonogashira coupling between **161** and iodide **162**, followed by Sharpless asymmetric dihydroxylation afforded the diol **164** in good yield and with excellent diastereoselectivity (*dr* > 20:1). Next, $AgBF_4$-promoted cyclization led to the desired *trans*-tetrahydrofuran **166**,[32] as a single diastereoisomer through the allenic intermediate **165**. It should be noted that this reaction worked very well even on a large scale (> 5 g) and could provide sufficient quantities of tetrahydrofuran for further synthesis. Subsequent silyl protection and selective cleavage of the enol benzoate with MeLi·LiBr produced the key intermediate **159**.



Scheme 44. Carter's Synthesis of the Key *trans*-Tetrahydrofuran **159**

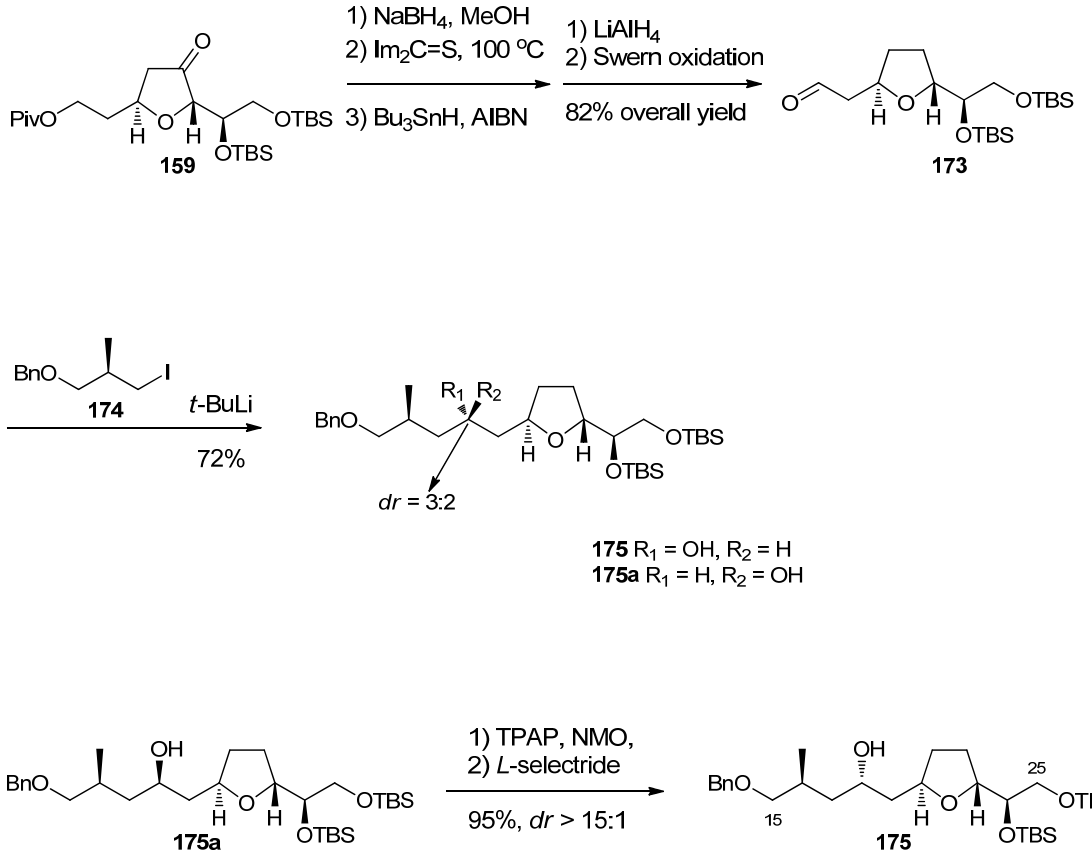
With the key intermediate **159** in hand, the next task was to construct both the C1-C14 fragment **157** (Scheme 45) and the C15-C29 fragment **158** (Scheme 47).

Direct diastereoselective alkylation of ketone **159** proved to be difficult, and so selective hydrogenation of enone **168**, which was derived from the tetrahydrofuran **159**, was considered. Hydrogenation of **168** using Wikinson's catalyst gave **169** in good yield and diastereoselectivity (*dr* = 10:1). After a further five steps, the aldehyde **170** was obtained in 59% overall yield. Treatment of iodide **171**[9a] with *n*-BuLi and addition of the lithiated intermediate to **170** produced the alcohol **172** in 61% yield as mixture (3:1) of two separable diastereoisomers. A further three steps were required to obtain the desired C1-C14 subunit **157**.



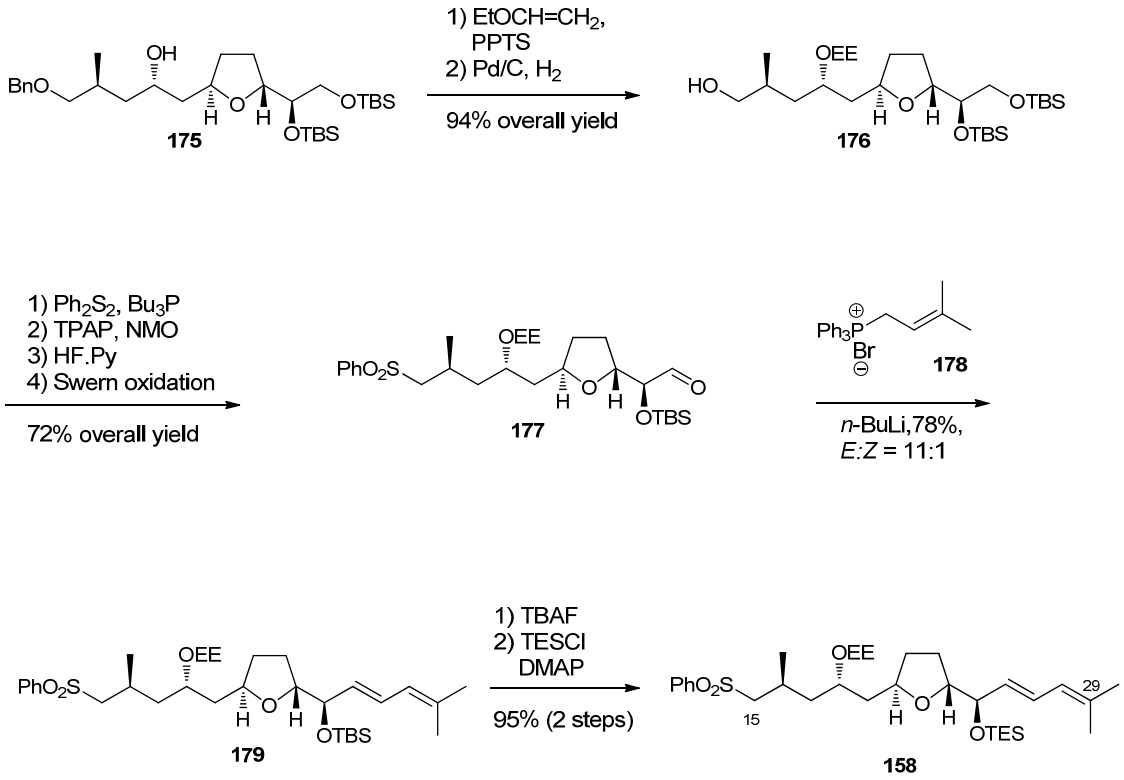
Scheme 45. Synthesis of C1-C14 Fragment **157**

The synthesis of the C15-C25 fragment is shown in Scheme 46. Aldehyde **173** was derived from the same ketone **159** in five steps with 82% over yield. Treatment of iodide **174** with *t*-BuLi and coupling of the resulting lithiated compound with aldehyde **173** gave an inseparable 3:2 mixture of two diastereoisomers (**175** and **175a**). The undesired diastereoisomer **175a**, could be converted into **175** in a diastereoselective manner (*dr* > 15:1), by oxidation followed by L-selectride reduction.



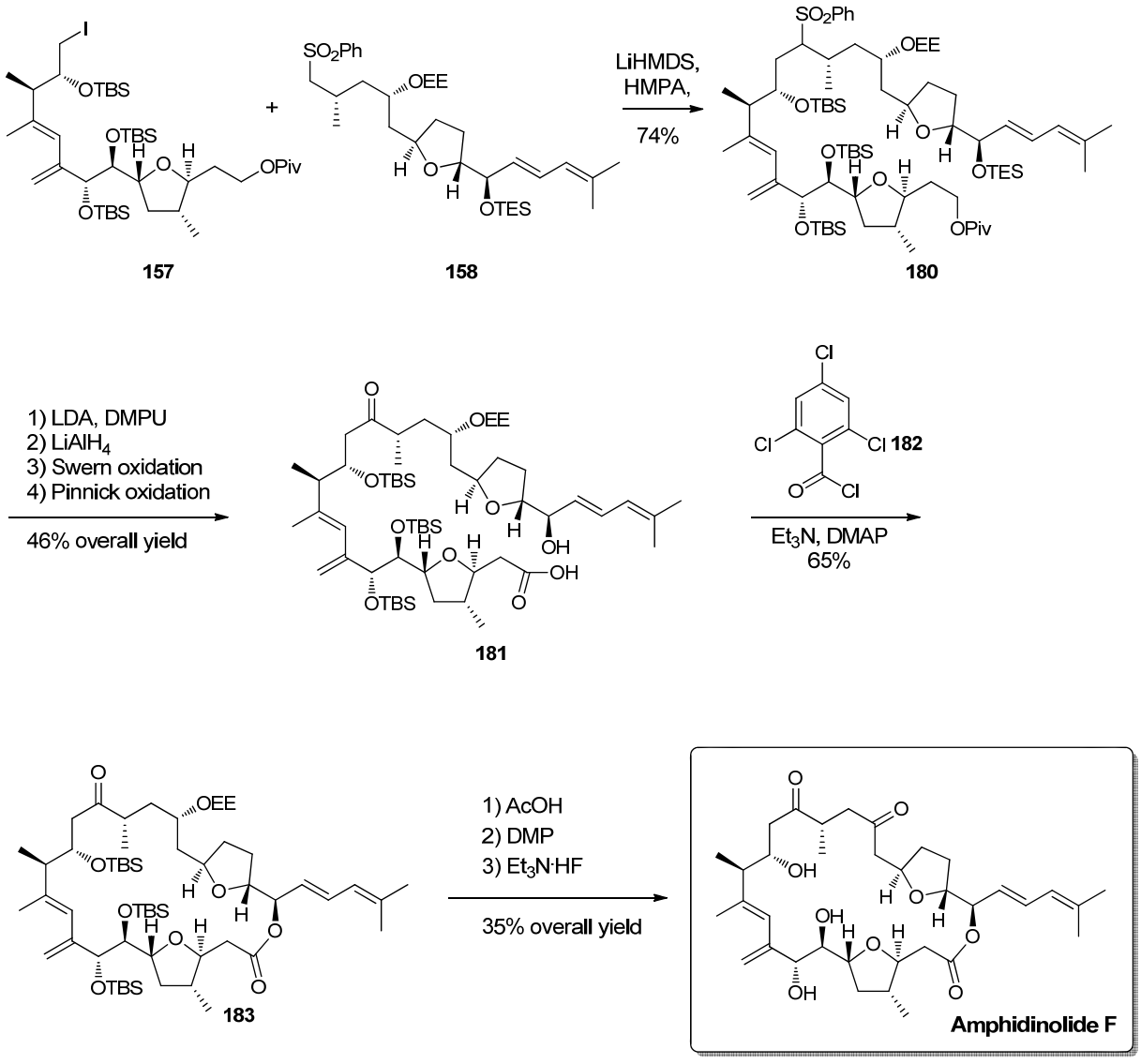
Scheme 46. Synthesis of C15-C25 Fragment **175**

A further six steps from **175** provided the aldehyde **177** in good yield (Scheme 47). Wittig reaction of **176** produced diene **179** with good stereoselectivity (*E*:*Z* = 11:1). Subsequent protecting group exchange afforded the C15-C29 fragment **158**.



Scheme 47. Synthesis of C15-C29 Fragment **158**

The completion of the total synthesis of amphidinolide F is shown in Scheme 48. The key fragment coupling reaction was accomplished by treatment of sulfone **158** with LiHMDS and HMPA followed by the addition of alkyl halide **157**, to form the C14–C15 coupled compound **180**. The acid **181** was then obtained in three steps from the pivaloyl ester **180** in good yield. This strategy had previously proved successful and had been reported by Carter earlier.[9a] Macrolactonisation under Yamaguchi conditions[33] led to the macrolide **183** in 65% yield. Further deprotection and fuctional group transformation finally resulted in the first total synthesis of amphidinolide F.

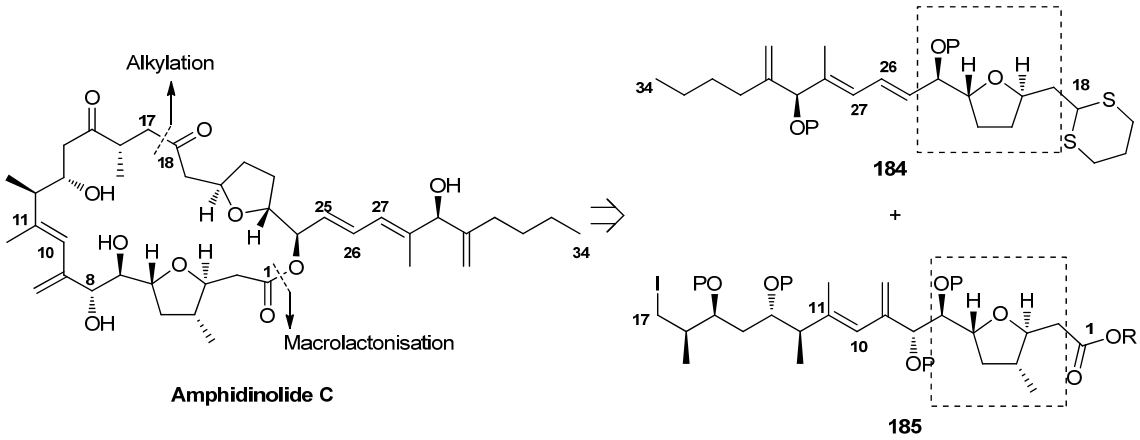


157 158 180 181 182 183

Scheme 48. Carter's Total Synthesis of Amphdinolide F

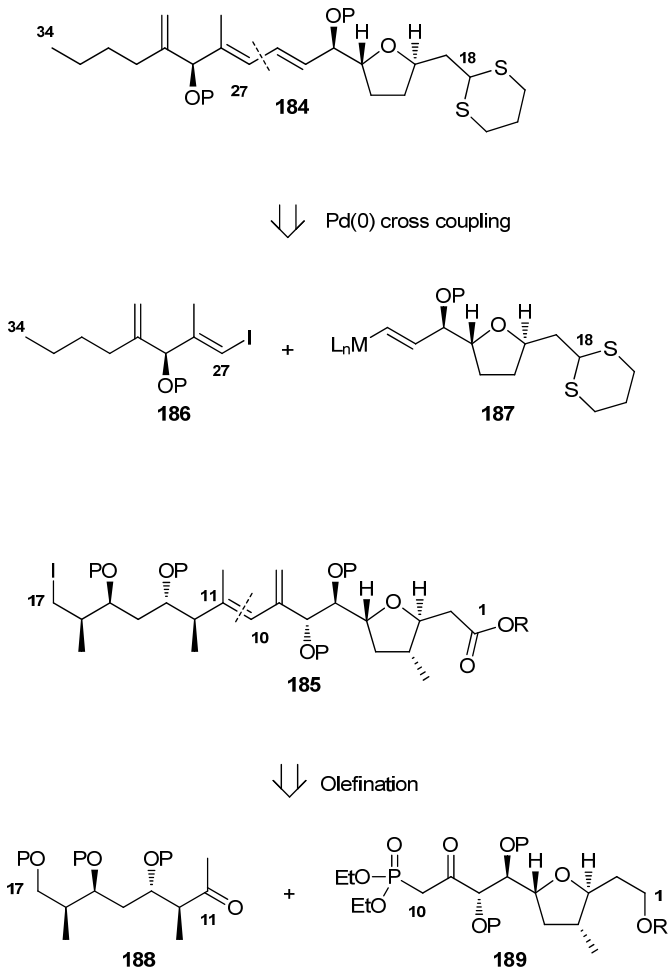
1.5 Retrosynthesis of Amphidinolide C

Our proposed synthetic route to amphidinolide C is highly convergent. A distinguishing feature of this strategy would be the use of a functionalised furanone as a key common intermediate for the construction of both the "northern" (**184**) and "southern" (**185**) hemispheres of amphidinolide C, thus exploiting the pseudo-symmetry. The retrosynthetic analysis commences with cleavage of the macrolactone C–O bond and disconnection between C17 and C18 to afford the the "northern" fragment **184** and "southern" fragment **185**, after implementation of additional functional group interconversions (Scheme 49).



Scheme 49. Retrosynthetic Analysis of Amphdinolide C

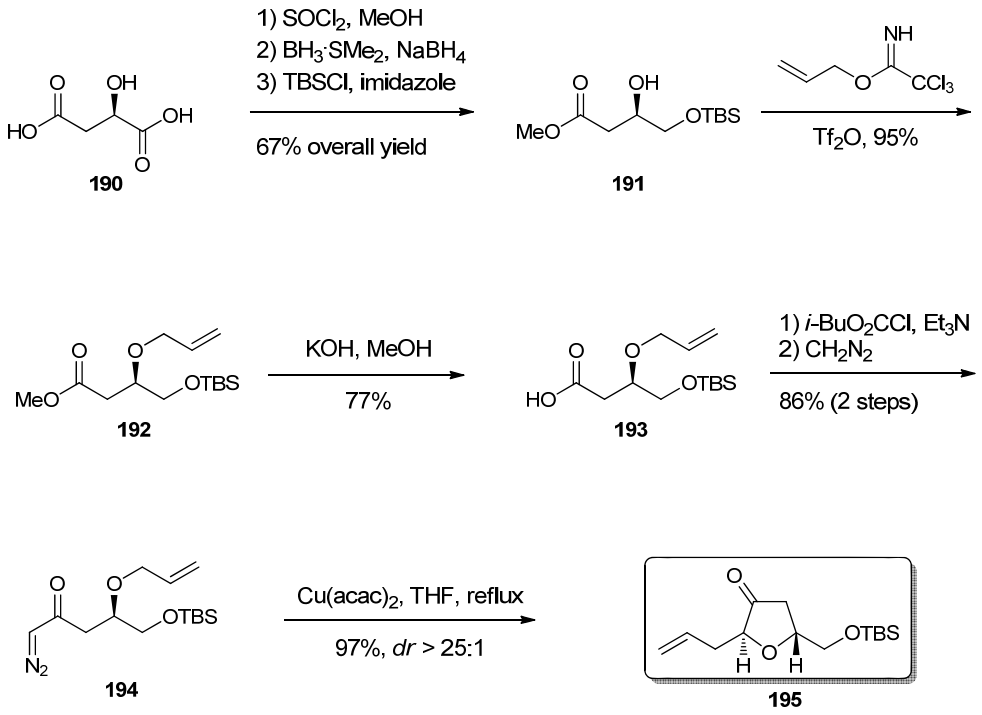
Disconnection of the key "northern" fragment **184** at the C26-C27 bond delivers the vinylic iodide **186** and vinylic organometallic **187**. This disconnection implies that the union of these fragments in the forward sense will be accomplished by a palladium-catalysed coupling reaction (Scheme 50). Further disconnection of the "southern" fragment **185** through the C10-C11 alkene leads to the phosphonate ester **189**, required for a Horner-Wadsworth-Emmons (HWE) olefination reaction, and the ketone coupling partner **188**.



Scheme 50. Retrosynthetic Analysis of the Northern and the Southern Fragment

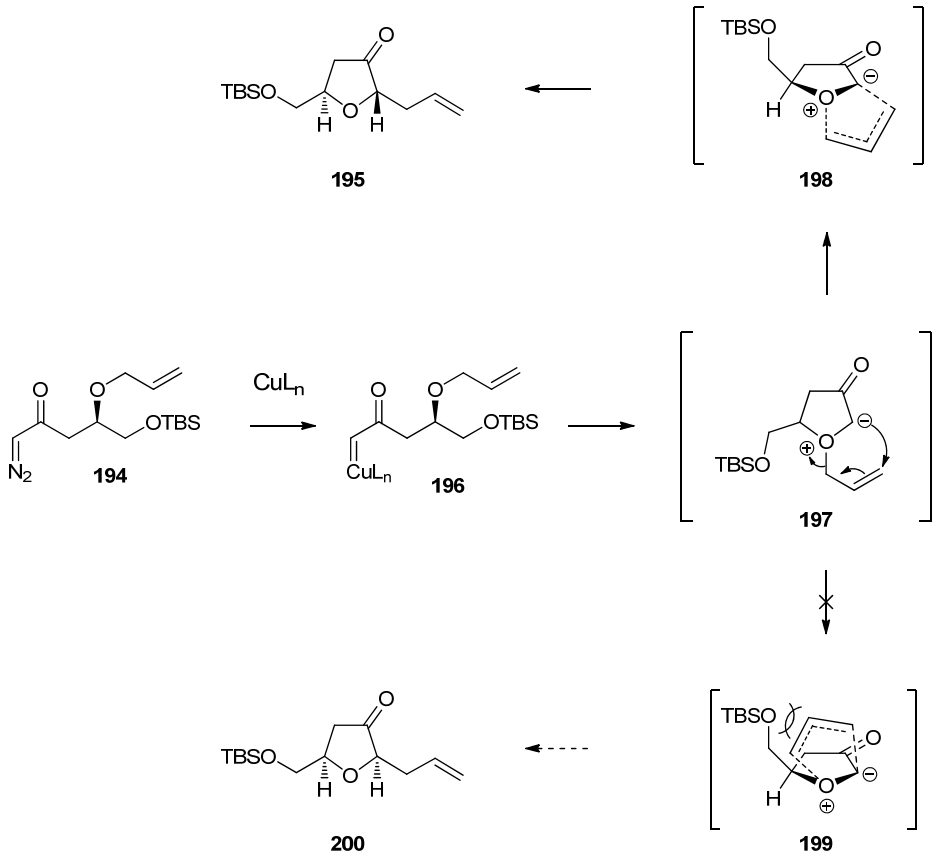
1.6 Previous Synthetic study on THF ring formation through Rearrangement of Diazoketone

Novel rearrangement methodology has been developed within the Clark group which allows the diastereoselective formation of substituted tetrahydrofuran systems.[34] The requisite dihydrofuranone was prepared from D-malic acid **190** (Scheme 47). The carboxylic acid **193**, which was derived from **190**, was actived as a mixed anhydride, followed by treatment with a solution of diazomethane gave the α-diazo ketone **194**. Treatment of this compound with $Cu(acac)_2$ in tetrahydrofuran at reflux afforded the dihydrofuranone **195** as a single diastereomer in high yield.[34]



Scheme 51. Clark's Synthesis of *trans*-THF Compound **195**

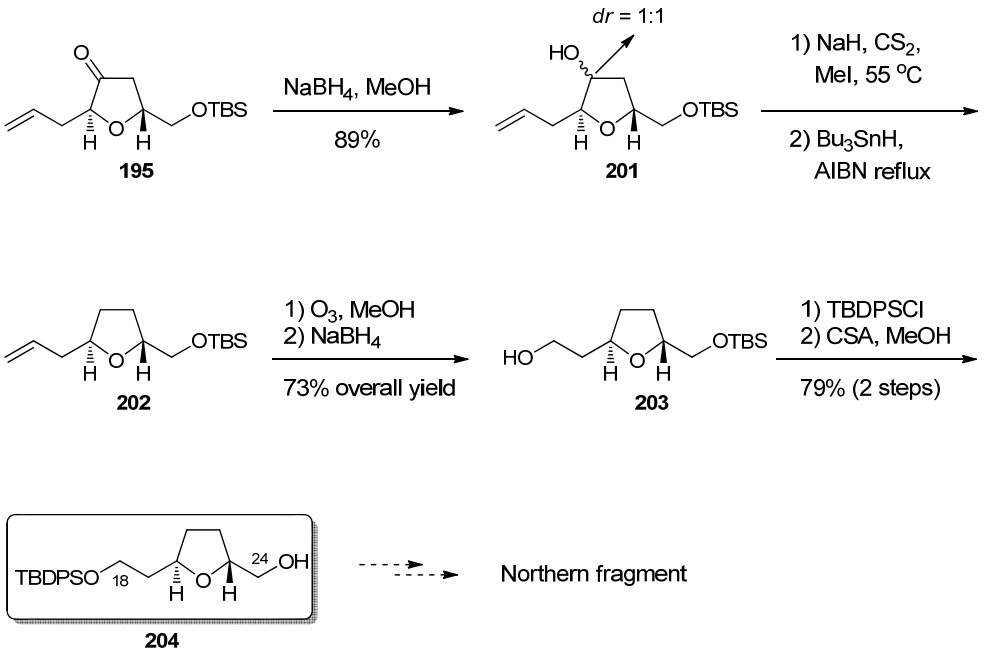
Previous studies in the Clark group have shown that $Cu(acac)_2$ is the complex of choice for the oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement from diazoketone **194** (Scheme 52).[35] In the predicted transition state, rearrangement from the bottom of the tetrahydrofuran as shown, is favoured due to steric effects. Thus, the transition state **198** leads to the desired 2,5-*trans* THF compound **195**.



Scheme 52. Explanation of Diastereoselectivity in the Tetrahydrofuran Formation

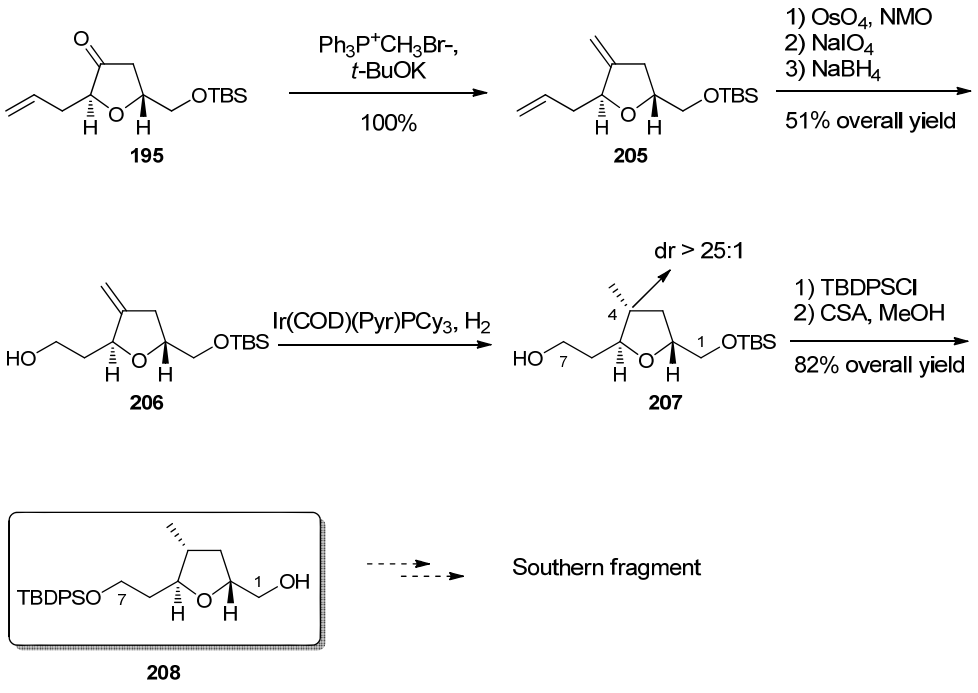
With the key intermediate **195** in hand, both of the required functionalized intermediates were synthesised.

On one hand, the ketone **195** was reduced to a diastereomeric mixture of alcohols **201** that were then converted into the corresponding xanthate esters (Scheme 53). Treatment of this mixture under Barton-McCombie conditions delivered the deoxygenated tetrahydrofuran **202**.[36] Ozonolysis and reduction then afforded the alcohol **202** in an overall yield of 73% over four steps, with minimal purification necessary. Protection of the primary alcohol as a *t*-butyldiphenylsilyl ether followed by selective acid-catalyzed removal of the TBS group generated the alcohol **204** as a key intermediate to the northern fragment.



Scheme 53. Clark's Synthesis of the Tetrahydrofuran Intermediate **204**

On the other hand, Wittig methylenation of the ketone **195** proceeded to afford diene **205** in quantitative yield (Scheme 54). Selective dihydroxylation of the side chain alkene was achieved in 64% yield and the resulting diol was then subjected to oxidative cleavage. The intermediate aldehyde was reduced with $NaBH_4$ to provide the alcohol **206**, which was to be subjected to diastereoselective hydrogenation of the methylene group to install the C4 methyl substituent. The use of homogenous catalysts to control the stereochemical outcome hydrogenation reactions through reversible coordination to hydroxyl or carbonyl groups is well precedented and gratifyingly this approach proved to be successful in this case. Hydrogenation of the alkene **206** using Crabtree's catalyst[37] afforded the saturated product as a single isomer and this compound was then converted into the alcohol **207** in good yield by silylation of the hydroxyl group with *t*-butyldiphenylsilyl chloride and subsequent cleavage of the TBS ether. Alcohol **208** would be the required intermediate for the southern fragment.

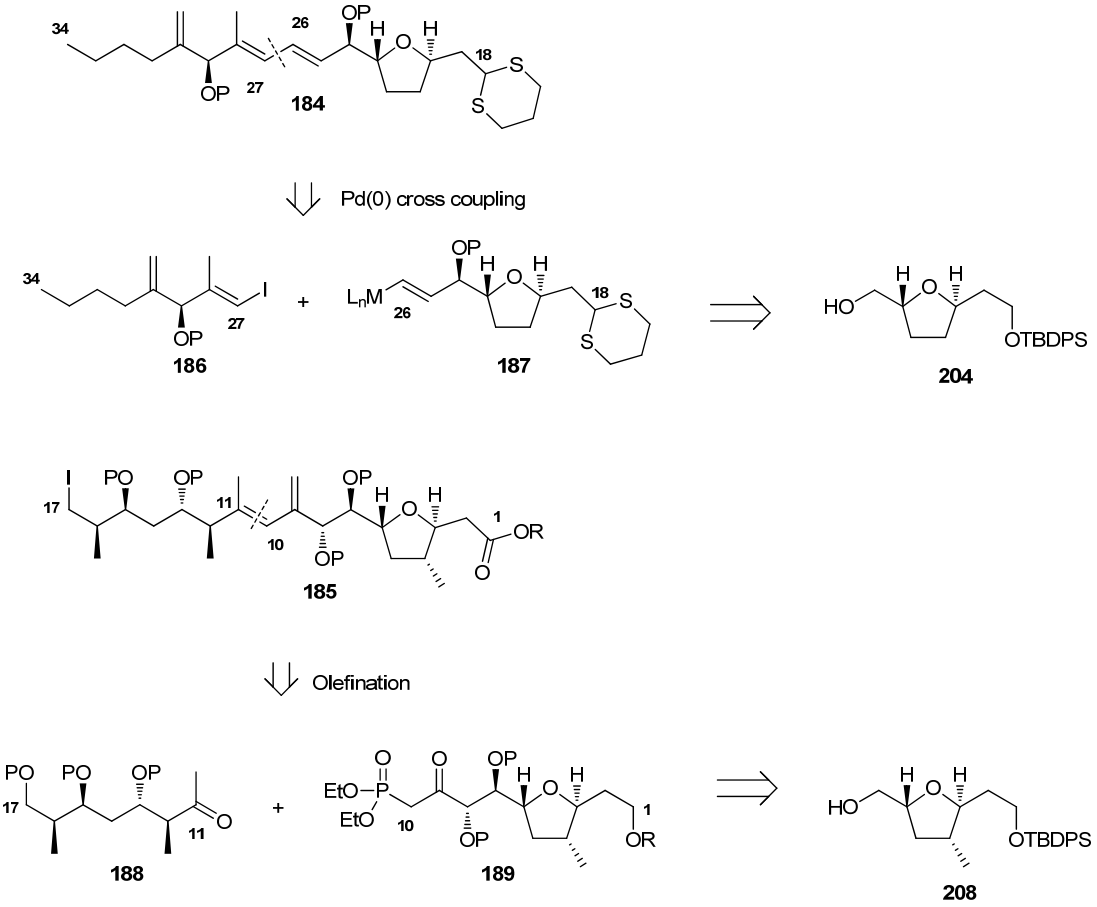


Scheme 54. Clark's Synthesis of the Tetrahydrofuran Intermediate **208**

2. Results and Discussion

2.1 Introduction

Following the successful synthesis of the *trans*-tetrahydrofuran **204** and **208**, the key task was their elaboration into fully-functionalised northern **184** and southern fragments **185** (Scheme 55).

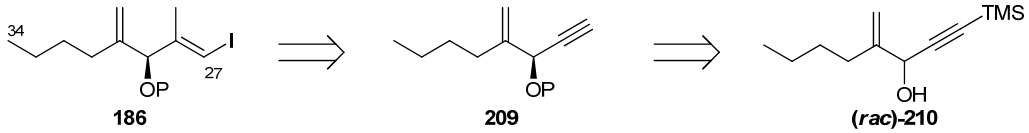


Scheme 55. Retrosynthetic Analysis of Northern **184** and Southern Fragment **189**

2.2 Synthetic Studies on Northern Fragment

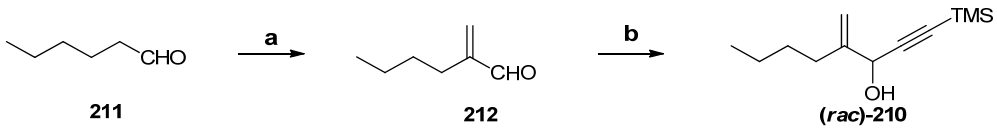
2.2.1 Synthesis of C27-34 Fragment

The C27-C34 fragment **186**, a precursor for the cross coupling reaction, could be obtained from enyne **209** under Negishi carboalumination conditions.[38] The required enantiomer could be obtained from racemic precursor **(*rac*)-210** (scheme 56).[39]



Scheme 56. Retrosynthetic Analysis of Fragment **186**

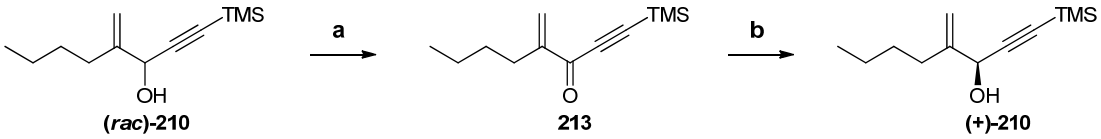
The forward synthesis started from commercially available hexnanal **211**, which could be transformed through a Mannich reaction into the volatile unsaturated aldehyde **212**. After direct Grignard addition to the crude aldehyde **212**, racemic intermediate **(*rac*)-210** was obtained in 73% overall yield (Scheme 57).



Reagents and conditions: **a** CH_2O, $Me_2NH{\cdot}HCl$, water, reflux; **b** *i*-PrMgCl, trimethylsilylacetylene, THF, 0 ºC to rt, 73% over 2 steps.

Scheme 57. Synthesis of Racemic Alcohol **(*rac*)-210**

With the intermediate **(*rac*)-210** in hand, the next challenge was to synthesise optically pure secondary alcohol **(+)-210**. Pagenkopf obtained this alcohol by Corey-Bakshi-Shibata (CBS) reduction of the corresponding enone **213**.[40] Initially, the same method was deployed in our synthesis (Scheme 58). Racemic alcohol **(*rac*)-210** was oxidized with MnO_2 to give the unsaturated enone **213**, which was not stable to storage. CBS reduction of the crude enone **213** led to alcohol **(+)-210**, which was isolated in 82% yield, and 92% *ee*. (*ee* determined by Mosher's method).[41]

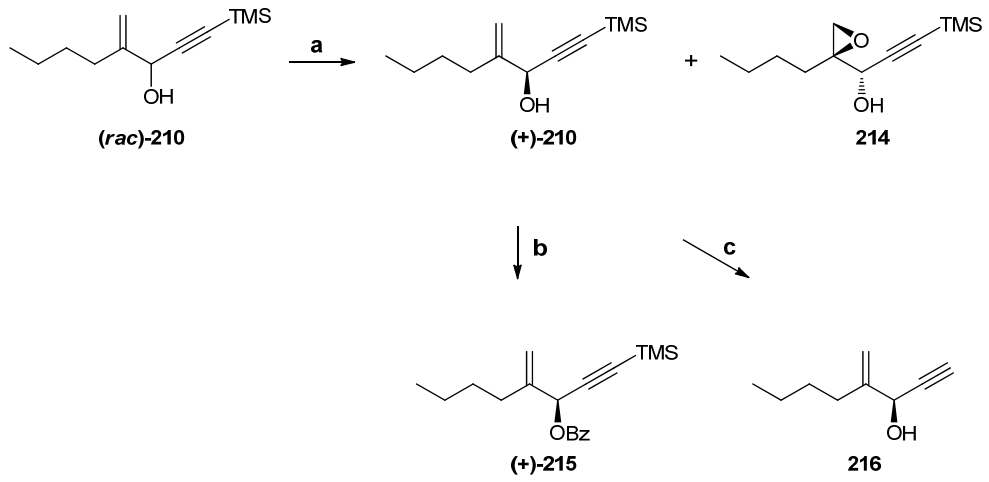


Reagents and conditions: **a** MnO_2, CH_2Cl_2, rt; **b** (*S*)-CBS, $SMe_2 \cdot BH_3$, THF, –10 ºC, 81% over 2 steps.

Scheme 58. Synthesis of **(+)-210** using CBS Reduction

Although this method delivered the allylic alcohol **(+)-210** with high selectivity, the fact that substantial quantities of a chiral reagent were required made this route too expensive to be used for the formation of large quantities of this early-stage intermediate.

We then explored the resolution of racemic allylic alcohol **(*rac*)-210** by a Sharpless kinetic resolution.[39] In this case, (+)-DET was used in order to access the desired (*S*)-alcohol **(+)-210**. Sub-stoichiometric amounts of (+)-DET and Ti(O*i*-Pr)$_4$ were added, followed by 0.7 equiv. TBHP. The reaction was monitored by ^{1}H NMR until conversion of the starting material **210** was greater than 65%. The resulting epoxide **214** and unreactive allylic alcohol **(+)-210** were separated by flash column chromatography. The *ee* value was verified using chiral HPLC. (The corresponding benzyl ester **(+)-215** was synthesised for HPLC experiments). Importantly, improved enantioselectivity was observed when this reaction was performed on a large scale (98% *ee* on 15 g scale, *cf.* 88% *ee* on 0.5 g scale). The TMS group was then removed under basic conditions to yield terminal propargylic alcohol **216**, which was the precursor for the Negishi carboalumination reaction (Scheme 59).

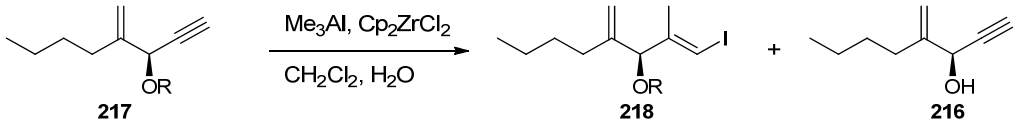


Reagents and conditions: **a** TBHP, (+)-DET, Ti(O*i*-Pr)$_4$, –20 ºC, 35%, 98% *ee*; **b** BzCl, Et$_3$N, DMAP, CH_2Cl_2, rt, 99%; **c** K_2CO_3, MeOH, rt, 93%; **b** PMBTCA, CSA, CH_2Cl_2, rt, 94%; **d** TBSCl, imidazole, DMF, rt, 99%.

Scheme 59. Kinetic Resolution to Afford **(+)-210**

The unprotected propargyl alcohol **216** was exposed to the standard conditions for carboalumination, but the desired product was not observed, even with the addition of water (1.5 equiv.) to accelerate the reaction (Table 2, Entries 1, 2).[42] Then the PMB protected compound was evaluated, but only deprotected alcohol **216** was isolated after the reaction (Entries 3, 4). A possible rationale for the failure of the carboalumination reaction **216** contains three active functionalities: a 1,1-disubstituted double bond, a terminal triple bond and a hydroxyl group. These functional groups could have strong coordinating capability with Zr, locking it away from the desired site of reaction. We introduced a silyl protecting group on secondary hydroxyl position with the expectation that this would reduce the chelating effect between hydroxyl and Zr. In this case, the desired product was formed, and the use of 4 equiv. of Me_3Al led to the best yield (Entries 5–7).

Table 2

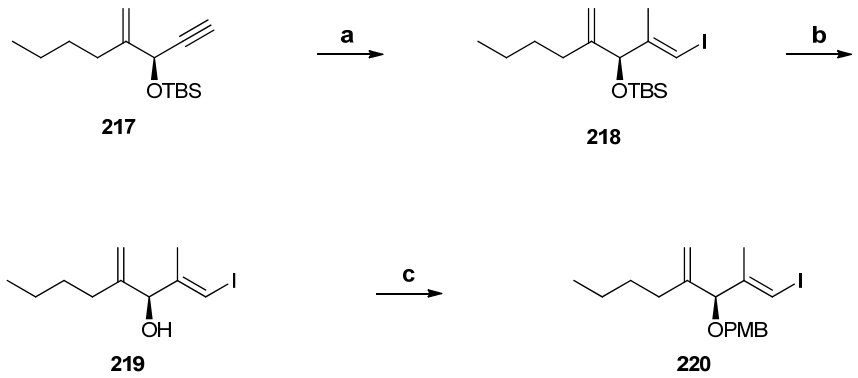


	R	T/°C	Cp_2ZrCl_2 (equiv.)	Me_3Al (equiv.)	H_2O (equiv.)[42]	**218**
1	H	–20	0.2	2	-	0%
2	H	–20	0.2	2	1.5	0%
3	PMB	–20	0.2	2	-	0%[a]
4	PMB	–20	0.2	2	1.5	0%[a]
5	TBS	–20	0.2	2	1.5	trace
6	TBS	–30	0.5	6	1.5	90%[b]
7	TBS	–30	0.5	4	1.5	91%[b]

[a] The PMB ether was cleaved to give **216**

[b] There was an inseparable unknown product contaminant. (4-8% based on ^1H NMR)

Following the success of the carboalumination reaction, a series of different cross-coupling precursors (**218, 219** and **220**) were synthesised (Scheme 60).



Reagents and conditions: **a** Cp_2ZrCl_2, Me_3Al, CH_2Cl_2, water, –30 °C, 91%; **b** TBAF, THF, rt, 42%; **c** PMBTCA, CSA, CH_2Cl_2, 80%.

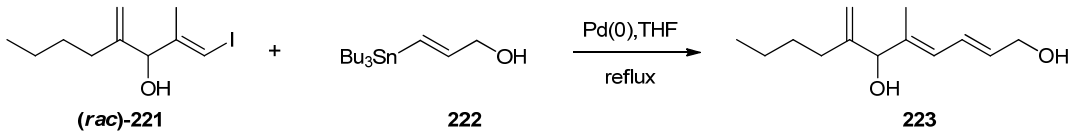
Scheme 60. Synthesis of the C27-C34 Fragments

2.2.2 Model Coupling of Northern Fragment

Initially, the viability of the Stille cross coupling reaction[43] was tested on a model system: racemic vinylic iodide **221** and vinylic stannane **222** (Table 3). The racemic vinylic iodide **221** was synthesized using the same route as for the enantiopure variant (See Scheme 60). The stannane **222** was synthesized by Pd(0)-catalyzed hydrostannylation of propargyl alcohol.[44]

Various conditions for cross-coupling reaction were screened, but in each case an unidentified side product, which might be due to a competing Heck reaction, was observed in conjunction with the desired compound (Table 3). The selectivity was not improved by increasing relative amount of organotin compound **222**.

Table 3

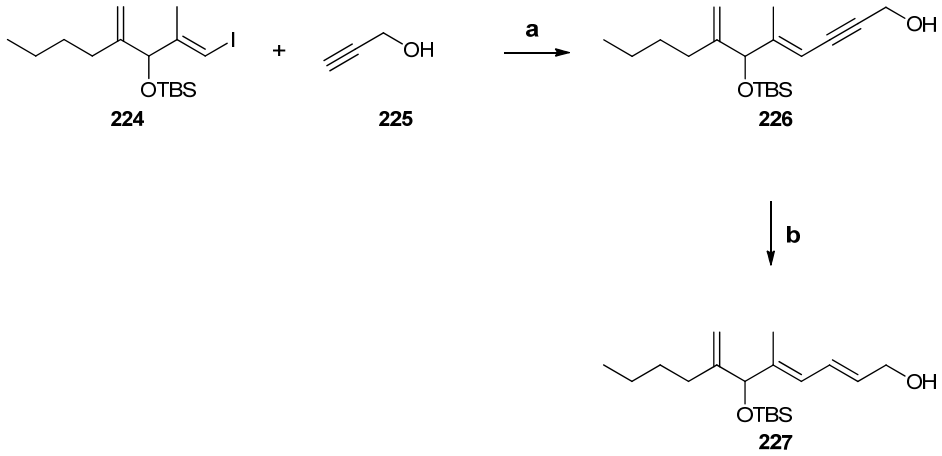


(*rac*)-221 222 223

	Catalyst	Additive	**222** (equiv.)	**221**	**223**
1	$PdCl_2(PPh_3)_2$	-	1.0	recovered	0%
2	$PdCl_2(PPh_3)_2$	PPh_3	1.0	recovered	0%
3	$Pd_2(dba)_3$	$AsPh_3$	1.0	0%	70%[a]
4	$Pd_2(dba)_3$	$AsPh_3$	2.0	0%	62%[a]

[a] Based on the crude NMR, there was an inseparable mixture with 1:1 ratio

As an alternative, the Sonogashira cross coupling[45] reaction was considered, because it is the only Pd-catalysed cross-coupling reaction which is not usually performed at an elevated temperature. Sonogashira reactions have been reported to proceed smoothly at room temperature. In this case, we envisaged that since the Sonogashira reaction could be performed at lower temperature, there would be fewer side reactions. Pleasingly, in the reaction between **224** and **225**, only the Sonogashira coupling product **226** was observed (Scheme 61). Following reduction of **226** by Red-Al, the *E*,*E*-conjugated diene **227** was formed in 65% yield and with excellent regioselectivity.



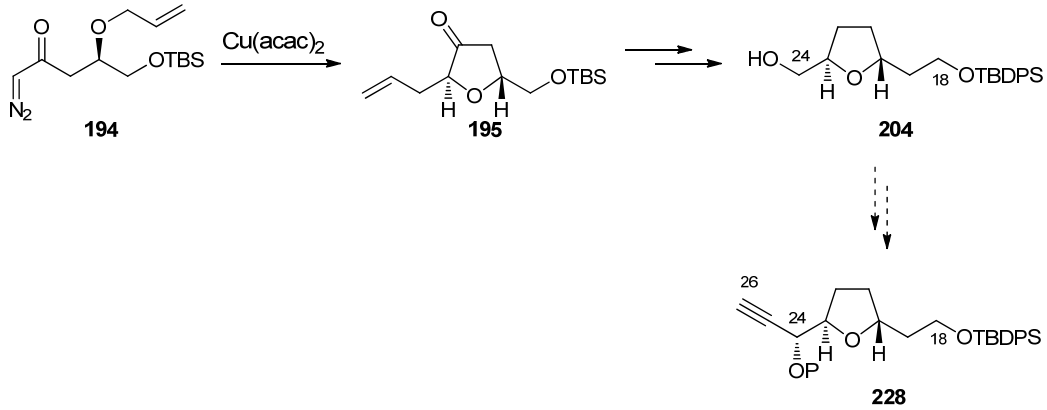
Reagents and conditions: **a** $Pd(PPh_3)_4$, CuI, Et_3N, rt, 85%; **b** Red-Al, Et_2O, 0 ºC to rt, 65%.

Scheme 61. Sonogashira Reaction Followed by Red-Al Reduction Strategy

2.2.3 Synthesis of C16-C28 Fragment

2.2.3.1 Alternative Method to Synthesise *trans*-Tetrahydrofurans

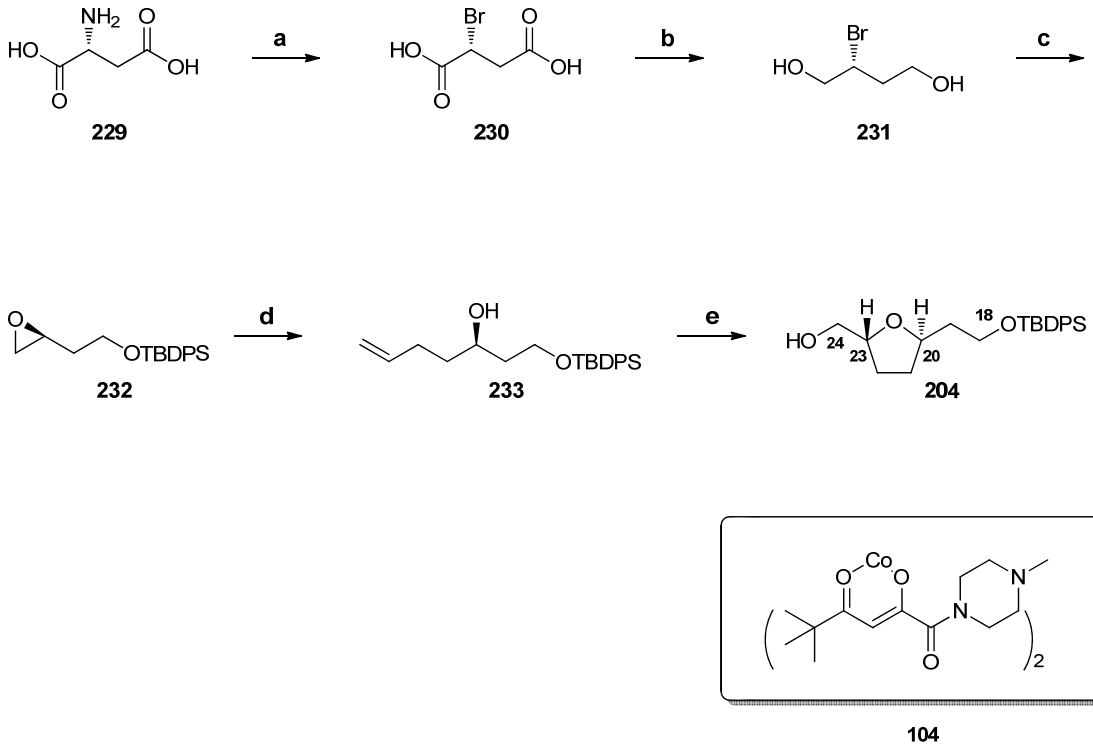
The next task was to prepare the alternative Sonogashira coupling partner **228** from the *trans*-tetrahydrofuran **204** (Scheme 62).



Scheme 62. Clark's Synthesis of *trans*-Tetrahydrofuran **228**

Previously, the *trans*-tetrahydrofuran systems had been obtained by copper-catalysed rearrangement of the diazo ketone **194** (Chapter 1.6).[35] However, this approach used diazomethane in the preparation of **194** and so for large scale work, an alternative approach was considered.

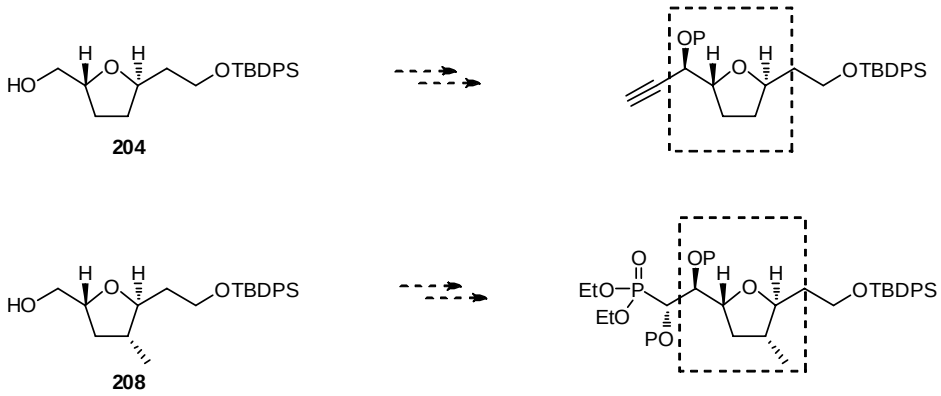
Pagenkopf and co-workers demonstrated a quick and efficient formation[7] of a *trans*-tetrahydrofuran using a Mukaiyama aerobic oxidative cyclisation reaction (Chapter 1.4.5).[39] We wanted to apply this method to this synthesis of fragment **204** (Scheme 63). Specifically, the diazotization of D-aspartic acid **229** using $NaNO_2$ and KBr in aqueous acid solution provided the bromide **230** in 86% yield.[46] Reduction of acid **230**, followed by treatment of diol **231** with NaH and TBDPSCl delivered the epoxide **232**. Opening the epoxide using allyl Grignard reagent gave alcohol **233** in 90% yield.



Reagents and conditions: **a** $NaNO_2$, H_2SO_4, KBr, water, 0 ºC to rt, 86%; **b** $BH_3 \cdot SMe_2$, THF, 0 ºC to rt, 80%; **c** NaH, TBDPSCl, THF, 0 ºC to rt, 97%; **d** allylmagnesium chloride, Et_2O, 0 ºC to rt, 90%; **e 104**, TBHP, O_2, *i*-PrOH, 55 ºC, 82%.

Scheme 63. Alternative Method to Synthesise of *trans*-Tetrahydrofuran **204**

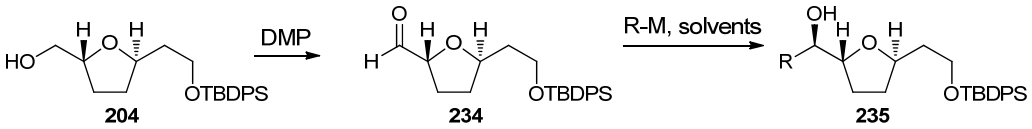
Due to the pseudo-symmetry of both northern and southern fragments, stereoselective introduction of the hydroxyl group at the α-positon of both tetrahydrofuran fragments was the next challenge (Scheme 64). Many efforts have been made to optimize the diastereometric control of a newly formed chiral centre adjacent to a 2,5 *trans*-tetrahydrofuran.



Scheme 64. Introduction of the Hydroxyl group at α-Positon of Tetrahydrofuran

In this case, direct Grignard addition was not highly stereoselective and delivered mixtures of two diastereoisomers (Table 4).

Table 4



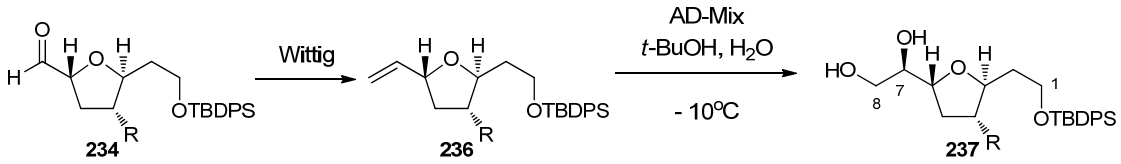
Entry	Conditions	Solvents	T/°C	R	Yield	*dr*[a]
1	HCCMgBr	Et_2O	0 to rt	HCC-	68%	3:2.3
2	TMSCCLi	THF	0 to rt	TMSCC-	71%	3:2[b]
3	TMSCCLi	TBME	–90	TMSCC-	35%	3:1[b]

[a] *dr* was indetifined based on crude ^{1}H NMR datas.

[b] The two diastereoisomers were separated by careful chromatography in silica gel. And the stereochemistry was confirmed based on comparison of the NMR datas with the Gleason's work.[47]

Next, Sharpless asymmetric dihydroxylation (AD) was investigated to introduce the new stereogenic centre. The use of AD-mix α did not deliver good levels of diastereocontrol (3:2) (Table 5, Entry 1) and use of AD-mix β led to the diol with undesired configuration at the newly created stereogenic centre as the major product (Table 5, Entries 2, 3).

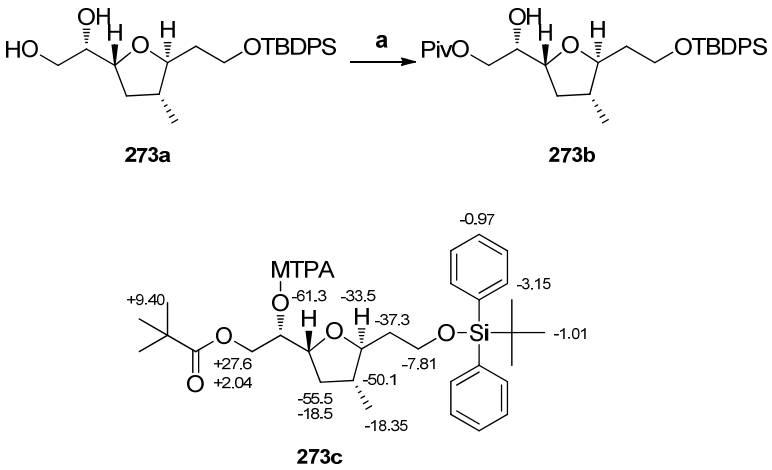
Table 5



Entry	R	Conditions	Yield	*dr*[a]
1	Me	AD-mix α	90%	1:0.67
2	Me	AD-mix β	91%	1:7[b]
3	H	AD-mix β	90%	1:7[b]

[a] *dr* was indentified based on the crude ^{1}H NMR datas.

[b] The stereochemistry of the major diastereoisomer was confirmed by Mosher's method (Scheme 65).[40]



Reagents and conditions: **a** PivCl, Et_3N, DMAP, CH_2Cl_2, rt, 53%.

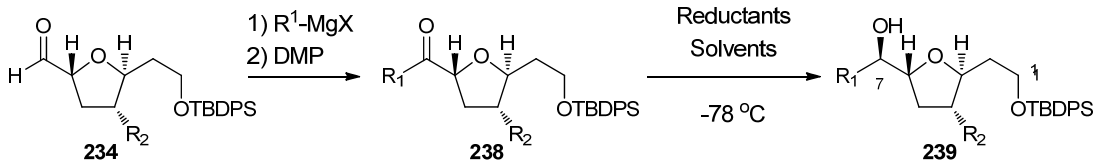
^{1}H NMR shift differences {δ [(R)-MTPA]-δ [(S)-MTPA]} reported in Hertz ($CDCl_3$, 500 MHz)

Scheme 65. Confirmation of the Stereochemistry of Diol **237a**

Due to the difficulties of introducing the hydroxyl group with R configuration at the new stereo centre, an alternative diastereoisomeric reduction strategy was considered.

Reduction of the appropriate ynone or enone with L-Selectride and $Na(OAc)_3BH$ did not result in high selectivity for the desired product (Table 6, Entries 1, 2, 3). However, Luche reduction of the enone led to the desired Felkin-Anh products with excellent selectivity (Table 6, Entries 4, 5).

Table 6



Entry	R_1	R_2	Conditions	yield	*dr*[c]
1	TMSCC-	H	L-Selectride, THF	81%	1.3:1[d]
2	TMSCC-	H	$Na(OAc)_3BH$, AcOH, MeCN	-[a]	1.2:1[d]
3	CH_2CH-	H	L-Selectride, THF	0%[b]	-
4	CH_2CH-	Me	$CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH	78%	10:1[e]
5	CH_2CH-	H	$CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH	78%,	>15:1[e]

[a] For ^{1}HNMR studies, no isolated yield available

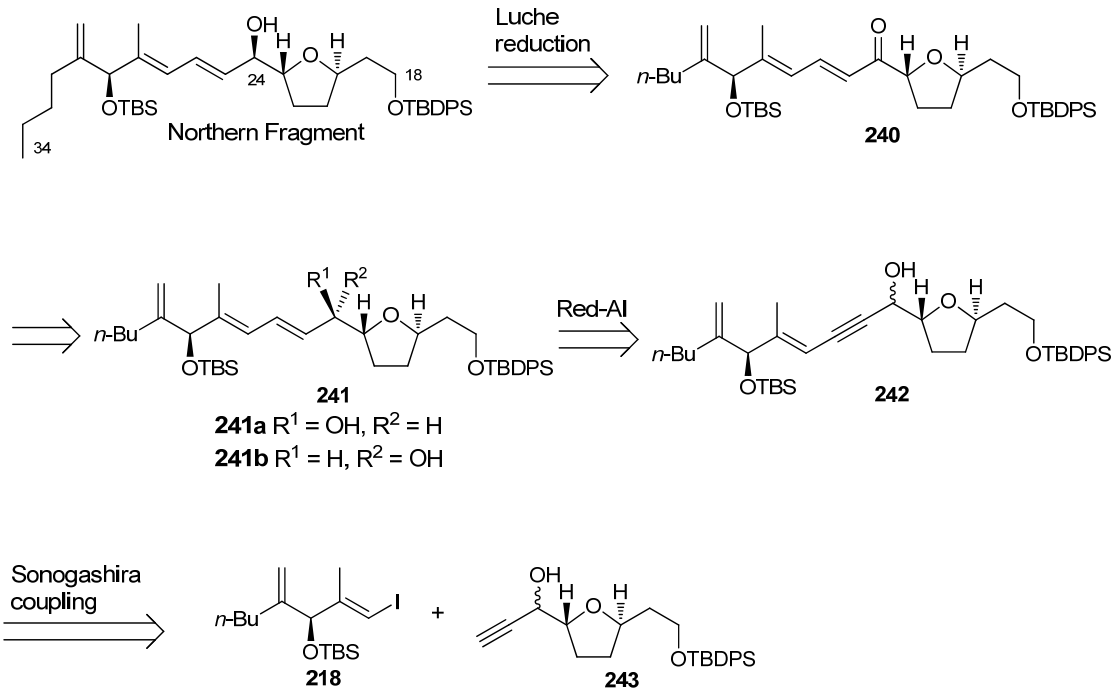
[b] Conjugate reduction was observed under these conditions

[c] *dr* was indentidied based on the crude ^{1}H NMR datas.

[d] The stereochemistry of newly formed alcohol was confirmed by comparison of the ^{1}H NMR datas with the Gleason's work.[47]

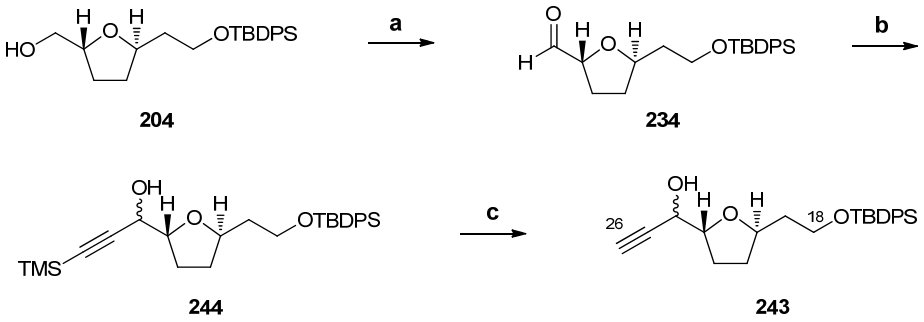
[e] The stereochemistry of newly formed alcohol was confirmed by comparison of the ^{1}H NMR datas with Spilling's work.[5b]

Following the success of the model system, the revised strategy for synthesis of the northern fragment is outlined in Scheme 66. The hydroxyl group at C24 of the northern fragment would be furnished by Luche reduction of the corresponding dienone **240**. The dienone would be derived from alcohol **241**, which would in turn be obtained by Red-Al reduction of enyne **242**. The compound **242** could be prepared by Sonogashira coupling between vinylic iodide **218** and propargylic alcohol **243**.



Scheme 66. Alternative Strategy for Synthesis of Northern Fragment

In a forward sense, the synthesis of compound **243** was straightforward (Scheme 67). Oxidation of the primary alcohol **204** using the Dess-Martin protocol provided the aldehyde **234**. Nucleophilic addition of an alkyne to the aldehyde **234** gave the propargyl alcohol **244** as a diastereoisomer mixture (*dr* = 3:4). Removal of the TMS protecting group in methanol in the presence of K_2CO_3 afforded the C18-C26 fragment **243**.

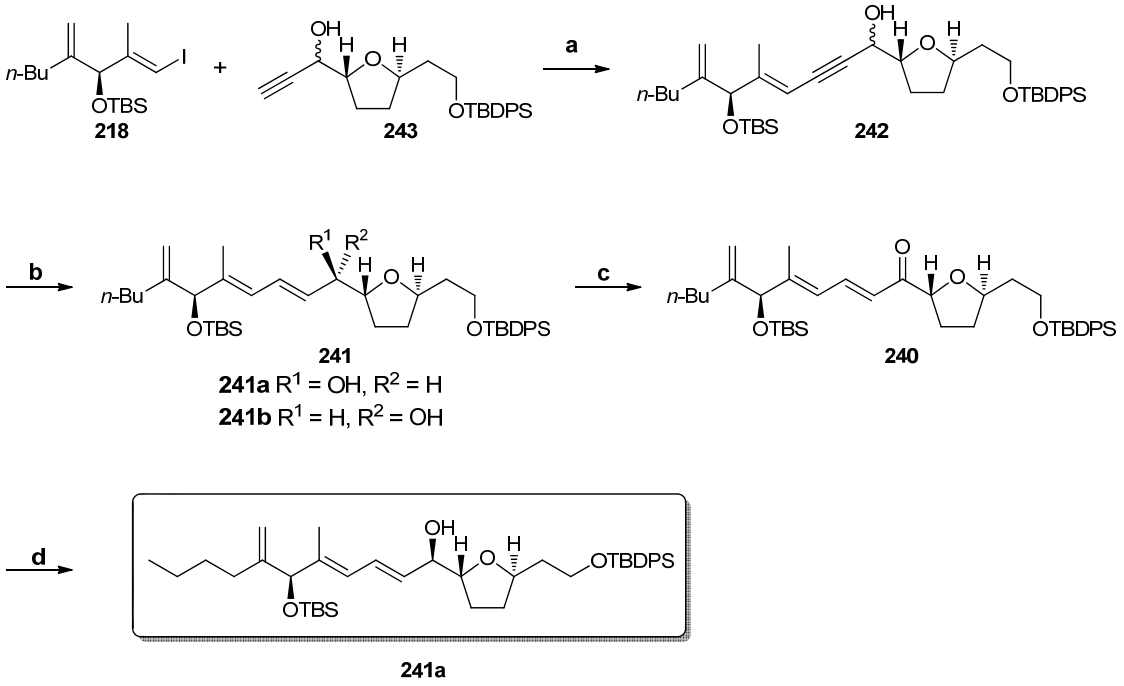


Reagents and conditions: **a** Dess-Martin periodinane, CH_2Cl_2, rt, 85%; **b** Me_3SiCCH, *n*-BuLi, –78 ºC, 75%; **c** K_2CO_3, MeOH, rt, 98%.

Scheme 67. Synthesis of the C18-C26 Fragment **243**

2.2.4 Coupling of the Northern Fragment

With both of the coupling partners **218** and **243** available, the next objective was to connect them using the Sonogashira coupling reaction (Scheme 68), the viability of which had been demonstrated using the model system.



Reagents and conditions: **a** $(Ph_3P)_2PdCl_2$, CuI, Et_3N, 50 ºC, 80%; **b** Red-Al, Et_2O, 0 ºC, 63%; **c** Dess-Martin periodinane, CH_2Cl_2, rt, 100%; **d** $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, –78 ºC, 82%.

Scheme 68. Synthesis of the Northern Fragment **241a**

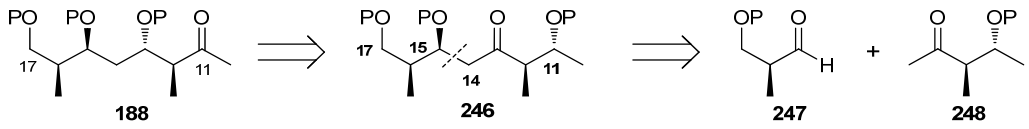
Coupling of the vinylic iodide **218** to a mixture of the propargylic alcohols **243** under Sonogashira conditions was achieved in 80% yield (Scheme 68). Practically, there were some problems during this procedure. The terminal alkyne fragment **243** was found to be very reactive with the CuI catalyst, which led to rapid dimerization. The process required oxygen-free conditions (degassing by bubbling Ar through the solution). To reduce the generation of this side product, the mixture of Pd(0) and vinylic iodide **218** was preheated to 50 °C and alkyne **243** was added dropwise using a syringe pump over 2 hours. This process allowed alkyne **243** to react as soon as it was added into the reaction flask. Lastly, TLC analysis always showed a complex mixture due to coordination of Pd(0) to the product. However, it was found that quenching the reaction with chloroform could reduce coordination and facilitate chromatography. Following the success of the Sonogashira reaction, the propargylic alcohol functionality of the coupled product **242** allowed regioselective alkyne reduction to be achieved using Red-Al, to give the desired *E*-configured alkene **241**. Oxidation of this diastereomeric mixture of allylic alcohols, to give the corresponding dienone **240**, was accomplished in quantitative yield using Dess-Martin periodinane. Subsequent stereoselective Luche reduction of the dienone **240** provided the alcohol **241a** in 82% yield as a single stereoisomer, which was the Felkin-Anh addition product. A similar reduction approach using L-Selectride was reported by Spilling and co-workers.[5b]

After optimisation, the functionalised northern fragment **245** was synthesised in an efficient manner. The synthesis described in this chapter proceeded in 12 steps with 13% overall yield.

2.3 Studies on Synthesis of Southern Fragment

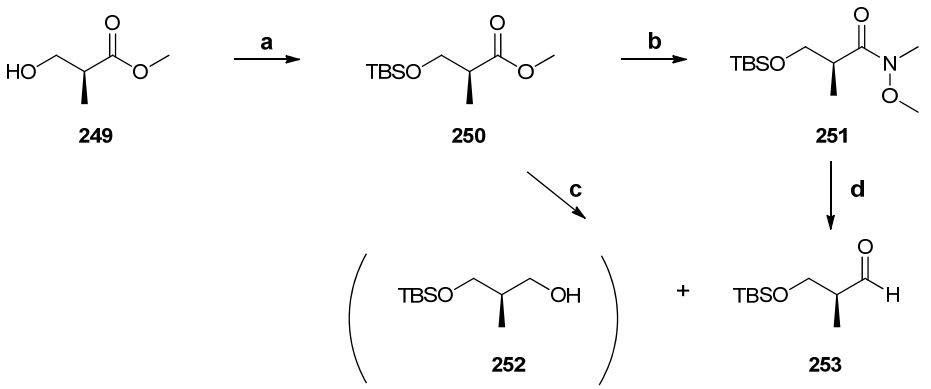
2.3.1 Synthesis of C11-C17 Fragment

The next challenge was the synthesis of the southern fragment. Recalling our retro-synthetic strategy, the C11-C17 carbon skeleton **246** was disconnected to deliver the aldehyde **247** and methyl ketone **248**, suggesting the use of a diastereoselective aldol reaction[48] to accomplish C–C bond formation in the forward direction (Scheme 69).



Scheme 69. Retrosynthetic Analysis of the C11-C17 Fragment **188**

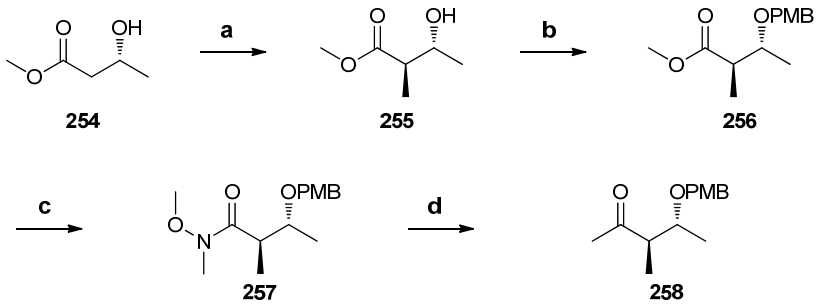
The synthesis began by preparing aldehyde **253**, using (*S*)–Roche ester **249** as starting material (Scheme 70). Protection of the primary alcohol afforded the TBS protected ester **250**. Direct reduction of ester **250** to the aldehyde **253** was difficult. Using 1.0 equiv. of DIBAL led to incomplete conversion. With more equivalents of DIBAL, the over-reduced product **252** was formed. Furthermore, aldehyde **253** was also found to undergo epimerization during purification on silica gel. To solve this, treatment of ester **250** with *N,O*-dimethyl hydroxylamine hydrochloride in the presence of *i*-PrMgCl as base, provided the Weinreb amide **251**. The aldehyde **253** was obtained by amide reduction using DIBAL, and was used for the next step without chromatographic purification.



Reagents and conditions: **a** TBSCl, imidazole, DMAP, CH_2Cl_2, rt, 97%; **b** Me(MeO)NH·HCl, *i*-PrMgCl, –15 ºC, 95%; **c** DIBAL, THF, –78 ºC; mixture of **252** and **253**; **d** DIBAL, THF, –78 ºC, 91% of **253**

Scheme 70. Synthesis of the Aldehyde **253**

Next, the other component for aldol reaction-methyl ketone **258** was synthesised in four steps (Scheme 71). Selective α-methylation of the commercially available alcohol **254**, provided the *anti*-product **255**.[49] PMB-protection of the secondary alcohol using the Lewis acid catalyst $La(OTf)_3$, gave the PMB ether **256**.[50] Weinreb amide formation from **256** using the same conditions as employed previously did not result in full conversion.[51] Starting material was always recovered after even increasing the amount of reagent or prolonging the reaction time. The best yield obtained was 67% yield over 2 steps. Grignard addition to Weinreb amide **257** was slow at room temperature, and heating the reaction up to 55 ºC was necessary to complete the reaction and deliver the desired methyl ketone **258** in good yield.

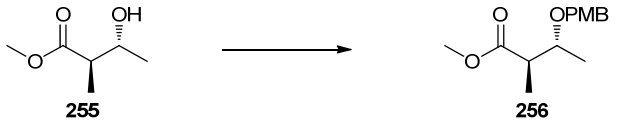


Reagents and conditions: **a** LDA, DMPU, MeI, THF, –78 ºC, 85%, *dr* = 10:1; **b** PMBTCA, $La(OTf)_3$, PhMe, rt; **c** Me(MeO)NH·HCl, *i*-PrMgCl, –15 ºC, 67% over 2 steps; **d** MeMgBr, THF, 55 ºC, 91%.

Scheme 71. Synthesis of the Ketone **258**

Various reaction conditions were investigated for the PMB protection (Table 7). Substrate **255** decomposed under basic conditions (Entry 1), and treatment with PMBCl and Ag_2O gave an inseparable mixture of products (Entry 2), so the use of PMBTCA with various acid catalysts was investigated. Using CSA or $La(OTf)_3$ delivered product **256** in the best yield (Entries 5, 6). However, shorter reaction time made $La(OTf)_3$ the most efficient catalyst for this reaction amongst those screened. Furthermore, purification proved to be difficult due to the presence of a decomposition compound arising from PMBTCA which had polarity similar to that of the product **256**. In this case, we decided to use the crude product in the next step directly.

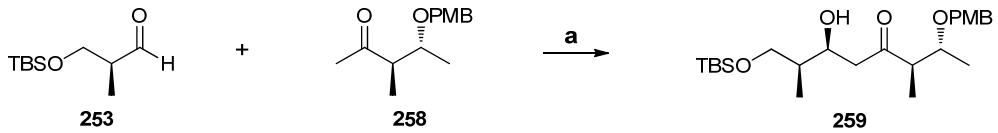
Table 7



Entry	Conditions	T	Solvents	Time/h	**256**
1	PMBCl (1.5 equiv.), NaH	0 ºC	Et_2O	1	0%
2	PMBCl (2.0 equiv.), Ag_2O	rt	THF	18	NA[a]
3	PMBTCA (2.0 equiv.), TFA	0 ºC	Et_2O	2	Trace
4	PMBTCA (2.0 equiv.), PPTS	rt	CH_2Cl_2	48	46%[b]
5	PMBTCA (2.0 equiv.), CSA	rt	CH_2Cl_2	10	85%[b]
6	PMBTCA (1.5 equiv.), $La(OTf)_3$	rt	PhMe	2	85%[b]

[a] Compound **256** and $(PMB)_2O$ was the same R_f value, making them difficult to separate by flash chromatography on silica gel.
[b] Crude yield, calculated by ^1H NMR.

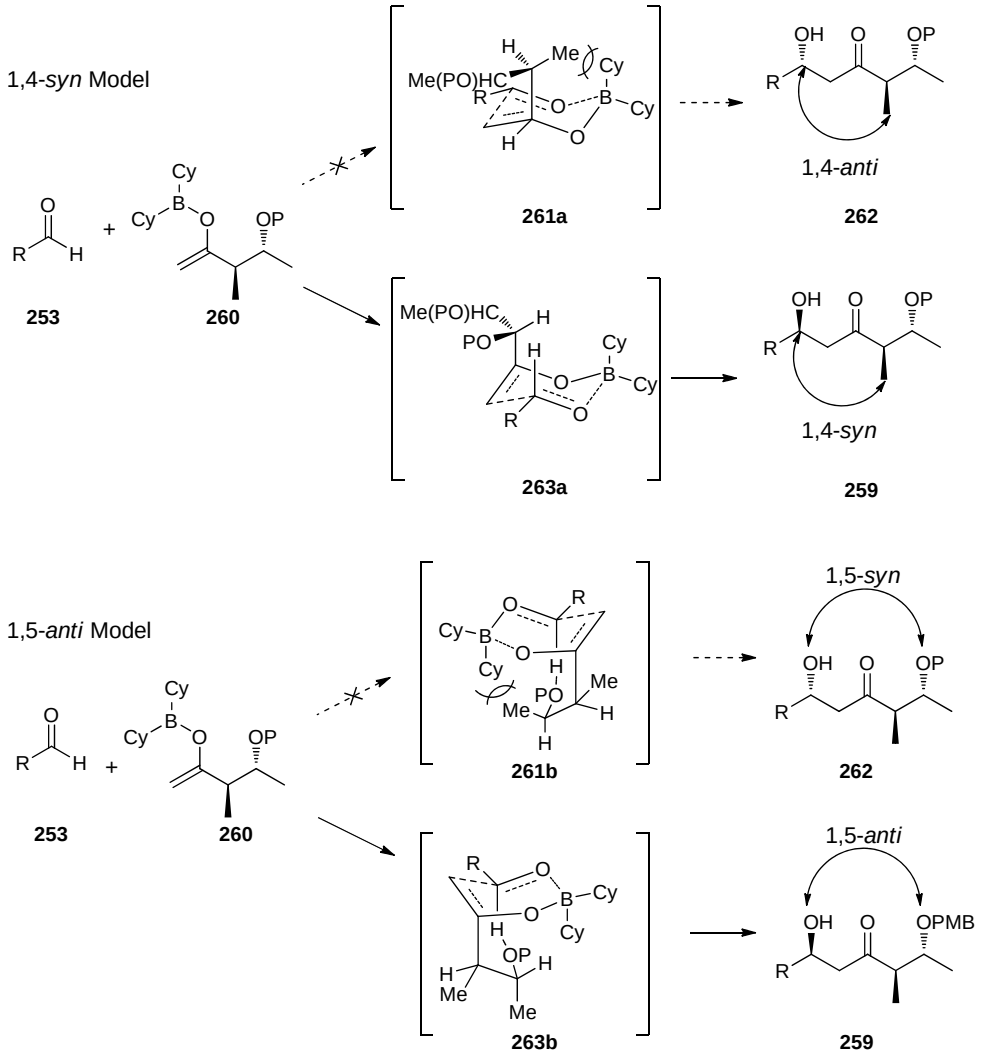
With both reactants in hand, the key aldol reaction could be investigated. Under Paterson's conditions a 1,5-*anti* aldol reaction was used to construct the carbon skeleton of the C11-C17 fragment (scheme 72).[48a]



Reagents and conditions: **a** (c-C_6H_{11})$_2$BCl, Et_3N, Et_2O, –78 ºC, 95%, *dr* > 20:1.

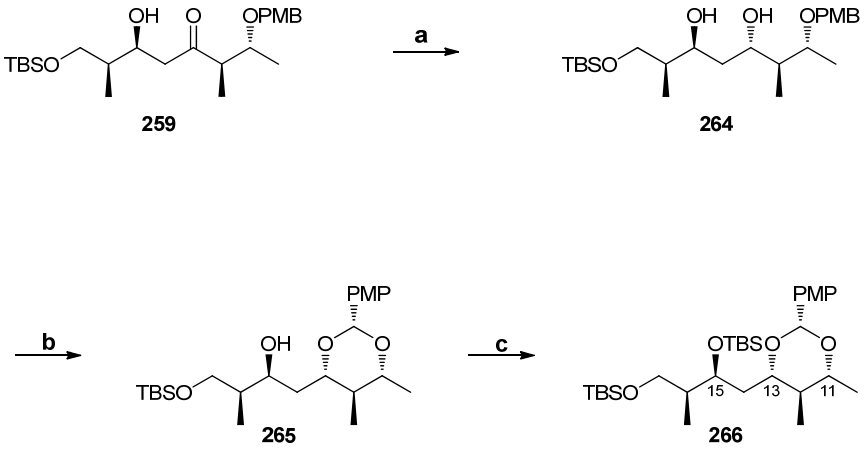
Scheme 72. Synthesis of the C11–C17 Fragment Using Aldol Reaction

The excellent diastereoselectivity of the reaction could be rationalised by reinforcement by both 1,4-*syn* and 1,5-*anti* control (Scheme 73).[48c] The transition states **263a** and **263b** were preferred due to the minimization of steric interactions between axial cyclohexyl group on boron and the axial side chain of the enolate.



Scheme 73. 1,4-*syn* and 1,5-*anti* Aldol Reaction

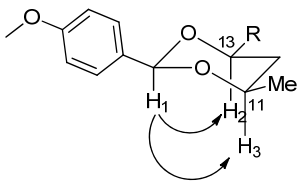
With the β-hydroxy ketone **259** in hand, a hydroxyl-directed reduction using tetramethylammonium triacetoxyborohydride, developed by Evans and co-workers, provided the 1,3-*anti* diol **264**.[52] Benzylic oxidation with DDQ in anhydrous CH_2Cl_2 and in the presence of molecular sieves led to the formation of PMP acetal **265** (Scheme 74).[53] Secondary alcohol protection then gave the fully protected intermediate **266**.



Reagents and conditions: **a** $Me_4NBH(OAc)_3$, AcOH, MeCN, –30 ºC, 91%; **b** DDQ, CH_2Cl_2, 0 ºC, 83%; **c** TBSCl, imidazole, DMF, rt, 94%.

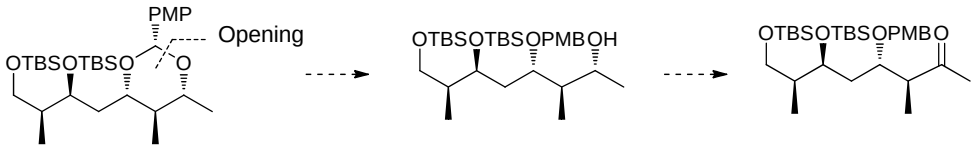
Scheme 74. Synthesis of the Acetal **266**

The NOE studies of acetal **266** suggested the *syn* relationship at C11 and C13. It indicated the 1,5-*anti* relationship between two hydroxyls at C11 and C15 (Scheme 75).



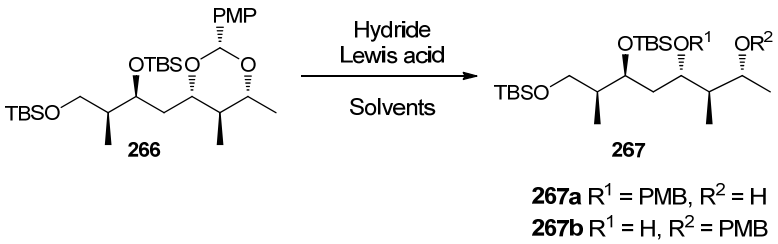
Scheme 75. NOE Study for the Acetal **266**

The next challenge was to open the PMP acetal in a regioselective manner (Scheme 76). If the PMP acetal could be cleaved at the desired position, the methyl ketone could then be readily synthesised.



Scheme 76. Proposed Approach for the Synthesis *via* an Acetal Cleavage

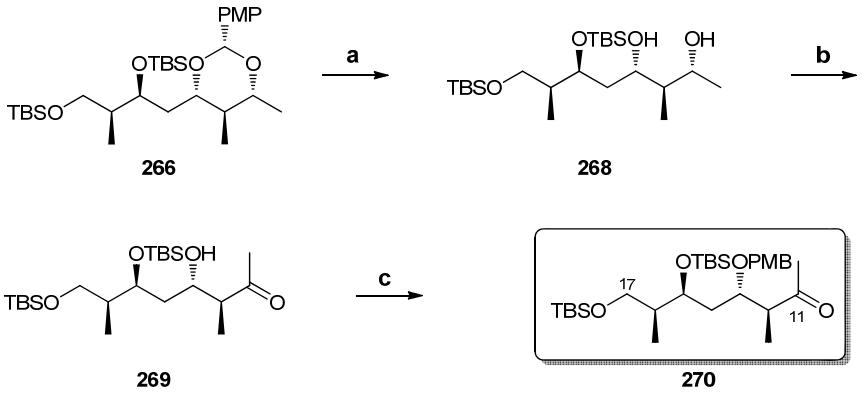
Many different conditions and reagents have been investigated to perform this acetal cleavage process.[54] In summary, the reaction requires a Lewis acid and a hydride source. Specifically, the Lewis acid coordinates the acetal to form an oxonium species, and hydride opens the ring by reduction.



Scheme 77. Proposed Approach for the Synthesis *via* an Acetal Cleavage

DIBAL is both a reducing reagent (hydride source) and a strong Lewis acid, but when the reaction was performed in toluene as solvent, only a small amount of the desired compound **267a** was observed; the TBS deprotected compound was formed as the major product. When the solvent was changed to DCM or THF, decomposition of starting material was observed without product formation. It was also observed that, with less than 10 equiv. of DIBAL,[54d] there was no consumption of the starting material. Alternatively, when Bu_3SnH was used in the presence of $MgBr_2 \cdot Et_2O$,[54c] the reaction gave 56% conversion. However, the result was disappointing; with 72% of the undesired product **267b** formed and 18% of products resulting from with migration of the TBS group. Borohydride derivatives: $NaBH_3CN$ and $NaBH(OAc)_3$ were also evaluated, but none of the desired product was observed.

Following this problem with the initial strategy, an alternative approach was examined. Removal of the PMP acetal under hydrogenolysis conditions using a catalytic amount $Pd(OH)_2$, provided diol **268** in 94% yield. Next, it was found that TEMPO oxidation led to the conversion of one secondary alcohol into ketone **269** with impressive regioselectivity.[55] The only drawback was that the reaction was slow, usually taking between two weeks and one month to complete. The possible reason for the selectivity might be that TEMPO reacted faster with the less hindered hydroxyl group. The remaining secondary hydroxyl group was protected with PMB under acidic conditions to deliver the C11-C17 fragment **270** (Scheme 78).



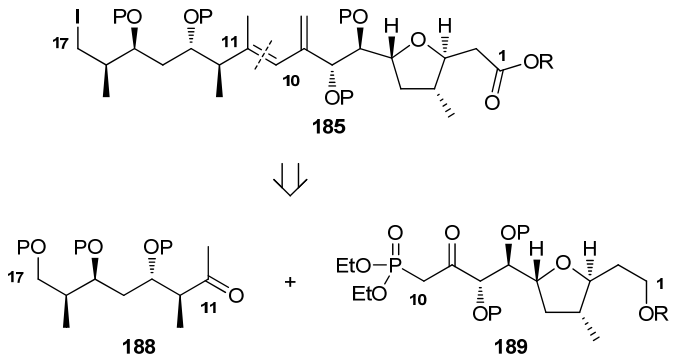
Reagents and conditions: **a** $Pd(OH)_2/C$, H_2, EtOAc, rt, 94%; **b** TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 94%; **c** PMBTCA, CSA, CH_2Cl_2, rt, 76%.

Scheme 78. Completing the Synthesis of the C11-C17 Fragment **270**

2.3.2 Model Studies on the Coupling of the Southern Fragment

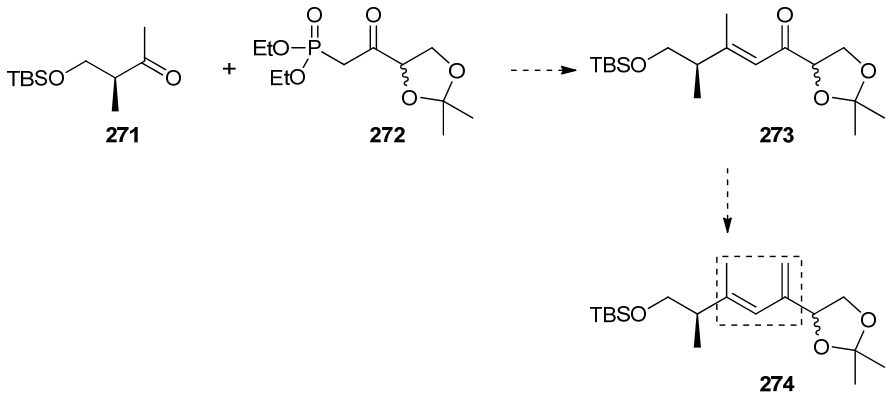
2.3.2.1 HWE Olefination Modeling

The original strategy for the synthesis of the southern fragment **185** was to use a HWE olefination coupling reaction between methyl ketone **188** and phosponate ester **189** (Scheme 79).



Scheme 79. Retrosynthetic Analysis of C1-C17 Fragment of Amphidinolide C

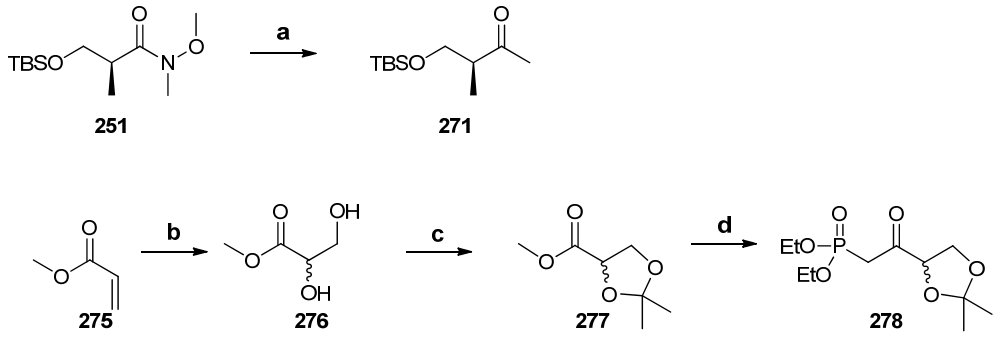
In order to evaluate the key coupling strategy, a HWE model for this key coupling reaction was considered (Scheme 80).



Scheme 80. HWE Models System

The synthesis of the starting materials was straightforward (Scheme 81). Addition of methylmagnesium bromide to the Weinreb amide **251** led to methyl ketone **271**.

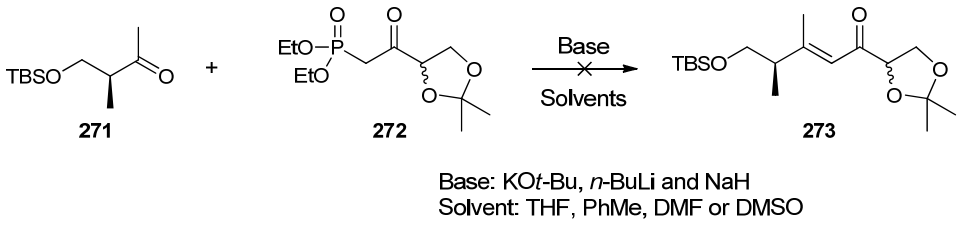
Dihydroxylation of methyl acrylate **275** gave the diol **276** in 34% yield. The low yield from the reaction was due to difficulties in isolation of the product as it was highly soluble in water. Acetonide formation of **276** provided acetal **277**. Treatment of **277** with diethyl methylphosphonate and *n*-BuLi gave the coupling partner **278**.



Reagents and conditions: **a** MeMgBr, THF, rt, 99%; **b** OsO_4, NMO, acetone, water, rt, 34%; **c** $Me_2C(OMe)_2$, CSA, rt, 93%; **d** $(EtO)_2P(O)Me$, *n*-BuLi, THF, –78 °C, 81%.

Scheme 81. Preparation the Starting Material for Model System

With both of the coupling substrates in hand, several coupling conditions were investigated (Scheme 82). The use of KO*t*-Bu, *n*-BuLi and NaH as base, along with THF, PhMe, DMF or DMSO as solvent was evaluated. In each case, there was no reaction at ambient temperature, and higher temperature (60 °C to reflux) led to decomposition of ketone **271**.

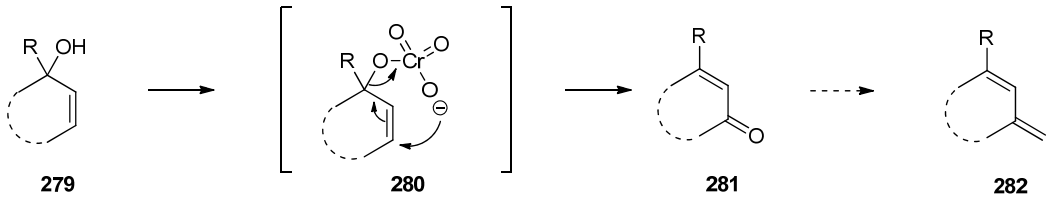


Scheme 82. Model Reactions between **271** and **272**

Based on all of the studies on the model systems, and due to the low reactivity of the ketone, HWE coupling were proved unsuitable for the coupling of units to give **273**.

2.3.2.2 Oxidative Rearrangement of Tertiary Allylic Alcohol

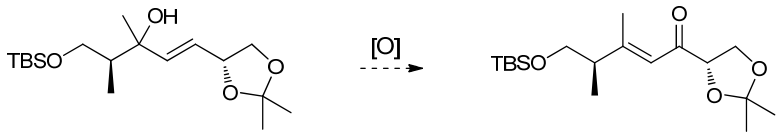
A new approach to the synthsis of diene **282** was considered. The idea was to synthesise an enone **281** through a rearrangement reaction promoted by Cr oxidants (Scheme 83).



Scheme 83. Proposed Approach *via* Enone **282**

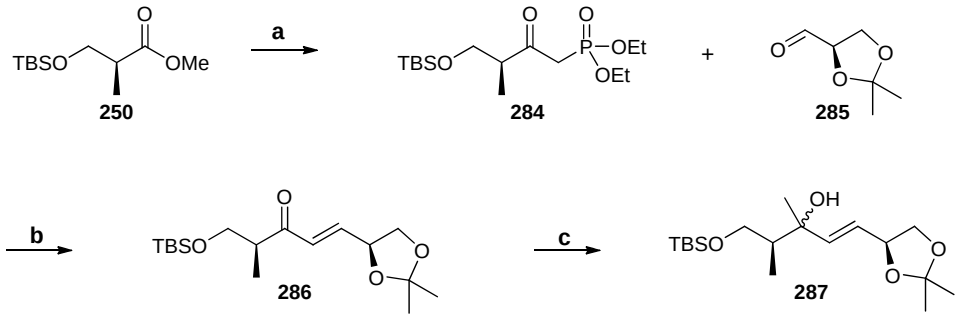
Many publications have documented the intramolecular oxidative rearrangement of tertiary allylic alcohols. [56-60] Treatment of the tertiary alcohol with Cr oxidant (such as PCC) induces oxidative rearrangement *via* the transition state **280** to yield the substituted conjugated enone **281** (scheme 86). In 2004, Iwabuchi and co-workers reported that 2-iodoxybenzoic acid (IBX) could be used instead of toxic Cr(VI) oxidants for the oxidative rearrangement of tertiary allylic alcohols.[56] In 2008, the same research group reported that TEMPO-derived oxoammonium salts ($TEMPO^{+}\cdot BF_4^{-}$and $TEMPO^{+}\cdot SbF_6^{-}$) were more effective as stoichiometric reagents for the transformation of acyclic tertiary allylic alcohols in acetonitrile.[57] Very recently, Iwabuchi's group used sub-stoichiometric amounts of TEMPO with $NaIO_4$-SiO_2 as a co-oxidant in dichloromethane.[58] Also, another rearrangement reaction was reported in which powdered Oxone ($2KHSO_5\cdot KHSO_4\cdot K_2SO_4$) was used in combination with sub-stoichiometric amounts (0.05–5 mol%) of 2-iodobenzenesulfonic acid or its sodium salt under non-aqueous conditions.[59]

These extensive studies encouraged us to utilise this approach to construct the key connection in the southern fragment. A new model was built to investigate this proposal (Scheme 84).



Scheme 84. Proposed Approach for the Model System

Synthesis of starting material **287** proved to be straightforward (Scheme 85). Treatment of the ester **250**, derived from the Roche ester, with *n*-BuLi and diethyl methylphosphonate produced phosphonate ester **285**. A stereoselective HWE reaction then coupled **285** and known aldehyde **284** in the presence of NaH to give the *E*-enone **287**.

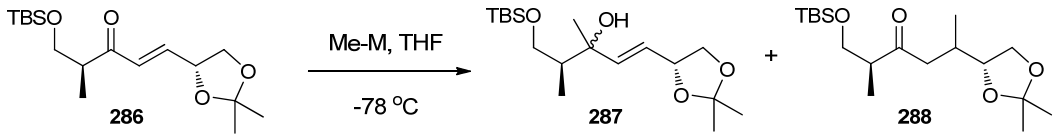


Reagents and conditions: **a** $(OEt)_2P(O)Me$, *n*-BuLi, THF, –78 °C, 77%; **b** NaH, THF, 0 °C to rt, 92%, **c** $CeCl_3$, MeLi, THF, 0 °C to rt, 88%.

Scheme 85. Synthesis of the Starting Materials for the Model System

Addition of methyl–metal reagents to the enone **286** was problematic (Table 8). Direct organolithium or Grignard addition gave the 1,4-addition product **288** as the major product (Entries 1 and 2). However, treatment of **286** with MeLi in the presence of anhydrous $CeCl_3$ led to the desired 1,2-addition product **287** exclusively (Entry 3).

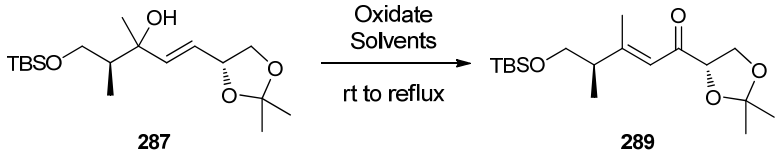
Table 8



Entry	Reagents	Additive	**287**	**288**
1	MeLi	NA	25%	40%
2	MeMgBr	NA	22%	50%
3	MeLi	$CeCl_3$	88%	0%

With the precursor **287** in hand, various oxidants were screened as reagents for the proposed desired oxidative rearrangement reaction (Table 9). Treatment of **287** with PDC produced only trace amount of product (less than 5%, observed by ^{1}H NMR), with mostly starting material remaining (Entry 1). The use of PCC gave full consumption of the starting material, but none of the desired product was observed (Entry 2). TEMPO and IBX did not react with allylic alcohol **287** (Entries 3, 4) and oxone led to decomposition of the starting material (Entry 5).

Table 9



Entry	Oxidants	Solvents	**289**
1	PDC	CH_2Cl_2	trace
2	PCC	CH_2Cl_2	0%[a]
3	TEMPO/$NaIO_4$	CH_2Cl_2	0% (Recovery of **287**)
4	IBX	DMSO	0% (Recovery of **287**)
5	Oxone	MeCN	0% (Decomposition of **287**)

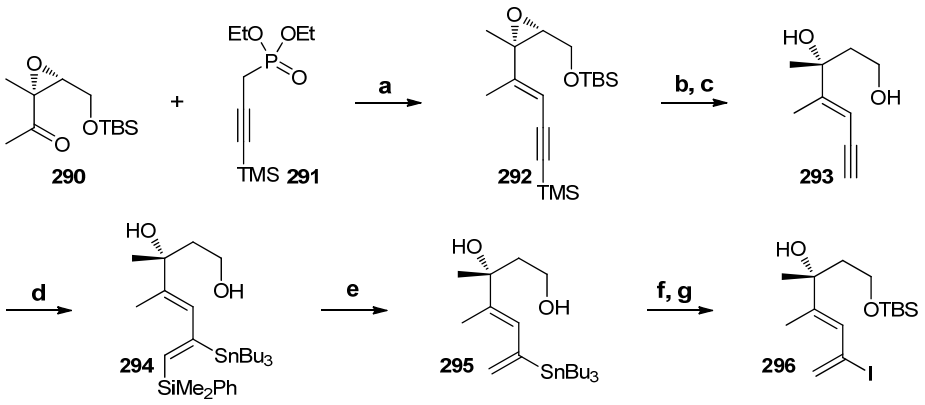
[a] **288** was completely consumed, but none of the desired product **289** was observed

Although much effort was invested in this oxidative rearrangement route, conditions could not be found which afforded the desired enone in a reasonable yield and so the route was abandoned.

2.3.2.3 Vinylic Halide Coupling

A report by Crews and coworkers concerning the synthesis of amphidinolide B gave us inspiration for a new approach.[61] Two different synthetic routes were reported for the preparation of an interesting conjugated vinylic iodide starting from a ketone (Schemes 86 and 87).

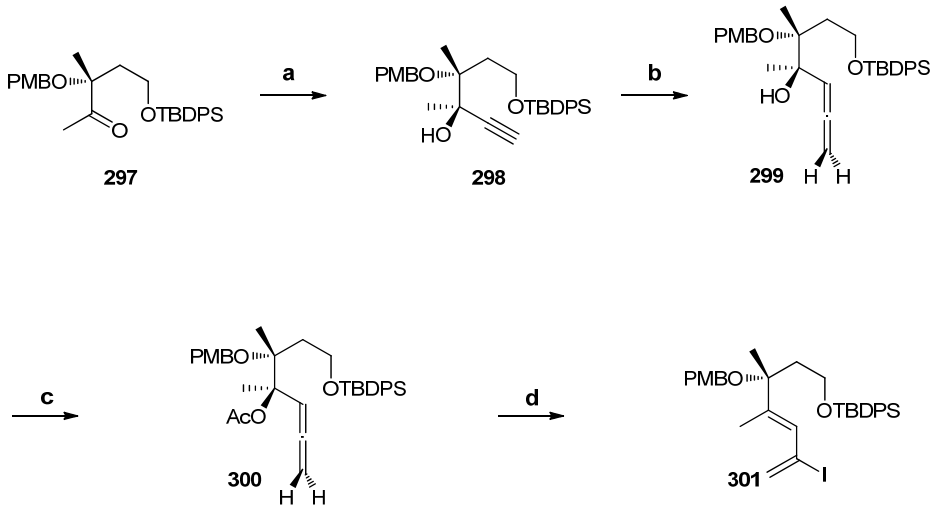
Firstly, the HWE reaction between compound **291** and ketone **290** in the presence of NaHMDS provided enyne **292** in good yield (*E*:*Z* = 6:1, Scheme 86).[61b] Simultaneous cleavage of the TBS ether and the TMS group using TBAF, followed by regioselective opening of the epoxide in the presence of $LiAlH_4$ furnished diol **293**. Silylstannation of the enyne with *n*-$Bu_3SnSiMe_2Ph$, using $Pd(PPh_3)_4$ as catalyst, produced the vinylic stannane **294** in both a regio- and stereoselective manner. TBAF removal of the silyl group then gave stannane **295** which upon reaction with I_2 and selective TBS protection of the primary alcohol finally yielded vinylic iodide **296**.



Reagents and conditions: **a** NaHMDS, THF, 82%; **b** TBAF, THF, 79%; **c** $LiAlH_4$, 79%; **d** *n*-$Bu_3SnSiMe_2Ph$, $Pd(PPh_3)_4$, THF, 76%; **e** TBAF, THF, 51%; **f** I_2, CH_2Cl_2; **g** TBSCl, imidazole, CH_2Cl_2, 80% over 2 steps.

Scheme 86. Crews' Synthesis of Vinylic Iodide **296**[61b]

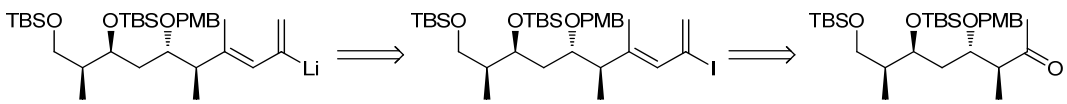
An alternative method was also reported (Scheme 87) within the same group.[61a] With the methyl ketone **297** available, a chelation-controlled addition of ethynylmagnesium bromide produced the ethynyl derivative **298** (*dr* = 9:1), which was homologated using paraformaldehyde and *i*-Pr_2NH in the presence of CuBr to afford allene **299**.[62] Acetylation of **299** provided acetate **300** and exposure of the acetate **300** to acetic acid and lithium iodide produced exclusively (*E*)-1,3-diene iodide fragment **301**.[63]



Reagents and conditions: **a** HCCMgBr, THF; **b** $(CH_2O)n$, CuBr, *i*-Pr_2NH; **c** Ac_2O, pyridine, 40 °C, 31% over 3 steps; **d** LiI, AcOH, 40 °C, 96%.

Scheme 87. Crews' Synthesis Vinylic Iodide **301**[61a]

Based on these reported results, our new strategy was to convert the methyl ketone into the corresponding 1,3-dienyl iodide, which would be coupled with the THF moiety to form the southern fragment (Scheme 88).

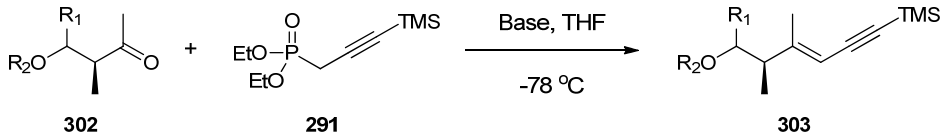


Scheme 88. Proposed Strategy for Synthesis of the Southern Fragment

First of all, the HWE reaction on a model system was studied (Table 10). Treatment of

phosphate ester **291** and various methyl ketones with bases led to the desired enynes. Use of NaHMDS delivered the best yield (Entries 2–5). It was also found that the β-substituted methyl group and not the protecting group, was the most important factor controlling the *E*:*Z* selectivity (Entries 3, 4). Thus, treatment of the β-substituted methyl ketone with NaHMDS led to a good yield and the *E*-product only (Entries 4, 5).

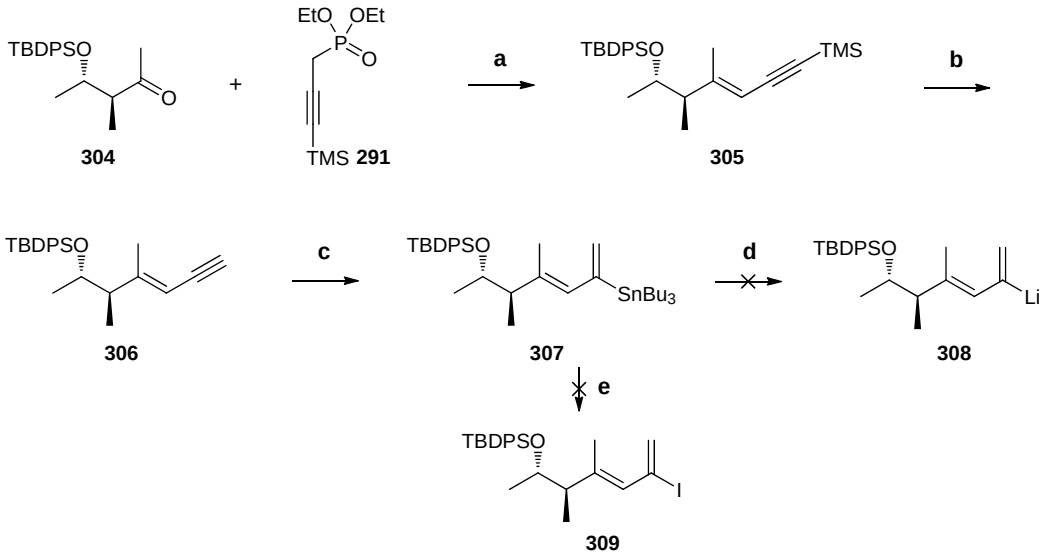
Table 10



302 **291** **303**

Entry	R_1	R_2	Bases	Yield	*E*:*Z*
1	H	TBS	*n*-BuLi	65%	3:1
2	H	TBS	NaHMDS	89%	4:1
3	H	PMB	NaHMDS	75%	6:1
4	Me	TBDPS	NaHMDS	84%	>15:1
5	Me	PMB	NaHMDS	90%	>15:1

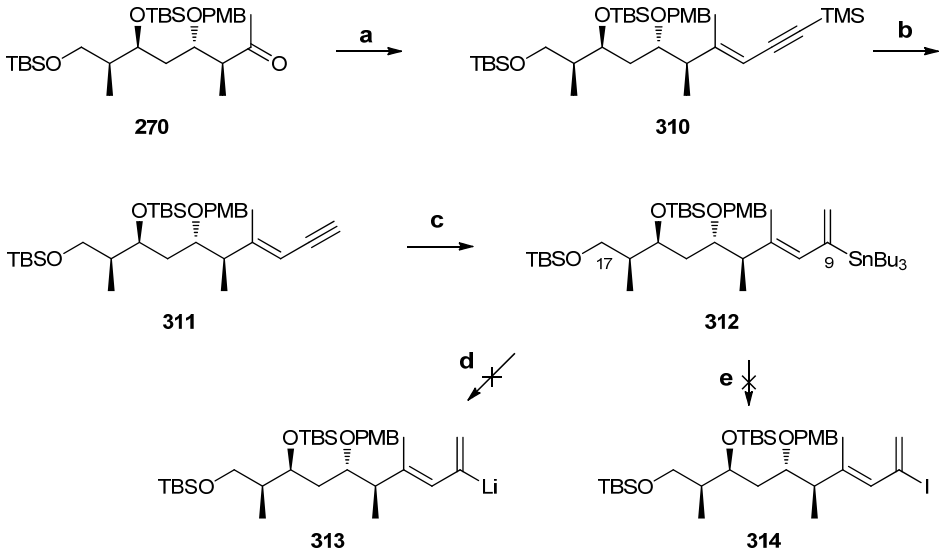
HWE transformation of methyl ketone **304** delivered the enyne **305** (Scheme 89). Basic removal of the TMS group followed by selective hydrostannation provided the desired stannane **307** under standard conditions. Unfortunately, the lithium-tin exchange reaction was unsuccessful, and treatment of **307** with I_2 in CH_2Cl_2 led only to decomposition of the substrate.



Reagents and conditions: **a** NaHMDS, THF, –78 °C, 84%; **b** K_2CO_3, MeOH, rt, 95%; **c** *n*-Bu_3SnH, $Pd(PPh_3)_4$, THF, rt, 85%; **d** *n*-BuLi or *t*-BuLi, THF, –78 °C; **e** I_2, CH_2Cl_2, 0 °C.

Scheme 89. Synthetic Study on Model System for Southern Fragment

At the same time, HWE transformation of **270** produced the enyne **310** in both good yield and regioselectiveity (Scheme 90). Cleavage of the TMS group in basic solution followed by selective hydrostannation in the presence of $Pd(Ph_3P)_4$ delivered the stannane **312**. Unfortunately, both lithium-tin and iodide-tin exchanges did not prove successful, as observed in the model system.

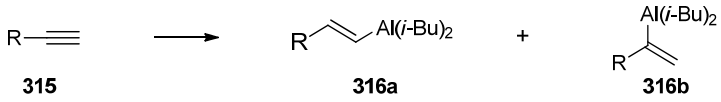


Reagents and conditions: **a** **291**, NaHMDS, THF, –78 °C, 77%; **b** K_2CO_3, MeOH, rt, 91%; **c** *n*-Bu_3SnH, $Pd(PPh_3)_4$, THF, rt, 76%. **d** *n*-BuLi or *t*-BuLi, THF, –78 °C; **e** I_2, CH_2Cl_2, 0 °C.

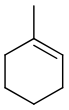
Scheme 90. Synthetic Study for the C9–C17 Fragment

Another potential approach to the synthesis was to convert enyne **315** into desired vinylalene **316b**, a process which was reported by Hoveyda and co-workers.[64] They reported a regioselective Ni(0) catalyzed method for hydroalumination of terminal alkynes (Table 13). Treatment of the terminal alkyne **315** with DIBAL in the presence of Ni(dppp)Cl_2 led to α-vinylalumination product **316b** in high yield and with high regio-selectivity (Entries 2, 3). The substrates chosen were mainly aromatic compounds, and only one enyne substrate was tested using this methodology (Entry 3).

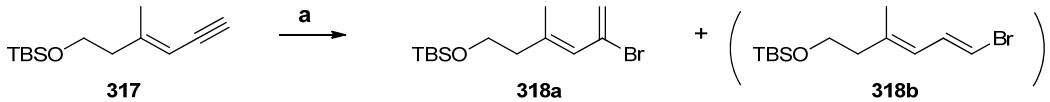
Table 11[64]



315 **316a** **316b**

Entry	R	Catalyst/ Reagent	Conversion	**a**:**b**
1	Ph	Ni(PPh_3)Cl_2/ DIBAL	>98	93:7
2	Ph	Ni(dppp)Cl_2/ DIBAL	>98	<2:98
3		Ni(dppp)Cl_2/ DIBAL	98	2:98

Since many different enynes had been synthesised from our previous studies, we attempted to apply Hoveyda's methodology to our synthesis. A very simple starting material **317** was chosen for preliminary model studies (Scheme 91). The hydroalumination reaction was very quick and clean for this substrate. The desired compound **318a** was isolated in 59% yield, with none of the regioisomer **318b** being observed.

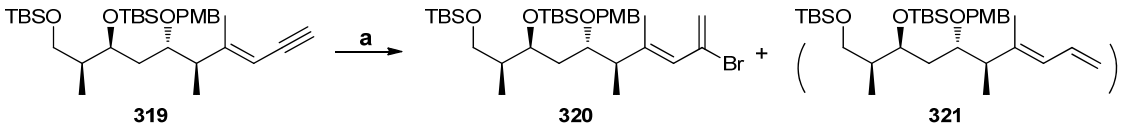


317 **318a** **318b**

Reagents and conditions: **a** Ni(dppp)Cl_2, DIBAL, THF, rt; then NBS, THF, rt, 59% of **318a**.

Scheme 91. Synthesis of Vinylic Bromide **318a**.

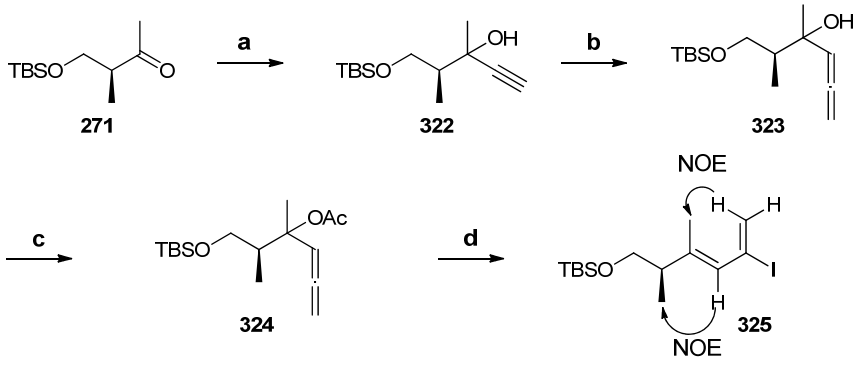
However, this catalytic process was not as successful when the substrate became more complex (Scheme 92). When enyne **319** was treated under the same reaction conditions, only 37% of the desired compound **320** was observed by ^{1}H NMR, and this was contaminated with 25% reduced product **321**. Furthermore, the product **320** was unstable to purification by chromatography on silica gel.



Reagents and conditions: **a** Ni(dppp)Cl_2, DIBAL, THF, rt,; then NBS, THF, rt, 37% yield of **320** over 2 steps.

Scheme 92. Synthetic Study on Alternative Apporoach

Because of the poor isolated yield obtained using this method, the alternative approach described by Crews was investigated, again using a simplified system (Scheme 93). The model substrate **325** was synthesised in four steps. Ethynyl Grignard addition to the ketone **271** produced the propargylic alcohol **322** as a 1:1 mixture of diastereoisomers. Treatment of **322** with formaldehyde and *i*-Pr_2NH in the presence of CuBr led to allene **323**. Acetylation followed by treatment of resulting ester **324** with LiI produced the vinylic iodide **325** (the geometry of the diene **325** was verified by NOE experiments).

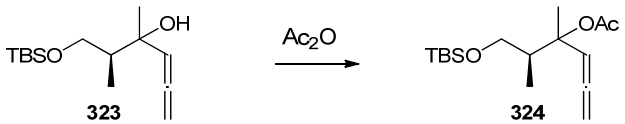


Reagents and conditions: **a** CHCMgBr, THF, 0 °C to rt, 75%; **b** $(CH_2O)n$, CuBr, *i*-Pr_2NH, 85%; **c** Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 71%; **d** LiI, AcOH, MeCN, rt, 64%.

Scheme 93. Synthesis of the Vinylic Iodide **325**

Acetylation of **323** proved to be non trivial (Table 12). Treatment of this alcohol with Ac_2O in the presence of a catalytic amount of TMSOTf led to decomposition of starting material (Entry 1).[65] Changing of the solvent to pyridine did not give full conversion (Entry 2). Reaction of the substrate **323** with excess Ac_2O and Et_3N with DMAP led to full conversion in yields of up to 71% yield.

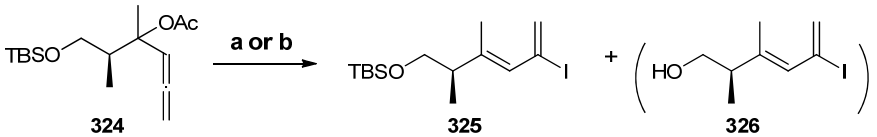
Table 12



323 324

Entry	Reagent and conditions	Results
1	TMSOTf, CH_2Cl_2, 0 °C to rt	decomposition
2	pyridine, 40 °C	37–45%
3	Et_3N, DMAP, CH_2Cl_2, rt	56–71%

Transformation of the allene into the vinylic iodide **325** was also problematic (Scheme 94). Standard conditions involve the use LiI and AcOH,[61b] but this caused the deprotection of the TBS ether. It was then found that when MeCN was used as a co-solvent with AcOH, the yield and *E*:*Z* selectivity were both improved. Furthermore the alkene isomers could be separated by flash chromatography on silica gel (the geometry of the diene **325** was verified by NOE experiment).

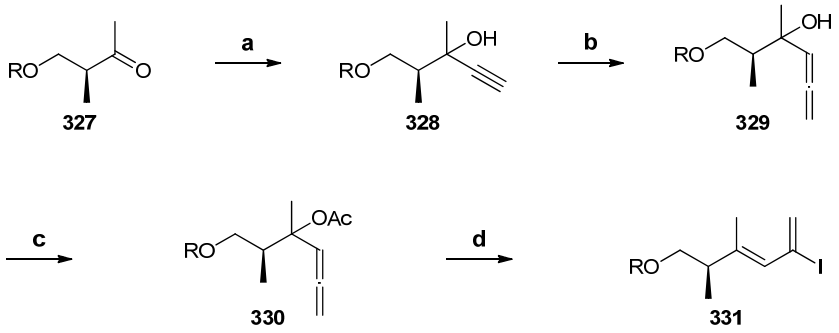


324 325 326

Reagents and conditions: **a** LiI, AcOH, 30% of **325**, (*E:Z* = 4:1), >50% of **326**; **b** LiI, AcOH/MeCN (1:1), 64% of **325**, (*E:Z* = 7:1), 5% of **326**;

Scheme 94. Synthesis of the Vinylic Iodide **325**

Fragments with different protecting groups were synthesized to test the tolerance of this four-step strategy (Scheme 95). Since the TBDPS ether was more stable than PMB and TBS ether under both basic and acidic conditions, the substrates with a TBDPS group gave higher yields in the acetylation and iodination steps.



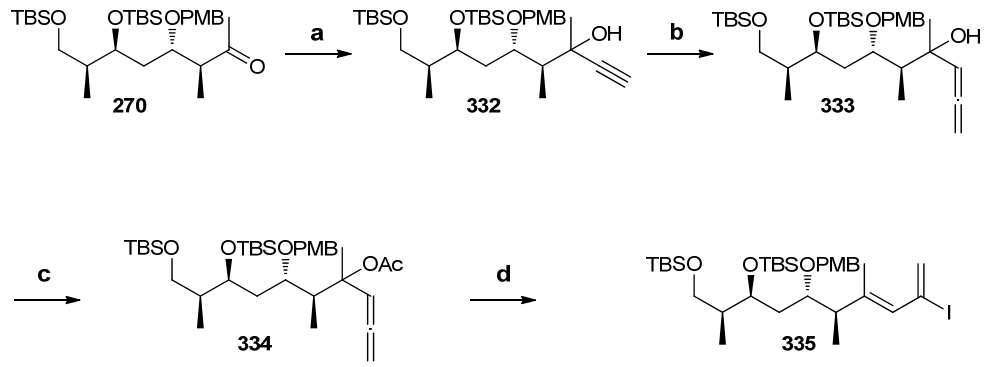
Reagents and conditions: **a** CHCMgBr, THF, 0 °C to rt; **b** $(CH_2O)_n$, CuBr, *i*-Pr_2NH; **c** Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt%; **d** LiI, AcOH, rt.

Scheme 95. Synthesis of Vinylic Iodide with Various Protecting Groups

Table 13

R	Step **a**	Step **b**	Step **c**	Step **d**	Combined yield
TBS	75%	85%	71%	64%	29%
PMB	99%	57%	37%	61%	23%
TBDPS	93%	75%	100%	70%	49%

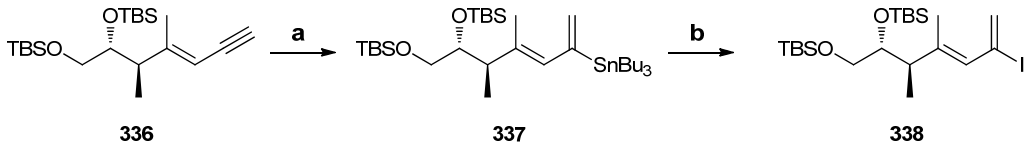
Following these successful model studies, the C11-C17 fragment synthesis began from the ketone **270** (Scheme 96). Treatment of **270** with ethynyl magnesium bromide provided the propargylic alcohol **332**. Reaction of **332** with formaldehyde and *i*-Pr_2NH in the presence of CuBr led to allene **333**. Acylation under the conditions optimized for the model system, followed by iodination produced the desired *E*-1,3-dienyl iodide **334**. However, this process was not reliable especially on large scale. Also the product **335** was found unstable to the purification by chromatography on silica gel.



Reagents and conditions: **a** CHCMgBr, THF, 0 °C to rt, 90%; **b** $(CH_2O)n$, CuBr, *i*-Pr_2NH, reflux, 57%; **c** Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 57%; **d** LiI, AcOH, MeCN, rt, 0-53%.

Scheme 96. Synthesis of the C9–C17 Fragment **335**

Information contained in a very recent publication from Carter and co-workers allowed us to salvage this strategy.[9b] They showed that silyl protected **337** could be converted into the desired diene iodide **338** successfully. Importantly, the authors indicated that the structure of both substrate and protecting group played an important role in stabilising the dienyl iodide product (Scheme 97).

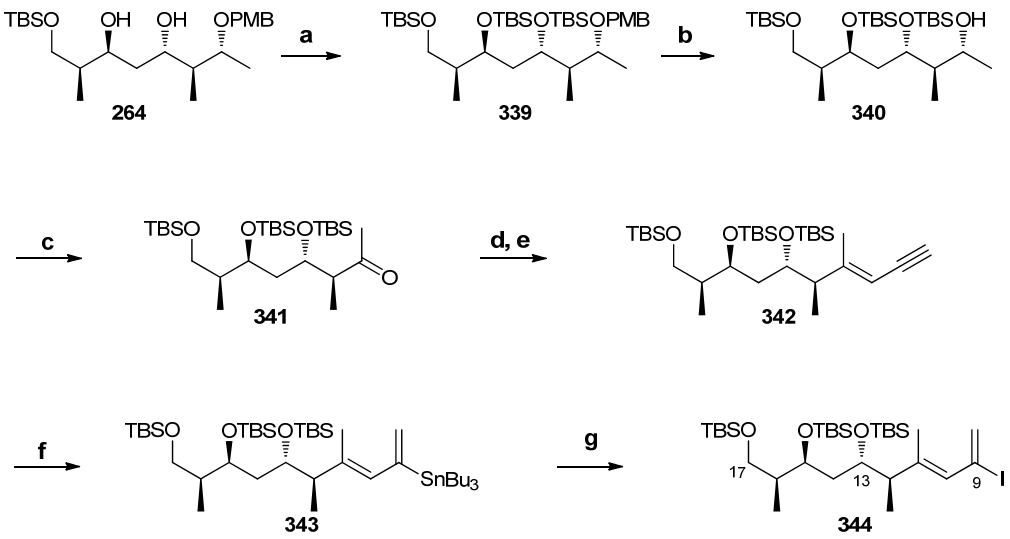


Reagents and conditions: **a** *n*-Bu_3SnH, $Pd(PPh_3)_4$, THF, rt, 72%; **b** I_2, CH_2Cl_2, 0 °C, 70%.

Scheme 97. Carter's Synthesis of Vinylic Iodide **338**[9b]

It was proposed that the use of silyl ether protecting groups could result in more stable substrates. A new substrate with silyl protecting groups was synthesized in order to test this theory (Scheme 98). Both of the hydroxyl groups in diol **264** were protected as TBS ethers. Cleavage of the PMB ether in the presence of DDQ them delivered alcohol **340**. Oxidation of alcohol **340** using the Dess-Martin protocol provided ketone **341** and then HWE transformation of **341** preceded both in good yield and with regioselectivity, as previously observed. Cleavage of the TMS group followed by selective hydrostannation of **342** in the presence of $Pd(PPh_3)_4$ delivered the stannane **343**. For this substrate, the iodide-tin exchange was successful and the stable

E-1,3-dienyl iodide **344** was obtained.

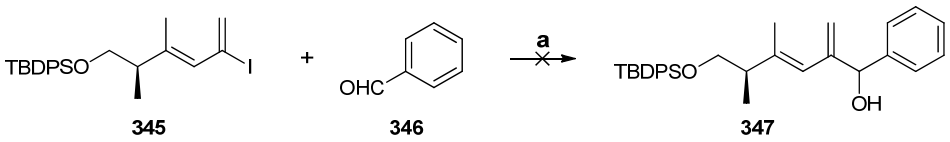


Reagents and conditions: **a** TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 86%; **b** DDQ, CH_2Cl_2, H_2O, rt, 92%; **c** Dess-Martin periodinane, CH_2Cl_2, rt, 75%; **d** NaHMDS, compound **291**, THF, –78 °C; **e** K_2CO_3, MeOH, rt, 77% over 2 steps; **f** $Pd(PPh_3)_4$, *n*-Bu_3SnH, THF, rt; **g** I_2, CH_2Cl_2, 0 °C to rt, 71% over 2 steps.

Scheme 98. Synthesis of C9–C17 Fragment **344**

Overall, by exchanging the PMB protecting group for a silyl group at C13, the stability of the C9–C17 fragment was significantly improved. Following by the successful synthesis of the fragment **344**, new coupling reactions for the formation of the southern fragment were investigated using model substrates.

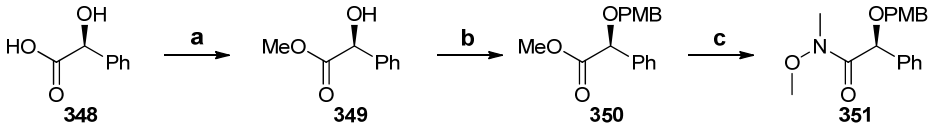
Firstly, the NHK reaction was evaluated by coupling the vinylic iodide **345** with benzaldehyde **346** (Scheme 99).[66] Unfortunately, the NHK conditions led to decomposition of the vinylic iodide. Inspection of the ^1H NMR spectrum of crude material, revealed that there were no signals corresponding to diene system. We propose that the Ni(0) catalyst may cause decomposition or polymerisation of the diene.



Reagents and conditions: **a** $NiCl_2$, $CrCl_2$, DMF or DMSO, 0 °C to 60 °C.

Scheme 99. Synthetic Study on NHK Reaction

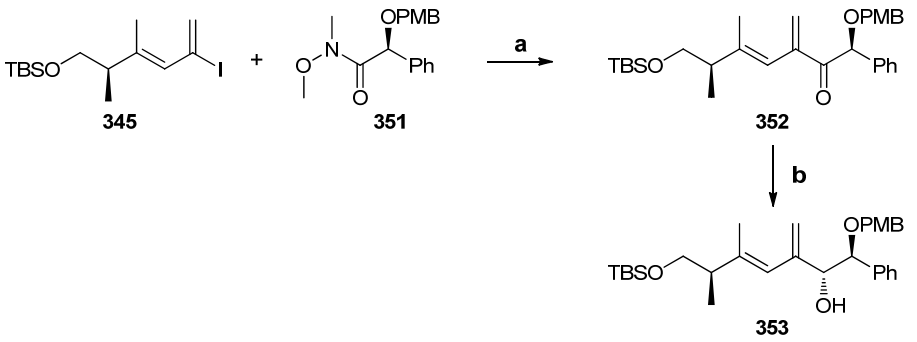
An alternative model was evaluated in which conversion of vinylic iodide into the vinyl lithium intermediate was followed by reaction with a Weinreb amide to form the new C–C bond. It was straightforward to synthesise the model starting material **351** in three steps (Scheme 100). Esterification of L-mandelic acid **348** gave **349** in 96% yield, and this was followed by PMB protection of the secondary alcohol to provide PMB ether **350**. Weinreb amide formation gave the coupling partner **351** in 35% yield over three steps.



Reagents and conditions: **a** $SOCl_2$, MeOH, 0 °C to rt, 96%; **b** PMBTCA, CSA, CH_2Cl_2, rt; **c** Me(MeO)NH·HCl, *i*-PrMgCl, –15 ºC, 35% over 2 steps

Scheme 100. Synthesis of the Starting Material for Model System

With both of the coupling partners in hand, dienyl iodide **345** was first treated with *n*-BuLi, and then added to Weinreb amide **351** to form enone **352** in 83% yield (Scheme 101). Following the success in constructing a new C–C bond, the next challenge was to introduce the desired configuration at the hydroxyl bearing stereocentre at the α-position of the diene. Pleasingly, it was found that Luche reduction led to the formation of the desired cram chelation product **353** as a single stereoisomer, (comparison of the ^{1}H NMR datas with Carter's work,[9b] the ^{1}H NMR of **353** was closely matched).



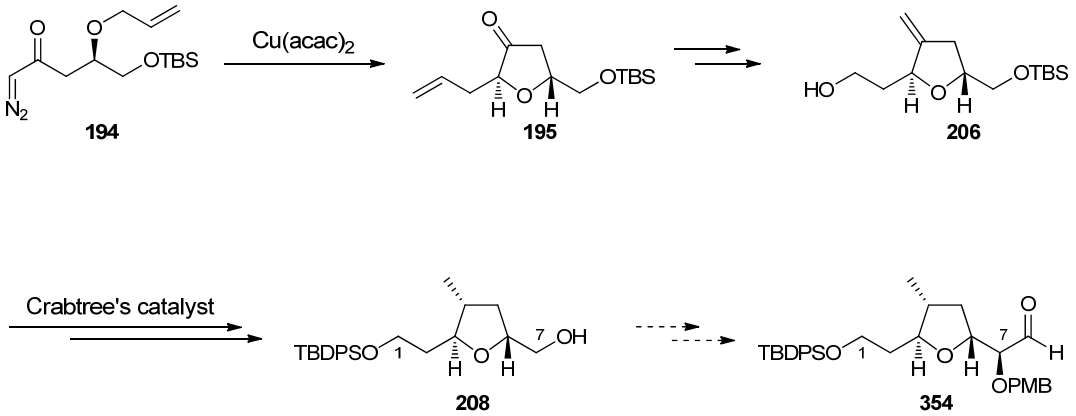
Reagents and conditions: **a** *n*-BuLi, THF, –78 °C to 0 °C, 83%; **b** $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, –78 °C, 75%.

Scheme 101. Synthetic Study on an Alternative Model System

The model studies above demonstrated that addition of the vinyl lithium species to the Weinreb amide was successful. They also showed that the Luche reduction strategy could be used to install the hydroxyl group with the desired stereochemistry for selective synthesis of the southern fragment.

2.3.4 Second Generation of Synthesis of C1-C8 Fragment

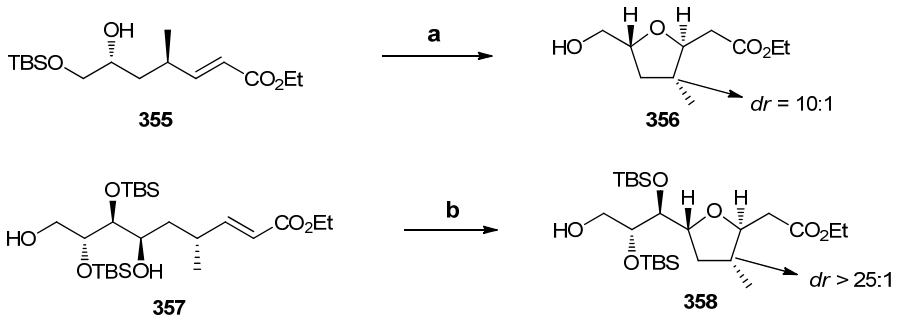
In this chapter, preparation of the alternative coupling partner **354** from the *trans*-tetrahydrofuran **208** is described (Scheme 105).



Scheme 102. Previous Synthesis of *trans*-Tetrahydrofuran **208** within Clark Group

Previously, the *trans*-tetrahydrofuran system was formed by copper-catalysed rearrangement of diazo ketone **194** (Chapter 1.6).[35] However, this approach used diazomethane and so it was desirable to find an alternative route for synthesis on a large scale.

Intramolecular conjugated addition of an oxygen nucleophile is often used for the formation of 2,5-*trans*-tetrahydrofurans. In 2008, Roush and co-workers reported a TBAF promoted cyclisation of **355**,[3b] which led to the *trans*-tetrahydrofuran **356** in 84% yield and with 10:1 *dr*. In 2010, Spilling and co-workers reported a similar approach;[5a] treatment of **357** with DBU in CH_2Cl_2 afforded the *trans*-tetrahydrofuran **358** was achieved in almost quantity yield as a single diastereoisomer (Scheme 103). We planned to utilise this method to synthesise the 2,5-*trans*-tetrahydrofuran.

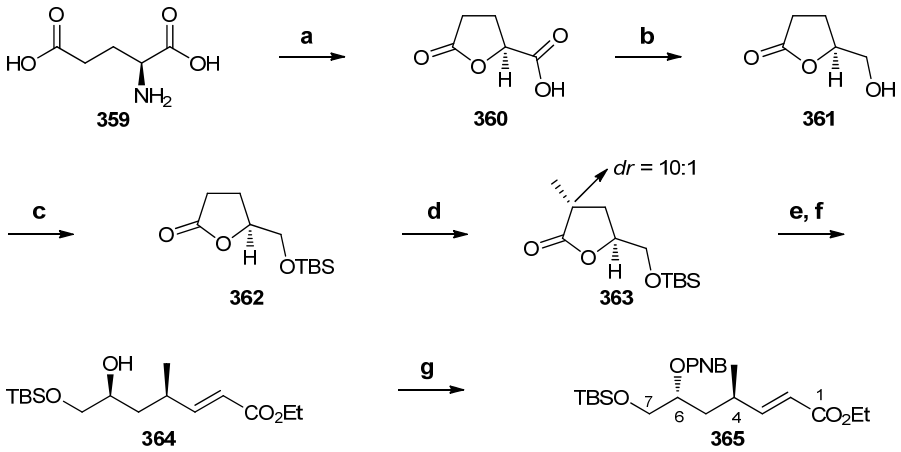


Reagents and conditions: **a** TBAF, THF, 0 °C to rt, 84%; **b** DBU, CH_2Cl_2, rt, 89%.

Scheme 103. Roush's[3b] and Spilling's[5a] *trans*-Tetrahydrofuran Formation

Our route began with diazotization of inexpensive *L*-glutamic acid **359** using $NaNO_2$ in acid aqueous solution to provide acid **360** (Scheme 104). Reduction of the acid with borane followed by protection of the primary alcohol of **361** delivered lactone **362**. Selective methylation of **362** using LiHMDS and MeI gave **363** as a mixture of two stereoiosmers (*dr* = 10:1), which could be separated by chromatography on silica gel. However, the purification would be very time-consuming due to the similar polarity of the isomers. The solution was to use the mixture directly for the next step, and separate the isomeric products at a later stage. With the mixture of two diastereoisomers in hand, DIBAL reduction followed by Wittig reaction produced the conjugated ester **364**. Mitsunobu reaction of hydroxyl group in **364** led to PNB ester **365** with the correct

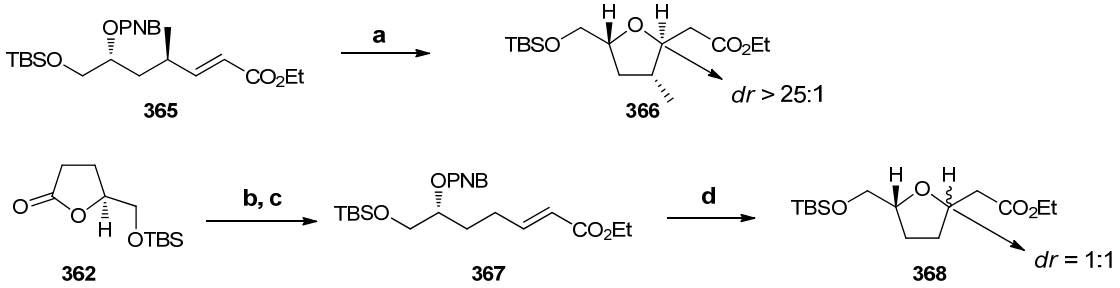
stereochemistry at C6.



Reagents and conditions: **a** $NaNO_2$, HCl, H_2O, 0 °C to rt; **b** $BH_3 \cdot SMe_2$, THF, 0 °C; **c** TBSCl, imidazole, DMAP, CH_2Cl_2, rt, 42% over 3 steps; **d** LiHMDS, MeI, THF, –78 °C, 80%; **e** DIBAL, –78 ºC; **f** $(Ph_3P)_3PCHCO_2Et$, PhMe, 80 °C, 85% over 2 steps; **g** Ph_3P, DIAD, *p*-nitrobenzoic acid, THF, 0 °C, 74% over 3 steps.

Scheme 104. New Synthetic Approach for *trans*-Tetrahydrofuran

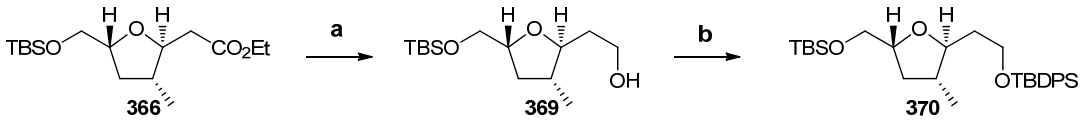
With ester **365** in hand, the *trans*-tetrahydrofuran **366** was formed through a domino hydrolysis and intramolecular Michael-type ring closure process in the presence of K_2CO_3. The methyl-bearing stereogenic centre played a very important role in controlling the stereochemical outcome of the reaction (Scheme 105). Under the same conditions, the ester **368** was obtained from the cyclisation of **367**, but with no diastereocontrol (the ester **367** was synthesised from lactone **362** using the same synthetic route as described in scheme 104).



Reagents and conditions: **a** K_2CO_3, EtOH, 55 °C, 85%; **b** DIBAL, –78 ºC; **c** $(Ph_3P)_3PCHCO_2Et$, PhMe, 80 °C; **d** K_2CO_3, EtOH, 55 °C.

Scheme 105. Investigation of the Effect from the Chiral Methyl Goup

Following the efficient synthesis of tetrahydrofuran **366**, reduction of ester **366** by $LiAlH_4$ delivered alcohol **369**. At this stage, the undesired stereoisomer could be separated easily by chromatography. Protection of the primary alcohol finally provided the *trans*-tetrahydrofuran **370**. Using these simple reactions, we were able to prepare 12 g of tetrahydrofuran compound **370**, with many of the reagents costing less than those used in the previous synthesis (Scheme 106).

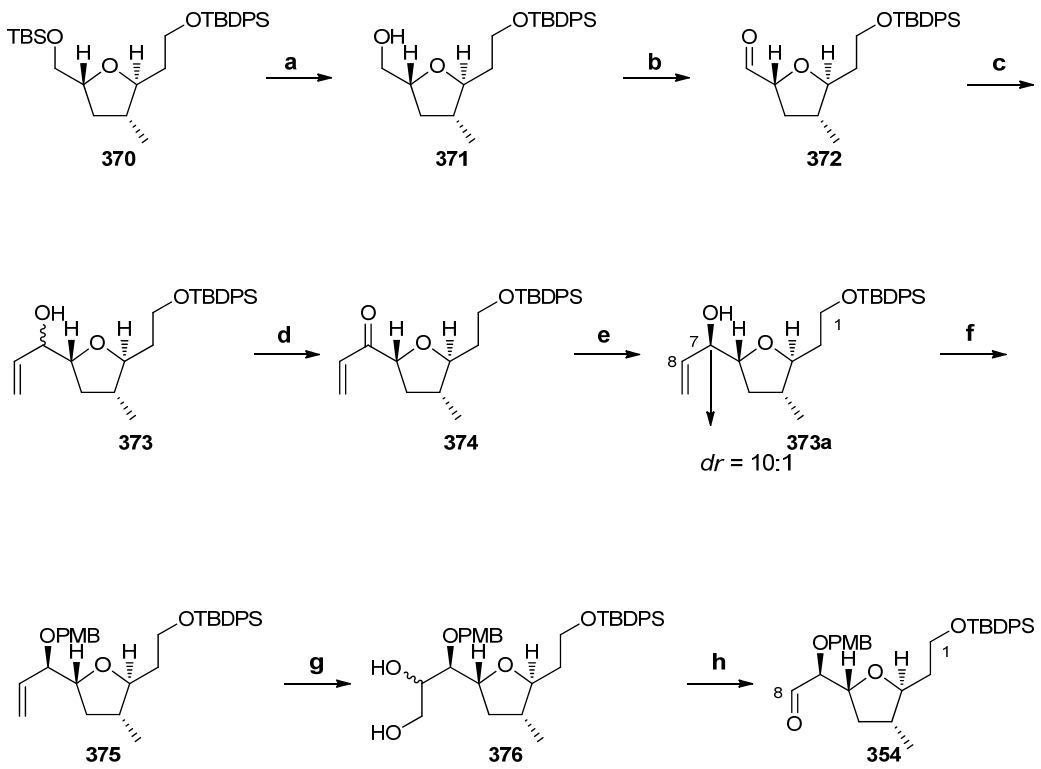


366 **369** **370**

Reagents and conditions: **a** $LiAlH_4$, THF, 0 °C to rt; **b** TBDPSCl, imidazole, DMAP, CH_2Cl_2, rt, 83% over 2 steps.

Scheme 106. Synthesis of the *trans*-Tetrahydrofuran **370**

With the intermediate **370** in hand, selective cleavage of the primary TBS ether delivered **371** (Scheme 107). Oxidation of **371** by Dess-Martin periodinane gave aldehyde **372**, and vinyl Grignard addition to **372** followed by oxidation of the intermediate allylic alcohol **373** produced the enone **374**. The enone was reduced under the Luche conditions to produce the product **373a** (*dr* = 10:1) as a result of the chelation control. Protection of **373a** on the secondary alcohol as the PMB ether provided **375**. Dihydroxylation followed by oxidative cleavage of the intermediate diol **376** led to aldehyde **354** as a coupling partner.

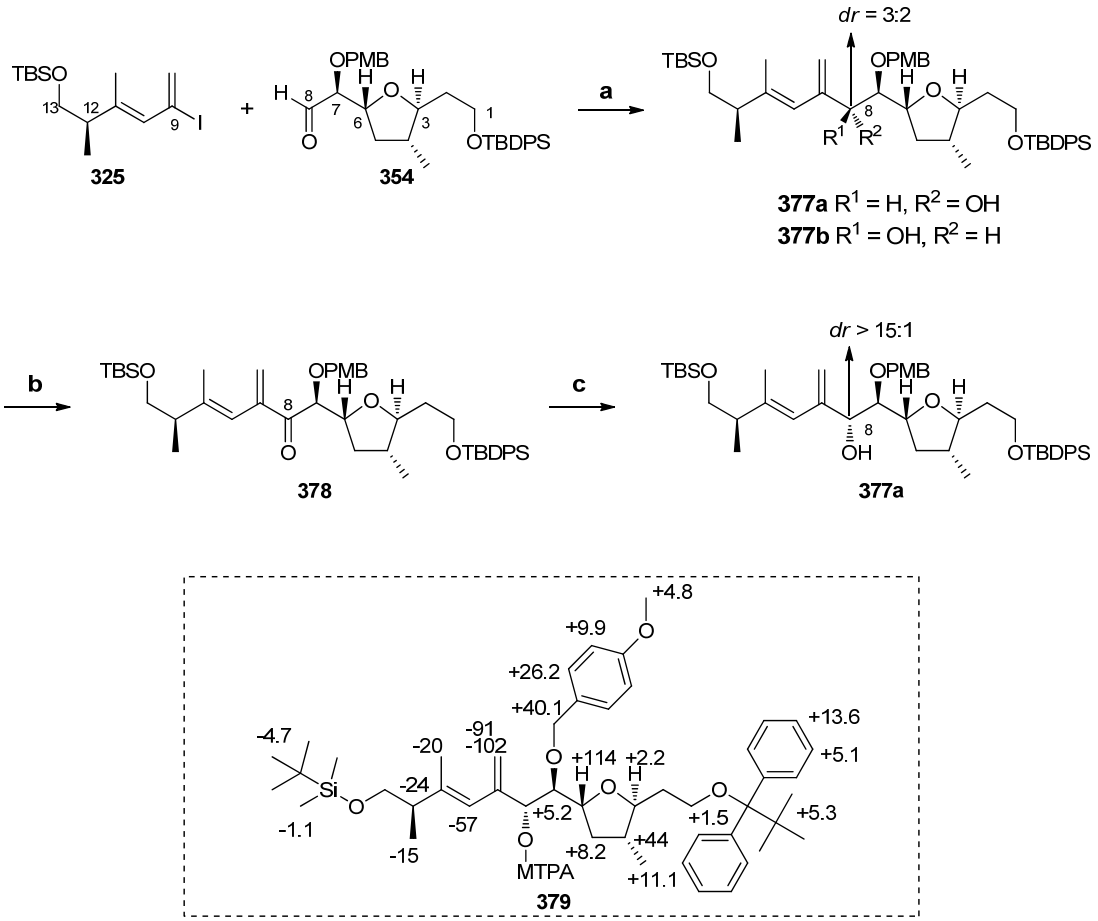


Reagents and conditions: **a** CSA, MeOH, –20 °C, 70%; **b** Dess-Martin periodinane, CH_2Cl_2, rt; **c** vinylmagnesium bromide, THF, 0 °C to rt; **d** Dess-Martin periodinane, CH_2Cl_2, rt, 53% over 2 steps; **e** $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, –78 ºC, 70%; **f** PMBTCA, $La(OTf)_3$, PhMe, rt, 84%; **g** OsO_4, NMO, acetone, H_2O, rt, 70%; **h** $NaIO_4$, THF, H_2O, rt, 88%.

Scheme 107. Synthesis of the C1-C8 Fragment **354**

2.3.5 Coupling Studies on the Southern Fragment

First of all, the coupling reaction between aldehyde **354** and vinylic iodide **325** was investigated (Scheme 108). Treatment of **325** with *n*-BuLi followed by addition to aldehyde **354** produced **377** as a 3:2 mixture of diastereoisomers. Oxidation of **377** using the Dess-Martin periodinane led to enone **378**. Luche reduction of **378** afforded the alcohol **377a** with correct stereochemistry at C8 as a single diastereoisomer (the absolute configuration was confirmed by Mosher's method[40]).

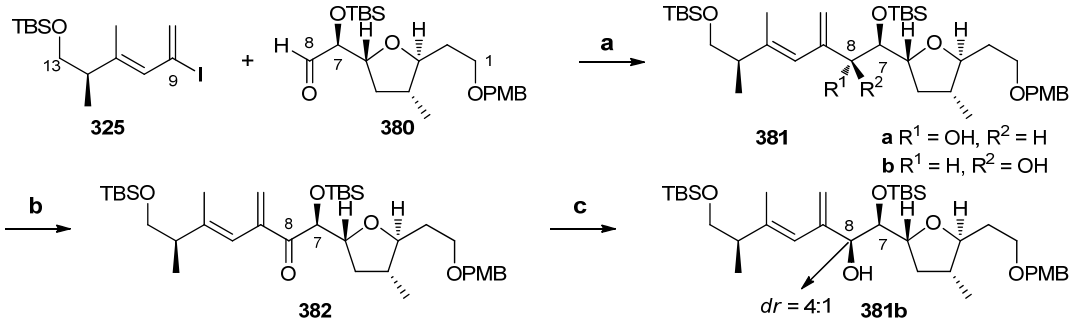


Reagents and conditions: **a** *n*-BuLi, THF, –78 ºC; **b** Dess-Martin periodinane, CH_2Cl_2, rt, 51% over 2 steps; **c** $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, –78 ºC, 78%.
^{1}H NMR shift differences {δ [(R)-MTPA]-δ [(S)-MTPA]} reported in Hertz ($CDCl_3$, 500 MHz)

Scheme 108. Synthesis of the Fragment **377a** by Luche Redution

We also synthesised the *trans*-tetrahydrofuran **380** bearing a TBS-protected alcohol for comparison purposes. It was found that a presence of a TBS ether at the C7 led to the mixture of two diastereoisomers **381** in which the product having the undesired

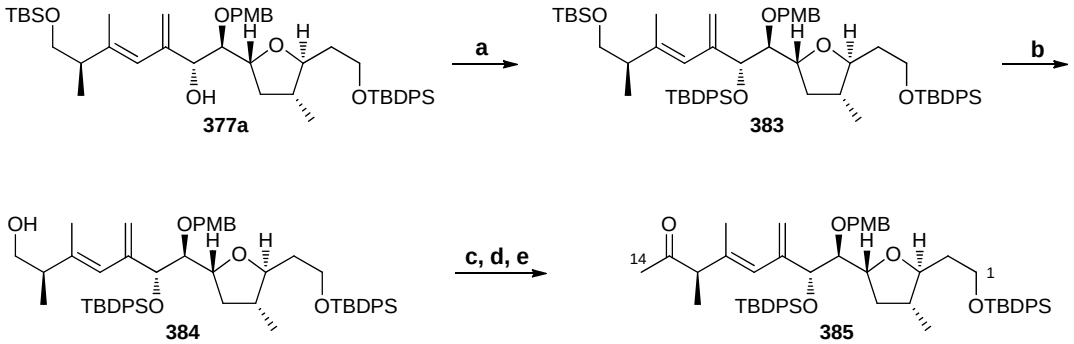
configuration at at C8 predominated (*dr* = 4:1) as Felkin-Anh product (Scheme 109). The steresochemistry of newly formed hydroxyl group was confirmed by comparison of the ^{1}H NMR datas of alcohol **381** with alcohol **377a** and Carter's report.[9b] It was also concluded that $CeCl_3 \cdot 7H_2O$ played an important role in chelating the ketone **378** at C8 and the oxygen atom at C7 (Scheme 108).



Reagents and conditions: **a** *n*-BuLi, THF, –78 ºC; **b** Dess-Martin periodinane, CH_2Cl_2, rt; **c** $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, –78 ºC.

Scheme 109. Different Results from the Fragment with TBS Protection at C7

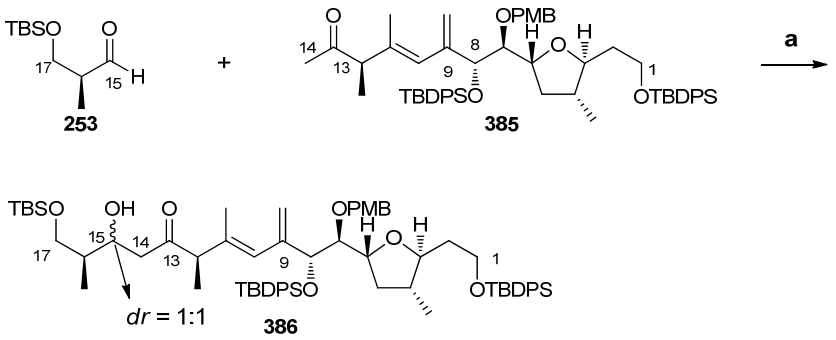
With the product **377a** in hand, the possibility of its conversion into a full fragment was evaluated (Scheme 110). Protection of the secondary alcohol gave TBDPS ether **383**. Selective cleavage of the primary TBS ether at low temperature provided alcohol **384** and sequential oxidation of **384** using Dess-Martin periodinane, addition of methylmagnesium bromide and Dess-Martin oxidation delivered methyl ketone **385**.



Reagents and conditions: **a** TBDPSCl, DMF, rt; **b** CSA, MeOH, –20 ºC, 56% over 2 steps; **c** Dess-Martin periodinane, CH_2Cl_2, rt; **d** methylmagnesium bromide, ether, 0 ºC to rt; **e** Dess-Martin periodinane, CH_2Cl_2, rt, 72% over 3 steps.

Scheme 110. Synthesis the Ketone **385**

Following the success of the sequence, the final southern fragment was close to completion, only requiring an aldol reaction[46a] between the ketone **385** and the aldehyde **253**. Unfortunately, under the conditions used previously, the aldol reaction gave a disappointing result (Scheme 111): a poor isolated yield (5%) of product **386** was observed with 1:1 ratio of two distereoisomers at the newly formed stereocentre (C15). And this results also indicated this aldol reaction did not follow the 1,4-*syn* aldol model.



Reagents and conditions: **a** (*c*-Hex)$_2$BCl, Et_3N, Et_2O, –78 ºC, 5%.

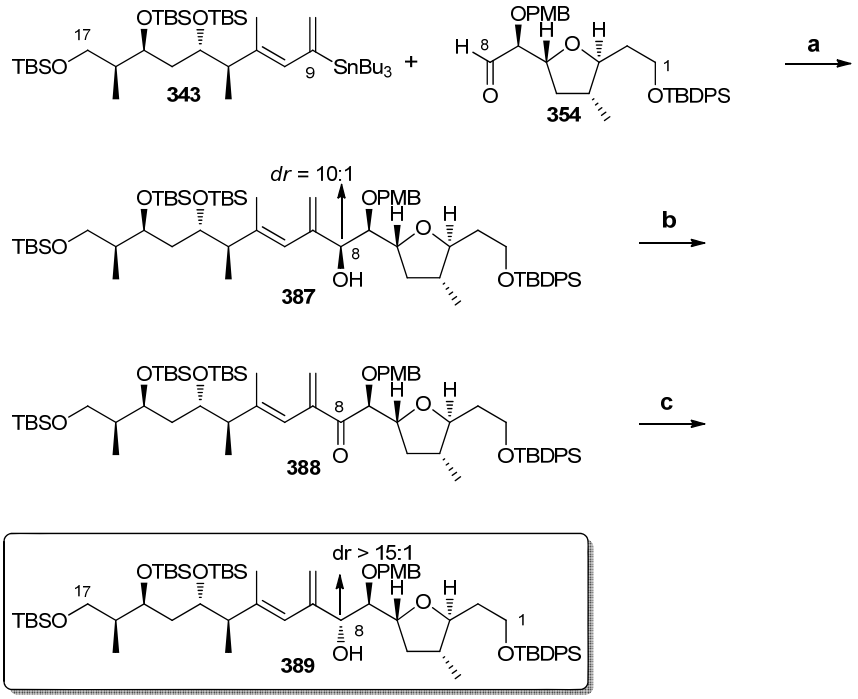
Scheme 111. Aldol Reaction Gave Poor Yield and Poor Diastereoselectivity

2.3.6 Completion of the Synthesis of the Southern Fragment

The aldol reaction was not suitable to construct the southern fragment in a diastereoselective way, so we decided to prepare the whole C9-C17 fragment before coupling with C1-C8 fragment **354**.

The synthesis of the entire C1–C17 fragment was completed as shown in Scheme 112. Subjecting the vinylic stannane **343** to tin-lithium exchange and addition of the lithiated intermediate to the aldehyde **354** afforded the alcohol **387** with high diastereoselectivity (*dr* = 10:1). Many efforts were made to verify the absolute configuration on C8 using the Mosher method. However, Mosher ester formation proved to be unsuccessful, presumably due to steric hindrance. The configuration of the newly created stereogenic center at C8 was assigned as *S* based on comparison of NMR data with that of closely related compounds prepared by Carter during their recent synthesis of amphidinolide F.[9b] Thus, it was clear that the diastereomer of the undesired alcohol had been obtained and inversion of configuration at the C8

stereogenic center was required. Oxidation of the alcohol with the Dess-Martin periodinane afforded the corresponding enone **388** and highly diastereoselective 1,2-reduction of the carbonyl group under Luche conditions afforded the alcohol **389** (*dr* > 15:1) with the required *R* configuration at the C8 stereogenic center. At this stage, the synthesis of the southern fragment was completed.



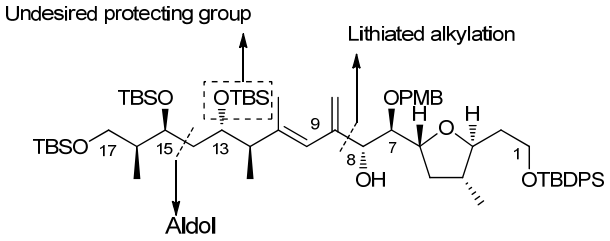
Reagents and conditions: **a** *n*-BuLi, THF, –78 ºC, 67% yield based on conversion; **b** Dess-Martin periodinane, CH_2Cl_2, rt, 89%; **c** $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, –78 ºC, 37%.

Scheme 112. Synthesis of the Southern Fragment **389**

After optimisation, the functionalised southern fragment **389** was finally synthesized in an efficient manner. The synthesis described in this chapter proceeded in 26 steps with 1.2% overall yield.

Compared with the northern fragment, the diastereoselective synthesis of southern fragment (C1-C17) was more complex (Scheme 113). First of all, the key connection was proved using model systems: C8-C9 formation (lithiated alkylation followed by selective Luche reduction) and C14-C15 formation (aldol condensation). Secondly, the coupling between C9-C13 fragment and C1-C8 fragment was proved more efficient. However, the aldol reaction between the C15-C17 and C1-C14 fragments failed. The only alternative for the synthesis was to selectively build C9-C17 fragment and then to

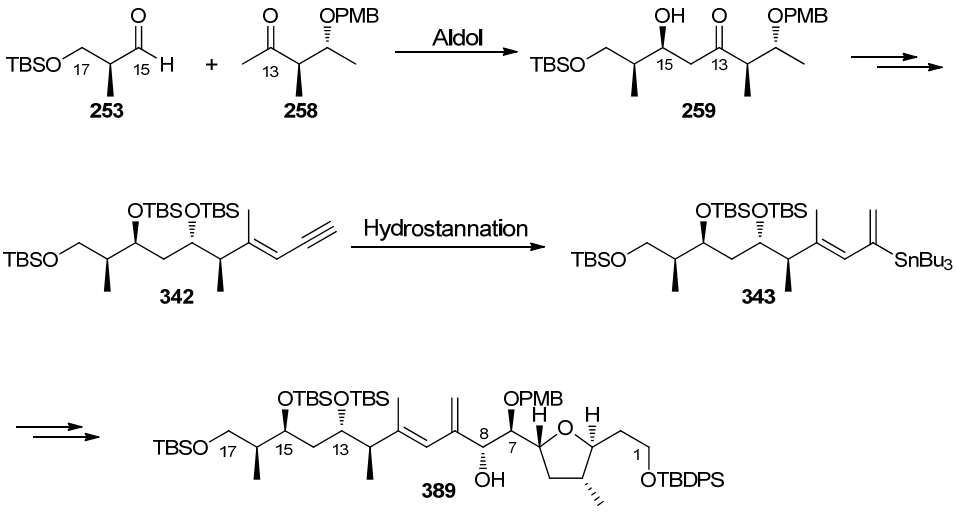
connect with C1-C8. Finally, during the synthesis of C9-C17, the protecting group at C13 played an important role in the stability of this fragment. In this synthesis, the protecting groups at C13 and C15 were TBS ethers, a strategy which prevents the continuation of the natural product synthesis. However, the convergent synthesis which has been developed will allow for fragments with different protecting groups at C13 and C15 to be prepared quickly and efficiently.



Scheme 113. Synthetic Analysis of C1-C17 Fragment

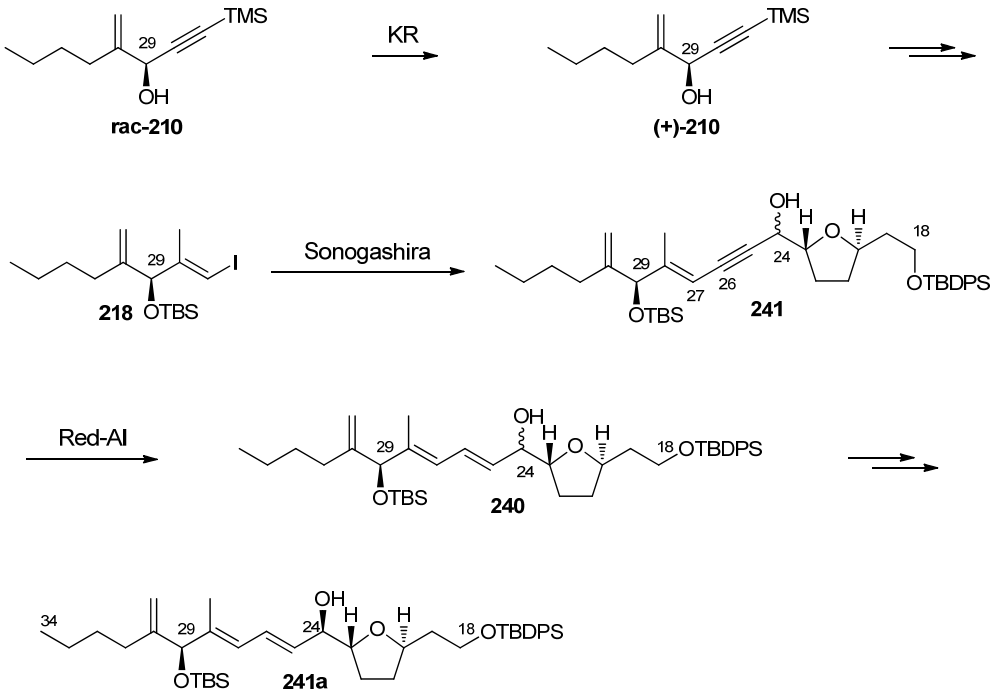
3. Conclusions and Outlook

The C1–C17 fragment of amphidinolide C has been prepared in an efficient and stereoselective fashion. Important features of the route include stereoselective boron-mediated aldol condensation between the chiral pool derived fragments **253** and **258** to produce the C1–C9 carbon backbone **259**, regioselective hydrostannylation of the enyne **342** to give the desired diene system, and addition of the lithiated stannane **343** to an aldehyde to deliver the C1-C17 fragment (Scheme 114).



Scheme 114. Summary of the Forward Synthesis of C1–C17 Fragment

On the other hand, the synthesis of the C18–C34 fragment of amphidinolide C included kinetic resolution under Sharpless asymmetric epoxidation conditions to furnish the enantionmericly pure hydroxyl at C29, Sonogashira coupling to form the C26-C27 bond, and Red-Al reduction of the enyne **241** to obtain the *E*,*E*-diene system. Finally, an oxidation and Luche reduction sequence furnished the system bearing the required stereochemistry at C24 (Scheme 115).



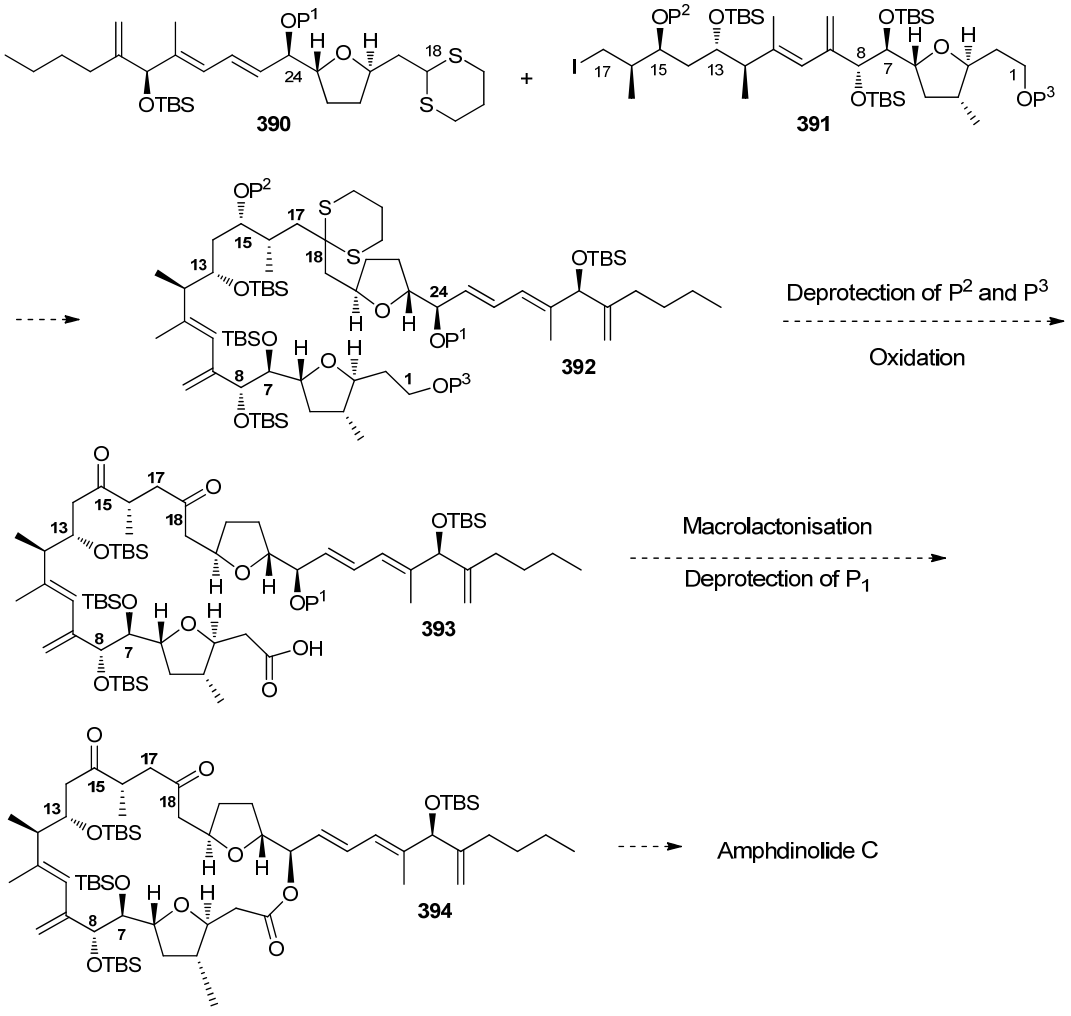
Scheme 115. Summary of the Forward Synthesis of C18–C34 Fragment

In summary, the synthesis of amphidinolide C fragments has proved to be very challenging and complex. In these syntheses, diastereoselective methodologies and synthetic strategies were developed based on the substrate-control. Most of the stereocentres were furnished using non-chiral reagents (for example, those at C4, C7, C8, C14, C13, C15 and C24). Furthermore the two *trans*-tetrahydrofurans (C3-C6 and C20-C23 frameworks) as well as two diene motifs (C9-C11 and C25-C28 frameworks) were prepared in a highly selective fashion.

Using the routes outlined in this work, the completion of a synthesis of amphidinolide

C might not be possible due to incompatible protecting groups. The next challenge is to redesign the route using the information gained during this work (Scheme 116).

If the northern **390** and southern fragments **391** are to be coupled using a dithiane anion, then selective deprotection of P^2 and P^3 followed by oxidation would afford the acid **393**. Cleavage of the P^1 followed by the macrolactonization would lead to the lactone **394**. Last step is removal of all the silyl ethers to complete the total synthesis of amphidinolide C.



Scheme 116. Protecting Group Considerations during the Synthesis of Amphidinolide C

Experimental Section

General comment

Air and/or moisture sensitive reactions were performed under an atmosphere of Argon in flame dried apparatus. Organic solvents were dried using a Pure Solv™ solvent purification systems. All reagents were purchased from commercial suppliers and used without further purification, unless otherwise stated. All reactions were monitored by thin layer chromatography using Merck silica gel 60 covered alumina plates F254. Thin layer chromatography plates were viewed under UV light or were visualised using either potassium permanganate solution or acidic ethanolic anisaldehyde solution. Column chromatography was performed under pressure using silica gel (Fluorochem LC60A, 35-70 micron, 60A) as solid support and HPLC-graded solvents as eluent. Petroleum ether used for column chromatography was 40-60 °C fraction.

IR spectra were recorded using a type IIa diamond single reflection element on a Shimadzu FTIR-8400 instrument. The IR spectrum of the compound (solid or liquid) was directly detected as a thin layer at ambient temperature.

^{1}H NMR spectra were recorded on a Bruker 400 MHz or 500 MHz Spectrospin spectrometer at ambient temperature. The carbon numbering drawn on the molecule corresponds to the cladiellin numbering used for the NMR signal assignment. IUPAC numbering is used for the molecule names. Data are reported as follows: chemical shift in ppm relative to $CHCl_3$ (7.27) on the δ scale, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, or a combination of these), coupling constant(s) J (Hz) and assignment.

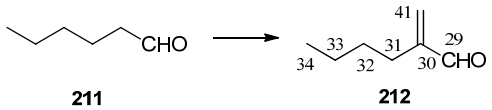
^{13}C NMR spectra were recorded on a Bruker 400 MHz or 500 MHz Spectrospin spectrometer at 100 MHz or 125 MHz at ambient temperature and multiplicities were obtained using a DEPT sequence. Data are reported as follows: chemical shift in ppm relative to $CHCl_3$ (77.16) on the δ scale and assignment.

High resolution mass spectra (HRMS) were obtained under EI, FAB, CI and ES conditions by the analytical services of the University of Glasgow on a Jeol MStation JMS-700 instrument. Low resolution mass spectra (LRMS) were carried out on the same instrument; the intensity of each peak is quoted as a percentage of the largest, where this information was available.

Elemental analyses were carried out on an Exeter Analytical Elemental Analyser EA 440.

Melting points were recorded with an Electrothermal IA 9100 apparatus.

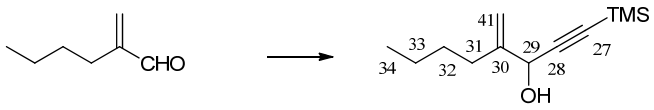
2-Methylenehexanal (212).[67]



211 **212**

Hexanal **211** (24 mL, 20 g, 0.20 mol), dimethylamine hydrochloride (19 g, 0.24 mol) and formaldehyde (19 g, 0.20 mol, 37% soln. in water) were heated together at 55 °C for 16 h. The mixture was cooled to rt and then diluted with brine (50 mL), extracted with ether (3 × 50 mL) and concentrated to afford the desired aldehyde **212** (20 g, 89%) as colourless oil. R_f = 0.60 (petroleum ether–ethyl acetate, 10:1); ν_{max} ($CHCl_3$) 2956, 2929, 2906, 2862, 1728, 1714, 1464, 1456, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H, CHO-C29), 6.24 (1H, d, J = 0.9 Hz, CH_2-C41), 5.98 (1H, d, J = 0.4 Hz, CH_2-C41), 2.24 (2H, t, J = 6.4 Hz, CH_2-C31), 1.52–1.48 (2H, m, CH_2-C32), 1.46–1.42 (2H, m, J = 7.2, 14.3 Hz, CH_2-C33), 0.90 (3H, t, J = 7.2 Hz, CH3-C34); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9 (C-C29), 150.5 (C-C30), 134.0 (CH_2-C41), 30.0 (CH_2-C31), 27.6 (CH_2-C32), 22.4 (CH_2-C33), 13.9 (CH_3-C34); LRMS (CI+, isobutane) *m/z* (intensity) 113.2 (100%) 101.2 (20%) 83.2 (10%) 71.1 (18%) 69.1 (9%) 61.0 (5%).

4-Methylene-1-(trimethylsilyl)oct-1-yn-3-ol (*rac*-210).[68]

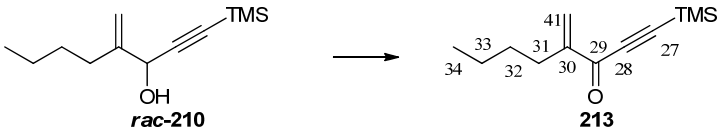


212 ***rac*-210**

Isopropylmagnesium bromide (116 mL of a 2.0 M solution in THF, 230 mmol) was added dropwise to a stirred solution of trimethylsilylacetylene (24.6 g, 251 mmol) in THF (50 mL) at 0 ºC. After complete addition of the Grignard reagent, the mixture was warmed to rt for 2 h before being added to a stirred solution of 2-methylenehexanal (20.0 g, 179 mmol) in THF (50 mL) at 0 ºC. The mixture was

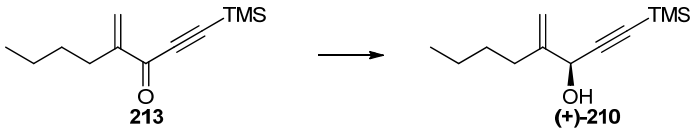
stirred for 30 min and then warmed to rt and stirred for a further 2 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (100 mL). The mixture was extracted with ether (3 × 100 mL) and organic extracts were combined then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether–ethyl acetate, 100:1 to 50:1) to afford the propargylic alcohol ***rac*-210** (30.2 g, 81%) as a pale yellow oil [full set of datas please see **(+)-210** below].

4-Methylene-1-(trimethylsilyl)oct-1-yn-3-one (213).[68]



To a solution of propargyl alcohol ***rac*-210** (4.0 g, 19 mmol) in CH_2Cl_2 (200 mL), was added powdered 4Å molecular sieves (10 g) and MnO_2 (2.5 g, 28 mmol) at rt. The resulting suspension was stirred at rt for 18 h. The solid was removed by filtration through the Celite® and the filtrate was concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 50:1) afforded the ketone **213** (3.2 g, 80%) as a yellow oil. To be noticed, this compound was not stable, and it should be used quickly for the next step. ν_{max} ($CHCl_3$) 2956, 2941, 2821, 1719, 1699, 1264, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.50 (1H, s, CH_2-C41), 5.98 (1H, s, CH_2-C41), 2.28 (2H, t, J = 7.2 Hz, CH_2-C31), 1.41–1.31 (4H, m, CH_2-C32, CH_2-C33), 0.89 (3H, t, J = 7.0 Hz, CH_3-C34), 0.25 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6 (CO-C29), 149.2 (C-C30), 130.5 (CH2-C41), 100.3 (C-C27), 98.2 (C-C28), 30.2 (CH_2-C31), 29.0 (CH_2-C32), 22.3 (CH_2-C33), 13.8 (CH_3-C34), –0.7 (TMS).

(*S*)-4-Methylene-1-(trimethylsilyl)oct-1-yn-3-ol [(+)-210].[68]



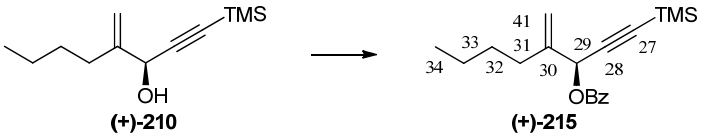
Ketone **213** (4.0 g, 19 mmol) was dissolved in THF (40 mL) at –30 °C was added (*S*)-CBS catalyst (1 M in THF, 3.0 mL, 3.0 mmol), followed by drop wise addition of BH_3·THF (1 M, 23 mL, 23 mmol) over 40 min. The reaction was stirred at –30 °C for 2 h until completion, indicated by TLC. MeOH was added (20 mL) at –30 °C, followed by pouring the solution into a half saturated solution of NH_4Cl (100 mL). The aqueous phase was extracted with Ethyl acetate (3 × 50 mL) and the combined organic extracts were washed with brine and dried with $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 20:1) to give title alcohol **(+)-210** (4.0 g, 100%) as colourless oil (full set of datas were below).

(*S*)-4-Methylene-1-(trimethylsilyl)oct-1-yn-3-ol [(+)-210].[68]

To a solution of racemic alcohol **3** (5.0 g, 24 mmol) and (+)-DET (0.74 g, 3.6 mmol) in CH_2Cl_2 (180 mL), was added powed 4Å molecular sieves (1.5 g). The mixture was cooled to between –20 to –30 ºC. Ti(O*i*-Pr)$_4$ (0.70 g, 2.4 mmol) was added quickly. The mixture was stirred for 1.5 h, and TBHP (5.6 M in CH_2Cl_2, 3.0 mL, 17 mmol) was then added. The resulting solution was stirred at –20 ºC for 4 days until NMR showed there was more than 65% conversion. The reaction was quenched by addition of an aqueous solution of NaOH (1 M, 100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and

concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 20:1) to give title alcohol **(+)-210** (1.8 g, 70%) as colourless oil. R_f = 0.54 (petroleum ether–ethyl acetate, 4:1); $[\alpha]_D^{25}$ +3.6 (*c* = 1.01, $CHCl_3$); ν_{max} ($CHCl_3$) 2958, 2931, 2173, 1379, 1249, 1041, 1008, 906, 839, 759, 731, 698, 671, 626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.27 (1H, s, CH_2-C41), 4.94 (1H, s, CH_2-C41), 4.81 (1H, d, *J* = 6.8 Hz, CH-C29), 2.19 (2H, t, *J* = 7.6 Hz, CH_2-C31), 1.92–1.86 (1H, m, OH), 1.54–1.45 (2H, m, CH_2-C32), 1.41–1.31 (2H, m, CH_2-C33), 0.92 (3H, t, *J* = 7.3 Hz, CH_3-C34), 0.18 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2 (C-C30), 111.5 (CH_2-C41), 104.8 (C-C27), 90.9 (C-C28), 66.2 (CH-C29), 31.6 (CH_2-C31), 30.2 (CH_2-C32), 22.6 (CH_2-C33), 14.1 (CH_3-C34), –0.1 (TMS). LRMS (CI+, isobutane) *m/z* (intensity) 211.3 (22%), 193.2 (100%).

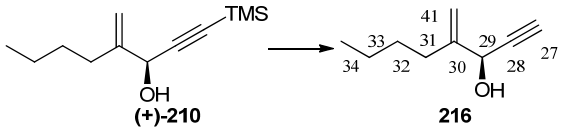
(*S*)-4-Methylene-1-(trimethylsilyl)oct-1-yn-3-yl benzoate [(+)-215].



The propargyl alcohol **(+)-210** (0.50 g, 2.4 mmol) was dissolved in CH_2Cl_2 (20 mL) and Et_3N (0.67 mL, 4.8 mmol) and DMAP (30 mg, 0.24 mmol) was added, followed by addition of BzCl (0.42 mL, 3.6 mmol). The yellow solution was stirred at rt for 2 h, and quenched by addition of NH_4Cl (20 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 20:1) to give the ester **(+)-215** (0.74 g, 99%) as colourless oil. ν_{max} ($CHCl_3$) 2957, 2931, 2861, 1724, 1601, 1451, 1315, 1248, 1093, 1067, 918, 840, 759, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (2H, dd, *J* = 8.4, 1.3 Hz, CH-Bz), 7.57 (1H, tt, *J* = 7.4, 1.3 Hz, CH-Bz), 7.46 (2H, t, *J* = 7.7 Hz, CH-Bz), 6.13 (1H, s, CH_2-C41), 5.39 (1H, s, CH_2-C41), 5.06 (1H, s, CH-C29), 2.28–2.16 (2H, m, CH_2-C31), 1.58–1.48 (2H, m, CH_2-C32), 1.36 (2H, m, CH_2-C33), 0.91

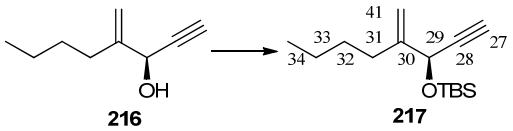
(3H, t, J = 7.3 Hz, CH_2-C34), 0.18 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (CO-Bz), 144.8 (C-C30), 133.4 (Ph-Bz), 130.2 (Ph-Bz), 128.7 (Ph-Bz), 128.7 (Ph-Bz), 114.2 (CH_2-C41), 101.2 (C-C27), 94.1 (C-C28), 67.6 (CH-C29), 32.0 (CH_2-C31), 30.1 (CH_2-C32), 22.6 (CH_2-C33), 14.2 (CH_3-C34), 0.1 (TMS); HRMS (CI) for $C_{19}H_{27}O_2Si$ ($[M+H]^+$) calcd. 315.1780, found 315.1781; Anal. calcd. for $C_{19}H_{26}OSi$: C 72.56%, H 8.33%, Found: C 72.61%, H 8.46%; HPLC, Chiralpak AD-H column (Hexane/*i*-PrOH, 0.2%, 0.5 ml min^{-1}), *S*-isomer elutes at 12.50 min, *R*-isomer elutes at 13.30 min.

(*S*)-4-Methyleneoct-1-yn-3-ol (216).[68]



A solution of alcohol **(+)-210** (1.7 g, 8.1 mmol) in MeOH (30 mL) was treated with K_2CO_3 (3.4 g, 24 mmol) and stirred for 2 h at rt. Petroleum ether (20 mL) was added and filtered. The solvent was removed in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 25:1) to yield title terminal alkyne **216** (1.0 g, 94%) as colourless oil. R_f = 0.29 (petroleum ether–ethyl acetate, 10:1); ν_{max} ($CHCl_3$) 3308, 2956, 2929, 2872, 2862, 1651, 1458, 1433, 1398, 1379, 1259, 1105, 1020, 991, 906, 860, 731, 648, 632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (1H, s, CH_2-C41), 4.97 (1H, s, CH_2-C41), 4.82 (1H, d, J = 6.4 Hz, CH-C29), 2.54 (1H, d, J = 2.2 Hz, CH-C27), 2.20 (2H, t, J = 7.6 Hz, CH_2-C31), 1.96 (1H, d, J = 6.4 Hz, OH), 1.50–1.48 (2H, m, CH_2-C32), 1.36 (2H, qt, J = 7.1, 14.3 Hz, CH_2-C33), 1.25 (3H, t, J = 7.2 Hz, CH_3-C34); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9 (C-C30), 111.6 (CH_2-C41), 83.2 (C-C27), 74.2 (C-C28), 65.6 (CH-C29), 31.5 (CH_2-C31), 30.1 (CH_2-C32), 22.6 (CH_2-C33), 14.1 (CH_3-C34); HRMS (CI, isobutane) for $C_9H_{15}OSi$ ($[M+H]^+$) calcd. 139.1123, found 139.1123.

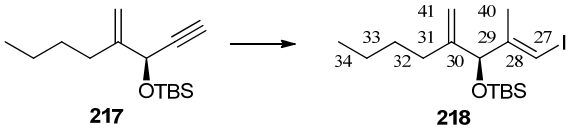
(*S*)-*tert*-Butyldimethyl(4-methyleneoct-1-yn-3-yloxy)silane (217).[68]



216 **217**

The alcohol **216** (0.90 g, 0.70 mmol) was dissolved in DMF (10 mL) and to this was added imidazole (1.2 g, 1.6 mmol) and TBSCl (1.3 g, 0.87 mmol) at 0 ºC. After addition, the reaction mixture was allowed to warm to rt and stirred for 18 h before the brine (15 mL) was added. The aqueous phase was extracted with petroleum ether (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 100:1) to give title TBS ether **217** (1.4 g, 87%) as colourless oil. R_f = 0.44 (petroleum ether–ethyl acetate, 4:1); $[\alpha]_D^{25}$ –29.2 (*c* = 1.05, $CHCl_3$); ν_{max} ($CHCl_3$) 3313, 2957, 2929, 2859, 1464, 1252, 1071, 835, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.22 (1H, s, CH_2-C41), 4.89–4.87 (1H, m, CH_2-C41), 4.81 (1H, s, CH-C29), 2.44 (1H, d, *J* = 2.2 Hz, CH-C27), 2.23–2.21 (2H, m, CH_2-C31), 1.52–1.44 (2H, m, CH_2-C32), 1.40–1.30 (2H, m, CH_2-C33), 0.92 (9H, s, CH_3C-TBS), 0.92 (3H, t, *J* = 7.2 Hz, CH_3-C34), 0.15 (3H, s, CH_3Si-TBS), 0.12 (3H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5 (C-C30), 110.4 (CH_2-C41), 84.2 (C-C28), 73.0 (CH-C27), 66.1 (CH-C29), 31.2 (CH2-C31), 30.1 (CH_2-C32), 25.9 (CH_3C-TBS), 22.7 (CH_2-C33), 18.5 (CCH_3-TBS), 14.2 (CH_3-C34), –4.6 (CH_3Si-TBS), –4.9 (CH_3Si-TBS); HRMS (CI) for $C_{15}H_{28}OSi$ ($[M+H]^+$) calcd. 253.1987, found 253.1983; LRMS (CI, isobutane) *m/z* (intensity) 253.5 (53), 251.5 (11), 195.4 (30), 154.2 (16), 121.3 (100), 93.1 (45), 79.2 (24); Anal. calcd. for $C_{15}H_{28}OSi$: C 71.36%, H 11.18%, Found: C 71.37%, H 11.24%.

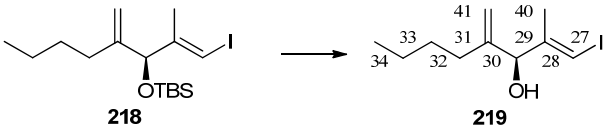
(*S*,*E*)-1-Iodo-2-methyl-4-methyleneoct-1-en-3-ol (218).



217 **218**

Trimethylaluminium (13 mL of a 2 M solution in hexane, 26 mmol) was added dropwise to a stirred solution of Cp_2ZrCl_2 (1.3 g, 4.4 mmol) in dichloromethane (30 mL) at –30 ºC. The mixture was stirred for 30 min and then water (0.17 mL, 8.7 mmol) was added dropwise followed by stirring for a further 30 min. A solution of the alkyne **217** (2.2 g, 8.7 mmol) in dichloromethane (5 mL) was added to the complex dropwise; stirring was continued until consumption of the starting material was observed by TLC. The solution was warmed to 0 ºC and a solution of iodine (2.7 g, 11 mmol) in THF (5 mL) was added dropwise. After stirring for a further 20 min the reaction was quenched by the addition of water (50 mL) and the organic material extracted with petroleum ether (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Residual material was purified by flash column chromatography on silica gel (hexane) to afford the unstable vinyl iodide **218** as pale yellow oil (3.1 g, 90%). R_f = 0.60 (petroleum ether); ν_{max} ($CHCl_3$) 2955, 2928, 2857, 1251, 937, 905, 866, 833, 775 cm^{-1}; $[\alpha]_D^{25}$ –21.8 (*c* = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.30–6.25 (1H, m, CH-C27), 5.12 (1H, d, *J* = 0.6 HzCH_2-C41), 4.89 (1H, d, *J* = 0.6 Hz, CH_2-C41), 4.51 (1H, s, CH-C29), 1.95–1.84 (2H, m, CH_2-C31), 1.67 (3H, d, *J* = 1.0 Hz, CH_3-C40), 1.42–1.24 (4H, m, CH_2-C32, CH_2-C33), 0.89 (3H, t, *J* = 7.2, CH_3-C34), 0.89 (9H, s, CH_3C-TBS), 0.03 (3H, s, CH_3Si-TBS), 0.02 (3H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8 (C-C30), 148.6 (C-C28), 110.8 (CH_2-C41), 80.5 (CH-C29), 77.9 (CH-C27), 30.4 (CH_2-C31), 30.2 (CCH_3-TBS), 25.9 (CH_3C-TBS), 22.7 (CH_2-C33), 19.9 (CH_3-C34), 14.2 (CH_3-C40), –5.0 (CH_3Si-TBS); HRMS (CI+, isobutane) calcd. for $C_{16}H_{32}OSiI$ ($[M+H]^+$) 359.1267, found 395.1259.

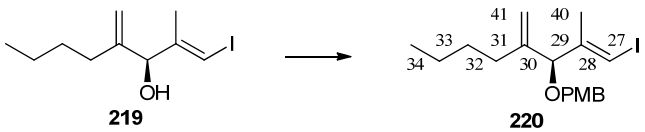
(*S*,*E*)-1-Iodo-2-methyl-4-methyleneoct-1-en-3-ol (219).



218 **219**

The iodide **218** (3.1 g, 7.9 mmol) was dissolved in THF (20 mL) and treated with TBAF (1 M in THF, 9.0 mL, 9.0 mmol) at rt for 2 h and then quenched by $NaHCO_3$ (50 mL). The aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 9:1) to give the alcohol **219** (1.2 g, 48%) as colourless oil. R_f = 0.25 (petroleum ether–ethyl acetate, 4:1); $[\alpha]_D^{25}$ –11.2 (*c* = 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39–6.41 (1H, m, CH-C27), 5.15 (1H, s, CH_2-C41), 4.98 (1H, s, CH_2-C41), 4.61 (1H, d, *J* = 3.4 Hz, CH-C29), 2.01–1.81 (2H, m, CH_2-C31), 1.73 (3H, s, CH_3-C40), 1.41–1.30 (4H, m, CH_2-C32, CH_2-C33), 0.90 (3H, t, *J* = 7.2, CH_3-C34); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5 (C-C30), 147.7 (C-C28), 111.1 (CH_2-C41), 79.5 (CH-C29), 79.3 (CH-C27), 31.3 (CH_2-C32), 30.2 (CH_2-C33), 22.6 (CH_2-C34), 20.1 (CH_3-C35), 14.1 (CH_3-C40).

(*S*,*E*)-1-{[(1-Iodo-2-methyl-4-methyleneoct-1-en-3-yl)oxy]methyl}-4-methoxybenzene (220).

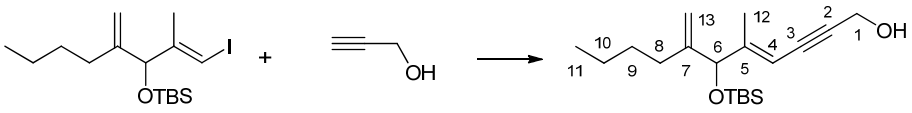


219 **220**

A solution of alcohol **219** (0.30 g, 1.1 mmol) in CH_2Cl_2 (15 mL) and PMBTCA (0.63 g, 2.2 mmol) and CSA (46 mg, 0.11 mmol) was added at rt. The resulting suspension was stirred at rt for 18 h before petroleum ether (50 mL) was poured in and solid was

removed by flitration. The filtrate was dried ($MgSO_4$) and concentrated *in vacuo*. The PMB ether **220** (0.38 g, 88%) was obtained as a colourless oil by flash column chromatography (petroleum ether–ethyl acetate, 100:3). R_f = 0.35 (petroleum ether–ethyl acetate, 9:1); $[\alpha]_D^{25}$ –36.9 (*c* = 0.73, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.7 Hz, Ph-PMB), 6.89 (2H, d, *J* = 8.7 Hz, Ph-PMB), 6.33 (1H, s, CH_2-C27), 5.16 (1H, s, CH-C41), 5.01 (1H, s, CH-C41), 4.36 (2H, s, CH_2O-PMB), 4.21 (1H, s, CH-C29), 3.81 (3H, s, CH_3O-PMB), 1.95–1.87 (2H, m, CH_2-C31), 1.71 (3H, s, CH_3-C41), 1.40–1.27 (4H, m, CH_2-C32, CH_2-C33), 0.89 (3H, t, *J* = 7.3 Hz, CH_3-C34); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 ($COCH_3$-PMB), 148.3 (C-C30), 130.4 (C-C28), 129.3 (CH-PMB), 127.7 (CCH_2-PMB), 113.9 (CH-PMB), 112.3 (CH-PMB), 85.9 (CH-C29), 79.3 (CH-C27), 69.9 (CH_2O-PMB), 55.4 (CH_3O-PMB), 31.1 (CH_2-31), 30.0 (CH_2-32), 26.1 (CH_2-33), 22.6 (CH_3-C34), 14.2 (CH_3-C40). HRMS (CI+, isobutane) calcd. $C_{18}H_{26}O_2I$ ($[M+H]^+$) 401.0977, found 401.0972.

(*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-5-methyl-7-methyleneundec-4-en-2-yn-1-ol (226).

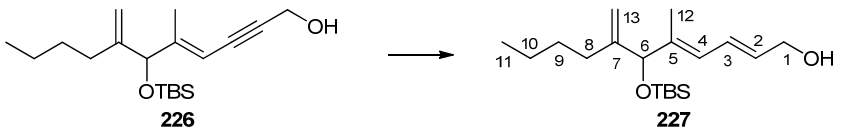


224 **225** **226**

$Pd(PPh_3)_4$ (6.0 mg, 0.0050 mmol) was added to a solution of racemic iodide **224** (70 mg, 0.25 mmol) in Et_3N (1.5 mL) followed by addition of CuI (5.0 mg, 0.03 mmol). Propargyl alcohol **225** (65 mg, 0.38 mmol) was added and strried at rt for 18 h. The reaction mixture was diluted with Et_2O (10 mL), and then washed with aqueous solution of HCl (1 M, 10 mL). Removal of solvent under reduced pressure and subsequently flash column chromatography on silica gel (petroleum ether–ethyl acetate, 20:1) furnished the title alcohol **226** (68 mg, 85%) as orange oil. R_f = 0.45 (petroleum ether–ethyl acetate, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (1H, brs, CH-C4), 5.07 (1H, brs, CH_2-C13), 4.88 (1H, s, CH_2-C13), 4.49–4.32 (3H, m, CH_2-C1,

CH-C6), 1.92 (1H, dt, J = 15.7, 7.8 Hz, CH_2-C8), 1.75 (1H, dt, J = 15.7, 7.8 Hz, CH_2-C8), 1.73 (3H, s, CH_3-C12), 1.52 (1H, t, J = 7.8 Hz, OH), 1.44–1.26 (4H, m, CH_2-C9, CH_2-C10), 0.89 (3H, t, J = 7.9 Hz, CH_3-C11), 0.89 (9H, s, CH_3C-TBS), 0.02 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6 (C-C7), 149.2 (C-C5), 111.0 (CH_2-C13), 104.8 (CH-C4), 91.0 (C-C3), 83.7 (C-C2), 80.2 (CH-C6), 52.0 (CH_2-C1), 30.1 (CH_2-C8), 30.0 (CH_2-C9), 25.9 (CH_3C-TBS), 22.8 (CH_2-C10), 18.4 (CCH_3-TBS), 15.4 (CH_3-C11), 14.2 (CH-C12), –4.9 (CH_3Si-TBS). HRMS (CI, isobutane) calcd. $C_{19}H_{35}O_2Si$ ($[M+H]^+$) 323.2406, found 323.2410.

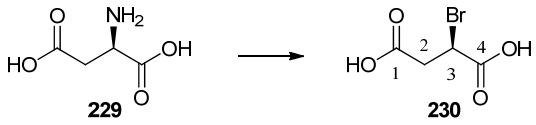
(2*E*,4*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-5-methyl-7-methyleneundeca-2,4-dien-1-ol (227).



To A solution of racemic propargylic alcohol **226** (25 mg, 0.078 mmol) in THF (2 mL) was added with Red-Al® (0.30 g, 0.15 mmol) at 0 °C. After the addition, the reaction mixture was allowed to warm to rt and stirred for 2 h before it was quenched by addition of saturated aqueous solution of sodium potassium tartrate (2 mL). The aqueous phase was extracted with Et_2O (2 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Further purification by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 20:1) afforded title *E*,*E*–diene **227** (16 mg, 65 %) as colourless oil; ν_{max} ($CHCl_3$) 2955, 2929, 1680, 1646, 1590, 1368, 1251, 1084, 985, 937, 902, 869 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (1H, ddt, J = 15.2, 11.4, 1.4 Hz, CH-C3), 6.10 (1H, d, J = 11.4 Hz, CH-C4), 5.83 (1H, dt, J = 11.4, 5.8 Hz, CH-C2), 5.11 (1H, brs, CH_2-C13), 4.88 (1H, s, CH_2-C13), 4.40 (1H, s, CH-C6), 4.22 (2H, t, J = 5.4 Hz, CH_2-C1), 1.92–1.75 (2H, m, CH_2-C8), 1.60 (3H, s, CH_3-C12), 1.42–1.23 (5H, m, CH_2-C9, CH_2-C10 and OH), 0.89 (9H, s, CH_3C-TBS), 0.88 (3H, t, J = 7.2 Hz, CH_3-C11), 0.02 (3H, s, CH_3Si-TBS), 0.01 (3H, s, CH_3Si-TBS);

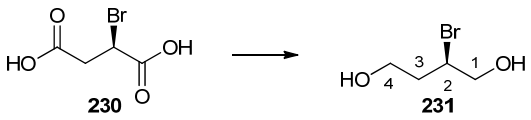
^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2 (C-C7), 142.1 (C-C5), 128.1 (CH-C2), 127.0 (CH-C3), 120.9 (CH-C4), 111.2 (CH_2-C13), 88.2 (CH-C6), 63.2 (CH_2-C1), 30.1 (CH_2-C8), 30.0 (CH_2-C9), 25.8 (CH_3C-TBS), 22.1 (CH_2-C10), 18.4 (CCH_3-TBS), 15.5 (CH_3-C11), 14.1 (CH-C12), –4.9 (CH_3Si-TBS); HRMS (CI, isobutane) calcd. $C_{19}H_{37}O_2Si$ ($[M+H]^+$) 325.2563, found 325.2560.

(*R*)-2-Bromosuccinic acid (230).[69]



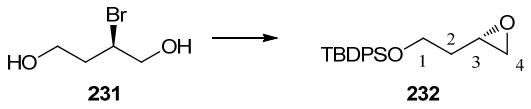
To a suspension of D-aspartic acid **229** (15 g, 0.11 mol) in water (300 mL) was added KBr (61 g, 0.51 mol) and concentrated H_2SO_4 (40 mL, 0.75 mol). The resulting solution was treated dropwise with a solution of $NaNO_2$ (14 g, 0.20 mmol) in water (40 mL) at 0 ºC over 1 hour. The reaction mixture was warmed to rt and stirred for 18 h. The aqueous phase was extracted with ethyl acetate (2 × 300 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo* to give the acid **230** (19 g, 86 %) as a white solid which was used without purification. M.p. = 172–174 °C (lit.[69]M.p. = 166–167 °C); $[\alpha]_D^{26}$ +68.1 (*c* = 0.95, $CHCl_3$) {lit.[69]$[\alpha]_D^{24}$ +60.83 (c = 0.90, MeOH)}; ^{1}H NMR (400 MHz, MeOD) δ 4.56 (1H, dd, *J* = 8.7, 6.2 Hz, CH-C3), 3.18 (1H, dd, *J* = 17.2, 8.7 Hz, CH_2-C2), 2.95 (1H, dd, *J* = 17.2, 6.2 Hz, CH_2-C2); ^{13}C NMR (100 MHz, MeOD) δ 173.2 (CO-C4), 172.3(CO-C1), 40.8 (CH-C3), 40.2 (CH_2-C2); HRMS (CI, isobutane) $C_4H_6BrO_6$ ($[M+H]^+$) calcd. 196.9449, found 196.9453; LRMS (CI, isobutane) *m*/*z* (intensity) 197.0 (100) 179.0 (32) 117.1 (18).

(*R*)-2-Bromobutane-1,4-diol (231).[69]



A solution of the acid **230** (6.5 g, 33 mmol) in THF (200 mL) was treated dropwise with borane dimethyl sulfide complex (9.0 mL of a 10 M solution, 0.10 mol) at 0 ºC. After gas evolution had ceased, the reaction mixture was warmed to rt and stirred for 18 h. The reaction was quenched by the addition of MeOH (100 mL) at 0 ºC, and the mixture was concentrated *in vacuo*. To remove boron residues, the crude material was washed with MeOH (2 × 100 mL) and then concentrated *in vacuo*. Purification by flash column chromatography on silica gel (ethyl acetate–MeOH, 20:1) gave the title diol **231** (5.5 g, 100%) as light yellow oil. R_f = 0.50 (ethyl acetate–MeOH, 50:1); $[\alpha]_D^{27}$ +30.2 (*c* = 1.15, $CHCl_3$) {lit.[69] $[\alpha]_D^{24}$ +33.30 (c = 15.19, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (1H, dq, *J* = 7.8, 5.3 Hz, CH-C2), 3.92–3.77 (4H, m, CH_2-C1, CH_2-C4), 310–1.96 (2H, m, OH), 2.19–2.05 (2H, m, CH_2-C3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.2 (CH_2-C1), 60.2 (CH_2-C4), 55.2 (CH-C2), 37.9 (CH_2-C3).

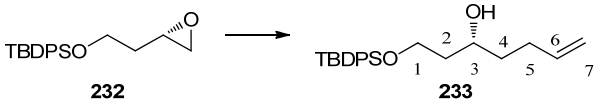
(*S*)-*tert*-Butyl[2-(oxiran-2-yl)ethoxy]diphenylsilane (232).[70]



The diol **231** (1.9 g, 11 mmol) was dissolved in THF (100 mL) and treated carefully with NaH (1.6 g of a 60% suspension in mineral oil, 37 mmol) at 0 ºC and the mixture was stirred for 30 min. TBDPSCl (3.4 mL, 13 mmol) was then added over 10 min at 0 ºC and the resulting mixture was warmed to rt for 2 h. Water (100 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The organic extracts were concentrated in *vacuo* and the residue was purified by flash column chromatography

on silica gel (petroleum ether–ethyl acetate, 100:1) to give the epoxide **232** (3.6 g, 97%) as a white solid. M.p. = 39–40 °C (lit.[69]M.p. = 39.7–41.2 °C); $[\alpha]_D^{27}$ –6.2 (*c* = 1.05, $CHCl_3$) {lit.[69]$[\alpha]_D^{25}$ –6.74 (*c* = 1.87, $CHCl_3$)}; ν_{max} ($CHCl_3$) 2931, 2858, 1473, 1427, 1388, 1107, 1037, 1006, 964, 910, 821, 736, 702, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.66 (4H, m, Ph-TBDPS), 7.45–7.37 (6H, m, Ph-TBDPS), 3.86–3.79 (2H, m, CH_2-C1), 3.10 (1H, tdd, *J* = 5.8, 4.1, 2.7 Hz, CH-C3), 2.78 (1H, dd, *J* = 5.0, 4.1 Hz, CH_2-C4), 2.51 (1H, dd, *J* = 2.7, 5.0 Hz, CH_2-C4), 1.77 (2H, m, CH_2-C2), 1.06 (9H, s, CH_3C-TBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (Ph-TBDPS), 135.7 (Ph-TBDPS), 133.8 (Ph-TBDPS), 129.7 (Ph-TBDPS), 127.8 (Ph-TBDPS) 61.1 (CH_2-C1), 50.3 (CH-C3), 47.4 (CH_2-C4), 35.9 (CH_2-C2), 27.0 (CH_3C-TBDPS), 19.3 (CCH_3-TBDPS); HRMS (CI, isobutane) $C_{20}H_{27}O_2Si$ ($[M+H]^+$) calcd. 327.1780, found 327.1782; LRMS (CI, isobutane) *m*/*z* (intensity) 327.3 (20) 269.2 (100) 249.2 (50) 239.2 (28) 207.2 (33) 193.2 (20) 161.1 (18) 131.2 (14) 71.1 (20).

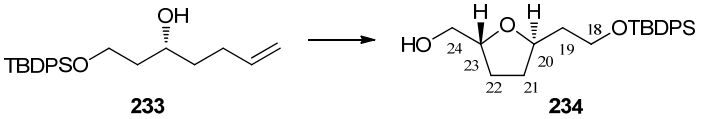
(*R*)-1-[(*tert*-Butyldiphenylsilyl)oxy]hept-6-en-3-ol (233).



A solution of epoxide **232** (2.2 g, 6.7 mmol) in Et_2O (75 mL) was treated dropwise with allylmagnesium chloride (7.0 mL of a 2.0 M solution in THF, 14 mmol) at 0 ºC. The reaction mixture was stirred at this temperature for 30 min and then warmed to rt for another 1 h. The reaction was quenched by addition of saturated aqueous solution of NH_4Cl (100 mL) and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 25:1) to give the alcohol **233** (2.2 g, 90%) as colourless oil. ν_{max} ($CHCl_3$) 3070, 2931, 2858, 2360, 2114, 1469, 1427, 1388, 1303, 1261, 1188, 1107, 995, 910, 821, 736, 702, 648, 613 cm^{-1}; $[\alpha]_D^{24}$ +8.2 (*c* = 1.21, $CHCl_3$); ^1H NMR (400 MHz,

$CDCl_3$) δ 7.69–7.66 (4H, m, Ph-TBDPS), 7.45–7.37 (6H, m, Ph-TBDPS), 5.85 (1H, ddt, J = 17.1, 10.1, 6.6 Hz, CH-C6), 5.04 (1H, ddt, J = 17.1, 2.1, 1.7 Hz, CH_2-C7), 4.97 (1H, ddt, J = 10.1, 2.1, 1.1, Hz, CH_2-C7), 3.98–3.86 (3H, m, CH-C3, CH_2-C1), 3.21 (1H, d, J = 2.8 Hz, OH), 2.21–2.14 (2H, m, CH_2-C5), 1.86–1.48 (4H, m, CH_2-C4, CH_2-C2), 1.05 (9H, s, CH_3C-TBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8 (CH-C6), 135.7 (Ph-TBDPS), 133.2 (Ph-TBDPS), 130.0 (Ph-TBDPS), 128.0 (Ph-TBDPS), 114.7 (CH_2-C7), 71.4 (CH-C3), 63.6 (CH_2-C1), 38.5 (CH_2-C4), 36.8 (CH_2-C5), 30.0 (CH_2-C2), 27.0 (CH_3C-TBDPS), 19.2 (CCH_3-TBDPS); HRMS (CI) for $C_{23}H_{33}O_2Si$ ($[M+H]^+$) calcd. 369.2250, found 329.2250; LRMS (CI, isobutane) *m/z* (intensity) 369.3 (100) 311.3 (25) 291.3 (32) 257.2 (10) 209.2 (15) 199.1 (12) 179.2 (5) 95.2 (29).

{(2*R*,5*R*)-[5-(2-*tert*-Butyldiphenylsilyloxy)ethyl]tetrahydrofuran-2-yl}methanol (234).

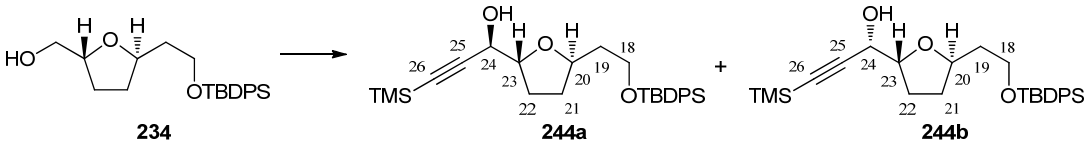


233 **234**

To a solution of alcohol **233** (6.7 g, 21 mmol) in *i*-PrOH (210 mL) was added $Co(nmp)_2$ (1.2 g, 2.1 mmol), TBHP (5.5 M in octane, 0.38 mL, 2.1 mmol) under O_2 atmosphere. The reaction was stirred at 55 ºC for 18 h. The solution was cooled to rt and treated with MeI (2.1 mL) and stirred at rt for 48 h. Water (300 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 9:1 to 4:1) to give the *trans*-tetrahydrofuran **234** (6.8 g, 97%) as colourless oil. $[\alpha]_D^{22}$ –11.0 (*c* = 0.96, $CHCl_3$); ν_{max} ($CHCl_3$) 2931, 2858, 1473, 1427, 1388, 1107, 1037, 1006, 964, 910, 821, 736, 702, 613 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.65 (4H, m, Ph-TBDPS), 7.44–7.36 (6H, m, Ph-TBDPS), 4.13 (1H, ddd, J = 13.2, 7.5, 5.8 Hz, CH-C20), 4.06 (1H, ddd, J = 14.0, 6.7, 3.5 Hz, CH-C23), 3.81–3.72 (2H, m,

CH_2-C18), 3.61 (1H, dt, J = 7.2, 3.5 Hz, CH_2-C24), 3.49–3.43 (1H, m, CH_2-C24), 2.07–1.50 (7H, m, CH_2-C21, CH_2-C22, CH_2-C19, OH), 1.05 (9H, s, CH_3C-TBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (Ph-TBDPS), 134.1 (Ph-TBDPS), 134.0 (Ph-TBDPS), 129.7 (Ph-TBDPS), 127.8 (Ph-TBDPS), 78.8 (CH-C20), 76.5 (CH-C23), 65.3 (CH_2-C24), 61.4 (CH_2-C18), 38.7 (CH_2-C19), 32.4 (CH_2-C21), 27.6 (CH_2-C22), 27.0 (CH_3C-TBDPS), 19.4 (CCH_3-TBDPS); HRMS (CI) $C_{23}H_{33}O_3Si$ ($[M+H]^+$) calcd. 385.2199, found 385.2200; LRMS (CI, isobutane) *m/z* (intensity) 385.3 (61) 327.3 (59) 307.3 (100) 229.2 (75).

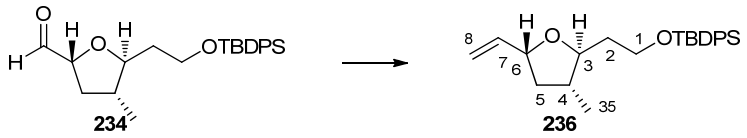
1-{(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl}-3-(trimethylsilyl)prop-2-yn-1-ol 244a and 244b



Alcohol **234** (0.20 g, 0.52 mmol) in CH_2Cl_2 (10 mL) was treated with Dess-Martin periodinane (0.28 g, 0.57 mmol) at rt. The reaction mixture was stirred for 3 h until there was no starting material left. The reaction was quenched by addition of saturated aqueous solution of $Na_2S_2O_3$ (20 mL) and Na_2CO_3 (20 mL). The aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo* to give the crude aldehyde as a yellow oil was used without further purification. To a solution of trimethylacetylene (0.44 mL, 3.1 mmol) in ether (10 mL) was slowly added with *i*-PrMgCl (2.0 M in THF, 1.4 mL, 2.8 mmol) at 0 ºC. After stirred at 0 ºC for 1 h, the resulting suspension was added to a solution of the aldehyde in ether (5 mL), which was prepared from last step. The reaction mixture was allowed to warm to rt for another 2 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (40 mL), and the aqueous phase was extracted with ether (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. Flash column chromatography on silica gel (petroleum ether–

ethyl acetate, 25:1 to 9:1) afforded a 3:4 mixture of (**244a**:**244b**) (0.18 g, 72%) as colourless oil. **244a** R_f = 0.28 (petroleum ether–ethyl acetate, 9:1); $[\alpha]_D^{24}$ –53.7 (*c* = 2.20, $CHCl_3$); ν_{max} ($CHCl_3$) 3410, 3070, 2955, 2936, 2889, 2862, 1465, 1427, 1389, 1249, 1103, 1080, 845, 698, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.68 (4H, m, Ph-TBDPS), 7.44–7.36 (6H, m, Ph-TBDPS), 4.17 (1H, dd, *J* = 7.5, 3.6 Hz, CH-C24), 4.16 (1H, ddd, *J* = 13.4, 7.5, 5.7 Hz, CH-C23), 4.00 (1H, td, *J* = 7.0, 6.9 Hz, CH-C20) 3.81–3.69 (2H, m, CH_2-C18), 2.31 (1H, d, *J* = 3.6 Hz, OH), 2.04–1.98 (2H, m, CH_2-C21), 1.88–1.68 (2H, m, CH_2-C19, CH_2-C22), 1.61–1.50 (1H, m, CH_2-C22), 1.04 (9H, s, CH_3C-TBDPS), 0.16 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (Ph-TBDPS), 134.1 (Ph-TBDPS), 129.8 (Ph-TBDPS), 127.7 (Ph-TBDPS), 103.4 (C-C25), 90.8 (C-C26), 81.9 (CH-C23), 77.1 (CH-C20), 66.1 (CH-C24), 61.2 (CH_2-C18) 38.5 (CH_2-C19), 32.1 (CH_2-C22), 28.4 (CH_2-C21), 27.1 (CH_3C-TBDPS), 19.4 (CCH_3-TBDPS), –0.01 (TMS); **244b** R_f = 0.29 (petroleum ether–ethyl acetate, 9:1); $[\alpha]_D^{24}$ +14.8 (c = 2.20, $CHCl_3$); ν_{max} ($CHCl_3$) 3406, 3075, 2955, 2936, 2889, 2862, 1469, 1427, 1388, 1249, 1099, 945, 841, 744, 698, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (4H, m, Ph-TBDPS), 7.44–7.36 (6H, m, Ph-TBDPS), 4.40 (1H, dd, *J* = 5.9, 3.3 Hz, CH-C24), 4.26 (1H, tt, *J* = 7.8, 5.7 Hz, CH-C20), 4.08 (1H, td, *J* = 7.4, 3.3 Hz, CH-C23) 3.81–3.69 (2H, m, CH_2-C18), 2.31 (1H, dd, *J* = 5.9, 1.3 Hz, OH), 2.12 (1H, dq, *J* = 11.7, 5.8 Hz, CH_2-C21), 2.04–1.97 (2H, m, CH_2-C21, CH_2-C19), 1.83 (1H, ddt, *J* = 13.2, 7.8, 5.8 Hz, CH_2-C22), 1.72 (1H, ddt, *J* = 13.2, 6.6, 5.8 Hz, CH_2-C22), 1.53 (1H, ddt, *J* = 11.7, 8.6, 5.7 Hz, CH_2-C19), 1.05 (9H, s, CH_3C-TBDPS), 0.15 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (Ph-TBDPS), 134.0 (Ph-TBDPS), 129.7 (Ph-TBDPS), 127.8 (Ph-TBDPS), 103.7 (C-C25), 91.0 (C-C26), 80.8 (CH-C23), 78.3 (CH-C20), 66.1 (CH-C24), 61.3 (CH_2-C18) 38.7 (CH_2-C19), 32.4 (CH_2-C22), 27.6 (CH_2-C21), 27.0 (CH_3C-TBDPS), 19.4 (CCH_3-TBDPS), –0.05 (TMS); HRMS (CI, isobutane) $C_{28}H_{41}O_3Si_2$ ($[M+H]^+$) calcd. 481.2594, found 481.2603; LRMS (CI, isobutane) *m/z* (intensity) 481.4 (100) 465.4 (24) 403.3 (78) 383.3 (22) 305.3 (22) 257.2 (31) 220.2 (15) 199.1 (14) 91.1 (12) 73.1 (10).

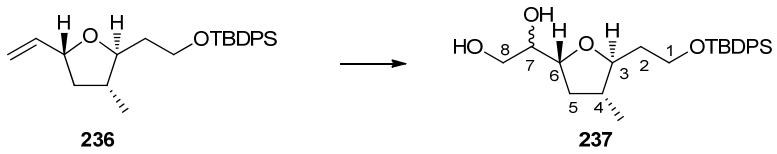
***tert*-Butyl{2-[(2*S*,3*R*,5*R*)-3-methyl-5-vinyltetrahydrofuran-2-yl]ethoxy}diphenylsilane (236).**



To a suspension of $MePh_3PBr$ (11 g, 32 mmol) in THF (100 mL) was added slowly *t*-BuOK (2.7 g, 24 mmol) at 0 ºC and the resulting mixture was stirred at 0 ºC for 1 h. A solution of aldehyde **234** (3.2 g, 8.0 mmol) in THF (10 mL) was then added dropwise and the mixture was allowed to warm to rt and stirred for 4 h before water (150 mL) was added to quench the reaction. The aqueous phase was extracted with Et_2O (2 × 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 500:3) afforded title olefin **236** (2.1 g, 72%) as colourless oil. $[\alpha]_D^{27}$ –4.2 (*c* = 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 2943, 2861, 2361, 2111, 1462, 1441, 1388, 1321, 1261, 1167, 1111, 995, 910, 820, 735, 710, 655, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.66 (m, 4H, Ph-TBDPS), 7.43–7.35 (6H, m, Ph-TBDPS), 5.84 (1H, ddd, *J* = 17.1, 10.3, 6.7 Hz, CH-C7), 5.20 (1H, ddd, *J* = 17.1, 1.6, 1.3 Hz, CH_2-C8), 5.06 (1H, ddd, *J* = 10.3, 1.6, 1.3 Hz, CH_2-C8), 4.34–4.32 (1H, m, CH-C6), 3.85–3.81 (2H, m, CH_2-C1), 3.65 (1H, dt, *J* = 8.4, 3.4 Hz, CH-C3), 2.22–2.17 (1H, m, CH_2-C5), 1.93–1.82 (1H, m, CH-C4), 1.84 (1H, ddt, *J* = 10.7, 7.3, 3.4 Hz, CH_2-C2), 1.70 (1H, ddt, *J* = 13.8, 8.4, 5.7 Hz, CH_2-C2), 1.35 (ddd, 1H, *J* = 12.1, 10.7, 9.5 Hz, CH_2-C5) 1.04 (9H, s, CH_3C-TBDPS), 1.03 (3H, d, *J* = 6.6 Hz, CH_3-C35); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1 (C-C7), 135.7 (Ph-TBDPS), 134.2 (Ph-TBDPS), 129.6 (Ph-TBDPS), 127.7 (Ph-TBDPS), 115.0 (CH_2-C8), 82.4 (CH-C20), 79.3 (CH-C23), 61.5 (CH_2-C18), 42.1 (CH_2-C5), 40.4 (CH-C4), 37.4 (CH-C2), 27.0 (CH_3C-TBDPS), 19.4 (CCH_3-TBDPS), 16.8 (CH_3-C35); HRMS (CI, isobutane) $C_{25}H_{35}O_2Si$ ($[M+H]^+$) calcd. 395.2406, found 395.2407; LRMS (CI,

isobutane) *m/z* (intensity) 395.2 (100) 305.3 (22) 199.1 (24) 91.1 (17) 73.1 (15).

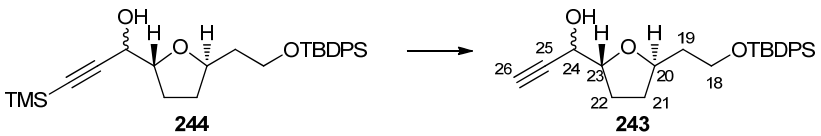
(*R*)-1-{(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl}ethane-1,2-diol (237).



236 **237**

The olefin **236** (0.21 g, 0.56 mmol) was dissolved in *t*-BuOH (5 mL) and water (5 mL), and added AD-mix-β (0.80 g, 0.62 mmol) at –10 ºC. The reaction was stirred at –10 ºC for 30 h and then was quenched by addition of saturated aqueous solutions of $Na_2S_2O_3$ (5 mL) and Na_2CO_3 (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. Flash column chromatography on silica gel (petroleum ether–ethyl acetate, 3:1 to 1:4) yielded the diol **237** (0.20 g, 88%) as colourless oil as a 1:6 mixture. This reaction was a quick test. The crude ^{1}H NMR was clear enough to investigate the diastereomeric ratio. So this synthetic route was abandoned. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.68 (4H, m, Ph-TBDPS), 7.44–7.36 (6H, m, Ph-TBDPS), 3.92–3.93 (1H, m, CH-C23), 3.93–3.56 (7H, m, CH_2-C8, CH-C7, CH-C6, CH-C3, CH_2-C1), 2.25 (1H, d, J = 4.4 Hz, OH), 2.11 (1H, dd, J = 7.1, 4.8 Hz, OH), 1.62 (1H, dt, J = 12.2, 6.2 Hz, CH_2-C5), 1.95–1.79 (2H, m, CH-C4, CH_2-C2), 1.66–1.43 (2H, m, CH_2-C2, CH_2-C5), 1.05 (9H, s, CH_3C-TBDPS), 1.03 (3H, d, J = 6.5 Hz, CH_3-C35).

1-{(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl}prop-2-yn-1-ol (243).

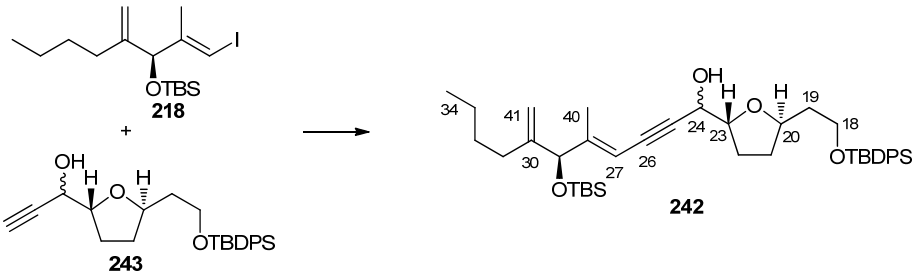


244 **243**

Alcohol **244** (0.75 g, 1.6 mmol) was dissolved in MeOH (20 mL), and K_2CO_3 (0.44 g,

3.2 mmol) was added at rt. The reaction mixture was stirred at rt for 2 h. Water (50 mL) was added, and the aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 9:1) to give the propargyl alcohol **243** (0.58 g, 91%) as colourless oil. R_f = 0.26 (petroleum ether–ethyl acetate, 3:1); $[\alpha]_D^{27}$ –0.73 (*c* = 2.15, $CHCl_3$); ν_{max} (liquid film) 3428, 3299, 3064, 2931, 2883, 2860, 1468, 1428, 1389, 1105, 941, 821, 741, 702 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 7.69–7.64 (4H, m, Ph-TBDPS), 7.46–7.35 (6H, m, Ph-TBDPS), 4.21– 4.12 (2H, m, CH-C24, CH-C23), 4.04 (1H, q, *J* = 6.9 Hz, CH-C20), 3.82–3.71 (2H, m, CH_2-C18), 2.48 (1H, brd, *J* = 4.2 Hz, OH), 2.42 (1H, d, *J* = 2.2 Hz, CH-C26), 2.14–2.01 (2H, m, CH_2-C21), 1.90–1.68 (3H, m, CH_2-C22 and CH_2-C19), 1.63–1.52 (1H, m, CH_2-C22), 1.05 (9H, s, CH_3C-TBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (Ph-TBDPS), 134.0 (Ph-TBDPS), 133.9 (Ph-TBDPS), 129.8 (Ph-TBDPS), 127.8 (Ph-TBDPS), 82.1 (C-C25), 81.4 (CH-C23), 77.2 (C-C26), 73.8 (CH-C20), 65.4 (CH-C24), 61.2 (CH_2-C18), 38.4 (CH_2-C19), 32.1 (CH_2-C22), 28.2 (CH_2-C21), 27.0 (CH_3C-TBDPS), 19.3 (CCH_3-TBDPS); HRMS (CI, isobutane) calcd. $C_{25}H_{33}O_3Si$ $[M+H]^+$ 409.2199 found 409.2200; LRMS (CI, isobutane) *m/z* (intensity) 409.4 (100), 383.4 (54), 331.4 (66), 305.4 (31), 253.3 (22).

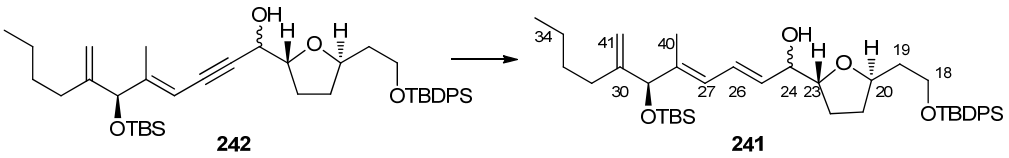
(6*S*,*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-{(2*R*,5*R*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl}-5-methyl-7-methyleneundec-4-en-2-yn-1-ol (242).



To a solution of vinyl iodide **218** (0.60 g, 1.5 mmol) in Et_3N (8.0 mL), was added with $Pd(PPh_3)_2Cl_2$ (14 mg, 0.0012 mmol), CuI (10 mg, 0.040 mmol) at rt. The yellow

suspension was bubbling with argon for 20 min. The reaction mixture was then allowed to warm to 55 ºC before a solution of propargyl alcohol **243** (0.40 g, 0.98 mmol) in Et_3N (2 mL) was added over 2 h. After complete addition, the suspension continued stirring for 1 h and quenched by water (20 mL). The aqueous phase was extracted with ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. Purification by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 25:1 to 20:1) furnished two diastereomeric mixture of propargyl alcohols **242** (0.54 g, 80%) as an orange oil which was used directly for the next step.

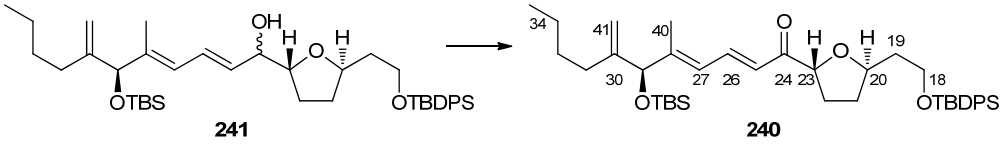
(2*E*,4*E*,6*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-{(2*R*,5*R*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl}-5-methyl-7-methyleneundeca-2,4-dien-1-ol (241).



Red-Al (0.33 g of a 65 wt. % solution in toluene, 1.2 mmol) was added to a solution of the diastereomeric propargylic alcohols **242** (0.20 g, 0.30 mmol) in THF (10 mL) at 0 ºC. The mixture was allowed to warm to rt for 30 min and the reaction was quenched by addition of a saturated aqueous solution of potassium sodium tartrate (40 mL). The mixture was extracted with ether (3 × 40 mL) and the combined extracts were dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on silica gel (petroleum ether/EtOAc, 20:1 to 9:1) to provide a diastereomeric mixture of dienols **241** (0.13 g, 65%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71–7.68 (4H, m, Ph-TBDPS), 7.44–7.38 (6H, m, Ph-TBDPS), 6.55 (1H, ddd, *J* = 15.2, 11.0, 0.8 Hz, CH-26), 6.07 (1H, d, *J* = 11.0 Hz, CH-C27), 5.58 (1H, dd, *J* = 15.2, 6.9 Hz, CH-C25), 5.11 (1H, s, CH_2-C41), 4.86 (1H, s, CH_2-C41), 4.40 (1H, s, CH-C29), 4.37–4.35 (1H, m, CH-C24) 4.16 (1H, ddt, *J* = 11.5, 7.6, 5.8

Hz, CH-C24), 3.95 (1H, dt, *J* = 7.0, 2.0 Hz, CH-C23), 3.86–3.74 (3H, m, CH-C20, CH_2-C18), 2.58 (1H, d, *J* = 2.7 Hz, OH), 2.24 (1H, d, *J* = 3.1 Hz, OH), 2.11–1.50 (8H, m, CH_2-C22, CH_2-C21, CH_2-C19, CH_2-C31), 1.60 (3H, s, CH_3-C40), 1.45–1.28 (4H, m, CH_2-C32, CH_2-C33), 1.06 (9H, s, CH_3C-TBDPS), 0.87 (9H, s, CH_3C-TBS), 0.85 (3H, t, *J* = 7.2 Hz, CH_3-C34), 0.02 (6H, s, CH_3Si-TBS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8 (C-C30), 139.7 (CH-C25), 139.5 (CH-C25), 135.7 (C-C28), 134.1 (Ph-TBDPS), 134.0 (Ph-TBDPS), 133.9 (Ph-TBDPS), 130.6 (Ph-TBDPS), 130.3 (Ph-TBDPS), 129.8 (Ph-TBDPS), 129.0 (Ph-TBDPS), 128.4 (Ph-TBDPS), 127.8 (CH-26), 125.0 (CH-C27), 109.9 (CH_2-C41), 81.9 (CH-C23), 81.3 (CH-C29), 80.8 (CH-C29), 76.6 (CH-C20), 75.7 (CH-C24), 73.5 (CH-C24), 61.3 (CH_2-C18), 38.9 (CH_2-C19), 38.6 (CH_2-C19), 32.4 (CH_2-C22), 30.9 (CH_2-C21), 30.2 (CCH_3-TBDPS), 28.3 (CCH_3-TBS), 27.0 (CH_3C-TBDPS), 25.7 (CH_3C-TBS), 26.0 (CH_3C-TBS), 22.7 (CH_2-C31), 19.4 (CH_2-C32), 18.5 (CH_2-C33), 14.2 (CH_3-C34), 12.2 (CH_3-C40), –4.8 (CH_3Si-TBS).

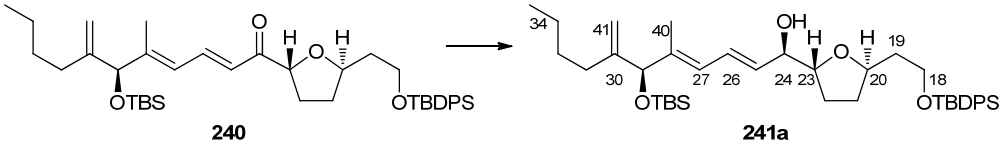
(*S*,2*E*,4*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-{(2R,5R)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl}-5-methyl-7-methyleneundeca-2,4-dien-1-one (240).



A solution of allylic alcohol **241** (0.12 g, 0.18 mmol) in CH_2Cl_2 (10 mL) was added Dess-Martin periodinane (0.12 g, 0.27 mmol) at rt. The reaction was stirred at rt for 1 h and was quenched by addition of saturated aqueous solution of $Na_2S_2O_3$ (10 mL) and Na_2CO_3 (10 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. Purification by flash column chromatography on silica gel (petroleum ether–ether, 25:1 to 20:1) afforded the enone **240** (0.12 g, 100%) as colourless oil. R_f = 0.70

(petroleum ether–ethyl acetate, 4:1); $[\alpha]_D^{24}$ +22.0 (c = 0.82, $CHCl_3$); ν_{max} ($CHCl_3$) 2955, 2929, 2856, 1683, 1626, 1587, 1388, 1251, 1084, 985, 937, 902, 869, 837, 823, 777, 738, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73–7.66 (4H, m, Ph-TBDPS), 7.67 (1H, dd, J = 15.2, 11.8 Hz, CH-C26), 7.45–7.36 (6H, m, Ph-TBDPS), 6.56 (1H, d, J = 15.2 Hz, CH-C27), 6.33 (1H, dq, J = 11.8, 0.8 Hz, CH-C25), 5.14 (1H, s, CH_2-C41), 4.91 (1H, d, J = 0.8 Hz, CH_2-C41), 4.53–4.47 (1H, m, CH-23), 4.48 (1H, s, CH-29), 4.35–4.27 (1H, m, CH-C20), 3.89–3.75 (2H, m, CH_2-C18), 2.29–2.22 (1H, m, CH_2-C22), 2.07–1.87 (4H, m, CH_2-C21, CH_2-C22, CH_2-C19), 1.83–1.73 (1H, m, CH_2-C19), 1.78 (3H, d, J = 0.8 Hz, CH_3-C40), 1.64–1.56 (1H, m, CH_2-C31), 1.44–1.22 (5H, m, CH_2-C31, CH_2-C32, CH_2-C33), 1.07 (9H, s, CH_3C-TBDPS), 0.91 (9H, s, CH_3C-TBDPS), 0.89 (3H, t, J = 7.2 Hz, CH_3-C34), 0.04 (3H, s, CH_3Si-TBS), 0.02 (3H, s, CH_3Si-TBS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6 (CO-C24), 151.6 (C-C30), 149.0 (C-C28), 139.9 (CH-C26), 135.7 (Ph-TBDPS), 135.7 (Ph-TBDPS), 134.0 (Ph-TBDPS), 133.9 (Ph-TBDPS), 129.7 (Ph-TBDPS), 127.8 (Ph-TBDPS), 124.0 (CH-C27), 123.9 (CH-25), 111.0 (CH_2-C41), 82.6 (CH-C23), 80.9 (CH-C29), 78.2 (CH-C20), 61.3 (CH_2-C18), 38.6 (CH_2-C19), 31.8 (CH_2-C22), 30.4 (CH_2-C21), 30.1 (CCH_3-TBDPS), 29.7 (CCH_3-TBS), 27.0 (CH_3C-TBDPS), 25.9 (CH_3C-TBS), 22.6 (CH_2-C31), 19.3 (CH_2-C32), 18.4 (CH_2-C33), 14.1 (CH_3-C34), 13.3 (CH_3-C40), –4.9 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{41}H_{63}O_4Si_2$ ($[M+H]^+$) calcd. 676.4365, found 676.4252.

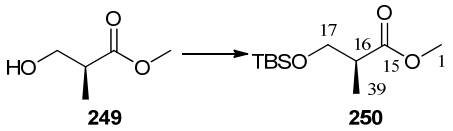
(1*R*,2*E*,4*E*,6*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-{(2*R*,5*R*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl}-5-methyl-7-methyleneundeca-2,4-dien-1-ol (241a).



To a stirred solution containing the purified dienone **240** (0.11 g, 0.16 mmol) and

$CeCl_3.7H_2O$ (0.15 g, 0.40 mmol), in MeOH (10 mL) at –78 ºC, was added sodium borohydride (27 mg, 0.7 mmol). The mixture was stirred for 30 min and the reaction was quenched by the addition of water (30 mL). The mixture was warmed to rt and then extracted with EtOAc (2 × 30 mL). The extracts were combined and dried ($MgSO_4$) then concentrated. The residual material was purified by chromatography on silica gel (pet. ether/ether, 25:1) to afford the alcohol **241a** (92 mg, 83%) as a single diastereomer. R_f = 0.66 (petroleum ether–ethyl acetate, 4:1); $[\alpha]_D^{27}$ –4.7 (*c* = 0.95, $CHCl_3$); ν_{max} ($CHCl_3$) 3311, 3292, 2956, 2858, 1653, 1464, 1388, 1251, 1111, 1070, 1004, 939, 906 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69–7.65 (4H, m, Ph-TBDPS), 7.46–7.35 (6H, m, Ph-TBDPS), 6.55 (1H, ddd, *J* = 15.2, 11.0, 0.8 Hz, CH-C27), 6.07 (1H, d, *J* = 11.0 Hz, CH-C26), 5.58 (1H, dd, *J* = 15.2, 6.8 Hz, CH-25), 5.11 (1H, s, CH_2-C41), 4.86 (1H, s, CH_2-C41), 4.40 (1H, s, CH-C29), 4.16 (1H, tt, *J* = 7.5, 5.8 Hz, CH-C24), 3.95 (1H, td, *J* = 7.0, 2.1 Hz, CH_2-C23), 3.83 (1H, q, *J* = 7.0 Hz, CH_2-C20), 3.82–3.72 (2H, m, CH_2-C18), 2.58 (1H, d, *J* = 2.7 Hz, OH), 2.09–1.50 (8H, m, CH_2-C19, CH_2-21, CH_2-C22, CH_2-C31), 1.60 (3H, s, CH_3-C40), 1.46–1.20 (4H, m, CH_2-32, CH_2-C33), 1.06 (9H, s, CH_3C-TBDPS), 0.90 (9H, s, CH_3C-TBS), 0.88 (3H, t, *J* = 7.2 Hz, CH_3-C34), 0.02 (3H, s, CH_3Si-TBS), 0.01 (3H, s, CH_3Si-TBS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8 (C-C30), 139.7 (CH-C25), 135.7 (C-C28), 134.1 (Ph-TBDPS), 130.6 (Ph-TBDPS), 129.8 (Ph-TBDPS), 129.0 (Ph-TBDPS), 127.8 (CH-26), 125.0 (CH-C27), 109.91 (CH_2-C41), 81.9 (CH-C23), 80.83 (CH-C29), 76.6 (CH-C20), 75.7 (CH-C24), 61.3 (CH_2-C18), 38.6 (CH_2-C19), 32.4 (CH_2-C22), 30.9 (CH_2-C21), 30.2 (CCH_3-TBDPS), 28.3 (CCH_3-TBS), 27.0 (CH_3C-TBDPS), 26.0 (CH_3C-TBS), 22.7 (CH_2-C31), 19.4 (CH_2-C32), 18.5 (CH_2-C33), 14.2 (CH_3-C34), 12.2 (CH_3-C40), –4.8 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{41}H_{63}O_3Si_2$ ($[M\text{-}OH_2]^+$) calcd. 659.4316, found 659.4315; LRMS (CI, isobutane) *m/z* (intensity) 659.6 (100) 583.5 (22) 527.5 (25) 457.4 (14) 449.5 (10) 353.3 (13) 257.3 (58) 239.3 (20) 205.3 (15) 107.2 (40).

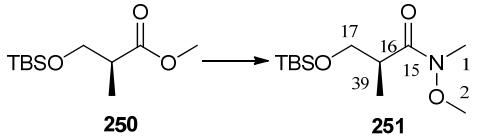
(*S*)-Methyl 3-(*tert*-butyldimethylsilyloxy)-2-methylpropanoate (250).[70]



249 **250**

A solution of (*S*)-Roche ester (5.0 g, 42 mmol), DMAP (0.13 g, 5.2 mmol), imidazole (6.9 g, 0.10 mol) in CH_2Cl_2 (45 mL) was cooled to 0 °C and then TBSCl (8.5 mL, 57 mmol) was added. The mixture was allowed to warm to rt and stirred for 2 h before a saturated aqueous solution of $NaHCO_3$ (50 mL) was added to the flask. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a residue that was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 50:1 to 20:1) to give the TBS ether **250** (9.5 g, 97%) as colourless oil. R_f = 0.90 (petroleum ether–ethyl acetate, 10:1); $[\alpha]_D^{22}$ +18.1 (*c* = 1.10, $CHCl_3$), {lit.[70] $[\alpha]_D^{22}$ +18.9 (*c* = 1.00, $CHCl_3$)}; ν_{max} 2953, 2929, 2859, 1742, 1462, 1251, 1197, 1174, 1092, 835, 816, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (1H, dd, *J* = 9.7, 6.9 Hz, CH_2-C17), 3.67 (3H, s, CH_3O-C1), 3.64 (1H, dd, *J* = 9.7, 6.0 Hz, CH_2-C17), 2.64 (1H, qdd, *J* = 7.0, 6.9, 6.0 Hz, CH-C16), 1.13 (d, 3H, *J* = 7.0 Hz, CH_3-C39), 0.86 (9H, s, CH_3C-TBS), 0.03 (3H, s, CH_3Si-TBS), 0.02 (s, 3H, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6 (CO-C15), 66.4 (CH_2-C17), 51.8 (CH_3-C1), 42.7 (CH-C16), 25.9 (CCH_3-TBS), 18.3 (CH_3C-TBS), 13.6 (CH_3-C39), –5.4 (CH_3Si-TBS); HRMS (ESI) for $C_{11}H_{24}NaO_3Si$ ($[M+Na]^+$) calcd. 255.1392, Found: 255.1387; Anal. calcd. for $C_{11}H_{24}O_3Si$: C 56.85%, H 10.41%, Found: C 56.83%, H 10.58%.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*,2-dimethylpropanamide (251).[71]

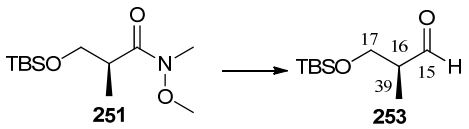


250 **251**

To a stirred slurry of *N*,*O*-dimethylhydroxylamine hydrochloride (6.0 g, 62 mmol)

and TBS ether (9.5 g, 41 mmol) in THF (50 mL) cooled to –15 °C was added *i*-PrMgCl (62 mL of a 2.0 M solution in THF, 0.12 mol). The mixture was stirred for 1 h and the reaction was then quenched by addition of a saturated aqueous solution of NH_4Cl (100 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in *vacuo* and the residue was purified by flash chromatography on silica gel (pet. ether/ethyl acetate, 6:1) to give the amide **251** (12 g, 95%) as colourless oil. R_f = 0.44 (petroleum ether–ethyl acetate, 4:1); ν_{max} (liquid film) 2955, 2930, 2884, 2857, 1662, 1097, 997, 835, 815, 775 cm^{-1}; $[\alpha]_D^{26}$ +23.9 (c = 1.10, $CHCl_3$) {Lit.[71] $[\alpha]_D^{26}$ +21.1 (c = 1.10, $CHCl_3$)}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (1H, dd, J = 9.5, 8.1 Hz, CH_2-C17), 3.70 (3H, s, CH_3O-C2), 3.52 (1H, dd, J = 9.5, 6.1 Hz, CH_2-C17), 3.21–3.11 (1H, m, CH-C16), 3.19 (3H, s, CH_3N-C1), 1.07 (3H, d, J = 6.9 Hz, CH_3-C39), 0.87 (9H, s, CH_3C-TBS), 0.04 (3H, s, CH_3Si-TBS), 0.03 (3H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2 (C-C17), 65.9 (CH_2-C15), 61.7 (CH_3O-C2), 38.2 (CH_3N-C1), 32.3 (CH-C16), 26.0 (CCH_3-TBS), 18.4 (CH_3C-TBS), 13.9 (CH_3-C39), –5.3 (CH_3Si-TBS); HRMS (ESI) for $C_{12}H_{27}NNaO_3Si$ ($[M+Na]^+$) calcd. 284.1658, found 284.1649. Anal. calcd. for $C_{12}H_{27}NO_3Si$: C 55.13%, H 10.41%, N 5.36%, Found: C 55.22%, H 10.51%, N 5.34%.

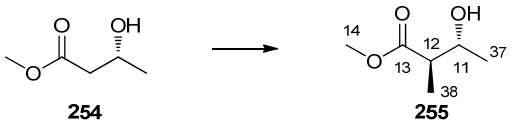
(*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropanal (253).



To a solution of the amide **251** (1.7 g, 6.5 mmol) in THF (10 mL) was added dropwise DIBAL (7.2 mL of a 1.0 M solution in CH_2Cl_2, 7.2 mmol) and the mixture was stirred for 1.5 h. The reaction mixture was then poured into a saturated aqueous solution of sodium, potassium tartrate (30 mL) and diluted with ether (20 mL). The mixture was stirred for 4 h until two clear phases were obtained. The aqueous phase was extracted

with ether (2 × 30 mL) and the organic extracts were combined and dried (Na_2SO_4), then concentrated to give the crude aldehyde **253**, which was used directly in the next step.

(2*R*,3*R*)-Methyl-3-hydroxy-2-methylbutanoate (255).[72]

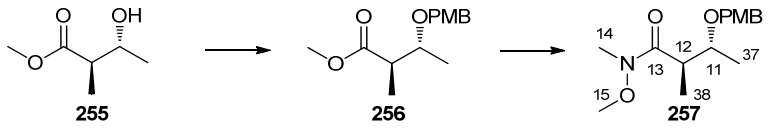


254 **255**

To a solution of diisopropylamine (15 mL, 0.11 mol) in anhydrous THF (250 mL) at –78 °C was added dropwise, *n*-butyllithium (37 mL of a 2.5 M solution in hexane, 92 mmol). The mixture was stirred at –78 °C for 30 min and then warmed to 0 °C for another 30 min. The solution of LDA was cooled to –78 °C and methyl 3(R)-(–)-3-hydroxybutyrate (5.0 g, 0.042 mol) was added over a period of 10 min. After complete addition, methyl iodide (3.1 mL, 0.50 mol) and DMPU (22 mL, 0.14 mol) were introduced at –78 °C and the solution was then stirred for 1 h and –40 °C for a further period of 1 h. The reaction was quenched by the addition of a saturated solution of NH_4Cl (150 mL) and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 4:1 to 1:1) to give the alcohol **255** (4.7 g, 85%) as a pale yellow oil. R_f = 0.40 (petroleum ether–ethyl acetate, 1:1). $[\alpha]_D^{19}$ –40.3 (*c* = 0.98, $CHCl_3$) {Lit.[72] $[\alpha]_D^{19}$ –34.7 (neat)}; ν_{max} ($CHCl_3$) 2976, 1732, 1451, 1437, 1261, 1197, 1172, 1112, 1078, 1045, 916, 860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.89 (1H, dqd, *J* = 7.3, 6.3, 5.4 Hz, CH-C11), 3.70 (3H, s, CH_3-C14), 2.69 (1H, d, *J* = 5.4 Hz, OH), 2.45 (1H, dq, *J* = 7.3, 7.2 Hz, CH-C12), 1.21 (d, 3H, *J* = 6.3 Hz, CH_3-C38), 1.17 (d, 3H, *J* = 7.2 Hz, CH_3-C37); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (C-C13), 69.5 (CH_3-C14), 51.9 (CH-C11), 47.0 (CH-C12), 20.9 (CH_3-C37), 14.2 (CH_3-C38);

HRMS (CI) for $C_6H_{13}O_3$ ($[M+H]^+$) calcd. 133.0865, found 133.0862.

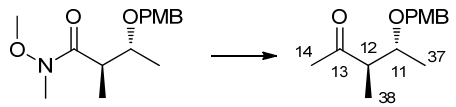
(2*R*,3*R*)-*N*-Methoxy-3-[(4-methoxybenzyl)oxy]-*N*, 2-dimethylbutanamide (257).



The alcohol **255** (5.0 g, 37 mmol) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (16 g, 56 mmol) were dissolved in toluene (75 mL). $La(OTf)_3$ (0.44 g, 0.74 mmol) was added at rt and the mixture was stirred for 18 h. Solid material was removed by filtration through Celite® and the crude product was obtained by concentration in vacuo. Purification of the residue by flash chromatography on silica gel (petroleum ether–ethyl acetate, 9:1) afforded the PMB ether **256** as yellow oil. To a slurry of *N*,*O*-dimethylhydroxylamine hydrochloride (5.4 g, 55 mmol) and PMB ether (11 g) in THF (50 mL) cooled to –15 °C was added *i*-PrMgCl (56 mL of a 2.0 M solution in THF, 0.11 mol) and the mixture was stirred for 1.5 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (100 mL). The aqueous phase was extracted with EtOAc (2 × 100 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in *vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 9:1 to 3:1) afforded the amide **257** (10 g, 95%) as a white solid. M.p.= 61.2–62.0 ºC; R_f = 0.34 (petroleum ether–ethyl acetate, 2:3); ν_{max} ($CHCl_3$) 2970, 2939, 2908, 1658, 1612, 1512, 1458, 1381, 1249, 1149, 1064, 1033, 995, 817 cm^{-1}; $[\alpha]_D^{20}$ –14.2 (*c* = 1.55, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (2H, d, *J* = 8.6 Hz, Ph-PMB), 6.84 (2H, d, *J* = 8.6 Hz, Ph-PMB), 4.48 (1H, d, *J* = 11.0 Hz, CH_2-PMB), 4.38 (1H, d, *J* = 11.0 Hz, CH_2-PMB), 3.81–3.76 (1H, m, CH-C11), 3.79 (3H, s, CH_3O-PMB), 3.64 (3H, s, CH_3O-C15), 3.21 (3H, s, CH_3N-C14), 3.12–3.05 (1H, m, CH-C12), 1.20 (3H, d, *J* = 6.2 Hz, CH-C37), 1.07 (3H, d, *J* = 7.0 Hz, CH_3-C38); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (C-C13), 159.0 (Ph-PMB), 131.2 (Ph-PMB), 129.8 (Ph-PMB), 113.6 (Ph-PMB), 77.3 (CH-C11), 71.3 (CH_2-PMB), 61.6 (CH_3O-C15), 55.4 (CH_3O-PMB), 41.5 (CH-C12), 32.1 (CH_3N-C14), 17.1 (CH_3-C37), 13.7 (CH_3-C38); HRMS (ESI) for $C_{15}H_{23}NNaO_4$

([M+Na]$^+$) calcd. 304.1525, found 304.1511.

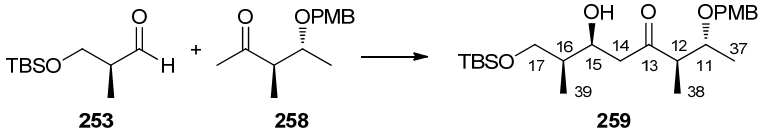
(3*R*,4*R*)-4-(4-Methoxybenzyloxy)-3-methylpentan-2-one (258).



257 **258**

The amide **257** (1.9 g, 6.7 mmol) was dissolved THF (20 mL) and treated dropwise with methylmagnesium bromide (10 mL of a 1.0 M solution in THF, 10 mmol) at 0 °C over a period of 20 min. The mixture was then warmed to 55 °C and stirred for 1.5 h. The reaction mixture was quenched by addition of a saturated aqueous solution of NH_4Cl (30 mL). The aqueous phase was extracted by EtOAc (3 × 30 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 8:1) to obtain the ketone **258** (1.6 g, 99%) as colourless oil. R_f = 0.57 (petroleum ether–ethyl acetate, 4:1); $[\alpha]_D^{27}$ –24.2 (*c* = 2.40, $CHCl_3$); ν_{max} ($CHCl_3$) 2972, 1711, 1613, 1586, 1512, 1456, 1377, 1354, 1246, 1173, 1107, 1034, 822 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (2H, d, *J* = 8.5 Hz, Ph-PMB), 6.86 (2H, d, *J* = 8.5 Hz, Ph-PMB), 4.48 (1H, d, *J* = 11.0 Hz, CH_2-PMB), 4.31 (1H, d, *J* = 11.0 Hz, CH_2-PMB) 3.79 (3H, s, CH_3O-PMB), 3.71 (1H, dq, *J* = 8.1, 6.2 Hz, CH-C11), 2.72 (1H, dq, *J* = 8.2, 7.0 Hz, CH-C12), 2.15 (3H, s, CH_3-C14) 1.17 (3H, d, *J* = 6.1 Hz, CH_3-C37), 1.02 (3H, d, *J* = 7.0 Hz, CH_3-C38); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3 (C-C13), 159.2 (Ph-PMB), 130.6 (Ph-PMB), 129.4 (Ph-PMB), 113.9 (Ph-PMB), 77.0 (CH-C11), 70.8 (CH_2-PMB), 55.4 (CH_3O-PMB), 53.8 (CH-C12), 30.3 (CH_2-C14), 16.8 (CH_3-C37), 12.8 (CH_3-C38); HRMS (ESI) for $C_{14}H_{20}NNaO_3$ ([M+Na]$^+$) calcd. 259.1310, found 259.1302.

(2*R*,3*R*,6*S*,7*S*)-8-(*tert*-Butyldimethylsilyloxy)-6-hydroxy-2-(4-methoxybenzyloxy)-3,7-dimethyloctan-4-one (259).

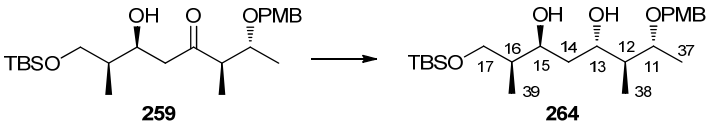


253 **258** **259**

The aldehyde **253** and the ketone **258** were dried prior to use by azetropic removal water by dissolving in toluene and concentrated in vacuo. Dicyclohexylboron chloride (16 mL of a 1.0 M solution in hexane, 16 mmol) was dissolved in dry ether (20 mL) and the solution was cooled to –78 °C. A solution of the ketone **258** (2.5 g, 11 mmol) in ether (5.0 m) was added dropwise to the solution of the Lewis acid at –78 °C followed by the addition of triethylamine (2.5 mL, 18 mmol). The mixture was stirred for 1 h and a solution of aldehyde **253** (4.3 g in 5.0 mL ether, 21 mmol) was then added at –78 °C. The reaction mixture was stirred for a further period of 2 h and the reaction was then quenched by the sequential addition of MeOH (10 mL), aqueous pH 7 buffer (20 mL) and H_2O_2 (20 mL of a 27% w/w aqueous solution). The mixture was stirred at rt for 4 h and then extracted with ether (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in *vacuo* and residual material was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1). The β-hydroxy ketone **259** was obtained (4.5 g, 95%) as a colourless liquid. R_f = 0.44 (petroleum ether–ethyl acetate, 4:1); $[\alpha]_D^{21}$ –39.9 (*c* = 1.15, $CHCl_3$); ν_{max} ($CHCl_3$) 2929, 2857, 1707, 1613, 1514, 1362, 1248, 1067, 1034, 835, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (2H, d, *J* = 8.6 Hz, Ph-PMB), 6.84 (2H, d, *J* = 8.6 Hz, Ph-PMB), 4.46 (1H, d, *J* = 10.9 Hz, CH_2-PMB), 4.28 (1H, d, *J* = 10.9 Hz, CH_2-PMB), 4.23 (1H, dddd, *J* = 8.8, 3.6, 3.3, 3.1 Hz, CH-C15), 3.79 (3H, s, CH_3O-PMB), 3.75–3.68 (1H, m, CH-C11), 3.65 (1H, dd, *J* = 9.8, 4.8 Hz), 3.60 (1H, dt, *J* = 9.8, 5.8 Hz), 3.25 (1H, d, *J* = 3.1 Hz, OH), 2.74 (1H, td, *J* = 7.0, 1.6 Hz, CH-C12), 2.67 (1H, dd, *J* = 17.1, 8.8 Hz, CH_2-C14), 2.58 (1H, dd, *J* = 17.1, 3.6 Hz, CH_2-C14), 1.70–1.61 (1H, m, CH-C16), 1.17 (3H, d, *J* = 6.2 Hz, CH_3-C37), 1.01 (3H, d, *J* = 7.0 Hz,

CH_3-C38), 0.89 (9H, s, CH_3C-TBS), 0.86 (3H, d, J = 7.0 Hz, CH_3-C39), 0.05 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.8 (C-C13), 159.3 (Ph-PMB), 130.5 (Ph-PMB), 129.6 (Ph-PMB), 113.9 (Ph-PMB), 77.5 (CH-C11), 71.0 (CH_2-PMB), 69.3 (CH-C15), 66.9 (CH_2-C17), 55.4 (CH_3O-PMB), 52.6 (CH-C12), 48.3 (CH_2-C14), 39.6 (CH-C16), 26.1 (CH_3C-TBS), 18.4 (CCH_3-TBS), 17.0 (CH_3-C37), 12.9 (CH_3-C38), 11.0 (CH_3-C39), –5.4 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{24}H_{43}O_5Si$ ($[M+H]^+$) calcd. 439.2880, found 439.2879; LRMS (CI) m/z (intensity) 441.6 (82) 121.2 (100).

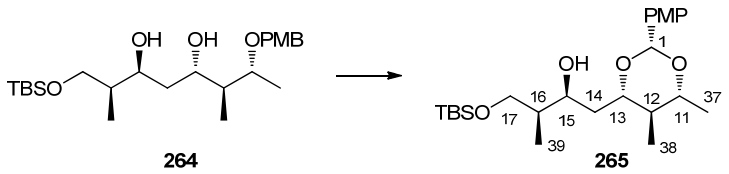
(2*S*,3*S*,5*S*,6*S*,7*R*)-1-(*tert*-Butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)-2,6-dimethyloctane-3,5-diol (264).



To a slurry of tetramethylammonium triacetoxyborohydride (12 g, 47 mmol) in acetonitrile (15 mL) at –30 °C was added acetic acid (15 mL) and and the mixture was stirred at this temperature for 30 min. The mixture was then added to a solution of the β-hydroxyl ketone 20 (2.5 g, 5.7 mmol) in acetonitrile (2 mL). The resulting solution was stirred for 20 h at –30 °C and the reaction was then quenched by addition of an aqueous solution of sodium, potassium tartrate (150 mL) followed by solid Na_2CO_3. The mixture was stirred at rt for 1 h and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in *vacuo*. Purification of residual material by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 12:1 to 8:1) afforded the diol (2.3 g, 91%) as colourless oil. R_f = 0.50 (petroleum ether–ethyl acetate, 3:2). $[\alpha]_D^{20}$ –30.1 (c = 0.98, $CHCl_3$); ν_{max} ($CHCl_3$) 2955, 2931, 2862, 1612, 1581, 1512, 1466, 1381, 1303, 1249, 1173, 1080, 1034, 833, 779 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, J = 8.6 Hz, CH-PMB), 6.86 (2H, d, J =

8.6 Hz, CH-PMB), 4.56 (1H, d, *J* = 11.0 Hz, CH_2-PMB), 4.39 (1H, d, *J* = 11. 0 Hz, CH_2-PMB) 4.17–4.09 (1H, m, OH), 4.17 (1H, d, *J* = 3.3 Hz, CH-C15), 3.85–3.76 (2H, m, CH-C13, CH-C11), 3.80 (3H, s, CH_3O-PMB), 3.73 (1H, dd, *J* = 9.8, 4.4 Hz, CH_2-C17), 3.68–3.63 (1H, m, CH_2-C17), 1.88–1.68 (3H, m, CH_2-C14, CH-C12), 1.44 (1H, ddd, *J* = 14.2, 7.7, 2.0 Hz, CH-C16), 1.22 (3H, d, *J* = 6.1 Hz, CH_3-C37), 0.93 (3H, d, *J* = 7.0 Hz, CH_3-C38), 0.89 (9H, s, CH_3C-TBS), 0.81 (3H, d, *J* = 6.9 Hz, CH_3-C39) 0.06 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (Ph-PMB) 130.3 (Ph-PMB), 129.4 (Ph-PMB), 113.8 (Ph-PMB), 79.3 (CH-C11), 73.0 (CH_2-PMB), 70.9 (CH-C15), 70.3 (CH_2-C17), 67.8 (CH-C13), 55.3 (CH_3O-PMB), 43.5 (CH-C12), 40.0 (CH-C16), 37.3 (CH_2-C14), 25.9 (CH_3C-TBS), 18.2 (CH_3-C37), 16.7 (CCH_3-TBS), 12.5 (CH_3-C38), 11.0 (CH_3-C39), –5.6 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{24}H_{44}O_5Si$ ($[M+H]^+$) calcd. 441.3042, found 441.3036; LRMS (CI, isobutane) *m*/*z* (intensity) 441.6 (82) 301.5 (16) 121.2 (100).

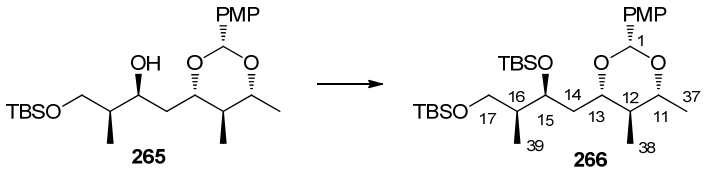
(2*S*,3*S*)-4-(*tert*-Butyldimethylsilyloxy)-1-[(2*R*,4*S*,5*R*,6*R*)-2-(4-methoxyphenyl)-5,6-dimethyl-1,3-dioxan-4-yl]-3-methylbutan-2-ol (265).



To a suspension of diol **264** (2.1 g, 4.7 mmol) and powdered molecular sieves in CH_2Cl_2 (20 mL) at –10 ºC was added dropwise a solution of DDQ (1.2 g, 5.2 mmol) in CH_2Cl_2 (50 mL). After 2 h, the mixture was filtered through Celite® and the filtrate was washed with a saturated aqueous solution of Na_2CO_3 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 10:1) gave the pure PMP acetal **265** (1.7 g, 83%) as colourless oil. R_f = 0.16 (petroleum ether–ethyl acetate,

9:1); $[\alpha]_D^{25}$ –21.2 (*c* = 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3510, 2955, 2931, 2854, 1612, 1589, 1519, 1465, 1388, 1303, 1249, 1172, 1080, 1033, 833, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (2H, d, *J* = 8.8 Hz, Ph-PMP), 6.87 (2H, d, *J* = 8.8 Hz, Ph-PMP), 5.55 (1H, s, CH-C1), 4.17 (1H, ddd, *J* = 9.5, 5.7, 2.4 Hz, CH-C13), 3.79 (3H, s, CH_3O-PMP), 3.77–3.72 (2H, m, CH-C11, CH_2-C17), 3.65 (1H, dd, *J* = 6.5, 3.7 Hz, CH_2-C17), 3.58 (1H, dd, *J* = 9.6, 6.1 Hz, CH-C15), 3.27 (1H, d, *J* = 3.7 Hz, OH), 1.89 (1H, ddd, *J* = 14.1, 10.2, 2.4 Hz, CH-C14), 1.78–1.73 (1H, m, CH-C12), 1.57–1.44 (2H, m, CH_2-C14, CH-C16), 1.32 (3H, d, *J* = 6.1 Hz, CH_3-C37), 0.92 (3H, d, *J* = 7.0 Hz, CH_3-C38), 0.90 (9H, s, CH_3C-TBS), 0.83 (3H, d, *J* = 6.7 Hz, CH_3-C39), 0.04 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9 (Ph-PMP), 131.7 (Ph-PMP), 127.5 (Ph-PMP), 113.7 (Ph-PMP), 100.3 (CH-C1), 79.2 (CH-C13), 78.6 (CH-C11), 70.3 (CH-C15), 68.1 (CH_2-C17), 55.4 (CH_3O-PMP), 40.7 (CH-C16), 39.7 (CH-C12), 37.3 (CH_2-C14), 26.0 (CH_3C-TBS), 19.6 (CH_3-C37), 18.3 (CCH_3-TBS), 12.6 (CH_3-C38), 10.9 (CH_3-C39), –5.4 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{24}H_{43}O_5Si$ ($[M+H]^+$) calcd. 439.2880, found 439.2876; LRMS (CI, isobutane) *m/z* (intensity) 439.6 (100) 137.2 (65) 212.2 (22) 73.2 (36).

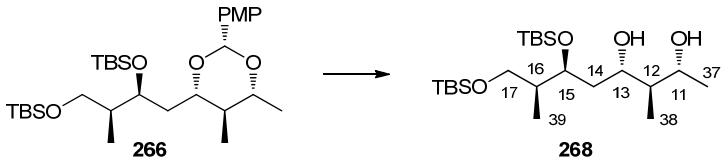
(5*S*,6*S*)-5-{[(2*R*,4*S*,5*R*,6*R*)-2-(4-Methoxyphenyl)-5,6-dimethyl-1,3-dioxan-4-yl]methyl}-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (266).



Alcohol **265** (1.7 g, 3.9 mmol) was dissolved in DMF (15 mL) and imidazole (1.9 g, 27 mmol) and TBSCl (2.9 g, 19 mmol) was then added at rt. The mixture was stirred at rt for 18 h before the brine (50 mL) was added. The aqueous phase was extracted with ethyl acetate (4 × 20 mL). The organic phase were dried (Na_2SO_4) and concentrated in *vacuo*. Purification of the residue by flash column chromatography on

silica gel (petroleum ether–ethyl acetate, 20:1) afforded TBS ether **266** (2.0 g, 94%) as colourless oil. R_f = 0.60 (petroleum ether–ethyl acetate, 9:1); $[\alpha]_D^{22}$ –48.6 (*c* = 0.99, $CHCl_3$); ν_{max} ($CHCl_3$) 2956, 2890, 2854, 1612, 1519, 1465, 1388, 1087, 1033, 918, 833, 771, 732, 671, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 8.7 Hz, Ph-PMP), 6.87 (2H, d, *J* = 8.7 Hz, Ph-PMP), 5.48 (1H, s, CH-C1), 4.13 (1H, td, *J* = 9.5, 2.5 Hz, CH-C15), 3.8 (3H, s, CH_3O-PMP), 3.61 (1H, dd, *J* = 9.7, 6.2 Hz, CH_2-C17), 3.54 (1H, dq, *J* = 6.8, 6.2 Hz, CH-C11), 3.51 (1H, td, *J* = 9.4, 1.4 Hz, CH-C13), 3.44 (1H, dd, *J* = 9.7, 7.0 Hz, CH_2-C17), 1.79 (1H, ddd, *J* = 14.1, 9.4, 1.4 Hz, CH_2-C14), 1.71 (1H, ddd, *J* = 13.4, 6.8, 2.9 Hz, CH-C12), 1.48–1.52 (1H, ddd, *J* = 14.1, 10.3, 2.5 Hz, CH_2-C14), 1.39–1.33 (1H, m, CH-C16), 1.31 (3H, d, *J* = 6.2 Hz, CH_3-C37), 0.90 (9H, s, CH_3C-TBS), 0.88 (9H, s, CH_3C-TBS), 0.85 (3H, d, *J* = 6.9 Hz, CH_3-C38), 0.83 (3H, d, J = 6.6 Hz, CH_3-C39), 0.04 (6H, s, CH_3Si-TBS), 0.02 (3H, s, CH_3Si-TBS), 0.03 (3H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8 (Ph-PMP), 131.8 (Ph-PMP), 127.4 (Ph-PMP), 113.6 (Ph-PMP), 100.0 (CH-C1), 78.7 (CH-C13), 78.6 (CH-C11), 68.9 (CH-C15), 64.5 (CH_2-C17), 55.4 (CH_3O-PMP), 42.2 (CH-C16), 41.1 (CH-C12), 38.1 (CH_2-C14), 26.2 (CH_3C-TBS), 19.6 (CH_3-C37), 18.4 (CCH_3-TBS), 12.7 (CH_3-C38), 11.7 (CH_3-C39), –3.9 (CH_3Si-TBS), –5.2 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{30}H_{57}O_5Si_2$ ($[M+H]^+$) calcd. 553.3745, found 553.2744; LRMS (CI, isobutane) *m/z* (intensity) 553.4 (100) 439.8 (32) 135.2 (45) 212.0 (12) 73.1 (16).

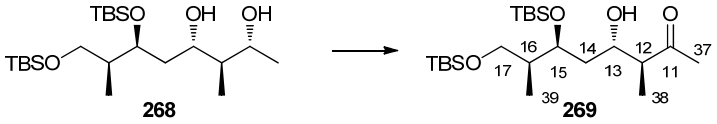
(2*R*,3*R*,4*S*,6*S*,7*S*)-6,8-Bis(*tert*-butyldimethylsilyloxy)-3,7-dimethyloctane-2,4-diol (268).



To a solution of acetal **266** (0.95 g, 1.7 mmol) in ethyl acetate (20 mL) was added palladium hydroxide on carbon (0.12 g, 20% palladium, 0.22 mmol). The atmosphere

of flask was exchanged three times by argon, and then was exchanged three times by hydrogen. The reaction was stirred for 18 h and filtered through a pad of Celite®. The filtrate was washed with ethyl acetate and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 8:1 to 4:1) to give the diol **268** (0.72 g, 94%) as a white solid. M. p. = 81.7–81.9 ºC; R_f = 0.20 (petroleum ether–ethyl acetate, 4:1); $[\alpha]_D^{22}$ –10.2 (*c* = 0.48, $CHCl_3$); ν_{max} ($CHCl_3$) 3348, 2955, 2928, 2885, 2856, 1471, 1462, 1380, 1359, 1250, 1086, 833, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.24 (1H, s, OH), 4.05 (1H, s, OH), 4.00–3.96 (1H, m, CH-C15), 3.86 (1H, ddd, *J* = 8.5, 6.8, 2.0 Hz, CH-C13), 3.80 (1H, dq, *J* = 14.2, 6.3 Hz, CH-C11), 3.56 (1H, dd, *J* = 9.9, 4.4 Hz, CH_2-C17), 3.45 (1H, dd, *J* = 9.9, 5.6 Hz, CH_2-C17), 1.94–1.83 (2H, m, CH-C16 and CH_2-C14), 1.65–1.58 (1H, m, CH_2-C14), 1.51–1.41 (1H, m, CH-C12), 1.17 (3H, d, *J* = 6.3 Hz, CH_3-C37), 0.98 (3H, d, *J* = 6.8 Hz, CH_3-C39), 0.90 (9H, s, CH_3C-TBS), 0.88 (9H, d, *J* = 2.8 Hz, CH_3C-TBS), 0.75 (3H, d, *J* = 7.2 Hz, CH_3-C38), 0.12 (3H, s, CH_3Si-TBS), 0.08 (3H, s, CH_3Si-TBS), 0.03 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.1 (CH-C13), 73.4 (CH-C15), 72.2 (CH-C11), 64.9 (CH_2-C17), 46.3 (CH-C12), 40.3 (CH-C16), 37.8 (CH2-C14), 26.0 (CH_3C-TBS), 21.4 (CH_3-C37), 18.4 (C-TBS), 14.3 (CH_3-C39), 13.2 (CH_3-C38), –4.2 (CH_3Si-TBS), –5.3 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{22}H_{51}O_4Si_2$ ($[M+H]^+$) calcd. 435.3248, found 435.3318; LRMS (CI, isobutane) *m*/*z* (intensity) 435.5 (15), 137.6 (6), 89.2 (100), 69.1 (21).

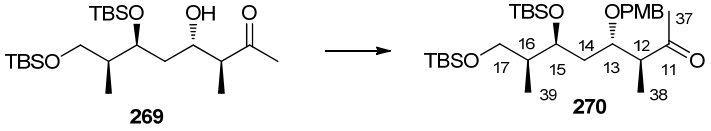
(3*S*,4*S*,6*S*,7*S*)-6,8-Bis(*tert*-butyldimethylsilyloxy)-4-hydroxy-3,7-dimethyloctan-2-one (269).



The diol **268** (0.59 g, 1.4 mmol) was dissolved in CH_2Cl_2 (15 mL), and iododiacetoxybenzene (0.48 g, 1.5 mmol) and TEMPO (22 mg, 0.14 mmol) was

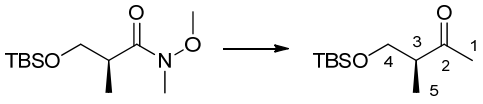
added at rt. The mixture was stirred for 90 h. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 6:1) to give the ketone **269** (0.47 g, 89%) as colourless oil. R_f = 0.67 (petroleum ether–ethyl acetate, 4:1); ν_{max} ($CHCl_3$) 2955, 2929, 2885, 2856, 1707, 1471, 1462, 1388, 1359, 1251, 1093, 1058, 1004, 939, 833, 808, 773, 742, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.99 (1H, ddd, J = 6.8, 5.2, 3.5 Hz, CH-C15), 3.93 (1H, tdd, J = 6.8, 4.3, 2.5 Hz, CH-C13), 3.57 (1H, dd, J = 9.8, 5.1 Hz, CH_2-C17), 3.47 (1H, dd, J = 9.8, 6.1 Hz, CH_2-C17), 3.24 (1H, d, J = 4.4 Hz, OH), 2.58 (1H, p, J = 7.2 Hz, CH-C12), 2.19 (3H, s, CH_3-C37), 1.86–1.76 (1H, m, CH_2-C14, CH-C16), 1.64 (1H, ddd, J = 14.3, 6.8, 2.4 Hz, CH_2-C14), 1.51 (1H, ddd, J = 14.3, 10.4, 3.4 Hz, CH_2-C14) 1.10 (3H, d, J = 7.2 Hz, CH_3-C38), 0.91 (3H, d, J = 6.9 Hz, CH_3-C39), 0.89 (9H, s, CH_3C-TBS), 0.88 (9H, s, CH_3C-TBS), 0.10 (3H, s, CH_3Si-TBS), 0.07 (3H, s, CH_3Si-TBS), 0.03 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5 (C-C11), 71.6 (CH-C15), 70.8 (CH-C13), 64.7 (CH_2-C17), 53.1 (CH-C12), 41.0 (CH-C16), 38.0 (CH-C14), 29.8 (CH_3-C37), 26.0 (CH_3C-TBS), 18.4 (CCH_3-TBS), 18.2 (CCH_3-TBS), 13.6 (CH_3-C38), 13.1 (CH_3-C39), –4.3 (CH_3Si-TBS), –5.3 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{22}H_{49}O_4Si_2$ ($[M+H]^+$) calcd. 433.3169, found 433.3170; LRMS (CI, isobutane) *m*/*z* (intensity) 433.5 (24), 317.4 (16), 285.4 (21), 283.4 (21), 229.4 (100), 133.3 (46), 97.2 (18), 73.1 (100); Anal. calcd. for $C_{22}H_{48}O_2Si_2$: C 61.05%, H 11.18%, Found: C 61.18%, H 11.24%.

(3*S*,4*S*,6*S*,7*S*)-6,8-Bis(*tert*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-3,7-dimethyloctan-2-one (270).



PMBTCA (0.59 g, 2.1 mmol) and the alcohol **269** (0.45 g, 1.1 mmol) were dissolved in CH_2Cl_2 (15 mL) and CSA (23 mg, 0.11 mmol) was added to the resulting solution at rt. The solution was stirred for 18 h before $NaHCO_3$ (25 mL) was added to quench the reaction. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the organic extracts were dried (Na_2SO_4) and solvent was removed in *vacuo*. The residual PMB ether **270** (0.33 g, 76%) was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 25:1) as colourless oil. R_f = 0.57 (petroleum ether–ethyl acetate, 10:1); R_f = 0.57 (petroleum ether–ethyl acetate, 10:1); $[\alpha]_D^{22}$ +0.5 (*c* = 1.10, $CHCl_3$); ν_{max} ($CHCl_3$) 2955, 2929, 2856, 1712, 1614, 1514, 1471, 1464, 1386, 1359, 1301, 1247, 1172, 1085, 1057, 1039, 939, 835, 773, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.7 Hz, Ph-PMB), 6.85 (2H, d, *J* = 8.7 Hz, Ph-PMB), 4.44 (2H, s, CH_2O-PMB), 4.00–3.98 (1H, m, CH-C15), 3.85 (1H, ddd, *J* = 8.8, 5.8, 2.7 Hz, CH-C13), 3.80 (3H, s, CH_3O-PMB), 3.58 (1H, dd, *J* = 9.6, 6.1 Hz, CH_2-C17), 3.38 (1H, dd, *J* = 9.6, 7.0 Hz, CH_2-C17), 2.94–2.88 (1H, m, CH-C12), 2.16 (3H, s, CH_3-C37), 1.74 (1H, ddd, *J* = 13.2, 6.8, 2.7 Hz, CH-C14), 1.71–1.62 (1H, m, CH_2-C16), 1.31 (1H, ddd, J = 14.5, 8.2, 2.7 Hz, CH_2-C14), 1.05 (3H, d, *J* = 6.9 Hz, CH_3-C38), 0.88 (9H, s, CH_3C-TBS), 0.88 (9H, s, CH_3C-TBS), 0.84 (3H, d, *J* = 6.9 Hz, CH_3-C39), 0.05 (6H, s, CH_3Si-TBS), 0.02 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8 (C-C11), 159.3 (Ph-PMB), 130.7 (Ph-PMB), 129.3 (Ph-PMB), 113.9 (Ph-PMB), 77.4 (CH-C13), 71.1 (CH_2O-PMB), 70.4 (CH-C15), 64.3 (CH_2-C17), 55.4 (CH_3O-PMB), 50.4 (CH-C12), 41.7 (CH-C16), 36.2 (CH_2-C14), 29.8 (CH_3-C37), 26.2 (CH_3C-TBS), 26.1 (CH_3C-TBS), 18.4 (CCH_3-TBS), 18.3 (CCH_3-TBS), 11.6 (CH_3-C39), 11.0 (CH_3-C38), –4.0 (CH_3Si-TBS), –4.2 (CH_3Si-TBS), –5.2 (CH_3Si-TBS), –5.4 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{30}H_{56}O_5Si_2$ ($[M+H]^+$) calcd. 553.3745, found 553.3745; LRMS (CI, isobutane) *m*/*z* (intensity) 553.7 (20), 433.6 (22), 415.6 (7), 283.4 (36), 229.4 (20), 121.2 (100), 73.2 (12); Anal. calcd. for $C_{30}H_{56}O_5Si_2$: C 65.17%, H 10.21%, Found: C 65.65%, H 10.08%.

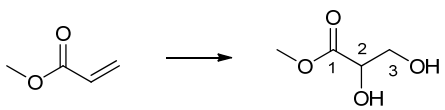
(*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-methylbutan-2-one (271).[71]



251 **271**

To a solution of the Weinreb amide **251** (2.8 g, 7.4 mmol) in THF (50 mL) was added MeMgCl (11 mL of 1.4 M in THF, 15 mmol) at 0 ºC over 20 min. After complete addition, the reaction mixture was allowed to warm to rt for 2 h. NH_4Cl (50 mL) was added and extracted with Et_2O (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 50:1) gave the ketone **271** (2.2 g, 93%) as colourless oil. R_f = 0.85 (petroleum ether–ethyl acetate, 9:1); ν_{max} ($CHCl_3$) 2930, 1717, 1092, 836 cm^{-1}; $[\alpha]_D^{26.2}$ + 32.9, (*c* = 0.95, $CHCl_3$), {lit.[71] $[\alpha]_D^{26.2}$ + 23.9, (*c* = 0.20, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (1H, dd, *J* = 9.8, 7.2 Hz, CH_2-C4), 3.64 (1H, dd, *J* = 9.8, 5.5 Hz, CH_2-C4), 2.77–2.71 (1H, m, CH-C3), 2.18 (3H, s, CH_3-C1), 1.05 (3H, d, *J* = 6.9 Hz, CH_3-C5), 0.88 (9H, s, CH_3C-TBS), 0.05 (3H, s, CH_3Si-TBS), 0.04 (3H, s, CH_3Si-TBS); ^{13}C NMR (400 MHz, $CDCl_3$) δ 211.5 (CO-C2), 65.1 (CH_2-C4), 48.9 (CH-C3), 29.1 (CH_3-C1), 26.3 (CH_3C-TBS), 19.4 (CCH_3-TBS), 12.5 (CH_3-C5), – 5.9 (CH_3Si-TBS).

Methyl 2,3-dihydroxypropanoate (276).

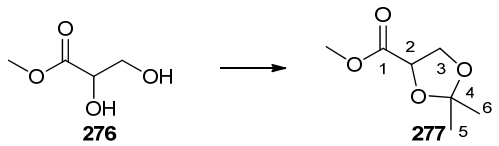


275 **276**

To a solution of methyl acrylate (5.0 mL, 58 mmol) in acetone (20 mL) and water (20 mL) NMO (10 g, 87 mmol) and OsO_4 (5% in water solution, 0.70 ml) was added at rt. The mixture was stirred over 48 h and the reaction was then quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$ (25 mL) and Na_2CO_3 (25 mL). The aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts

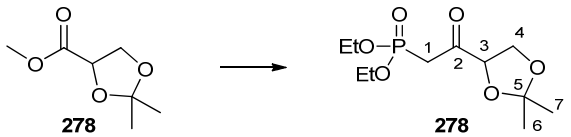
were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (ethyl acetate) to give the diol (1.7 g, 34%) as colourless oil. R_f = 0.20 (ethyl acetate); ν_{max} ($CHCl_3$) 1732, 1437, 1213, 1112, 1060, 970, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.28 (1H, dd, *J*= 8.3, 4.0 Hz, CH-C2), 3.74 (2H, dd, *J* = 4.0, 2.0 Hz, CH_2-C3), 3.65 (3H, s, CH_3-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9 (CO-C1), 69.2 (CH-C2), 64.1 (CH_2-C3), 53.1 (CH_3-OMe); HRMS (CI, isobutane) for $C_4H_9O_4$ ($[M+H]^+$) calcd. 121.0501, found 121.0500.

Methyl 2,2-dimethyl-1,3-dioxolane-4-carboxylate (277).



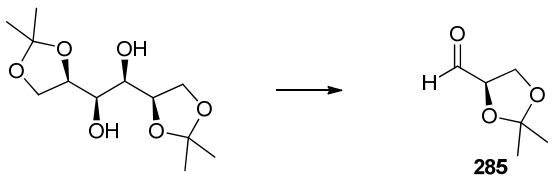
To a solution of diol (0.50 g, 4.2 mmol) in 2,2-dimethoxypropane (15 mL) was added CSA (98 mg, 0.42 mmol) at rt. The reaction mixture was stirred at rt for 18 h and was quenched by addition of Na_2CO_3 (2 g). Solid material was removed by filtration and the solution was concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 2:1) to give the acetal (0.62 g, 93%) as colourless oil. R_f = 0.25 (petroleum ether–ethyl acetate, 4:1); ν_{max} ($CHCl_3$) 1712, 1474, 1464, 1247, 1172, 1085, 939, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (1H, dd, *J* = 7.2, 5.2 Hz, CH-C2), 4.24 (1H, dd, *J* = 8.6, 7.2 Hz, CH_2-C3), 4.11 (1H, dd, *J* = 8.6, 5.2 Hz, CH_2-C3), 3.78 (3H, s, CH_3-OMe), 1.50 (3H, s, CH_3-C5), 1.40 (3H, s, CH_3-C6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (CO-C1), 111.5 (C-C4), 74.2 (CH-C2), 67.4 (CH_2-C3), 52.5 (CH_3-Me), 25.9 (CH_3-C6), 25.7 (CH_3-C6); HRMS (CI, isobutane) for $C_7H_{13}O_4$ ($[M+H]^+$) calcd. 161.0814, found 161.0816.

Diethyl [2-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxoethyl]phosphonate (278).



A solution of diethyl methylphosphonate (0.88 mL, 6.0 mmol) in THF (20 mL) was treated with *n*-BuLi (2.6 mL of a 2.5 M solution in hexane, 5.5 mmol) at –78 °C and the mixture was stirred for 30 min. The resulting yellow solution was added dropwise a solution of acetal (0.81 g, 5.0 mmol) in THF (5 mL) at –78 °C and the mixture was stirred for 1 h before being warmed to rt and stirred for another 1 h. A saturated aqueous solution of NH_4Cl (15 mL) was added and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. Flash column chromatography on silica gel (petroleum ether–ethyl acetate, 4:1 to 1:1) delivered the phosphate ester **278** (1.2 g, 86%) as colourless oil. R_f = 0.20 (petroleum ether–ethyl acetate, 1:1); ν_{max} ($CHCl_3$) 2987, 2931, 2910, 1718, 1190, 1014, 974, 840, 812 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.56 (1H, dd, J = 7.3, 5.5 Hz, CH-C3), 4.20–4.13 (6H, m, CH_2-Et, CH_2-C1), 3.51 (1H, dd, J = 22.7, 14.0 Hz, CH_2-C4), 3.15 (1H, dd, J = 22.0, 14.0 Hz, CH_2-C4), 1.50 (3H, s, CH_3-C6), 1.40 (3H, s, CH_3-C7), 1.34 (6H, t, J = 7.1 Hz, CH_3-Et); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6 (CO-C1), 111.3 (C-C5), 80.2 (CH-C3), 66.1 (CH_2-Et), 62.8 (CH_2-C1), 62.7 (CH_2-C1), 38.3 (CH_2-C4), 26.2 (CH_3-C6), 25.2 (CH_3-C7), 16.5 (CH_3-Et); HRMS (CI, isobutane) for $C_{11}H_{22}O_6P$ ($[M+H]^+$) calcd. 281.1154, found 281.1161; LRMS (CI, isobutane) *m*/*z* (intensity) 281.1 (15) 209.3 (25) 179.1 (54) 137.2 (27) 123.1 (100) 109 (69);

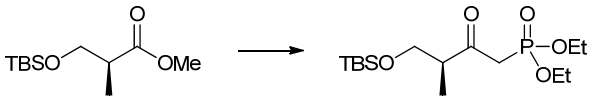
(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (285).



1,2,5,6-Di-*O*-isopropylidene-D-mannitol (1.0 g, 4.0 mmol) was dissolved in CH_2Cl_2

(10 mL) and treated with $NaIO_4$ (1.7 g, 8.0 mmol) followed by a saturated aqueous solution of $NaHCO_3$ (0.4 mL). The reaction mixture was stirred for 2 h and excess solid $MgSO_4$ was added to quench the reaction. The solid was removed by filtration; the filtrate was concentrated *in vacuo* to afford the crude aldehyde **285** (0.67 g, 67 %) as colourless oil, which was used without purification.

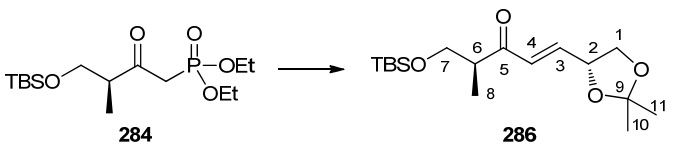
(*S*)-Diethyl-{4-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-2-oxobutyl}phosphonate (284).



250 **284**

A solution of diethyl methylphosphonate (1.2 mL, 8.0 mmol) in THF (15 mL) was treated slowly with *n*-BuLi (2.5 M in hexane, 2.5 mL, 6.5 mmol) at –78 °C for 30 min. The ester **250** (1.2 g, 4.2 mmol) was added at –78 °C and allowed to warm to 0 °C for 1 h. NH_4Cl (50 mL) was added and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 1:1) to give the title compound **285** (1.4 g, 77%) as colourless oil, which was used directly for the next step.

(*S*,*E*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-methylpent-1-en-3-one (286).

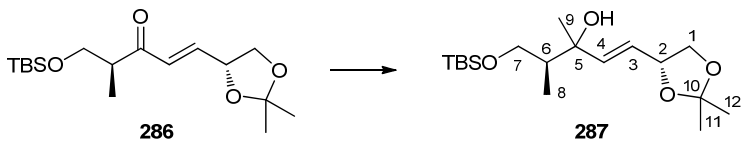


284 **286**

To a solution of phosphonate ester **284** (1.4 g, 4.0 mmol) in THF (15 mL) was added NaH (0.16 g of a 60% suspension in mineral oil, 3.9 mmol) at 0 °C. After gas release had subsided, a solution of the known aldehyde **296** was added. The mixture was then

stirred at 0 °C for 2 h and then the reaction was quenched by addition of an aqueous solution of NH_4Cl (50 mL). The aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 20:1) to give the olefin **298** (1.2 g, 92%) as colourless oil. ν_{max} ($CHCl_3$) 2990, 2967, 2936, 2876, 1698, 1681, 1639, 1457, 1384, 1375, 1256, 1230, 1185, 1063, 978, 813, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (1H, dd, J = 15.7, 5.7 Hz, CH-C3), 6.46 (1H, dd, J = 15.7, 1.3 Hz, CH-C4), 4.67 (1H, td, J = 7.0, 1.3 Hz, CH-C2), 4.18 (1H, dd, J = 8.1, 6.6 Hz, CH_2-C1), 3.79 (1H, dd, J = 9.8, 7.2 Hz, CH_2-C1), 3.66 (1H, dd, J = 8.1, 7.4 Hz, CH_2-C7), 3.61 (1H, dd, J = 9.8, 6.0 Hz, CH_2-C7) 3.02–2.97 (1H, m, CH-C6), 1.44 (3H, s, CH_3-C10), 1.41 (3H, s, CH_3-C11), 1.07 (3H, d, J = 7.0 Hz, CH_3-C8), 0.85 (9H, s, CH_3C-TBS), 0.02 (3H, s, CH_3Si-TBS), 0.01 (3H, s, CH_3Si-TBS); ^{13}C NMR (400 MHz, $CDCl_3$) δ 199.6 (CO-C5), 141.8 (CH-C3), 129.8 (CH-C4), 109.7 (C-C9), 75.1 (CH-C2), 68.4 (CH_2-C1), 66.4 (CH_2-C7), 43.5 (CH-C6), 26.4 (CH_3-Me), 25.9 (CH_3-Me), 25.6 (CCH_3-TBS), 18.3 (CH_3C-TBS), 13.6 (CH_3-C8), –5.4 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{17}H_{33}O_4Si$ ($[M+H]^+$) calcd. 329.2148, found 329.5270.

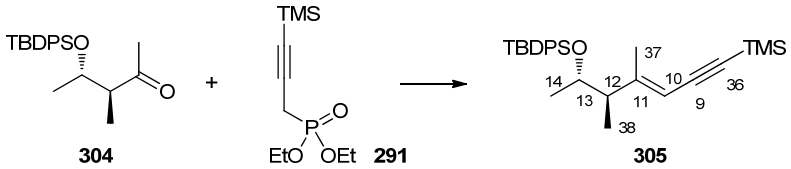
(4*S*,*E*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3,4-dimethylpent-1-en-3-ol (287).



$CeCl_3 \cdot 7H_2O$ (0.17 g, 0.45 mmol) was stirred under vacuum at 130 °C for 2.5 h. THF (2 mL) was then added and the mixture was stirred for another 1 h at rt. The reaction mixture was cooled to 0 °C, and treated dropwise with MeLi (0.28 mL of 1.6 M solution in THF, 0.45 mmol) at 0 °C for 1 h. The ketone **286** (0.10 g, 0.31 mmol) in THF (1 mL) was added at 0 °C and the mixture was stirred for 1 h. A saturated

aqueous solution of NH_4Cl (10 mL) was added and the mixture was extracted with Et_2O (2 × 10 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Flash column chromatography on silica gel (petroleum ether–ethyl acetate, 8:1) afforded the alcohol **287** (91 mg, 88%) as colourless oil which was a mixture of two diastereoisomers (*dr* = 1:1). ν_{max} ($CHCl_3$) 3541, 2957, 2930, 2885, 2857, 1253, 1051, 939, 833, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90–5.72 (4H, m, CH-C3, CH-C4), 4.57–4.52 (2H, m, CH-C2), 4.15–4.06 (4H, m, CH_2-C7), 3.84 (1H, dd, J = 10.0, 3.5 Hz, CH_2-C1), 3.69 (1H, dd, J = 10.0, 4.0 Hz, CH_2-C1) 3.63–3.58 (4H, m, CH_2-C1, OH), 1.91–1.83 (1H, m, CH-C6), 1.72–1.64 (1H, m, CH-C6), 1.43 (3H, s, CH_3-C11), 1.41 (3H, s, CH_3-C12), 1.40 (6H, s, CH_3-C9), 1.26 (3H, s, CH_3-C11), 1.22 (3H, s, CH3-C12,), 0.98 (3H, d, J = 7.1 Hz, CH_3-C8), 0.90 (9H, s, CH_3C-TBS), 0.90 (9H, s, CH_3C-TBS), 0.84 (3H, d, J = 7.1 Hz, CH_3-C8), 0.08 (3H, s, CH_3Si-TBS), 0.08 (3H, s, CH_3Si-TBS), 0.07 (3H, s, CH_3Si-TBS), 0.05 (3H, s, CH_3Si-TBS); HRMS (CI, isobutane) for $C_{18}H_{37}O_4Si$ ($[M+H]^+$) calcd. 345.2461, found 345.2463.

tert-Butyl{[(2*S*,3*R*,*E*)-3,4-dimethyl-7-(trimethylsilyl)hept-4-en-6-yn-2-yl]oxy}diphenylsilane (303).

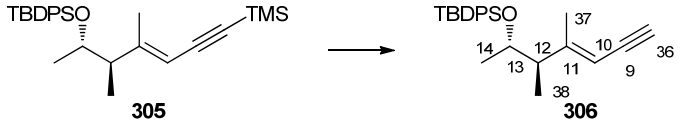


304 **291** **305**

The phosphonate **304** (0.89 g, 3.7 mmol) was dissolved in THF (25 mL) and NaHMDS (3.4 mL of 1.0 M in THF, 3.4 mmol) was added at –78 °C. The reaction mixture was stirred at –78 °C for 30 min and then a solution of the ketone (1.0 g, 2.8 mmol) in THF (5 mL) was added. The mixture was stirred at –78 °C for a further period of 2 h and the reaction was then quenched by addition of aqueous solution of NH_4Cl (50 mL). The aqueous phase was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether–ethyl

acetate, 20:1) to give the enyne **305** (1.2 g, 95%) as colourless oil. R_f = 0.85 (petroleum ether–ethyl acetate, 20:1); ν_{max} ($CHCl_3$) 2958, 2858, 2133, 1400, 1377, 1249, 1107, 1037, 840, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.65 (4H, m, Ph-TBDPS), 7.44–7.35 (6H, m, Ph-TBDPS), 5.30 (1H, brs, CH-C10), 3.84 (1H, dq, J = 7.0, 6.0 Hz, CH-C13), 2.25 (1H, dq, J = 6.5, 6.2 Hz, CH-C12), 1.71 (3H, d, J = 0.9 Hz, CH_3-C37), 1.05 (9H, s, CH_3C-TBDPS), 1.01 (3H, d, J = 7.0 Hz, CH_3-C14), 0.94 (3H, d, J = 6.2 Hz, CH_3-C38), 0.12 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8 (C-C11), 136.1 (Ph-TBDPS), 134.8 (Ph-TBDPS), 129.7 (Ph-TBDPS), 127.7 (Ph-TBDPS), 106.2 (C-C9), 103.8 (C-C10), 97.3 (C-C36), 71.4 (CH-C13), 49.0 (CH-C12), 27.2 (CH_3C-TBDPS), 19.7 (CH_3C-TBDPS), 19.4 (CH_3-C14), 18.4 (CH_3-C37), 13.4 (CH_3-C38), 0.3 (TMS); HRMS (CI, isobutane) for $C_{28}H_{41}OSi_2$ ($[M+H]^+$) calcd. 449.2696, found 449.2693; LRMS (CI, isobutane) *m/z* (intensity) 449.4 (10) 391.3 (10) 283.3 (100) 193.2 (10) 157.1 (9).

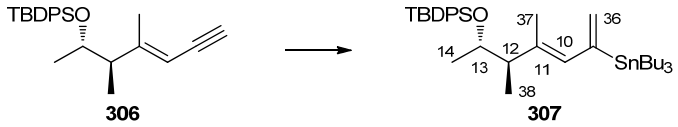
***tert*-Butyl{[(2*S*,3*R*,*E*)-3,4-dimethylhept-4-en-6-yn-2-yl]oxy}diphenylsilane (306).**



To a solution of alkyne **305** (1.2 g, 2.7 mmol) in MeOH (20 mL) was added K_2CO_3 (1.4 g, 10 mmol) at rt. The reaction mixture was stirred at rt for 2 h before water (50 mL) was added. The aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 50:1) to give the terminal alkyne **306** (1.0 g, 100%) as colourless oil. R_f = 0.79 (petroleum ether–ethyl acetate, 20:1); $[\alpha]_D^{20}$ –7.8 (c = 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3290, 2966, 2931, 2858, 2094, 1735, 1427, 1377, 1107, 1037, 821, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (4H, m, Ph-TBDPS), 7.43–7.34 (6H, m,

Ph-TBDPS), 5.26 (1H, brs, CH-C10), 3.84 (1H, dq, *J* = 6.3, 6.1 Hz, CH-C13), 3.03 (1H, d, *J* = 2.2 Hz, CH-C36), 2.26 (1H, dq, *J* = 7.0, 6.1 Hz, CH-C12), 1.73 (3H, s, CH_3-C37), 1.05 (9H, s, CH_3C-TBDPS), 1.02 (3H, d, *J* = 7.0 Hz, CH_3-C14), 0.95 (3H, d, *J* = 6.3 Hz, CH_3-C38); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1 (C-C11), 135.9 (Ph-TBDPS), 134.7 (Ph-TBDPS), 129.6 (Ph-TBDPS), 127.5 (Ph-TBDPS), 104.8 (CH-C10), 81.8 (C-C9), 80.0 (CH-C36), 71.2 (CH-C13), 48.9 (CH-C12), 26.9 (CCH_3-TBDPS), 19.6 (CH_3C-TBDPS), 19.2 (CH_3-C14), 17.9 (CH_3-C37), 13.4 (CH_3-C38); HRMS (CI, isobutane) for $C_{25}H_{33}OSi_2$ ($[M+H]^+$) calcd. 377.2301, found 377.2302; LRMS (CI, isobutane) *m/z* (intensity) 377.4 (10) 319.3 (10) 283.3 (95) 257.3 (48) 199.2 (15) 179.2 (15) 157.1 (100) 141.1 (15) 81.1 (11) 69.1 (15).

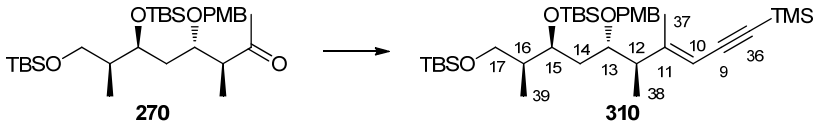
tert-Butyl{[(2*S*,3*R*,*E*)-3,4-dimethyl-6-(tributylstannyl)hepta-4,6-dien-2-yl]oxy}diphenylsilane (307).



To a solution of alkyne **306** (0.25 g, 0.65 mmol) in THF (20 mL) was added $Pd(Ph_3P)_4$ (23 mg, 0.020 mmol) at rt. The resulting yellow solution was treated with *n*-Bu_3SnH (0.21 mL, 0.80 mmol) at rt for 30 min. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 250:1) to give the stannane **307** (0.52 g, 100%) as colourless oil. R_f = 0.85 (petroleum ether–ethyl acetate, 20:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.68 (4H, m, Ph-TBDPS), 7.44–7.34 (6H, m, Ph-TBDPS), 5.58 (1H, s, CH-C10), 5.57 (1H, dd, *J* = 3.5, 1.8 Hz, CH_2-C36), 5.27 (1H, dd, *J* = 3.5, 1.2 Hz, CH_2-C36), 3.92 (1H, dq, *J* = 6.2, 4.7 Hz, CH-C13), 2.20 (1H, td, *J* = 11.3, 6.8 Hz, CH-C12), 1.53–1.45 (15H, m, CH_3-37, CH_2-Bu), 1.32–1.26 (9H, m, CH_3-C14, CH_2-Bu), 1.06 (9H, s, CH_3C-TBDPS), 1.06 (3H, d, *J* = 6.8 Hz, CH_3-C38), 0.98–0.84 (9H, m, CH_3-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1 (Ph-TBDPS), 135.6 (C-C11), 135.1 (C-C9), 134.5

(C-C36), 130.1 (Ph-TBDPS), 129.7 (Ph-TBDPS), 127.6 (Ph-TBDPS), 127.5 (CH_2-C36), 126.7 (CH-C10), 71.1 (CH-C13), 49.0 (CH-C12), 30.1 (CCH_3-TBDPS), 29.2 (CH_2-Bu), 27.6 (CH_3-C14), 27.5 (CH_2-Bu), 27.2 (CH_3C-TBDPS), 16.4 (CH_3-C37), 13.8 (CH_2-Bu), 13.2 (CH_3-C38), 10.1 (CH_3-Bu).

(5*S*,6*S*)-5-{(2*S*,3*R*,*E*)-2-[(4-Methoxybenzyl)oxy]-3,4-dimethyl-7-(trimethylsilyl)hept-4-en-6-yn-1-yl}-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (310).

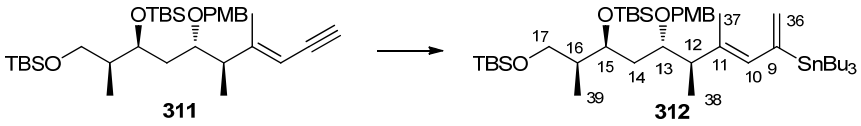


The phosphonate **291** (0.40 g, 1.6 mmol) was dissolved in THF (10 mL) and NaHMDS (1.0 M in THF, 1.3 mL, 1.3 mmol) was added at –78 °C. The reaction mixture was stirred at –78 °C for 30 min and then a solution of the ketone (0.60 g, 1.1 mmol) in THF (2 mL) was added. The mixture was stirred at –78 °C for a further period of 2 h and the reaction was then quenched by addition of aqueous solution of NH_4Cl (10 mL). The aqueous phase was extracted with Et_2O (2 × 10 mL) and the organic extracts were combined, dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether–ethyl acetate, 250:1 to 50:1) to give the enyne **310** (0.54 g, 77%) as colourless oil.

(5*S*,6*S*)-5-{(2*S*,3*R*,*E*)-2-[(4-Methoxybenzyl)oxy]-3,4-dimethylhept-4-en-6-yn-1-yl}-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (311).

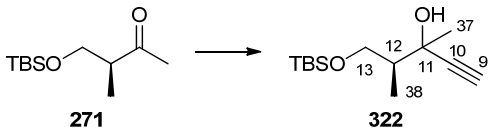
The alkyne **310** (0.54 g, 0.84 mmol) was dissolved in MeOH (10 mL) and K_2CO_3 (0.34 g, 2.5 mmol) was added at rt. The reaction mixture was stirred at rt for 2 h before water (25 mL) was added. The aqueous phase was extracted with Et_2O (3 × 25 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 50:1) to give the terminal alkyne **311** (0.43 g, 90%) as colourless oil. R_f = 0.82 (petroleum ether–ethyl acetate, 20:1); ν_{max} ($CHCl_3$) 3290, 2966, 2931, 2858, 2094, 1735, 1427, 1377, 1107, 1037, 821, 702 cm^{-1}; $[\alpha]_D^{19}$ –12.8 (*c* = 0.40, $CHCl_3$); ν_{max} ($CHCl_3$) 2956, 2929, 2852, 1514, 1464, 1249, 1041, 810, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.6 Hz, Ph-PMB), 6.87 (2H, d, *J* = 8.6 Hz, Ph-PMB), 5.37 (1H, s, CH-C10), 4.44 (1H, d, *J* = 10.8 Hz, CH_2-PMB), 4.39 (1H, d, *J* = 10.8 Hz, CH_2-PMB), 3.94 (1H, ddd, *J* = 7.6, 5.3, 2.4 Hz, CH-C15), 3.80 (3H, s, CH_3O-PMB), 3.58–3.53 (2H, m, CH-C13, CH_2-C17), 3.39 (1H, dd, *J* = 9.6, 6.8 Hz, CH_2-C17), 3.1 (1H, d, *J* = 2.1 Hz, CH-C36), 2.59–2.54 (1H, m, CH-C12), 1.95 (3H, s, CH_3-C37), 1.71 (1H, ddd, *J* = 13.5, 6.8, 2.4 Hz, CH-C16), 1.62 (1H, ddd, *J* = 14.0, 8.5, 5.3 Hz, CH_2-C14), 1.43–1.35 (1H, m, CH_2-C14), 1.03 (3H, d, *J* = 7.0 Hz, CH_2-C38), 0.88 (9H, s, CH_3C-TBS), 0.87 (9H, s, CH_3C-TBS), 0.83 (3H, d, *J* = 6.8 Hz, CH_3-C39), 0.03 (12H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (Ph-PMB), 155.7 (C-C11), 131.2 (Ph-PMB), 129.2 (Ph-PMB), 113.9 (Ph-PMB), 105.4 (CH-C10), 81.9 (C-C9), 80.6 (CH-C36), 78.5 (CH-C13), 70.8 (CH_2-PMB), 70.5 (CH-C15), 64.7 (CH_2-C17), 55.4 (CH_3O-PMB), 44.2 (CH-C12), 41.3 (CH-C16), 35.5 (CH_2-C14), 26.1 (CH_3C-TBS), 26.0 (CH_3C-TBS), 18.7 (CH_3-C37), 18.4 (CCH_3-TBS), 18.3 (CCH_3-TBS), 13.7 (CH_3-C38), 11.1 (CH_3-C39), –4.0 (CH_3Si-TBS), –5.2 (CH_3Si-TBS); HRMS (ESI) for $C_{33}H_{58}NaO_4Si_2$ ($[M+Na]^+$) calcd 597.3771, found 597.3770.

(5*S*,6*S*)-5-{(2*S*,3*R*,*E*)-2-[(4-Methoxybenzyl)oxy]-3,4-dimethyl-6-(tributylstannyl)hepta-4,6-dien-1-yl}-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (312).



The alkyne **311** (0.14 g, 0.25 mmol) was dissolved into THF (5 mL) and $Pd(PPh_3)_4$ (7 mg, 0.01 mmol) was added at rt. The resulting yellow solution was treated with *n*-Bu_3SnH (80 mg, 0.28 mmol) at rt for 30 min. Solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 250:3) to give the stannane **312** (0.16 g, 76%) as colourless oil. R_f = 0.80 (petroleum ether–ethyl acetate, 20:1); ν_{max} ($CHCl_3$) 2955, 2928, 2854, 1514, 1464, 1247, 1039, 908, 835, 773, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.6 Hz, Ph-PMB), 6.86 (2H, d, *J* = 8.6 Hz, Ph-PMB), 5.93 (1H, s, CH-C10), 5.62 (2H, dd, *J* = 3.3, 1.8 Hz, CH_2-C36), 5.31 (1H, ddd, *J* = 3.3, 1.1 Hz, CH-C15), 4.50 (1H, d, *J* = 10.7 Hz, CH_2-PMB), 4.39 (1H, d, *J* = 10.7 Hz, CH_2-PMB), 3.98–3.92 (1H, m, CH-C15), 3.80 (3H, s, CH_3O-PMB), 3.61–3.53 (2H, m, CH-C13, CH_2-C17), 3.39 (1H, dd, *J* = 9.6, 7.1 Hz, CH_2-C17), 2.54–2.47 (1H, m, CH-C12), 1.77–1.67 (1H, m, CH-C16), 1.71 (3H, s, CH_3-C37), 1.52–1.42 (8H, m, CH_2-C14, CH_2-Bu), 1.30 (6H, dq, *J* = 14.3, 7.2 Hz, CH_2-Bu), 1.02 (3H, d, *J* = 7.0 Hz, CH_2-C38), 0.83 (32H, m, CH_3C-TBS, CH_2-Bu, CH_3-Bu), 0.83 (3H, d, *J* = 6.9 Hz, CH_3-C39), 0.03 (12H, s, CH_3Si-TBS); HRMS (ESI) for $C_{45}H_{86}NaO_4Si_2Sn$ ($[M+Na]^+$) calcd 889.4984, found 889.4990.

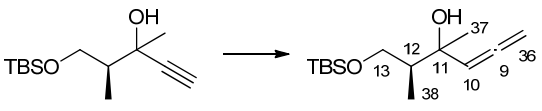
(4*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3,4-dimethylpent-1-yn-3-ol (322).



To a solution of methyl ketone **271** (2.0 g, 6.3 mmol) in ether (50 mL) was added slowly with ethynyl magnesium bromide (15 mL of a 0.5 M solution in THF, 7.5

mmol) at 0 ºC. After addition, the reaction mixture was allowed to warm to rt for another 2 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (50 mL). The aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 500:15) to give a diastereomeric alcohols **322** (2.0 g, 93%) as colourless oil. R_f = 0.41 and 0.40 (petroleum ether–ethyl acetate, 9:1); ν_{max} ($CHCl_3$) 2955, 2929, 2858, 1471, 1388, 1253, 1060, 1033, 1003, 831, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.45 (1H, s, OH), 4.42 (1H, s, OH), 4.25 (1H, dd, J = 3.4, 10.0 Hz, CH_2-C13), 3.92 (1H, t, J = 10.2 Hz, CH_2-C13), 3.70–3.65 (2H, m, CH_2-C13), 2.45 (1H, s, CH-C9), 2.42 (1H, s, CH-C9), 1.98–1.80 (1H, m, CH-C12), 1.48 (3H, s, CH_3-C37), 1.08 (3H, d, J = 3.0 Hz, CH_3-C38), 0.91 (9H, s, CH_3C-TBS), 0.90 (9H, s, CH_3C-TBS), 0.84 (3H, d, J = 6.9, CH_3-C38) 0.10 (6H, s, CH_3Si-TBS), 0.09 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.5 (C-C10), 85.6 (C-C10), 72.4 (CH-C11), 72.2 (CH-C11), 71.3 (CH-C9), 71.1 (CH-C9), 68.1 (CH_2-C13), 67.3 (CH_2-C13), 44.0 (CH-C12), 42.8 (CH-C12), 28.9 (CH_3-C37), 28.8 (CH_3-C37), 25.9 (CH_3C-TBS), 18.3 (CCH_3-TBS), 12.8 (CH_3-C38), 11.7 (CH_3-C38), –5.4 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{13}H_{27}O_2Si$ ($[M+H]^+$) calcd 243.1780, found 243.1777; LRMS (CI, isobutane) *m/z* (intensity) 243.3 (20) 217.3 (100) 133.2 (15) 85.2 (23) 61 (56).

(2*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-2,3-dimethylhexa-4,5-dien-3-ol (323).

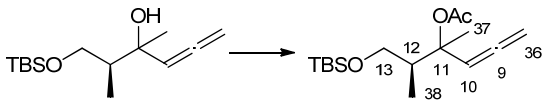


322 **323**

To a solution of propargyl alcohol **322** (3.2 g, 13 mmol) in dioxane (80 mL) was added paraformaldehyde (1.2 g, 40 mmol), CuBr (0.95 g, 6.6 mmol) and *i*-Pr_2NH (1.9 mL, 13 mmol). The resulting mixture was heated at reflux for 18 h. The black solid

was removed by filtration, and the filtrate was washed with water (100 mL). The aqueous phase was extracted with ethyl acetate (2 × 100 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 25:1 to 9:1) to give the allene **323** (2.8 g, 85%) as a yellow oil. R_f = 0.40 (petroleum ether–ethyl acetate, 9:1); ν_{max} (neat) 2956, 2929, 2856, 1957, 1471, 1253, 1060, 831, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.27 (1H, dd, J = 13.2, 6.6 Hz, CH-C10), 5.26 (1H, dd, J = 13.2, 6.6 Hz, CH-C10), 4.84 (2H, d, J = 6.7 Hz, CH_2-C36), 4.83 (2H, dd, J = 6.7, 1.0 Hz, CH_2-C36), 4.66 (1H, s, OH), 4.21 (1H, s, OH), 3.91 (1H, dd, J = 10.1, 4.1, Hz, CH_2-C13), 3.70–3.63 (1H, m, CH_2-C13), 1.98–1.75 (2H, m, CH-C12), 1.31 (3H, s, CH_3-C37), 1.27 (3H, s, CH_3-C37), 0.96 (3H, d, J = 7.0 Hz, CH_3-C38), 0.90 (9H, s, CH_3C-TBS), 0.90 (9H, s, CH_3C-TBS), 0.82 (3H, d, J = 7.0 Hz, CH_3-C38), 0.09 (3H, s, CH_3Si-TBS), 0.09 (3H, s, CH_3Si-TBS), 0.08 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9 (C-C9), 206.4 (C-C9), 99.8 (CH-C10), 96.0 (CH-C10), 77.7 (CH_2-C36), 74.7 (CH-C11), 74.4 (CH-C11), 67.3 (CH_2-C13), 67.0 (CH_2-C13), 44.2 (CH-C12), 43.0 (CH-C12), 27.4 (CH_3-C37), 25.9 (CH_3C-TBS), 24.0 (CH_3-C37), 18.2 (CCH_3-TBS), 12.7 (CH_3-C38), 12.6 (CH_3-C38), –5.5 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{14}H_{29}O_2Si$ ($[M+H]^+$) calcd. 257.1937, found 257.1940; LRMS (CI, isobutane) *m/z* (intensity) 240.3 (22) 239.3 (100) 217.3 (84) 113.2 (13) 73.1 (41).

(2*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,3-dimethylhexa-4,5-dien-3-yl acetate (324).

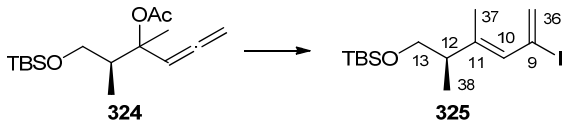


323 **324**

To a solution of allene **323** (1.8 g, 7.2 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (20 mL) and acetic anhydride (4.4 mL, 47 mmol). The solution was treated with DMAP (1.8 g, 14 mmol) and then stirred at rt for 18 h. The reaction mixture was poured into

a saturated aqueous solution of $NaHCO_3$ (100 mL). The aqueous phase was extracted with ethyl acetate (2 × 100 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 100:1) to give the acetate ester **324** (1.5 g, 71%) as colourless oil. R_f = 0.70 (petroleum ether–ethyl acetate, 20:1); ν_{max} ($CHCl_3$) 2955, 2928, 2856, 1972, 1734, 1471, 1363, 1244, 1074, 1006, 815, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.54 (1H, t, J = 6.7 Hz, CH-C10), 5.49 (1H, t, J = 6.7 Hz, CH-C10), 4.93–4.82 (4H, m, CH_2-C36), 3.76 (1H, dd, J = 10.0, 4.2 Hz, CH_2-C13), 3.71 (1H, dd, J = 10.0, 4.0 Hz, CH_2-C13), 3.57 (1H, dd, J = 10.0, 6.4 Hz, CH_2-C13), 3.54-3.51 (1H, m, CH_2-C13), 2.35-2.24 (2H, m, CH-C12), 2.15 (3H, s, CH_3-Ac) 1.99 (3H, s, CH_3-Ac), 1.50 (3H, s, CH_3-C37), 1.46 (3H, s, CH_3-C37), 1.02 (3H, d, J = 6.9 Hz, CH_3-C38), 0.96 (3H, d, J = 6.9 Hz, CH_3-C38), 0.89 (9H, s, CH_3C-TBS), 0.88 (9H, s, CH_3C-TBS), 0.04 (3H, s, CH_3Si-TBS), 0.04 (3H, s, CH_3Si-TBS), 0.03 (3H, s, CH_3Si-TBS), 0.02 (3H, s, CH_3Si-TBS); HRMS (CI, isobutane) for $C_{13}H_{27}O_2Si$ ($[M+H]^+$) calcd. 243.1780, found 243.1777; LRMS (CI, isobutane) *m/z* (intensity) 243.3 (20) 217.3 (100) 133.2 (15) 85.2 (23) 61 (56).

(*R*,*E*)-*tert*-Butyl[(5-iodo-2,3-dimethylhexa-3,5-dien-1-yl)oxy]dimethylsilane (325).

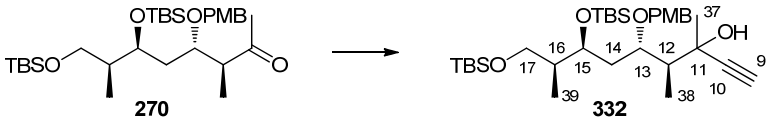


324 **325**

A solution of the acetate ester **324** (1.0 g, 3.4 mmol) in acetic acid (25 mL) and acetonitrile (25 mL) was treated with lithium iodide (1.4 g, 10 mmol) at rt. The mixture was stirred in the dark for 3 h and then poured into a saturated aqueous solution of $NaHCO_3$ (100 mL). The aqueous phase was extracted with ethyl acetate (2 × 100 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on

silica gel (petroleum ether–Et_2O, 250:1 to 500:3) to give vinylic iodides **325** (0.69 g, 58%) as colourless oil. R_f = 0.15 (petroleum ether); v_{max} ($CHCl_3$) 2953, 2921, 2881, 2865, 1603, 1472, 1256, 1113, 1095, 1063, 831, 773 cm^{-1}; $[\alpha]_D^{25}$ +9.1 (*c* = 0.86, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6) δ 5.98 (1H, brs, CH-C10), 5.81 (1H, brs, CH_2-C36), 5.72 (1H, t, *J* = 1.4 Hz, CH_2-C36), 3.40 (1H, dd, *J* = 6.8, 9.8 Hz, CH_2-C13), 3.30 (1H, dd, *J* = 6.3, 9.8 Hz, CH_2-C13), 2.13 (1H, h, *J* = 6.5 Hz, CH-C12), 1.60 (3H, d, *J* = 1.4 Hz, CH-C37), 0.96 (9H, s, CH_3C-TBS), 0.84 (3H, d, *J* = 6.9 Hz, CH_3-C38), 0.01 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, C_6D_6) δ 142.6 (C-C11), 130.7 (CH_2-C36), 128.3 (CH-C10), 104.2 (C-C9), 66.6 (CH_2-C13), 44.7 (CH-C12), 26.1 (CH_3C-TBS), 18.5 (CCH_3-TBS), 15.5 (CH_3-C37), 15.3 (CH_3-C38), –5.3 (CH_3Si-TBS).

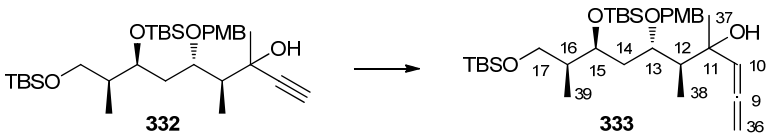
(4*S*,5*S*,7*S*,8*S*)-7,9-bis[(*tert*-Butyldimethylsilyl)oxy]-5-[(4-methoxybenzyl)oxy]-3,4, 8-trimethylnon-1-yn-3-ol (332).



To a solution of methyl ketone **281** (0.51 g, 0.90 mmol) in ether (10 mL) was added slowly ethynyl magnesium bromide (2.2 mL of a 0.5 M in THF solution, 1.1 mmol) at at 0 ºC. After addition, the reaction mixture was allowed to warm to rt for 2 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (50 mL). The aqueous phase was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 500:15) to give the alcohol **332** (0.48 g, 90%) as colourless oil. R_f = 0.55 (petroleum ether–ethyl acetate, 20:1); v_{max} ($CHCl_3$) 2953, 2929, 2856, 1614, 1514, 1406, 1249, 1039, 835, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (2H, d, *J* = 8.6 Hz, Ph-PMB), 6.86 (2H, d, *J* = 8.6 Hz, Ph-PMB), 5.44 (1H, s, OH), 4.71 (1H, d, *J* = 9.8 Hz, CH_2-PMB), 4.53

(1H, d, *J* = 9.8 Hz, CH_2-PMB), 4.08 (1H, td, *J* = 6.3, 2.5 Hz, CH-C15), 3.86–3.78 (1H, m, CH-C13), 3.81 (3H, s, CH_3O-PMB), 3.62 (1H, dd, *J* = 9.7, 6.3 Hz, CH_2-C17), 3.45 (1H, dd, *J* = 9.7, 6.6, Hz, CH_2-C17), 2.48 (1H, s, CH-C9), 1.90–1.72 (4H, m, CH_2-C14, CH-C16, CH-C12), 1.44 (3H, s, CH_3-C37), 0.96 (3H, d, *J* = 6.9 Hz, CH_3-C38), 0.90 (3H, d, *J* = 6.9 Hz, CH_3-C39), 0.90 (9H, s, CH_3C-TBS), 0.88 (9H, s, CH_3C-TBS), 0.11 (3H, s, CH_3Si-TBS), 0.08 (3H, s, CH_3Si-TBS), 0.04 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5 (Ph-PMB), 130.0 (Ph-PMB), 129.9 (Ph-PMB) 114.1 (Ph-PMB), 87.3 (C-C10), 82.0 (C-C11), 72.3 (CH-C13), 72.1 (CH-C15), 71.4 (CH_2-PMB), 71.3 (CH-C9), 64.1 (CH_2-C17), 55.4 (CH_3O-PMB), 48.3 (CH-C12), 41.8 (CH-C16), 39.3 (CH_2-C14), 29.1 (CH_3-C37), 26.1 (CH_3C-TBS), 26.0 (CH_3C-TBS), 18.4 (CCH_3-TBS), 18.3 (CCH_3-TBS), 13.9 (CH_3-C38), 11.8 (CH_3-C39), –3.5(CH_3Si-TBS), –4.4 (CH_3Si-TBS), –5.2 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{32}H_{59}O_5Si_2$ ($[M+H]^+$) calcd. 579.3901, found 579.3899; LRMS (CI, isobutane) *m/z* (intensity) 579.4 (10), 427.1 (13), 243.1 (40) 217.3 (100) 133.2 (15) 85.2 (23) 61 (56).

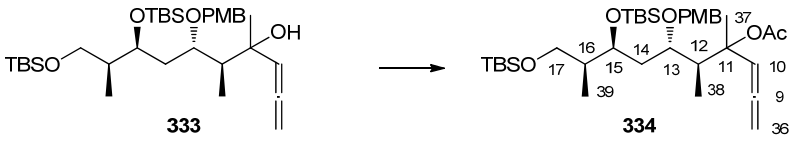
(5*S*,6*S*,8*S*,9*S*)-8,10-bis[(*tert*-Butyldimethylsilyl)oxy]-6-[(4-methoxybenzyl)oxy]-4,5,9-trimethyldeca-1,2-dien-4-ol (333).



Propargyl alcohol **332** (0.47 g, 0.80 mmol) was dissolved in dioxane (45 mL) and paraformaldehyde (72 mg, 2.4 mmol), CuBr (60 mg, 0.40 mmol) and *i*-Pr_2NH (0.10 mL, 0.80 mmol) was added at rt. The resulting mixture was then heated at reflux for 18 h. The black solid was removed by filtration; the filtrates were washed with water (100 mL). The aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–

ethyl acetate, 100:3) to give allene **333** (0.27 g, 56%) as yellow oil. R_f = 0.89 (petroleum ether–ethyl acetate, 20:1); ν_{max} ($CHCl_3$) 2953, 2929, 2856, 1960, 1471, 1456, 1251, 1039, 835, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 8.6 Hz, Ph-PMB), 6.86 (2H, d, J = 8.6 Hz, Ph-PMB), 5.30 (1H, t, J = 6.7 Hz, CH-C10), 4.85 (2H, d, J = 6.6 Hz, CH_2-C36), 4.50 (1H, d, J = 10.4 Hz, CH_2-PMB), 4.42 (1H, d, J = 10.4 Hz, CH_2-PMB), 4.03–4.00 (1H, m, CH-C15), 4.01 (1H, s, OH), 3.79 (3H, s, CH_3O-PMB), 3.71 (1H, td, J = 6.5, 4.1 Hz, CH-C13), 3.61 (1H, dd, J = 9.6, 6.3 Hz, CH_2-C17), 3.43 (1H, dd, J = 9.6, 6.8 Hz, CH_2-C17), 1.96 (1H, dq, J = 6.9, 6.9 Hz, CH-C12), 1.81–1.71 (3H, m, CH_2-C14, CH-C16), 1.31 (3H, s, CH_3-C37), 0.91 (3H, d, J = 7.2 Hz, CH_3-C38), 0.89–0.88 (21H, m, CH_3C-TBS, CH_3-C39), 0.07 (3H, s, CH_3Si-TBS), 0.06 (3H, s, CH_3Si-TBS), 0.03 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5 (C-C9), 159.4 (Ph-PMB), 130.0 (Ph-PMB), 129.9 (Ph-PMB), 114.1 (Ph-PMB), 97.3 (CH-C10), 79.8 (CH-C13), 74.1 (CH-C11), 71.2 (CH_2-C36), 70.6 (CH-C15), 64.3 (CH_2-C17), 55.4 (CH_3O-PMB), 46.8 (CH-C12), 41.6 (CH_2-C14), 37.9 (CH-C16), 27.8 (CH_3-C37), 26.2 (CH_3C-TBS), 26.1 (CH_3C-TBS), 18.4 (CCH_3-TBS), 18.3 (CCH_3-TBS), 12.2 (CH_3-C38), 11.7 (CH_3-C39), –3.6 (CH_3Si-TBS), –4.2 (CH_3Si-TBS), –5.2 (CH_3Si-TBS).

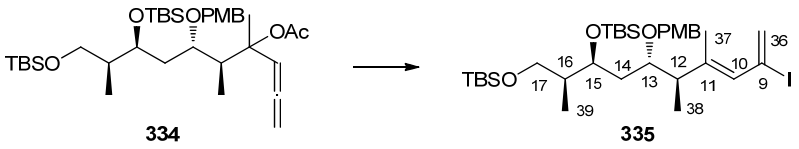
(5S,6S,8S,9S)-8,10-bis[(*tert*-Butyldimethylsilyl)oxy]-6-[(4-methoxybenzyl)oxy]-4,5,9-trimethyldeca-1,2-dien-4-yl acetate (334).



To a solution of allene **333** (10 mg, 0.17 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (0.20 mL, 1.4 mmol) and acetic anhydride (0.10 mL, 0.68 mmol). DMAP (50 mg, 0.17 mmol) was then added and the mixture was then stirred at rt for 18 h. The reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ (5 mL). The aqueous phase was extracted with ethyl acetate (2 × 5 mL) and the combined

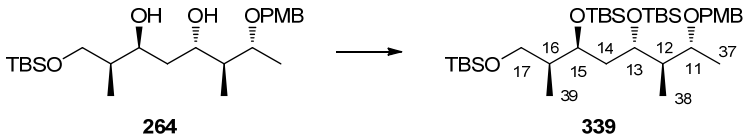
organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 250:3) to give the acetate ester **334** (6 mg, 54%) as colourless oil.

(5S,6S)-5-{(2S,3R,*E*)-6-Iodo-2-[(4-methoxybenzyl)oxy]-3,4-dimethylhepta-4,6-dien-1-yl}-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (335).



To a solution of the acetate ester **334** (11 mg, 0.016 mmol) in acetic acid (0.50 mL) and acetonitrile (1 mL) was added lithium iodide (25 mg, 0.18 mmol) at rt. The reaction mixture was stirred in the dark for 3 h before the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ (2 mL). The aqueous phase was extracted with ethyl acetate (2 × 2 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ether, 250:1) to give the iodide **335** (7 mg, 58%) as colourless oil. To be noticed, this iodide was decomposed very quickly. And this procedure was not repeatable. R_f = 0.89 (petroleum ether–ethyl acetate, 20:1); ^{1}H NMR (400 MHz, C_6D_6) δ 7.30 (2H, d, J = 8.6 Hz, Ph-PMB), 6.85 (2H, d, J = 8.6 Hz, Ph-PMB), 6.10 (1H, brs, CH-C10), 5.84 (1H, s, CH_2-C36), 5.78 (1H, s, CH_2-C36), 4.40 (1H, d, J = 10.9 Hz, CH_2-PMB), 4.35 (1H, d, J = 10.9 Hz, CH_2-PMB), 4.16 (1H, ddd, J = 7.9, 5.1, 2.7 Hz, CH-C15), 3.78 (1H, dd, J = 9.6, 6.7 Hz, CH_2-C17), 3.68–3.62 (1H, m, CH-C13), 3.55 (1H, dd, J = 9.6, 6.7 Hz, CH_2-C17), 3.32 (3H, s, CH_3O-PMB), 2.46–2.40 (1H, m, CH-C12), 2.22 (1H, m, CH-C16), 1.82 (3H, d, J = 1.1 Hz, CH_3-C37), 1.78 (1H, ddd, J = 14.1, 8.7, 5.1 Hz, CH_2-C14), 1.58 (1H, ddd, J = 14.1, 7.9, 3.4 Hz, CH_2-C14), 1.02 (9H, s, CH_3C-TBS), 0.97–1.01 (12H, m, CH_3C-TBS, CH_3-C38), 0.98 (3H, d, J = 7.0 Hz, CH_3-C39), 0.03 (12H, s, CH_3Si-TBS).

(5*S*,7*S*,8*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-5-{(2*R*,3*R*)-3-[(4-methoxybenzyl)oxy]butan-2-yl}-2,2,3,3,8,11,11,12,12-nonamethyl-4,10-dioxa-3,11-disilatridecane (339).

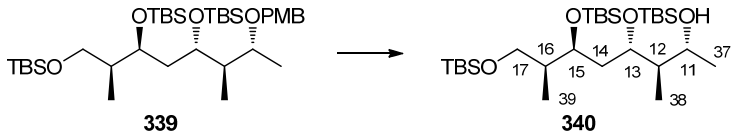


264 **339**

To a solution of the diol (1.2 g, 2.7 mmol) in CH_2Cl_2 (50 mL) was added TBSOTf (1.6 mL, 6.8 mmol), and 2,6-lutidine (1.8 mL, 16 mmol) at rt and the mixture was stirred for 2 h. A saturated aqueous solution of $NaHCO_3$ (100 mL) was then added and the phases were separated. The aqueous phase was extracted with ether (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 50:1) to give the TBS ether (1.7 g, 93%) as colourless oil. R_f = 0.82 (petroleum ether–ethyl acetate, 20:1); $[\alpha]_D^{27}$ –12.5 (*c* = 1.15, $CHCl_3$); ν_{max} ($CHCl_3$) 2953, 2929, 2857, 1514, 1472, 1463, 1387, 1360, 1248, 1171, 1040, 1005, 938, 835, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.7 Hz, Ph-PMB), 6.85 (2H, d, *J* = 8.7 Hz, Ph-PMB), 4.55–4.30 (2H, m, CH_2-PMB), 3.93 (1H, td, *J* = 6.4, 3.4 Hz, CH-C13), 3.90 (1H, td, *J* = 6.4, 2.3 Hz, CH-C15), 3.80 (3H, s, CH_3O-PMB), 3.60 (1H, dd, *J* = 9.6, 6.3 Hz, CH_2-C17), 3.49 (1H, dq, *J* = 6.3, 6.2 Hz, CH-C11), 3.37 (1H, dd, *J* = 9.6, 7.3 Hz, CH_2-C17), 1.87 (1H, dd, *J* = 6.9, 3.4 Hz, CH-C12), 1.75 (1H, dq, *J* = 6.9, 2.1 Hz, CH-C16), 1.57 (2H, t, *J* = 6.3 Hz, CH_2-C14), 1.14 (3H, d, *J* = 6.2 Hz, CH_3-C37), 0.89 (2H, d, *J* = 7.0 Hz, CH_3-C39), 0.88 (18H, s, CH_3C-TBS), 0.85 (9H, s, CH_3C-TBS), 0.83 (3H, d, *J* = 6.9 Hz, CH_3-C38), 0.08 (3H, s, CH_3Si-TBS), 0.06 (3H, s, CH_3Si-TBS), 0.03 (3H, s, CH_3Si-TBS), 0.02 (3H, s, CH_3Si-TBS), 0.02 (3H, s, CH_3Si-TBS), 0.01 (3H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2

(Ph-PMB), 131.8 (Ph-PMB), 128.9 (Ph-PMB), 113.9 (Ph-PMB), 76.1 (CH-C11), 71.9 (CH-C13), 71.0 (CH-C15), 65.3 (CH_2-C17), 55.5 (CH_3O-PMB), 44.1 (CH_2-PMB), 41.3 (CH-C12), 38.7 (CH-C14), 26.2 (CH_3C-TBS), 18.5 (CCH_3-TBS), 18.3(CH-C16) 17.2 (CH_3-C37), 11.1 (CH_3-C38), 11.0 (CH3-C39), –3.6 (CH_3Si-TBS), –3.8 (CH_3Si-TBS), –4.3 (CH_3Si-TBS), –5.2 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{36}H_{73}O_5Si_3$ ($[M+H]^+$) calcd. 669.4766, found 669.4758; LRMS (CI, isobutane) *m/z* (intensity) 669.5 (65) 549.4 (30) 491.3 (25) 405.3 (28) 359.3 (27) 317.2 (13) 267.2 (20) 137.2 (18) 119.0 (100).

(2*R*,3*R*,4*S*,6*S*,7*S*)-4,6,8-tris[(*tert*-Butyldimethylsilyl)oxy]-3,7-dimethyloctan-2-ol (340).



The PMB ether **339** (1.6 g, 1.1 mmol) was dissolved in CH_2Cl_2 (20 mL) and DDQ (0.31 g, 1.3 mmol) and water (10 mL) were added at rt. The resulting solution was stirred at rt for 2 h and the reaction was then quenched by addition of a saturated aqueous solution of $NaHCO_3$ (50 mL). The phases were separated and the aqueous phase was extracted with ether (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in *vacuo*. Residual material was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 100:2 to 100:3) to give the alcohol **340** (1.3 g, 99%) as colourless oil. R_f = 0.70 (petroleum ether–ethyl acetate, 9:1); $[\alpha]_D^{27}$ –9.1 (*c* = 1.60, $CHCl_3$); ν_{max} ($CHCl_3$) 2957, 2930, 2885, 2857, 1253, 1051, 939, 833, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.91–3.86 (2H, m, CH-C13, CH-C15), 3.64 (1H, ddd, *J* = 8.3, 6.2, 4.0 Hz, CH-C11), 3.59 (1H, dd, *J* = 9.5, 6.3 Hz, CH_2-C17), 3.38 (1H, dd, *J* = 9.5, 6.9 Hz, CH_2-C17), 2.25 (1H, d, *J* = 3.8 Hz, OH), 1.74 (1H, dq, *J* = 6.8, 2.2 Hz, CH-C12), 1.67–1.54 (3H, m, CH-C16, CH_2-C14), 1.20 (3H, d, *J* = 6.2 Hz, CH_3-C37), 0.89 (9H, s, CH_3C-TBS), 0.89 (9H, s, CH_3C-TBS),

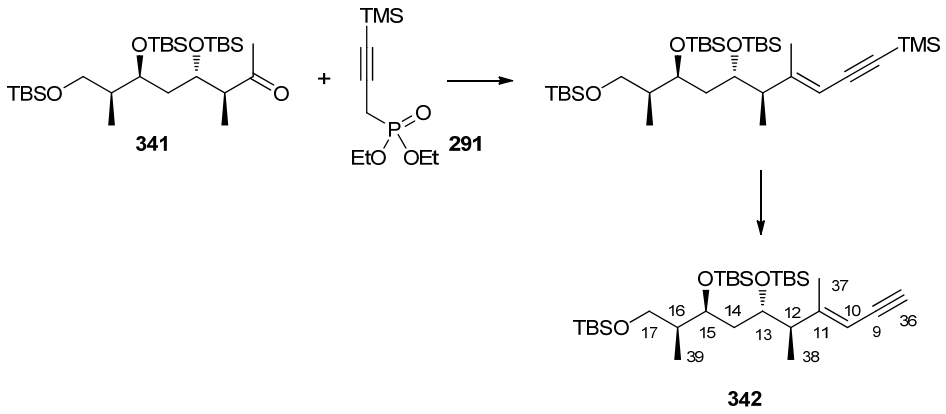
0.88 (9H, s, CH_3C-TBS), 0.84 (3H, d, J = 6.9 Hz, CH_3-C38), 0.83 (3H, d, J = 6.9 Hz, CH_3-C39), 0.09 (3H, s, CH_3Si-TBS), 0.09 (3H, s, CH_3Si-TBS), 0.07 (3H, s, CH_3Si-TBS), 0.07 (3H, s, CH_3Si-TBS), 0.03 (3H, s, CH_3Si-TBS), 0.02 (3H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.8 (CH-C13), 71.1 (CH-C15), 70.3 (CH-C11), 64.8 (CH_2-C17), 46.1 (CH-C12), 41.1 (CH-C16), 39.3 (CH_2-C14), 26.1 (CH_3C-TBS), 21.9 (CH_3-C37), 18.4 (CCH_3-TBS), 12.8 (CH_3-C38), 11.2 (CH_3-C39), –3.7 (CH_3Si-TBS), –4.0 (CH_3Si-TBS), –4.2 (CH_3Si-TBS), –5.2 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{28}H_{65}O_4Si_3$ ($[M+H]^+$) calcd. 549.4191, found 549.4197; LRMS (CI, isobutane) *m/z* (intensity) 549.5 (100) 491.4 (12) 417.4 (98) 373.4 (17) 359.3 (17) 285.3 (57) 241.2 (32) 217.2 (21) 133.1 (45) 73.1 (25).

(3*S*,4*S*,6*S*,7*S*)-4,6,8-tris[(*tert*-Butyldimethylsilyl)oxy]-3,7-dimethyloctan-2-one (341).

340 341

The alcohol **340** (1.2 g, 2.2 mmol) was dissolved in CH_2Cl_2 (30 mL) and Dess–Martin peroiodiane (1.5 g, 3.3 mmol) was added at rt. The mixture was stirred at rt for 2 h and the reaction was then quenched by addition of saturated aqueous solutions of $Na_2S_2O_3$ (50 mL) and $NaHCO_3$ (50 mL). The aqueous phase was extracted with Et_2O (2 × 100 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in *vacuo* to deliver the ketone (1.2 g, 100%) as colourless oil, which was used in the next step without purification.

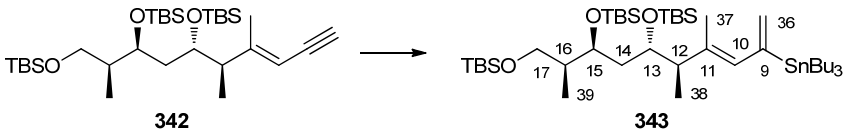
(5*S*,7*S*,8*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-2,2,3,3,8,11,11,12,12-nonamethyl-5-[(*R*,*E*)-3-methylhex-3-en-5-yn-2-yl]-4,10-dioxa-3,11-disilatridecane (342).



The phosphonate **291** (0.20 g, 0.82 mmol) was dissolved in THF (25 mL) and NaHMDS (0.39 mL of a 2.0 M solution in THF, 0.78 mmol) was added at –78 °C. The reaction mixture was stirred at –78 °C for 30 min and then a solution of the ketone (0.30 g, 0.55 mmol) in THF (5 mL) was added. The mixture was stirred at –78 °C for a further period of 2 h and the reaction was then quenched by addition of aqueous solution of NH_4Cl (50 mL). The aqueous phase was extracted with Et_2O (2 × 50 mL) and the organic extracts were combined, dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether–ethyl acetate, 250:1) to give the enyne (0.27 g, 77%) as colourless oil. The enyne (0.27 g, 0.42 mmol) was dissolved in MeOH (5 mL) and K_2CO_3 (0.3 g, 2.0 mmol) was added at rt. The mixture was stirred at rt until all starting material had been consumed. Water (20 mL) was added and the aqueous phase was extracted with ether (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether–ethyl acetate, 500:3) to give the the enyne 23 (0.23 g, 97%) as colourless oil. R_f = 0.70 (petroleum ether–ethyl acetate, 9:1); $[\alpha]_D^{28}$ +13.4 (*c* = 1.60, $CHCl_3$); ν_{max} ($CHCl_3$) 2957, 2932, 2859, 1742, 1254, 1045, 1005, 835, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41–5.39 (1H, m, CH-C10), 3.89 (1H, ddd, *J* = 8.0, 6.2, 2.0 Hz, CH-C13), 3.73 (1H, ddd, *J* = 7.2, 5.9, 3.3 Hz, CH-C15), 3.55 (1H, dd, *J* = 9.6,

7.3 Hz, CH_2-C17), 3.37 (1H, dd, *J* = 9.6, 6.5 Hz, CH_2-C17), 3.03 (1H, d, *J* = 2.0 Hz, CH-C36), 2.32 (1H, dq, *J* = 6.9, 3.2 Hz, CH-C12), 1.97 (3H, d, *J* = 0.6 Hz, CH_3-C37), 1.65 (1H, dqd, *J* = 13.8, 6.8, 1.9 Hz, CH_2-C14), 1.61 (1H, ddd, *J* = 13.8, 7.8, 5.9 Hz, CH_2-C14), 1.52 (1H, ddd, *J* = 13.6, 7.1, 6.3 Hz, CH-C16), 1.06 (3H, d, *J* = 7.0 Hz, CH_3-C38), 0.91 (9H, s, CH_3C-TBS), 0.91 (9H, s, CH_3C-TBS), 0.89 (9H, s, CH_3C-TBS), 0.82 (3H, d, *J* = 6.9 Hz, CH_3-C39), 0.10 (3H, s, CH_3Si-TBS), 0.08 (3H, s, CH_3Si-TBS), 0.06 (3H, s, CH_3Si-TBS), 0.05 (9H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8 (C-C11), 106.1 (CH-C10), 81.9 (CH-C9), 80.5 (CH-C36), 73.2 (CH-C13), 69.6 (CH-C15), 65.3 (CH-C17), 46.5 (CH-C12), 40.3 (CH-C16), 39.5 (CH_2-C14), 26.2 (CH_3C-TBS), 18.7 (CH_3-C37), 18.5 (CCH_3-TBS), 18.3 (CCH_3-TBS), 18.2 (CCH_3-TBS), 15.3 (CH_3-C38), 10.3 (CH_3-C39), –3.8 (CH_3Si-TBS), –4.0 (CH_3Si-TBS), –4.2 (CH_3Si-TBS), –4.5 (CH_3Si-TBS), –5.2 (CH_3Si-TBS); HRMS (CI, isobutane) $C_{31}H_{65}O_3Si_3$ ($[M+H]^+$) calcd. 569.4242, found 543.4247.

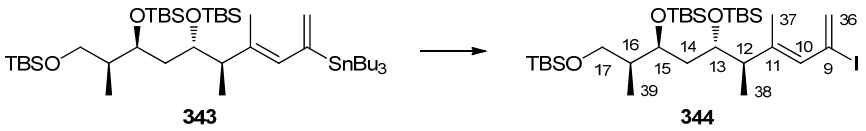
(5S,7S,8S)-7-[(*tert*-Butyldimethylsilyl)oxy]-2,2,3,3,8,11,11,12,12-nonamethyl-5-[(R,*E*)-3-methyl-5-(tributylstannyl)hexa-3,5-dien-2-yl]-4,10-dioxa-3,11-disilatridecane (343).



To a solution of alkyne **342** (0.64 g, 1.1 mmol) in THF (40 mL) was added with $Pd(Ph_3P)_4$ (63 mg, 0.050 mmol) at rt. The resulting yellow solution was treated with *n*-Bu_3SnH (0.35 mL, 1.3 mmol) at rt for 30 min. Solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 250:1) to give the stannane **343** (0.70 g, 72%) as colourless oil. R_f = 0.30 (petroleum ether–ethyl acetate, 50:1); $[\alpha]_D^{28}$ +22.6, (*c* = 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 2955, 2928, 2856, 1462, 1385, 1251, 1043, 835, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (1H, brs, CH-C10), 5.64 (1H, dd, *J* = 3.4, 1.7 Hz,

CH_2-C36), 5.32 (1H, dd, *J* = 3.4, 1.1 Hz, CH_2-C36), 3.88 (1H, td, *J* = 7.2, 1.8 Hz, CH-C13), 3.73 (1H, td, *J* = 6.4, 3.0 Hz, CH-C15), 3.56 (1H, dd, *J* = 9.6, 6.9 Hz, CH_2-C17), 3.36 (1H, dd, *J* = 9.6, 6.9 Hz, CH_2-C17), 2.25–2.18 (1H, m, CH-C12), 1.71 (3H, d, *J* = 1.1 Hz, CH_3-C37), 1.67 (1H, dq, *J* = 6.9, 1.8 Hz, CH-C16), 1.61–1.43 (14H, m, CH_2-Bu, CH_2-C14), 1.34–1.27 (6H, m, CH_2-Bu), 1.03 (3H, d, *J* = 7.0 Hz, CH_3-C38), 0.92–0.85 (36H, m, CH_3-Bu, CH_3C-TBS), 0.82 (3H, d, *J* = 6.7 Hz, CH_3-C39), 0.09 (3H, s, CH_3Si-TBS), 0.08 (3H, s, CH_3Si-TBS), 0.04 (3H, s, CH_3Si-TBS), 0.03 (3H, s, CH_3Si-TBS), 0.02 (3H, s, CH_3Si-TBS), 0.01 (3H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8 (C-C11), 135.6 (C-C9), 131.9 (CH-C10), 127.2 (CH_2-C36), 73.3 (CH-C13), 69.8 (CH-C15), 65.3 (CH-C17), 47.1 (CH-C12), 40.4 (CH-C16), 38.7 (CH_2-C14), 29.2 (CH_2-Bu), 27.5 (CH_2-Bu), 26.1 (CH_3C-TBS), 18.4 (CH_2-Bu), 18.3 (CCH_3-TBS), 16.8 (CH_3-C37), 15.2 (CH_2-Bu), 13.9 (CH_3-C38), 10.4 (CH_3-Bu), 10.1 (CH_3-C39), –3.8 (CH_3Si-TBS), –4.0 (CH_3Si-TBS), –4.1 (CH_3Si-TBS), –4.5 (CH_3Si-TBS), –5.2 (CH_3Si-TBS); HRMS (ESI) $C_{43}H_{92}NaO_3Si_3Sn$ ($[M+Na]^+$) calcd. 883.5274, found 883.5268.

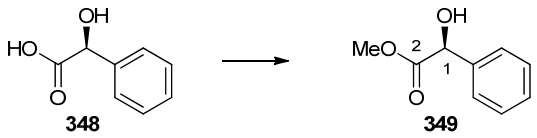
(5*S*,7*S*,8*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-5-[(*R*,*E*)-5-iodo-3-methylhexa-3,5-dien-2-yl]-2,2,3,3,8,11,11,12,12-nonamethyl-4,10-dioxa-3,11-disilatridecane (344).



A solution of stannane **343** (0.30 g, 0.35 mmol) in CH_2Cl_2 (20 mL) was treated dropwise with a solution of I_2 (0.11 g, 0.42 mmol) in CH_2Cl_2 (5 mL) at 0°C over 10 min. The reaction was completed when the colour of I_2 did not fade. The reaction mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ (40 mL) and $NaHCO_3$ (20 mL). The aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether)

to give the vinyl iodide **344** (0.20 g, 71%) as colourless oil. R_f = 0.85 (petroleum ether–ethyl acetate, 100:1); v_{max} ($CHCl_3$) 2956, 2929, 2883, 2854, 1623, 1603 1472, 1254, 1111, 1095,1063, 835, 773 cm^{-1}; $[\alpha]_D^{28}$ +22.6 (*c* = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.00 (1H, brs, CH-C10), 5.94 (1H, s, CH_2-C36), 5.92 (1H, brs, CH_2-C36), 3.86 (1H, td, *J* = 6.9, 2.0 Hz, CH-C13), 3.75 (1H, td, *J* = 6.4, 3.2 Hz, CH-C15), 3.56 (1H, dd, *J* = 9.6, 6.9 Hz, CH_2-C17), 3.36 (1H, dd, *J* = 9.6, 6.7 Hz, CH_2-C17), 2.24 (1H, qd, *J* = 6.9, 2.9 Hz, CH-C12), 1.83 (3H, d, *J* = 1.3 Hz, CH_3-C37), 1.69–1.32 (3H, m, CH_2-C14, CH-C16), 1.04 (3H, d, *J* = 7.0 Hz, CH_3-C38), 0.90 (18H, s, CH_3C-TBS), 0.86 (9H, s, CH_3C-TBS), 0.82 (3H, d, *J* = 6.9 Hz, CH_3-C39), 0.09 (3H, s, CH_3Si-TBS), 0.08 (3H, s, CH_3Si-TBS), 0.01 (12H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4 (C-C11), 131.4 (CH-C10), 127.9 (CH_2-C36), 104.0 (C-C9), 73.2 (CH-C13), 70.1 (CH-C15), 66.1 (CH_2-C17), 46.8 (CH-C12), 40.7 (CH-C16), 38.8 (CH_2-C14), 29.3 (CH_3-C37), 26.2 (CH_3C-TBS), 18.5 (CCH_3-TBS), 18.3 (CCH_3-TBS), 13.7 (CH_3-C38), 10.7 (CH_3-C39), –3.8 (CH_3Si-TBS), –4.0 (CH_3Si-TBS), –4.1 (CH_3Si-TBS), –4.5 (CH_3Si-TBS), –5.2 (CH_3Si-TBS).

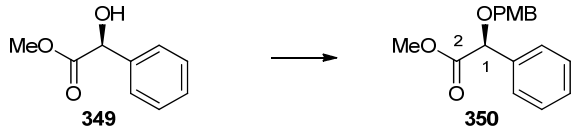
(*S*)-Methyl 2-hydroxy-2-phenylacetate (349).



To a solution of (*S*)-2-hydroxy-2-phenylacetic acid **348** (3.5 g, 23 mmol) in MeOH (50 mL) was added $SOCl_2$ (2 drops). The reaction refluxed for 4 h before the resulting solution was concentrated in *vacuo* to afford the title compound **349** (3.7 g, 96%) as white solid without any further purification. R_f = 0.30 (petroleum ether–ethyl acetate, 1:4); M.p. = 56–57 °C, (lit.[70]M.p. = 53–55 °C); $[\alpha]_D^{28}$ +151.6 (*c* = 1.20, methanol) {Lit.[70]$[\alpha]_D^{20}$ +140.8 (*c* = 0.39, methanol)}; v_{max} ($CHCl_3$) 1735, 1456, 1363, 1217, 1068, 734, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.44 (m, 5H, Ph), 5.18 (d, 1H, *J* =

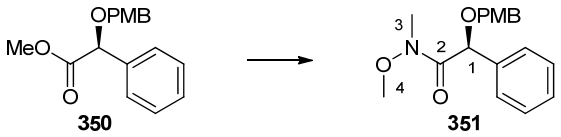
5.6 Hz, CH-C1), 3.76 (s, 3H, CH_3O-Me), 3.50 (d, 1H, J = 5.6 Hz, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 (CO-C2), 138.3 (Ph), 128.6 (Ph) 128.4 (Ph), 126.6 (Ph), 72.8 (CH-C1), 53.1 (CH_3O-Me); HRMS (CI, isobutane) $C_9H_{11}O_3$ ($[M+H]^+$) calcd. 167.0708, found 167.0710.

(*S*)-Methyl 2-[(4-methoxybenzyl)oxy]-2-phenylacetate (350).



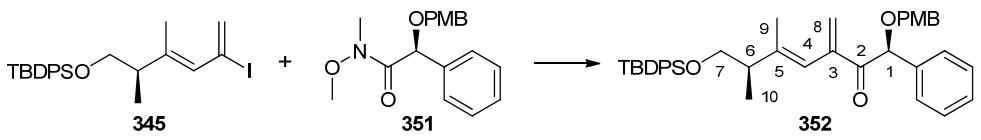
Ester **349** (3.0 g, 18 mmol) was dissolved in CH_2Cl_2 (40 mL) and PMBTCA (10 g, 36 mmol) and CSA (0.15 g, 3.6 mmol) were then added at rt. The mixture was stirred at rt for 18 h. The solid was removed by filtration and the liquor was concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 9:1) to give the compound **350** (5.2 g, 100%) as yellow oil. R_f = 0.25 (petroleum ether–ethyl acetate, 9:1); $[\alpha]_D^{22}$ +82.2 (c = 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 1747, 1612, 1435, 1246, 1207, 1170, 1095, 1030, 819, 783, 729, 696, 638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.33 (5H, m, Ph), 7.27 (2H, d, J = 8.7 Hz, Ph-PMB), 6.88 (2H, d, J = 8.7 Hz, Ph-PMB), 4.91 (1H, s, CH-C1), 4.54 (1H, d, J = 11.8 Hz, CH_2-PMB), 4.50 (1H, d, J = 11.8 Hz, CH_2-PMB), 3.81 (3H, s, CH_3O-PMB), 3.70 (3H, s, CH_3O-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5 (CO-C2), 159.6 (Ph-PMB), 136.5 (Ph), 130.0 (Ph), 129.4 (Ph), 129.3 (Ph), 128.8 (Ph), 127.6 (Ph), 114.0 (Ph-PMB), 79.3 (CH-C1), 70.9 (CH_2-PMB), 55.4 (CH_3O-PMB), 52.4 (CH_3O-Me); HRMS (CI, isobutane) $C_{17}H_{19}O_4$ ($[M+H]^+$) calcd. 287.1283, found 287.1283.

(S)-*N*-Methoxy-2-[(4-methoxybenzyl)oxy]-*N*-methyl-2-phenylacetamide (351).



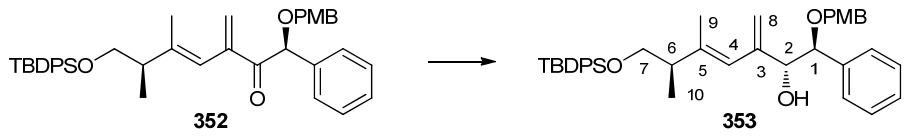
A stirred slurry of *N,O*-dimethylhydroxylamine hydrochloride (1.2 g, 13 mmol) and ester **350** (2.4 g, 8.4 mmol) in THF (50 mL) at –15 ºC was treated with *i*-PrMgCl (13 mL of a 2.0 M solution in THF, 26 mmol) in order to maintain the internal temperature below –15 ºC. After stirred for 1 h at –15 ºC, the reaction mixture was quenched by addition of a saturated aqueous solution of NH_4Cl solution (100 mL). The aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 4:1 to 1:1) to give the Weinreb amide **351** (0.90 g, 35%) as colourless oil. R_f = 0.15 (petroleum ether–ethyl acetate, 1:1); ν_{max} (neat) 1668, 1612, 1512, 1456, 1301, 985, 817, 754, 696, 630, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.33 (5H, m, Ph), 7.30 (2H, d, J = 8.7 Hz, Ph-PMB), 6.88 (2H, d, J = 8.7 Hz, Ph-PMB), 5.27 (1H, s, CH-C1), 4.54 (2H, s, CH_2-PMB), 3.81 (3H, s, CH_3O-PMB), 3.33 (3H, brs, CH_3O-C4), 3.70 (3H, s, CH_3N-C3); HRMS (CI, isobutane) $C_{17}H_{19}O_4$ ($[M+H]^+$) calcd. 287.1283, found 287.1283.

(1*S*,6*R*,*E*)-7-[(*tert*-Butyldiphenylsilyl)oxy]-1-[(4-methoxybenzyl)oxy]-5,6-dimethyl-3-methylene-1-phenylhept-4-en-2-one (352).



Iodide **345** (40 mg, 0.13 mmol) was dissolved in Et_2O (2 mL) and the solution was treated dropwise with *n*-BuLi (0.050 mL of a 2.5 M solution in hexane, 0.12 mmol) at –78 °C. The resulting yellow solution was stirred at –78 °C at 30 min and then added a solution of amide **351** (50 mg, 0.11 mmol) in ether (1 mL) at –78 °C. The reaction mixture was then allowed to warm to rt slowly for another 4 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl solution (10 mL). The aqueous phase was extracted with ethyl acetate (2 × 10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 20:1 to 8:1) to give enone **352** (53 mg, 83%) as colourless oil. R_f = 0.35 (petroleum ether–ethyl acetate, 4:1); v_{max} ($CHCl_3$) 2956, 2929, 2832, 1774, 1612, 1512, 1456, 1282, 900, 817, 775, 754, 696, 621 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.61 (4H, m, Ph-TBDPS), 7.45–7.31 (11H, m, Ph-6.84 (1H, d, *J* = 8.7 Hz, Ph-PMB),TBDPS and Ph), 7.25 (2H, d, *J* = 8.7 Hz, Ph-PMB), 6.81 (1H, d, *J* = 8.7 Hz, Ph-PMB), 6.01 (1H, brs, CH-C4), 5.83 (1H, brs, CH_2-C8), 5.42 (1H, brs, CH_2-C8), 5.31 (1H, s, CH-C1), 4.47 (2H, q, *J* = 11.6 Hz, CH_2-PMB), 3.80 (3H, s, CH_3O-PMB), 3.58 (1H, dd, *J* = 9.9, 6.7 Hz, CH_2-C7), 3.48 (1H, dd, *J* = 9.9, 6.7 Hz, CH_2-C7), 2.36 (1H, m, CH-C6), 1.40 (3H, d, *J* = 1.4 Hz, CH_3-C9), 1.02 (9H, s, CH_3C-TBDPS), 0.99 (3H, d, *J* = 6.9 Hz, CH_3-C10).

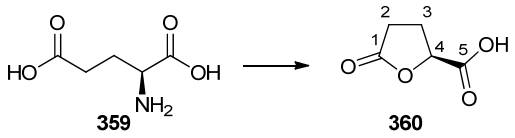
(1*S*,2*R*,6*R*,*E*)-7-[(*tert*-Butyldimethylsilyl)oxy]-1-[(4-methoxybenzyl)oxy]-5,6-dimethyl-3-methylene-1-phenylhept-4-en-2-ol (353).



To a solution of ketone **352** (20 mg, 0.033 mmol) in MeOH (2 mL) was added $CeCl_3 \cdot 7H_2O$ (18 mg, 0.049 mmol) at –78 °C. The reaction was stirred for 30 min and $NaBH_4$ was then added (4.0 mg, 0.1 mmol) at –78 °C. The reaction mixture was

stirred for 1 h, and the reaction was quenched by addition of water (5 mL). The aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 9:1) to give the alcohol **353** (15 mg, 75%) as colourless oil. R_f = 0.30 (petroleum ether–ethyl acetate, 4:1); ν_{max} ($CHCl_3$) 2956, 2929, 2832, 1614, 1514, 1464, 1249, 1111, 1089, 1037, 837, 775, 696, 605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (4H, m, Ph-TBDPS), 7.45–7.31 (11H, m, Ph-TBDPS and Ph), 7.17 (2H, d, J = 8.6 Hz, Ph-PMB), 6.84 (2H, d, J = 8.7 Hz, Ph-PMB), 5.63 (1H, brs, CH-C4), 5.09 (1H, brs, CH_2-C8), 4.88 (1H, brs, CH_2-C8), 4.40–4.32 (3H, m, CH-C1, CH-C2, CH_2-PMB), 4.17 (1H, d, J = 11.2 Hz, CH_2-PMB), 3.78 (3H, s, CH_3O-PMB), 3.62 (1H, dd, J = 9.9, 6.8 Hz, CH_2-C7), 3.50 (1H, dd, J = 9.9, 6.7 Hz, CH_2-C7), 2.38 (1H, m, CH-C6), 2.07 (1H, d, J = 3.9 Hz, OH) 1.62 (3H, d, J = 1.3 Hz, CH_3-C9), 1.04 (9H, s, CH_3C-TBDPS), 1.00 (3H, d, J = 6.9 Hz, CH_3-C10); HRMS (CI, isobutane) $C_{40}H_{49}O_4Si$ ($[M+H]^+$) calcd. 621.3400, found 621.3398.

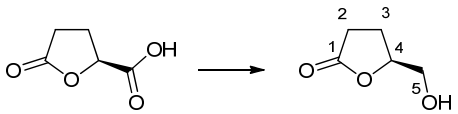
(*S*)-5-Oxotetrahydrofuran-2-carboxylic acid (360).



To a flask charged L-glutamic acid (30 g, 0.20 mol) in water (200 mL) was added concentrated HCl solution (30 mL). The resulting solution was then treated dropwise with a solution of $NaNO_2$ (18 g, 0.27 mol) in water (100 mL) at 0 ºC over 1 hour. The reaction mixture was warmed to rt and stirred for 18 h. Water was removed under reduced pressure. The solid was washed with acetone (2 × 100 mL) and the washings were dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo*. The residue was then dried in high vaccum for 18 h to give lactone **360** (21 g, 92%) as a yellow solid. The solid was used directly for the next step. M.p. = 71–73 ºC (lit.[71] M.p. = 70–72 ºC);

$[\alpha]_D^{22}$ +14.3 (*c* = 1.50, MeOH) {lit.[71] $[\alpha]_D^{25}$ +16.02 (*c* = 4.6, MeOH)}; ^{1}H NMR (400 MHz, DMSO) δ 9.52 (1H, brs, COOH), 5.02–4.99 (1H, m, CH-C4), 2.69–2.53 (3H, m, CH-C2, CH_2-C3) 2.43–2.37 (1H, m, CH_2-C3); ^{13}C NMR (100 MHz, DMSO) δ 175.9 (CO-C5), 174.8 (CO-C1), 75.2 (CH-C4), 26.8 (CH-C2), 26.0 (CH_2-C3).

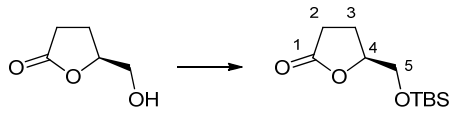
(*S*)-5-(Hydroxymethyl)dihydrofuran-2(3H)-one (361).



360 **361**

To a solution of acid **360** (21 g, 165 mmol) in THF (150 mL) was added dropwise borane methyl sulfide complex (33 mL of a 10 M solution, 0.33 mol) at 0 ºC. After gas released, the reaction mixture was allowed to warm to rt and then stirred for 18 h. The reaction was quenched by careful addition of MeOH (100 mL) at 0 ºC. The solvent was then removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate-MeOH, 20:1) to give the alcohol **361** (8.8 g, 42% over 2 steps) as colourless oil. $[\alpha]_D^{25}$ +30.3 (*c* = 1.5, MeOH) {lit.[72] $[\alpha]_D^{26}$ +31.9 (*c* = 3.2, EtOH)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66–4.60 (1H, m, CH-C4), 3.89 (1H, d, *J* = 12.8 Hz, CH_2-C5), 3.64 (1H, dd, *J* = 12.8, 3.5 Hz, CH_2-C5), 2.85–2.48 (3H, m, CH_2-C2 and OH), 2.30–2.12 (2H, m, CH_2-C3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (CO-C1), 80.9 (CH-C4), 64.2 (CH_2-C5), 28.8 (CH_2-C2), 23.3 (CH_2-C3).

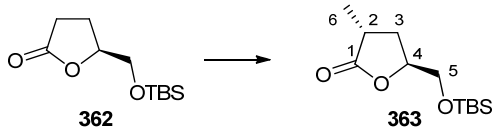
(*S*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}dihydrofuran-2(3H)-one (362).



361 **362**

The alcohol **361** (4.8 g, 41 mmol) was dissolved in CH_2Cl_2 (100 mL) and imidazole (6.8 g, 99 mmol), TBSCl (7.5 g, 50 mmol) and DMAP (0.50 g, 4.1 mmol) was added and the mixture was stirred at rt for 2 h. The reaction was then quenched by addition of brine (100 mL). The aqueous phase was extracted with Et_2O (2 × 100 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purified of the residue by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 20:1 to 9:1) afforded the TBS ether **362** (8.5 g, 89%) as colourless oil. R_f = 0.35 (petroleum ether–ethyl acetate, 9:1); $[\alpha]_D^{25}$ +12.8 (*c* = 1.00, $CHCl_3$) {lit.[73] $[\alpha]_D^{20}$ +12.8 (*c* = 1.00, $CDCl_3$)}; ν_{max} ($CHCl_3$) 2931, 2862, 1774, 1465, 1357, 1257, 1172, 1118, 1087, 995, 833, 779, 663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.58 (1H, ddt, *J* = 8.1, 5.1, 3.2 Hz, CH-C4), 3.86 (1H, dd, *J* = 11.3, 3.2 Hz, CH_2-C5), 3.68 (1H, dd, *J* = 11.3, 3.1 Hz, CH_2-C5), 2.61 (1H, ddd, *J* = 17.5, 10.2, 7.3 Hz, CH_2-C2), 2.46 (1H, ddd, *J* = 17.5, 10.2, 7.3 Hz, CH_2-C2), 2.31–2.13 (2H, m, CH_2-C3), 0.89 (9H, s, CH_3C-TBS), 0.07 (3H, s, CH_3Si-TBS), 0.06 (3H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (CO-C1), 80.2 (CH-C4), 65.0 (CH_2-C5), 28.7 (CH_2-C2), 25.9 (CH_3C-TBS), 23.7 (CH_2-C3), 18.4 (CCH_3-TBS), –5.3 (CH_3Si-TBS); HRMS (CI, isobutane) for $C_{11}H_{23}O_3Si$ ($[M+H]^+$) calcd. 231.1416, found 231.1403; LRMS (CI, isobutane) *m*/*z* (intensity) 231.2 (72) 200.21 (10) 107.1 (21) 81.1 (58) 73.1 (100) 69.1 (85).

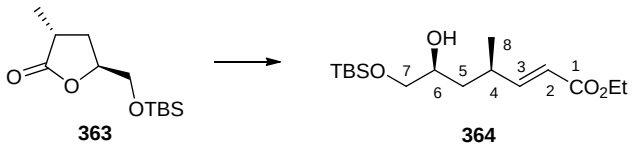
(3*R*,5*S*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-methyldihydrofuran-2(3H)-one (363).



A solution of lactone **362** (14 g, 69 mmol) in THF (150 mL) was treated dropwise with LiHMDS (69 mL of a 1.0 M solution in THF, 69 mmol) at –78 ºC for 1 h. MeI (17 mL, 277 mmol) was added and the mixture was stirred at –78 ºC for another 2 h

before NH_4Cl (200 mL) was added. The aqueous phase was extracted with Et_2O (2 × 200 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 100:3) to give the lactone **363** (8.9 g, 64%) as colourless oil. R_f = 0.20 (petroleum ether–ethyl acetate, 9:1); $[\alpha]_D^{26}$ +38.7 (*c* = 0.95, $CHCl_3$) {lit.[74] $[\alpha]_D^{28}$ +20.7 (*c* = 0.18, $CHCl_3$)}; ν_{max} ($CHCl_3$) 2931, 2862, 1774, 1465, 1357, 1257, 1126, 1026, 933, 840, 779, 663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.52 (1H, dq, *J* = 8.9, 3.1 Hz, CH-C4), 3.84 (1H, dd, *J* = 11.2, 3.1 Hz, CH_2-C5), 3.67 (1H, dd, *J* = 11.2, 3.1 Hz, CH_2-C5), 2.79 (1H, tq, *J* = 9.5, 7.3 Hz, CH-C2), 2.40 (1H, ddd, *J* = 12.6, 9.5, 2.9 Hz, CH_2-C3), 1.94 (1H, dt, *J* = 12.6, 9.0 Hz, CH_2-C3), 1.26 (3H, d, *J* = 7.3 Hz, CH_3-C6), 0.88 (9H, s, CH_3C-TBS), 0.06 (3H, s, CH_3Si-TBS), 0.06 (3H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6 (CO-C1), 77.8 (CH-C4), 65.2 (CH_2-C5), 34.4 (CH-C2), 32.4 (CH_2-C3), 25.9 (CH_3C-TBS), 18.4 (CCH_3-TBS), 16.6 (CH_3-C6), –5.3 (CH_3Si-TBS); HRMS (CI, isobutane) $C_{12}H_{25}O_3Si$ ($[M+H]^+$) calcd. 245.1573, found 245.1564; LRMS (CI, isobutane) *m/z* (intensity) 245.3 (100) 73.1 (20).

(4*R*,6*S*,*E*)-Ethyl-7-((tert-butyldimethylsilyl)oxy)-6-hydroxy-4-methylhept-2-enoate (364).

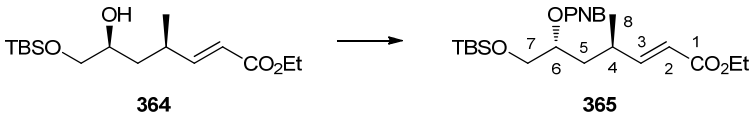


363 **364**

The lactone **363** (8.7 g, 40 mmol) was dissolved in CH_2Cl_2 (100 mL) and the solution was treated slowly with DIBAL (44 mL of a 1.0 M solution in CH_2Cl_2, 44 mmol) at –78 ºC for 2 h. The reaction was quenched by MeOH (5 mL) at –78 ºC and then the mixture was poured into a saturated aqueous solution of sodium potassium tartrate (500 mL). The mixture was stirred for 4 h until two clear layers separated. The aqueous phase was extracted with Et_2O (2 × 500 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated in *vacuo* to give the crude semi acetal as colourless oil which could be used without purification. To a solution of

crude product which was prepared from last step in toluene (100 mL) was added (carbethoxymethylene)triphenylphosphorane (17 g, 48 mmol) at rt. And the reaction mixture was heated to 80 ºC for 18 h. The solvent was removed under reduced pressure and the residuewas purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 50:1 to 20:1) to afford the olefin **364** (10.4 g, 84%) as colourless oil. R_f = 0.75 (petroleum ether–ethyl acetate, 4:1); $[\alpha]_D^{27}$ –30.6 (*c* = 0.85, $CHCl_3$); ν_{max} ($CHCl_3$) 2956, 2929, 2856, 1718, 1653, 1464, 1301, 1251, 1103, 1035, 833, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.82 (1H, dd, *J* = 15.6, 8.6 Hz, CH-C3), 5.85 (1H, d, *J* = 15.6 Hz, CH-C2), 4.18 (2H, q, *J* = 7.1 Hz, CH_2-Et), 3.65–3.59 (2H, m, CH_2-C7), 3.35 (1H, dd, *J* = 7.4, 9.7 Hz, CH-C6), 2.70–2.59 (1H, m, CH-C4), 2.37 (1H, d, *J* = 2.8 Hz, OH), 1.49 (1H, ddd, *J* = 14.0, 9.7, 4.5 Hz, CH_2-C5), 1.34 (1H, ddd, J = 14.0, 9.7, 2.5 Hz, CH_2-C5) 1.29 (3H, t, *J* = 7.1 Hz, CH_3-Et), 1.09 (3H, d, *J* = 6.8 Hz, CH_3-C8), 0.90 (9H, s, CH_3C-TBS), 0.06 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (CO-C1), 153.6 (CH-C3), 120.7 (CH-C2), 69.7 (CH-C6), 67.6 (CH_2-C7), 60.4 (CH_2-Et), 39.3 (CH_2-C5), 33.3 (CH-C4), 26.0 (CH_3C-TBS), 20.7 (CH_3-Et), 18.5 (CCH_3-TBS), 14.4 (CH_3-C8), –5.2 (CH_3Si-TBS); HRMS (ESI) for $C_{16}H_{32}NaO_4Si$ ($[M+Na]^+$) calcd. 339.1968, found 339.1962.

(2*R*,4*R*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]-7-ethoxy-4-methyl-7-oxohept-5-en-2-yl 4-nitrobenzoate (365).

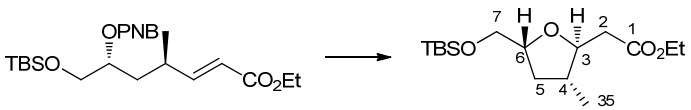


364 **365**

To a solution of alcohol **364** (10 g, 34 mmol) in THF (150 mL) was added Ph_3P (11 g, 41 mmol) and 4-nitrobenzonic acid (6.9 g, 41 mmol) at –10 ºC. DIAD (8.0 mL, 41 mmol) was added over 20 min. The mixture was stirred for 2 h and then the mixture was poured into a saturated aqueous solution of $NaHCO_3$ (150 mL). The aqueous phase was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were

dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ether, 25:1) to give the ester **365** (13.5 g, 87%) as yellow oil. R_f = 0.51 (petroleum ether–ethyl acetate, 9:1); $[\alpha]_D^{24}$ –27.3 (*c* = 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 2955, 2929, 2855, 1716, 1527, 1269, 1101, 1043, 833, 815, 775, 717, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (2H, d, *J* = 9.0 Hz, Ph-PNB), 8.18 (2H, d, *J* = 9.0 Hz, Ph-PNB), 6.87 (1H, dd, *J* = 15.7, 8.1, Hz, CH-C3), 5.75 (1H, dd, *J* = 15.7, 1.0 Hz, CH-C2), 5.25 (1H, td, *J* = 9.0, 4.9 Hz, CH-C6), 4.06 (2H, qd, *J* = 7.1, 1.0 Hz, CH_2-Et), 3.75 (2H, d, *J* = 4.9 Hz, CH_2-C7), 2.45 (1H, m, CH-C4), 1.91 (1H, ddd, *J* = 14.4, 9.2, 7.1 Hz, CH_2-C5), 1.77 (1H, ddd, *J* = 14.4, 7.1, 4.0 Hz, CH_2-C5), 1.21 (3H, t, *J* = 7.1 Hz, CH_3-Et), 1.12 (3H, d, *J* = 6.7 Hz, CH_3-C8), 0.85 (9H, s, CH_3C-TBS), 0.01 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6 (CO-C1), 164.3 (CO-PNB), 153.4 (CH-C3), 150.7 (Ph-PNB), 135.8 (Ph-PNB), 130.9 (Ph-PNB), 123.6 (Ph-PNB), 120.0 (CH-C2), 74.6 (CH-C6), 64.4 (CH_2-C7), 60.4 (CH_2-Et), 36.9 (CH-C4), 33.9 (CH_2-C5), 25.9 (CH_3C-TBS), 19.9 (CH_3-C8), 18.3 (CCH_3-TBS), 14.3 (CH_3-Et), −5.3 (CH_3Si-TBS); HRMS (ESI) $C_{23}H_{35}NaO_7Si$ ($[M+Na]^+$) calcd. 488.2080, found 488.2075.

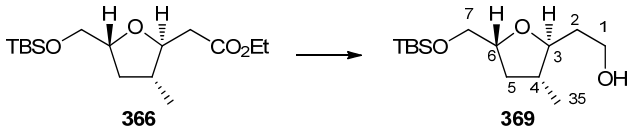
Ethyl-2-[(2*S*,3*R*,5*R*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-methyltetrahydro furan-2-yl]acetate (366).



The ester **365** (13 g, 0.030 mol) was dissolved in ethanol (100 mL) and K_2CO_3 (12 g, 0.090 mol) was added at rt. The reaction mixture was then heated to 55 ºC for 30 min. The solid was removed by filtration and the filtrate was then concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ether, 500:15) to give the *trans*-tetrahydrofuran **366** (7.9 g, 89%) as colourless

oil. $[\alpha]_D^{24}$ –13.8 (*c* = 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 2956, 2929, 2858, 1735, 1458, 1251, 1103, 1041, 833, 775, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.14 (2H, q, *J* = 7.1 Hz, CH_2-Et), 4.05 (1H, ddt, *J* = 9.1, 6.4, 4.7 Hz, CH-C6), 3.83 (1H, m, CH-C3), 3.61 (2H, ddd, *J* = 14.6, 10.6, 4.8 Hz, CH_2-C7), 2.48 (2H, qd, *J* = 14.7, 6.1 Hz, CH_2-C2), 2.13 (1H, m, CH-C4), 1.93 (1H, m, CH_2-C5), 1.46 (1H, m, CH_2-C5), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-Et), 1.03 (3H, d, *J* = 6.5 Hz, CH_3-C35), 0.89 (9H, s, CH_3C-TBS), 0.05 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (CO-C1), 81.9 (CH-C3), 78.8 (CH-C6), 66.1 (CH_2-C7), 60.6 (CH_2-Et), 40.1 (CH_2-C2), 39.7 (CH-C4), 37.2 (CH_2-C5), 26.1 (CH_3C-TBS), 18.5 (CCH_3-TBS), 16.5 (CH_3-Et), 14.4 (CH_3-C35), –5.2 (CH_3Si-TBS); HRMS (ESI) for $C_{16}H_{32}NaO_4Si$ ($[M+Na]^+$) calcd. 339.1968, found 339.1962.

2-[(2*S*,3*R*,5*R*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-methyltetrahydrofuran-2-yl]ethanol (369).

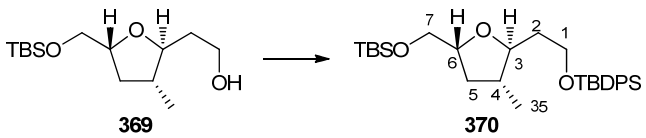


366 369

$LiAlH_4$ (0.95 g, 25 mmol) was added slowly into Et_2O (120 mL) at 0 ºC. The ester (7.0 g, 23 mmol) in THF (25 mL) was then added dropwise into the resulting suspension at 0 ºC and the mixture was allowed to warm to rt for 2 h. Water (1 mL) was added at 0 ºC, followed by addition of 1M NaOH solution (1.0 mL) and stirred at 0 ºC for 15 min. The reaction mixture was warmed to rt and water (3 mL) was added and the mixture was stirred for another 15 min. Solid $MgSO_4$ was then added, and the solid was removed by filtration. The solvent was evaporated under reduced pressure to give the title alcohol as yellow oil (5.6 g, 95%) without any further purification. R_f = 0.15 (petroleum ether–ether, 4:1); $[\alpha]_D^{23}$ –2.9 (*c* = 0.99, $CHCl_3$); ν_{max} ($CHCl_3$) 2955, 2928, 2856, 1462, 1251, 1103, 1049, 939, 833, 773, 669 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 4.08 (1H, ddt, J = 9.1, 6.6, 4.7 Hz, CH-C6), 3.83−3.74 (2H, m, CH_2-C1), 3.62 (2H, d, J = 4.7 Hz, CH_2-C7), 3.57 (1H, td, J = 9.1, 2.8 Hz, CH-C3), 2.82 (1H, dd, J = 7.0, 4.0 Hz, OH), 2.10 (1H, m, CH-C4), 1.95−1.82 (2H, m, CH_2-C2), 1.65 (1H, dddd, J = 14.0, 9.1, 8.0, 4.7 Hz, CH_2-C5), 1.41 (1H, ddd, J = 12.2, 10.9, 9.1 Hz, CH_2-C5), 1.02 (3H, d, J = 6.5 Hz, CH_3-C35), 0.91 (9H, s, CH_3C-TBS), 0.07 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.0 (CH-C3), 79.1 (CH-C6), 66.2 (CH_2-C7), 62.0 (CH_2-C1), 40.3 (CH_2-C5), 36.7 (CH-C4), 35.4 (CH_2-C2), 26.0 (CH_3C-TBS), 18.4 (CCH_3-TBS), 16.1 (CH_3-C35), –5.2 (CH_3Si-TBS); HRMS (ESI) for $C_{14}H_{30}NaO_3Si$ ($[M+Na]^+$) calcd. 297.1862, found 297.1852.

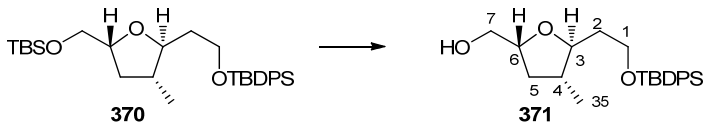
tert-Butyl{2-[(2S,3R,5R)-5-{[(tert-butyldimethylsilyl)oxy]methyl}-3-methyltetrahydrofuran-2-yl]ethoxy}diphenylsilane (370).



To a solution of the alcohol **369** (6.3 g, 24 mmol) in CH_2Cl_2 (150 mL) was added TBDPSCl (7.6 mL, 29 mmol), imidazole (3.9 g, 58 mmol) and DMAP (0.3 g, 2.4 mmol) at rt and the mixture was stirred for 2 h. The reaction was then quenched by $NaHCO_3$ (150 mL). The aqueous phase was extracted with Et_2O (2 × 150 mL), dried ($MgSO_4$) and concentrated in *vacuo*. Purified by flash column chromatography on silica gel (petroleum ether–ether, 100:1) afforded the TBDPS ether **370** (12 g, 100%) as colourless oil. R_f = 0.55 (petroleum ether–ether, 4:1); $[\alpha]_D^{27}$ −12.8 (c = 1.02, $CHCl_3$); ν_{max} (liquid film) 2955, 2929, 2885, 2857, 1472, 1428, 1252, 1107, 834, 776, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.65 (4H, m, Ph-TBDPS), 7.44−7.34 (6H, m, Ph-TBDPS), 3.98 (1H, ddt, J = 9.0, 6.3, 5.0 Hz, CH-C6), 3.87−3.75 (2H, m, CH_2-C1), 3.62 (1H, dd, J = 10.5, 5.0 Hz, CH_2-C7), 3.55 (1H, dd, J = 10.5, 5.0 Hz, CH_2-C7), 3.53 (1H, dd, J = 8.7, 3.2 Hz, CH-C3), 2.10 (1H, dt, J = 12.2, 6.7 Hz, CH_2-C5), 1.90−1.78 (2H, m, CH-C4, CH-C2), 1.72−1.62 (1H, m, CH-C2), 1.36 (1H,

ddd, J = 12.2, 10.8, 8.9 Hz, CH_2-C5), 1.04 (9H, s, CH_3C-TBDPS), 1.00 (3H, d, J = 6.5 Hz, CH_3-C35), 0.88 (9H, s, CH_3C-TBS), 0.04 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (Ph-TBDPS), 134.3 (Ph-TBDPS), 134.2 (Ph-TBDPS), 129.6 (Ph-TPDPS), 127.7 (Ph-TBDPS), 82.3 (CH-C3), 78.5 (CH-C6), 66.4 (CH_2-C7), 61.6 (CH_2-C1), 40.0 (CH-C4), 37.7 (CH_2-C5), 37.3 (CH_2-C2), 27.0 (CH_3C-TBDPS), 26.1 (CH_3C-TBS), 19.3 (CCH_3-TBDPS), 18.5 (CCH_3-TBS), 16.5 (CH_3-C35), −5.0 (CH_3Si-TBS), −5.1 (CH_3Si-TBS).

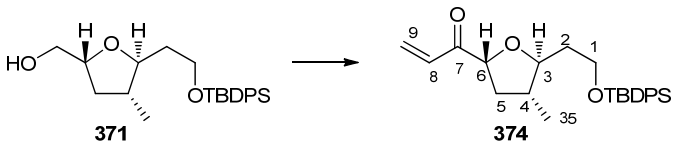
[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]methanol (371).



The crude bis-silyl ether was dissolved in a mixture of CH_2Cl_2 (30 mL) and MeOH (30 mL) and cooled to −10 °C. Solid CSA (0.16 g, 0.68 mmol) was added and the resulting mixture was stirred for 3 h. The reaction was quenched by the addition of Et_3N (0.20 mL, 1.4 mmol) and warmed to rt. The volatiles were removed in vacuo and the residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 9:1 to 3:1) to provide the alcohol **371** (2.7 g, 71%) as colourless oil. R_f = 0.22 (petroleum ether–ethyl acetate, 6:1); $[\alpha]_D^{27}$ −17.4 (c = 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3435, 2956, 2929, 2857, 1473, 1427, 1111, 1083, 822, 736, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77−7.73 (4H, m, Ph-TBDPS), 7.40−7.32 (6H, m, Ph-TBDPS), 4.03 (1H, dtd, J = 9.4, 6.3, 3.2 Hz, CH-C6), 3.87−3.80 (2H, m, CH_2-C1), 3.66−3.50 (2H, m, CH-C3, CH_2-C7), 3.48−3.42 (1H, m, CH_2-C7), 2.08 (1H, dt, J = 12.1, 6.2 Hz, CH_2-C5), 1.98–1.81 (3H, m, CH_2-C2, CH-C4), 1.35 (1H, ddd, J = 12.1, 10.7, 9.4 Hz, CH_2-C5), 1.07 (9H, s, CH_3C-TBDPS), 1.02 (3H, d, J = 6.5 Hz, CH_3-C35); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9 (Ph-TBDPS), 134.3 (Ph-TBDPS), 134.3 (Ph-TBDPS), 129.9 (Ph-TBDPS), 128.0 (Ph-TBDPS), 82.3 (CH-C3), 78.6 (CH-C6), 65.6 (CH_2-C7),

61.5 (CH_2-C1), 40.4 (CH-C4), 37.4 (CH_2-C2), 36.9 (CH_2-C5), 27.2 (CH_3C-TBDPS), 19.6 (CCH_3-TBDPS), 16.7 (CH_3-C35); HRMS (ESI) $C_{24}H_{34}NaO_3Si$ ($[M+Na]^+$) calcd. 421.2175, found 421.2169.

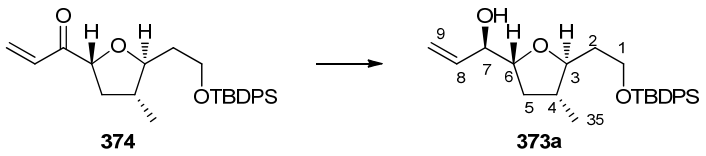
1-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]prop-2-en-1-one (374).



The alcohol **371** (5.5 g, 15 mmol) was dissolved in CH_2Cl_2 (75 mL) and treated with Dess-Martin periodinane (9.3 g, 22 mmol) at rt for 2 h and then quenched by $Na_2S_2O_3$ (50 mL) and $NaHCO_3$ (50 mL). Extracted with ethyl acetate (2 × 100 mL) dried ($MgSO_4$) and concentrated in *vacuo* to obtain crude aldehyde as yellow oil. A solution of aldehyde in ether (50 mL) was added slowly with vinyl magnesium bromide (1N in THF, 22 ml, 22 mmol) at 0 ºC. After addition, the reaction mixture was allowed to warm to rt for another 2 h. NH_4Cl (100 mL)was added and extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo* to give crude allylic alcohol as orange oil. The alcohol was dissolved into CH_2Cl_2 (75 mL). The resulting solution was treated with dess-martin periodinane (7.5 g, 18 mmol) at rt for 1 h and then quenched by $Na_2S_2O_3$ (50 mL) and $NaHCO_3$ (50 mL). The aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. Purified by flash column chromatography on silica gel (petroleum ether–ethyl acetate, 25:1) delivered the enone **374** (3.0 g, 52% over 3 steps) as colourless oil. R_f = 0.18 (petroleum ether–ethyl acetate, 25:1); $[\alpha]_D^{26}$ +25.1 (c = 1.50, $CHCl_3$); ν_{max} (neat) 3071, 2957, 2932, 2862, 1697, 1612, 1466, 1427, 1427, 1396, 1103, 702, 609 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (4H, m, Ph-TBDPS), 7.45–7.35 (6H, m, Ph-TBDPS), 6.74 (1H, dd, J = 17.5, 10.6 Hz, CH-C8), 6.38 (1H, dd, J = 17.5, 1.7 Hz,

CH_2-C9), 5.76 (1H, dd, J = 10.6, 1.7 Hz, CH_2-C9), 4.50 (1H, dd, J = 8.8, 7.7 Hz, CH-C6), 3.88–3.83 (2H, m, CH_2-C1), 3.72 (1H, td, J = 8.6, 3.3 Hz, CH-C3), 2.39 (1H, dt, J = 12.5, 7.5 Hz, CH_2-C5), 2.00–1.85 (2H, m, CH-C4, CH_2-C2), 1.70 (1H, ddt, J = 13.9, 8.4, 5.4 Hz, CH_2-C2), 1.59 (1H, ddd, J = 12.5, 10.3, 8.8, Hz, CH_2-C5), 1.05 (9H, s, CH_3C-TBDPS), 1.02 (3H, d, J = 6.6 Hz, CH_3-C35); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3 (C-C7), 135.7 (Ph-TBDPS), 135.7 (Ph-TBDPS), 134.1 (Ph-TBDPS), 134.0 (Ph-TBDPS), 131.6 (CH-C8), 129.7 (Ph-TBDPS), 129.7 (CH_2-C9), 127.8 (Ph-TBDPS), 83.7 (CH-C3), 81.6 (CH-C6), 61.1 (CH_2-C1), 39.7 (CH-C4), 38.3 (CH_2-C5), 36.8 (CH_2-C2), 27.0 (CH_3C-TBDPS), 19.4 (CCH_3-TBDPS), 16.3 (CH_3-C35); HRMS (CI, isobutane) calcd $C_{26}H_{35}O_3Si$ $[M+H]^+$ 423.2355, found 423.2359.

(*R*)-1-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]prop-2-en-1-ol (373a).

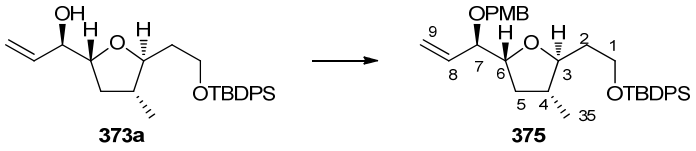


374 **373a**

To a solution of enone (0.26 g, 0.63 mmol) and $CeCl_3.7H_2O$ (0.25 g, 0.68 mmol) in MeOH (63 mL) at −78 °C was added solid $NaBH_4$ (26 mg, 0.68 mmol) in a single portion. The mixture was stirred for 1 h, warmed to rt and concentrated in *vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL), the organic phase isolated and the extracted with further CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated to afford the desired allylic alcohol (0.27 g, 99%, *dr* > 9:1) as a colourless oil. R_f = 0.16 (petroluem ether–ethyl acetate, 20:1); $[\alpha]_D^{24}$ −12.0 (c = 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 3460, 3071, 2958, 2930, 2858, 1697, 1427, 1109, 703, 613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.65 (4H, m, Ph-TBDPS), 7.45–7.36 (6H, m, Ph-TBDPS), 5.76 (1H, ddd, J = 17.2, 10.6, 6.1 Hz, CH-C8), 5.36 (1H, dt, J = 17.2, 1.5 Hz, CH_2-C9), 5.19

(1H, dt, *J* = 10.6, 1.4 Hz, CH_2-C9), 3.93–3.87 (1H, m, CH-C7), 3.84–3.74 (3H, m, CH CH_2-C1,CH-C6), 3.59 (1H, td, *J* = 8.9,2.9 Hz, CH-C3), 2.48 (1H, d, *J* = 3.0 Hz, OH), 2.10–2.02 (1H, m, CH-C5), 1.95–1.82 (2H, m, CH_2-C2 and CH-C4), 1.63 (1H, ddt, *J* = 13.9, 8.9, 5.2 Hz, CH_2-C2), 1.32 (1H, ddd, *J* = 12.2, 10.8, 9.1 Hz, CH-C5), 1.05 (9H, s,CH_3C-TBDPS), 1.01 (3H, d, *J* = 6.5 Hz, CH_3-C35); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7 (CH-C8), 135.7 (Ph-TBDPS), 134.1 (Ph-TBDPS), 134.0 (Ph-TBDPS), 129.7 (Ph-TBDPS), 127.8 (Ph-TBDPS), 117.1 (CH_2-C9), 82.1 (CH-C6), 81.0 (CH-C3), 76.3 (CH-C7), 61.2 (CH_2-C1), 40.4 (CH-C4), 37.5 (CH_2-C5), 37.0 (CH_2-C2), 27.0 (CH_3C-TBDPS), 19.4 (CCH_3-TBDPS), 16.4 (CH_3-C35); HRMS (CI, isobutane) $C_{26}H_{37}O_3Si$ $[M+H]^+$ calcd 425.2512, found 425.2509.

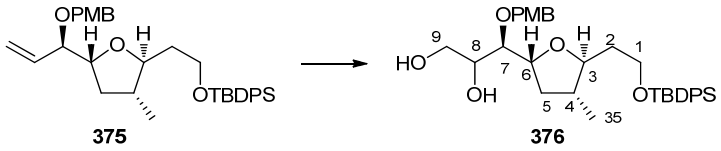
***tert*-Butyl{2-[(2S,3R,5R)-5-{(R)-1-[(4-methoxybenzyl)oxy]allyl}-3-methyltetrahydrofuran-2-yl]ethoxy}diphenylsilane (375).**



To a stirred solution of allylic alcohol (0.10 g, 0.24 mmol) and *p*-methoxybenzyltrichloroacetimidate (99 mg, 0.35 mmol) in CH_2Cl_2 (10 mL) was added $La(OTf)_3$ (7.2 mg, 0.012 mmol) and the mixture stirred for 6 h at rt. The reaction was quenched by the addition of water (5 mL), extracted with CH_2Cl_2 (3 × 5 mL), washed with brine (10 mL) and dried ($MgSO_4$). Concentration afforded a residue that was purified by chromatography on silica gel (petroleum ether–EtOAc, 98:2) to yield desired ether **375** (0.11 g, 82%) as a colourless oil. R_f = 0.35 (petroleum ether–ether, 9:1); $[\alpha]_D^{24}$ −19.4 (*c* = 0.98, $CHCl_3$); ν_{max} (liquid film) 3071, 2956, 2931, 2857, 1612, 1513, 1246, 1108, 1084, 1035, 999, 926, 822, 739, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (4H, m, Ph-TBDPS), 7.43–7.33 (6H, m, Ph-TBDPS), 7.24 (2H, d, *J* = 8.7 Hz, Ph-PMB), 6.81 (2H, d, *J* = 8.7 Hz, Ph-PMB), 5.79–5.69 (1H, m, CH-C8), 5.30–5.24 (2H, m, CH_2-C9), 4.59 (1H, d, *J* = 11.9 Hz, CH_2-PMB), 4.40

(1H, d, J = 11.9 Hz, CH_2-PMB), 4.00 (1H, dt, J = 9.4, 6.3 Hz, CH-C6), 3.89–3.78 (2H, m, CH_2-C1), 3.77 (3H, s, CH_3O-PMB), 3.75–3.70 (1H, m, CH-C7), 3.54 (1H, td, J = 8.6, 3.3 Hz, CH-C3), 1.99 (1H, dt, J = 12.3, 6.7 Hz, CH_2-C5), 1.90–1.78 (2H, m, CH_2-C2, CH-C4), 1.69 (1H, ddt, J = 13.7, 8.3, 5.8 Hz, CH_2-C2), 1.42–1.28 (1H, m, CH_2-C5), 1.04 (9H, s, J = 2.8 Hz, CH_3C-TBDPS), 0.98 (3H, d, J = 6.5 Hz, CH_3-C35); ^{13}C NMR (100s MHz, $CDCl_3$) δ 159.1 (Ph-PMB), 135.7 (Ph-TBDPS), 135.6 (CH-C8), 134.3 (Ph-TBDPS), 134.2 (Ph-PMB), 131.0 (Ph-PMB), 129.6 (Ph-TBDPS), 129.6 (Ph-TBDPS), 129.3 (Ph-PMB), 127.7 (Ph-TBDPS), 118.6 (CH_2-C9), 113.8 (Ph-PMB), 82.5 (CH-C7), 82.3 (CH-C3), 79.9 (CH-C6), 70.2 (CH_2-PMB), 61.6 (CH_2-C1), 55.4 (CH_3-PMB), 39.7 (CH-C4), 37.4 (CH_2-C5), 37.1 (CH_2-C2), 27.0 (CH_3C-TBDPS), 19.4 (CCH_3-TBDPS), 16.4 (CH_3-C35); HRMS (CI+, isobutane) $C_{34}H_{45}O_4Si$ $[M+H]^+$ calcd 545.3087, found 545.3079.

(3R)-3-[(2R,4R,5S)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]-3-[(4-methoxybenzyl)oxy]propane-1,2-diol (376).



A solution of alkene (82 mg, 0.15 mmol) and NMO (19 mg, 0.16 mmol) dissolved in a mixture of THF (2.0 mL) and water (0.2 mL) was treated with OsO_4 (17 μl of a 4% aqueous solution, 3.0 μmol) and the solution was stirred for 18 h at rt. The reaction was quenched by the addition of solid Na_2SO_3 (60 mg) and the mixture was stirred for 30 min. The organic component was extracted with CH_2Cl_2 (3 × 10 mL) and this was washed with brine (15 mL), dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography on silica gel (petroluem ether–EtOAc, 3:1 to EtOAc) to afford the title diol (76 mg, 88%) as a viscous yellow oil. R_f = 0.19 (petroluem ether–ethyl acetate, 4:1); $[\alpha]_D^{23}$ −1.3 (c = 0.96, $CHCl_3$); ν_{max} (liquid film) 3404, 2954, 2931, 2855, 1514, 1247, 1105, 1084, 1035, 823, 701, 614 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.68–7.62 (4H, m, Ph-TBDPS), 7.44–7.32 (6H, m, Ph-TBDPS), 7.23 (2H, d, J = 8.7 Hz, Ph-PMB), 6.85 (2H, d, J = 8.7 Hz, Ph-PMB), 4.63 (1H, d, J = 11.2 Hz, CH_2-PMB), 4.55 (1H, d, J = 11.2 Hz, CH_2-PMB), 4.14 (1H, dt, J = 14.0, 4.4 Hz, CH-C6), 3.81–3.75 (3H, m, CH_2-C1, CH-C8), 3.80 (3H, s, CH_3O-PMB), 3.71–3.64 (3H, m, CH-C3, CH_2-C9), 3.54 (1H, t, J = 5.2 Hz, CH-C7), 3.28 (1H, d, J = 6.3 Hz, OH), 2.32 (1H, dd, J = 6.7, 5.8 Hz, OH), 2.03 (1H, dt, J = 12.2, 6.6 Hz, CH_2-C5), 1.94–1.77 (2H, m, CH_2-C2, CH-C4), 1.67–1.58 (1H, m, CH_2-C2), 1.56–1.48 (1H, m, CH_2-C5), 1.02 (1H, d, J = 6.5 Hz, CH_3-C35), 1.04 (9H, s, CH_3C-TBDPS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7 (Ph-PMB), 135.9 (Ph-TBDPS), 134.30 (Ph-TBDPS), 134.2 (Ph-TBDPS), 130.7 (Ph-PMB), 129.9 (Ph-PMB), 129.90 (Ph-TBDPS), 128.0 (Ph-TBDPS), 114.2 (Ph-PMB), 82.9 (CH-C3), 80.7 (CH-C7), 79.2 (CH-C6), 73.9 (CH_2-PMB), 71.7 (CH-C8), 64.1 (CH_2-C9), 61.5 (CH_2-C1), 55.6 (CH_3O-PMB), 39.9 (CH-C4), 37.4 (CH_2-C2), 37.2 (CH_2-C5), 27.2 (CH_3C-TBDPS), 19.5 (CCH_3-TBDPS), 16.6 (CH_3-C35).

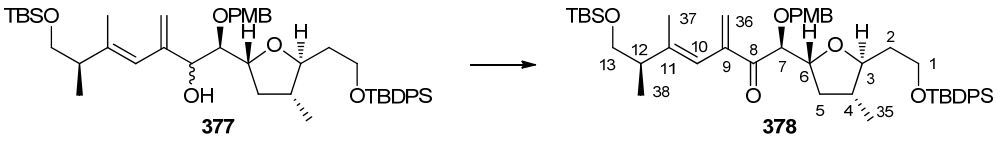
(*S*)-2-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]-2-[(4-methoxybenzyl)oxy]acetaldehyde (354).

Sodium periodate (73 mg, 0.34 mmol) was added to a solution of diol (0.10 g, 0.17 mmol) in a mixture of THF (2.6 mL) and water (0.30 mL) at rt. The mixture was stirred for 30 min at rt and then diluted with water (3 mL). The mixture was extracted with CH_2Cl_2 (4 × 4 mL) and the organic extracts were dried ($MgSO_4$). The mixture was concentrated to afford the crude aldehyde which was used directly in the following step.

(1*R*,2*R*,6*R*,*E*)-7-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]-1-[(4-methoxybenzyl)oxy]-5,6-dimethyl-3-methylenehept-4-en-2-ol (377).

A solution of iodide **325** (0.55 g, 1.4 mmol) in Et_2O (10 mL) was treated with *n*-BuLi (1.1 mL of a 1.6 M solution in hexane, 1.1 mmol) at –78 °C for 30 min. The aldehyde **354** (0.40 g, 0.72 mmol) in Et_2O (3 mL) was then added at –78 °C and warmed to rt for 3 h. A saturated solution of NH_4Cl (20 mL) was added and the mixture was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo* to afford the crude product, which was used for next step directly.

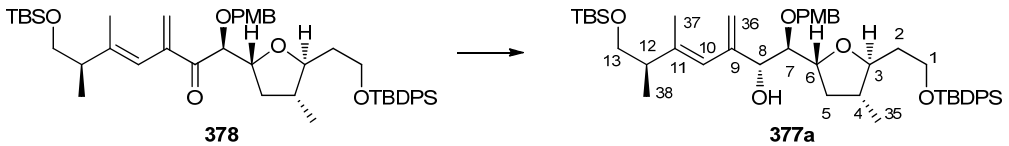
(1S,6R,E)-7-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2R,4R,5S)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]-1-[(4-methoxybenzyl)oxy]-5,6-dimethyl-3-methylenehept-4-en-2-one (378).



To a solution of crude product **377** in CH_2Cl_2 (10 mL) was added Dess-Martin periodiane (0.47 g, 1.1 mmol) at rt and the mixture was stirred for 2 h. The reaction was then quenched by the addition of saturated aqueous solutions of $Na_2S_2O_3$ (10 mL) and $NaHCO_3$ (10 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The

residue was purified by flash column chromatography on silica gel (petroleum ether–ether, 100:3 to 20:1) gave the enone **378** (0.39 g, 51% over 2 steps) as colourless oil. R_f = 0.57 (petroleum ether–ethyl acetate, 4:1); ν_{max} ($CHCl_3$) 2956, 2933, 2856, 1739, 1516, 1249, 1107, 1087, 837, 773, 619 cm^{-1}; $[\alpha]_D^{24}$ –22.6 (c = 0.60, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.64 (4H, m, Ph-TBDPS), 7.42–7.34 (6H, m, Ph-TBDPS), 7.21 (2H, d, J = 8.6 Hz, Ph-PMB), 6.81 (2H, d, J = 8.6 Hz, Ph-PMB), 6.28 (1H, s, CH-C10), 5.94 (1H, s, CH_2-C36), 5.61 (1H, s, CH_2-C36), 4.60 (1H, d, J = 11.5 Hz, CH_2-PMB), 4.39 (1H, d, J = 11.5 Hz, CH_2-PMB), 4.21 (1H, d, J = 5.6 Hz, CH-C7), 4.25 (1H, td, J = 5.6, 9.1 Hz, CH-C6), 3.83–3.74 (2H, m, CH_2-C1), 3.76 (3H, s, CH_3O-PMB), 3.59 (1H, dd, J = 9.8, 6.3 Hz, CH_2-C13), 3.54 (1H, td, J = 8.8, 3.2 Hz, CH-C3), 3.44 (1H, dd, J = 9.8, 7.1 Hz, CH_2-C13), 2.38–2.33 (1H, m, CH-C12), 1.97–1.93 (1H, m, CH-C4), 1.83–1.75 (2H, m, CH_2-C2), 1.66 (3H, d, J = 1.2 Hz, CH_3-C37), 1.67–1.55 (1H, m, CH_2-C5), 1.40 (1H, dd, J = 21.4, 10.8 Hz, CH_2-C5), 1.04 (9H, s, CH_3C-TBDPS), 1.03 (3H, d, J = 7.2 Hz, CH_3-C35), 0.96 (3H, d, J = 6.5 Hz, CH_3-C38), 0.87 (9H, s, CH_3C-TBS), 0.03 (3H, s, CH_3Si-TBS), 0.02 (3H, s, CH_3Si-TBS); HRMS (CI, isobutane) $[M+H]^+$ calcd. for $C_{37}H_{65}O_6Si_2$ 661.4320, found 661.4318; LRMS (CI, isobutane) *m/z* (intensity) 531.5 (10) 181.3 (18) 125.2 (100) 121.2 (10).

(1*R*,2*R*,6*R*,*E*)-7-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]-1-[(4-methoxybenzyl)oxy]-5,6-dimethyl-3-methylenehept-4-en-2-ol (377a).



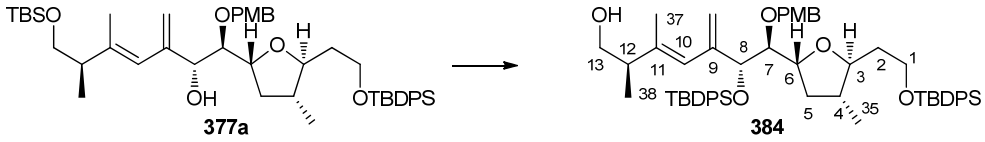
To a solution of the enone (0.27 g, 0.30 mmol) in MeOH (50 mL) was added $CeCl_3 \cdot 7H_2O$ (0.32 g, 0.86 mmol) at –78 °C. The reaction was stirred for 30 min and $NaBH_4$ (23 mg, 0.60 mmol) was added. The resulting suspension was stirred at

–78 °C for 4 h before water (50 mL) was added to quench the reaction. The aqueous phase was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ether, 100:3 to 50:3) to give the alcohol **377a** (0.21 g, 78%) as colourless oil. R_f = 0.45 (petroleum ether–ethyl acetate, 4:1); $[\alpha]_D^{26}$ +9.8 (*c* = 0.73, $CHCl_3$); ν_{max} ($CHCl_3$) 2955, 2929, 2856, 1514, 1471, 1249, 1111, 1089, 837, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.65 (4H, m, Ph-TBDPS), 7.42–7.35 (6H, m, Ph-TBDPS), 7.25 (2H, d, *J* = 8.6 Hz, Ph-PMB), 6.84 (2H, d, *J* = 8.6 Hz, Ph-PMB), 5.53 (1H, s, CH-C10), 5.42 (1H, d, *J* = 1.3 Hz, CH_2-C36), 4.99 (1H, s, CH_2-C36), 4.66 (1H, d, *J* = 11.6 Hz, CH_2-PMB), 4.46 (1H, d, *J* = 11.6 Hz, CH_2-PMB), 4.39 (1H, dd, *J* = 7.2, 3.4 Hz, CH-C8), 4.12 (1H, ddd, *J* = 9.1, 6.2, 2.5 Hz, CH-C6), 4.07 (1H, d, *J* = 7.2 Hz, OH), 3.79 (3H, s, CH_3O-PMB) , 3.80–3.77 (2H, m, CH_2-C1), 3.68 (1H, td, *J* = 8.6, 3.2 Hz, CH-C3), 3.56 (1H, dd, *J* = 9.8, 6.5 Hz, CH_2-C13), 3.42 (1H, dd, *J* = 9.8, 7.0 Hz, CH_2-C13), 3.27–3.25 (1H, m, CH-C7), 2.32–2.28 (1H, m, CH-C12), 1.87–1.76 (4H, m, CH_2-C2 CH-C4, CH_2-C5), 1.70 (3H, d, *J* = 1.3 Hz, CH_3-C37), 1.65–1.61 (1H, m, CH_2-C5), 1.03 (9H, s, CH_3C-TBDPS), 0.99 (3H, d, *J* = 6.5 Hz, CH_3-C35), 0.98 (3H, d, *J* = 6.9 Hz, CH_3-C38), 0.88 (9H, s, CH_3C-TBS), 0.03 (6H, s, CH_3Si-TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7 (Ph-PMB), 145.6 (C-C9), 135.7 (Ph-PMB), 134.1 (C-C11), 134.1 (Ph-TBDPS), 130.5 (Ph-TBDPS), 129.7 (Ph-PMB), 129.7 (Ph-TBDPS), 127.8 (Ph-TBDPS), 127.8 (Ph-TBDPS), 123.1 (CH-C10), 114.1 (Ph-PMB) 113.8 (CH_2-C36), 83.1 (CH-C3), 78.5 (CH-C7), 77.8 (CH-C6), 74.7 (CH-C8), 71.5 (CH_2-PMB), 67.1 (CH_2-C13), 61.4 (CH-C1), 55.4 (CH_3O-PMB), 45.8 (CH-C12), 39.3 (CH-C4), 37.1 (CH_2-C5), 36.9 (CH_2-C2), 27.0 (CH_3C-TBDPS), 26.1 (CH_3C-TBS), 19.3 (CCH_3-TBDPS), 18.4 (CCH_3-TBS), 16.3 (CH_3-C37), 16.0 (CH_3-C38), 15.9 (CH_3-C35), –5.2 (CH_3Si-TBS); HRMS (CI) $[M+Na]^+$ $C_{47}H_{70}NaO_6Si_2$ calcd. 809.4609, found 809.4614.

(5*R*,6*S*,10*R*,*E*)-5-[(2*R*,4*R*,5*S*)-5-{2-[(4-Methoxybenzyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]-2,2,3,3,9,10,13,13,14,14-decamethyl-7-methylene-4,12-dioxa-3,13-disilapentadec-8-en-6-ol (381b).

To a solution of the enone (0.12 g, 0.18 mmol) in MeOH (50 mL) was added $CeCl_3 \cdot 7H_2O$ (0.21 g, 0.55 mmol) at –78 °C. The reaction was stirred for 30 min and $NaBH_4$ (17 mg, 0.46 mmol) was added. The resulting suspension was stirred at –78 °C for 4 h before water (50 mL) was added to quench the reaction. The aqueous phase was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo* to give the crude alcohol (0.46 mg, 38%) as colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 8.6 Hz, Ph-PMB), 6.84 (2H, d, J = 8.6 Hz, Ph-PMB), 5.55 (1H, s, CH-C10), 5.34 (1H, d, J = 1.3 Hz, CH_2-C36), 5.01 (1H, s, CH_2-C36), 4.48–4.39 (2H, m, CH_2-PMB), 4.01 (1H, ddd, J = 9.9, 7.3, 6.2 Hz, CH-C6), 3.89 (1H, d, J = 9.2 Hz, CH-C8), 3.80 (3H, s, CH_3O-PMB), 3.64–3.42 (6H, m, CH_2-C13, CH_2-C1, CH-C3, CH-C7), 3.56 (1H, dd, J = 9.8, 6.5 Hz, CH_2-C13), 2.93 (d, J = 9.2 Hz, OH), 2.36–2.30 (1H, m, CH-C12), 2.12 (1H, dt, J = 12.3, 6.2 Hz, CH_2-C5) 2.01–1.90 (3H, m, CH_2-C2 CH-C4), 1.76 (3H, d, J = 1.3 Hz, CH_3-C37), 1.58–1.51 (1H, m, CH_2-C5), 1.04 (3H, d, J = 6.8 Hz, CH_3-C38), 1.00 (3H, d, J = 6.5 Hz, CH_3-C35), 0.89 (9H, s, CH_3C-TBS), 0.87 (9H, s, CH_3C-TBS), 0.08 (3H, s, CH_3Si-TBS), 0.04 (6H, s, CH_3Si-TBS), 0.00 (3H, s, CH_3Si-TBS). After comparison of ^{1}H NMR with alcohol **371a** and Cater's work,[9b] it was confirmed the major product was **381b** as a mixture of two diastereoisomers (*dr* = 4:1).

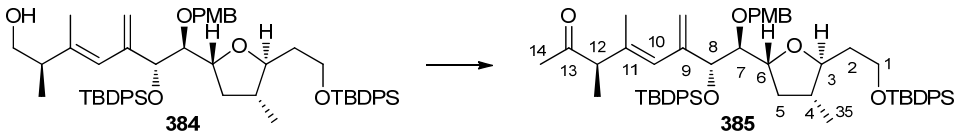
(2*R*,6*R*,7*S*,*E*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-7-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]-7-[(4-methoxybenzyl)oxy]-2,3-dimethyl-5-methylenehept-3-en-1-ol (384).



The alcohol **377a** (70 mg, 0.90 mmol) was dissolved in DMF (10 mL) and TBDPSCl (0.71 mL, 2.7 mmol), imidazole (0.37 g, 5.4 mmol) and DMAP (10 mg) was added at rt and the mixture stirred for 18 h. The reaction was quenched by the addition of brine (20 mL) and the aqueous was extracted with Et_2O (2 × 20 mL) and concentration in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ether, 100:3 to 20:1) to give the crude product, which was contaminated with TBDPSCl. The crude silyl ether was dissolved in MeOH (20 mL) and treated with CSA (60 mg, 0.25 mmol) at –20 °C for 4 h. A saturated aqueous solution of $NaHCO_3$ (20 mL) was added and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ether, 20:1 to 7:1) to give the alcohol **384** (45 mg, 56% over 2 steps). R_f = 0.32 (petroleum ether–ethyl acetate, 4:1); $[\alpha]_D^{28}$ –14.1 (*c* = 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.62 (8H, m, Ph-TBDPS), 7.44–7.32 (12H, m, Ph-TBDPS), 7.22 (2H, d, *J* = 8.6 Hz, Ph-PMB), 6.74 (2H, d, *J* = 8.6 Hz, Ph-PMB), 6.00 (1H, s, CH-C10), 4.98 (1H, s, CH_2-C36), 4.88 (1H, s, CH_2-C36), 4.17 (1H, d, *J* = 3.6 Hz, CH-C8), 4.61 (2H, dd, *J* = 16.5, 5.2 Hz, CH_2-PMB), 3.89 (1H, td, *J* = 9.5, 7.1 Hz, CH-C6), 3.84–3.76 (2H, m, CH_2-C1), 3.75 (3H, s, CH_3O-PMB), 3.41 (2H, d, *J* = 6.8 Hz, CH_2-C13), 3.31 (1H, td, *J* = 8.8, 2.8 Hz, CH-C3), 3.19 (1H, dd, *J* = 7.1, 3.6 Hz, CH-C7), 2.35–2.33 (1H, m, CH-C12), 1.53–1.83 (5H, m, CH-C4, CH_2-C5, CH_2-C2), 1.64 (3H, d, *J* = 1.2 Hz, CH_3-C37), 1.07 (9H, s, CH_3C-TBDPS), 1.05 (9H, s, CH_3C-TBDPS), 0.95 (3H, d, *J* = 6.9 Hz, CH_3-C38), 0.83 (3H, d, *J* = 6.5

Hz, CH_3-C35); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9 (Ph-PMB), 144.2 (C-C9), 139.6 (C-C11), 137.3 (Ph-TBDPS), 135.7 (Ph-TBDPS), 135.0 (Ph-TBDPS), 134.3 (Ph-TBDPS), 134.1 (Ph-TBDPS), 133.8 (Ph-TBDPS), 131.7 (Ph-TBDPS), 129.8 (Ph-TBDPS), 129.7 (Ph-PMB), 129.6 (Ph-PMB), 127.9 (Ph-TBDPS), 127.7 (Ph-TBDPS), 127.6 (Ph-TBDPS), 127.5 (Ph-TBDPS), 125.7 (CH-C10), 116.4 (CH_2-C36), 113.6 (Ph-PMB), 85.4 (CH-C7), 81.3 (CH-C3), 78.6 (CH-C6), 77.8 (CH-C8), 74.2 (CH2-PMB), 65.5 (CH-C13), 61.7 (CH-C1), 55.4 (CH_3O-PMB), 46.1 (CH-C12), 39.9 (CH-C4), 38.1 (CH_2-C2), 37.1 (CH_2-C5), 27.2 (CH_3C-TBDPS), 27.0 (CH_3C-TBDPS), 19.5 (CCH_3-TBDPS), 19.4 (CCH_3-TBDPS), 16.1 (CH_3-C37), 15.39 (CH_3-C38), 15.24 (CH_3-C35); HRMS (ESI) $[M+Na]^+$ calcd. for $C_{57}H_{74}NaO_6Si_2$ 993.4922, found 993.4916.

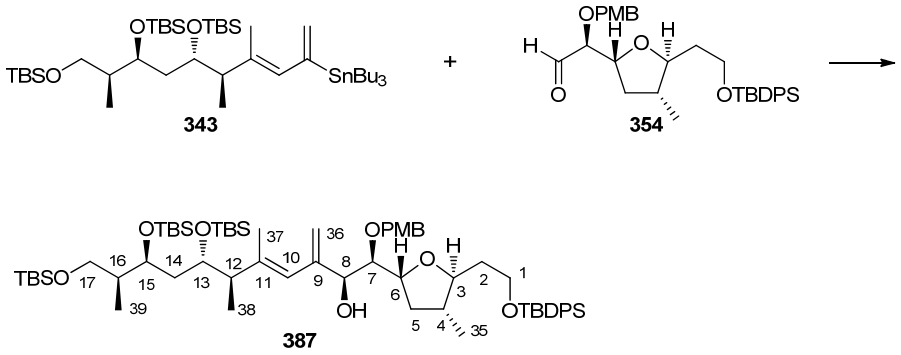
(3*R*,7*R*,8*S*,*E*)-7-[(*tert*-Butyldiphenylsilyl)oxy]-8-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]-8-[(4-methoxybenzyl)oxy]-3,4-dimethyl-6-methyleneoct-4-en-2-one (385).



To a solution of alcohol **384** (50 mg, 0.055 mmol) in CH_2Cl_2 (2 mL) was added Dess-Martin periodiane (35 mg, 0.083 mmol) at rt. The mixture was stirred for 2 h and then the reaction was quenched by the addition of saturated aqueous solutions of $Na_2S_2O_3$ (5 mL) and $NaHCO_3$ (5 mL). The mixture was extracted with Et_2O (2 × 10 mL) and then concentrated in *vacuo* to afford the crude aldehyde as yellow oil. The crude aldehyde was dissolved in THF (10 mL) and added dropwise to methylmagnesium bromide (0.1 mL of 1 M in THF, 0.1 mmol) at 0 °C. The reaction was stirred at this temperature over 1 h and then quenched by the addition of saturated aqueous solution of NH_4Cl (10 mL). The aqueous phase was extracted with Et_2O (2 × 10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in

vacuo to give the crude alcohol as colourless oil. To a solution of crude alcohol in CH_2Cl_2 (5 mL) was added Dess-Martin periodiane (35 mg, 0.083 mmol) at rt and the mixture was stirred for 2 h. The reaction was quenched by the addition of aqueous solutions of $Na_2S_2O_3$ (5 mL) and $NaHCO_3$ (5 mL). The aqueous phase was extracted with Et_2O (2 × 10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether–ether, 25:1 to 20:1) delivered the methyl ketone **385** (36 mg, 72%). R_f = 0.85 (petroleum ether–ethyl acetate, 4:1); $[\alpha]_D^{27}$ –40.6 (*c* = 0.85, $CHCl_3$); ν_{max} ($CHCl_3$) 2956, 2933, 2856, 1716, 1516, 1248, 1215, 1111, 833, 775, 713 619 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.62 (8H, m, Ph-TBDPS), 7.44–7.32 (12H, m, Ph-TBDPS), 7.23 (2H, d, *J* = 8.6 Hz, Ph-PMB), 6.77 (2H, d, *J* = 8.6 Hz, Ph-PMB), 6.11 (1H, s, CH-C10), 5.02 (1H, s, CH_2-C36), 4.88 (1H, s, CH_2-C36), 4.63–4.57 (2H, m, CH_2-PMB), 4.20 (1H, d, *J* = 3.7 Hz, CH-C8), 3.91 (1H, td, *J* = 9.3, 7.1 Hz, CH-C6), 3.84–3.76 (2H, m, CH_2-C1), 3.76 (3H, s, CH_3O-PMB), 3.35 (1H, td, *J* = 8.9, 2.8 Hz, CH-C3), 3.21 (1H, dd, *J* = 7.1, 3.7 Hz, CH-C7), 3.10 (1H, q, *J* = 6.8 Hz, CH-C12), 1.95 (3H, s, CH_3-C14), 1.83–1.56 (4H, m, CH-C4, CH_2-C5, CH_2-C2), 1.58 (3H, d, *J* = 1.1 Hz, CH_3-C37), 1.08 (3H, d, *J* = 7.0 Hz, CH3-C38), 1.08 (3H, s, CH_3C-TBDPS), 1.05 (3H, s, CH_3C-TBDPS), 0.86 (3H, d, *J* = 6.5 Hz, CH_3-C35), 0.81 (1H, dd, *J* = 21.1, 11.1 Hz, CH_2-C5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0 (CO-C13), 159.0 (Ph-PMB), 144.3 (C-C9), 137.3 (C-C11), 136.3 (Ph-PMB), 135.7 (Ph-TBDPS), 134.3 (Ph-TBDPS), 134.0 (Ph-TBDPS), 133.8 (Ph-TBDPS), 131.8 (Ph-TBDPS), 129.9 (Ph-TBDPS), 129.8 (Ph-TBDPS), 129.7 (Ph-TBDPS), 129.6 (Ph-PMB), 129.4 (Ph-TBDPS), 127.6 (CH-C10), 127.5 (Ph-TBDPS), 117.0 (CH_2-C36), 113.6 (Ph-PMB), 86.0 (CH-C7), 81.3 (CH-C3), 78.3 (CH-C6), 74.7 (CH-C8), 61.7 (CH_2-PMB), 57.8 (CH_2-C2), 55.4 (CH-C12), 40.0 (CH_3O-PMB), 38.1 (CH-C4), 37.1 (CH_2-C5), 29.9 (CH_2-C2), 27.9 (CH_3-C37), 27.2 (CH_3C-TBDPS), 27.0 (CH_3C-TBDPS), 19.5 (CCH_3-TBDPS), 19.4 (CCH_3-TBDPS), 16.1 (CH_3-C35), 15.7 (CH_3-C14), 14.2 (CH_3-C38); HRMS (CI) $[M+Na]^+$ $C_{58}H_{74}NaO_6Si_2$ calcd. 945.4922, found 945.4916.

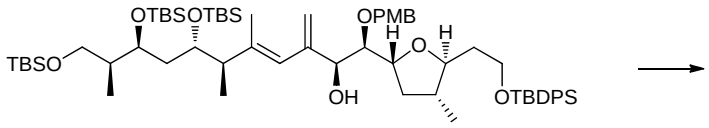
(1*R*,6*R*,7*S*,9*S*,10*S*,*E*)-7,9,11-tris[(*tert*-butyldimethylsilyl)oxy]-1-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]-1-[(4-methoxybenzyl)oxy]-5,6,10-trimethyl-3-methyleneundec-4-en-2-ol (387).



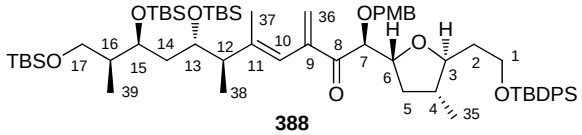
To a solution of the stannane **343** (0.28 g, 0.30 mmol) in THF (7 mL) was added dropwise *t*-BuLi (0.16 mL of a 1.9 M solution in hexane, 0.30 mmol) at –78 °C over 30 min. The 22 mixture was warmed to 0 °C and stirred at this temperature for 4 h to give a pale yellow solution. A solution of the aldehyde **354** (0.10 mg, 0.19 mmol) in THF (3 mL) was then added to the solution of the anion at 0 °C. The mixture was stirred at 0 °C for 1 h and then warmed to rt and stirred for a further period of 3 h before the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (15 mL). The aqueous phase was extracted with ether (2 × 15 mL) and the organic extracts were combined and dried ($MgSO_4$), then concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether–ether, 5:1 to 4:1) to give the alcohol 25 (57 mg, 67% based on the conversion) as colourless oil and unreacted aldehyde **387** was recovered. R_f = 0.20 (petroleum ether–ethyl acetate, 9:1); $[\alpha]_D^{27}$ –9.5 (c = 0.75, $CHCl_3$); ν_{max} ($CHCl_3$) 2955, 2930, 2857, 1613, 1514, 1472, 1462, 1389, 1302, 1249, 1105, 1041, 1006, 939, 835, 773, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68–7.63 (4H, m, Ph-TBDPS), 7.42–7.30 (6H, m, Ph-TBDPS), 7.19 (2H, d, *J* = 8.7 Hz, Ph-PMB), 6.80 (2H, d, *J* = 8.7 Hz, Ph-PMB), 5.75 (1H, brs, CH-C10), 5.43 (1H, brs, CH_2-C36), 5.01 (1H, brs, CH_2-C36), 4.62 (1H, d, *J* = 10.6 Hz, CH_2-PMB), 4.45 (2H, d, *J* = 10.6 Hz, CH_2-PMB), 4.12 (1H, dt, *J* = 6.1, 9.6 Hz,

CH-C6), 4.06–4.01 (1H, m, CH-C8), 3.87–3.74 (4H, m, CH_2-C1, CH-C15, CH-C13), 3.78 (3H, s, CH_3O-PMB), 3.60 (1H, td, *J* = 8.9, 3.0 Hz, CH-C3), 3.55 (1H, dd, *J* = 9.6, 6.6 Hz, CH_2-C17), 3.55 (1H, dd, *J* = 9.6, 7.0 Hz, CH_2-C17), 3.29 (1H, dd, *J* = 6.1, 2.4 Hz, CH-C7), 2.99 (1H, d, *J* = 7.0 Hz, OH), 2.33–2.32 (1H, m, CH-C12), 2.12–2.04 (1H, m, CH_2-C5), 1.86 (3H, d, *J* = 0.8 Hz, CH_3-C37), 1.86–1.79 (1H, m, CH_2-C2), 1.73–1.62 (3H, m, CH_2-C2, CH-C4, CH-C16), 1.54–1.48 (2H, m, CH_2-C14), 1.38–1.28 (1H, m, CH_2-C5), 1.05 (9H, s, CH_3C-TBDPS), 1.00 (3H, d, *J* = 6.5 Hz, CH_3-C38), 0.90 (9H, s, CH_3C-TBS), 0.88 (9H, s, CH_3C-TBS), 0.85 (9H, s, CH_3C-TBS), 0.84 (3H, d, *J* = 6.3 Hz, CH_3-C35), 0.82 (3H, d, *J* = 6.9 Hz, CH_3-C39), 0.10 (3H, s, CH_3Si-TBS), 0.09 (3H, s, CH_3Si-TBS), 0.02 (12H, s, CH_3Si-TBS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3 (Ph-PMB), 145.6 (C-C9), 142.1 (C-C11), 135.7 (Ph-TBDPS), 134.2 (Ph-TBDPS), 131.0, 129.7 (Ph-TBDPS), 129.7 (Ph-PMB) 129.7 (Ph-PMB), 127.8 (Ph-TBDPS), 123.6 (CH-C10), 113.9 (CH_2-C36), 113.8 (Ph-PMB), 82.1 (CH-C3), 81.8 (CH-C7), 80.3 (CH-C6), 74.9 (CH-C8), 74.5 (CH_2-PMB), 72.7 (CH-C15), 70.4 (CH-C13), 65.1 (CH_2-C17), 61.6 (CH_2-C1), 55.4 (CH_3O-PMB), 47.8 (CH-C12), 40.9 (CH-C16), 39.9 (CH-C4), 38.2 (CH_2-C14), 38.0 (CH_2-C5), 37.3 (CH_2-C2), 27.0 (CH_3C-TBDPS), 26.1 (CH_3C-TBS), 26.0 (CH_3C-TBS), 19.4 (CCH_3-TBDPS), 19.2 (CCH_3-TBS), 18.4 (CCH_3-TBS), 18.3 (CH_3-C37), 16.5 (CH_3-C38), 14.4 (CH_3-C39), 10.7 (CH_3-C35), –3.6 (CH_3Si-TBS), –4.0 (CH_3Si-TBS), –4.4 (CH_3Si-TBS), –5.2 (CH_3Si-TBS); HRMS (ESI) $[M+Na]^+$ calcd. for $C_{64}H_{108}O_8Si_4$ 1139.7019, found 1139.7013.

(1*S*,6*R*,7*S*,9*S*,10*S*,*E*)-7,9,11-*tris*-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl)-1-[(4-methoxybenzyl)oxy]-5,6,10-trimethyl-3-methyleneundec-4-en-2-one (388).



387

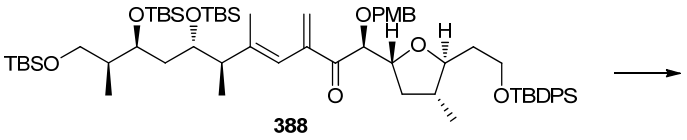


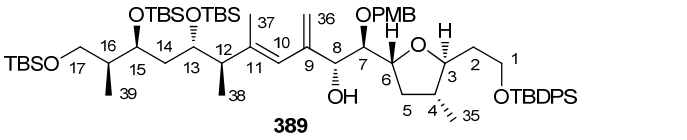
388

To a solution of the alcohol **387** (27 mg, 0.024 mmol) in CH_2Cl_2 (2 mL) was added Dess-Martin periodiane (15 mg, 0.036 mmol) and $NaHCO_3$ (10 mg) at rt. The mixture was stirred for 1.5 h and the solvent was removed in vacuo. Purification of the residual material by flash column chromatography on silica gel (pet. ether/ether, 100:3) afforded the ketone (24 mg, 89%) as colourless oil. R_f = 0.55 (petroleum ether–ethyl acetate, 9:1); $[\alpha]_D^{27}$ –1.3 (c = 1.20, $CHCl_3$); ν_{max} ($CHCl_3$) 2955, 2930, 2857, 1670, 1612, 1514, 1462, 1249, 1093, 1041, 835, 775, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.76–7.74 (4H, m, Ph-TBDPS), 7.42–7.34 (6H, m, Ph-TBDPS), 7.20 (2H, d, *J* = 8.6 Hz, Ph-PMB), 6.81 (2H, d, *J* = 8.6 Hz, Ph-PMB), 6.42 (1H, s, CH_2-C36), 6.02 (1H, s, CH-C10), 5.70 (1H, s, CH_2-C36), 4.60 (1H, d, *J* = 11.5 Hz, CH_2-PMB), 4.39 (2H, d, *J* = 11.5 Hz, CH_2-PMB), 4.26 (1H, dt, *J* = 9.3, 6.0 Hz, CH-C6), 4.18 (1H, d, *J* = 5.7 Hz, CH-C7), 3.87–3.75 (4H, m, CH_2-C1, CH-C15, CH-C13), 3.77 (3H, s, CH_3O-PMB), 3.58–3.55 (1H, m, CH-C3), 3.55 (1H, dd, *J* = 9.5, 6.6 Hz, CH_2-C17), 3.36 (1H, dd, *J* = 9.5, 7.1 Hz, CH-C7), 2.35–2.28 (1H, m, CH-C12), 1.94 (1H, dt, *J* = 12.2, 6.7 Hz, CH-C4), 1.86–1.77 (3H, m, CH_2-C5, CH_2-C2), 1.74 (3H, s, CH_3-C37), 1.70–1.63 (2H, m, CH_2-C2, CH-C16), 1.57–1.44 (2H, m, CH_2-C14), 1.43–1.32 (1H, m, CH_2-C5), 1.07 (3H, d, *J* = 7.0 Hz, CH_3-C38), 1.04 (9H, s, CH_3C-TBDPS), 0.96 (3H, d, *J* = 6.5 Hz, CH_3-C35), 0.90 (9H, s, CH_3C-TBS), 0.89 (9H, s, CH_3C-TBS),

0.84 (9H, s, CH_3C-TBS), 0.82 (3H, d, J = 6.9 Hz, CH_3-C39), 0.09 (3H, s, CH_3Si-TBS), 0.08 (3H, s, CH_3Si-TBS), 0.03 (6H, s, CH_3Si-TBS), 0.02 (3H, s, CH_3Si-TBS), 0.01 (3H, s, CH_3Si-TBS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.9 (C-C8), 159.3 (Ph-PMB), 143.6 (C-C9), 143.5 (C-C11), 135.7 (Ph-TBDPS), 134.2 (Ph-TBDPS), 130.0 (Ph-PMB), 129.6 (Ph-TBDPS), 128.1 (CH_2-C36), 127.7 (Ph-TBDPS), 122.0 (CH-C10), 113.8 (Ph-PMB), 85.5 (CH-C7), 82.4 (CH-C3), 78.7 (CH-C6), 72.9 (CH-C15), 72.1 (CH_2-PMB), 69.9 (CH-C13), 65.2 (CH_2-C17), 61.5 (CH_2-C1), 55.4 (CH_3O-PMB), 47.9 (CH-C12), 40.5 (CH-C16), 39.7 (CH-C4), 38.6 (CH_2-C14), 37.2 (CH_2-C5), 37.0 (CH_2-C2), 27.0 (CH_3C-TBDPS), 26.1 (CH_3C-TBS), 19.4 (CH_3C-TBS), 18.5 (CH_3C-TBS), 18.2 (CH_3C-TBS), 17.8 (CH_3-C37), 16.2 (CH_3-C38), 14.7 (CH_3-C39), 10.5 (CH_3-C35), –3.6 (CH_3Si-TBS), –4.0 (CH_3Si-TBS), –4.5 (CH_3Si-TBS), –5.2 (CH_3Si-TBS); HRMS (ESI+) $[M+Na]^+$ calcd. for $C_{64}H_{106}O_8Si_4$ 1137.6862, found 1137.6788.

(1*R*,2*R*,6*R*,7*S*,9*S*,10*S*,*E*)-7,9,11-*tris*-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]-1-[(4-methoxybenzyl)oxy]-5,6,10-trimethyl-3-methyleneundec-4-en-2-ol (389).





The enone (24 mg, 0.022 mmol) was dissolved in methanol (1 mL) and the solution was cooled to –78 °C. Solid $CeCl_3 \cdot 7H_2O$ (40 mg, 0.11 mmol) and $NaBH_4$ (6 mg, 0.18 mmol) were at added to the solution of the enone –78 °C. The mixture was stirred at this temperature for 30 min and then warmed to rt and stirred for an additional period

of 2 h. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel (petroleum ether–ether, 25:1) to give the alcohol **389** (9 mg, 37%) as colourless oil. R_f = 0.22 (petroleum ether–ethyl acetate, 9:1); $[\alpha]_D^{26}$ +2.2 (c = 0.90, $CHCl_3$); ν_{max} ($CHCl_3$) 2953, 2930, 2856, 1508, 1464, 1249, 1107, 1078, 1043, 835, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68–7.64 (4H, m, Ph-TBDPS), 7.43–7.32 (6H, m, Ph-TBDPS), 7.24 (2H, d, *J* = 8.7 Hz, Ph-PMB), 6.83 (2H, d, *J* = 8.7 Hz, Ph-PMB), 5.57 (1H, s, CH-C10), 5.50 (1H, brs, CH_2-C36), 5.02 (1H, brs, CH_2-C36), 4.70 (1H, d, *J* = 11.5 Hz, CH_2-PMB), 4.42 (2H, d, *J* = 11.5 Hz, CH_2-PMB), 4.17 (1H, d, *J* = 7.6 Hz, CH-C8), 4.12–4.06 (1H, m, CH-C6), 3.90–3.65 (5H, m, CH_2-C1, CH-C15, CH-C13, CH-C3), 3.79 (3H, s, CH_3O-PMB), 3.57–3.48 (1H, m, CH_2-C17), 3.34 (1H, dd, *J* = 9.6, 6.7 Hz, CH_2-C17), 3.23–3.20 (1H, m, CH-C7), 2.81 (1H, d, *J* = 5.2 Hz, OH), 2.25–2.20 (1H, m, CH-C12), 1.85–1.75 (1H, m, CH_2-C5), 1.77 (3H, d, *J* = 1.0 Hz, CH_3-C37), 1.68–1.58 (3H, m, CH_2-C2, CH-C4), 1.54–1.46 (3H, m, CH_2-C14, CH-C16), 1.28–1.24 (1H, m, CH_2-C5), 1.03 (9H, s, CH_3C-TBDPS), 0.97 (3H, d, *J* = 6.3 Hz, CH_3-C38), 0.89 (18H, s, CH_3C-TBS), 0.85 (9H, s, CH_3C-TBS), 0.83 (3H, d, *J* = 7.0 Hz, CH_3-C35), 0.81 (3H, d, *J* = 6.9 Hz, CH_3-C39), 0.09 (3H, s, CH_3Si-TBS), 0.07 (3H, s, CH_3Si-TBS), 0.04 (3H, s, CH_3Si-TBS), 0.03 (3H, s, CH_3Si-TBS), 0.00 (6H, s, CH_3Si-TBS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3 (Ph-PMB), 145.1 (C-C9), 142.1 (C-C11), 135.7 (Ph-TBDPS), 134.2 (Ph-TBDPS), 130.5 (Ph-TBDPS), 129.7 (Ph-TBDPS), 129.7 (Ph-PMB), 127.8 (Ph-TBDPS), 124.6 (CH-C10), 113.9 (CH_2-C36), 113.8 (Ph-PMB), 100.1 (CH-C7), 83.2 (CH-C3), 77.6 (CH-C6), 74.3 (CH-C8), 73.1 (CH_2-PMB), 71.3 (CH-C15), 69.1 (CH-C13), 65.3 (CH_2-C17), 61.4 (CH_2-C1), 55.4 (CH_3O-PMB), 47.8 (CH-C12), 47.5 (CH-C12), 40.2 (CH-C16), 39.2 (CH-C4), 37.1 (CH_2-C14), 36.9 (CH_2-C5), 29.9 (CH_2-C2), 27.0 (CH_3C-TBDPS), 26.1 (CH_3C-TBS), 26.0 (CH_3C-TBS), 19.3 (CCH_3-TBDPS), 18.4 (CCH_3-TBS), 18.4 (CH_3-C37), 18.2 (CCH_3-TBS), 17.3 (CH_3-C38), 16.3 (CH_3-C39), 10.2 (CH_3-C35), –3.6 (CH_3Si-TBS), –3.9 (CH_3Si-TBS), –4.6 (CH_3Si-TBS), –5.2 (CH_3Si-TBS); HRMS (ESI) $[M+Na]^+$ calcd. for $C_{64}H_{108}O_8Si_4$ 1139.7019, found 1139.7013.

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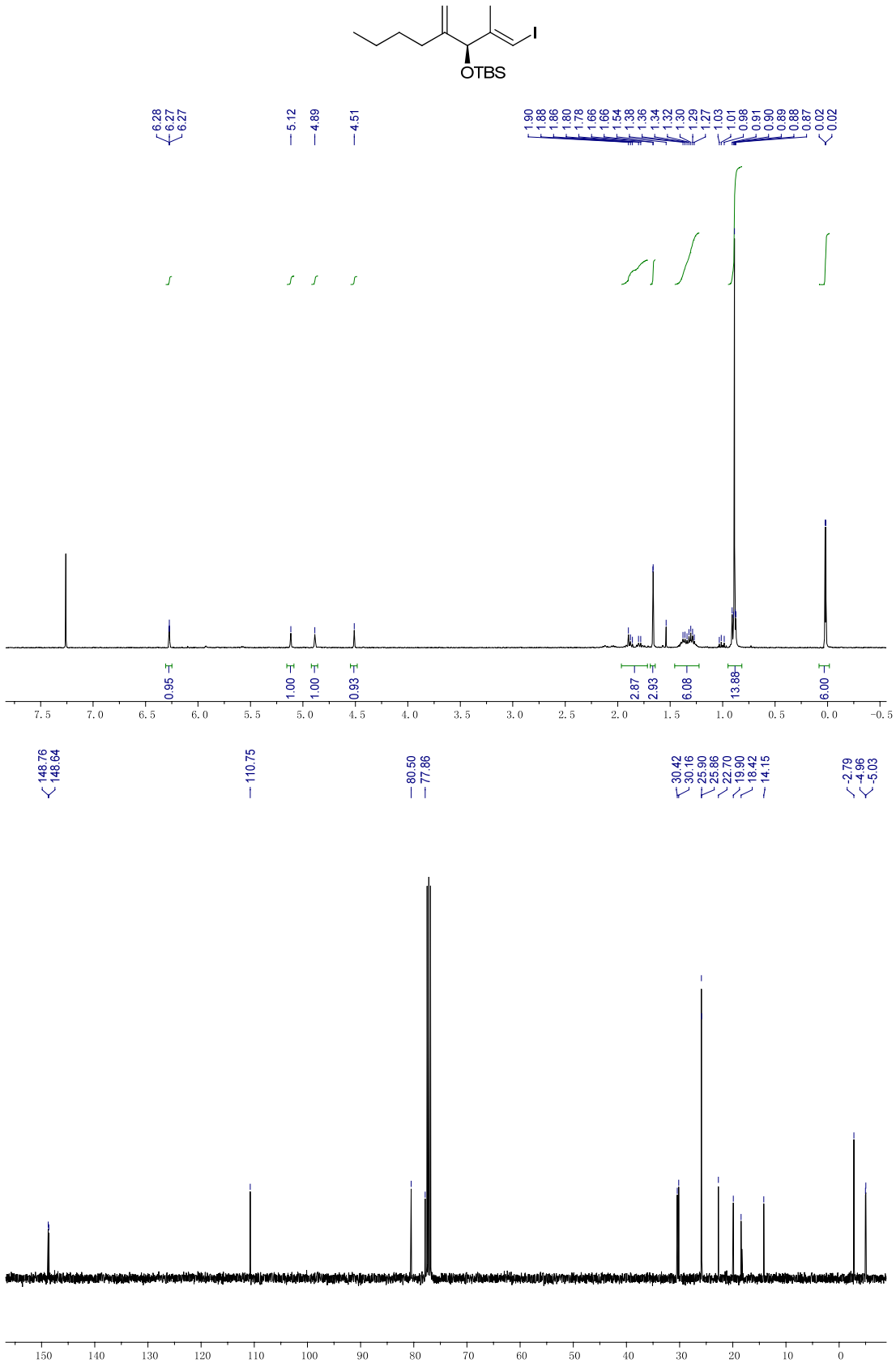
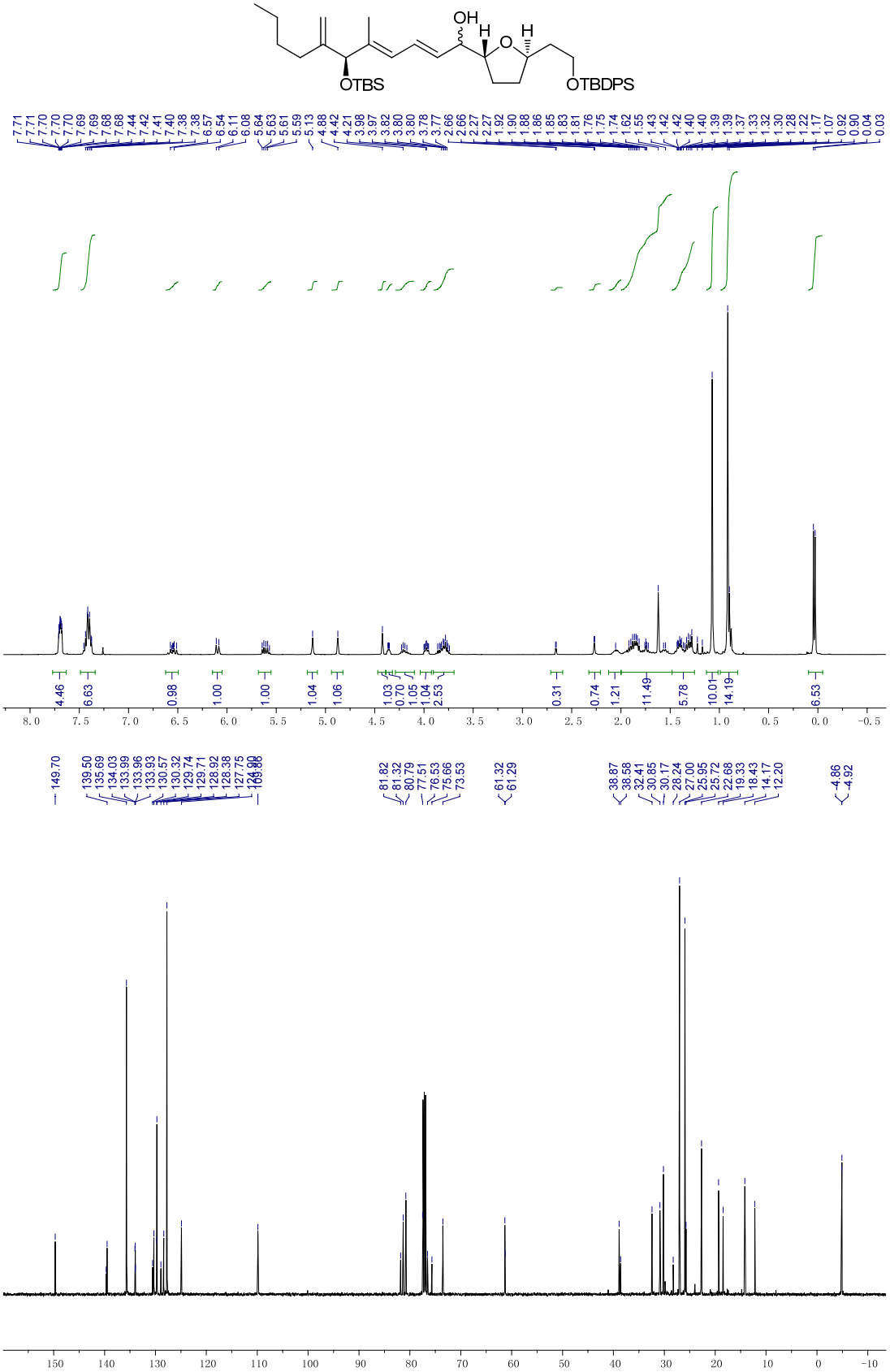
Appendices

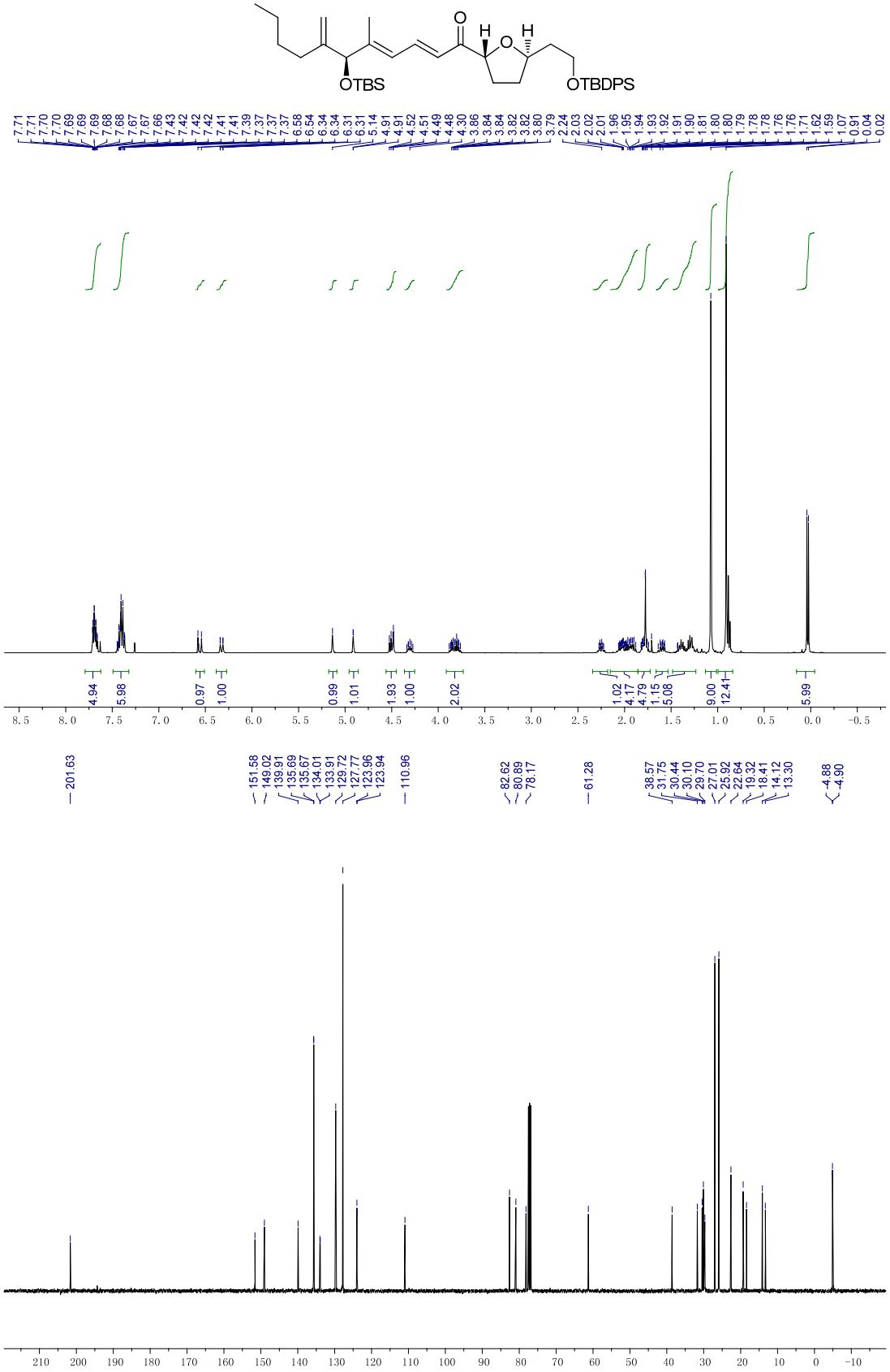
Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **218**



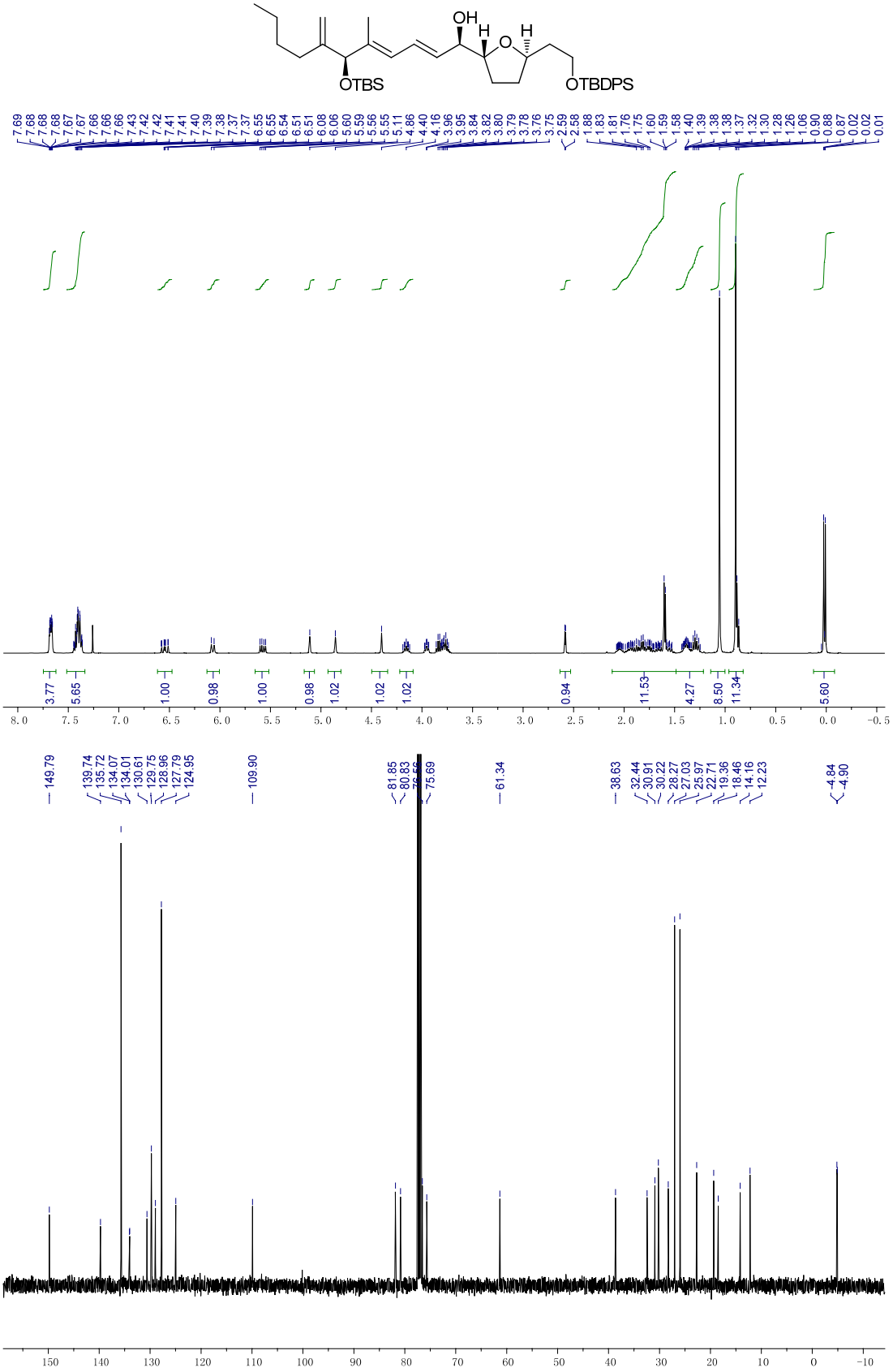
Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **241**



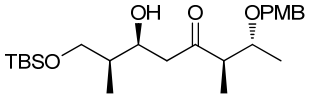
Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **240**

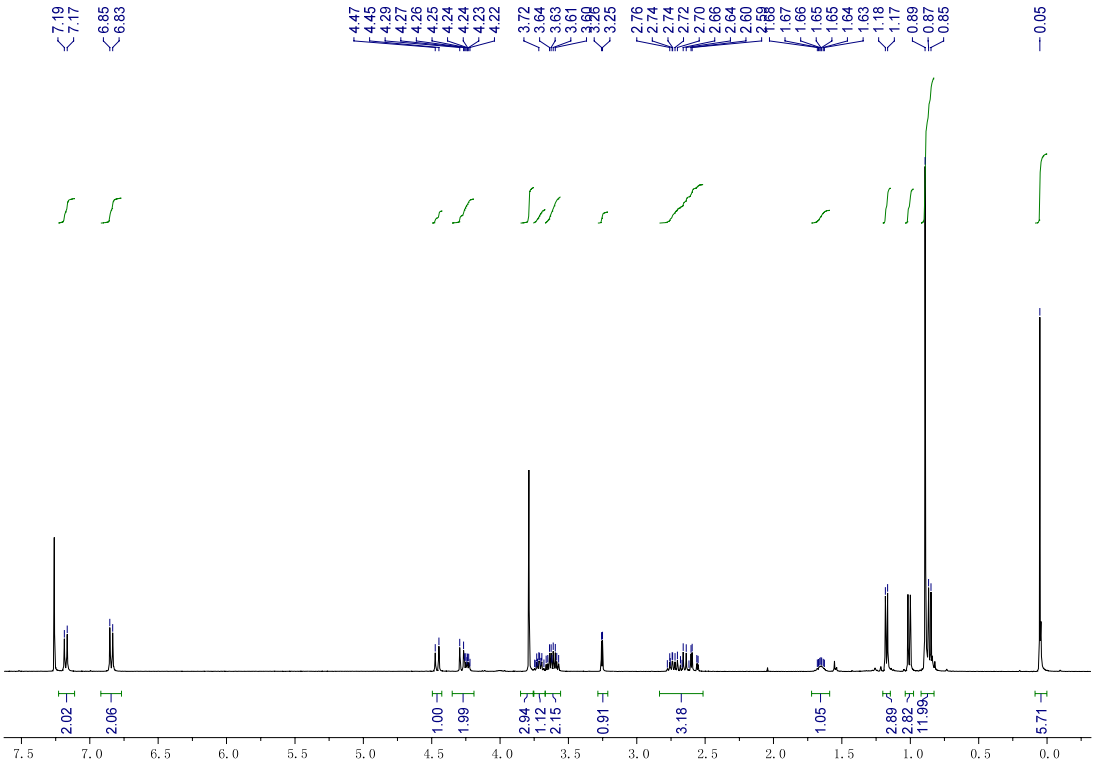


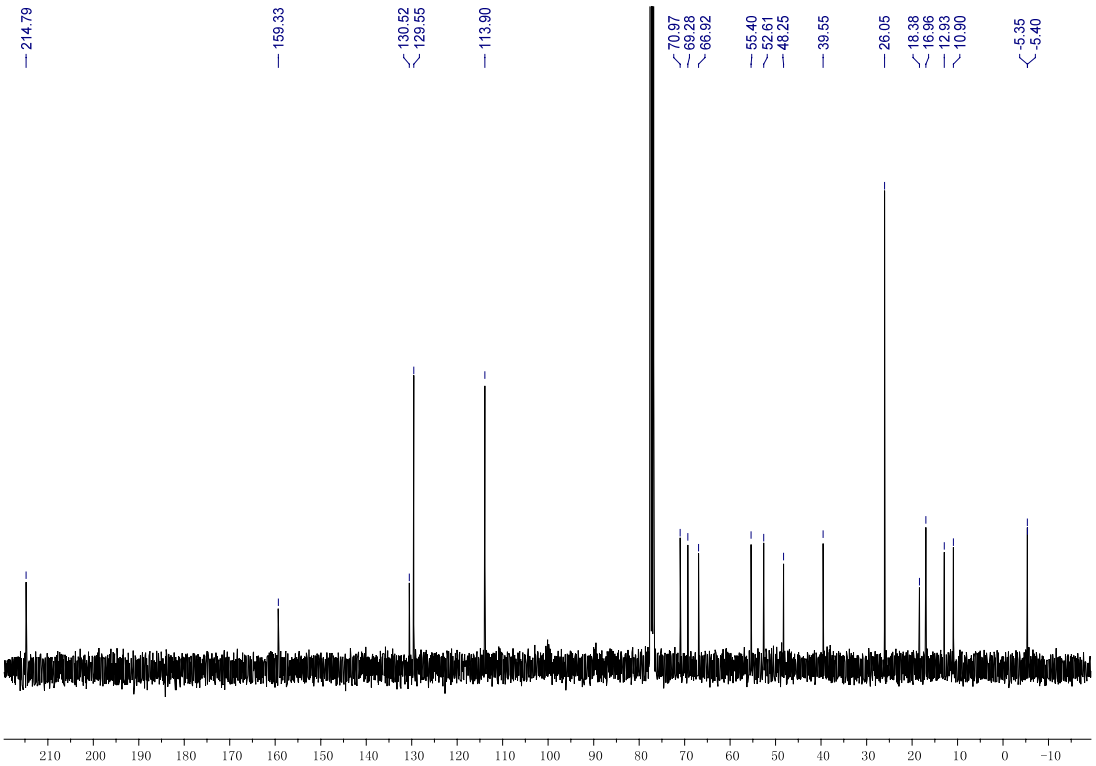
Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **241a**



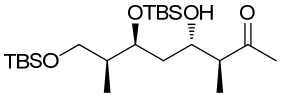
Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **259**

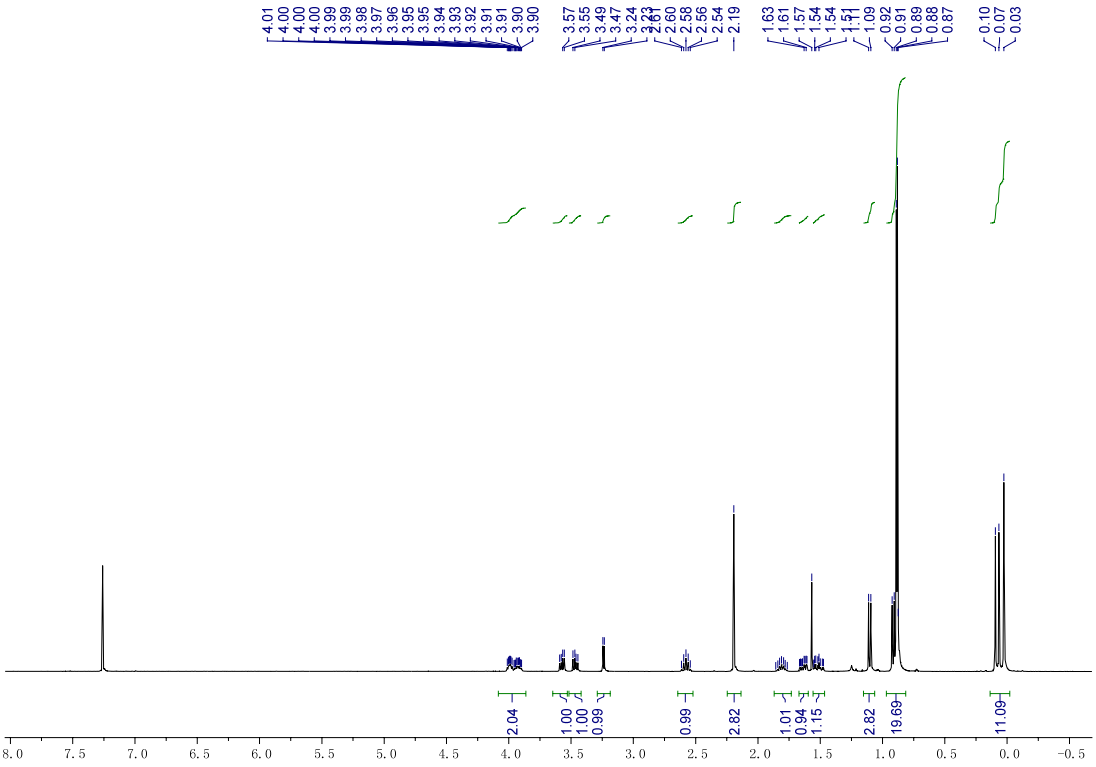


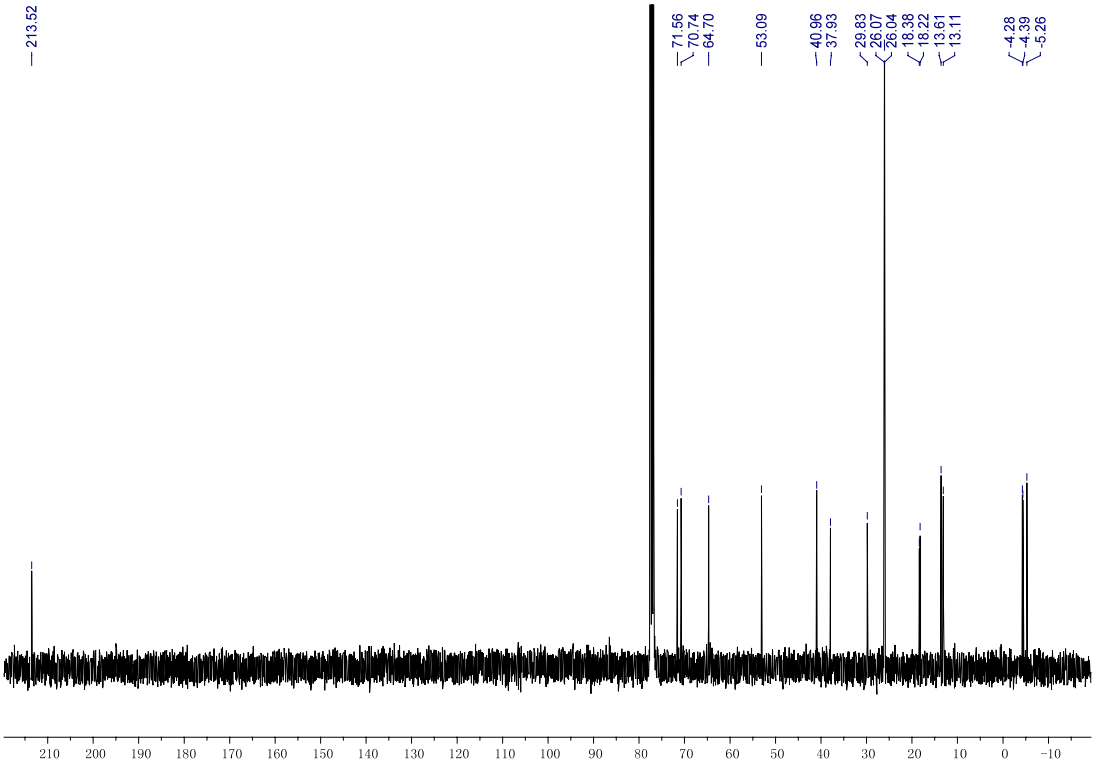




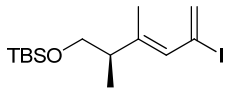
Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **269**

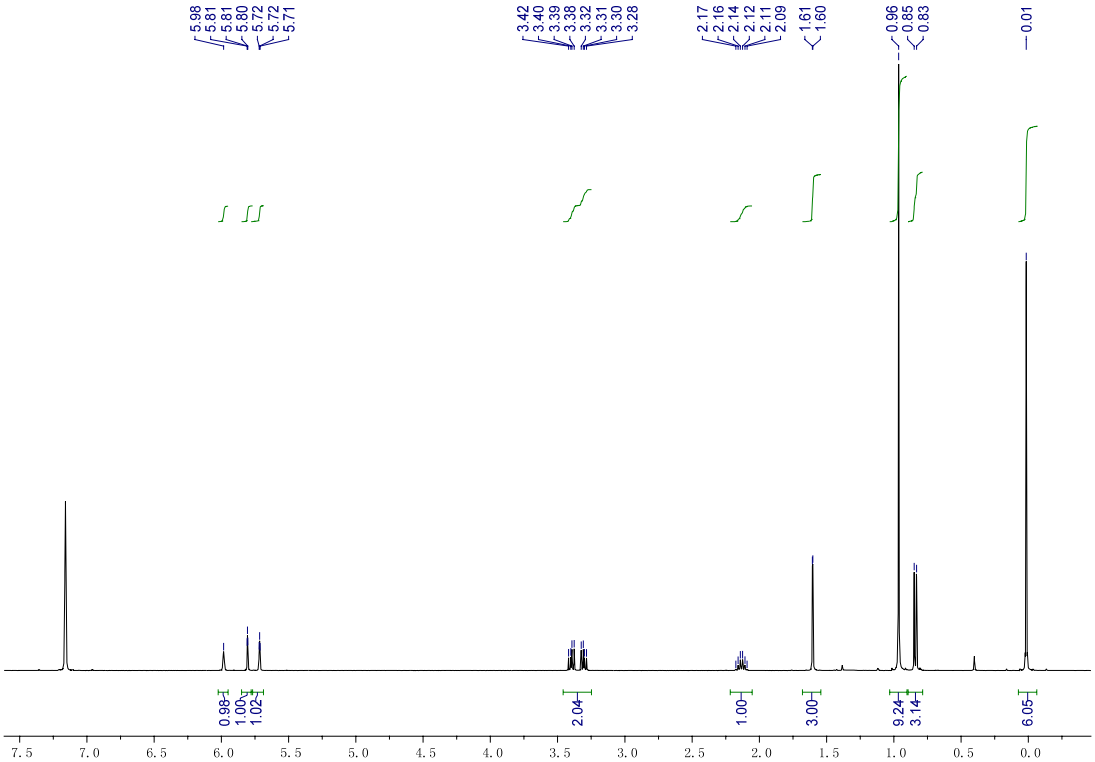


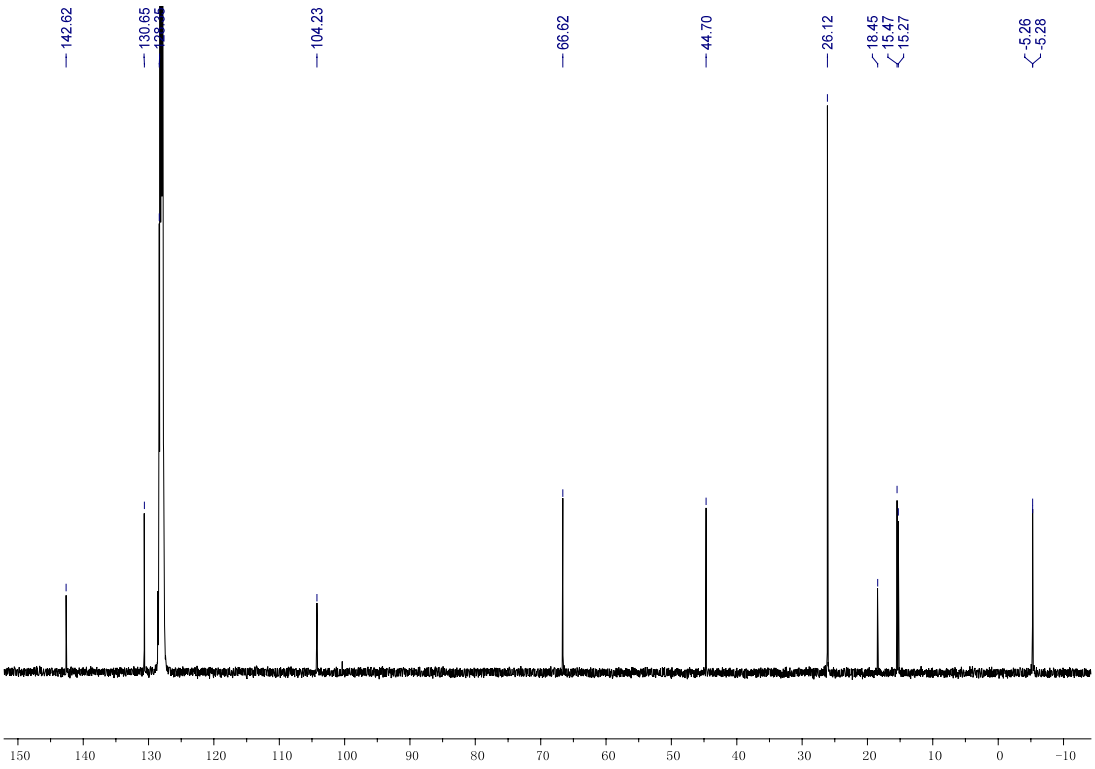




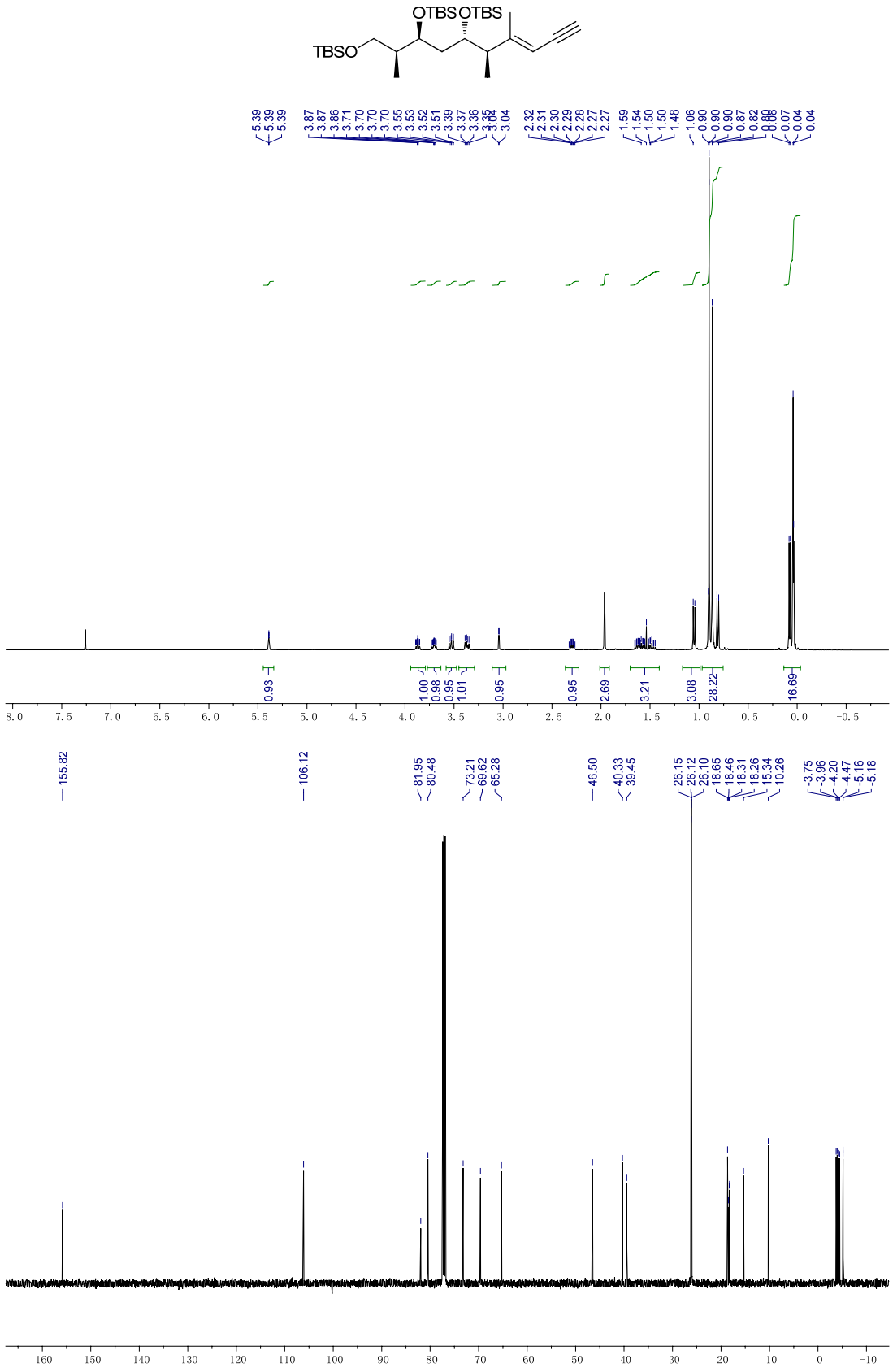
Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **336**



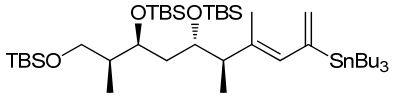


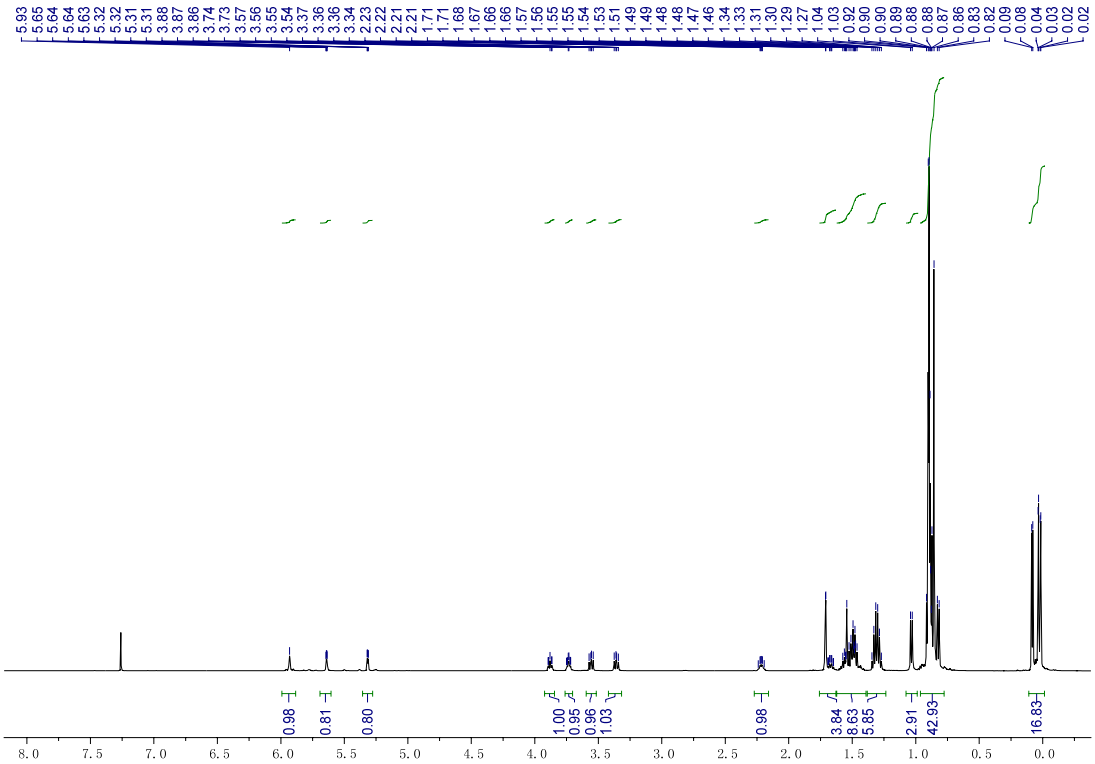


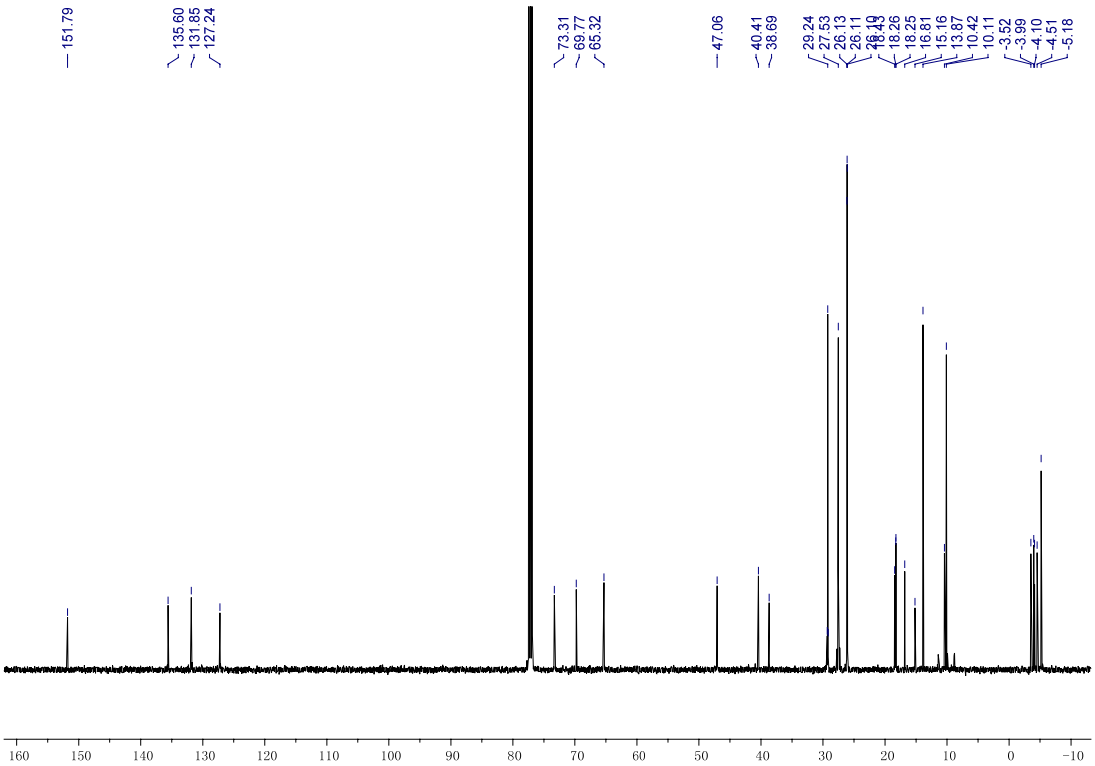
Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **353**



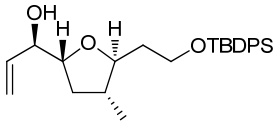
Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **354**

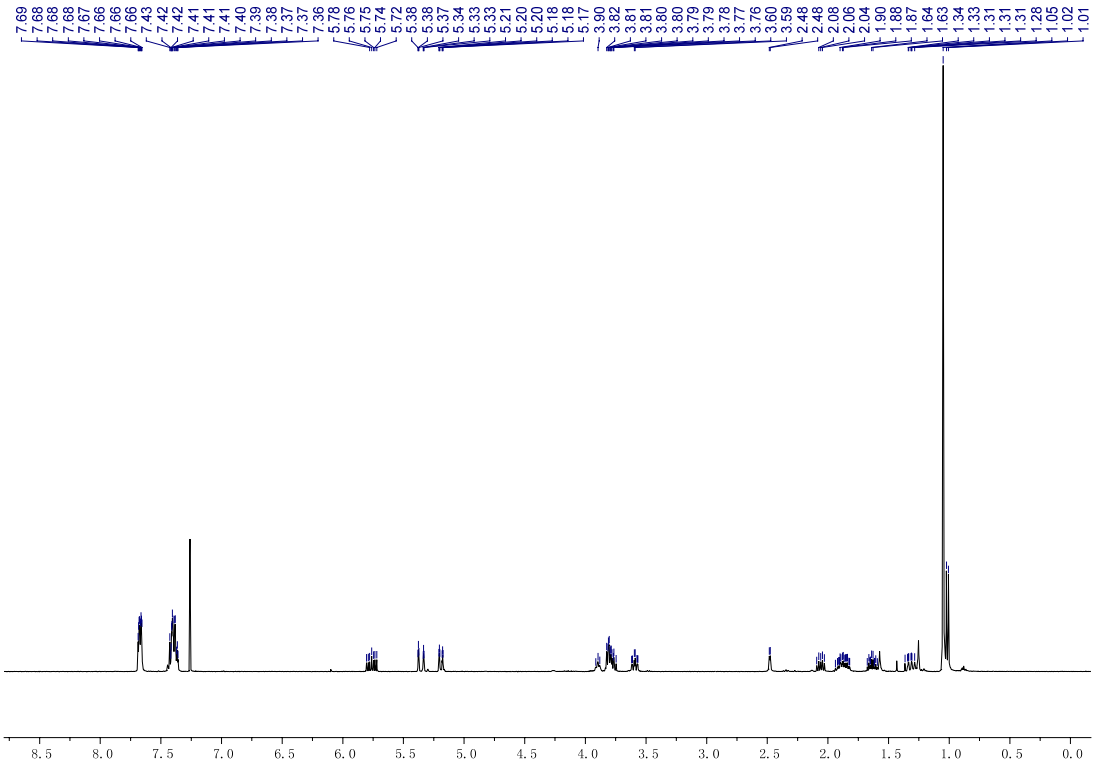


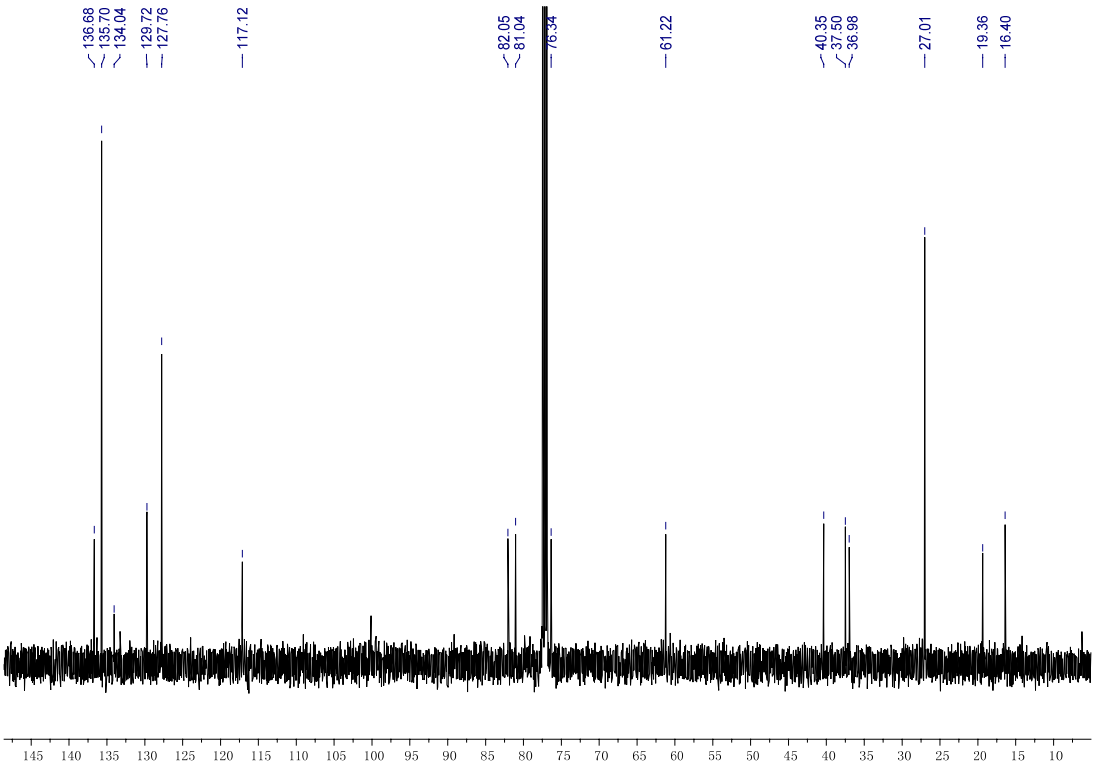




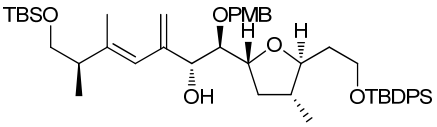
Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **384**

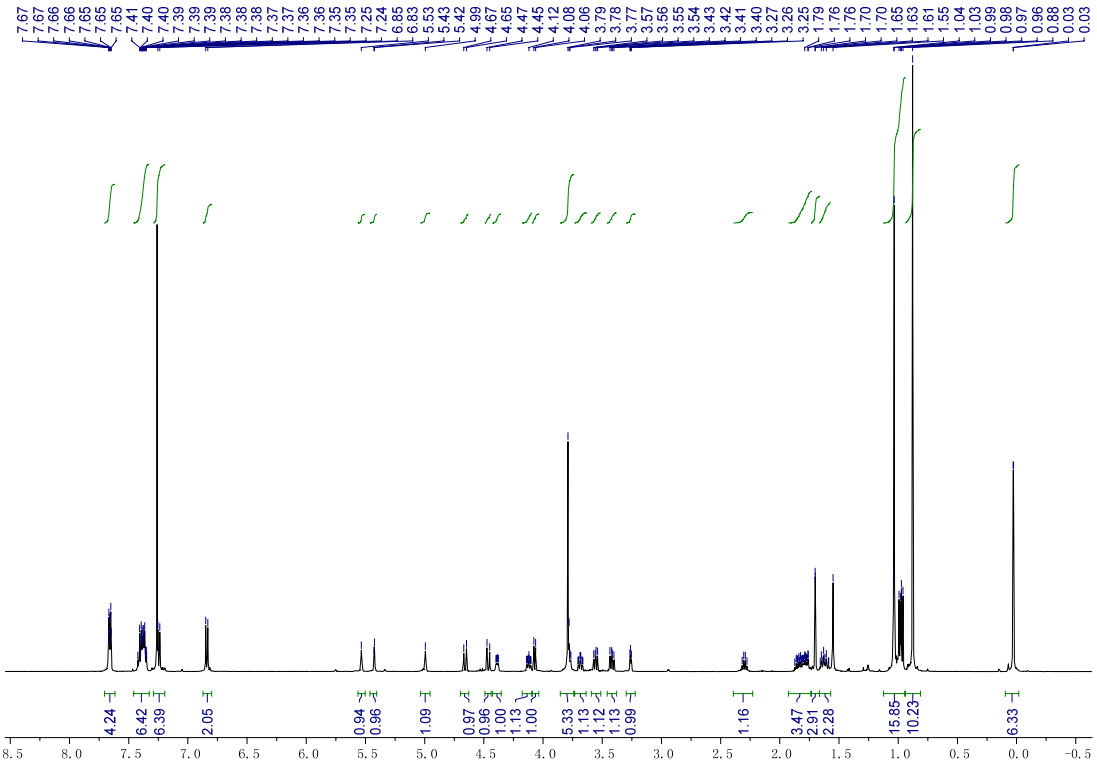


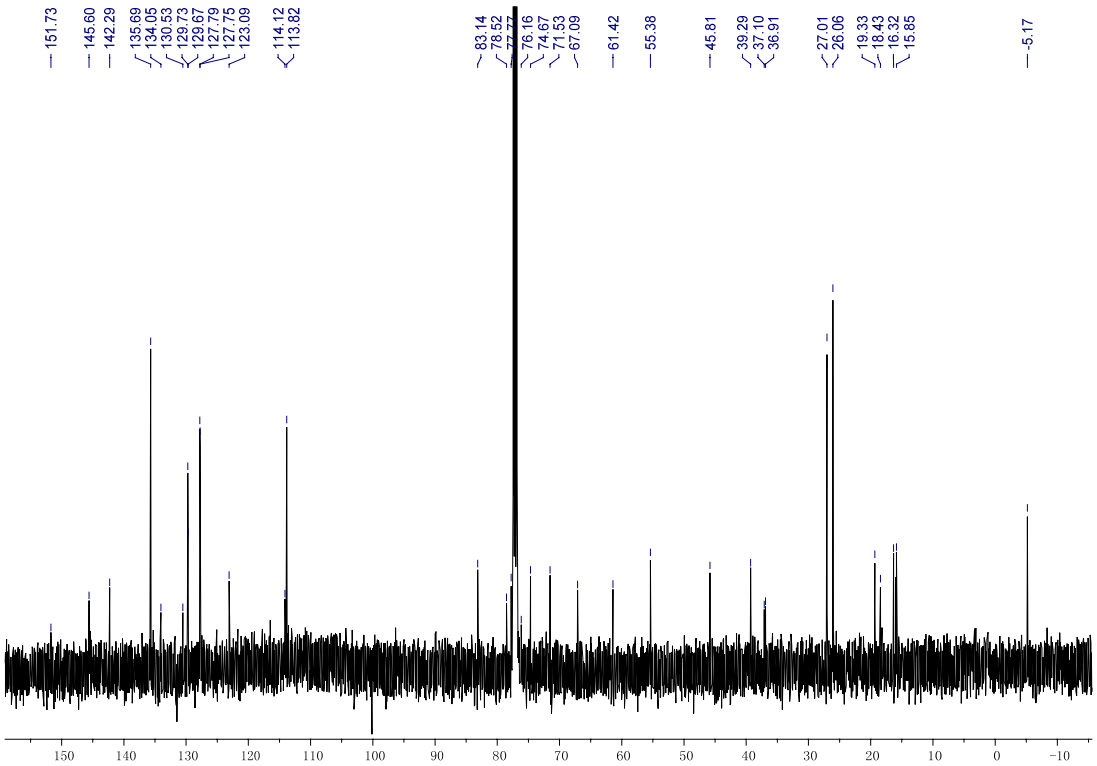




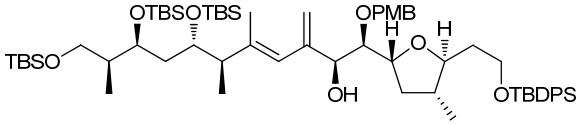
Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **388a**

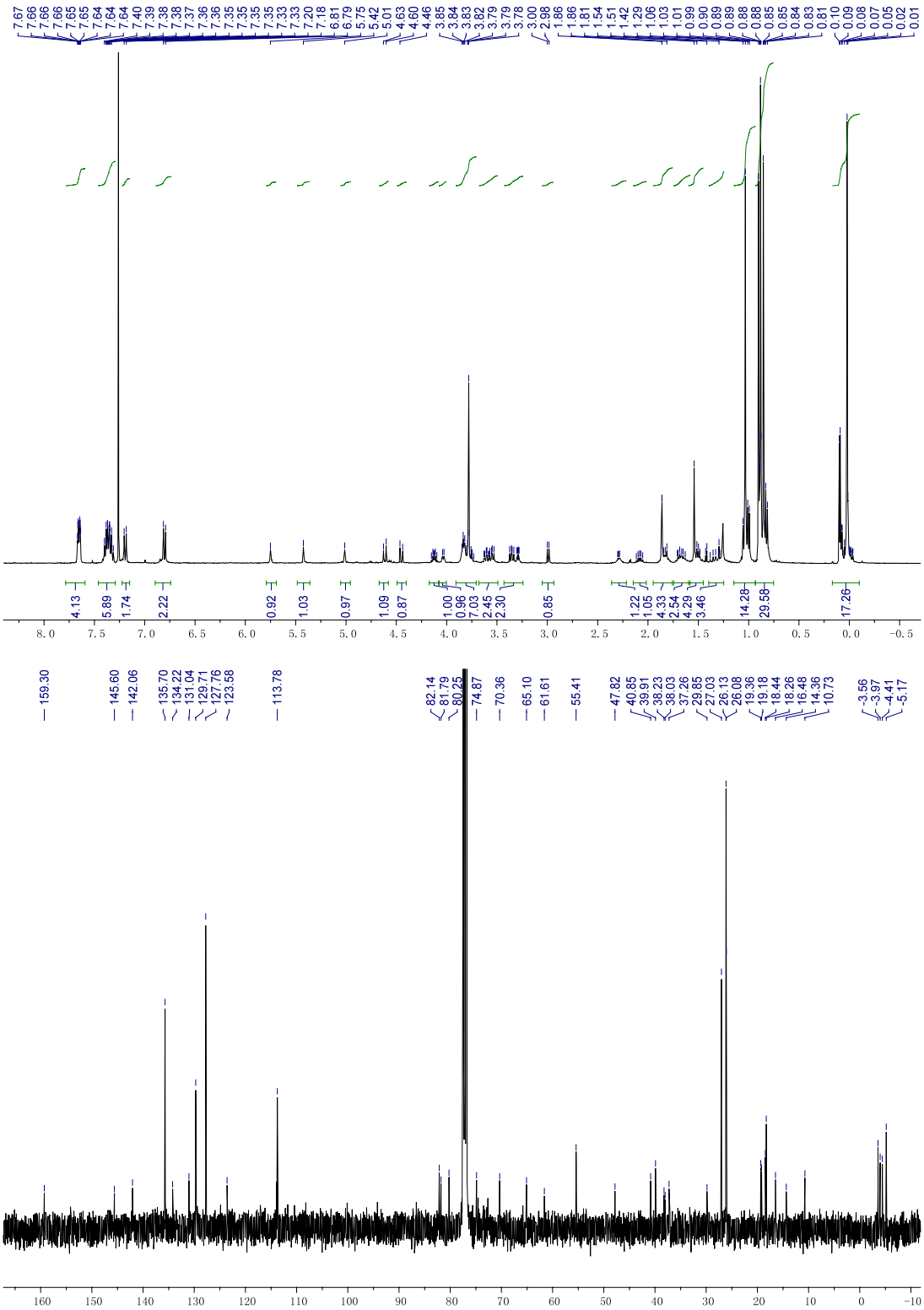




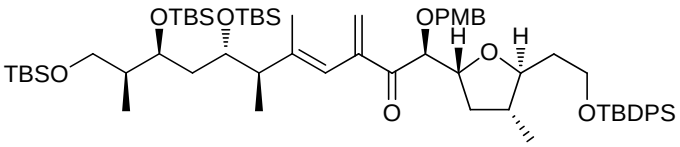


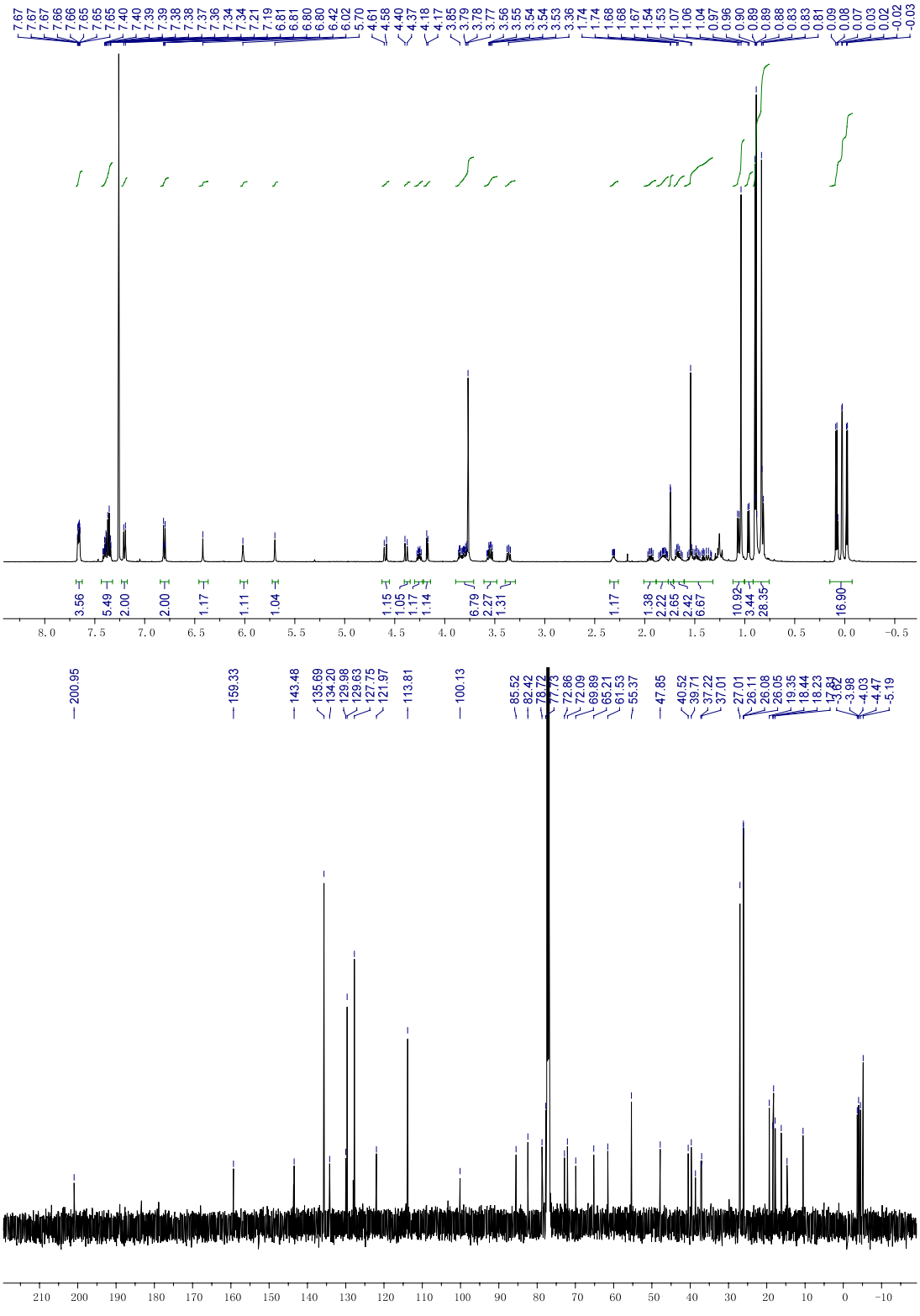
Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **398**





Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **399**





Appendix 1: ^{1}H and ^{13}C NMR spectra of compound **400**