Studies Towards the Total Synthesis of the Amphidinolide C Family of Natural Products

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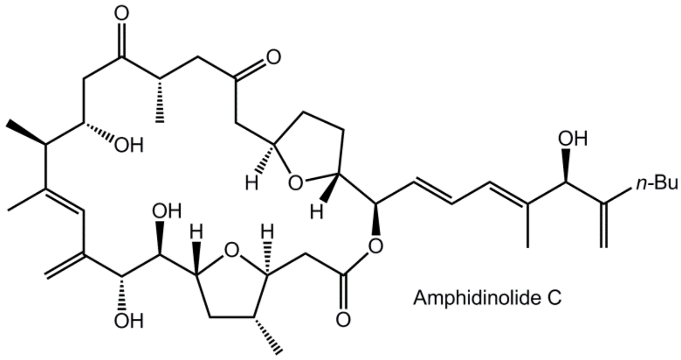
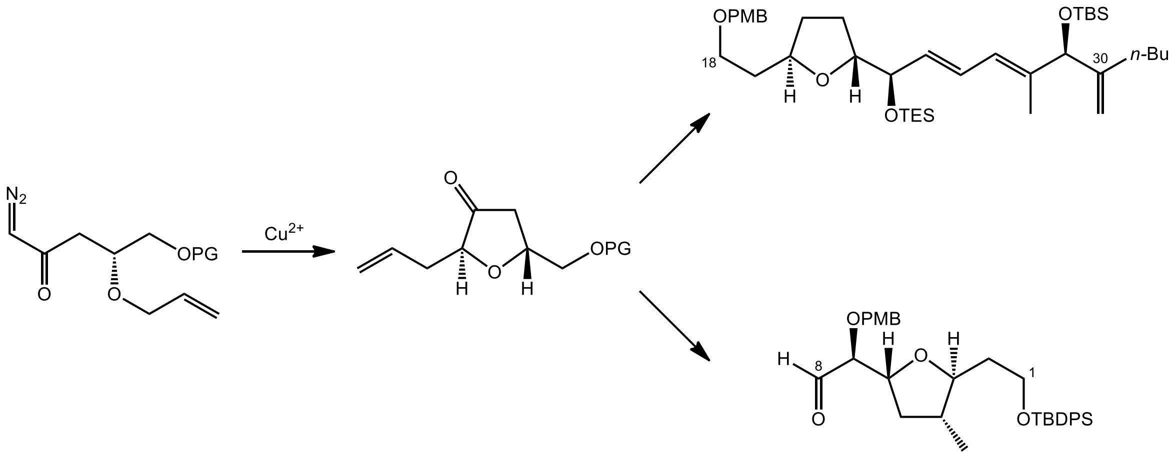
Abstract

The amphidinolide compounds represent an extensive array of marine natural products, a number of which demonstrate potent anti-cancer bioactivity *in vitro*. Amphidinolide C represents an attractive synthetic target due to a combination of potent bioactivity and complex molecular architecture. This project deals with a modular and convergent total synthesis approach to amphidinolide C from which two synthetic fragments of similar size and complexity, termed 'northern' and 'southern', were synthesised in a stereoselective fashion. The stereochemical commonality between the branched chains of the 2,5-*trans* tetrahydrofuran systems found within both fragments, led to the conclusion that a keystone common intermediate could be applied to the synthesis of each. Previous efforts within the group have shown that 2,5-*trans* tetrahydrofuran-3-ones could be prepared through a diastereoselective rearrangement of a free or metal-bound oxonium ylide generated from a metal carbenoid.





This thesis details the scalable preparation of the intermediate tetrahydrofuranone through tandem oxonium ylide and [2,3]-sigmatropic rearrangement. Subsequent discussions show the applicability of the intermediate to forming the C-(18)—C-(34) fragment of amphidinolide C and the C-(18)—C-(29) fragment of amphidinolide F, through the use of palladium cross-coupling methodology; alternative methods found to prepare the 'northern' fragment are also discussed. Additionally, the C-(1)—C-(8) fragment was prepared from the common intermediate system, the key steps in this synthesis involved introduction of the C-(4) methyl group through homogeneous catalytic hydrogenation and Luche reduction to afford the C-(7) alcohol.

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Acknowledgements

Fruitful projects in chemistry are never wholly the result a single researcher's blood, sweat and swearing in the lab (as much as we would like to think so), but are instead built upon a combination of good synthetic planning and a remarkable supporting cast.

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"Always do sober what you said you'd do drunk. That will teach you to keep your mouth shut."

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The most significant thanks of all are left for my beautiful wife Jane, who knows how much I love her and what she means to me and really has no need to read about it here.

Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is being concurrently submitted, in candidature for any other degree.

I also declare that the work presented in this thesis is the result of my own investigations and when the work of other investigators has been used, this has been fully acknowledged in the text.

Andrew P. Osnowski

Professor J. S. Clark

Abbreviations Used in Text

Ac	acetyl
acac	acetylacetonate
ACHN	1,1′-azobis(cyclohexanecarbonitrile)
AD	asymmetric dihydroxylation
AIBN	2,2′-azobis(isobutyronitrile)
Anal.	Analysis
Ar	aryl
atm	atmosphere
ATP	adenosine triphosphate
B_2pin_2	bis(pinacolato)diborane
Bn	benzyl
Bp	boiling point
Bu	butyl
calcd.	calculated
CAN	ceric ammonium nitrate
CBS	Corey-Bakshi-Shibata ligand
CIDNP	chemically induced dynamic nuclear polarization
cm	centimetre
CSA	camphorsulfonic acid
Cy	cyclohexyl
DBA	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDBNP	6,6′-didodecylbinaphtholphosphate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutyl aluminium hydride
DMAP	4-dimethylaminopyridine
DMPU	*N*,*N*′-dimethyl-*N*,*N*′-propylene urea
DPEPhos	(oxydi-2,1-phenylene)bis(diphenylphosphine)
DMF	dimethylformamide
DMS	dimethylsulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EE	1-ethoxyethoxy

ESR	electron spin resonance
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
hfacac	hexafluoroacetylacetonate
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
HWE	Horner–Wadsworth–Emmons
Hz	hertz
IBX	2-iodoxybenzoic acid
IC_{50}	inhibitory concentration of 50%
imid.	imidazole
IR	infrared
L-selectride	lithium tri-*sec*-butylborohydride
LDA	lithium diisopropylamide
lit.	literature
LRMS	low resolution mass spectroscopy
μg	microgram
M	molar
mbar	millibar
m-CPBA	*meta*-chloroperoxybenzoic acid
MLn	generalised metal-ligand centre
Me	methyl
MHz	megahertz
mL	millilitre
MOM	methoxymethyl
MPPIM	methyl phenylpropyl imidazolidinecarboxylate
Mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
NHK	Nozaki–Hiyama–Kishi
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Pet.	petroleum

PG	generalised protecting group
Ph	phenyl
Piv	pivaloyl
Pr	propyl
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
PTTL	*N*-phthaloyl-*tert*-leucinate
Pyr	pyridine
R	Generalised group
rac.	Racemic
R_f	retention factor
rt	room temperature
Red-Al	sodium bis(2-methoxyethoxy)aluminum dihydride
SAR	structure activity relationship
SET	single electron transfer
sp.	species
TES	triethylsilyl
Tf	trifluoromethanesulfonate
TBAI	tetra-*n*-butylammonium iodide
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBSP	*tert*-butylphenylsulfonyl pyrrolidinecarboxylate
Temp.	temperature
tfacac	trifluoroacetylacetonate
tfacam	trifluoroacetamide
TFPPTL	*N*-tetrafluorophthaloyl-*tert*-leucinate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate

Chapter 1: Introduction

1 Marine Natural Products and Total Synthesis

The genesis of life on the Earth is proposed to have begun between 3.9 to 3.5 billion years ago in the primordial oceans of the early planet, leading over time from simple prokaryotic beginnings to the complex biodiversity that is seen in our world today.[1] The success and permanency of marine organisms over this timeframe, in conjunction with evolutionary requirements for intra-species molecular signalling and the essential toxins required for both offensive and defensive purposes, have led to a plethora of complex chemical entities present within the marine environment.

In contrast to terrestrial creatures whose messenger pheromones are by necessity of air transmission relatively simple, low-weight and therefore volatile, marine organisms can extrude much more complex structures into their saline surroundings with the only caveats being the requirement for solubility and potency towards their target. These drug-like attributes of biological potency and aqueous solubility, in addition to the volume of unique chemical structures, have led to the pursuance of marine natural products as possible ligands for receptors associated with human disease states.

Since the completion of the Human Genome Project in 2004,[2] the current consensus is that of the approximate 30,000 proteins coded by the human genome, around 3,000 are designated as disease modifying genes, while only 10% of the total genome is considered 'druggable' *i.e.* susceptible to binding orally bioavailable ligands.[3] The overlap between disease modifying and druggable genes provides a targetable genome of between 600 to 1500 proteins that are amenable to small molecule therapy. The application of natural products as both drugs and lead compounds for drug development is a well-established process within the pharmaceutical industry, and has led to wide-spread screening of numerous marine natural compounds in the challenging search for the drugs of tomorrow.[4]

As of 2012, the structures of approximately 22,000 individual marine natural products have been published of which eight have overcome the hurdles of clinical trials to attain drug approval by US and European regulatory authorities, with numerous others in various phases of clinical development.[5] These compounds span a broad range of structural classes, modes of action and have utilities ranging from anti-cancer to pain relief. Due to the number and array of compound types isolated from the marine environment thus far, combined with the relatively small genomic locus associated with disease states and current capabilities in high-throughput screening, it is axiomatic that marine natural products will continue to play an important role in the pharmaceutical industry as both drugs and lead compounds in the foreseeable future.

Due to the efforts required to isolate relatively small quantities of pure compound from substantial amounts of natural resources, in combination with the necessity of providing a regular supply of bioactive material, modern synthetic techniques are required to supply sufficient quantities of these potentially precious materials for pharmaceutical testing.

2 Amphidinolides: Isolation, Bioactivity and Structure

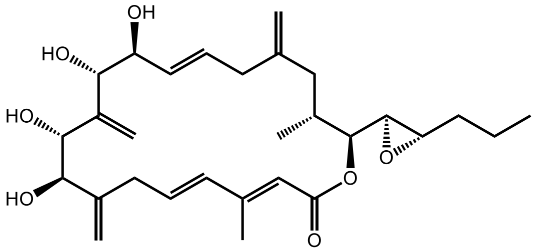
The amphidinolides are a set of 34 distinct macrolide compounds, harvested from the microalgae *amphidinium sp.* a symbiont found within the inner cells of the flatworm *amphiscolops sp.*, native to the coral reefs of the Okinawan archipelago in southern Japan. Isolation and characterisation of these complex polyoxygenated natural products has been accomplished entirely by Kobayashi and co-workers who have disclosed a structurally diverse range of macrolactones exhibiting, in certain cases, excellent cytotoxic efficacy against tumour cell lines.[6]

Initial assays of amphidinium metabolites were conducted using crude extract mixtures and demonstrated promising anti-neoplastic effects against two distinct cell lines, namely mouse lymphoma L1210 and human epidermoid carcinoma KB. The encouraging cytotoxic activity observed (70–90% inhibition at 3 μg mL^{-1}) led to large-scale harvesting of various microalgae strains and separation of the molecular components by HPLC. The Y-5 strain of *amphidinium* sp. has proved to be the richest source of amphidinolide macrolides with no less than 15 individual compounds isolated, of which amphidinolides N, B and C (**6**, **2** and **3**) have proven to be amongst the most bioactive members.[6a] To date the cytotoxic mode of action of the amphidinolides remains undetermined though amplified cytotoxicity is more prevalent amongst those macrolides composed of 25 to 27 atoms, as illustrated in *Table 1*.

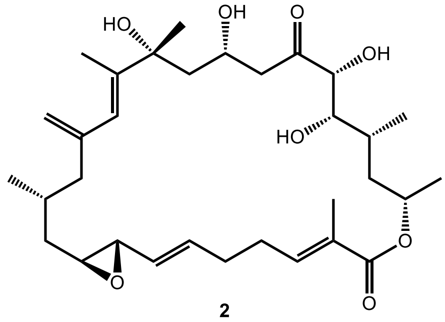
Structurally, the macrolactone systems of the amphidinolides vary in size from 12 membered, in the case amphidinolides Q[7] and W,[8] through to the largest known 29 membered amphidinolide M.[9] Despite overall structural differences present within the group, several common features such as multiple sites of unsaturation, the presence of 1,1-disubstituted alkenes and the occurrence of oxacycles (e.g. epoxides, tetrahydrofurans and pyrans) within the macrolactone ring, are manifest throughout the family (*Figure 1*).

Amphidinolide		Macrolactone Size	Cytotoxicity (IC$_{50}$, μg mL^{-1}) Murine Lymphoma L1210	Cytotoxicity (IC$_{50}$, μg mL^{-1}) Human Epidermoid Carcinoma KB
A	**1**	20	2.0	5.7
B	**2**	26	1.4×10^{-4}	4.2×10^{-3}
C	**3**	25	5.8×10^{-3}	4.6×10^{-3}
D		26	1.9×10^{-2}	0.08
E		19	2.0	10
F		25	1.5	3.2
G		27	5.4×10^{-3}	5.9×10^{-3}
H	**4**	26	4.8×10^{-4}	5.2×10^{-4}
J		15	2.7	3.9
K		19	1.7	2.9
L	**5**	27	9.2×10^{-2}	0.1
M		29	1.1	0.4
N	**6**	26	5.0×10^{-5}	6.0×10^{-5}
O		15	1.7	3.6
P		15	1.6	5.8
Q		12	6.4	>10
R		15	1.4	0.7
S		16	4.0	6.5
T1	**7**	19	18	>20
U	**8**	20	12	>20
V		14	3.2	7
W	**9**	12	3.9	>10
X		16	0.6	7.5
Y		17	0.8	8.0

Table 1



1
Amphidinolide A



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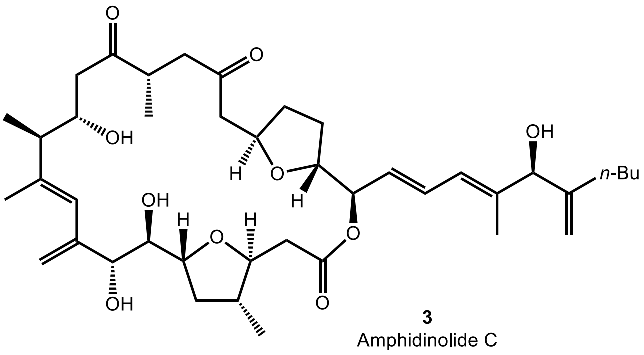

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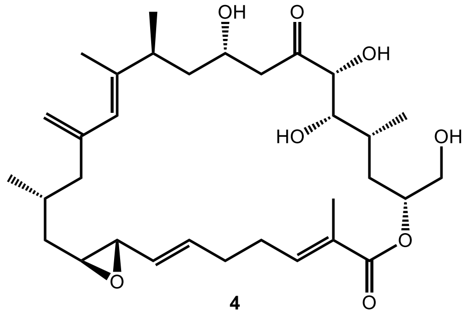
Amphidinolide C



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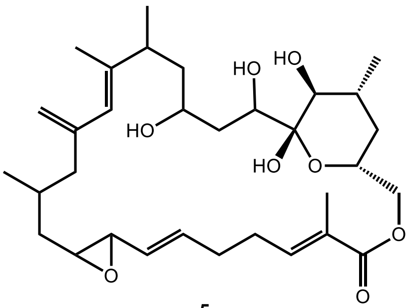
Amphidinolide H



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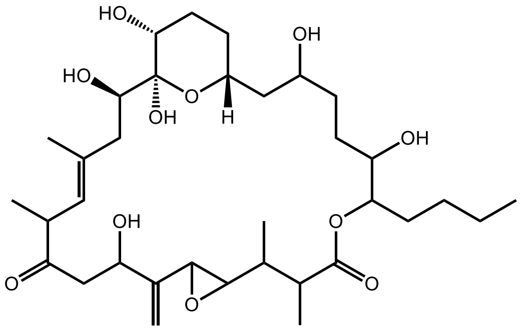
Amphidinolide L



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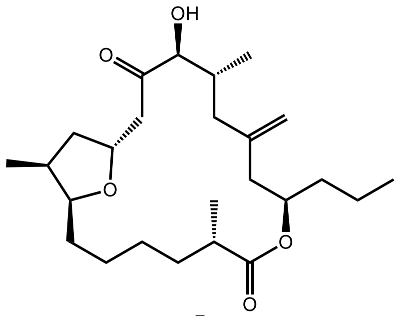
Amphidinolide N



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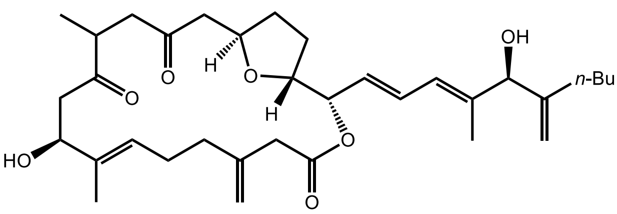
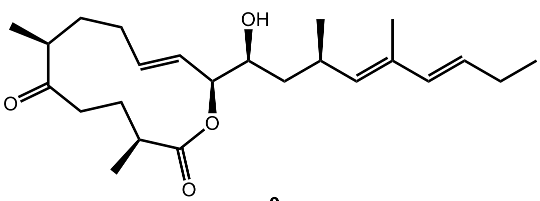
Amphidinolide T1



8
Amphidinolide U



9
Amphidinolide W

Figure 1

3 Amphidinolide C and Related Compounds

3.1 Discovery, Bioactivity and Structure

Amphidinolide C **3** was the earliest 25-membered macrolide isolated from *amphidinium sp*. by Kobayashi *et al*. in 1988.[10] Originally obtained as a component of the Y-5 strain of the microalga it was later also found in Y-26, Y-56 and Y-71 strains leading to significant isolable quantities of material that were used subsequently to determine the structure and absolute stereochemistry.[6a]

The novel macrolide was tested against both murine lymphoma L1210 and epidermoid carcinoma KB cell lines, exhibiting IC_{50} values of 5.8×10^{-3} and 4.6×10^{-3} μg mL^{-1} respectively.[10] Interestingly, a brief remark also described the ability of amphidinolide C to activate rabbit skeletal muscle actomyosin ATPase activity.[11]

On the assignment of the absolute stereochemistry, again by Kobayashi *et al.*, amphidinolide C was shown to a be structurally complex natural product comprising a core 25-membered macrolactone ring, which contains two embedded 2,5-*trans* substituted tetrahydrofurans and a C-(25)—C-(34) exocyclic tail unit.[12] The macrolactone possesses eleven stereocentres, three of which are secondary hydroxyl groups, two ketone units and a diene system between C-(9)—C-(11) bearing an exocyclic 1,1-disubstituted olefin. The tail fragment accommodates an (*E*,*E*)-diene system, a doubly allylic alcohol at the C-(29) position as well as the compound's second 1,1-disubstuted alkene unit, located at C-(30) (*Figure* 2).[12]

The core macrolide of amphidinolide C is shared by three closely related congeners C2,[13] C3[14] and F[15] shown in *Table 2*. The apparent structural similarity between these compounds does not translate into comparable *in vitro* bioactivity, the significant difference in biological activity between amphidinolides C, C2 and C3, and the chain-truncated amphidinolide F, lies within the tail region of the compound. The doubly allylic alcohol of C-(29) confers potent bioactivity but in its absence, or the removal of the H-bond donor capacity by acetylation, the activity of the parent compound is reduced by approximately 1000 fold. This surprisingly tight SAR illustrates the key importance of the tail region of the compound but does not provide insight into the requisite functionality of the macrolactone in binding to the as yet unknown target receptor. This observation suggests that edited portions of amphidinolide C, particularly those around the northern hemisphere and tail of the compound, may elicit a response in cytotoxicity assays.

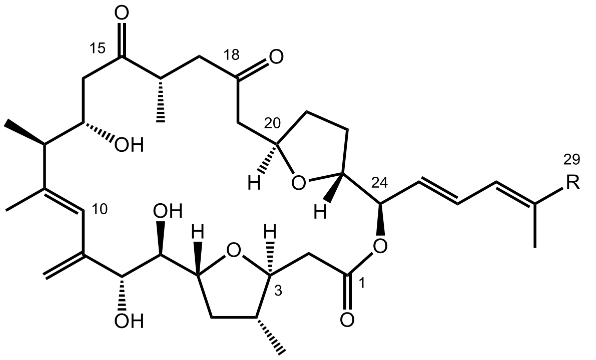


Figure 2

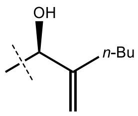
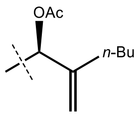
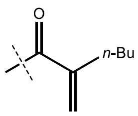
		Cytotoxicity (IC$_{50}$, μg mL^{-1})	
Amphidinolide	R	Murine Lymphoma L1210	Human Epidermoid Carcinoma KB
C[10] **3**		5.8×10^{-3}	4.6×10^{-3}
C2 **10**		0.8	3.0
C3 **11**		7.6	10
F **12**	Me	1.5	3.2

Table 2.

4 Synthetic Efforts Towards the Total Synthesis of Amphidinolide C and Congeners

4.1 General Remarks

The potent *in vitro* cytotoxic activity displayed by amphidinolide C *in vitro,* in combination with the complex molecular architecture of the compound, and the relatively small quantities of material available for study, have made it an attractive target for total synthesis. Due to the high degree of structural overlap between congeners of the amphidinolide C and amphidinolide F, efforts towards the synthesis of both compounds are of interest when reviewing the current state of literature regarding these fascinating targets.

Numbering of the amphidinolide C family begins at the carboxy unit of the macrolactone ester C-(1) and continues in a counter-clockwise fashion terminating in the terminal carbon of the exocyclic tail unit, C-(29) in the case of amphidinolide F and C-(34) in that of amphidinolide C. Retrosyntheses of these particular natural products tend towards two very specific starting disconnections, the first along the macrolactone bond and the second on either of the flanking bonds of the C-(18) ketone. These disconnections lead to what will subsequently be described as 'northern' and 'southern' fragments, for the sake of generality.

The majority of syntheses have focussed on the construction of the 2,5-*trans* tetrahydrofuran units embedded within the macrolide system as a basis for building outwards towards more developed intermediate fragments. To date, no total synthesis of amphidinolide C, C2 or C3 has been disclosed, though a total synthesis of amphidinolide F has been published recently. The ensuing sections detail the work on the synthesis of both 'northern' and 'southern' fragments of amphidinolide C and F. Where a single group has published on both sections the work is discussed in conjunction.

4.2 The Roush Group

4.2.1 Synthesis of C-(11)—C-(29) Fragment of Amphidinolide F

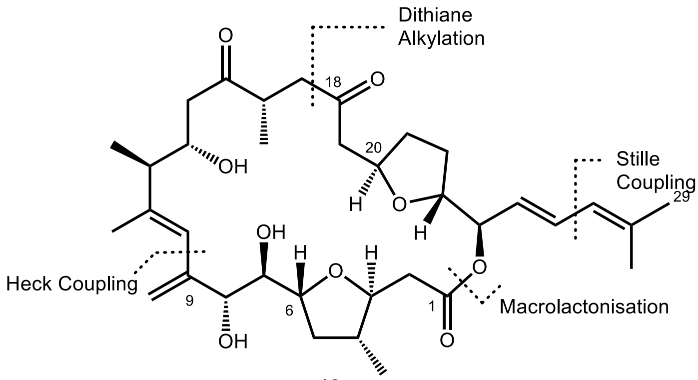


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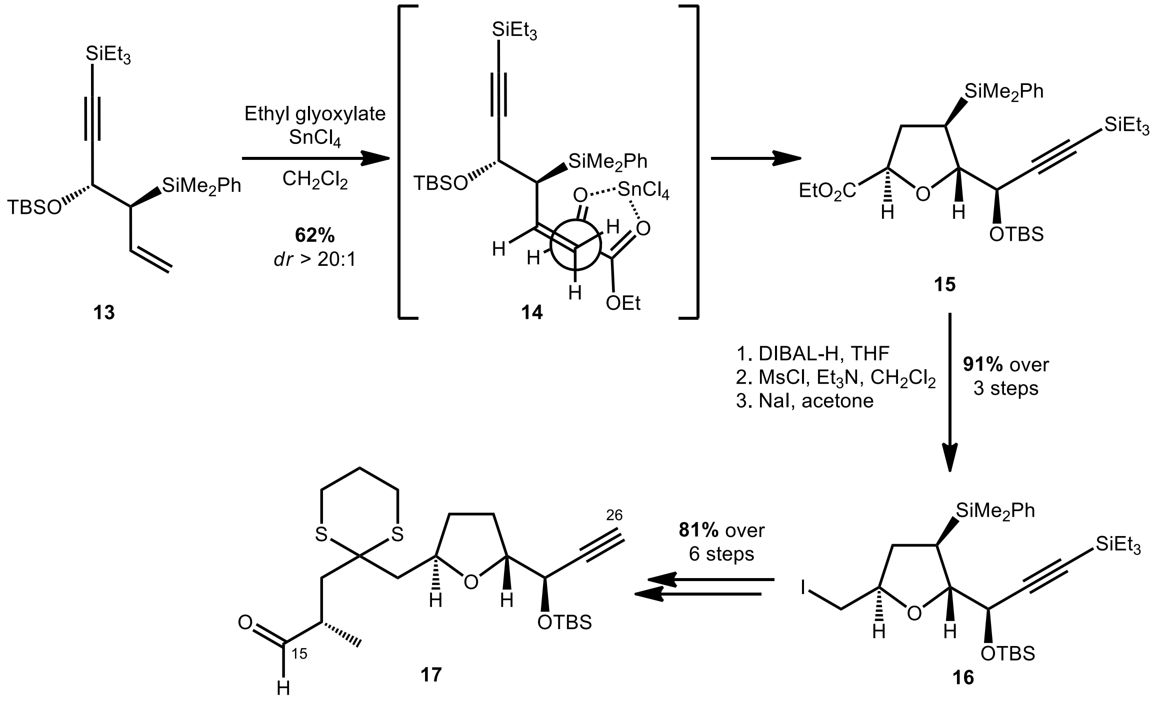
Figure 3

Roush and co-workers envisaged the retrosynthetic analysis of amphidinolide F shown in *Figure 3*.[16] Disconnection across the lactone bond and the C-(9)—C-(10) diene system led to a structurally complex C-(10)—C-(29) fragment from which the forward connections were predicted to be achievable through Yamaguchi macrolactonisation and Heck coupling respectively.

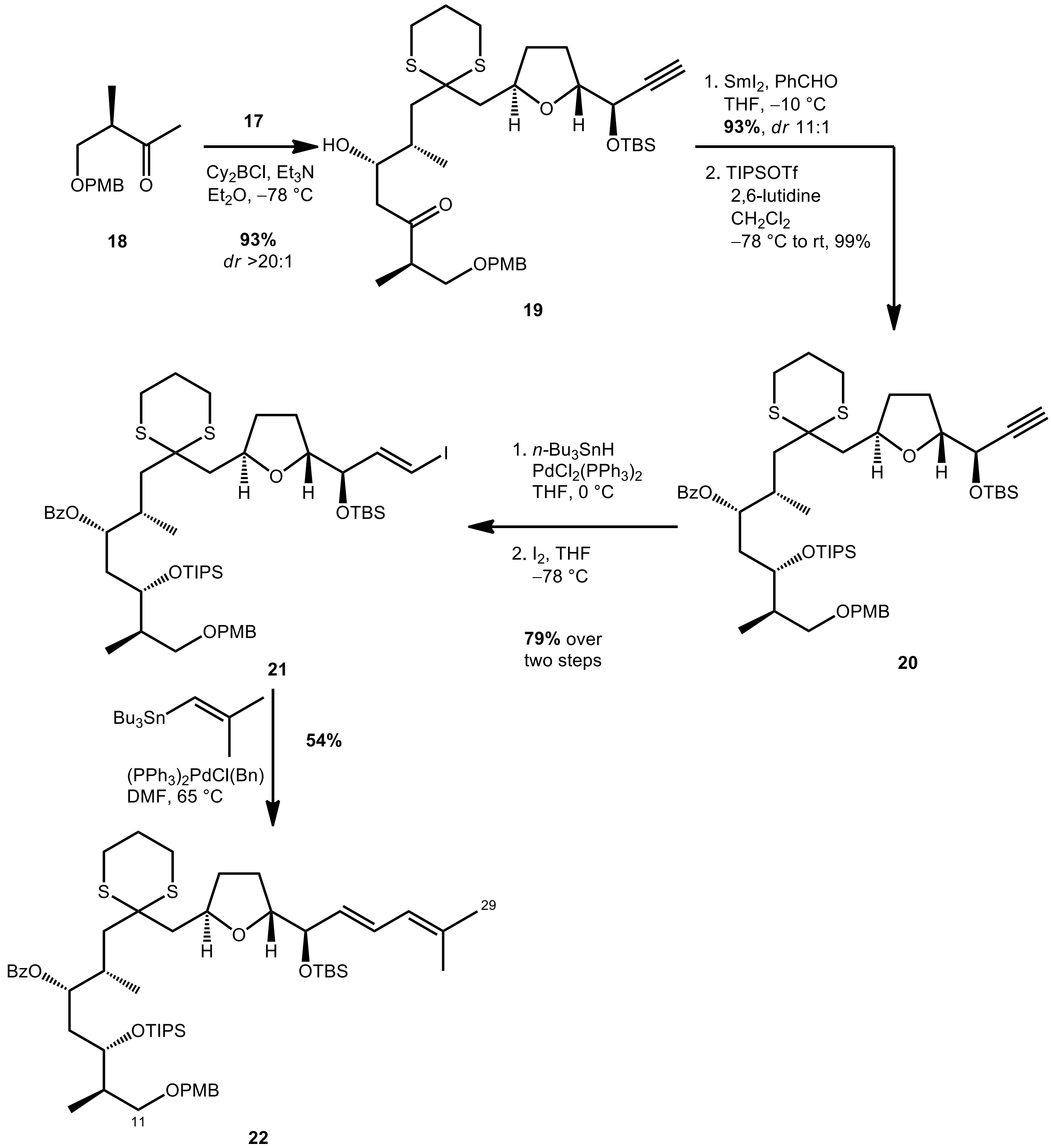
The group's interest in chelate controlled [3+2] annulation reactions between chiral allylic silanes and aldehydes, led to the belief that the 2,5-*trans* stereochemistry of the northern tetrahydrofuran could be formed using this methodology. The synthesis of tetrahydrofuran **15** was accomplished through tin activation of ethyl glyoxylate and treatment of the complex with allylsilane **13**. The desired [3+2]-annulation proceeded in good yield and excellent diastereoselectivity to afford the desired 2,5-*trans* tetrahydrofuran **15**, shown in *Scheme 1*, the stereochemical outcome of the reaction is guided by the *syn*-synclinal intermediate **14.**[17]

Reduction of the ester functionality was followed by two-step conversion of the alcohol product to alkyl iodide 16 which upon iodide displacement, protiodisilation of the C-Si bond and functional group interchange afforded aldehyde **17**.



Scheme 1

The synthesis was completed in a further six steps beginning from the boron mediated aldol condensation of the aldehyde with methylketone **18** which proceeded under Felkin-Anh control. The yield and diastereomeric ratio of the addition proved to be excellent, allowing progression of the route through an Evans-Tishchenko reduction of the resultant ß-hydroxy ketone.[18] After further manipulation of functional groups, vinyl iodide **21** was ultimately cross-coupled to a stannane under Stille conditions to afford the C-(11)—C-(29) carbon framework of amphidinolide F (*Scheme* 2).

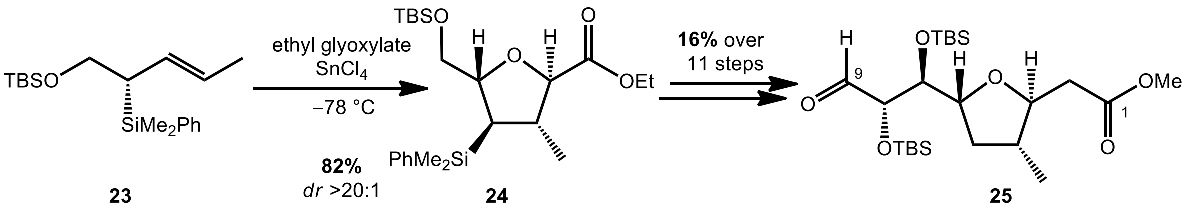


Scheme 2

4.2.2 Synthesis of the C-(1)—C-(9) Fragment of Amphidinolides C and F

Encouraged by the success of their tin mediated [3+2] annulation in forming the key C-(20)—C-(23) tetrahydrofuran of the Northern fragment of amphidinolide F, Roush and co-workers subsequently focussed on the application of the same methodology to the C-(1)—C-(9) Southern fragment of the macrolactone ring.[19] The greater molecular intricacies of this section of the target, particularly regarding the exocyclic C-(35) methyl group, provided complications in the observed diastereocontrol of the annulation reaction when aldehydes other than ethyl glyoxylate were used (*Scheme 3*). Although aldehyde **25** was prepared in eleven steps from the 2,5-*trans* tetrahydrofuran

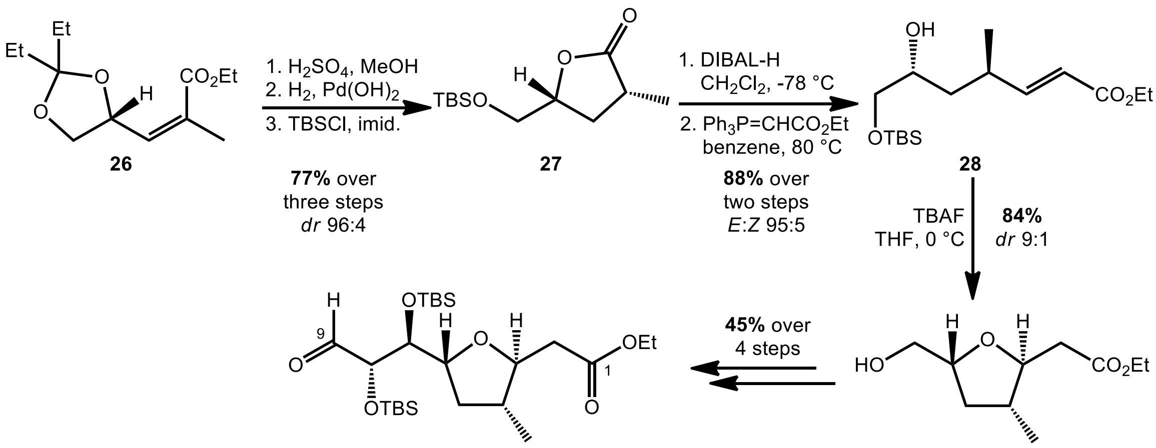
24, the route was considered to be too long and low yielding for practical use in a total synthesis. An alternative method was sought.



Scheme 3

Prior work conducted by Kobayashi and co-workers towards evaluation of the absolute stereochemistry of amphidinolide C, used a stereocontrolled intramolecular oxa-Michael reaction to construct the C-(3)—C-(6) tetrahydrofuran unit.[12b]

Roush and co-workers employed an analogous methodology when developing a second generation synthesis of their target tetrahydrofuran (*Scheme 4*). The α,β-unsaturated ester **26** was prepared by Still-Genari olefination of isopentyl ketal glyceraldehyde thereby providing a chiral-pool starting point for the synthesis. Acid-catalysed ketal deprotection and lactonisation was followed by stereoselective hydrogenation of the endocyclic double bond with Pearlman's catalyst, TBS protection of the extant hydroxyl gave the lactone **27** as a single diastereoisomer. Reduction of the lactone group delivered an aldehyde which upon treatment with (carbethoxymethylene)-triphenylphosphorane yielded α,β-unsaturated ester **28**, the precursor compound required to deliver the 2,5-*trans* tetrahydrofuran. Treatment of the intermediate with TBAF led to intramolecular cyclisation of the compound in good yield and with a high degree of stereocontrol.[12b]



Scheme 4

The high ratio of 2,5-*trans* tetrahydrofuran formation over the *cis* diastereomer is largely controlled by the steric effect of the C-(35) methyl group on the preferred conformer of compound **28** generated through 1,3-allylic strain, as illustrated in *Figure 4*. The stereocontrolled installation of the C-(7)—C-(8) diol was accomplished through the application of Brown's γ-borylallylborane[20] and was followed by a Tamao-Fleming oxidation. Overall the sequence illustrated in *Scheme 4* provided a shorter and higher-yielding synthesis than that of the [3+2] annulation methodology discussed in *Scheme 3*.

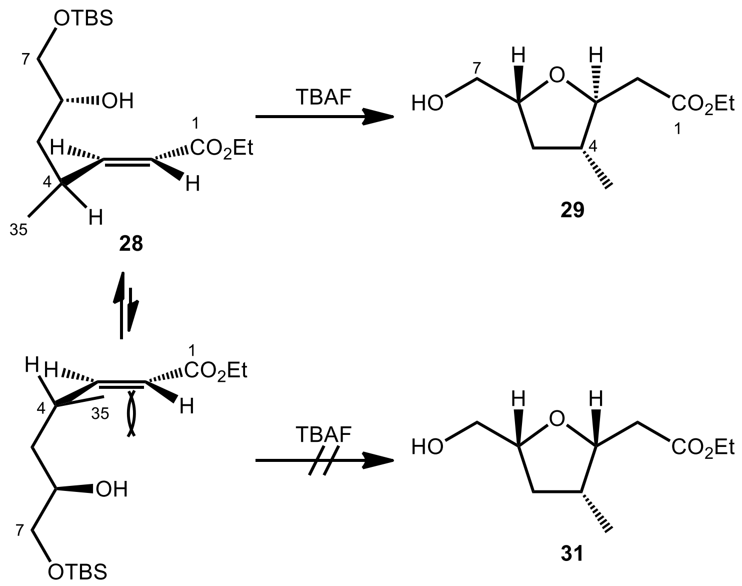


Figure 4

4.3 The Mohapatra Group

4.3.1 Synthesis of the C-(19)—C-(34) Fragment of Amphidinolide C

The initial disconnections in Mohapatra's strategy for the synthesis of amphidinolide C, were analogous to those previously exploited in Roush's disconnection of amphidinolide F, leading to a target C-(19)—C-(34) fragment highlighted in *Figure 5*.[21]

Scheme 5 shows the forward synthesis of the 2,5-*trans* tetrahydrofuran ring system. Generally, syntheses of the 2,5-*trans* tetrahydrofuran functionality of amphidinolide C are conducted in a diastereoselective fashion, unusually Mohapatra's group decided to pre-form the enatiopure C-(20) and C-(23) stereocentres and combine both through a regioselective, copper triflate catalysed ring opening of the allylic oxirane **33**.[22]

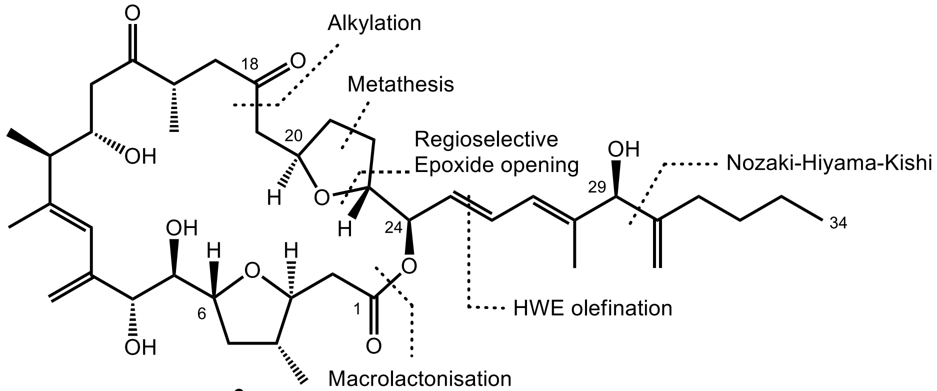
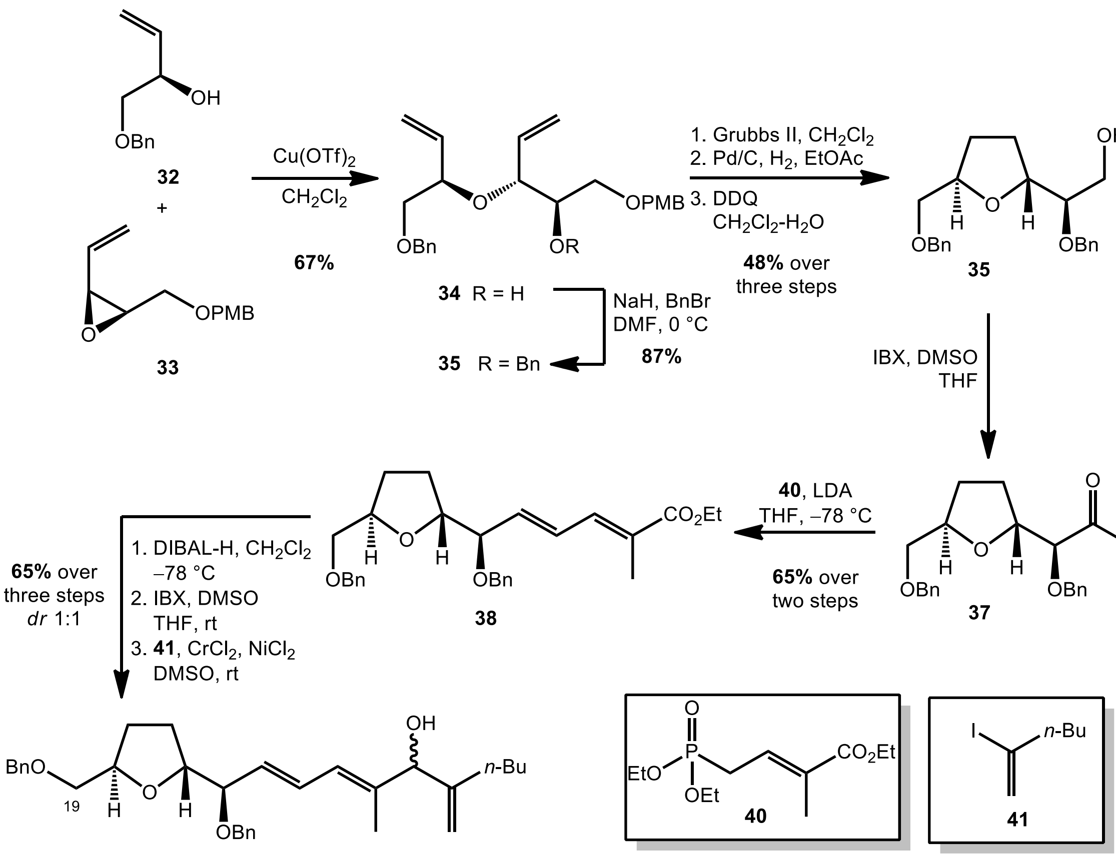


Figure 5

In forming diene **34**, the desired stereochemistry at C-(20), C-(23) and C-(24) was introduced early in the synthesis through inexpensive chiral starting materials. The terminal olefins were united by means of metathesis, catalysed by Grubbs second generation catalyst, and the resultant endocyclic olefin reduced by hydrogenation.



Scheme 5

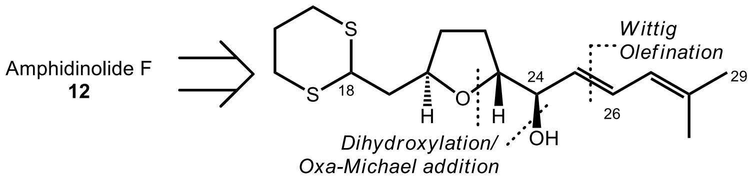
Further manipulation of the compound afforded aldehyde **37** which was olefinated with phosphonate ester **40**, thereby permitting access to the unsaturated *E*:*E* diene ester **38**. The synthesis was completed in a further three reactions, the key step of which was the

Nozaki-Hayama-Kishi coupling of the intermediate aldehyde with vinyl iodide **41**, providing the C-(19)—C-(34) fragment **39** as a 1:1 mixture of separable C-(29) diastereomers.

4.4 The Armstrong Group

4.4.1 Synthesis of the C-(18)—C-(29) Fragment of Amphidinolide F

2009 saw the publication by Armstrong and co-workers of their work concerning the synthesis of the northern fragment of amphidinolide F, comprising a short synthesis of the 2,5-*trans* tetrahydrofuran system, and unification of the formed fragment with the C-(26)—C-(29) truncated tail section through Wittig olefination.[23] These workers also reflected on the possibility of expanding the C-(18)—C-(29) northern construct of amphidinolide F to enable synthesis of the C-(29)—C-(34) tail of amphidinolide C.



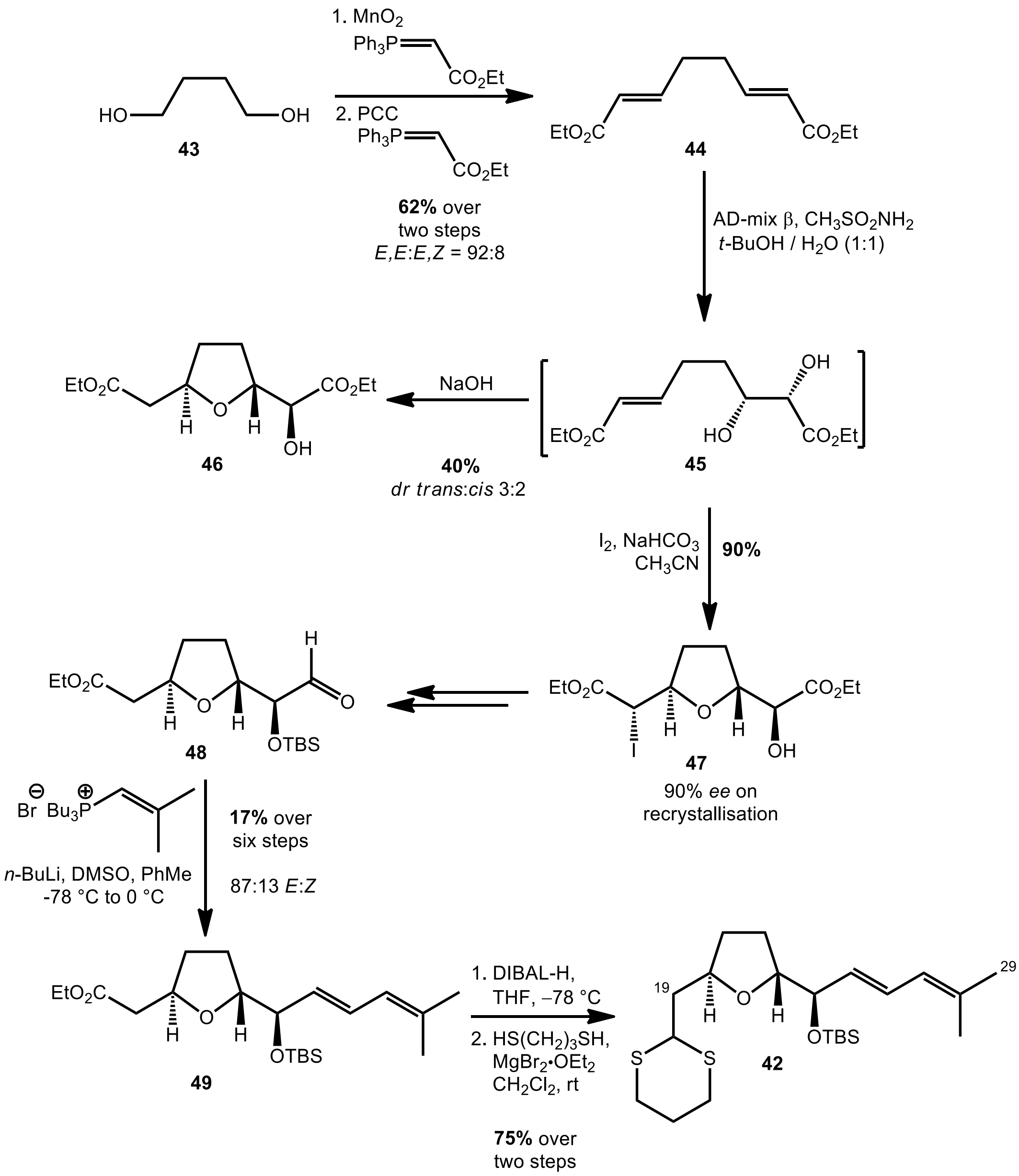
42

Figure 6

Armstrong's retrosynthetic analysis of amphidinolide F followed the prevalent convention of disconnection at the macrolactone bond and adjacent to the C-(18) ketone, in this case between the C-(17)—C-(18) bond, leading to the C-(18)—C-(29) fragment **42**, shown in *Figure 6*.

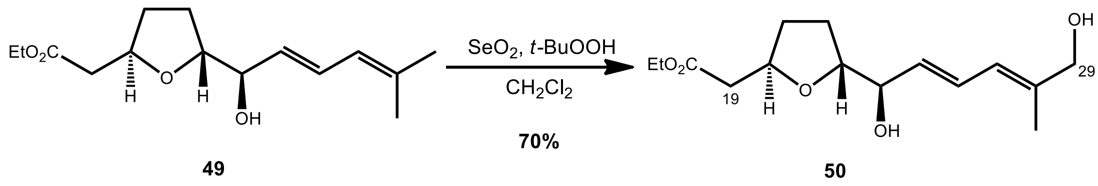
Synthesis of fragment **42** commenced using the oxidation-olefination procedures of Graham *et al.*[24] from which dienoate **44** was isolated in acceptable yield with good *E*:*Z* selectivity. Attention subsequently turned to the development of methodology for the selective monodihydroxylation of the diene and subsequent oxa-Michael cyclisation used to form the 2,5-*trans* tetrahydrofuran **46**. In the absence of base, the major product isolated from the Sharpless asymmetric dihydroxylation of **44** was diol **45**, but in the presence of NaOH the cyclisation reaction proceeded to afford tetrahydrofuran **46**. Although the cyclisation reaction occurred in poor yield and with a low diastereomeric ratio, no 6-*exo* trig cyclisation was reported. Isolation of diol **45** and base mediated cyclisation of the purified material was attempted but no discernible improvement in the diastereomeric ratio of *cis* and *trans* isomers was observed. Iodo etherification of alkene **45** did not provide a markedly better diasteromeric ratio of iodotetrahydrofuran

47 (*trans*:*cis* 3:1) but did allow for enrichment of the desired enantiomer by means of product recrystallization.



Scheme 6

Following several transformations, including radical deiodination, the carbon framework of the C-(18)—C-(29) fragment of amphidinolide F was completed following Wittig olefination of aldehyde **48**. A two-step conversion of the ester into dithiane **42** provided the final compound of the sequence. Attempts to extend the potential utility of diene **49** for the synthesis of amphidinolide C were realised through the provision of a synthetic handle on the C-(29) position. As shown in *Scheme 7*, selenium mediated allylic oxidation afforded the desired allylic alcohol **50** in 70% yield.



Scheme 7

4.5 The Spilling Group

4.5.1 Synthesis of the C-(18)—C-(34) Fragment of Amphidinolide C

Spilling's retrosynthetic analysis of the macrolactone ring of amphidinolide C adhered to the standard disconnection strategy leading to the C-(18)—C-(34) fragment **51**.[25] Construction of the 2,5-*trans* tetrahydrofuran ring was envisaged as the result of an intramolecular, palladium-catalysed cyclisation of an allylcarbonate with a suitably functionalised alcohol, while introduction of the C-(25)—C-(26) diene by use of phosphonate olefination chemistry was expected. The applicability of HWE olefination to the functionalization of various aldehydes was noted as a potential route towards accessing a number of synthetic analogues, including that of the abbreviated tail region of amphidinolide F. Introduction of the extended C-(29)—C-(34) side chain was anticipated to be performed by Nozaki–Hiyama–Kishi coupling of a suitable vinylic iodide with the appropriate C-(29) aldehyde, in an identical approach to that used by Mohapatra.[21]

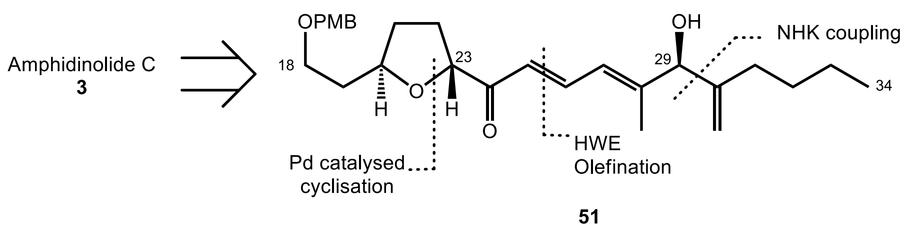
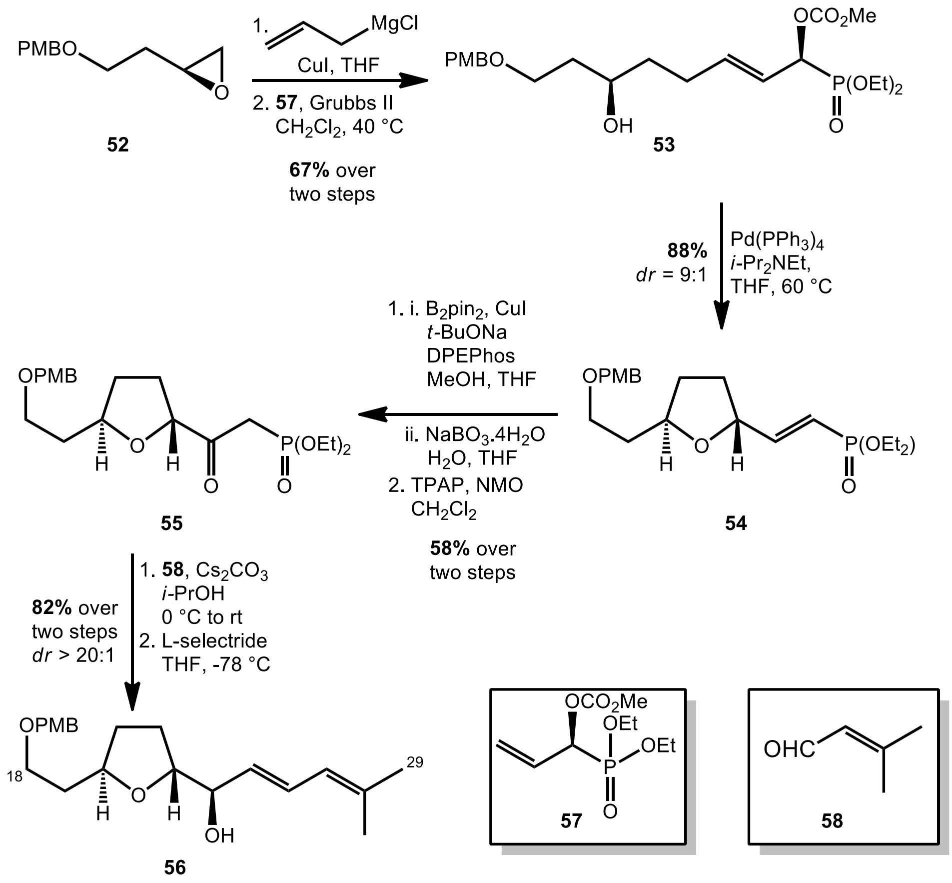


Figure 7

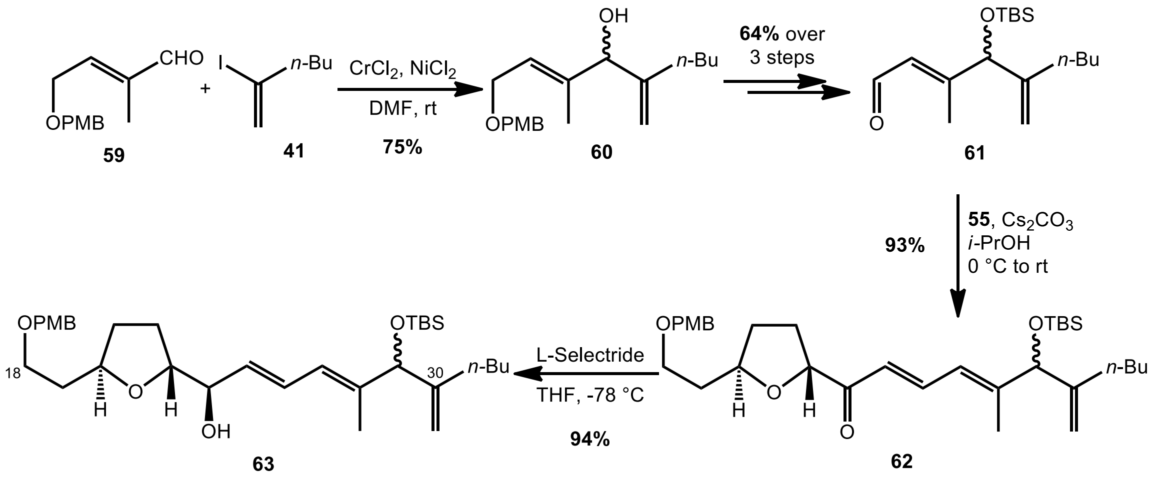
Forward synthesis began from epoxide **52**, formed in three steps from 3-buten-1-ol and resolved from the racemic epoxide by use of Jacobsen's methodology.[26] Ring opening with allylmagnesium chloride provided a terminal alkene, which on metathesis with enantiomerically pure phosphonoallylic carbonate **57** using Grubbs' second generation catalyst yielded *E*-olefin **53**. Palladium catalysed decarboxylation of the allylcarbonate led to intramolecular cyclisation through the C-(20) secondary hydroxyl group, thereby forming the 2,5-*trans* tetrahydrofuran diastereomer **54** preferentially. The resultant *E*-vinylphosphonate underwent hydroboration-oxidation with diboron pinacol ester and sodium perborate to afford a 1:1 mixture of C-(24) secondary alcohols, which upon TPAP oxidation provided the ß-ketophosphonate **55** in good yield.



Scheme 8

With the ß-ketophosphonate in hand, attention turned to synthesis of an aldehyde coupling partner and optimisation of the coupling methodology. Prior to construction of the C-(26)—C-(34) segment of amphidinolide C, the group decided to test the viability of using HWE olefination to construct the C-(25)—C-(26) bond by fashioning the northern fragment of amphidinolide F from commercially available 3-methyl-crotonaldehyde **58**. A number of ineffective conditions, in which various solvent-base combinations were employed, were examined before the optimal system comprising caesium carbonate and anhydrous isopropanol, permitted access to the desired dieneone. Felkin-Anh controlled 1,2-reduction of the C-(24) ketone functionality was then accomplished by use of L-selectride, providing the C-(18)—C-(29) northern fragment of amphidinolide F **56** as a single diastereoisomer.

The success of the HWE protocol channelled subsequent efforts into the synthesis of an aldehyde that would form the backbone of the C-(26)—C-(34) tail of amphidinolide C. Nozaki-Hiyami-Kishi coupling of aldehyde **59** and vinyl iodide **41** afforded a racemic mixture of doubly allylic alcohol **60** in good yield, the PMB ether was further manipulated to afford the germane aldehyde for provision of the C-(25)—C-(26) bond-forming olefination reaction. Application of the previously optimised HWE conditions allowed for high-yielding formation of an intermediate dieneone **62** and subsequentby L-selectride reduction afforded the desired C-(18)—C-(34) fragment of amphidinolide C.



Scheme 9

4.5.2 Synthesis of the C-(1)—C-(9) Fragment of Amphidinolides C and F

Spilling's synthesis of the C-(1)—C-(9) fragment of amphidinolides C and F harnessed the power of a nickel catalysed, homoallylic addition reaction of a 1,3-diene to an aldehyde, in order to provide the precursor framework of the southern 3-methyl 2,5-*trans* tetrahydrofuran fragment of the natural product.[27] As shown in the retrosynthesis (*Figure 8*), access to the 2,5-*trans* tetrahydrofuran was viewed as being possible through an intramolecular oxa-Michael addition of α,β-unsaturated ester **65**, analogous to that previously employed by Kobayashi[12b] and Roush.[19]

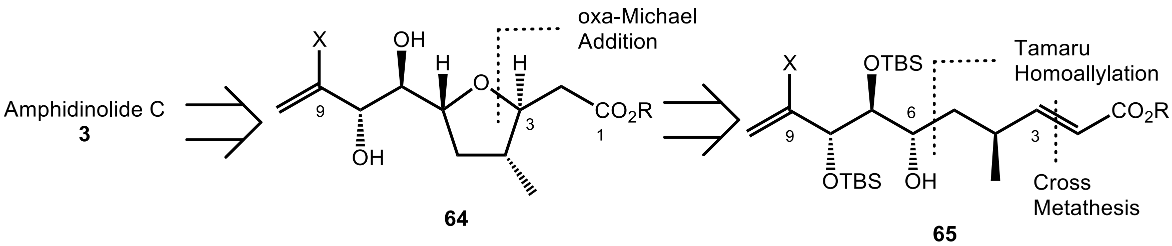
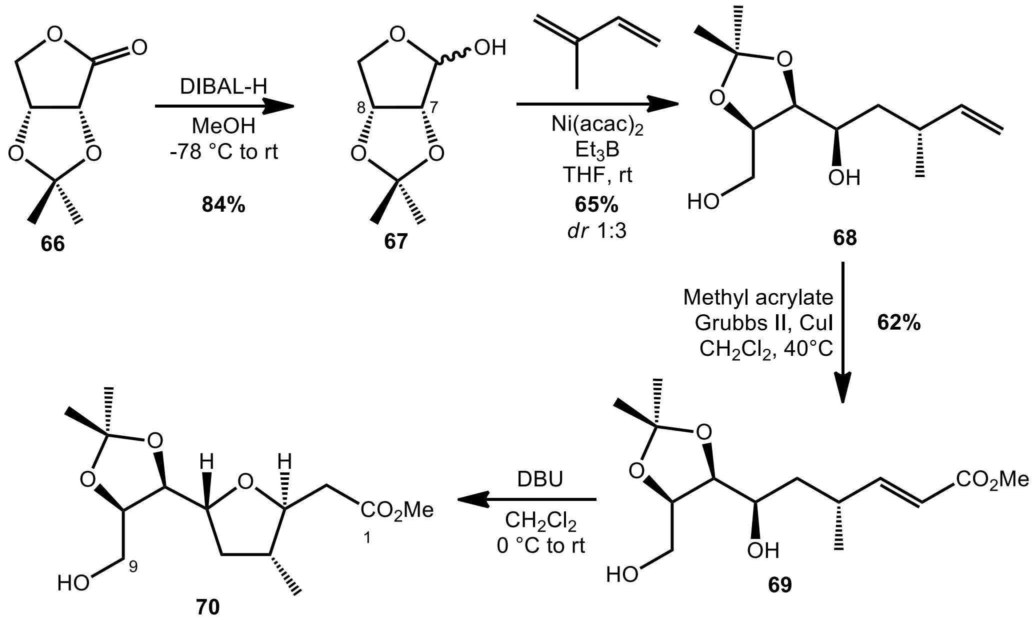


Figure 8

The synthesis commenced from the commercially available lactone **66**, which underwent DIBAL-H reduction to hemiacetal **67**, thereby providing a masked aldehyde bearing the required C-(7)—C-(8) diol stereochemistry of the natural product, for the key homoallylation step (*Scheme 10*).



Scheme 10

Isoprene underwent stereoselective addition to form **68** through the application of catalytic Ni(acac)$_2$ and stoichiometric triethylborane, to afford a 3:1 mixture of C-(6),C-(7) *anti* products in favour of the undesired diastereoisomer. The C-(1)—C-(9) fragment **70** was obtained from the isolated minor isomer through cross metathesis of the alkene **68** with methyl acrylate, followed by an oxa-Michael addition to the α,β-unsaturated ester. Stereocontrol of the cyclisation reaction was, as previously discussed, induced by the presence of the C-(35) methyl group (*cf*. *Figure 3*).

4.6 The Pagenkopf Group

4.6.1 Synthesis of the C-(18)—C-(34) Fragment of Amphidinolide C

The disconnections employed by Pagenkopf and Mora, illustrated in *Figure 9*, followed the orthodox macrolactone and C-(17)—C-(18) bond breakages to provide the C-(18)—C-(34) fragment **71** bearing suitable protecting groups.[28] The disconnection between the 2,5-*trans* tetrahydrofuran and tail region was envisioned to be the result of a stereoselective alkynylation reaction between an aldehyde and an enyne which would be followed by propargylic reduction, while formation of the central tetrahydrofuran was viewed as the product of the intramolecular, cobalt catalysed, oxidative radical cyclisation.

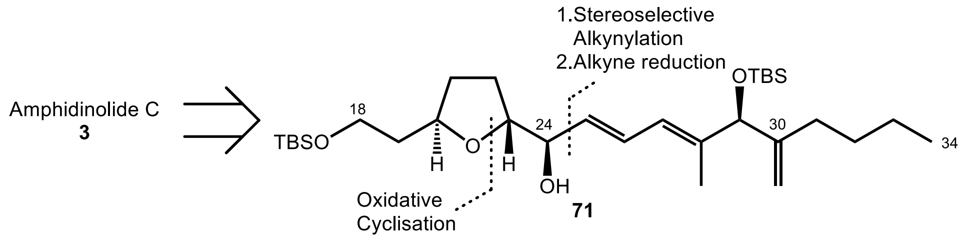
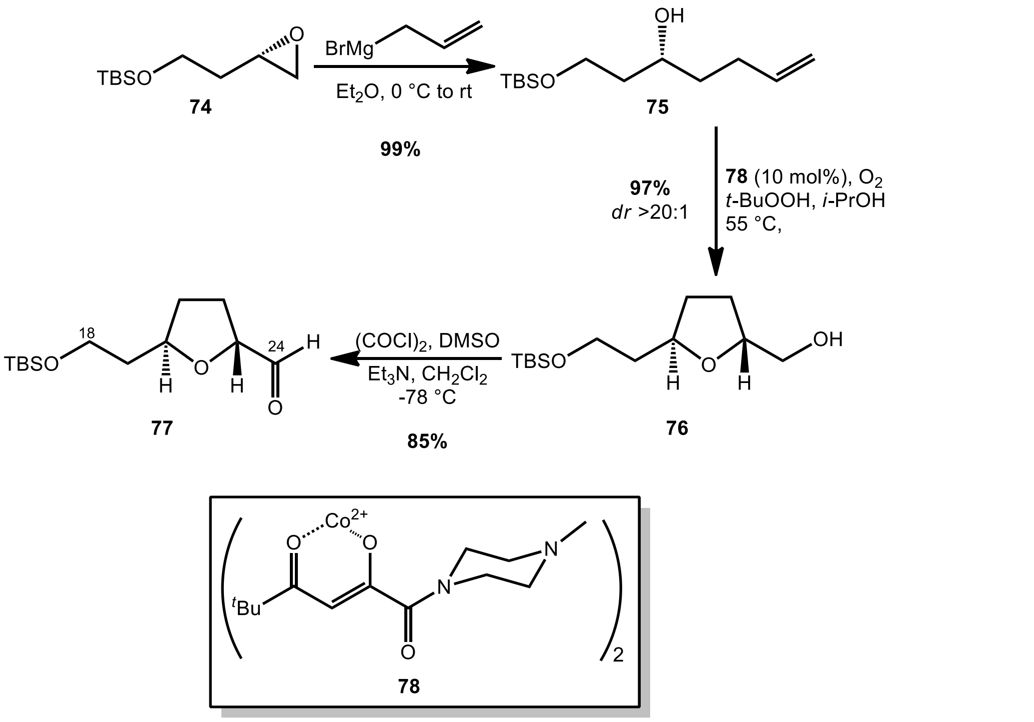


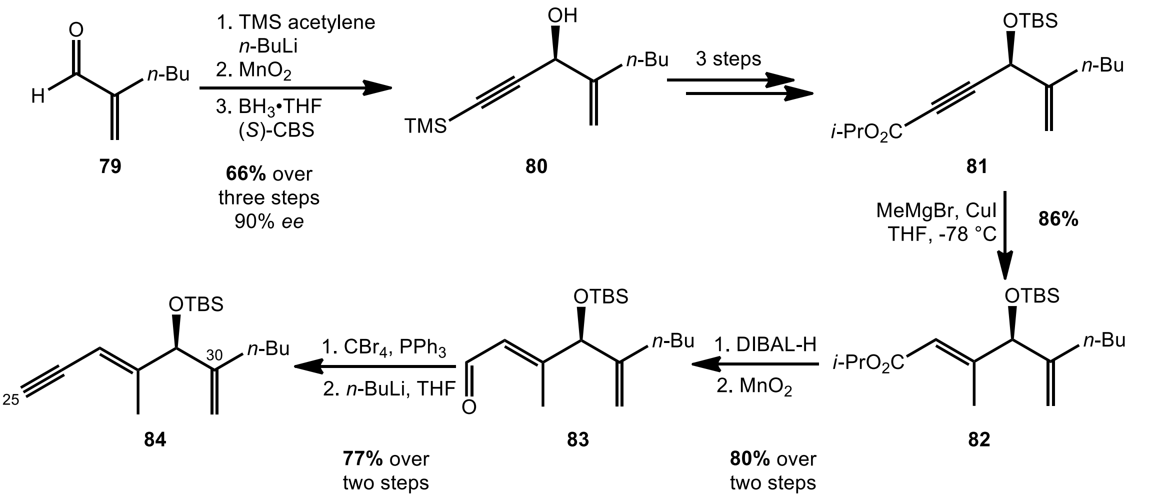
Figure 9

This synthesis is one of the more succinct routes to access the northern fragment of amphidinolide C allowing for an extremely rapid access to the 2,5-*trans* tetrahydrofuran using inexpensive starting materials, through an efficient cobalt(II) mediated cyclisation reaction which proceeds with remarkable stereoselectivity (*Scheme 11*). The same authors have recently reported on the utility of the cobalt cyclisation methodology for the preparation of the C-(3)—C-(6) tetrahydrofuran of the southern fragment of amphidinolide C.[29]

The construction of enyne **82** was accomplished through the nine step sequence detailed in *Scheme 12*. Installation of the C-(29) stereochemistry was accomplished through reagent controlled reduction, using the (*S*)-enantiomer of the Corey-Bakshi-Shibata reagent of an intermediate enone system, to provide allylic alcohol **78** in good yield and enantiomeric excess. Manipulation of the silyl protecting groups and formation of the propargylic ester **79** yielded a substrate that was amenable to the copper mediated 1,4-addition of a methyl group, affording the synthetic equivalent of the C-(40) methyl of the natural product. The C-(25)—C-(34) carbon backbone of the tail region of amphidinolide C was completed in a further four steps utilising Corey-Fuchs methodology to afford enyne **82**.

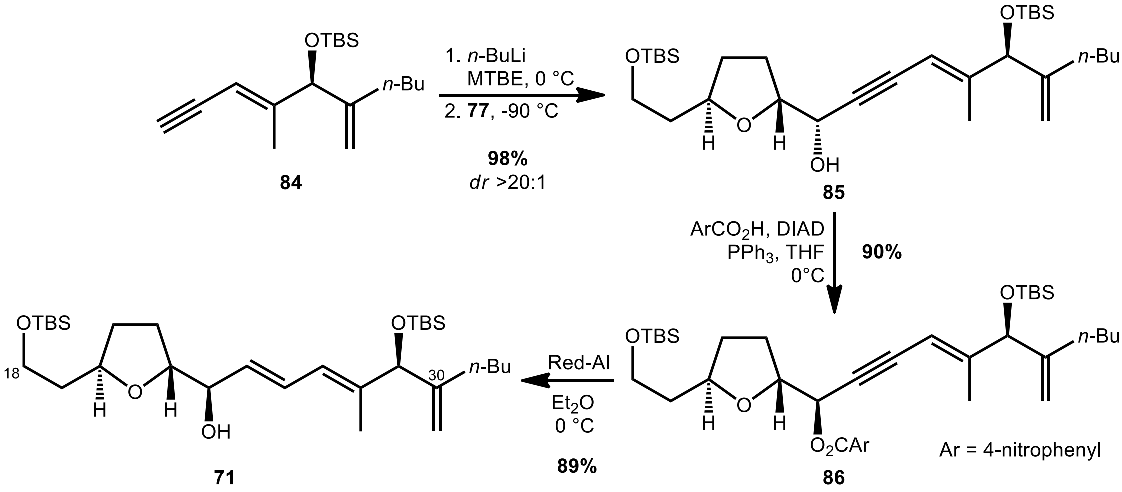


Scheme 11



Scheme 12

The stereoselective addition of lithiated alkyne **84** to aldehyde **77** was accomplished, after painstaking optimisation, to afford the C-(23)—C-(24) 1,2-*anti* diastereomer **85** as the sole product, in 93% yield (*Scheme 13*). Mitsunobu inversion of the C-(24) hydroxyl group was followed by treatment with Red-Al, leading to reduction of both the 4-nitrobenzoate group and the propargylic alcohol to form the required 2*E*,4*E*-dienol **71**. This sequence was reported to allow rapid access to gram scale quantities of the C-(18)—C-(34) fragment of amphidinolide and provides a concise sequence for construction of the 2,5-*trans* tetrahydrofuran core using cobalt catalysis.



Scheme 13

4.7 The Ferrié Group

4.7.1 Synthesis of the C-(1)—C-(9) Fragment of Amphidinolides C and F

2010 saw the publication of Ferrié and Figadére's route towards the C-(1)—C-(9) fragment of the macrolide core of amphidinolide C.[31] The disconnection at the lactone bond and at the C-(9)—C-(10) diene locus suggested vinyl stannane **87** as the synthetic goal of the project. Integration of the C-(1) methyl ester was envisaged as the product of C-glycosylation of an acylated hemiacetal, whilst the required 1,2-*anti* relationship of the C-(6) and C-(7) stereocentres was expected to result from a stereoselective Mukaiyama aldol reaction of a siloxyfuran and a suitably protected enatiopure aldehyde.

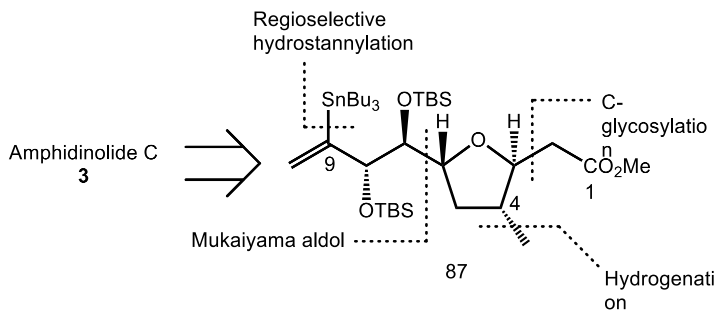
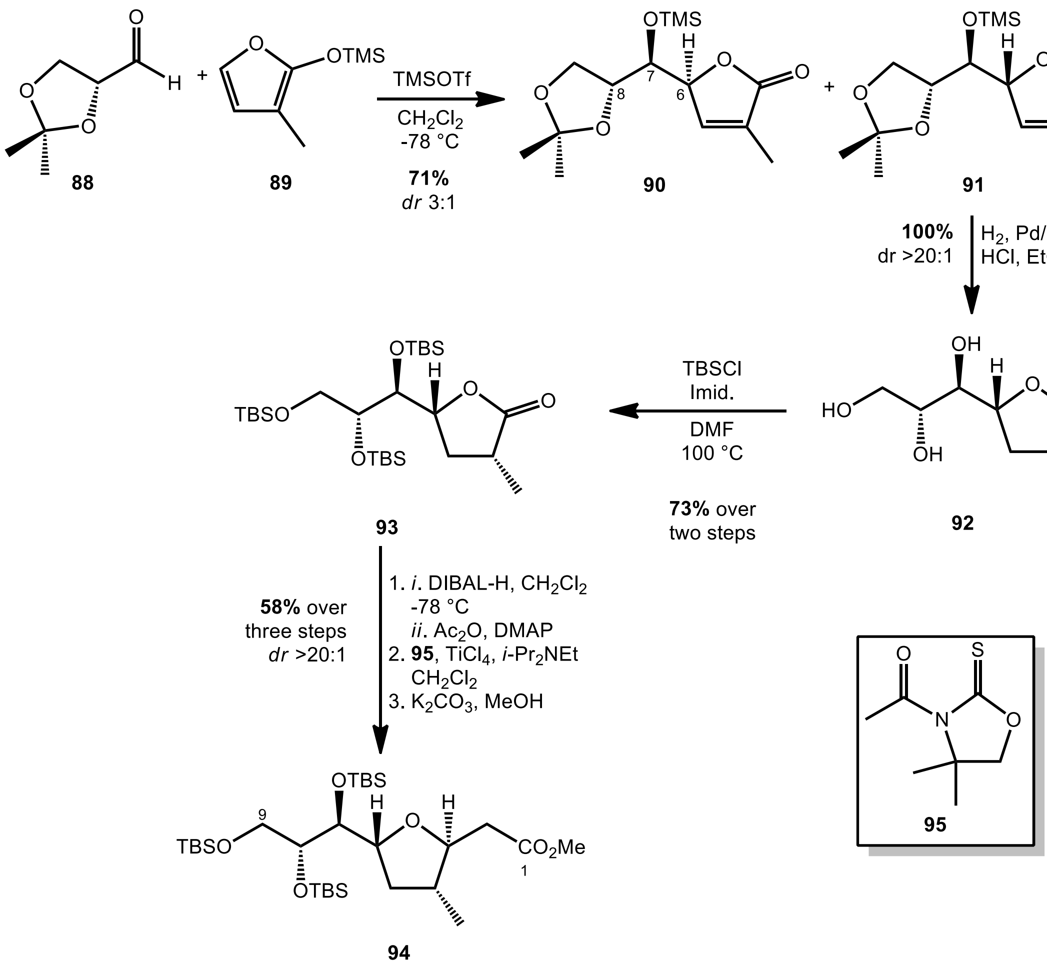


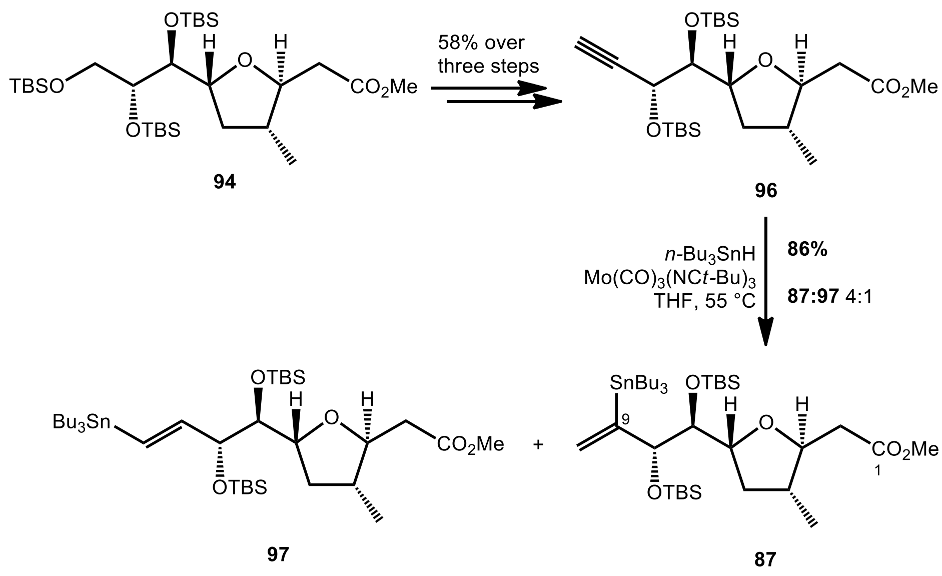
Figure 10

The approach taken towards the target **87** began from the TMS triflate catalysed aldol reaction of oxyfuran **89** and D-glyceraldehyde acetonide **88**, *Scheme 14*. The separable diastereomers resulting from the addition reaction, both provided the required 1,2-*anti*-relationship associated with the C-(7)—C-(8) diol, but were formed in a 3:1 mixture of C-(6) isomers. Hydrogenation of the endocyclic alkene bond from the least hindered face generated the required C-(35) methyl stereochemistry, whilst the acidic solvent system led to removal of both the acetonide and TMS groups. Threefold reprotection of the resultant triol **92** with TBS chloride afforded lactone **93**, which upon reduction and acetylation provided a protected hemiacetal precursor to the key $TiCl_4$ facilitated C-glycoslation reaction. Treatment of the intermediate with the titanium enolate of oxazolidinone **95** resulted in stereoselective access to the desired C-(3) isomer corresponding to the natural product.



Scheme 14

The completion of the synthesis was instigated through cleavage of the terminal TBS ether, partial oxidation of the resulting alcohol and homologation of the resultant aldehyde using the Bestmann-Ohira reagent to provide the alkyne **94** in good yield. The conversion of the alkyne into a synthetic handle for future assembly of the C-(9)—C-(10) bond was accomplished by formation of vinyl stannane **85** through regioselective, molybdenum catalysed hydrostannylation.[32]



Scheme 15

4.8 The Carter Group

4.8.1 Total Synthesis of Amphidinolide F

2012 saw publication by Carter and Mahapatra on the total synthesis of amphidinolide F, the first member of this sub-family of the amphidinolides to be synthesised.[33] The elegant methodology disclosed in the paper, built upon the solid foundations of a preceding publication in which the stereoselective construction of the C-(7)—C-(20) fragment of the macrolactone ring system was described.[34] The prior paper had excluded the construction of the 2,5-*trans* tetrahydrofuran ring systems, in favour of defining methodology for the synthesis of the C-(9)—C-(11) diene system, which they noted was difficult to prepare through conventional palladium cross-coupling methodology.[35]

The key strategic aspect of the total synthesis lay in the realisation that both the C-(3)—C-(6) and C-(20)—C-(23) tetrahydrofuran systems bore identical stereochemistry, and comparable functionalization on their neighbouring branched chains. This observation suggested that a common intermediate could be used as a keystone compound for the preparation of both northern and southern fragments, thereby reducing both the timeframe and cost of synthesis. The retrosynthesis of amphidinolide F, shown in *Figure 11*, details the requisite northern and southern fragments, in addition to the intermediate **100** that was hoped would be the antecedent to both.

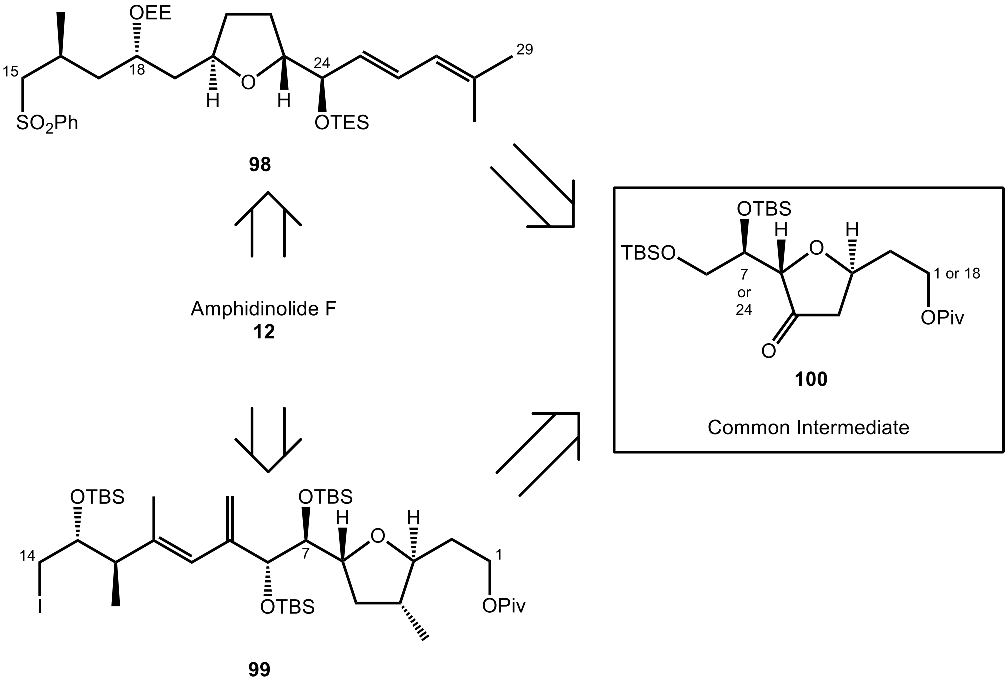
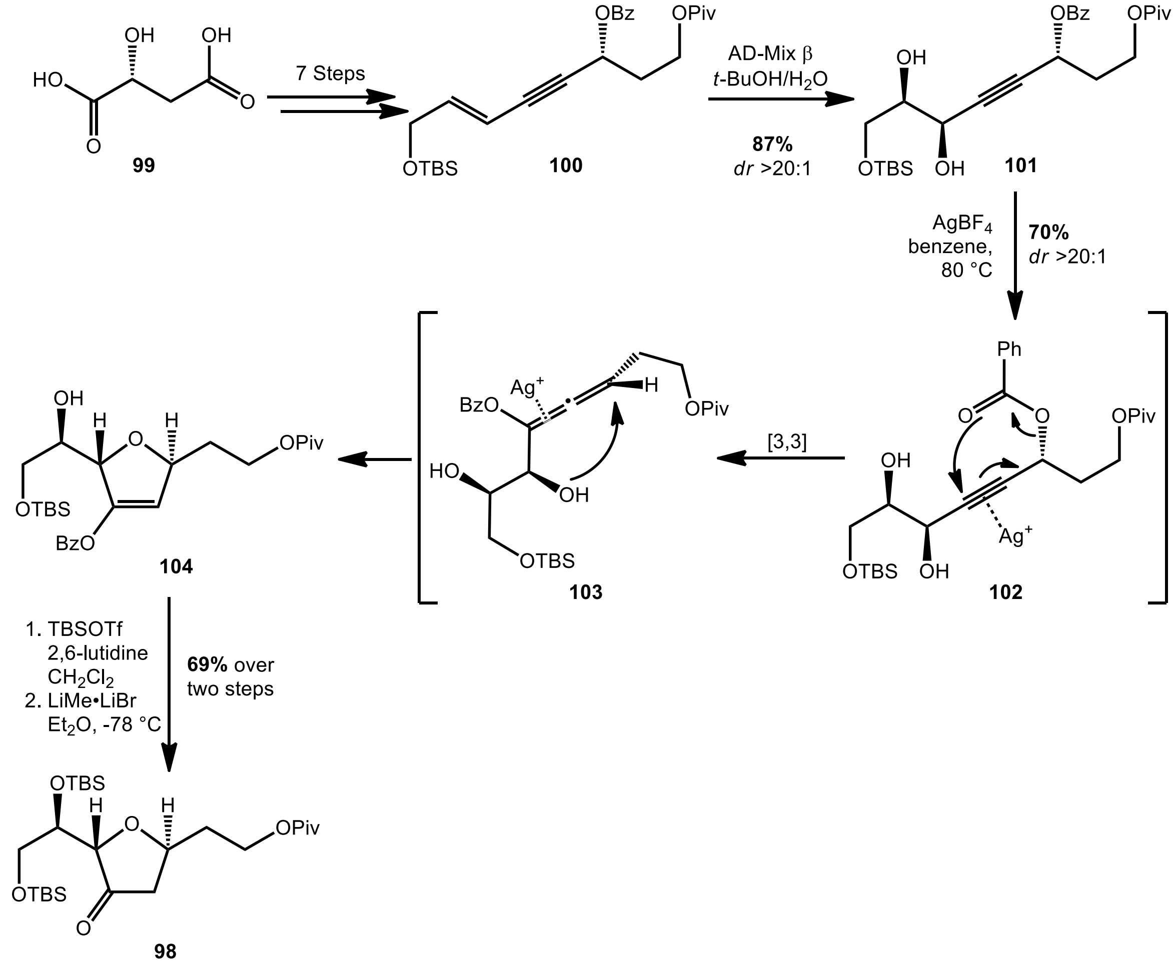


Figure 11

4.8.1.1 Synthesis of Common Intermediate

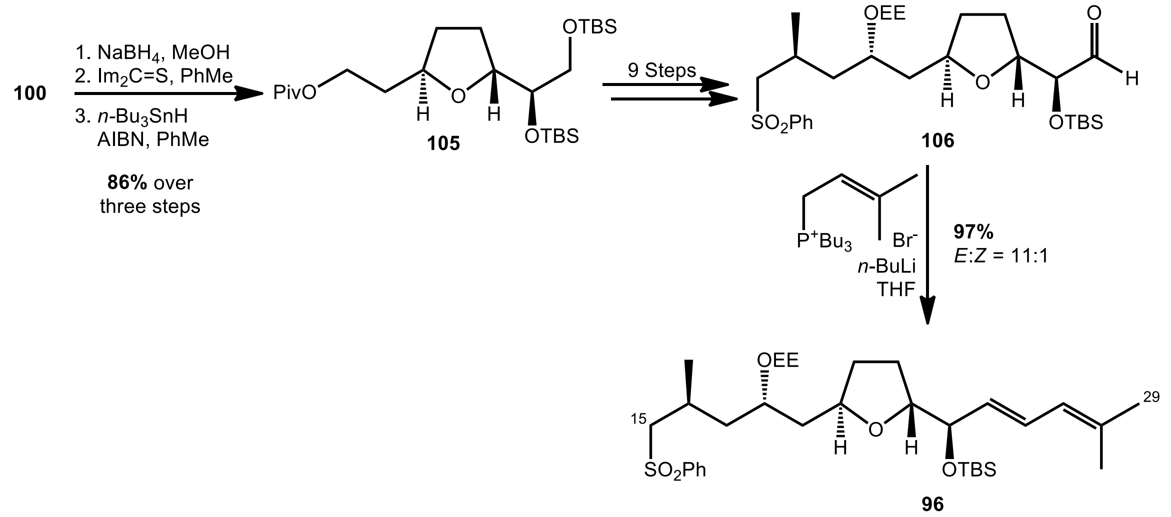
The approach adopted to synthesise the common intermediate began from enyne **100**, prepared in seven steps from D-malic acid **101**. Sharpless asymmetric dihydroxylation of the *E*-olefin provided diol **103** as a single diastereoisomer, thereby establishing what would later become the C-(6) and C-(23) stereocentres of the natural product. Treatment of the propargylic alcohol with a sub-stoichiometric quantity of silver tetrafluoroborate, in refluxing benzene, resulted in the the [3,3]-sigmatropic rearrangement of the intermediate silver complex **104** (*Scheme 16)*. The initial stereochemistry and suprafacial shift of the benzoyl ester provided transfer of stereogenicity to the allenyl intermediate **105** allowing for a stereospecific 5-*endo-trig* cyclisation to the desired dihydrofuran **106**. On protection of the secondary alcohol and methanolysis of the benzoyl ester, 2,5-*trans* tetrahydrofuranone **100** was isolated as a single diastereoisomer.



Scheme 16

4.8.1.2 Diversification of Common Intermediate to the C-(15)—C-(29) Northern Fragment

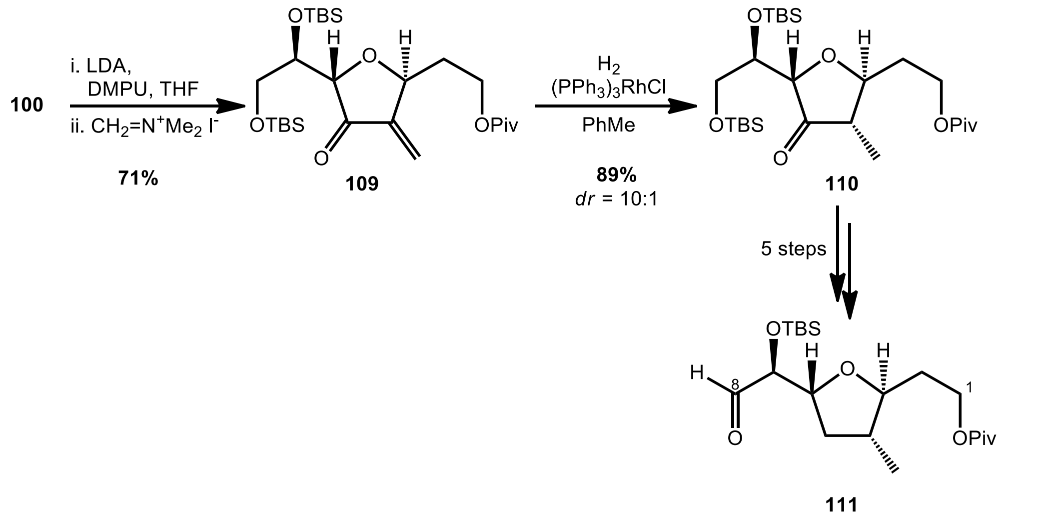
Synthesis of the C-(15)—C-(25) backbone of the Northern fragment began with deletion of the C-(21) carbonyl group. This transformation was achieved through reduction of the group to give a mixture of diastereomeric alcohols followed by radical deoxygenation of the thiocarbamates produced from the alcohols to afford tetrahydrofuran **107** (*Scheme 17*). Further manipulation of functionality led to aldehyde **108** which underwent Wittig olefination in excellent yield, providing the required diene **98** with the C-(25)—C-(28) **(***E*,*E*)-stereochemistry found in the natural product.



Scheme 17

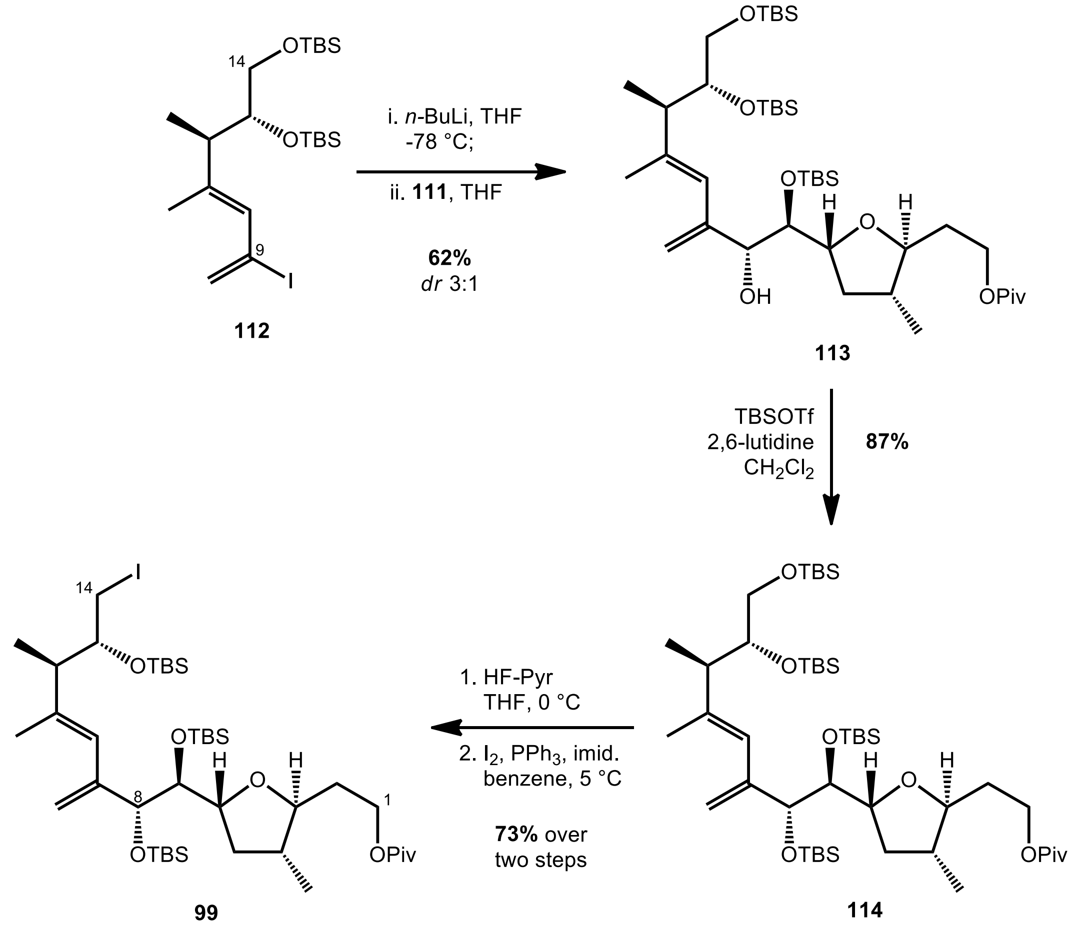
4.8.1.3 Diversification of Common Intermediate to the C-(1)—C-(14) Southern Fragment

Installation of the C-(35) methyl group was achieved through Mannich reaction of the lithium enolate of **100** with Eschenmoser's salt, and stereoselective hydrogenation using Wilkinson's catalyst thereby affording intermediate **110**. Deletion of the superfluous carbonyl functionality was again achieved through the use of radical hydride substitution methodology (*Scheme 18*).



Scheme 18

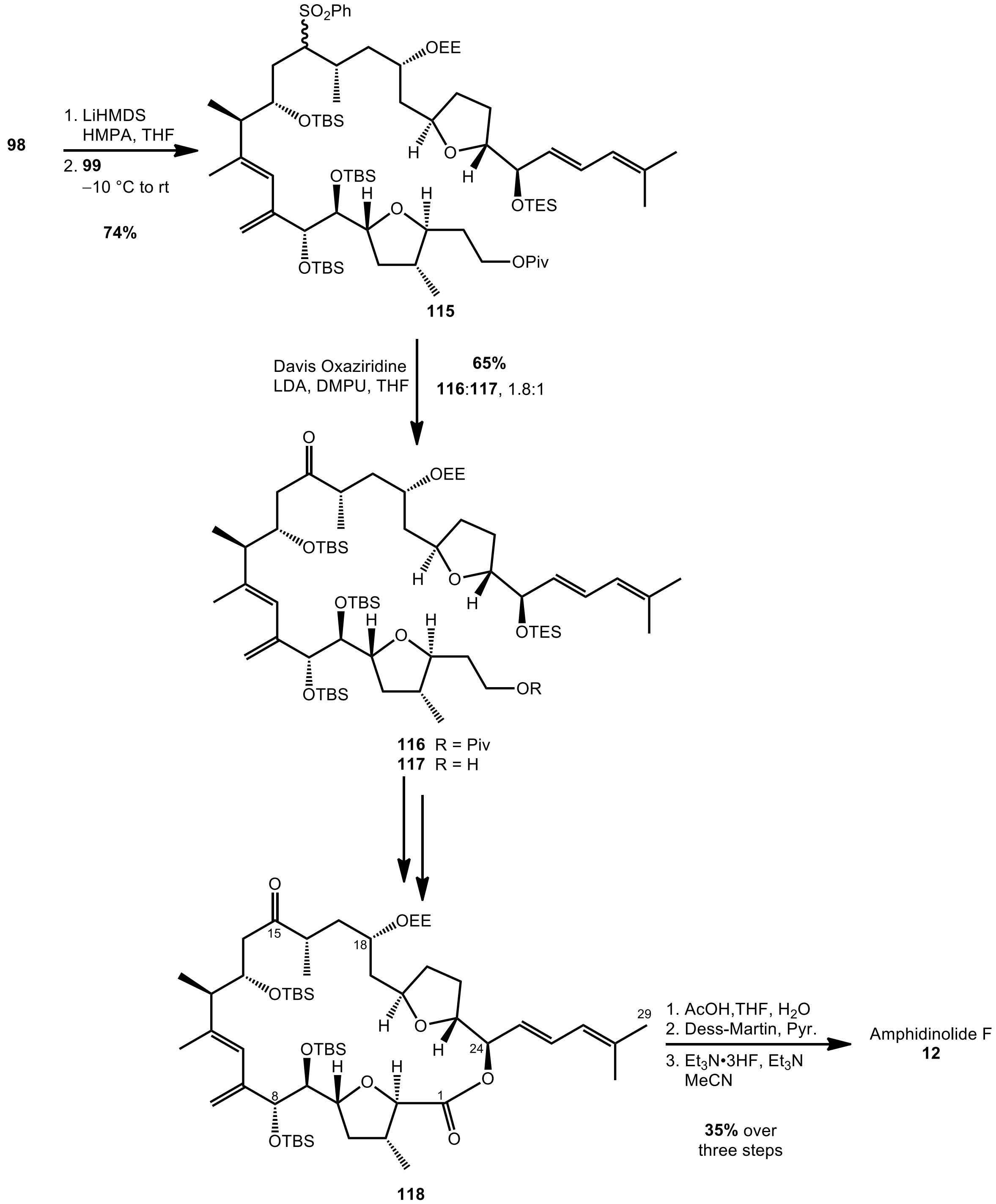
The C-(9)—C-(14) vinylic iodide **112**, prepared using chemistry developed within the group previously,[34] was activated through lithium-halogen exchange and added to aldehyde **111**. Alcohol **113**, bearing the required C-(8) stereochemistry was fashioned through Felkin-Anh controlled addition and protected as a TBS ether. Further functionalization of compound **114** led to alkyl iodide **99**, the electrophilic coupling partner required for the key C-(14)—C-(15) sulfone alkylation step.



Scheme 19

4.8.1.4 Union of Northern and Southern Fragments and Completion of Synthesis

Alkylation of sulfone **98** with alkyl iodide **99** proceeded in good yield to provide the C-(1)—C-(29) fragment **115**. However, subsequent oxidative desulfurisation, although leading to the clean formation of the C-(18) ketone, afforded a mixture of C-(1) pivaloyl ester protected and deprotected products **116** and **117**. Independent manipulation of both compounds to form the pertinent carboxylic acid, was followed by C-(24) TES deprotection setting the stage for a Yamaguchi macrolactonisation which afforded **118** in 65% yield. The synthesis of amphidinolide F **12** was completed in a further three operations comprising the removal of the C-(15) ethoxyethyl ether, oxidation of the resultant secondary alcohol and universal cleavage of the extant TBS ethers.


98
1. LiHMDS HMPA, THF
2. 99 −10 °C to rt
74%
SO2Ph
OEE
OTBS
OTES
OPiv
115
Davis Oxaziridine LDA, DMPU, THF
65%
116:117, 1.8:1
OR
116 R = Piv
117 R = H
118
1. AcOH,THF, H2O
2. Dess-Martin, Pyr.
3. Et3N•3HF, Et3N MeCN
35% over three steps
Amphidinolide F
12

Scheme 20

5 Carbenes and Metal Carbenoids

5.1 Carbene Structure

Carbenes have been postulated as reaction intermediates since the early days of organic synthesis, when the decomposition of relatively simple precursors led to products that were explainable only through invocation of such transient species. At the most basic level carbenes are divalent carbon species containing a neutral carbon atom bearing two unshared valence electrons.[36] Methylene, the simplest member of the family, is a highly reactive and difficult to control reactive intermediate that was first definitively identified and studied in the early 1960s.[37] Subsequent studies of functionalised carbenes, have led to a greater understanding of the reactivity of this unique species and have even led to the isolation and study of so-called persistent carbenes. Carbenes can exist in one of two possible electronic structures, namely the singlet and triplet states, shown in *Figure 12*.[38]

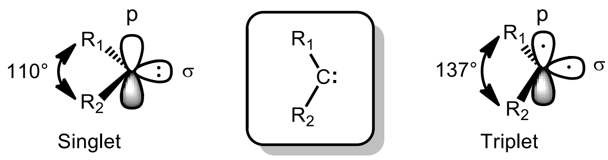


Figure 12

The triplet state contains two unpaired electrons within the σ and p orbitals and resembles a diradical carbon centre in which the dihedral angle between the R groups is generally within the range of 130 to 150°. The triplet state exists when the energy gap between the σ and p orbitals is small allowing for an electron to remain unpaired and inhabit each of the orbitals in accordance with Hund's rule of maximum multiplicity. By virtue of the unpaired nature of electrons in the triplet state, carbenes of this type are paramagnetic and can be identified by ESR spectroscopy, provided the lifetime of the species is sufficiently long lived.[38]

In contrast, if the energy gap between the σ and p orbitals is large the electrons will pair within the σ orbital leading to singlet carbenes. This paired configuration of electrons provides a neutral carbon centre of ambiphilic character (*i.e.* exemplified by the ability to exhibit both carbocationic and carbanionic behaviour) due to the s orbital lone pair and the vacant p orbitals. The singlet state is generally of higher energy and is therefore of greater reactivity than the triplet state. The increased energy cost of pairing electrons can be mitigated through the ability of the empty p orbital to accept electron density from adjacent electronegative atoms, as illustrated in *Figure 13*, thereby perturbing the originally degenerate orbitals on the carbon centre and stabilising the singlet carbene.[39]

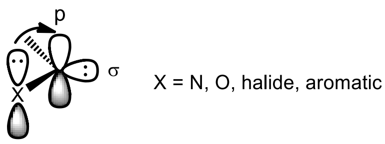
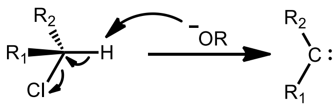


Figure 13

5.2 The Generation of Carbenes

Carbenes are generally prepared by base induced α-elimination of haloalkanes or through controlled decomposition of nitrogen from a stabilised intermediate. Historically, carbenes were postulated as plausible reaction intermediates based upon experimental observations. Butlerov's experiments concerning the reaction of copper with methyl iodide afforded ethylene, which was considered to be the result of the dimerization of methylene.[40] As early as 1862, Geuther proposed that the basic hydrolysis of chloroform provided dichloromethylene,[41] a result that has since been substantiated to proceed via an α-elimination mechanism, as shown in *Scheme 21*.[42]

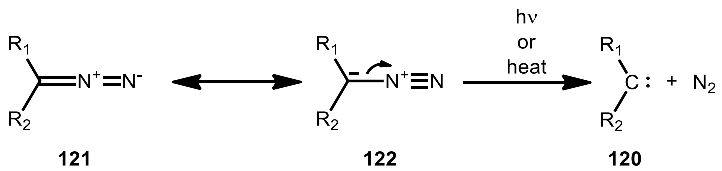
Trihalomethanes generally provide the best precursor compounds for this type of reaction providing dihalocarbenes as the intermediates. Chloroform can be used to form dichlorocarbene using hydroxide as the base, but formation of alkyl carbenes from alkyl halides requires a more powerful base such as *t*-BuLi due to the possibility of alkene formation through ß-elimination.[43]



119 **120**

Scheme 21

The early years of the 20th century saw work published by Buchner[44] and Staudinger[45] on the decomposition of diazo compounds and reactions of the intermediate carbene species. Diazo groups can be liberated in the form of nitrogen gas from suitable starting materials through thermolysis and photolysis (*Scheme 22*). The inherent instability of alkyl diazo groups, and the safety issues associated with their explosive potential and carcinogenicity,[46] led to work on more stable precursors such as diazirines[47] and sulfonyl hydrazine salts[48] which can also undergo photolytic and thermolytic decomposition to form carbenes. Upon formation, free carbenes are promiscuous in their behaviour towards various functional groups which limits their application in useful synthesis to all but the most simple of compounds.



Scheme 22

5.3 Metal Carbenoids

The potential of carbenes to accomplish various synthetically valuable procedures was realised in the early days of organic synthesis, but it was not until the 1960's when Fischer[49] and Schrock[50] independently stabilised carbenes within the coordination spheres of metal centres, that carbene chemistry became of significant practical use. Metal carbenoids, or metallocarbenes, are reactive intermediates formed by the nucleophilic attack of a diazo compound into the empty orbital of Lewis acidic transition metal centre as shown in *Figure 14*. Loss of nitrogen from the complex results in a transient metallocarbene species, which is stabilised by back donation from the d-orbitals of the metal centre to the vacant p-orbitals of the carbon centre. Despite exhibiting corresponding reactivity, metal carbenoids have fully tetravalent carbons and cannot therefore be described absolutely as carbenes. In the presence of electron-rich substrates (S:) a reaction proceeds whereby a new carbon—substrate bond is formed and the metal-ligand complex returned to the catalytic cycle.[51]

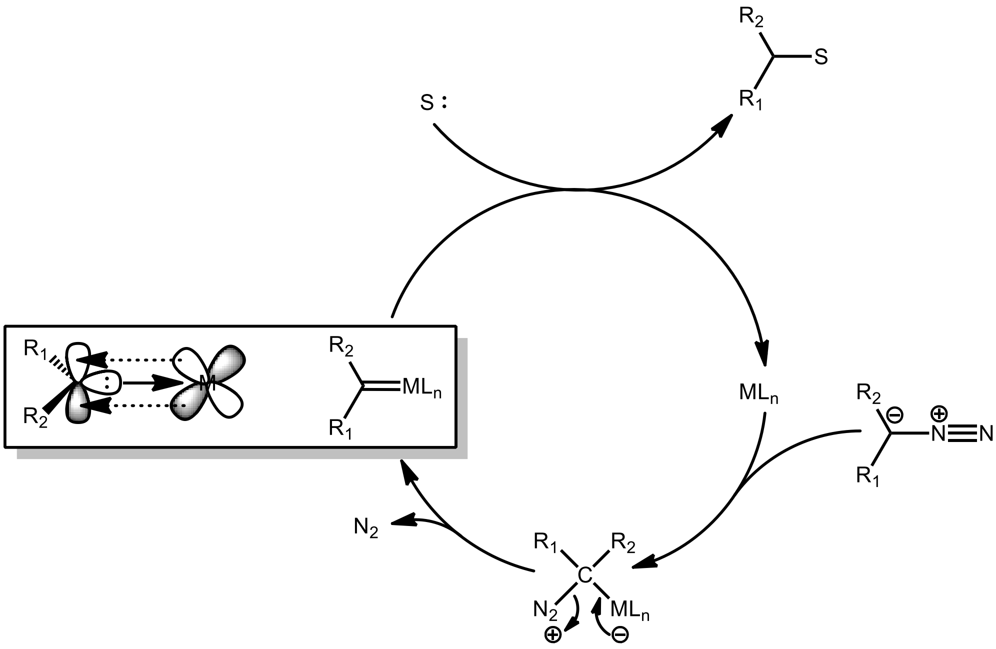
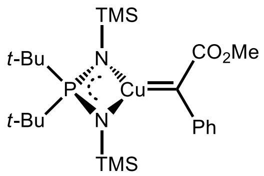


Figure 14

The high reactivities of metal carbenoids means that they are transient species, generally formed within the reaction and used *in situ* to form the desired products. However, 2001 saw the publication of work by Hofmann in which the relatively long-lived copper carbenoid **123** was prepared and detected in solution by NMR spectroscopy.[52] In the same year a stable rhodium carbenoid was isolated by the groups of Snyder and Arduengo and was analysed by X-ray crystallography, providing the first incontrovertible proof of metallocarbene structure.[53]



123

Figure 15

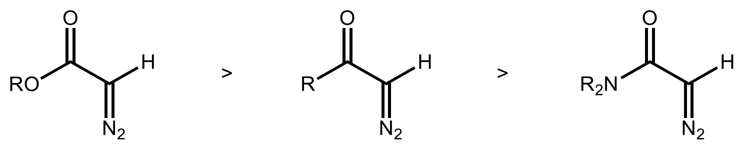
5.4 Diazo compounds as Metal Carbenoid Precursors

5.4.1 Electronic character of Metal Carbenoids

The electrophilicity of metallocarbene intermediates has been shown to be of key importance in controlling the chemo-, regio- and stereoselective outcomes of reactions, particularly those involving C-H insertion. The electrophilic character of the intermediate species is determined partly from the ligands used on the metal catalyst and partly from the substituents of the parent diazo compound.[54] Metallocarbenes possesing low electrophilic character display inferior reactivity in comparison to their more electron-poor analogues, but superfluous electrophilicity can lead to significant side-product formation. The mesomeric effect of flanking electron-withdrawing groups offers stabilisation to diazo compounds, thereby providing viable synthetic intermediates for subsequent transformations.[55] The dinitrogen of the diazo functionality is easily liberated by application of photo or thermolytic excitation, and is decomposed readily in the presence of acid catalysis. In the case of alkyl diazo compounds, such as diazomethane, this facile decomposition presents significant safety risks and hence α-diazo carbonyl substrates are the preferred option for the generation of metal carbenoids due to their improved safety profile.[56] Modern synthetic techniques tend towards the preparation of α-diazo carbonyl compounds as a means of both stabilising the diazo group and tuning the electrophilicity of the compounds to deliver useful reactivity. Metallocarbenes derived from these types of compounds can be subdivided into three categories:

1. Acceptor substrates containing an electron-withdrawing group. Generation of metal carbenoid intermediates can be achieved by reaction of various metal catalysts with diazo compounds of the type shown in *Figure 16*. The general trend of decreasing reactivity of metallocarbenes derived from these types of compounds progresses from α-diazoacetates **124**, through α-diazoketones **125** to α-diazoacetamides **126**.[57]

Extrusion of nitrogen from these compounds can be achieved using a variety of metals to provide moderate electrophilicity in the resulting metal carbenoid, and hence high degrees of reactivity are noted within this class of compound.

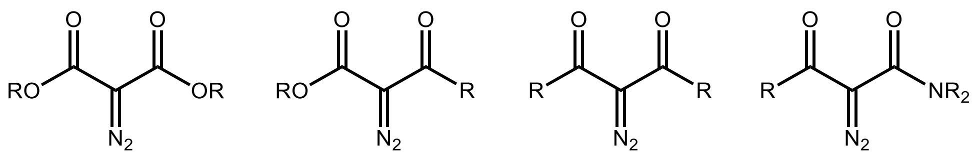


124 **125** **126**

Figure 16

2. Acceptor-acceptor substrates containing two electron-withdrawing groups.

Metallocarbenes derived from compounds of the type shown in *Figure 17* demonstrate enhanced stability, due to the presence of two electron-withdrawing groups flanking the carbenoid centre. The presence of two electron-withdrawing groups deactivates these compounds towards forming metallocarbenes, hence there is a requirement for highly reactive metal complexes in order to decompose the diazo functionality. The highly electrophilic nature of the resultant species provides increased reactivity when compared to those generated from a single acceptor substrate.[58]

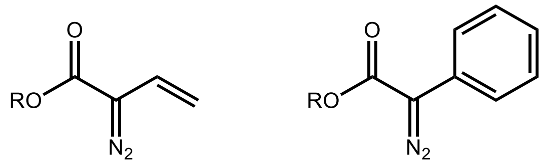


127 128 129 130

Figure 17

3. Those containing an electron-withdrawing group and an electron-donating group (acceptor-donor substrate)

The third category of metallocarbenes is that covering intermediates derived from α-diazo compounds of type **131** and **132**. These compounds remained relatively unexplored until the work of Davies in 1997, when the first example of C-H insertion was reported using these reagents.[59] The stabilising influence of the electron-withdrawing group when combined with the resonance donation of an adjacent π-system provides a push-pull system which affords a stabilised metallocarbene. Due to the increased stability of the starting materials, highly reactive metal catalysts are required to convert the diazo functionality into metallocarbenes, but the reactivity of the formed intermediate is moderated, leading to greater chemoselectivity in subsequent transformations.[60]



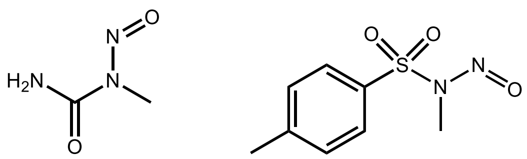
131 **132**

Figure 18

5.5 Formation of α-Diazo Compounds

5.5.1 Diazomethane Formation and Application to α-Diazoketone Formation

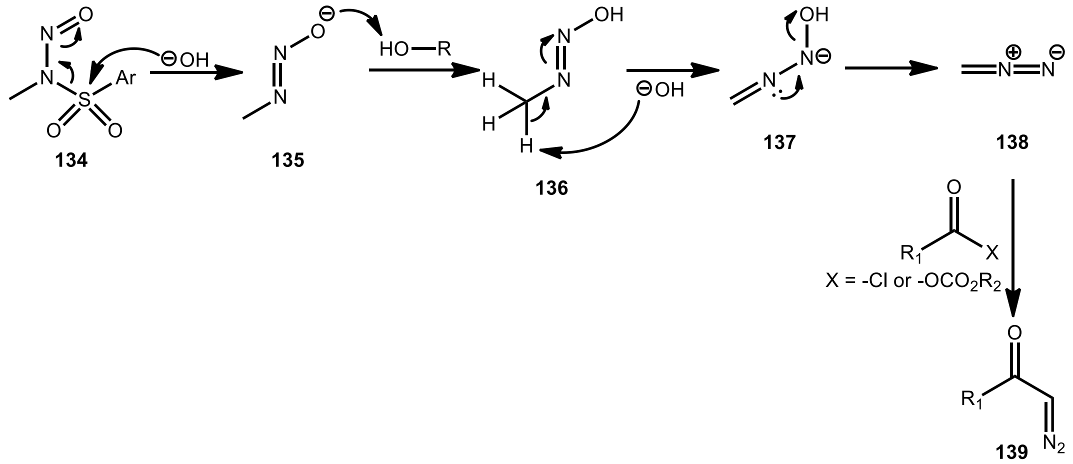
In order to access the key diazo functionality, required for the preparation of metal carbenoids, several methods have been developed to introduce the moiety into synthetically useful compounds. The simplest alkyl diazo compound is diazomethane **138** which was traditionally prepared by the base mediated decomposition of *N*-nitroso-*N*-methylurea **133** through the method of von Pechmann.[61]



133 **134**

Figure 19

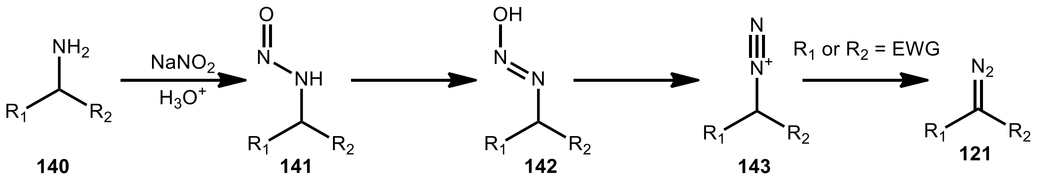
The instability of this precursor to shock and temperatures greater than 20 °C led to the development of Diazald® **134** (*N*-Methyl-*N*-(*p*-tolylsulfonyl)nitrosamide) as a more stable alternative.[62] The mechanism of diazald decomposition to diazomethane **138**, and its subsequent use for the synthesis of α-diazocarbonyl compounds, is shown in *Scheme 23*. Diazomethane is toxic and explosive, although the risk can be minimised by confining the decomposition reaction within specialised glassware and co-distilling the product with diethyl ether.[63] Diazomethane is never isolated pure, but is instead used as a dilute ethereal solution in subsequent transformations. In the case of α-diazo carbonyls **139**, this routinely involves the introduction of an activated acetyl group, typically an acid chloride or mixed anhydride, into the bulk solution of diazomethane.



Scheme 23

5.5.2 Diazotisation of Amines

Diazo groups can be accessed by treatment of amines with nitrous acid, normally generated through reaction of nitrite salts and aqueous acid at low temperature (*Scheme 24*).

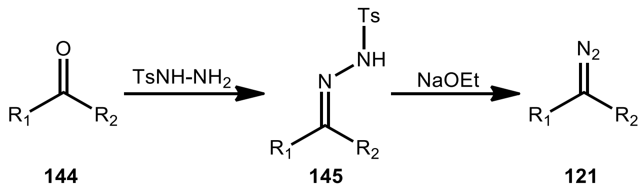


Scheme 24

In the presence of flanking electron-withdrawing groups the resultant diazonium salt can undergo elimination of the acidic proton leading to formation of an α-diazo carbonyl species. Curtius prepared ethyl diazoacetate from glycine ethyl ester hydrochloride using this method as early as 1883.[64] Alternatively, alkyl nitrite reagents can be used to produce α-diazo carbonyl compounds in cases where an organic soilvent is preferred over the traditional aqueous solvent systems.[65]

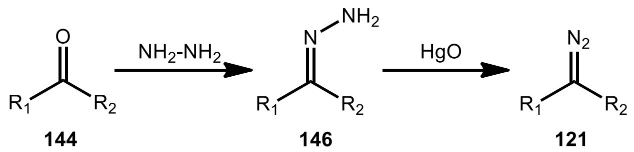
5.5.3 Decomposition of Hydrazones and Oximes

The Bamford-Stevens reaction is a method for the preparation of diazo compounds from corresponding ketones and aldehydes. The preliminary step in the sequence, shown in *Scheme 25*, requires the formation of a tosyl hydrazone **145** which upon exposure to base decomposes to form the diazo compound **121**, through deprotonation and elimination of the *p*-toluenesulfinate ion. The Bamford-Stevens reaction is generally conducted at elevated temperature and so only stabilised diazo compounds, such as those bearing adjacent aryl substitutions, can be isolated from this reaction. Nonstabilised alkyl diazo intermediates undergo thermal decomposition, leading to a carbene based rearrangement of the compound to form olefins.[66]



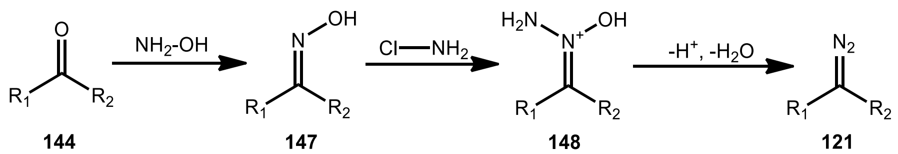
Scheme 25

Oxidation of hydrazones offers an alternative route for the preparation of the diazo functionality (*Scheme 26*). Initially this reaction was reported by Curtius in 1889 using mercuric oxide in the preparation.[67] Subsequent work demonstrated that other heavy metal salts such as $Pb(OAc)_4$,[68] MnO_2[55] and AgO[69] can promote the same transformation. A less toxic variant, in which Swern oxidation conditions are employed, was recently published by Brewer and Javed.[70]



Scheme 26

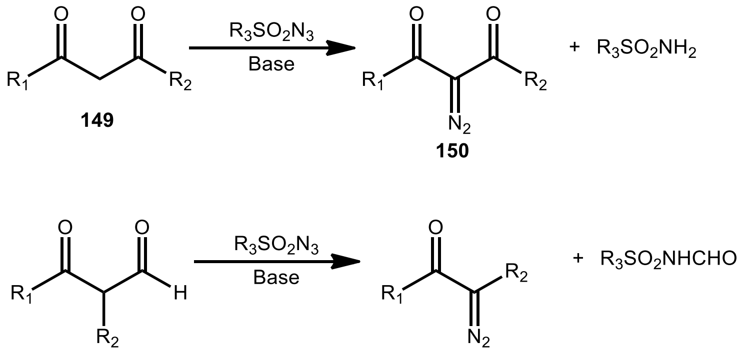
An associated reaction is the Forster Reaction in which an oxime is treated with chloroamine to afford the intermediate **148**, which readily decomposes to the related diazo compound (*Scheme 27*). Although diazomethane can be prepared from formaldehyde by this method it has not found widespread applicability.[71]



Scheme 27

5.5.4 Regitz Diazo Transfer

Arenesulfonyl azides were shown by Regitz to transfer diazo functionality to suitably activated carbonyl systems (*Scheme 28*).[72] This methodology is limited to compounds such as malonates and β-ketoesters where the α-protons are sufficiently acidic for the reaction to proceed. The scope of the Regitz methodology can be augmented through the use of an aldehyde as the second activating group, in which case deacetylation leads to α-diazo compounds of type **152**.[73]



Scheme 28

6 Metal Carbenoid Transformations

The stabilising influence of the metal-ligand complex in metallocarbenes has led to a proliferation of their synthetic uses over the course of the last thirty years. The three major transformations in which they have been used are cyclopropanation, insertion reactions and in the formation of ylides coupled with their subsequent rearrangement chemistry.

6.1 Carbenoid Mediated Cyclopropanation

Addition of a carbene species to olefin has long been known to afford a cyclopropane, a recurrent motif amongst natural products occurring in plant defence and in synthetic insecticides. In 1958, Simmons and Smith described the reaction of methylene carbenoid, generated by reaction of diiodomethane and a zinc-copper couple, adding to various alkenes to provide cyclopropanes.[74] Subsequent advances in metal carbenoid formation, through decomposition of diazo compounds with chiral metal complexes, has led the way to both enatio- and diasteroselective transformations but a thorough review of which remains outwith the scope of this narrative. Various metals, including Cu, Rh, Ru, Mo, Fe, Co, Ir and Pd have been shown to generate metal carbenoids from diazo compounds,[75] which subsequently undergo cyclopropanation in the presence of alkenes, or cyclopropenation when reacted with alkynes. Additionally, numerous ligands have been developed which can impart chiral information to these reactions leading to enantioselective transformations in both inter and intramolecular fashion.

As shown in *Figure 20*, upon formation of the metal carbenoid and introduction to an olefin, the complex undergoes concerted [2+1] cycloaddition to afford the cyclopropane system with regeneration of the catalyst.[51, 76] Palladium complexes can also be used to decompose diazo compounds to form palladium carbenoids, which although undergoing cyclopropanation reactions, do so through an alternative mechanism involving a formal [2+2] addition of the carbenoid across the alkene, followed by reductive elimination of the metal centre.[77]

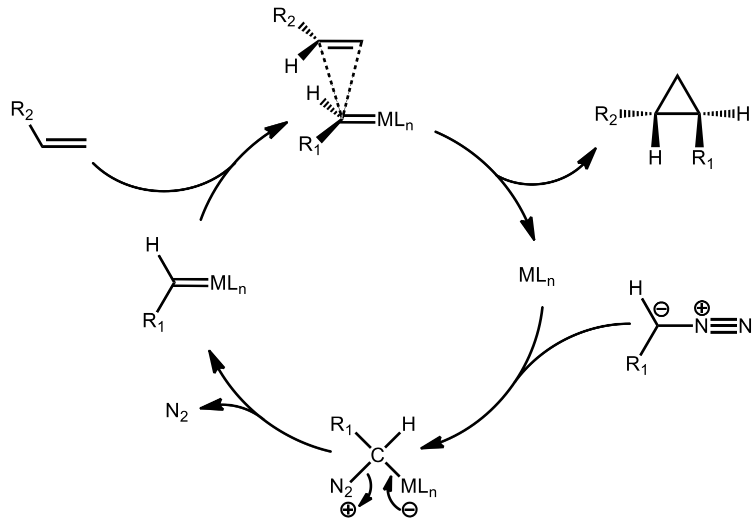
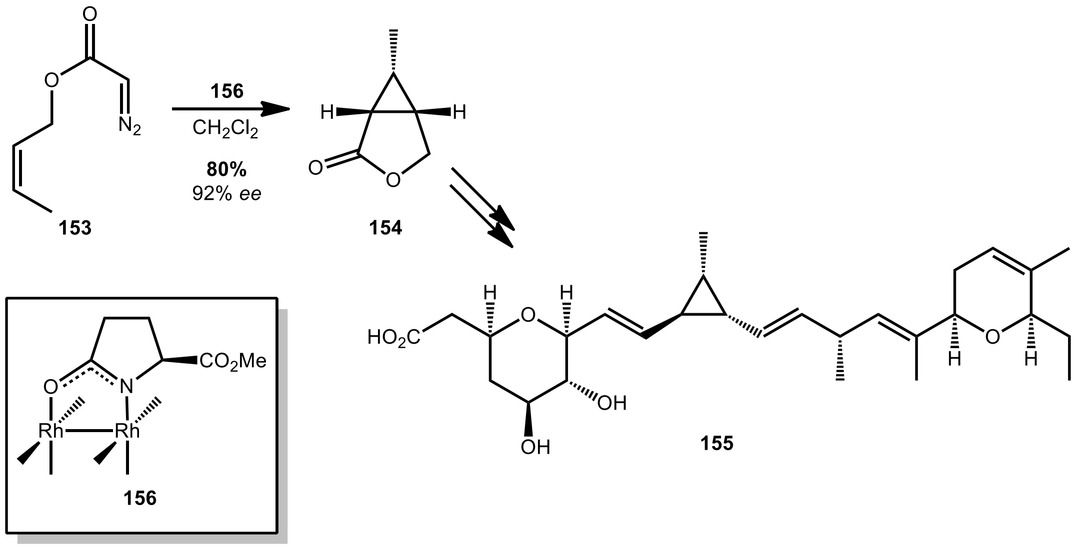


Figure 20

The use of metal carbenoid catalysed cyclopropanation is widespread within literature due to the many applications of the methodology in the total syntheses of natural products. A good example of the synthetic utility of this reaction is Martin's total synthesis of (+)-ambruticin S **155**, an antibiotic derived from *Polyangium cellulosum*. The central divinyl cyclopropane unit of the synthetic product was prepared through an intramolecular, asymmetric dirhodium carboxamide catalysed, cyclopropanation of alkene **153** (*Scheme 29*).[78]



Scheme 29

6.2 Carbenoid Insertion Reactions

The ability of a carbenoid to insert into R-H bonds (R = C, S, Si, O, N) is a long recognized phenomenon in the field.[79] Early work on carbene C-H insertion reactions focussed on the ability of the carbenes methylene and dichloromethylene to react with simple aliphatic acyclic and cyclic systems. These reactions were found to be chemoselectively and regioselectively uncontrollable, leading to the comment by Doering that *"methylene must be classified as the most indiscriminate reagent known in organic chemistry"*.[80] The relative stability of metal carbenoids has circumvented this promiscuous behaviour resulting in more controllable reactivity and synthetic utility, in which specific bonds are activated for insertion.[79] Classical C-H insertion reactions were traditionally carried out using copper activation, but the advent of dirhodium complexes as catalysts for the formation of metal carbenoids has led to advances in both the regio- and stereocontrol of this reaction.

Doyle suggested a mechanism for C-H insertion, in which overlap of the p-orbitals of the metal bound centre of the carbenoid with the σ-orbital of the activated C-H bond initiates a three- or four-membered cyclic transition state. The dissociation of the carbenoid-stabilising metal proceeds with concerted migration of the hydrogen atom thereby providing the insertion product and regenerating catalyst (*Figure 21*).[81]

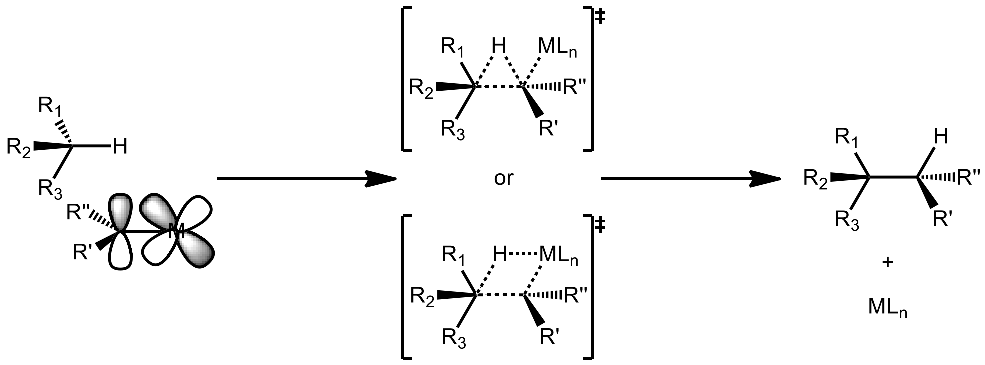


Figure 21

C-H insertion reactions involving carbenoid intermediates are generally conducted intramolecularly on systems bearing restricted molecular geometry, in order to control the diastereoselectivity of the reaction. C-H Insertion reactions tend towards the formation of five-membered cyclic systems through a pseudo-chair transition state first propose by Taber and co-workers (*Figure 22*).[82]

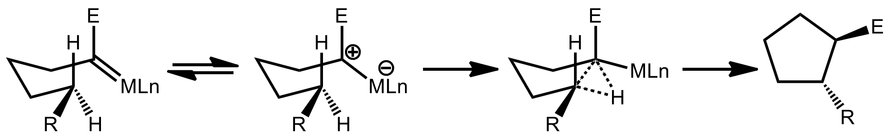


Figure 22

6.3 Ylide Formation

In the presence of Lewis bases, metallocarbenoids have been shown to form ylides or ylide-like intermediates that are prone to undergo subsequent rearrangement chemistry.[83] Ethers, sulfides, tertiary amines, carbonyls and imines have all been shown to provide non-bonding electrons for formation of these short lived intermediates (*Figure 23*).[84]

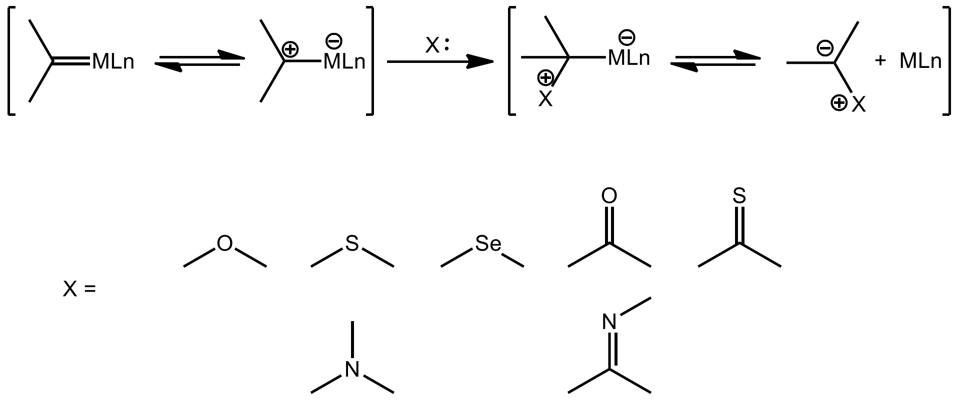


Figure 23

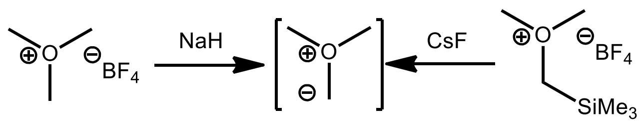
7 Oxonium Ylides

At the most basic level, oxonium ylides are a species bearing a positively charged oxygen atom adjacent to negatively charged carbon atom. Unlike their ammonium and sulfonium counterparts, oxonium ylides are a short lived species which have never been isolated and whose existence is imputed only through isolation of the products they form. Recent years have seen great interest in oxonium ylides as transient synthetic species through the simplified methodologies used in their generation and a better understanding of the synthetic outcomes of their use.[83]

7.1 Formation of Oxonium Ylides

7.1.1 Generation of Oxonium Ylides from Oxonium Salts

Two profoundly different methods have been used for the generation of oxonium ylides from readily accessible starting materials, the most prevalent being treatment of a metal carbenoid with an ether. An alternative methodology which gave the earliest verifiable example of oxonium ylide formation, results from the manipulation of simple oxonium salts. Olah reported in the early 1980's that trimethyloxonium tetrafluoroborate **157** could be deprotonated using sodium hydride to yield methoxyethane **159**, the result of a [1,2]-shift of a methyl group from the oxonium centre. This result, combined with the isolation of a product mixture consistant with the transient formation of the oxonium ylide **158**, provided evidence of the putative intermediate species (*Scheme 30*).[85]



157 158 160

159

Scheme 30

Supplementary work on the fluoride mediated decomposition of α-silated oxonium salts **160** provided further evidence for the short-lived oxonium ylide species.[85] The synthetic utility of the methodology was, however, severely limited by the restricted functional group tolerance and the high reactivity of the starting materials towards the methylation of nucleophiles.

7.1.2 Generation of Oxonium Ylides from Metal Carbenoids

The oxygen atom of an ether group, by virtue of its non-bonding electrons, acts as a weak Lewis base. Within the confines of conventional chemistry this limits the potential of ethers as nucleophiles, but within the sphere of metallocarbenoid chemistry, ether lone pairs are effective in forming oxonium ylide intermediates. The interaction between the two species is believed to be weak, with the equilibrium lying towards the discrete ether and metallocarbenoid pair (*Figure 24*).[86] This is corroborated by the ability of metal carbenoids to undergo both cyclopropanation and insertion reactions in ethereal solvents.[87]

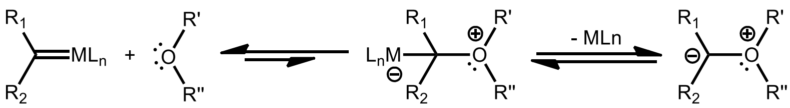


Figure 24

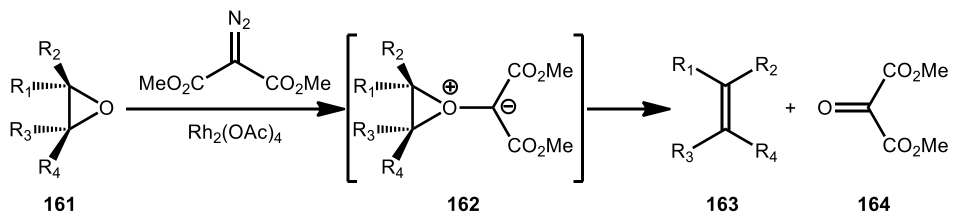
Although the intermolecular formation of oxonium ylides is usually disfavoured with repect to competitive pathways, the intramolecular formation of cyclic ylide systems, especially when subsequent rearrangement reactions are efficient, can push the equilibrium towards product formation. This type of transformation can be tuned by the choice of both metal and ligand in the carbenoid species.[88]

7.2 Reactivity of Oxonium Ylides

Upon formation, oxonium ylides can undergo a synthetically useful [2,3]-sigmatropic rearrangement or [1,2]-shift (Stevens rearrangement) in the presence of suitable migrating functionality. Side reactions such as ß-hydride elimination and deoxygenation of epoxides are also possible. When combined with the competitive reactivity of the parent metal carbenoid, the disadvantages of employing this methodology are evident. However, despite these apparent limitations, valuable studies concerning oxonium ylide chemistry published by several groups, have led to the methodology becoming a useful tool in modern organic synthesis.

7.2.1 Deoxygenation of Epoxides

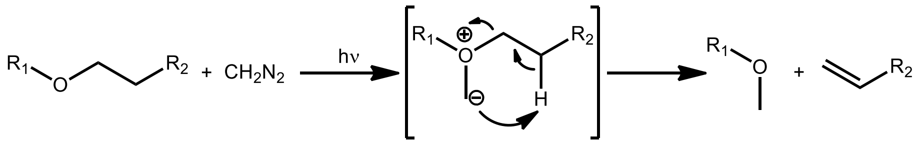
Wittig and Schlosser described the deoxygentation of phenyloxirane to form styrene using a copper generated carbene in 1962.[89] Subsequent work by Martin and Ganem established a more robust deoxygenation reaction for conversion of epoxides into their associated alkenes using a carbenoid generated from dimethyl diazomalonate and $Rh_2(OAc)_4$, or alternatively $Rh_2(Piv)_4$. The decomposition of ephemeral oxonium ylide **162**, illustrated in *Scheme 31*, provided good isolated yields of isomerically pure olefins **163** in the presence of labile functionalities such as halides, ketones, acetates and TMS ethers but without secondary cyclopropanation occurring.[90]



Scheme 31

7.2.2 ß-Hydride Elimination of Oxonium Ylides

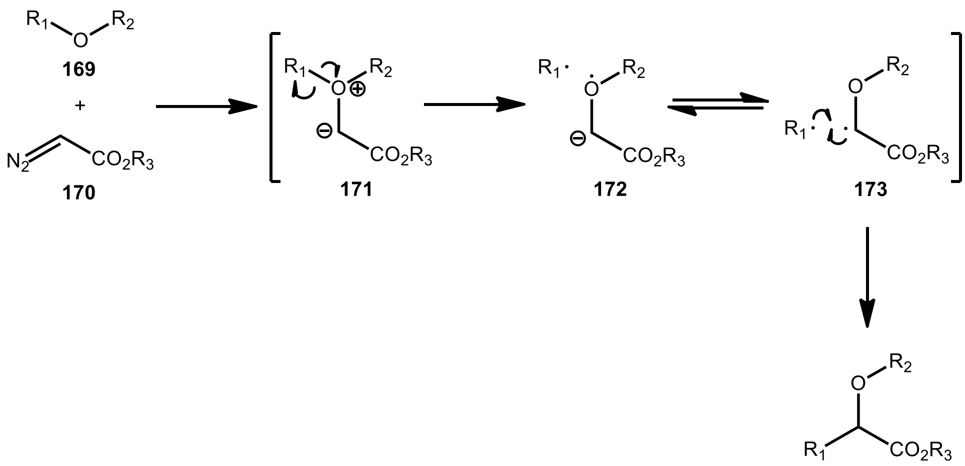
Several significant migratory reaction pathways can be followed upon the formation of an oxonium ylide. The first of these, ß-hydride elimination, results in the degradation of the parent ylide **166** to form an ether **167** and an olefin **168**, a generalised sequence for which is illustrated in *Scheme 32*. This reaction was first reported by Franzen and Fikentscher from the reaction of methylene with diethyl ether.[91]



Scheme 32

7.2.3 Stevens Rearrangement of Oxonium Ylides

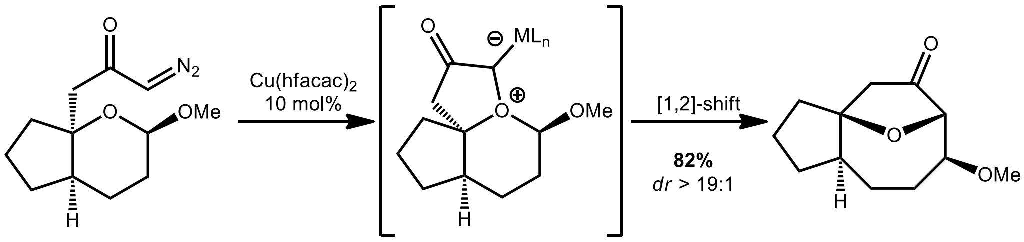
A more synthetically useful reaction of an oxonium ylide is the Stevens rearangement, which involves the formal [1,2]-shift of an alkyl group adjacent to the ylide. The net result of the Stevens rearrangement is equivalent to the insertion of a carbene into a C-O ether bond (*Scheme 33*). The reaction was originally discovered in 1928, during Stevens' work on ammonium ylides.[92]



Scheme 33

The Stevens Rearrangement is a high-energy, symmetry-forbidden process under the rules of Woodward and Hoffmann[93] and hence mechanistic explanations have traditionally tended towards rationalisations involving radical pairs.[94] CIDNP analysis of the reaction by Iwamura suggested that a singlet radical pair is formed through homolytic degradation of the transient ylide species **171**, followed by a recombination of the radicals within the solvent cage to afford the [1,2]-shift product **174.**[95]

Use can be made of the [1,2]-shift reaction of oxonium ylides in forming oxo-bridged ring systems, as has been demonstrated by West and co-workers (*Scheme 34*).[96] Use of rhodium dimers in generating the metal carbenoid intermediate from α-diazoketone **175** led predominantly to C-H insertion products, in preference to oxonium ylide formation. Conversely, $Cu(hfacac)_2$ afforded the oxo-bridged system **177**, through [1,2]-shift of oxonium ylide **176**, with retention of starting material stereochemistry. This stereochemical result was ascribed to the rapid recombination of the putative radical species during rearrangement.

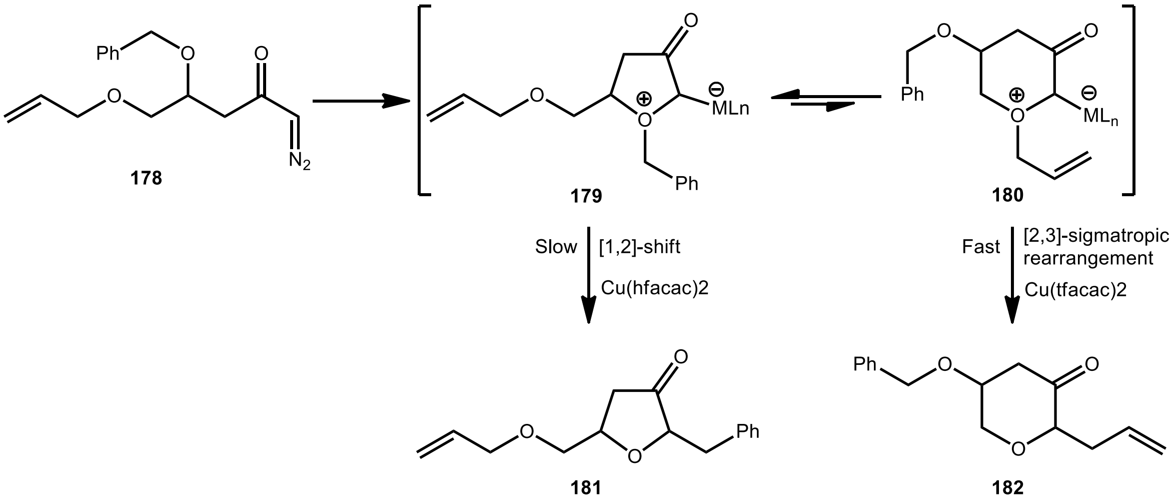


175 176 177

Scheme 34

7.2.4 Competitive [1,2]-Stevens Rearrangement and [2,3]-Sigmatropic Rearrangement

Although most alkyl groups can migrate in the [1,2]-shift of oxonium ylide systems, benzyl groups have found widespread use as migrating functionality in Stevens rearrangement reactions. West conducted a study, summarised in *Scheme 35*, on the effect of catalyst selection on the outcome of oxonium ylide rearrangement, in which both the [1,2]-shift of a benzyl group and the [2,3]-sigmatropic rearrangement of an allylic ether function were possible.[97] The study showed that there is a defined preference for formation of the five-membered oxonium ylide **179**, where rhodium dimers and Cu(hfacac)$_2$ are used for the formation of the metal carbenoid. In these cases, formation of tetrahydrofuranone **181** resulted from [1,2]-shift of the benzyl group, but generation of the metal carbenoid with Cu(tfacac)$_2$ afforded the six-membered pyranone **182** preferentially. This result is suggestive of an equilibration between five and six-membered oxonium ylides **179** and **180**, which allows for formation of the pyranone preferentially when the migratory group facilitates rapid rearrangement.



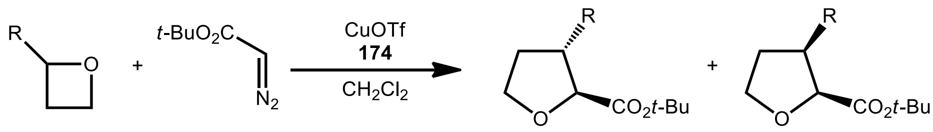
Scheme 35

The preference for the rhodium catalysts for the formation of the furanone system was attributed towards to either, a shift in equilibrium through a stabilisation of the five-membered ylide by the metal centre or a lack of preference towards migrating group where rhodium carbenoids are involved. The differences in reactivity observed through changes to both the metal and ligand in the catalyst suggest that the metal centre is associated with the transient oxonium ylide species.

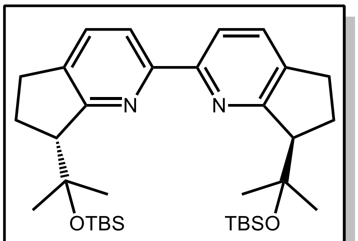
7.2.4.1 Asymmetric Induction of [1,2]-shifts of Oxonium Ylides

The use of chiral ligands to influence the stereochemical outcome of the [1,2]-shift of oxonium ylides has been explored. Inspired by the moderately enantioselective, intermolecular oxonium ylide ring expansion reactions of Nozaki,[98] Katsuki and co-workers investigated the asymmetric ring expansion of oxetanes, to form tetrahydrofurans. Bipyridine ligand **187** was applied to the copper-catalysed reaction of *t*-butyl diazoacetate with oxetane **183** and subsequent intermolecular oxonium ylide formation.[99]

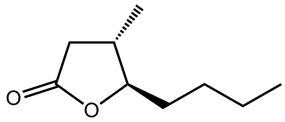
Use of racemic **183** (*Scheme 32*, entry 1) was expected to result in the kinetic resolution of one enantiomer, yet the ratio of *trans* **185** and *cis* products **186** was essentially equimolar. The high degree of enantiomeric excess obtained for each product suggested that the catalyst was interacting in a stereodivergent fashion with each enantiomer of the starting material resulting in a highly enantioselective transformation upon [1,2]-shift. Use of chiral (*R)*-oxetane (entry 2) led to diastereoselective formation of the *trans* product with high levels of enatioselectivity, equally use of the (*S*)-oxetane resulted in preferential formation of the *cis* diastereomer, with a correspondingly remarkable level of asymmetric induction (entry 3).



183 184 185 186



187



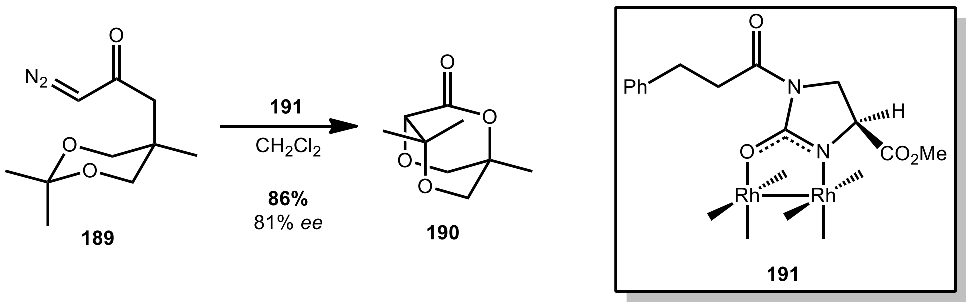
188

Entry	R	*dr* **185**:**186**	*ee* (%) *trans*	*ee* (%) *cis*	*ee* (%) recovered oxetane
1	Ph	59:41	75	81	5
2	(*R*)-Ph	89:11	92	16	87
3	(*S*)-Ph	25:75	11	93	87

Scheme 36

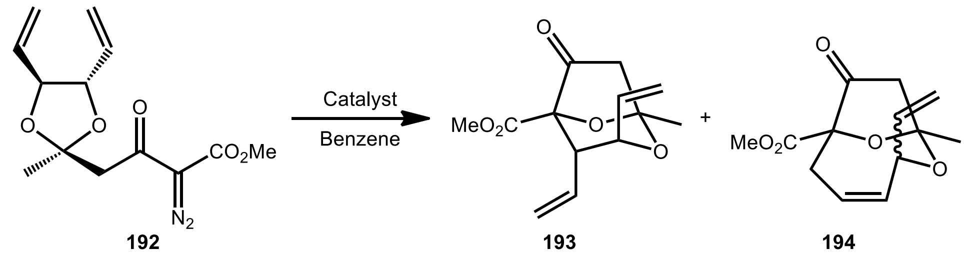
The catalyst was believed to induce the formation of a chiral oxonium ylide which underwent [1,2]-rearrangement before oxonium inversion could occur. The group would later apply their ring-expanding [1,2]-shift to a total synthesis of *trans*-whiskey lactone **188**.[100]

Doyle *et al*. reported the desymmetrisation of acetonide **189** using the chiral rhodium carboxylate dimer Rh_2(4*S*-MPPIM)$_4$ **191**. High yields of the [1,2]-shift product **190** were reported, with an enantiomeric excess of 81%. Small quantities of C-H insertion side products were also produced (*Scheme 37*).[101]



Scheme 37

The stereoselective [1,2]-shift of an oxonium ylide formed from an acetal, was also explored by Zercher and co-workers in their studies concerning the synthesis of complex bridged bicyclic acetals. Reaction of α-diazo-β-ketoester **192** with $Rh_2(OAc)_4$ resulted in the formation the desired [1,2]-shift product **193**, which the group noted was the core carbon structure found in the zaragozic acid family of natural products. Employment of Cu(hfacac)$_2$ to generate the oxonium ylide resulted in both the required Stevens rearrangement product as well as the undesired [2,3]-sigmatropic rearrangement product, diene **194**.[102]

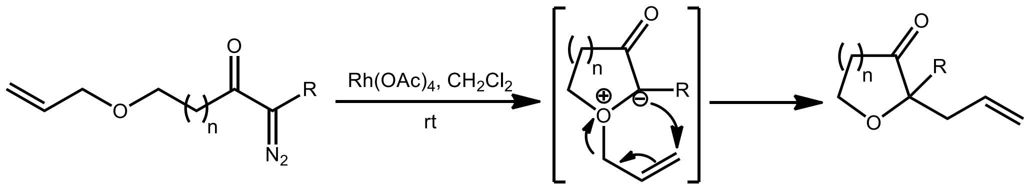


			Yield (%)	
Entry	Catalyst	Temp. (°C)	**193**	**194**
1	$Rh_2(OAc)_4$	80	64	-
2	Cu(hfacac)$_2$	25	42	20

Scheme 38

7.3 [2,3]-Sigmatropic Rearrangements of Oxonium Ylides

As discussed briefly in the preceding section, when oxonium ylides are formed in the presence of an allylic function, [2,3]-sigmatropic rearrangement of the intermediate can occur. The initial report of this transformation, by Kirmse and Kapps in 1968, described the intermolecular reaction between allyl ether and the copper derived carbenoid of diazomethane. The major product of the reaction was the mono cyclopropanated adduct, with [2,3]-rearrangement providing the minor side product.[103] The synthetic utility of such rearrangements came to the fore in 1986 when Johnson and Pirrung independently reported the intramolecular cyclisation of allylic ethers bearing α-diazo carbonyl group when treated with rhodium acetate. Formation of furanones and pyranones were demonstrated to be achievable through rearrangements of oxonium ylides of type **196**, as illustrated in *Scheme 39*.[104]

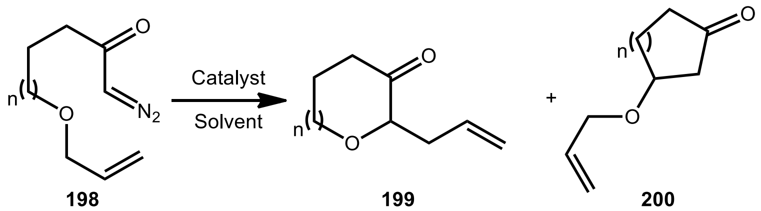


195 **196** **197**

Entry	R	n	Yield **197** (%)
1	CO_2Me	1	91
2	H	1	70
3	CO_2Me	2	53
4	H	2	33

Scheme 39

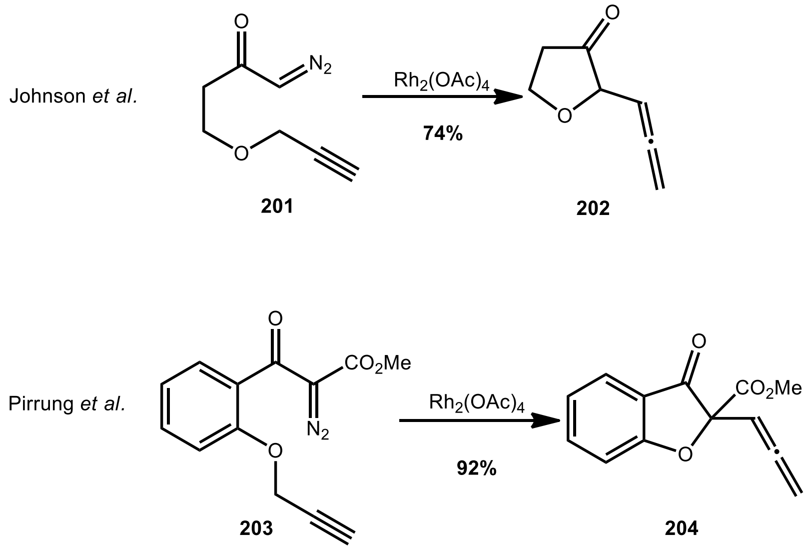
The methodology was extended by Clark and co-workers during studies concerning both rhodium and copper catalysis, for the formation of 2,6-tetrahydropyran-3-ones and larger ring systems.[105] Initial studies, based upon the reaction of α-diazoketones of type **198** with various catalysts, demonstrated that tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement was best facilitated by the use of electrophilic copper catalysts, in particular $Cu(hfacac)_2$. *Scheme 40* shows that use of rhodium carboxylate dimers and less electrophilic copper complexes promoted formation of the C-H insertion by-products **200**. Application of the optimal copper catalyst to chain extended diazoketone precursors allowed an oxepane-3-one (entry 7) and an oxocan-3-one (entry 8) to be formed, albeit with attendant C-H insertion (entry 7) and in modest yield (entry 8).



Entry	n	Catalyst	Solvent	Temp.	Yield **199** (%)	Yield **200** (%)
1	1	$Rh_2(OAc)_4$	CH_2Cl_2	rt	37	22
2	1	$Rh_2(OAc)_4$	THF	reflux	58	12
3	1	$Cu(acac)_2$	CH_2Cl_2	reflux	61	12
4	1	$Cu(tfacac)_2$	CH_2Cl_2	reflux	78	0
5	1	$Cu(hfacac)_2$	CH_2Cl_2	reflux	83	0
6	2	$Cu(acac)_2$	CH_2Cl_2	reflux	18	61
7	2	$Cu(hfacac)_2$	CH_2Cl_2	reflux	76	3
8	3	$Cu(hfacac)_2$	CH_2Cl_2	reflux	40	-

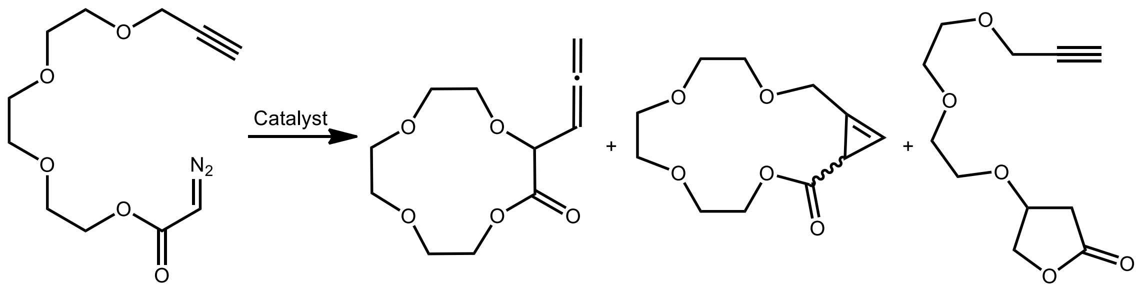
Scheme 40

The [2,3]-sigmatropic rearrangement of oxonium ylides does not occur on allylic functionality exclusively, Johnson and Pirrung demonstrated the applicability of the methodology to the formation tetrahydrofuranones bearing a pendant allene, the result of the [2,3]-rearrangement of a propargylic ether (*Scheme 41*).[104]



Scheme 41

Doyle subsequently reported on the application of the [2,3]-sigmatropic rearrangement reaction of propargylic ethers to the formation of allene bearing macrocycle **206** using copper catalysis (*Scheme 43*). Reaction of rhodium(II) acetate with diazoester **205** led to selective cyclopropenation of the alkyne in a clear example of the importance of catalyst choice in the face of competing reactions.[106]



205 **206** **207** **208**

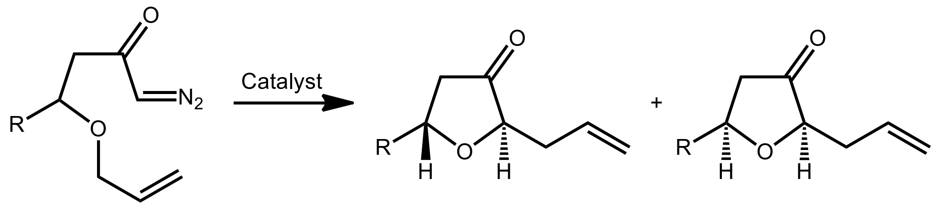
Entry	Catalyst	Combined Yield (%)	Product Distribution		
			206	**207**	**208**
1	$Cu(MeCN)_4PF_6$	61	75	0	25
2	$Rh(OAc)_4$	62	0	96	4

Scheme 42

7.4 Diastereoselectivity of Intramolecular [2,3]-Sigmatropic Rearrangements

7.4.1 Application to 2,5-*trans* tetrahydrofuran-3-one Formation

Johnson and Roskamp's initial report of intramolecular cyclisation reactions through transient oxonium ylides demonstrated that, upon formation of 2,5-tetrahydrofuran-3-ones the 2,5-*trans* diastereomer predominated when dirhodium acetate was employed as the catalyst (*Scheme 43*, entry 1).[104b] Clark later reported that copper catalysts could be used in analogous transformations providing both higher yields of the desired products, as well as improved diastereocontrol in forming the 2,5-*trans* diastereoisomer **210** (entries 2 and 3).[107]



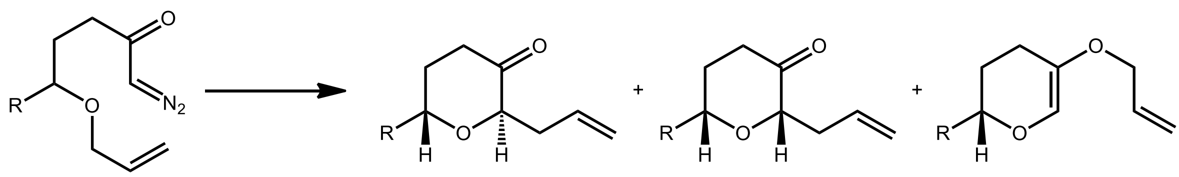
209 210 211

Entry	R	Catalyst	Combined Yield (%)	*dr* **210:211**
1	Me	$Rh_2(OAc)_4$	65	92:8
2	*i*-Pr	$Cu(acac)_2$	85	>97:3
3	*i*-Pr	$Cu(acac)_2$	83	>97:3

Scheme 43

7.4.2 Application to 2,6-*trans* Tetrahydropyran-3-one Formation

Studies by Clark, the results of which were published in 2003, explored the effect of catalyst choice on the stereoselectivity of 2,6-tetrahydropyran-3-one formation from diazoketones of type **210** (*Scheme 44*).[108]



212 213 214 215

Entry	Catalyst	R	Yield (%) **213+214**	dr **213:214**	Yield (%) **215**
1	$Cu(acac)_2$	Me	28	92:8	4
2	$Cu(acac)_2$	*i*-Pr	40	96:4	7
3	$Cu(tfacac)_2$	*i*-Pr	64	94:6	9
4	$Cu(hfacac)_2$	*i*-Pr	65	76:24	13
5	$Rh_2(OAc)_4$	*i*-Pr	17	21:79	0

Scheme 44

Copper catalysis was again found to promote the formation of oxonium ylides and provide the desired 2,6-*trans* tetrahydropyran-3-one systems upon [2,3]-sigmatropic rearrangement. The catalyst of choice for 2,5-*trans* tetrahydrofuran-3-one formation, $Cu(acac)_2$, afforded good stereoselectivity when applied to diazoketones of type **212** providing the 2,6-*trans* diastereomer **213** as the major product albeit in a low yield (entries 1 and 2). Increasing the electrophilic character of the metal carbenoid resulted in increased product yields, augmented formation of the 2,6-*trans* diastereomer and slightly increased formation of the [1,4]-rearranged side-product **215** (entries 2 and 3), whereas use of a rhodium dimer catalyst reversed the ratio of products to favour the 2,6-*cis* isomer over the *trans* diastereomer (entry 5).

7.4.3 Rationalisation of Diastereomeric Outcome

Two models exist to explain the diastereoselectivity of the rearrangement reactions of the oxonium ylides, based on models of a free oxonium ylide, under which [2,3]-rearrangement occurs in a classical fashion and an alternative in which the ylide is associated with the metal-ligand complex of the parent carbenoid.

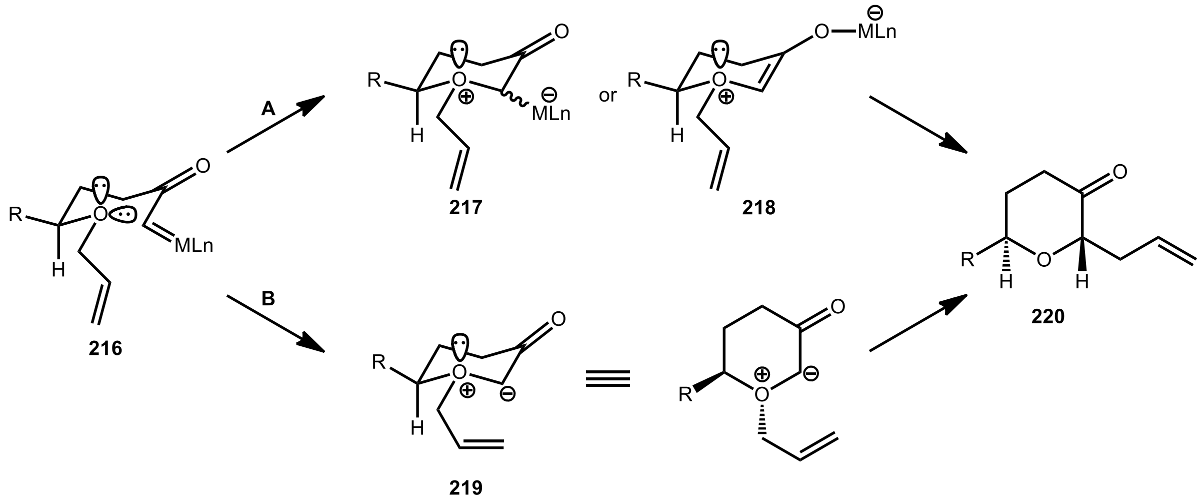


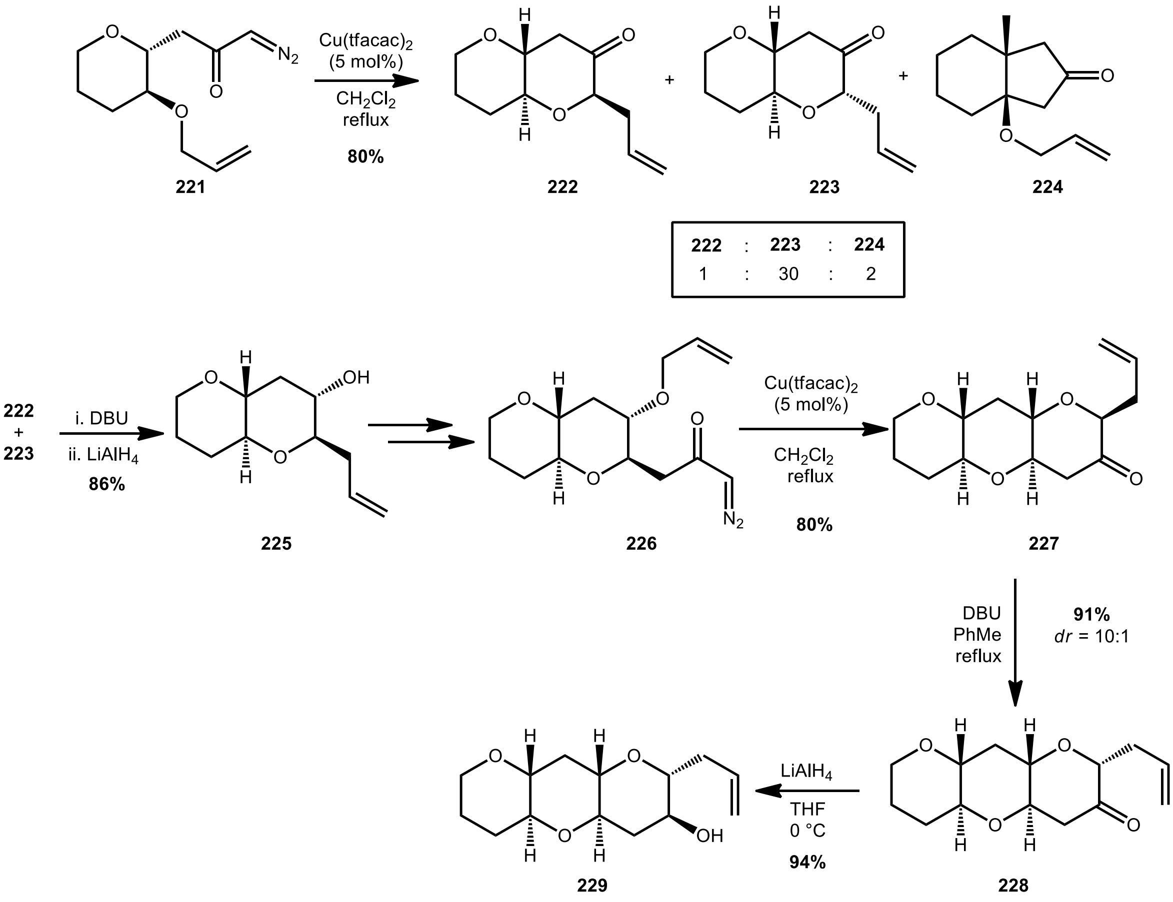
Figure 25

Although the possibility exists for attack of the metal carbenoid **216** through either of the diastereotopic ether lone pairs, in practise one predominates to form the energy minimised transition state, in which the R substituent and migrating allylic functionality are located in equatorial positions (*Figure 25*). The diastereoselectivity of the rearrangement product is believed to originate from migration occurring on the least hindered face of the transition state *i.e.* that opposite to the bulky R substituent. Preferential formation of the 2,6-*trans* product suggests [2,3]-sigmatropic rearrangement occurs swiftly upon formation of the oxonium ylide. Furthermore, the *trans* to *cis* ratio variation with catalyst system implies that the oxonium ylide is associated to some degree with the metal centre. The stereochemical outcome can be envisaged as proceeding *via* one of the two possible pathways illustrated. Pathway **A** shows attack through an etheric lone pair onto the newly formed metal carbenoid and the resulting metal associated product then rapidly rearranges with concomitant loss of the associated metal-ligand centre. The nature of metal association and stabilisation is not well understood and could derive from either the carbon-metal bond of **217** or the metal enolate **218**.

A second possibility exists in which the metal-ligand centre is lost completely to provide a free chiral oxonium ylide **219**. Rapid rearrangement of the chiral oxonium system would follow along pathway **B** to provide the identical kinetic product gained through pathway **A**. Inversion of an oxonium centre is a phenomenon that is describe within the literature[109] and provides the possibility of isomeric chiral oxonium ylides, which upon thermodynamic equilibration would afford diasteromeric product mixtures. The equilibrium between the oxonium ylide and its parent compounds (*Figure 24*), in addition to the product distributions obtained from intramolecular cyclisation reactions tending towards the predominance of a single diastereoisomer, means that the metal associated model is more likely than formation of a free oxonium ylide. However progression *via* pathway **B** and a free oxonium ylide cannot, as yet, be completely discounted.

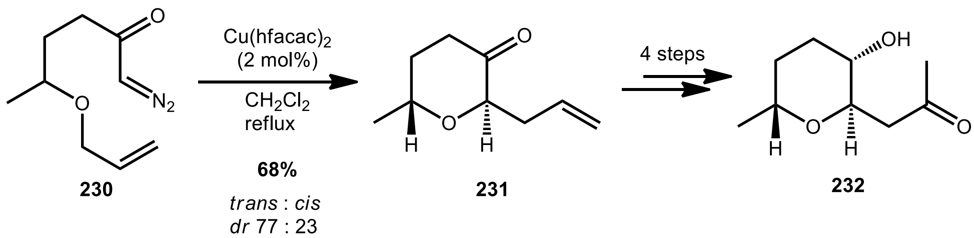
7.4.4 Application of Diastereoselective [2,3]-Rearrangements to Total Synthesis

West's studies on the formation of *trans*-fused polycyclic ethers, of the type found in marine natural products such as gambierol, led to the publication of an iterative approach to the formation of polyethers (*Scheme 45*).[110] Diazoketone **221** was treated under optimised conditions to afford a diasteromeric mixture of oxabicycles **219** and **223**, resulting from the formation of an oxonium ylide and subsequent [2,3]-sigmatropic rearrangement, as well as the C-H insertion product **224**. Epimerisation of ketones **222** and **223** was followed by stereoselective reduction of the carbonyl group to afford the alcohol **225**. Stepwise modification of the pendant groups afforded diazoketone **226**, a precursor to a second tandem oxonium ylide-rearrangement sequence, providing access to tricyclic ketone **226**.



Scheme 45

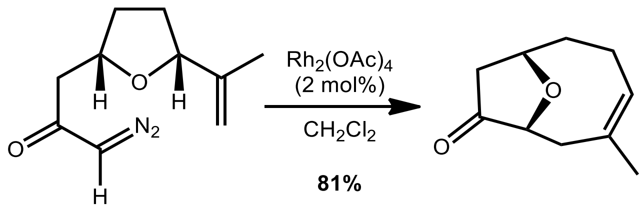
The Clark group demonstrated the efficacy of the [2,3]-rearrangement reaction of oxonium ylides in total synthesis by using the reaction to construct of the 2,6-*trans* tetrahydrofuran-3-one core of (±)-decarestrictine L **232** (*Scheme 46*).[111]



Scheme 46

7.5 Bicyclic Ring Formation through Stereoselective [2,3]-Sigmatropic Rearrangment

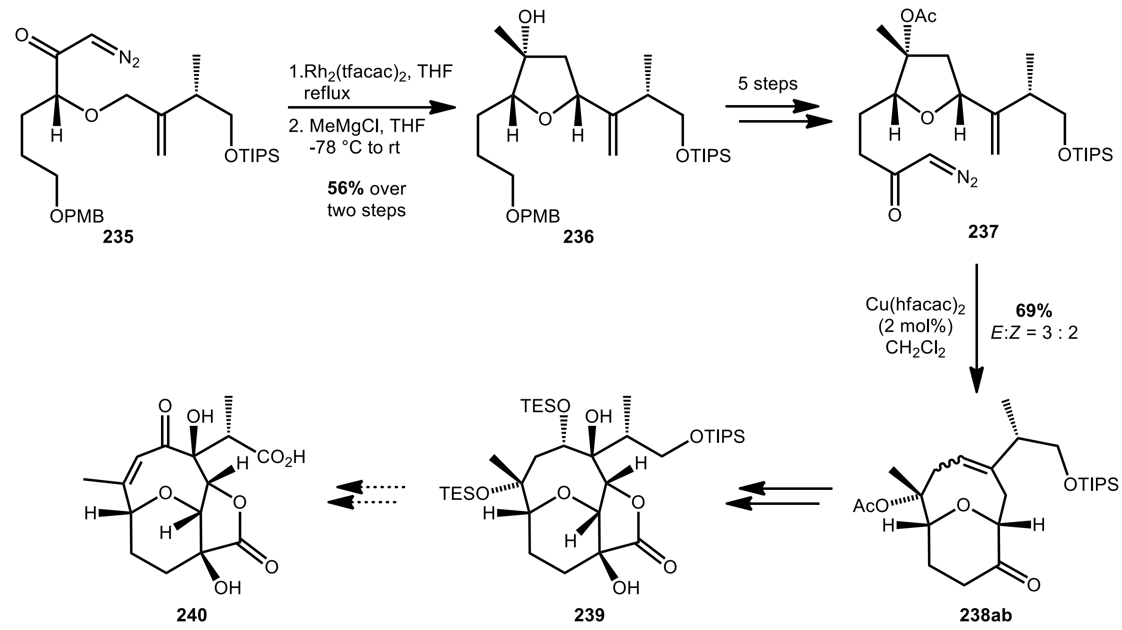
The creation of bicyclic ring systems from suitably fashioned cyclic ethers can be accomplished through use of a tandem oxonium ylide formation/rearrangement strategy. Pirrung demonstrated an efficient route for the preparation of an eight-membered bicyclic ketone **234** from the 2,5-*trans* tetrahydrofuran **230** (*Scheme 47*).[104a]



233 **234**

Scheme 47

An early example of the utility of this ring expansion reaction was published by Clark, who used the methodology to prepare the core bicyclic structure of neoliacinic acid **240**.[112] The reaction sequence, shown in *Scheme 48*, used two key carbenoid transformations in the preparation of strategic oxacyclic intermediates. The primary transformation involved the $Rh_2(hfacac)_4$ catalysed C-H insertion of diazoketone **235** to form a 2,5-*cis* tetrahydrofuran-3-one, which was treated with methylmagnesium chloride to afford alcohol **236**. After further manipulation of the pendant groups, the stage was set for the second carbenoid transformation, the copper-catalysed oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement reaction of diazoketone **237**. Application of $Cu(hfacac)_2$ to **237** afforded a mixture of the [1,2]-shift product as well as the desired [2,3]-sigmatropic rearrangement, albeit as a mixture of both *E* and *Z* isomers **238ab**. The 2,6-*cis* stereochemistry of the bridgehead protons results from the spatial orientation of the nucleophilic centre with respect to the pendant allylic groups in the transition state (*Figure 26*). Nucleophilic attack of the allylic group, during the [2,3]-rearrangement is achieved from the proximal position of the six-membered oxonium system, leading to the formation of the *cis* isomer preferentially.



Scheme 48

Both olefin isomers are produced as a consequence of the capacity of the oxonium ylide to rearrange through either of the oxonium ylides **242** or **243** shown in *Figure 26*. The 3:2 ratio of *E* and *Z* isomers is suggestive of a small energy difference in the equilibrium of the transition states that is easily overcome. Subsequent work by Clark on the cladiellin family of natural products showed that the choice of metal and ligand in the carbenoid species is of prime importance in determining the outcome of olefin geometry in this type of transformation, providing evidence of metal association adjacent to the site of oxonium ylide formation.[113] Following isolation of the products, conversion of the *E* olefin into the more stable *Z* isomer was found to be achievable using mercaptoethanol and a radical initiator. A similar oxonium ylide rearrangement strategy was also utilised in Clark's synthesis of the tricyclic core **247** of labiatin A (*Scheme 49*).[114]

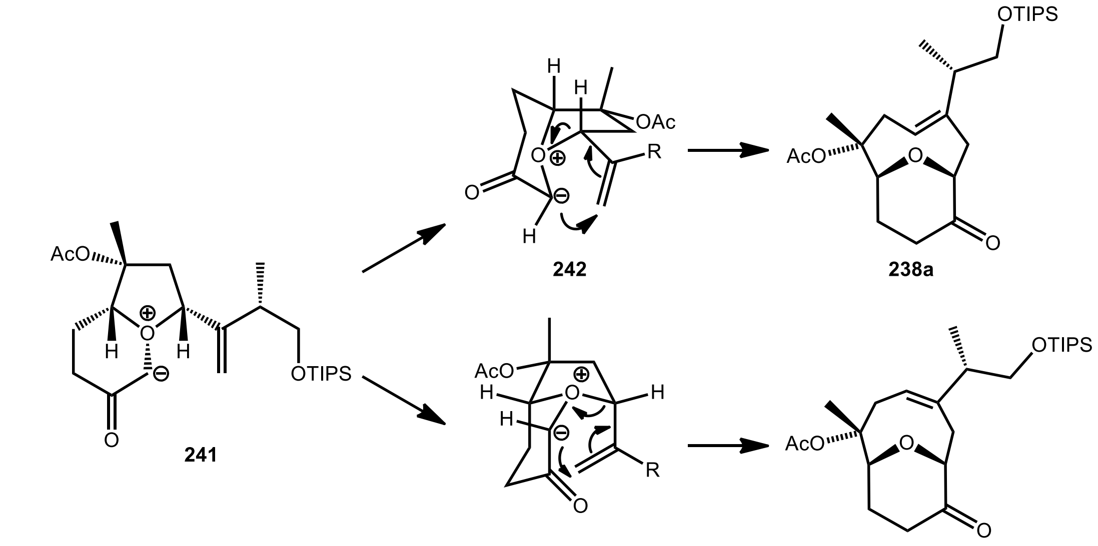
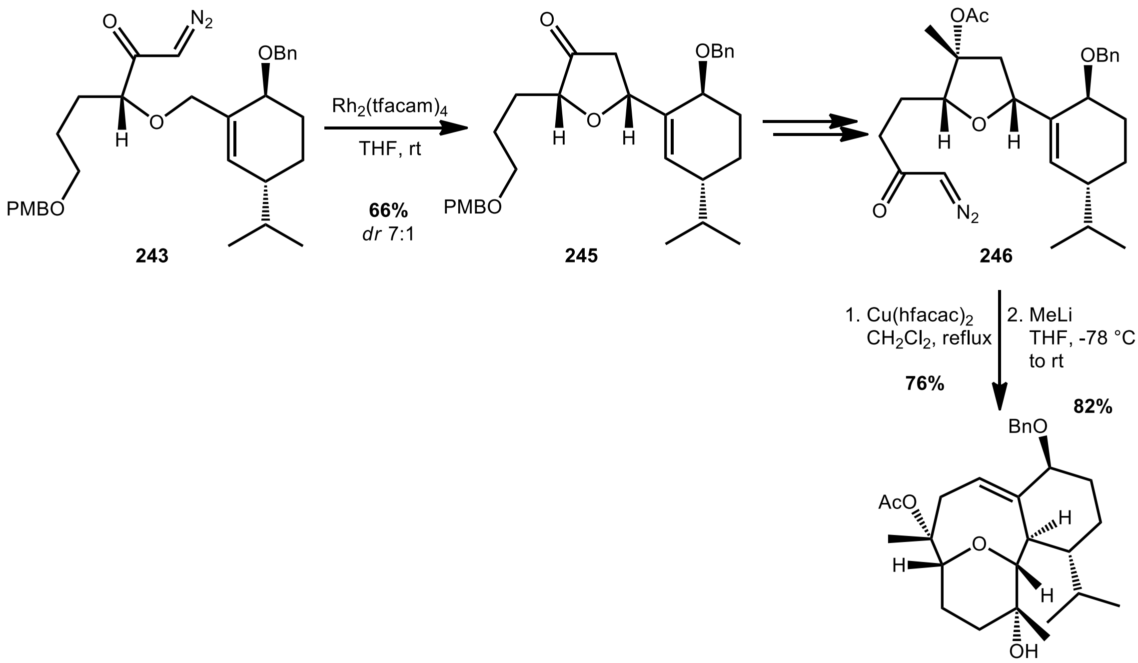
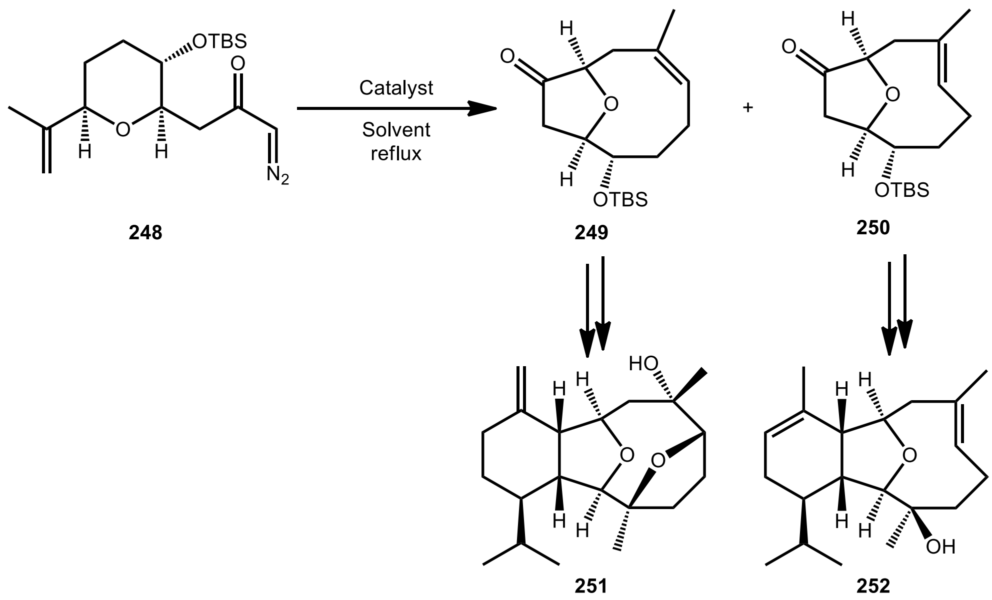


Figure 26



Scheme 49

In an elegant example of convergent total syntheses, a recent paper by Clark and co-workers demonstrated how the ratio of *E*/*Z* isomers could be tuned through the judicious selection of solvent, temperature and most importantly catalyst. Reaction of $Rh_2(O_2CCPh_3)_4$ with diazoketone **248** afforded practical quantities of *E*-olefin **250** which was used to prepare eight members of the cladiellen family of natural products, the skeleton of which (**252**) is shown in *Scheme 50*.[113]



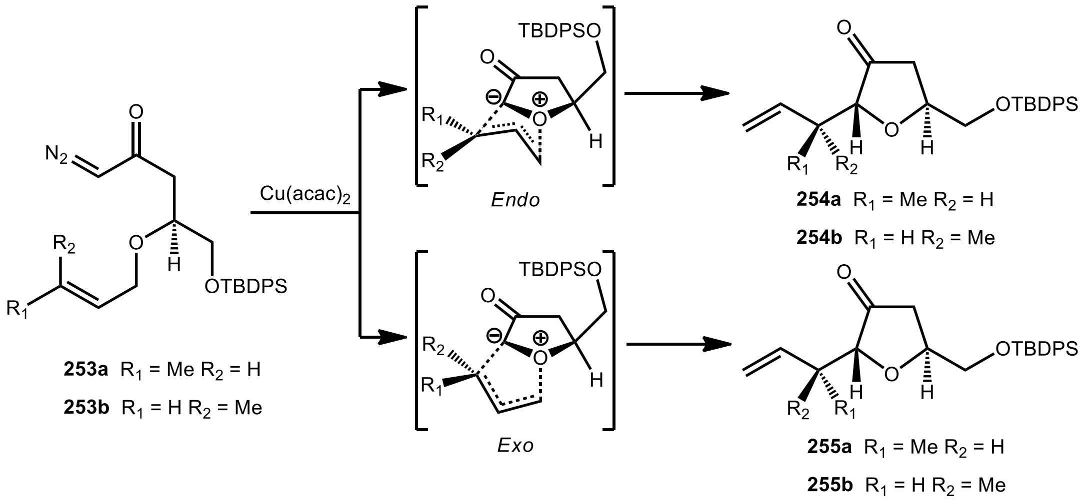
Entry	Catalyst	Solvent	Yield (%)	*Z*:*E* ratio
1	Cu(hfacac)$_2$	THF	74	6.9:1.0
2	$Rh_2(O_2CCPh_3)_4$	1,2-dichloroethane	56	1.0:6.3

Scheme 50

The use of electrophilic ligands in copper catalysis has allowed the fine tuning of the oxonium ylide formation and rearrangement reaction to afford primarily the *Z*-olefin **249**, previously employed by Clark and co-workers in their synthesis of vigulariol **251**.[115] These examples distinctly illustrate the effect of the metal centre on the diastereoselectivity of the reaction and provide further substantiation to a metal associated oxonium ylide intermediate.

7.6 Stereochemistry of [2,3]-Rearranged Allylic Substituents

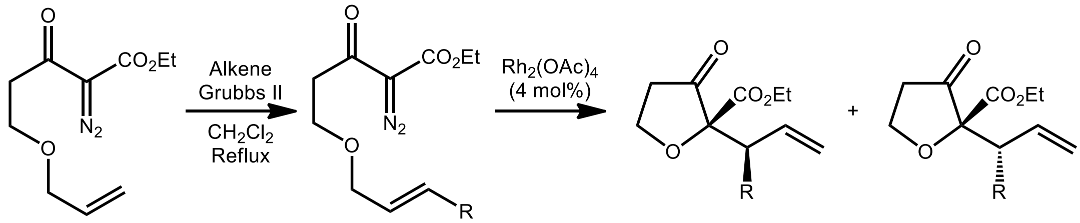
A study on the transition states generated through oxonium ylide generation and [2,3]-rearrangement of substituted olefins was conducted by Clark and co-workers in 2004.[116] The formation of 2,5-tetrahydrofuran-3-ones, as has been seen, was a well-studied reaction within the group, but the generation of stereochemistry in the allylic substituent through the [2,3]-rearrangement of the ephemeral oxonium ylide was relatively unexplored. An understanding of the nature of the rearrangement transition state, either *endo* or *exo*, was therefore of key importance in delivering the desired stereochemistry to the allylic position. In order to access the required stereochemistry of the product, the *E*-crotyl ether starting material **253a** would have to rearrange through the *endo* transition state shown in *Scheme 51*, alternatively the *Z* crotyl ether **253b** would have to pass through an *exo* transition state.



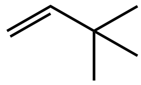
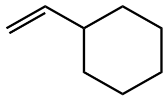
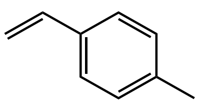
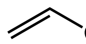
Scheme 51

To evaluate the course of the tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement reaction, the *E* and *Z*-crotyl ethers **253a** and **253b** were prepared and treated independently with Cu(acac)$_2$. As discussed previously, the cyclic oxonium ylide formed from allylic ethers such as **253** rearrange preferentially to afford 2,5-*trans* tetrahydrofuran-3-ones and this diastereoselective outcome was again observed from the experiments conducted. Rearrangement of Z-crotyl ether **253b** afforded the unwanted diastereomer **254b** in good yield and excellent diastereoselective control (75%, *dr* 95:5), indicating an *endo* transition state predominated the transformation. The desired isomeric product **255a** was prepared in both excellent yield and with a high diastereomeric ratio from the *E* crotyl ether starting material **253a** (88%, *dr* >92:8). Again, this outcome supported the occurrence of an *endo* transition state during the rearrangement reaction.

The work of Hodgson and co-workers concerning the total synthesis of hyperolactone, an anti-HIV agent, relied upon a similar type of rearrangement reaction to afford the desired stereochemistry at the allylic position. Initial studies on model systems, shown in *Scheme 52*, supported the preference for an *endo* transition state in the [2,3]-rearrangement of cyclic oxonium ylides, thereby affording tetrahydrofuranones of type **258** in good yield and diastereoselective ratio.[117] Optimisation of the reaction conditions for the one-pot process was subsequently allowed for an enantioselective preparation of (−)-hyperolactone.[118]



256 257 258 259

Entry	Alkene	Yield (%)	*dr* **258:259**
1		49	94:6
2		79	90:10
3		63	98:2
4		82	98:2

Scheme 52

7.7 Asymmetric Induction of Tandem Oxonium Ylide Formation and [2,3]-Rearrangement

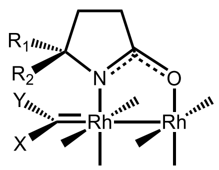
The field of asymmetric induction in carbene reactions has been of intense interest to researchers for many years. Although both cyclopropanation and C-H insertion reactions have been well studied, the application of asymmetric induction in the case of oxonium ylide formation and rearrangement has only advanced within the last two decades. Several reports emerged in the early 1990's regarding enantio-induction in the [2,3]-sigmatropic rearrangement reaction of chalcogen ylides, particularly those of sulfur and selenium, by means of chiral rhodium, copper and cobalt complexes.[119] Work on oxonium ylides, by comparison, has been sparser.

7.7.1 Intramolecular Enantioselective Transformations

McKervey published the first report of a [2,3]-sigmatropic rearrangement of the oxonium ylide derived from α-diazo-β-ketoesters of type **261a** using the binol-phosphate dirhodium(II) complex **263**. This reaction afforded 90% isolated yield of the [2,3]-rearranged product **262a** with a moderate 30% *ee* (*Scheme 53,* entry 1).[120] Both the yield and enantio-induction of the reaction were improved by using the rhodium dimer

264, the ligand of which was derived from D-*tert*-leucine.[121] Augumented stereoselectivity, through the use of chiral complexes, provides supplementary evidence for the transitional species being a metal-bound oxonium ylide in which the chiral ligands are proximal to the reacting centre. Aromatic α-diazo-β-keto esters, of type **261**, have proved to be suitable substrates for comparative studies of enantioselective oxonium ylide and [2,3]-sigmatropic rearrangements, and have been used in several experiments.

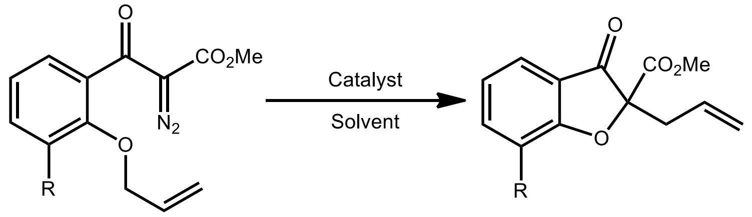
Doyle had previously observed that rhodium(II) carboxamide dimers, despite being inferior substrates, apropos diazo decomposition, delivered higher degrees of asymmetric induction in subsequent reactions when compared to rhodium complexes bearing carboxylate ligands.[101] The improved stereochemical outcomes from application of these catalysts were understood to be the result of the closer proximity of the reacting metal centre to the chiral appendages of the ligand, as illustrated by the generalised rhodium carboxamide carbenoid **260**.



260

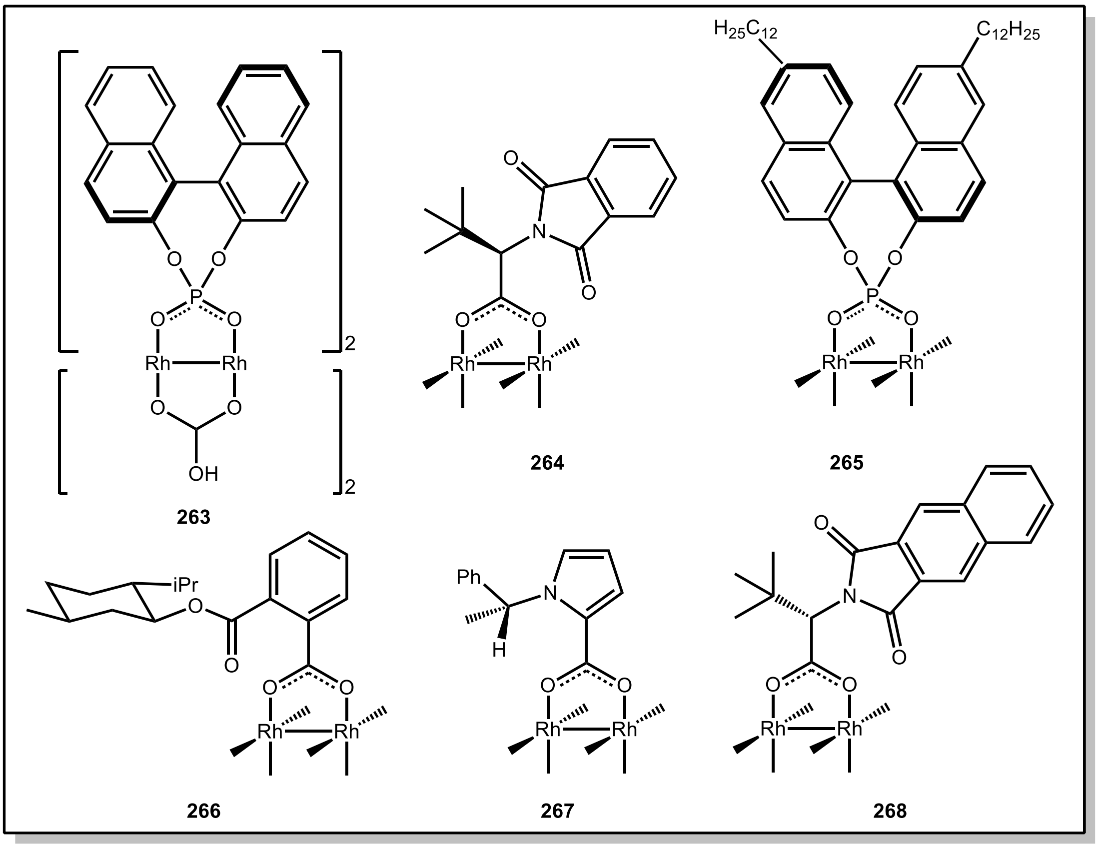
Figure 27

Inspired by these findings, the group of Moody prepared several chiral rhodium(II) carboxylates, such as **263** and **264**, designed to facilitate the rapid decomposition of the diazo moiety to the metal carbenoid, but which secured the pendant chiral ligands in a comparable spatial position to those of carboxamide ligands. *Scheme 53* (entries 4 and 5) shows that these ligands provided good conversion of the starting material into the oxonium ylide resulting in the formation of the [2,3]-rearranged product, albeit with low levels of enantioinduction.[122] Hodgson established that enantiomeric excesses of 62% could be achieved by the employment of $Rh_2[(R)\text{-DDBNP}]_4$ **265** as a catalyst (entry 3),[123] whilst the work of Hashimoto and co-workers led to the development of $Rh_2[(S)\text{-PTTL}]_4$ catalyst **268** (entry 6) which afforded **262a** in 76% *ee* when the reaction was conducted at low temperature.[124]



261a R=Me
261b R=H

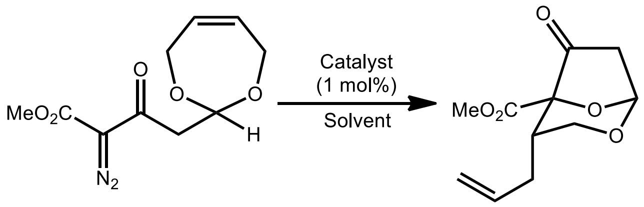
262a R=Me
262b R=H



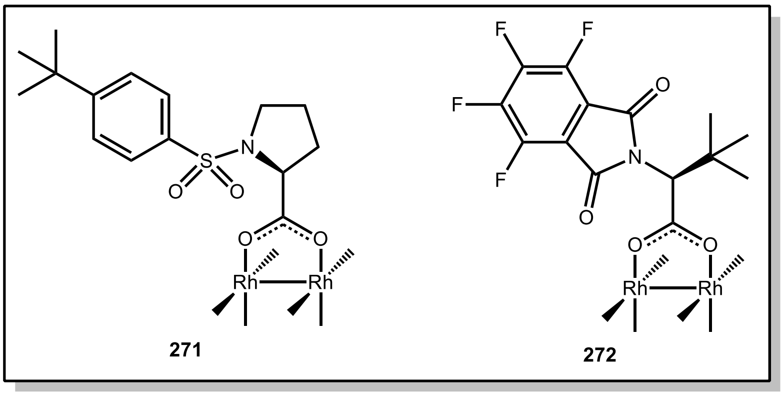
Entry	Catalyst	R	Solvent	Temp.	Yield (%)	*ee* (%)
1	**263**	Me	CH_2Cl_2	reflux	92	30
2	**264**	H	Hexane	20 °C	96	60
3	**265**	H	Benzene	25 °C	46	62
4	**266**	Me	CH_2Cl_2	reflux	92	13
5	**267**	Me	CH_2Cl_2	reflux	92	12
6	**268**	Me	Toluene	−10 °C	54	76

Scheme 53

Calter and Sugathapala demonstrated that an enantioselective rearrangement of an allylic acetal, to form bicyclic ether **270**, could be accomplished in moderate yield and with modest *ee* when performed using Davies' Rh_2[*S*-TBSP]$_4$ complex **271** as the catalyst (*Scheme 54*).[125] Hashimoto subsequently performed an analogous transformation using the Rh_2(*S*-TFPTTL)$_4$ dimer **272** as the catalyst, thereby improving dramatically both the yield and enantioselectivity of this novel transformation.[126]



269 **270**

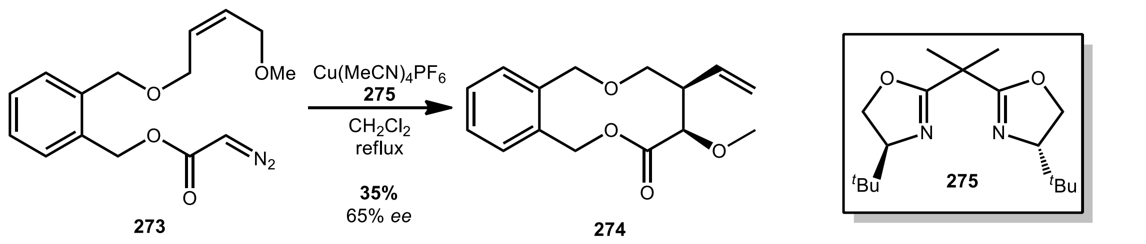


271 **272**

Entry	Catalyst	Solvent	Temp.	Yield (%)	*ee* (%)
1	**271**	Benzene	reflux	34	34
2	**272**	Toluene	0 °C	93	93

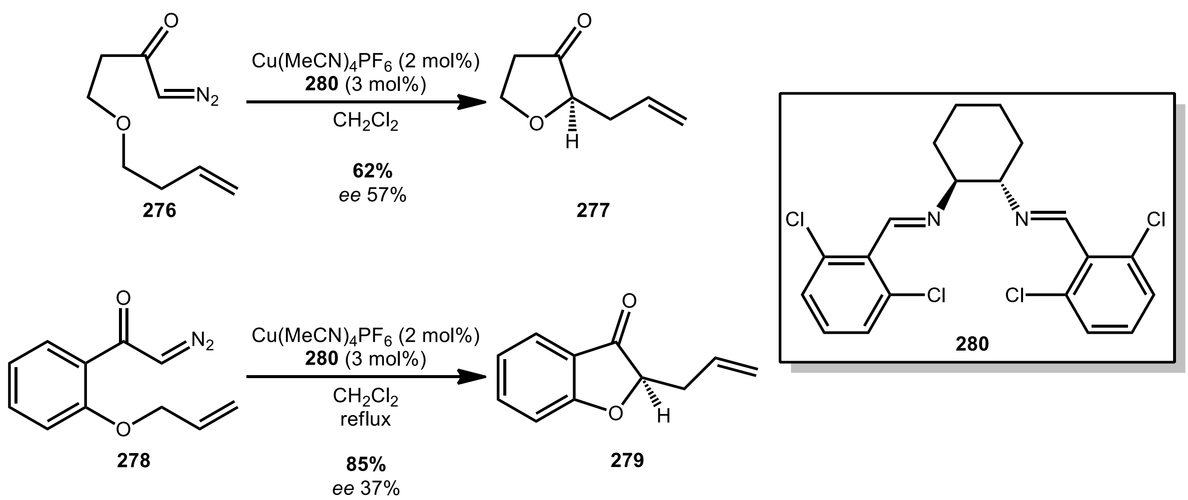
Scheme 54

The stereoselective formation of *cis*-macrocyclic structure **274** was achieved by Doyle in 1998.[127] Application of chiral bis-oxazoline ligand **275** and a copper(I) salt, to achiral α-diazoester **273** provided chemoselective oxonium ylide formation and [2,3]-rearrangement, the only notable by-product being cyclopropanation of the olefin bond (*Scheme 55*). Although the reaction proceeded in low yield, the levels of enantioselectivity are notable for a poly-oxygenated system. Replacement of the copper catalyst with a chiral rhodium dimer was ineffective, resulting only in formation of trace amounts of **274**.



Scheme 55

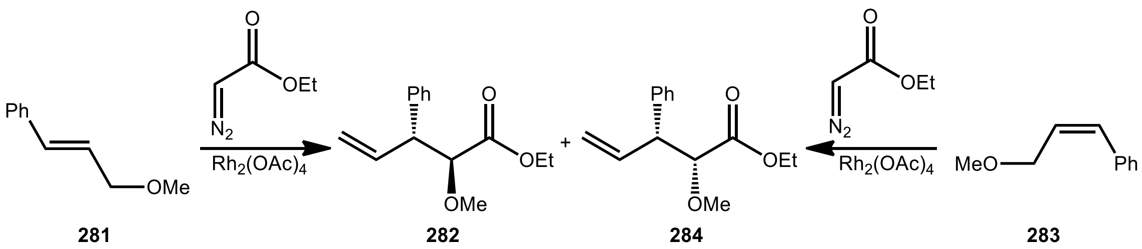
In a rare example of copper-catalysed enantioselective tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement, Clark established that tetrahydrofuran-3-ones could be constructed asymmetrically through decomposition of diazoketone **276**, using a catalyst formed *in situ* from Cu(MeCN)$_4$PF$_6$ and diimine ligand **280**, to afford **277** in reasonable yield and enantiomeric excess (*Scheme 56*).[128] The modest induction of asymmetry in aliphatic substrates was also observed when the same catalyst system was applied to aromatic substrate **278**. Although a higher yield of benzofuranone **279** was achieved, a decrease in enantiomeric excess was also observed when compared to the non-aromatic substrate **276**. The variance in asymmetric induction between substrates was attributed to differences in the reaction pathways, from which high enantiomeric excess was ascribed to a significant metal association with the oxonium ylide, whilst low induction was thought to result from a transition state whose structure corresponded to a free ylide from which partial oxonium inversion occurred.



Scheme 56

7.7.2 Intermolecular Stereoselective [2,3]-Rearrangements

Although intramolecular cyclisation reactions involving oxonium ylides have been well studied in terms of reaction outcome and stereochemistry, the intermolecular variant of this type of reaction has, by comparison, received limited attention. The $Rh_2(OAc)_4$-catalysed decomposition of ethyl diazoaceate in the presence of either the *cis* or *trans* isomer of cinnamyl methyl ether was investigated by Doyle *et al.* in 1988. The outcome of the resultant tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement reaction, illustrated in *Scheme 57*, provided evidence that the geometry of the alkene starting material translates into a preference for the 1,2-*anti* or 1,2-*syn* product.[129]



Scheme 57

In the case of *trans* cinnamyl methyl ether **281** the major product is the 1,2-*anti* diastereomer **282**, whereas the reaction employing the *cis* isomer **283** results predominantly in the 1,2-*syn* isomer **284**; the major side product of the reaction was the competitive cyclopropanation of the olefin. Doyle rationalised the highly diastereoselective nature of the reaction through application of the transition state models illustrated in *Figure 28*.

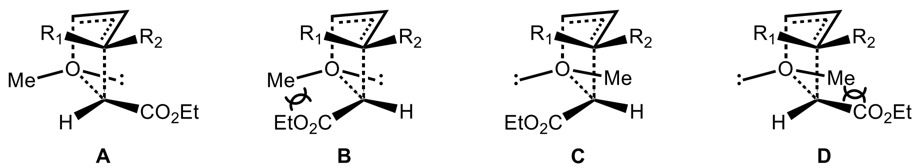
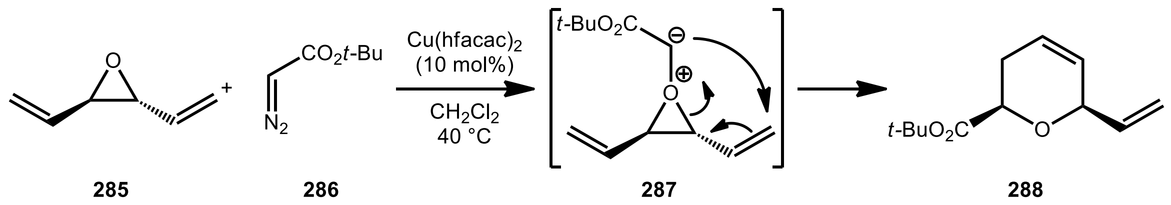


Figure 28

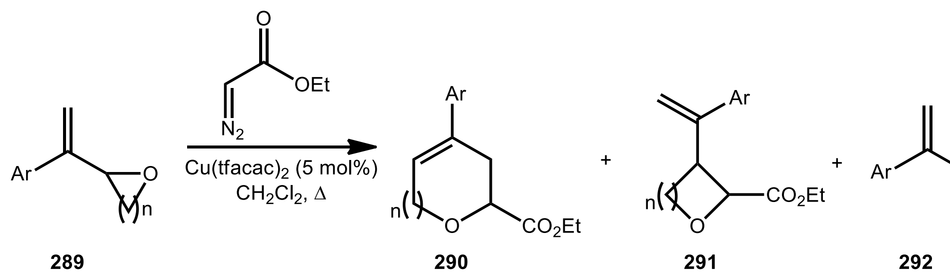
The highest energy transition states are those in which an eclipsed conformation exists between the ester group and that of the methyl group, hence transition states **B** and **D** are energetically disfavoured over **A** and **C**. The *cis* cinnamyl methyl ether (R^1=Ph, R^2=H) reacts preferentially to form the 1,2-*syn* product through transition state **A** due to the minimised steric clash between the ester and phenyl groups, whereas in the case of the *trans* olefin (R^1=H, R^2=Ph), the 1,2-*anti* diastereomer is formed preferentially where transition state **C** is energetically minimised.

In 2006 Quinn *et al*. published a paper in which stereoselective three-carbon ring expansion of *trans* divinyl epoxides was accomplished using a [2,3]-sigmatropic rearrangement of an intermolecularly formed oxonium ylide.[130] *Scheme 58* illustrates that the C_2-symmetry of the epoxide **285**, when converted to an intermediate ylide species **287** allows for stereospecific rearrangement to dihydropyran **288** only.



Scheme 58

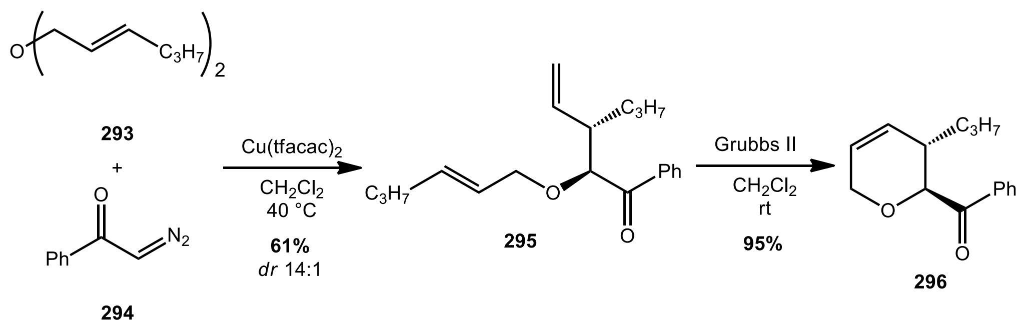
Recent attempts by Njardarson and co-workers, to follow the ring expansion chemistry established by Quinn, demonstrated that oxonium ylides formed intermolecularly from variously sized, asymmetric oxygen containing heterocycles of type **289** and ethyl diazoacetate, did not efficiently undergo [2,3]-rearranged ring expansion, but instead provided a mixture of the desired rearrangement products **290** and the [1,2]-shift products **291**.[131] Moreover, epoxides (entry 1) underwent preferential carbenoid-mediated deoxygenation to afford diene **292** (*Scheme 59*).



Entry	n	Ar	Combined Yield (%) **290**+**291**	Product Distribution	
				290	**291**
1	1	4-MePh	26	1	1.2
2	2	Ph	72	1	2.5 (3:1, *trans*:*cis*)
3	3	Ph	74	6	1 (*trans* only)

Scheme 59

Despite the disappointing results of their ring expansion chemistry, the group refocused their attention on the reactivity of ylides generated from symmetric allylic ether **293** (*Scheme 60*). In accordance with the results of Doyle[129] the *trans* stereochemistry of the olefin bonds translated into the preferential formation of the *anti* diastereomer **295** upon [2,3]-sigmatropic rearrangement of the transient ylide. Both rhodium and copper-catalysed decomposition of diazo acetophenone resulted in the the formation of oxonium ylides and [2,3]-rearrangement to afford the *anti* diastereomer preferentially. However, the optimal combination of yield and diastereomeric ratio was found to result from the use of $Cu(tfacac)_2$ as the catalyst. The group introduced this reaction as the first stage of their two-step, one-pot, stereoselective formation of dihydropyran **296**.



Scheme 60

8 Overview

Metal carbenoid chemistry has, over the past three decades, added a set of highly controllable reactions to the toolkit of organic chemists. The application of a range of metal catalysts, particularly copper and rhodium complexes, for the controlled decomposition of diazo compounds has paved the way towards tuneable reactivity in three key areas, namely cyclopropanation, insertion and ylide formation.

Oxonium ylide formation, and the attendant [1,2]-shift and [2,3]-sigmatropic rearrangement reactions of the short-lived intermediate, have shown excellent practical application to the diastereoselective formation of oxygen-containing hetereocycles; of particular note is the formation of 2,5-*trans* tetrahydrofuran and 2,6-*trans* tetrahydropyran systems, which are motifs common to a number of isolated natural products.

One such example is amphidinolide C, a structurally complex marine natural product, which shows promising anti-cancer bioactivity. Several groups have published syntheses of fragments of the natural product, in which various methodologies have been used to construct the two, 2,5-*trans* tetrahydrofurans embedded within the macrolactone system. However, until recently the application of oxonium ylide rearrangement towards this target has not been explored.

9 Addendum

Subsequent to completion of this manuscript, a number of papers were published detailing partial and total syntheses of amphidinolides C and F. Primarily, Carter and Mahapatra used methodology analogous to that successfully applied to their synthesis of amphidinolide F to afford the first total synthesis of amphidinolide C.[224]

September 2013 saw the publication by Fürstner and co-workers on the second total synthesis of amphidinolide F.[225] Forsyth and Wu have also published details of their work on the preparation of the C-(1)–C-(14) and C-(15)–C-(25) fragments of amphidinolide C.[226]

Chapter 2: Results and Discussion

10 Clark Group Approach to the Total Synthesis of Amphidinolide C

Since the inception of this project in 2009, the approach towards the synthesis of amphidinolide C within the Clark group has been designed to be both modular and convergent. In common with Carter and Mahapatra's approach, our strategy took into account the 'hidden symmetry' of the macrolide-embedded 2,5-*trans* tetrahydrofuran rings. The key feature of our strategy is the use of a common intermediate for the construction of both 'northern' and 'southern' hemisphere fragments in order that rapid construction of the macrocyclic skeleton could be achieved. The initial retrosynthetic analysis developed by the group, and shown in *Figure 29*, commences with the two almost ubiquitous disconnections across the lactone bond of the macrolactone and the C-(17)—C-(18) bond adjacent to the ketone of C-(18), thereby affording 'northern hemisphere' fragment **297** and 'southern hemisphere' fragment **298**. Both resultant fragments are of similar size and complexity leading to a highly convergent synthesis. Forward connection would be facilitated firstly at C-(17)—C-(18) through a dithiane alkylation of **297** with alkyl iodide **298** and followed by Yamaguchi macrolactonisation.

The northern hemisphere fragment **297** was further disconnected across the C-(26)—C-(27) bond, with forward connection envisaged through a Heck or Stille coupling reaction, to afford vinyl iodide **300** and a vinyl organometallic reagent **299**. Further disconnection of the iodide leads to a strategy involving Negishi carboalumination of alkyne **301**. A Stille reagent of type **299** can be envisaged as being derived from hydrostannylation of a propargylic group, which itself is preparable through nucleophilic attack of a suitable alkyne onto an aldehyde at the C-(24) position. An aldehyde of this type can be prepared through various fuctional group interchanges on 2,5-*trans* dihydrofuran-3-one **306** which is the product of a copper-catalysed formation and rearrangement reaction of an oxonium ylide, or metal-bound ylide intermediate, formed from α-diazoketone **307**, a reaction well studied within the group.

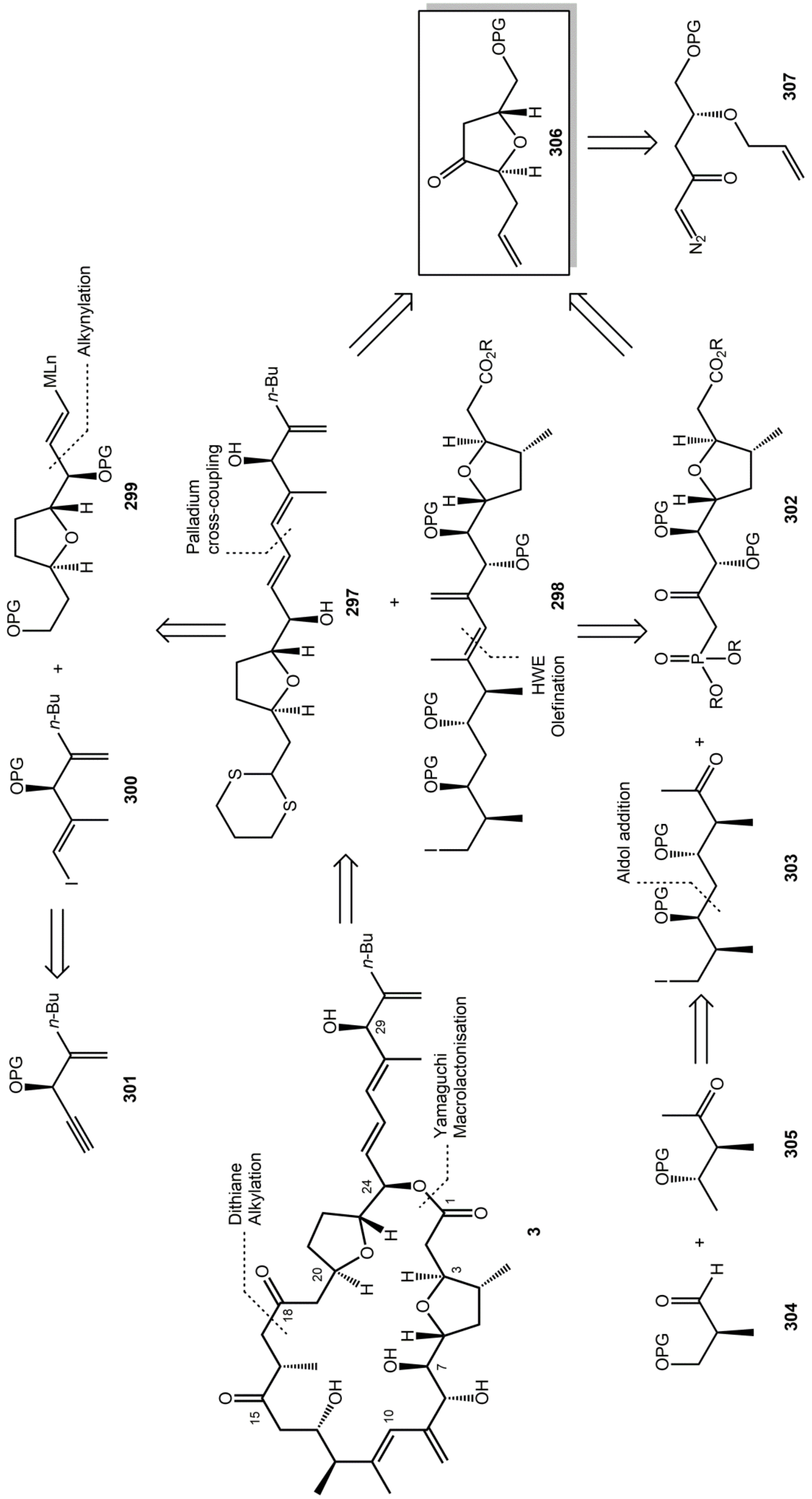

Alkynylation
299
300
301
Palladium cross-coupling
297
HWE Olefination
298
302
Aldol addition
303
304
305
306
307
Dithiane Alkylation
Yamaguchi Macrolactonisation
3

Figure 29

Southern hemisphere fragment **298** was developed from the same dihydrofuran-3-one through disconnection of the C-(10)—C-(11) alkene bond to afford a putative Horner-Wadsworth-Emmons intermediate **302** and methyl ketone **303**. The ß-ketophosphonate was disconnected along the protected diol C-(7)—C-(8) bond and the methyl appendage of the furan ring at C-(4), again providing the 2,5-*trans* dihydrofuranone substrate **306** as the key intermediate in the synthesis. The ketone coupling partner for the HWE reagent was disconnected along the C-(14)-C-(15) bond and can be seen as an advanced intermediate derived from a stereoselective aldol coupling of intermediates **304** and **305**.

11 Preparation of a Common Intermediate

11.1 Acetonide Protected Target

An early candidate for a common intermediate system, incorporating the simplified introduction of the required C-(24) stereochemistry, was acetonide **309**; this compound was believed to be accessible from the early stage enantiopure glyceraldehyde **88**. The use of this starting material would allow, upon tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement of α-diazoketone **308**, access to the desired diastereomer from an inexpensive chiral pool starting material at an early stage in the synthesis. In addition to the early establishment of the C-(24) stereochemistry, facile oxidative cleavage of the deprotected diol would afford an aldehyde, which upon manipulation could deliver the foundation of the C-(7)—C-(8)-*anti* diol subunit of the macrolactone core.

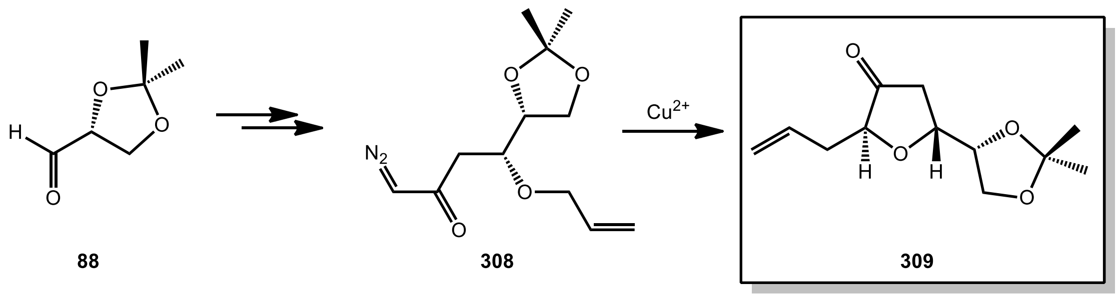
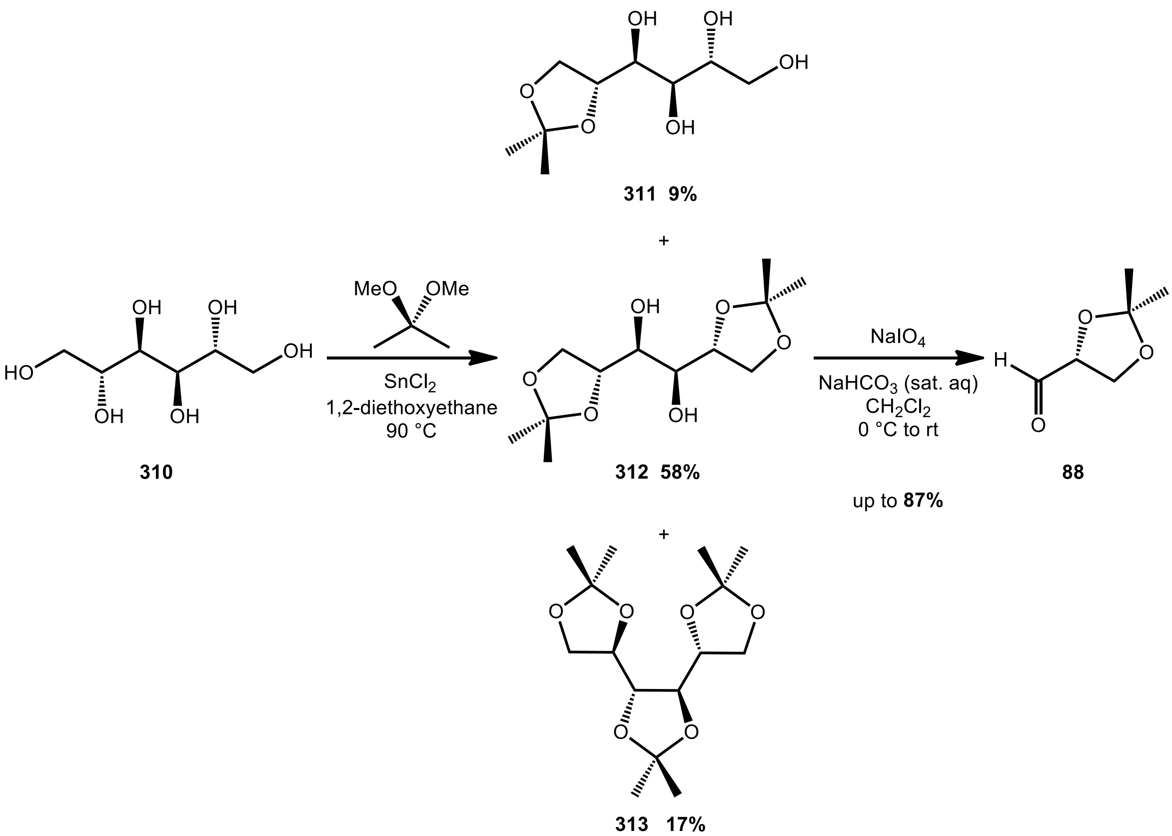


Figure 30

11.1.1 Formation of ß-hydroxyester Intermediate - Reduction Methodology

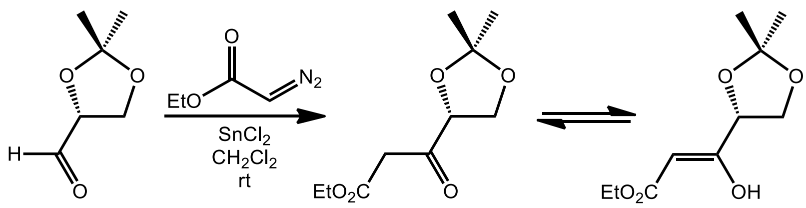
The starting material for this synthetic pathway was 1,2;5,6-diisopropylidene-D-mannitol **310**, an easily accessible derivative of D-mannitol (*Scheme 61*). The bis-acetonide protection of the two terminal 1,2-diol units of D-mannitol was accomplished using 2,2-dimethoxypropane and catalytic tin(II) chloride in refluxing 1,2-dimethoxyethane according to the methods of Schmid and co-workers.[132] The reaction afforded the required 1,2;5,6-diacetal **312** in 58% isolated yield in addition to the 1,2-monoacetal product **311** and the triacetalated material **313** in 9% and 17% yields, respectively. Upon isolation, the diol **312** was subjected to oxidative cleavage, using sodium periodate, to afford the enantiopure (*R*)-glyceraldehyde acetonide **88**. As the procedures became standardised, isolation of the aldehyde, through vacuum distillation, routinely afforded the required compound in yields of up to 87%, with analysis consistant with that described in the literature.[132]



Scheme 61

(*R*)-Glyceraldehyde acetonide is known to have poor stability and is prone to polymerisation even at low temperatures under a nitrogen atmosphere. In addition to the polymerisation problems, it is also known to form a highly water soluble hydrate in the presence of moisture, resulting in overall loss of material if not handled or stored correctly.[132] Generally, subsequent reactions were performed with freshly distilled material to minimise the potential for loss of aldehyde on prolonged storage.

Attainment of sufficient quantities of aldehyde **88** allowed investigations to turn to construction of the 2,5-*trans* tetrahydrofuran-3-one system **309**, for which we required the precursor α-diazoketone **308**. Introduction of the ester functionality required for formation of the required α-diazoketone began by reaction of aldehyde **88** with ethyl diazoacetate in the presence of a Lewis acid, to provide β-ketoester **314a**. Various Lewis acids have been shown to be useful in achieving this type of C-H insertion reaction, including $BF_3{\cdot}OEt_2$,[133] $SnCl_2$[134] and $NbCl_5$;[135] alternative approaches to effecting this transformation have used Cu(II) and Rh(III) exchanged clays[136] and zeolite catalysts.[137] Initial efforts to effect the formation of **314a** employed $BF_3{\cdot}OEt_2$ as the catalyst afforded complex reaction mixtures from which the desired β-ketoester was isolated in an unsatisfactory 16% yield. The ^{1}H NMR spectrum of the isolated product showed an equilibrium mixture of β-ketoester **314a** and tautomeric enol form **314b**. A transformation using stannous chloride as the catalyst, as described originally by Roskamp and Holmquist,[134] resulted in a cleaner reaction and a much improved isolated yield of 81%.



88 **314a** **314b**

Scheme 62

In order to introduce the required C-5 *R*-stereochemistry to the target, 2,5-*trans* tetrahydrofuran-3-one **309**, the ketone functionality of **314** was required to undergo stereoselective reduction. Pleasingly, Chikashita and co-workers had previously described an identical reduction reaction in 1989. Their work detailed the low temperature application of L-selectride [LiBH(*sec*-Bu)$_3$] for the stereoselective reduction of a series of β-ketoesters, one of which resulted in the attainment of 1,2-*syn* diastereomer **315a** in moderate yield and with excellent diastereocontrol.[138] The mechanistic rationale for the stereoselective reduction relied on chelation of the lithium cation with both the carbonyl and the β-ether groups of the acetonide, allowing preferential attack from the less hindered *si* face. In this fashion, 1,2-*syn* diasteromer **315a** is formed as the major product, whereas coordination through the α-ether and reduction from the *re* face results in the undesired 1,2-*anti* diastereomer **315b**; both outcomes are illustrated in *Figure 31*. The results of Chikashita support the conclusion that high facial selectivity is engendered by use of reagents capable of chelation control, whilst reductants composed of poorly chelating metals, such as aluminium (DIBAL-H) and sodium ($NaBH_4$) show only marginal preference for the 1,2-*syn* diastereomer.

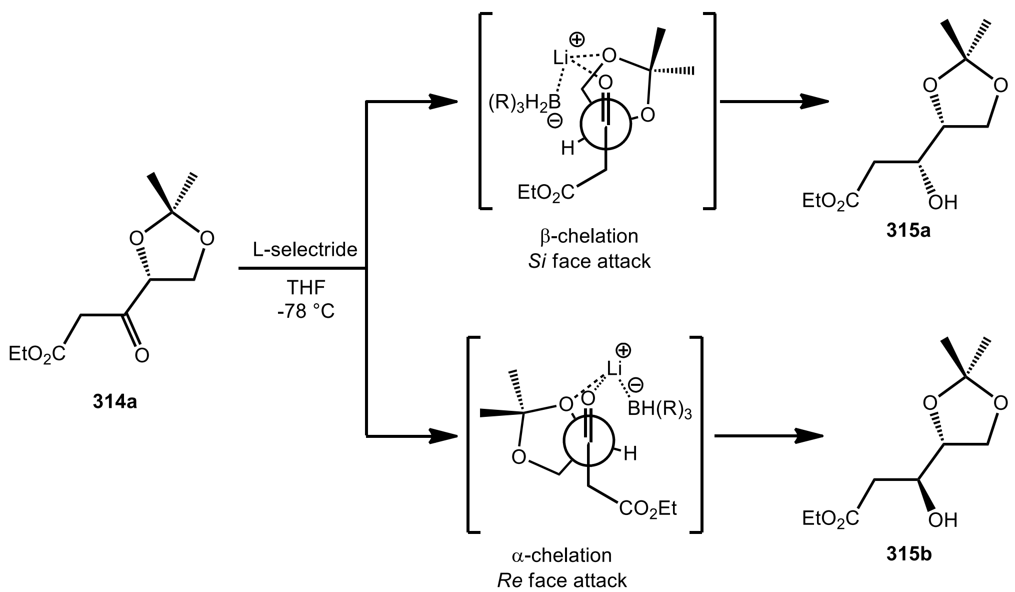
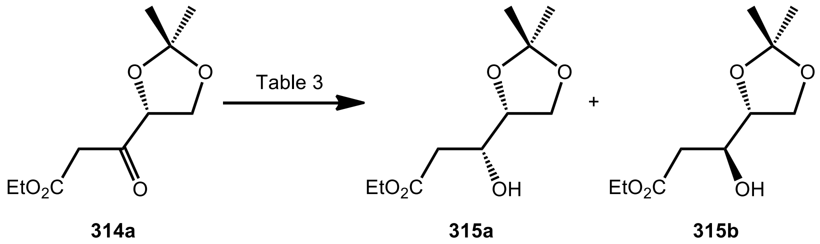


Figure 31

In our hands, efforts to replicate these results were unsuccessful despite the use of various batches of L-selectride, solvents, temperatures and work-up conditions; a selection of results are illustrated in *Table 3*. Reductions using L-selectride and superhydride (entries 1 to 4 and entry 9 respectively) were monitored by TLC upon complete addition of the reductant, at the temperatures specified. In each case TLC analysis indicated consumption of the starting material and conversion to a more polar product. However, on work-up TLC analysis showed only a single spot of identical polarity to the starting material. ^{1}H NMR analysis of isolated material showed that this was indeed the keto-enol **314**, with no desired reduction having taken place. Increasing the concentration of reductant and variation of batch afforded no reaction nor did the extension of reaction time. Allowing the reaction to warm to ambient temperature (entry 3) led only to an intractable mixture from which the reduced product could not be isolated. The change in TLC profile observed during the reaction suggested that coordination of the substrate and reductant was occurring, but was not followed by delivery of the hydride to the carbonyl group.



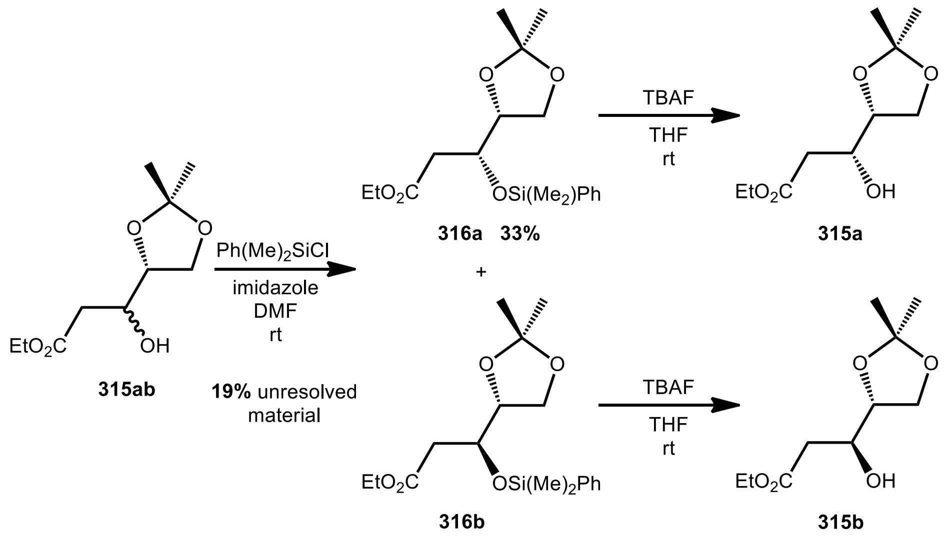
Scheme 63

Entry	Reductant	Eq. mol.	Solvent	Temp. (°C)	Time (min)	Yield (%) **315a:315b**	*dr* **315a:315b**
1	Li(*sec*-Bu)$_3$BH	2.0	THF	−78	180	–	–
2	Li(*sec*-Bu)$_3$BH	2.0	THF	−78	360	–	–
3	Li(*sec*-Bu)$_3$BH	4.0	THF	−78 to rt	300	Decomp.	–
4	Li(*sec*-Bu)$_3$BH	3.0	Et_2O	−78	60	–	–
5	$NaBH_4$	1.1	EtOH	−78	30	95	56:44
6	$NaBH_4$	1.1	EtOH	0	30	94	50:50
7	$LiBH_4$	1.5	EtOH	−78	30	90	50:50
8	$LiBH_4$	1.3	THF	0	30	–	–
9	$LiBHEt_3$	1.1	THF	−40	120	–	–

Table 3

Less sterically encumbered reducing reagents were then applied to the system. As expected, $NaBH_4$ delivered full reduction of the ketone but with no stereoselectivity even at low temperature (*dr* 56:44 *syn*:*anti*). $LiBH_4$ in ethanol (entry 7) afforded no stereoselectivty in the reduction, but like $NaBH_4$ fully reduced the starting material. Attempts to repeat the reduction in THF at 0 °C did not proceed most likely due to the poor solubility of the reductant (entry 9). Further attempts to pre-chelate the β-ketoester with salts of lithium or zinc prior to reduction were unsuccessful in terms of diasteromeric outcome.

In an effort to advance the synthesis and test subsequent reactivity, efforts were made to isolate each of the diastereomeric ß-hydroxyesters **315ab**. During the course of purifying the products of reduction, attempts were made to separate the mixture by chromatography, but on each occasion attempted isolation was met with failure. It was found that derivatisation of the secondary alcohols as dimethylphenylsilyl ethers, as shown in *Scheme 64*, allowed for successful part-separation of the diastereomers on a 100 mg scale. On isolation, the discrete products were treated with TBAF to regenerate the secondary alcohols and assignment of structure made by comparison to Herrera's data for the 1,2-*anti* diastereomer **315b**.[139]

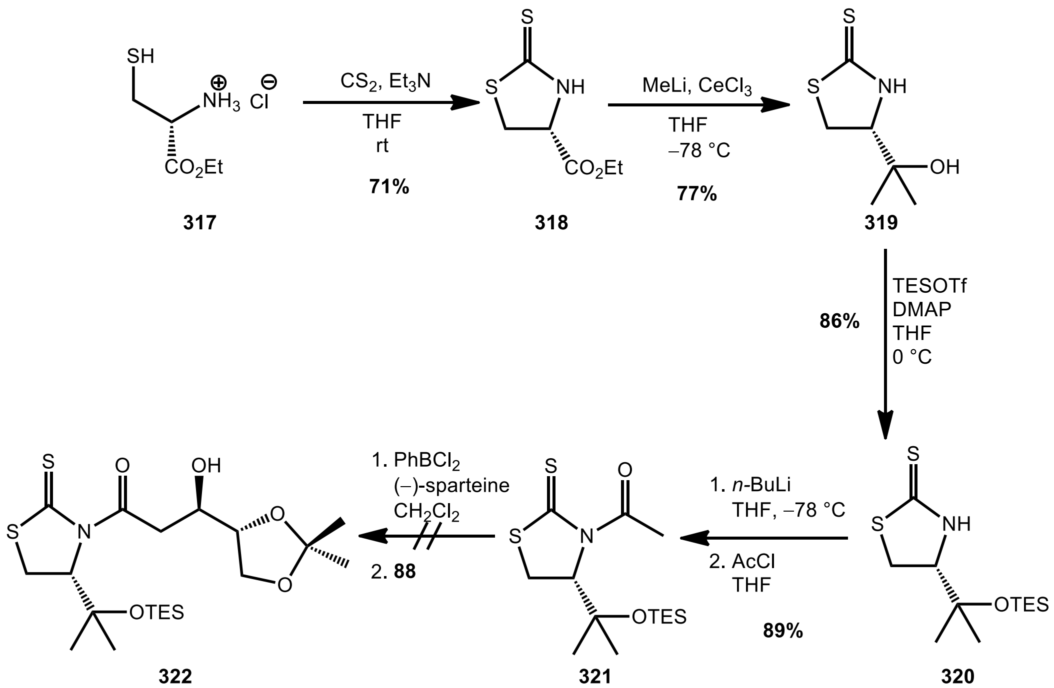


Scheme 64

11.1.2 Formation of ß-hydroxyester - Chiral Auxilliary Methodology

Efforts to render formation of ß-hydroxyester **315a** stereoselective were undertaken using the chiral auxiliary procedures established by Sammakia and Zhang.[140] *Scheme 65* illustrates the synthesis of the acetylated auxiliary unit **321**, beginning from commercially available cysteine ethyl ester hydrochloride **317**. Conversion of the starting material through reaction with carbon disufide allowed access to thiazolidinethione **318** in reasonable yield; an identical transformation was also accomplished with 1 1-thiocarbonyldiimidazole in a comparable 66% isolated yield.

Tertiary alcohol **319** was formed by the addition of a methylcerium nucleophile, generated by combination of methyllithium and anhydrous cerium trichloride, a side-step necessary due to epimerisation of the α-stereocentre through enolisation when using more basic nucleophiles. Addition of the cerium reagent to the ester group provided the required alcohol in 77% yield after recrystallisation from toluene. The synthesis was completed by TES protection of the extant alcohol and acylation of the thiazolidinethione ring system.

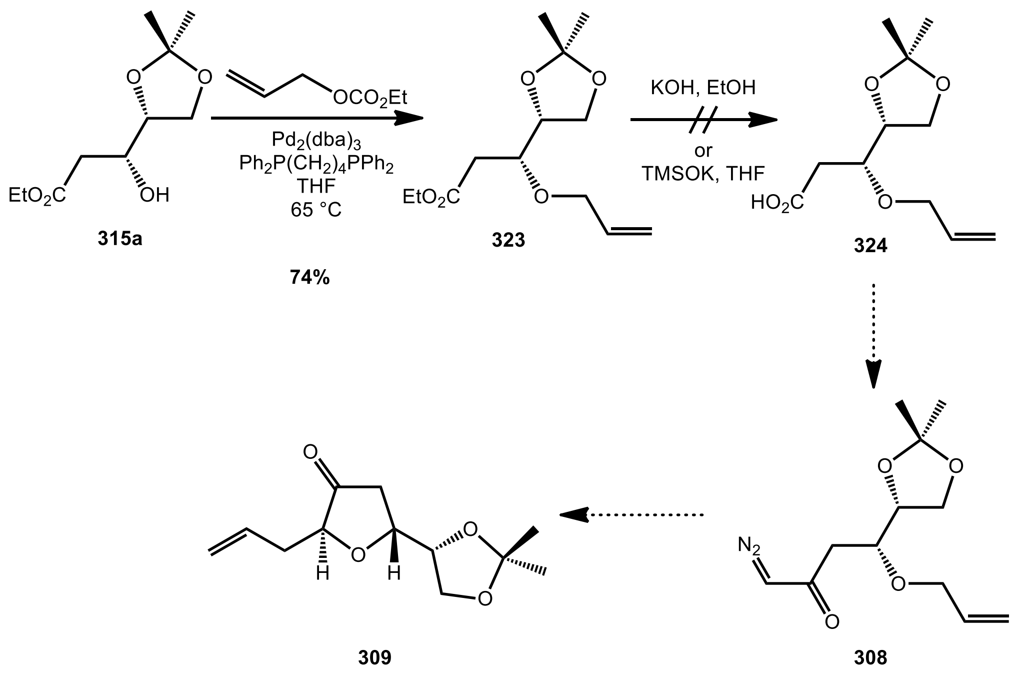


Scheme 65

Attempts were made to accomplish the aldol addition of **321** to aldehyde **88** using dichlorophenylborane and (−)-sparteine to generate the enolate. Despite closely following the protocol of Sammakia, only complex reaction mixtures were obtained in each instance. Attempted purification of the reaction residues produced small amounts of material that, by ^{1}H NMR analysis, contained the pertinent peaks of the product, as indicated by comparison to literature values, but also included many other artefacts that were inconsistent with the desired reactivity. Notwithstanding the disappointment of this initial result, a further attempt was made to effect the transformation using stannous triflate and *N*-ethylpiperidine to form the enolate at −78 °C, prior to addition of a freshly prepared batch of aldehyde. Analysis of an aliquot of reaction mixture showed only the presence of the auxiliary, the aldehyde appearing to have decomposed over a short period of time under the reaction conditions.

11.1.3 Subsequent Syntheses of the ß-ketoester Intermediate

As a quantity of the required ß-hydroxyester **315a** had been isolated cleanly through silyl ether derivitisation, efforts were made to allylate the free hydroxyl function using various procedures. Although treatment of alcohols with allyl bromide in the presence of silver(I) oxide has been used for the mild allylation of various diverse substrates including ß-hydroesters,[97] in our case no reaction was observed to occur when similar conditions were employed. An alternative approach, in which the allyl cation is generated *in situ* from allyl trichloroacetimidate in the presence of an acid catalyst has previously been used to form allylic ethers.[141] Standard catalysts for this type of transformation include sulfonic acids, but in the case of compounds bearing acetal groups these conditions are too harsh, leading to loss of the protecting group. In related examples, Lewis acids have demonstrated useful reactivity in the formation of benzyl ethers from trichloroacetimidate precursors.[142] It was hoped that treatment of alcohol **315a** with a freshly prepared batch of allyl trichloroacetimidate in toluene, using $Sc(OTf)_3$ as the catalyst, would afford allyl ether **323**. Disappointingly, on prolonged stirring the starting material remained unreacted.



Scheme 66

Allylation of the secondary alcohol was ultimately accomplished via palladium-catalysed generation of the allyl cation from allyl ethyl carbonate in degassed THF,[143] as shown in *Scheme 66*. These conditions allowed high isolable yields of stereopure allyl ether **323** to be obtained. When analogous conditions were applied to a diastereomeric mixture of ß-hydroxyesters **315ab** an isolated yield of 98% was achieved, but unfortunately the product diastereomers proved impossible to separate by chromatography.

Attention subsequently turned to the conversion of the ethyl ester to an α-diazoketone via activation of carboxylic acid **324**. Frustratingly, when ester **323** was exposed to hydrolysis using potassium hydroxide in alcohol, decomposition of the substrate ensued; the alternative use of potassium trimethylsilanolate as the nucleophile resulted in a sluggish reaction. At this stage, efforts to prepare an acetonide protected common intermediate were abandoned in favour a more practical route towards such an early stage intermediate.

11.2 TBS and TBDPS Protected Targets

The difficulties encountered during the attempted synthesis of **309**, from the laborious preparation of aldehyde **88**, through the non-stereoselective formation of desired ß-hydroxyester **315a** and decomposition of the ester **323** on exposure to basic hydrolysis conditions had guided the project towards two significant conclusions. Firstly, the route used to introduce the stereochemistry, into what would become the C-5 position of the target 2,5-*trans* tetrahydrofuran-3-one, had to be amenable to scalable synthesis due to the early stage nature of the intermediate. Secondly, it was necessary to use a protecting group of greater stability than the originally chosen acetonide; in this case the use of silyl ethers was considered advantageous (*Figure 32*).

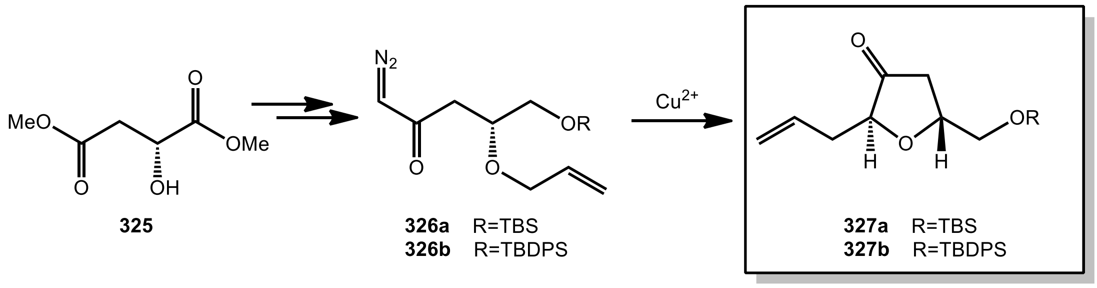
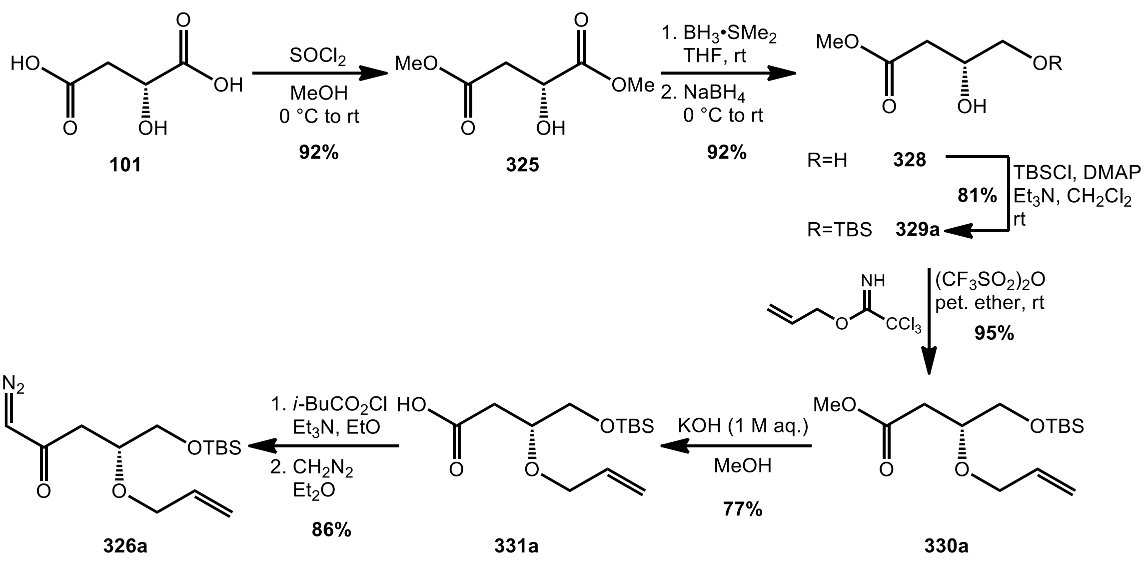


Figure 32

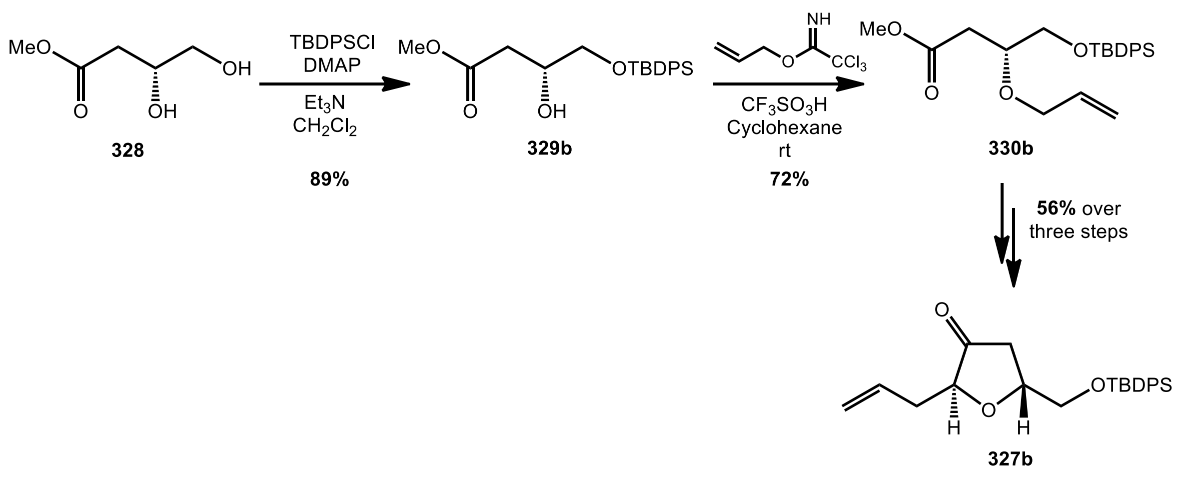
The restructured synthetic route began from the commercially available chiral pool starting material D-malic acid, the enantiomer of which had proved to be a versatile starting material for a previous total synthesis project within the group.[144] The keystone TBS-protected common intermediate **326a** was prepared rapidly in seven steps from D-malic acid **101** (*Scheme 67*). Bis-esterification of the carboxylic acids with methanol and thionyl chloride[145] yielded D-methyl malate **325**, the α-hydroxyester of which was selectively reduced using a combination of borane-DMS complex and sodium borohydride through the protocol of Saito and co-workers.[146] The primary alcohol of the resulting diol **328**, thus formed, was selectively protected using TBSCl, setting the stage for allylation of the secondary hydroxyl group.



Scheme 67

In the course of preparing a supplementary compound set, in which a TBDPS ether was used in place of the TBS protecting group, it had been found that allylation of this type of secondary alcohol could be achieved using the triflic acid catalysed activation of an allyl trichloroacetimidate (*Scheme 68*).[147] Using this strategy, 2,5-*trans* tetrahydrofuran-3-one **327b** was prepared in seven steps and with an overall 36% yield.

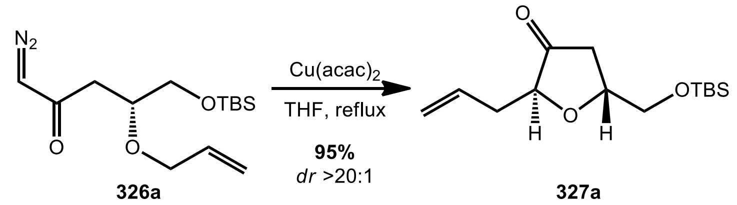
An initial attempt to convert TBS analogue **329a** to allyl ether **330a**, using triflic acid as the catalyst, led to a mixture of products through acidic cleavage of the TBS protecting group and non-selective allylation of the resultant diol **328**. Further efforts employing CSA or PPTS as the catalyst did not furnish the desired allylated compound. However, high yields of **330a** were obtained when the reaction was catalysed by triflic anhydride over the course of five days.[148] An alternative allylation strategy, using the palladium-catalysed decomposition of allyl ethyl carbonate, afforded an inseparable product mixture containing the desired material and a product that appeared to have resulted from migration of the silyl protecting group to the secondary hydroxyl group.



Scheme 68

Attempted hydrolysis of the methyl ester **330a** by exposure to potassium trimethylsilanolate in THF, proved to be too sluggish for an acceptably reproducible procedure (*Scheme 67*). In contrast saponification using potassium hydroxide proceeded smoothly to afford the carboxylic acid **331a**. Subsequent activation of the acid, either as the acid chloride or as a mixed anhydride, and treatment of the intermediate with freshly prepared diazomethane permitted access to the α-diazoketone **326a**. The diazoketone was isolated as a green oil, indicating light absorbance in the visible spectrum, whilst the IR spectrum of the compound showed an intense absorbtion at 2101 cm^{-1} corresponding to the diazo functionality.[149] Both the ^{1}H and ^{13}C NMR spectra showed the presence of the newly formed $CH=N_2$ group with signals at 5.34 and 55.5 ppm respectively, thereby demonstrating the isolated material was the desired α-diazoketone.

As discussed in the previous chapter, α-diazocarbonyl compounds undergo extrusion of nitrogen to form metal carbenoids in the presence of metal catalysts. In cases of acyclic substrates where allylic ethers are present, these intermediates can then undergo oxonium ylide formation followed by a [2,3]-sigmatropic rearrangement, thereby forming oxygen-containing heterocycles in a highly diastereoselective fashion. In this case, α-diazoketone **326a**, when exposed to $Cu(acac)_2$ in refluxing THF, followed this pathway to afford 2,5-*trans* tetrahydrofuran-3-one **327a** in excellent yield and as a single diastereomer (*Scheme 69*). As shown in *Scheme 68*, an analogous transformation was conducted to form the TBDPS protected substrate **327b** and the NMR data of the compound again showed formation of a single diastereoisomer. Numerous examples within the group have shown that the rearrangement of oxonium ylides of this type provide the desired 2,5-*trans* stereochemistry shown, the data for the isolated compound **327b** was supported by these analyses and differed from data corresponding to the alternative 2,5-*cis* diastereomer.[147] Further confirmation of the stereochemistry came from comparison of the data of advanced synthetic intermediates, to those of known compounds and will be discussed presently.



Scheme 69

While the benefits of forming 2,5-*trans* tetrahydrofuranones through the diastereoselective rearrangement of oxonium ylides is immediately apparent, the practical aspects of the synthesis require brief discussion. The safety hazards of diazomethane generation, both in terms of potential toxicity and explosive risk, require that distillation of the compound is conducted in a well-ventilated fume hood using apparatus with fire-polished jointed glassware. The glassware within our group limits the decomposition of Diazald to 100 mmol, which without loss would provide the equivalent molar concentration of diazomethane. The formation of diazoketone **326a** from the mixed anhydride of **331a** requires around 10 equivalent moles of diazomethane to maximise product yield, thereby limiting the scale of reaction to 10 mmol scale, equating to 2.7 g of acid **331a** as starting material. As 2,5-*trans* tetrahydrofuranone **327a** is a relatively early stage intermediate in our process this scale issue constitutes an early bottleneck in the synthesis. The synthesis of diazoketone **326a** was typically conducted in duplicate, and the reactions combined for work up and purification prior to the tandem oxonium ylide and [2,3]-sigmatropic rearrangement reaction.

The decomposition of diazoketone **326a**, and rearrangement of the intermediate oxonium ylide to form the 2,5-*trans* tetrahydrofuran-3-one, generally occurred within thirty minutes if vigorous reflux was maintained throughout the course of the reaction. On occasion the reaction did not proceed, possibly due to inactive catalyst, but in such cases the starting α-diazoketone could be re-isolated almost quantitatively by column chromatography thereby showing the robust stability of **326a** to thermolysis alone. The 2,5-*trans* tetrahydrofuran-3-one **327a** was isolated through simple concentration of the solution and direct purification of the residue; isolable yields of 85% to 95% were regularly achieved on reactions of up to 4 grams of α-diazoketone, with no observable trace of the undesired 2,5-*cis* diastereomer. Although the possibility existed for a C-H insertion side reaction to form **332**, or for an alternative six-membered oxonium ylide formation through **333**, the products of neither outcome were observed (*Figure 33*).

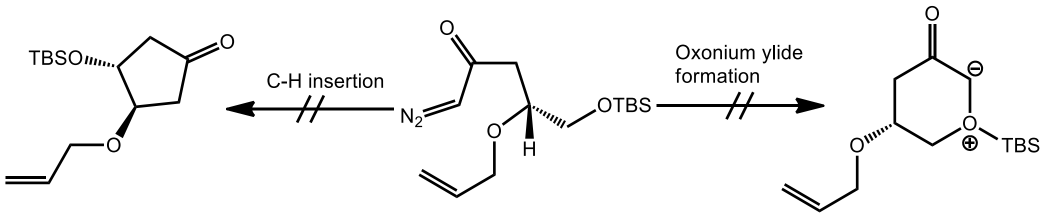


Figure 33

12 Diversification of Common Intermediate

12.1 Synthesis of C-(18)-C-(24) Fragment of Amphidinolide C — C-(21) Ketone Removal

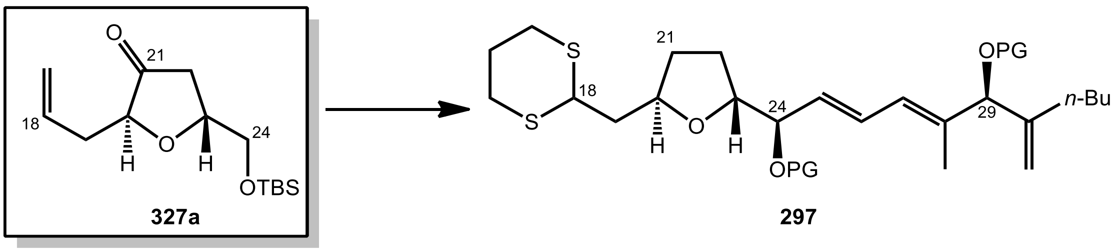
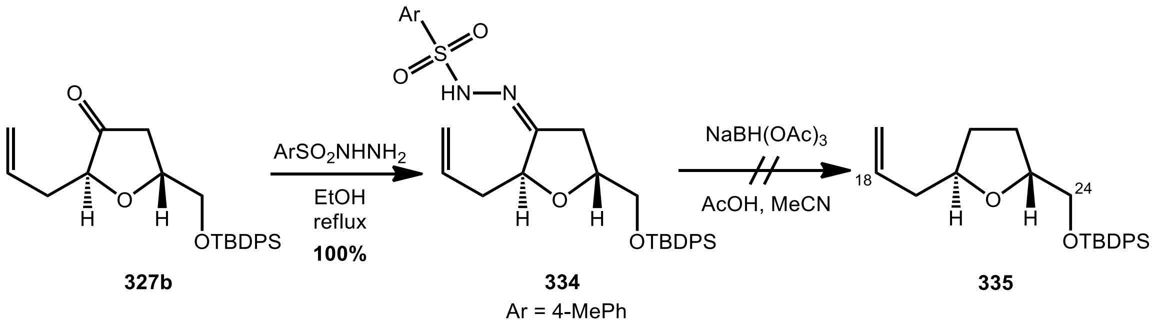


Figure 34

12.1.1 Reductive Removal of C-(21) Ketone Functionality

In differentiating the common intermediate **323a** to provide the 'northern' construct **297** (*Figure 34*), the immediate goal was deletion of the ketone group on what would become the C-(21) position of the natural product. Initial work on this problem was geared towards removal of the functionality through formation of the tosyl hydrazone followed by reduction of the intermediate species; an example of equivalent reactivity on tetrahydrofuranones was reported by McLaughlin in 2002.[150] Although synthesis of the tosyl hydrazone **334** proved facile, reductive removal of the functionality using a number of reducing agents, including $NaBH(OAc)_3$,[150] $NaBH_3CN$,[151] and $NaBH_4$,[152] proved impossible, leading only to intractable product mixtures in each case (*Scheme 70*).



Scheme 70

12.1.2 Radical Deoxygenation of C-(21) Functionality

An alternative approach to the problem was sought through the radical substitution methodology of Barton and McCombie[153] whereby the ketone would be converted into a functional group that would undergo radical cleavage and hydride reduction. Initial anxieties concerning the possibility of cyclisation of the intermediate radical species with the pendant olefin in a 4-*exo* or 5-*endo*-trig fashion,[154] would prove to be unfounded in practise (*Figure 35*).

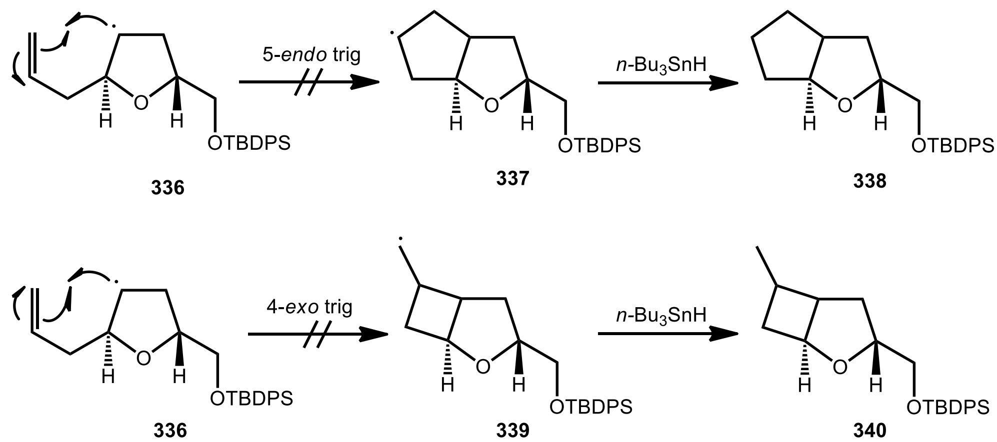
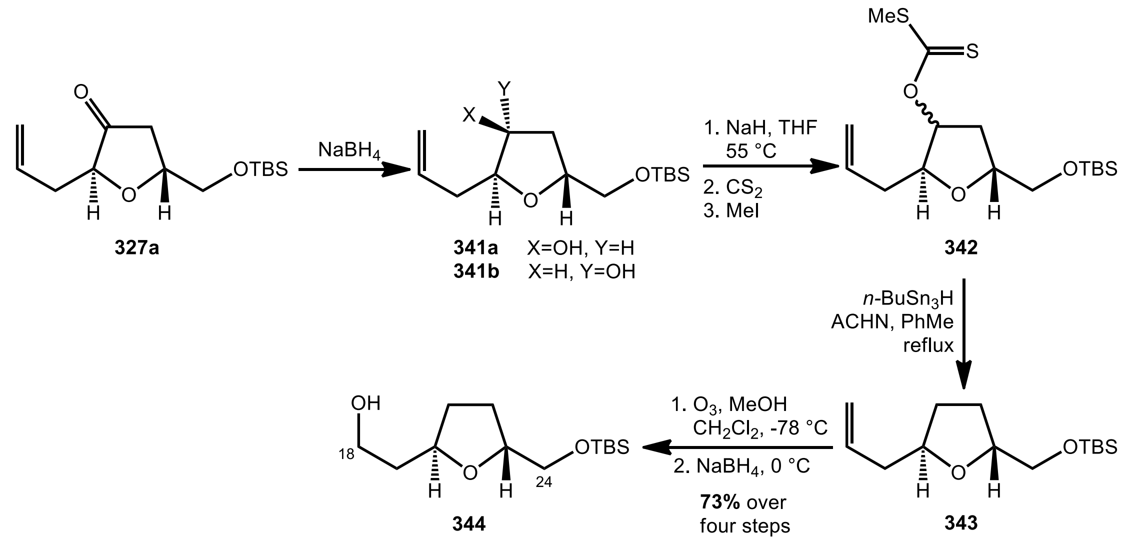


Figure 35

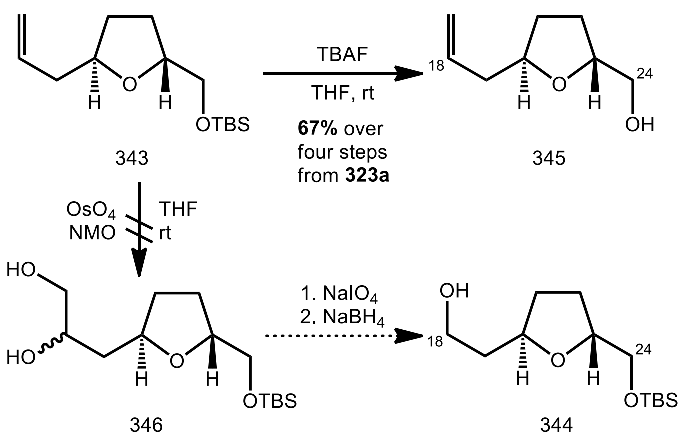
Work on the sequence began with borohydride reduction of the ketone carbonyl group to form a diastereomeric mixture of alcohols on the C-(21) carbon. The diastereomers **341a** and **341b** were separable by column chromatography and confirmation of absolute stereochemistry of the system was possible by comparison of the data for the 1,2-*syn* isomer **341a** with that of a previously characterised sample prepared by Pagenkopf and Wang.[155] Subsequent work on the compounds was conducted using the diastereomeric mixture of both alcohols.

The alcohols were converted to their respective xanthate esters **342** by stepwise treatment with base, carbon disulfide and methyl iodide. This intermediate was not purified but used directly in the subsequent deoxygenation step following work-up and concentration. Using tri-*n*-butyltin hydride and a radical initiator, both AIBN and ACHN proving germane, tetrahydrofuran **342** was deoxygenated smoothly to afford **343**. Although the reaction proceeded cleanly to afford the required material, the compound could not be isolated by chromatography without the presence of a malodorous sulfur-containing impurity.



Scheme 71

Isolation of unadulterated tetrahydrofuran substrate was accomplished by fluoride deprotection of TBS ether **343**, column chromatography of the resultant alcohol **345** allowing separation of the product from the foul-smelling impurity (*Scheme 72*). Although this alcohol was used in subsequent test reactions, alcohol **344** was the preferred and strategically required intermediate hence a consequent reprotection of the primary alcohol **345** was necessary, rendering this route synthetically superfluous.

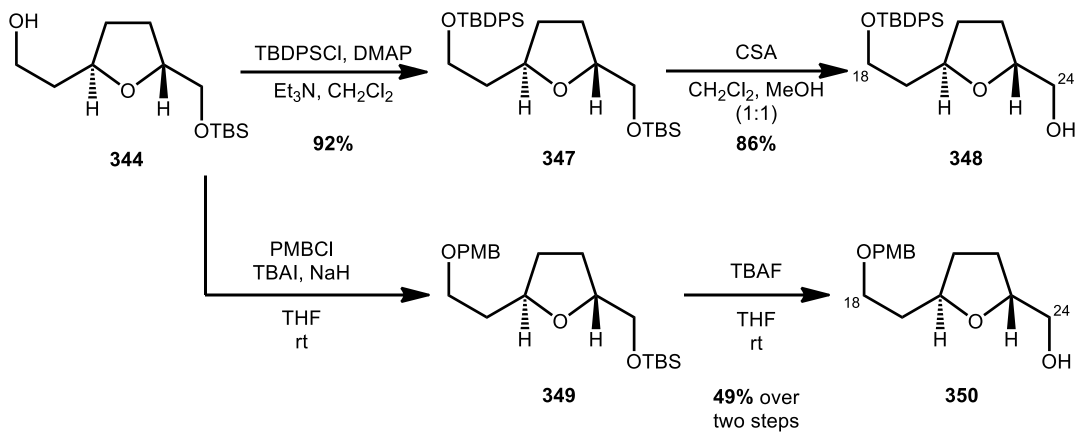


Scheme 72

As the impurity had been shown to be separable from the desired system by rendering the tetrahydrofuran compound more polar, a second approach involving direct transformation of the allyl functionality to primary alcohol **344** was investigated (*Scheme 72*). Preliminary attempts to effect this transformation involved dihydroxylation of the olefin, with subsequent oxidative cleavage of the intermediate 1,2-diol and reduction of the resultant aldehyde affording alcohol **344** (*Scheme 72*). Disappointingly, formation of diol **346** failed possibly due to poisoning of the osmium, by the sulphur-based impurity, and so the reaction sequence was abandoned. An alternative approach, in which ozonolysis of the double bond was followed by borohydride reduction of the intermediate trioxolane, gratifyingly allowed access to alcohol **340** in 73% yield over four steps from ketone **327a** (*Scheme 71*). The removal of the C-(21) oxygen substituent to form the desired tetrahydrofuran was confirmed by signals in the ^{1}H NMR spectra at 2.11-2.02 and 1.63–1.53 ppm, integrating to one proton each for the newly formed CH_2 group. A single peak in the ^{13}C NMR spectrum at 32.4 ppm, showing HSQC correlation with both C-H signals confirmed the structure of the product.

12.1.3 Orthogonal Protection of the C-(18)—C-(24) Fragment

Masking of the primary alcohol of **344** was accomplished with two distinct protecting groups, namely TBDPS and PMB, in order to expand the potential late stage deprotection strategies for the C-(18) hydroxyl group. Upon protection of the pendant alcohol, the C-(24) TBS ether was removed selectively by means of CSA-catalysed deprotection in the case of bis-silyl ether **347**, and by exposure to the fluoride anion in the case of PMB ether **349**.

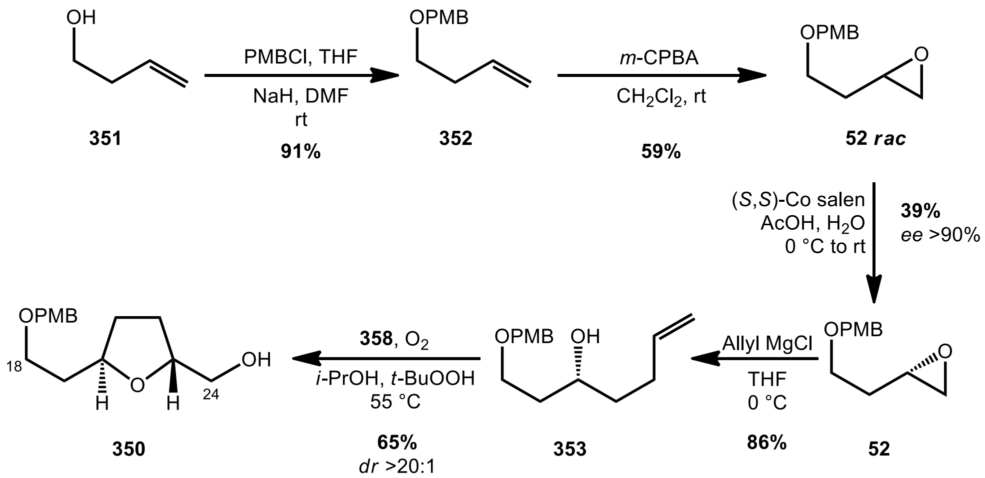


Scheme 73

TBDPS ether **348** was used in the preliminary stages of construction of the C-(18)—C-(34) fragment of the natural product, however the optimisation of an orthogonal protecting group strategy for this northern fragment would later require the exploitation of PMB protected ether **350**. To this end, an alternative strategy towards the bulk synthesis of the fragment was investigated.

12.1.4 Alternative Strategy in Forming C-(18)—C-(24) Fragment

Due to the strictures of time at the final stages of the project, a more concise approach to the generation of the 'Northern' tetrahydrofuran **350** was sought which condensed the synthesis timeframes over those required for the previously discussed diazoketone rearrangement and Barton-McCombie deoxygenation steps. A variation on the procedure of Pagenkopf and Morra[28] was used to form **350** in five steps from commercially available 1-buten-4-ol, as shown in *Scheme 74*. Protection of the alcohol with a PMB group proceeded in good yield and was followed by epoxidation of the alkene using standard *m*-CPBA methodology. Hydrolytic kinetic resolution of the racemic mixture, using the protocol of Jacobsen,[26, 156] delivered the desired oxirane in a 39% yield, the data for which corresponded directly with that previously reported by Spilling and Roy.[27] Epoxide ring opening was achieved by the addition of allylmagnesium chloride, and the isolated compound again complemented literature data for the 5-hydroxypent-1-ene **353**.[27] A diastereoselective, cobalt catalysed cyclisation then delivered the 2,5-*trans* tetrahydrofuran **350** in a 65% yield, the data for which matched precisely with that of the compound generated through the route involving tandem oxonium ylide and [2,3]-sigmatropic rearrangement chemistry as previously discussed.



Scheme 74

Cobalt-catalysed cyclisations of this type had been investigated in the early 1990's by Mukaiyama *et al.*[157] In their original paper they reported an oxidative cyclisation of a number of α-substituted 5-hydroxypent-1-ene starting materials **354**, to form 2-hydroxytetrahydrofurans **360** with varying C-5 substitutions (*Figure 36*).

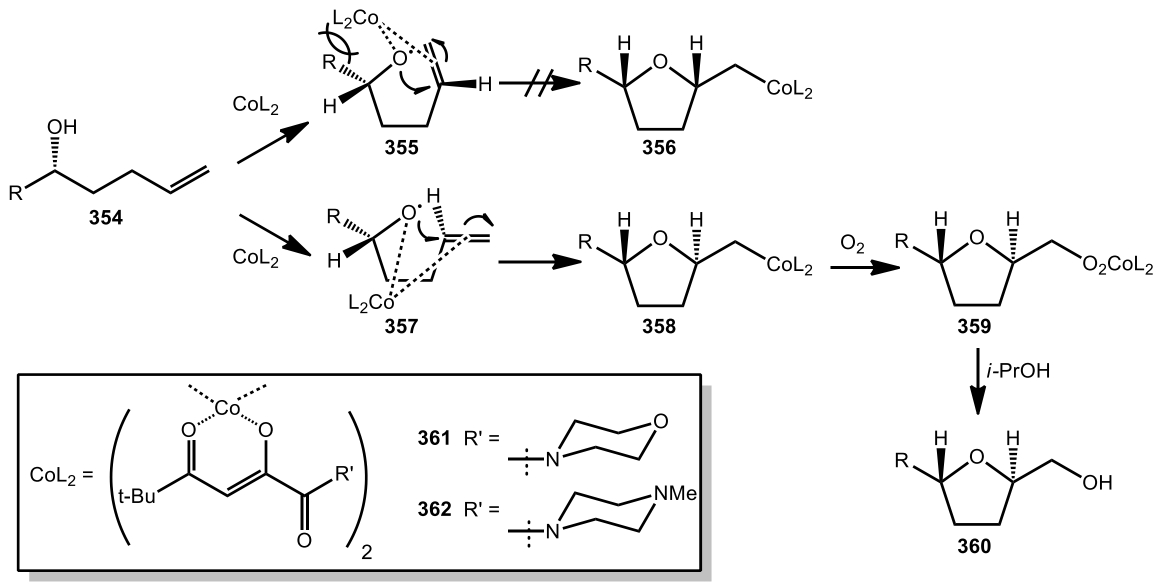
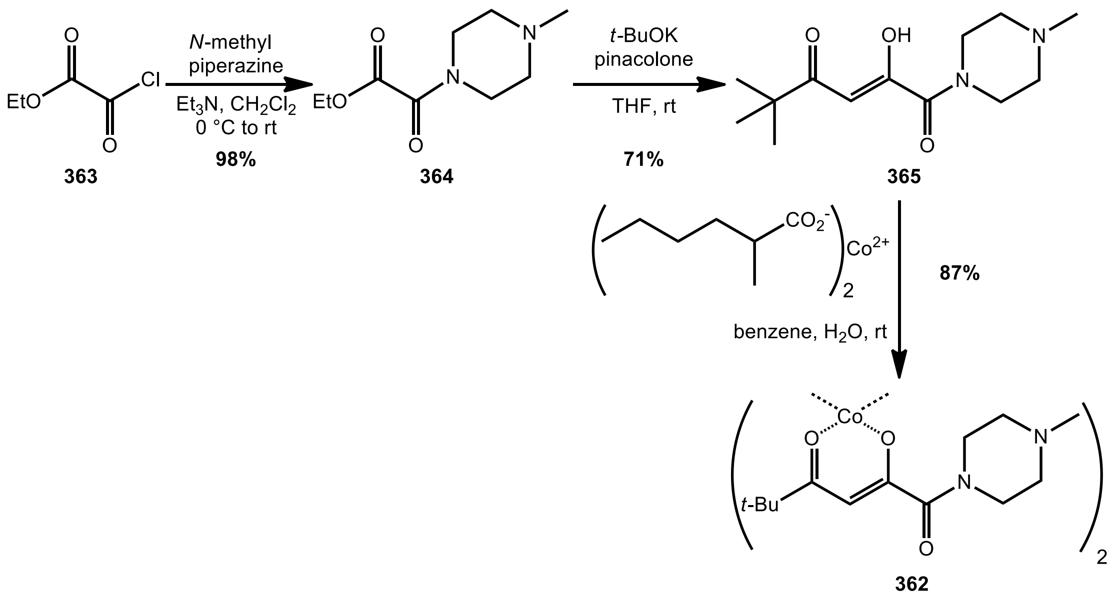


Figure 36

The excellent stereocontrol of the reaction, affording exclusively the 2,5-*trans* product, was believed to derive from the minimised steric repulsion encountered between the α-substituent at the 5-position of the radical intermediate **357** and the bound cobalt-ligand complex in the cyclisation step. The NMM catalyst **366** used by Mukaiyama was improved by Pagenkopf by substitution of the NMM amide with NMP to give complex **362**. The diastereoselectivity of both catalysts were equivalent, but the NMP group was preferred due to the propensity of the tertiary amine to quaternarise in the presence of alkyl halides. The improved aqueous solubility of the quaternary amine facilitated removal of the catalyst system through simple extraction techniques.

The catalyst was prepared, through the method of Pagenkopf, in three steps, beginning from formation of glyoxylate amide **364** through reaction of ethyl chlorooxoacetate **363** and 1-methylpiperazine.[158] The ester was subsequently reacted with the potassium enolate of pinacolone to afford ligand **365**. Ligand exchange to form the cobalt(II) NMP_2 catalyst **362** was accomplished through reaction with cobalt(II) ethylhexanoate, the product being easily isolated by decanting off the mother liquor and washing the product with hexane (*Scheme 75*).



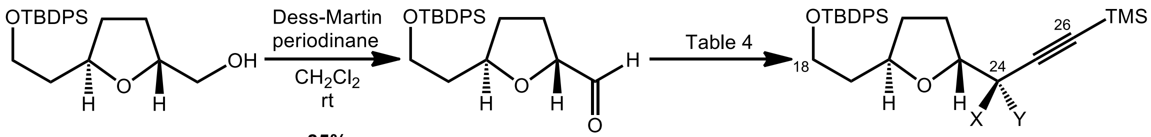
Scheme 75

12.2 Synthesis of C-(18)—C-(26) Fragment — Introduction of C-(24) Stereochemistry

12.2.1 Substrate Controlled Alkynylation

With a range of tetrahydrofuryl alcohols in hand, attention turned to establishment of the C-(24) hydroxyl stereochemistry and the introduction of a synthetic handle to allow access to the C-(25)—C-(28) diene functionality. Formation of propargylic alcohol **363a** was envisaged as a route towards creating this synthetic handle, as regio- and stereoselective hydrostannylation of the alkyne would permit test reactions to be conducted on future Stille cross-coupling methodology.

Investigations into the creation of the desired C-(24) stereochemistry began by focussing on the ability of the aldehyde **366** to exert substrate control during the alkynylation through the α-chiral centre at the C-(23) position. It was hoped that through the use of chelation control, *Figure 37*, that the alkynylation would proceed to afford the desired C-(24) stereochemistry exclusively. To this end, magnesium and lithium acetylides were generated and added to aldehyde **366**.



348 **366** **367a:** X = OH; Y = H **367b**: X = H; Y = OH

Scheme 76

Entry	Acetylide	Additive	Temp (°C)	Solvent	Yield (%)	*dr* **367a: 367b**
1	TMS—≡⊖ ⊕Li	–	−78	Et_2O/ Et_3N	47	1:2
2	TMS—≡⊖ ⊕Li	–	−78	THF	68	1:2
3	TMS—≡⊖ ⊕MgBr	–	−78	THF	72	2:1
4	TMS—≡⊖ ⊕MgBr	–	0	THF	72	2:1
5	TMS—≡⊖ ⊕Li	$MgBr_2$	−30	Et_2O	71	1:1
6	TMS—≡⊖ ⊕Li	$MgBr_2$	−78	Et_2O	71	1:2
7	TMS—≡⊖ ⊕Li	$ZnCl_2$	−78	–	–	–

Table 4

Frustratingly, no combination of reagent, additive, temperature or solvent system permitted stereoselective addition of the nucleophile to the aldehyde (*Table 4*). A single example of the addition of a structurally similar aldehyde to the lithium acetylide in THF at −78 °C afforded a *dr* of 9:1 in favour of the undesired stereochemistry, albeit in 38% yield; the reaction proved irreproducible when applied to aldehyde **366** (entry 2). The use of a magnesium acetylide (entries 3 and 4) allowed marginal preference for the formation of the desired C-(23)—C-(24) 1,2-*syn* diastereomer. In contrast, attempts to pre-chelate the aldehyde and tetrahydrofuran ether with magnesium bromide did not provide the desired chelated intermediate for addition of the alkyne nucleophile (entries 5 and 6) and proceeded with a slight preference for the 1,2-*anti* diastereomer **367b** on addition of the nucleophile.

Use of zinc chloride as a ligating additive did not afford either of the propargylic alcohol products, providing only unreacted aldehyde (entry 7). Pagenkopf and Morra would later report that stereoselective addition of a lithium acetylide to a similar aldehyde system at −90 °C, using MTBE as solvent, offers a practical route towards the undesired C-(23)—C-(24) 1,2-*anti* diastereomer, by Felkin-Anh controlled addition.[159]

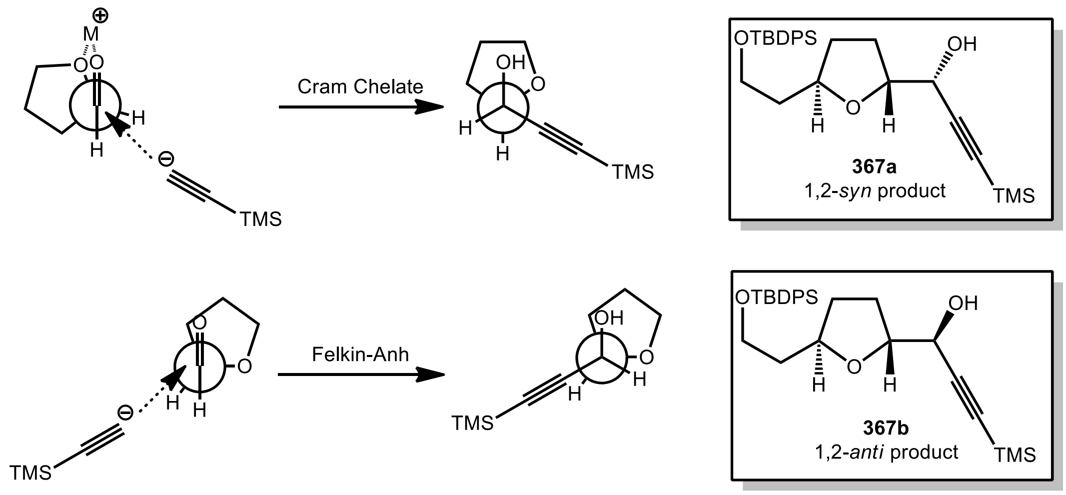


Figure 37

12.2.2 Reagent Controlled Alkynylation Reaction

The addition of zinc acetylides into aldehydes is a well-precedented reaction within the literature and has been rendered stereoselective through the use of numerous chiral ligands.[160] Alkylzinc compounds have long been known to coordinate to the π-electrons of acetylenes, leaving the terminal hydrogen susceptible to deprotonation by weak tertiary amines. The nucleophiles thus formed can undergo stereoselective addition to carbonyl groups enabled by the ability of the zinc centres to coordinate to the chiral ligand, alkyne and the electrophile.[161]

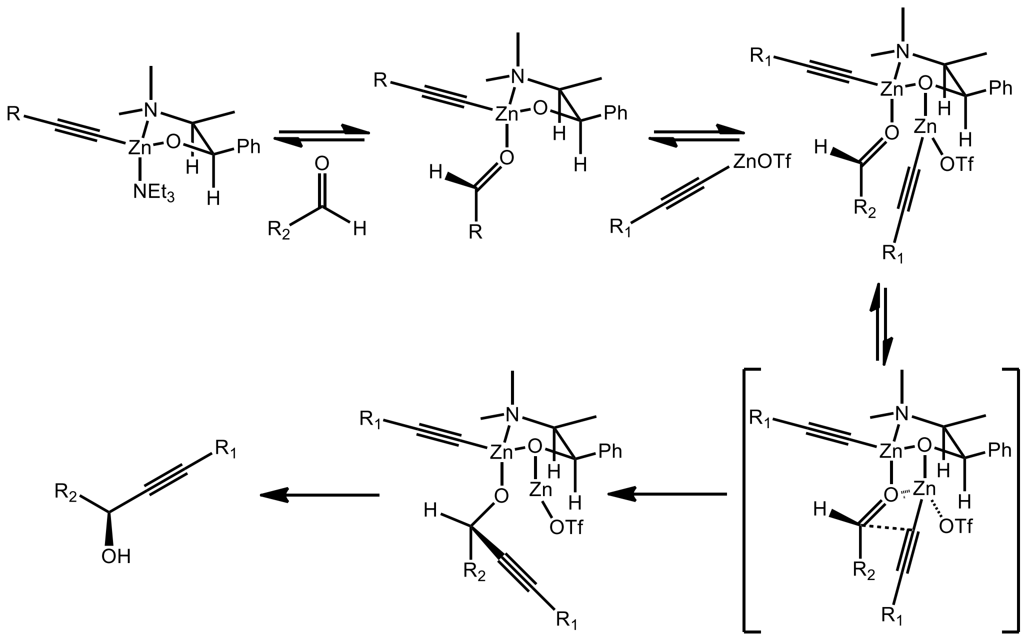
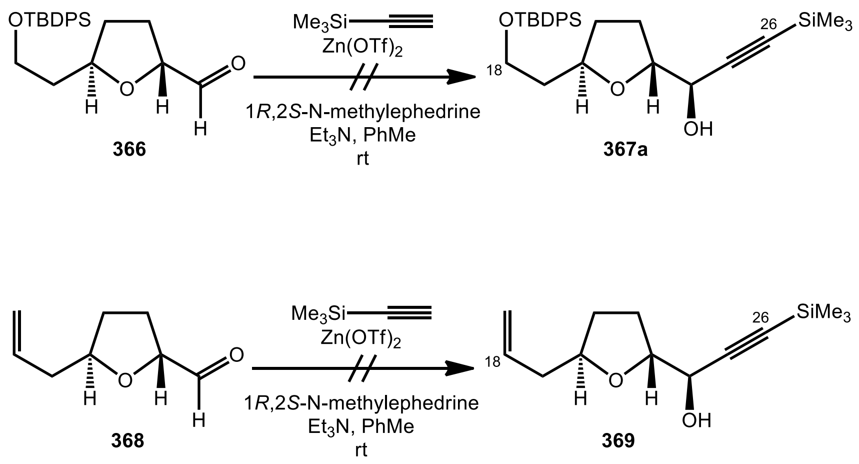


Figure 38

Carreira and co-workers eliminated the requirement for pyrophoric alkylzinc reagents, through replacement of the metal source with zinc triflate, and made the addition of the resultant zinc acetylide to aldehydes asymmetric through the use of *N*-methylephedrine derived ligands.[162] Tanaka *et al* would later apply Carreira's methodology to the addition of zinc acetylides to 2-tetrahydrofuranaldehehydes, thereby synthesising propargylic alcohols of the type required for our total synthesis in a stereoselective manner.[163] The proposed generalised asymmetric mechanism required to form the desired diastereomer is shown in *Figure 38*.

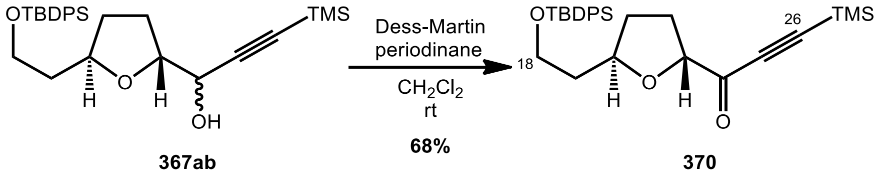


Scheme 77

Both primary alcohols **345** and **348** were used in the investigation of the reaction sequence shown in *Scheme 77*. Oxidation of the alcohol **348** to aldehyde **366** was accomplished in good yield using Dess-Martin periodinane as the oxidant. The analogous oxidation of **345** proceeded in 83% yield, with both compounds exhibiting the CHO proton signal at ~9.7 ppm in their respective ^{1}H NMR spectra. Various attempts to effect the asymmetric introduction of trimethylsilyl acetylene using Carreira's methodology failed, despite meticulous purification of reagents and intermediates, and careful drying of the zinc(II) triflate before use. Three separate batches of zinc(II) triflate were applied to the reaction, because disparities in results obtained from reagent batches was noted in the literature,[164] but in each case the tested aldehyde always remained unreacted.

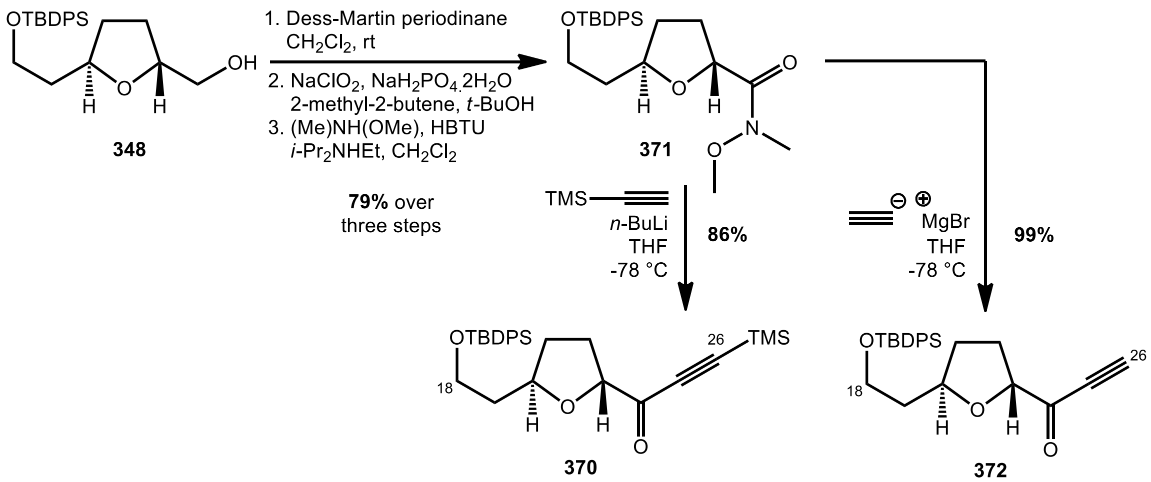
12.2.3 Stereoselective Reductions of Ynones

An alternative approach was taken to generate the C-(24) secondary alcohol stereoselectively through the reduction of an ynone functionality. The reduction of two ynone substrates, TMS protected substrate **370** and deprotected analogue **372**, were tested using a variety of reducing reagents. The TMS protected product was prepared easily through the Dess-Martin oxidation of diastereomeric mixtures of propargylic alcohols generated previously (*Scheme 78*).



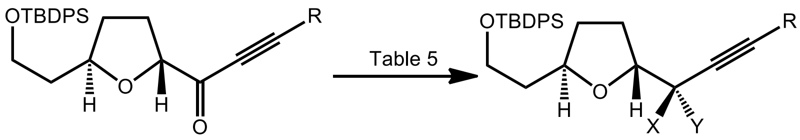
Scheme 78

The second substrate **372** was formed by addition of commercially available ethynylmagnesium bromide to the Weinreb amide **371** (*Scheme 79*). This approach was found to be necessary because oxidation of propargylic alcohols lacking the terminal alkyne TMS group afforded difficult to resolve reaction mixtures; moreover, possible epimerisation of the adjacent C-(23) sterocentre could result from basic methanolysis of the TMS group of ynone **370**. Weinreb amide **371** could also be used to prepare ynone **370**, providing an improved yield over the propargylic alcohol oxidation method illustrated in *Scheme 78*.



Scheme 79

With ynone substrates **370** and **372** in hand, attention turned to the stereoselective reduction of the carbonyl functionality using a variety of reagents (*Scheme 80*). Use of chelating reducing reagents was expected to deliver the undesired 1,2-*anti* diastereomer through formation of the Cram chelate model, whereas non-chelating reductants under Felkin-Anh control should have allowed for preferential formation of 1,2-*syn* product. A number of reductants were tested on both systems to assay the selectivity of the reduction; the results are shown in *Table 5*.



370 R = TMS

367a: X = OH; Y = H; R=TMS
367b: X = H; Y = OH; R=TMS

372 R = H

378a: X = OH; Y = H; R=H
378b: X = H; Y = OH; R=H

Scheme 80

The use of L-selectride on ynone **370**, provided a marginal preference for the undesired 1,2-*anti* diastereomer (Table 5, entry 1), however application to **372** yielded a mixture of products in a 1:1 ratio (entry 5). The use of Luche reduction conditions with both **370** and **372** afforded a slight excess of the 1,2-*syn* product which corresponds to the Felkin-Anh model of reduction (entries 2 and 6). This result was surprising when measured against a similar reduction applied to concurrent work on the 'southern' fragment, in which an analogous enone system was reduced with excellent levels of diastereocontrol; this work will be discussed subsequently (Section 12.5, *Scheme 109*). CBS reduction using both enantiomers of Corey's methyl-oxazaborolidine ligands, which have previously demonstrated their usefulness in the stereoselective reduction of prochiral ynones,[30] failed to deliver either diastereomer in good ratio (entries 3 and 4).

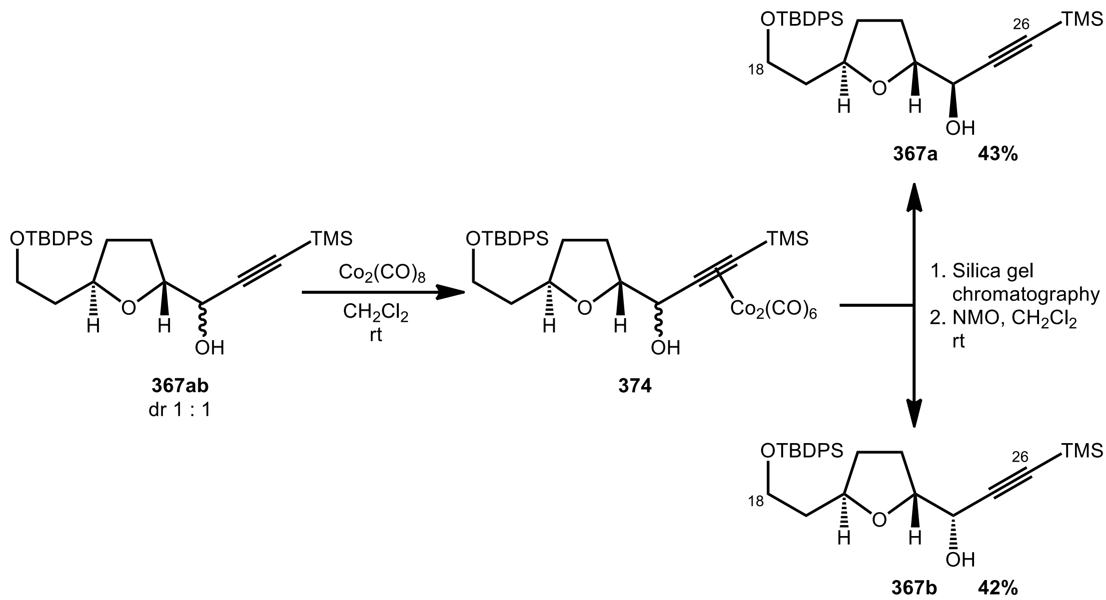
Entry	Ynone	Reductant	Temp.	Solvent	Combined Yield (%)	*dr* **367a : 367b**
1	**370**	L-selectride	−78 °C	THF	82	2 : 3
2	**370**	$NaBH_4$, $CeCl_3 \cdot 7H_2O$	−78 °C	MeOH	90	3 : 2
3	**370**	$BH_3 \cdot$THF (*R*)-Me CBS ligand	−78 °C	THF	94	1 : 2
4	**370**	$BH_3 \cdot$THF (*S*)-Me CBS ligand	−78 °C	THF	84	1 : 1
						dr **378a : 378b**
5	**372**	L-selectride	−78 °C	THF	90	1 : 1
6	**372**	$NaBH_4$, $CeCl_3 \cdot 7H_2O$	−78 °C	MeOH	95	3 : 2

Table 5

12.2.4 Resolution of Propargylic Alcohols

Notwithstanding the disappointing results obtained when trying to control the C-(24) stereocentre, we had demonstrated that the C-(18)—(26) carbon backbone could be accessed through the chemistry discussed previously, albeit as an inseparable mixture of diastereomeric C-(24) alcohols; a methodology was subsequently sought to deliver the discrete compounds. 2001 saw publication of a paper by Gleason and Ajamianon on the use of a cobalt-mediated cycloisomerisation reaction in the formation of dihydrofuran systems.[165] This paper proved to be of particular interest as it discussed the chromatographic isolation of intermediate dicobalt hexacarbonyl-alkyne complexes, the propargylic alcohols of which bore structural similarity to the diastereomeric mixture that we sought to separate.

Treatment of a diasteromeric mixture of propargylic alcohols **367ab** with dicobalt octacarbonyl in dichloromethane provided a mixture of separable brown oils, which upon independent oxidation of the complex with NMO allowed for recovery of the isolated compounds as single diastereomers. Curiously, this technique was found to be unsuccessful when applied to diasteromeric mixtures of propargylic alcohols **378ab** in which the alkyne terminus was unprotected.



Scheme 81

Assignment of the C-(24) hydroxyl stereochemistry was accomplished by analysis of the coupling constants between the C-(23) and C-(24) carbons, and comparison with the literature available for similar systems.[166] The C-(23)—C-(24) *syn* coupling of the desired diastereomer **367a** was measured at $^3J_{HH}$=7.5 Hz, whereas that of the *anti* product **363b** was determined to be $^3J_{HH}$=3.3 Hz. In structurally similar α-tetrahydrofurylpropargylic alcohols, the *erythro* diastereomer exhibits vicinal coupling constants that are smaller ($^3J_{HH}$ = 2-4 Hz) than that of the *threo* diastereomer ($^3J_{HH}$=6-8 Hz).[167] A demonstrative example from the work of Gleason is shown in *Figure 40*.

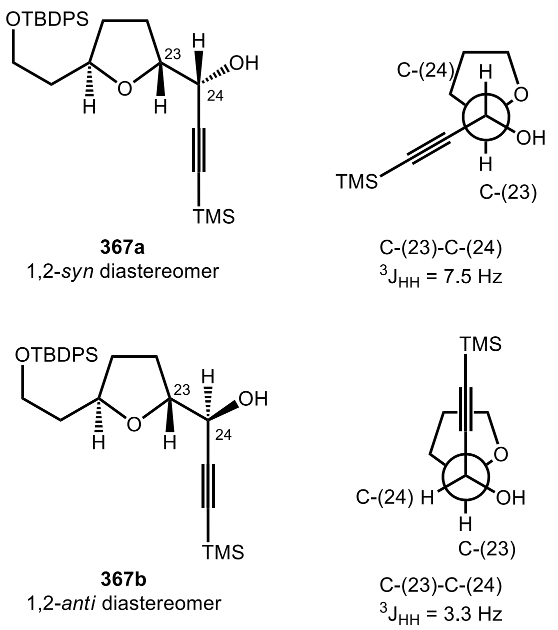


Figure 39

The Newman projections of compounds **367a** and **367b**, illustrated in *Figure 39*, demonstrate that the disparity in vicinal coupling constants is a product of the dihedral bond angle difference between the two protons.

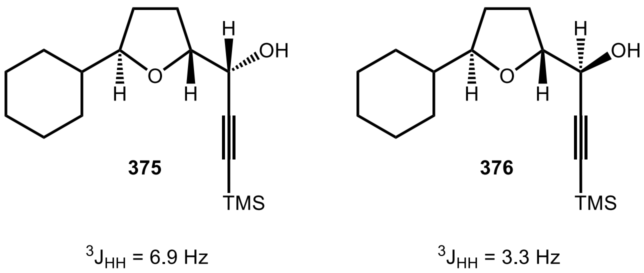
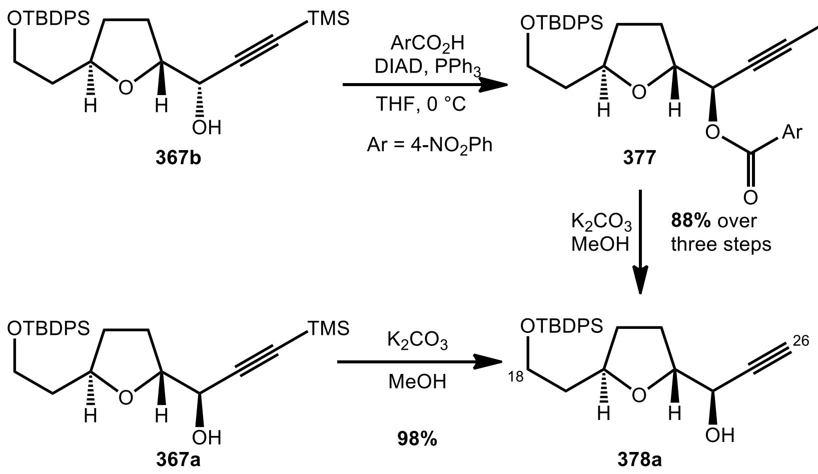


Figure 40

12.3 Inversion of the 1,2-*anti* Diastereomer, Hydrostannylation and Attempted Stille Coupling

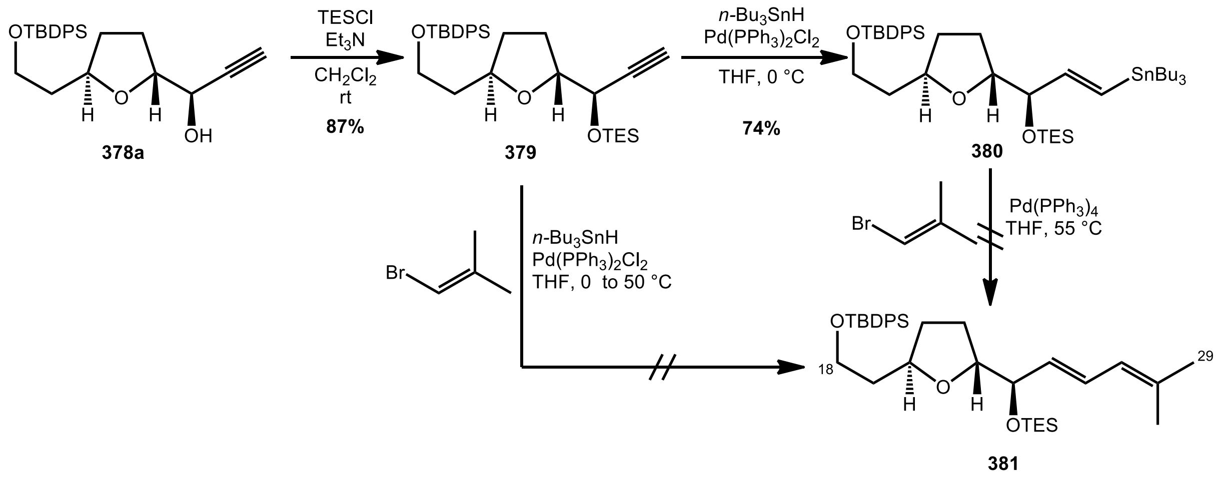
With both C-(24) diastereomers in hand, attention turned to conversion of the alkyne functionality into a coupling partner for a palladium-catalysed coupling reaction. The original intention of the project was to use a Stille coupling reaction to connect the C-(26) and C-(27) carbons of amphidinolide C. This was originally envisaged as being achievable through transformation of the C-(25)—C-(26) terminal alkyne to a vinyl stannane through a palladium catalysed hydrostannylation. To this end, the TMS protecting group of **367a** was cleaved from the alkyne under basic methanolysis conditions, affording propargylic alcohol **378a** in excellent yield. In order to maximise the available quantity of alkyne **378a**, the undesired stereochemistry of the 1,2-*anti* diastereomer **367b** was inverted through the protocol of Mitsunobu (*Scheme 82*).[168] On work-up, the intermediate 4-nitrobenzoate **377** was not isolated but was instead treated with potassium carbonate and methanol to afford simultaneous cleavage of the terminal TMS and 4-nitrobenzoate groups. This two-pot three-step sequence proceeded in 88% yield to provide maximal quantities of alkyne **378a** for subsequent work.



Scheme 82

Propargylic alcohol **378a** was protected as a TES silyl ether and the alkyne converted into *E*-vinylstannane **380** through a palladium-catalysed hydrostannylation.[169] The regio- and stereochemistry of vinylstannane **380** was confirmed by analysis of the ^{1}H NMR spectrum, the vicinal coupling of the C-(25) and C-(26) alkene protons was measured at $^3J_{HH}$=19.1 Hz, indicating a *trans* alkene relationship.

The vinyl iodide partner, required to afford the C-(18)—C-(34) fragment of amphidinolide C upon cross-coupling, had previously been synthesised by Yang but showed signs of instability on prolonged storage.[170] It was decided at this stage to use the commercially available isocrotyl bromide to test the key Stille reaction. The benefit of this strategy extended beyond the safeguarding of precious stock of vinyl iodide precursor as it would also afford access to the C-(18)—C-(29) fragment **381** of amphidinolide F, if the cross-coupling methodology was effective (*Scheme 83*).



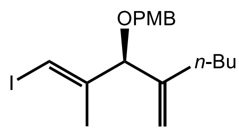
Scheme 83

Initial attempts at the Stille cross-coupling of isocrotyl bromide and vinylstannane **380** were entirely unsuccessful, resulting only in the recovery of starting material. Variation in palladium catalyst, as well as an attempted one-pot conversion of alkyne **379** directly into diene **381**, in the presence of *n*-Bu_3SnH and isocrotyl bromide,[169] afforded only unreacted vinylic stannane **380**.

12.4 Synthesis of C-(27)—C-(34) Fragment of Amphidinolide C

The construction of the PMB protected tail fragment **382** of amphidinolide C was originally accomplished by Yang in six steps from hexanal.[170] In the initial stages of the project, an orthogonal protection strategy was envisaged in which a PMB ether was to be used as the protecting group of choice for this C-(29) hydroxyl group and to this end a Lewis acid catalysed activation of PMB imidate was used to shield the allylic alcohol. Reports of problematic PMB deprotection of allylic alcohols in the presence of conjugated dienes,[171] which would exist in the C-(25)—C-(29) locus of amphidinolide C, led us to subsequently explore alternative protecting groups for the C-(29) hydroxyl group. Nevertheless, palladium-catalysed methodologies were tested with this analogue in exploratory cross-coupling chemistry with alkyne **378a**.

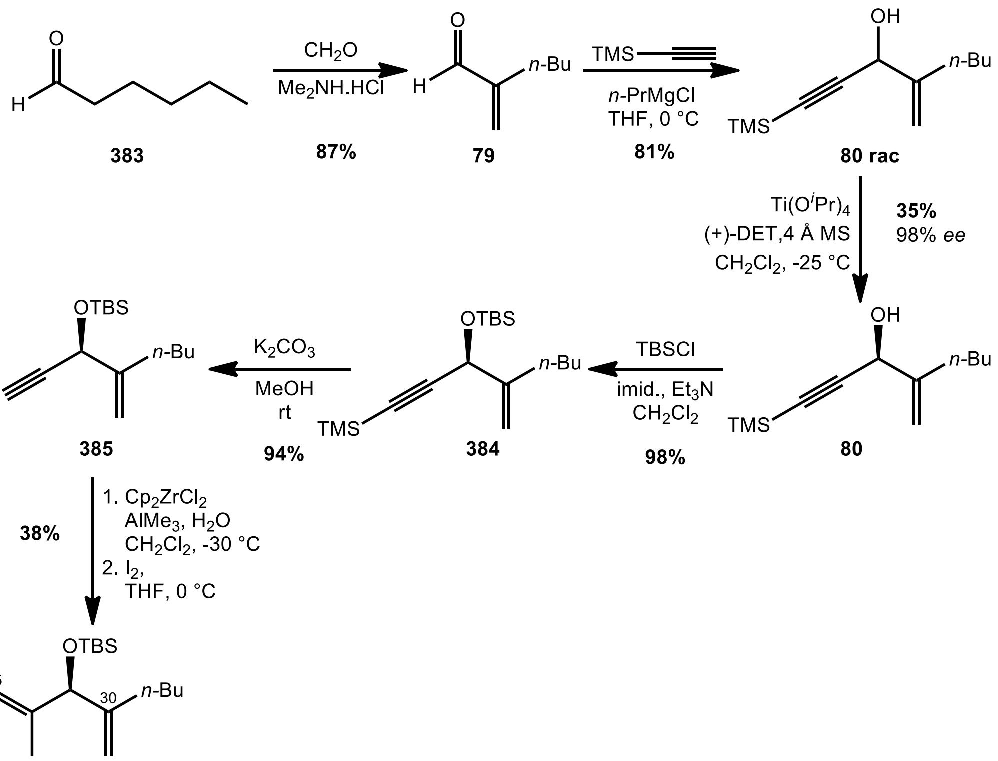
The route to PMB protected vinylic iodide **382** was replicated, with minor variation in step order and alteration of protecting group, to afford the TBS protected analogue **386**, as shown in *Scheme 84*.



382

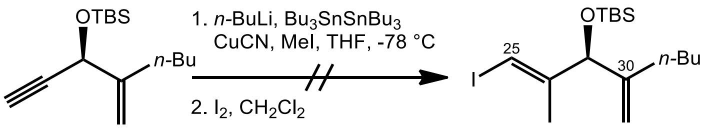
Figure 41

Mannich methylenation of hexanal afforded enal **79** which upon treatment with the magnesium acetylide of trimethylsilylacetylene, yielded the racemic allylic alcohol **80rac**. Enantiopure **80** was then obtained *via* kinetic resolution of the racemate through Sharpless asymmetric epoxidation of the undesired C-(29) (*R*)-enantiomer.[172] The highly conjugated secondary alcohol was protected as a TBS ether in excellent yield, affording intermediate **380**.



Scheme 84

Removal of the terminal TMS group was accomplished under methanolysis conditions using potassium carbonate as base. Propargylic alcohol **385** was then converted into vinyl iodide **386** through the zirconium-catalysed carboalumination chemistry pioneered by Negishi *et al.*[173] The water accelerated variant of this reaction described by Wipf[174] was used in our case, providing methylated vinyl iodide **386** in poor yield. Although this conversion was reported by Yang to proceed with yields of up to 90%,[170] these results proved impossible to duplicate despite numerous attempts. An alternative preparation of **386** from alkyne **385** using carbostannation/iodination procedures, as previously employed in Fürstner's synthesis of amphidinolide B1,[175] failed to deliver the required vinyl iodide (*Scheme 85*).



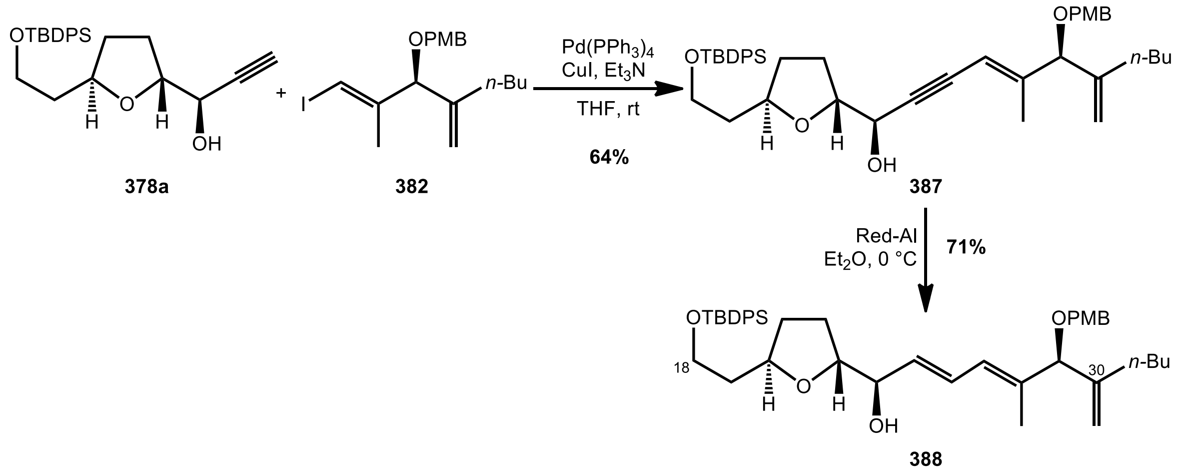
385 **386**

Scheme 85

12.5 Preparation of the C-(18)—C-(34) Fragment of Amphidinolide C: Sonogashira Cross-Coupling

Our disappointment at the failure of Stille cross-coupling to effect the union of fragment **379** with isocrotyl bromide (*Scheme 83*) led us to explore alternative procedures to construct the C-(26)—C-(27) bond. Inspection of the intermediate components available to us, led to the conclusion that a possible palladium-catalysed cross-coupling could result from the direct reaction of vinyl halides and alkyne **379**.

In 1975, publications from Heck,[176] Cassar[177] and Sonogashira[178] appeared concerning palladium-catalysed couplings of aryl and vinyl halides to terminal alkynes. Heck and Cassar showed that the cross-coupling reaction could occur in the absence of copper if elevated temperatures were employed for the transformation, while Sonogashira proved that the reaction is accelerated if a copper(I) co-catalyst is employed. The use of copper to couple alkynes was previously known from the Glaser[179] and Cadiot-Chodkiewicz[180] reactions and was exploited by Sonogashira, in combination with the palladium catalytic cycle, to provide a powerful methodology to the organic synthesis community. The Sonogashira coupling, as we were to find, often suffers from the shortcoming of latent alkyne homo-coupling, affording dimeric side-products through the Glaser reaction.



Scheme 86

The preliminary work progressed well, as shown in *Scheme 86*. A test coupling reaction of 7 mg alkyne **378a** with the PMB protected vinyl iodide **382** delivered the desired enyne **387** in 64% yield, the coupling of the fragments was confirmed by ^{1}H and ^{13}C NMR analysis of the product. Although the NMR data was in accordance with the desired structure, the sample was visibly contaminated with brown residue, originating from either the palladium catalyst or copper(I) co-catalyst. The crude product was taken forward to the subsequent step, the Red-Al reduction of the propargylic alcohol, to afford the desired *(E,E)*-dienol **388** in 71% yield. Pagenkopf and Morra had previously demonstrated that this propargylic reduction was a feasible route to forming the C-(25)—C-(28) dienol bonds of amphidinolide C.[159]

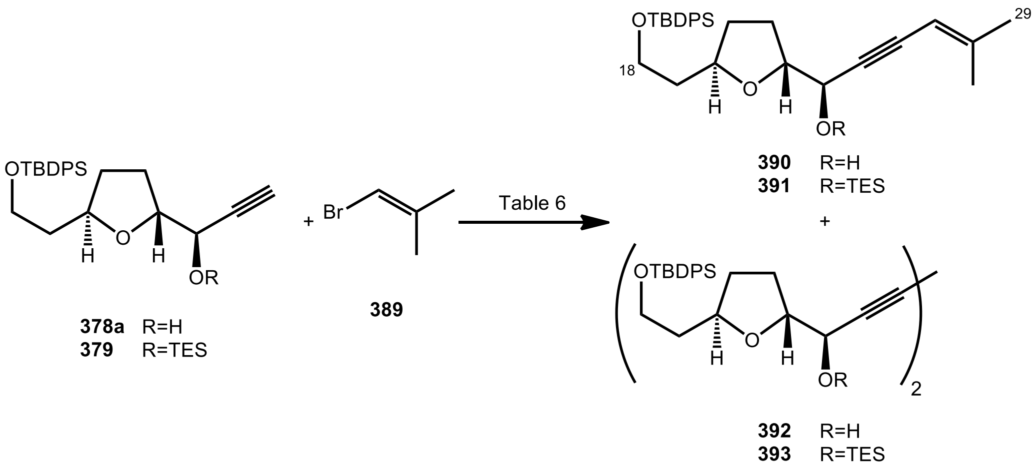
A further batch of C-(29) PMB protected vinyl iodide **382** was prepared by Guang Yang and attempts to repeat the coupling on larger scale were undertaken. Unfortunately, the reaction did not proceed efficiently allowing only for recovery of starting alkyne **378**. The synthesis of **382**, through Negishi carboalumination and subsequent PMB protection, was a delicate operation and isolation of the product hampered by the lipophilicity of the reaction residue on chromatography. Additionally, the instability of the vinyl iodide did not facilitate an easy transformation. Initially it was believed that residual PMB-trichloroacetimidate artefacts, resulting from the protection step, were responsible for poisoning the catalyst through coordination of the complex. In order to test this hypothesis, simultaneous Sonogashira couplings of alkyne **378a** were undertaken with unprotected racemic and PMB protected enatiopure vinyl iodides. The desired coupling occurred with the unprotected species, albeit in a disappointing 29% yield, whilst the PMB protected intermediate failed to undergo cross-coupling. It was decided at this stage to move the strategy away from the use of the PMB protected vinyl iodide towards a substrate bearing a protecting group with greater amenability to the synthesis, namely the TBS ether **386** described in *Scheme 84*.

12.6 Synthesis of the C-(18)—C-(29) Fragment of Amphidinolide F: Palladium Cross-Coupling Methodology

Although cross-coupling of alkyne **378a** with vinyl iodide **382** had proved possible, the reaction sequence was largely irreproducible, varying from batch to batch of vinyl iodide. In an attempt to develop a more reproducible methodology, we turned our attention towards the cross-coupling of alkyne **378a** with commercially available isocrotyl bromide. In this way, it was hoped that access to the northern fragment of amphidinolide F could be attained before employing the optimised methodology to couple alkyne **378a** with the vinyl iodide fragment **386**. The conditions previously illustrated in *Scheme 83*, demonstrate that Stille cross-coupling had failed to provide the C-(18)—C-(29) fragment of amphidinolide F, through reaction of isocrotyl bromide with a vinyl stannane. Despite this failure, it was hoped that palladium-catalysed alkyne cross-coupling could be used to effect an equivalent transformation. The resulting enyne intermediate would then undergo an equivalent C-(24) hydroxyl-controlled propargylic reduction, resulting in the formation of the (*E*,*E*)-dienol present in the natural product.

12.6.1 Amphidinolide F: C-(18)—C-(29) Fragment: Copper co-catalysed Palladium Cross-Couplings

We anticipated that Sonogashira methodology would be an appropriate means of cleanly cross-coupling our alkyne and the commercially available isocrotyl bromide coupling partner. Significant problems with this methodology quickly became apparent, when initial test reactions resulted in alkyne dimerisation in the presence of Cu(I) salts and the desired cross-coupled product proved highly elusive at the early stages of the investigation.



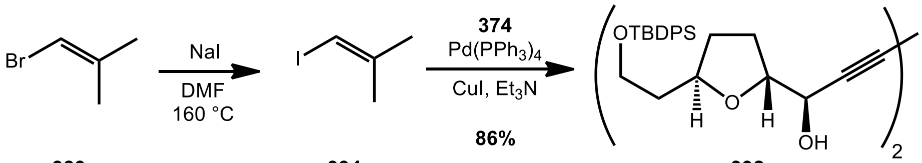
Scheme 87

The initial reaction was undertaken using the standard Sonogashira conditions which resulted in cross-coupling of alkyne **378a** to vinyl iodide **382** (*Scheme 86*). TLC analysis showed complete conversion of the alkyne to an unexpectedly *more* polar product when the reaction was conducted at ambient temperature, using a combination of $Pd(PPh_3)_4$ and copper(I) iodide catalysts (*Scheme 87, Table 6*). Upon isolation and analysis of the newly formed product, it was found that the Glaser homo-coupled product **392** was the sole isolable material from the reaction (entry 1). Variation of catalyst loading, base and temperature were undertaken in accordance with diverse literature procedures (entries 2 to 6). Frustratingly, each adaptation failed to deliver the desired enyne system and the sole result of each of these experiments was, again, Glaser homo-coupling of the starting alkyne. Characterisation of the unwanted product was signposted in the ^1H NMR spectrum through loss of the terminal alkyne proton signal at 2.24 ppm, whilst all other signals remained; disappearance of the corresponding alkyne C-H stretch in the FT-IR spectrum, previously observed at 3299 cm^{-1}, further substantiated evidence of homo-coupling. The order of addition of reagents was explored, as was pre-stirring of the vinyl bromide with catalyst before slow addition of the alkyne in rigorously degassed solvents. The latter experiment did not result in any reaction under an argon atmosphere, but on brief exposure to oxygen the homo-coupled dimer formed rapidly. Attempts to convert isocrotyl bromide **385** into the more reactive isocrotyl iodide **390**, through treatment with sodium iodide in DMF at 160 °C following the procedures of Liu,[181] did not deliver appreciable amounts of the cross-coupled product when the putative vinyl iodide was used in the Sonogashira reaction (*Scheme 88*).

Entry	Alkyne	Catalyst System	Solvent Base	Temp.	Yield (%) **390**	Yield (%) **392**
1	**378a**	$Pd(PPh_3)_4$ [10 mol%] Cu(I)I [10 mol%]	THF Et_3N	rt	0	84
2	**378a**	$Pd(PPh_3)_4$ [10 mol%] Cu(I)I [5 mol%]	THF Et_3N	rt	0	Not isolated[d]
3	**378a**	$Pd(PPh_3)_4$ [10 mol%] Cu(I)Br [5 mol%]	THF Et_3N	rt	0	Not isolated[d]
4	**378a**	$Pd(PPh_3)_4$ [10 mol%] Cu(I)I [5 mol%]	THF Et_3N	50 °C	0	80
5[a]	**378a**	$Pd(PPh_3)_4$ [10 mol%] Cu(I)I [10 mol%]	Benzene *n*-$BuNH_2$	rt	0	Not isolated[d]
6[b]	**378a**	$Pd(PPh_3)_2Cl_2$ [10 mol%] Cu(I)I [5 mol%]	*i*-Pr_2NH	rt	0	Not isolated[d]
7[c]	**378a**	$Pd(PPh_3)_4$ [5 mol%]	Pyrrolidine	50 °C	75	N/A
					Yield (%) **391**	Yield (%) **393**
8	**379**	$Pd(PPh_3)_4$ [5 mol%]	Pyrrolidine	50 °C	64	N/A

For examples of similar conditions see; a. Burke *et al;*[182] b. Echavarren *et al;*[183] c. Linstrumelle *et al;*.[184] d. Structure determined from analysis of the crude ^{1}H NMR spectrum.

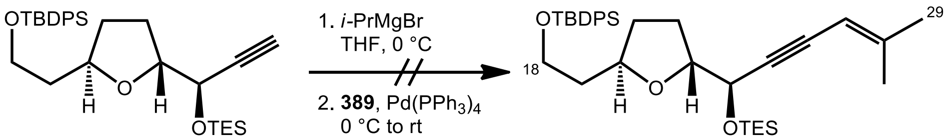
Table 6



Scheme 88

12.6.2 Amphidinolide F: C-(18)—C-(29) Fragment: Copper Free Palladium Cross-Couplings

In order to remove copper from the cross-coupling protocols two procedures were investigated. Kumada-type cross-coupling[185] did not result in reaction between TES-protected alkyne **379** and isocrotyl bromide (*Scheme 89*). We subsequently explored the application of the Heck alkynylation reaction, sometimes referred to in the literature as a 'copper-free Sonogashira' coupling.[186]



Scheme 89

A number of authors have shown that the cross-coupling of alkynes to aryl and vinyl halides can be accomplished in the presence of Pd^0 catalyst and a judicious choice of base.[186] The traditionally accepted mechanism for the copper-associated Sonogashira coupling is shown in *Figure 41*. The sequence comprises two catalytic cycles, the upper palladium cycle and the lower copper cycle.

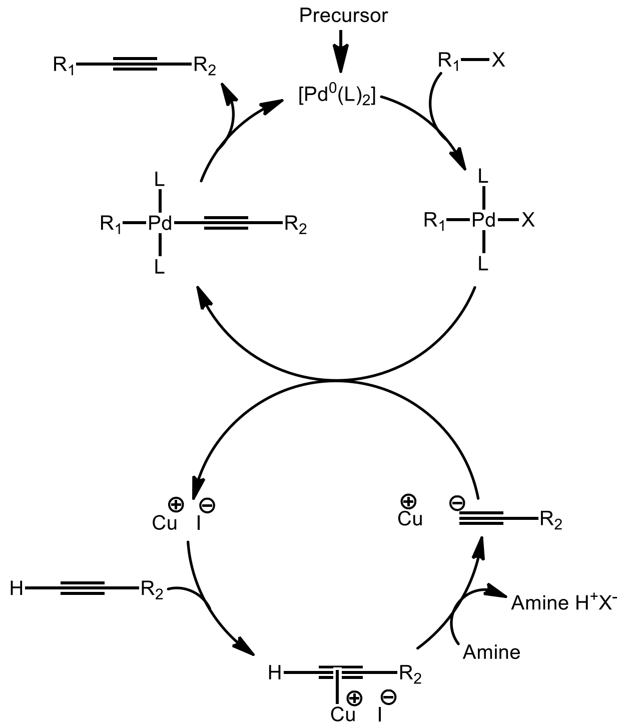


Figure 42

Activation of the alkyne is believed to result from the formation of a copper(I) π-complex, which renders the terminal hydrogen more acidic, and therefore more labile to deprotonation by the ubiquitous amine base. Upon deprotonation and formation of the terminal copper acetylide, the intermediate can then undergo transmetallation with the active palladium complex, formed through oxidative insertion of the Pd^0 catalyst into the aryl or vinyl halide starting material. Reductive elimination of palladium provides the cross-coupled compound and regenerates the palladium catalyst for further catalytic cycles.

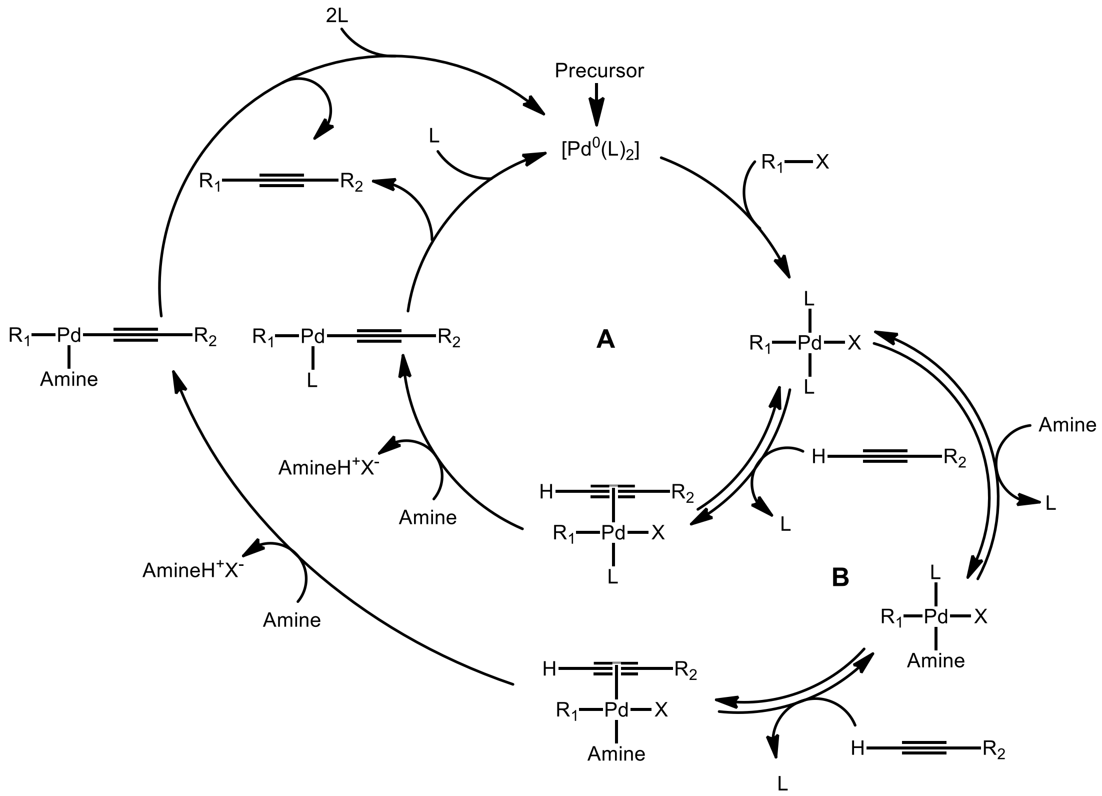
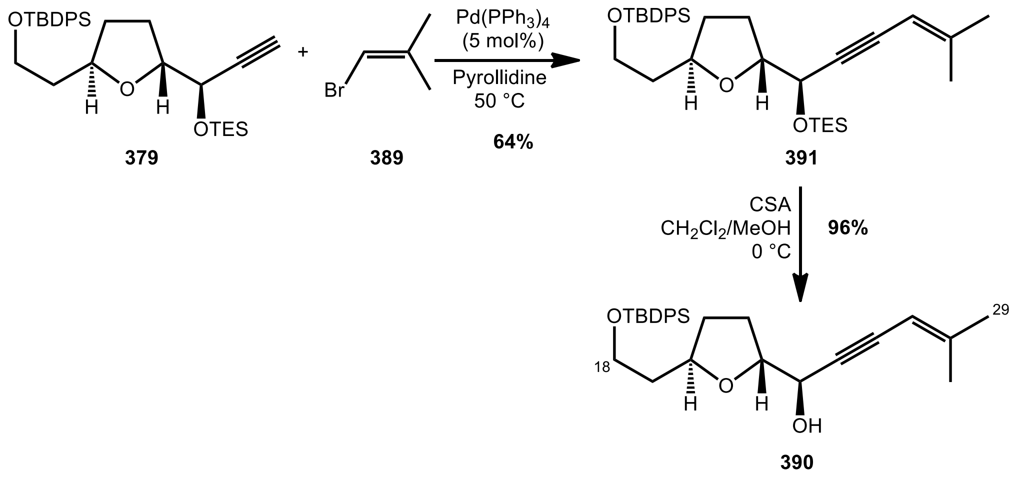


Figure 43

Various groups have demonstrated that the use of copper(I) is not necessary to afford equivalent reactivity and that cross-coupling can proceed in the presence of a Pd^0 catalyst and an amine alone.[186] Jutand and co-workers studied the course of this cross-coupling methodology and proposed two catalytic cycles that were dependent upon the ability of the amine to act as a ligand for the palladium centre, both cycles are shown in *Figure 43*.[187] Pathway A occurs where the alkyne provides a better ligand to the palladium complex than the amine, resulting in an acetylide that can be deprotonated by the excess base and form the desired product upon reductive elimination. Pathway B is the result of the amine being able to act as a better ligand to the palladium(II) complex than the alkyne, thereby forming a more active intermediate that can accelerate the π-complexation of the alkyne. Deprotonation of the intermediate complex is followed by reductive elimination to form the cross-coupled product and regeneration of the catalyst. The pathway the reaction takes is determined by which complexation is faster, either that of the alkyne or amine, but the net result is the formation of the same cross-coupled product without the possibility of side reaction through Glaser coupling.

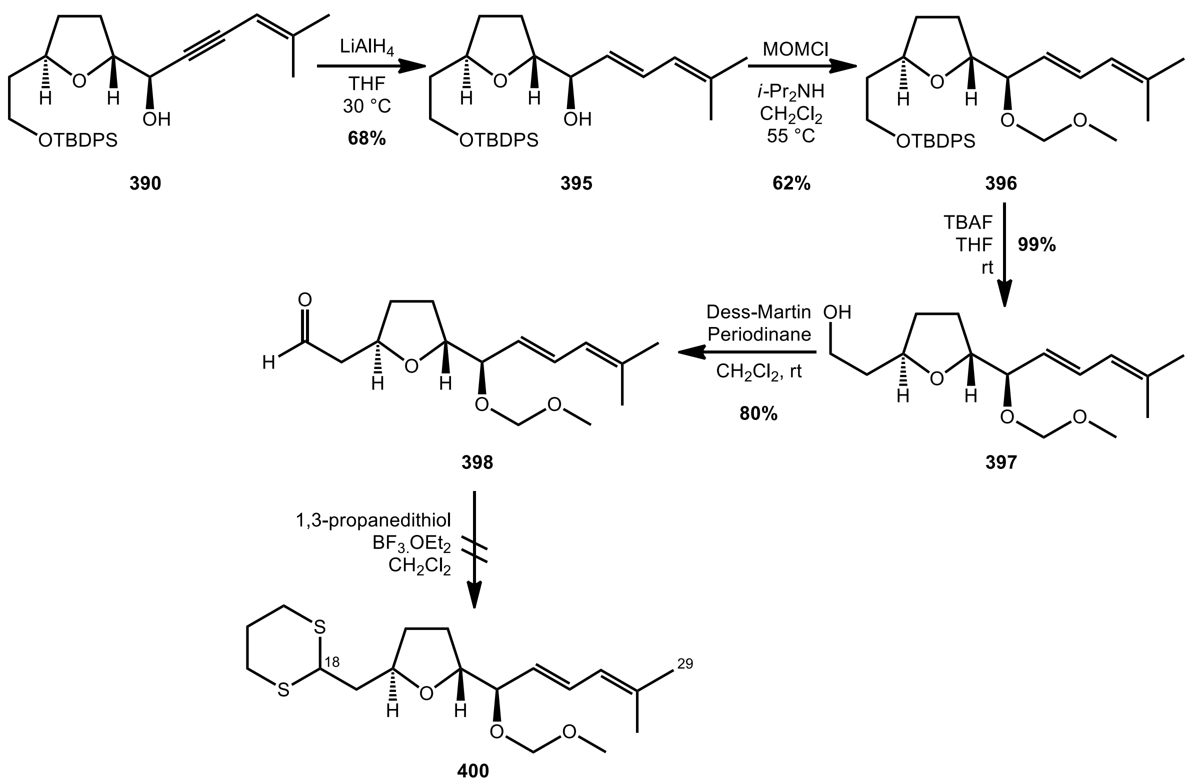
Using the procedure of Linstrumelle *et al*,[184] where pyrrolidine was employed as the reaction solvent and base, TES-protected alkyne **379** was successfully coupled to isocrotyl bromide **389** in 64% yield (*Table 6*, entry 8). The TES ether was shown to be cleavable on short exposure to CSA to afford the desired, diastereomerically pure, propargylic alcohol **390** in 96% isolated yield. A further cross-coupling with the free hydroxyl propargylic alcohol **378** gratifyingly allowed direct access to the C-(18)—C-(29) carbon backbone of amphidinolide F **390** in 75% yield (entry 7).



Scheme 90

12.6.3 Amphidinolide F: Completion of C-(18)—C-(29) Fragment

The stereospecific formation of (2*E*,4*E*)-dienol **395** was accomplished through the application of aluminium hydride reagents; both $LiAlH_4$ at 30 °C and Red-Al at 0 °C provided the required compound in good yield and with excellent olefin geometry control (*Scheme 91*). The stereospecificity of this reduction is controlled by the proximal alcohol group, which upon chelation to the aluminium centre allows for transmetallation of the alkyne in a *syn* fashion.[188] Upon hydrolysis of the vinylic aluminium intermediate, the complex decomposed to liberate the C-(25)—C-(26) *trans* alkene **395**. Although in practice both reagents deliver the required dienol system the use of Red-Al was considered to be preferential in this sequence owing to the more facile work-up procedures employed for isolation of the product. The stereochemical assignment of (*E*)-alkene formation was ascribed based upon the C-(25)—C-(26) coupling constant ($^3J_{HH}$=15.2 Hz) and comparison of our data to that of previous literature data for compounds used in amphidinolide F fragment preparation.[23, 25]

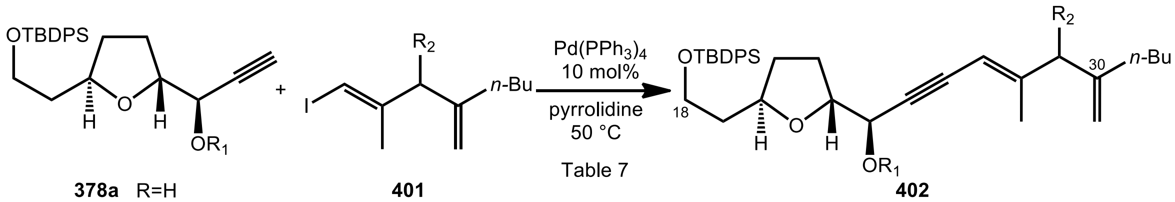


Scheme 91

With dieneol **395** in hand, test reactions were attempted in order to access C-(18) dithane target **400**. MOM ether protection of the secondary alcohol was accomplished smoothly, as was the subsequent fluoride-mediated deprotection of TPDPS ether to afford primary alcohol **397**. Partial oxidation of the alcohol yielded aldehyde **398**, a potential C-(18) coupling partner for later syntheses. However, subsequent efforts to form dithiane **400** by treatment of the aldehyde with 1,3-propanedithiol, under Lewis acid catalysis, led to decomposition of the small amount of isolated material. The large loss of sample mass engendered by the removal of the TBDPS group, in conjunction with time limitations, meant that only a single attempt was made to prepare the dithiane **400**.

12.6.4 Amphidinolide C: C-(18)—C-(34) Fragment *via* Copper Free Cross-Couplings

The success of the pyrrolidine-aided cross-coupling reaction in preparing the 'northern' C-(18)—C-(29) fragment of amphidinolide F led us to apply the same methodology to the preparation of the C-(18)—C-(39) of amphidinolide C. *Table 7* shows the results of the test reactions conducted on various alkyne analogues and vinyl iodide substrates in the preparation of Markush structure **402** (*Scheme 92*).

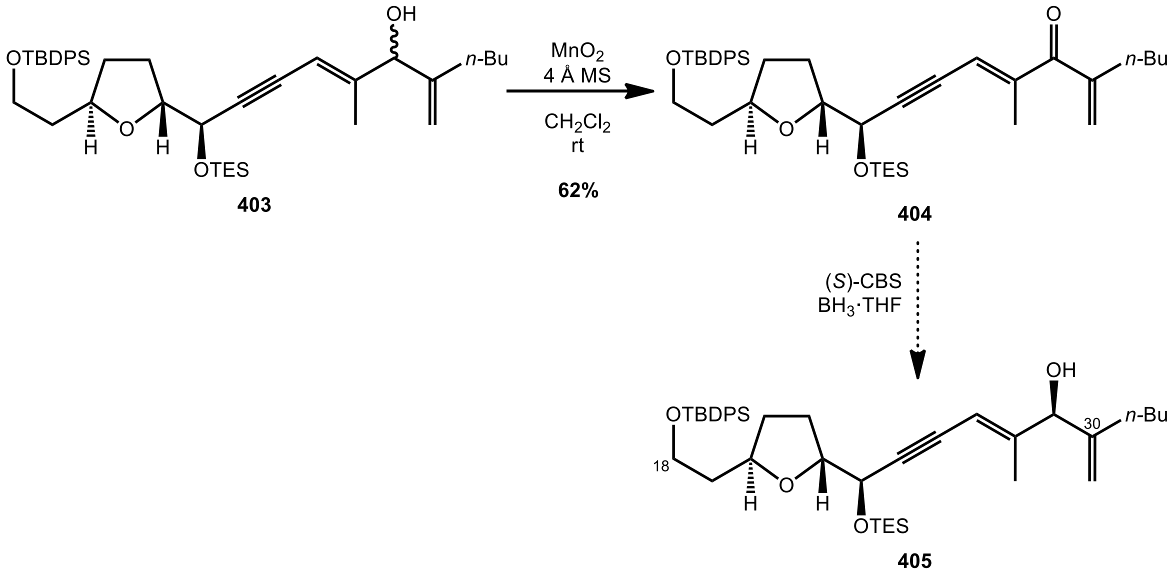


Scheme 92

Entry	Alkyne	R1	R2	Yield (%) **402**
1	**378a**	H	*(rac)*-OH	77
2	**379**	TES	*(rac)*-OH	71
3	**378a**	H	*(S)*-OTBS	36

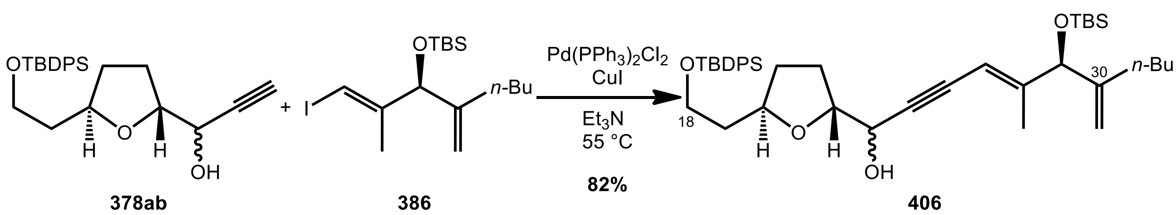
Table 7

As the racemic variant of the C-(29) unprotected vinyl iodide was readily available at the time of testing, two trial cross-couplings were conducted on this substrate. Application of the palladium-catalysed, pyrrolidine-solvated alkynylation methodology to the reaction of alkynes **378a** and **379** with the racemic vinyl iodide afforded the cross-coupled product in good yield (*Table 7,* entries 1 and 2). Although the use of a racemic vinyl iodide initially seems to be of little synthetic value, the application of the methodology to the functionisation of TES-protected alkyne **379** (entry 2) potentially provided a substrate that, it was hoped, could be advantageously exploited through the reaction sequence shown in *Scheme 93.* A Corey-Bakshi-Shibata reagent-controlled stereoselective reduction of an analogue of the highly conjugated enone system **404** has precedent in the literature and it was hoped that this reaction would deliver the desired C-(29) stereochemistry.[159] As discussed formerly (Section 10.4, *Scheme 84*), our route towards generating this stereocentre required removal of the undesired enantiomer of **80rac** by kinetic resolution, which resulted in substantial loss of potentially useful material. Although the highly unsaturated ketone **404** was isolable from the oxidation of **403** using manganese dioxide, the intermediate was prone to decomposition on standing, rendering it unusable for the proposed reduction.



Scheme 93

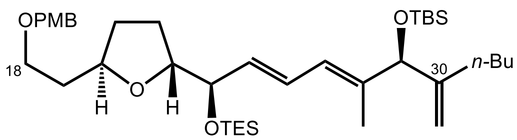
Synthesis of the C-(29) (*S*)-TBS protected vinyl iodide **381** was accomplished (section 10.4, *Scheme 85*) and it was subjected to the cross-coupling under the copper-free conditions discussed previously (*Table 6*, entry 7). Although full consumption of the starting alkyne **374** was observed during the course of the reaction, the isolated yield of the cross-coupled product was only 36%. A second product, in which cross-coupling occurred but from which anomalous loss of the C-(29) OTBS group was also apparent, was also isolated; the structure of this by-product remains undetermined. Yang would subsequently demonstrate that slow addition of alkyne **378ab**, facilitated by a syringe pump, to a heated solution of vinyl iodide **386**, $Pd(PPh_3)_2Cl_2$ and Cu(I) resulted in Sonogashira cross-coupling of the reactants in a yield of 82% (*Scheme 94*).[170]



Scheme 94

12.7 Amphidinolide C: C-(18)—C-(34) Fragment *via* Alkynylation Methodology

Although it had been established that palladium cross-coupling methods could be used to prepare the 'northern' fragments of both amphidinolides C and F, an alternative methodology was developed concurrently, involving alkynylation of a suitably functionalised tetrahydrofuran, to generate the C-(18)—C-(34) fragment of amphidinolide C.



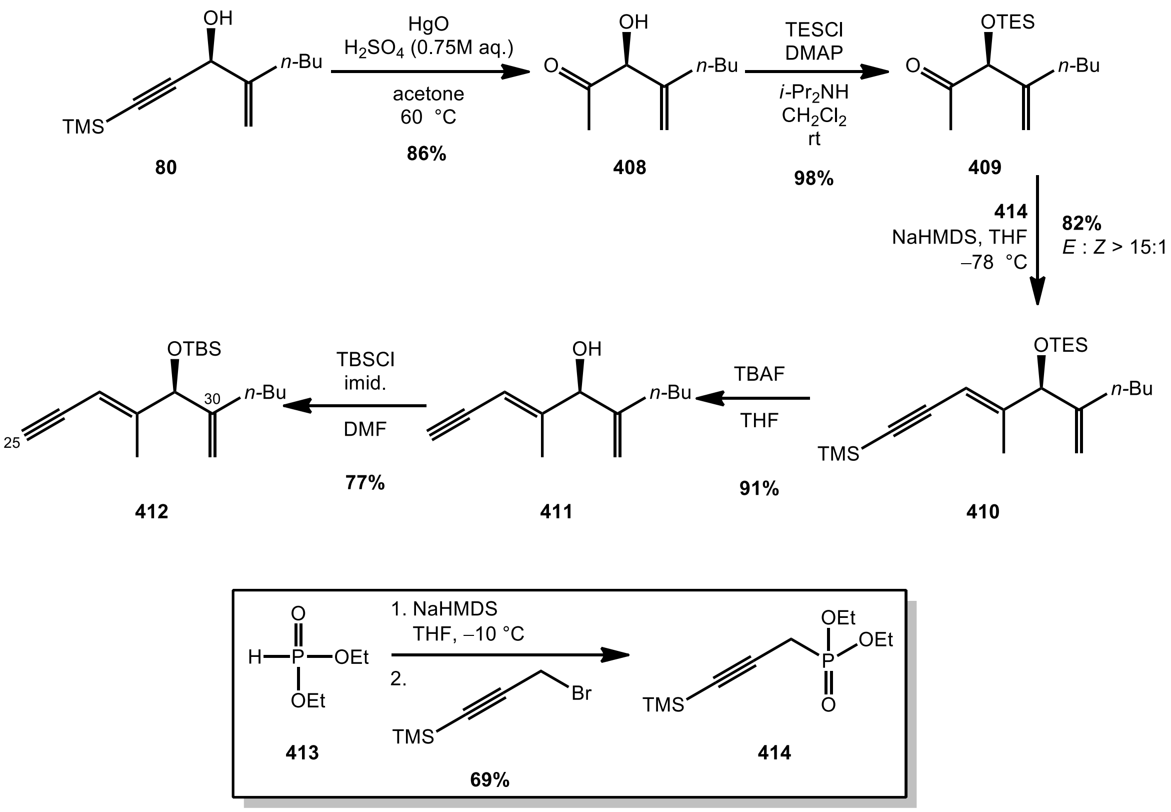
407

Figure 44

We had previously discounted the use of a PMB ether to protect the C-(29) hydroxyl group, due to potential difficulties with removal of the group whilst adjacent to the C-(25)—C-(28) (*E*,*E*)-diene. A C-(29) hydroxyl protection as a TBS ether was an appropriate alternative, necessitating the use of a protecting group of greater lability on the C-(24) hydroxyl. This alteration was required as the C-(24) alcohol was required for Yamaguchi esterification at an advanced stage of the synthesis. As both silyl ethers were of inferior stability to the previously used C-(18) TBDPS group, it became strategically necessary to alter the C-(18) functionality to better enable selective deprotection of this key position; as shown previously the C-(18) PMB ether had been prepared from alcohol **344** (Section 10.1.3, *Scheme 73*). It was decided to use this compound, in the hope that its remoteness from the C-(25)—C-(28) (*E*,*E*)-diene would not cause unwanted reactivity during deprotection. The target compound **407** is shown in *Figure 44*.

12.7.1 Amphidinolide C: Synthesis of the C-(25)—C-(34) Fragment

Construction of the enyne C-(25)—C-(34) fragment was accomplished from the enatiomerically pure alkyne **80** (*Scheme 95*), an intermediate that had been prepared during the synthesis of vinyl iodide **386**. The preliminary reaction in the sequence involved the mercury-catalysed hydrolysis of the terminal alkyne to afford α-hydroxy ketone **408**. The possibility of acid-catalysed epimerisation of the adjacent secondary alcohol was a source of concern at this early stage, but other researchers had previously shown that the integrity of an α-chiral centre was preserved in hydrolysis reactions of this type.[189] The methodology of Ley and co-workers in their synthesis of tetronasin was applied to alkyne **80**, allowing isolation of the enantiopure α-hydroxy ketone **408** in good yield.[190] Although enolisation of the α-hydroxy stereocentre did not occur, the compound was not amenable to prolonged storage and was used in the following step immediately.



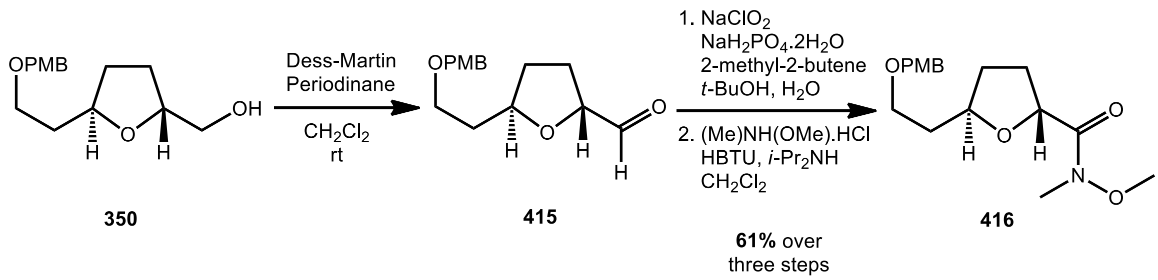
Scheme 95

The C-(29) hydroxyl required the protection of a TBS ether and so attempts were made to directly protect alcohol **408** using either TBS chloride or TBS triflate. However, this approach was found to be impractical through a combination of slow silation, possibly owing to steric factors, and the instability of the starting material. Protection of the secondary hydroxyl was deemed to be advantageous in the ensuing olefination step and so an alternative protecting group was sought. In contrast to the aborted TBS protection, we found that reaction of **408** with TES chloride resulted in full conversion of the starting material into the desired product in less than two hours and in excellent yield.

Horner-Wadsworth-Emmons olefination of methyl ketone **409** with propargylic phosphanate ester **414**,[191] provided the desired enyne **410**. Universal deprotection of the silyl groups was accomplished using a fluoride source and the integrity of the C-(29) hydroxyl stereochemistry was confirmed by Mosher ester analysis of compound **411**.[192] Clean isolation of **411** was complicated by co-elution with triethysilyl fluoride during column chromatography but the impurity was found to be removable through protracted drying under high vacuum. As with the attempted TBS protection of **408**, the conversion of alcohol **411** into target **412** did not progress with complete conversion. On stirring for three days under the indicated conditions, the desired TBS ether was isolated in an overall 77% yield with 14% recovery of the starting alcohol.

12.8 Synthesis of C-(18)—C-(24) PMB Protected Tetrahydrofuran Electrophiles

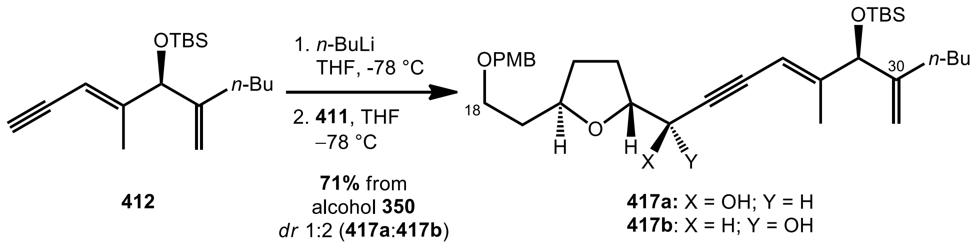
Two C-(24) electrophiles were prepared from alcohol **350** in order to explore the chemistry of the C-(18)—C-(34) fragment synthesis. Partial oxidation of the primary alcohol using Dess-Martin periodinane furnished aldehyde **415**, which could be subjected to the direct addition of a metallated acetylide to afford the united fragment bearing a C-(24) alcohol. As an alternative, the intermediate aldehyde was further oxidised to the associated carboxylic acid, which upon treatment with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of HBTU, yielded Weinreb amide **416** as a stable intermediate. The highly conjugated ketone, resulting from coupling of this species to the metallated acetylide of **412**, would subsequently be used to explore reductive methodology to deliver the desired C-(24) hydroxyl stereochemistry.



Scheme 96

12.9 Amphidinolide C: Synthesis of C-(18)—C-(34) Fragment *via* Aldehyde Alkynylation

Direct addition of the lithium acetylide to aldehyde **415** at −78 °C provided a diastereomeric mixture of C-(24) alcohols favouring of the undesired C-(24)—C-(25)-*anti* product. This result did not improve upon the stereoselectivity of acetylide addition reaction discussed previously (Section 10.2.1), but did accord with the previous observation of moderate preference for the undesired *anti* diastereomer (*Scheme 97*).



412

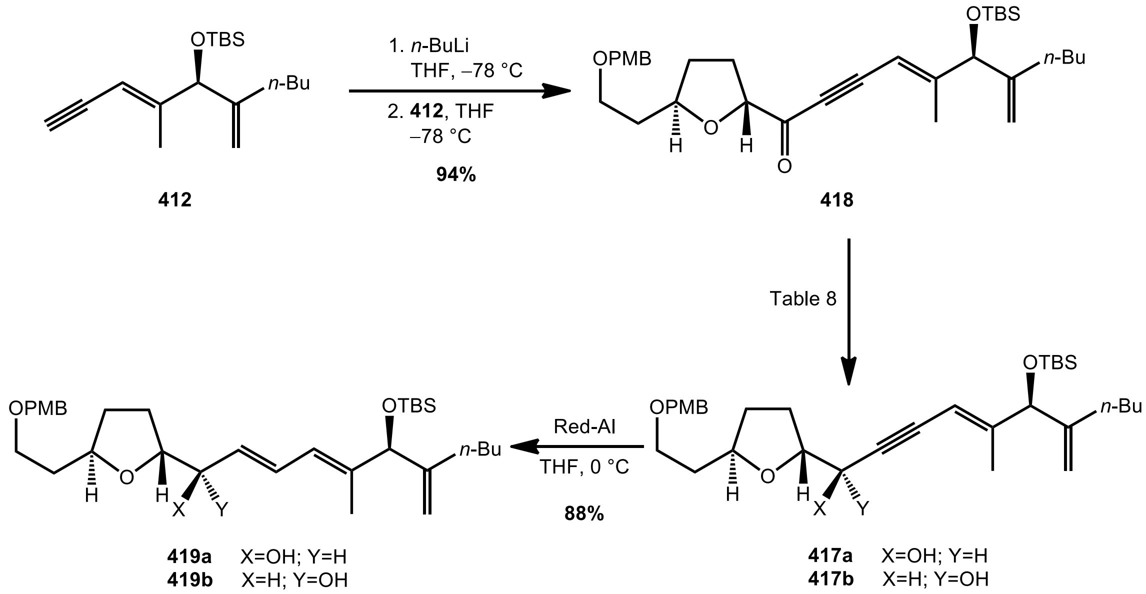
417a: X = OH; Y = H
417b: X = H; Y = OH

Scheme 97

12.10 Amphidinolide C: Synthesis of C-(18)—C-(34) Fragment *via* Weinreb Amide Alkynylation

Addition of the lithium acetylide of enyne **412** to Weinreb amide **416** afforded the C-(24) ketone **418** in excellent yield (*Scheme 98*). The product was then subjected to various reducing agents to determine the diastereoselectivity of the 1,2-reduction reaction. Despite the previously unexceptional diastereomeric ratios gained through reduction of similar ynonic systems (Section 11.2.3, *Scheme 80*), results on a related dienone indicated that a stereoselective reduction of **418** might be possible (Section 12.5, *Scheme 109*).

The results of both the Luche and L-selectride reductions (Table 8, entries 1 and 2) were similar to those recorded previously for substrates **370** and **372** (Table 5). The direct introduction of Red-Al to ynone **418** was expected to result in the 1,2-reduction of the ketone with successive reduction of the consequential propargylic group affording (*E*,*E*)-dienol **419**. When the reaction was conducted at 0 °C, a marginal preference for the C-(24)—C-(25)-*syn* diastereomer **419a** was observed (entry 3). It was hoped that through reduction of reaction temperature, the diastereoselectivity of the reduction could be improved but the diastereomeric ratio remained constant and afforded only 1,2-carbonyl reduction to the alcohol **417** as a mixture of isomers without the ensuing alkyne reduction.



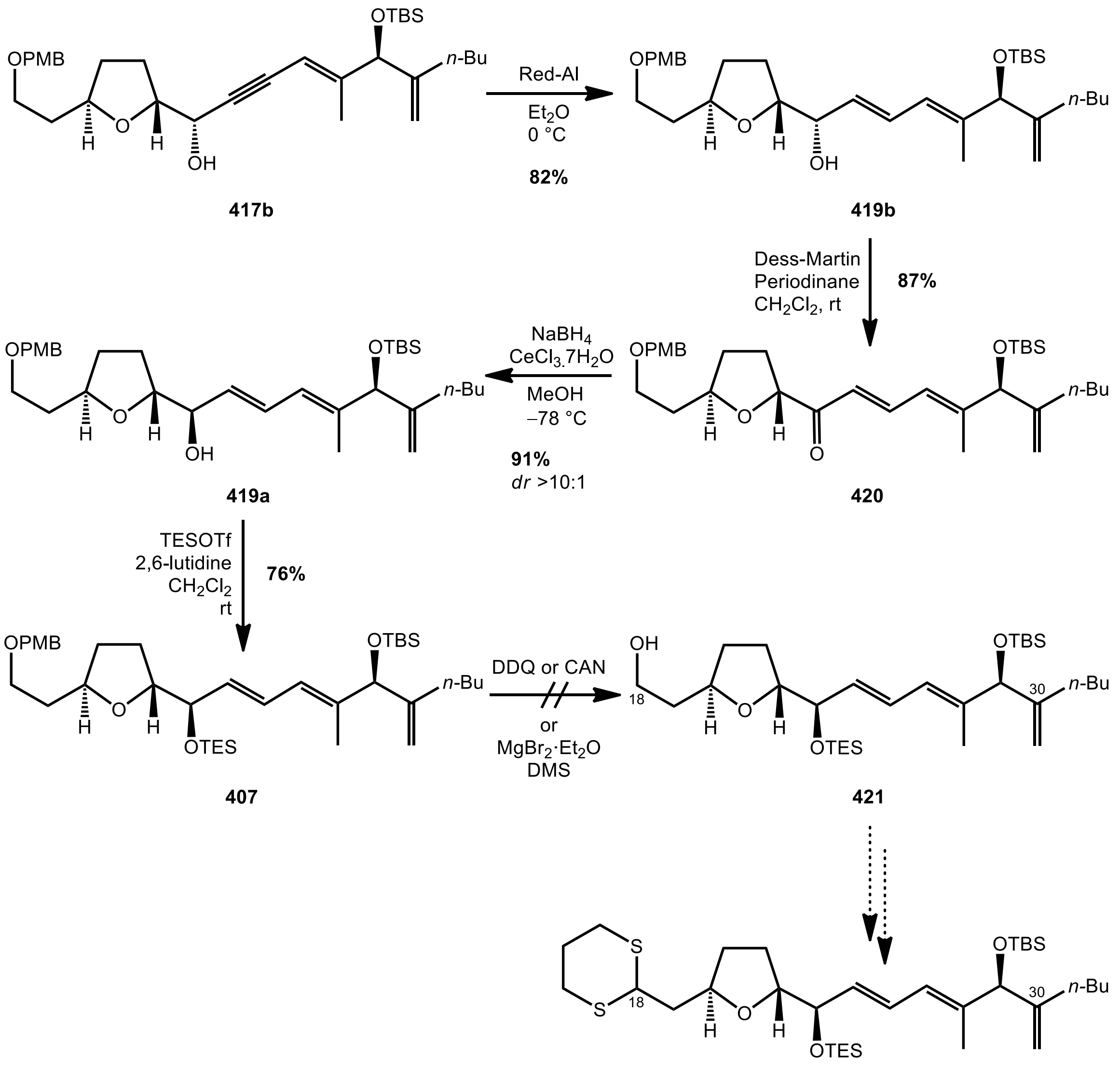
Scheme 98

Entry	Reductant	Solvent	Temp. (°C)	Yield (%)	*dr* **417a:417b**
1	$NaBH_4$ $CeCl_3.7H_2O$	MeOH	−78	100	2:1
2	L-selectride	THF	−78	66	1:1
3	Red-Al	Et_2O	0	79	2:1 **419a:419b**
4	Red-Al	Et_2O	−78	87	2:1

Table 8

12.11 Amphidinolide C: Completion of C-(18)—C-(34) Fragment

Although no diastereocontrol had been observed, in either addition of a lithium acetylide to aldehyde **415** or through reduction of ynone **418**, significant quantities of both C-(24) diastereomers had been generated in the course of this work. Painstaking chromatography of the mixture allowed for the partial separation of a reasonable quantity of the unwanted 1,2-*anti* product **417b**. Concurrent work on the 'southern' fragment had shown that the reduction of a C-5 enone system vicinal to a 2,5-*trans* tetrahydrofuran, could be accomplished under Felkin-Anh control using Luche reduction conditions (Section 12.5, *Scheme 109*). The stereoselectivity of this reduction was in direct contrast to the reduction of ynonic systems, previously discussed in *Schemes 80* and *98*, and suggested a possible solution to the generation of the desired C-(24) stereocentre.



Scheme 99

Propargylic alcohol **417b** was reduced with Red-Al to afford the stereopure (*E*,*E*)-dienol **419b** in good yield. Upon acquisition of the analysis for the C-(24) (*S*)-diastereomer, oxidation was accomplished using either Dess-Martin periodinane or MnO_2, to provide dienone **420** in 87% or 83% yield depending upon the oxidation technique employed. The 1,2-reduction of the carbonyl group proceeded in excellent yield and with high levels of diastereocontrol under Luche conditions, thereby providing the required (*R*)-stereochemistry at the C-(24) stereocentre. This sequence was subsequently shown to be applicable to diasteromeric mixtures of **419a** and **419b**, thereby rendering the previous attempt to introduce the desired stereochemistry at an early stage in the synthesis entirely obsolete. Protection of the extant C-(24) secondary alcohol as a TES ether was accomplished with TES triflate in 76% yield, after attempts to afford the same transformation with TES chloride met with incomplete conversion.

With the fully protected C-(18)—C-(34) fragment **407** in hand, the stage was set for what we believed would be the simple removal of the PMB ether and introduction of a dithiane at the C-(18) position. Initial attempts to remove the PMB functionality using traditional single electron transfer reagents such as DDQ and CAN resulted in the decomposition of the precious starting material. It was believed that this type of deprotection strategy was incompatible in the presence of the C-(25)—C-(28) (*E*,*E*)-diene system, a belief reinforced by similar observations by Iwasaki *et al* in their total synthesis of curacin A.[193] Their observation that dienes of this type, even those remote from the PMB group, are incompatible with DDQ and CAN deprotection conditions led them to develop milder conditions to effect the desired transformation.[194] Attempts to replicate Iwasaki's conditions, using a combination of magnesium bromide diethyl etherate and dimethyl sulfide, resulted in decomposition of the C-(18)—C-(34) fragment **407**. Due to the paucity of late-stage material at this point in the project, in combination with the constrained time-frames no further attempts were made to remove the PMB ether from **407**.

13 Amphidinolide C: Synthesis of the C-(1)—C-(17) Fragment

Early synthetic planning for the creation of the C-(1)—C-(17) fragment of the macrolide, proposed a disconnection between the C-(10) and C-(11) bonds, which would be constructed through Horner–Wadsworth–Emmons olefination of β-ketophosphonate **302** and an appropriately functionalised methyl ketone. Initial work on this segment of the compound began in the belief that such a connection would be viable, and hence efforts were made to transform the common intermediate **327a** into β-ketophosphonate **302**, with emphasis on stereoselective formation of the C-(35) methyl group and introduction of the C-(7)—C-(8)-*anti* diol system.

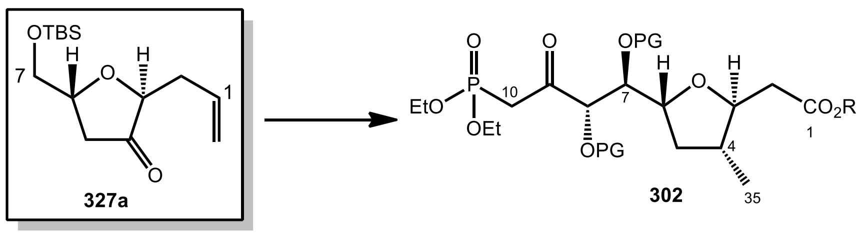
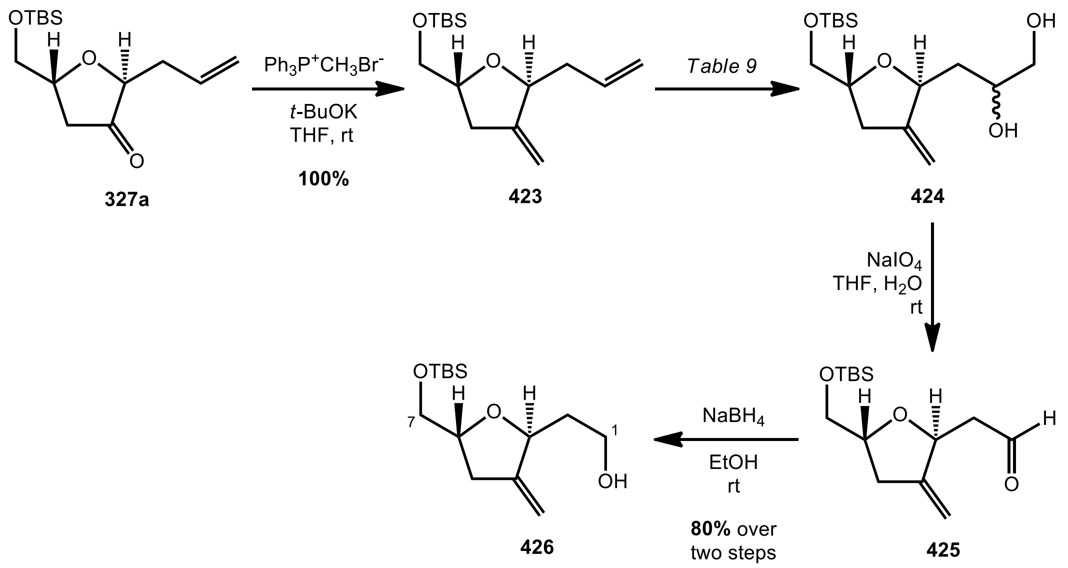


Figure 45

13.1 Amphidinolide C: Synthesis of the C-(1)—C-(7) Fragment and Introduction of C-(4) Stereochemistry

The primary goal of the synthesis was incorporation of the methyl group situated at C-(35) with the required C-(4) stereochemistry. To this end, the ketone of the common intermediate **327a** was methylenated using a Wittig reaction and gratifyingly diene **423** was afforded in quantitative yield on the first attempt, rendering the testing of alternative olefination methodologies redundant (*Scheme 100*). It was believed that introduction of the C-(4) stereochemistry could be facilitated by the application of homogeneous catalytic hydrogenation, facially directed by a C-(1)-positioned hydroxyl group. To form this intermediate, the pendant allylic group required conversion to the alcohol **426**, without disruption to the newly formed 1,1-disubstituted olefin group (*Scheme 100*). Unlike the oxidative cleavage of the allyl group in the 'northern' fragment, compound **343**, which was achieved through ozonolysis, transformation of diene **423** required a more selective approach; we believed that sequential dihydroxylation and periodate cleavage offered a suitable alternative methodology.

Examples in the literature of allylic mono-dihydroxylation in the presence of 1,1-dienes are sparse, with only two examples from the groups of Corey[195] and Trost[196] detailing equivalent reactivity. Nevertheless we considered that the less hindered allylic appendage should present the most accessible site for dihydroxylation in our case. A number of dihydroxylation experiments were undertaken, the first using Upjohn conditions[197] and the second and third employing commercially available Sharpless asymmetric dihydroxylation reagents;[156] the outcomes are summarised in *Table 9*.

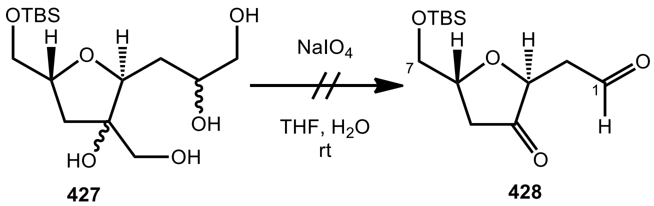


Scheme 100

Entry	Conditions	Solvent	Temp.	Yield (%) **424**
1	OsO_4 (2mol%) NMO (1.1 eq)	THF, H_2O	rt	64
2	AD-Mix α	*t*-BuOH, H_2O	0 °C	41
3	AD-Mix ß	*t*-BuOH, H_2O	0 °C	43
4	OsO_4 (2 mol%) $NaIO_4$ (2.1 eq)	THF, H_2O	rt	—

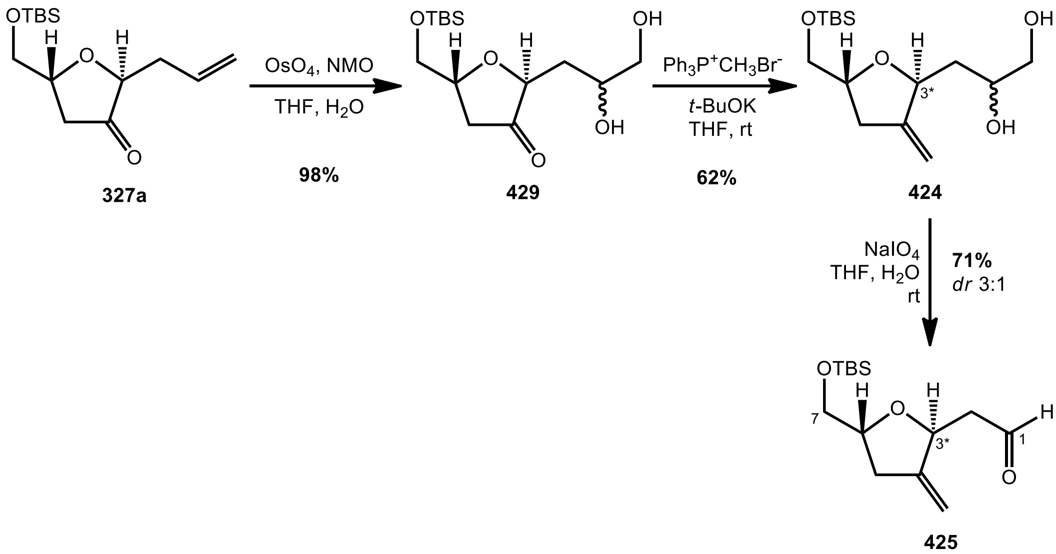
Table 9

Dihydroxylation using the standard Upjohn conditions (entry 1) afforded a 64% yield of the desired dihydroxylation product with a diastereomeric ratio of 1:1, as judged by ^1H NMR spectroscopy, and 7% recovery of the starting diene. Under these conditions the reaction could not be forced to completion through the addition of further co-oxidant, without a concomitant drop in the isolated yield of the desired product. These results suggested bis-dihydroxylation was taking place in the presence of excess reagent, leading to lower isolable quantities of the desired product. The use of Sharpless asymmetric dihydroxylation procedures (entries 2 and 3) provided diminished isolated yields of **424** in the case of both α and β mixtures. Application of the Lemieux-Johnson protocol[198] in an attempt to directly access aldehyde **425**, through a one-pot dihydroxylation and diol cleavage promoted by sodium periodate, led to a complex reaction mixture from which none of the desired product was isolated.



Scheme 101

In an effort to maximise product recovery, we attempted to isolate the putative tetraol **427** thought to be responsible for loss of material in the dihydroxylation step. Stripping of chromatography columns with dichloromethane and methanol, subsequent to isolation of the diol **424**, afforded artefacts of the reaction, the complex ^{1}H NMR spectrum of which contained signals corresponding to TBS and tetrahydrofuran groups. Attempts to oxidatively cleave the vicinal diols of the isolated material, thereby affording the dicarbonyl product **428**, which it was hoped could be recycled back into the reaction sequence, gave a complex reaction mixture from which the desired material was not isolated (*Scheme 101*).

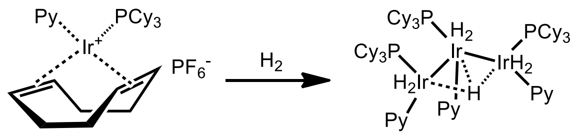


Scheme 102

In an attempt to avaoid tetraol formation, the sequence of methylenation and dihydroxylation was reversed. *Scheme 102* shows that although the dihydroxylation of alkene **327a** was accomplished in excellent yield, subsequent Wittig olefination of the ketone was problematic, not only in terms of the moderate yield of the reaction, but also because partial epimerisation of the adjacent C-(3) tetrahydrofuranyl stereocentre was observed. At this stage we concluded that Upjohn dihydroxylation of diene **423** was a reasonable method for advancing the synthesis. The synthetic sequence was completed through oxidative cleavage of the 1,2-diol **424** and reduction of the intermediate aldehyde **425**, providing C-(1) primary alcohol **426** (*Scheme 100*).

13.2 Installation of C-(4) Methyl Stereochemistry through Asymmetric Hydrogenation

With sufficient alkene **426** in hand, the stage was set to introduce the C-(4) stereochemistry, by means of a hydroxyl controlled reduction of the 1,1-disubstituted olefin. From the earliest stage of the project, Crabtree's complex **430** was identified as the catalyst of choice for this transformation due to its ability to deliver stereoselective hydrogenation through chelation to carbonyl and alcohol groups.[199] In our case, we believed that the pendant alkyl alcohol could act as a ligand for the catalyst, thereby delivering hydrogen from the corresponding face.

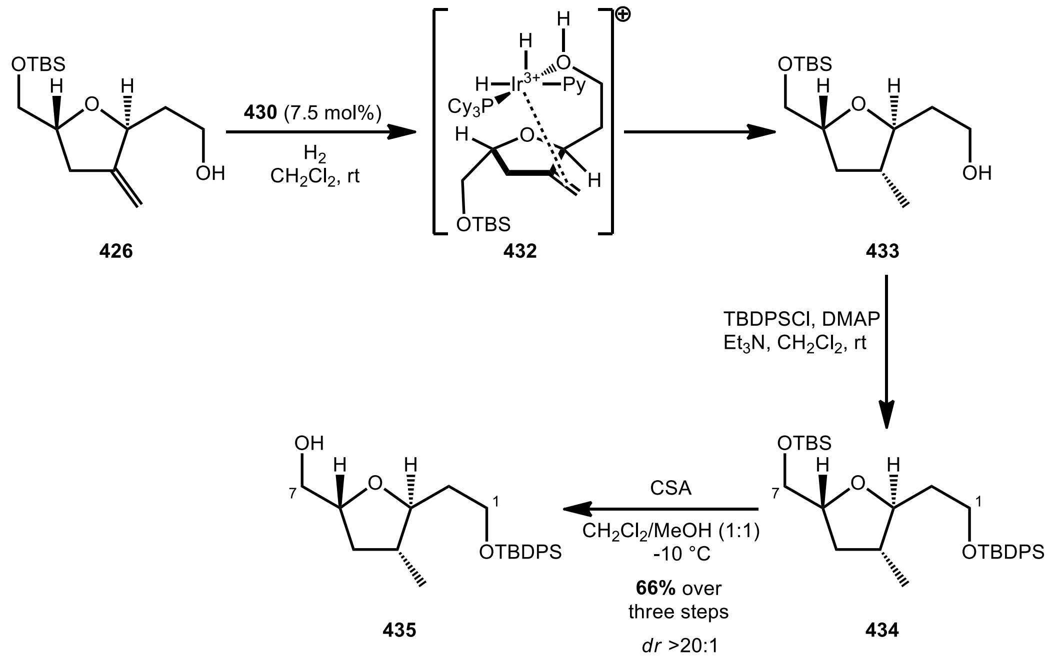


430 **431**

Figure 46

Early work proved positive with regard to the stereoselective outcome, but the reaction suffered from incomplete conversion. Previous reports had documented the deactivation of catalyst through the formation of a stable and inactive trimeric iridium complex on prolonged exposure to hydrogen (*Figure 46*).[200] Assorted reaction conditions were assayed, including variation in the non-coordinating solvent employed, reaction concentration and the rigorous degassing of all solutions used in the transformation. It was found that briefly exposing the catalyst to a hydrogen atmosphere, prior to rapid, dropwise introduction of the olefin, allowed for complete conversion of the samples in less than two hours. The reaction was monitored through ^{1}H NMR analysis of reaction aliquots, until disappearance of the olefin signals (5.01 and 4.44 ppm), and formation of the C-(4) methyl (doublet at 1.3 ppm) was observed.

The catalyst loading in the preliminary reaction was 12 mol% but it was subsequently found that a loading of 7.5 mol% was as efficacious in terms of both stereoselectivity and yield. It is believed that further reduction in the amount of catalyst could afford equivalent reactivity, though this hypothesis remains untested. In addition to the cost benefit of decreased catalyst loading, anomalous deprotection of the TBS group occurred during column chromatography of the products, where the sample was visibly contaminated with residual catalyst artefacts. Although initially problematic, this issue proved resolvable through minimisation of the required purification steps in the sequence between **426** and **435** (*Scheme 103*). Upon completion of the hydrogenation reaction, the extant alcohol was directly protected as a TBDPS ether in the same pot. Aqueous acidic work-up of bis-silyl ether **434** and CSA-catalysed deprotection of the C-(7) TBS ether subsequently furnished alcohol **435**, in a yield of 66% over three steps.

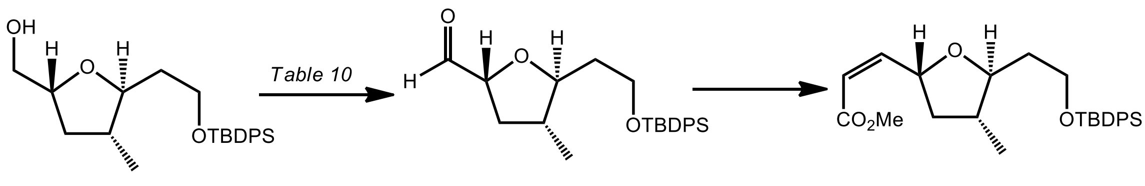


Scheme 103

13.3 Installation of the C-(7)—C-(8) Diol through Dihydroxylation

With alcohol **435** in hand, attention was turned to the formation of the β-ketophosphonate retron **302** bearing the desired 1,2-*anti* diol in the C-(7)—C-(8) locus of the natural product (*Figure 29*). To this end, we planned to test the suitability of applying the Sharpless asymmetric dihydroxylation reaction to the (*Z*)-α,β-unsaturated ester **437**.

Oxidation of alcohol **435** to its associated aldehyde allowed access to olefin **437** through either Wittig reaction with a phosphorane in an alcoholic solvent, or through the Still-Gennari modification of the Horner–Wadsworth–Emmons olefination. Exposure of (methoxycarbonyl)methylenetriphenylphosphorane to the intermediate aldehyde allowed for selective formation of the desired (*Z*)-isomer in good yield (*Table* 10, entry 1).[201] A one-pot reaction involving tandem oxidation and olefination in dichloromethane, led to a reversal in the stereoselectivity (entry 2),[202] whereas application of the Still-Genarri reagent[203] to the pre-formed aldehyde gave the optimal ratio favouring the (*Z*)-isomer **437** and the best yield over all three experiments. The (*E*) and (*Z*)-isomers proved sufficiently separable by column chromatography to allow access to pure samples of each.

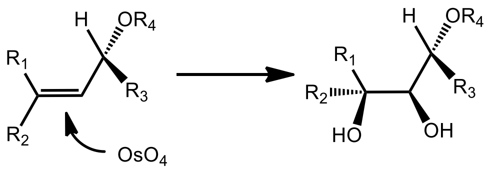


Scheme 104

Entry	Conditions	Yield (%)	*Z*:*E*
1	i. Dess-Martin periodinane, CH_2Cl_2, rt ii. $Ph_3P{=}CHCO_2Me$, MeOH, rt	70	95:5
2	Dess-Martin periodinane, $Ph_3P{=}CHCO_2Me$ CH_2Cl_2, rt	71	5:95
3	i. Dess-Martin periodinane, CH_2Cl_2, rt ii. $(F_3CCH_2O)_2POCH_2CO_2Me$, THF, −78 °C	77	99:1

Table 10

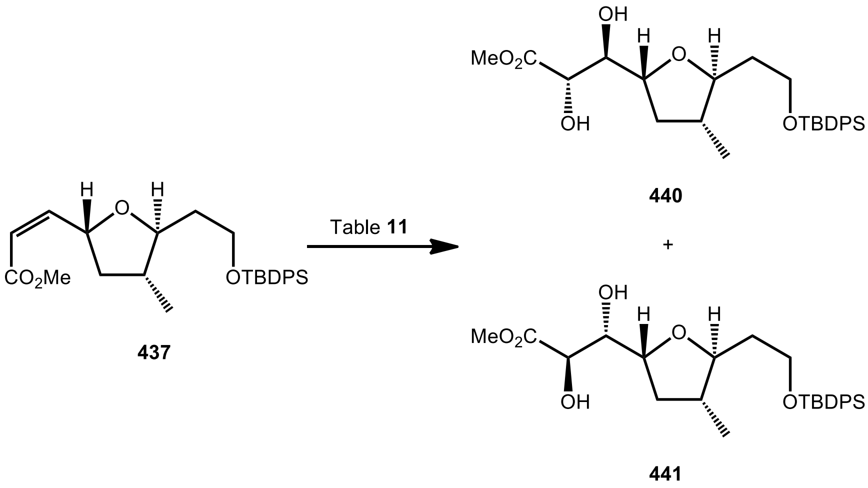
Efforts to dihydroxylate (*Z*)-alkene **437**, to generate the C-(7)—C-(8) 1,2-*anti* diol, began in the knowledge that Kishi's empirical model of allylic dihydroxylation, *Figure 47*, predicted that substrate control would deliver the wrong diastereomer as the major product.[204] The model is based upon the least sterically encumbered, eclipsed conformation **438** being most kinetically accessible prior to, and during, the osmylation transition state.



438 **439**

Figure 47

In this case, the dihydroxylation reagent approaches the face opposite that of the allylic oxygen substituent, due to a minimisation of the electronic repulsion between reactant and substrate. It was hoped, in our case, that the use of the Sharpless' ligands could override the substrate bias and deliver the desired diastereomer **440**. The three reactions shown in *Table 11* proceeded in good yield but with poor stereocontrol, dihydroxylation with AD-mix β (entry 2) afforded a mild preference for the unwanted C-(7)—C-(8) (*S*, *R*)-diastereomer **441** while AD-mix α afforded equivalent amounts of the diastereomers (entry 1). Most surprisingly, Upjohn dihdroxylation (entry 3), which was expected to deliver the undesired product, according to the Kishi model of allylic substituent control, gave equivalent amounts of each diastereomer. The diastereomers were isolable by careful chromatography and the relative configurations assigned by reduction of the ester group to form triol **442**. Comparison of the 1,2,3-triol with a sample of known absolute stereochemistry (sample preparation described in *Section 12.5, Scheme 110*), as shown in *Scheme 106*, allowed for structural assignment of each of the products.

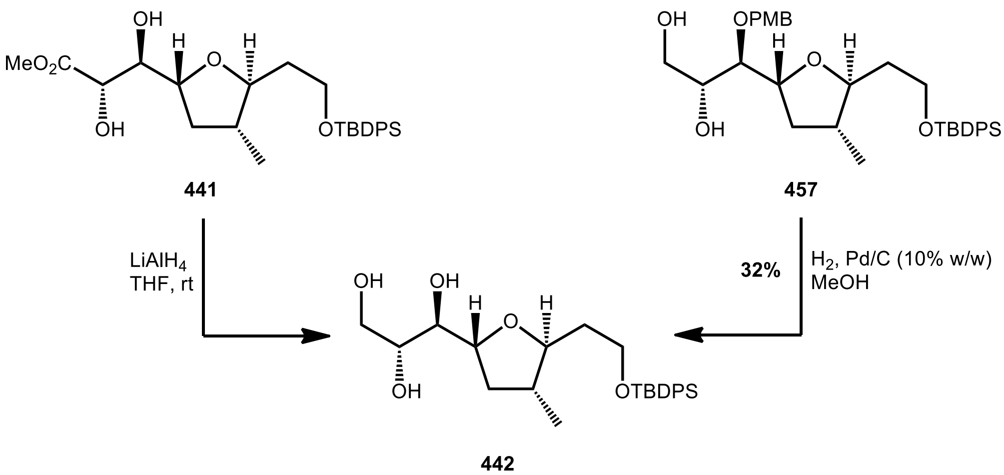


Scheme 105

Entry	Conditions	Solvent	Yield (%) 440+441	*dr* 440:441
1	AD-Mix α, $MeSO_2NH_2$	*t*-BuOH, H_2O	71	1:1
2	AD-Mix β, $MeSO_2NH_2$	*t*-BuOH, H_2O	71	1:2
3	OsO_4, NMO	THF, H_2O	81	1:1

Table 11

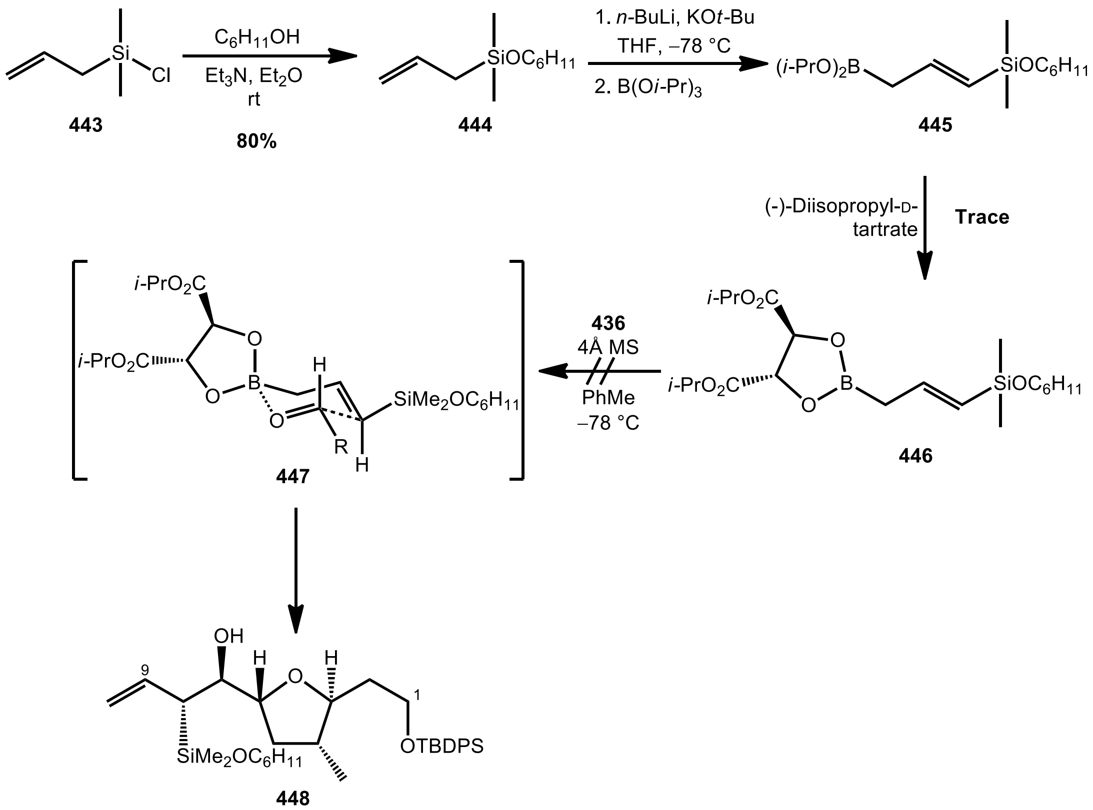
In an effort to drive the synthesis forward towards the formation of β-ketophoshonate **456**, bis-PMB protection of diol **436** was attempted using PMB-trichloroacetimidate and PMB chloride alkylation techniques. Unfortunately both the acid and base mediated reactions afforded intractable mixture of products in each case.



Scheme 106

13.4 Installation of the C-(7)—C-(8) Diol through Allylboration

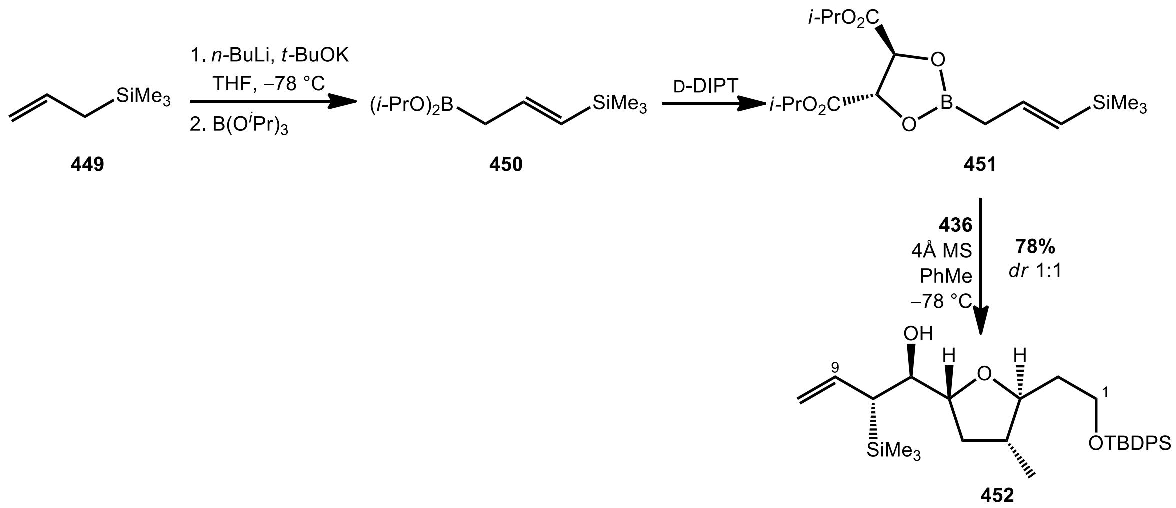
Following disappointing results when attempting to form the C-(7)—C-(8)-*anti* diol **437** through dihydroxylation methodology, our attention briefly turned to effecting a similar transformation through allylboration procedures. Roush has described the application of γ-alkoxyallylboron reagents to deliver 1,2-*anti* silanols, which upon Tamao-Fleming oxidation afforded the associated 1,2-anti diol. An example from a 1991 paper inspired us to apply the methodology towards our synthesis of the C-(7)—C-(8) stereocentres.[205]



Scheme 107

Formation of chiral allylboronate **446** began with synthesis of allyl silanol **444** through the reaction of allyl chlorodimethylsilane **443** and cyclohexanol using the procedure of Cella (*Scheme 107*).[206] Upon deprotonation of the allylic group using Schlosser's base,[207] the solution was observed to turn from clear to orange-yellow indicating formation of the allylic anion. Subsequent sequential addition of triisopropylborane and (−)-dii*so*propyl D-tartrate was expected to deliver γ-alkoxyallylborane **446**. In practice, ^{1}H NMR analysis of the reactions showed mixtures of allylsilane **444** and excess tartrate ester; trace peaks of the desired intermediate, identified by comparison to Roush's data, were observed but were insubstantial components of the reaction mixtures. Variation of base, temperature, solvent and reaction time failed to deliver the desired product; where pertinent peaks were observed in the ^{1}H NMR spectrum, addition of aldehyde **436** was undertaken, on each attempt formation of the desired C-(7)—C-(8) silanol **448** was not observed.

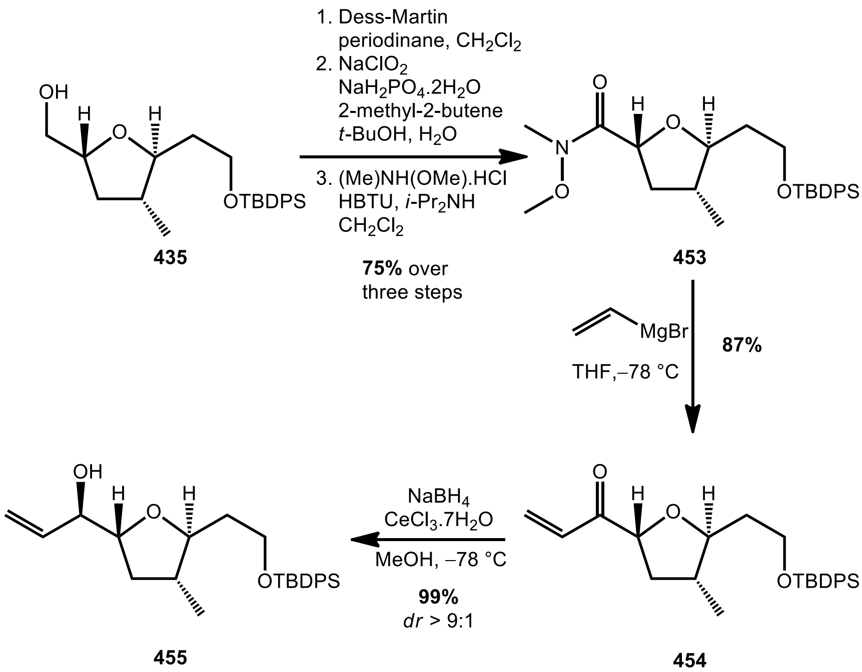
A variant of the procedure used in *Scheme 107* was attempted in which allyltrimethylsilane was used as the source of the allyl functionality. Following equivalent deprotonation and boration procedures to those used previously, aldehyde **436** was added to the reaction mixture. In this case two separable products were formed cleanly from the reaction. The ^{1}H and ^{13}C NMR spectra of the isolated compounds supports the formation of compound **452** and its diastereomer however the diastereoselectivity of the allylboration reaction was poor, yielding what was essentially an equivalent mixture of products. This sequence was not pursued further owing to the poor diastereoselectivity of the reaction; the relative stereochemistry of the products remains undetemined. Mechanistic considerations, whereby the reaction proceeds via a transition state of type **447**, would suggest that the products are the C-(7)—C-(8)-*anti* diastereomers indicated (*Scheme 108*).



Scheme 108

13.5 Installation of C-(7) Hydroxyl Stereochemistry

The poor diastereoselectivity resulting from the preceding dihydroxylation and allylboration methodologies led us to explore stepwise introduction of the C-(7) and C-(8) stereocentres. This approach began with formation of enone **454** by addition of vinylmagnesium bromide to Weinreb amide **453**, prepared in excellent yield by sequential step-wise oxidation of alcohol **435** and HBTU-facilitated coupling of the resultant carboxylic acid to *N*,*O*-dimethylhydroxylamine hydrochloride. This piecemeal sequence proved necessary as the alternative approach of vinylmagnesium bromide addition to the intermediate aldehyde **436**, followed by an allylic oxidation of the diasteromeric mixture of allylic alcohols (*dr* 1:1), afforded mixtures that were difficult to purify and delivered significantly lower yields of enone **454** (45% over three steps).



Scheme 109

The efficacious, stereocontrolled introduction of the C-(7) hydroxyl group proved possible through Felkin-Anh reduction of enone **454** under Luche conditions. Excellent isolated yields of allylic alcohol **455** were afforded along with exceptional levels of diastereocontrol. The absolute stereochemistry of the alcohol was determined by application of the modified Mosher protocol.[192]

The difference in stereoselectivity of this reduction reaction over that of the previously discussed ynone systems is difficult to rationalise as the two systems offer similar prochiral faces for the approach of a reducing reagent. Logically, if the enone confers greater stereocontrol to the reduction, the pendant olefin group must play a decisive role in the approach of the hydride ion. The C-C bond rotation between the carbonyl and olefin groups allows for several possible conformers to exist, the extremes of which, **A** and **B**, are illustrated in *Figure 48*. At low temperature, and under the Felkin-Anh model, the lowest energy conformation is posited to be **B**, where the olefin is positioned to minimise allylic strain with the C-(6) ß-tetrahydrofuranyl hydrogen. In this way, hydride approach from the *si* face is reinforced and stereocontrol is amplified over that of the Felkin-Anh modelled ynone system **C**.

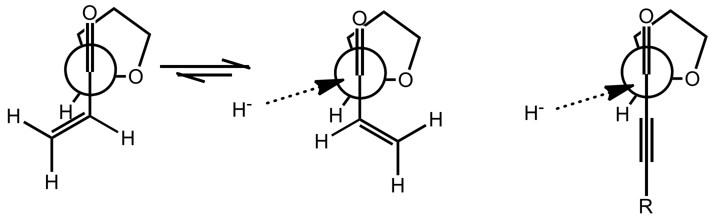
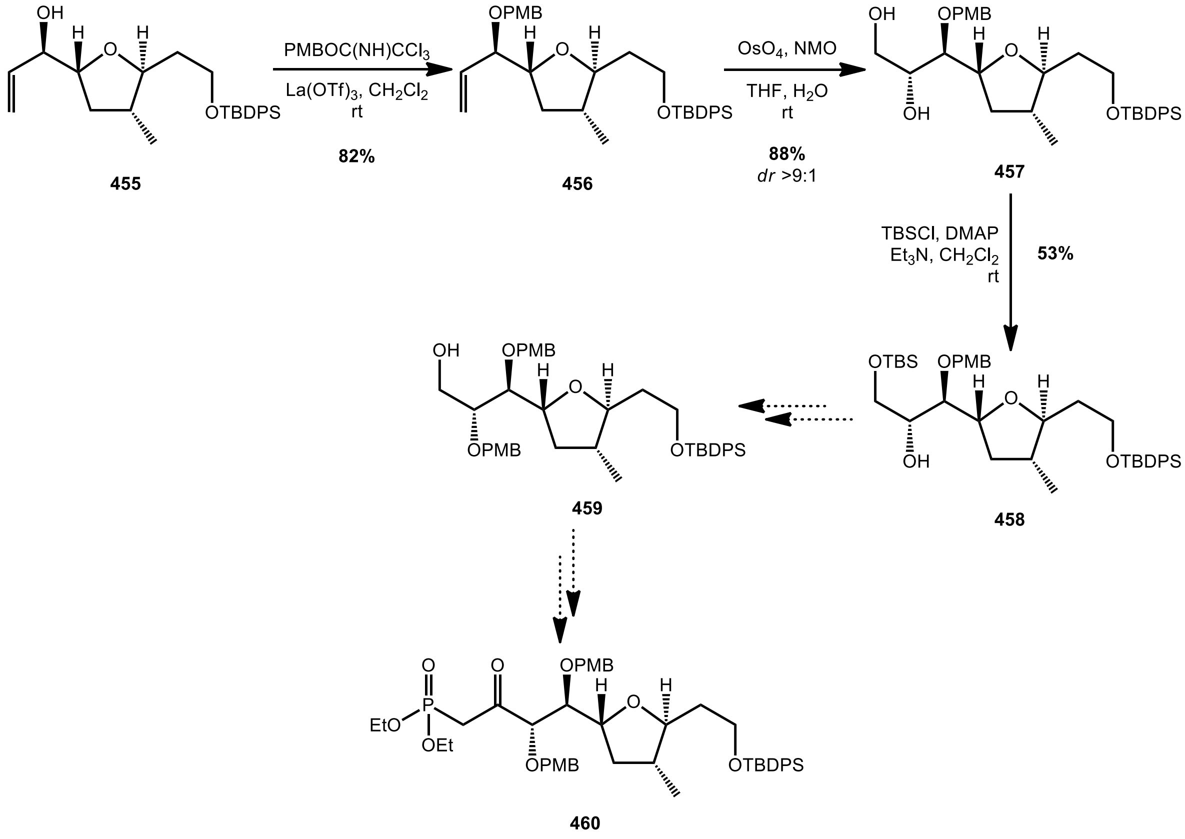


Figure 48

Protection of the secondary alcohol was accomplished by Lewis acid catalysed activation of PMB-trichloroacetimidate with lanthanum(III) triflate, and the olefin was then dihydroxylated under Upjohn conditions (*Scheme 110*). As expected, under the allylic dihydroxylation model of Kishi discussed previously, the C-(8) hydroxyl was introduced stereoselectively to afford diol **457**. The absolute stereochemistry of the C-(8) stereocentre was determined through selective TBS protection of the C-(9) primary alcohol and application of the modified Mosher protocol to the remaining secondary alcohol.[192] Removal of the PMB ether by hydrogenolysis afforded triol **438**, as shown in *Scheme 106*, allowing a determination of the absolute stereochemistry of the α,ß-dihydroxyesters **440** and **441** prepared previously. Following protection of the C-(8) secondary alcohol and removal of the terminal TBS group, further steps could have progressed the synthesis towards advanced intermediates such as the ß-ketophosphonate **460** or the vinyl stannane **87** prepared by Ferrié[31] (*Scheme 15*). By this stage in the project however, the proposal of forming the C-(9)—C-(11) diene functionality through Horner-Wadsworth-Emmons methodology had been beset by the failure of model reactions to accomplish the required coupling.

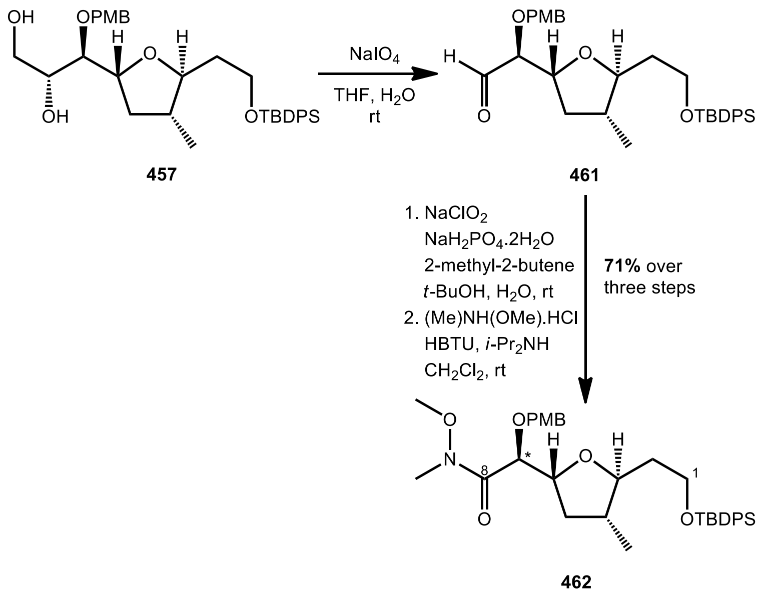

OH
OPMB
OTBDPS
PMBOC(NH)CCl3
La(OTf)3, CH2Cl2
rt
82%
455
456
OsO4, NMO
THF, H2O
rt
88%
dr >9:1
457
TBSCl, DMAP
Et3N, CH2Cl2
rt
53%
OTBS
458
459
EtO
OEt
460

Scheme 110

13.6 Alternative Methodolgy Towards the Formation of C-(1)—C-(17) Fragment

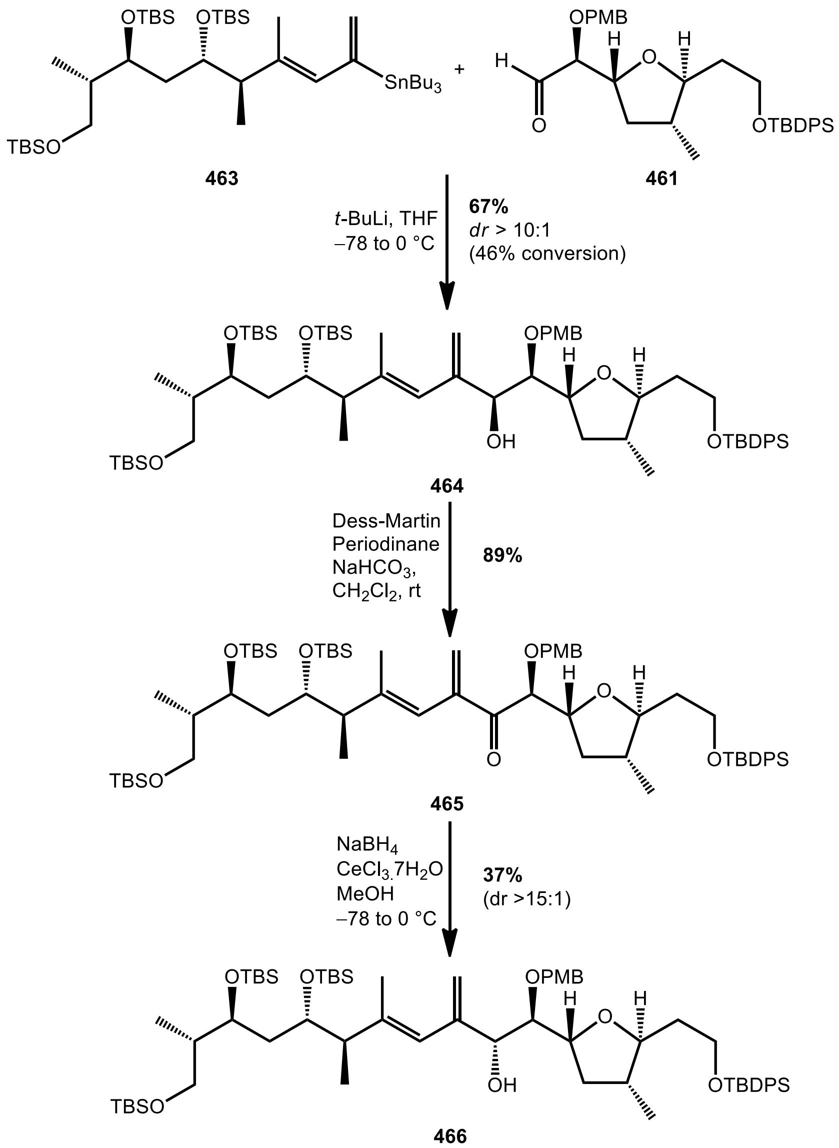
A revised synthetic plan required the creation of a fragment encompassing the necessary stereochemistry and diene geometry of the C-(9)—C-(17) locus of the natural product's macrolide ring. The generation of a nucleophile from this fragment and addition to a suitably functionalised C-(1)—C-(8) fragment, was believed to be an appropriate method by which to access the desired C-(1)—C-(17) 'southern' component of amphidinolide C. The revised synthetic plan required the formation of an electrophilic moiety positioned at C-(8) and to this end, both aldehyde **461** and Weinreb amide **462** were prepared (*Scheme 111*).

Aldehyde **461** was prepared through oxidative cleavage of the 1,2-diol **457** and was used immediately in the subsequent reaction with the C-(9)—C-(17) fragment **463** prepared by Guang Yang. The Weinreb amide **462** was constructed through Pinnick oxidation of the intermediate aldehyde and condensation of the resultant carboxylic acid with *N*,*O*-dimethylhydroxylamine hydrochloride. Although compound **462** was isolated in good yield, partial epimerisation of the PMB protected C-(7) stereocentre was observed intermittently. The problematic reproducibility of this reaction necessitated reliance on aldehyde **461** as the electrophilic moiety required for formation of the C-(8)—C-(9) bond.



Scheme 111

The completion of the C-(1)—C-(17) fragment **466**, accomplished by Yang, is shown in *Scheme 112* and commenced from the tin-lithium exchange of fragment **463**. After formation of the nucleophile, through treatment of stannane **463** with *t*-butyl lithium, it was added to aldehyde **461**. The reaction proceeded in good yield and with excellent levels of stereocontrol, but unfortunately the undesired C-(7)—C-(8) *syn* diastereomer **464** predominated. The correct stereochemistry was subsequently introduced through oxidation of alcohol **464** to give ketone **465** followed by Luche reduction, under Felkin-Anh control, to provide the C-(1)—C-(17) fragment of the macrolide core with the required stereochemistry. Although the reaction afforded the correct diastereomer, the slow rate of reduction led to a substantial loss of material through decomposition and resulted in a lower than anticipated isolated yield of **466**.



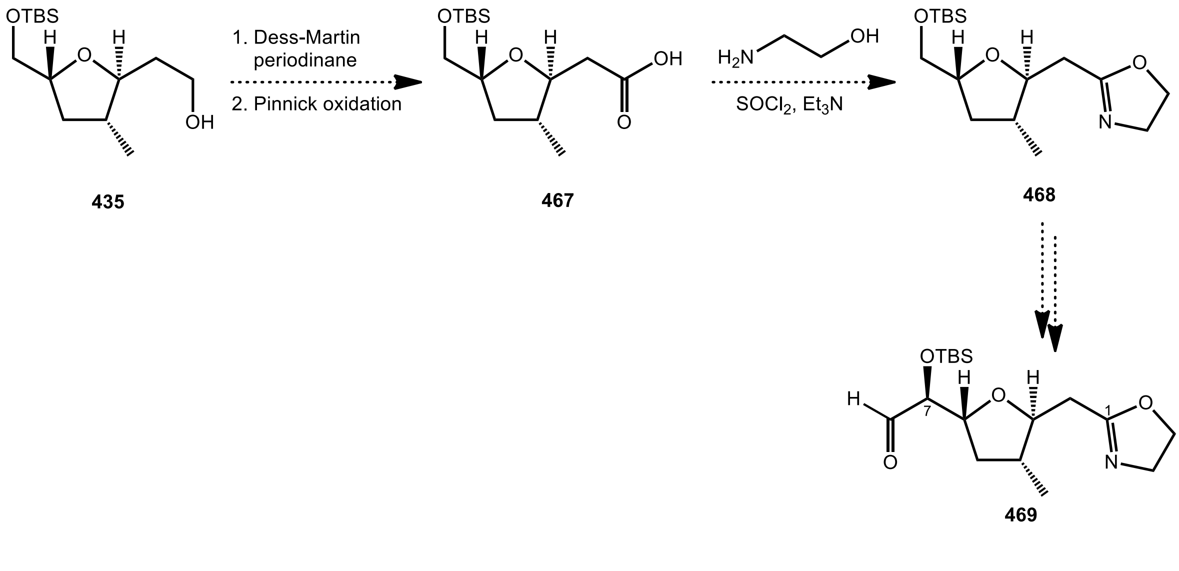
Scheme 112

14 Future Work

Although the complexities of amphidinolide C have been largely addressed in the work described herein, a total synthesis of the natural product remains an elusive goal. The major difficulty at present lies within the realm of protecting group chemistry, particularly those associated with the C-(1), C-(13) and C-(15) positions.

14.1 C-(1) Protection

Presently, the choice of TBDPS on the C-(1) locus is impractical, owing to the increased stability of this functionality over the other silyl ethers within the two most advanced fragments **407** and **466**. As the C-(1) position is destined to become the carboxylic acid precursor required for Yamaguchi cyclisation, it would be beneficial to have this locus protected in an equivalent oxidation state as early as possible to negate the requirement for oxidation at a later, more complex, stage in the synthesis. To this end, a suitable alternative could involve the formation of an oxazoline group at the C-(1) position, as shown in Scheme *113*. This hetereocycle is stable against nucleophilic attack and generally requires forcing conditions of mineral acid and heat to restore the masked carboxylic acid. Removal of the group under mild conditions can be accomplished if an iminium salt is formed through reaction with an alkyl halide, and the salt treated with aqueous base; an example of this type of deprotection reaction has been used by the Kallmerten group during studies on the synthesis of nargenicins.[208]

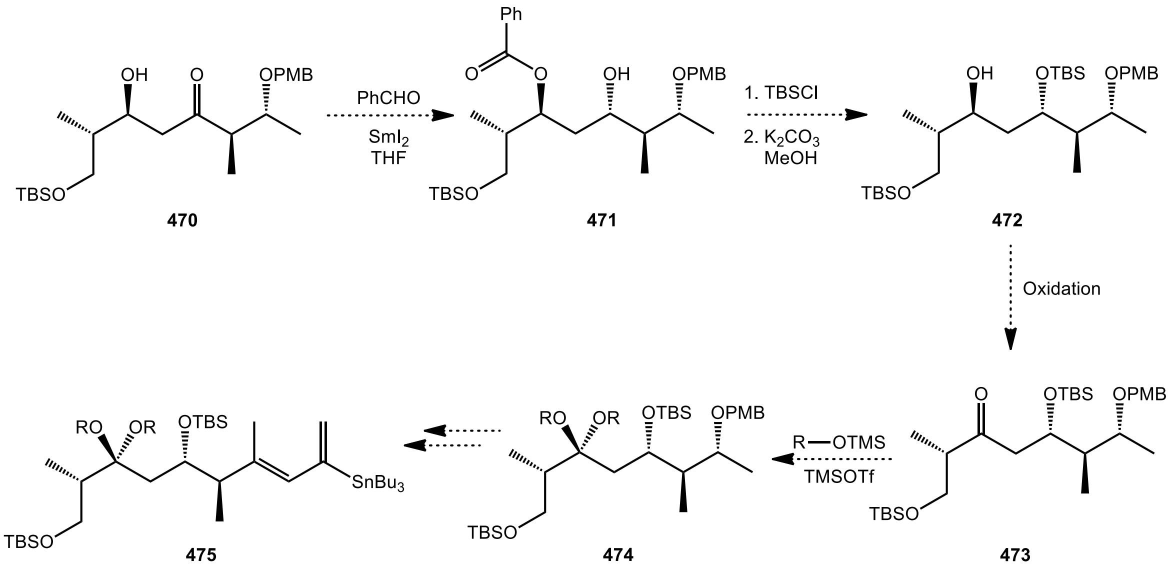


Scheme 113

Although the current C-(7)-containing fragment **456** is protected as a PMB ether, it would be beneficial to test current methodologies where a TBS protecting group is used in its place. Elimination of PMB ethers from the synthesis may be highly advantageous to negate the problematic reactivity associated with diene functionality of both 'northern' and 'southern' fragments. Protection of the C-(7)—C-(8) diol as bis TBS ethers would greatly assist in late-stage global deprotection.

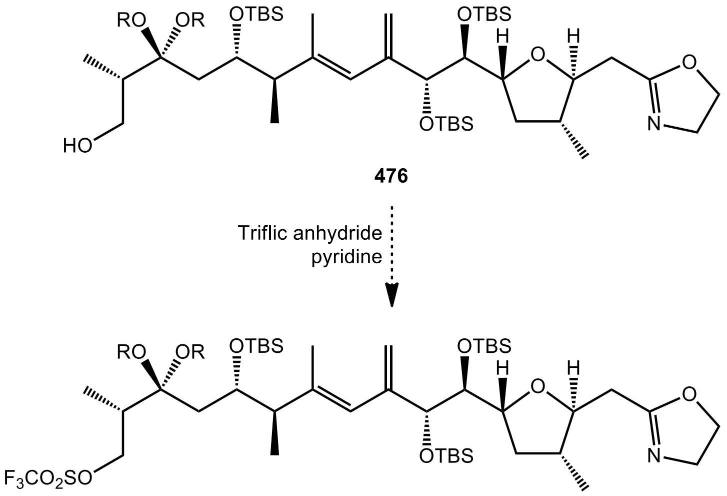
14.2 C-(13) and C-(15) Protection

The 1,3-*anti* stereochemistry of the C-(13) and C-(15) hydroxyl groups was previously introduced using Evans $Me_4NHB(OAc)_3$ reagent,[209] but this generates a 1,3-diol which is difficult to protect in a selective fashion.[170] An alternative approach would involve the C-(15) hydroxyl controlled Evans-Tishchenko reduction of ketone **470**, an intermediate previously prepared by Guang Yang, which should afford the 1,3-*anti* product preferentially with the additional benefit of protecting the C-(15) position as an ester; this would allow for the subsequent differential protection of the C-(13) position. As the C-(15) position of amphidinolide C bears a ketone, the stereochemistry of this position is obsolete and hence this site could be protected as a ketal following oxidation of the secondary alcohol (*Scheme 114*).



Scheme 114

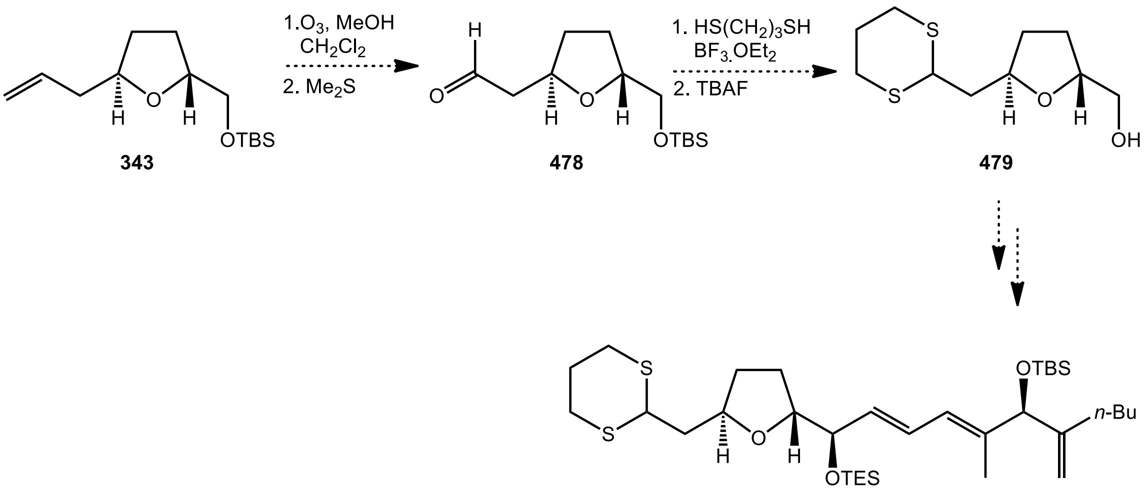
Upon combination of **475** and **469**, formation of the desired C-(8) stereochemistry and protection of the secondary alcohol could be followed by selective cleavage of the C-(17) TBS ether. Conversion of the C-(17) hydroxyl into a leaving group would allow for subsequent formation of the C-(17)—C-(18) bond through dithiane alkylation.



Scheme 115

14.3 C-(18) Protection

Although the synthesis of the C-(18)—C-(34) fragment of amphidinolide C had been accomplished, we were unable to deprotect the PMB group of compound **407** using established SET reagents or a combination of $MgBr_2$ and DMS. Although the literature abounds with methods for removal of PMB groups, the C-(24) and C-(29) hydroxyl protecting groups, in addition to the highly conjugated tail region renders the majority of methodologies unsuitable. A possible approach to effect this deprotection involves the use of Birch reduction, an example of this was reported by Bittman and co-workers in their synthesis of plasmalogens.[210]

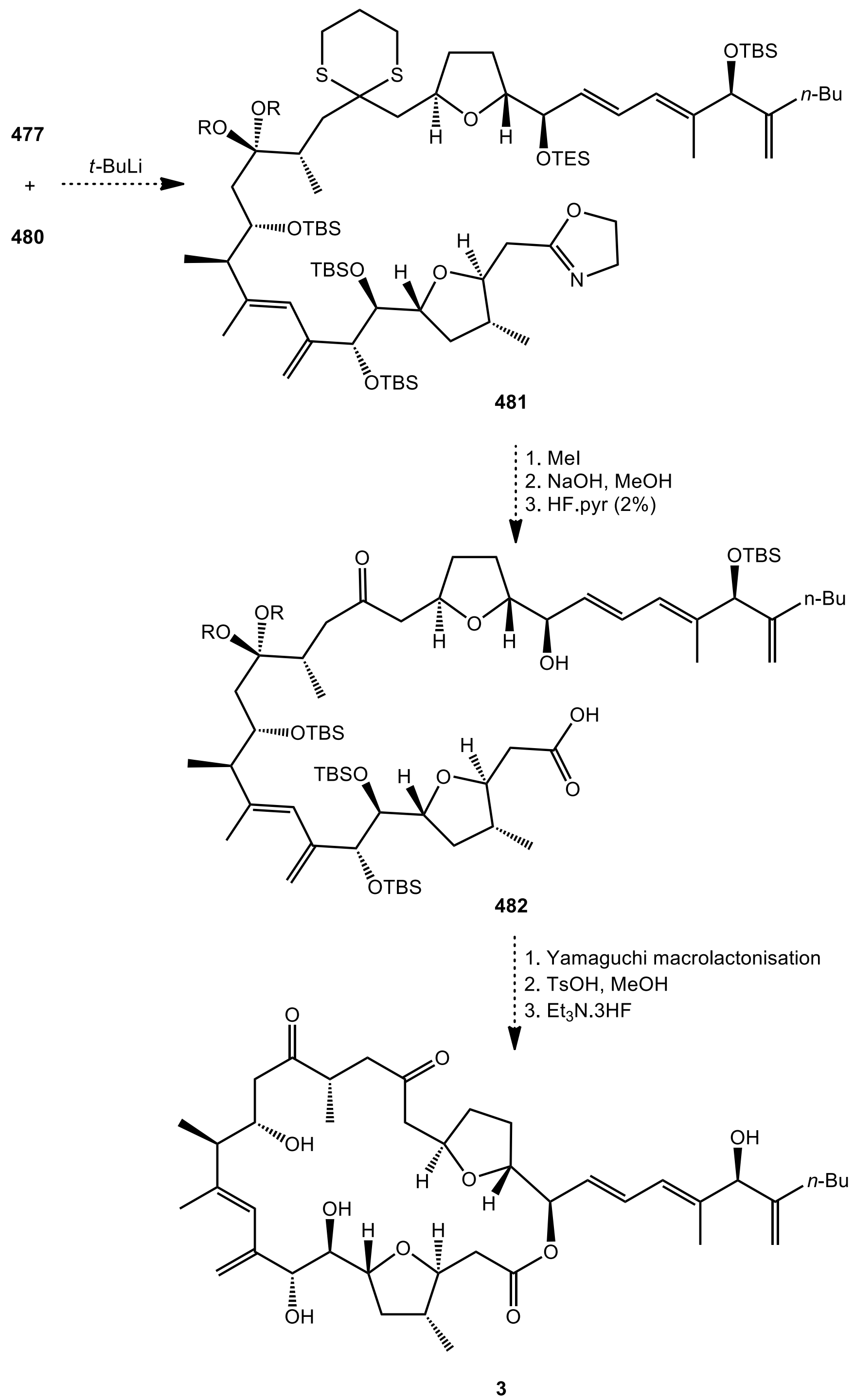


Scheme 116

Alternatively, as the primary strategy towards formation of the C-(17)—C-(18) linkage relies upon the alkylation of a dithiane, it may be possible to introduce this functionality early in the synthesis, thereby using it as both an alkylation precursor and the C-(18) protecting group. This change could be implemented at the ozonolysis stage through modification of the work-up from sodium borohydride to dimethyl sulfide to afford an intermediate aldehyde **478**. Formation of the dithiane and deprotection of the C-(24) TBS group could be accomplished as shown in *Scheme 116*. Alteration of either of the existing routes, *i.e.* palladium cross-coupling or alkynylation of the C-(24) position, would afford the C-(18)—C-(34) construct **480**; a caveat being amendment of the C-(24) alcohol oxidation protocols, from the current Dess-Martin procedure, to a more dithiane friendly alternative.

14.4 Completion of Amphidinolide C Total Synthesis

Alkylation of the dithiane **480** with **477** would set the stage for Yamaguchi lactonisation of the substrate, upon deprotection of the oxazoline and TES moieties. Fragmentation of the oxazoline group, as discussed previously, using a two-step process of alkyl iminium salt formation and mild treatment with aqueous base, would afford the C-(1) carboxylic acid. In our case, the application of methyl iodide to system **481** is likely to lead to concomitant loss of the C-(18) dithiane. On Yamaguchi macrolactonisation of the deprotected carboxylic acid with the C-(24) hydroxyl, the challenge would then be deprotection of the ketal and extant TBS ethers. Ketal hydrolysis could be accomplished by simple exposure of the moiety to catalytic acid and would be followed by universal removal of the remaining silyl ethers, using the $Et_3N{\cdot}3HF$ protocol adopted by Carter and Mahapatra in the final step of their synthesis of amphidinolide F (*Scheme 117*).

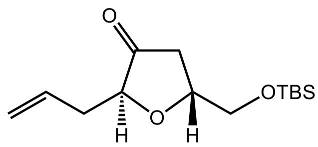

477
+
480
t-BuLi
481
1. MeI
2. NaOH, MeOH
3. HF.pyr (2%)
482
1. Yamaguchi macrolactonisation
2. TsOH, MeOH
3. Et3N.3HF
3

Scheme 117

15 Summary and Conclusions

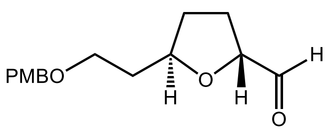
Methodology has been developed which has enabled access to two fragments comprising the complete carbon skeleton of amphidinolides C and F. This thesis has dealt specifically with the stereoselective synthesis of the C-(18)—C-(34) fragment of amphidinolide C **407**, the C-(18)—C-(29) fragment of amphidinolide F **397** and the C-(1)—C-(8) fragment **461** of the common macrolide ring system. A key point in the total synthesis work outlined was the employment of a modular synthesis, whereby the natural product was divided into two fragments of equivalent complexity, termed 'Northern' and 'Southern'. Each fragment was constructed through building outwards from a 2,5-*trans* substituted tetrahydrofuran, both ring systems of which were identified as being advanced synthetic products of an antecedent common intermediate.

The synthesis of the common intermediate **327a** was achieved in seven steps from the chiral pool starting material D-malic acid, in an overall 41% yield and with excellent diastereocontrol. The key step of this synthesis was the diastereoselective [2,3]-sigmatropic rearrangement of an intermediate oxonium ylide, formed through the copper-catalysed decomposition of an α-diazoketone. The common intermediate provided the foundation for the construction of both 'Northern' and 'Southern' fragments through alteration of the 2,5-vicinal carbon chains and the C-3 positioned ketone.

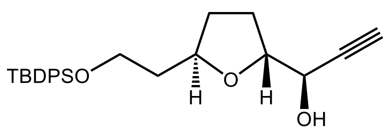


327a

The C-(18)—C-(34) 'Northern' fragments were assembled in a further eleven linear steps from the common intermediate through two methodologies, namely palladium-catalysed cross-coupling of alkyne **378** or alkynylation of aldehyde **415**. Transformation of intermediate **327a** to either intermediate necessitated deletion of the C-(21) ketone moiety; this was accomplished through the application of radical deoxygenation techniques.

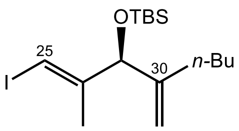


415

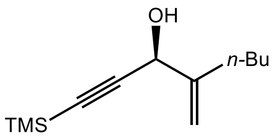


378

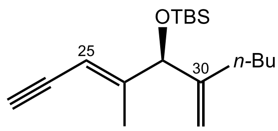
The vinylic iodide cross-coupling partner and alkynylation precursor were both derived from a common propargylic alcohol **80**. The C-(29) stereochemistry of this intermediate was achieved through kinetic resolution of the racemic alcohol *via* the Sharpless asymmetric epoxidation protocol.



386

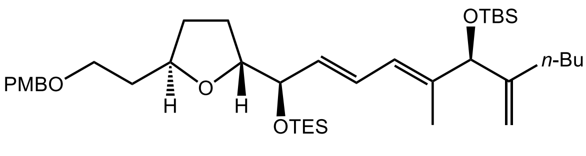


80

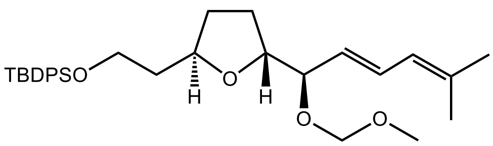


412

Use of Sonogashira or Heck alkynylation cross-couplings between propargylic alcohol **378** and vinyl iodide **386**, or through alkynylation of aldehyde **415** using the lithium acetylide of **412**, allowed access to systems of type **407**, the carbon backbone of the C-(19)—C-(34) fragment of amphidinolide C. Heck alkyne cross-coupling of **378** with commercial isocrotyl bromide afforded access to the C-(18)—C-(29) carbon backbone of amphidinolide F. The desired C-(25)—C-(26) olefin geometry of both fragments was introduced through hydroxyl-controlled propargylic reduction, and the C-(24) stereochemistry of **407** established through Felkin-Anh controlled reduction of a C-(24) dienone. The deprotection of the C-(18) group has provided some problematic reactivity issues, which it is hoped can be resolved in future work. A recent publication from our group has discussed the use of palladium cross-couplings in forming these fragments of amphidinolide C and F.[211]

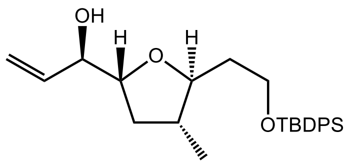


407

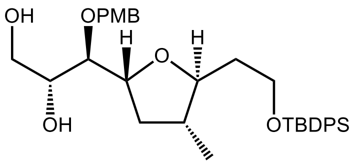


396

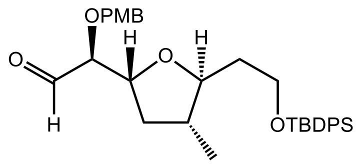
The synthesis of the 'Southern' C-(1)—C-(8) fragment required the stereoselective introduction of the C-(4) methyl group. This was achieved through a sequence of methylenation, selective dihydroxylation and a substrate controlled hydrogenation reactions. Introduction of the C-(7) and C-(8) *anti* diol chemistry was attempted with both dihydroxylation and allylboration chemistry. Although both methodologies afforded the desired reactivity, the diastereoselective outcomes were insufficient for a total synthesis route. Stepwise introduction of the C-(7) and C-(8) stereocentres was shown to be achievable through the stereoselective reduction of an intermediate enone, thereby delivering allylic alcohol **455**. The C-(8) stereochemistry was introduced through a stereoselective dihydroxylation, the resulting diol **457** proved to be amenable to a change in project strategy by providing the precursor to aldehyde **461**.



455

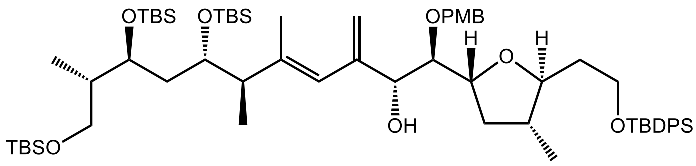


457



461

Nucleophilic addition of Yang's C-(9)—C-(17) fragment into aldehyde **461** allowed, with subsequent modification, access to the 'Southern' C-(1)—C-(17) fragment of the macrolide ring **466**. This synthesis was recently published in tandem with that of the 'Northern' fragment.[212]



466

In summary, a stereoselective formation of the C-(18)—C-(34) fragment of amphidinolide C, the C-(18)—C-(34) fragment of amphidinolide F and the C-(1)—C-(8) fragment common to both macrolides has been achieved. Two of the nine stereocentres discussed in the work originate from the use of D-malic acid as the starting material for a common intermediate species. The remaining stereocentres were introduced through substrate controlled reactions, with the only exception being the C-(29) hydroxyl of amphidinolide C, which was introduced through Sharpless epoxidation resolution chemistry. The combined efforts of the Clark group have yielded two fragments corresponding to the complete carbon skeletons of amphidinolides C, C2, C3 and F, with union of 'Northern' and 'Southern' fragments the last hurdle to be overcome in a total synthesis of these fascinating natural products.

Chapter 3: Experimental Section

General comments

Air and/or moisture sensitive reactions were performed under an atmosphere of Argon in flame dried apparatus. Organic solvents were dried using 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.

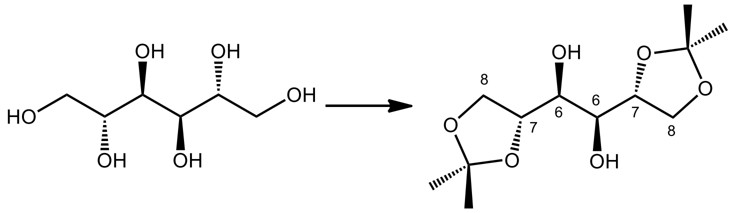
IR spectra were recorded using a type IIa diamond single reflection element on a Shimadzu FTIR-8400 instrument. The IR spectrum of the compound (solid or liquid) was directly detected as a thin layer at ambient temperature.

^{1}H NMR spectra were recorded on a Bruker 400 MHz or 500 MHz Spectrospin spectrometer at ambient temperature. The carbon numbering used for the NMR signal assignment of the molecules corresponds to the amphidinolide numbering protocol assigned by Kobayashi;[12] where possible, intermediates are assigned based upon concluding position within the amphidinolide structure. IUPAC numbering is used for the molecule names and generated using ChemAxon's MarvinSketch 5.12.2 software. Data is reported as follows: chemical shift in ppm relative to $CDCl_3$ (7.26) on the δ scale, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, ap = apparent, 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 is 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 ESI 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.

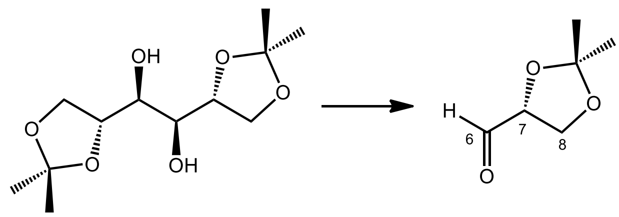
Elemental analyses were carried out on an Exeter Analytical Elemental Analyser EA 440.

1,2:5,6-Di-*O*-isopropylidene-D-mannitol.[213] (312)



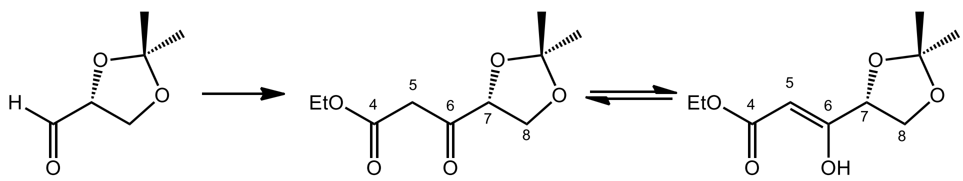
To a slurry of D-mannitol (50 g, 0.27 mol) in 1,2-dimethoxyethane (120 mL) was added 2,2-dimethoxypropane (80 mL, 0.65 mol) and $SnCl_2$ (50 mg, 0.26 mmol). The mixture was warmed to 95 °C until a clear solution was obtained (45 minutes approx.) and the heating continued for a further 30 minutes. The reaction was removed from heat and pyridine (100 µl) was added to the solution whilst warm; the reaction was then allowed to cool to rt. The volatile component was removed by distillation at 100 °C (1 atm). The crude material was slurried in CH_2Cl_2 (360 mL) for 1.5 h, filtered to remove the colourless solid [1,2-isopropylidene-D-mannitol **311** (5.4 g, 9%)] and the filtrate concentrated to a clear oil which crystallised on standing. Purification of the two-component mixture was achieved by chromatography (pet. ether/EtOAc, 4:1 to 1:1) to provide the desired diacetal **312** as colourless solid (42 g, 58%) and 1,2:3,4:5,6-di-*O*-isopropylidene-D-mannitol **313** (13.8 g, 17%) also as a colourless solid. R_f = 0.15 (pet. ether/EtOAc, 1:1); $[\alpha]_D^{16}$ +3.1 (c = 0.96, $CHCl_3$); Mp 120–122 °C [lit. 118-120 °C][213]; ν_{max} (powder) 3394, 3279, 2978, 2886, 1373, 1258, 1204, 1065, 856, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.20–4.13 (2H, m, CH-C8), 4.14-4.08 (2H, m, CH-C7), 3.97 (2H, dd, *J* = 8.4, 5.4 Hz, CH-C8), 3.79-3.69 (2H, m, CH-C6), 2.77 (2H, d, *J* = 6.7 Hz, OH-C6), 1.40 (6H, s, CH_3-Me acetonide), 1.34 (6H, s, CH_3- Me acetonide); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.7 (C-C acetonide), 76.5 (CH-C7), 71.4 (CH-C6), 67.0 (CH-C8), 27.0 (CH_3-Me acetonide), 25.5 (CH_3-Me acetonide); HRMS (CI+, isobutane) calcd for $C_{12}H_{23}O_6$ $[M+H]^+$ 263.1494, found 263.1494 (Δ −0.3 ppm); LRMS (CI+, isobutane) *m/z* (intensity); 263.4 (100%), 205.3 (45%), 147.2 (20%); Anal. calcd for $C_{12}H_{22}O_6$ C 54.95%, H 8.45%, found C 54.89%, H 8.52%.

(4*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde.[213] (88)



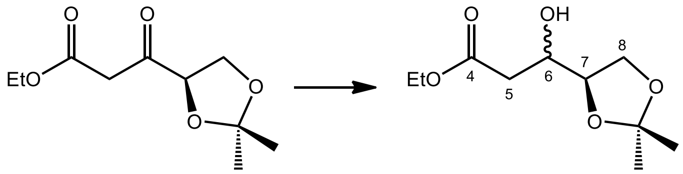
Sodium periodate (16 g, 76 mmol) was added to a stirred solution of diol **312** (10 g, 38 mmol) in CH_2Cl_2 (75 mL) and saturated aqueous $NaHCO_3$ (4 mL) at 0 °C; the ice bath was then removed and the mixture stirred for 3 h at rt. $MgSO_4$ (4.9 g) was added to the reaction mixture, stirred for 20 minutes and removed by filtration. The solids were washed with further CH_2Cl_2 (20 mL) and the solution carefully concentrated at ambient temperature on a rotary evaporator. Distillation of the crude mixture *in vacuo* afforded the desired aldehyde **88** (8.6 g, 87%) as a clear, colourless oil. $[\alpha]_D^{26}$ +72.0 (c = 1.30, $CHCl_3$); Bp 45-48 °C (13 mbar) [lit. 72-74 °C (44 mbar)][213]; ν_{max} (liquid film) 3442, 2989, 1734, 1373, 1211, 1065, 840, 601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.70 (1H, d, *J* = 1.9 Hz, CH-C6), 4.41–4.30 (1H, m, CH-C7), 4.15 (1H, dd, *J* = 8.8, 7.4 Hz, CH-C8), 4.08 (1H, dd, *J* = 8.8, 4.7 Hz, CH-C8), 1.47 (3H, s, CH_3-Me acetonide), 1.40 (3H, s, CH_3-Me acetonide); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1 (CH-C6), 111.6 (C-C acetonide), 80.2 (CH-C7), 65.9 (CH_2-C8), 26.6 (CH_3-Me acetonide), 25.4 (CH_3-Me acetonide); HRMS (CI+, isobutane) calcd for $C_6H_{11}O_3$ $[M+H]^+$ 131.0708, found 131.0711 (Δ +2.2 ppm); LRMS (CI+, isobutane) *m/z* (intensity); 131.2 (100%).

Ethyl 3-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-oxopropanoate.[215] (314)



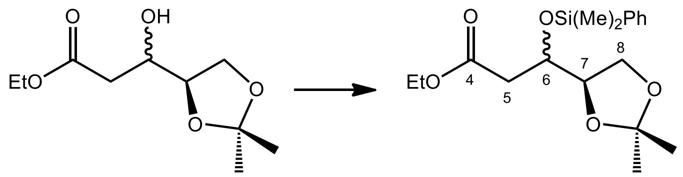
Aldehyde **88** (8.8 g, 68 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a solution of ethyl diazoacetate (7.5 mL, 71 mmol) and $SnCl_2$ (1.3 g, 6.8 mmol) in CH_2Cl_2 (290 mL) at rt. Upon complete addition the mixture was stirred for 1h before the reaction was quenched with brine (150 mL). The mixture was extracted with Et_2O (2 × 150 mL), dried ($MgSO_4$), filtered and concentrated to a yellow oil. Purification of the residue by chromatography (pet. ether to pet. ether/EtOAc, 19:1) afforded a keto-enol mixture of **314** (8.2 g, 56%) as a clear, colourless oil. R_f = 0.39 (pet. ether, EtOAc, 4:1); $[\alpha]_D^{25}$ +80.4 (c = 1.03, $CHCl_3$) [lit. $[\alpha]_D^{26}$ +73.7 (c = 1.5, $CHCl_3$)][215]; ν_{max} (liquid film) 2988, 2901, 1745, 1720, 1208, 1061, 843, cm^{-1}; **Ketone:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (1H, dd, *J* = 7.8, 5.2 Hz, CH-C7), 4.23–4.16 (3H, m, CH-C8 and CH_2-OEt), 4.09 (1H, dd, *J* = 8.8, 5.2 Hz, CH-C8), 3.66 (1H, d, *J* = 16.4 Hz, CH_2-C5), 3.52 (1H, d, *J* = 16.4 Hz, CH_2-C5), 1.48 (3H, s, CH_3-Me acetonide), 1.38 (3H, s, CH_3-Me acetonide), 1.28 (3H, t, *J* = 7.2 Hz, CH_3-OEt); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4 (C-C6), 167.3 (C-C4), 111.6 (C-C acetonide), 80.2 (CH-C7), 66.9 (CH_2-C8), 61.8 (CH_2-OEt), 46.1 (CH-C5), 26.3 (CH_3-Me acetonide), 25.1 (CH_3-Me acetonide), 14.4 (CH_3-OEt); **Enol:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (1H, s, OH-C6), 5.37 (1H, d, *J* = 0.8 Hz, CH-C5), 4.56–4.52 (1H, m, CH-C7), 4.28–4.18 (3H, m, CH-C8 and CH_2-OEt), 3.99 (1H, dd, *J* = 8.5, 5.8 Hz, CH-C8), 1.48 (3H, s, CH_3-Me acetonide), 1.40 (3H, s, CH_3-Me acetonide), 1.28 (3H, t, *J* = 7.2 Hz, CH_3-OEt); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6 (C-C6), 173.1 (C-C4), 111.0 (C-C acetonide), 88.6 (CH-C5), 74.8 (CH-C7), 68.4 (CH_2-C8), 60.7 (CH_2-OEt), 26.4 (CH_3-Me acetonide), 25.7 (CH_3-Me acetonide), 14.6 (CH_3-OEt); HRMS (CI+, isobutane) calcd for $C_{10}H_{17}O_5$ $[M+H]^+$ 217.1076, found 217.1078 (Δ +0.9 ppm); LRMS (CI+, isobutane) *m*/*z* (intensity); 217.2 (100%), 199.2 (21%), 159.2 (30%).

Ethyl 3-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-(*R*,*S*)-hydroxypropanoate. (315)



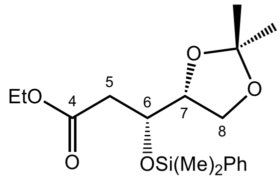
NaBH$_4$ (0.9 g, 25 mmol) was added to a solution of ketone **314a** (4.9 g, 23 mmol) in EtOH (130 mL) at 0 °C and the mixture stirred for 15 minutes. The volatiles were removed *in vacuo* and the residue partitioned between Et_2O (50 mL) and brine (50 mL). The organic phase was isolated and the aqueous back-extracted with further Et_2O (2× 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated before purification of the residue by chromatography (pet. ether/EtOAc, 9:1 to 4:1) to give a diasteromeric mixture of alcohols **315a** and **315b** (4.1 g, 83%, *dr* 1:1) as a clear oil.

Resolution of β-hydroxy esters through silyl ether derivatisation.



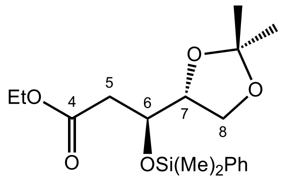
To a stirred solution of diasteromeric alcohols **315** (0.11 g, 0.46 mmol) in DMF (5 mL) at rt was added chloro(dimethyl)phenylsilane (0.11 mL, 0.69 mmol) and imidazole (0.62 g, 0.92 mmol). The mixture was stirred for 1.5 h, concentrated *in vacuo* and purified by chromatography (pet. ether/EtOAc, 97:3) to provide silyl ethers **316a** (34 mg, 21%), **316b** (53 mg, 33%) and a diastereomeric mixture of both (31 mg, 19%) all as clear, colourless oils.

Ethyl (3*R*)-3-{[dimethyl(phenyl)silyl]oxy}-3-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]propanoate. (316a)



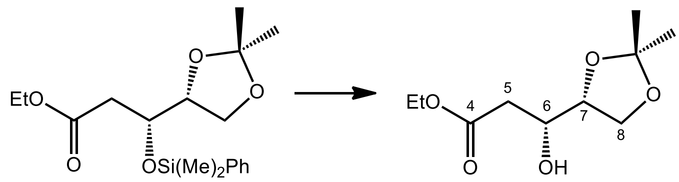
R_f = 0.40 (pet. ether, EtOAc, 9:1); $[\alpha]_D^{25}$ +25.0 (c = 1.09, $CHCl_3$); ν_{max} (liquid film) 2984, 2902, 1734, 1373, 1208, 1250, 1071, 823, 785, 731, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.55 (2H, m, CH-PhSi), 7.47–7.29 (3H, m, CH-PhSi), 4.45–4.22 (1H, m, CH-C6), 4.11-4.00 (3H, m, CH_2-OEt and CH-C7), 3.92 (1H, dd, *J* = 8.4, 6.9 Hz, CH-C8), 3.77 (1H, dd, *J* = 8.4, 6.6 Hz, CH-C8), 2.50 (1H, dd, *J* = 15.2, 4.0 Hz, CH-C5), 2.42 (1H, dd, *J* = 15.2, 8.5 Hz, CH-C5), 1.38 (3H, s, CH_3-Me acetonide), 1.30 (3H, s, CH_3-Me acetonide), 1.21 (3H, t, *J* = 7.1 Hz, CH_3-OEt), 0.40 (3H, s, CH_3-SiMe), 0.39 (3H, s, CH_3-SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7 (C-C4), 138.3 (C-PhSi), 133.8 (CH-PhSi), 129.9 (CH-PhSi), 128.1 (CH-PhSi), 109.9 (C-C acetonide), 78.0 (CH-C7), 70.6 (CH-C6), 65.5 (CH_2-C8), 60.9 (CH_2-OEt), 38.4 (CH_2-C5), 26.6 (CH_3-Me acetonide), 25.3 (CH_3-Me acetonide), 14.5 (CH_3-OEt), −0.8 (CH_3-MeSi), −1.0 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{18}H_{29}O_5Si$ $[M+H]^+$ 353.1784, found 353.1788 (Δ +1.1 ppm); LRMS (CI+, isobutane) *m/z* (intensity); 353.3 (5%), 219.2 (100%), 179.2 (23%), 161.2 (44%), 133.2 (24).

Ethyl (3*S*)-3-{[dimethyl(phenyl)silyl]oxy}-3-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]propanoate. (316b)



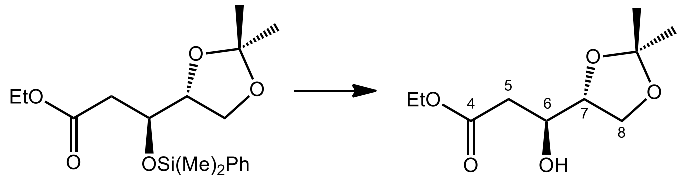
R_f = 0.44 (pet. ether, EtOAc, 9:1); $[\alpha]_D^{24}$ −5.2 (c = 1.07, $CHCl_3$); ν_{max} (liquid film) 2985, 2908, 1735, 1373, 1250, 1072, 824, 787, 733, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.54 (2H, m, CH-PhSi), 7.40–7.33 (3H, m, CH-PhSi), 4.17 (1H, ddd, *J* = 7.8, 6.7, 4.1 Hz, CH-C7), 4.05–3.91 (4H, m, CH_2-OEt, CH-C6 and CH-C8), 3.72 (1H, dd, *J* = 7.8, 5.5 Hz, CH-C8), 2.61 (1H, dd, J = 15.4, 4.1 Hz, CH-C5), 2.46 (1H, dd, J = 15.4, 7.7 Hz, CH-C5), 1.34 (3H, s, CH_3-Me acetonide), 1.31 (3H, s, CH_3-Me acetonide), 1.20 (3H, t, J = 7.2 Hz, CH_3-OEt), 0.40 (3H, s, CH_3-SiMe), 0.40 (3H, s, CH_3-SiMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (C-C4), 138.2 (C-PhSi), 133.7 (CH-PhSi), 130.0 (CH-PhSi), 128.1 (CH-PhSi), 109.8 (C-C acetonide), 78.7 (CH-C7), 71.2 (CH-C6), 67.1 (CH_2-C8), 60.8 (CH_2-OEt), 40.3 (CH_2-C5), 26.9 (CH_3-Me acetonide), 25.6 (CH_3-Me acetonide), 14.5 (CH_3-OEt), −0.76 (CH_3-SiMe), −0.86 (CH_3-SiMe); HRMS (CI+, isobutane) calcd for $C_{18}H_{29}O_5Si$ $[M+H]^+$ 353.1784, found 353.1783 (Δ −0.2 ppm); LRMS (CI+, isobutane) m/z (intensity); 353.3 (8%), 337.3 (47%), 295.2 (100%), 275.2 (53%), 217.2 (28%).

Ethyl (3*R*)-3-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxypropanoate. (315a)



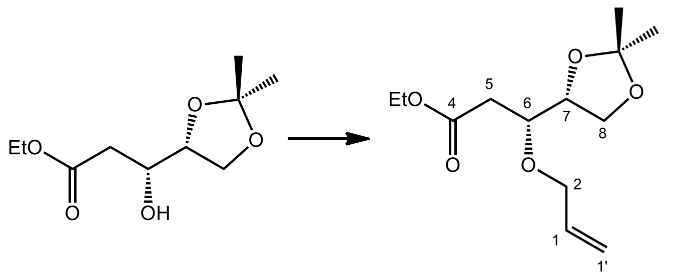
TBAF (3.4 mL of a 1 M solution in THF, 3.4 mmol) was added dropwise to a stirred solution of **316a** (1.1 g, 3.1 mmol) in THF (10 mL) at rt and the mixture was stirred for 30 minutes. The reaction was quenched by the addition of H_2O (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated to a clear oil. Purification of the residue by chromatography (pet. ether/EtOAc/Et_3N, 80:20:1) yielded alcohol **315a** (0.58 g, 86%) as a single diastereomer. R_f = 0.17 (pet. ether/EtOAc, 2:1); $[\alpha]_D^{24}$ +15.7 (c = 1.14, $CHCl_3$); ν_{max} (liquid film) 3472, 2986, 2901, 1729, 1373, 1250, 1067, 849, 609 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (2H, q, J = 7.1 Hz, CH_2-OEt), 4.12 (1H, td, J = 6.5, 4.6 Hz, CH-C7), 4.08–4.00 (2H, m, CH-C6 and CH-C8), 3.85 (1H, dd, J = 8.3, 6.5 Hz, CH-C8), 2.81 (1H, d, J = 5.6 Hz, OH-C6), 2.54 (1H, dd, J = 16.0, 8.3 Hz, CH-C5), 2.48 (1H, dd, J = 16.0, 4.5 Hz, CH-C5), 1.44 (3H, s, CH_3-Me acetonide), 1.36 (3H, s, CH_3-Me acetonide), 1.27 (3H, t, J = 7.1 Hz, CH_2-OEt); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2 (C-C4), 110.0 (C-C acetonide), 78.0 (CH-C7), 68.7 (CH-C6), 66.0 (CH_2-C8), 61.2 (CH_2-OEt), 38.6 (CH_2-C5), 26.7 (CH_3-Me acetonide), 25.5 (CH_3-Me acetonide), 14.5 (CH_3-OEt); HRMS (CI+, isobutane) calcd for $C_{10}H_{19}O_5$ $[M+H]^+$ 219.1232, found 219.1230 (Δ −1.0 ppm); LRMS (CI+, isobutane) m/z (intensity); 219.2 (100%), 161.2 (70%); Anal. calcd for $C_{10}H_{18}O_5$ C 55.03%, H 8.31%, found C 54.95%, H 8.48%.

Ethyl (3*S*)-3-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxypropanoate.[216] (315b)



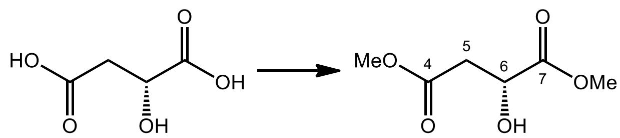
The procedure used to prepare **315a** provided **315b** as a clear, colourless oil in 91% yield. R_f = 0.17 (pet. ether, EtOAc, 2:1); $[\alpha]_D^{25}$ −13.5 (c = 0.95, $CHCl_3$), [lit. $[\alpha]_D^{22}$ −11.8 (c = 0.6, $CHCl_3$)][216] ; v_{max} (liquid film) 3464, 2986, 2909, 1728, 1373, 1157, 1064, 848, 787 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.18 (2H, q, *J* = 7.1 Hz, CH_2-OEt), 4.12–4.05 (1H, m, CH-C8), 4.02–3.92 (3H, m, CH-C6, CH-C7 and CH-C8), 3.15 (1H, d, *J* = 3.7 Hz, OH-C6), 2.70 (1H, dd, *J* = 16.7, 2.8 Hz, CH-C5), 2.47 (1H, dd, *J* = 16.7, 8.6 Hz, CH-C5), 1.41 (3H, s, CH_3-Me acetonide), 1.34 (3H, s, CH_3-Me acetonide), 1.28 (3H,t, *J* = 7.1 Hz, CH_3-OEt); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2 (C-C4), 109.9 (C-C acetonide), 77.9 (CH-C7), 69.6 (CH-C6), 67.0 (CH_2-C8), 61.2 (CH_2-OEt), 37.9 (CH_2-C5), 27.0 (CH_3-Me acetonide), 25.5 (CH_3-Me acetonide), 14.5 (CH_3-OEt); HRMS (CI+, isobutane) calcd for $C_{10}H_{19}O_5$ $[M+H]^+$ 219.1232, found 219.1234 (Δ +0.6 ppm); LRMS (CI+, isobutane) *m/z* (intensity); 219.2 (100%), 161.2 (65%), 133.2 (26%).

Ethyl (3*R*)-3-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-(prop-2-en-1-yloxy)propanoate. (323)



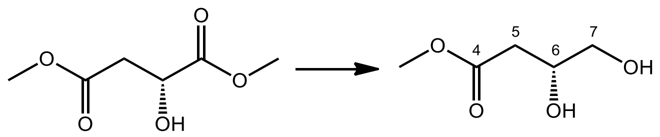
$Pd_2(dba)_2$ (10 mg, 0.011 mmol) and 1,4-bis(diphenylphosphino)butane (20 mg, 0.046 mmol) were stirred together in degassed THF (2 mL) at rt for 5 minutes. A solution of alcohol **315a** (0.10 g, 0.46 mmol) and allyl ethyl carbonate (0.24 g, 1.8 mmol) in degassed THF (1 mL) was added to the catalyst complex and the mixture was heated at 65 °C for 18 h. On cooling to rt the reaction mixture was concentrated and the residue purified directly by chromatography (pet. ether/EtOAC, 20:1 to 9:1) to afford the title allylic ether **323** (89 mg, 75%) as a clear, yellow oil. R_f = 0.57 (pet. ether, EtOAc, 3:1); $[\alpha]_D^{25}$ +23.2 (c = 1.04, $CHCl_3$); v_{max} (liquid film) 2985, 2901, 1736, 1373, 1257, 1180, 1064, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (1H, ddt, *J* = 17.1, 10.4, 5.7 Hz, CH-C1), 5.25 (1H, dd, *J* = 17.1, 1.6 Hz, CH-C1' *trans*), 5.15 (1H, dd, *J* = 10.4, 1.6 Hz, CH-C1' *cis*), 4.26 (1H, dt, *J* = 6.7, 5.6 Hz, CH-C7), 7.31 (2H, q, *J* = 7.1 Hz, CH_2-OEt), 4.11-4.17 (2H, m, CH_2-C2), 4.03-3.95 (2H, m, CH-C6 and CH-C8), 3.79 (1H, dd, *J* = 8.5, 6.6 Hz, CH-C8), 2.53 (1H, dd, *J* = 15.7, 4.7 Hz, CH-C5), 2.47 (1H, dd, *J* = 15.7, 7.9 Hz, CH-C5), 1.42 (3H, s, CH_3-Me acetonide), 1.35 (3H, s, CH_3-Me acetonide), 1.27 (3H, t, *J* = 7.1 Hz, CH_3-OEt); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (C-C4), 135.0 (CH-C1), 117.4 (CH_2-C1'), 109.9 (C-C acetonide), 76.8 (CH_2-C2), 76.2 (CH-C7), 72.4 (CH-C6), 65.5 (CH_2-C8), 60.9 (CH_2-OEt), 36.4 (CH_2-C5), 26.8 (CH_3-Me acetonide), 25.4 (CH_3-Me acetonide), 14.5 (CH_3-OEt); HRMS (CI+, isobutane) calcd for $C_{13}H_{23}O_5$ $[M+H]^+$ 259.1545, found 259.1540 (Δ −2.2 ppm); LRMS (CI+, isobutane) *m/z* (intensity); 259.3 (63%), 201.2 (100%); Anal. calcd for $C_{13}H_{22}O_5$ C 55.03%, H 8.31%, found C 54.95%, H 8.48%.

1,4-Dimethyl (2*R*)-2-hydroxybutanedioate.[217] (325)



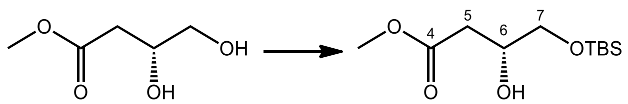
Thionyl chloride (30 mL, 0.41 mol) was added dropwise over 30 minutes to a solution of D-malic acid (25 g, 0.19 mol) in methanol (466 mL) at 0 °C and the mixture was stirred for 18 hours at rt. The volatile material was then removed *in vacuo* and the resulting residue partitioned between CH_2Cl_2 (200 mL) and saturated aqueous $NaHCO_3$ (200 mL). The organic phase was isolated and the aqueous back-extracted with further CH_2Cl_2 (100 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and concentrated to provide the title diester **325** (28 g, 92%) as a pale yellow oil. R_f = 0.48 (EtOAc); $[\alpha]_D^{23}$ +16.7 (c = 0.98, MeOH), [lit. $[\alpha]_D^{25}$ +9.6 (c = 2.3, EtOH)][218]; ν_{max} (liquid film) 3493, 2958, 1730, 1438, 1264, 1212, 1167, 1103 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54-4.47 (1H, m, CH-C6), 3.81 (3H, s, CH_3-MeO), 3.71 (3H, s, CH_3-MeO), 3.22 (1H, d, *J* = 5.6 Hz, OH-C6), 2.87 (1H, dd, *J* = 16.5, 4.4 Hz, CH -C5), 2.79 (1H, dd, *J* = 16.5, 6.1 Hz, CH-C5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5 (C-C4), 170.7 (C-C7), 67.0 (CH-C6), 52.7 (CH-MeO), 51.8 (CH_3-MeO), 38.2 (CH_2-C5); HRMS (CI+, isobutane) calcd for $C_6H_{11}O_5$ $[M+H]^+$ 163.0606, found 163.0603 (Δ −2.1 ppm); LRMS (CI+, isobutane) *m/z* (intensity); 163.2 (100%), 131.2 (24%), 103.2 (30%); Anal. calcd for $C_6H_{10}O_5$ C 44.45%, H 6.22%, found C 44.27%, H 6.28%.

Methyl (3*R*)-3,4-dihydroxybutanoate.[219] (328)



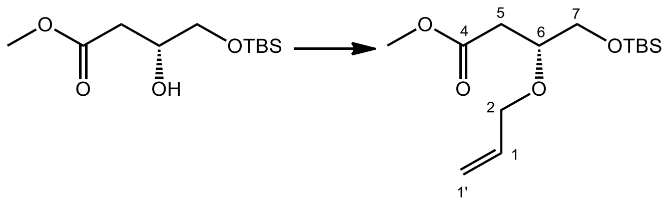
$BH_3 \cdot Me_2S$ (17 mL, 0.18 mol) was added dropwise to a stirred solution of α-hydroxyester **325** (28 g, 0.18 mol) in THF (336 mL) at rt. After complete addition and cessation of gas evolution, the reaction was stirred for 30 minutes. $NaBH_4$ (0.66 g, 18 mmol) was added to the solution in two equal portions at 0 °C, at an interval of five minutes, and the reaction stirred for 3 hours at rt. The reaction was quenched by the addition of methanol (200 mL) and stirred for 10 minutes. The resulting solution was concentrated *in vacuo* and purified by chromatography (EtOAc) to provide the diol **328** (19 g, 83%) as a clear colourless oil. R_f = 0.23 (EtOAc); $[\alpha]_D^{22}$ +13.8 (c = 0.99, $CHCl_3$) [lit. $[\alpha]_D^{20}$ +13.8 (*c* = 2.27, $CHCl_3$)][8]; ν_{max} (liquid film) 3379, 2955, 2886, 1720, 1442, 1165, 1034, 864 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.16–4.09 (1H, m, CH-C6), 3.72 (3H, s, CH_3-MeO), 3.71–3.64 (1H, m, CH-C7), 3.57–3.48 (1H, m, CH-C7), 3.40–3.33 (1H, m, OH-C6), 2.57 (1H, dd, *J* = 16.5, 8.5 Hz, CH-C5), 2.50 (1H, dd, *J* = 16.5, 4.1 Hz, CH-C5), 2.46–2.33 (1H, m, OH-C7); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2 (C-C4), 68.6 (CH-C6), 65.8 (CH_2-C7), 52.1 (CH_3-MeO), 37.5 (CH_2-C5); HRMS (CI+, isobutane) calcd for $C_5H_{11}O_4$ $[M+H]^+$ 135.0657, found 135.0656 (Δ −0.9 ppm); LRMS (CI+, isobutane) *m/z* (intensity); 135.2 (82%), 103.2 (100%); Anal. calcd for $C_5H_{10}O_4$ C 44.77%, H 7.51%, found C 44.45%, H 7.51%.

Methyl (3*R*)-4-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxybutanoate.[219] (329a)



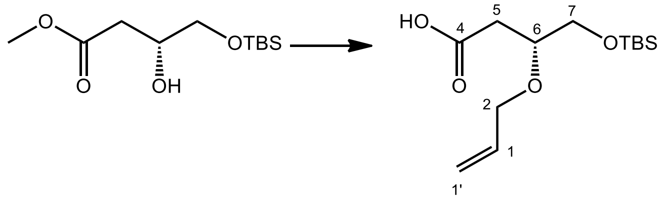
To a stirred solution of the diol **328** (7.59 g, 56.6 mmol) in CH_2Cl_2 (60 mL) at 0 °C were added sequentially *tert*-butyldimethylsilyl chloride (8.96 g, 59.4 mmol), triethylamine (15.8 mL, 113 mmol) and DMAP (1.38 g, 11.3 mmol). The mixture was stirred for 16 h at rt and then diluted with CH_2Cl_2 (40 mL). The reaction was quenched by the addition of 1MHCl (120 mL). The mixture was extracted with CH_2Cl_2 (3 × 75 mL) and the organic phases were combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (pet. ether/EtOAc, 20:1) to provide the silyl ether **329a** (11.4 g, 80%) as a colourless oil. R_f = 0.15 (pet. ether/EtOAc, 9:1); $[\alpha]_D^{23}$ +11.2 (*c* = 1.01, $CHCl_3$), [lit $[\alpha]_D^{23}$ +7.38 (*c* = 1.00, CH_2Cl_2)][219]; ν_{max} (liquid film) 3472, 2932, 2862, 1736, 1250, 1173, 1119, 1065, 833, 779 cm–1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12–4.03 (1H, m, CH-C6) 3.71 (3H, s, CH_3-MeO), 3.63 (1H, dd, *J* = 10.0, 4.8 Hz, CH-C7), 3.57 (1H, dd, *J* = 10.0, 5.7 Hz, CH-C7), 2.85 (1H, d, *J* = 4.9 Hz, OH-C6), 2.54 (1H, dd, *J* = 16.0, 5.2 Hz, CH_2-C5), 2.49 (1H, dd, *J* = 16.0, 7.4 Hz, CH_2-C5), 0.89 (9H, s, CH_3-^{t}BuSi), 0.06 (6H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7 (C-C4), 68.7 (CH-C6), 66.3 (CH_2-C7), 51.9 (CH_3-MeO), 37.9 (CH_2-C5), 26.0 (CH_3-^{t}BuSi), 18.4 (C-^{t}BuSi), −5.3 (CH_3-MeSi), −5.3 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{11}H_{25}O_4Si$ $[M+H]^+$ 249.1522, found 249.1519 (Δ −1.2 ppm); LRMS (CI+, isobutane) *m/z* (intensity) 249.2 (100%). Anal. calcd for $C_{11}H_{24}O_4Si$ C 53.19%, H 9.74%, found C 53.03%,H 9.83%.

Methyl (3*R*)-4-[(*tert*-butyldimethylsilyl)oxy]-3-(prop-2-en-1-yloxy)butanoate. (330a)



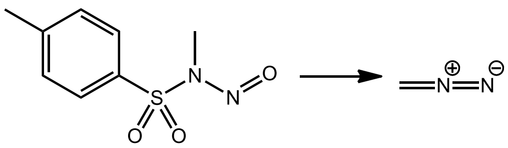
To a solution of the alcohol **329a** (5.02 g, 20.1 mmol) and allyl trichloroacetimidate (8.72 g, 40.3 mmol) in pet. ether (25 mL) at rt was added triflic anhydride (4 drops). After stirring for 5 days the mixture was filtered, concentrated and purified directly by chromatography (pet. ether/EtOAc, 97.5:2.5) to provide the allyl ether **330a** (5.53 g, 95%) as a pale yellow oil. R_f = 0.33 (pet. ether/EtOAc, 9:1); $[\alpha]_D^{23}$ +11.2 (c = 1.01, $CHCl_3$); $\nu_{max.}$ (liquid film) 2932, 2862, 1744, 1250, 1080, 1003, 833, 779, 671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (1H , ddt, *J* = 17.1, 10.4, 5.7 Hz, CH_2-C1), 5.25 (1H, dq, *J* = 17.1, 1.5 Hz, CH-C1’ *trans*), 5.14 (1H, dq, *J* = 10.4, 1.5 Hz, CH-C1’ *cis*), 4.14–4.03 (2H, m, CH_2-C2), 3.90–3.83 (1H, m, CH-C6), 3.71 (1H, dd, *J* = 10.4 Hz, 9.5 Hz, CH-C7), 3.68 (3H, s, CH_3-MeO), 3.54 (1H, dd, *J* = 10.4 Hz, 6.1 Hz, CH-C7), 2.61 (1H, dd, *J* = 15.6, 4.8 Hz, CH-C5), 2.48 (1H, dd, *J* = 15.6, 7.8 Hz, CH-C5), 0.89 (9H, s, CH_3-^{t}BuSi), 0.05 (6H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3 (C-C4), 135.2 (CH-C1), 117.0 (CH_2-C1’), 76.5 (CH-C6), 71.6 (CH_2-C2), 64.8 (CH_2-C7), 51.7 (CH_3-MeO), 37.5 (CH_2-C5), 26.0 (CH_3-^{t}BuSi), 18.4 (C-^{t}BuSi), −5.3 (CH_3-MeSi), −5.3 (CH_3-MeSi); Anal. calcd for $C_{14}H_{28}O_4Si$ C 58.29%, H 9.78%, found C 58.19%, H 9.71%.

(3*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3-(prop-2-en-1-yloxy)butanoic acid. (331a)



To a stirred solution of the ester **330a** (26.8 g, 92.9 mmol) in methanol (500 mL) at rt was added a 1 M aqueous solution of KOH (112 ml, 112 mmol). The solution was stirred for 5 h at rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (300 mL) and adjusted to pH 2 with 1 M aqueous HCl. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 250 mL). The organic phases were combined, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (pet. ether/EtOAc, 4:1) to provide the desired carboxylic acid **331a** (19.6 g, 77%) as a pale yellow oil. R_f = 0.27 (pet. ether/EtOAc, 1:1); $[\alpha]_D^{24}$ +20.4 (c = 1.02, $CHCl_3$); ν_{max} (liquid film) 3086, 2862, 17482, 1713, 1466, 1257, 1080, 833, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.02 (1H, br s, CO_2H), 5.89 (1H, ddt, *J* = 17.2, 10.4, 5.7 Hz, CH-C1), 5.27 (1H, qd, *J* = 17.2, 1.8 Hz, CH-C1'*trans*), 5.17 (1H, qd, J = 10.4, 1.8 Hz, CH-C1'*cis*), 4.17–4.06 (2H, m, CH_2-C2), 3.89–3.82 (1H, m, CH-C6), 3.73 (1H, dd, *J* = 10.4, 5.0 Hz, CH-C7), 3.58 (1H, dd, *J* = 10.4, 6.0 Hz, CH-C7), 2.68 (1H, dd, *J* = 15.9, 5.0 Hz, CH-C5), 2.55 (1H, dd, *J* = 15.9, 7.4 Hz, CH-C5), 0.89 (9H, s, CH_3-^{t}BuSi), 0.06 (6H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6 (C-C4), 134.8 (CH-C1), 117.4 (CH_2-C1'), 76.2 (CH-C6), 71.6 (CH_2-C2), 64.7 (CH_2-C7), 37.4 (CH_2-C5), 26.0 (CH_3-^{t}BuSi), 18.4 (C-^{t}BuSi), −5.3 (CH_3-MeSi), −5.3 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{13}H_{27}O_4Si$ $[M+H]^+$ 275.1678, found 275.1681 (Δ +0.7 ppm); LRMS (CI+, isobutane) *m*/*z* (intensity) 275.3 (6%), 143.2 (100%). Anal. calcd for $C_{13}H_{26}O_4Si$ C 56.90%, H 9.55%, found C 57.03%, H 9.64%.

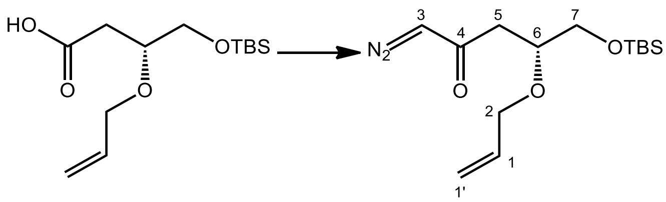
Diazomethane (138)



Note - Diazomethane was generated from Diazald® within a Sigma Aldrich Daizald kit with fire-polished Clear-Seal® joints. The kit was inspected for cracks and/or chips prior to each use. Each distillation was conducted behind a blast shield.

Solid KOH (13.5 g, 241 mmol) was dissolved in water (52 mL) to which was added Et_2O (67 mL) and 2-ethoxyethanol (67 mL). The flask was warmed to 70 ˚C in a water bath and a solution of Diazald (17.2 g, 80.2 mmol) in Et_2O (134 mL) was added dropwise over 30 minutes to the basic solution. The ethereal solution of diazomethane was distilled into a conical flask pre-chilled in an ice-bath. Upon completion of the diazomethane distillation, the solution was stored at 0 ˚C under an argon atmosphere until required.

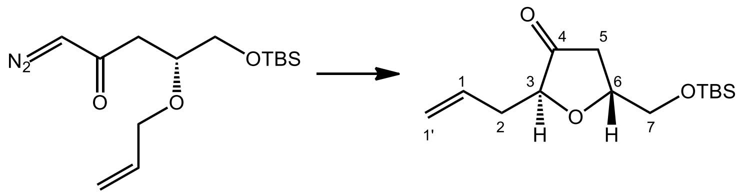
(4*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1-diazo-4-(prop-2-en-1-yloxy)pentan-2-one. (326a)



The reaction sequence was performed in duplicate and material was combined for work-up and purification. To a stirred solution of the carboxylic acid **331a** (2.5 g, 9.1 mmol) in ether (90 mL), at rt, was added triethylamine (1.3 ml, 9.1 mmol) and isobutylchloroformate (1.3 ml, 9.6 mmol). The reaction mixture was stirred vigorously for 2 h then filtered, to remove precipitates, and added to a freshly distilled ethereal solution of diazomethane (91.1 mmol) at 0 °C. The resultant solution was allowed to stir for 16 h at rt and quenched by the addition of acetic acid (4 mL). The solution was added carefully to a solution of saturated aqueous $NaHCO_3$ (200 mL) and the ether layer isolated. The aqueous phase was back-extracted with ether (100 mL) and the organic phases were combined, dried ($MgSO_4$) and concentrated. The residue purified by chromatography (pet. ether/EtOAc, 20:1 to 9:1) to provide the diazo ketone **326a** (4.7 g, 86%); $[\alpha]_D^{25}$ +39.6 (c = 1.02, $CHCl_3$); ν_{max} (liquid film) 2955, 2930, 2857, 2101, 1640, 1362, 1346, 1111, 1091, 833, 814, 775 cm−1; ^1H NMR(400 MHz, $CDCl_3$) δ 5.88 (1H, ddt, *J* = 17.2, 10.4, 5.7 Hz, CH-C1), 5.34 (1H, br s, CH-C3), 5.25 (1H, dq, *J* = 17.2, 1.4 Hz, CH-

C1' *trans*), 5.15 (1H, dq, *J* = 10.4, 1.4 Hz, CH-C1' *cis*), 4.12 (1H, ddt, *J* = 12.6, 5.7, 1.4 Hz, CH-C2), 4.06 (1H, ddt, *J* = 12.6, 5.7, 1.4 Hz, CH-C2), 3.92–3.84 (1H, m, CH-C6), 3.68 (1H, dd, *J* = 10.5, 5.1 Hz, CH-C7), 3.58 (1H, dd, *J* = 10.5, 5.5 Hz, CH-C7), 2.63–2.42 (2H, m, CH_2-C5), 0.89 (9H, s, CH_3-^{t}BuSi), 0.05 (6H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3 (C-C4), 135.1 (CH-C1), 117.0 (CH_2-C1'), 76.8 (CH-C6), 71.6 (CH_2-C2), 64.9 (CH_2-C7), 55.5 (CH-C3), 43.7 (CH_2-C5), 26.0 (CH_3-^{t}BuSi), 18.4 (C-^{t}BuSi), −5.2 (CH_3-MeSi); LRMS (FAB) *m/z* (intensity) 299.0 (100%). Anal. calcd for $C_{14}H_{26}N_2O_3Si$ C 56.34%, H 8.78%, N 9.39% found C 56.29%, H 8.80%, N 9.41%.

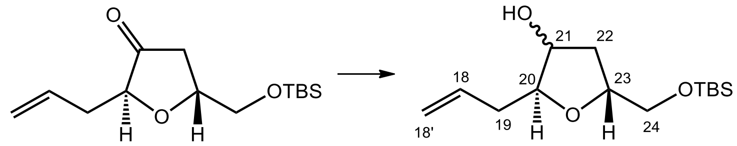
(2*S*,5*R*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-2-(prop-2-en-1-yl)tetrahydrofuran-3-one. (327a)



Diazoketone **326a** (1.9 g, 6.4 mmol) in THF (160 mL) was added dropwise to a stirred solution of $Cu(acac)_2$ (0.33 g, 1.3 mmol) in THF (160 mL) at reflux. Following complete addition, the solution was heated for a further 40 minutes and cooled to rt. Concentration *in vacuo* afforded a residue which was purified directly by chromatography (pet. ether/EtOAc, 20:1) to provide the furanone **327a** (1.64 g, 95%, *dr*>20:1) as a colourless oil. R_f = 0.59 (pet. ether/EtOAc, 4:1); $[\alpha]_D^{21}$ −70.2 (c = 1.02, $CHCl_3$); ν_{max} (liquid film) 2932, 2862, 2100, 1759, 1466, 1404, 1257, 1087, 833, 779 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, CH-C1), 5.26–5.02 (2H, m, CH_2-C1'), 4.50–4.44 (1H, m, CH-C6), 4.13 (1H, dd, *J* = 7.2, 4.5 Hz, CH-C3), 3.91 (1H, dd, *J* = 10.9, 3.0 Hz, CH-C7), 3.66 (1H, dd, *J* = 10.9, 2.6 Hz, CH-C7), 2.56–2.42 (3H, m, CH-C2 and CH_2-C5), 2.32–2.23 (1H, m, CH-C2), 0.86 (9H, s, CH_3-^{t}BuSi), 0.05 (3H, s, CH_3-MeSi), 0.04 (3H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.5 (C-C4), 133.3 (CH-C1), 118.1 (CH_2-C1'), 79.7 (CH-C3), 75.8 (CH-C6), 66.8 (CH_2-C7), 38.3 (CH_2-C2), 36.4 (CH_2-C5), 25.8 (CH_3-^{t}BuSi), 18.2 (C-^{t}BuSi), −5.5 (CH_3-MeSi), −5.6 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{14}H_{27}O_3Si$ $[M+H]^+$ 271.1729, found 271.1731 (Δ +0.4 ppm); LRMS (CI+, isobutane) *m/z* (intensity) 271.4 (100%). Anal. calcd for $C_{14}H_{26}O_3Si$ C 62.18%, H 9.69% found C 62.20%, H 9.81%.

(2*S*,3*S*,5*R*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-2-(prop-2-en-1-yl) tetrahydrofuran-3-ol. (341a)

(2*S*,3*R*,5*R*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-2-(prop-2-en-1-yl) tetrahydrofuran-3-ol (341b)

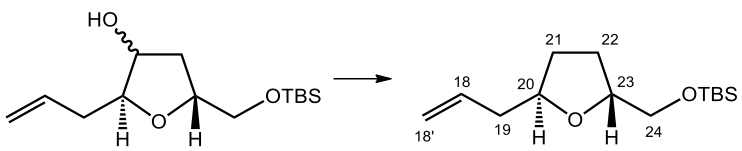


Sodium borohydride (365 mg, 9.66 mmol) was added to a solution of ketone **327a** (2.5 g, 9.2 mmol) in ethanol (157 mL) at rt. After stirring for 15 minutes the volatiles were removed *in vacuo* and the residue was partitioned between CH_2Cl_2 and H_2O (100 mL of each). The resulting diastereomeric mixture of the alcohols was extracted with CH_2Cl_2 (2 × 100 mL) and the combined extracts were washed with brine. The organic phase was dried ($MgSO_4$) and concentrated to give a colourless oil. The crude material was used in the subsequent step without purification and a small sample of the diastereomeric mixture of alcohols (*dr* 4:1) was purified (pet. ether/EtOAc 95:5 to 9:1) for characterisation purposes.

341a (C20-C21-*syn*).[220] R_f = 0.27 (pet. ether/EtOAc, 20:1); $[\alpha]_D^{22}$ +6.4 (c = 1.12, $CHCl_3$); ν_{max} (liquid film) 3409, 2953, 2929, 2897, 2857, 1254, 1085, 833, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (1H, dddd, *J* = 17.2, 10.2, 7.2, 6.6 Hz, CH-C18), 5.17 (1H, dq, *J* = 17.2, 1.6 Hz, CH-C18' *trans*), 5.10–5.06 (1H, m, CH-C18' *cis*), 4.32–4.24 (2H, m, CH-C23 and CH-C21), 3.89 (1H, td, *J* = 7.1, 2.8 Hz, CH-C20), 3.68 (1H, dd, *J* = 10.8, 4.3 Hz, CH-C24), 3.61 (1H, dd, *J* = 10.8, 4.1 Hz, CH-C24), 2.50–2.34 (2H, m, CH_2-C19), 2.08 (1H, ddd, *J* = 13.4, 8.6, 4.7 Hz, CH-C22), 1.99 (1H, ddd, *J* = 13.4, 7.0, 1.1 Hz, CH-C22), 1.57 (1H, d, *J* = 6.0 Hz, OH-C21), 0.89 (9H, s, CH_3-^{t}BuSi), 0.05 (6H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9 (CH-C18), 117.1 (CH_2-C18'), 82.1 (CH-C20), 77.6 (CH-C23), 73.5 (CH-C21), 65.7 (CH_2-C24), 37.2 (CH_2-C22), 33.9 (CH_2-C19), 26.1 (CH_3-^{t}BuSi), 18.5 (C-^{t}BuSi), −5.2 (CH_3-MeSi), −5.2 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{14}H_{29}O_3Si$ $[M+H]^+$ 273.1886, found 273.1887 (Δ +0.3 ppm); LRMS (CI+, isobutane) *m/z* (intensity) 273.4 (100%). Anal. calcd for $C_{14}H_{28}O_3Si$ C 61.72%, H 10.36% found C 61.32%, H 10.55%.

341b (C20-C21-*anti*).R_f = 0.31 (pet. ether/EtOAc, 20:1); $[\alpha]_D^{22}$ −40.7 (c = 1.06, $CHCl_3$); ν_{max} (liquid film) 3445, 2953, 2929,2857, 1472, 1254, 1088, 832, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (1H, ddt, *J* = 17.2, 10.3, 7.0 Hz, CH-C18), 5.12–5.05 (2H, m, CH_2-C18'), 4.29–4.24 (1H, m, CH-C23), 4.23 (1H, d, *J* = 10.9 Hz, OH-C21), 4.10-4.01 (1H, m, CH-C20), 3.99 (1H, ap dd, J = 10.9, 5.8 Hz, CH-C21), 3.86 (1H, dd, J = 10.9, 2.3 Hz, CH-C24), 3.53 (1H, dd, J = 10.9, 1.8 Hz, CH-C24), 2.36 (1H, ddd, J = 14.1, 9.8, 5.8 Hz, CH-C22), 2.20–2.05 (2H, m, CH_2-C19), 1.86 (1H, dd, J = 14.1, 2.6 Hz, CH-C22), 0.92 (9H, s, CH_3-^{t}BuSi), 0.12 (6H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6 (CH-C18), 117.3 (CH_2-C18'), 87.7 (CH-C20), 78.1 (CH-C23), 74.6 (CH-C21), 66.1 (CH_2-C24), 38.4 (CH_2-C19), 35.6 (CH_2-C22), 26.1 (CH_3-^{t}BuSi), 18.7 (C-^{t}BuSi), −5.3 (CH_3-MeSi), −5.4 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{14}H_{29}O_3Si$ $[M+H]^+$ 273.1886, found 273.1888, (Δ +0.9 ppm); LRMS (CI+, isobutane) m/z (intensity) 273.4 (100%). Anal. calcd for $C_{14}H_{28}O_3Si$ C 61.72%, H 10.36% found C 61.62%, H 10.51%.

***tert*-Butyldimethyl{[(2*R*,5*R*)-5-(prop-2-en-1-yl)tetrahydrofuran-2-yl]methoxy}silane. (343)**

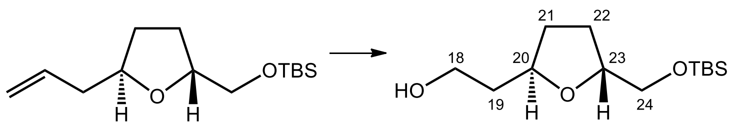


A diastereomeric mixture of the alcohols **341** (1.95 g, 7.16 mmol, *dr* 70:30) in THF (2 mL) was added dropwise to a stirred suspension of NaH (1.51 g of a 60% dispersion in mineral oil, 37.8 mmol) in THF (143 mL) at 55 °C. Following complete addition, the mixture was heated at reflux for 30 minutes and carbon disulfide (4.30 mL, 71.6 mmol) was added. The mixture was heated for a further 30 minutes and iodomethane (4.52 mL, 71.6 mmol) was added dropwise. Heating was continued for an additional 2 h and the mixture was then cooled to rt and the reaction was quenched by slow addition of H_2O (100 mL). The organic component was extracted with ether (3 × 120 mL) and the extracts were washed with brine (100 mL) then dried ($MgSO_4$) and concentrated. The residual crude xanthate was used without further purification.

The crude xanthate was dissolved in toluene (243 mL) and 1,1′-azobis(cyclohexanecarbonitrile) (1.38 g, 5.66 mmol) and n-Bu_3SnH (5.80 mL, 21.5 mmol) were added sequentially. The mixture was placed in a pre-heated oil bath at 110 °C and and the mixture was heated at reflux for 2 h. The mixture was cooled to rt and concentrated *in vacuo*. The resultant dark residual material was purified directly by chromatography (pet. ether/EtOAc, 99:1) to give the tetrahydrofuran **343** contaminated with a malodorous impurity. A small amount of material was purified for characterization purposes and the rest was used in the subsequent step without further purification. R_f = 0.46 (pet. ether/EtOAc, 9:1); $[\alpha]_D^{21}$ −10.4 (c = 1.00, $CHCl_3$); ν_{max} (liquid film) 2955, 2928, 2857, 1471, 1252, 1084, 833, 775, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$)

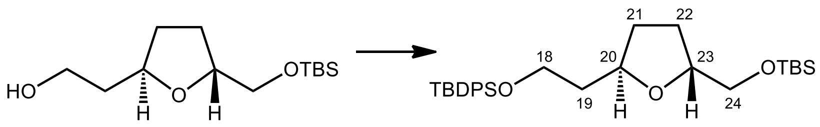
δ 5.81 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz, CH-C18), 5.12–5.01 (2H, m, CH_2-C18'), 4.06 (1H, tt, *J* = 6.7, 5.0 Hz, CH-C23), 4.01 (1H, ddt, *J* = 7.7, 6.4, 6.1 Hz, CH-C20), 3.63 (1H, dd, *J* = 10.5, 4.6 Hz, CH-C24), 3.55 (1H, dd, *J* = 10.5, 5.4 Hz, CH-C24), 2.39–2.30 (1H, m, CH-C19), 2.25–2.16 (1H, m, CH-C19), 2.04–1.93 (2H, m, CH-C21 and CH-C22), 1.80–1.68 (1H, m, CH-C22), 1.62–1.51 (1H, m, CH-C21), 0.89 (9H, s, CH_3-^{t}BuSi), 0.05 (6H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3 (CH-C18), 116.8 (CH_2-C18'), 79.4 (CH-C23), 78.9 (CH-C20), 66.1 (CH_2-C24), 40.4 (CH_2-C19), 31.4 (CH_2-C21), 28.2 (CH_2-C22), 26.1 (CH_3-^{t}BuSi), 18.5 (C-^{t}BuSi), −5.1 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{14}H_{29}O_2Si$ $[M+H]^+$ 257.1937 found 257.1934 (Δ −1.00 ppm); LRMS (CI+, isobutane) *m/z* (intensity) 257.4 (100%); Anal. calcd for $C_{14}H_{28}O_2Si$ C 65.57%, H 11.00% found C 65.81%, H 11.05%.

2-[(2*R*,5*R*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}tetrahydrofuran-2-yl]ethan-1-ol. (344)



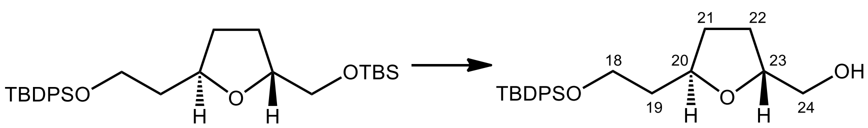
Ozone was bubbled through a solution of the alkene **343** dissolved in a mixture of methanol and CH_2Cl_2 (50% v/v, 120 mL) until the solution turned a purple/blue color. The solution was purged with argon for 15 minutes to dissipate the colour, warmed to 0 °C and sodium borohydride (1.60 g, 43.0 mmol) was then added slowly in small portions over 10 minutes. The mixture was then stirred for 1 h and the reaction was quenched by the addition of solid NH_4Cl (4 g). The precipitated solids were removed by vacuum filtration and the solvent was evaporated to give an opaque white oil that was then purified by chromatography (pet. ether/EtOAc, 4:1 to 1:1) to afford alcohol **344** (1.36 g, 73% over 4 steps) as a colourless oil. R_f = 0.39 (pet. ether/EtOAc, 1/1); $[\alpha]_D^{23}$ −2.9 (c = 0.99, $CHCl_3$); ν_{max} (liquid film) 3440, 2953, 2930, 2857, 1469, 1253, 1079, 834, 775, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19–4.06 (2H, m, CH-C20 and CH-C23), 3.84–3.76 (2H, m, CH_2-C18), 3.59 (2H, d, *J* = 4.8 Hz, CH_2-C24), 2.96 (1H, dd, *J* = 6.6, 4.3 Hz, OH-C18), 2.11–2.02 (1H, m, CH-C21), 2.02–1.92 (1H, m, CH-C22), 1.79–1.69 (3H, m, CH_2-C19 and CH-C22), 1.63–1.53 (1H, m, CH-C21), 0.89 (9H, s, CH_3-^{t}BuSi), 0.06 (6H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.1 (CH-C23), 79.6 (CH-C20), 65.9 (CH_2-C24), 62.1 (CH_2-C18), 37.4 (CH_2-C19), 32.4 (CH_2-C21), 27.8 (CH_2-C22), 26.1 (CH_3-^{t}BuSi), 18.5 (C-^{t}BuSi), −5.2 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{13}H_{29}O_3Si$ $[M+H]^+$ 261.1886 found 261.1883, (Δ −1.20 ppm); LRMS (CI+, isobutane) *m/z* (intensity) 261.4 (100%), 203.3 (22%), 129.3 (14%); Anal. calcd for $C_{13}H_{28}O_3Si$ C 59.95%, H 10.84% found C 59.99%, H 10.89%.

***tert*-Butyl({[(2*R*,5*R*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]methoxy})dimethylsilane. (347)**



A solution of alcohol **344** (0.26 g, 1.0 mmol), *tert*-butyldiphenylsilyl chloride (0.29 mL, 1.1 mmol), Et_3N (0.21 ml, 1.5 mmol) and DMAP (25 mg, 0.20 mmol) in CH_2Cl_2 (10 mL) was stirred for 17 h at rt. The reaction was quenched by the addition of 1 M aqueous HCl (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were then dried ($MgSO_4$) and concentrated. Chromatographic purification of the residual material by chromatography (pet. ether/EtOAc, 99:1) afforded the desired silyl ether **347** (466 mg, 92%) as a colourless oil. R_f = 0.47 (pet. ether/EtOAc, 3:1); $[\alpha]_D^{21}$ −1.9 (c = 0.98, $CHCl_3$); ν_{max} (liquid film) 2955, 2929, 2856, 1471, 1256, 1082, 1006, 835, 775, 736, 699, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (4H, m, CH-PhSi), 7.44–7.34 (6H, m, CH-PhSi), 4.13–4.06 (1H, m, CH-C20), 4.04 (1H, tt, *J* = 6.9, 5.0 Hz, CH-C23), 3.80–3.70 (2H, m, CH_2-C18), 3.62 (1H, dd, *J* = 10.5, 5.0 Hz, 1H, CH-C24), 3.53 (1H, dd, *J* = 10.5, 5.0 Hz, CH-C24), 2.05–1.82 (3H, m, CH-C21, CH-C22 and CH-C19), 1.76–1.63 (2H, m, CH-C19 and CH-C22), 1.55–1.45 (1H, m, CH-C21), 1.07 (9H, s, CH_3-^{t}BuSi), 0.92 (9H, s, CH_3-^{t}BuSi), 0.08 (6H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CH-PhSi), 134.1 (C-PhSi), 134.1 (C-PhSi), 129.7 (CH-PhSi), 127.7 (CH-PhSi), 79.0 (CH-C23), 76.8 (CH-C20), 66.2 (CH_2-C24), 61.6 (CH_2-C18), 38.8 (CH_2-C19), 32.1 (CH_2-C21), 28.3 (CH_2-C22), 27.0 (CH_3-^{t}BuSi), 26.1 (CH_3-^{t}BuSi), 19.3 (C-^{t}BuSi), 18.5 (C-^{t}BuSi), −5.1 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{29}H_{47}O_3Si_2$ $[M+H]^+$ 499.3063 found 499.3062 (Δ −0.5 ppm); LRMS (CI+, isobutane) *m*/*z* (intensity) 499.6 (68%), 421.5 (100%).

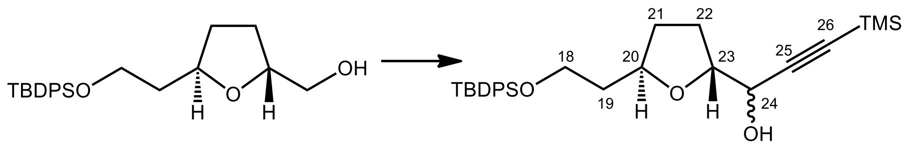
[(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]methanol. (348)



To a solution of the bis silyl ether **347** (0.10 g, 0.20 mmol) in a mixture of methanol and CH_2Cl_2 (2 ml, 50% v/v) at 0 °C was added camphor sulfonic acid (14 mg, 0.06 mmol). The mixture was stirred for 2 h and the reaction was quenched by the addition of triethylamine (0.01 mL). The mixture was concentrated *in vacuo* and the residual material was purified by chromatography (pet. ether/EtOAc, 3:1) to provide the alcohol

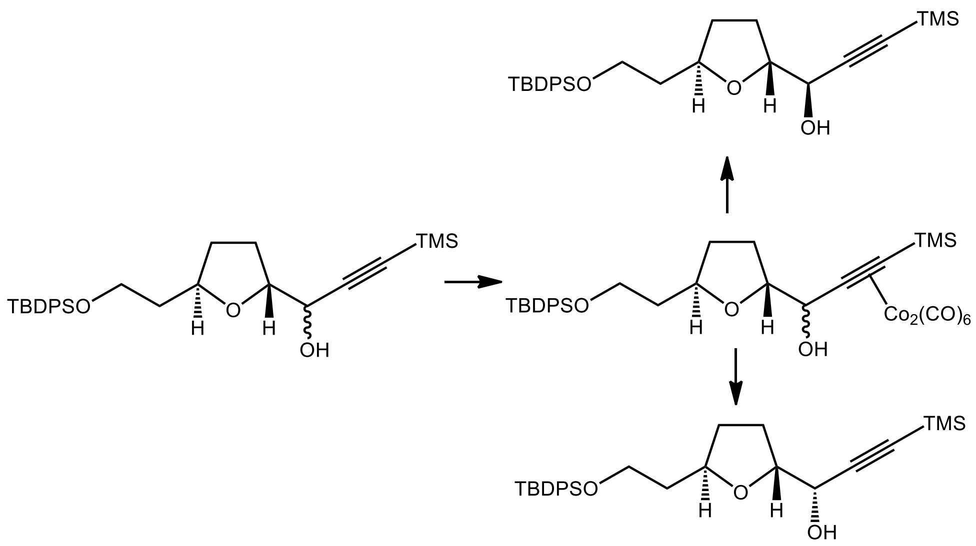
348 (66 mg, 86%) as a colourless oil. R_f = 0.35 (pet. ether/EtOAc, 9:1); $[\alpha]_D^{22}$ −10.9 (c = 0.96, $CHCl_3$); ν_{max} (liquid film) 3433, 3055, 2931, 2862, 1466, 1389, 1265, 1088, 818, 702, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77–7.61 (4H, m, CH-PhSi), 7.49–7.31 (6H, m, CH-PhSi), 4.18–4.09 (1H, m, CH-C20), 4.06 (1H, qd, *J* = 6.9, 3.2 Hz, CH-C23), 3.84–3.72 (2H, m, CH_2-C18), 3.66–3.57 (1H, m, CH-C24), 3.51–3.43 (1H, m, CH-C24), 2.08–1.50 (7H, m, CH_2-C19, CH_2-C21, CH_2-C22 and OH-C24), 1.06 (9H, s, CH_3-^{t}BuSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CH-PhSi), 134.1 (C-PhSi), 134.0 (C-PhSi), 129.7 (CH-PhSi), 127.7 (CH-PhSi), 78.8 (CH-C23), 76.5 (CH-C20), 65.2 (CH_2-C24), 61.4 (CH_2-C18), 38.6 (CH_2-C19), 32.4 (CH_2-C21), 27.6 (CH_2-C22), 27.0 (CH_3-^{t}BuSi), 19.3 (C-^{t}BuSi); HRMS (CI+, isobutane) calcd for $C_{23}H_{33}O_3Si$ $[M+H]^+$ 385.2199 found 385.2200 (Δ +0.3 ppm); LRMS (CI+, isobutane) *m*/*z* (intensity) 385.4 (76%), 327.3 (27%), 307.4 (100%), 229.3 (40%).

1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]-3-(trimethylsilyl)prop-2-yn-1-ol. (367)



Alcohol **348** (50 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (4 mL) and the solution was treated with a single portion of Dess-Martin periodinane (79 mg, 0.19 mmol) for 1 h at rt. The volatiles were removed *in vacuo* and the resulting residue suspended in ether (5 mL). The precipitates were removed by filtration and the mixture was concentrated. The crude aldehyde **362** was dissolved in an ethereal solution of magnesium bromide, prepared by the dropwise addition of 1,2-dibromoethane (0.10 mL, 1.1 mmol) to magnesium turnings (27 mg, 1.1 mmol) in ether (0.8 mL) at rt. A solution of MeLi (0.35 mL of a 1.6 M solution in THF, 0.56 mmol) was cooled to 0 °C in an ice bath and ethynyltrimethylsilane (0.09 mL, 0.6 mmol) was then added dropwise. The mixture was cooled to −30 °C and a second batch of ethereal magnesium bromide solution (prepared as before) was added and the mixture stirred for 5 minutes. The magnesium-aldehyde complex was added to the solution of the metallated alkyne at −78 °C and the mixture was stirred for an additional 30 minutes. The mixture was allowed to slowly warm to rt over 45 minutes and the reaction was quenched by addition of saturated aqueous NH_4Cl solution (7 mL). The organics were extracted with ether (3 × 5 mL), dried ($MgSO_4$) and concentrated. Purification of the residual material by chromatography afforded a mixture (70:30) of the diastereomeric alcohols **367ab** (48 mg, 71%) as a colourless liquid.

Diastereomer separation by formation of cobalt hexacarbonyl complexes.



A mixture of propargylic alcohols (0.21 g, 0.44 mmol, *dr* 1:1) and dicobalt octacarbonyl (0.18 g, 0.52 mmol) in CH_2Cl_2 (5 mL) was allowed to stir for 1.5 h at ambient temperature. The volatiles were removed *in vacuo* and the resulting brown residue was purified directly by chromatography (pet. ether/EtOAc, 97.5:2.5) to provide separate cobalt hexacarbonyl complexes of the diastereomeric propargylic alcohols. The complexes, thus formed, were dissolved individually in CH_2Cl_2 (5 mL) and treated with NMO (615 mg, 5.25 mmol). After stirring for 1 h at rt the resulting purple mixtures were concentrated and purified directly by chromatography (pet. ether/EtOAc, 3:1) to afford the alcohols **363a** (92 mg, 43%) and **363b** (87 mg, 42%) as colourless oils.

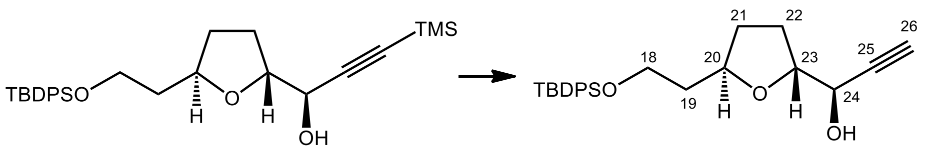
(1*R*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]-3-(trimethylsilyl)prop-2-yn-1-ol. (367a)

R_f = 0.21 (pet. ether/EtOAc, 9:1); $[\alpha]_D^{24}$ −53.7 (c = 2.20, $CHCl_3$); ν_{max} (liquid film) 3410, 3070, 2955, 2936, 2889, 2862, 1465, 1427, 1389, 1249, 1103, 1080, 845, 698, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (4H, m, CH-PhSi), 7.45–7.35 (6H, m, CH-PhSi), 4.20–4.10 (2H, m, CH-C20 and CH-C24), 4.00 (1H, ap q, *J* = 6.8 Hz, CH-C23), 3.82–3.71 (2H, m, CH_2-C18), 2.44 (1H, d, *J* = 3.5 Hz, OH-C24), 2.13–2.00 (2H, m, CH-C21 and CH-C22), 1.90–1.68 (3H, m, CH_2-C19 and CH-C22), 1.62–1.52 (1H, m, CH-C21), 1.05 (9H, s, CH_3-^{t}BuSi), 0.17 (9H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CH-PhSi), 134.0 (C-PhSi), 129.8 (CH-PhSi), 127.8 (CH-PhSi), 103.5 (C-C25), 90.7 (C-C26), 81.7 (CH-C23), 77.1 (CH-C20), 66.2 (CH-C24), 61.3 (CH_2-C18), 38.5 (CH_2-C19), 32.1 (CH_2-C21), 28.3 (CH_2-C22), 27.0 (CH_3-^{t}BuSi), 19.4 (C-^{t}BuSi), 0.0 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{28}H_{41}O_3Si_2$ $[M+H]^+$ 481.2594, found 481.2592 (Δ −0.4 ppm); LRMS (CI+, isobutane) *m*/*z* (intensity) 481.5 (94%), 403.4 (100%).

(1*S*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]-3-(trimethylsilyl)prop-2-yn-1-ol. (367b)

R_f = 0.22 (pet. ether/EtOAc, 9:1); $[\alpha]_D^{26}$ +14.8 (c = 2.20, $CHCl_3$); ν_{max} (liquid film) 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 7.70–7.65 (4H, m, CH-PhSi), 7.45–7.36 (6H, m, CH-PhSi), 4.41 (1H, dd, *J* = 5.9, 3.3 Hz, CH-C24), 4.27 (1H, tt, *J* = 7.7, 5.8 Hz, CH-C20), 4.09 (1H, td, *J* = 7.4, 3.3 Hz, CH-C23), 3.81–3.72 (2H, m, CH_2-C18), 2.34 (1H, dd, *J* = 5.9, 1.3 Hz, OH-C24), 2.12 (1H, dq, *J* = 11.7, 5.8 Hz, CH-C21), 2.04–1.97 (2H, m, CH_2-C22), 1.84 (1H, ddt, *J* = 13.2, 7.9, 5.7 Hz, CH-C19), 1.72 (1H, dq, *J* = 13.2, 6.6 Hz, CH-C19), 1.62-1.53 (1H, m, CH-C21), 1.05 (9H, s, CH_3-^{t}BuSi), 0.16 (9H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CH-PhSi), 134.0 (C-PhSi), 134.0 (C-PhSi), 129.7 (CH-PhSi), 127.8 (CH-PhSi), 103.7 (C-C25), 90.9 (C-C26), 80.7 (CH-C23), 78.3 (CH-C20), 65.1 (CH-C24), 61.4 (CH_2-C18), 38.8 (CH_2-C19), 32.4 (CH_2-C21), 27.0 (CH_3-^{t}BuSi), 26.7 (CH_2-C22), 19.3 (C-^{t}BuSi), 0.0 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{28}H_{41}O_3Si_2$ $[M+H]^+$ 481.2594 found 481.2593, (Δ −0.2 ppm); LRMS (CI+, isobutane) *m/z* (intensity) 481.5 (93%), 403.4 (100%).

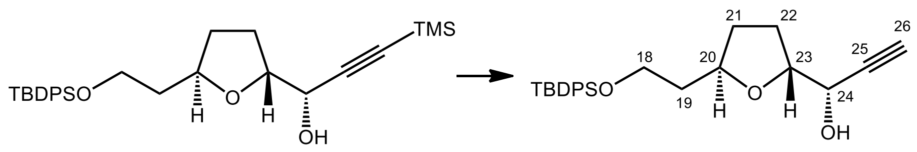
(1*R*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl} tetrahydrofuran -2-yl]prop-2-yn-1-ol. (378a)



To a stirred solution of the TMS protected alkyne **367a** (600 mg, 1.25 mmol) in wet methanol (34 mL) was added solid K_2CO_3 (431 mg, 3.12 mmol). The mixture was stirred for 2 h at rt after which time the volatiles were removed *in vacuo* and residual material was partitioned between CH_2Cl_2 (20 mL) and saturated NH_4Cl solution (20 mL). The organic phase was isolated and the aqueous phase extracted with further CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and filtered. Removal of solvent gave a residue which was purified by chromatography (pet. ether/EtOAc, 3:1) to afford the alkyne **378a** (499 mg, 98%) as a colourless oil. R_f = 0.26 (pet. ether/EtOAc, 3:1); $[\alpha]_D^{26}$ −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 (400 MHz, $CDCl_3$) δ 7.69–7.64 (4H, m, CH-PhSi), 7.46–7.35 (6H, m,CH- PhSi), 4.21– 4.12 (2H, m, CH-C20 and CH-C24), 4.04 (1H, ap q, *J* = 6.9 Hz, CH-C23), 3.82–3.71 (2H, m, CH_2-C18), 2.48 (1H, br d, *J* = 4.2

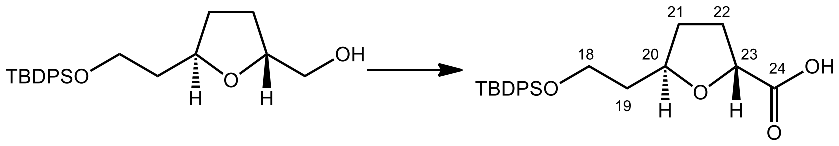
Hz, OH-C24), 2.42 (1H, d, *J* = 2.2 Hz, CH-C26), 2.14–2.01 (2H, m, CH-C21 and CH-C22), 1.90–1.68 (3H, m, CH_2-C19 and CH-C22), 1.63–1.52 (1H, m, CH-C21), 1.05 (9H, s, CH_3-^{t}BuSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CH-PhSi), 134.0 (C-PhSi), 133.9 (C-PhSi), 129.8 (CH-PhSi), 127.8 (CH-PhSi), 82.1 (C-C25), 81.4 (CH-C23), 77.2 (CH-C20), 73.8 (C-C26), 65.4 (CH-C24), 61.2 (CH_2-C18), 38.4 (CH_2 –C19), 32.1 (CH_2-C21), 28.2 (CH_2-C22), 27.0 (CH_3-^{t}BuSi), 19.3 (C-^{t}BuSi); HRMS (CI+, isobutane) $[M+H]^+$ calcd for $C_{25}H_{33}O_3Si$ 409.2199 found 409.2200 (Δ +0.3 ppm); LRMS (CI+, isobutane) *m/z* (intensity) 409.4 (100%), 383.4 (54%), 331.4 (66%), 305.4 (31%), 253.3 (22%).

(1*S*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]prop-2-yn-1-ol. (378b)



The procedure used to prepare **378a** was used to provide **378b** in 88% yield. R_f = 0.26 (pet.ether/EtOAc, 3:1); $[\alpha]_D^{25}$ +1.0 (c = 1.75, $CHCl_3$); ν_{max} (liquid film) 3401, 3306, 2957, 2931, 2857, 1427, 1085, 823 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.67 (4H, m, CH-PhSi), 7.48–7.37 (6H, m, CH-PhSi), 4.42 (1H, ddd, *J* = 6.2, 3.5, 2.3 Hz, CH-C24), 4.35-4.27 (1H, m, CH-C20), 4.10 (1H, td, *J* = 7.4, 3.5 Hz, CH-C23), 3.84–3.73 (2H, m, CH_2-C18), 2.40 (1H, d, *J* = 2.2 Hz, CH-C26), 2.32 (1H, d, *J* = 6.2 Hz, OH-C24), 2.17–2.08 (1H, m, CH-C21), 2.07–1.97 (2H, m, CH_2-C21 and CH-C22), 1.90–1.81 (1H, m, CH-C19), 1.79-1.70 (1H, m, CH-C19), 1.64–1.53 (1H, m, CH-C22), 1.05 (9H, s, CH_3-^{t}BuSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CH-PhSi), 134.0 (C-PhSi), 134.0 (C-PhSi), 129.7 (CH-PhSi), 127.8 (CH-PhSi), 82.0 (C-C25), 80.6 (CH-C23), 78.1 (CH-C20), 74.2 (C-C26), 64.7 (CH-C24), 61.3 (CH_2-C18), 38.7 (CH_2-C19), 32.4 (CH_2-C21), 27.0 (CH_3-^{t}BuSi), 26.9 (CH_2-C22), 19.4 (C-^{t}BuSi); HRMS (CI+, isobutane) calcd for $C_{25}H_{33}O_3Si$ $[M+H]^+$ 409.2199 found 409.2201 (Δ +0.4 ppm); LRMS (CI+, isobutane) *m/z* (intensity) 409.4 (65%), 383.4 (51%), 351.4 (36%), 331.4 (100%), 305.4 (66%), 253.3 (27%), 227.3 (15%), 199.2 (9%); Anal. calcd for $C_{25}H_{32}O_3Si$ C 73.49%, H 7.89% found C 73.38%, H 7.78%.

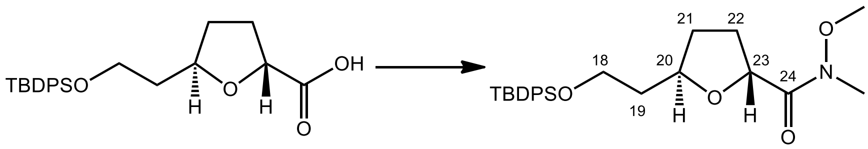
(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl} tetrahydrofuran -2-carboxylic acid.



A single portion of Dess-Martin periodinane (1.37 g, 3.23 mmol) was added to a solution of alcohol **348** (1.04 g, 2.71 mmol) in CH_2Cl_2 (51 mL) and the mixture stirred for 2 h at rt. The reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL) and the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude residue was passed through a plug of silica gel (pet. ether/EtOAC, 9:1) and the concentrated solution was used as isolated in the following step.

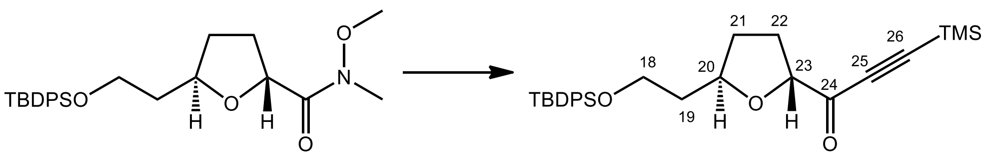
To a solution of the aldehyde and 2-methyl-2-butene (2.30 mL, 21.7 mmol) in *t*-BuOH (13.5 mL) was added a prepared solution of $NaClO_2$ (1.83 g, 16.2 mmol, 80% pure) and $NaH_2PO_4.2H_2O$ (2.76 g, 17.7 mmol) in H_2O (27 mL). The mixture was stirred for 1.5 h at rt, concentrated *in vacuo* and partitioned between CH_2Cl_2 (30 mL) and H_2O (30 mL). The organic phase was isolated and the aqueous phase was back-extracted with further CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to give a clear, colourless oil that was used directly in the following step. R_f = 0.15 (EtOAc); $[\alpha]_D^{24}$ +16.1 (c = 1.15, $CHCl_3$); ν_{max} (liquid film) 2957, 2957, 2934, 2875, 1734, 1468, 1428, 1267, 1107, 1082, 736, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69–7.63 (4H, m, CH-PhSi), 7.47–7.36 (6H, m, CH-PhSi), 4.47 (1H, dd, *J* = 8.0, 6.3 Hz, CH-C23), 4.38-4.31 (1H, m, CH-C20), 3.83-3.73 (2H, m, CH_2-C18), 2.41–2.32 (1H, m, CH-C22), 2.14–2.03 (2H, m, CH-C21 and CH-C22), 1.91–1.83 (1H, m, CH-C19), 1.75 (1H, td, *J* = 13.5, 6.0 Hz, CH-C19), 1.67–1.59 (1H, m, CH-C21), 1.05 (9H, s, CH_3-^{t}BuSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5 (C-C24), 135.7 (CH-PhSi), 133.8 (C-PhSi), 133.7 (C-PhSi), 129.8 (CH-PhSi), 127.8 (CH-PhSi), 78.9 (CH-C20), 76.3 (CH-C23), 61.0 (CH_2-C18), 38.2 (CH_2-C19), 31.6 (CH_2-C21), 30.1 (CH_2-C22), 27.0 (CH_3-^{t}BuSi), 19.3 (C-^{t}BuSi); HRMS (CI+, isobutane) calcd for $C_{23}H_{31}O_4Si$ $[M+H]^+$ 399.1991 found 399.1995, (Δ +0.9 ppm).

(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-N-methoxy-N-methyl tetrahydrofuran-2-carboxamide. (371)



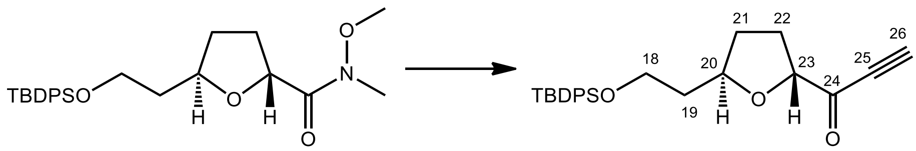
The crude carboxylic acid was dissolved in CH_2Cl_2 (21 mL) to which was added sequentially DIPEA (1.34 mL, 7.71 mmol), *N,O*-dimethylhydroxylamine (341 mg, 3.49 mmol) and HBTU (1.51 g, 3.49 mmol) at rt. The mixture was stirred for 18 h and the reaction was quenched with 1 M HCl (15 mL). This mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Purification of the resultant residue was achieved by chromatography (pet. ether/EtOAc, 2:1) to afford the title Weinreb amide **371** (949 mg, 79% over three steps) as a clear, colourless oil. R_f = 0.15 (pet. ether/EtOAc, 1:1); $[\alpha]_D^{24}$ −2.2 (c = 1.00, $CHCl_3$); ν_{max} (liquid film) 2957, 2933, 2875, 1677, 1469, 1428, 1109, 1078, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (4H, m, CH- PhSi), 7.44–7.34 (6H, m, CH- PhSi), 4.84–4.77 (1H, m, CH-C23), 4.35–4.25 (1H, m, CH-C20), 3.77 (2H,t, *J* = 6.7 Hz, CH_2-C18), 3.68 (3H, s, CH_3-MeO), 3.18 (3H, s, CH_3-MeN), 2.24–2.00 (3H, m, CH_2-C22 and CH-C21), 2.00–1.91 (1H, m, CH-C19), 1.75 (1H, dq, *J* = 13.3, 6.7 Hz, CH-C19), 1.61–1.51 (1H, m, CH-C21), 1.04 (9H, s, CH_3-^{t}BuSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 (C-C24), 135.6 (CH-PhSi), 134.0 (C-PhSi), 133.9 (C-PhSi), 129.6 (CH-PhSi), 127.7 (CH- PhSi), 78.2 (CH-C20), 74.8 (CH-C23), 61.5 (CH_2-C18), 61.4 (CH_3-MeO), 38.5 (CH_2-C19), 32.4 (CH_3-MeN), 31.7 (CH_2-C21), 29.4 (CH_2-C22), 26.9 (CH_3-^{t}BuSi), 19.2 (C-^{t}BuSi); HRMS (CI+, isobutane) calcd for $C_{25}H_{36}NO_4Si$ $[M+H]^+$ 442.2413 found 442.2413 (Δ −0.1 ppm); LRMS (CI+, isobutane) *m/z* (intensity) 442.5 (72%), 363.4 (100%).

1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]-3-(trimethylsilyl)prop-2-yn-1-one. (370)



To a solution of *n*-BuLi (1.1 mL of a 2.5 M soln. in hexanes, 2.8 mmol) in of THF (1 mL) at 0 °C was added dropwise trimethylsilylacetylene (0.45 mL, 3.2 mmol). The reaction mixture was stirred for 30 minutes and transferred to a solution of Weinreb amide **371** (0.95 g, 2.2 mmol) in THF (60 mL) at −78 °C. The mixture was stirred for 1 h then the reaction was quenched by the addition of 1 M aqueous HCl (10 mL) and the mixture was allowed to warm to rt. The solution was extracted with CH_2Cl_2 (3 × 30 mL), dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography (pet. ether/EtOAc, 20:1 to 9:1) to yield the desired ynone **370** (0.88 g, 86%) as a clear, colourless oil. R_f = 0.34 (pet. ether/EtOAc, 9:1); $[\alpha]_D^{25}$ +7.8 (c = 1.00, $CHCl_3$); ν_{max} (liquid film) 2957, 2933, 2875, 1677, 1469, 1428, 1109, 1078, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.65 (4H, m, CH-PhSi), 7.44–7.36 (6H, m, CH-PhSi), 4.47 (1H, dd, *J* = 8.4, 6.0 Hz, CH-C23), 4.33 (1H, dq, J = 8.1, 6.3 Hz, CH-C20), 3.77 (2H, t, *J* = 6.5 Hz, CH_2-C18), 2.33–2.25 (1H, m, CH-C22), 2.11–2.02 (2H, m, CH-C21 and CH-C22), 1.95 (1H, dq, *J* = 13.3, 6.5 Hz, CH-C19), 1.74 (1H, dq, *J* = 13.3, 6.5 Hz, CH-C19), 1.64–1.55 (1H, m, CH-C21), 1.04 (9H, s, CH_3-^{t}BuSi), 0.22 (9H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (C-C24), 135.7 (CH-PhSi), 133.9 (C-PhSi), 133.9 (C-PhSi), 129.7 (CH-PhSi), 127.8 (CH-PhSi), 101.8 (C-C25), 100.3 (C-C26), 83.7 (CH-C23), 78.9 (CH-C20), 61.4 (CH_2-C18), 38.5 (CH_2-C19), 31.4 (CH_2-C21), 29.6 (CH_2-C22), 27.0 (CH_3-^{t}BuSi), 19.3 (C-^{t}BuSi), −0.7 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{28}H_{39}O_3Si_2$ $[M+H]^+$ 479.2437 found 479.2434, (Δ −0.8 ppm).

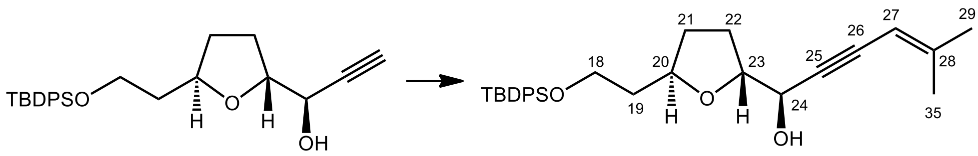
1-[(2*R*,5*R*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]prop-2-yn-1-one. (372)



A solution of Weinreb amide **371** (160 mg, 0.36 mmol) in THF (10 mL) was cooled to −78 °C and ethynylmagnesium bromide (1.1 mL, 0.54 mmol) was added dropwise. The mixture was stirred for 2.5 h and the reaction was quenched with 1 M aqueous HCl (5 mL). The mixture was allowed to warm to rt and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to afford a residue that was purified by chromatography (pet. ether/EtOAc, 9:1) to provide the desired ynone **372** as a clear, colourless oil (131 mg, 90%). R_f = 0.18 (pet. ether/EtOAc, 9:1); $[\alpha]_D^{27}$ +2.8 (c = 1.00, $CHCl_3$); ν_{max} (liquid film) 3269, 2956, 2932, 2878, 2092, 1677, 1469, 1427, 1109, 1078, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.64 (4H, m, CH-PhSi), 7.45–7.35 (6H, m, CH-PhSi), 4.47 (1H, dd, *J* = 8.3, 6.1 Hz, CH-C23), 4.41–4.30 (1H, m, CH-C20), 3.85–3.71 (2H, m, CH_2-C18), 3.26 (1H, s, CH-C26), 2.37–2.24 (1H, m, CH-C22), 2.13–2.01 (2H, m, CH-C21 and CH-C22), 1.94–1.87 (1H, m, CH-C19), 1.76 (1H, td, *J* = 13.6, 6.1 Hz, CH-C19), 1.66–1.55 (1H, m, CH-C21), 1.08–1.02 (9H, m, CH_3-^{t}BuSi); ^{13}C

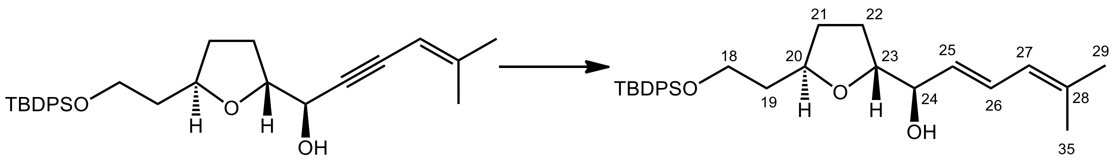
NMR (125 MHz, $CDCl_3$) δ 189.0 (C-C24), 135.9 (CH-PhSi), 134.1 (C-PhSi), 134.1 (C-PhSi), 130.0 (CH-PhSi), 128.0 (CH-PhSi), 83.8 (CH-C23), 81.9 (CH-C26), 80.1 (C-C25), 79.0 (C-C20), 61.4 (CH_2-C18), 38.5 (CH_2-C19), 31.6 (CH_2-C21), 29.6 (CH_2-C22), 27.2 (CH_3-^{t}BuSi), 19.5 (C-^{t}BuSi).

(1R*)*-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]-5-methylhex-4-en-2-yn-1-ol. (390)



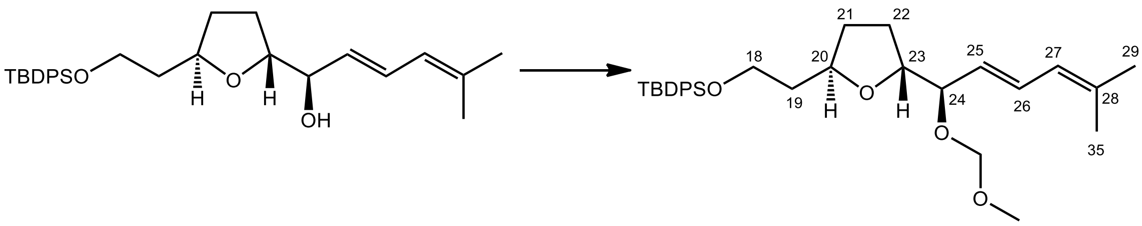
1-Bromo-2-methyl-1-propene (0.25 mL, 2.4 mmol) was added to a suspension of $Pd(PPh_3)_4$ (4.3 mg, 3.9 μmol) in pyrrolidine (0.70 mL) and the mixture was stirred until homogeneous. The alkyne **378** (32 mg, 0.78 mmol) in pyrrolidine (0.70 mL) was added to the solution and the reaction mixture was warmed to 50 °C in a pre-heated oil bath for 20 h. The mixture was cooled to rt and the reaction was quenched by the addition of saturated NH_4Cl solution (3 mL) and extracted with ether (3 × 3 mL). The organic extracts were combined and dried ($MgSO_4$). Purification of the residue by chromatography (pet. ether/ether, 1:1) afforded the enyne **390** (27 mg, 75%) of a colourless oil. R_f = 0.15 (pet.ether/ether, 3:1); $[\alpha]_D^{21}$ +4.4 (c = 1.20, $CHCl_3$); ν_{max} (liquid film) 3414, 2958, 2930, 2858, 1471, 1428, 1389, 1100, 823, 704 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.64 (4H, m, CH-PhSi), 7.45–7.36 (6H, m, CH-PhSi), 5.27–5.25 (1H, m, CH-C27), 4.34–4.30 (1H, m, CH-C24), 4.19–4.12 (1H, m, CH-C20), 4.03 (1H, ap q, *J* = 7.1 Hz, CH-C23), 3.81–3.73 (2H, m, CH_2-C18), 2.44 (1H, d, *J* = 3.7 Hz, OH-C24), 2.13–2.02 (2H, m, CH-C21 and CH-C22), 1.86–1.68 (3H, m, CH_2-C19 and CH-C22), 1.87 (3H, s, CH_3-C29), 1.79 (3H, s, CH_3-C35), 1.61–1.53 (1H, m, CH-C21), 1.04 (9H, s, CH_3-^{t}BuSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6 (C-C28), 135.7 (CH-PhSi), 134.0 (C-PhSi), 134.0 (C-PhSi), 129.8 (CH-PhSi), 127.8 (CH-PhSi), 104.7 (CH-C27), 89.0 (C-C26), 83.8 (C-C25), 81.9 (CH-C23), 77.0 (CH-C20), 66.4 (CH-C24), 61.3 (CH_2-C18), 38.5 (CH_2-C19), 32.2 (CH_2-C21), 28.4 (CH_2-C22), 27.0 (CH_3-^{t}BuSi), 24.9 (CH_3-C29), 21.2 (CH_3-C35), 19.4 (C-^{t}BuSi); HRMS (CI+, isobutane) calcd for $C_{29}H_{39}O_3Si$ $[M+H]^+$ 463.2668 found 463.2673, (Δ +0.9 ppm); LRMS (CI+, isobutane) *m*/*z* (intensity) 463.7 (17%), 445.3 (100%).

(1*R*,2*E*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]-5-methylhexa-2,4-dien-1-ol. (395)



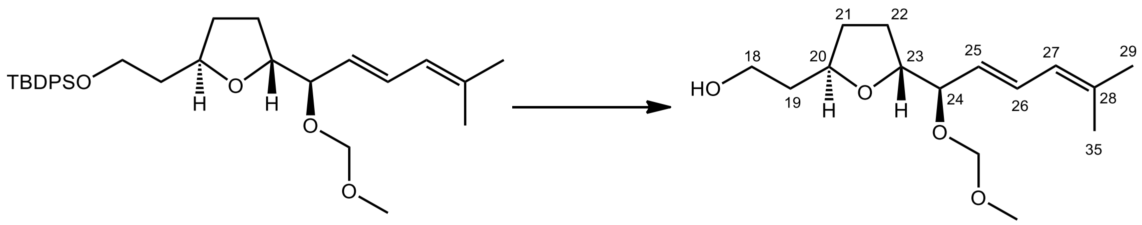
Lithium aluminium hydride (0.22 mL of a 1 M solution in THF, 0.22 mmol) was added dropwise to a stirred solution of alkyne **390** (50 mg, 0.11 mmol) in THF (2 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and then at 30 °C for an additional 1 h. The reaction was quenched at 0 °C by the addition of H_2O (1 mL) followed sequentially by 10% aq. NaOH (2 mL) and further H_2O (3 ml). The mixture was diluted with Et_2O (7 mL) and $MgSO_4$ (200 mg) was added; the mixture was then stirred for 15 minutes. The solids were removed by filtration and washed with further Et_2O. The filtrate was concentrated and the resultant residue was purified by chromatography (pet. ether/Et_2O, 2:1) to yield the diene **395** (35 mg, 70%) as a colourless oil. R_f = 0.21 (pet.ether/ether, 3:1); $[\alpha]_D^{21}$ +3.6 (c = 1.50, $CHCl_3$); ν_{max} (liquid film) 3456, 2957, 2928, 2909, 2857, 1471, 1427, 1081, 957, 822, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70–7.64 (4H, m, CH-PhSi), 7.45–7.35 (6H, m, CH-PhSi), 6.53 (1H, ddd, *J* = 15.2, 11.0, 0.8 Hz, CH-C26), 5.83 (1H, dd, *J* = 11.0, 0.8 Hz, CH-C27), 5.46 (1H, dd, *J* = 15.2, 6.9 Hz, CH-C25), 4.18–4.10 (1H, m, CH-C20), 3.96–3.90 (1H, m, CH-C24), 3.83–3.71 (3H, m, CH_2-C18 and CH-C23), 2.53 (1H, d, *J* = 2.6 Hz, OH-C24), 2.07–1.99 (1H, m, CH-C21), 1.97–1.88 (1H, m, CH-C22), 1.88–1.80 (1H, m, CH-C19), 1.79 (3H, s, CH_3-C29), 1.77 (3H, s, CH_3-C35), 1.76–1.70 (1H, m, CH-C19), 1.67–1.48 (m, 2H, CH-C21 and CH-C22), 1.07 (9H, s, CH_3-^{t}BuSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2 (C-C28), 135.8 (CH-PhSi), 134.3 (C-PhSi), 134.2 (C-PhSi), 129.7 (CH-PhSi), 129.3 (CH-C26), 128.8 (CH-C25), 127.8 (CH-PhSi), 124.8 (CH-C27), 82.0 (CH-C23), 76.6 (CH-C20), 75.7 (CH-C24), 61.5 (CH_2-C18), 38.8 (CH_2-C19), 32.4 (CH_2-C21), 28.2 (CH_2-C22), 27.1 (CH_3-^{t}BuSi), 26.1 (CH_3-C29), 19.4 (C-^{t}BuSi), 18.5 (CH_3-C35); HRMS (ESI+) calcd for $C_{29}H_{41}O_3Si$ $[M]^+$ 464.2747 found 464.2737, (Δ −2.0 ppm).

{[(1*R*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]prop-2-yn-1-yl]oxy}triethylsilane. (396)



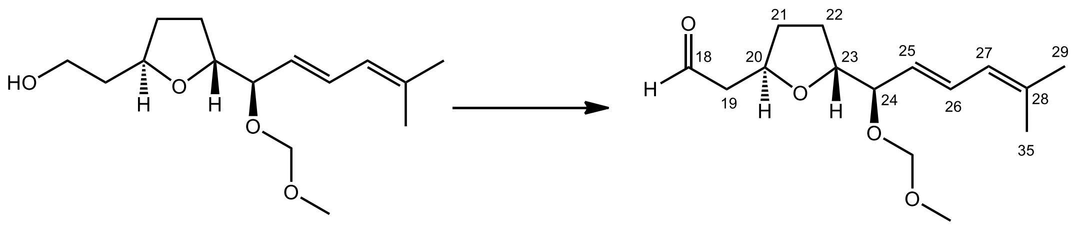
A solution of alcohol **395** (26 mg, 0.056 mmol), chloromethyl methyl ether (21 μl, 0.28 mmol) and DIPEA (58 μl, 0.34 mmol) in CH_2Cl_2 (2 mL) was heated at 55 °C for 15 h. The mixture was cooled to rt and the reaction was quenched with saturated aqueous NH_4Cl (3 mL) and extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated and the residue was purified by chromatography (pet. ether/Et_2O, 9:1) to afford the desired MOM ether **396** (24 mg, 84%). R_f = 0.36 (pet. ether/Et_2O, 3:1); $[\alpha]_D^{26}$ −35.6 (c = 1.10, $CHCl_3$); ν_{max} (liquid film) 2957, 2931, 2884, 2857, 2362, 1472, 1428, 1109, 1037, 823, 704 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.64 (4H, m, CH-PhSi), 7.44–7.35 (6H, m, CH-PhSi), 6.45 (1H, dd, *J* = 15.2, 11.0 Hz, CH-C26), 5.83 (1H, d, *J* = 11.0 Hz, CH-C27), 5.38 (1H, dd, *J* = 15.2, 7.6 Hz, CH-C25), 4.72 (1H, d, *J* = 6.7 Hz, CH-MOM), 4.58 (1H, d, *J* = 6.7 Hz, CH-MOM), 4.16–4.08 (1H, m, CH-C20), 4.04–3.96 (2H, m, CH-C23 and CH-C24), 3.82–3.70 (2H, m, CH_2-C18), 3.36 (3H, s, CH_3-MOM), 1.99 (1H, tdd, *J* = 8.3, 5.7, 3.2 Hz, CH-C21), 1.94–1.86 (2H, m, CH-C19 and CH-C22), 1.78 (3H, s, CH_3-C35), 1.76 (3H, s, CH_3-C29), 1.74–1.62 (2H, m, CH-C-19 and CH-C22), 1.54–1.45 (1H, m, CH-C21), 1.04 (9H, s, CH_3 ^{t}BuSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8 (C-C28), 135.9 (CH-PhSi), 134.3 (C-PhSi), 131.2 (CH-C26), 129.9 (CH-PhSi), 127.9 (CH-PhSi), 126.8 (CH-C25), 124.8 (CH-C27), 93.9 (CH_2-MOM), 80.8 (CH-C23), 79.4 (CH-C24), 77.0 (CH-C20), 61.8 (CH_2-C18), 55.6 (CH_3-MOM), 38.9 (CH_2-C19), 32.4 (CH_2-C21), 28.7 (CH_2-C22), 27.2 (CH_3-^{t}BuSi), 26.4 (CH_3-C29), 19.5 (C-^{t}BuSi), 18.7 (CH_3-C35).

2-[(2*R*,5*R*)-5-[(1*R*,2*E*)-1-(Methoxymethoxy)-5-methylhexa-2,4-dien-1-yl]tetrahydrofuran-2-yl]ethan-1-ol. (397)



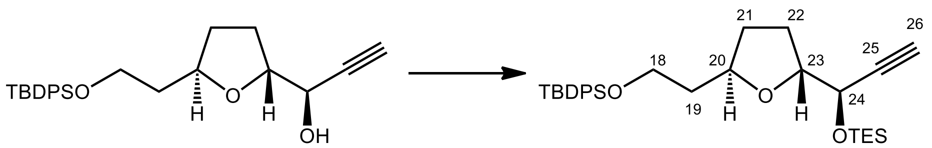
To a stirred solution of silyl ether **396** (24 mg, 47 µmol) in THF (1 mL) was added TBAF (52 µl of a 1 M soln. in THF, 52 µmol). The mixture was stirred for 4 h at rt and the reaction was quenched with saturated aqueous NH_4Cl (2 mL). The reaction mixture was extracted with Et_2O (3 × 5 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (pet. ether/ Et_2O, 1:3) provided alcohol **397** (12 mg, 99%) as a pale yellow oil. R_f = 0.22 (pet. ether/Et_2O, 1:2); $[\alpha]_D^{26}$ −47.0 (c = 1.20, $CHCl_3$); ν_{max} (liquid film) 3426, 2917, 2882, 2853, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.45 (1H, dd, *J* = 15.2, 11.0 Hz, CH-C26), 5.82 (1H, dd, *J* = 11.0, 0.7 Hz, CH-C27), 5.37 (1H, dd, *J* = 15.2, 8.0 Hz, CH-C25), 4.72 (1H, d, *J* = 6.7 Hz, CH-MOM), 4.57 (1H, d, *J* = 6.7 Hz, CH-MOM), 4.16 (1H, dq, *J* = 8.3, 6.1 Hz, CH-C20), 4.07 (1H, dd, *J* = 14.2, 6.5 Hz, CH-C23), 4.02 (1H, dd, *J* = 14.2, 8.0 Hz, CH-C24), 3.81–3.75 (2H, m, CH_2-C18), 3.39 (3H, s, CH_3-MOM), 2.85 (1H, br s, OH-C18), 2.09–2.01 (1H, m, CH-C21), 1.97–1.88 (1H, m, CH-C22), 1.80–1.65 (3H, m, CH_2-C19 and CH-C22), 1.78 (3H, s, CH_3-C35), 1.76 (3H, s, CH_3-C29), 1.56 (1H, ddt, *J* = 11.9, 9.9, 8.2 Hz, CH-C21); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1 (C-C28), 131.4 (CH-C26), 126.5 (CH-C25), 124.7 (CH-C27), 94.0 (CH_2-MOM), 81.4 (CH-23), 79.9 (CH-C20), 79.3 (CH-C24),62.1 (CH_2-C18), 55.7 (CH_3-MOM), 37.7 (CH_2-C19), 32.6 (CH_2-C21), 28.4 (CH_2-C22), 26.3 (CH_3-C29), 18.7 (CH_3-C35).

2-[(2*R*,5*R*)-5-[(1*R*,2*E*)-1-(Methoxymethoxy)-5-methylhexa-2,4-dien-1-yl]tetrahydrofuran-2-yl]acetaldehyde. (398)



Dess-Martin Periodinane (45 mg, 89 µmol) was added in one portion to a stirred solution of alcohol **397** (24 mg, 0.11 mmol) in CH_2Cl_2 (1.5 mL) and stirred for 1 h at rt. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 mL) and the mixture was extracted with Et_2O (3 × 2 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated to give a residue that was purified by chromatography (pet. ether/Et_2O, 1:2) affording the title acetaldehyde **398** as a colourless, opaque oil (19 mg, 80%). R_f = 0.29 (pet. ether/Et_2O, 1:2); ν_{max} (liquid film) 2916, 2887, 2848, 1725, 1442, 1378, 1149, 1098, 1032cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (1H, t, *J* = 2.2 Hz, CH-C18), 6.46 (1H, dd, *J* = 15.2, 11.0 Hz, CH-C26), 5.83 (1H, dd, *J* = 11.0, 0.7 Hz, CH-C27), 5.37 (1H, dd, *J* = 15.2, 8.2 Hz, CH-C25), 4.73 (1H, d, *J* = 6.7 Hz, CH-MOM), 4.58 (1H, d, *J* = 6.7 Hz, CH-MOM), 4.41 (1H, ddt, *J* = 8.4, 6.9, 5.7 Hz, CH-C20), 4.08 (1H, dd, *J* = 14.1, 6.8 Hz, CH-C23), 4.05–3.99 (1H, m, CH-C24), 3.39 (3H, s, CH_3-MOM), 2.72 (1H, ddd, *J* = 16.4, 6.9, 1.9 Hz, CH-C19), 2.57 (1H, ddd, *J* = 16.4, 5.7, 1.9 Hz, CH-C19), 2.19–2.10 (1H, m, CH-C21), 2.01–1.92 (1H, m, CH-C22), 1.78 (3H, s, CH_3-C29 or C35), 1.76 (3H, s, CH_3-C29 or C35), 1.76–1.70 (1H, m, CH-C22), 1.55 (1H, ddt, *J* = 12.1, 9.7, 8.4 Hz, CH-C21); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5 (CH-C18), 137.2 (C-C28), 131.6 (CH-C26), 126.4 (CH-C25), 124.7 (CH-C27), 93.9 (CH_2-MOM), 81.5 (CH-C23), 79.3 (CH-C24), 74.6 (CH-C20), 55.6 (CH_3-MOM), 49.8 (CH_2-C19), 32.5 (CH_2-C21), 28.6 (CH_2-C22), 26.3 (CH_3-C29), 18.7 (CH_3-C35).

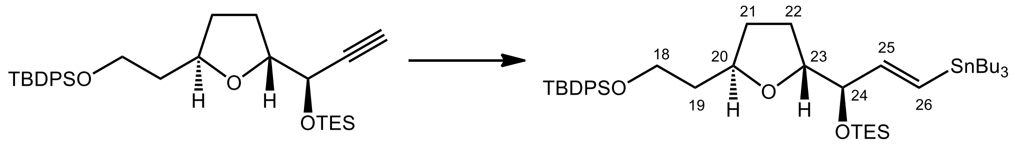
***tert*-Butyldiphenyl{2-[(2*R*,5*R*)-5-{(*R*)-1-[(triethylsilyl)oxy]prop-2-yn-1-yl} tetrahydro furan-2-yl]ethoxy}silane. (379)**



To a stirred solution of propargylic alcohol **378** (62 mg, 0.15 mmol), Et_3N (42 µl, 0.30 mmol) and DMAP (1.6 mg, 0.26 µmol) in CH_2Cl_2 (2 mL) was added TESCl (33 µl, 0.20 mmol). The mixture was stirred for 1.5 h at rt and the reaction was quenched by the addition aqueous 0.5 M HCl (3 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated. Purification of the residue was achieved by chromatography (pet. ether/EtOAc, 20:1) yielding the desired silyl ether **379** (71 mg, 91%) as a clear, colourless oil. R_f = 0.45 (pet. ether/Et_2O, 9:1); $[\alpha]_D^{25}$ −9.3 (c = 0.99, $CHCl_3$); ν_{max} (liquid film) 3310, 2956, 2932, 2875, 1472, 1428, 1083, 824, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.61 (4H, m, CH-PhSi), 7.44 –7.35 (6H, m, CH-PhSi), 4.39 (1H, dd, *J* = 5.8, 2.1 Hz, CH-C24), 4.22-4.14 (1H, m, CH-C20), 4.01 (1H, td, *J* = 7.0, 5.8 Hz, CH-C23), 3.79–3.70 (2H, m, CH_2-C18), 2.33 (1H, d, *J* = 2.1 Hz, CH-C26), 2.10 –2.00 (2H, m, CH-C21 and

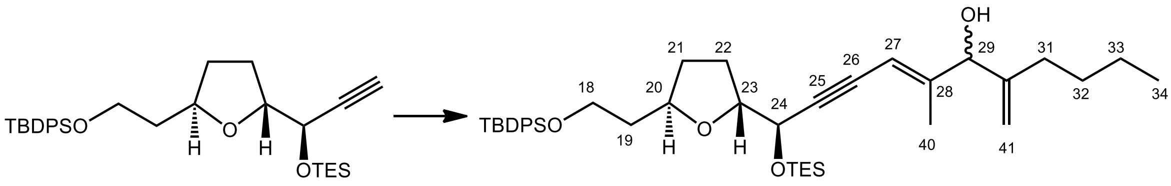
CH-C22), 1.99–1.83 (2H, m, CH-C19 and CH-C22), 1.69 (1H, m, CH-C19), 1.54–1.45 (1H, m, CH-C21), 1.04 (9H, s, CH_3-^{t}BuSi), 0.96 (9H, t, *J* = 7.9 Hz, CH_3-EtSi), 0.64 (6H, q, *J* = 7.9 Hz, CH_2-EtSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9 (CH-PhSi), 134.3 (C-PhSi), 129.9 (CH-PhSi), 127.9 (CH-PhSi), 83.8 (C-C25), 81.5 (CH-C23), 77.6 (CH-C20), 73.4 (CH-C26), 66.1 (CH-C24), 61.7 (CH_2-C18), 38.9 (CH_2-C19), 32.5 (CH_2-C21), 28.1 (CH_2-C22), 27.2 (CH_3-^{t}BuSi), 19.5 (C-^{t}BuSi), 7.0 (CH_3-EtSi), 5.1 (CH_2-EtSi).

{[(1*R*,2*E*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]-3-(tributylstannyl)prop-2-en-1-yl]oxy}triethylsilane. (380)



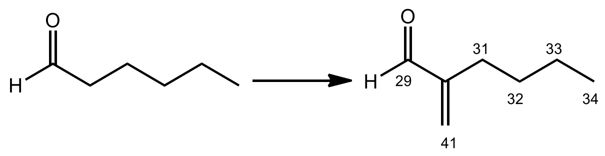
To a stirred solution of alkyne **379** (30 mg, 57 µmol) in THF (0.5 mL) at 0 °C was added $Pd(PPh_3)_2Cl_2$ (0.4 mg, 0.6 µmol) and *n*-Bu_3SnH (17 µL, 63 µmol). The reaction was stirred for 15 minutes before direct purification by column chromatography (pet. ether/Et_3N, 99:1) to afford vinyl stannane **380** (35 mg, 74%) as a clear, colourless oil. R_f = 0.35 (pet. ether); $[\alpha]_D^{24}$ +0.62 (c = 0.97, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.63 (4H, m, CH-PhSi), 7.44 –7.34 (6H, m, PhSi), 6.21 (1H, dd, *J* = 19.1, 1.2 Hz, CH-C26), 5.98 (1H, dd, *J* = 19.1, 5.4 Hz, CH-C25), 4.09–4.00 (2H, m, CH-C20 and CH-C24), 3.90-3.96 (1H, m, CH-C23), 3.75 (2H, t, *J* = 6.5 Hz, CH_2-C18), 1.98–1.90 (1H, m, CH-C21), 1.90–1.80 (2H, m, CH-C19 and CH-C22), 1.73–1.64 (2H, m, CH-C19 and CH-C22), 1.52–1.41 (7H m, CH-C21 and CH_2-^{n}BuSn), 1.35-1.24 (6H, m, CH_2-^{n}BuSn), 1.04 (9H, s, CH_3-^{t}BuSi), 0.93 (9H, t, *J* = 7.9 Hz, CH_2-EtSi), 0.90–0.85 (15H m, CH_2-^{n}BuSn and CH_3-^{n}BuSn), 0.58 (6H, q, *J* = 7.9 Hz, CH_2-EtSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7 (CH-C25), 135.7 (CH-PhSi), 134.1 (C-PhSi), 134.0 (C-PhSi), 129.6 (CH-PhSi), 129.3 (CH-C26), 127.7 (CH-PhSi), 81.9 (CH-C23), 78.4 (CH-C24), 76.8 (CH-C20), 61.7 (CH-C18), 38.9 (CH_2-C19), 32.4 (CH-C21), 29.3 (^{n}BuSn), 27.4 (^{n}BuSn), 27.0 (CH_3-^{t}BuSi), 19.3 (C- ^{t}BuSi), 13.9 (^{n}BuSn), 9.6 (^{n}BuSn), 7.0 (CH_3-EtSi), 5.08 (CH_2-EtSi); HRMS (ESI+, MeOH:H_2O) calcd for $C_{43}H_{74}O_3Si_2Sn$ $[M+Na]^+$ 837.4096, found 837.4091, (Δ +4.7 ppm).

(1*R*,4*E*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]-5-methyl-7-methylidene-1-[(triethylsilyl)oxy]undec-4-en-2-yn-6-ol. (402)



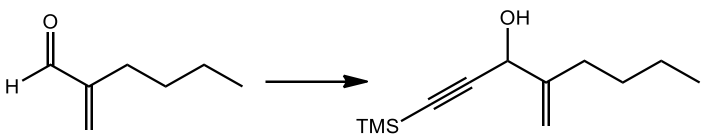
To a stirred solution of vinyl iodide **80rac** (30 mg, 0.11 mmol), $Pd(PPh_3)_4$ (3.0 mg, 0.024 mmol) Et_3N (0.65 mL) and CuI (1.2 mg, 0.049 mmol) in THF (2 mL) was added alkyne **375** (25 mg, 0.049 mmol) in THF (0.5 mL) dropwise. The mixture was stirred at rt for 16 h and the reaction was quenched by the addition of 0.5 M aqueous HCl (2 mL). The organic component was extracted with CH_2Cl_2 (2 × 5 mL), dried ($MgSO_4$) and concentrated. The resultant brown residue was purified by chromatography (pet. ether/EtOAc, 3:1) to afford the enyne **402** (12 mg, 45%) as a brown oil. R_f = 0.60 (pet. ether/Et_2O, 1:1); ν_{max} (liquid film) 3439, 2956, 2931, 2875, 2364, 1461, 1429, 1110, 1085, 739, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68–7.64 (4H, m, CH-PhSi), 7.44–7.35 (6H, m, CH-PhSi), 5.65 (1H, d, *J* = 0.9 Hz, CH-C27), 5.11 (1H, s, CH-C41), 4.96 (1H, s, CH-C41), 4.59-4.51 (1H, m, CH-C24), 4.50 (1H, s, CH-C29), 4.16 (1H, td, *J* = 12.3, 6.2 Hz, CH-C20), 4.04 (1H, td, *J* = 12.9, 6.9 Hz, CH-C23), 3.75 (2H, t, *J* = 6.5 Hz, CH_2-C18), 2.10–2.01 (2H, m, CH-C21 and CH-C22), 1.99–1.81 (4H, m, CH-C19, CH-C22 and CH_2-C31), 1.75 (3H, s, CH_3-C40), 1.74–1.64 (1H, m, CH-C19), 1.61 (1H, br s, OH-C29), 1.50 (1H, dq, *J* = 11.3, 8.8 Hz, CH-C21), 1.44–1.35 (2H, m, CH_2-C32), 1.36–1.26 (2H, m, CH_2-C33), 1.04 (9H, s, CH_3-^{t}BuSi), 0.96 (9H, t, *J* = 7.9 Hz, CH_3-EtSi), 0.89 (3H, t, *J* = 7.3 Hz, CH_3-C34), 0.64-0.59 (6H, m, CH_2-EtSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7 (C-C30), 149.2 (C-C28), 135.9 (CH-PhSi), 135.9 (CH-PhSi), 134.3 (C-PhSi), 134.3 (C-PhSi), 129.9 (CH-PhSi), 129.8 (CH-PhSi), 128.0 (CH-PhSi), 111.4 (CH_2-C41), 106.8 (CH-C27), 93.4 (C-C25), 82.6 (C-C26), 81.8 (CH-C23), 79.3 (CH-C29), 77.5 (CH-C20), 66.9 (CH-C24), 61.8 (CH_2-C18), 38.9 (CH_2-C19), 32.5 (CH_2-C21), 31.5 (CH_2-C31), 30.4 (CH_2-C32), 28.3 (CH_2-C22), 27.2 (CH_3-^{t}BuSi), 22.9 (CH_2-C33), 19.5 (C-^{t}BuSi), 15.5 (CH_3-C40), 14.3 (CH_3-C34), 7.1 (CH_3-EtSi), 5.1 (CH_2-EtSi); HRMS (FAB+, NOBA, NaI) calcd for $C_{41}H_{62}O_4Si_2Na$ $[M+Na]^+$ 697.4085, found 697.4073, (Δ −1.6 ppm).

2-Methylidenehexanal.[221] (79)



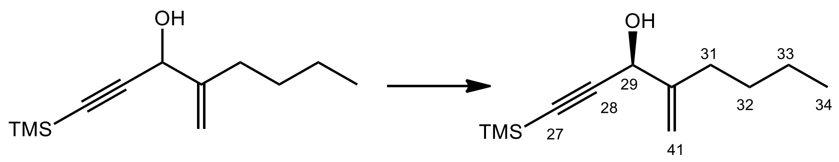
Hexanal (24.0 mL, 20.0 g, 200 mmol), dimethylamine hydrochloride (19.6 g, 240 mmol) and formaldehyde (19.4 g, 240 mmol, 37% w/w soln. in H_2O) were heated together at 55 °C for 16 hours. The mixture was cooled to rt and extracted with Et_2O (3 x 50 mL) and concentrated to afford the desired aldehyde **79** (19.6g, 87%) as a clear, pale yellow oil. R_f = 0.42 (pet. ether/EtOAC, 9:1); ν_{max} (liquid film) 2957, 2929, 2862, 1696, 1463, 945 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.53 (s, 1H, CH-C29), 6.24 (1H, d, *J* = 0.5 Hz, CH-C41), 5.98 (1H, *J* = 0.5 Hz CH-C41), 2.24 (2H, t, *J* = 7.6 Hz, CH_2-C31), 1.45–1.35 (2H, m, CH_2-C32), 1.35–1.23 (2H, m, CH_2-C33), 0.91 (3H, t, *J* = 7.2 Hz, CH_3-C34); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9 (CH-C29), 150.6 (C-C30), 134.0 (CH_2-C41), 30.0 (CH_2-C32), 27.6 (CH_2-C31), 22.4 (CH_2-C33), 13.9 (CH_2-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-Methylidene-1-(trimethylsilyl)oct-1-yn-3-ol. (*rac*-80)



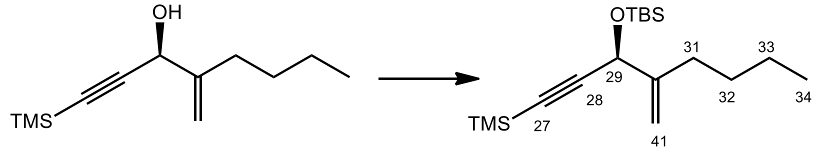
Isopropylmagnesium bromide (116 mL of a 2.0 M solution in THF, 0.23 mol) was added dropwise to a stirred solution of trimethylsilylacetylene (24.6 g, 251 mmol) in THF (50 mL) at 0 °C. After complete addition of the Grignard reagent, the mixture was warmed to rt for 2 h before being added to a stirred solution of 2-methylidenehexanal **79** (20.0 g, 179 mmol) in THF, (50 mL) at 0 °C. The mixture was stirred for 30 minutes 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 Et_2O (3 × 100 mL) and the organic extracts were combined and dried (Na_2SO_4) then concentrated *in vacuo*. The residue was purified by chromatography (pet. ether/EtOAc, 100:1 to 50:1) to afford the propargylic alcohol ***rac*-80** (30.2 g, 81%) as a pale yellow oil.

(3*S*)-4-Methylidene-1-(trimethylsilyl)oct-1-yn-3-ol.[28] (80)



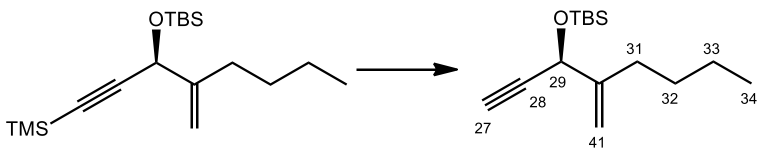
To a solution of racemic allyl alcohol **rac-80** (12.7 g, 60.6 mmol) and (+)-DET (1.55 mL, 9.08 mmol) in CH_2Cl_2 (454 mL), was added powdered 4 Å molecular sieves (3.8 g). The mixture was cooled to −30 °C and freshly distilled Ti(O*i*-Pr)$_4$ (1.79 mL g, 6.06 mmol) was added. The mixture was stirred for 2 h before addition of TBHP (3.0 mL of a 5.6 M solution in CH_2Cl_2, 17 mmol). The resulting solution was placed at −20 °C until ^{1}H NMR showed > 65% conversion of starting material to product. The reaction was quenched by the addition of aqueous 1 M NaOH (250 mL) and extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were washed with brine (250 mL), dried ($MgSO_4$) concentrated *in vacuo*. The residue was purified by flash chromatography (pet. ether/EtOAc, 20:1) to give of enantiopure allyl alcohol **80** (4.51 g, 35%, 98% *ee*) as a colourless oil. $[\alpha]_D^{25}$ +3.6 (c = 1.01, $CHCl_3$); R$_f$ = 0.54, (pet. ether/EtOAc, 4:1); ν_{max} (liquid film) 2958, 2931, 2173, 1379, 1249, 1041, 1008, 906, 839, 759, 731, 698, 671, 626 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (1H, s, CH-C41), 4.94 (1H, s, CH-C41), 4.81 (1H, d, *J* = 6.3 Hz, CH-C29), 2.19 (2H, t, *J* = 7.6 Hz, CH_2-C31), 1.92–1.86 (1H, m, OH-C29), 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, CH_3-MeSi); ^{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_2-C34), -0.1 (CH_3-C1 TMS); LRMS (CI+, isobutane) *m/z* (intensity) 211.2 (20%) 193.2 (100%), 151.2 (72%).

[(3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-methylideneoct-1-yn-1-yl]trimethylsilane.[28] (384)



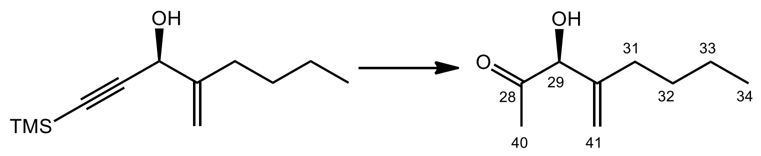
To a solution of alcohol **80** (0.40 g, 1.9 mmol) in CH_2Cl_2 (27 mL) was added imidazole (0.30 g, 4.4 mmol), DMAP (23 mg, 0.19 mmol) and tert-butyldimethylsilyl chloride (1.3 g, 0.87 mmol) at 0 °C, the reaction mixture was allowed to warm to rt and stirred for 25 h. The reaction was quenched by the addition of 1 M aqueous HCl (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The extracts were combined, washed with brine, dried ($MgSO_4$) and concentrated. The resulting residue was purified by chromatography (pet. ether/Et_2O, 99:1) to give the desired silyl ether **384** (0.61 g, 98%) as a colourless oil. R_f = 0.76 (pet. ether/ether, 40:1); $[\alpha]_D^{29}$ −40.9 (c = 1.05, $CHCl_3$); ν_{max} (liquid film) 2958, 2929, 2857, 1653, 1464, 1249, 1070, 1029, 834, 775, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.23 (1H, s, CH-C41), 4.87–4.85 (1H, m, CH-C29), 4.80 (1H, s, CH-C41), 2.14 (2H, dd, *J* = 8.2, 7.2 Hz, CH_2-C31), 1.53–1.43 (2H, m, CH_2-C32), 1.39-1.30 (2H, m, CH_2-C33), 0.92 (9H, s, CH_3-^{t}BuSi), 0.91 (3H, t, *J* = 7.3 Hz, CH_3-C34), 0.16 (9H, s, CH_3-MeSi), 0.15 (3H, s, CH_3-MeSi), 0.13 (3H, s, CH_3-MeSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5 (C-C30), 110.4 (CH_2-C41), 105.9 (C-C27), 89.9 (C-C28), 66.6 (CH-C29), 31.5 (CH_2-C31), 30.2 (CH_2-C32), 26.0 (CH_3-^{t}BuSi), 22.7 (CH_2-C33), 18.5 (C- ^{t}BuSi), 14.1 (CH_2-C34), -0.1 (CH_3-MeSi), −4.2 (CH_3-MeSi), −4.6 (CH_3-MeSi).

***tert*-Butyldimethyl{[(3*S*)-4-methylideneoct-1-yn-3-yl]oxy}silane.[28] (385)**



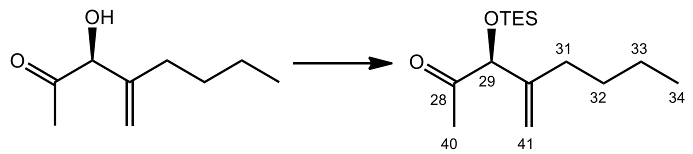
To a solution of the TMS-protected alkyne **384** (892 mg, 2.75 mmol) in wet MeOH (25 mL) was added K_2CO_3 (950 mg, 6.85 mmol) at rt. The mixture was stirred for 2 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and 1 M aqueous HCl (20 ml) and the organic phase isolated. The aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were then dried ($MgSO_4$) and concentrated. The resulting crude material was purified by chromatography (pet. ether/EtOAc, 99:1) to provide the alkyne **385** (652 mg, 94%) as a colourless oil. R_f = 0.65 (pet. ether/EtOAc, 20:1); $[\alpha]_D^{20}$ -29.1 (c = 1.02, $CHCl_3$); ν_{max} (liquid film) 3313, 2957, 2929, 2859, 1464, 1252, 1071, 835, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.22 (1H, s, CH-C41), 4.89–4.87 (1H, m, CH-C29), 4.81 (1H, s, CH-C41), 2.44 (1H, d, *J* = 2.2 Hz, CH-C27), 2.23–2.11 (2H, m, CH_2-C31), 1.52–1.42 (2H, m, CH_2-C32), 1.40–1.30 (2H, m, CH_2-C33), 0.92 (3H, t, *J* = 7.2 Hz, CH_3-C34), 0.92 (9H, s, CH_3-^{t}BuSi), 0.15 (3H, s, CH_3-MeSi), 0.12 (3H, s, CH_3-MeSi); ^{13}C NMR (125 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 (CH_2-C31), 30.1 (CH_2-C32), 25.9 (CH_3-^{t}Bu TBS), 22.7 (CH_2-C33), 18.5 (C- ^{t}BuSi), 14.1 (CH_2-C34), −4.6 (CH_3-MeSi), −5.0 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{15}H_{29}OSi$ $[M+H]^+$ 253.1987, found 253.1983 (Δ −2.0 ppm); LRMS (CI+, isobutane) *m*/*z* (intensity) 253.3 (100%), 195.2 (63%), 121.2 (64%); Anal. calcd for $C_{15}H_{28}OSi$ C 71.36%, H 11.18%, found: C 71.37%, H 11.24%.

(3*S*)-3-Hydroxy-4-methylideneoctan-2-one. (408)



To a solution of alkyne **80** (1.2 g, 5.7 mmol) in acetone (57 mL), was added in one portion, a predissolved solution of yellow HgO (0.62 g, 2.9 mmol) in 0.75 M aqueous H_2SO_4 (27 mL). The mixture was warmed to 60 °C for 30 minutes, cooled to rt and the reaction was quenched by the addition of 1 M aqueous HCl (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL), dried ($MgSO_4$) and concentrated. Flash chromatography purification of the residue (pet. ether/Et_2O, 3:1) provided ketone **408** (0.77 g, 86%) as a clear colourless oil R_f = 0.32 (pet. ether/Et_2O, 1:1); $[\alpha]_D^{26}$ +340.5 (c = 1.18, $CHCl_3$); ν_{max} (liquid film) 3457, 2958, 2930, 2864, 1714, 1357, 1182, 1084 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.22 (1H, s, CH-C41), 5.12 (1H, s, CH-C41), 4.59 (1H, d, *J* = 4.4 Hz, CH-C29), 3.84 (1H, d, *J* = 4.4 Hz, OH-C29), 2.18 (3H, s, CH_3-C40), 2.15–1.98 (1H, m, CH-C31), 1.84–1.74 (1H, m, CH-C31), 1.47-1.36 (2H, m, CH_2-C32), 1.35-1.25 (2H, m, CH_2-C33), 0.89 (3H, t, *J* = 7.3 Hz, CH_3-C34); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4 (C–C28), 146.8 (C–C30), 115.9 (CH_2–C41), 82.7 (CH–C29), 30.1 (CH_2–C31), 29.9 (CH_2-C32), 24.9 (CH_3-C40), 22.6 (CH_2-C33), 14.0 (CH_3-C34); HRMS (CI+, isobutane) calcd for $C_9H_{16}O_2$ $[M+H]^+$ 157.1228, found 157.1232 (Δ +2.0 ppm); LRMS (CI+, isobutene) *m*/*z* (intensity); 157.3 (100%), 139.2 (42%).

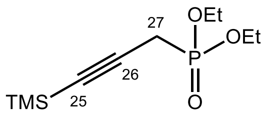
(3*S*)-4-Methylidene-3-[(triethylsilyl)oxy]octan-2-one. (409)



Chloro triethylsilane (1.2 mL, 7.4 mmol) was added dropwise, at 0 °C, to a solution containing alcohol **408** (0.77 g, 4.9 mmol), DIPEA (1.3 mL, 7.4 mmol) and DMAP (0.60 g, 4.9 mmol) in CH_2Cl_2 (10 mL). Upon complete addition the solution was warmed to rt and stirred for 90 minutes. The reaction was quenched by addition of H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The resultant residue was purified by chromatography (pet. ether/Et_2O, 99:1) to provide the title silyl ether **409** (1.3 g, 98%) as a pale yellow oil. R_f = 0.51 (pet. eth./Et_2O, 20:1); $[\alpha]_D^{27}$ −140.2 (c = 0.96, $CHCl_3$); ν_{max} (liquid film) 2955, 2938, 2877, 1719, 1237, 1070, 1003, 726 cm^{-1}; ^1H NMR (500 MHz,

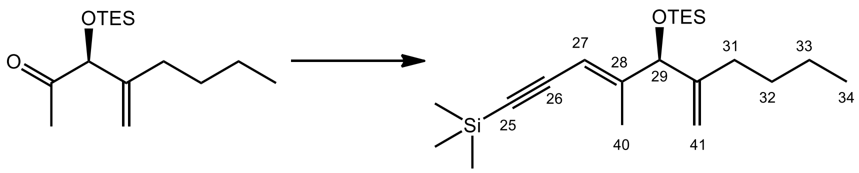
$CDCl_3$) δ 5.33 (1H, s, CH-C41), 5.06–4.95 (1H, m, CH-C41), 4.38 (1H, s, CH-C329), 2.11 (3H, s, CH_3-C40), 2.01-1.97 (1H, m, CH-C31), 1.95–1.87 (1H, m, CH-C31), 1.51–1.24 (4H, m, CH_2-C32 and CH_2-C33), 0.94 (9H, t, *J* = 7.9 Hz, CH_3-EtSi), 0.89 (3H, t, J = 7.2 Hz, CH_3-C34), 0.60 (6H, q, J = 7.9 Hz, CH_2-EtSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5 (C-C28), 146.9 (C-C30), 111.6 (CH_2-C41), 82.2 (CH-C29), 31.4 (CH_2-C31), 29.9 (CH_2-C32), 23.7 (CH_3-C40), 22.6 (CH_2-C33), 14.1 (CH_3-C34), 6.8 (CH_3- EtSi), 4.8 (CH_2- EtSi).

Diethyl (3-(trimethylsilyl)prop-2-yn-1-yl)phosphonate.[222] (414)



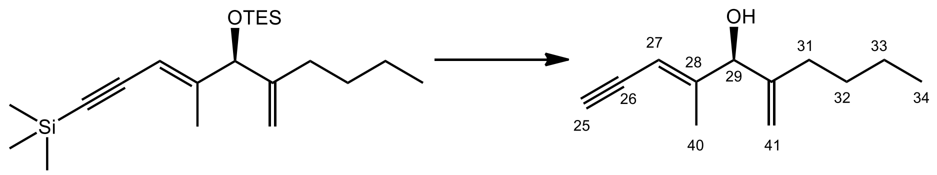
To a solution of diethyl phosphite (5.7 mL, 44 mmol) in THF (14 mL) was added dropwise NaHMDS (44 mL of a 1 M soln. in THF, 44 mmol) at −10 °C and stirred for 1 h. Propargyl bromide (7.2 mL, 44 mmol) was added dropwise to the solution and the mixture was stirred for a further 1 h. The reaction was quenched by the addition of H_2O (50 mL) and the mixture was extracted with Et_2O (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Purification of the residue by flash chromatography (pet. ether/Et_2O, 9:1 to 1:4) provided **414** (7.6 g, 69%) as a pale yellow oil; R_f = 0.25 (Et_2O); ν_{max} (liquid film) 2982, 2961, 2933, 2900, 2179, 1248, 1019, 837, 759, 640 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23–4.15 (4H, m, CH_2-OEt), 2.80 (1H, d, *J* = 22.3 Hz, CH_2-C27), 1.36 (1H, t, *J* = 7.1 Hz, CH_3-OEt), 0.16 (9H, s, CH_3-MeSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 96.1 (C-C26), 88.3 (C-C25), 63.2 (CH_2-OEt), 63.1 (CH_2-OEt), 19.6 (d, *J* = 144.7 Hz, CH_2-C27), 16.5 (CH_3-OEt), 0.0 (CH_3-MeSi); HRMS (EI+) calcd for $C_{10}H_{21}O_3PSi$ $[M]^+$ 248.0998, found 248.0989, (Δ −3.3 ppm); LRMS (EI+) *m/z* (intensity); 248.0 (12%), 233.3 (100%), 205.0 (30%), 177.0 (84%).

Triethyl({[(3*E*,5*S*)-4-methyl-6-methylidene-1-(trimethylsilyl)dec-3-en-1-yn-5-yl]oxy})silane. (410)



To a solution of diethyl (3-(trimethylsilyl)prop-2-yn-1-yl)phosphonate **414** (2.4 g, 9.7 mmol) in THF (10 mL) at −78 °C was added dropwise NaHMDS (7.3 mL of a 1 M soln. in THF, 7.3 mmol). The reaction was then stirred for 30 minutes before the dropwise addition of a precooled solution of ketone **409** (1.3 g, 4.8 mmol) in THF (10 mL). The reaction was stirred for a further 30 minutes and the reaction was quenched by the addition of H_2O (15 mL). The mixture was warmed to rt and extracted with Et_2O (3 x 15mL). The combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). The solution was filtered, concentrated and the residue was purified by chromatography (pet. ether/Et_2O, 99:1) to provide the title enyne **410** (1.4 g, 82%) as a clear, colourless oil. R_f = 0.73 (pet. Ether/Et_2O, 20:1); $[\alpha]_D^{27}$ +2.1 (c = 1.00, $CHCl_3$); ν_{max} (liquid film) 2956, 2877, 2137, 1458, 1248, 1103, 1073, 839, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.72-5.69 (1H, m, CH-C27), 5.07 (1H, s, CH-C41), 4.87 (1H, s, CH-C41), 4.44 (1H, s, CH-C29), 1.98–1.87 (1H, m, CH-C31), 1.81–1.76 (1H, m, CH-C31), 1.74 (3H, s, CH_3-C40), 1.42–1.34 (2H, m, CH_2-C32), 1.34–1.24 (2H, m, CH_2-C33), 0.93 (9H, t, *J* = 7.9 Hz, CH_3-EtSi), 0.89 (3H, t, *J* = 7.2 Hz, CH_3-C34), 0.57 (6H, q, *J* = 7.9 Hz, CH_2-EtSi), 0.01 (9H, s, CH_3-MeSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1 (C-C28), 149.3 (C-C30), 110.6 (CH_2-C41), 105.3 (CH-C27), 103.2 (C-C26), 97.8 (C-C25) 79.7 (CH-C29), 29.9 (CH_2-C32), 29.7 (CH_2-C31), 25.6 (CH_2-C33), 15.3 (CH_3-C40), 14.0 (CH_3-C34), 6.8 (CH_3-EtSi), 4.7 (CH_2-EtSi), 0.1 (CH_2-TMS); HRMS (CI+, isobutane) calcd for $C_{21}H_{41}OSi_2$ $[M+H]^+$ 365.2696, found 365.2698, (Δ +0.2 ppm); LRMS (CI+, isobutane) *m/z* (intensity); 365.4 (25%), 233.3 (9%), 113.2 (32%), 73.1 (100%); Anal. calcd for $C_{21}H_{40}OSi_2$ C 69.16%, H 11.05%, found C 68.93%, H 11.12%.

(3*E*,5*S*)-4-Methyl-6-methylidenedec-3-en-1-yn-5-ol. (411)



To a solution of silyl alkyne **410** (0.31 g, 0.84 mmol) in THF (5 mL) at rt was added TBAF (1.8 mL of a 1 M solution in THF, 1.8 mmol). The mixture was stirred for 30 minutes and the reaction was quenched by the addition of H_2O (5 mL). The mixture was extracted with Et_2O (3 x 5mL), the combined extracts washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (pet. ether/Et_2O, 20:1 to 9:1) provided the title compound **411** (0.14 g, 91%) as of clear, colourless oil; R_f = 0.30 (pet. eth./Et_2O, 3:1); $[\alpha]_D^{25}$ +4.8 (c = 1.02, $CHCl_3$); ν_{max} (liquid film) 3359, 3310, 2957, 2872, 2860, 2103, 1648, 1024, 904, 633, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.67-5.65 (1H, m, CH-C27), 5.13 (1H, s, CH-C41), 4.99-4.97 (1H, m, CH-C41), 4.54 (1H, d, *J* = 3.0 Hz, CH-C29), 3.11 (1H, d, *J* = 2.2 Hz, CH-C25), 1.98 (1H, dt, *J* = 15.6, 7.7 Hz, CH-C31), 1.87 (1H, dt, *J* = 15.6, 7.7 Hz, CH-C31), 1.81 (3H, s, CH_3-C40), 1.67 (1H, m, C29-OH), 1.48–1.37 (2H, m, CH_2-C32), 1.37–1.27 (2H, m, CH_2-C33), 0.90 (3H, t, *J* = 7.3 Hz, CH_3-C34); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8 (C–C28), 148.9 (C–C30), 111.5 (CH_2–C41),

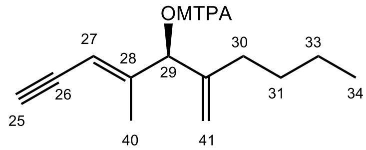
105.6 (CH–C27), 81.5 (CH–C25), 81.2 (C–C26), 79.1 (CH-C29), 31.2 (CH_2-C31), 30.2 (CH_2-C32), 22.7 (CH_2-C33), 15.5 (CH_3-C40), 14.1 (CH_3-C34); HRMS (CI+, isobutane) calcd for $C_{12}H_{19}O$ $[M+H]^+$ 179.1436, found 179.1434 (Δ −0.2 ppm); LRMS (CI+, isobutene) *m/z* (intensity); 179.2 (12%), 161.2 (100%).

Mosher Ester Preparation—General Procedure

To a solution of secondary alcohol (0.012 mmol) dissolved CH_2Cl_2 (1 mL) was added Et_3N (3.0 μL, 0.018 mmol) and a single crystal of DMAP. (*S*)-MTPA chloride (3.6 mg, 0.014 mmol) was added to the solution and the mixture stirred overnight at rt. The reaction was quenched by the addition of water (1mL) and extracted with Et_2O (2 × 2 mL). The organic layer was washed sequentially with 1 M HCl (1 mL), $NaHCO_3$ sat. aq. (1 mL) and brine (1 mL). The solution was dried over $MgSO_4$, and concentrated. The (*R*)-MTPA ester was purified by flash chromatography on silica gel and analysed by ^{1}H-NMR on isolation.

The (*S*)-MTPA ester was prepared from (*R*)-MTPA chloride using an identical procedure.

Mosher Ester Analysis of 411

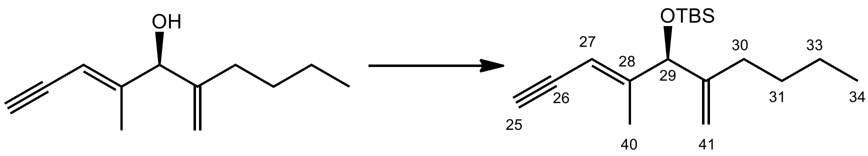


	δ *S*-ester (PPM)	δ *R*-ester (ppm)	Δδ *SR* (=δ*S*−δ*R*) ppm	Hz (400 MHz)
CH-C25	3.16	3.13	0.03	+12
CH-C27	5.80	5.81	0.13	+4
CH_3-C40	1.84	1.74	0.10	+40
CH-C41	4.98	5.05	−0.07	−28
CH-C41	5.01	5.16	−0.15	−60
CH_2-C31	1.82	1.91	−0.09	−36
CH_2-C32	1.36	1.42	−0.06	−24
CH_2-C33	1.25	1.30	−0.05	−20
CH_2-C34	0.87	0.89	−0.025	−8

(*S*)-MTPA ester*:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.45 (2H, m, CH-Ph MTPA), 7.44–7.34 (3H, m, CH-Ph MTPA), 5.80 (1H, s, CH-C27), 5.00-4.97 (1H, m, CH-C41), 5.01 (1H, s, CH-C41), 4.98 (1H, s, CH-C29), 3.54 (3H, s, MeO MTPA), 3.16 (1H, d, *J* = 2.2 Hz, CH-C25), 1.84 (3H, s, CH_3-C40), 1.84-1.79 (2H, m, CH_2-C31), 1.42–1.30 (2H, m, CH_2-C32), 1.30–1.17 (2H, m, CH_2-C33), 0.87 (2H, t, *J* = 7.2 Hz, CH_3-C34).

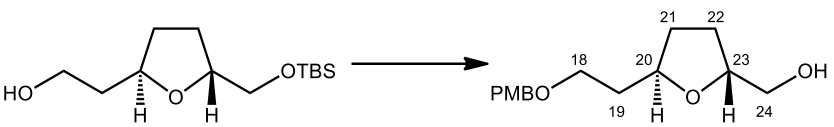
(*R*)-MTPA ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.45 (2H, m, CH-Ph MTPA), 7.44–7.36 (3H,m, CH-Ph MTPA), 5.81 (1H, s, CH-C27), 5.07-5.04 (1H, m, CH-C41), 5.16 (1H,s, CH-C41), 5.05 (1H, s, CH-C29), 3.54 (3H, s, CH_3-MeO MTPA), 3.13 (1H, d, *J* = 2.2 Hz, CH-C25), 1.93-1.90 (2H, m, CH_2-C31), 1.74 (3H, s, CH_3-C40), 1.47–1.35 (2H, m, CH_2-C32), 1.37–1.18 (2H, m, CH_2-C33), 0.89 (3H, t, *J* = 7.3 Hz, CH_3-C34).

***tert*-Butyldimethyl{[(3*E*,5*S*)-4-methyl-6-methylidenedec-3-en-1-yn-5-yl]oxy}silane.[28] (412)**



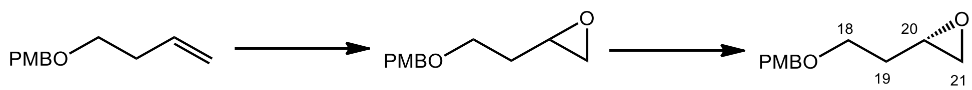
To a solution of allylic alcohol **411** (0.36 g, 2.0 mmol) in DMF (10 mL) was added imidazole (0.27 g, 4.0 mmol) and TBSCl (0.36 g, 2.4 mmol) and the mixture stirred for 36 h at rt. The reaction was quenched by the addition of H_2O (5 mL) and the mixture was extracted with pet. ether (3 x 10 mL). The combined organic extracts were washed sequentially with aqueous 1 M HCl (15 mL) and saturated aqueous $NaHCO_3$ (15 mL) and dried ($MgSO_4$). The solution was concentrated and the residue was purified by chromatography (pet. ether to pet. ether/Et_2O, 3:1) to provide the title compound **412** as a clear colourless oil (0.45 g, 77%) and recovered starting material (49 mg, 14%); R_f = 0.40 (pet. eth); $[\alpha]_D^{28}$ +8.2 (c = 1.00, $CHCl_3$); ν_{max} (liquid film) 3315, 2929, 2858, 2109, 1647, 1427, 1252, 1091, 869, 834, 774, 675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66-5.63 (1H, m, CH-C27), 5.07 (1H, s, CH-C41), 4.89 (1H, d, *J* = 1.2 Hz, CH-C41), 4.44 (1H, s, CH-C29), 3.08 (1H, d, *J* = 2.2 Hz, CH-C25), 1.97–1.87 (1H, m, CH-C31), 1.83–1.76 (1H,m, CH-C31), 1.76 (3H, s, CH_3-C40), 1.45–1.35 (2H, m, CH_2-C32), 1.35–1.24 (2H, m, CH_2-C33), 0.87 (3H, t, *J* = 7.2 Hz, CH_3-C34), 0.89 (9H, s, CH_3-^{t}BuSi), 0.03 (3H, s, CH_3-MeSi), 0.02 (3H, s, CH_3-MeSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9 (C–C28), 149.2 (C–C30), 111.1 (CH_2-C41), 104.5 (CH–C27), 81.7 (C–C26), 80.9 (CH–C25), 80.2 (CH–C29), 30.1 (CH_2-C31), 29.9 (CH_2-C32), 25.9 (CH_3-^{t}BuSi), 22.7 (CH_2-C33), 18.4 (C-^{t}BuSi), 15.4 (CH_3-C40), 14.2 (CH_3-C34), −4.9 (CH_3–MeSi), −5.0 (CH_3–MeSi); HRMS (CI+, isobutane) calcd for $C_{18}H_{33}OSi$ $[M+H]^+$ 293.2300, found 293.2307, (Δ +0.6 ppm); LRMS (CI+, isobutene) *m/z* (intensity); 293.4 (100%), 279.4 (41%), 253.3 (58%), 161.2 (46%); Anal. calcd for $C_{18}H_{32}OSi$ C 73.90%, H 11.03%, found C 74.16%, H 11.15%.

[(2*R*,5*R*)-5-{2-[(4-Methoxyphenyl)methoxy]ethyl}tetrahydrofuran-2-yl]methanol. (350)



To a suspension of NaH (7.5 mg, 0.18 mmol) in THF (3mL) was added alcohol **344** (24 mg, 0.092 mmol) in THF (0.5 mL). The suspension was stirred for 5 minutes at rt before addition of TBAI (3.3 mg, 0.009 mmol) and PMBCl (16 mL, 0.11 mmol). The mixture was stirred for 16 hours and the reaction was quenched by the addition of H_2O (3 mL). The reaction mixture was extracted with Et_2O (3 x 5 mL), washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The crude residue was dissolved in THF (2 mL) and TBAF (0.1 mL of a 1 M solution in THF, 0.1 mmol) was added and the mixture stirred for 30 minutes at rt. The reaction was quenched with H_2O (2 mL) and the mixture extracted with Et_2O (3 x 2 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated and the crude residue purified by column chromatography (pet. eth/Et_2O, 9:1) to afford alcohol **350** (17 mg, 49% over two steps) as a clear, colourless oil. R_f = 0.25 (Et_2O); $[\alpha]_D^{24}$ −21.9 (c = 0.96, $CHCl_3$); ν_{max} (liquid film) 3440, 2937, 2866, 1612, 1512, 1244, 1081, 1031, 818cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 6.88 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 4.44 (2H, s, CH_2-PMB alkyl), 4.13–4.03 (2H, m, CH-C20 and CH-C23), 3.80 (3H, s, CH_3-PMB alkyl), 3.62 (1H, ddd, *J* = 11.4, 7.1, 3.3 Hz, CH-C24), 3.56 (1H, m, CH-C18), 3.54 (1H, m, CH-C18), 3.52–3.44 (1H, m, CH-C24), 2.10–2.01 (1H, m, CH-C21), 2.01–1.82 (2H, m, CH-C22 and CH-C19), 1.77 (1H, dtd, *J* = 12.4, 7.0, 5.4 Hz, CH-C19), 1.71–1.51 (2H, m, CH-C21 and CH-C22); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3 (C-PMB Ar), 130.8 (C-PMB Ar), 129.4 (CH-PMB Ar), 113.9 (CH-PMB Ar), 79.0 (CH-C23), 76.8 (CH-C20), 72.8 (CH_3-PMB alkyl), 67.4 (CH_2-C24), 65.2 (CH_2-C18), 55.4 (CH_3-PMB alkyl), 36.0 (CH_2-C19), 32.4 (CH_2-C21), 27.6 (CH_2-C22); HRMS (EI+) calcd for $C_{15}H_{21}O_4$ $[M]^+$ 266.1518, found 266.1515, (Δ −0.3 ppm).

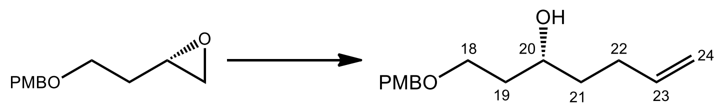
(2S)-2-{2-[(4-Methoxyphenyl)methoxy]ethyl}oxirane.[25] (52)



m-CPBA (18 g, 0.11 mol) was added portionwise over 15 minutes to a solution of alkene **352** (10 g, 52 mmol) in CH_2Cl_2 (120 mL) at 0 °C, on warming to rt the mixture was stirred for 14 h. The resultant precipitates were removed by filtration and washed with cold CH_2Cl_2 (50 mL). The filtrate was concentrated and pet. ether (150 mL) was added to the flask and the mixture stirred for a further 30 minutes at rt. Filtration and concentration yielded a yellow solid that was purified by chromatography (pet. ether/Et_2O, 9:1 to 4:1) to afford the intermediate racemic epoxide (6.4 g, 59%) as a yellow oil.

To a solution of (*S*,*S*)-N,N'-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt (II) (0.15 g, 0.25 mmol) in CH_2Cl_2 (3.1 mL) was added AcOH (28 μl, 0.50 mmol), under an open atmosphere, and the mixture was stirred for 30 minutes at rt. Concentration of the mixture *in vacuo* afforded a black residue, which was then dried for 20 minutes under high vacuum and dissolved in THF (7 mL). The catalyst solution was added to the concentrated epoxide (5.3 g, 25 mmol) and stirred until uniform mixing was achieved. The mixture was cooled to 0 °C and H_2O (0.25 mL, 14 mmol) was added dropwise over 15 minutes, the mixture was then stirred for 72 h at rt and purified directly by chromatography (pet. ether/Et_2O, 9:1 to 4:1) to yield the enantiopure epoxide **52** (2.1 g, 39%, *ee* >90%) as a clear, colourless oil (R_f = 0.32 (pet. ether/Et_2O, 1:1); $[\alpha]_D^{24}$ −14.9 (c = 1.02, $CHCl_3$) [lit. $[\alpha]_D^{26}$ −13.9 (c = 1.0, $CHCl_3$)][14]; ν_{max} (liquid film) 2998, 2933, 2837, 1611, 1512, 1244, 1086, 1032, 818 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (2H,d, *J* = 8.6 Hz, CH-PMB Ar), 6.88 (2H,d, *J* = 8.6 Hz, CH-PMB Ar), 4.46 (2H,s, CH_2-PMB alkyl), 3.81 (3H,s, CH_3-PMB alkyl), 3.62–3.57 (2H,m, CH_2-C18), 3.08–3.04 (1H,m, CH-C20), 2.78 (1H,dd, *J* = 4.8, 4.1 Hz, CH-C21), 2.52 (1H, dd, *J* = 4.8, 2.7 Hz, CH-C21), 1.93–1.87 (1H,m, CH-C19), 1.77 (1H,m, CH-C19); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6 (C-PMB Ar), 130.8 (C-PMB Ar), 129.6 (CH-PMB Ar), 114.2 (CH-PMB Ar), 73.1 (CH_2-PMB alkyl), 67.1 (CH_2-C18), 55.6 (CH_3-PMB alkyl), 50.4 (CH-C20), 47.4 (CH_2-C21), 33.3 (CH_2-C19).

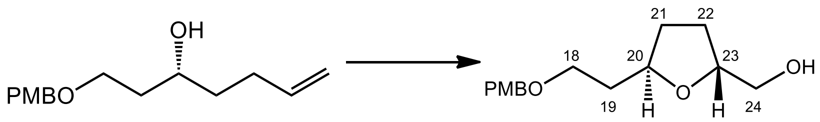
(3*R*)-1-[(4-Methoxyphenyl)methoxy]hept-6-en-3-ol.[25] (353)



Allylmagnesium chloride (6.7 mL of a 2 M solution, 13.4 mmol) was added dropwise, over 10 minutes to a stirred solution of epoxide **52** (1.8 g, 1.9 mmol) in THF (81 mL) at 0 °C. The mixture was stirred for 1 hand the reaction was quenched with saturated aqueous NH_4Cl (50 mL). The mixture was extracted with Et_2O (3 × 50 mL), washed with brine (75 mL), dried ($MgSO_4$) and concentrated. The resultant residue was purified by column chromatography (pet. ether/Et_2O, 9:1 to 3:1) to afford the desired secondary alcohol **353** (1.9 g, 86%) as a clear oil. R_f = 0.19 (pet. ether/Et_2O, 1:1); $[\alpha]_D^{24}$ +12.7 (c = 1.01, $CHCl_3$); ν_{max} (liquid film) 2998, 2933, 2837, 1611, 1512, 1244, 1086, 1032, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 6.88 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 5.84 (1H, ddt, *J* = 17.1, 10.2, 6.7 Hz, CH-C23), 5.03 (1H, ddd, *J* = 17.1, 3.4, 1.6 Hz, CH-C24 *trans*), 4.96 (1H, ddd, *J* = 10.2, 3.4, 1.2 Hz, CH-C24 *cis*), 4.45 (2H, s, CH_2-PMB alkyl), 3.85–3.78 (1H, m, CH-C20), 3.80 (3H, s, CH_3-PMB alkyl), 3.73-3.67 (1H, m, CH-C18), 3.66-3.59 (1H, m, CH-C18), 2.92 (1H, d, *J* = 3.2 Hz, OH-C20), 2.26–2.06 (2H, m, CH_2-C22), 1.76–1.71 (2H, m, CH_2-C19), 1.64–1.46 (2H, m, CH_2-C21); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (C-PMB Ar), 138.8 (CH-C23), 130.2 (C-PMB Ar), 129.5

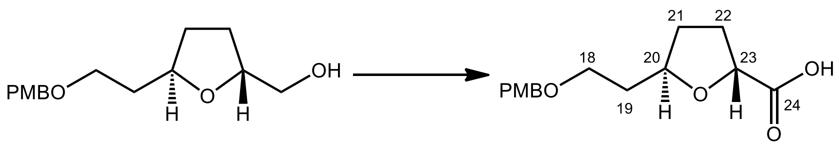
(CH-PMB Ar), 114.7 (CH-C24), 114.0 (CH-PMB Ar), 73.1 (CH_2-PMB alkyl), 71.1 (CH-C20), 69.1 (CH_2-C18), 55.4 (CH_3-PMB alkyl), 36.7 (CH_2-C21), 36.5 (CH_2-C19), 30.1 (CH_2-C22); HRMS (EI+) $[M]^+$ calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1574 (Δ +1.1 ppm).

[(2*R*,5*R*)-5-{2-[(4-Methoxyphenyl)methoxy]ethyl}tetrahydrofuran-2-yl]methanol. (350)



To a solution of $Co(NMP)_2$ **358** (0.43 g, 0.76 mmol)[223] in *i*-PrOH (76 mL) under an O_2 atmosphere was added alkenol **349** (1.9 g, 7.6 mmol) in *i*-PrOH (5 mL) and *t*-BuOOH. The mixture was heated at 55 °C for 17 h, cooled to rt and MeI (0.47 mL, 7.6 mmol) was added to the mixture. The reaction was quenched by the addition of H_2O (50 mL), and the mixture was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were dried ($MgSO_4$), concentrated to give a residue that was purified by column chromatography (pet. ether/Et_2O, 4:1 to 1:1) to afford tetrahydrofuran **346** (1.3 g, 65%) as a clear oil. The ^1H, ^{13}C NMR and optical rotation data matches the previously characterised sample.

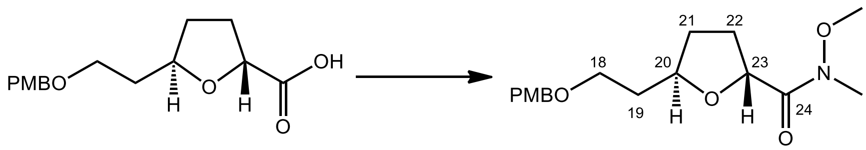
(2*R*,5*R*)-5-{2-[(4-Methoxyphenyl)methoxy]ethyl}tetrahydrofuran-2-carboxylic acid.



Dess-Martin periodinane (0.94 g, 2.2 mmol) was added to a solution of alcohol **350** (0.45 g, 1.7 mmol) of CH_2Cl_2 (22 mL). The mixture was stirred for 2 h at rt and the reaction was quenched with $NaHCO_3$ (10 mL). The mixture was extracted with Et_2O (3 × 30 mL) and the combined layers were dried ($MgSO_4$) and concentrated before filtration through a silica gel pad (pet. ether/Et_2O, 1:1) to provide a clear, colourless oil. The product was dissolved in a solution of *t*-BuOH (8.5 mL) and 2-methyl-2-butene (1.4 mL, 13.6 mmol) to which was added dropwise a solution of $NaClO_2$ (0.92 g, 10.2 mmol) and $NaH_2PO_4.2H_2O$ (1.7 g, 11.1 mmol) in H_2O (17 mL). The mixture was stirred for 2 h at rt and then the reaction was concentrated *in vacuo* and partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic phase was isolated and the aqueous phase was back-extracted with further CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to provide the intermediate carboxylic acid (0.33 g, 69% over two steps) as a clear, colourless oil. R_f = 0.14 (Et_2O); $[\alpha]_D^{25}$ +12.5 (c = 1.02, $CHCl_3$);

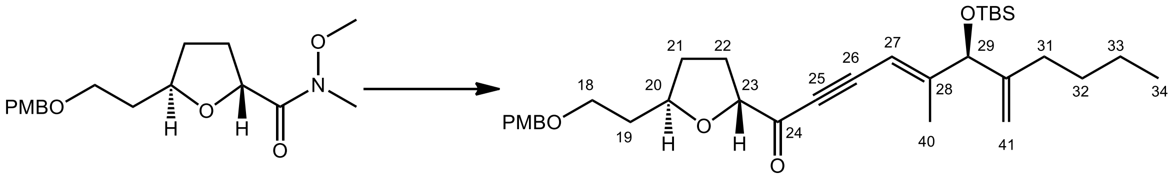
ν_{max} (liquid film) 2938, 2932, 2870, 1723, 1512, 1245, 1080, 818, 751 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 6.88 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 4.52–4.47 (1H, m, CH-C23), 4.44 (2H, s, CH_2-PMB alkyl), 4.33–4.26 (1H, m, CH-C20), 3.81 (3H, s, CH_3-PMB alkyl), 3.60–3.53 (2H, m, CH_2-C18), 2.43–2.34 (1H, m, CH-C22), 2.14–2.04 (2H, m, CH-C21 and CH-C22), 1.93–1.78 (2H, m, CH_2-C19), 1.70–1.61 (1H, m, CH-C21); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6 (C-C24), 159.6 (C-PMB Ar), 130.7 (C-PMB Ar), 129.4 (CH-PMB Ar), 114.1 (CH-PMB Ar), 79.2 (CH-C20), 76.6 (CH-C23), 73.0 (CH_2-PMB alkyl), 66.9 (CH_2-C18), 55.5 (CH_3-PMB alkyl), 35.5 (CH_2-C19), 31.7 (CH_2-C21), 30.0 (CH_2-C22); HRMS (EI+, isobutane) calcd for $C_{15}H_{20}O_5$ $[M+H]^+$ 280.1311, found 280.1314, (Δ +1.2 ppm).

(2*R*,5*R*)-N-Methoxy-5-{2-[(4-methoxyphenyl)methoxy]ethyl}-N-methyltetrahydrofuran-2-carboxamide. (416)



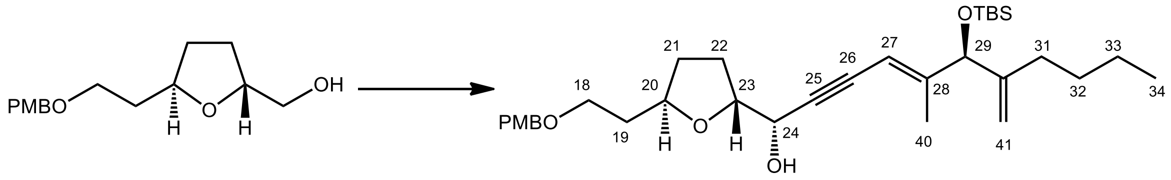
A solution of the carboxylic acid (0.32 g, 1.1 mmol), *N*,*O*-dimethyhydroxylamine.HCl (0.21 g, 2.2 mmol), HBTU (0.43 g, 2.2 mmol) and DIPEA (0.84 mL, 4.8 mmol) in CH_2Cl_2 (13 mL) was stirred for 16 h at rt. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were dried ($MgSO_4$), concentrated and the resultant residue was purified by column chromatography (pet. ether/Et_2O 1:1 to Et_2O) to afford of the Weinreb amide **416** (0.33 g, 88%) as a clear, colourless oil. R_f = 0.27 (Et_2O); $[\alpha]_D^{24}$ −3.63 (c = 1.17, $CHCl_3$); ν_{max} (liquid film) 2938, 2857, 1674, 1513, 1247, 1079, 1033, 819 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 6.87 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 4.85–4.79 (1H, m, CH-C23), 4.43 (1H, s, CH_2-PMB alkyl), 4.42 (1H, s, CH_2-PMB alkyl),4.28 (1H, ddd, *J* = 13.1, 7.3, 5.7 Hz, CH-C20), 3.80 (3H, s, CH_3-PMB alkyl), 3.70 (3H, s, CH_3-MeO), 3.62–3.53 (2H, m, CH_2-C18), 3.19 (3H, s, CH_3-MeN), 2.24–2.16 (1H, m, CH-C22), 2.16–2.02 (2H, m, CH-C21 and CH-C22), 1.93 (1H, ddd, *J* = 12.8, 10.3, 6.4 Hz, CH-C19), 1.82 (1H, dtd, *J* = 12.8, 7.3, 5.7 Hz, CH-C19), 1.62–1.53 (1H, m, CH-C21); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2 (C-C24) 159.4 (C-PMB Ar), 131.0 (C-PMB Ar), 129.3 (CH-PMB Ar), 114.0 (CH-PMB Ar), 78.4 (CH-C20), 75.1 (CH-C23), 72.9 (CH_2-PMB alkyl), 67.7 (CH_2-C18), 61.5 (CH_3-MeO), 55.5 (CH_3-PMB alkyl), 35.9 (CH_2-C19), 31.8 (CH_3-MeN and CH_2-C21), 29.4 (CH_2-C22); HRMS (CI+, isobutane) calcd for $C_{17}H_{26}NO_5$ $[M+H]^+$ 324.1811, found 324.1806, (Δ−1.4 ppm); LRMS (CI+, isobutene) *m*/*z* (intensity); 324.3 (17%), 292.2 (16%), 241.2 (16%), 216.2 (10%), 204.2 (20%), 172.2 (28%), 121.1 (100%).

(4*E*,6*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2*R*,5*R*)-5-{2-[(4-methoxyphenyl) methoxy]ethyl}tetrahydrofuran-2-yl]-5-methyl-7-methylideneundec-4-en-2-yn-1-one. (414)



To a stirred solution of alkyne **412** (0.36 g, 1.2 mmol) in of THF (4 mL) at 0 °C was added dropwise *n*-BuLi (0.37 mL of a 2.5 M solution in hexane, 1.2 mmol). The reaction was stirred 30 minutes and transferred to a precooled −78 °C solution of Weinreb amide **416** (0.20 g, 0.62 mmol) in of THF (4 mL). The solution was stirred for a further 30 minutes and the reaction was quenched with a saturated aqueous solution of NH_4Cl (5 mL). The mixture was extracted with Et_2O (2 x 10 mL), the combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography (pet. ether to pet. ether/Et_2O, 2:1) to provide ynone **418** as a clear, colourless oil (0.33 g, 95%).R_f = 0.46 (pet. ether/Et_2O, 2:1); $[\alpha]_D^{25}$ +19.2 (c = 1.00, $CHCl_3$); ν_{max} (liquid film) 2954, 2929, 2857, 1664, 1614, 1513, 1247, 1086, 867, 835, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 6.87 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 5.86 (1H, s, CH-C27), 5.08 (1H, s, CH-C41), 4.93 (1H, d, *J* = 1.3 Hz, CH-C41), 4.55–4.49 (2H, m, CH-23 and CH-C29), 4.44 (2H, d, *J* = 5.4 Hz, CH_2-PMB alkyl), 4.33–4.25 (1H, m, CH-C20), 3.80 (3H, s, CH_3-PMB alkyl), 3.63–3.53 (2H, m, CH_2-C18), 2.35–2.25 (1H, m, CH-C22), 2.14–2.03 (2H, m, CH-C21 and CH-C22), 2.00–1.90 (2H, m, CH-C19 and CH-C31), 1.86 (3H, s, CH_3-C40), 1.85–1.75 (2H, m, CH-C19 and CH-C31), 1.68–1.56 (1H, m, CH-C21), 1.46–1.36 (2H, m, CH_2-C32), 1.36–1.25 (2H, m, CH_2-C33), 0.91 (9H, s, CH_3-^{t}BuSi), 0.90 (3H, t, *J* = 7.2 Hz, CH_3-C34), 0.04 (3H, s, CH_3-MeSi), 0.04 (3H, s, CH_3-MeSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.3 (C-C24), 161.0 (C-C28), 159.5 (C-PMB Ar), 148.9 (C-C30), 130.9 (C-PMB Ar), 129.3 (CH-PMB Ar), 114.1 (CH-PMB Ar), 112.1 (CH_2-C41), 103.5 (CH-C27), 92.9 (C-C25), 90.9 (C-C26), 83.9 (CH-C29), 80.5 (CH-C23), 78.9 (CH-C20), 72.9 (CH_2-PMB alkyl), 67.5 (CH_2-C18), 55.5 (CH_3-PMB alkyl), 35.9 (CH_2-C19), 31.5 (CH_2-C21), 30.2 (CH_2-C32), 29.8 (CH_2-C31), 29.7 (CH_2-C22), 25.9 (CH_3-^{t}BuSi), 22.7 (CH_2-C33), 18.4 (C-^{t}BuSi), 16.5 (CH_3-C40), 14.1 (CH_3-C34), −4.8 (CH_3-MeSi), −5.0 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{33}H_{51}O_5Si$ $[M+H]^+$ 555.3506, found 555.3511, (Δ +0.9 ppm); LRMS (CI+, isobutene) *m*/*z* (intensity); 555.3 (100%).

(1*S*,4*E*,6*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2*R*,5*R*)-5-{2-[(4-methoxyphenyl) methoxy]ethyl}tetrahydrofuran-2-yl]-5-methyl-7-methylideneundec-4-en-2-yn-1-ol. (417b)

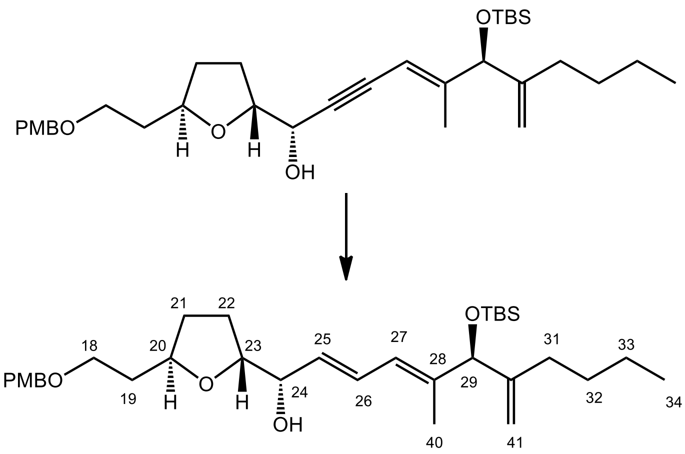


Dess-Martin periodinane (0.21 g, 0.48 mmol) was added as a single portion to a stirred solution of alcohol **350** (0.10 g, 0.38 mmol) in CH_2Cl_2 (5 mL) at rt. The mixture was stirred for 2 h and the reaction was quenched by the addition of a saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with Et_2O (3 × 5 mL) and the organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (pet. ether/Et_2O, 1:1) to afford the corresponding aldehyde.

The aldehyde was dissolved in THF (1.5 mL) and cooled to -78 °C. *n*-BuLi (0.16 mL of a 2.5 M solution in hexanes, 0.40 mmol) was added dropwise to a solution of alkyne **412** (0.12 g, 0.40 mmol) in THF (2 mL) at 0 °C and the mixture was stirred for 15 minutes before cooling to −78 °C. A solution of the aldehyde in THF (1.5 mL) was added dropwise to the alkyne anion and the mixture was stirred for a further 15 minutes before the reaction was quenched by the addition of saturated aqueous NH_4Cl (3 mL). On warming to rt the mixture was extracted with Et_2O (3 × 5mL) and the organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (pet. ether/Et_2O, 2:1) to afford a diastereomeric mixture of propargylic alcohols (0.15 g, 71%, *dr* C-23-C24 *anti*:*syn*, 3:2). Partial separation of the isomers by chromatography (pet. ether/Et_2O, 4:1) allowed for isolation of the pure C23,C24-*anti* diastereomer **417b**. R_f = 0.25 (pet. ether/Et_2O, 1:1); $[\alpha]_D^{25}$ +13.1 (c=2.05, $CHCl_3$); ν_{max} (liquid film) 3491, 2955, 2929, 2857, 2364, 1613, 1513, 1247, 1080, 871, 835, 775, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.6 Hz, CH-PMB Ar), 6.87 (2H, d, *J* = 8.6 Hz, CH-PMB Ar), 5.65 (1H, s, CH-C27), 5.07 (1H, s, CH-C41), 4.87 (1H, d, *J* = 1.4 Hz, CH-C41), 4.61-4.55 (1H, m, CH-C24), 4.43 (3H, s, CH_2-PMB alkyl and CH-C29), 4.22 (1H, tt, *J* = 7.7, 5.5 Hz, CH-C20), 4.16 (1H, td, *J* = 7.3, 3.4 Hz, CH-C23), 3.80 (3H, s, CH_3-PMB alkyl), 3.54 (2H, t, *J* = 6.5 Hz, CH_2-C18), 2.36 (1H, d, *J* = 5.4 Hz, OH-C24), 2.15–2.07 (1H, m, CH-C21), 2.07–1.99 (2H, m, CH_2-C22), 1.96–1.83 (2H, m, CH-C19 and CH-C31), 1.81–1.73 (2H, m, CH-C19 and CH-C31), 1.71 (3H, s, CH_3-C40), 1.66–1.53 (1H, m, CH-C21), 1.38 (2H, m, CH_2-C32), 1.34–1.23 (2H, m, CH_2-C33), 0.89 (3H, t, *J* = 7.2 Hz, CH_3-C34), 0.89 (9H, s, CH_3-^{t}BuSi), 0.01 (6H, s, CH_3-MeSi); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 159.3 (C- PMB Ar), 152.6 (C-C30), 149.2 (C-C28), 130.7 (C-PMB Ar), 129.4 (CH-PMB Ar), 113.9 (CH-PMB Ar), 111.0 (CH_2-C41), 104.9 (CH-C27), 90.7 (C-C26), 83.8 (C-C25), 81.0 (CH-C23), 80.1 (CH-C29), 78.4 (CH-C20), 72.8 (CH_2-PMB alkyl), 67.4 (CH_2-C18), 65.3 (CH-C24), 55.4 (CH_3-PMB alkyl), 36.0 (CH_2-C19), 32.4 (CH_2-C21), 30.1 (CH_2-C32), 30.0 (CH_2-C31), 26.8 (CH_2-C22), 25.9 (CH_3-^{t}BuSi), 22.7 (CH_2-C33), 18.4 (C-^{t}BuSi), 15.4 (CH_3-C40), 14.2 (CH_3-C34), −4.9 (CH_3-MeSi), −5.0 (CH_3-MeSi); HRMS (FAB+, NOBA) calcd for $C_{33}H_{53}O_5Si$ $[M+H]^+$ 557.3662, found 557.3662, (Δ +0.0 ppm).

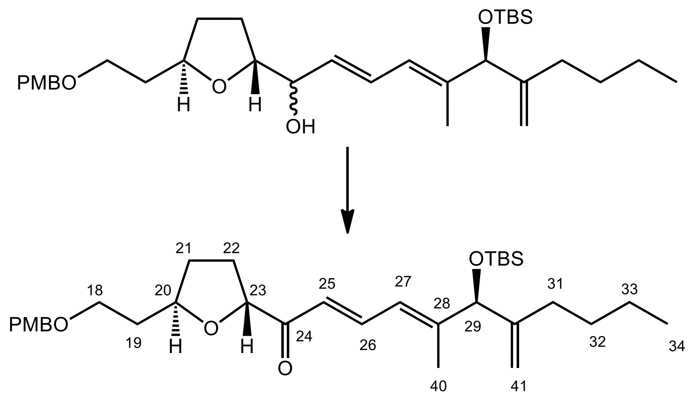
(1*S*,2*E*,4*E*,6*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2*R*,5*R*)-5-{2-[(4-methoxyphenyl) methoxy]ethyl}tetrahydrofuran-2-yl]-5-methyl-7-methylideneundeca-2,4-dien-1-ol. (419b)



To a solution of propargylic alcohol **417b** (68 mg, 0.12 mmol) in Et_2O (2 mL) at 0 °C was added Red-Al (74 mg of a >65% wt. solution in toluene, 0.24 mmol) and the solution stirred for 45 minutes. The reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and the mixture was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated. The crude residue was purified (pet. ether/Et_2O, 1:1) to provide of the desired dienol **419b** (59 mg, 88%) as a clear, colourless oil (88%). R_f = 0.23 (pet. ether/Et_2O, 1:1); $[\alpha]_D^{23}$ −7.3 (c = 1.01, $CHCl_3$); ν_{max} (liquid film) 3432, 2955, 2929, 2857, 1613, 1513, 1247, 1074, 834, 774, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 6.88 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 6.52 (1H, ddd, *J* = 15.2, 11.0, 1.2 Hz, CH-C26), 6.07 (1H, d, *J* = 11.0 Hz, CH-C27), 5.59 (1H, dd, *J* = 15.2, 6.6 Hz, CH-C25), 5.10 (1H, s, CH-C41), 4.85 (1H, s, CH-C41), 4.44 (2H, s, CH_2-PMB alkyl), 4.40 (1H, s, CH-C29), 4.32-4.39 (1H, m, CH-C24), 4.14 (1H, tdd, *J* = 11.4, 6.8, 4.5 Hz, CH-C20), 4.04–3.98 (1H, m, CH-C23), 3.80 (3H, s, CH_3-PMB alkyl), 3.55 (2H, t, *J* = 6.5 Hz, CH_2-C18), 2.20 (1H, br s, OH-C24), 2.11–2.02 (1H, m, CH-C21), 1.93–1.83 (4H, m, CH-C19, CH_2-C22 and CH-C31), 1.83–1.72 (2H, m, CH-C19 and CH-C31), 1.60 (3H, d, *J* = 0.8 Hz,

CH_3-C40), 1.59–1.50 (1H, m, CH-C21), 1.42–1.34 (2H, m, CH_2-C32), 1.33–1.24 (2H, m, CH_2-C33), 0.89 (9H, s, CH_3-^{t}BuSi), 0.88 (3H, t, *J* = 7.4 Hz, CH_3-C34), 0.02 (3H, s, CH_3-MeSi), 0.01 (3H, s, CH_3-MeSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3 (C-PMB Ar), 149.7 (C-C30), 139.6 (C-C28), 130.7 (C-PMB Ar), 130.3 (CH-C25), 129.4 (CH-PMB Ar), 128.4 (CH-C26), 124.9 (CH-C27), 113.9 (CH-PMB Ar), 109.9 (CH_2-C41), 81.5 (CH-23), 80.8 (CH-C29), 77.8 (CH-C20), 73.6 (CH-C24), 72.8 (CH_2-PMB alkyl), 67.4 (CH_2-C18), 55.4 (CH_3-PMB alkyl), 36.2 (CH_2-C19), 32.4 (CH_2-C21), 30.9 (CH_2-C31), 30.2 (CH_2-C32), 26.0 (CH_3-^{t}BuSi), 25.7 (CH_2-22), 22.7 (CH_2-C33), 18.4 (C-^{t}BuSi), 14.2 (CH_3-C34), 12.2 (CH_3-C40), −4.9 (CH_3-MeSi), −4.9 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{33}H_{55}O_5Si$ $[M+H]^+$ 559.3819, found 559.3808, (Δ −1.9 ppm).

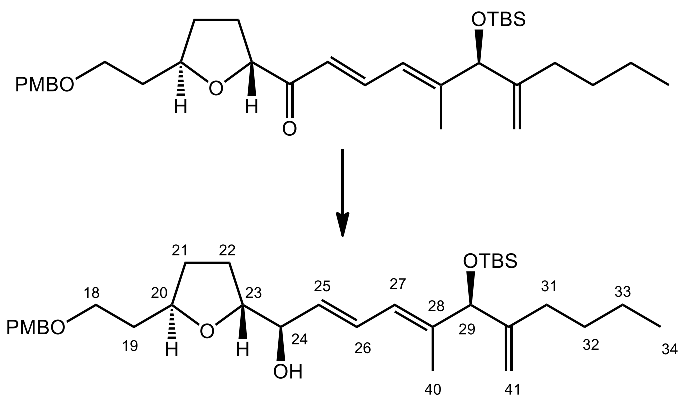
(2*E*,4*E*,6*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2*R*,5*R*)-5-{2-[(4-methoxyphenyl) methoxy]ethyl}oxolan-2-yl]-5-methyl-7-methylideneundeca-2,4-dien-1-one. (420)



Dienol **419** (0.19 g, 0.34 mmol, *dr* 1:1) was dissolved in CH_2Cl_2 (6 mL) to which was added Dess-Martin periodinane (0.17 g, 0.40 mmol) and mixture allowed to stir for 1 h at rt. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and the mixture was extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (pet. ether/Et_2O, 4:1) yielded the title dienone **420** (0.16 g, 87%) as a clear, colourless oil. R_f = 0.25 (pet. ether/Et_2O, 3:1); $[\alpha]_D^{24}$ +15.1 (c = 0.98, $CHCl_3$); ν_{max} (liquid film) 2954, 2929, 2857, 1681, 1613, 1585, 1247, 1079, 835, 775, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (1H, dd, *J* = 15.2, 11.8 Hz, CH-C26), 7.26 (2H, d, *J* = 8.7 Hz, CH_2-PMB Ar), 6.88 (2H, d, *J* = 8.7 Hz, CH_2-PMB Ar), 6.52 (1H, d, *J* = 15.2 Hz, CH-C25), 6.32 (1H, dd, *J* = 11.8, 0.8 Hz, CH-C27), 5.11 (1H, s, CH-C41), 4.90 (1H, d, *J* = 1.0 Hz, CH-C41), 4.57–4.50 (1H, m, CH-C23), 4.47 (1H, s, CH-C29), 4.45 (2H, s, CH_2-PMB alkyl), 4.44 (2H, s, CH_2-PMB alkyl), 4.23 (1H, ddd, *J* = 13.1, 7.2, 5.8 Hz, CH-C20), 3.80 (3H, s, CH_3-PMB alkyl), 3.59 (2H, t, *J* = 6.5 Hz, CH_2-C18), 2.32–2.21 (1H, m, CH-C22), 2.09–1.72 (6H, m, CH_2-C19, CH-C21, CH-C22 and CH_2-C31), 1.76 (3H, d, *J* = 1.0 Hz, CH_3-C40), 1.66–1.55 (1H, m, CH-

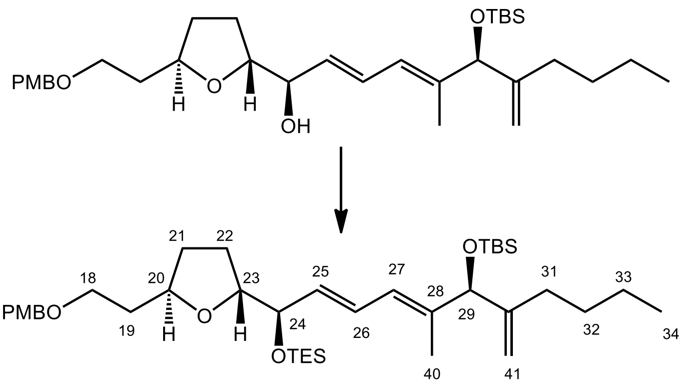
C21), 1.43–1.33 (2H, m, CH_2-C32), 1.33–1.23 (2H, m, CH_2-C33), 0.90 (9H, s, CH_3-^{t}BuSi), 0.87 (3H, t, J = 7.2 Hz, CH_3-C34), 0.03 (3H, s, CH_3–MeSi), 0.02 (3H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6 (C-C24), 159.3 (C-PMB Ar), 151.7 (C-C30), 149.1 (C-C28), 140.0 (CH-C26), 130.7 (C-PMB Ar), 129.4 (CH-PMB Ar), 124.0 (CH-C25), 123.9 (CH-C27), 113.9 (CH-PMB Ar), 111.0 (CH_2-C41), 82.7 (CH-C23), 80.9 (CH-C29), 78.4 (CH-C20), 72.9 (CH_2-PMB alkyl), 67.4 (CH_2-C18), 55.4 (CH_3-PMB alkyl), 35.8 (CH_2-C19), 31.7 (CH_2-C21), 30.4 (CH_2-C32), 30.1 (CH_2-C31), 29.7 (CH_2-C22), 25.9 (CH_3-^{t}BuSi), 22.7 (CH_2-C33), 18.4 (C-^{t}BuSi), 14.1 (CH_3-C34), 13.4 (CH_3-C40), −4.9 (CH_3-MeSi), −4.9 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{33}H_{53}O_5Si$ $[M+H]^+$ 557.3662, found 557.3661,(Δ −0.9 ppm); LRMS (CI+, isobutene) *m/z* (intensity); 557.5 (100%), 425.4 (32%), 243.3 (39%).

(1*R*,2*E*,4*E*,6*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2R,5*R*)-5-{2-[(4-methoxyphenyl) methoxy]ethyl}tetrahydrofuran-2-yl]-5-methyl-7-methylideneundeca-2,4-dien-1-ol. (419a)



To a solution of dienone **420** (0.16 g, 0.30 mmol) and $CeCl_3.7H_2O$ (0.15 g, 0.41 mmol) in methanol (34 mL) at −78 °C was added, in one portion, $NaBH_4$ (16 mg, 0.41 mmol). The reaction mixture was stirred for 30 minutes, concentrated and partitioned between Et_2O (10 mL) and saturated aqueous NH_4Cl (10 mL). The organic layer was isolated and the aqueous phase back-extracted with further Et_2O (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to afford dienol **419a** (0.16 g, 100%, *dr*>10:1) as a clear, colourless oil. R_f = 0.33 (pet. ether/Et_2O, 1:1); $[\alpha]_D^{24}$ −9.8 (c = 1.90, $CHCl_3$); ν_{max} (liquid film) 3438, 2954, 2929, 2857, 1612, 1513, 1247, 1073, 834, 774, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 8.6 Hz, CH-PMB Ar), 6.88 (2H, d, J = 8.6 Hz, CH-PMB Ar), 6.54 (1H,ddd, J = 15.1, 11.0, 0.8 Hz, CH-C26), 6.07 (1H, d, J = 11.0 Hz, CH-C27), 5.57 (1H, dd, J = 15.1, 7.2 Hz, CH-C25), 5.11 (1H, s, CH-C41), 4.85 (1H, s, CH-C41), 4.44 (2H, s, CH_2-PMB alkyl), 4.40 (1H, s, CH-C29), 4.09 (1H, dt, J = 7.6, 6.5 Hz, CH-C20), 3.96 (1H, t, J = 7.2 Hz, CH-C24), 3.87 (1H, ap q, J = 7.2 Hz, CH-C23), 3.80 (3H, s, CH_3-PMB alkyl), 3.56-3.53 (2H, m, CH_2-C18), 2.62 (1H, br s, OH-C24), 2.11–2.00 (1H, m, CH-C21), 2.00–1.72 (5H, m, CH_2-C19, CH-C22 and CH_2-C31), 1.71–1.50 (2H, m, CH-C21 and CH-C22), 1.60 (3H, s, CH_3-C40), 1.42–1.33 (2H, m, CH_2-C32), 1.33–1.22 (2H, m, CH_2-C33), 0.89 (9H, s, CH_3-^{t}BuSi), 0.87 (3H, t, J = 7.2 Hz, CH_3-C34), 0.02 (3H, s, CH_3-MeSi), 0.00 (3H, s, CH_3-MeSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5 (C-PMB Ar), 149.9 (C-C30), 140.0 (C-C28), 130.9 (C-PMB Ar), 130.7 (CH-C25), 129.6 (CH-PMB Ar), 129.2 (CH-C26), 125.1 (CH-C27), 114.1 (CH-PMB Ar), 110.1 (CH_2-C41), 82.1 (CH-C23), 81.0 (CH-C29), 76.9 (CH-C20), 75.9 (CH-C24), 73.0 (CH_2-PMB alkyl), 67.6 (CH_2-C18), 55.6 (CH_3-PMB alkyl), 36.1 (CH_2-C19), 32.6 (CH_2-C21), 31.1 (CH_2-C31), 30.4 (CH_2-C32), 28.4 (CH_2-C22), 26.2 (CH_3-^{t}BuSi), 22.9 (CH_2-C33), 18.6 (C-^{t}BuSi), 14.4 (CH_3-C34), 12.4 (CH_3-C40), −4.67 (CH_3-MeSi), −4.72 (CH_3-MeSi); HRMS (EI+) calcd for $C_{33}H_{52}O_4Si$ $[M{-}H_2O]^+$ 540.3630, found 540.3639,(Δ +0.7 ppm).

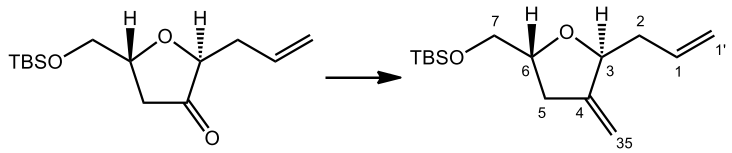
(5*S*,6*E*,8*E*,10*R*)-12,12-Diethyl-5-(hex-1-en-2-yl)-10-[(2*R*,5*R*)-5-{2-[(4-methoxyphenyl)methoxy]ethyl}tetrahydrofuran-2-yl]-2,2,3,3,6-pentamethyl-4,11-dioxa-3,12-disilatetradeca-6,8-diene. (407)



To a stirred solution of alcohol **419a** (47 mg, 0.08 mmol) and 2,6-lutidine (29 µl, 0.25 mmol) in CH_2Cl_2 (2 mL) at rt was added TES triflate (23 µl, 0.10 mmol). The solution was stirred for 2 h and the reaction was quenched with 0.5 M aqueous HCl (5 mL). The mixture was extracted with Et_2O (2 × 5 mL), the combined organic layers were dried ($MgSO_4$) and concentrated to a crude residue that was purified by chromatography (pet. ether/Et_2O, 3:1) to yield of the title compound **407** (43 mg, 76%) as a clear colourless oil and unreacted starting alcohol (10 mg, 21%). R_f = 0.36 (pet. ether/Et_2O, 9:1); $[\alpha]_D^{25}$ −9.5 (c = 1.00, $CHCl_3$); ν_{max} (liquid film) 2954, 2929, 2875, 2857, 1613, 1513, 1247, 1078, 834, 774, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 8.7 Hz, CH-PMB Ar), 6.87 (2H, d, J = 8.7 Hz, CH-PMB Ar), 6.46 (1H, ddd, J = 15.2, 11.0, 1.2 Hz, CH-C26), 6.05 (1H, d, J = 11.0 Hz, CH-C27), 5.65 (1H, dd, J = 15.2, 6.2 Hz, CH-C25), 5.12 (1H, s, CH-C41), 4.85 (1H, s, CH-C41), 4.45 (1H, d, J = 11.5 Hz, CH-PMB alkyl), 4.41 (1H, d, J = 11.5 Hz, CH-PMB alkyl), 4.40 (1H, s, CH-C29), 4.16 (1H, t, J = 5.5 Hz, CH-C24), 4.04-3.97

(1H, m, CH-C20), 3.97-3.92 (1H, m, CH-C23), 3.80 (3H, s, CH_3-PMB alkyl), 3.60–3.50 (2H, m, CH_2-C18), 2.00–1.93 (1H, m, CH-C21), 1.92–1.67 (6H, m, CH_2-C19, CH_2-C22 and CH_2-C31), 1.58 (3H, d, *J* = 0.9 Hz, CH_3-C40), 1.53–1.44 (1H, m, CH-C21), 1.42–1.34 (2H, m, CH_2-C32), 1.33–1.24 (2H, m, CH_2-C33), 0.95 (9H, t, *J* = 7.9 Hz, CH_3-EtSi), 0.89 (9H, s, CH_3-^{t}BuSi), 0.87 (3H, t, *J* = 7.2 Hz, CH_3-C34), 0.60 (6H, q, *J* = 7.9 Hz, CH_2-EtSi), 0.01 (3H, s, CH_3-MeSi), 0.00 (3H, s, CH_3-MeSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3 (C-PMB Ar), 149.8 (C-C30), 138.4 (C-C28) 132.3 (CH-C25), 130.9 (C-PMB Ar), 129.4 (CH-PMB Ar), 127.4 (CH-C26), 125.5 (CH-C27), 113.9 (CH-PMB Ar), 109.7 (CH_2-C41), 82.1 (CH-C23), 80.8 (CH-C29), 77.0 (CH-C20), 75.8 (CH-C24), 72.8 (CH_2-PMB alkyl), 67.8 (CH_2-C18), 55.7 (CH_3-PMB alkyl), 36.1 (CH_2-C19), 32.4 (CH_2-C21), 31.1 (CH_2-C31), 30.3 (CH_2-C32), 27.6 (CH_2-22), 26.0 (CH_3-^{t}BuSi), 22.7 (CH_2-C33), 18.4 (C-^{t}BuSi), 14.2 (CH_3-C34), 12.0 (CH_3-C40), 7.0 (CH_3-EtSi), 5.1 (CH_2-EtSi), −4.9 (CH_3-MeSi), −4.9 (CH_3-MeSi); HRMS (EI+) $[M]^+$ calcd for $C_{39}H_{68}O_5Si_2$ 672.4605, found 672.4612, (Δ +1.0 ppm).

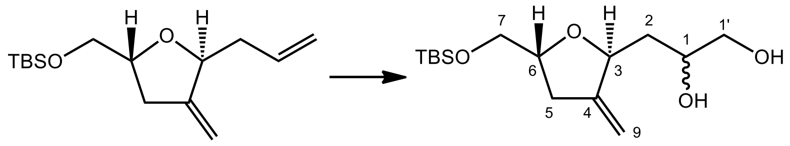
***tert*-Butyldimethyl{[(2*R*,5*S*)-4-methylidene-5-(prop-2-en-1-yl)tetrahydrofuran-2-yl]methoxy}silane. (423)**



t-BuOK (25 mL of a 2 M solution in THF, 50 mmol) was added to a suspension of methyltriphenylphosphonium bromide (18 g, 50 mmol) in THF (83 mL) at rt and stirred for 1 h. A solution of the ketone **327a** (4.5 g, 17 mmol) in THF (65 mL) was added to the suspension of the ylide at rt and the mixture was stirred for 30 minutes. The reaction was quenched by the addition of H_2O (100 mL) and the mixture was extracted with EtOAc (3 × 200 mL). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*, and the residue was purified by chromatography (pet. ether/EtOAc, 20:1) to provide the desired diene **423** (4.5 g, 100%) as a colourless oil. R_f = 0.49 (pet. ether/EtOAc, 20:1); $[\alpha]_D^{22}$ −53 (*c* = 0.99, $CHCl_3$); $\nu_{max.}$ (liquid film) 3078, 2954, 2929, 2858, 1667, 1641, 1471, 1254, 1077, 834, 814, 775, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, CH-C1), 5.14–5.04 (2H, m, CH_2-C1’), 5.00 (1H, q, *J* = 2.2 Hz, CH-C35), 4.86 (1H, q, *J* = 2.2 Hz, CH-C35), 4.50–4.43 (1H, m, CH-C3), 4.18-4.11 (1H, m, CH-C6), 3.64 (1H, dd, *J* = 10.4, 4.6 Hz, CH-C7), 3.53 (1H, dd, *J* = 10.4, 6.1 Hz, CH-C7), 2.69–2.61 (1H, m, CH-C5), 2.54–2.46 (1H, m, CH-C5), 2.41–2.25 (2H, m, CH_2-C2), 0.88 (9H, s, CH_3-^{t}BuSi), 0.05 (6H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8 (C-C4), 134.8 (CH-C1), 117.2 (CH_2-C1’), 105.2 (CH_2-C35), 80.1 (CH-C3), 78.1 (CH-C6), 65.5 (CH_2-C7), 40.3 (CH_2-C2), 35.2 (CH_2-C5), 26.0 (CH_3-^{t}BuSi), 18.5 (C-^{t}BuSi), −5.2 (CH_3-

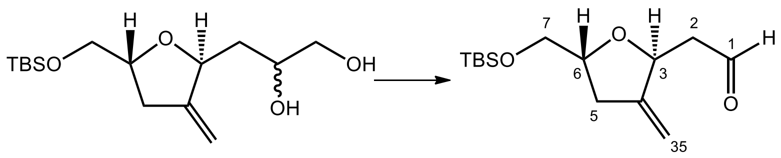
MeSi); HRMS (CI+, isobutane) calcd for $C_{15}H_{29}O_2Si$ $[M+H]^+$ 269.1937, found 269.1933 (Δ −1.3 ppm). Anal. calcd for $C_{15}H_{28}O_2Si$ C 67.11%, H 10.51%, found C 67.10%, H 10.57%.

3-[(2*S*,5*R*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-methylidenetetrahydrofuran-2-yl]propane-1,2-diol. (424)



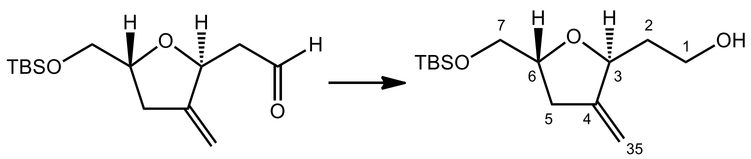
OsO_4 (0.88 mL of a 4% aqueous solution, 0.15 mmol) was added to a solution of diene **423** (2.2 g, 8.2 mmol) and NMO (1.2 g, 10 mmol) in a mixture of THF (100 mL) and H_2O (11 mL), and the mixture was stirred for 16 h at rt. The reaction was quenched by the addition of solid Na_2SO_3 (3.2 g) and the mixture was allowed to stir for 30 minutes before being partitioned between CH_2Cl_2 (125 mL) and H_2O (100 mL). The organic phase was extracted with CH_2Cl_2 (2 × 100 mL), dried ($MgSO_4$)and concentrated. The residue was purification by chromatography (pet. ether/EtOAc, 1:1 to 1:3) to give a diasteromeric mixture of diols **424** (1.6 g, 64%, *dr* = 1:1) as a colourless oil. Analyses were conducted on a diastereomeric mixture of C-1 alcohols. R_f = 0.21 (pet. ether/EtOAc, 1:1); $\nu_{max.}$ (liquid film) 3387, 3078, 2954, 2931, 2862, 1667, 1249, 1072, 833, 779, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.03 (0.5H, q, *J* = 2.2 Hz, CH-C35), 5.01 (0.5H, q, *J* = 2.2 Hz, CH-C35), 4.86 (0.5H, q, *J* = 2.2 Hz, CH-C35), 4.84 (0.5H, q, *J* = 2.3 Hz, CH-C35), 4.71–4.62 (1H, m, CH-C3), 4.23–4.15 (1H, m, CH-C6), 4.03–3.91 (1H, m, CH-C1), 3.87 (0.5H, d, *J* = 1.6 Hz, OH-C1), 3.69–3.50 (4H, m, CH_2-C1’ and CH_2-C7), 3.15 (0.5H, d, *J* = 4.1 Hz, OH-C1), 2.73–2.60 (1H, m, CH_2-C5), 2.58–2.45 (1H, m, CH_2-C5), 2.37 (0.5H, t, *J* = 5.9 Hz, OH-C1’), 2.20 (0.5H, t, *J* = 6.2 Hz, OH-C1’), 1.92 (0.5H, dd, *J* = 8.2, 3.3 Hz, CH-C2), 1.88 (0.5H, dd, *J* = 8.2, 3.3 Hz, CH-C2), 1.78–1.63 (1.5H, m), 0.89 (4.5H, s, CH_3-^{t}BuSi), 0.88 (4.5H, s, CH_3-^{t}BuSi), 0.06 (3H, s, CH_3-MeSi), 0.05 (3H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8 (C-C4), 150.5 (C-C4), 105.4 (CH-C35), 105.3 (CH-C35), 80.3 (CH-C3), 78.4 (CH-C6), 78.4 (CH-C6), 78.2 (CH-C3), 71.6 (CH-C1), 70.0 (CH-C1), 67.0 (CH_2-C1’), 66.6 (CH_2-C1’), 65.4 (CH_2-C7), 65.3 (CH_2-C7), 38.3 (CH_2-C2), 37.7 (CH_2-C2), 34.9 (CH_2-C5), 34.5 (CH_2-C5), 26.0 (CH_3-^{t}BuSi), 18.4 (C-^{t}BuSi), −5.2 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{15}H_{31}O_4Si$ $[M+H]^+$ 303.1991, found 303.1996 (Δ +1.4 ppm). Anal. calcd for $C_{15}H_{30}O_4Si$ C 59.56%, H 10.00%, found C 59.26%, H 9.95%.

2-[(2*S*,5*R*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-methylidenetetrahydrofuran-2-yl]acetaldehyde. (425)



Sodium periodate (3.5 g, 16 mmol) was added to a stirred solution of the diol **424** (2.5 g, 8.3 mmol) in a mixture of THF (141 mL) and H_2O (35 mL) and the mixture was stirred for 1.5 h at rt. The mixture was diluted with H_2O and extracted with Et_2O (2 × 75 mL). The organic extracts were dried ($MgSO_4$) and concentrated, and the resulting crude aldehyde was used in the following step. A small sample was purified by chromatography (pet. ether/EtOAc, 4:1) for characterization purposes. $\nu_{max.}$ (liquid film) 2953, 2931, 2894, 2857, 1666, 1727, 1254, 1076, 836, 775, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, t, *J* = 2.3 Hz, CH-C1), 5.06 (1H, q, *J* = 2.2 Hz, CH-C35), 4.93–4.88 (1H, m, CH-C3), 4.87 (1H, q, *J* = 2.2 Hz, CH–C35), 4.18 (1H, dddd, *J* = 7.3, 5.6, 5.2, 4.5 Hz, CH-C6), 3.64 (1H, dd, *J* = 10.6, 4.5 Hz, CH–C7), 3.60 (1H, dd, *J* = 10.6, 5.2 Hz, CH–C7), 2.73–2.64 (3H, m, CH_2–C2 and CH–C5), 2.62–2.54 (1H, m, CH–C5), 0.88 (9H, s, CH_3-^{t}BuSi), 0.05 (3H, s, CH_3-MeSi), 0.05 (3H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3 (C–C1), 150.3 (C-C4), 105.9 (CH_2-C35), 78.5 (CH–C6), 75.8 (CH-C3), 65.5 (CH_2-C7), 49.3 (CH_2-C5), 34.7 (CH_2-C2), 26.0 (CH_3-^{t}BuSi), 18.5 (C-^{t}BuSi), −5.2 (CH_3-MeSi), −5.2 (CH_3-MeSi).

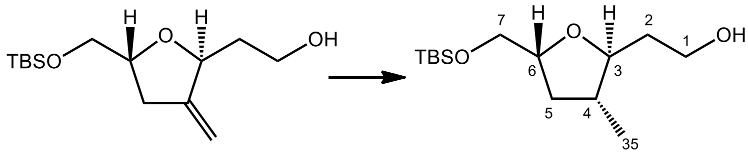
2-[(2*S*,5*R*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-methylidenetetrahydrofuran-2-yl]ethan-1-ol. (426)



The crude aldehyde **425** was dissolved in wet EtOH (92 mL) and solid $NaBH_4$ (0.33 g, 8.7 mmol) was added. The mixture was stirred for 1 h at rt, concentrated and then partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL). The phases were separated and the aqueous phase was extracted with further CH_2Cl_2 (2 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (pet. ether/EtOAc, 3:1) to provide the alcohol **426** (1.8 g, 80% over two steps) as a colourless oil. R_f = 0.19 (pet. ether/EtOAc, 4:1); $[\alpha]_D^{26}$ −42.8 (*c* = 1.00, $CHCl_3$); $\nu_{max.}$ (liquid film) 3426, 3078, 2931, 2855, 1667, 1466, 1249, 1065, 833, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (1H, q, *J* = 2.2 Hz, CH-C35), 4.84 (1H, q, *J* = 2.2 Hz, CH-

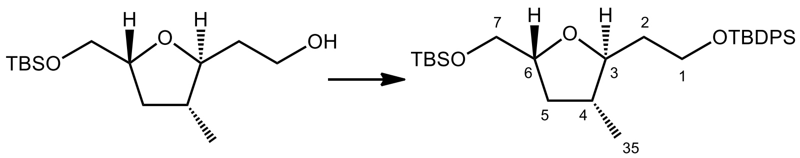
C35), 4.65–4.59 (1H, m, CH-C3), 4.17 (1H, dddd, J = 7.1, 6.1, 5.1, 5.0 Hz, CH-C6), 3.88–3.76 (2H, m, CH_2-C1), 3.63 (1H, dd, J = 10.6, 5.0 Hz, CH_2-C7), 3.59 (1H, dd, J = 10.6, 5.1 Hz, CH_2-C7), 2.84 (1H, dd, J = 7.0, 4.2 Hz, OH-C1), 2.69–2.61 (1H, m, CH-C5), 2.55–2.47 (1H, m, CH-C5), 1.89–1.74 (2H, m, CH_2-C2), 0.88 (9H, s, CH_3-^{t}BuSi), 0.05 (6H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0 (C-C4), 105.1 (CH_2-C35), 81.0 (CH-C6), 78.2 (CH-C3), 65.3 (CH_2-C7), 61.7 (CH_2-C1), 37.1 (CH-C2), 34.8 (CH_2-C5), 26.0 (CH_3-^{t}BuSi), 18.4 (C-^{t}BuSi), −5.2 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{14}H_{29}O_3Si$ $[M+H]^+$ 273.1886, found 273.1885 (Δ −0.4 ppm); Anal. calcd for $C_{14}H_{28}O_3Si$ C 61.72%, H 10.36%, found C 61.71%, H 10.41%.

2-[(2*S*,3*R*,5*R*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-methyltetrahydrofuran-2-yl]ethan-1-ol.[21] (433)



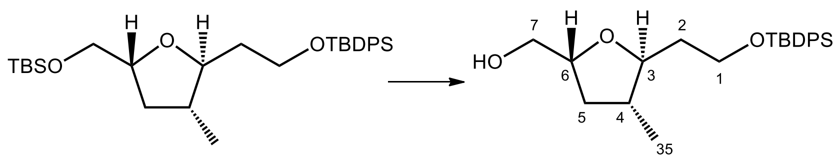
Crabtree's catalyst (0.25 g, 0.27 mmol) was dissolved in CH_2Cl_2 (160 mL) under an atmosphere of argon. The argon was evacuated and replaced with H_2; purging/H_2 replacement was repeated twice more. The mixture stirred for under the hydrogen atmosphere until a visible lessening in color intensity was observed (~10 min), at which point the alkene **426** (1.00 g, 3.67 mmol) in CH_2Cl_2 (6 mL) was added dropwise to the solution of the catalyst. After 2 h, an aliquot (0.3 mL) was removed from the reaction vessel, dried *in vacuo* and analyzed by ^{1}H NMR to ensure that alkene reduction had occurred. The reaction mixture was used directly in the following step; an aliquot was purified for characterization purposes. R_f = 0.21 (pet. ether/EtOAc, 4:1); $[\alpha]_D^{25}$ −14.0 (c = 1.01, $CHCl_3$). $\nu_{max.}$ (liquid film) 3425, 2956, 2928, 2903, 2857, 1473, 1251, 1103, 1049, 938, 833, 814, 774 cm^{-1}; ^{1}H NMR (500 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-C1), 2.10 (1H, dt, J = 12.2, 6.6 Hz, CH_2-C5), 1.95–1.88 (1H, m, CH-C4), 1.88–1.82 (1H, m, CH_2-C2), 1.65 (1H, dddd, J = 14.0, 9.1, 8.0, 4.7 Hz, CH_2-C2), 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_3-^{t}BuSi), 0.07 (6H, s, CH_3-MeSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 86.0 (CH-C3), 79.1 (CH-C6), 66.2 (CH_2-C7), 62.0 (CH_2-C1), 40.4 (CH-C4), 37.0 (CH_2-C5), 35.7 (CH_2-C2), 26.1 (CH_3-^{t}BuSi), 18.5 (C-^{t}BuSi), 16.2 (CH_3 -C35), −5.1 (CH_3-MeSi), −5.2 (CH_3-MeSi); HRMS (CI+, isobutane) calcd for $C_{14}H_{31}O_3Si$ $[M+H]^+$ 275.2042, found 275.2041 (Δ −0.5 ppm).

***tert*-Butyl({[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]methoxy})dimethylsilane. (434)**



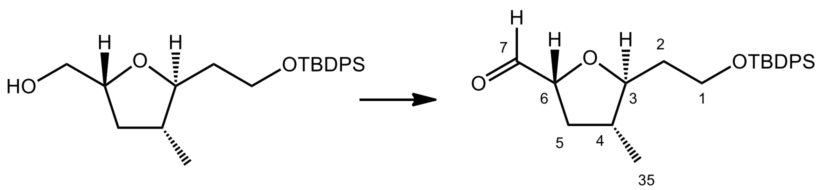
The H_2 amosphere was replaced with argon before the sequential addition of Et_3N (0.47 mL, 3.39 mmol), TBDPSCl (1.05 mL, 4.03 mmol) and DMAP (0.12 g, 0.94 mmol). The resulting mixture was stirred for 36 h at rt and then concentrated. The residue was partitioned between CH_2Cl_2 (50 mL) and 1 M aqueous HCl (50 mL), the phases were separated and the organic extracts were further extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The reaction mixture was used directly in the following step; an aliquot was purified for characterization purposes. R_f = 0.55 (pet. ether/EtOAc, 4:1); $[\alpha]_D^{24}$ −12.8 (*c* = 1.02, $CHCl_3$); $\nu_{max.}$ (liquid film) 2955, 2929, 2885, 2857, 1472, 1428, 1252, 1107, 834, 776, 737, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.65 (4H, m, CH-PhSi), 7.44–7.34 (6H, m, CH-PhSi), 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-C7), 3.55 (1H, dd, *J* = 10.5, 5.0 Hz, CH-C7), 3.53 (1H, dd, *J* = 8.7, 3.2 Hz, CH-C3), 2.10 (1H, dt, *J* = 12.2, 6.7 Hz, CH-C5), 1.90–1.78 (2H, m, CH-C4 and CH-C2), 1.72-1.62 (1H, m, CH-C2), 1.36 (1H, ddd, *J* = 12.2, 10.8, 9.0 Hz, CH-C5), 1.04 (9H, s, CH_3-^{t}BuSi), 1.00 (3H, d, *J* = 6.5 Hz, CH_3-C35), 0.88 (9H, s, CH_3-^{t}BuSi), 0.04 (6H, s, CH_3-MeSi); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CH-PhSi), 134.3 (C-PhSi), 134.2 (C-PhSi), 129.6 (CH-PhSi), 127.7 (CH-PhSi), 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_3-^{t}BuSi), 26.1 (CH_3-^{t}BuSi), 19.3 (C-^{t}BuSi), 18.5 (C-^{t}BuSi), 16.5 (CH_3-C35), −5.0 (CH_3-MeSi), −5.1 (CH_3-MeSi); Anal. calcd for $C_{30}H_{48}O_3Si_2$ C 70.26%, H 9.43% found C 70.38%, H 9.56%.

[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]methanol. (435)



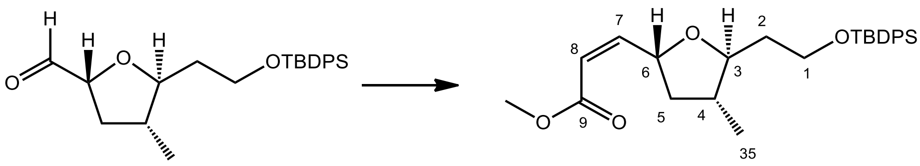
The crude bis-silyl ether **434** was dissolved in a mixture of CH_2Cl_2 (50 mL) and MeOH (50 mL) and cooled to −10 °C. Solid CSA (0.16 g, 0.68 mmol) was added and the resulting mixture was stirred for 3 h. The reaction was quenched by the addition of Et_3N (0.40 mL, 2.9 mmol) and warmed to rt. The volatiles were removed *in vacuo* and the residue was purified by flash chromatography (pet. ether/EtOAc, 9:1 to 3:1) to provide the alcohol **435** (0.98 g, 66% over 3 steps). R_f = 0.22 (pet. ether/EtOAc, 3:1); $[\alpha]_D^{24}$ −17.4 (*c* = 1.00, $CHCl_3$); $\nu_{max.}$ (liquid film) 3435, 2956, 2930, 2857, 1473, 1427, 1111, 1083, 823, 737, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (4H, m, CH-PhSi), 7.45–7.35 (6H, m, CH-PhSi), 4.03 (1H, dtd, *J* = 9.3, 6.3, 3.2 Hz, CH-C6), 3.86–3.77 (2H, m, CH_2-C1), 3.61 (1H, ddd, *J* = 11.5, 7.1, 3.2 Hz, CH-C7), 3.58 (1H, td, *J* = 8.8, 3.1 Hz, CH-C3), 3.49-3.41 (1H, m, CH-C7), 2.10-2.02 (1H, m, CH-C5), 1.96–1.80 (2H, m, CH-C4 and CH-C2), 1.70-1.60 (1H, m, CH-C2), 1.33 (1H, ddd, *J* = 12.1, 10.7, 9.3 Hz, CH-C5), 1.05 (9H, s, CH_3-^{t}BuSi), 1.02 (3H, d, *J* = 6.5 Hz, CH_3-C35); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (CH-PhSi), 134.1 (C-PhSi), 134.1 (C-PhSi), 129.7 (CH-PhSi), 127.8 (CH-PhSi), 82.1 (CH-C3), 78.4 (CH-C6), 65.4 (CH_2-C7), 61.3 (CH_2-C1), 40.2 (CH-C4), 37.2 (CH_2-C2), 36.7 (CH_2-C5), 27.0 (CH_3-^{t}BuSi), 19.4 (C-^{t}BuSi), 16.5 (CH_3-C35); HRMS (CI+, isobutane) calcd for $C_{24}H_{35}O_3Si$ $[M+H]^+$ 399.2355, found 399.2354, (Δ −0.5 ppm).

(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-carbaldehyde. (436)



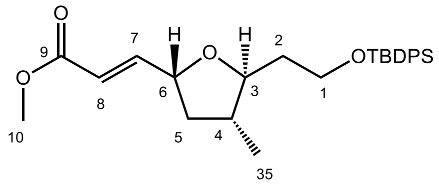
Dess-Martin periodinane (96 mg, 0.22 mmol) was added to a solution of alcohol **435** (45 mg, 0.11 mmol) in CH_2Cl_2 (6 mL) at rt and the reaction mixture was stirred for 2 hours at rt. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and the mixture was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried ($MgSO_4$), concentrated and used crude in the following step. ^1H NMR (400 MHz, $CDCl_3$) δ 9.62 (1H, d, *J* = 2.2 Hz, CH-C7), 7.70–7.65 (4H,m, CH-PhSi), 7.45 – 7.36 (6H, m, CH-PhSi), 4.22 (1H, td, *J* = 8.2, 2.2 Hz, CH-C6), 3.85 (2H, dd, *J* = 7.3, 5.4 Hz, CH_2-C1), 3.69 (1H,td, *J* = 8.5, 3.2 Hz, CH-C3), 2.33 (1H, dt, *J* = 12.6, 7.6 Hz, CH-C5), 1.99-1.83 (3H, m, CH_2-C2 and CH-C4), 1.60–1.52 (1H, m, CH-C5), 1.05 (9H, s, CH_3-^{t}BuSi), 1.03 (3H, d, *J* = 6.6 Hz, CH_3-C35); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4 (C-C7), 135.7 (CH-PhSi), 135.7 (CH-PhSi), 134.0 (C-PhSi), 133.9 (C-PhSi), 129.7 (CH-PhSi), 127.8 (CH-PhSi), 84.0 (CH-C3), 81.8 (CH-C6), 61.1 (CH_2-C1), 39.4 (CH-C4), 36.8 (CH_2-C2), 36.2 (CH_2-C5), 27.0 (CH_3-^{t}BuSi), 19.4 (C- ^{t}BuSi), 16.4 (CH_3-C35).

Methyl (2*Z*)-3-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]prop-2-enoate. (437)



To a solution of methyl *P*,*P*-bis(2, 2, 2-trifluoroethyl)phosphonoacetate (23 μL, 0.11 mmol) and 18-crown-6 (0.15 g, 0.55 mmol) in THF (1.5 mL) cooled to −78 °C was added a solution of KHMDS (0.18 mL of a 0.6 M solution in THF, 0.11 mmol). The reaction mixture was stirred for 10 minutes before the addition of the crude aldehyde **436** (0.22 mmol) in THF (2 mL). Stirring was continued for 1 hour at −78 °C before the mixture was warmed to rt and quenched with aqueous saturated NH_4Cl (5 mL). The mixture was extracted with Et_2O (3 x 5 mL), dried ($MgSO_4$) and concentrated to provide a clear oil containing *Z*/*E* isomers in a ratio of 99:1.The mixture was purified on SiO_2 (pet. ether/EtOAc 30/1) to provide *Z*-unsaturated ester **437** (38 mg, 77%) as a clear, colourless oil. R_f = 0.38 (pet. ether/ EtOAc, 9:1); $[\alpha]_D^{29}$ −6.4 (c = 2.05, $CHCl_3$); ν_{max} (liquid film) 2955, 2923, 2856, 1720, 1427, 1196, 1178, 1105, 1088, 1007, 822, 700, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69–7.66 (4H, m, CH-PhSi), 7.44–7.34 (6H, m, CH-PhSi), 6.29 (1H, dd, *J* = 11.7, 7.3 Hz, CH-C7), 5.74 (1H, dd, *J* = 11.7, 1.5 Hz, CH-C8), 5.40–5.34 (1H, m, CH-C6), 3.85–3.80 (2H, m, CH_2-C1), 3.70 (3H, s, CH_3-MeO), 3.68 (1H, td, *J* = 8.6, 3.2 Hz, CH-C3), 2.51 (1H, dt, *J* = 12.1, 6.7 Hz, CH-C5), 2.00–1.89 (1H, m, CH-C4), 1.85 (1H, dtd, *J* = 13.9, 7.4, 3.2, CH-C2) 1.68 (1H, dtd, *J* = 13.9, 8.6, 5.5 Hz, CH-C2), 1.28 (ddd, *J* = 12.1, 10.3, 7.5 Hz, 1H, CH-C5), 1.05 (9H, s, CH_3-^{t}BuSi), 1.02 (3H, d, *J* = 6.5 Hz, CH_3-C35); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5 (C-C9), 152.8 (CH-C7), 135.7 (CH-PhSi), 134.2 (C-PhSi), 134.2 (C-PhSi) 129.6 (CH-PhSi), 127.8 (CH-PhSi), 118.3 (CH-C8), 82.6 (CH-C3), 74.9 (CH-C6), 61.4 (CH_2-C1), 51.4 (CH_3-OMe), 41.5 (CH_2-C5), 40.1 (CH-C4), 37.2 (CH_2-C2), 27.0 (CH_3-^{t}BuSi), 19.4 (C-^{t}BuSi), 16.6 (CH_3-C35); HRMS (CI+, isobutane) $[M+H]^+$ calcd for $C_{27}H_{37}O_4Si$ 453.2461, found 453.2462 (Δ +0.1 ppm); LRMS (CI+, isobutane) *m*/*z* (intensity); 453.5 (76%), 375.4 (100%).

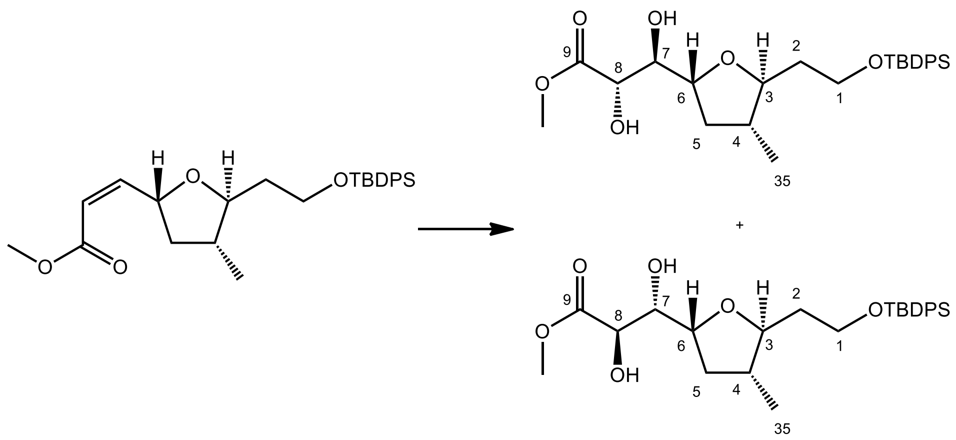
Methyl (2*E*)-3-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]prop-2-enoate.



The *E* isomer was isolated from mixtures resulting from the reaction of aldehyde **436** and methyl (triphenylphosphoranylidene)acetate (*Scheme 104*). R_f = 0.25 (pet. ether/ EtOAc, 9:1); $[\alpha]_D^{24}$ +9.8 (c = 2.15, $CHCl_3$); ν_{max} (liquid film) 2955, 2929, 2857, 1724, 1427, 1269, 1109, 1088, 823, 700, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71–7.67 (4H,m, CH-PhSi), 7.47–7.31 (6H, m, CH- PhSi), 6.92 (1H, dd, *J* = 15.6, 5.2 Hz, CH–C7), 6.02 (1H, dd, *J* = 15.6, 1.5 Hz, CH-C8), 4.55–4.49 (1H, m, CH-C6), 3.83 (2H, dd, *J* = 7.4, 5.5 Hz, CH_2-C1), 3.74 (3H, s, CH_3-OMe), 3.68 (1H, td, *J* = 8.8, 3.1 Hz, CH-C3), 2.30 (1H, dt, *J* = 12.1, 6.7 Hz, CH-C5), 1.94 (1H, ddt, *J* = 10.4, 8.8, 6.7 Hz, CH-C4), 1.87 (1H, dtd, *J* = 13.9, 7.4, 3.1 Hz, CH-C2), 1.67 (1H, ddt, *J* = 13.9, 8.6, 5.4 Hz, CH-C2), 1.42–1.34 (1H, m, CH-C5), 1.05 (9H, s, CH_3-^{t}BuSi), 1.02 (3H, d, *J* = 6.5 Hz, CH_3-C35); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9 (C-C9), 149.5 (CH-C7), 135.7 (CH- PhSi), 134.2 (C-PhSi), 134.2 (C-PhSi), 129.7 (CH-PhSi), 127.8 (CH-PhSi), 119.3 (CH-C8), 82.7 (CH-C3), 76.7 (CH-C6), 61.2 (CH_2-C1), 51.7 (CH_3-OMe), 41.4 (CH_2-C5), 40.4 (CH-C4), 37.2 (CH_2-C2), 27.0 (CH_3-^{t}BuSi), 19.4 (C-^{t}BuSi), 16.4 (CH_3-C35); HRMS (CI+, isobutane) $[M+H]^+$ calcd for $C_{27}H_{37}O_4Si$ 453.2461, found 453.2465 (Δ +0.8 ppm); LRMS (CI+, isobutane) *m*/*z* (intensity); 453.5 (26%), 375.4 (100%).

Methyl (2*S*,3*R*)-3-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]-2,3-dihydroxypropanoate. (440)

Methyl (2*R*,3*S*)-3-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]-2,3-dihydroxypropanoate. (441)

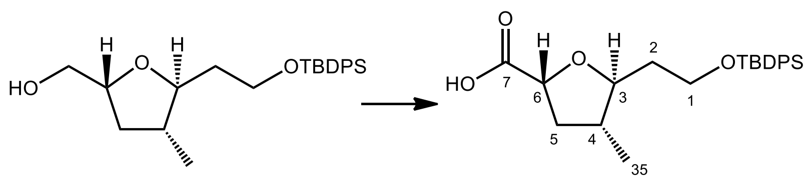


OsO_4 (5.0 μL of a 4% aqueous solution 0.86 μmol) was added to a solution of α,β-unsaturated ester **437** (19 mg, 0.043 mmol) and NMO (6.1 mg, 0.051 mmol) in a solution of in THF (1 mL) and H_2O (0.1 mL). The mixture was stirred for 3 days at rt and quenched by the addition of solid Na_2SO_3 (22 mg). On stirring for 30 minutes the solution was diluted with CH_2Cl_2 (3 mL) and H_2O (2 mL), the organic phase isolated and the aqueous phase back-extracted with further CH_2Cl_2 (2 × 5 mL). The solution was dried ($MgSO_4$), filtered and concentrated before purification by chromatography (pet. ether/EtOAc, 3:1) to afford 7,8-anti diols **440** (9 mg, 43%) and **441** (8 mg, 38%) both as clear oils.

440: R_f = 0.29 (pet. ether/EtOAc, 2:1); $[\alpha]_D^{25}$ −16.8 (c = 1.15, $CHCl_3$); ν_{max} (liquid film) 3464, 2955, 2930, 2858, 1739, 1429, 1269, 1107, 1082, 823, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.62 (4H, m, CH-PhSi), 7.44 –7.35 (6H, m, CH-PhSi), 4.26 (1H, dd, *J* = 9.4, 4.2 Hz, CH-C8), 4.00 (1H, ddd, *J* = 9.7, 6.1, 3.6 Hz, CH-C6), 3.80–3.76 (2H, m, CH_2-C1), 3.74 (3H, s, CH_3-MeO), 3.74-3.68 (1H, m, CH-C7), 3.61 (1H, td, *J* = 8.8, 3.0 Hz, CH-C3), 3.27 (1H, d, *J* = 9.4 Hz, OH-C8), 2.62 (1H, d, *J* = 8.2 Hz, OH-C7), 2.10 (1H, dt, *J* = 12.3, 6.1 Hz, CH-C5), 1.93–1.78 (2H, m, CH-C2 and CH-C4), 1.65 –1.56 (2H, m, CH-C2 and CH-C5), 1.04 (9H, s, CH_3-^{t}BuSi), 1.02 (3H, d, *J* = 6.5 Hz, CH_3-C35); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (C-C9), 135.7 (CH-PhSi), 134.0 (C-PhSi), 134.0 (C-PhSi), 129.8 (CH-PhSi), 129.8 (CH-PhSi), 127.8 (CH-PhSi), 127.8 (CH-PhSi), 83.3 (CH-C3), 77.8 (CH-C6), 73.7 (CH-C7), 73.6 (CH-C8), 61.2 (CH_2-C1), 52.5 (CH_3-MeO), 39.9 (CH-C4), 37.4 (CH_2-C5), 37.1 (CH_2-C2), 27.0 (CH_3-^{t}BuSi), 19.3 (C-^{t}BuSi), 16.2 (CH_3-C35); HRMS (CI+, isobutane) calcd for $C_{27}H_{39}O_6Si$ $[M+H]^+$ 487.2516, found 487.2517 (Δ +0.2 ppm); LRMS (CI+, isobutane) *m*/*z* (intensity); 487.4 (100%), 409.4 (40%), 375.4 (26%), 331.3 (53%).

441: R_f = 0.18 (pet. ether/EtOAc, 2:1); $[\alpha]_D^{25}$ −23.6 (c = 0.95, $CHCl_3$); ν_{max} (liquid film) 3441, 2955, 2929, 2857, 1738, 1429, 1259, 1225, 1107, 1084, 822, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.63 (4H, m, CH-PhSi), 7.45–7.35 (6H, m, CH-PhSi), 4.34-4.25 (1H, m, CH-C8), 3.99 (1H, ddd, *J* = 9.0, 7.8, 6.4 Hz, CH-C6), 3.80–3.68 (3H, m, CH_2-C1 and CH-C7), 3.67 (3H, s, CH_3-MeO), 3.51 (1H, td, *J* = 8.8, 3.1 Hz, CH-C3), 3.21 (1H, d, *J* = 5.3 Hz, OH-C7), 2.38 (1H, d, *J* = 7.2 Hz, OH-C8), 2.25 (1H, dt, *J* = 12.7, 6.4 Hz, CH-C5), 1.92–1.83 (1H, m, CH-C4), 1.83–1.72 (1H, m, CH-C2), 1.66–1.47 (2H, m, CH-C2 and CH-C5), 1.04 (9H, s, CH_3-^{t}BuSi), 1.01 (3H, d, *J* = 6.5 Hz, CH_3-C35); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 (C-C9), 135.7 (CH-PhSi), 135.7 (CH-PhSi), 134.1 (C-PhSi), 129.7 (CH-PhSi), 127.8 (CH-PhSi), 82.8 (CH-C3), 77.3 (CH-C6), 75.5 (CH-C7), 72.7 (CH-C8), 61.4 (CH_2-C1), 52.6 (CH_3-MeO), 40.1 (CH-C4), 38.7 (CH_2-C5), 37.2 (CH_2-C2), 27.0 (CH_3-^{t}BuSi), 19.3 (C-^{t}BuSi), 16.4 (CH_3-C35); HRMS (CI+, isobutane) calcd for $C_{27}H_{39}O_6Si$ $[M+H]^+$ 487.2516, found 4487.2514 (Δ −0.5 ppm); LRMS (CI+, isobutane) *m*/*z* (intensity); 487.4 (88%), 409.4 (44%), 375.4 (30%), 331.3 (100%).

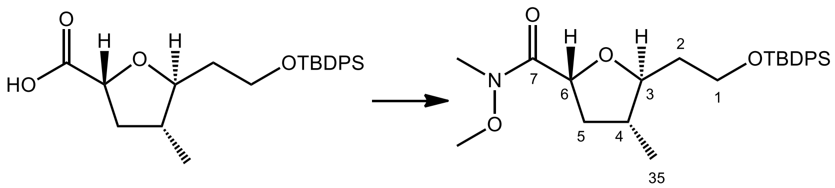
(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-carboxylic acid.



Dess-Martin periodinane (498 mg, 1.18 mmol) was added in a single portion to a stirred solution of alcohol **435** (390 mg, 0.98 mmol) in CH_2Cl_2 (18 mL). The mixture was stirred at rt for 1.5 h, quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (2 × 25 ml). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated and the residue used directly in the following step.

To a solution of aldehyde and 2-methyl-2-butene (0.83 mL, 7.8 mmol) in *t*-BuOH (4.8 mL) was added dropwise a solution of $NaClO_2$ (0.67 g, 80% purity, 6.0 mmol) and NaH_2PO_4·$2H_2O$ (1.0 g, 6.4 mmol) in H_2O (9.7 mL). The mixture was stirred at rt for 1 h, concentrated and partitioned between CH_2Cl_2 (20 mL) and H_2O (15 mL). The aqueous phase was isolated and extracted with further CH_2Cl_2 (20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give the title carboxylic acid which was used directly in the following step. R_f = 0.12 (pet. ether/EtOAc, 1:1); $[\alpha]_D^{25}$ +11.9 (*c* = 2.70, $CHCl_3$); $\nu_{max.}$ (liquid film) 3050, 2957, 2930, 2857, 1721, 1427, 1107, 1088, 937, 823, 736, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68–7.64 (4H, m, CH-PhSi), 7.46–7.37 (6H, m, CH-PhSi), 4.42-4.33 (1H, m, CH-C6), 3.84–3.77 (3H, m, CH_2-C1 and CH-C3), 2.53 (1H, dt, *J* = 12.8, 7.4 Hz, CH-C5), 2.03–1.94 (1H, m, CH-C4), 1.87 (dtd, *J* = 14.4, 7.4, 3.1 Hz, 1H, CH-C2), 1.74–1.63 (2H, m, CH-C2 and CH-C5), 1.05 (9H, s, CH_3-^{t}BuSi), 1.04 (3H, d, *J* = 6.6 Hz, CH_3-C35); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5 (C-C7), 135.7 (CH-PhSi), 133.8 (C-PhSi), 133.8 (C-PhSi), 129.9 (CH-PhSi), 129.8 (CH-PhSi), 127.9 (CH-PhSi), 127.8 (CH-PhSi), 84.4 (CH-C3), 75.8 (CH-C6), 60.8 (CH_2-C1), 39.9 (CH-C4), 38.6 (CH_2-C5), 36.6 (CH_2-C2), 27.0 (CH_3-^{t}BuSi), 19.3 (C-^{t}BuSi), 16.1 (CH_3-C35); HRMS (CI+, isobutane) calcd for $C_{24}H_{33}O_4Si$ $[M+H]^+$ 413.2148, found 413.2151, (Δ +0.7 ppm).

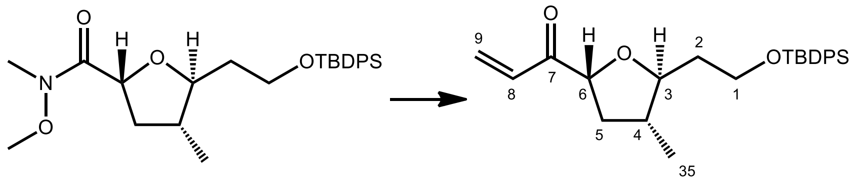
(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-N-methoxy-N,4-dimethyltetrahydrofuran-2-carboxamide. (453)



To a solution of the intermediate carboxylic acid (crude 0.98 mmol) in CH_2Cl_2 (8 mL) was added sequentially DIPEA (0.48 mL, 2.7 mmol), N,O-dihydroxylamine hydrochloride (0.12 g, 1.3 mmol) and HBTU (0.55 g, 1.3 mmol). The resulting mixture was stirred for 19 h at rt and the reaction was quenched with 1 M HCl (10 mL). The mixture was extracted with CH_2Cl_2 (2 × 20 mL) and the organic phases were combined and washed with brine (20 mL), then dried ($MgSO_4$) and concentrated. Purification of the residue by chromatography (pet. ether/EtOAc, 9:1 to 4:1) afforded the desired the Weinreb amide **453** (0.33 g, 75% over three steps) as a colourless oil. R_f = 0.16 (pet. ether/EtOAc, 3:1). $[\alpha]_D^{23}$ −10.3 (*c* = 1.24, $CHCl_3$). $\nu_{max.}$ (liquid film) 3050, 2958, 2933, 2857, 1672, 1467, 1427, 1109, 1089, 740, 705, 613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69–7.64 (4H, m, CH-PhSi), 7.43–7.33 (6H, m, CH-PhSi), 4.79–4.70 (1H, m, CH-C6), 3.90–3.78 (2H, m, CH_2-C1), 3.73 (1H, td, *J* = 8.5, 3.5 Hz, CH-C3), 3.64 (3H, s, CH_3-MeO), 3.18 (3H, s, CH_3-MeN), 2.34 (1H, dt, *J* = 12.2, 7.4 Hz, CH-C5), 1.96–1.85 (2H, m, CH-C4 and CH-C2), 1.80–1.70 (2H, m, CH-C2 and CH-C5), 1.04 (9H, s, CH_3-^{t}BuSi), 1.03 (3H, d, *J* = 6.5 Hz, CH_3-C35); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1 (C-C7), 135.7 (CH-PhSi), 135.6 (CH-PhSi), 134.2 (C-PhSi), 134.0 (C-PhSi), 129.6 (CH-PhSi), 127.7 (CH-PhSi), 127.7 (CH-PhSi), 83.5 (CH-C3), 74.2 (CH-C6), 61.5 (CH_2-C1), 61.5 (CH_3-MeO), 39.7 (CH-C4), 38.1 (CH_2-C5), 36.8 (CH_2-C2), 32.5 (CH_3-MeN), 27.0 (CH_3-^{t}BuSi), 19.3 (C-^{t}BuSi), 16.1 (CH_3-C35); HRMS (CI+, isobutane) calcd for

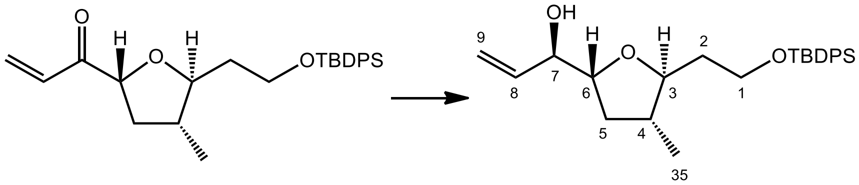
$C_{26}H_{38}NO_4Si$ $[M+H]^+$ 456.2570, found 456.2571 (Δ +0.2 ppm).

1-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]prop-2-en-1-one. (454)



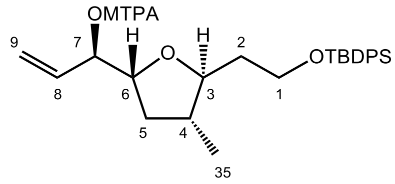
To a solution of Weinreb amide **453** (2.5 g, 5.5 mmol) in THF (150 mL) at −78 °C was added dropwise vinylmagnesium bromide (7.2 mL of a 1 M solution in THF, 7.2 mmol). The mixture was stirred for 1 h and the reaction was then quenched by the addition of 1 M aqueous HCl (75 mL). The mixture was allowed to warm slowly to rt and the organic component was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$) and then concentrated. Purification of the residue by chromatography (pet. ether/EtOAc, 9:1) afforded the title enone **454** (2.2 g, 86%) as a colourless oil. R_f = 0.16 (pet. ether/EtOAc, 20:1); $[\alpha]_D^{25}$ +20.5 (*c* = 1.50, $CHCl_3$); $\nu_{max.}$ (liquid film) 3071, 2932, 2862, 1697, 1612, 1466, 1427, 1396, 1103, 702, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (4H, m, CH-PhSi), 7.45–7.35 (6H, m, CH-PhSi), 6.74 (1H, dd, *J* = 17.5, 10.6 Hz, CH-C8), 6.38 (1H, dd, *J* = 17.5, 1.7 Hz, CH-C9 *trans*), 5.76 (1H, dd, *J* = 10.6, 1.7 Hz, CH-C9 *cis*), 4.50 (1H, dd, *J* = 8.8, 7.6 Hz, CH-C6), 3.88–3.83 (2H, m, CH_2-C1), 3.72 (1H, td, *J* = 8.5, 3.3 Hz, CH-C3), 2.39 (1H, dt, *J* = 12.5, 7.6 Hz, CH-C5), 2.00–1.85 (2H, m, CH-C4 and CH-C2), 1.70 (1H, ddt, *J* = 13.9, 8.5, 5.4 Hz, CH-C2), 1.59 (1H, ddd, *J* = 12.5, 10.3, 8.8 Hz, CH-C5), 1.05 (9H, s, CH_3 -^{t}BuSi), 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 (CH-PhSi), 135.7 (CH-PhSi), 134.1 (C-PhSi), 134.0 (C-PhSi), 131.6 (CH-C8), 129.7 (CH-PhSi), 129.7 (CH_2-C9), 127.8 (CH-PhSi), 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_3-^{t}BuSi), 19.4 (C-^{t}BuSi), 16.3 (CH_3-C35); HRMS (CI+, isobutane) calcd for $C_{26}H_{35}O_3Si$ $[M+H]^+$ 423.2355, found 423.2359 (Δ +0.9 ppm).

(1*R*)-1-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]prop-2-en-1-ol. (455)



To a solution of enone **454** (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 at −78 °C and then warmed to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL), the organic phase isolated and the aqueous phase was 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 **455** (0.27 g, 99%, *dr* > 9:1) as a colourless oil. R_f = 0.40 (pet. ether/EtOAc, 3:1); $[\alpha]_D^{24}$ −12.0 (*c* = 1.00, $CHCl_3$); $\nu_{max.}$ (liquid film) 3466, 3071, 2958, 2930, 2858, 1427, 1109, 1089, 1027, 994, 926, 823, 739, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.65 (4H, m, CH-PhSi), 7.45–7.36 (6H, m, CH-PhSi), 5.76 (1H, ddd, *J* = 17.2, 10.5, 6.1 Hz, CH-C8), 5.36 (1H, dt, *J* = 17.2, 1.5 Hz, CH-C9 *trans*), 5.19 (1H, dt, *J* = 10.5, 1.5 Hz, CH-C9 *cis*), 3.93–3.87 (1H, m, CH-C7), 3.84–3.74 (3H, m, CH_2-C1 and CH-C6), 3.59 (1H, td, *J* = 8.9, 2.9 Hz, CH-C3), 2.48 (1H, d, *J* = 3.0 Hz, OH-C7), 2.10–2.02 (1H, m, CH-C5), 1.95–1.82 (2H, m, CH-C2 and CH-C4), 1.63 (1H, ddt, *J* = 13.9, 8.9, 5.2 Hz, CH-C2), 1.32 (1H, ddd, *J* = 12.2, 10.8, 9.1 Hz, CH-C5), 1.05 (9H, s, CH_3-^{t}BuSi), 1.01 (3H, d, *J* = 6.5 Hz, CH_3-C35); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7 (CH-C8), 135.7 (CH-PhSi), 134.1 (C-PhSi), 134.0 (C-PhSi), 129.7 (CH-PhSi), 127.8 (CH-PhSi), 117.1 (CH_2-C9), 82.1 (CH-C3), 81.0 (CH-C6), 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_3-^{t}BuSi), 19.4 (C-^{t}BuSi), 16.4 (CH_3-C35); HRMS (CI+, isobutane) calcd for $C_{26}H_{37}O_3Si$ 425.2512 $[M+H]^+$, found 425.2509 (Δ −0.7 ppm).

Mosher Analysis of Alcohol 455

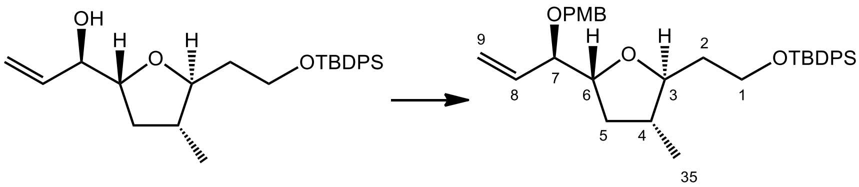


	δ *S*-ester (PPM)	δ *R*-ester (ppm)	Δδ *SR* (=$\delta_S-\delta_R$)	
			ppm	Hz (400 MHz)
CH-C9 *trans*	5.42	5.26	0.16	+64
CH-C9 *cis*	5.31	5.22	0.09	+36
CH-C8	5.84	5.65	0.19	+76
CH-C6	4.02	4.01	0.01	+4
CH-C5	1.97	2.06	-0.09	-36
CH-C5	1.23	1.29	-0.06	-24
CH-C4	1.84	1.90	-0.06	-24
CH_3-C35	0.92	1.00	-0.08	-32
CH-C3	3.49	3.54	-0.05	-20
CH-C2	1.78	1.82	-0.04	-16
CH-C2	1.62	1.66	-0.04	-16
CH_2-C1	3.75	3.76	-0.01	-4
^{t}Bu-C1 ^{t}BuSi	1.03	1.03	0.00	0

(*S*)-MTPA ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.63 (4H, m, CH-PhSi), 7.54–7.50 (2H, m, CH-Ph MTPA), 7.43–7.33 (6H, m, CH-PhSi), 7.33–7.27 (3H, m, CH-Ph MTPA), 5.84 (1H, ddd, *J* = 17.5, 10.6, 7.1 Hz, CH-C8), 5.46-5.38 (2H, m, CH-C7 and CH-C9 *trans*), 5.31 (1H, d, *J* = 10.6 Hz, CH-C9 *cis*), 4.02 (1H, td, *J* = 9.2, 6.4 Hz, CH–C6), 3.81–3.69 (2H, m, CH_2-C1), 3.49 (1H, dd, *J* = 8.9, 3.0 Hz, CH–C3), 3.46 (3H, d, *J* = 0.8 Hz, CH_3-MeO MTPA), 2.02–1.94 (1H, m, CH–C5), 1.87 – 1.81 (1H, m, CH–C4), 1.81–1.75 (1H, m, CH–C2), 1.67-1.58 (1H, m, CH–C2), 1.28–1.18 (1H, m, CH-C5), 1.03 (9H, s, CH_3-^{t}BuSi), 0.92 (3H, d, *J* = 6.5 Hz, CH_3-C35).

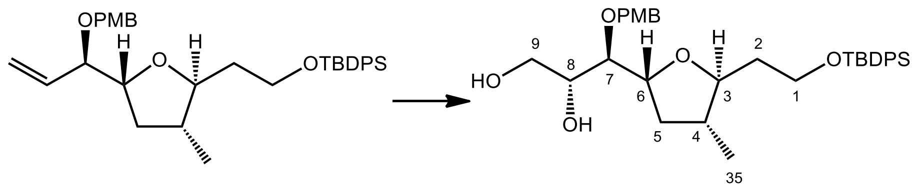
(*R*)-MTPA ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.62 (m, 4H, PhSi), 7.56–7.52 (m, 2H, Ph MTPA), 7.43–7.33 (6H, m, PhSi), 7.33–7.28 (3H, m, Ph MTPA), 5.65 (1H, ddd, *J* = 17.3, 10.6, 6.8 Hz, CH–C8), 5.37 (1H, t, *J* = 7.4 Hz, CH–C7), 5.26 (1H, dt, *J* = 17.3, 1.2 Hz, CH-C9 *trans*), 5.22 (1H, dt, *J* = 10.6, 1.2 Hz, CH–C9 *cis*), 4.05–3.97 (1H, m, CH-C6), 3.82-3.69 (2H, m, CH_2-C1), 3.54 (1H, td, *J* = 9.0, 2.9 Hz, CH-C3), 3.47 (3H, d, *J* = 1.0 Hz, CH_3-MeO MTPA), 2.10–2.01 (1H, m, CH–C5), 1.93–1.86 (1H, m, CH–C4), 1.86–1.78 (1H, m, CH-C2), 1.71–1.60 (1H, m, CH–C2), 1.33–1.24 (1H, m, CH–C5), 1.03 (9H, s, CH_3-^{t}BuSi), 1.00 (3H, d, *J* = 6.5 Hz, CH_3-C35).

***tert*-Butyl({2-[(2*S*,3*R*,5*R*)-5-[(1*R*)-1-[(4-methoxyphenyl)methoxy]prop-2-en-1-yl]-3-methyltetrahydrofuran-2-yl]ethoxy})diphenylsilane. (456)**



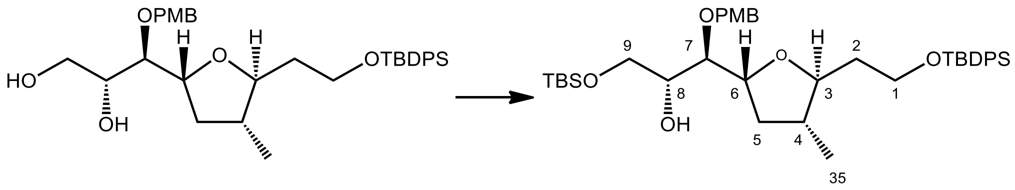
To a stirred solution of allylic alcohol **455** (0.10 g, 0.24 mmol) and *p*-methoxybenzyltrichloroacetimidate (99 mg, 0.35 mmol) in CH_2Cl_2 (10 mL) was added $La(OTf)_3$ (7.2 mg, 0.012 mmol) and the mixture stirred at rt for 6 h. The reaction was quenched by the addition of H_2O (5 mL) and the mixture 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 (pet. ether/EtOAc, 98:2) to yield the title ether **456** (0.11 g, 82%) as a colourless oil. R_f = 0.72 (pet. ether/EtOAc, 3:1); $[\alpha]_D^{24}$ −19.1 (*c* = 0.98, $CHCl_3$); $\nu_{max.}$ (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, CH-PhSi), 7.43–7.33 (6H, m, CH–PhSi), 7.24 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 6.81 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 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-PMB alkyl), 4.40 (1H, d, *J* = 11.9 Hz, CH-PMB alkyl), 4.00 (1H, dt, *J* = 9.4, 6.4 Hz, CH-C6), 3.89–3.78 (2H, m, CH_2-C1), 3.77 (3H, s, CH_3-PMB alkyl), 3.75–3.70 (1H, m, CH-C7), 3.54 (1H, td, *J* = 8.4, 3.3 Hz, CH-C3), 1.99 (1H, dt, *J* = 12.3, 6.4 Hz, CH-C5), 1.90–1.78 (2H, m, CH-C2 and CH-C4), 1.69 (1H, ddt, *J* = 13.7, 8.4, 5.8 Hz, CH-C2), 1.42-1.28 (1H, m, CH-C5), 1.04 (9H, s, CH_3-^{t}BuSi), 0.98 (3H, d, *J* = 6.5 Hz, CH_3-C35); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (C-PMB Ar), 135.7 (CH-PhSi), 135.6 (CH-C8), 134.3 (C-PhSi), 134.2 (C-PhSi), 131.0 (C-PMB Ar), 129.6 (CH-PhSi), 129.6 (CH-PhSi), 129.3 (CH-PMB Ar), 127.7 (CH-PhSi), 118.6 (CH_2-C9), 113.8 (CH-PMB Ar), 82.5 (CH-C7), 82.3 (CH-C3), 79.9 (CH-C6), 70.2 (CH_2-PMB alkyl), 61.6 (CH_2-C1), 55.4 (CH_3-PMB alkyl), 39.7 (CH-C4), 37.4 (CH_2-C5), 37.1 (CH_2-C2), 27.0 (CH_3-^{t}BuSi), 19.4 (C-^{t}BuSi), 16.4 (CH_3-C35); HRMS (CI+, isobutane) calcd for $C_{34}H_{45}O_4Si$ $[M+H]^+$ 545.3087, found 545.3079 (Δ −1.5 ppm).

(2*R*,3*R*)-3-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyl tetrahydrofuran-2-yl]-3-[(4-methoxyphenyl)methoxy]propane-1,2-diol. (457)



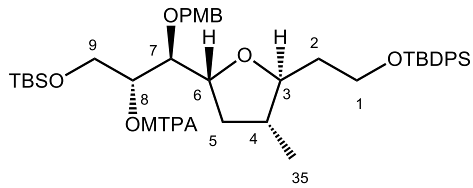
A solution of alkene **456** (82 mg, 0.15 mmol) and NMO (19 mg, 0.16 mmol) dissolved in a mixture of THF (2.0 mL) and H_2O (0.2 mL) was treated with OsO_4 (17 µl of a 4% aqueous solution, 3.0 µmol) and the solution was stirred for 18 h at rt. The reaction was quenched by the addition of solid Na_2SO_3 (60 mg) and the mixture was stirred for 30 minutes. The mixture 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 (pet. ether/EtOAc, 3:1 to EtOAc) to afford the title diol **457** (76 mg, 88%) as a viscous yellow oil. R_f = 0.21 (pet. ether/EtOAc, 1:1); $[\alpha]_D^{23}$ −1.3 (*c* = 0.96, $CHCl_3$); $\nu_{max.}$ (liquid film) 3404, 2954, 2931, 2855, 1612, 1514, 1247, 1105, 1084, 1035, 823, 737, 701, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.62 (4H, m, CH-PhSi), 7.44–7.32 (6H, m, CH-PhSi), 7.23 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 6.85 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 4.63 (1H, d, *J* = 11.2 Hz, CH-PMB alkyl), 4.55 (1H, d, *J* = 11.2 Hz, CH-PMB alkyl), 4.14 (1H, dt, *J* = 10.0, 5.5 Hz, CH-C6), 3.82–3.74 (3H, m, CH_2-C1 and CH-C8), 3.79 (3H, s, CH_3-PMB alkyl), 3.71–3.63 (3H, m, CH-C3 and CH_2-C9), 3.54 (1H, t, *J* = 5.5 Hz, CH-C7), 3.28 (1H, d, *J* = 6.3 Hz, 1H, OH-C8), 2.32 (1H, dd, *J* = 6.7, 5.8 Hz, OH-C9), 2.03 (1H, dt, *J* = 12.2, 5.5 Hz, CH-C5), 1.94–1.77 (2H, m, CH-C2 and CH-C4), 1.67–1.58 (1H, m, CH-C2), 1.56–1.48 (1H, m, CH-C5), 1.02 (3H, d, *J* = 6.5, CH_3-C35), 1.04 (9H, s, CH_3-^{t}BuSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5 (C-PMB Ar), 135.7 (CH-PhSi), 134.1 (C-PhSi), 134.0 (C-PhSi), 130.5 (C-PMB Ar), 129.7 (CH-PMB Ar), 129.7 (CH-PhSi), 127.8 (CH-PhSi), 114.0 (CH-PMB Ar), 82.7 (CH-C3), 80.5 (CH-C7), 79.0 (CH-C6), 73.7 (CH_2-PMB alkyl), 71.5 (CH-C8), 63.9 (CH_2-C9), 61.3 (CH_2-C1), 55.4 (CH_3-PMB alkyl), 39.7 (CH-C4), 37.2 (CH_2-C2), 37.0 (CH_2-C5), 27.0 (CH_3-^{t}BuSi), 19.3 (C-^{t}BuSi), 16.4 (CH_3-C35); Anal. calcd for $C_{34}H_{46}O_6Si$ C 70.55%, H 8.17%, found C 70.61%, H 8.01%.

***tert*-butyl[(2*R*,3*R*)-3-[(2*R*,4*R*,5*S*)-5-{2-[(tert-butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]-2-hydroxy-3-[(4-methoxyphenyl)methoxy] propoxy]dimethylsilane. (458)**



To a solution of diol **457** (69 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was added sequentially Et_3N (25 µl, 0.18 mmol), DMAP (1.5 mg, 0.012 mmol) and TBSCl (20 mg, 0.13 mmol) and the mixture was stirred for 24 h at rt. The reaction was quenched with 1 M aqueous HCl (5 mL), extracted with CH_2Cl_2 (2 × 5 mL) and dried ($MgSO_4$). On filtration and concentration, the residue was purified by chromatography (pet. ether/EtOAc, 99:1 to 9:1) to yield the silyl ether **458** (44 mg, 53%) as a clear colourless oil. R_f = 0.29 (pet. ether: EtOAc, 9:1); $[\alpha]_D^{23}$ −8.5 (c = 1.85, $CHCl_3$); ν_{max} (liquid film) 3480, 2951, 2931, 2860, 1248, 1078, 1035, 829, 699, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.63 (4H, m, CH-PhSi), 7.42–7.32 (6H, m, CH-PhSi), 7.24 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 6.83 (2H, d, *J* = 8.7 Hz, CH-PMB Ar), 4.59 (2H, s, CH_2-PMB), 4.19 (1H, ddd, *J* = 10.0, 6.2, 4.2 Hz, CH-C6), 3.85–3.76 (3H, m, CH_2-C1 and CH-C8), 3.79 (3H, s, CH_3-PMB), 3.68 (2H,m, CH_2-C9), 3.67-3.64 (1H, td, *J* = 8.6, 3.3 Hz, CH-C3), 3.42 (1H,dd, *J* = 5.0, 4.2 Hz, CH-C7), 3.07 (1H,d, *J* = 5.8 Hz, OH-C8), 2.00 (1H, dt, *J* = 12.0, 6.2 Hz, CH-C5), 1.90–1.77 (2H, m, CH-C2 and CH-C4), 1.70–1.61 (1H, m, CH-C2), 1.61–1.53 (1H, m, CH-C5), 1.03 (9H, s, CH_3-^{t}BuSi), 1.00 (3H, d, *J* = 6.5 Hz, CH_3-C35), 0.88 (9H, s, CH_3-^{t}BuSi), 0.05 (3H,s, CH_3-MeSi), 0.04 (3H, s, CH_3-MeSi); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3 (C-PMB Ar), 135.7 (CH-PhSi), 134.2 (C-PhSi), 134.1 (C-PhSi), 130.9 (C-PMB Ar), 129.7 (CH-PMB Ar), 129.6 (CH-PhSi), 127.7 (CH-PhSi), 113.8 (CH-PMB Ar), 82.5 (CH-C3), 79.6 (CH-C7), 78.6 (CH-C6), 73.2 (CH_2-PMB alkyl), 72.2 (CH-C8), 64.3 (CH_2-C9), 61.5 (CH_2-C1), 55.4 (CH_3-PMB alkyl), 39.8 (CH-C4), 37.3 (CH_2-C2), 37.3 (CH_2-C5), 27.0 (CH_3-^{t}BuSi), 26.1 (CH_3-^{t}BuSi), 19.3 (C-^{t}BuSi), 18.4 (C-^{t}BuSi), 16.4 (CH_3-C35), −5.2 (CH_3-MeSi), −5.2 (CH_3-MeSi); HRMS (FAB, NOBA) calcd for $C_{40}H_{61}O_6Si_2$ $[M+H]^+$ 693.4006, found 693.4011, (Δ +0.7 ppm).

Mosher Ester Analysis of Alcohol 458

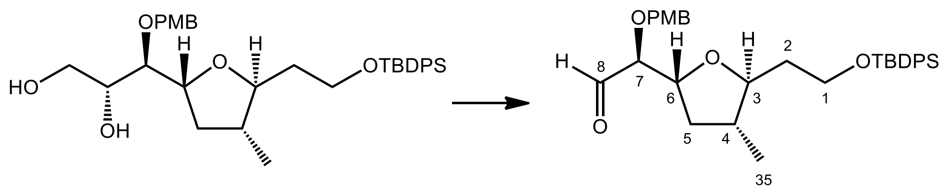


	δ *S*-ester (PPM)	δ *R*-ester (ppm)	Δδ *SR* (=δ_S - δ_R) ppm	Δδ *SR* (=δ_S - δ_R) Hz (500 MHz)
CH_3-C9 MeSi	0.05	0.02	0.03	+15
CH_3-C9 MeSi	0.04	0.02	0.02	+10
CH_3-C9 ^{t}BuSi	0.85	0.83	0.02	+10
CH-C9	4.00	3.96	0.04	+20
CH-C9	3.87	N/A	N/A	NA
CH-C7	3.43	3.61	-0.18	-90
CH-C7 PMB-CH_2	4.34	4.57	-0.23	-115
CH-C7 PMB-CH_2	4.29	4.53	-0.24	-120
CH-C7 PMB-CH_3	3.76	3.78	-0.02	-10
CH-C7 PMB-Ar	7.03	7.17	-0.14	-70
CH-C7 PMB-Ar	6.74	6.8	-0.06	-30
CH-C6	3.91	4.04	-0.13	-65
CH-C5	1.93	2.02	-0.09	-45
CH-C5	1.45	1.51	-0.06	-30
CH-C4	Not assignable			
CH_3-C35	0.97	0.99	-0.02	-10
CH-C3	3.55	3.57	-0.02	-10
CH-C2	Not assignable			
CH-C2	1.62	1.64	-0.02	-10
CH_3-C1 ^{t}BuSi	1.03	1.04	-0.01	-5

(*S*)-MTPA ester: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.64 (4H, m, CH-PhSi), 7.64–7.59 (2H,m, CH-Ph MTPA), 7.43–7.31 (9H, m, CH-PhSi and CH-Ph MTPA), 7.03 (2H,d, *J* = 8.6 Hz, CH-PMB Ar), 6.74 (2H, d, *J* = 8.6 Hz, CH-PMB Ar), 5.22 (1H, dt, *J* = 7.3, 3.3 Hz, CH-C8), 4.34 (1H, d, *J* = 10.9 Hz, CH-PMB alkyl), 4.29 (1H, d, *J* = 10.9 Hz, CH-PMB alkyl), 4.00 (1H,dd, *J* = 11.8, 2.8 Hz, CH-C9), 3.95-3.86 (1H, m, CH-C6), 3.87 (1H,dd, *J* = 11.8, 7.3 Hz, CH-C9), 3.85–3.77 (2H, m, CH_2-C1), 3.76 (3H, s, CH_3-PMB alkyl), 3.62 (3H, s, CH_3-MeO MTPA), 3.55 (1H, td, *J* = 8.8, 2.9 Hz, CH-C3), 3.43 (1H, dd, *J* = 5.0, 3.3 Hz, CH-C7), 1.93 (1H, dt, *J* = 11.6, 6.6 Hz, CH-C5), 1.84 –1.75 (2H, m, CH-C2 and C4), 1.66–1.58 (1H, m, CH-C2), 1.49–1.41 (1H, m, CH-C5), 1.03 (9H, s, CH_3-^{t}BuSi), 0.97 (3H, d, *J* = 6.4 Hz, CH_3-C35), 0.85 (9H, s, CH_3 -^{t}BuSi), 0.05 (3H, s, CH_3-MeSi), 0.04 (3H,s, CH_3-MeSi).

(*R*)-MTPA ester: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.63 (4H, m, CH-PhSi), 7.58–7.55 (2H, m, CH-Ph MTPA), 7.42–7.31 (9H, m, CH-PhSi and CH-Ph MTPA), 7.17 (2H, d, *J* = 8.6 Hz, CH-PMB Ar), 6.80 (2H, d, *J* = 8.6 Hz, CH-PMB Ar), 5.21 (1H,dt, *J* = 7.3, 3.5 Hz, CH-C8), 4.57 (1H, d, *J* = 11.1 Hz, CH-PMB alkyl), 4.53 (1H, d, *J* = 11.1 Hz, CH-PMB alkyl), 4.04 (1H, dt, *J* = 9.8, 5.7 Hz, CH-C6), 3.96 (1H, dd, *J* = 11.6, 3.5 Hz, CH-C9), 3.88–3.79 (3H, m, CH_2-C1 and CH-C9), 3.78 (3H, s, CH_3-PMB alkyl), 3.64–3.58 (1H, m, CH-C7), 3.57 (1H, td, *J* = 8.8, 2.9 Hz, CH-C3), 3.49 (3H, s, CH_3-MeO MTPA), 2.02 (1H, dt, *J* = 11.8, 6.6 Hz, CH-C5), 1.88–1.78 (2H, m, CH-C2 and CH-C4), 1.68–1.60 (1H, m, CH-C2), 1.54–1.48 (1H, m, CH-C5), 1.04 (9H, s, CH_3-^{t}BuSi TBDPS), 0.99 (3H, d, *J* = 6.5 Hz, CH_3-C35), 0.83 (9H, s, CH_3-^{t}BuSi), -0.02 (3H, s, CH_3-MeSi), -0.02 (3H, s, CH_3-MeSi).

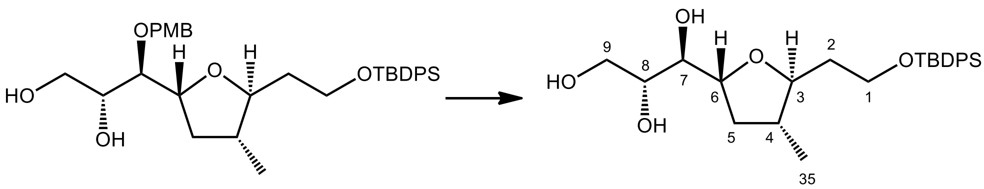
(2*S*)-2-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]-2-[(4-methoxyphenyl)methoxy]acetaldehyde. (461)



Sodium periodate (73 mg, 0.34 mmol) was added to a solution of diol **457** (0.10 g, 0.17 mmol) in a mixture of THF (2.6 mL) and H_2O (0.30 mL) at rt. The mixture was stirred for 30 minutes at rt and then diluted with H_2O (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. R_f = 0.41 (pet. ether/EtOAc, 1:1). $\nu_{max.}$ (liquid film) 2957, 2931, 2857, 1731, 1612, 1513, 1248, 1105, 1034, 1008, 909, 822, 732, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (1H, d, *J* = 1.7 Hz, CH-C8), 7.70–7.63 (4H, m, CH-PhSi), 7.45–7.33 (6H, m, CH-PhSi), 7.26 (2H, d, *J* = 8.6 Hz, CH-PMB Ar), 6.86 (2H, d, *J* = 8.6 Hz, CH-PMB Ar), 4.68 (1H, d, *J* =

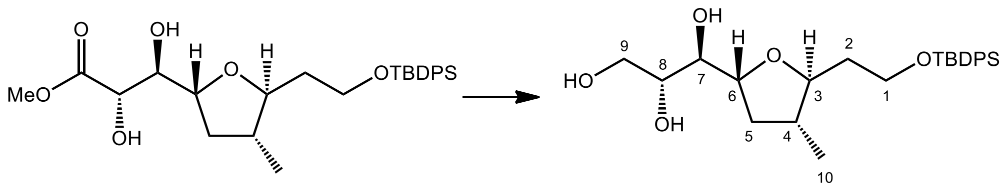
11.7 Hz, CH-PMB alkyl), 4.56 (1H, d, *J* = 11.7 Hz, CH-PMB alkyl), 4.24 (1H, ddd, *J* = 9.3, 6.3, 4.5 Hz, CH-C6), 3.80 (3H, s, CH_3-PMB alkyl), 3.82–3.71 (3H, m, CH_2-C1 and CH-C7), 3.64 (1H, td, *J* = 8.6, 3.1 Hz, 1H, CH-C3), 2.06 (1H, dt, *J* = 12.2, 6.7 Hz, CH-C5), 1.89–1.79 (2H, m, CH-C4 and CH-C2), 1.69–1.52 (2H, m, CH-C2 and CH-C5), 1.05 (9H, s, CH_3-^{t}BuSi), 1.02 (3H, d, *J* = 6.5 Hz, CH_3-C35); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7 (C-C8), 159.6 (C-PMB Ar), 135.7 (CH-PhSi), 134.2 (C-PhSi), 134.1 (C-PhSi), 129.9 (CH-PhSi), 129.7 (CH-PMB Ar), 129.5 (C-PMB Ar), 127.7 (CH-PhSi), 114.0 (CH-PMB Ar), 84.9 (CH-C7), 82.8 (CH-C3), 77.7 (CH-C6), 73.0 (CH_2-PMB alkyl), 61.3 (CH_2-C1), 55.4 (CH_3-PMB alkyl), 39.6 (CH-C4), 37.0 (CH_2-C2), 36.7 (CH_2-C5), 27.0 (CH_3-^{t}BuSi TBDPS), 19.3 (C-^{t}BuSi), 16.2 (CH_3-C35).

(1*R*,2*R*)-1-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyl methyltetrahydrofuran -2-yl]propane-1,2,3-triol. (442)



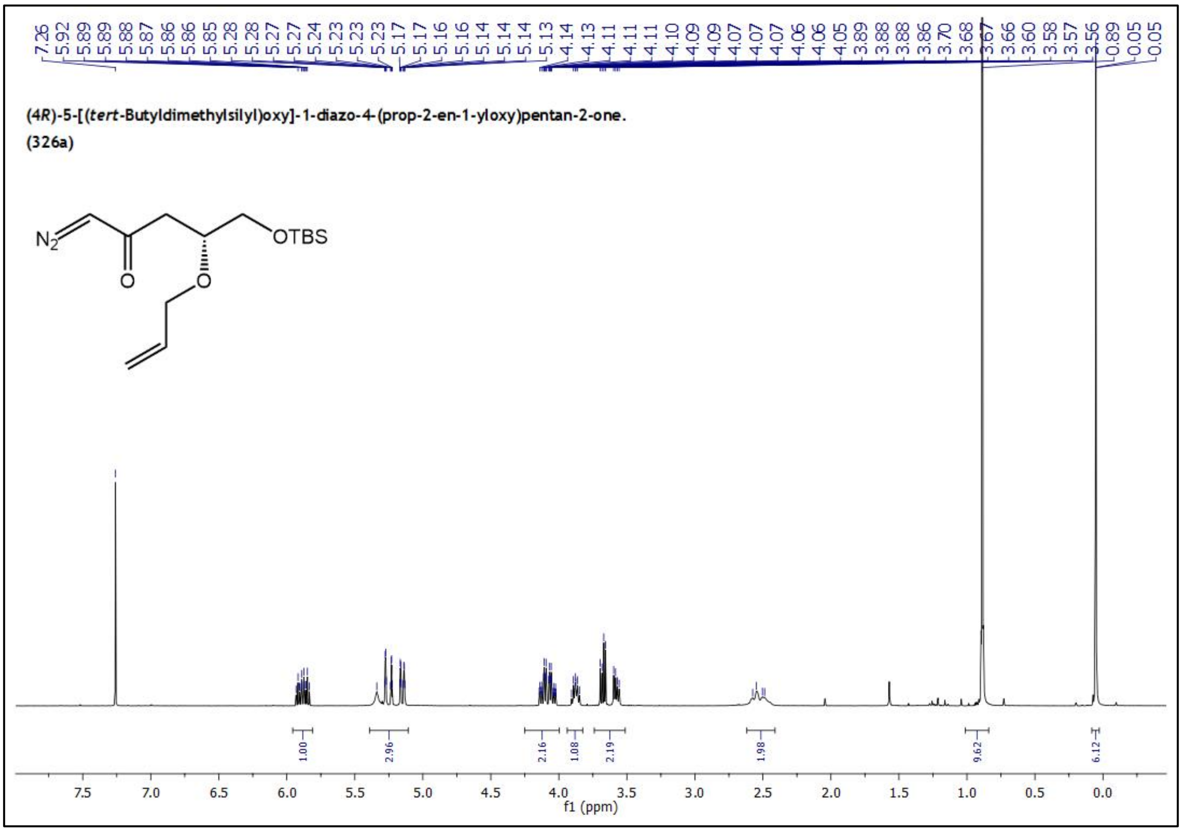
Palladium on carbon (14 mg, 10% wt.%) was added to a solution of PMB ether **457** (137 mg, 0.24 mmol) in methanol (2.5 mL) under a nitrogen atmosphere. The flask was purged and refilled with hydrogen and the process repeated two times. The mixture was stirred for 16 h at rt and the reaction mixture was filtered through celite, concentrated and purified by chromatography (pet. ether/Et_2O, 1:3) to afford triol **442** (35 mg, 32%) as a clear oil. R_f = 0.22 (Et_2O); $[\alpha]_D^{28}$ −18.3 (c = 1.70, $CHCl_3$); $\nu_{max.}$ (liquid film) 3401, 2957, 2930, 2857, 1473, 1427, 1072, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.64 (4H, m, CH-PhSi), 7.45–7.35 (6H, m, PhSi), 4.06 (1H, ddd, *J* = 9.8, 6.2, 3.8 Hz, CH-C6), 3.85–3.77 (2H, m, CH_2-C1), 3.72 (2H, t, *J* = 5.3 Hz, CH_2-C9), 3.66–3.60 (2H, m, CH-C3 and CH-C8), 3.53 (1H, ddd, *J* = 7.2, 5.5, 3.8 Hz, CH-C7), 2.66 (1H, d, *J* = 7.3 Hz, OH-C8), 2.46 (1H, d, *J* = 7.2 Hz, OH-C7), 2.31-2.22 (1H, m, OH-C9), 2.07 (1H, dt, *J* = 12.4, 6.2 Hz, CH-C5), 1.97–1.90 (1H, m, CH-C4), 1.89–1.82 (1H, m, CH-C2), 1.69–1.59 (2H, m, CH-C2 and CH-C5), 1.07 (9H, s, CH_3-^{t}BuSi), 1.04 (3H, d, *J* = 6.5 Hz, CH_3-C35); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8 (CH-PhSi), 134.2 (C-PhSi), 134.2 (C-PhSi), 129.8 (CH-PhSi), 127.8 (CH-PhSi), 83.2 (CH-C3), 78.1 (CH-C6), 74.1 (CH-C7), 73.3 (CH-C8), 64.1 (CH_2-C9), 61.3 (CH_2-C1), 40.2 (CH-C4), 37.6 (CH_2-C5), 37.4 (CH_2-C2), 27.1 (CH_3-^{t}BuSi), 19.4 (C-^{t}BuSi), 16.3 (CH_3-C35); HRMS (CI+, isobutane) calcd for $C_{26}H_{39}O_5Si$ $[M+H]^+$ 459.2567, found 459.2561 (Δ −1.3 ppm).

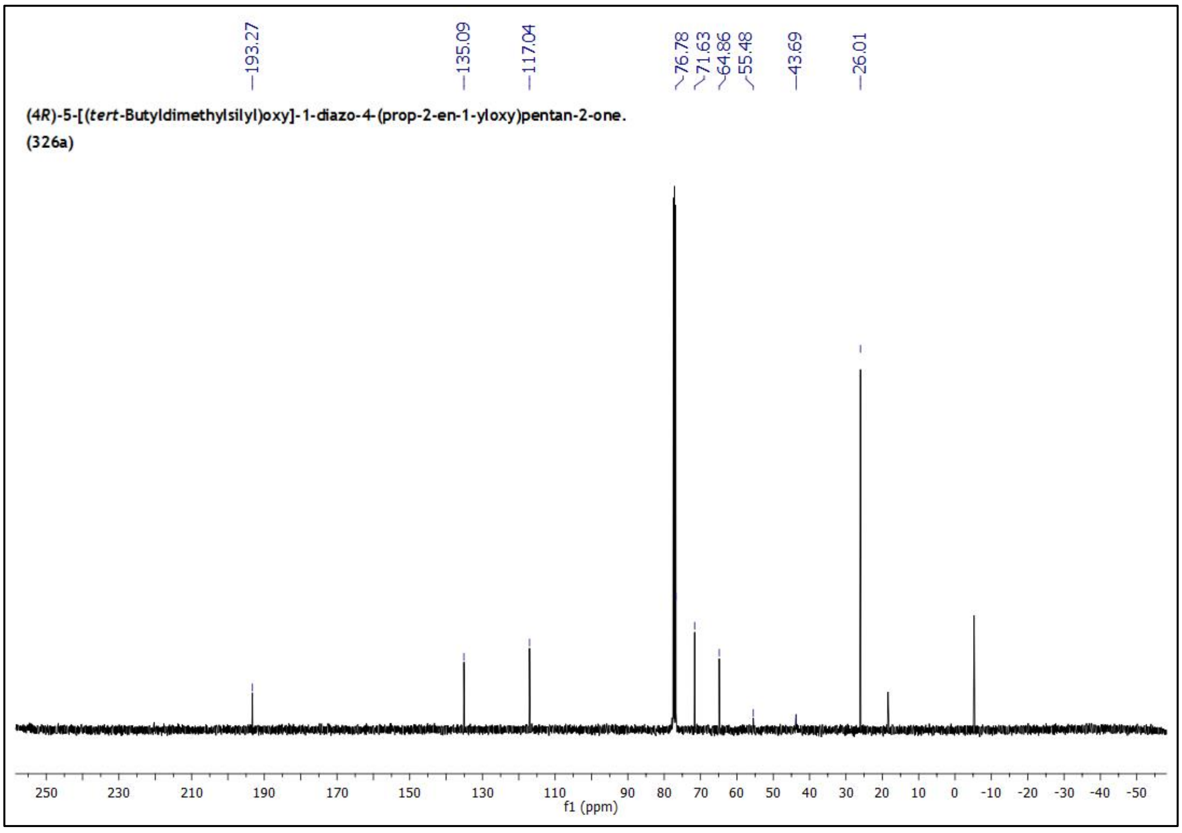
(1*R*,2*R*)-1-[(2*R*,4*R*,5*S*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}-4-methyl methyltetrahydrofuran -2-yl]propane-1,2,3-triol. (442)

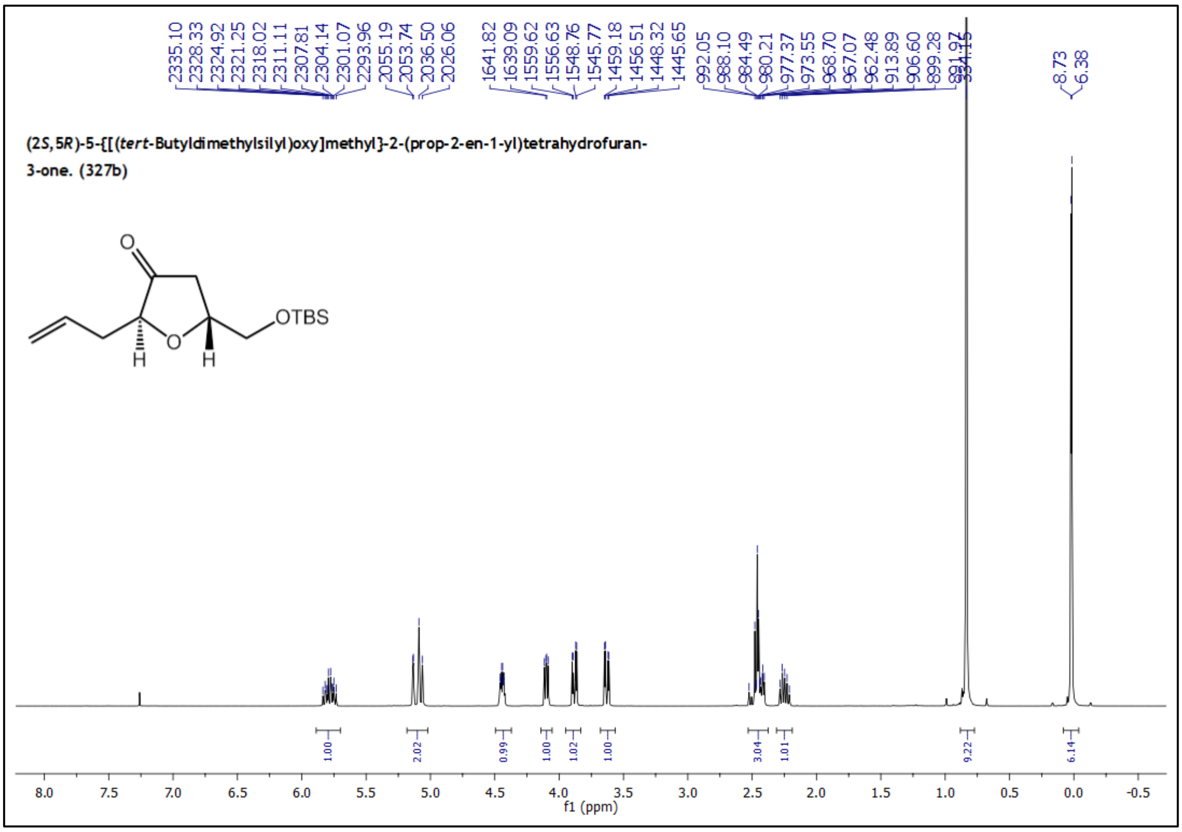


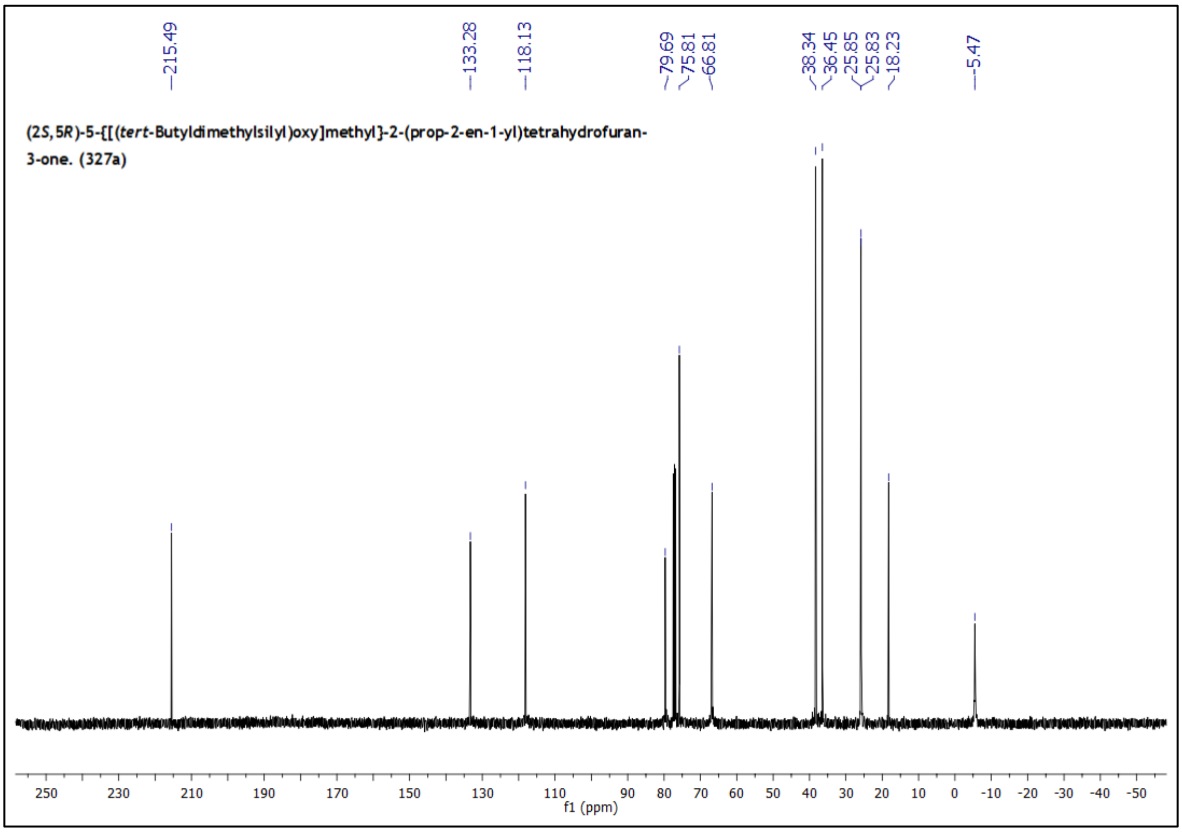
$LiAlH_4$ (2.0 mg, 0.53 mmol) was added to a stirred solution of ester **441** (17 mg, 0.035 mmol) in THF (1 ml) at rt. The mixture was stirred for 1 h and was quenched by the sequential addition of H_2O (0.1 mL), 10% aqueous NaOH (0.1 mL), H_2O (0.1 mL) and $MgSO_4$ (0.2 g). The solution was filtered and the ^{1}H NMR spectra of the compound matched that of the previously characterised material.

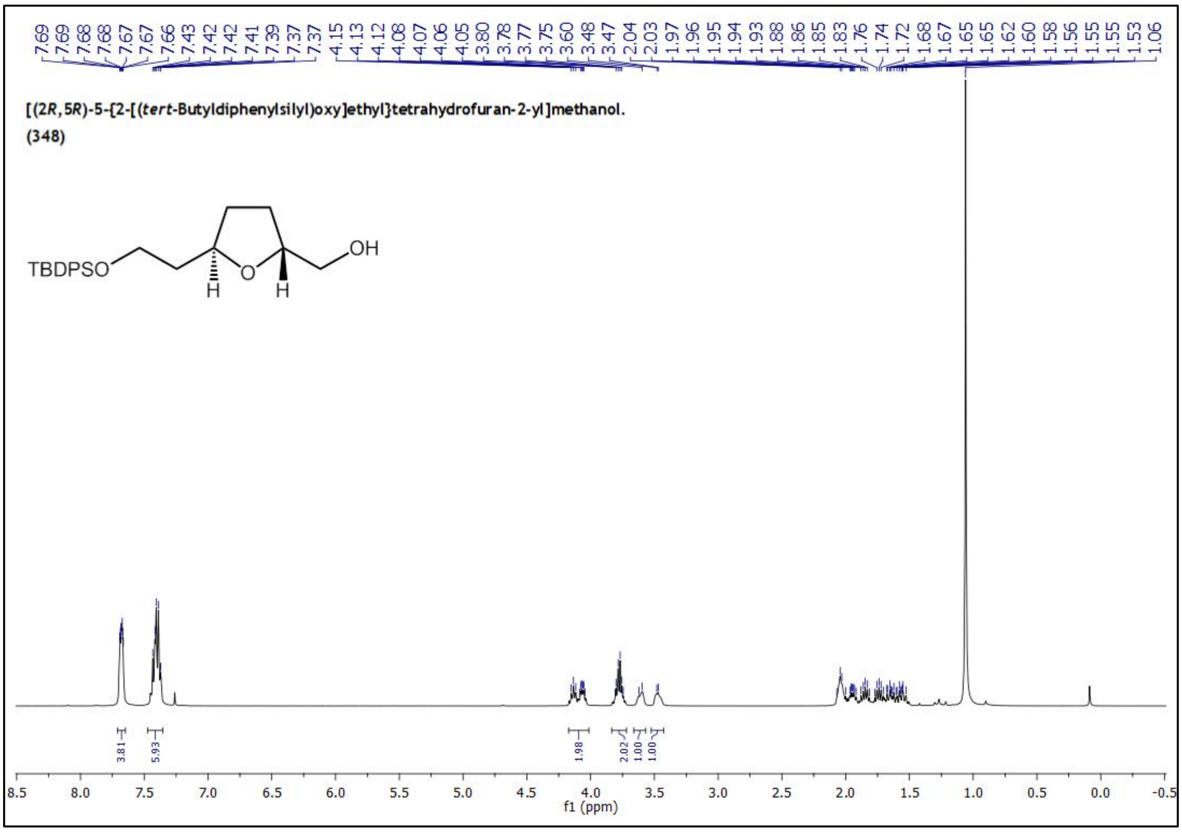
Appendices

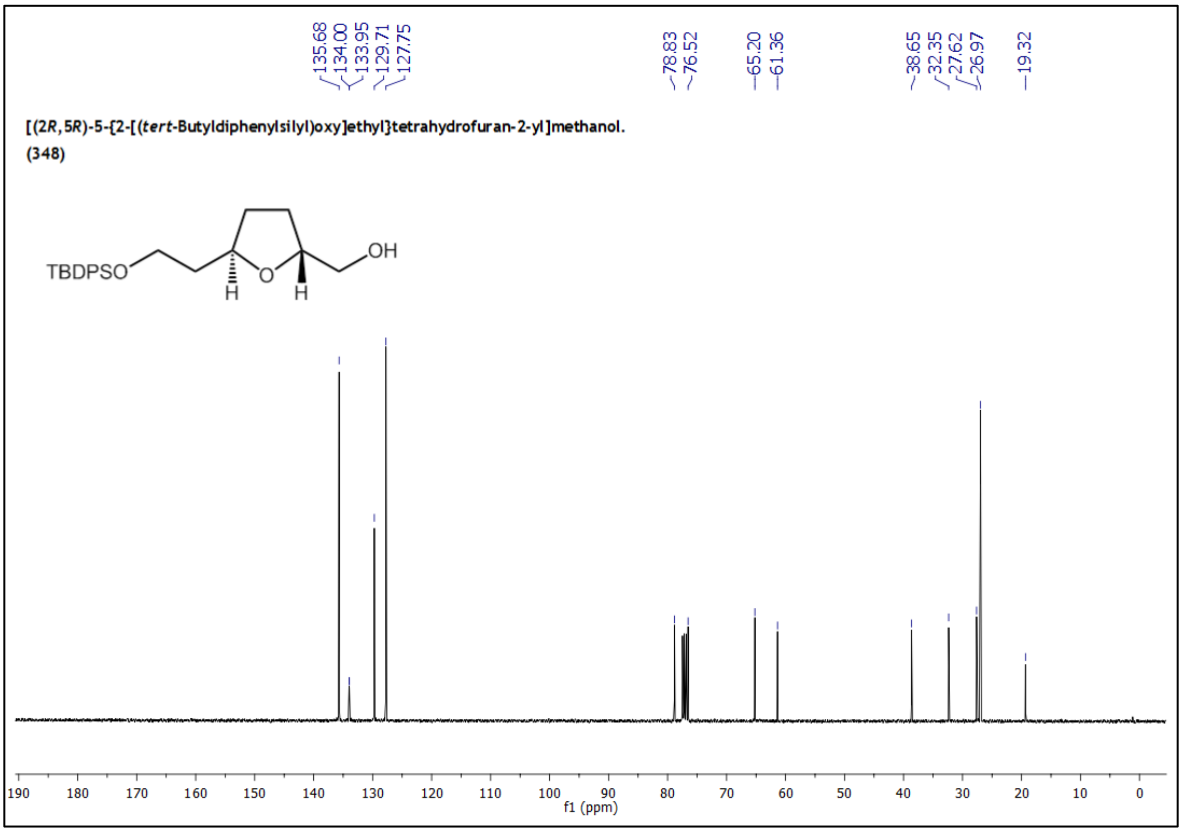

7.26 5.92 5.89 5.89 5.88 5.87 5.86 5.86 5.85 5.28 5.28 5.27 5.24 5.23 5.23 5.23 5.17 5.17 5.16 5.14 5.14 5.14 5.13 4.14 4.14 4.13 4.11 4.11 4.11 4.10 4.09 4.09 4.07 4.07 4.07 4.06 4.06 4.05 3.89 3.88 3.88 3.86 3.70 3.68 3.67 3.66 3.60 3.58 3.57 3.56 0.89 0.05 0.05
(4*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1-diazo-4-(prop-2-en-1-yloxy)pentan-2-one.
(326a)
N2
O
O
OTBS
1.00
2.96
2.16
1.08
2.19
1.98
9.62
6.12
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

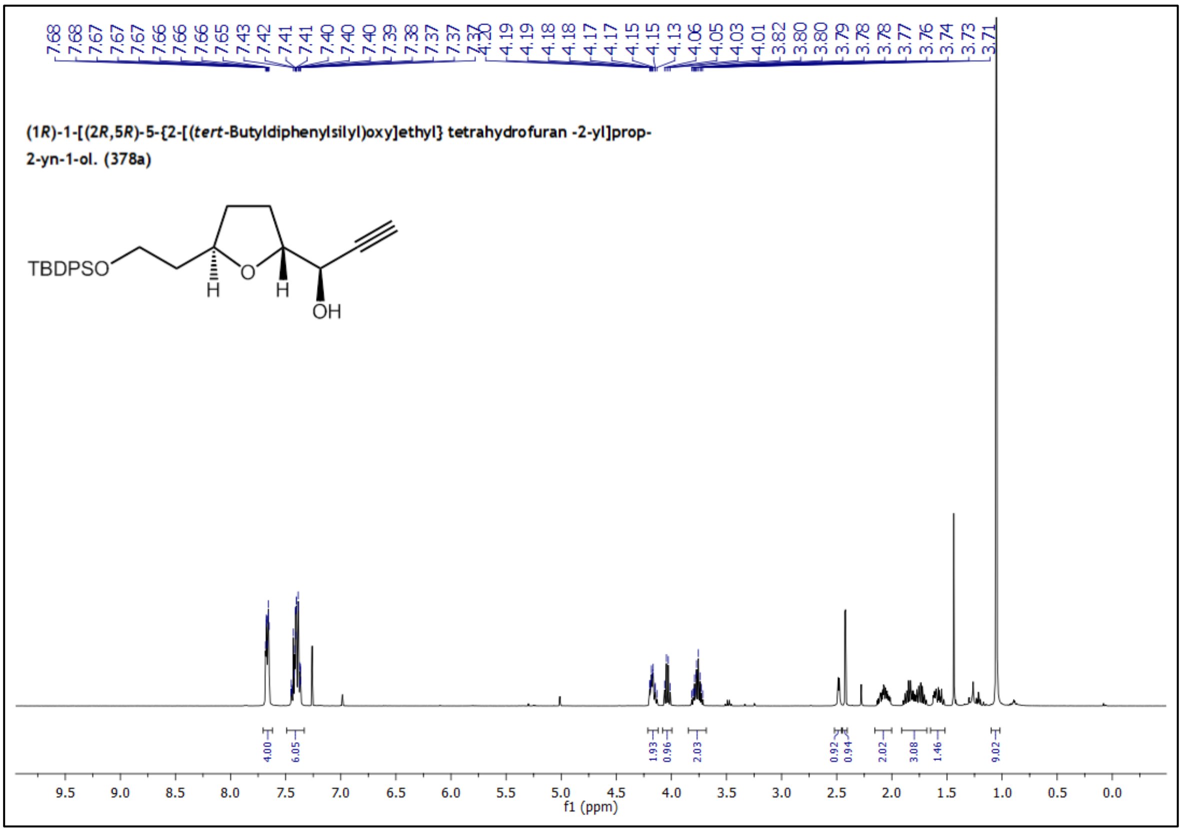

193.27
135.09
117.04
76.78
71.63
64.86
55.48
43.69
26.01
(4*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1-diazo-4-(prop-2-en-1-yloxy)pentan-2-one.
(326a)
250 230 210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50
f1 (ppm)

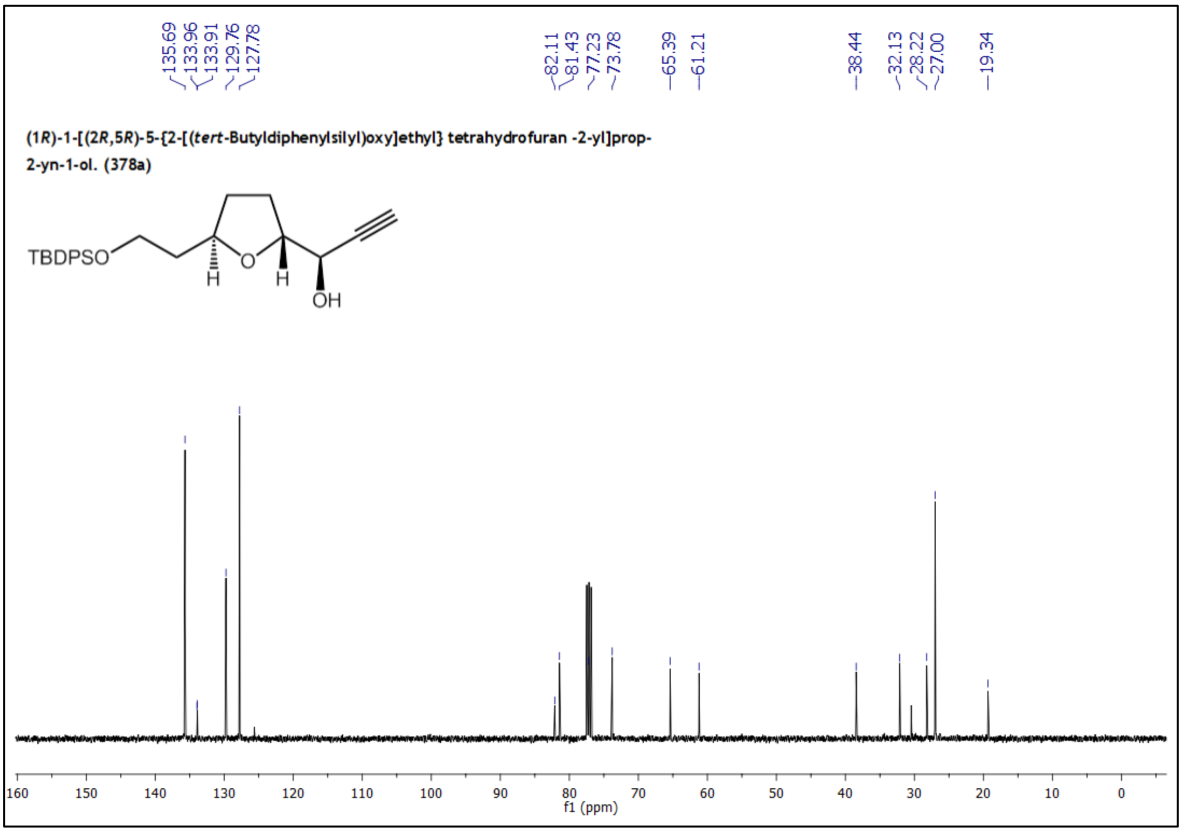

(2S,5R)-5-{[(tert-Butyldimethylsilyl)oxy]methyl}-2-(prop-2-en-1-yl)tetrahydrofuran-3-one. (327b)
O
OTBS
H
H
f1 (ppm)

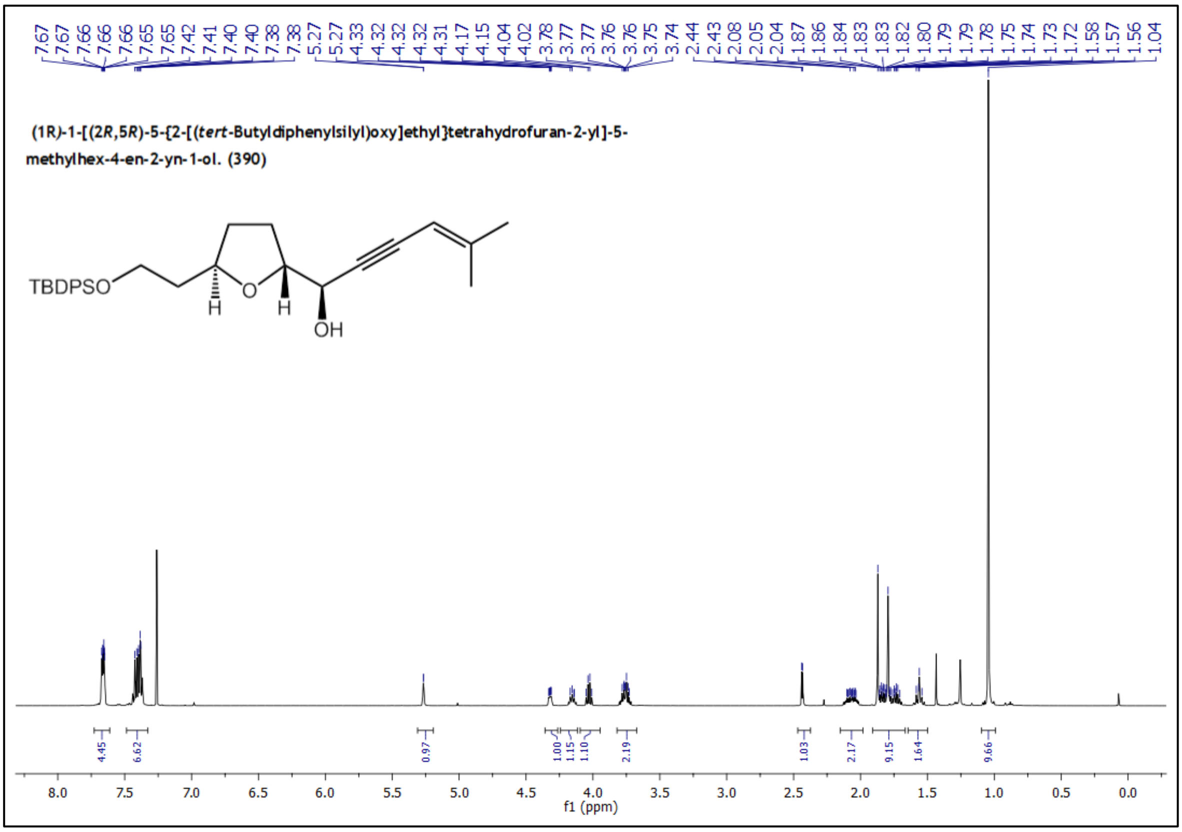

(2S,5R)-5-{[(tert-Butyldimethylsilyl)oxy]methyl}-2-(prop-2-en-1-yl)tetrahydrofuran-3-one. (327a)
215.49
133.28
118.13
79.69
75.81
66.81
38.34
36.45
25.85
25.83
18.23
-5.47
f1 (ppm)

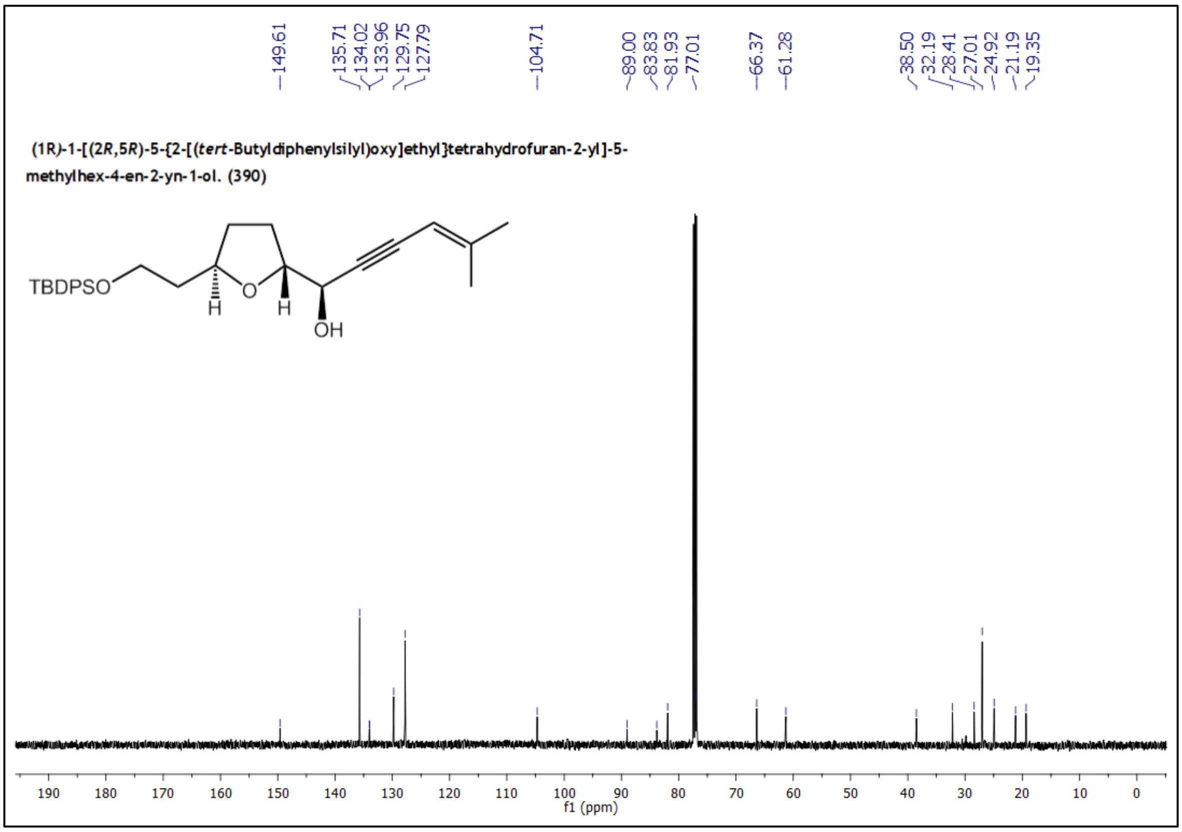

7.69 7.69 7.68 7.68 7.67 7.67 7.66 7.43 7.42 7.42 7.41 7.39 7.37 7.37 4.15 4.13 4.12 4.08 4.07 4.06 4.05 3.80 3.78 3.77 3.75 3.60 3.48 3.47 2.04 2.03 1.97 1.96 1.95 1.94 1.93 1.88 1.86 1.85 1.83 1.76 1.74 1.72 1.68 1.67 1.65 1.65 1.62 1.60 1.58 1.56 1.55 1.55 1.53 1.06
[(2R,5R)-5-{2-[(tert-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]methanol.
(348)
TBDPSO
OH
O
H
H
3.81
5.93
1.98
2.02
1.00
1.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

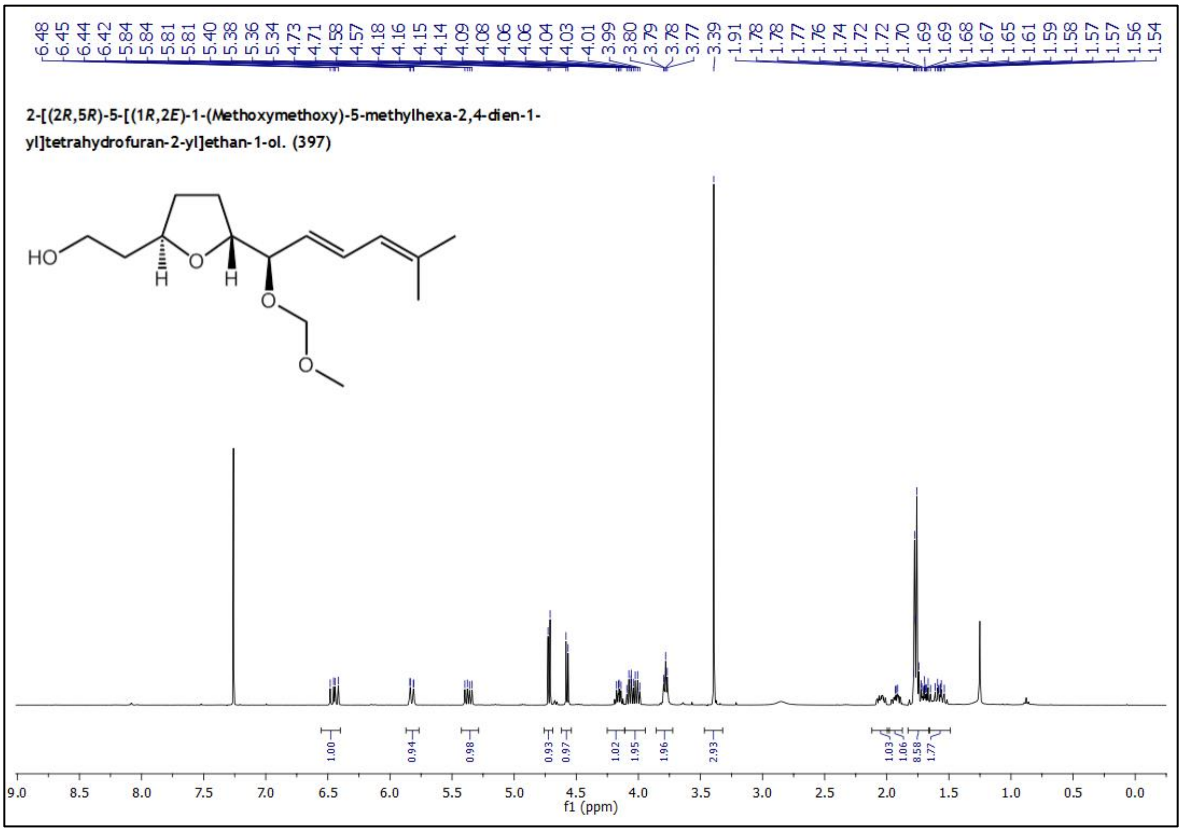

135.68 134.00 133.95 129.71 127.75
78.83 76.52
65.20 61.36
38.65 32.35 27.62 26.97
19.32
[(2R,5R)-5-{2-[(tert-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]methanol.
(348)
TBDPSO
OH
O
H
H
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

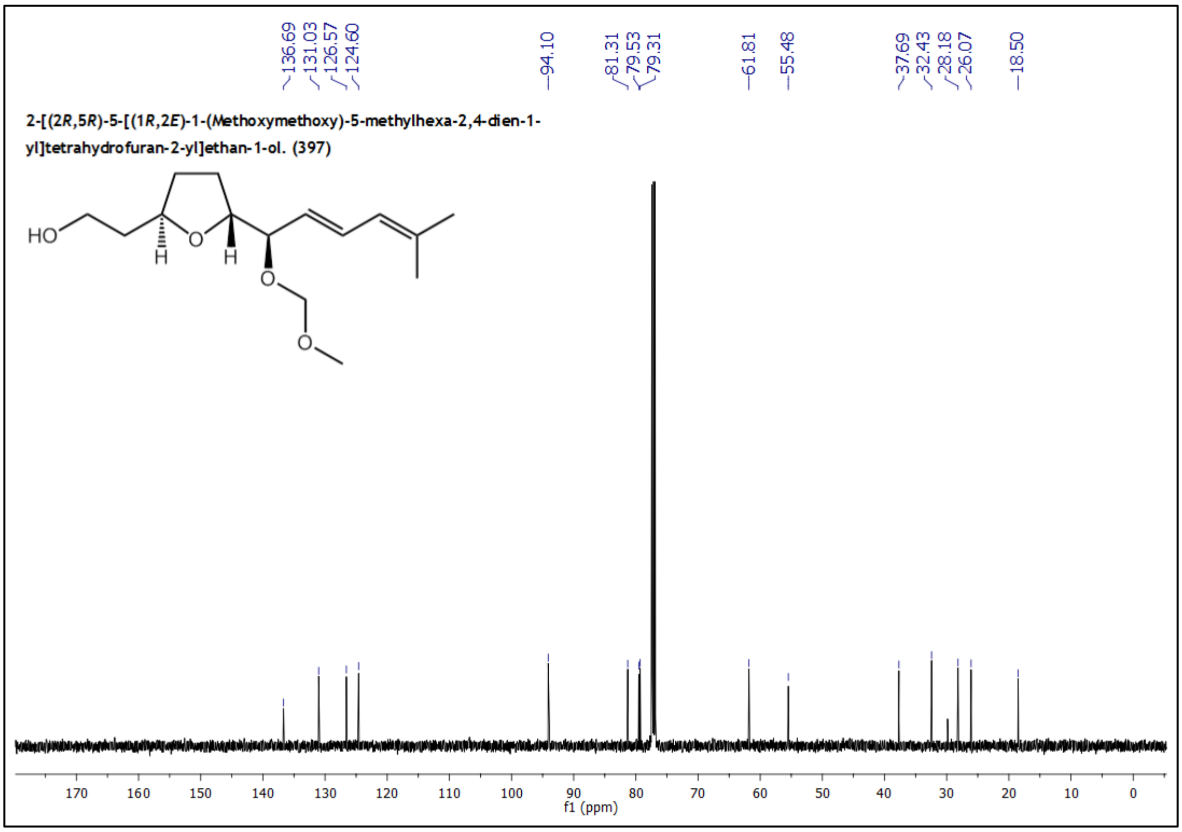

7.68
7.68
7.67
7.67
7.67
7.66
7.66
7.66
7.65
7.43
7.42
7.41
7.41
7.40
7.40
7.39
7.38
7.37
7.37
7.37
4.20
4.19
4.19
4.18
4.18
4.17
4.17
4.15
4.15
4.13
4.06
4.05
4.03
4.01
3.82
3.80
3.80
3.79
3.78
3.78
3.77
3.76
3.74
3.73
3.71
(1*R*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl} tetrahydrofuran -2-yl]prop-2-yn-1-ol. (378a)
TBDPSO
H
O
H
OH
4.00
6.05
1.93
0.96
2.03
0.92
0.94
2.02
3.08
1.46
9.02
f1 (ppm)

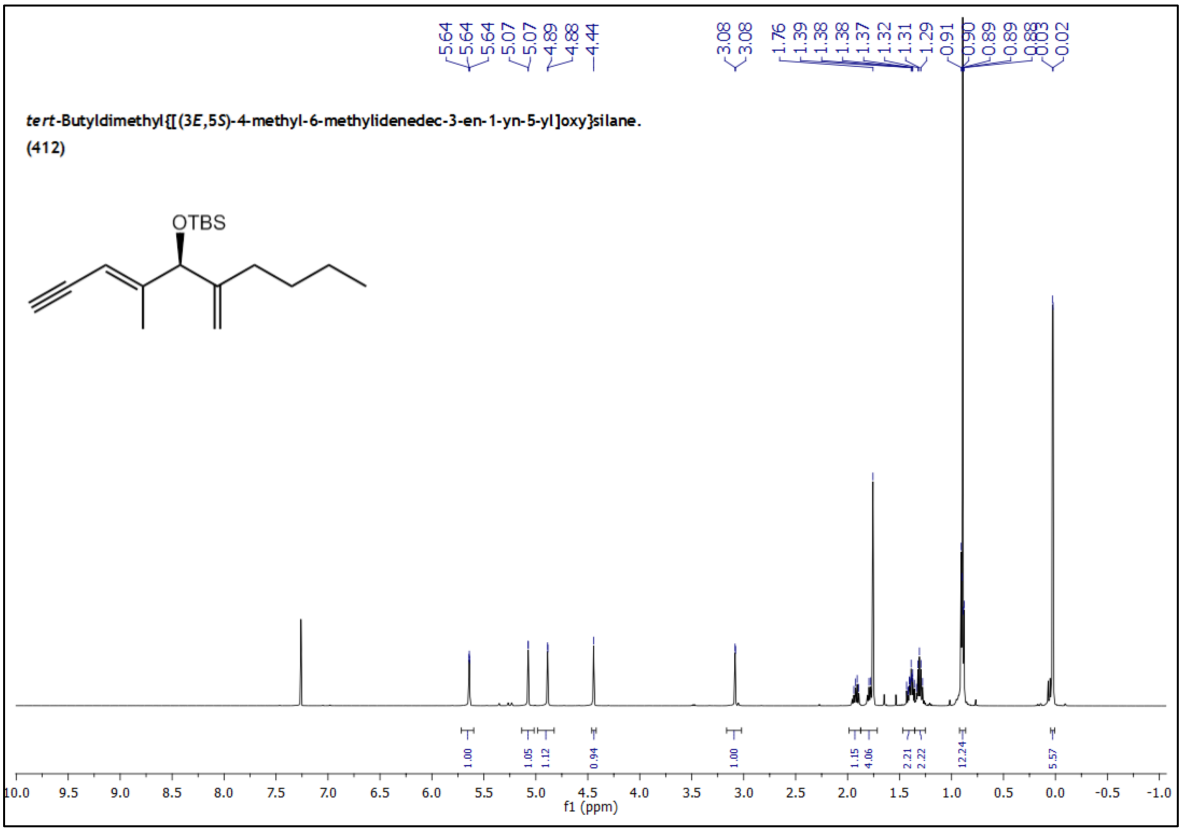

135.69
133.96
133.91
129.76
127.78
82.11
81.43
77.23
73.78
65.39
61.21
38.44
32.13
28.22
27.00
19.34
(1*R*)-1-[(2*R*,5*R*)-5-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl} tetrahydrofuran -2-yl]prop-2-yn-1-ol. (378a)
TBDPSO
H
O
H
OH
f1 (ppm)

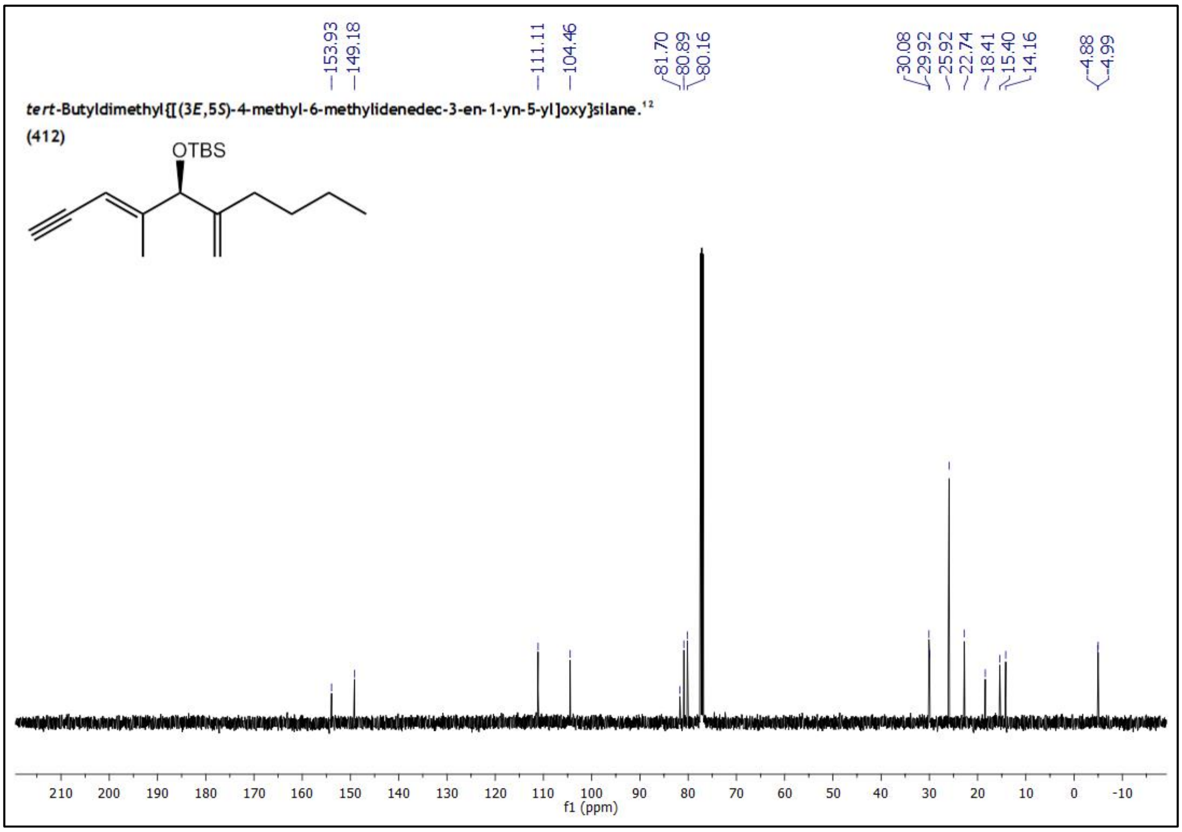

7.67
7.67
7.66
7.66
7.66
7.65
7.65
7.42
7.41
7.40
7.40
7.38
7.38
5.27
5.27
4.33
4.32
4.32
4.32
4.31
4.17
4.15
4.04
4.02
3.78
3.77
3.77
3.76
3.76
3.75
3.74
2.44
2.43
2.08
2.05
2.04
1.87
1.86
1.84
1.84
1.83
1.83
1.82
1.80
1.79
1.79
1.78
1.75
1.74
1.73
1.72
1.58
1.57
1.56
1.04
(1R)-1-[(2R,5R)-5-{2-[(tert-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]-5-methylhex-4-en-2-yn-1-ol. (390)
TBDPSO
H
O
H
OH
4.45
6.62
0.97
1.00
1.15
1.10
2.19
1.03
2.17
9.15
1.64
9.66
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

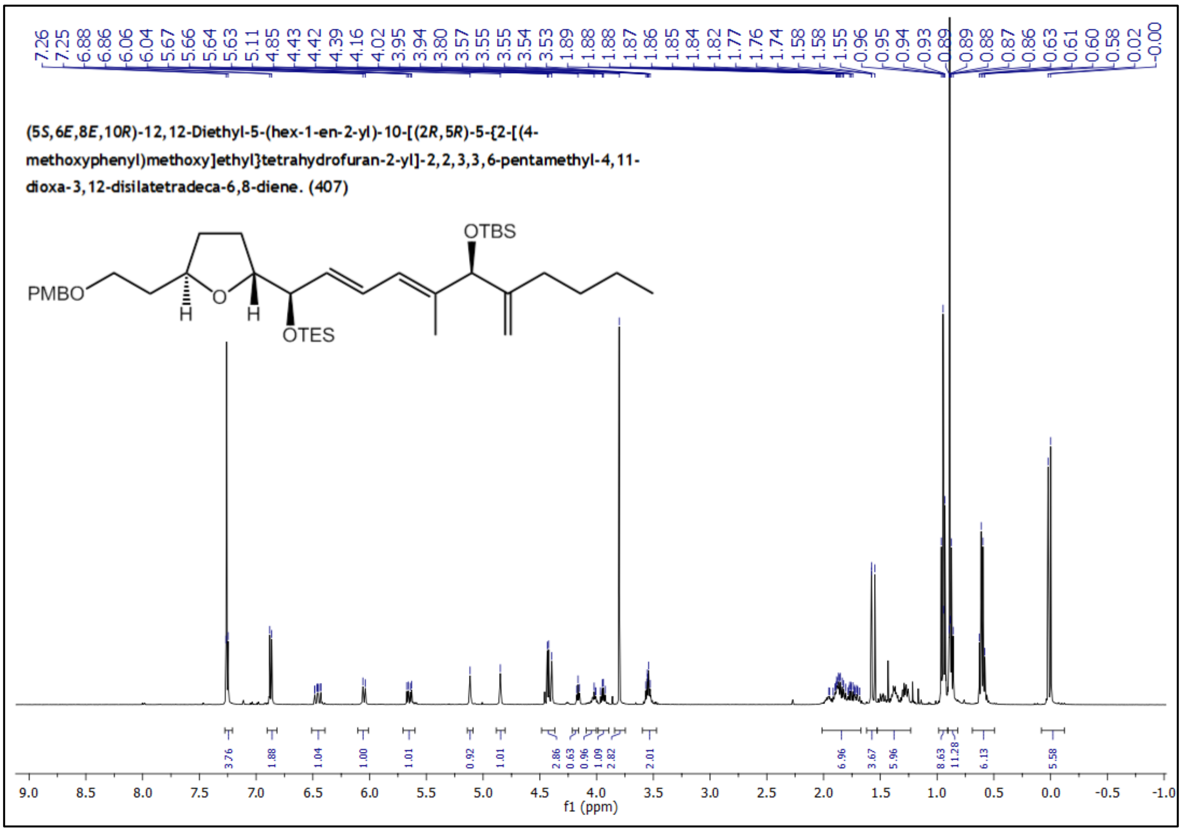

149.61
135.71
134.02
133.96
129.75
127.79
104.71
89.00
83.83
81.93
77.01
66.37
61.28
38.50
32.19
28.41
27.01
24.92
21.19
19.35
(1R)-1-[(2R,5R)-5-{2-[(tert-Butyldiphenylsilyl)oxy]ethyl}tetrahydrofuran-2-yl]-5-methylhex-4-en-2-yn-1-ol. (390)
TBDPSO
H
O
H
OH
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

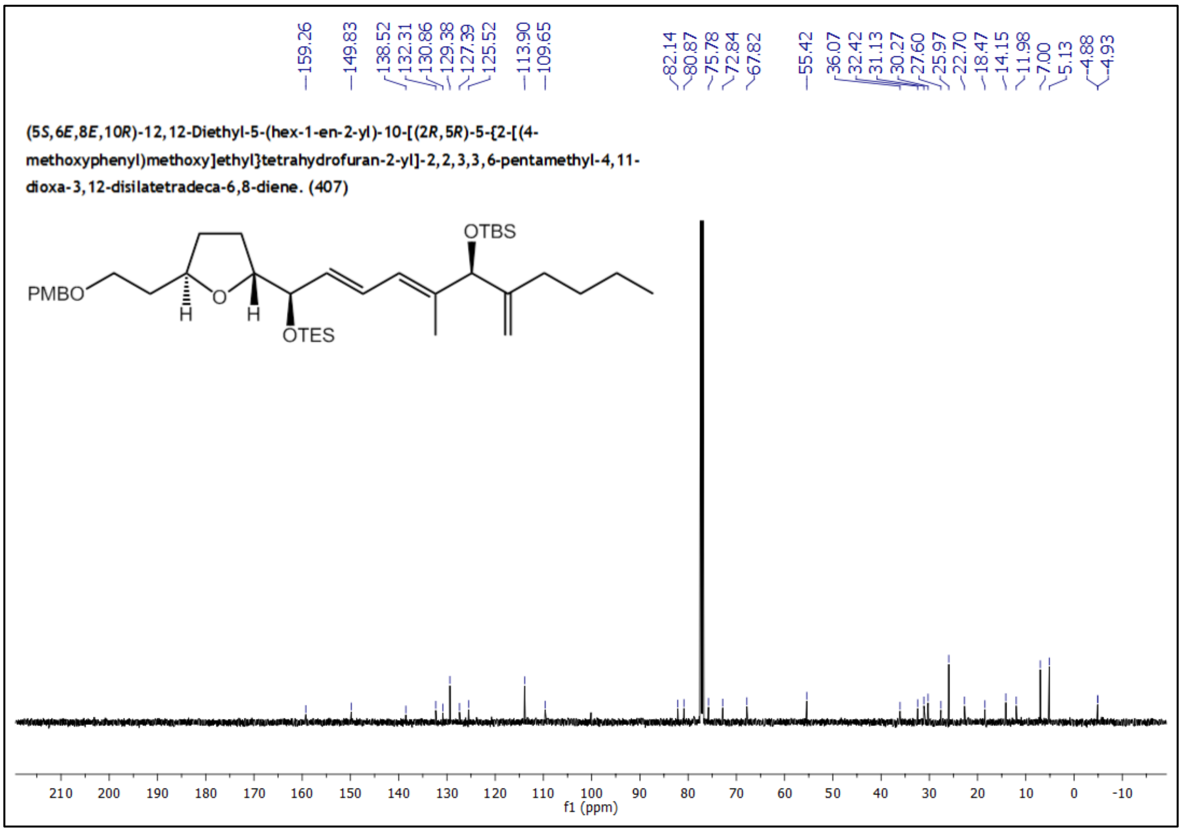

2-[(2R,5R)-5-[(1R,2E)-1-(Methoxymethoxy)-5-methylhexa-2,4-dien-1-yl]tetrahydrofuran-2-yl]ethan-1-ol. (397)
f1 (ppm)

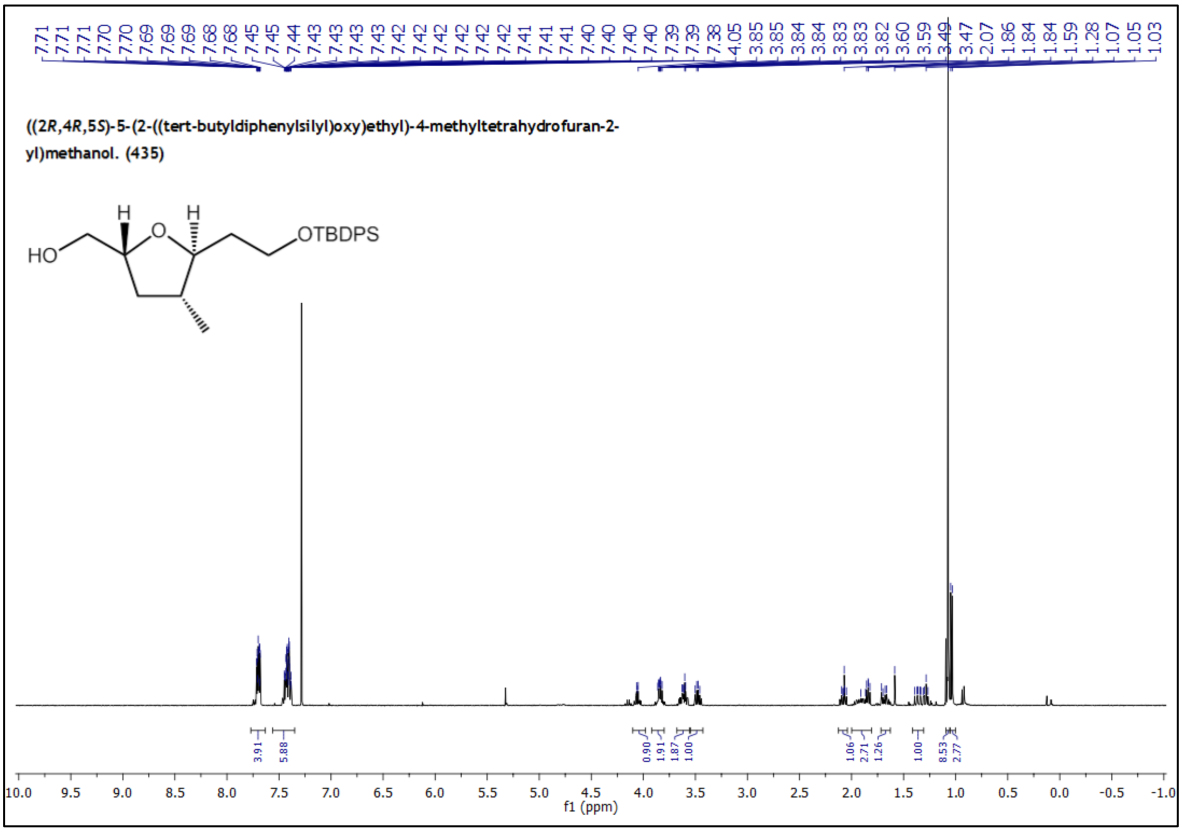

2-[(2R,5R)-5-[(1R,2E)-1-(Methoxymethoxy)-5-methylhexa-2,4-dien-1-yl]tetrahydrofuran-2-yl]ethan-1-ol. (397)
136.69
131.03
126.57
124.60
94.10
81.31
79.53
79.31
61.81
55.48
37.69
32.43
28.18
26.07
18.50
f1 (ppm)


5.64
5.64
5.64
5.07
5.07
4.89
4.88
4.44
3.08
3.08
1.76
1.39
1.38
1.38
1.37
1.32
1.31
1.29
0.91
0.90
0.89
0.89
0.88
0.03
0.02
tert-Butyldimethyl{[(3*E*,5*S*)-4-methyl-6-methylidenedec-3-en-1-yn-5-yl]oxy}silane.
(412)
OTBS
1.00
1.05
1.12
0.94
1.00
1.15
4.06
2.21
2.22
12.24
5.57
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


153.93
149.18
111.11
104.46
81.70
80.89
80.16
30.08
29.92
25.92
22.74
18.41
15.40
14.16
-4.88
-4.99
tert-Butyldimethyl{[(3*E*,5*S*)-4-methyl-6-methylidenedec-3-en-1-yn-5-yl]oxy}silane.[12]
(412)
OTBS
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


(5S,6E,8E,10R)-12,12-Diethyl-5-(hex-1-en-2-yl)-10-[(2R,5R)-5-{2-[(4-methoxyphenyl)methoxy]ethyl}tetrahydrofuran-2-yl]-2,2,3,3,6-pentamethyl-4,11-dioxa-3,12-disilatetradeca-6,8-diene. (407)
OTBS
PMBO
H
O
H
OTES
f1 (ppm)


(5S,6E,8E,10R)-12,12-Diethyl-5-(hex-1-en-2-yl)-10-[(2R,5R)-5-{2-[(4-methoxyphenyl)methoxy]ethyl}tetrahydrofuran-2-yl]-2,2,3,3,6-pentamethyl-4,11-dioxa-3,12-disilatetradeca-6,8-diene. (407)
OTBS
PMBO
H
O
H
OTES
f1 (ppm)


7.71
7.71
7.71
7.70
7.69
7.69
7.69
7.68
7.68
7.45
7.45
7.44
7.43
7.43
7.43
7.43
7.42
7.42
7.42
7.42
7.42
7.41
7.41
7.40
7.40
7.40
7.39
7.39
7.38
4.05
3.85
3.85
3.84
3.84
3.83
3.83
3.82
3.60
3.59
3.49
3.47
2.07
1.86
1.84
1.84
1.59
1.28
1.07
1.05
1.03
((2R,4R,5S)-5-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-methyltetrahydrofuran-2-yl)methanol. (435)
HO
H
O
H
OTBDPS
3.91
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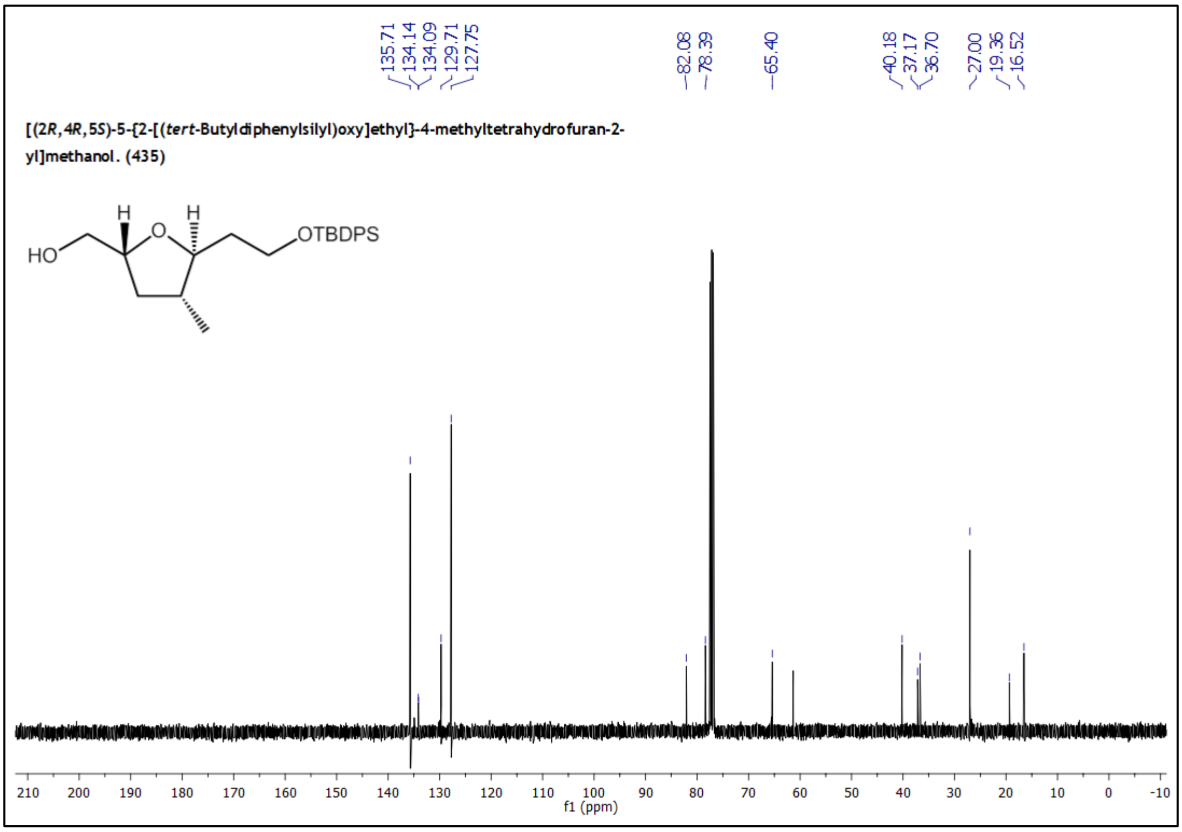
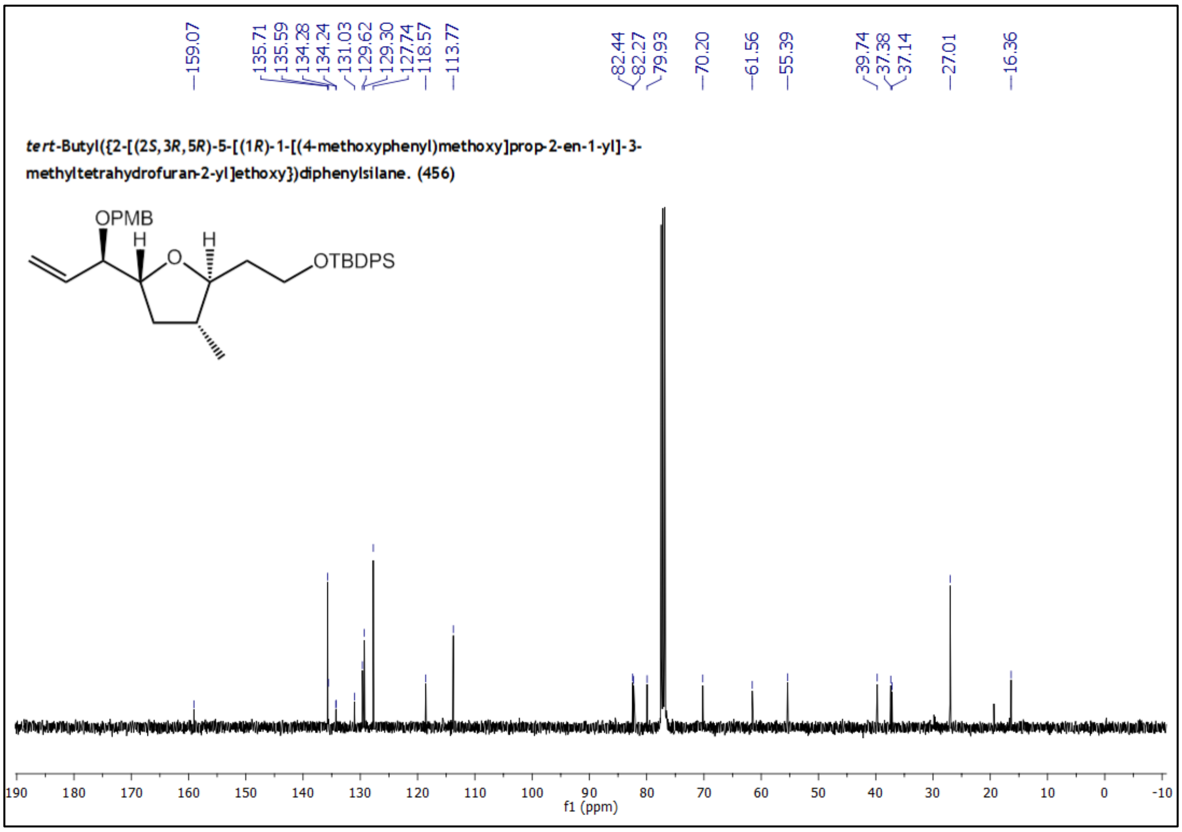
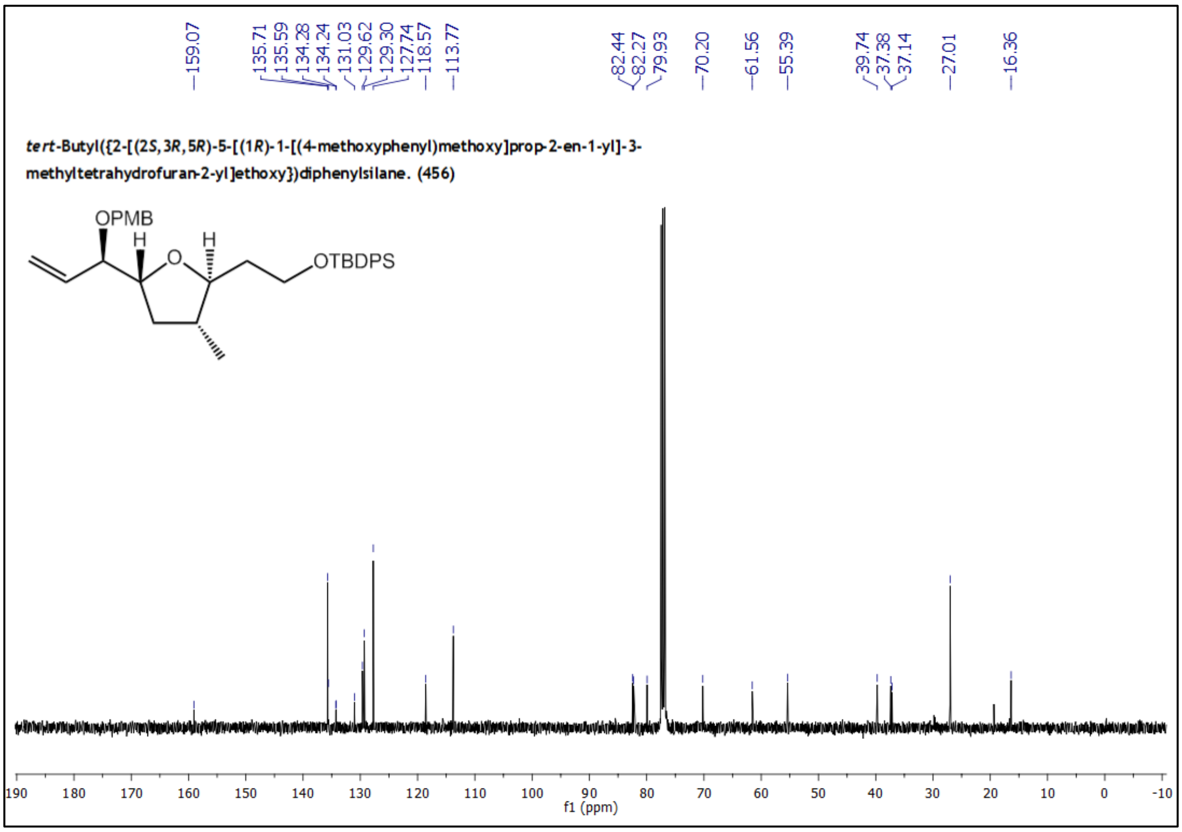
0.90
1.91
1.87
1.00
1.06
2.71
1.26
1.00
8.53
2.77
f1 (ppm)


135.71
134.14
134.09
129.71
127.75
82.08
78.39
65.40
40.18
37.17
36.70
27.00
19.36
16.52
[(2R,4R,5S)-5-{2-[(tert-Butyldiphenylsilyl)oxy]ethyl}-4-methyltetrahydrofuran-2-yl]methanol. (435)
HO
H
O
H
OTBDPS
f1 (ppm)


159.07
135.71
135.59
134.28
134.24
131.03
129.62
129.30
127.74
118.57
113.77
82.44
82.27
79.93
70.20
61.56
55.39
39.74
37.38
37.14
27.01
16.36
tert-Butyl({2-[(2*S*,3*R*,5*R*)-5-[(1*R*)-1-[(4-methoxyphenyl)methoxy]prop-2-en-1-yl]-3-methyltetrahydrofuran-2-yl]ethoxy})diphenylsilane. (456)
OPMB
H
O
H
OTBDPS
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


159.07
135.71
135.59
134.28
134.24
131.03
129.62
129.30
127.74
118.57
113.77
82.44
82.27
79.93
70.20
61.56
55.39
39.74
37.38
37.14
27.01
16.36
tert-Butyl({2-[(2*S*,3*R*,5*R*)-5-[(1*R*)-1-[(4-methoxyphenyl)methoxy]prop-2-en-1-yl]-3-methyltetrahydrofuran-2-yl]ethoxy})diphenylsilane. (456)
OPMB
H
O
H
OTBDPS
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

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Synthesis of the C-18–C-34 Fragment of Amphidinolides C, C2, and C3

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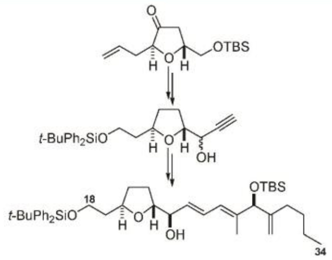
Received February 21, 2013

ABSTRACT



The C-18–C-34 fragment of amphidinolides C, C2, and C3 and the C-18–C-29 fragment of amphidinolide F have been constructed from a *trans*-2,5-disubstituted dihydrofuran. This key intermediate was prepared from a dihydrofuranone formed by diastereoselective rearrangement of a free or metal-bound oxonium ylide generated from a metal carbenoid. The side chains found in amphidinolides C and F were introduced using Sonogashira coupling reactions.

The amphidinolides are macrolide natural products extracted from symbiotic dinoflagellates of the genus *Amphidinium* cultivated from the Okinawan flatworms of the *Amphiscolops* species. Several members of this diverse group of macrolides exhibit potent cytotoxicity and possess other biological activities, but in most cases the substantial quantities of material required in order to fully establish their therapeutic potential are not available.[1] Amphidinolide C[2] (**1**) and the closely related congeners amphidinolides C2[3] (**2**), C3[4] (**3**), and F[5] (**4**) are particularly attractive targets for total synthesis because of their powerful *in vitro* activities and the synthetic challenges that their complex molecular architectures present (Figure 1). Several groups have reported syntheses of fragments of these natural products,[2b–d,6] but only very recently has a total synthesis of one member of the family, amphidinolide F (**4**), been published.[7]

Amphidinolide C was isolated by Kobayashi et al. in 1988 and was found to possess cytotoxic activity against both murine lymphoma and epidermoid carcinoma KB cell lines.[2] Subsequently, the absolute and relative configurations of this and the other natural products in the series were established and their bioactivities were determined,

(1) (a) Kobayashi, J.; Ishibashi, M. *Chem. Rev.* **1993**, *93*, 1753. (b) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77. (c) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451. (d) Kobayashi, J. *J. Antibiot.* **2008**, *61*, 271.

(2) (a) Kobayashi, J.; Ishibashi, M.; Wälchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. *J. Am. Chem. Soc.* **1988**, *110*, 490. (b) Ishiyama, H.; Ishibashi, M.; Kobayashi, J. *Chem. Pharm. Bull.* **1996**, *44*, 1819. (c) Kubota, T.; Tsuda, M.; Kobayashi, J. *Org. Lett.* **2001**, *3*, 1363. (d) Kubota, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 1613.

(3) Kubota, T.; Sakuma, Y.; Tsuda, M.; Kobayashi, J. *Mar. Drugs* **2004**, *2*, 83.

(4) Kubota, T.; Suzuki, A.; Yamada, M.; Baba, S.; Kobayashi, J. *Heterocycles* **2010**, *82*, 333.

(5) Kobayashi, J.; Tsuda, M.; Ishibashi, M.; Shigemori, H.; Yamasu, T.; Hirota, H.; Sasaki, T. *J. Antibiot.* **1991**, *44*, 1259.

(6) (a) Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2004**, *6*, 3865. (b) Mohapatra, D. K.; Rahaman, H.; Chorghade, M. S.; Gurjar, M. K. *Synlett* **2007**, *4*, 567. (c) Bates, R. H.; Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2008**, *10*, 4343. (d) Armstrong, A.; Pyrkotis, C. *Tetrahedron Lett.* **2009**, *50*, 3325. (e) Mahapatra, S.; Carter, R. G. *Org. Biomol. Chem.* **2009**, *7*, 4582. (f) Paudyal, M. P.; Rath, N. P.; Spilling, C. D. *Org. Lett.* **2010**, *12*, 2954. (g) Ferrié, L.; Figadère, B. *Org. Lett.* **2010**, *12*, 4976. (h) Roy, S.; Spilling, C. D. *Org. Lett.* **2010**, *12*, 5326. (i) Morra, N. A.; Pagenkopf, B. L. *Org. Lett.* **2011**, *13*, 572.

(7) Mahapatra, S.; Carter, R. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7948.

10.1021/ol400482j
Published on Web 03/25/2013

providing insights into the structure–activity relationships (SARs) within this unique set of compounds.

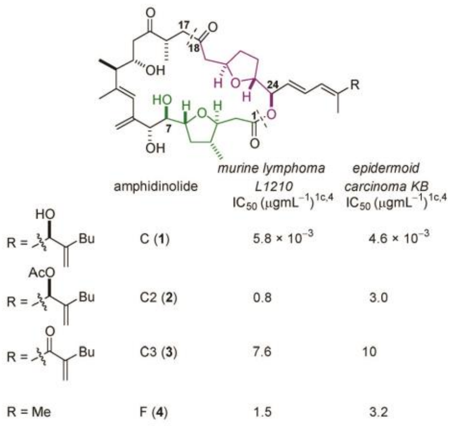
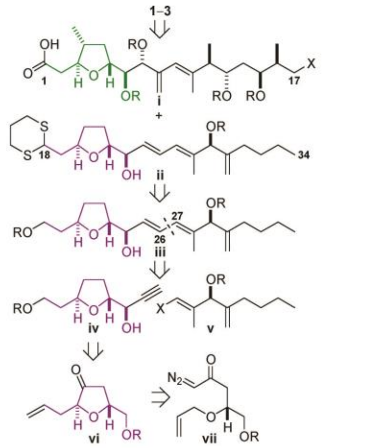


Figure 1. Amphidinolides C, C2, C3, and F.

The 25-membered macrolactone core of amphidinolide C contains two 2,5-*trans* substituted tetrahydrofurans embedded in its structure and an unsaturated side chain (C-25 to C-34). The significant differences in biological activity between amphidinolides C, C2, and F result from structural variations in the side-chain region of these compounds.[1] The C-29 hydroxyl group confers potent bioactivity on amphidinolide C, and the absence of this substituent or removal of its H-bond donor capacity by acetylation results in a 1000-fold reduction in activity (Figure 1). This observation regarding the SAR encouraged us to adopt a modular synthetic approach in which the side chain of amphidinolide C and analogues would be constructed using Pd-catalyzed coupling reactions.

The retrosynthetic analysis of amphidinolide C is shown in Scheme 1. Initial disconnection of the lactone C–O bond and the C-17–C-18 bond leads to the 'southern' and 'northern' fragments **i** and **ii** respectively. Simplification of the 'northern' fragment **ii** leads to the diene **iii**, and further disconnection of the C-26–C-27 bond provides a vinylic halide **v** and a propargylic alcohol **iv**. The latter can be obtained from a *trans* 2,5-disubstituted dihydrofuranone **vi** of a type generated by a highly diastereoselective metal-mediated reaction of the diazo ketone **vii**.[8] In the overall synthetic plan, it is expected that dihydrofuranone **vi** will serve as a precursor to the C-1 to C-7 portion of the southern fragment **i**, allowing both key tetrahydrofuran-containing fragments to be prepared from a common intermediate.[9] A similar strategy was employed by Carter and Mahaparta in their very recent total synthesis of amphidinolide F.[7]

Scheme 1. Retrosynthetic Analysis of Amphidinolide C



The requisite dihydrofuranone was prepared from dimethyl D-malate (Scheme 2). Selective reduction of the α-hydroxy ester using the procedure by Saito et al. provided a diol,[10] the primary hydroxyl group of which was protected to give the TBS ether **6**. The remaining secondary hydroxyl group was then allylated using the acid-catalyzed reaction of an imidate to afford the allyl ether **7**.[11] Saponification of the ester provided the carboxylic acid **8**, and activation of this as a mixed anhydride followed by treatment with a solution of diazomethane gave the α-diazo ketone **9**. Treatment of this compound with $Cu(acac)_2$ in THF at reflux afforded the dihydrofuranone **10** as a single isomer in high yield.[8]

Following the synthesis of the ketone **10**, the first challenge was the deletion of the carbonyl group from the ring to provide the tetrahydrofuran corresponding to the C-18 to C-24 subunit of amphidinolide C. Initial attempts to perform removal of the ketone were undertaken by formation of a tosyl hydrazone followed by

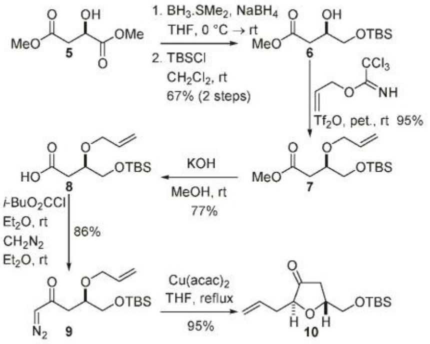
(8) (a) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060. (b) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062. (c) Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193. (d) Clark, J. S.; Krowiak, S. A.; Street, L. J. *Tetrahedron Lett.* **1993**, *34*, 4385. (e) Clark, J. S.; Whitlock, G. A. *Tetrahedron Lett.* **1994**, *35*, 6381. (f) Clark, J. S.; Whitlock, G.; Jiang, S.; Onyia, N. *Chem. Commun.* **2003**, 2578. (g) Clark, J. S.; Fessard, T. C.; Wilson, C. *Org. Lett.* **2004**, *6*, 1773. (h) Clark, J. S.; Fessard, T. C.; Whitlock, G. A. *Tetrahedron* **2006**, *62*, 73.

(9) Clark, J. S.; Yang, G.; Osnowski, A. P. *Org. Lett.* **2013**, *15*, DOI: 10.1021/ol4004838.

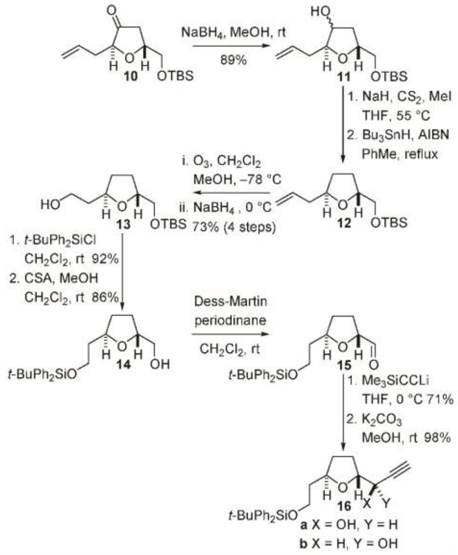
(10) (a) Saito, S.; Hasegawa, M.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389. (b) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067.

(11) (a) Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247. (b) Krüger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499.

Scheme 2. Synthesis of *trans*-Dihydrofuranone **10**



Scheme 3. Synthesis of Propargylic Alcohol **16**



reduction.[12] However, this approach was unsuccessful and so the use of radical deoxgenation methods was explored (Scheme 3). The ketone **10** was reduced to a diastereomeric mixture of alcohols **11** that were then converted into the corresponding xanthate esters. Treatment of this mixture under Barton–McCombie conditions delivered the deoxygenated tetrahydrofuran **12**.[13] Ozonolysis and reduction then afforded the alcohol **13** in an overall yield of 73% over four steps, with minimal purification necessary. Protection of the primary alcohol as a *tert*-butyldiphenylsilyl ether followed by selective acid-catalyzed removal of the TBS group generated the alcohol **14**. Oxidation of the primary alcohol using the Dess-Martin protocol provided the aldehyde **15** required for the addition of an alkyne nucleophile.

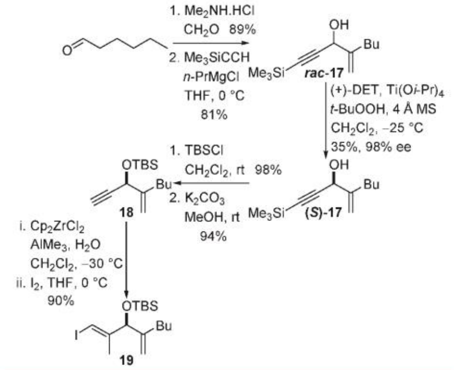
Several sets of reaction conditions were examined in an effort to perform a stereoselective nucleophilic attack on the aldehyde **15**. Attempted reagent-controlled introduction of the alkyne using Carriera's alkynylation protocol[14] did not proceed efficiently. Efforts to achieve substrate control by using various alkyne nucleophiles and reaction conditions were not successful; a 1.5:1 mixture of the diastereomeric propargylic alcohols **16a** and **16b** was obtained from the reaction performed with magnesium trimethylsilylacetylide in THF at −78 °C. Oxidation of the mixture of alcohols to the corresponding ynone proceeded in good yield, but attempted stereoselective ketone reduction using L-selectride or under Luche conditions at −78 °C resulted in little stereocontrol (1:1 and 1.5:1 of **16a**:**16b**, respectively) .

Following preparation of the propargylic alcohols **16a,b**, attention turned to the synthesis of the vinylic iodide coupling partner **19** (Scheme 4). Hexanal was methylenated under Mannich conditions,[15] and the resulting enal was subjected to the Grignard addition of TMS acetylene to provide a racemic mixture of propargylic alcohols **17**. Kinetic resolution was then performed using Sharpless asymmetric epoxidation, and the allylic alcohol **(*S*)-17** was obtained with 98% ee.[16] TBS protection of the secondary alcohol, removal of the TMS group, and subjection of the resulting terminal alkyne to modified Negishi carboalumination and iodination conditions[17] provided the unstable *E*-vinylic iodide **19** stereoselectively and in good yield.

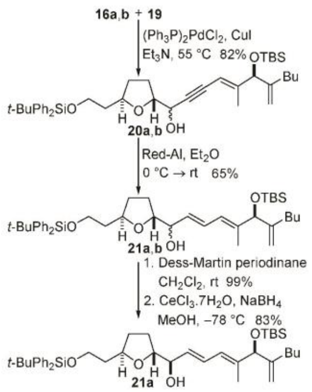
Although it was possible to separate the diastereomeric alcohols **16a,b**, the mixture was used in the subsequent step. Coupling of the vinylic iodide **19** to a mixture of the propargylic alcohols **16a,b** under Sonogashira conditions was achieved in 82% yield (Scheme 5).[18] The propargylic alcohol functionality of the coupled products **20a,b** allowed stereoselective reduction of the alkyne to be achieved using Red-Al to give the desired *E*-configured alkenes **21a,b**.[6i] Oxidation of the diastereomeric mixture of allylic alcohols to give the enone was accomplished in quantitative yield using the Dess-Martin periodinane. A subsequent stereoselective Luche reduction of the dienone provided the alcohol **21a** corresponding to the entire C-18

(12) (a) Caglioti, L. *Tetrahedron* **1966**, *22*, 487. (b) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662.
(13) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(14) (a) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (b) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605.
(15) Ragoussis, V.; Giannikopoulos, A.; Skoka, E.; Grivas, P. *J. Agric. Food Chem.* **2007**, *55*, 5050.
(16) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
(17) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068.
(18) (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874. (b) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.

Scheme 4. Stereoselective Synthesis of Vinylic Iodide **19**



Scheme 5. Completion of the C-18−C-34 Fragment of Amphidinolide C



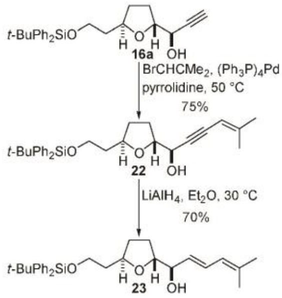
to C-34 fragment in 83% yield as a single stereoisomer through Felkin−Anh control.

(19) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403.

(20) Alcohol **16a** could be obtained as a single diastereomer by addition of lithium trimethylsilylacetylide to the aldehyde **15**, treatment of resulting diastereomeric alcohols with dicobalt octacarbonyl, chromatographic separation of the diastereomeric cobalt complexes, and oxidative removal of cobalt followed by desilylation (see Supporting Information for full details).

The power of the Sonogashira coupling reaction for the installation of a range of tail units was further illustrated by the construction of the C-18−C-29 fragment of amphidinolide F (Scheme 6). In this case, a copper-free variant of the Sonogashira reaction[19] was used to couple 1-bromo-2-methylpropene to the alkyne **16a**.[20] This modification to the procedure was required because significant homocoupling of the alkyne was encountered when the reaction was performed in the presence of copper iodide. When pyrrolidine was used as the solvent, clean coupling occurred to provide **22** in 75% yield. The propargylic alcohol was reduced to the corresponding *E*-allyl alcohol **23** in an analogous manner to the reduction of **20a,b** (Scheme 5).

Scheme 6. Completion of the C-18−C-29 Fragment of Amphidinolide F



In summary, we have synthesized the C-18−C-34 fragment of amphidinolide C and the C-18−C-29 fragment of amphidinolide F using routes in which diastereoselective rearrangement of the diazo ketone **9** is used to construct the key *trans*-2,5-disubstituted tetrahydrofuran. The entire 'northern' fragments **21a** and **23** were constructed from **16** using Sonogashira coupling reactions to install the side chains found in the natural products. Stereoselective enone reduction was used to control the stereochemistry at C-24 in the case of the C-18−C-34 fragment of amphidinolide C.

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Supporting Information Available. Experimental procedures and data for **7**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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Synthesis of the C-1–C-17 Fragment of Amphidinolides C, C2, C3, and F

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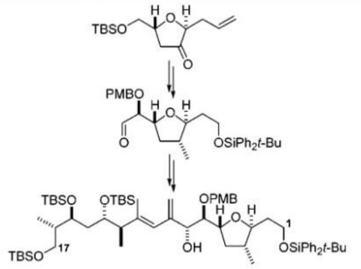
ABSTRACT



The C-1–C-17 fragment of amphidinolides C, C2, C3, and F has been constructed from a *trans*-2,5-disubstituted dihydrofuranone prepared by diastereoselective rearrangement of a free or metal-bound oxonium ylide generated from a metal carbenoid. The dihydrofuranone was converted into an aldehyde corresponding to the C-1–C-8 framework, and this was coupled to the C-9–C-17 unit by nucleophilic addition of a vinylic anion.

Amphidinolides C, C2, C3, and F are structurally related members of a large family of marine natural products isolated from microalgae of *amphidinium* sp. (Figure 1). Amphidinolide C possesses substantial anticancer activity (IC_{50} values $<0.01\ \mu g\ mL^{-1}$ against certain cell lines).[1]

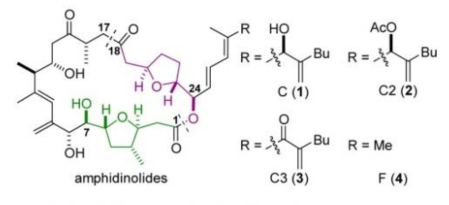


Figure 1. Amphidinolides C, C2, C3, and F.

The unique structures and bioactivities of amphidinolides C,[2] C2,[3] C3,[4] and F[5] have aroused significant interest in their syntheses, and several groups have reported syntheses of fragments of the compounds.[6] Very recently, Carter and Mahapatra completed a synthesis of amphidinolide F in which a common intermediate was used to prepare both tetrahydrofurans.[7]

(1) (a) Kobayashi, J. *J. Antibiot.* **2008**, *61*, 271. (b) Kobayashi, J.; Ishibashi, M. *Chem. Rev.* **1993**, *93*, 1753. (c) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77. (d) Kobayashi, J.; Shimbo, K.; Kubota, T.; Tsuda, M. *Pure Appl. Chem.* **2003**, *75*, 337.

(2) (a) Kobayashi, J.; Ishibashi, M.; Wälchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. *J. Am. Chem. Soc.* **1988**, *110*, 490. (b) Ishiyama, H.; Ishibashi, M.; Kobayashi, J. *Chem. Pharm. Bull.* **1996**, *44*, 1819. (c) Kubota, T.; Tsuda, M.; Kobayashi, J. *Org. Lett.* **2001**, *3*, 1363. (d) Kubota, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 1613.

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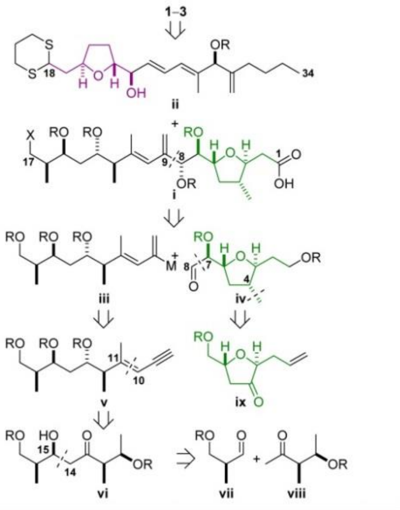
The macrolactone common to amphidinolides C, C2, C3, and F (**1**–**4**, Figure 1) contains two *trans*-2,5-disubstituted tetrahydrofurans. The similarity of the rings inspired us to design a synthesis in which a readily accessible dihydrofuranone bearing suitable functionality would serve as a common intermediate for the construction of two acyclic fragments of similar size and complexity, thus laying the foundations for convergent and efficient total syntheses of all four natural products. This approach has been validated recently by Mahapatra and Carter who completed their total synthesis of amphidinolide F from a common tetrahydrofuranyl intermediate.[7]

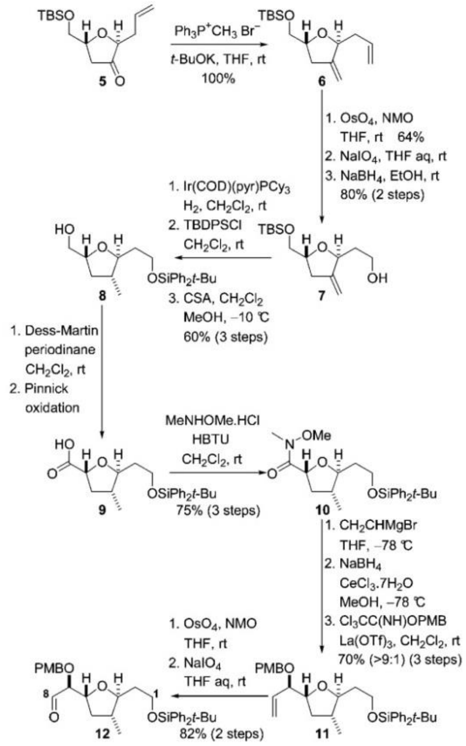
Scheme 1. Retrosynthetic Analysis of Amphidinolide C



The retrosynthetic analysis of amphidinolide C is shown in Scheme 1. As described in the preceding paper,[8] initial disconnection of the lactone C–O bond and the C-17–C-18 bond gives the 'northern' and 'southern' fragments **ii** and **i**. Disconnection of the 'southern' fragment **i** through the C-8–C-9 bond leads to the vinylic organometallic compound **iii** and the aldehyde **iv**. The vinylic organometallic compound **iii** can be converted into the enyne **v**, implying regioselective hydrometalation of the alkyne in the forward direction. Disconnection through the C-10–C-11 alkene and oxidation at C-13 then reveals the β-hydroxy ketone **vi**. Subsequent aldol disconnection between C-14 and C-15 leads to the aldehyde **vii** and the ketone **viii**, both of which can be prepared from chiral pool materials. The aldehyde **iv** can undergo two one-carbon disconnections to give the ketone **ix** which corresponds to the intermediate used in our synthesis of the 'northern' fragment.[8] Consequently, the intermediate prepared by diastereoselective rearrangement of a free or metal-bound oxonium ylide, generated by intramolecular cyclization of a copper carbenoid,[9] will be used for the preparation of both the 'northern' and 'southern' fragments **ii** and **i**.

(8) Clark, J. S.; Yang, G.; Osnowski, A. P. *Org. Lett.* **2013**, *15*, DOI: 10.1021/ol400482j.

Scheme 2. Construction of the C-1–C-8 Fragment



The dihydrofuranone **5** corresponding to the C-1–C-7 fragment was prepared from dimethyl D-malate in six steps as described in the preceding paper.[8] Wittig methylenation of the ketone **5** proceeded to afford diene **6** in quantitative yield (Scheme 2). Selective dihydroxylation of the

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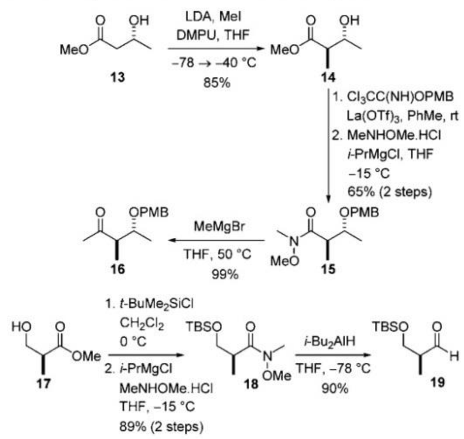
side-chain alkene was achieved in 64% yield, and the resulting diol was then subjected to oxidative cleavage. The intermediate aldehyde was reduced with $NaBH_4$ to provide the alcohol **7**, which was to be subjected to hydrogenation of the methylene group to install the C-4 methyl substituent. The use of homogeneous catalysts to control the stereochemical outcome hydrogenation reactions through reversible coordination to hydroxyl or carbonyl groups is precedented,[10] and gratifyingly this approach proved to be successful in our case. Hydrogenation of the alkene **7** using Crabtree's catalyst (12 mol %) afforded the saturated product as a single isomer, and this compound was then converted into the alcohol **8** in good yield by silylation of the hydroxyl group with *tert*-butyldiphenylsilyl chloride and subsequent cleavage of the TBS ether.

The carboxylic acid **9** was prepared from the alcohol **8** by sequential Dess-Martin and Pinnick oxidation reactions. Subsequent HBTU-mediated coupling of the carboxylic acid **9** to *N,O*-dimethylhydroxylamine afforded the Weinreb amide **10**. Treatment of this amide with vinylmagnesium bromide resulted in the formation of the corresponding enone. An alternative synthesis of the enone by sequential oxidation of alcohol **8** to the aldehyde, addition of vinylmagnesium bromide, and oxidation of the resulting diastereomeric mixture of alcohols afforded material that was difficult to purify in 53% yield. A Luche reduction of the enone resulted in the clean formation of the required diastereomer ($dr > 9{:}1$) and was followed by PMB protection of the allylic alcohol by a Lewis acid catalyzed reaction with a trichloroacetimidate.[11] Construction of the aldehyde **12**, which corresponds to the C-1–C-8 fragment, was completed by dihydroxylation of the alkene followed by oxidative cleavage of the 1,2-diol.

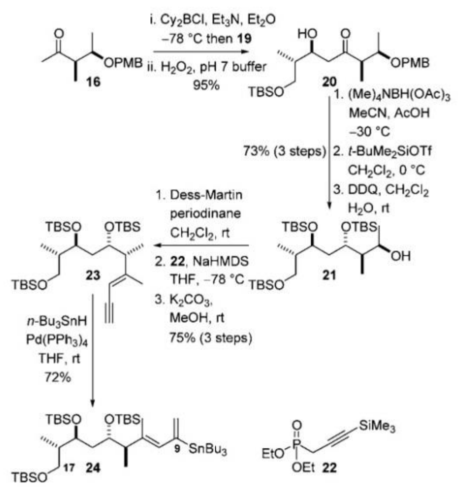
Scheme 3. Synthesis of Ketone **16** and Aldehyde **19**



Synthesis of the C-9–C-17 fragment began with construction of the fragments shown in Scheme 3. The commercially available ester **13** was first α-methylated stereoselectively ($dr > 10{:}1$) and in high yield.[12] The hydroxyl group of the resulting *β*-hydroxy ester **14** was then protected, and the ester was converted into the Weinreb amide **15**.[13] Transformation of the amide into the target methyl ketone **16** was accomplished cleanly and in high yield by reaction of the amide **15** with methylmagnesium bromide. Aldehyde **19**, the requisite aldol coupling partner, was prepared from the Roche ester **17**. Protection of the hydroxyl group as a TBS ether was followed by conversion of the ester into the Weinreb amide **18**. Reduction of the Weinreb amide with DIBAL-H at low temperature afforded the aldehyde **19**.

Aldol condensation of the aldehyde **19** with the boron enolate generated from the methyl ketone **16** proceeded in excellent yield and afforded the *β*-hydroxy ketone **20** as a single diastereoisomer (Scheme 4), presumably as a consequence of reinforcing 1,4- and 1,5-stereoinduction.[14] Stereoselective directed ketone reduction with tetramethylammonium triacetoxyborohydride afforded the *anti*-1,3-diol with a high level of diastereocontrol ($dr > 25{:}1$).[15] Silylation of both hydroxyl groups was accomplished by treatment of the diol with *tert*-butyldimethylsilyl triflate, and the PMB ether was cleaved with DDQ under standard conditions. Oxidation of the resulting secondary alcohol **21** afforded the corresponding methyl ketone, and this was subjected to Horner–Wadsworth–Emmons olefination with phosphonate **22** ($E/Z > 15{:}1$).[16] Removal of the trimethylsilyl group with potassium carbonate in wet methanol afforded the terminal alkyne **23**, and subsequent palladium-catalyzed hydrostanylation with tributyltin hydride afforded the vinylic stannane **24** in good yield.[17]

Scheme 4. Construction of the C-9–C-17 Fragment

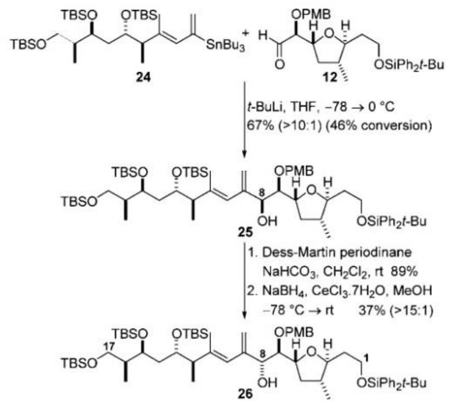


(10) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.

Fragment coupling to complete the entire C-1–C-17 fragment was performed as shown in Scheme 5. Subjection of the vinyl stannane **24** to tin–lithium exchange and addition of the lithiated intermediate to the aldehyde **12** afforded the alcohol **25** with high diastereoselectivity (*dr* > 10:1). The configuration of the newly created stereogenic center at C-8 was assigned as *S* based on comparison of NMR data with those of closely related compounds prepared by Carter and Mahapatra during their recently reported total synthesis of amphidinolide F.[7,18] Thus, it was clear that the diastereomer of the required alcohol had been obtained and inversion of configuration at the C-8 stereogenic center was required. Oxidation of the alcohol with the Dess-Martin periodinane afforded the corresponding enone, and highly diastereoselective 1,2-reduction of the carbonyl group under Luche conditions afforded the alcohol **26** (*dr* > 15:1) with the required *R* configuration at the C-8 stereogenic center. The stereochemical outcome of the ketone reduction reaction was confirmed by comparison of the ^1H and ^{13}C NMR data obtained for the diastereomeric alcohols **25** and **26** with those of the closely related compound (C-1–C-14 fragment) prepared by Mahapatra and Carter.[7,18]

In summary, the C-1–C-17 fragment of amphidinolide C has been prepared in an efficient and stereoselective fashion. An important feature of this synthesis is the use of dihydrofuranone **5**, a starting material from which the carbon frameworks of both 'northern' and 'southern' fragments of the natural products have been synthesized. Other key transformations include stereoselective boron-mediated aldol condensation between the chiral pool derived fragments **16** and **19** to produce the C-1–C-9 unit, regioselective hydrostannylation of the enyne **23**, and tin–lithium exchange of the stannane **24** followed by nucleophilic addition to aldehyde **12**.

Scheme 5. Coupling to Complete the C-1–C-17 Fragment



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Supporting Information Available. Experimental procedures and data for **6–12**, **14–16**, **18–21**, and **23–26**, plus intermediate compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(18) For tabulated selected NMR data, see Supporting Information.
(19) Luche reduction of the enone prepared from the alcohol **25** was very slow, and some decomposition occurred. The yield of 37% is unoptimized.

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