Total Synthesis of Members of the Amphidinolide Family of Natural Products

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Dottore Magistrale in Farmacia (*cum laude*)

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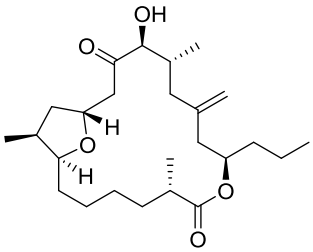
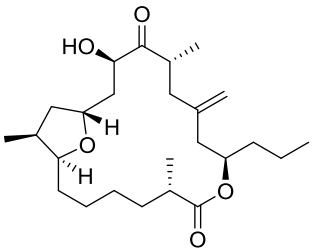
Abstract

The amphidinolides are macrolide natural products isolated from marine dinoflagellates of the genus *Amphidinium* and most of them display potent cytotoxic activities *in vitro*. Amphidinolides C-C3, F and T1-5 represent attractive synthetic targets due to a combination of potent bioactivity and complex molecular architecture.


amphidinolide T1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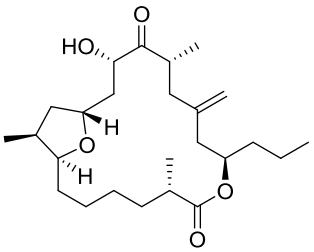
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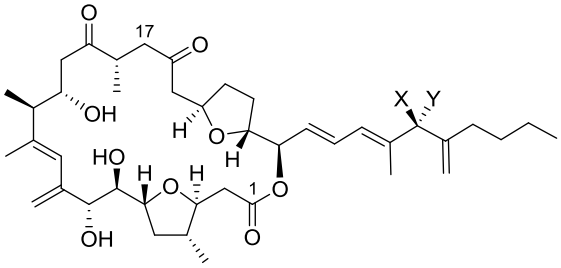
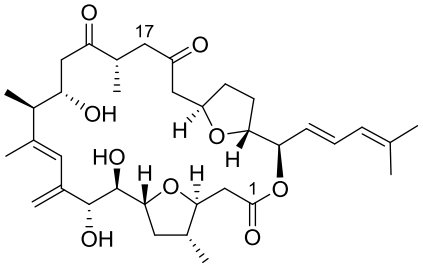

amphidinolide C X=OH Y=H
amphidinolide C2 X=OAc Y=H
amphidinolide C3 X,Y=O


amphidinolide F

This thesis describes the total syntheses of amphidinolides T1, T3 and T4, and the preparation of the C1-C17 fragment of amphidinolides C and F.

Concise and high-yielding total syntheses of amphidinolides T1, T3, and T4 have been completed using an alkynyl macrolactone as a common late-stage intermediate. The α-hydroxy ketone motif was installed by sequential alkyne hydrosilylation, epoxidation, and Fleming–Tamao oxidation. A tandem oxonium ylide formation [2,3]-sigmatropic rearrangement reaction was used to construct the trisubstituted tetrahydrofuran core found within the natural products.

The C1-C17 fragment of amphidinolides C, C2, C3 and F was synthesised employing [2,3]-sigmatropic rearrangement of an oxonium ylide generated by decomposition of 1-sulfonyl-triazole to construct the trisubstituted tetrahydrofuran ring found in the natural products. The two main segments were conjoined using a Stille cross-coupling reaction that allowed simultaneous installation of the isomerization-prone 1,3-diene unit.

Declaration

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

A portion of the work described herein has been published elsewhere as listed below.

"Total Syntheses of Amphidinolides T1, T3, and T4" J. Stephen Clark, Filippo Romiti *Angew. Chem. Int. Ed.*, **2013**, *52*, 10072-10075.

Filippo Romiti

Prof. J. Stephen Clark

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Travagli, Stefano “Lombardino” “Dinho” Lombardi, Francesca “Fra” “Francelli” Bedogni, Riccardo “Riky” Colle, Giacomo “Bego” “Begozzi” Beghini and Davide “Tinto” “Tenorio” Tintori. I would also like to thank my friends Gian Paolo “Paul” “GABA” Vallerini, Andrea “Greeends” Grandi and Eddi “Fabrizio” “Bidello Pazzo” Lazzarin for coming in Scotland several times to visit me.

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Finally, thanks to myself… *“I’m happy when life’s good and when it’s bad I cry, I’ve got values but I don’t know how or why. They call me the seeker, I’ve been searching low and high, I won’t get to get what I’m after till the day I die”*

Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	2,2'-azo*bis*isobutyronitrile
Ar	aryl
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BOM	benzyloxymethyl
bp	boiling point
brsm	based on recovered starting material
Bu	butyl
c	cyclo
CBS	Corey-Bakshi-Shibata
cod	1,5-cyclooctadiene
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
CSA	camphorsulfonic acid
CuTc	copper(I) thiophene-2-carboxylate
Cy	cyclohexyl
dba	dibenzylideneacetone
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
$(DHQD)_2PHAL$	*bis*(dihydroquinidino)phthalazine
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPM	3,4-dimethoxybenzyl
DMPU	*N*,*N*-dimethyl propylene urea
DMSO	dimethylsulfoxide
dppb	1,4-*bis*(diphenylphosphino)butane
dr	diastereomeric ratio

EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	enantiomeric excess
EE	ethoxyethyl
Et	ethyl
GI	Grubbs first generation catalyst
GII	Grubbs second generation catalyst
hfacac	hexafluoroacetylacetonate
HGII	Hoveyda-Grubbs second generation catalyst
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
i	iso
IC_{50}	half maximal inhibitory concentration
Ipc	isopinocampheyl
LDA	lithium diisopropylamide
m	*meta*
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
MOM	methoxymethyl
mp	melting point
Ms	mesyl (methanesulfonyl)
n	normal (e.g. unbranched alkyl chain)
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
nmp	5,5-dimethyl-1-(4-methylpiperazin-1-yl)hexane-1,2,4-trione
NMR	nuclear magnetic resonance
o	*ortho*
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
pfm	heptafluoro butanamide
p	*para*
PG	generalised protecting group
Ph	phenyl

PHT	pyrrolidone hydrotribromide
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PMBTCA	*p*-methoxybenzyl-2,2,2-trichloroacetimidate
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
Py (pyr)	pyridine
quant.	quantitative
R	generalised group
RCAM	ring-closing alkyne metathesis
RCM	ring-closing metathesis
R_f	retention factor in chromatography
rt	room temperature
t	*tert*
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TCBC	2,4,6-trichlorobenzoyl chloride
temp.	temperature
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
tfacac	trifluoroacetylacetonate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	*p*-tolyl
tpa	triphenylacetate
TPAP	tetra-*n*-propylammonium perruthenate
Tr	trityl (triphenylmethyl)
Ts	tosyl (*p*-toluenesulfonyl)
VAZO	1,1'-azo*bis*(cyclohexanecarbonitrile)
X_c	chiral auxiliary

Table of Contents

1 Introduction and Background

1.1 The Amphidinolide Family of Natural Products

The amphidinolides are cytotoxic macrolide natural products isolated from marine dinoflagellates of the genus *Amphidinium* which are endosymbionts found in the inner wall cells of *Amphiscolops* flatworms, living in Okinawan coral reefs.[1] These microorganisms can be cultivated in the laboratory and feature particularly prolific biosynthetic machinery, which makes them amenable to more detailed studies.[2] To date, more than 35 structurally diverse members of the amphidinolide family have been isolated and identified by Kobayashi and co-workers (Figure 1).[3]

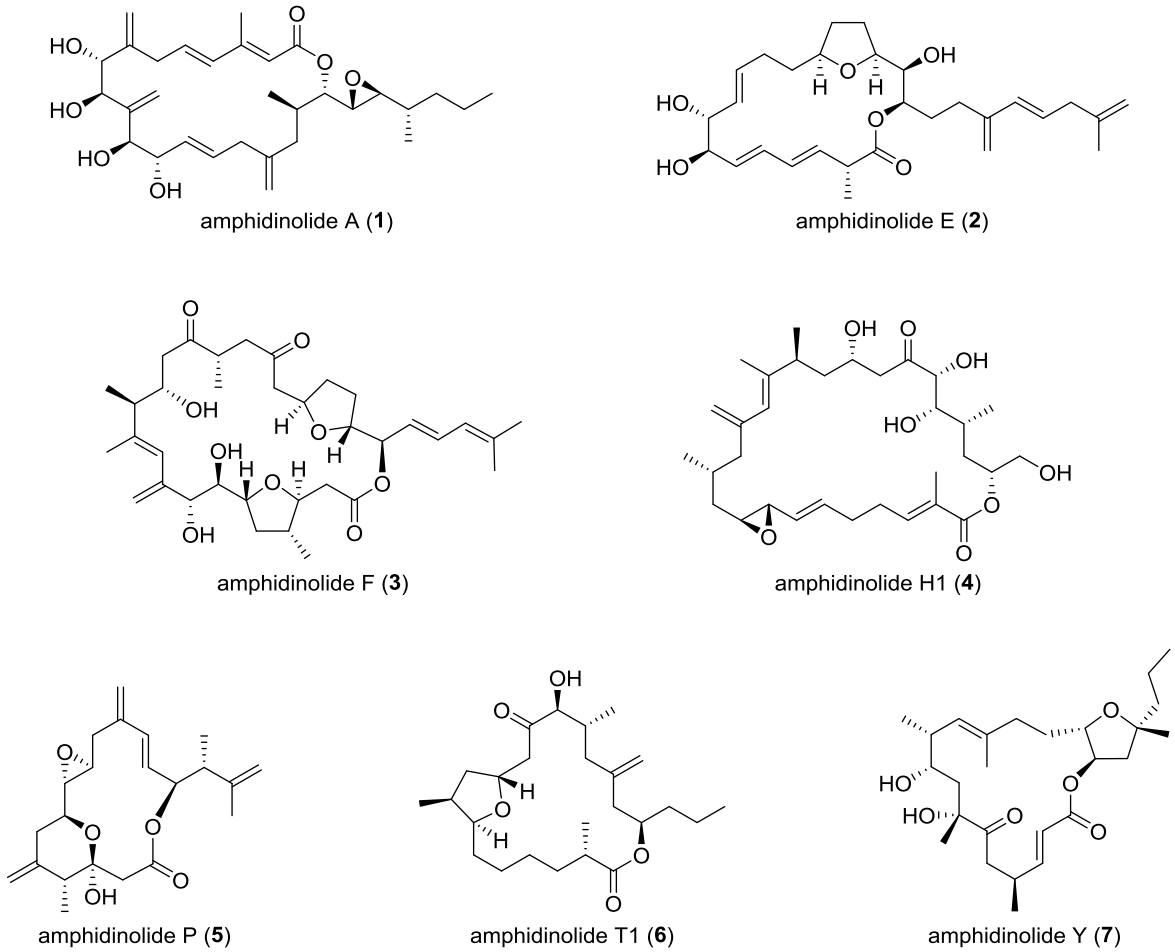


Figure 1

In general, the amphidinolides are distinguished by a pronounced cytotoxic activity against various cancer cell lines, particularly L1210 murine lymphoma

cells and KB human epidermoid carcinoma cells; some of them possess potencies comparable to those of the most cytotoxic compounds known to date.[4] Some of the amphidinolides also possess other biological activities, but in most cases the substantial quantities of material that would be required in order to fully establish their therapeutic potential are not available.

The structural features of amphidinolides are as intriguing as their biological activities. In contrast to macrolide antibiotics derived from terrestrial microorganisms, the majority of amphidinolides features an *odd*-numbered macrolactone ring ranging in size from 12 to 29 atoms. Individual amphidinolides differ considerably from each other in structural terms, but multiple sites of unsaturation and the presence of small oxacycles such as epoxides, tetrahydrofurans and pyrans are common features throughout the family.

In the Clark group, we are particularly interested in those amphidinolides featuring a *trans*-tetrahydrofuran ring such as amphidinolide F (**3**) and amphidinolide T1 (**6**), because of the expertise developed in our group over the last 20 years to synthesize this motif using a [2,3]-sigmatropic rearrangement of an oxonium ylide.

1.2 Amphidinolides T: Isolation, Structure and Bioactivity

The five closely related amphidinolides of the T subgroup are compact 19-membered macrolactones possessing seven or eight stereogenic centres, an exocyclic double bond, an α-hydroxy ketone moiety and a trisubstituted THF ring (Figure 2).

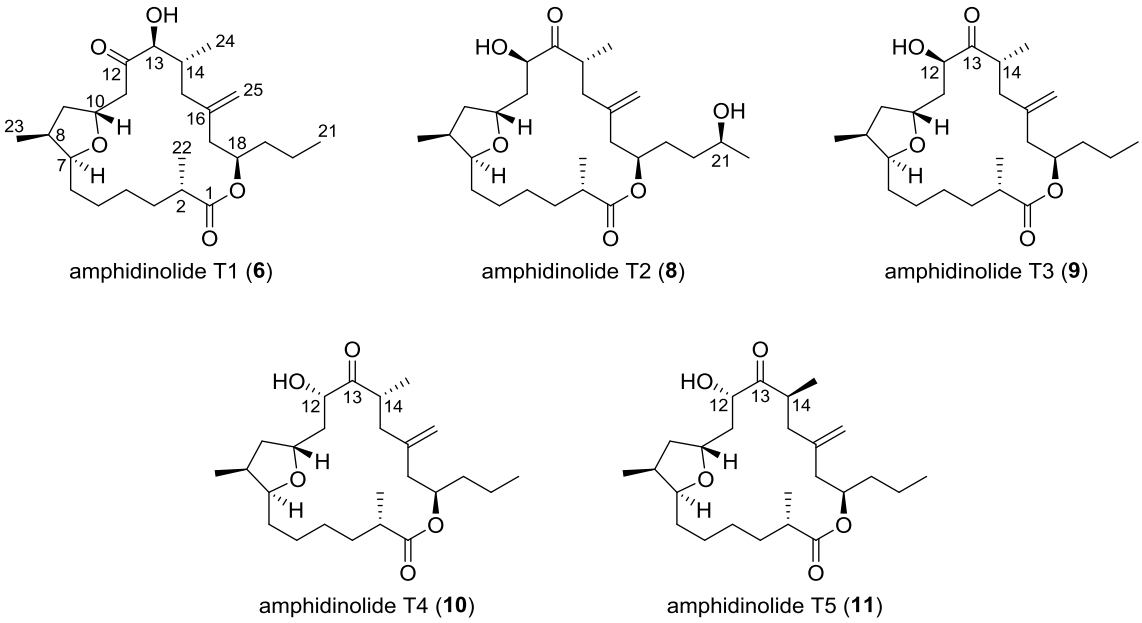


Figure 2

The five members of the amphidinolide T series differ only in the oxygenation pattern and stereochemistry of the C12–C14 region with the exception of amphidinolide T2 (**8**), which possesses a longer, C21-hydroxylated side chain. Amphidinolide T2 (**8**) is the sole member of the T family that is not an isomer of another member.

In 2000, the Kobayashi group isolated and identified amphidinolide T1 (**6**), which was the first macrolide of the series to be fully characterised.[5] Initially, the structure and stereochemistry of amphidinolide T1 was determined by extensive NMR studies and Mosher ester analysis of the segments derived from its degradation.[6] Subsequently, the structure was confirmed by single crystal X-ray diffraction studies.[7] Amphidinolide T1 (**6**) features a ketone on C12 flanked by a hydroxyl group with an *S* absolute configuration at C13.

In 2001, Kobayashi and co-workers isolated amphidinolides T2–T5.[7,8] The elucidation of the structure of these natural products was achieved as result of

detailed NMR studies and Mosher ester analysis of fragments produced by their degradation. Interestingly, amphidinolides T3–5 are constitutional isomers of T1, displaying a reversal of the hydroxy ketone pattern (ketone at C-13, hydroxyl group at C-12), and they possess diastereomeric relationships at C-12 and C-14.

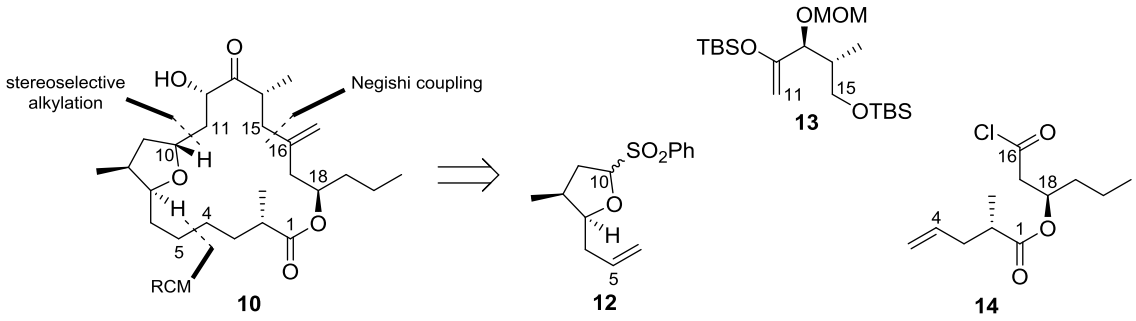
Although amphidinolides T1–T5 are not the most potent members of amphidinolide family, they still exhibit appreciable cytotoxic activities with IC_{50} values of 7–18 μg/mL against L1210 murine lymphoma cells and of 10–35 μg/mL against KB human epidermoid carcinoma cells.[8] To the best of our knowledge, their biological activities with respect to other diseases have not been studied, mainly because the substantial quantities of material that would be required in order to fully establish their therapeutic potential are not available.

1.3 Previous Syntheses of Amphidinolides T

The challenging structures and intriguing bioactivities of the amphidinolides T make them very attractive synthetic targets.[3,9] Consequently, several total syntheses of amphidinolides T1–T5 have been reported. Fürstner and co-workers completed the synthesis of amphidinolide T4 in 2002 and then used their elegant strategy to synthesize amphidinolides T1, T3, and T5.[10] The groups of Ghosh (T1),[11] Jamison (T1 and T4),[12] Zhao (T3),[13] Yadav (T1),[14] and Dai (T1, T2, T3 and T4)[15] have also completed syntheses of members of the family.

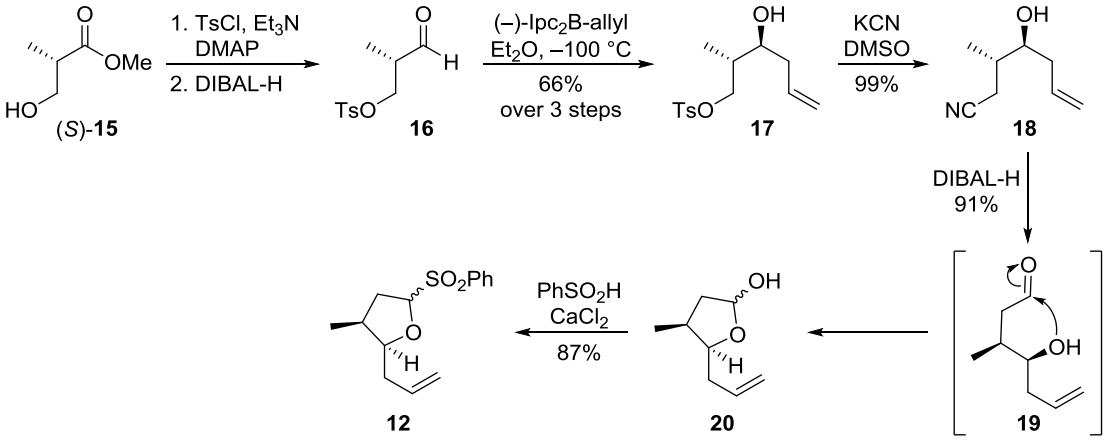
1.3.1 Fürstner: Acyl-Negishi Coupling and Ring-Closing Metathesis

Only one year after Kobayashi and co-workers reported the structural elucidation of the amphidinolide T family, Fürstner *et al*. completed the first total synthesis of amphidinolide T4.[10a] The group completed the syntheses of amphidinolides T1, T3 and T5 thereafter, using the same strategy.[10b] Fürstner's approach was highly convergent, and involved the coupling of three building blocks of similar size and complexity by stereoselective Lewis acid-mediated alkylation of a sulfone and Negishi acyl chloride coupling (Scheme 1). A pivotal ring-closing metathesis reaction was employed to close the 19-membered macrocycle.



Scheme 1

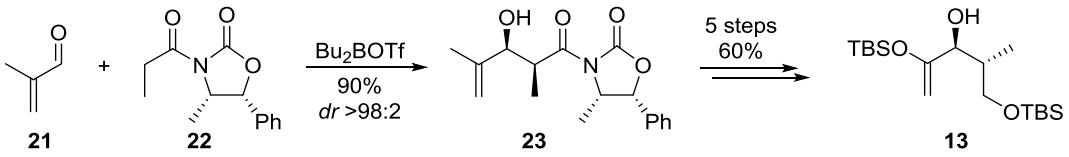
The synthesis of the key fragment **12** bearing the THF moiety commenced from commercially available (*S*)-Roche ester **15** (Scheme 2). Tosylation of the primary hydroxyl group followed by selective reduction of the methyl ester delivered the corresponding aldehyde **16**, which was subjected to an asymmetric allyl addition reaction by treatment with (−)-Ipc_2B-allyl at low temperature to afford alcohol **17** as single diastereoisomer.



Scheme 2

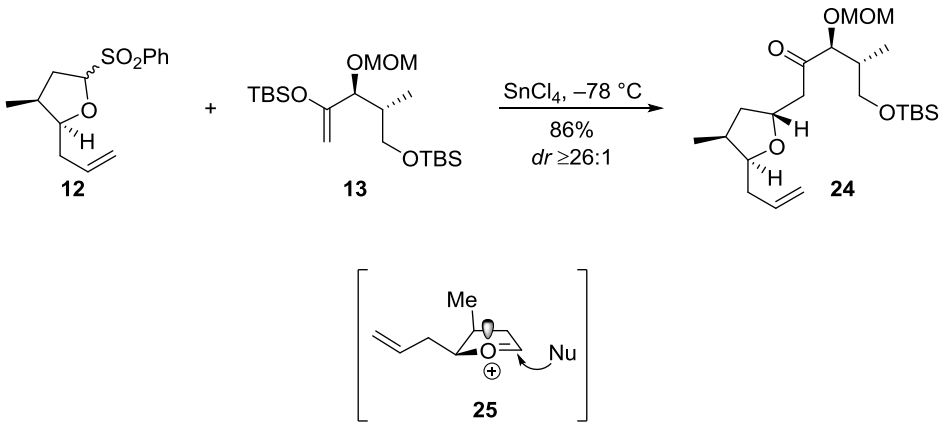
Displacement of the tosylate using potassium cyanide delivered nitrile **18**, which was reduced to the aldehyde **19** that spontaneously cyclised to form the hemiacetal **20**. The hemiacetal **20** was then converted into sulfone **12** upon treatment with $PhSO_2H$ in the presence of $CaCl_2$ as dehydrating agent. Thus, the THF ring fragment was assembled in just 6 steps from chiral hydroxy ester (S)-**15**.

The silyl enol ether **13** was prepared in a high-yielding 6-step sequence employing an Evans aldol reaction with methacrolein **21** to install the required stereochemistry (Scheme 3).[16]



Scheme 3

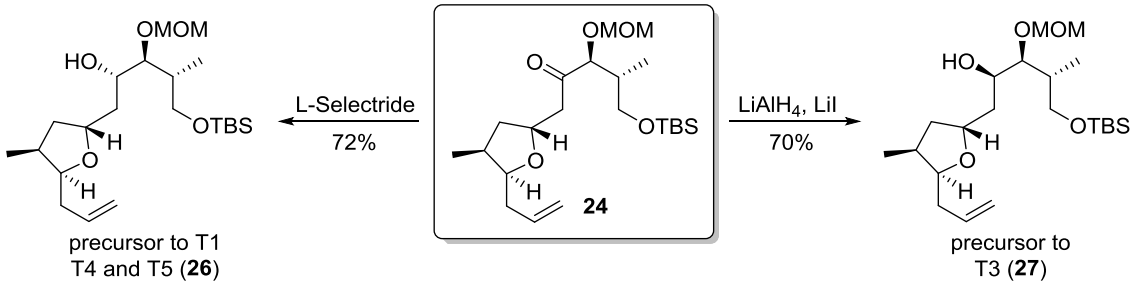
Coupling of the two fragments was achieved by activation of sulfone **12** with $SnCl_4$ and trapping of the resulting oxonium intermediate **25b** with silyl enol ether **13** (Scheme 4). This method delivered the desired *trans*-tetrahydrofuran product **24** in 86% yield and with excellent diastereoselectivity.



Scheme 4

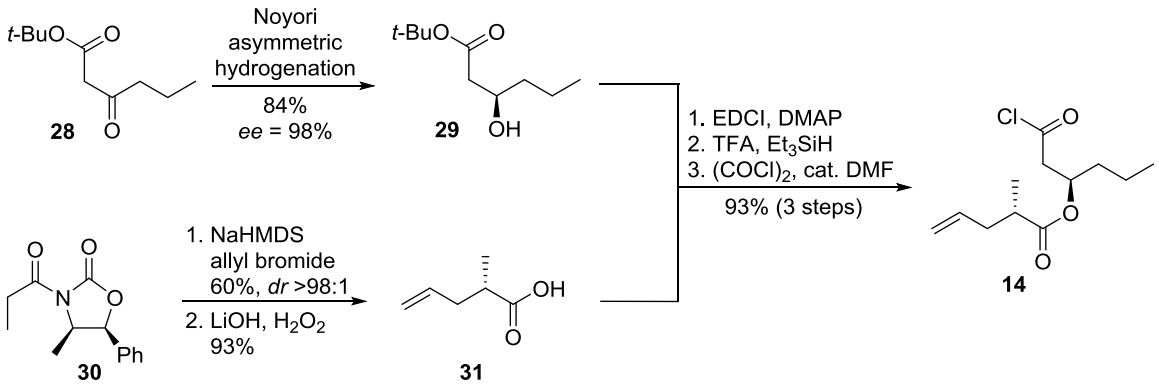
The stereochemical outcome of this reaction was explained by the presence of the methyl group in an axial position in the furanoid oxonium ion intermediate **25**, which was sufficient to bias nucleophilic attack of the silyl enol ether to the opposite face.[17]

This highly efficient coupling procedure provided the ketone **24**, a common precursor to all of the targets. By performing stereoselective reduction reactions, Fürstner *et al*. were able to access the advanced precursors of amphidinolides T1 and T3–5 (Scheme 5). Reduction of ketone **24** with L-Selectride afforded the alcohol precursor of amphidinolides T1, T4 and T5 (**26**). On the other hand, the use of $LiAlH_4$ in combination with LiI, in order to generate a Li^+-rich medium, inverted the stereochemical outcome of the reaction with preferential formation of the alcohol precursor of amphidinolides T3 (**27**).[18]



Scheme 5

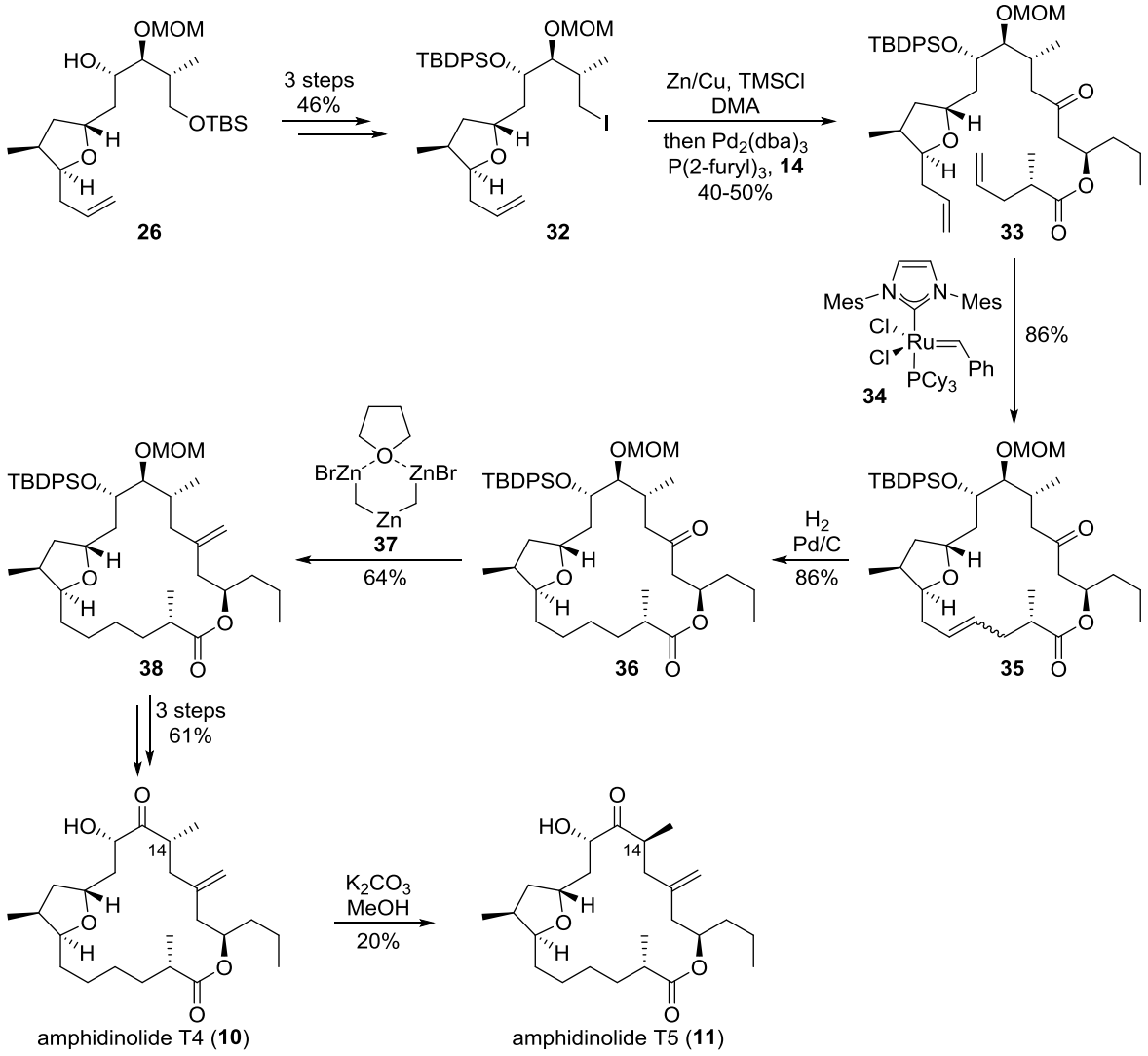
The third building block, ester **14**, was easily assembled from readily available starting materials (Scheme 6). The hydroxy ester **29** was prepared by Noyori asymmetric reduction of the corresponding ß-keto ester **28** to set the desired stereochemistry.[19] The carboxylic acid **31** was prepared from oxazolidinone **30** using the well-known Evans alkylation procedure.[20] Esterification of the alcohol **29** with the acid **31**, followed by conversion of the *tert*-butyl ester functionality into the corresponding acyl chloride gave the remaining building block **14**.



Scheme 6

Fragment **26** was converted into the corresponding iodide **32** in three steps and coupling of the fragments was achieved by a palladium-catalysed acyl-Negishi reaction using zinc-copper couple to generate the organozinc intermediate (Scheme 7). The 19-membered macrolactone **36** was formed by highly efficient RCM using the Nolan catalyst **34**[21] to give macrocycle **35** followed by alkene hydrogenation. Conversion of the ketone group into the *exo*-methylene group of the target proved to be very challenging because of the steric hindrance around the ketone functionality in lactone **36**. The methylenation issue was overcome using the Nysted reagent **37**, which allowed formation of the product **38** in 64%

yield. The synthesis of amphidinolide T4 was finally completed by an efficient deprotection/oxidation/deprotection sequence.



Scheme 7

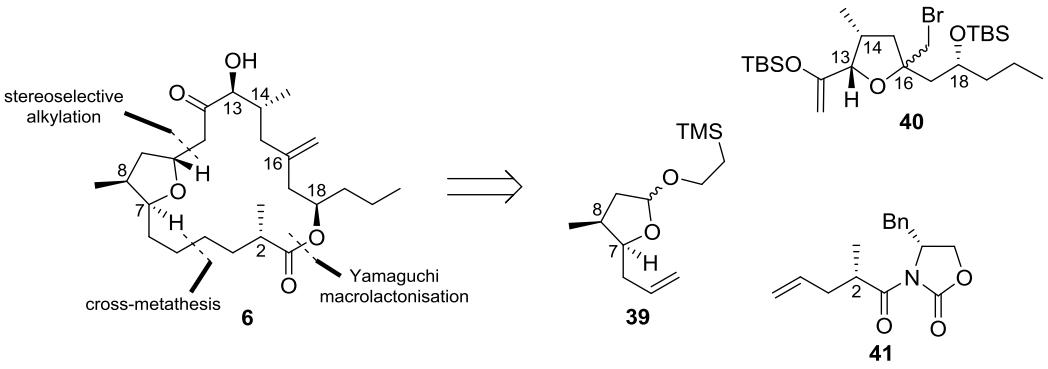
As previously shown by Kobayashi, epimerisation of amphidinolide T4 at C14 upon treatment with potassium carbonate in MeOH afforded amphidinolide T5.[7] Amphidinolide T1 was obtained using the same synthetic pathway and inverting the order of orthogonal deprotection of the diol functionality of macrolactone **38**. The same strategy was also used to synthesize amphidinolide T3 from precursor **27**.

Applying this strategy, Fürstner and co-workers completed the syntheses of amphidinolides T1, T3, T4 and T5 in 17-19 steps and with overall yields of 1.5%, 1.7%, 2.1% and 0.4% respectively. Fürstner's synthesis is remarkable for several reasons. Firstly, a common route leads to four structurally complex natural

products in a highly diastereocontrolled manner and in a convergent way. Secondly, it is impressive that the synthesis of amphidinolide T4 was published only two years after the original structural elucidation of amphidinolide T1 and one year after the characterisation of amphidinolide T4.

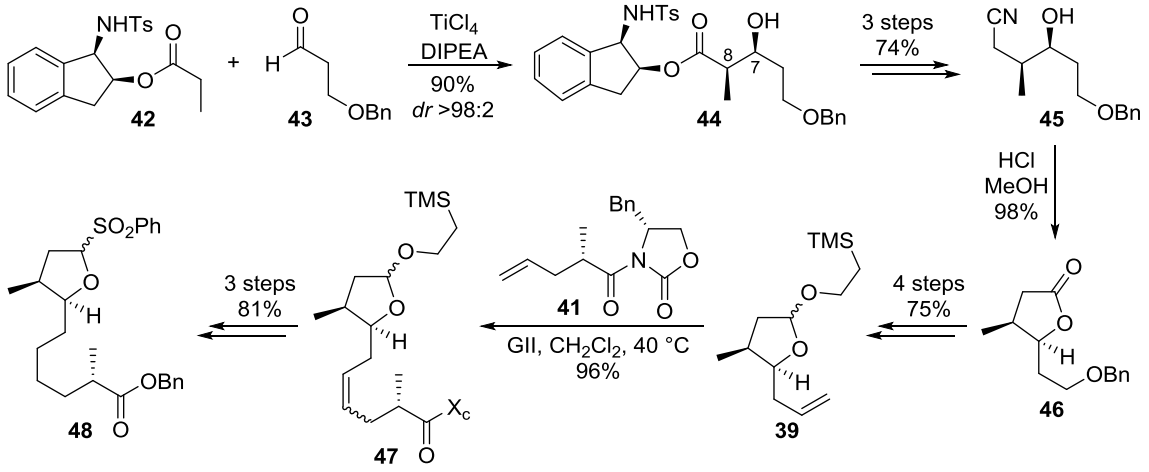
1.3.2 Ghosh: Lewis Acid-Mediated Alkylation and Macrolactonisation

A few months after Fürstner and co-workers reported their synthesis of amphidinolide T4, the Ghosh group published the first total synthesis of amphidinolide T1.[11] Ghosh *et al*. disconnected amphidinolide T1 into three main fragments to be coupled by cross-metathesis and stereoselective Lewis acid-mediated alkylation reactions. The Yamaguchi macrolactonisation protocol was envisioned as the method to be used to form the macrocycle (Scheme 8).[22]



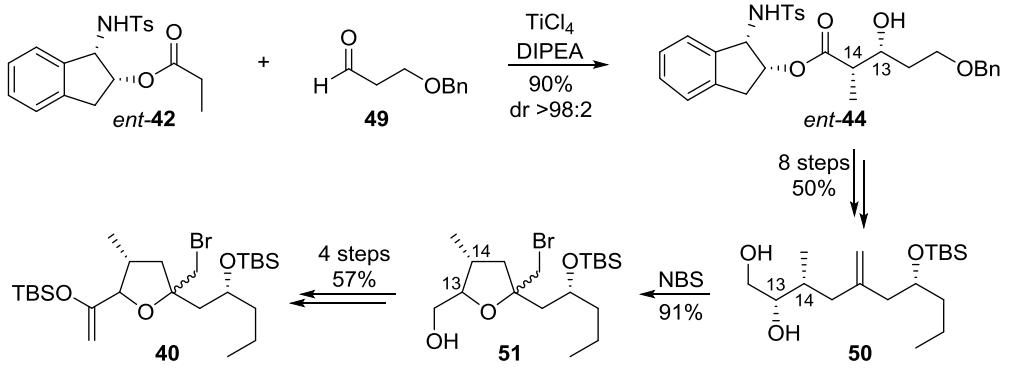
Scheme 8

Ghosh and co-workers employed the high-yielding aldol condensation reaction of an enolate bearing an indanyl-derived chiral auxiliary developed within the group to set the desired stereochemistry at C7 and C8 with complete diastereocontrol (Scheme 9).[23] With regard to construction of the THF ring, a similar strategy to Fürstner's was employed. The aldol product **44** was converted into the nitrile **45** and subsequent acidic hydrolysis of the nitrile group resulted in spontaneous cyclisation to afford the lactone **46** in 98% yield. Lactone **46** was transformed into the protected lactol **39**, which underwent cross-metathesis with oxazolidinone derivative **41** to give the coupled product **47**. Further elaboration of lactol **47** delivered sulfone **48** in 3 steps.



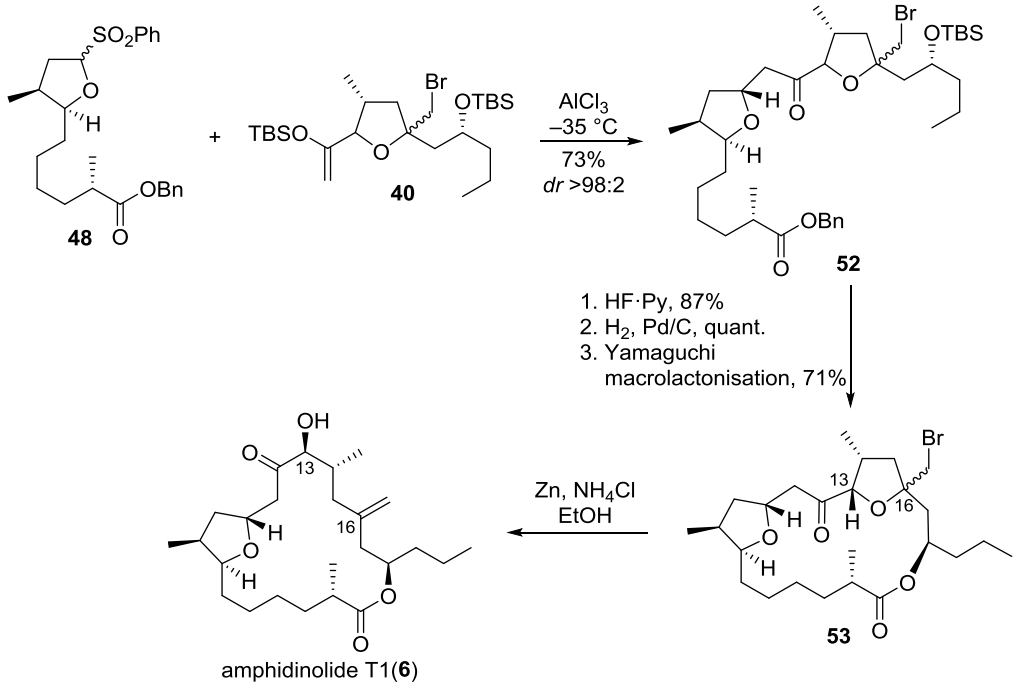
Scheme 9

For the synthesis of the fragment **40**, Ghosh again chose to use the aldol condensation reaction developed by his group to install the stereocentres at C13 and C14 (Scheme 10). Importantly, a bromoether motif was formed to protect the C13 hydroxyl group as well as the sensitive *exo*-methylene group at C16 (**50**→**51**).



Scheme **10**

The fragments **48** and **40** were coupled by oxocarbenium ion-mediated alkylation, using an excess of $AlCl_3$ as the Lewis acid to promote this transformation (Scheme 11). Under these conditions the desired coupled product **52** was obtained in 73% yield as a single diastereoisomer. In the end, formation of the macrolactone ring by sequential Yamaguchi esterification[22] and unmasking of the bromoether with Zn and NH_4Cl in ethanol provided amphidinolide T1.[24] This protection/deprotection strategy overcame the difficulty of ketone methylenation encountered by Fürstner's group.

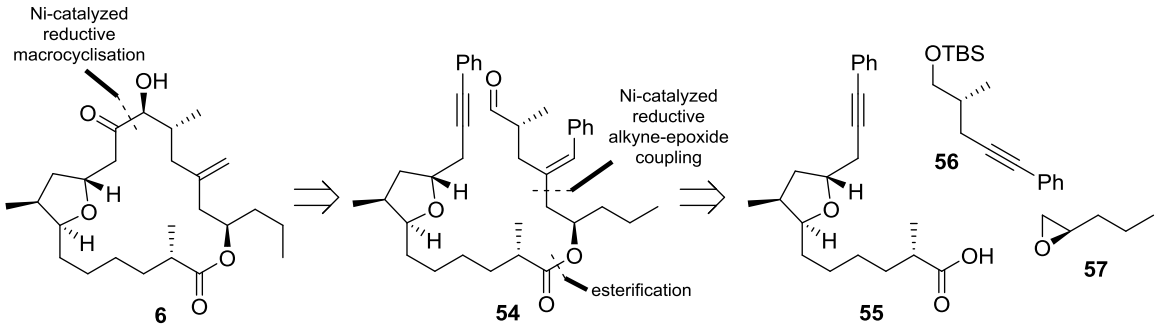


Scheme 11

Ghosh completed the synthesis of amphidinolide T1 in 19 steps (longest linear sequence) with an overall yield of 5.8%. The high overall yield obtained by Ghosh can be explained by the fact that his strategy is highly convergent and there is full functionalization of each fragment to avoid any lower-yielding steps after fragment coupling.

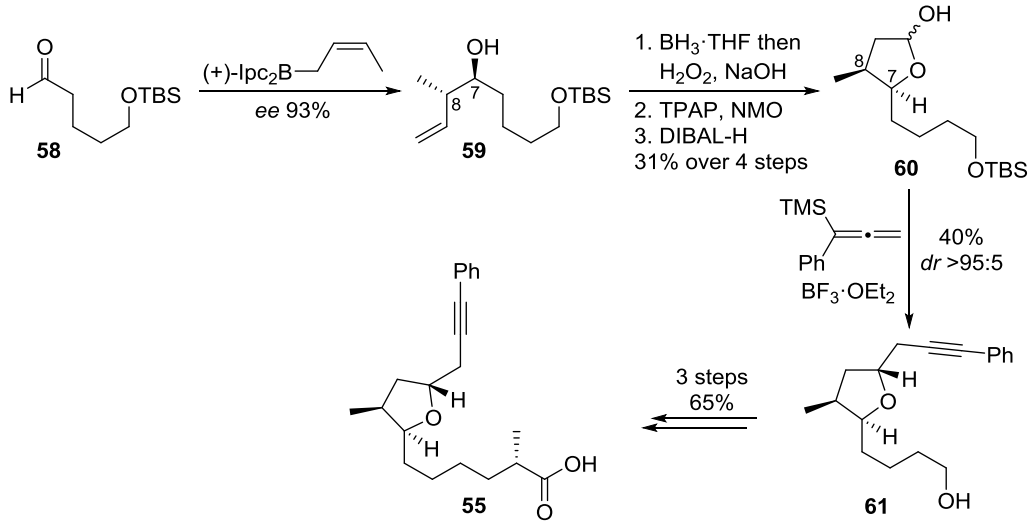
1.3.3 Jamison: Nickel-Catalyzed Reductive Coupling

The approach to amphidinolides T1 and T4 by the Jamison group relied upon the use of a nickel-catalysed reductive coupling reaction developed in their laboratory (Scheme 12).[12,25] Jamison's synthetic plan involved the coupling of the main fragments by esterification followed by simultaneous macrocycle formation and stereogenic centre creation employing a nickel-catalysed reductive alkyne-aldehyde coupling reaction.[25]



Scheme 12

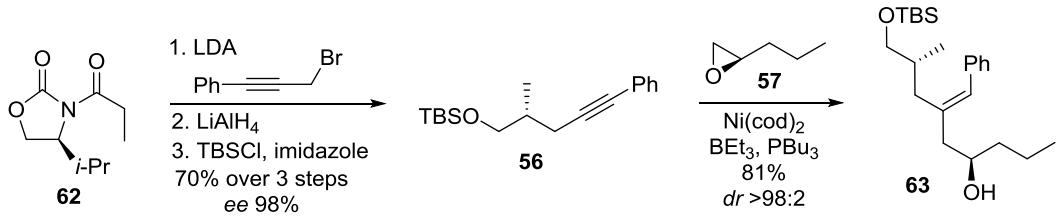
Jamison *et al*. assembled the substituted THF ring in a similar fashion to that of Fürstner and Ghosh. The synthesis started with a Brown asymmetric crotylation reaction of aldehyde **58** to form the C7—C8 bond with simultaneous introduction of the absolute stereochemistry at these positions (Scheme 13). The resulting homoallylic alcohol **59** was then subjected to hydroboration, oxidative cyclisation, and partial reduction to give lactol **60**. Lewis acid-mediated allenylsilane addition to the oxocarbenium ion derived from lactol **60** delivered tetrahydrofuran **61** in a modest yield of 40% but with complete diastereocontrol. Alcohol **61** was then converted into carboxylic acid **55**.



Scheme 13

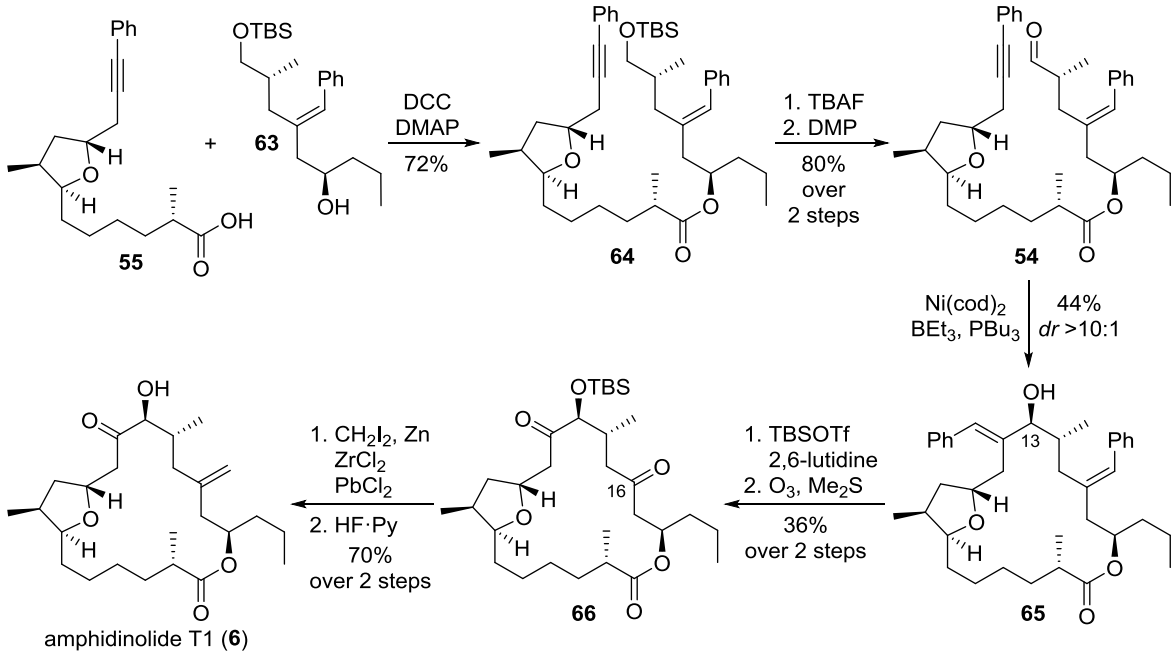
The major improvement that nickel-catalysed reductive alkyne-epoxide coupling provided was that it allowed access to advanced intermediate **63** in only 4 steps (Scheme 14).[26] Aryl alkyne **56** was prepared efficiently from the imide **62** using the Evans alkylation protocol.[20] The epoxide coupling partner **57** was accessed in enantioenriched form using Jacobsen's hydrolytic kinetic resolution procedure.[27]

Nickel-catalysed reductive coupling of the alkyne **56** and the epoxide **57** afforded the homoallylic alcohol **63** in 81% yield, with excellent regioselectivity (>95:5) with respect to both epoxide opening and alkyne addition.



Scheme 14

After coupling of the carboxylic acid **55** with alcohol **63** by means of DCC-mediated esterification, the macrocycle was formed by stereoselective nickel-catalysed reductive alkyne-aldehyde coupling, setting the stereochemistry at C13 (Scheme 15). When intermediate **54** was treated under optimised conditions, the 19-membered lactone **65** was obtained in 44% yield and with good diastereoselectivity. It is noteworthy that the sense of induction followed the Felkin-Anh model for the nucleophilic addition to an α-chiral aldehyde.

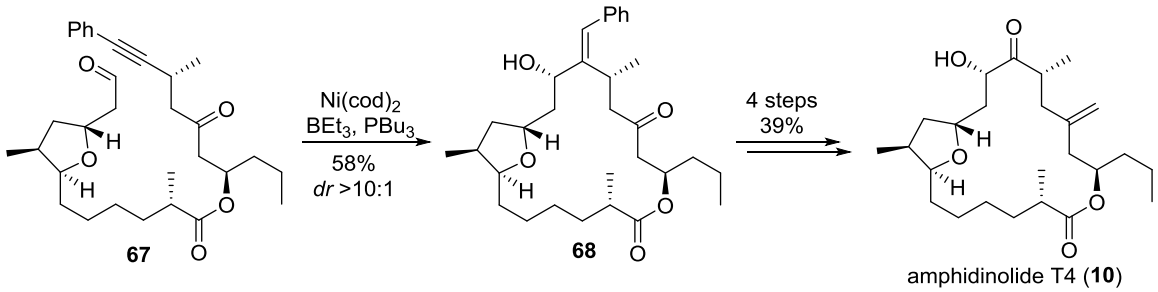


Scheme 15

Alcohol protection followed by ozonolysis afforded the diketone **66** in low yield. Differences in steric hindrance around the carbonyl groups allowed selective methylenation of the C16 ketone using a modified Takai olefination reaction.

Subsequent deprotection delivered amphidinolide T1 in 17 steps with an overall yield of 1.1%.

Jamison and co-workers adopted a slightly different strategy in order to complete the synthesis of amphidinolide T4. Reversal of the positions of the aldehyde and alkyne groups prior to cyclisation resulted in an exchange of positions of the alcohol and the trisubstituted alkene in the macrolactone **68** after stereoselective nickel-catalysed reductive alkyne-aldehyde coupling (Scheme 16). The sequence employed in the amphidinolide T1 route was then used to complete the synthesis of amphidinolide T4 in a total of 15 steps with an overall yield of 1.7%.



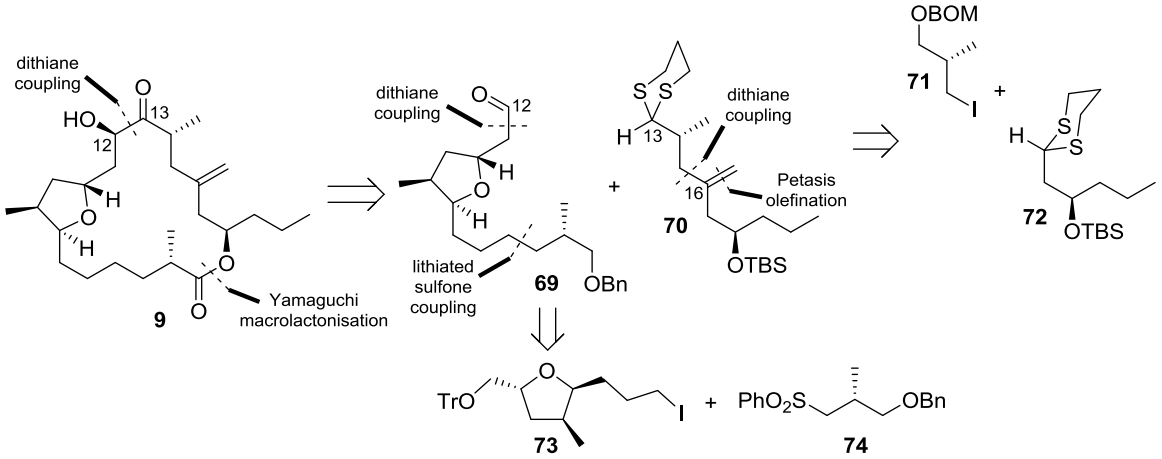
Scheme 16

In his syntheses of amphidinolides T1 and T4, Jamison took the opportunity to showcase the synthetic utility of the nickel-catalysed reductive coupling developed by his group.[25] Jamison and co-workers applied the synthetic strategy described above to the synthesis of other members of the amphidinolide T family of natural products. However, the approach proved unsuccessful for the synthesis of amphidinolide T2.[28]

1.3.4 Zhao: Umpolung Chemistry

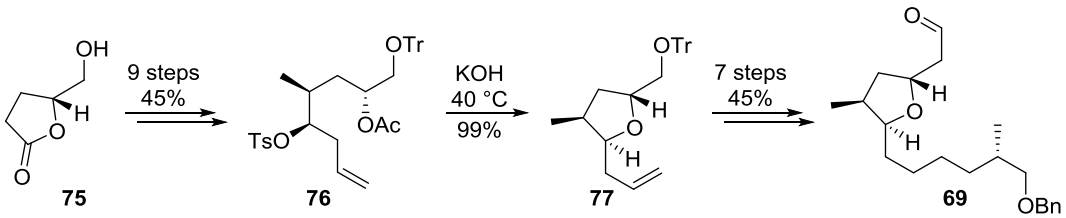
The Zhao group developed a very different strategy to synthesise amphidinolide T3 relying upon an extensive use of umpolung chemistry (Scheme 17).[13] They envisaged using a dithiane addition reaction to couple the main fragments **69** and **70**, by forming the C12—C13 bond, and Yamaguchi macrolactonisation to close the ring. Zhao *et al*. planned to introduce the *exo*-methylene group at C16

by performing Petasis olefination at an early stage in the synthesis in order to overcome the problems encountered by Fürstner's group.



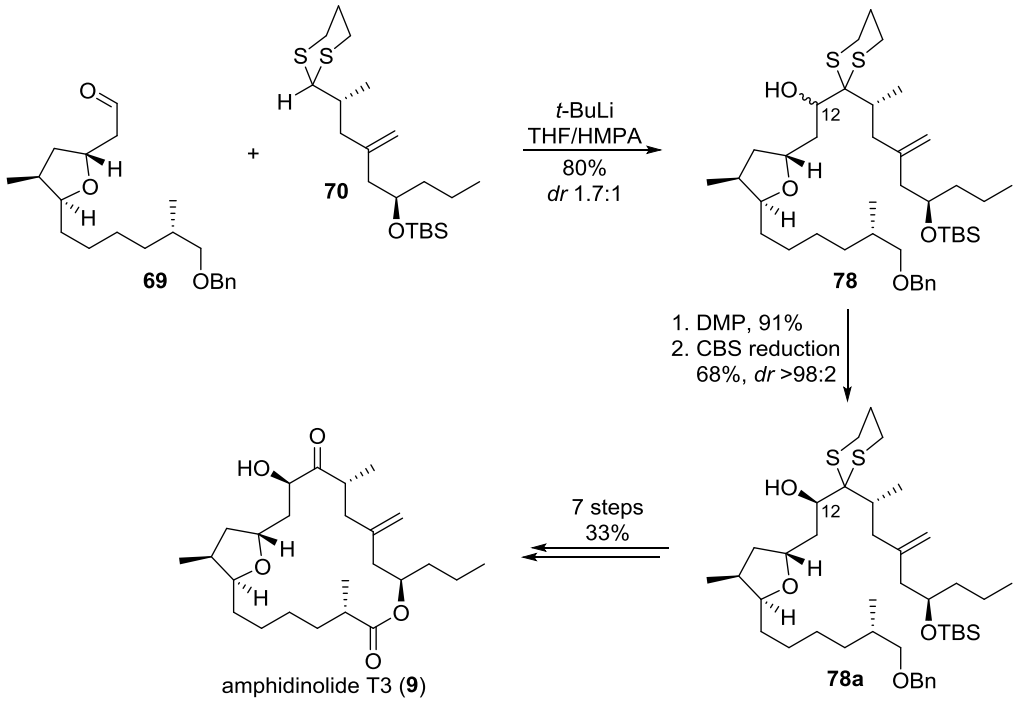
Scheme 17

The strategy used by Zhao to prepare the trisubstituted THF ring involved intramolecular displacement of a tosylate by an alkoxide (Scheme 18). A further 7 steps were required to convert the tetrahydrofuran **77** into the aldehyde **69**.



Scheme 18

The two main fragments were assembled by deprotonation of dithiane **70** with *t*-BuLi and addition of the resulting anion to aldehyde **69** (Scheme 19). Under these conditions alcohol **78** was obtained in 80% yield but with a poor *dr* of 1.7:1. An oxidation/reduction sequence using the Corey-Bakshi-Shibata asymmetric reduction protocol allowed the selective formation of alcohol **78a** featuring the required stereochemistry at C12. Although advanced intermediate **78a** contains the entire carbon skeleton of the natural product, seven additional steps, mainly involving protecting group manipulation and changes in oxidation state, were required for its transformation into amphidinolide T3.

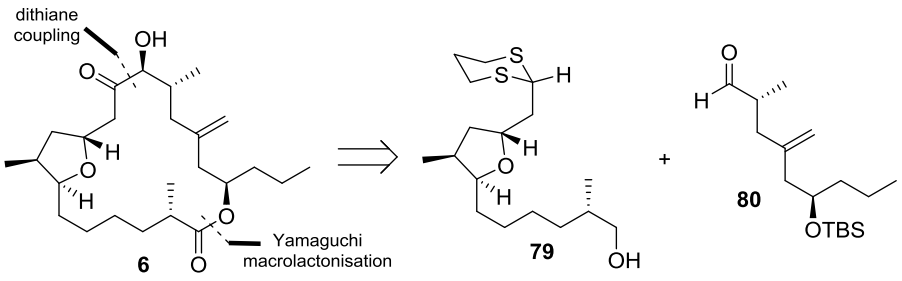


Scheme 19

The synthesis of amphidinolide T3 was completed in 27 steps with an overall yield of 4.3%. This approach could also be applied to the synthesis of amphidinolide T4.

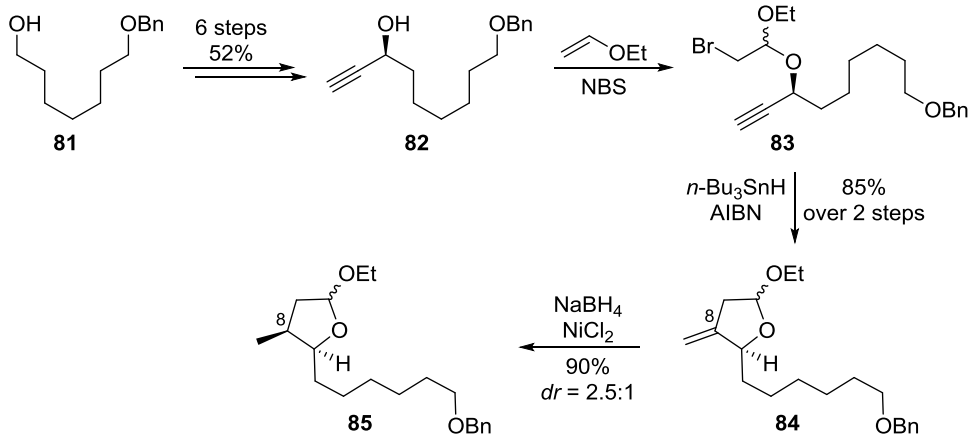
1.3.5 Yadav: Radical Cyclisation and Dithiane Coupling

Yadav and co-workers reported the synthesis of amphidinolide T1 employing a radical cyclisation reaction developed by their group to build the THF ring.[14,29] The main disconnections were similar to that employed by Zhao; for example, a reversed dithiane coupling reaction was to be used to form the C12—C13 bond and Yamaguchi lactonisation was used to construct the macrocycle (Scheme 20).



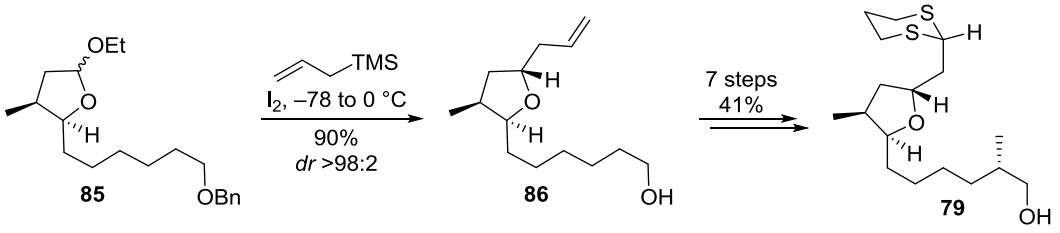
Scheme 20

The synthesis started with readily available benzyl ether **81**, which was converted into the propargylic alcohol **82** in six steps (Scheme 21). Alkynol **82** was then reacted with ethyl vinyl ether in the presence of NBS to deliver the bromoacetal **83**, which underwent radical cyclisation to give the acetal **84**.[29] Next, reduction of the *exo*-methylene group afforded the acetal **85** in 90% yield but with only 2.5:1 diastereoselectivity at C8.



Scheme 21

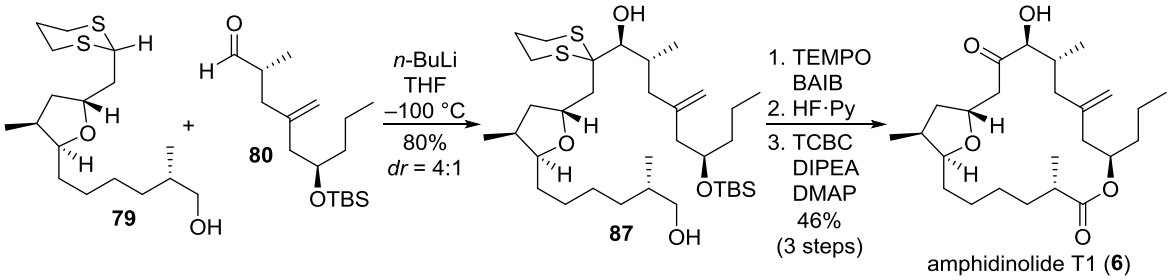
Treatment of the acetal **85** with allyltrimethylsilane in the presence of an excess of iodine resulted in allylation with concomitant debenzylation to deliver the trisubstituted THF **86** in excellent yield with complete diastereoselectivity (Scheme 22). The alcohol **86** was then converted into the dithiane **79** ready for coupling.



Scheme 22

Coupling of the fragments was achieved by deprotonation of the dithiane **79** with *n*-BuLi and addition of the resulting anion to the aldehyde **80** (Scheme 23). When the reaction was performed at −100 °C, the alcohol **87** was obtained in 80% yield with a diastereoselectivity of 4:1 in favour of the desired Felkin-Anh adduct. Regioselective oxidation of the primary alcohol, with concomitant

cleavage of the dithiane, followed by TBS deprotection and Yamaguchi macrolactonisation completed the synthesis of amphidinolide T1.

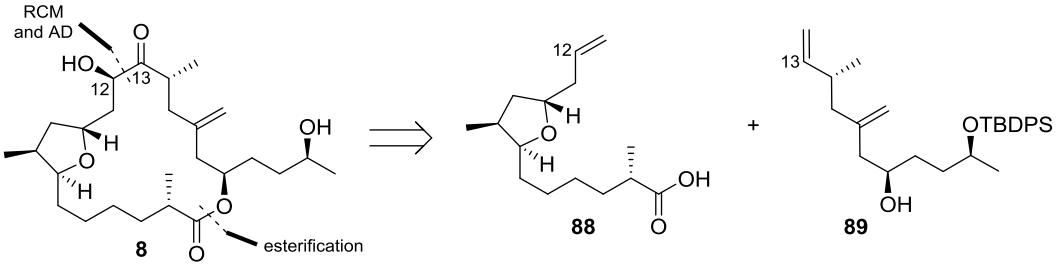


Scheme 23

Employing this strategy, Yadav *et al*. completed the synthesis of amphidinolide T1 in 23 steps with an overall yield of 4.1%.

1.3.6 Dai: Ring-Closing Metathesis and Asymmetric Dihydroxylation

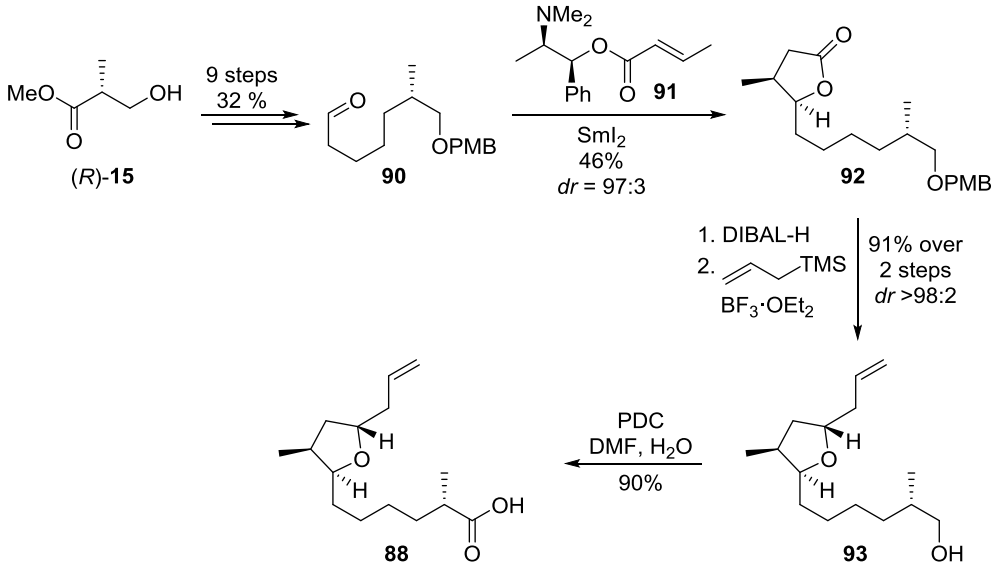
Dai and co-workers developed a synthetic strategy that allowed them to access all the members of the amphidinolide T family. In 2010, they were the first to complete the synthesis of amphidinolide T2 (**8**).[15a] Dai's approach relies on the key sequence of RCM and asymmetric dihydroxylation to assemble the C12/C13 α-hydroxy ketone subunit (Scheme 24).



Scheme 24

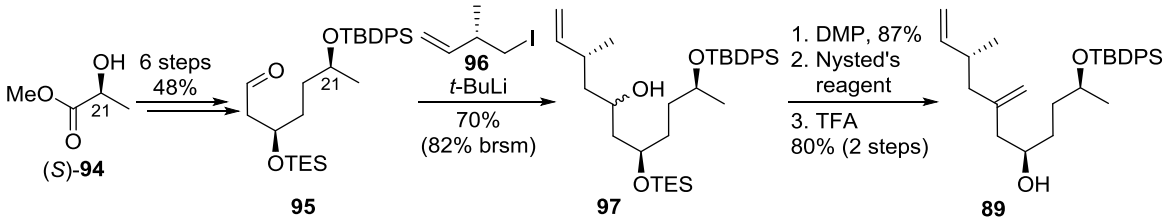
Dai and co-workers synthesised the THF ring moiety by employing a samarium diiodide mediated cyclisation (Scheme 25).[30] The aldehyde precursor **90** was prepared in 9 steps starting from the (*R*)-Roche ester **15**. SmI_2-mediated reductive coupling of aldehyde **90** with the *N*-methylephedrine-derived crotonate **91** delivered the *cis*-3,4-disubstituted γ-butyrolactone **92** in moderate yield with a very high level of diastereocontrol. Partial reduction of the lactone

to give the corresponding lactol followed by diastereoselective Lewis acid-mediated allylation with concomitant PMB cleavage delivered the *trans*-THF **93** in 91% yield as a single diastereoisomer. The alcohol **93** was then oxidised to give the carboxylic acid **88**.



Scheme 25

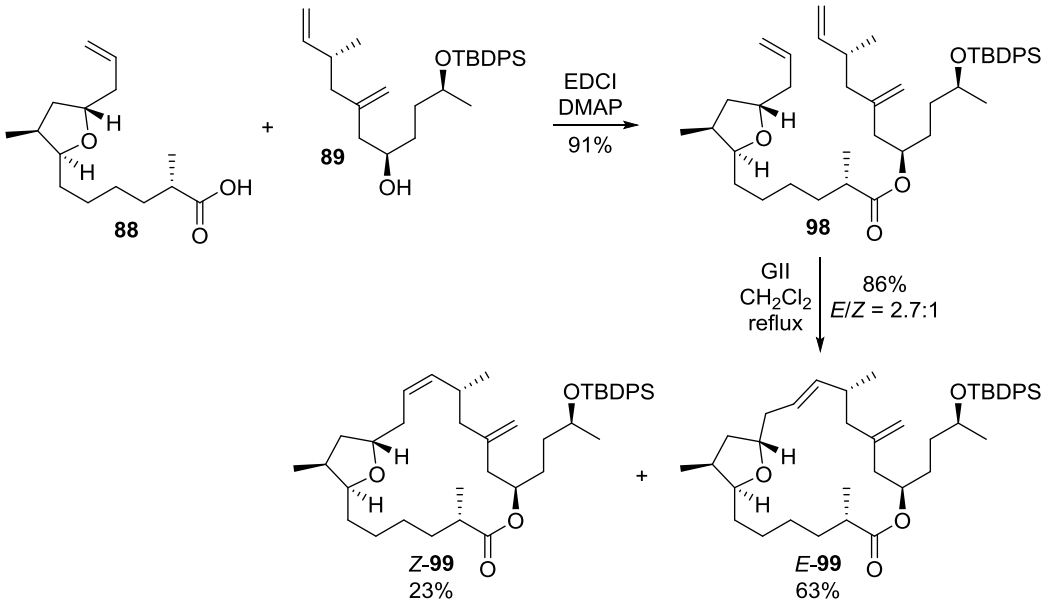
The synthesis of alcohol fragment **89** commenced with (*S*)-methyl lactate **94**, which was transformed into aldehyde **95** in 6 steps (Scheme 26). Addition of the alkyllithium reagent, prepared from the iodide **96**, to the aldehyde **95** delivered an inconsequential diastereomeric mixture of alcohols **97,** which was oxidised using DMP. Methylenation of the resulting ketone using Nysted's reagent followed by TES cleavage by exposure to TFA delivered the final alcohol fragment **89** in good yield.



Scheme 26

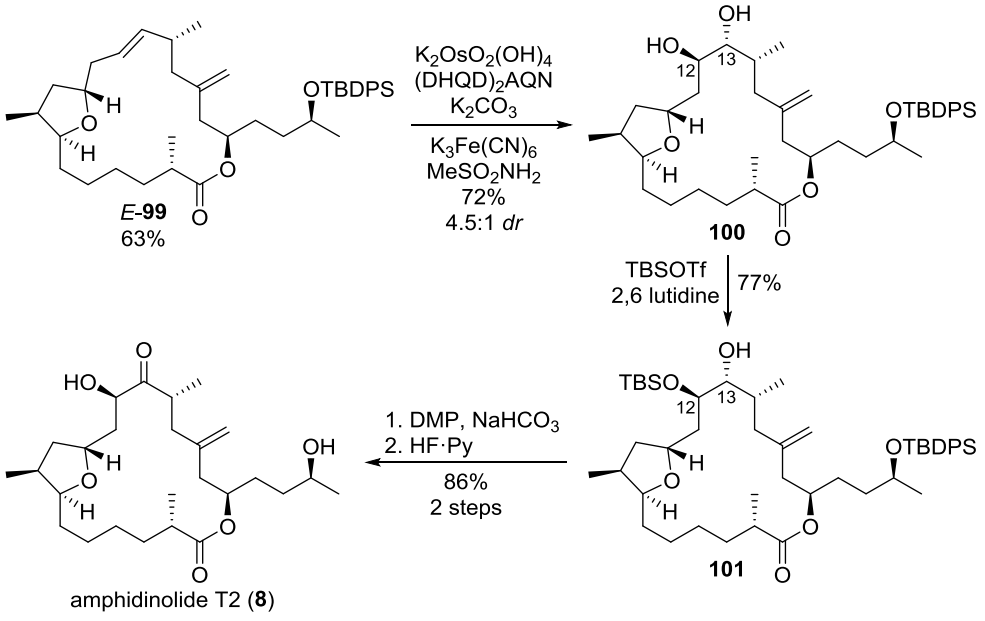
An EDCI-mediated esterification reaction was employed to couple fragments **88** and **89**, followed by closure of the macrocycle using RCM (Scheme 27). After careful screening of reaction conditions and catalysts, the best result was

obtained by treating the triene **98** with the Grubbs second generation catalyst in CH_2Cl_2 at reflux. Under these conditions the macrolactone **99** was obtained in 86% combined yield as a separable 2.7:1 mixture in favour of the *E* alkene.



Scheme 27

The next step involved the regio- and diastereoselective dihydroxylation of *E*-**99** (Scheme 28). Of all the chiral ligands screened, $(DHQD)_2AQN$ gave the best result, furnishing the product in good yield and with a 4.5:1 diastereomeric ratio.



Scheme 28

Under optimised reaction conditions the desired isomer **100** was obtained in 59% yield. In contrast, *Z*-**99** proved to be an unsuitable substrate for the asymmetric dihydroxylation reaction. Selective protection of C12 hydroxyl group of the diol **100** and oxidation of the C13 hydroxyl functionality of the resulting alcohol **101**, followed by global desilylation completed the total synthesis of amphidinolide T2. The first total synthesis of amphidinolide T2 was accomplished in 19 steps with an overall yield of 4.2%.

Dai's strategy was particularly suitable for amphidinolide T2 but proved to be more problematic when applied to the synthesis of the other members of the amphidinolide T family. Indeed, dihydroxylation reactions and selective protection occurred with poor selectivity and several steps were required to convert mixtures of isomeric products into each natural product.[15b,c] As result of these problems, a lower overall yield was obtained. Applying his RCM and asymmetric dihydroxylation strategy, Dai completed the synthesis of amphidinolide T1, T3 and T4 in 19-21 steps with overall yields of 1.3%, 1.9% and 3.3% respectively.

1.3.7 Summary of the Total Syntheses of Amphidinolides T

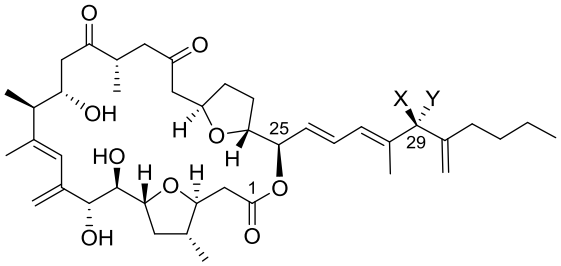
The total syntheses of members of amphidinolide T family described in the preceding discussion present a wide range of interesting chemistry and different approaches to the formation of the *trans*-THF ring. The most popular method was a Lewis acid promoted diastereoselective oxocarbenium alkylation, employed by Fürstner, Ghosh, Jamison, Dai and Yadav (Schemes 4, 10, 13, 22 and 25). Zhao's strategy involved a classic intramolecular displacement of a tosylate by a hydroxyl group (Scheme 18).

In many of these syntheses, substituents and stereocentres in the C12–C14 region were introduced before or during formation of the macrocycle, which has meant that the route to each member is differentiated at an early stage or that several steps are required to change oxidation states or invert stereocentres in order to access more than one natural product. The exception is the route of Dai and co-workers in which RCM was used to close the macrocycle with C12—C13 bond formation and the resulting alkene was dihydroxylated. This strategy was

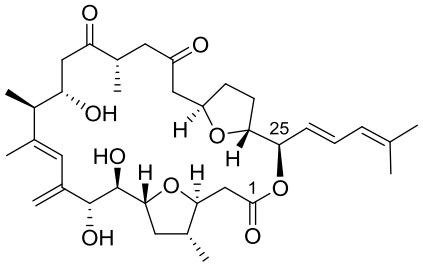
particularly suitable for the synthesis of amphidinolide T2. However, in the case of amphidinolides T1, T3 and T4, the RCM and dihydroxylation reactions were not stereoselective and several steps were required to convert mixtures of isomeric products into each natural product.

1.4 Amphidinolides C and F: Isolation, Structure and Bioactivity

Amphidinolide C (**102**), C2 (**103**), C3 (**104**) and F (**3**) form a subgroup of four closely related compounds sharing the same 25-membered macrocyclic core but exhibiting different side chains (Figure 3). Amphidinolides C and F possess complex and densely functionalized structures featuring 11 or 12 stereogenic centres, two *trans*-tetrahydrofuran rings and two 1,3-diene units.



amphidinolide C (**102**) X=OH Y=H
amphidinolide C2 (**103**) X=OAc Y=H
amphidinolide C3 (**104**) X,Y=O



amphidinolide F (**3**)

Figure 3

Amphidinolide C (**1**) was the first member of this subgroup to be isolated by Kobayashi and co-workers in 1988.[31] Its relative stereochemistry was determined by 1D and 2D NMR experiments and the absolute stereochemistry was established through degradation and Mosher ester analysis.[6] More recently, two additional variants, amphidinolides C2[32] and C3,[33] have been identified. They differ from amphidinolide C at C29 featuring an acetate group in the case of amphidinolide C2, and a ketone functionality in the case of amphidinolide C3. In 1991, amphidinolide F was also isolated by Kobayashi *et al.* in very limited quantities (0.00001% wet weigh yield).[34] The structure and absolute stereochemistry of amphidinolide F was fully established only in 2012 when its first total synthesis was reported by Carter.[35]

Despite the structural homology, these compounds exhibit different levels of biological activity. Amphidinolide C is one of the most potent of all the amphidinolides, exhibiting impressive cytotoxic activity against murine lymphoma L1210 cells (IC_{50} = 5.8 ng/mL) and human epidermoid carcinoma KB cells (IC_{50} = 4.6 ng/mL).[31] The other three member of the subgroup are up to three orders of magnitude less potent.[32,33,34] These preliminary results highlight the key importance of the side chain for the biological activity. Because of the

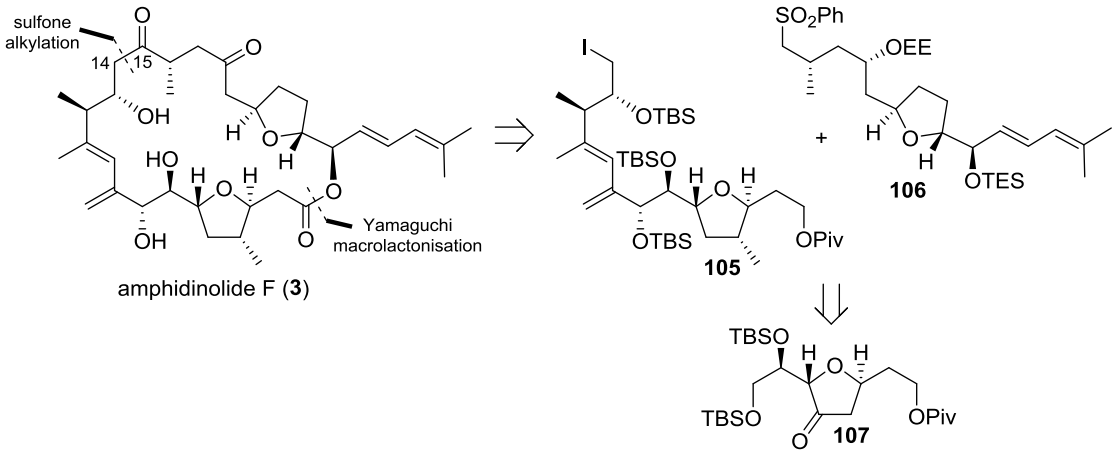
limited quantities isolated, it was not possible to test if their cytotoxicity extends to a larger panel of tumour cell lines.

1.5 Previous Syntheses of Amphidinolides C and F

Their extremely promising bio-profile, challenging complex molecular architecture and the very limited material supply for studies have made amphidinolides C and F very popular targets among the synthetic community.[36] Despite this, in the 20 years after their isolation neither amphidinolide C nor amphidinolide F was successfully synthesized. The first total synthesis of amphidinolide F was reported by Carter in 2012,[35] followed in 2013 by Fürstner.[37] Both Carter and Fürstner also applied their strategy to complete the synthesis of amphidinolide C.[38,39]

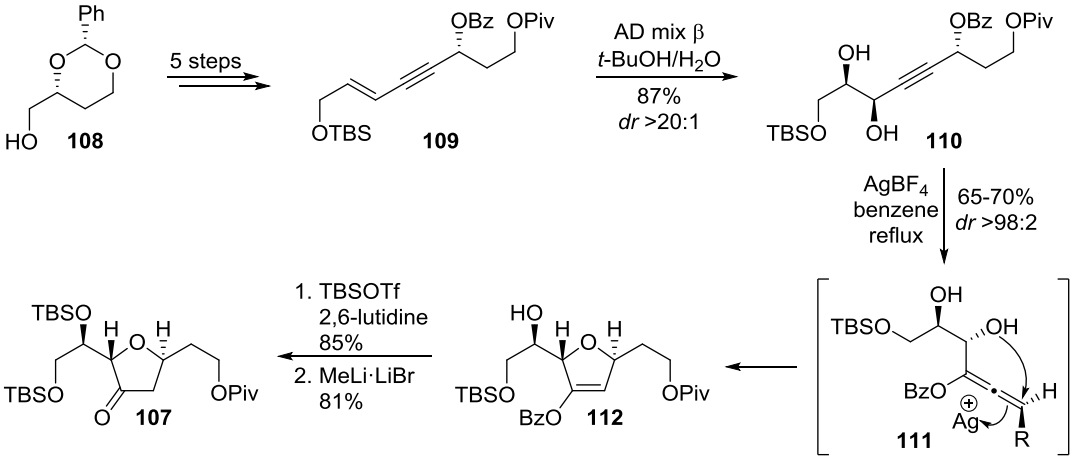
1.5.1 Carter: Use of Latent Symmetry

Carter's strategy relies on the similarity of functionalization, oxidation states and stereochemistry around the two tetrahydrofuran rings within the macrocyclic core of amphidinolide C and F. Carter's retrosynthetic plan involves disconnections at the C—O macrolactone bond and at the C14—C15 bond revealing two main fragments, the sulfone **106** and the iodide **105**, which can both be accessed from a common intermediate dihydrofuranone **107** (Scheme 29).



Scheme 29

The synthesis of the common intermediate **107** started with known alcohol **108**, which is easily accessible in two steps from D-malic acid (Scheme 30).[40] The alcohol **108** was converted into enyne **109** in 5 steps, which was then subjected to Sharpless asymmetric dihydroxylation to afford the diol **110** in excellent yield and diastereoselectivity. Formation of dihydrofuran **112** was accomplished by silver-catalysed cyclisation *via* chiral allene intermediate **111** to deliver the desired product in good yield as a single diastereoisomer. Silyl protection and cleavage of the enol benzoate by treatment with MeLi·LiBr completed the synthesis of the pivotal dihydrofuranone **107**.

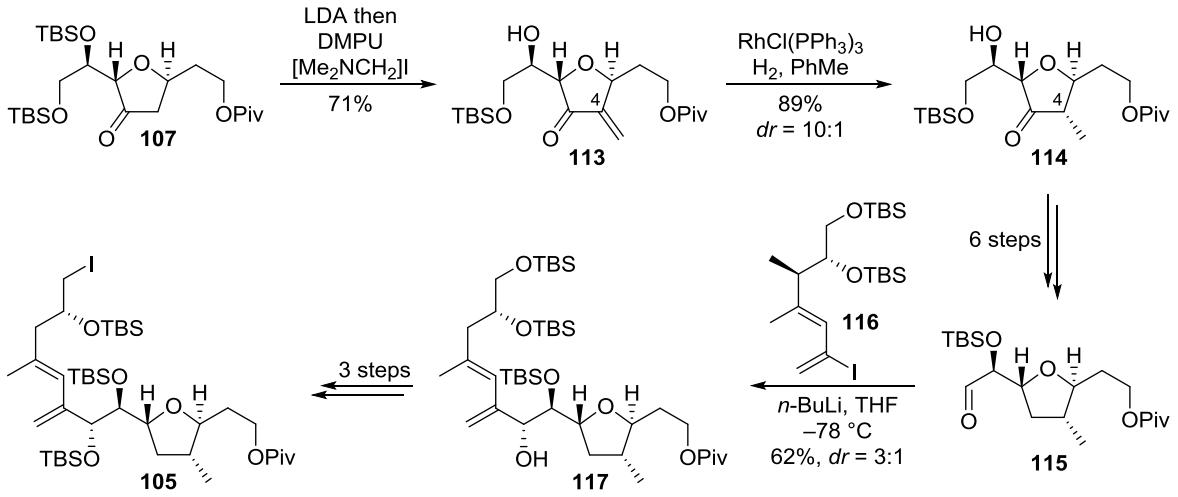


Scheme 30

Dihydrofuranone **107** was then employed for the preparation of both iodide **105** and sulfone **106**.

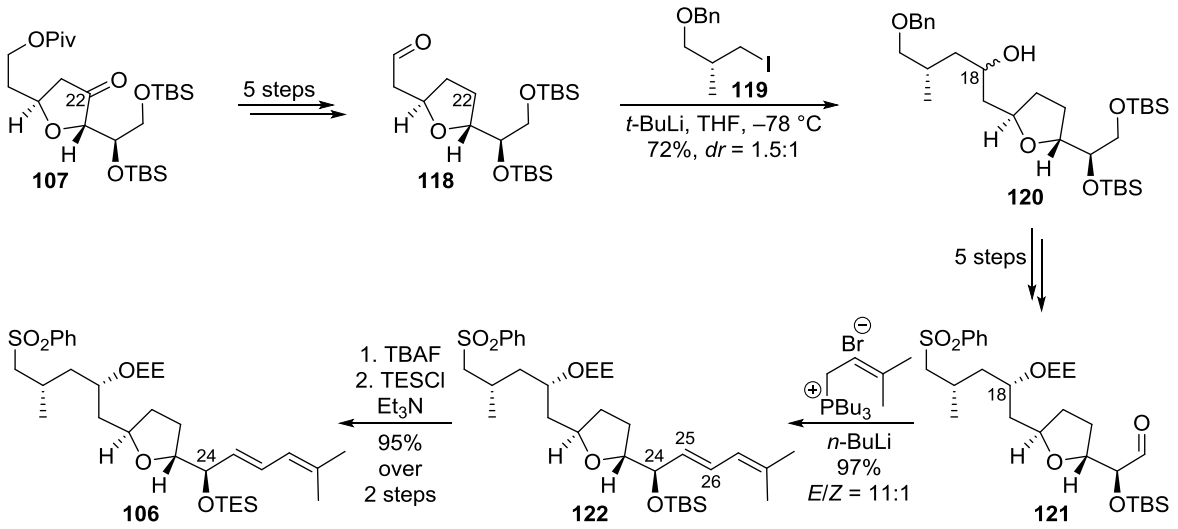
The methyl group present in the tetrahydrofuran ring of the iodide fragment **105** was installed by trapping the enolate formed by deprotonation of ketone **107** with Eschenmoser's salt followed by reduction of the resulting double bond using Wilkinson's catalyst (Scheme 31). The dihydrofuranone **114** was then transformed into aldehyde **115** in which the ketone group in the THF ring had been removed by deoxygenation. Addition of the vinyl lithium species, prepared from the iodide **116**, to the aldehyde **115** gave the alcohol **117** in good yield but modest diastereoselectivity (*dr* = 3:1) in favour of the desired isomer. Interestingly, under the optimised reaction conditions, there was no evidence of 1,3-metallotropic shift by the organolithium reagent to generate the corresponding allenyl lithium species with scrambling of the geometry of the

double bond.[41] The alcohol **117** was then easily converted into the final iodide fragment **105**.



Scheme 31

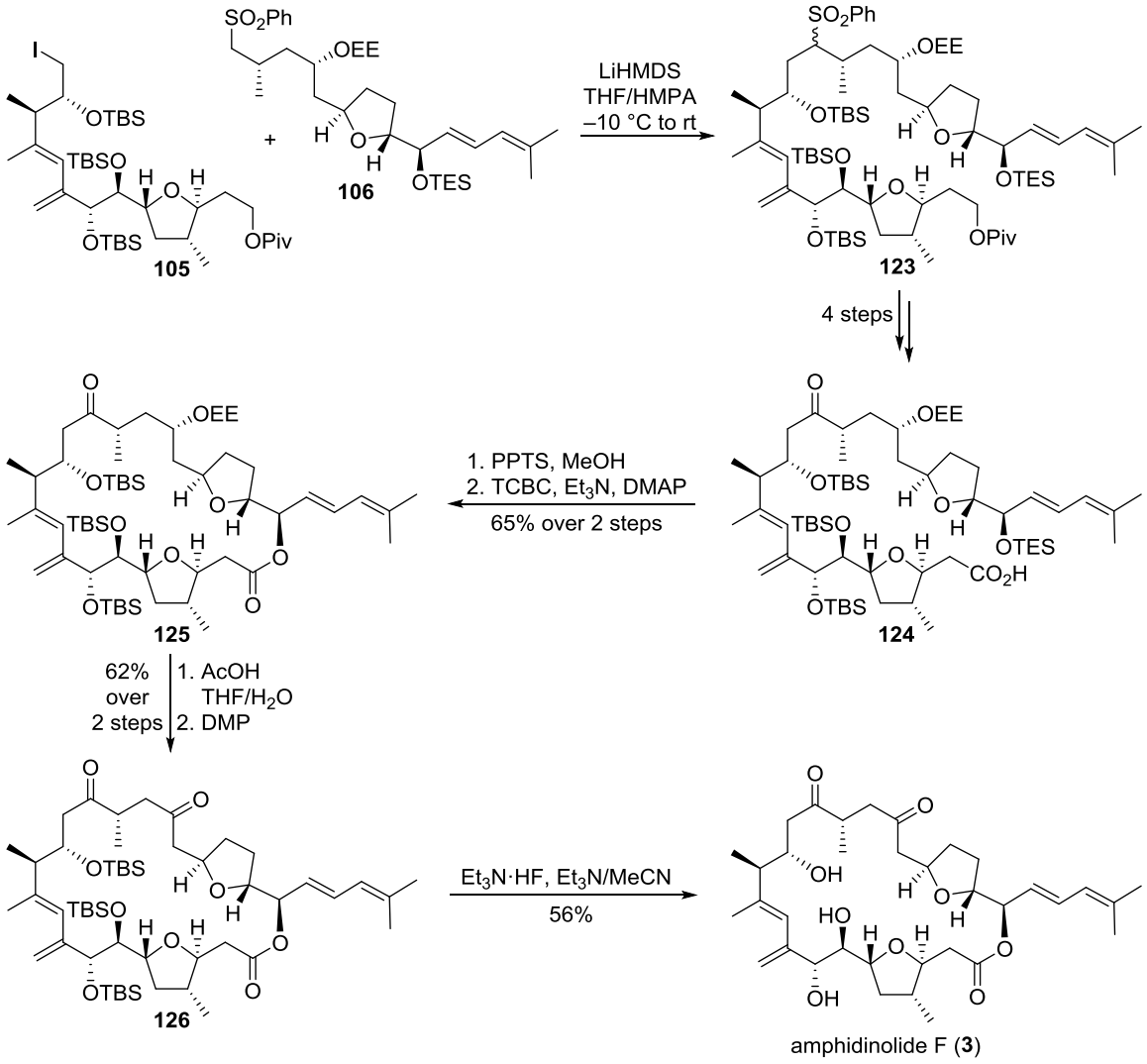
In the synthetic route toward sulfone **106**, the common intermediate **107** was deoxygenated at C22 and converted into aldehyde **118** (Scheme 32). Addition of the alkyl lithium species derived from the iodide **119** to the aldehyde **118** delivered alcohol **120** in 72% yield as an inseparable 1.5:1 mixture of diastereoisomers. Both diastereoisomers were suitable for completion of the synthesis; however, for practical reasons, Carter chose to perform an oxidation/reduction sequence to convert the mixture into the single EE-protected alcohol **121** with the *S* configuration at C18.



Scheme 32

The benzyl ether functionality was converted into the corresponding sulfone during the transformation of the alcohol **120** into the key α-oxy aldehyde **121**. Olefination of aldehyde **121** using Tamura/Vedejs conditions allowed selective formation of the desired *E* alkene at C25-C26 and accomplished introduction of the side chain.[42] Exchange of silyl protecting groups at C24 completed the synthesis of sulfone fragment **106**.

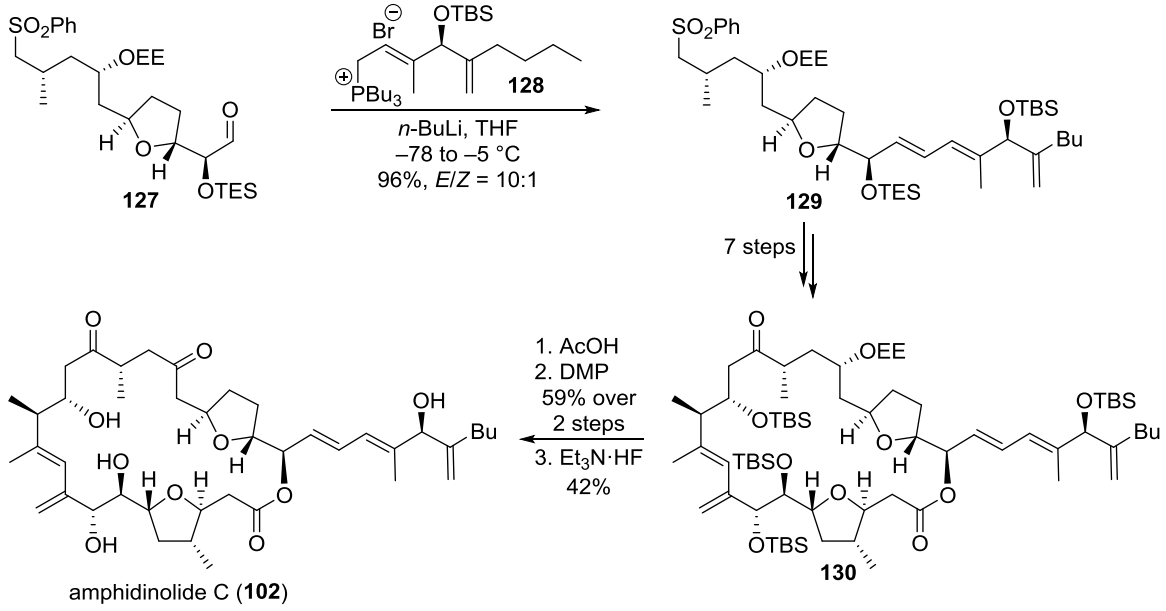
Coupling of the fragments was realised by displacing the iodide present in **105** with the anion generated by deprotonation of the sulfone **106** using LiHMDS in the presence of HMPA (Scheme 33). The coupled product **123** was then converted into acid **124** after manipulation of the protecting groups and oxidation. Selective removal of the TES group followed by Yamaguchi macrolactonisation provided macrocycle **125** in good yield.



Scheme 33

The total synthesis of amphidinolide F (**3**) was completed by selective cleavage of the EE protecting group, oxidation of the resulting alcohol, and global deprotection.

Carter applied the same strategy to the total synthesis of amphidinolide C. Selective formation of the desired *E* alkene at C25-C26 during introduction of the side chain was achieved by Tamura/Vedejs olefination of the α-oxy aldehyde **127** employing tributylphosphonium salt **128** (Scheme 34).[42] Sulfone **129** was used in the same synthetic pathway described above to complete the synthesis of amphidinolide C (**102**).



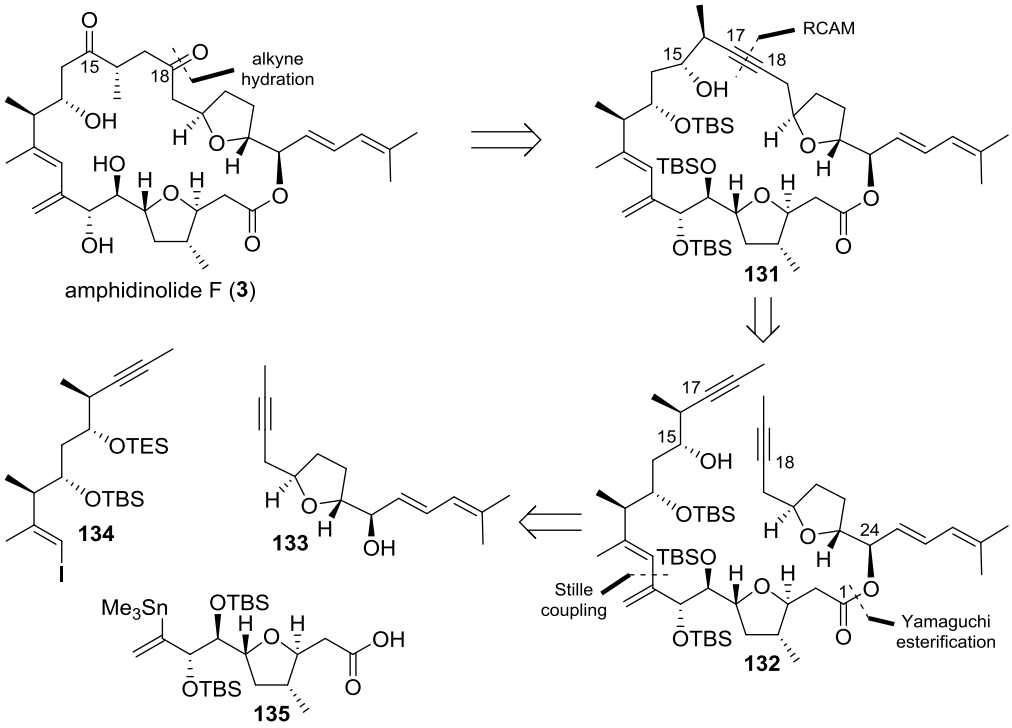
Scheme 34

Exploiting the latent symmetry within the macrocyclic core of amphidinolides C and F, Carter completed the first total synthesis of amphidinolide F in 34 steps and of amphidinolide C in 33 steps with an overall yield of 0.3% and 0.2% respectively.

1.5.2 Fürstner: Ring-Closing Alkyne Metathesis and Alkyne Hydration

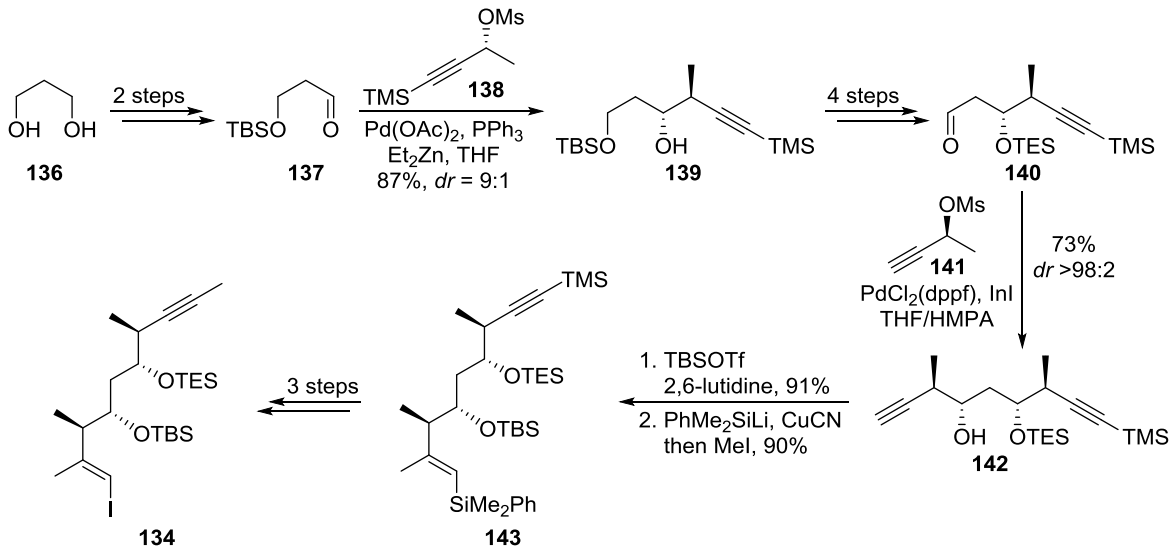
Fürstner and co-workers showcased the synthetic utility of ring-closing alkyne metathesis (RCAM) by applying this methodology to the total synthesis of amphidinolides F and C. Fürstner's approach is highly convergent, involving the coupling of three building blocks of similar size and complexity by esterification

and Stille cross-coupling (Scheme 35). A key RCAM reaction was employed to close the macrocycle and a directed noble-metal catalysed alkyne hydration reaction was used to install the 1,4-diketone moiety at C15 and C18.



Scheme 35

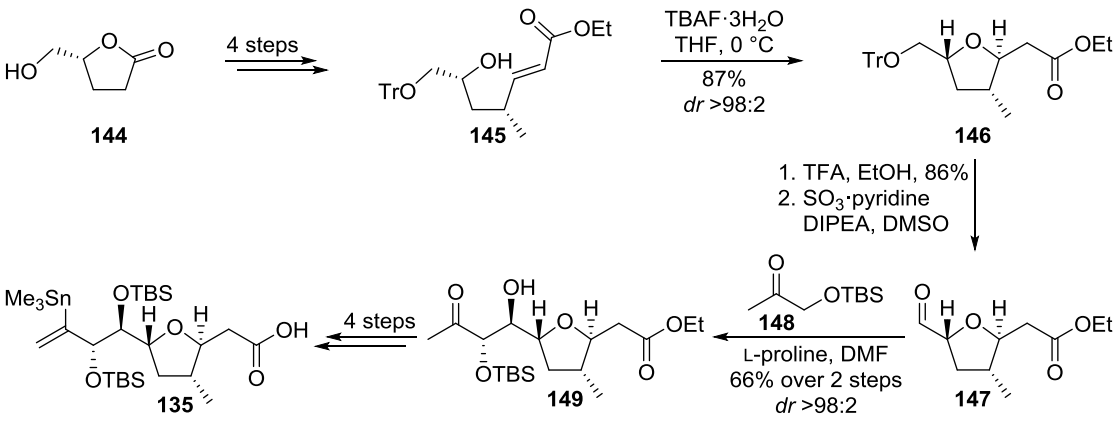
The synthesis of the vinylic iodide **134** started with 1,3-propanediol **136** and employed two different *anti*-propargylation reactions, developed by Marshall, to set the stereogenic centres (Scheme 36).[43]



Scheme 36

A first zinc-mediated propargylation of aldehyde **137** delivered alcohol **139** in high yield with a *dr* = 9:1. A second indium-mediated propargylation of aldehyde **140** provided the alcohol **142** in 73% yield as a single diastereoisomer. The free hydroxyl group was TBS protected, and then the terminal alkyne was subjected to regioselective silylcupration followed by quenching with methyl iodide to deliver the vinyl silane **143** in excellent yield. The silane **143** was then converted in a few steps into the vinylic iodide **134**, which proved to be light-sensitive and was formed as required from its immediate precursor.

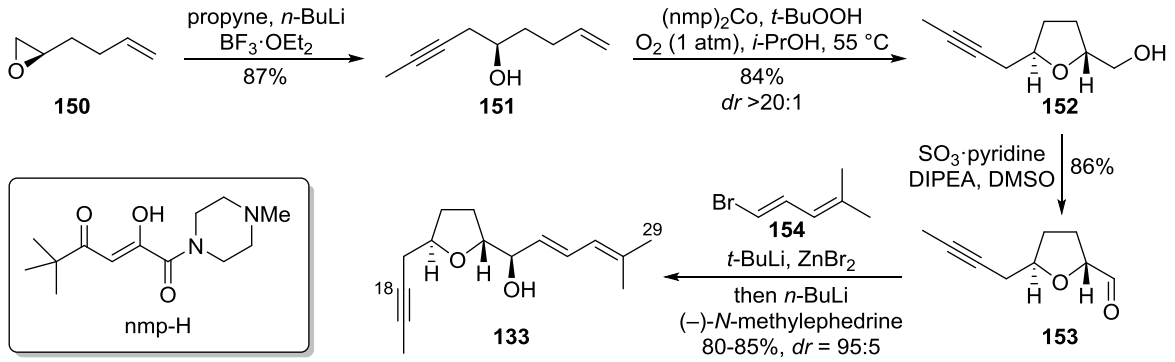
The vinylic stannane **135** was prepared from commercially available chiral lactone **144** (Scheme 37). The lactone **144** was converted into α,ß-unsaturated ester **145** in four steps. The ester **145** underwent intramolecular oxa-Michael reaction upon exposure to TBAF to give the desired 2,5-*trans*-THF **146** as a single diastereoisomer in 87% yield. The required stereochemistry of the *anti*-aldol product **149** was set with complete diastereocontrol by proline-catalysed aldol reaction between the ketone **148** and the aldehyde **147**.[44] The preparation of carboxylic acid **135** was completed by conversion of the methyl ketone functionality of intermediate **149** into the corresponding vinylic stannane and saponification of the ester moiety.



Scheme 37

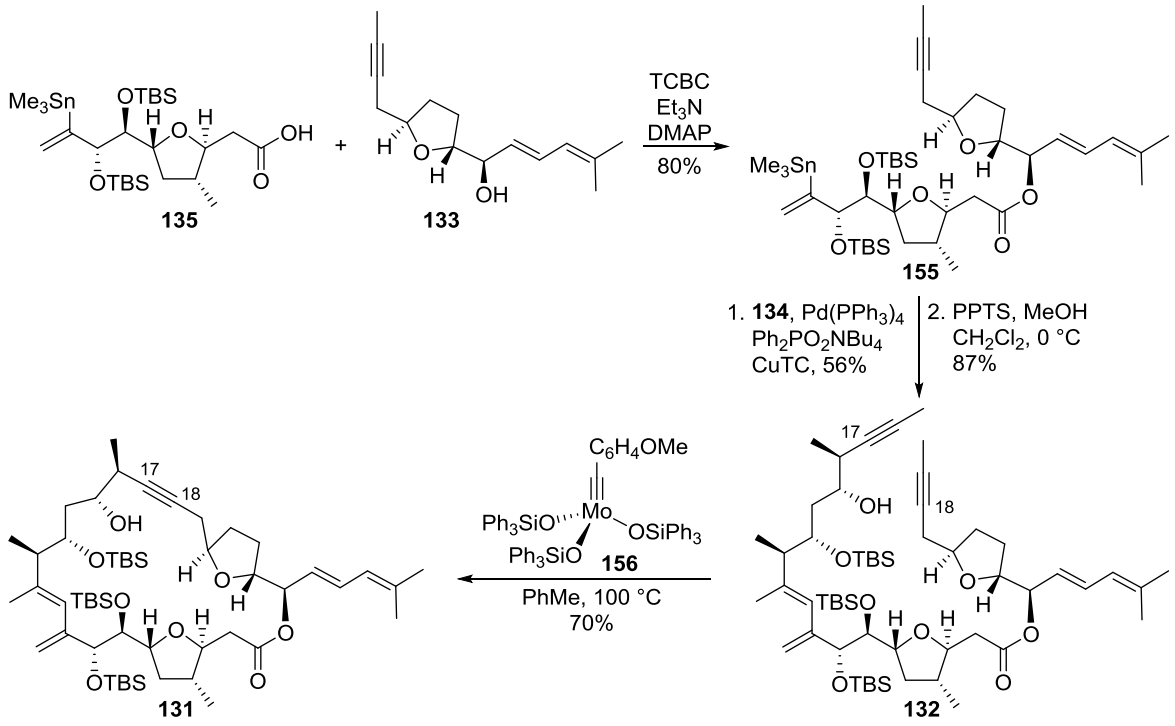
The tetrahydrofuran segment **133** was assembled from chiral epoxide **150** in only four steps exploiting an oxidative Mukaiyama cyclisation, a powerful synthetic tool that exploits molecular oxygen as stoichiometric oxidant to convert γ,δ-unsaturated alcohols into *trans*-THF rings (Scheme 38).[45] Fürstner and co-worker used a cobalt catalyst carrying nmp ligands, developed by Pagenkopf, to promote this transformation. Under these conditions, the desired

trans-tetrahydrofuran **152** was obtained in high yield as a single diastereoisomer. It is important to note that Pagenkopf *et al*. had previously reported model studies towards amphidinolide C applying a very similar strategy.[36k,l] The side chain of amphidinolide F was installed by chelate-controlled *N*-methylephedrine-assisted addition of the organozinc reagent formed from the dienyl bromide **154** to the aldehyde **153**.[46]



Scheme 38

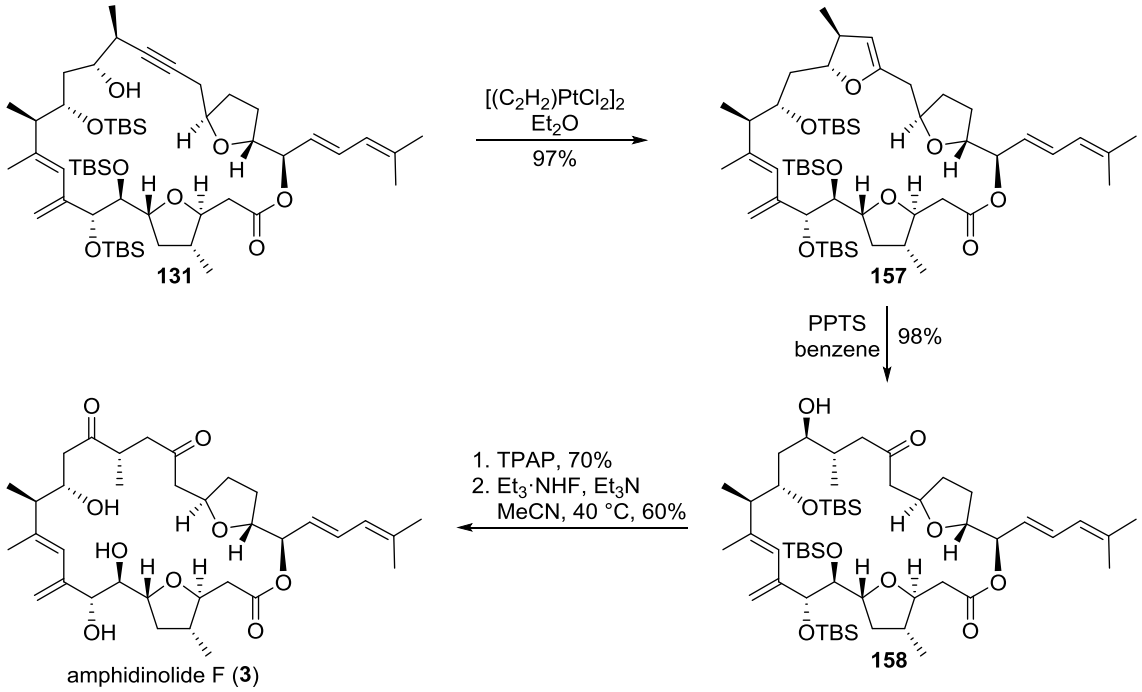
The carboxylic acid **135** and the alcohol **133** were coupled by Yamaguchi esterification. Stille coupling of the resulting stannane **155** with iodide **134** allowed the challenging 1,3-diene functionality of the ester **132** to be assembled in 56% yield (Scheme 39).



Scheme 39

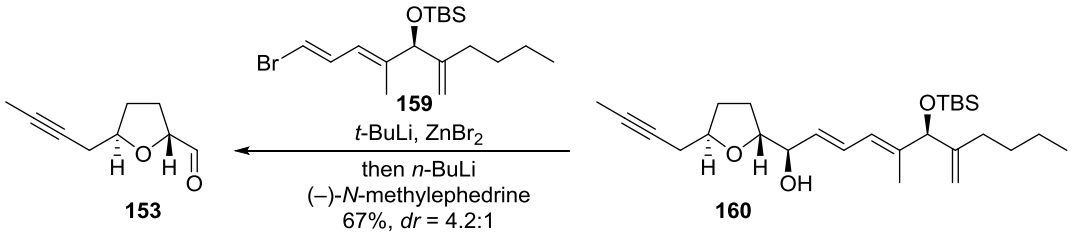
Ring-closing alkyne metathesis of the diyne **132** in the presence of the molybdenum complex **156** was used to close the macrocycle to deliver the macrocyclic alkyne **131** in 70% yield.

Next, transannular alkyne hydration under platinum catalysis gave enol ether **157**, which was then hydrolysed to afford the corresponding γ-hydroxy ketone **158** in almost quantitative yield by exposure to PPTS in wet benzene(Scheme 40).[47] Oxidation of the free hydroxyl group followed by global deprotection afforded amphidinolide F (**3**).



Scheme 40

Fürstner and co-workers utilised the same strategy to complete the synthesis of amphidinolide C (Scheme 41). Addition of the organozinc species prepared from the bromide **159** to the aldehyde **153** gave the alcohol **160** in good yield and with moderate diastereoselectivity in favour of the desired product.



Scheme 41

Alcohol **160** was then used in the same synthetic sequence described above to complete the synthesis of amphidinolide C (**102**).

Fürstner and co-worker completed the synthesis of amphidinolide C and F in only 21 steps with an overall yield of 3.2% and 2.2% respectively, thus showcasing the utility of RCAM in natural product synthesis.

1.5.3 Summary of the Total Syntheses of Amphidinolides C and F

The total syntheses of amphidinolides C and F described in the preceding discussion present an array of interesting chemistry and different approaches to form the two *trans*-THF rings within the macrocyclic core.

Carter formed *trans*-dihydrofuranone **107**, precursor for both THF rings, by silver-catalysed cyclisation *via* a chiral allene intermediate (Scheme 30). Carter exploited the latent symmetry around the two tetrahydrofuran rings; however, transformation of dihydrofuranone **107** in each THF segment required several manipulations adding several steps to the synthetic route.

Fürstner employed a highly diastereoselective intramolecular oxa-Michael reaction to assemble the trisubstituted tetrahydrofuran ring (Scheme 37) and a powerful oxidative Mukaiyama cyclisation to build the disubstituted THF ring (Scheme 38). Fürstner's strategy is highly convergent, involving the coupling of three building blocks of similar size and complexity. This approach allowed Fürstner and co-workers to complete the synthesis of amphidinolides C and F in only 21 steps.

1.6 Oxonium Ylide Generation and Rearrangement

1.6.1 Tetrahydrofuran Motif in Bioactive compounds

The tetrahydrofuran motif is ubiquitous across many natural product families and synthetic analogues that exhibit remarkable bioactivity.[48] In particular, over the last 20 years, a significant number of THF-containing polyketide macrolides have been isolated from marine organisms (Figure 4). The intriguing chemical structure and promising biological activities of these secondary metabolites make them potential lead compounds for drug development or pharmacological tools for fundamental studies in the life sciences.[48]

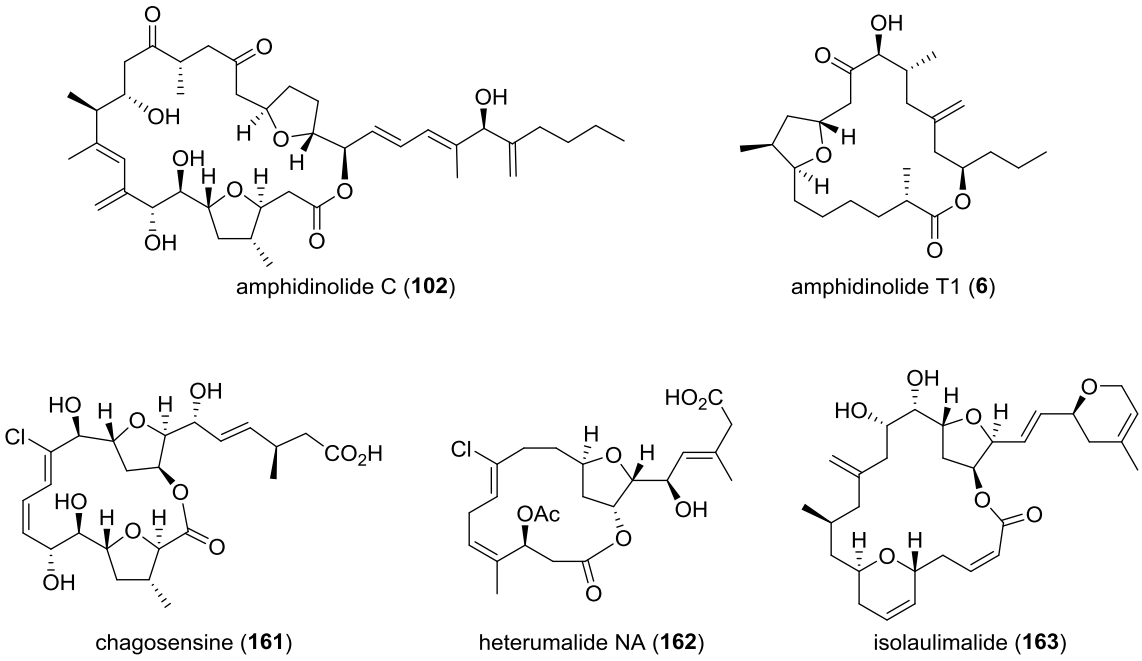


Figure 4

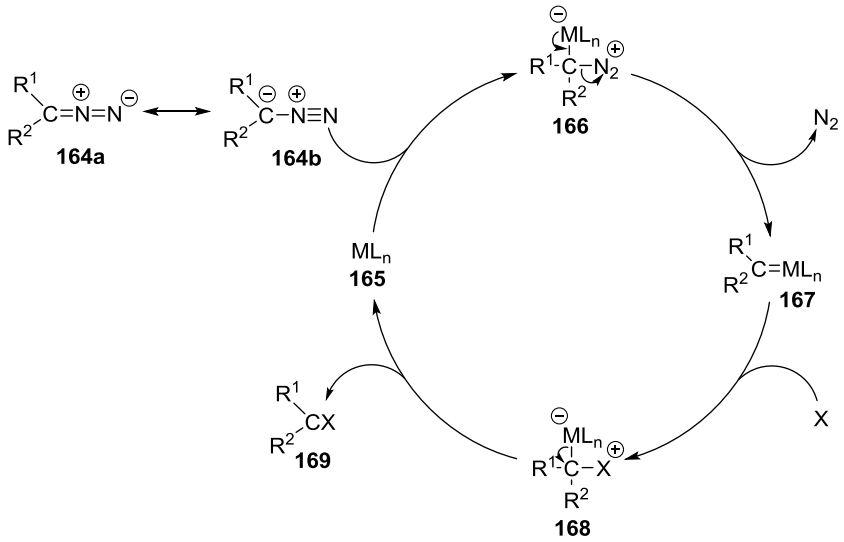
The ability to form THF rings in an efficient and diastereoselective manner is crucial for the synthesis of these natural products. This issue has driven synthetic organic chemists to develop numerous methodologies for the formation of this motif.[49]

Over the last 20 years, in the Clark group we have developed expertise in the synthesis of *trans*-tetrahydrofuran rings using [2,3]-sigmatropic rearrangement of catalytically generated oxonium ylides. This transformation will be discussed in detail.

1.6.2 Metal Carbenoid Reactions

Carbenes are divalent carbon species containing a neutral carbon atom bearing two unshared valence electrons.[50] Based upon empirical observations, they were first postulated as plausible reaction intermediates in the early days of organic synthesis.[51] The use of free carbenes in organic synthesis has been limited by the harsh conditions that are usually required for their generation coupled with the instability and high reactivity of the carbene intermediates and low selectivities of the reactions in which they are involved. It was not until the 1960s, when Fischer[52] and Schrock[53] independently found that transition metals can stabilise carbenes and attenuate their reactivity by forming complexes, commonly referred to as metal carbenoids or metallocarbenes, that carbene chemistry became of significant synthetic utility. Since then, reactions involving a metal carbenoid have become increasingly useful for carbon-carbon bond formation.

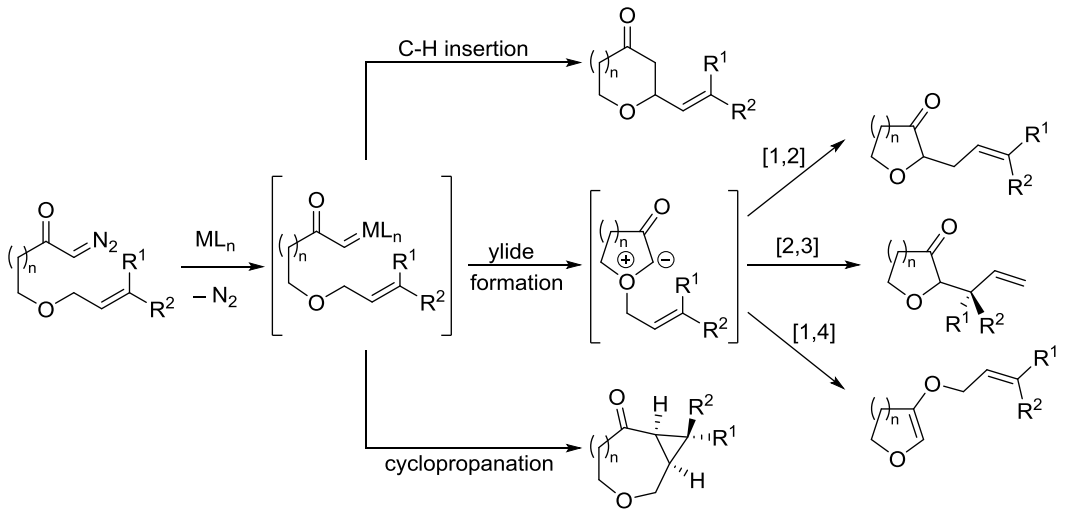
Traditionally, metal carbenoids are formed using Lewis acidic transition metals that are capable of catalysing the decomposition of diazo compounds (Scheme 42). The formation of the metal carbenoid **167** is achieved by nucleophilic attack of the diazo compound **164** onto the metal centre of complex **165** followed by back donation of electrons by the metal and consequent loss of molecular nitrogen from intermediate **166**.



Scheme 42

Transfer of the electrophilic carbene to an electron-rich substrate X regenerates the catalyst and completes the cycle with the formation of the new carbon-carbon bond in the product **169**.

Although the use of transition metal catalysts for the decomposition of diazo compounds has been known for more than 100 years,[54] only in the past 30 years has the use of diazo compounds as precursors for metal carbenoid transformations received significant attention. The reasons for this are related to the development of new transition metal catalysts, which have proved capable of giving access to relatively stable metal-carbene complexes reducing the problems of selectivity and reactivity associated with the use of free carbenes. The catalytic activity of the transition metal complexes depends on coordinative unsaturation at the metal centre which allows them to react as electrophiles with diazo compounds. To create such metal carbenoids, a complex possessing sufficient electron-withdrawing ligands around an electron deficient metal is required. Furthermore, it is possible to tune the reactivity of a metal carbenoid by using different metal-ligand combinations. In fact, the metal carbenoid generated by decomposition of an α-diazo carbonyl compound can follow various reaction pathways such as cyclopropanation, X-H insertion (X = C, O, S, N, Si) or ylide generation followed by rearrangement depending on the transition metal complex employed. Consequently, catalyst selection is crucial for the outcome of a carbenoid reaction (Scheme 43).



Scheme 43

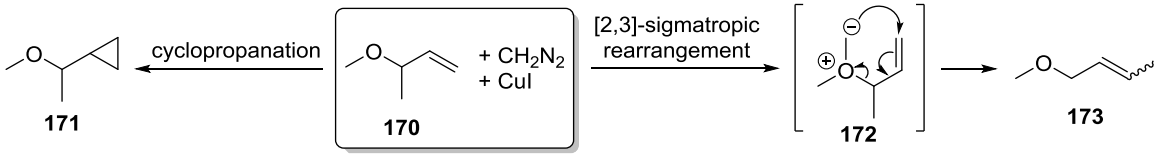
A wide range of transition metal complexes have been used for the decomposition of α-diazo carbonyl compounds; among them copper and rhodium complexes are the most effective catalysts and an increasing number of chemical transformations are based on these complexes.

The key step in our strategy for the synthesis of members of amphidinolide T family of natural products is [2,3]-sigmatropic rearrangement of an oxonium ylide generated by decomposition of an α-diazo carbonyl compound, which will be discussed in detail in the next section.

1.6.3 [2,3]-Sigmatropic Rearrangement of Oxonium Ylides

The reaction of an electron-deficient carbenoid with the non-bonding electron pair of a Lewis base generates a metal complex-associated ylide or a free ylide. Ylides are species bearing a positively charged heteroatom directly bonded to a negatively charged carbon atom.[55] Nitrogen, halogen, oxygen, phosphorus, and sulfur are the most common Lewis basic heteroatoms used to generate ylides. Even though they are highly reactive dipolar compounds, ammonium,[56] phosphonium[57] and sulfonium[58] ylides have been isolated. However, unlike their ammonium, phosphonium and sulfonium counterparts, oxonium ylides have never been isolated due to their reactivity, which results in an extremely short lifetime. Their existence is postulated only through isolation of the products resulting from their subsequent reactions. Common reactions involving ylides include: [2,3]-sigmatropic rearrangement of allylic, propargylic and allenic ylides, [1,2]-shift (Stevens rearrangement) and [1,4]-shift.

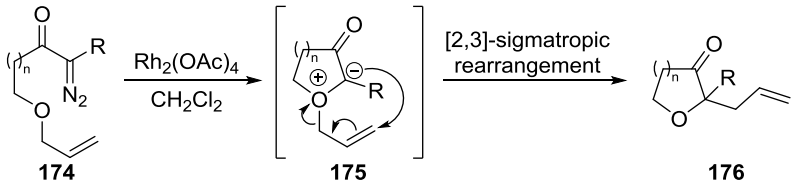
When oxonium ylides are generated from the reaction of a metal carbenoid with an allylic ether or propargylic ether, [2,3]-sigmatropic rearrangement occurs spontaneously. This behaviour was first observed by Kirmse and Kapps who reported the formation of the rearranged product **173** as a minor product during the cyclopropanation of allyl ether **170** by treatment with diazomethane in the presence of copper iodide (Scheme 44).[59]



Scheme 44

The synthetic utility of such rearrangement reactions was showcased in 1986 when Pirrung and Johnson independently published methods for the intramolecular cyclisation of allyloxy diazo ketones in the presence of rhodium acetate dimer to produce five- and six-membered cyclic ethers (Table 1).[60,61] Pirrung and Johnson demonstrated that the furanones and pyranones are formed by tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement.

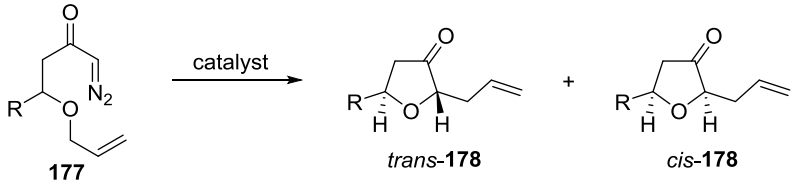
Table 1



entry	R	n	yield
1	CO_2Me	1	91%
2	H	1	70%
3	CO_2Me	2	53%
4	H	2	33%

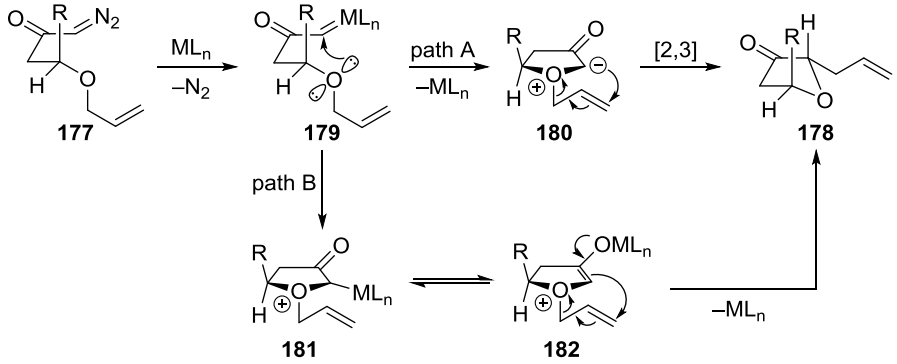
In the early nineties the methodology was extended by Clark, who investigated the diastereoselective transformation of diazo ketones of type **177** into 2,5-dialkyl dihydrofuranones of type **178** using both rhodium and copper catalysis (Table 2).[62] The copper-mediated transformation proceeded with improved yields and excellent diastereoselectivity compared to the corresponding rhodium mediated process. It was assumed that the greater electrophilicity of the intermediate copper carbenoid compared to a rhodium metallocarbene favoured the oxonium ylide generation. In summary, Clark developed efficient tandem copper-catalysed chemoselective ylide formation followed by highly diastereoselective [2,3]-sigmatropic rearrangement.

Table 2



entry	R	catalyst	yield	*trans*:*cis*
1	*n*-Pr	$Rh_2(OAc)_4$	68%	81:19
2	*i*-Pr	$Rh_2(OAc)_4$	51%	65:35
3	*n*-Pr	$Cu(acac)_2$	83%	>97:3
4	*i*-Pr	$Cu(acac)_2$	85%	>97:3

Although the exact mechanism has not been fully elucidated, two different pathways have been proposed based on the results obtained (Scheme 45).

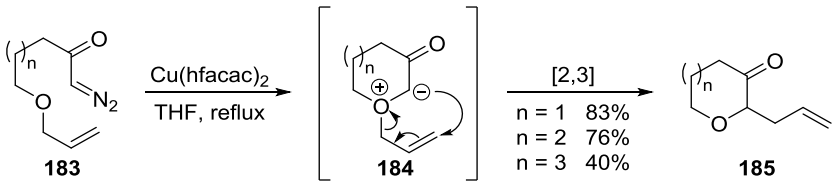


Scheme 45

According to the proposed mechanism, exposure of diazo ketone **177** to a transition metal catalyst results in formation of the corresponding metal carbenoid **179** with loss of dinitrogen. Pathway A involves the selective attack of one of the diastereotopic lone pairs of the ether oxygen onto the metal carbenoid displacing the metal with an efficient transfer of stereochemical information to form free oxonium ylide **180**. As a consequence of this process, ylide **180** is characterised by a *trans* relationship between the allyl group bonded to the oxygen and the R substituent. In the alternative proposed mechanism (pathway B), the metal complex directs ylide rearrangement by remaining on the structure *via* intermediates **181** and **182**.

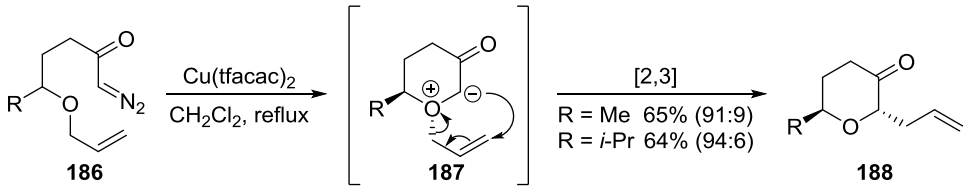
Clark and co-workers further extended the methodology to the formation of six-, seven- and eight-membered cyclic ethers (Scheme 46).[63] Formation of these

products is particularly challenging because competing C-H insertion reactions are possible. Both the catalyst and the solvent system dramatically influenced the outcome of the reaction. Copper was found to be the metal of choice because of its ability to promote oxonium ylide formation over C-H insertion.



Scheme 46

The role of the catalyst has not been fully elucidated but it appears that increasing the electron demand of the catalyst ligands has a beneficial effect in terms of promoting the reaction. It was postulated that the high yield obtained using $Cu(hfacac)_2$ is a consequence of increased stabilisation of the metal-bound ylide intermediate. This would result in the suppression of the reformation of the carbenoid species or in the reduction of the energetic barrier between the metal-bound ylide-species and the transition state of the rearrangement step. Clark and co-workers also studied the stereochemical outcome of the formation of 2,6-tetrahydropyran-3-ones (Scheme 47).[64]

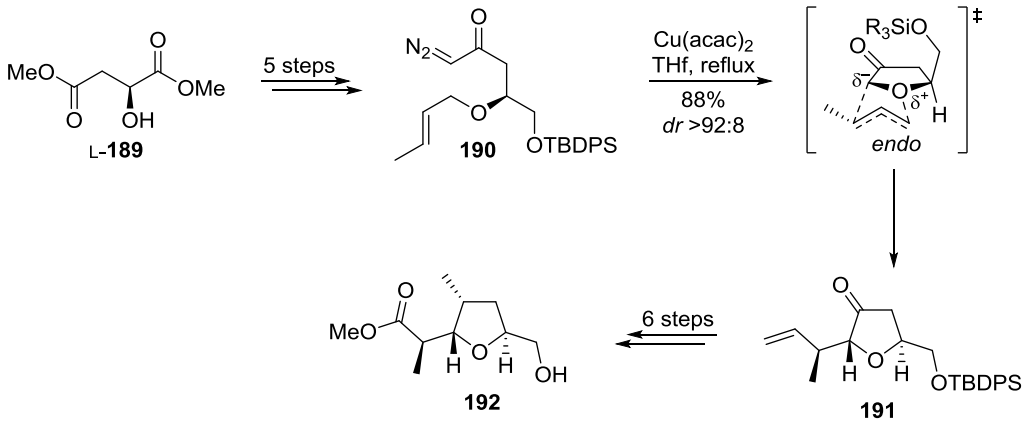


Scheme 47

After extensive optimisation studies, Clark and co-workers found that the best results were obtained treating diazo ketone **186** with $Cu(tfacac)_2$ in CH_2Cl_2 at reflux. Under the optimal conditions, *trans*-2,6-tetrahydropyran-3-ones of type **188** were obtained in moderate yield and with high diastereoselectivity.

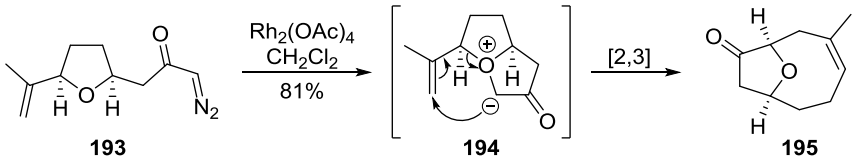
The utility of the [2,3]-sigmatropic rearrangement of oxonium ylide has been demonstrated by Clark and co-workers who have applied this transformation as a key step in the synthesis of several natural products. For example, this methodology was used for the preparation of the A-ring fragment of the gambieric acids **192** (Scheme 48).[65] The synthesis started from commercially

available L-dimethyl malate **189** which was converted in five steps into the pivotal diazo ketone **190**. Diazo ketone **190** underwent tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement upon treatment with $Cu(acac)_2$ in refluxing THF to afford dihydrofuranone **191** in 88% yield and with excellent diastereoselectivity. The stereochemistry of furanone **191** was extablished by X-ray analysis, confirming that [2,3] rearrangement had occurred *via* the *endo* transition state. Ketone **191** was then further elaborated to give the final tetrahydrofuran **192**.



Scheme 48

The tandem oxonium ylide formation/rearrangement strategy can be used for the formation of bicyclic ring systems from suitably fashioned cyclic ethers as demonstrated by Pirrung (Scheme 49).[60]

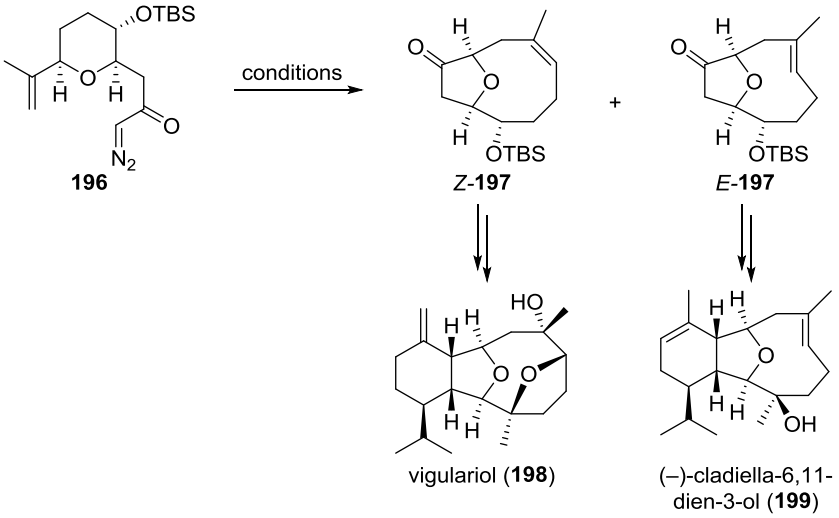


Scheme 49

Recently, Clark and co-workers showed the utility of this ring expansion reaction employing the methodology as pivotal step in the development of an elegant general strategy for the synthesis of the cladiellin family of natural products (Table 3).[66] Extensive screening of solvents, temperature and catalysts, using diazo ketone **196** as substrate, demonstrated that the ratio of *E*/*Z* isomers could be tuned to obtain the desired product. The use of copper complexes bearing electron-withdrawing ligands as catalysts allowed preferential formation of the product featuring the *Z*-alkene functionality. Ketone *Z*-**197** was the key

intermediate employed by Clark and co-workers in their synthesis of vigulariol (**198**).

Table 3

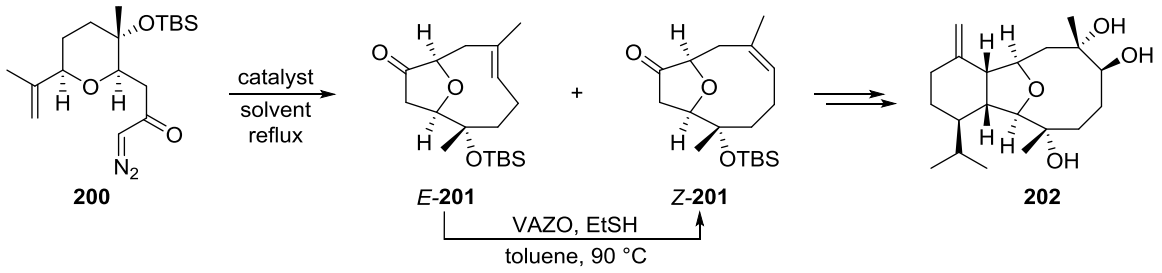


entry	catalyst	solvent	temp.	yield	*Z*:*E*
1	$Cu(hfacac)_2$	CH_2Cl_2	rt	94%	5.9:1
2	$Cu(hfacac)_2$	THF	reflux	74%	6.9:1
3	$Rh_2(tpa)_4$	DCE	reflux	56%	1:6.3

When diazo ketone **196** was treated with $Rh_2(tpa)_4$ in refluxing DCE the bicyclic ketone *E*-**197** was formed preferentially. Ketone *E*-**197** was the common intermediate used to complete the syntheses of (−)-cladiella-6,11-dien-3-ol (**199**) and a further seven members of the cladiellin family of natural products.

In their synthesis of the purported structure of sclerophytin F (**202**), Clark *et al*. explored the metal-mediated cyclization and ring-expanding rearrangement of the α-diazo ketone **200** to give the isomeric bridged bicyclic ethers *E*-**201** and *Z*-**201** (Table 4).[67] In this case, the use of $Cu(hfacac)_2$ to promote the reaction resulted in the formation of the product in excellent yield (98%) but as a 1.8:1 mixture of *Z*:*E* isomers. Rhodium catalysis resulted in preferential or exclusive formation of the bicyclic ether featuring the *Z*-olefin, although in a moderate or low yield. Interestingly, it was possible to isomerize the ketone *E*-**201** to give *Z*-**201** upon exposure to a mixture of VAZO and a sub-stoichiometric amount of ethanethiol in toluene. Bicyclic ketone *Z*-**201** was the key intermediate employed by Clark *et al*. to complete the synthesis of the purported structure of sclerophytin F (**202**).[67]

Table 4



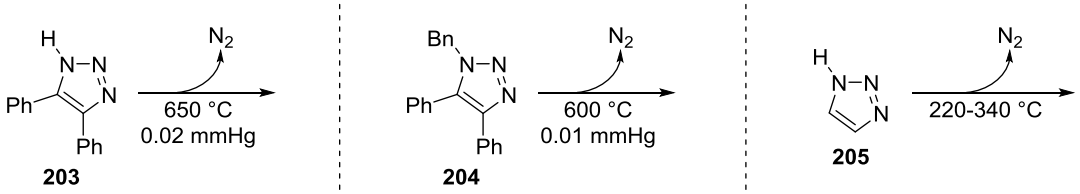
entry	catalyst	solvent	yield	*Z*:*E*
1	$Cu(hfacac)_2$	CH_2Cl_2	98%	1.8:1
2	$Rh_2(OAc)_4$	CH_2Cl_2	42%	7.9:1
3	$Rh_2(tpa)_4$	CH_2Cl_2	14%	>20:1
4	$Rh_2(pfm)_4$	THF	31%	>20:1

These results illustrate the influence of the choice of metal and ligand on the diastereoselectivity of the reaction, and provide evidence to support a pathway that proceeds *via* a metal-associated oxonium ylide intermediate.

1.6.4 1-Sulfonyl-1,2,3-Triazoles as Metal Carbenoid Precursors

The decomposition of diazo compounds using transition metal catalysis to generate metallocarbene intermediates has been exploited in a wide range of synthetically useful transformations.[68] Inspired by the utility of metal carbenoids as reactive intermediates for organic synthesis, the synthetic community has investigated the possibility of employing readily accessible *N*-sulfonyl-1,2,3-triazoles as precursors for the formation of imino metal carbenoid intermediates.[69]

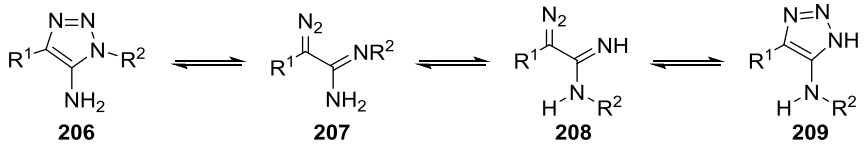
1,2,3-Triazoles are five-membered aromatic heterocycles featuring three adjacent nitrogen atoms and two carbon atoms. The 1,2,3-triazole ring is a very robust and stable structure compared to other nitrogen-rich heterocycles. However, pyrolysis or *vacuum* pyrolysis at higher temperatures leads to loss of molecular nitrogen and decomposition of the triazole unit (Scheme 50).[70,71]



Scheme 50

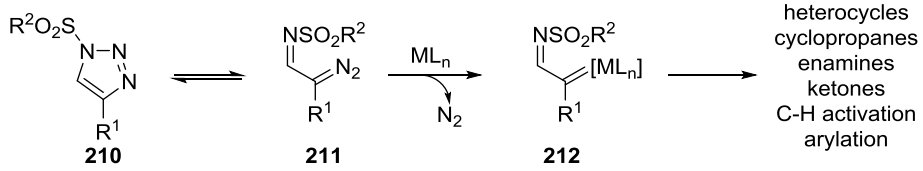
In 2006, Katritzky carried out several experiments to determinate the thermal stability of 1,2,3-triazole (**205**) and showed that it decomposes at temperatures of 220-340 °C.[72]

However, substituents have a large influence on thermal stability and reactivity, and suitably substituted 1,2,3-triazoles have been shown to undergo tautomerisation between the ring-closed and the open chain forms. 5-Amino-1,2,3-triazoles **206** can rearrange to the isomeric triazoles **209** *via* the imino diazo intermediates **207** and **208**: this reaction is the well-known Dimroth rearrangement (Scheme 51).[73]



Scheme 51

The presence of a strongly electron-withdrawing group, such as a sulfonyl group, at the N1 position tends to drive the equilibrium towards the ring-opened imino diazo form.[74] Recently it was demonstrated that the Dimroth-type equilibrium of 1-sulfonyl-1,2,3-triazoles (**210**⇌**211**) can be exploited to generate metal carbenoid species (Scheme 52).



Scheme 52

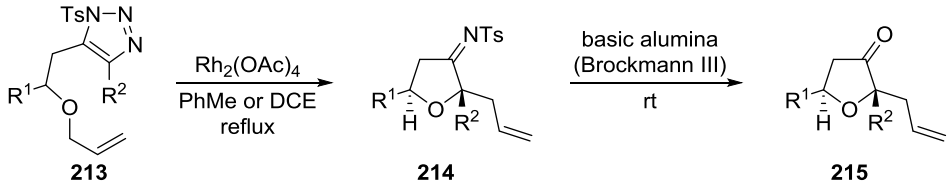
Pioneering work by Gevorgyan and Fokin demonstrated that in the presence of a suitable transition-metal catalyst, 1-sulfonyl-1,2,3-triazoles **210** undergo denitrogenative decomposition generating the reactive imino carbenoid

intermediates **212**.[75] These metallocarbene intermediates then can be used in a wide range of synthetically useful transformations by careful choice of reaction conditions.[69]

As discussed previously, one area in which the use of carbenoids derived from the decomposition of diazo ketones has been extensively exploited is the synthesis of *trans*-2,5-disubstituted dihydrofuran-3-ones, which are particularly attractive targets due to the ubiquitous presence of the tetrahydrofuran motif in natural products and biologically active compounds.[76] The main drawback of this transformation is that diazomethane is usually used in order to prepare the α-diazo ketone from an acid chloride or anhydride, which discourages those without specialist training and equipment from using this reaction.

Inspired by the potential of using triazoles as carbenoid precursors, Boyer reported the rhodium(II)-catalysed transformation of 5- and 4,5-substituted-1-sulfonyl-1,2,3-triazoles **213** into *trans*-dihydrofuran-3-ones **215** (Table 5).[77] Treatment of triazoles **213** with $Rh_2(OAc)_4$ in refluxing toluene or DCE resulted in the stereocontrolled formation of dihydrofuran-3-imines **214**, which were then hydrolysed by stirring in the presence of basic alumina (Brockmann activity III) at rt to give the corresponding ketones **215**.

Table 5



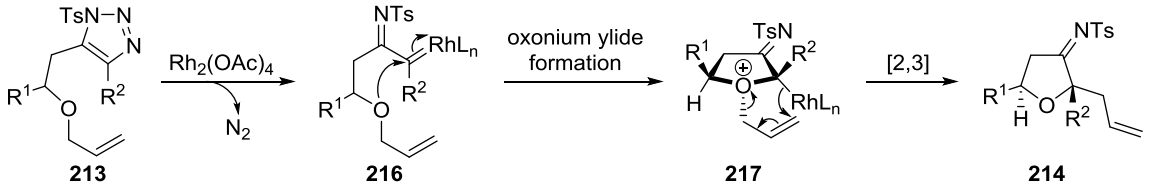
213 **214** **215**

entry	R^1	R^2	yield	*trans*:*cis*
1	Me	H	70%	9:1
2	*i*-Pr	H	83%	>20:1
3	$TBDPSOCH_2$	H	78%	>20:1
4	$TBDPSOCH_2$	Me	62%	>20:1
5	Me_2CH	CH_2CHCH_2	51%	–

This method provided the dihydrofuranones **215** with superior yields and diastereoselectivities than those obtained from the corresponding rhodium(II)-catalysed reactions of α-diazo ketones, and with comparable yields and

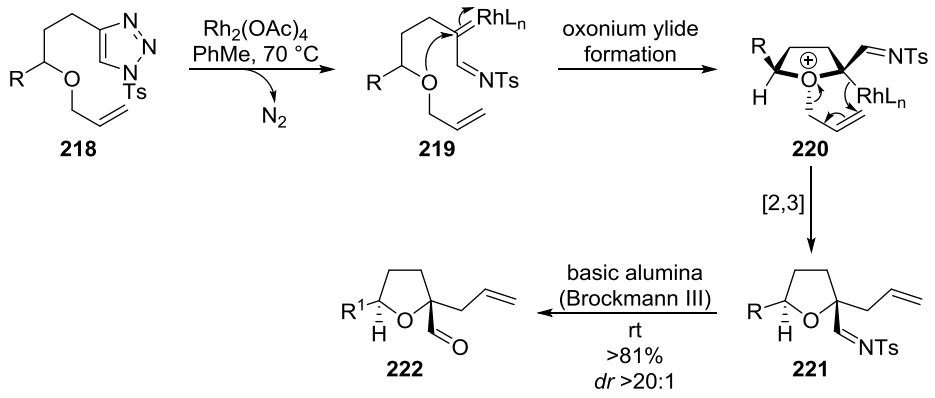
selectivities to those obtained from the copper(II)-catalysed ones (see Table 2). Importantly, this transformation not only provides a simple alternative to the use of α-diazo ketones, it also allows the diastereoselective formation of products with a 2-tetrasubstituted centre when 4,5-disubstituted-1-sulfonyl-1,2,3-triazoles are used as substrates (entries 4, 5). The corresponding reaction with α-diazo ketones derived from higher diazo alkanes has not been reported.

The proposed mechanism for this transformation involves the formation of a rhodium(II) iminocarbenoid intermediate **216** by $Rh_2(OAc)_4$ catalysed denitrogenation of the 1-sulfonyl-1,2,3-triazole **213** (Scheme 53). Selective attack of one of the diastereotopic lone pairs of the ether oxygen onto the metal carbenoid generates the metal-bound oxonium ylide **217**, which undergoes [2,3]-sigmatropic rearrangement to generate dihydrofuran-3-imine **214**.



Scheme 53

Boyer further extended this methodology by developing a complementary reaction for the synthesis of 2-tetrasubstituted tetrahydrofurans **222** from the 1-sulfonyl-1,2,3-triazoles **218** bearing a γ-allyloxy group at the 4-position (Scheme 54).[78] Importantly, it is not possible to employ traditional α-diazo aldehyde starting materials to access these products.[79]



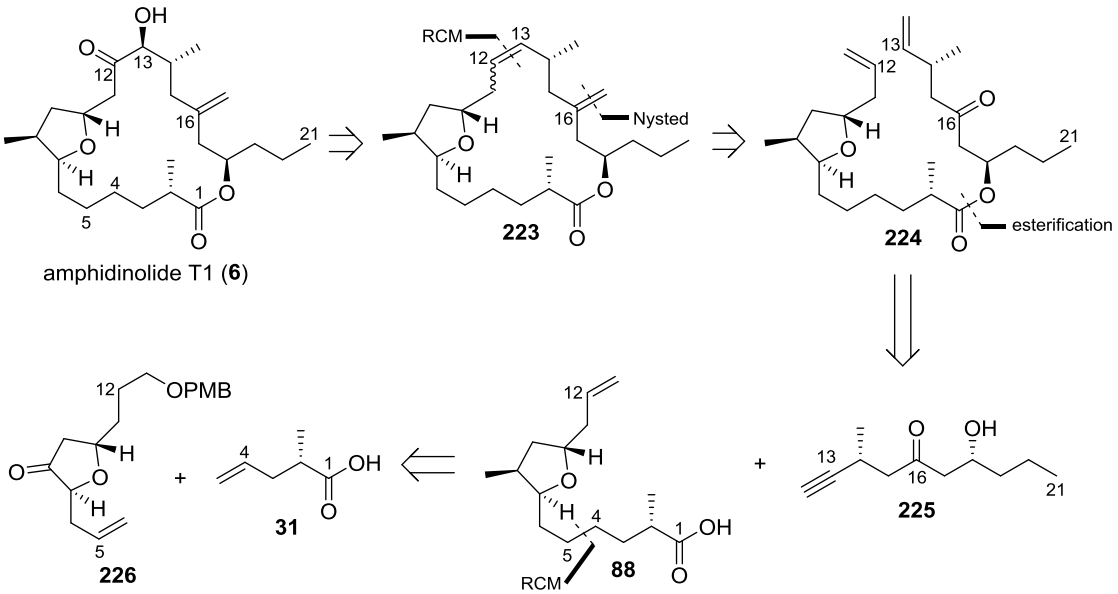
Scheme 54

In this reaction, rhodium(II)-catalysed denitrogenation of sulfonyl triazole **218** generates the carbenoid intermediate **219** and then one of the diastereotopic lone pairs of the ether oxygen attacks the rhodium carbenoid to generate the metal-bound oxonium ylide **220**. The resulting ylide undergoes [2,3]-sigmatropic rearrangement forming tetrahydrofuran **221** bearing a tosyl imino group, which is hydrolysed into the corresponding aldehyde **222** by treatment with basic alumina (Brockmann activity III).

2 Results and Discussion

2.1 Previous Work in the Clark Group towards Amphidinolides T

The aim of the project was to develop a synthetic strategy that would enable amphidinolides T1, T3, T4 and T5 to be prepared from a single common late stage intermediate because of the structural similarity between the amphidinolides T. In the initial approach, the C12/C13 α-hydroxy ketone moiety would be derived from macrocyclic *E*- or *Z*-alkene **223**, which was envisioned as the common precursor for the natural targets (Scheme 55).

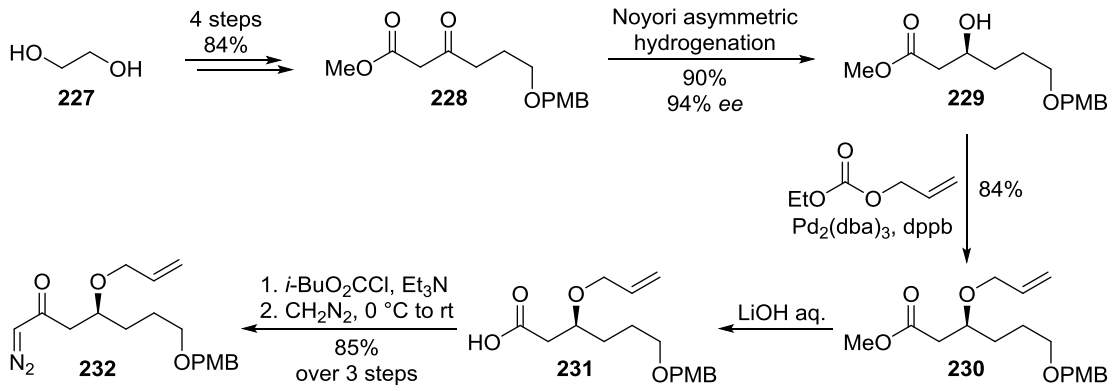


Scheme 55

Disconnection through the C12—C13 double bond by RCM and the *exo*-methylene group revealed intermediate **224**. Subsequent disconnection through the lactone C—O bond of intermediate **224** revealed two main fragments: the carboxylic acid **88** and the alcohol **225**. With regard to the acid fragment **88**, it could be prepared from the known acid **31**, previously used in Fürstner's syntheses of amphidinolides T, and dihydrofuranone **226**. The required 2,5-*trans*-dihydrofuranone **226** could be synthesized using Clark's oxonium ylide rearrangement methodology (Section 1.6.3).[62]

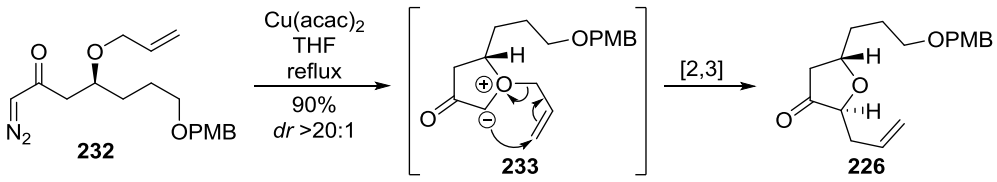
Initially, efforts were focused on the synthesis of the C1-C12 fragment **88**.[80] The synthesis of the fragment commenced with diol **227**, which was converted into the ß-keto ester **228** using a high-yielding 4-step sequence (Scheme 56). Next,

Noyori reduction of the ß-keto ester led to formation of the ß-hydroxy ester **229** in excellent yield and with 94% *ee*.[19] *O*-Allylation proved to be more challenging than expected, and a palladium-catalysed reaction of alcohol **229** with allyl ethyl carbonate was required to perform this transformation. The resulting ester **230** was saponified to deliver the corresponding carboxylic acid **231** and this was converted into the key diazo ketone **232** by mixed anhydride formation and subsequent reaction with diazomethane.



Scheme 56

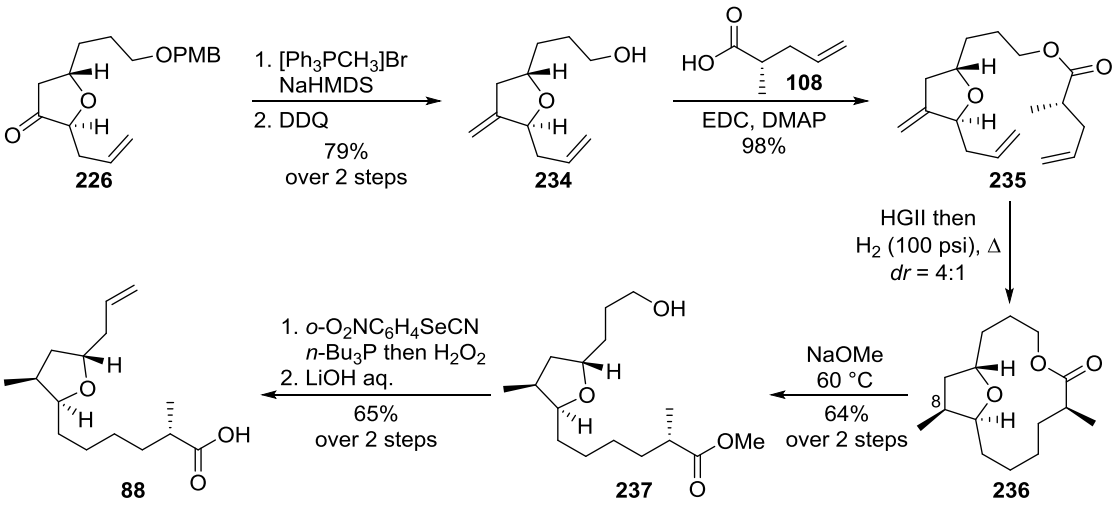
The pivotal diastereoselective THF construction was accomplished by copper catalysed decomposition of diazo ketone **232**, followed by formation and subsequent [2,3]-sigmatropic rearrangement of the putative oxonium ylide **233** (Scheme 57). This transformation provided ketone **226** in high yield and as a single diastereoisomer, showcasing the efficiency of the oxonium ylide rearrangement methodology (Section 1.6.3).[62]



Scheme 57

Methylenation of the ketone **226** followed by cleavage of the PMB group afforded the alcohol **234** (Scheme 58). Coupling of the alcohol **234** with the carboxylic acid **31** was realized by EDC-mediated esterification, affording the desired ester **235** in 98% yield. At this stage, various RCM processes were investigated and the best result was obtained with a one-pot metathesis and

hydrogenation protocol using Hoveyda-Grubbs second generation catalyst.[81] Treatment of the resulting macrolactone **236** with sodium methoxide afforded methyl ester **237** in 64% yield over 2 steps with a 4:1 *dr* at C8 in favour of the desired product. The level of diastereocontrol during hydrogenation was similar to that obtained when macrolactone **236** was prepared using a two-step process in which hydrogenation of the intermediate diene was accomplished using Wilkinson's catalyst.

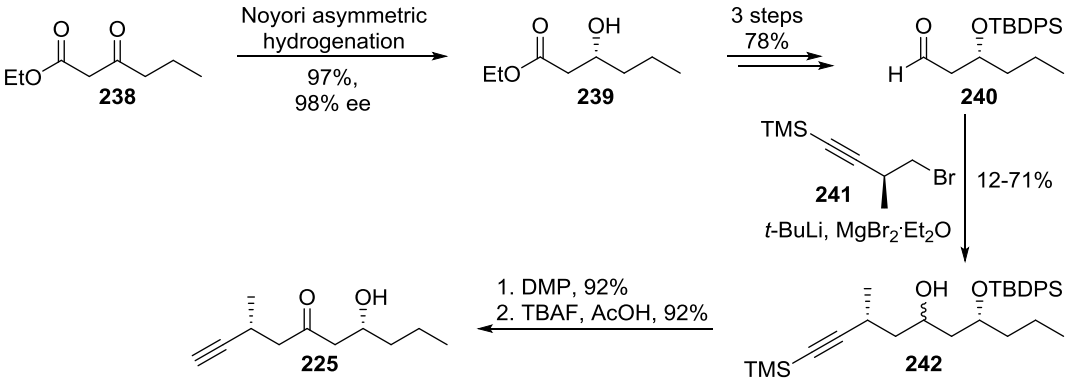


Scheme 58

Conversion of the alcohol **237** into the corresponding selenide under conditions described by Grieco,[82] followed by treatment with hydrogen peroxide resulted in selenoxide formation and elimination. Subsequent ester saponification completed the synthesis of the known carboxylic acid **88**, which is the intermediate used by Dai *et al.* in their syntheses of amphidinolides T.[15]

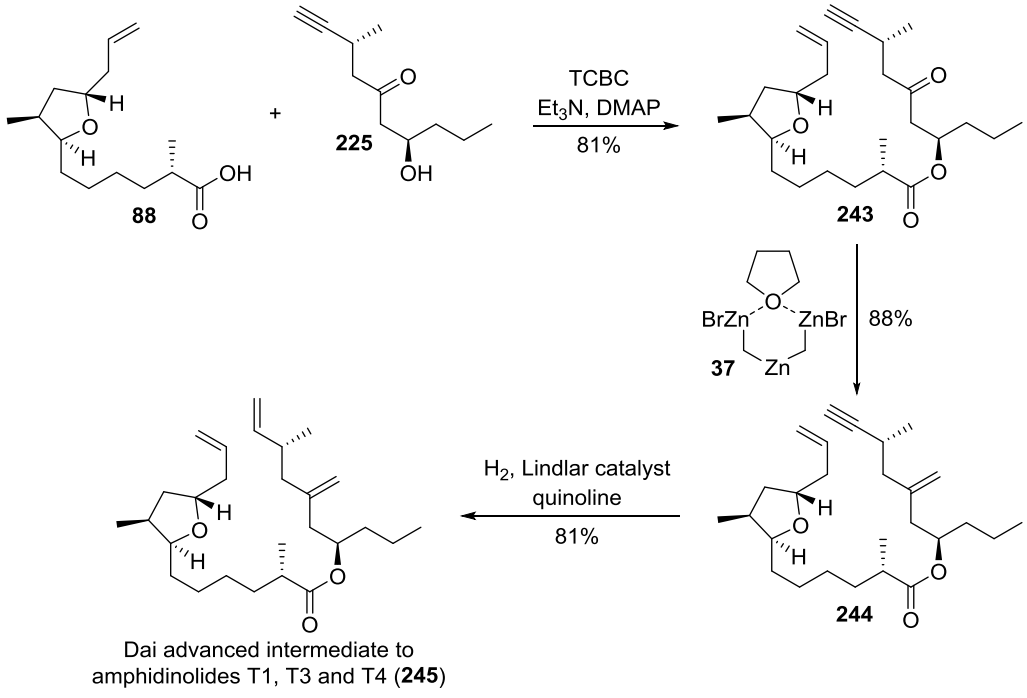
With regard to the hydroxyketone fragment **225**, the aldehyde **240** was prepared from commercially available ethyl 3-oxohexanoate **238** in a high-yielding 4-step sequence using Noyori asymmetric reduction to set the desired stereochemistry (Scheme 59).[19] Subsequent addition of a Grignard reagent, prepared from bromide **241**, to aldehyde **240** proved to be very problematic. After an extensive screening of various reaction conditions, the coupled product **242** was isolated in 71% yield.[80b] The optimised procedure involves a bromine-lithium exchange followed by transmetallation to form the Grignard reagent *in situ*, which is then reacted with aldehyde **240**. Although these reaction conditions allowed the product to be obtained in good yield, this result proved to be

difficult to reproduce and alcohol **242** was formed with yields ranging between 12% and 71%. The synthesis of the alcohol fragment **225** was completed by DMP oxidation and global desilylation.



Scheme 59

Coupling of the alcohol **225** with carboxylic acid **88** was accomplished by esterification under Yamaguchi conditions, delivering the desired product **243** in 81% yield (Scheme 60). Unfortunately, attempts to close the macrocycle by enyne RCM were unsuccessful.



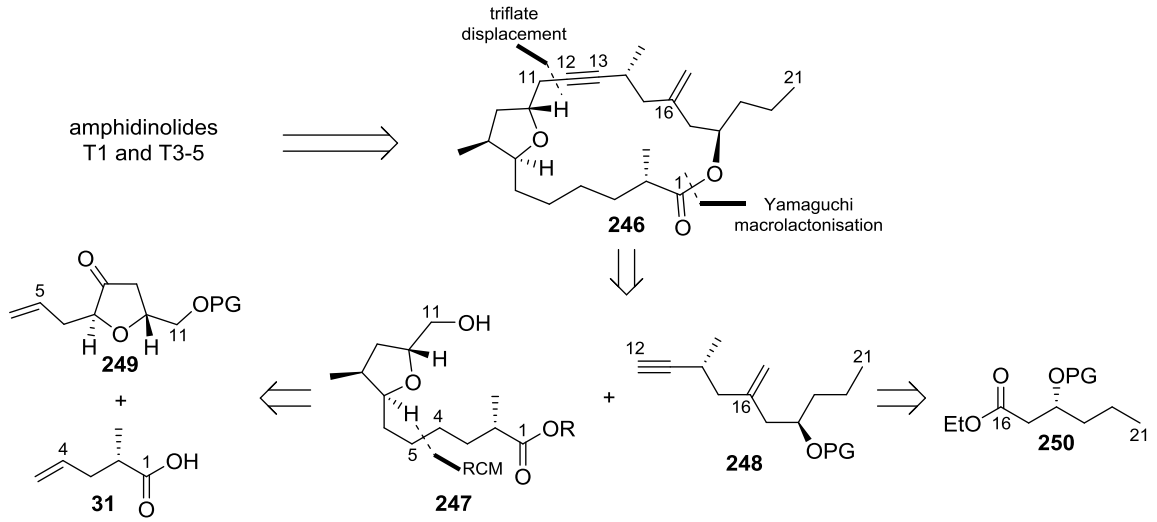
Scheme 60

However, methylenation of the ketone moiety at C16 using Nysted's reagent **37** and subsequent partial reduction of the alkyne under Lindlar conditions intercepted the advance intermediate **245** employed by Dai and co-workers

during their synthesis of amphidinolides T1, T3 and T4.[15b,c] In conclusion, a formal synthesis of these three members of the amphidinolide T family was achieved.

2.2 Evolution of the Strategy towards Amphidinolides T

The main goal of the project remained the total synthesis of amphidinolides T1, T3, T4 and T5 from a single late stage precursor. Macrocyclic alkyne **246** was identified as new common intermediate because the alkyne functionality represented an optimal handle to access the required C12/C13 α-hydroxy ketone moiety typical of the amphidinolide T series (Scheme 61). Disconnection of the lactone C—O bond and the C11—C12 bond in the common intermediate **246** revealed the C1-C11 alcohol fragment **247** and the C12-C21 alkyne fragment **248**. The C1-C11 fragment **247** can be prepared from the known acid **31** and the *trans* 2,5-disubstituted dihydrofuranone **249**, which is readily accessible as a single diastereoisomer by oxonium ylide rearrangement.[22] The C12-C21 fragment **248** can be accessed from the protected ß-hydroxy ester **250**.

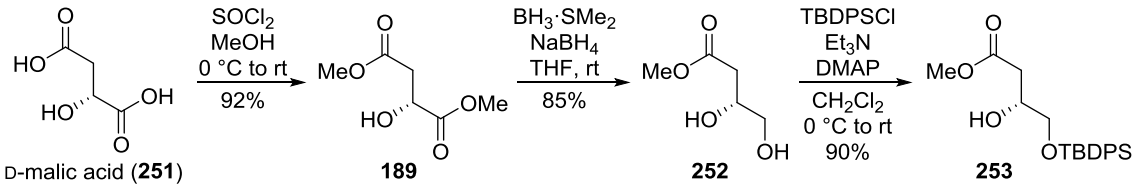


Scheme 61

2.3 Amphidinolides T: Synthesis

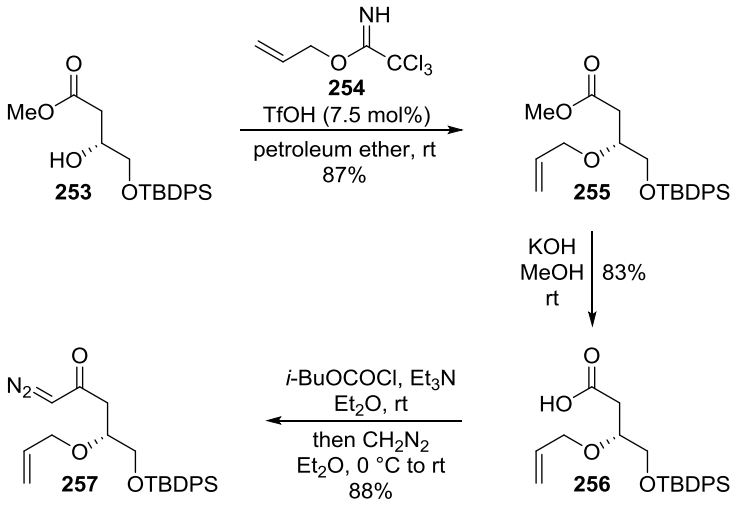
2.3.1 Synthesis of the Tetrahydrofuran Core of Amphidinolides T

The initial efforts were focused on the preparation of the tetrahydrofuran core. The synthesis commenced with readily available alcohol **253**, which can be obtained from D-malic acid **251** in three steps (Scheme 62).[83,84] D-Malic acid **251** was converted into dimethyl D-malate **189** by treatment with thionyl chloride in methanol. Regioselective reduction of dimethyl D-malate **189** by treatment with one equivalent of borane-dimethyl sulfide complex in the presence of a sub-stoichiometric amount of $NaBH_4$ proceeded very efficiently affording the desired diol **252** in 85% yield; neither the triol nor the other possible diol was detected. The regioselectivity of this reaction can be explained by the complexation between borane and the free hydroxyl group, which directs the reduction on the proximal ester functionality. The reduction of esters to alcohols with borane is known to be relatively slow.[85] However, Brown and co-workers showed that the reducing power of borane can be remarkably increased by the presence of a small amount of $NaBH_4$.[86] Selective TBDPS protection of the primary alcohol was achieved by treatment of diol **252** with TBDPSCl, triethylamine and catalytic DMAP to afford alcohol **253** in high yield.



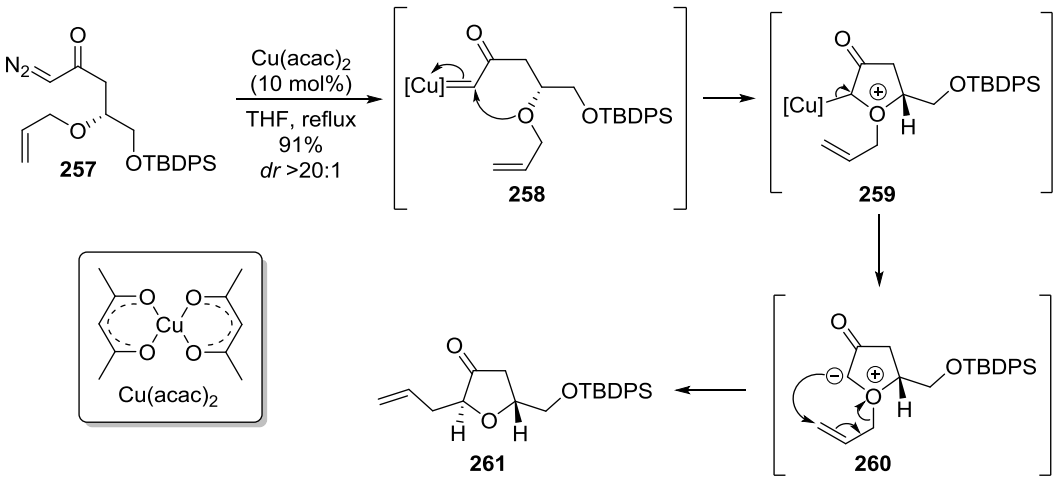
Scheme 62

O-Allylation of the alcohol **253** was performed under acidic conditions to avoid the competitive retro-aldol reaction (Scheme 63). The selected procedure involved the use of allyl trichloroacetimidate **254** as allylating agent in the presence of triflic acid as a catalyst. Under these conditions the ester **255** was obtained in 87% yield. Next, ester **255** was hydrolysed to give the corresponding carboxylic acid **256** by treatment with potassium hydroxide in methanol. The acid **256** was then activated by conversion into a mixed anhydride and this was exposed to a freshly prepared ethereal solution of diazomethane at 0 °C to give key α-diazo ketone **257** in 88% yield.[87]



Scheme 63

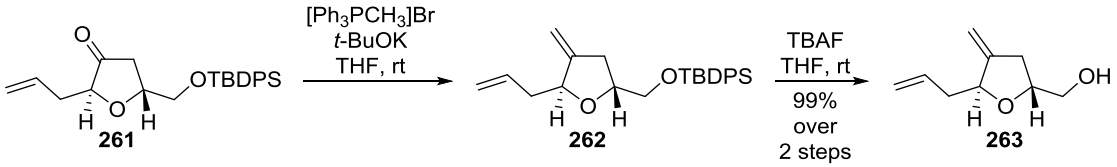
The next step was the formation of the tetrahydrofuran by rearrangement of an oxonium ylide or its metal-bound equivalent (Scheme 64).[62] Treatment of diazo ketone **257** with 10 mol% of copper(II) acetylacetonate in THF at reflux resulted in denitrogenation and formation of the corresponding copper carbenoid **258** followed by formation and subsequent [2,3]-sigmatropic rearrangement of the free oxonium ylide **260** or its metal-bound equivalent **259** (Section 1.2.2). This process afforded the desired product **261** as a single diastereoisomer in 91% yield.



Scheme 64

Methylenation of ketone **261** by treatment with the ylide generated from the reaction of triphenylphosphoniummethyl bromide with potassium *tert*-butoxide and subsequent TBDPS cleavage upon exposure to TBAF provided the desired alcohol **263** in 99% yield over 2 steps (Scheme 65). Purification of the product

262, resulting from the Wittig reaction, required tedious flash chromatography on silica gel. However, simple filtration of the reaction mixture through a short pad of silica in order to remove the triphenylphosphine oxide side-product allowed the product to be obtained with sufficient purity for use in the next step without affecting the efficiency of the process.

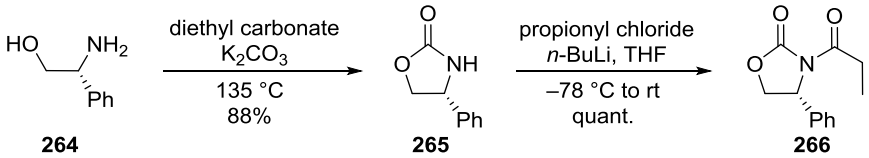


Scheme 65

Using the [2,3]-sigmatropic rearrangement reaction of an oxonium ylide as pivotal step, *trans*-THF fragment **263** was prepared from alcohol **253** in 6 steps with an overall yield of 57%.

2.3.2 Preparation of the C1-C4 Fragment

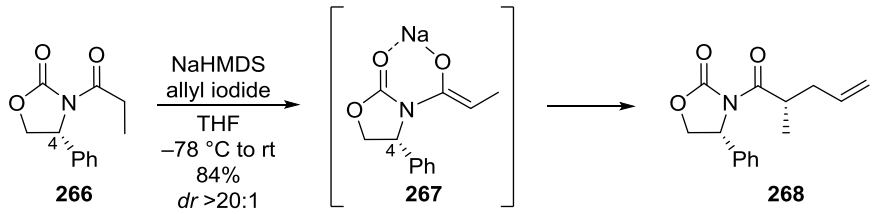
The strategy adopted for the synthesis of the known acid **31** relied on the highly diastereoselective Evans alkylation reaction.[20] The application of Evans' protocol required the preparation of the oxazolidinone chiral auxiliary **265**, which was synthesised by a condensation reaction between the commercially available enantiopure *D*-(−)-α-phenylglycinol (**264**) and diethyl carbonate (Scheme 66).[88] The mixture of reagents was heated neat for 2.5 hours at 135 °C to distil the ethanol formed during the reaction and force the equilibrium in favour of the desired oxazolidinone **265**. Oxazolidinone **265** was then acylated using freshly distilled propionyl chloride after deprotonation with *n*-BuLi to obtain acyl oxazolidinone **266** in quantitative yield.



Scheme 66

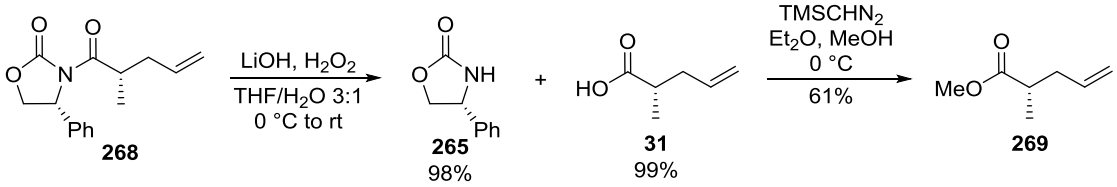
Deprotonation of the acyl oxazolidinone **266** using NaHMDS and subsequent alkylation of the sodium enolate **267** with freshly distilled allyl iodide delivered

the desired diastereoisomer **268** in 84% isolated yield with a *dr* >20:1 (Scheme 67). The stereochemical outcome of the reaction is readily explained by formation of a metal-chelated *Z*-enolate, with C—N bond rotation blocked by the sodium chelation, where diastereoface selection is dictated by the C4-substituent on the oxazolidinone ring, which hinders *si*-face approach of the electrophile.



Scheme 67

The synthesis of the C1-C4 fragment **31** was completed by treatment of **268** with lithium hydroperoxide resulting in hydrolytic cleavage of the chiral auxiliary (Scheme 68). The work-up conditions were optimised to recover oxazolidinone **265**, by washing the organic layer at pH 12, and isolating the carboxylic acid **31** in almost quantitative yield, by acidification until pH 2 and back extraction of the aqueous phase using ethyl acetate. The carboxylic acid **31** could also be converted into the corresponding methyl ester by exposure to $TMSCHN_2$. The modest yield of the ester **269** obtained by using this transformation is mainly due to the product volatility.



Scheme 68

In conclusion, the carboxylic acid **31** was prepared in a highly diastereoselective 4-step sequence and in 73% overall yield. Furthermore, the precious chiral oxazolidinone **265** was recovered almost completely at the end of the sequence.

2.3.3 Completion of the C1-C11 Fragment

The initial plan was to form the C4—C5 bond by a cross metathesis reaction that would guarantee a rapid access to the final C1-C11 fragment.[89] This idea was inspired by a similar process employed by Ghosh and Liu during their synthesis of amphidinolide T1 (Section 1.3.2).[11] This transformation was investigated by screening the three ruthenium-based catalysts that are most commonly employed for olefin metathesis: Grubbs first-generation catalyst (GI), Grubbs second-generation catalyst (GII), and Hoveyda-Grubbs second-generation catalyst (HGII) (Figure 5).

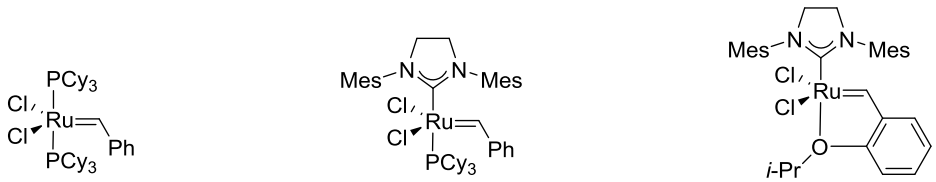
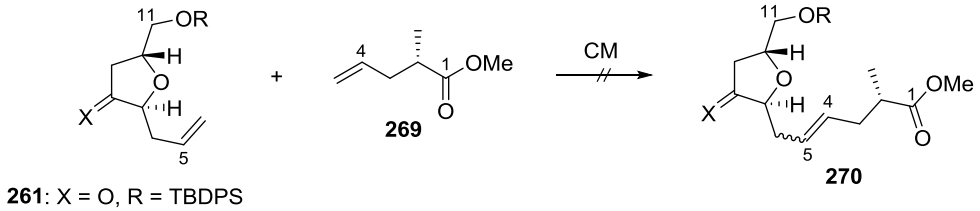


Figure 5

Disappointingly, even though several THF-containing terminal alkene substrates (**261**-**263**) were subjected to the cross-metathesis reaction with ester **269**, the desired product **270** was not observed in any case (Scheme 69). In each case, both of the starting materials were recovered at the end of the reaction along with variable amounts of the homodimer of ester **269**.

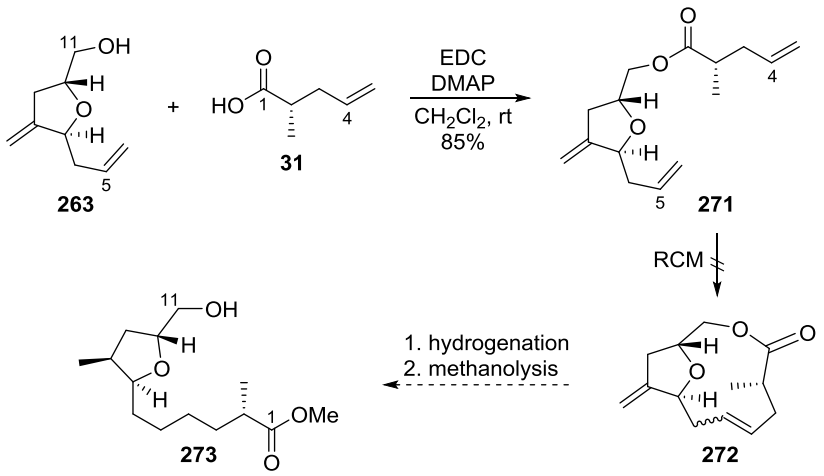


261: X = O, R = TBDPS
262: X = CH_2, R = TBDPS
263: X = CH_2, R = H

Scheme 69

Because of the failure of the cross-metathesis reaction, a different strategy based on the use of the more efficient RCM to form the C4—C5 bond was required. Following this plan, alcohol **263** and carboxylic acid **318** were coupled by EDC-mediated esterification to afford ester **271** in 85% yield (Scheme 70). Subsequent RCM and methanolysis of the resulting macrolactone **272** was expected to complete the synthesis of the C1-C11 fragment **273**. Unfortunately,

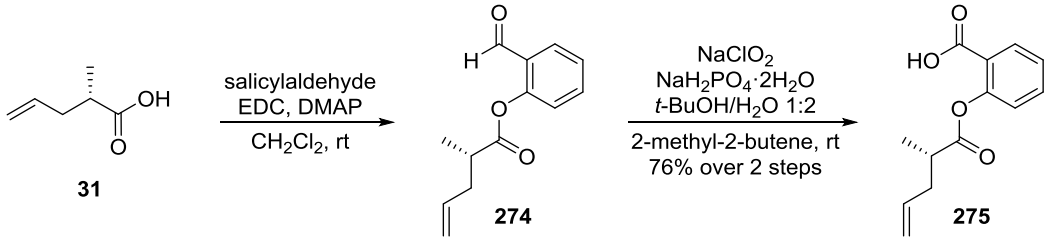
RCM reactions performed on ester **271** using Hoveyda-Grubbs second generation catalyst and Grubbs second generation catalyst were unsuccessful; formation of desired product **272** was not observed and there was almost complete recovery of the starting material.



Scheme 70

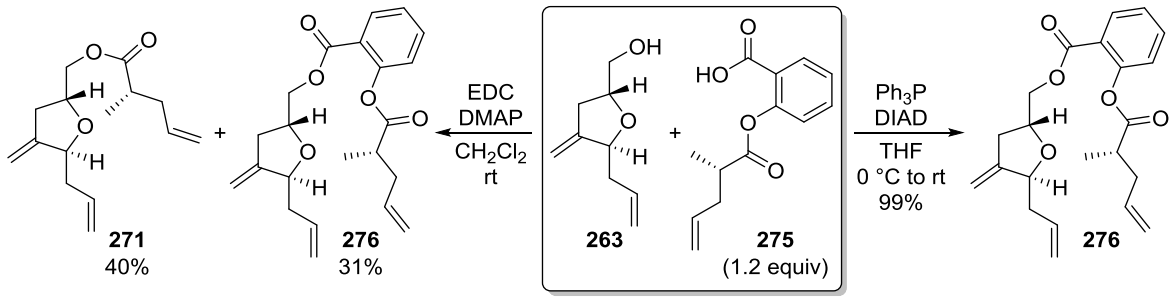
The inherent strain of the 11-membered lactone made it extremely difficult to form macrolactone **272** by RCM. Although there are examples of RCM being used to form 11-membered rings, they generally involve systems in which ring closure is facilitated by conformational bias and they are less common than those that lead to less strained ring systems.[90]

As a consequence of the failure of the RCM reaction of the triene **271**, an alternative synthetic route was explored, in which a spacer would be used to facilitate the RCM process. The spacer system chosen was a salicylic acid for two main reasons. First, the use a salicylic spacer allows the formation of a less strained 15-membered ring system. Second, the flat phenyl group of salicylic acid and the conformational rigidity it confers should have a beneficial effect on the efficiency of the RCM process. With this plan in mind, the carboxylic acid **31** was coupled with salicylaldehyde by EDC-mediated esterification (Scheme 71). Subsequent Pinnick oxidation of the resulting crude aldehyde **274** afforded carboxylic acid **275** in 76% yield over 2 steps.



Scheme 71

Attempted coupling of the alcohol **263** to the acid **275** by EDC-mediated esterification resulted in the formation of the desired product **276** in only 31% yield with concomitant formation of transesterification product **271** in 40% yield (Scheme 72).

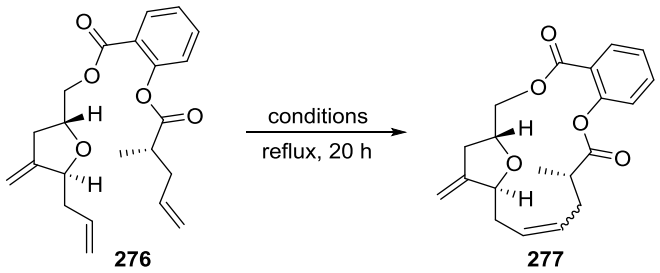


Scheme 72

The coupling of the fragments was accomplished instead by employing a Mitsunobu reaction[91] in which the role of the two coupling partners is reversed. The Mitsunobu reaction was very successful; the first attempt was performed using 2.0 equiv. of acid **275** and resulted in the formation of the desired diester **276** in 99% yield. The amount of carboxylic acid **275** used was successively reduced to 1.2 equiv. without affecting the yield.

The crucial next step was the formation of the macrocycle **277** from triene **276** by ring closing metathesis (Table 6). Pleasingly, the first attempt to perform RCM using 20 mol% of Grubbs second generation catalyst in DCE at reflux provided the desired diene **277** in 94% yield showcasing the success of the spacer strategy (Table 6, entry 1). This represents the first example of the use of salicylic acid as spacer in order to improve the efficiency of an RCM process. The RCM reaction was optimised by screening various catalysts and reaction conditions.

Table 6



276 277

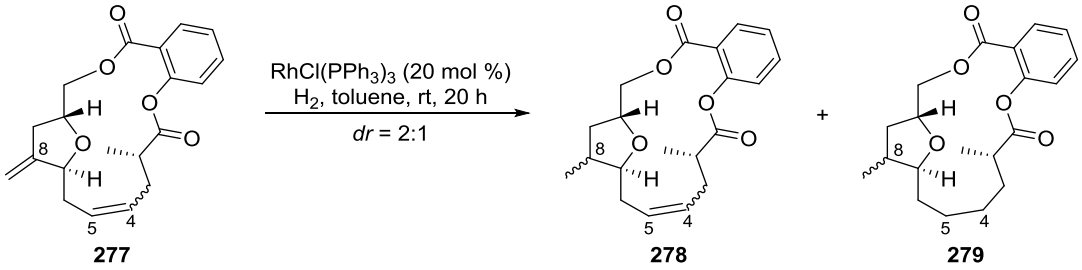
entry	catalyst	equiv. of catalyst[a]	solvent	**276**	**277**	*E*:*Z*
1	GII	0.20	DCE	–	94%	1:1
2	HGII	0.20	DCE	–	83%	1:1
3	GI	0.20	DCE	–	88%	3:1
4	GII	0.15	DCE	–	94%	1:1
5	GII	0.12	DCE	–	91%	1:1
6	GII	0.10	DCE	14%[b]	81%[b]	1:1
7	GII	0.12	CH_2Cl_2	–	96%	1.2:1
8	GI	0.12	CH_2Cl_2	30%[b]	63%[b]	3:1

[a] In all cases, the catalyst was added in four equal portions at 2 hour intervals

[b] the yield is approximate because **276** and *Z*-**277** were not separable by flash chromatography

Initial screening experiments were performed using 20 mol% of catalyst and revealed that the Grubbs second generation catalyst was the best to promote this transformation (entries 1-3), thus further optimisation studies where carried out with this catalyst. The catalyst loading could be reduced to 12 mol% without affecting the yield (entry 5). However, when only 10 mol% of GII was used the reaction did not go to completion (entry 6) and prolonging the reaction time was not beneficial. The best result was obtained when triene **276** was treated with 12 mol % of GII in CH_2Cl_2 at reflux. Under these conditions the desired product **277** was isolated in 96% yield as an inconsequential 1.2:1 mixture of *E* and *Z* isomers (entry 7). When the reaction was performed in the presence of 12 mol % of the less expensive GI, product **277** was obtained in 63% yield and 30% of starting triene **276** was recovered. As expected, the methylene group of the THF ring was unaffected by the RCM process because 1,1-disubstituted alkenes are considerably less reactive than terminal alkenes towards the ruthenium catalysts.[89]

With diene **277** in hand, the next challenge was to hydrogenate both alkenes simultaneously, installing the desired stereochemistry at C8. The first attempt was performed using Wilkinson's catalyst following the procedure used in previous studies in our group (Scheme 73).[80b] Unfortunately, the macrocycle **277** proved to be an unsuitable substrate for Wilkinson hydrogenation. Indeed, when diene **277** was treated with 20 mol% of Wilkinson's catalyst under atmosphere of hydrogen in toluene at room temperature for 20 h a 1:1 mixture of the desired product **279** and the monoreduced product **278** was obtained, as determined by ^{1}H NMR analysis of the crude mixture.



Scheme 73

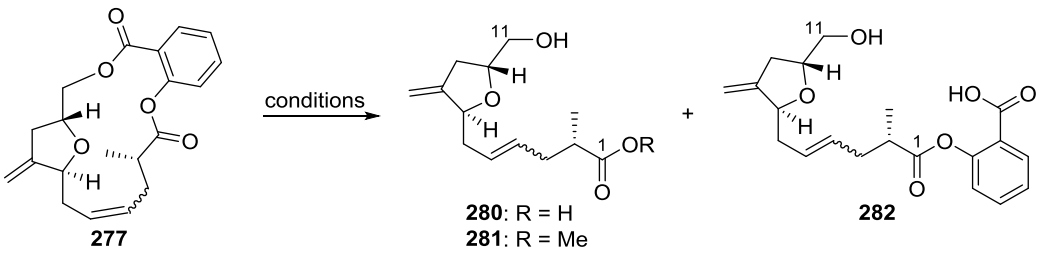
The major drawback of this hydrogenation reaction was the fact that the *dr* of both products **278** and **279**, with respect to the absolute configuration of the stereocentre at C8, was only 2:1 as determined by ^{1}H NMR. No further studies were carried out to establish definitively the configuration of the major product due to the unsatisfactory diastereoselectivity of the reaction.

An alternative method was proposed in order to set the correct stereochemistry at C8. The new strategy involved the cleavage of the spacer group that had been used to facilitate the RCM process by basic hydrolysis followed by directed hydrogenation of the exocyclic alkene using Crabtree's catalyst.[92]

The removal of the spacer proved to be more challenging than expected. The initial plan was to hydrolyse both of the ester groups present in diene **277** to obtain the resulting acid **280** (Table 7). Disappointingly, various conditions were explored in attempts to obtain the carboxylic acid **280**, but none of them proved to be effective. The major problem encountered during this reaction was the formation of half-hydrolysed product **282** when LiOH, LiOOH or TMSOK were used (entries 1-4). Furthermore, attempts to convert this compound into the carboxylic acid **280** or the methyl ester **281** were unsuccessful. Treatment of

macrocycle **277** with potassium hydroxide in a 3:2 mixture of MeOH and THF resulted in the formation of methyl ester **281** in 80% yield, along with a small amount of carboxylic acid **280** (entry 5). Surprisingly, when KOH was used in pure THF, only decomposition of the starting material was observed (entry 6). Fortunately, treatment of macrocycle **277** with potassium hydroxide in methanol at room temperature afforded selectively methyl ester **281** in 95% yield (entry 7). This compound later proved to be an excellent substrate for the Crabtree hydrogenation reaction and so it was to be an important intermediate in the synthesis.

Table 7

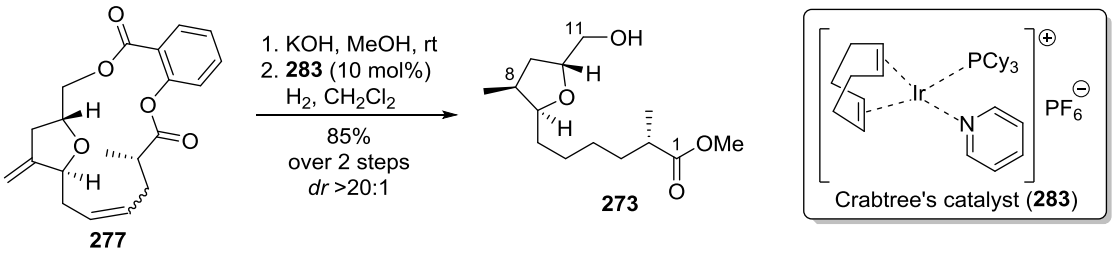


entry	base	equiv. of base	temp.	solvent	**280**	**281**	**282**
1	LiOH	20.0	rt	MeOH/THF 3:2	–	–	86%
2	LiOH	40.0	rt	MeOH/THF 3:2	30%	–	60%
3	LiOOH	2.0	0 °C to rt	THF/H_2O 3:1	–	–	73%
4	TMSOK	2.5	rt	THF	30%	–	50%
5	KOH	2.0	rt	MeOH/THF 3:2	12%	80%	–
6	KOH	2.0	rt	THF	nd[a]	nd[a]	nd[a]
7	KOH	2.0	rt	MeOH	–	95%	–

[a] After complete consumption of the starting material only decomposition was observed

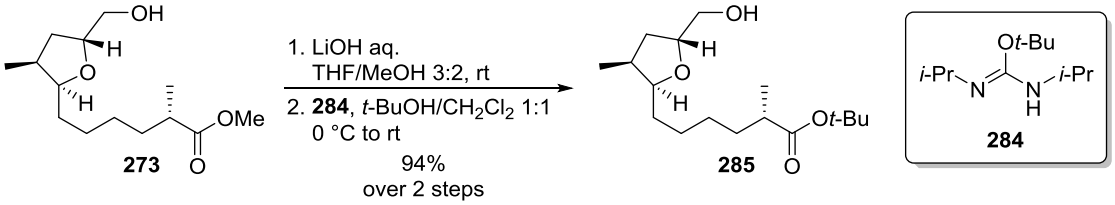
The expectation was to use Crabtree's catalyst **283** in order exploit the directing effect due to a coordination of the C11 hydroxyl group with the iridium centre of the catalyst and so direct the hydrogenation reaction to the desired face. Pleasingly, hydrogenation of the crude methyl ester **281** in the presence of Crabtree's catalyst **283** afforded the desired C1-C11 fragment **273** in 85% yield over two steps and as a single diastereoisomer (Scheme 74). The absolute configuration at C8 was established by ^{1}H-^{1}H NOESY experiment. Thus, the C1-

C11 fragment **273** was prepared efficiently from alcohol **253** in 10 steps and 46% overall yield.



Scheme 74

Considering that the plan was to assemble the two main fragments by displacement of the triflate derived from the alcohol at C11 with an alkynyl lithium species, an analogous C1-C11 fragment was prepared featuring a *tert*-butyl ester (Scheme 75). The more bulky *tert*-butyl group was chosen in order to protect the ester group from the nucleophilic attack. Preparation of the *tert*-butyl ester **285** was achieved by hydrolysis of the methyl ester **273** by treatment with lithium hydroxide, followed by esterification.



Scheme 75

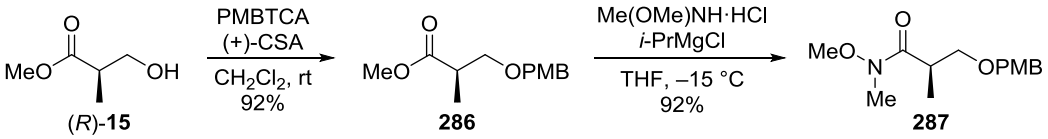
Of the conditions investigated for the formation of the *tert*-butyl ester **285** the use of *N*,*N*'-diisopropyl-*O*-*tert*-butylisourea **284** delivered the best results. Using this procedure, the ester **285** was obtained in 94% yield over two steps.

2.3.4 Preparation of the C12-C21 Fragment

Following the synthesis of the C1-C11 fragment, efforts were then focused on the preparation of the C12-C21 fragment.

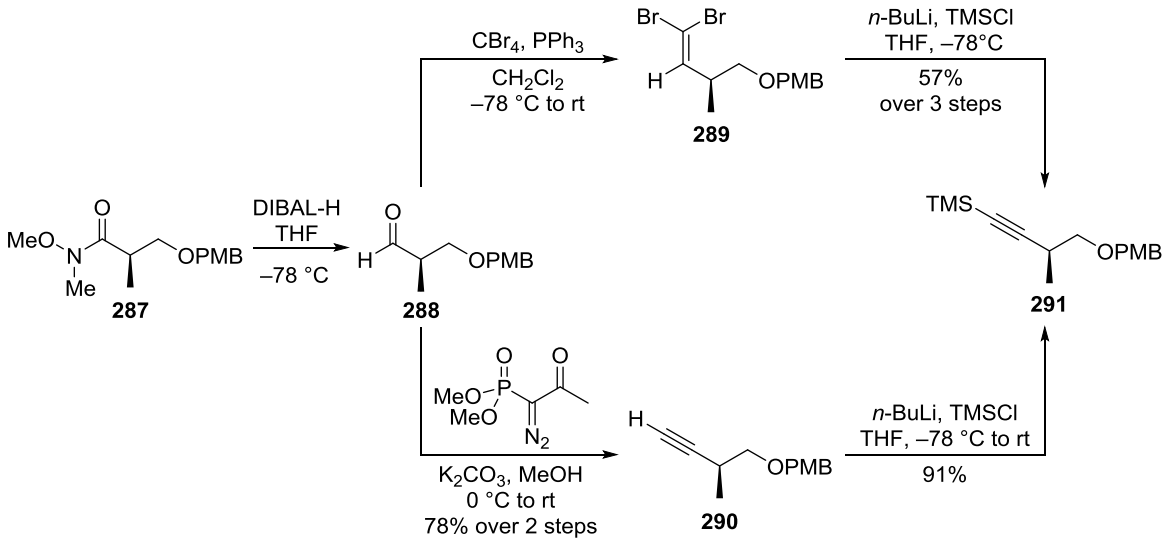
2.3.4.1 First-Generation Synthesis

The initial plan was to improve and optimise a route previously developed in our group (Section 2.1).[80b] The synthesis of the C12-C21 fragment commenced from the commercially available (*R*)-Roche ester (**15**) as a chiral starting material, which was converted into the corresponding PMB-ether **286** upon exposure to PMBTCA in the presence of a catalytic amount of (+)-CSA (Scheme 76). Subsequently, treatment of ester **286** with *N,O*-dimethylhydroxylamine hydrochloride in the presence of isopropyl magnesium chloride as base furnished the Weinreb amide **287** in 92% yield.



Scheme 76

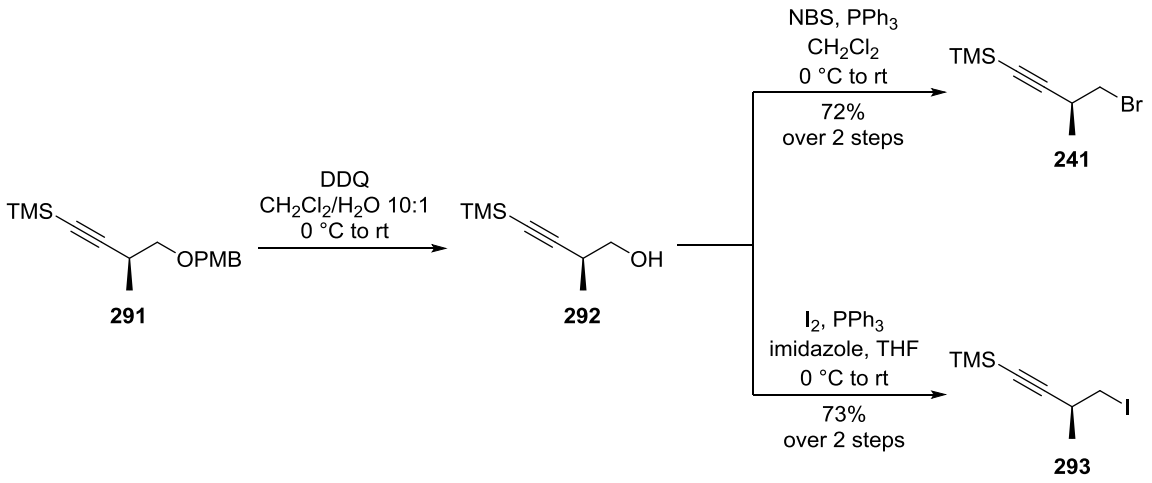
The Weinreb amide **287** was then converted into the alkyne **291** *via* the corresponding aldehyde **288** in two possible ways: use of the Corey-Fuchs[93] or the Bestmann-Ohira[94] protocol, with subsequent TMS protection of the terminal alkyne **290** in the latter case (Scheme 77).



Scheme 77

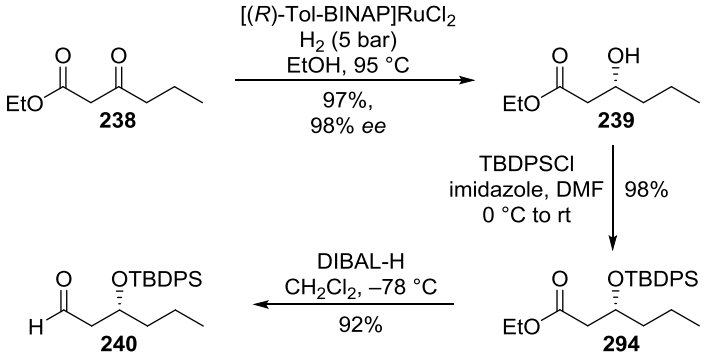
Use of the Corey-Fuchs reaction delivered the TMS-alkyne **291** in 57% yield over 3 steps, but the reaction proved to be difficult to reproduce on large scale, with yields ranging from 15% to 57%. The Bestmann-Ohira route afforded the product **291** in 71% yield over three steps in a more reproducible way. Thus, the Bestmann-Ohira protocol was the preferred synthetic pathway.

Alkyne **291** was converted into the bromide **241** or the iodide **293** ready for coupling with the segment constituting the C12-C21 fragment (Scheme 78). Oxidative cleavage of the PMB protecting group followed by treatment of the resulting primary alcohol **292** with freshly recrystallized NBS and triphenylphosphine provided the bromide **241** in 72% yield over two steps. The primary alcohol **292** could be also converted into the corresponding iodide upon exposure to iodine in the presence of triphenylphosphine and imidazole. This procedure delivered the iodide **293** in 73% yield over 2 steps.



Scheme 78

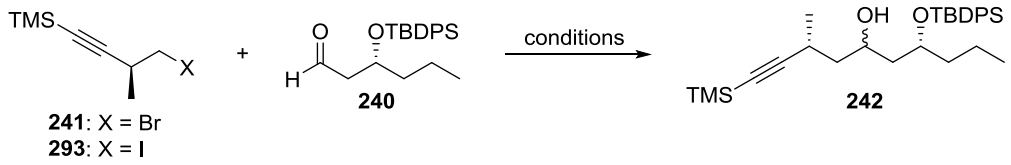
The coupling partner, aldehyde **240**, was synthesised from the commercially available ethyl 3-oxohexanoate **238** (Scheme 79). Noyori asymmetric reduction of ß-keto ester **238** afforded alcohol **239** in 97% yield and with 98% ee.[19] TBDPS protection followed by reduction of the ester functionality using DIBAL-H delivered aldehyde **240** in excellent yield. Selective reduction of the ester **294** to afford the aldehyde **240**, without prior conversion into the corresponding Weinreb amide, allowed the length of the synthetic sequence to be reduced and the overall yield to be improved.



Scheme 79

The next step was the challenging coupling reaction between the aldehyde **240** and the bromide **241** or iodide **293**. Initially, conditions that had delivered the product in good yield during previous work carried out in the group were tested (Table 8, entry 1).[80b] This procedure involves bromine-lithium exchange and subsequent transmetallation to form the Grignard reagent *in situ*, which then reacts with the aldehyde. Under these conditions, the coupled product **242** was isolated in 71% yield, but the reaction still remained capricious and yields ranged from 12% to 71%.

Table 8



entry	X	reagents	solvent	temp.	**242**	**240**	other
1	Br	*t*-BuLi, $MgBr_2 \cdot OEt_2$	Et_2O	−78 °C to rt	71%	–	–
2	Br	*t*-BuLi	THF	−78 °C to rt	8%	45%	a
3	I	*t*-BuLi	Et_2O	−78 °C to rt	3%	43%	a
4	Br	Mg, LiCl	Et_2O	0 °C to rt	–	32%	b
5	Br	SmI_2, NiI_2	THF	0 °C to rt	–	40%	c
6	I	SmI_2, NiI_2	THF	0 °C to rt	–	36%	c

a = elimination

b = Würtz coupling

c = decomposition

Several other reaction conditions that had not been explored previously were investigated, but unfortunately they were unsuccessful and resulted in the

formation of various by-products (Figure 6). The use of *t*-BuLi without addidion of $MgBr_2 \cdot OEt_2$ afforded only traces of the desired product **242**; furthermore, deprotonation at the α-position of the aldehyde and partial elimination of the protected hydroxyl group to produce the corresponding α,ß-unsaturated aldehyde occurred (entries 2,3). When the Grignard reagent was formed by treatment of the bromide **241** with magnesium turning in the presence of lithium chloride, only the Würtz coupling product was obtained and aldehyde **240** was partially recovered (entry 4). The use of SmI_2 in the presence of a catalytic amount of NiI_2 resulted mainly in decomposition (entries 5,6).

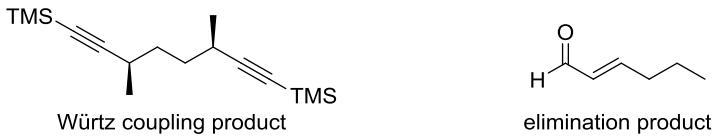


Figure 6

In order to circumvent reliability problems encountered during the Grignard reaction, a new synthetic route toward the C12-C21 fragment was explored.

2.3.4.2 Second-Generation Synthesis

The key features of the new approach are the installation of the 1,1-disubtituted olefin at C16 in the early stage of the synthesis using a Peterson olefination reaction and the employment of an Evans alkylation reaction[20] to set the methyl at C14 with the desired stereochemistry (Figure 7).

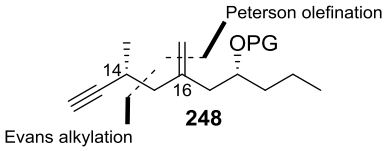
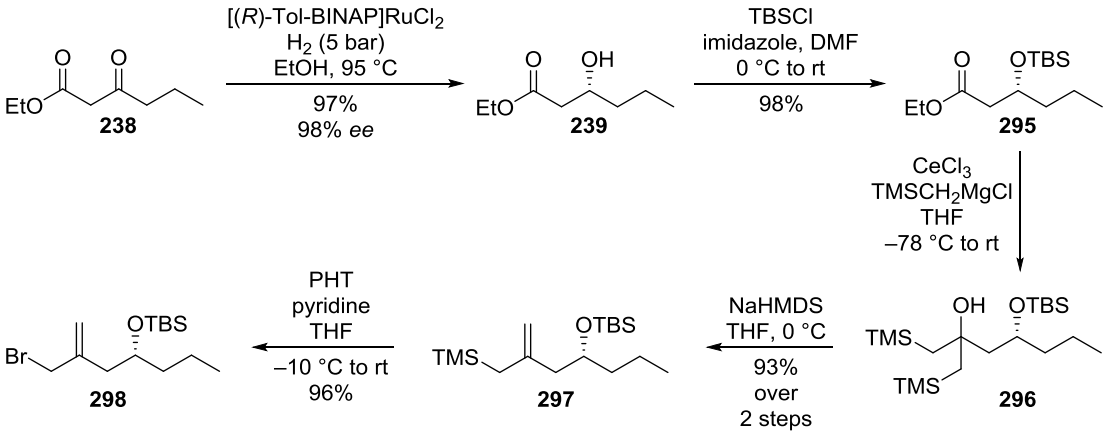


Figure 7

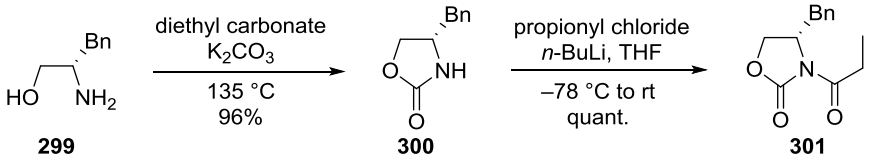
The second generation synthesis of the C12-C21 fragment commenced, as previously, with Noyori asymmetric reduction of ethyl 3-oxohexanoate **238** to give the ß-hydroxy ester **239**, which was then TBS protected under standard conditions to afford silyl ether **295** (Scheme 80). Treatment of the ester **295** with 3 equivalents of the organocerium reagent generated by reaction of trimethylsilylmethylmagnesium chloride with anhydrous cerium(III) chloride[95]

resulted in double Grignard addition.[96] Workup and exposure of the crude tertiary alcohol **296** to NaHMDS facilitated Peterson elimination and delivered the allylic silane **297** in excellent yield.[97] Reaction of the allylic silane **297** with pyrrolidone hydrotribromide (PHT) in THF, with careful control of the temperature, then delivered the required allylic bromide **298**.[98]



Scheme 80

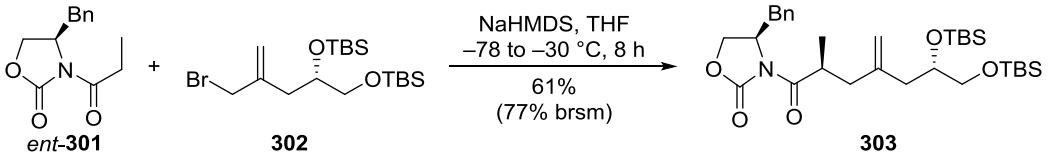
The allylic bromide **298** was then employed in an Evans alkylation reaction.[20] The application of the Evans protocol required the preparation of the oxazolidinone chiral auxiliary **300**, which was synthesised by a condensation reaction between the commercially available enantiopure *L*-(−)-phenylalaninol (**299**) and diethyl carbonate (Scheme 81).[88] After recrystallization, the chiral oxazolidinone was obtained in 96% yield and the measured specific rotation was in agreement to that reported in literature.



Scheme 81

The oxazolidinone **300** was then acylated using freshly distilled propionyl chloride after deprotonation with *n*-butyllithium. Trituration of the product in petroleum ether delivered the acyl oxazolidinone **301** in quantitative yield.

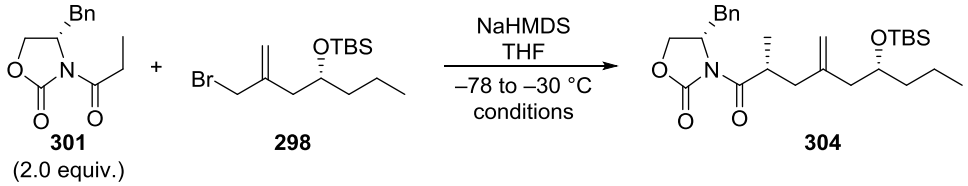
The choice of this particular Evans alkylation reaction was inspired by a similar example reported by Mulzer *et al.* (Scheme 82).[99] In this case, the electrophile was similar to the allylic bromide **298** but incomplete reaction with the enolate was observered.



Scheme 82

The reaction of the enolate **301** with the allylic bromide **298** reaction proved to be even more challenging than expected and various conditions had to be screened in order to obtain the product in good yield and with high diastereoselectivity (Table 9).

Table 9

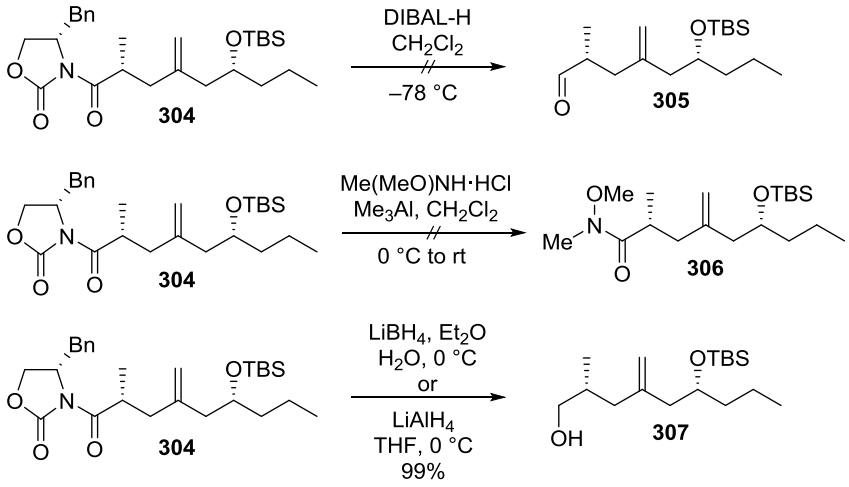


entry	time	additive	conversion	*dr*	yield desired isomer
1	8 h	–	36%	15:1	24%
2	18 h	–	53%	15:1	39%
3	18 h	HMPA	100%	3:1	61%
4	18 h	TBAI	79%	15:1	60%

Applying exactly the same conditions reported by Mulzer *et al.* resulted in poor conversion and the desired product was isolated in only 24% yield (entry 1). Prolonging the reaction time resulted in an improvement in the level of conversion, but the desired product was still obtained in a poor yield (entry 2). In order to improve the efficiency of this transformation the effect of various additives was investigated. Addition of freshly distilled HMPA to the reaction mixture, immediately after addition of the allylic bromide **298**, resulted in a dramatic improvement in the level of conversion and the yield, but there was a drop in the diastereoselectivity of the reaction (entry 3). Among the various

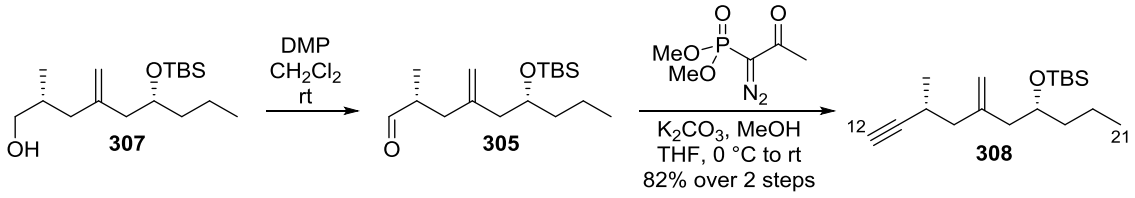
reaction conditions investigated, the best result was obtained employing TBAI as additive (entry 4). Under these conditions, 79% conversion was observed and the product was obtained with 15:1 *dr*. The two diastereoisomers could be separated by careful column chromatography and this allowed the isolation of the desired isomer **260** in 60% yield (76% brsm), which is comparable to the results reported by Mulzer and co-workers.

The next step involved the cleavage of the chiral Evans auxiliary (Scheme 83). Attempting to cleave the chiral auxiliary using DIBAL-H to obtain the desired aldehyde **305** resulted in mainly decomposition along with a by-product which was consistent with the opening of the oxazolidinone ring. Decomposition was observed when the combination of Me(MeO)NH·HCl and Me_3Al was used in an attempt to convert oxazolidinone **304** into the corresponding Weinreb amide **306**. Pleasingly, cleavage of the Evans auxiliary using either $LiBH_4$ or $LiAlH_4$ delivered alcohol **307** in almost quantitative yield.



Scheme 83

To complete the C12-C21 fragment, the alcohol **307** was oxidised to give the aldehyde **305**, which was converted to the corresponding terminal alkyne **308** using the Bestmann-Ohira reagent in 82% yield over 2 steps (Scheme 84).[94]



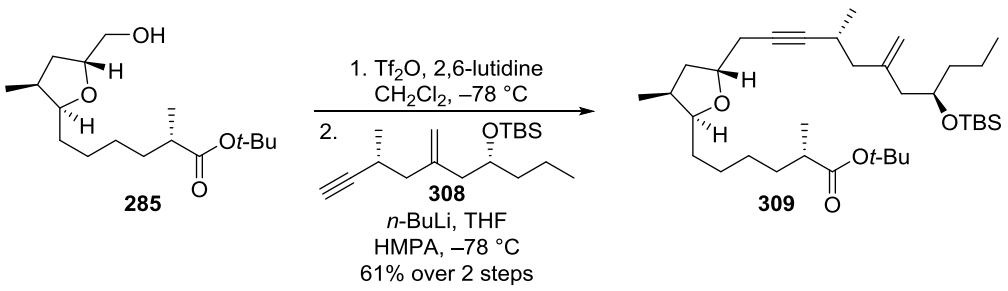
Scheme 84

The C12-C21 fragment **308** was prepared in 9 steps with an overall yield of 41% using the synthetic route described above. Furthermore, the reaction sequence was performed on multigram scale without loss of efficiency. Following the synthesis of both fragments, efforts were then focused on the coupling of the fragments and the preparation of the common late stage intermediate.

2.3.5 Fragment Coupling and Macrocyclisation

Initially, coupling of the two main fragments and preparation of the common late-stage intermediate was investigated employing the *tert*-butyl ester of the C1-C11 fragment **285**. The ability of the bulky *tert*-butyl group to protect the ester functionality from the attack by nucleophile was the reason behind this choice.

Coupling of the two fragments involved the conversion of the alcohol functionality present in the *tert*-butyl ester **285** into the corresponding triflate. Subsequent triflate displacement by the lithium acetylide species generated from C12-C21 fragment **308** would deliver the alkyne **309** (Scheme 85).

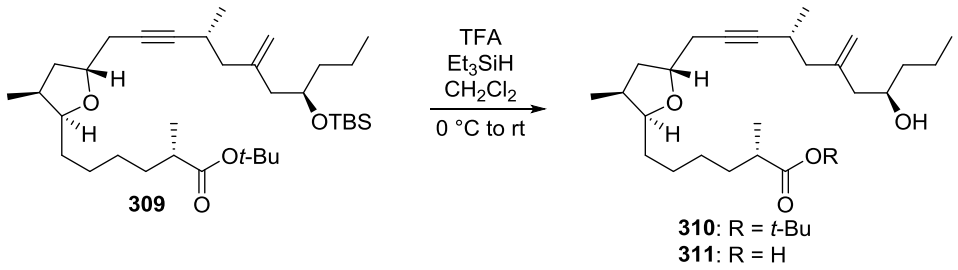


Scheme 85

The conversion of alcohol **285** into the corresponding triflate proceeded smoothly upon treatment with Tf_2O and 2,6-lutidine. The resulting triflate proved to be prone to decomposition and had to be used immediately after rapid purification by filtration on a short pad of silica gel. The subsequent coupling reaction required 2 equivalents of alkyne **308** and the use of HMPA as additive in order to obtain the desired product **309** in good yield. The use of the *tert*-butyl ester motif within **285** successfully prevented the attack by the acetylide anion derived from alkyne **308** despite the use of 2 equivalents of acetylide. However,

it transpired that the *tert*-butyl ester functionality was incompatible with subsequent transformations.

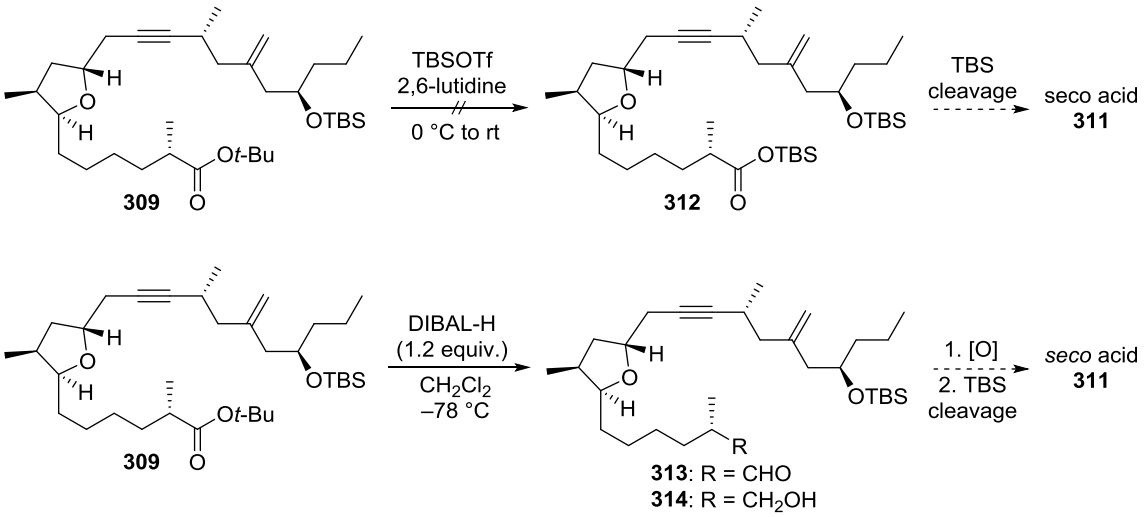
The next challenge was the cleavage of both the *tert*-butyl ester and TBS protecting groups in order to convert the ester **309** into the desired *seco* acid **311** ready for macrolactonisation. Since both protecting groups can be removed under acidic conditions, simultaneous cleavage was attempted by exposure of ester **309** to TFA in the presence of Et_3SiH as a carbocation scavenger (Scheme 86).[100]



Scheme 86

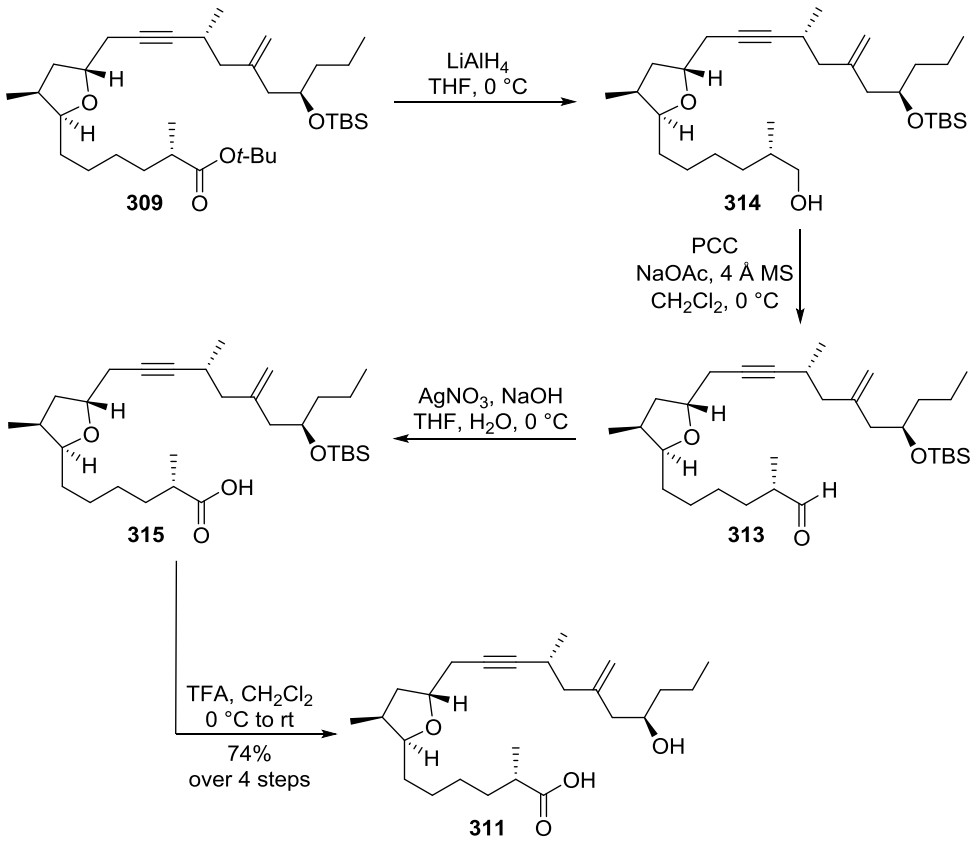
After 1 h, ^1H NMR analysis of a small aliquot of the reaction mixture showed that complete consumption of starting material **309** had occurred with formation of the *tert*-butyl ester **310** and the desired *seco* acid **311** in a 3:1 ratio. The reaction was then stirred until complete consumption of *tert*-butyl ester **310** was evident (monitoring by TLC). After column chromatography on silica gel the only compound isolated was an unknown by-product possessing the same R_f as the desired *seco* acid **311**. The reaction had been performed on a small scale and so the by-product was not identified.

In light of this result, various conditions for the removal of the *tert*-butyl ester were explored (Scheme 87). An attempt to cleave the *tert*-butyl ester by exposure to a Lewis acid such as TBSOTf proved to be unsuccessful and only decomposition of the starting material was observed.[101] Another possibility was to reduce the ester to give the corresponding aldehyde **313**, which could then be converted into *seco* acid **311** by oxidation and TBS cleavage. Unfortunately, this route was also unsuccessful. In fact, when compound **309** was treated with 1.2 equivalents of DIBAL-H in CH_2Cl_2 at −78 °C, ^1H NMR analysis of a small aliquot of the reaction revealed the formation of a mixture of the aldehyde **313** and the alcohol **314** before the *tert*-butyl ester **309** had been consumed completely.



Scheme 87

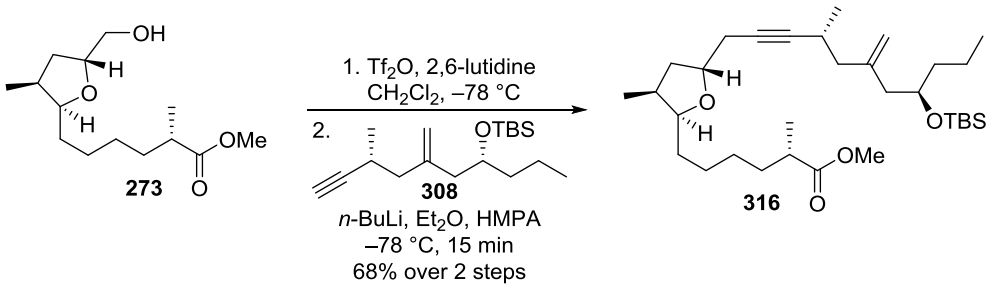
To circumvent these problems, the ester **309** was reduced to give the corresponding alcohol **314** by treatment with excess of $LiAlH_4$ (Scheme 88). Alcohol **314** was then oxidised to the corresponding carboxylic acid **315** *via* the aldehyde **313**. Cleavage of the TBS group by exposure to TFA then afforded the *seco* acid **311** in 74% yield over 4 steps.



Scheme 88

This synthetic route allowed the conversion of compound **309** into the desired *seco* acid **311** in 4 steps and in excellent overall yield. However, this approach also added several extra steps to the synthetic route.

The *tert*-butyl ester group had proved to be unsuitable for a concise and efficient synthesis of the amphidinolides T1 and T3-5, and so the possibility of coupling the methyl ester **273** to the alkyne **308** was explored (Scheme 89). This type of reaction was likely to present an additional challenge, because the methyl ester is more susceptible to nucleophilic attack than a *tert*-butyl ester. For this reason, a reduced amount of the lithium acetylide formed from alkyne **308** was employed in the reaction in order to minimise its addition to the methyl ester functionality. After careful optimisation of the reaction conditions, the best result was obtained treating the triflate derived from alcohol **273** with 1 equivalent of acetylide formed from alkyne **308** in Et_2O at −78 °C for 15 min. Under these conditions the desired coupled product **316** was obtained in 68% yield over 2 steps. Pleasingly, by-products resulting from the nucleophilic attack of the lithiated acetylide on the methyl ester were not detected.

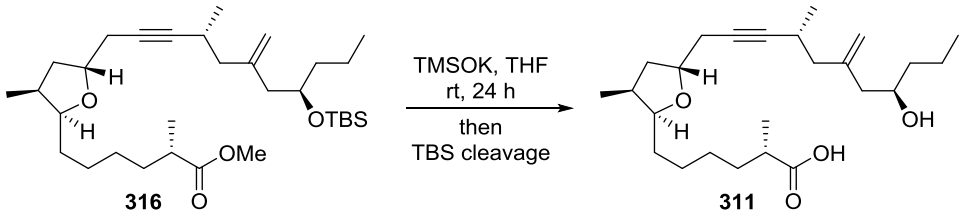


Scheme 89

With compound **316** in hand, the next challenge was one-pot formation of the *seco* acid **311** by hydrolysis of the methyl ester functionality and cleavage of the TBS protecting group (Table 10). TMSOK[102] was chosen for the cleavage of the methyl ester for two reasons: firstly, the cleavage reaction using TMSOK can be performed in THF, which is compatible with the most common methods of TBS ether cleavage; secondly, the reaction conditions are very mild minimising epimerization at the methyl-bearing stereocentre at the ester α position. Technically, it is not correct to refer to this ester cleavage as hydrolysis because the reaction occurs under non-aqueous conditions and the use of dry solvent is crucial. The product of the reaction is the potassium salt which is converted into

the corresponding carboxylic acid following acidic work-up. According to this plan, methyl ester **316** was treated with 10 equivalents of TMSOK in THF and when the starting material was consumed completely (24 h), the reagent used to cleave the TBS group was added directly to the reaction mixture.

Table 10

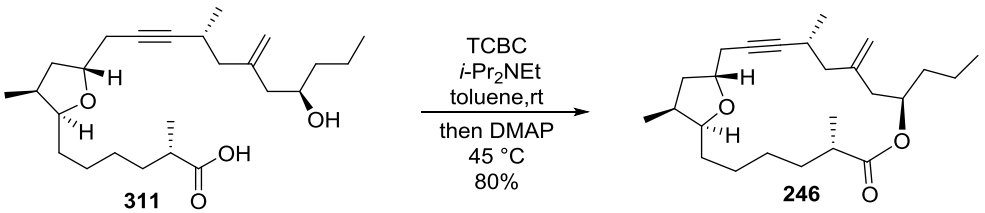


entry	TBS cleavage conditions	time	yield
1	HF·pyridine (100 equiv.)	24 h	75%
2	TBAF (50 equiv.), AcOH	48 h	80%
3	HCl conc. (100 equiv.)	1 h	86%
4	TFA (20 equiv.)	1 h	0%[a]

[a] 90 % of the acid with the TBS protected alcohol was obtained

Cleavage of the TBS group using HF·pyridine was effective but slow (entry 1). Deprotection with TBAF delivered the product in 80% yield (entry 2), but the time required to achieve complete desilylation was even longer (48 h). Surprisingly, the addition of 20 equivalents of TFA to the reaction mixture resulted in no TBS cleavage (entry 4). The best result was obtained by quenching the TMSOK reaction with concentrated HCl and stirring the resulting mixture for an additional hour (entry 3). Under these conditions the desired *seco* acid **311** was obtained in 86% yield.

With the *seco* acid **311** now available, the synthesis of the common late-stage intermediate **201** was completed by macrolactonisation (Scheme 90).[22]



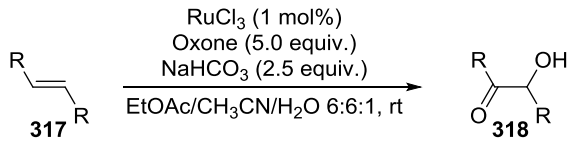
Scheme 90

The Yamaguchi protocol was chosen because it had been employed in previous total syntheses of members of the amphidinolide T family of natural products.[11,13,14] Pleasingly, treatment of the acid **311** under Yamaguchi conditions delivered the pivotal macrolactone **246** in 80% yield.

The common intermediate **246** was thus prepared from alcohol **253** in 14 steps with an overall yield of 21.6% and the stage was set for the completion of the syntheses of amphidinolides T1, T3, T4 and T5.

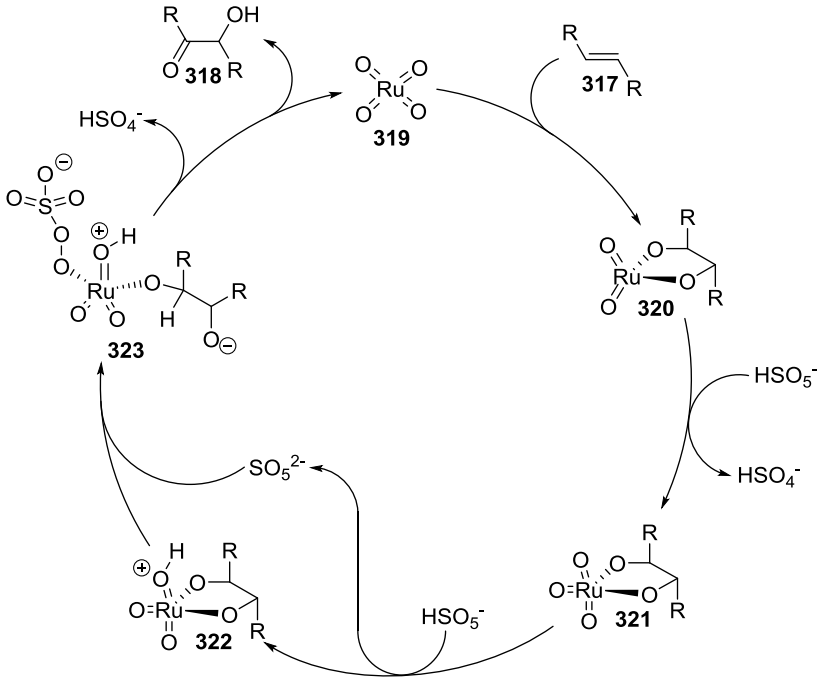
2.3.6 First Attempt to Complete the Syntheses

The first attempt to complete the synthesis was based on a direct oxidation of an alkene to the corresponding α-hydroxy ketone by exposure to RuO_4 (Scheme 91).[103] The reagent RuO_4 is formed *in situ* from a mixture of $RuCl_3$ and Oxone.



Scheme 91

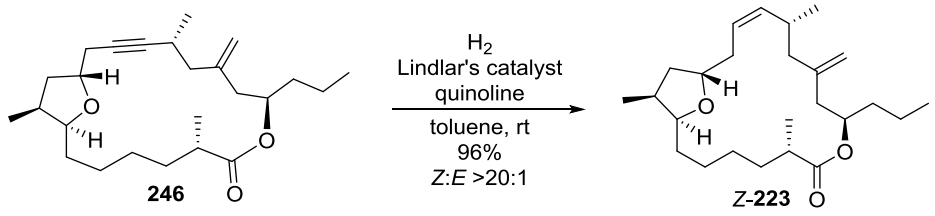
The proposed mechanism for this reaction involves a [3+2] cycloaddition between RuO_4 and the double bond and subsequent oxidation of the ruthenium(VI) compound **320** to afford the ruthenate **321** (Scheme 92).



Scheme 92

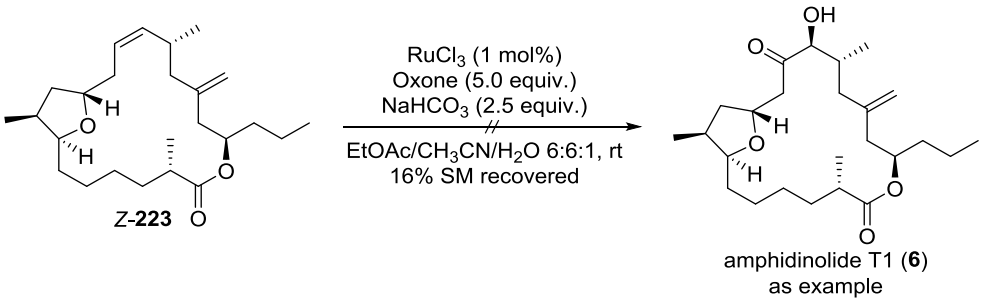
After activation of ruthenate **321** by protonation, SO_5^{2-} adds to the metal centre in **322** with concomitant cleavage of one of the two metal–oxygen bonds. The resulting mixed peroxoruthenate **323** then rearranges to give α-hydroxy ketone **318** and regenerate the active catalyst **319**.

With this procedure in mind, the triple bond present in macrolactone **246** was selectively reduced to the corresponding *Z*-alkene using Lindlar's catalyst[104] affording known macrolactone *Z*-**223**[15b] in excellent 96% yield (Scheme 93).



Scheme 93

Unfortunately, when the diene *Z*-**223** was subjected to the ketohydroxylation conditions developed by Plietker, significant decomposition was observed (Scheme 94). Small amounts of two uncharacterized by-products were obtained but none of the natural products were obtained from the reaction.

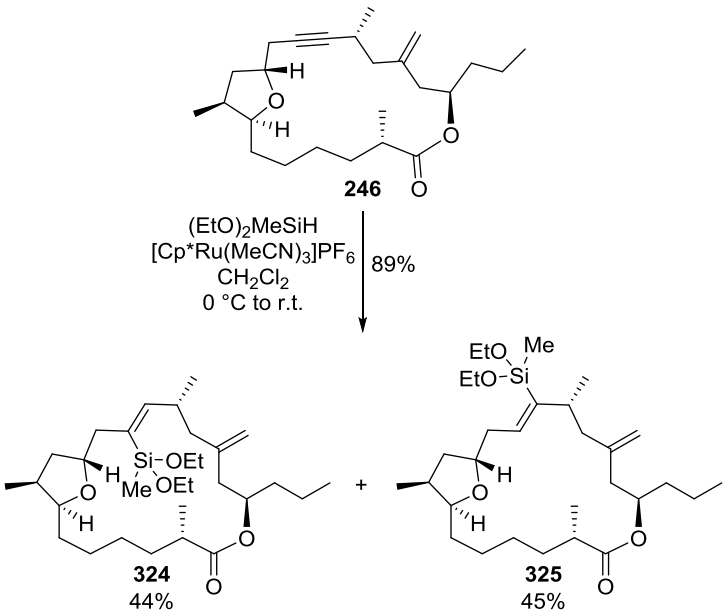


Scheme 94

Further investigations into the use of the ruthenium-mediated ketohydroxylation reaction were not carried out. There were two main reasons for this decision: first of all, the reaction was repeated twice and in both cases none of the desired amphidinolides were detected in the reaction mixture; secondly, although the ketohydroxylation reaction could, in principle, afford the desired natural products, it would be extremely difficult to control both the regiochemical and stereochemical outcome of the reaction.

2.3.7 Hydrosilylation

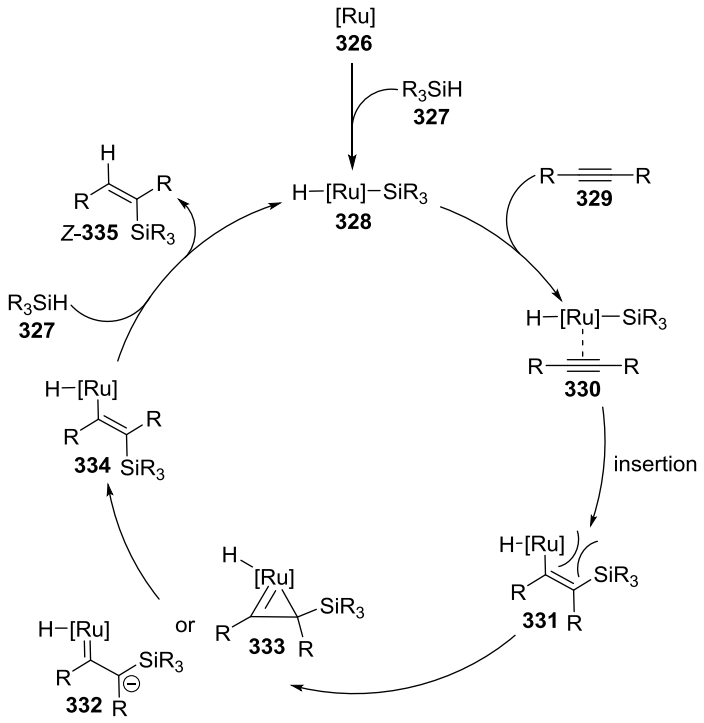
Following the failure of the direct alkene oxidation approach, efforts were focused on a different route to complete the syntheses of amphidinolides T1 and T3-5. This alternative strategy involved hydrosilylation of the alkyne in the common intermediate **246** followed by sequential epoxidation and Tamao-Fleming oxidation of the resulting silane.[105] A protocol developed by Trost *et al.*,[106] in which $[Cp^*Ru(CH_3CN)_3]PF_6$ is employed as the catalyst, was chosen as the first method for the hydrosilylation of the common intermediate (Scheme 95).



Scheme 95

Treatment of alkyne **246** with 10 mol% of the ruthenium(II) complex in the presence of methyldiethoxysilane delivered the corresponding *Z*-vinylsilanes **324** and **325** as a 1:1 mixture of separable regioisomers in a combined yield of 89%.

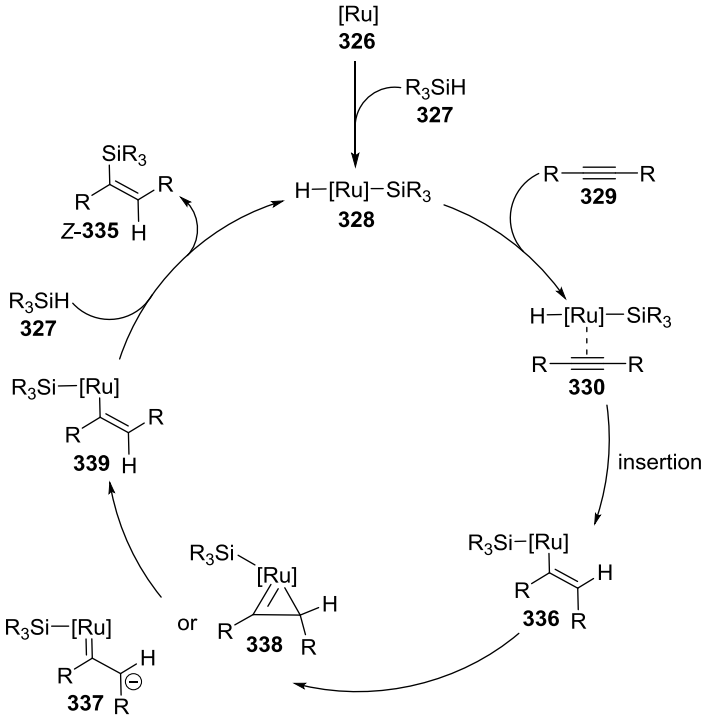
The selective formation of the *Z*-vinylsilane under the reaction conditions could be explained with the modified Chalk-Harrod mechanism[107] proposed independently by Crabtree[108] and Ojima[109] (Scheme 96). According to this proposed mechanism the *anti-addition* product **335** is formed by initial insertion of the alkyne substrate into the Ru—Si bond. This is followed by isomerization of the initially formed vinyl complex **331** to a less sterically congested and thermodynamically favoured intermediate of type **332** or **333**.



Scheme 96

Crabtree *et al.* suggested the metallocyclopropene intermediate **333** as the most likely intermediate for this isomerization, but Ojima *et al.* proposed the alternative metal alkylidene **332**. Noteworthy is the proposed 'monohydride'-type mechanism (by analogy to homogeneous hydrogenation) that permits *E*/*Z* isomerization to out-compete reductive elimination, which must occur by intermolecular reaction with a molecule of the silane **327**.

More recently, Trost and co-workers proposed a different mechanism based on computational studies to explain the selectivity of the hydrosilylation reaction catalyzed by cationic ruthenium complexes (Scheme 97).[106c] They suggested that hydride-insertion to deliver intermediate of type **336** is favored over silyl-insertion. The *trans* addition stereochemistry should result from the formation of a metal carbene type **337** or metallocyclopropene intermediate **338** upon hydride-insertion followed by a stereospecific counterclockwise rotation of the C_α–C_β bond. The intermediate then undergoes a facile α-silyl migration through a metallocyclopropene-like transition structure to give the *trans* addition product **335**.

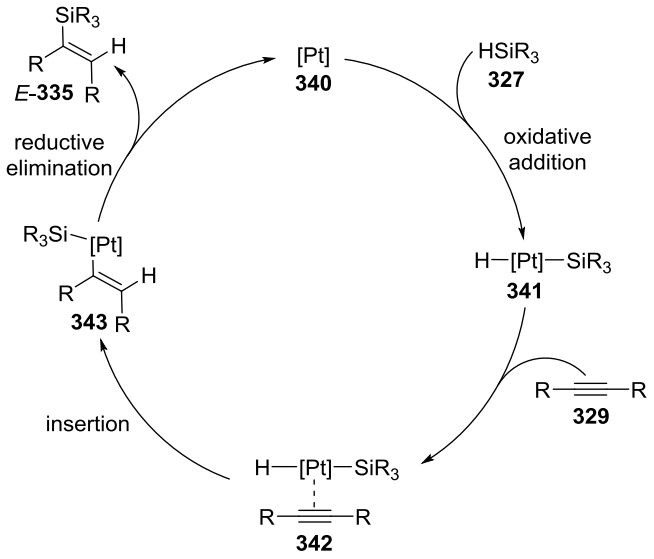


Scheme 97

The result obtained from the ruthenium-catalysed hydrosilylation reaction was very satisfying. In fact, Trost's method allowed the regioisomeric *Z*-vinylsilanes **324** and **325** to be obtained in excellent yield as a separable 1:1 mixture. Both of these regioisomers are required to complete the syntheses of all four target products (*vide infra*).

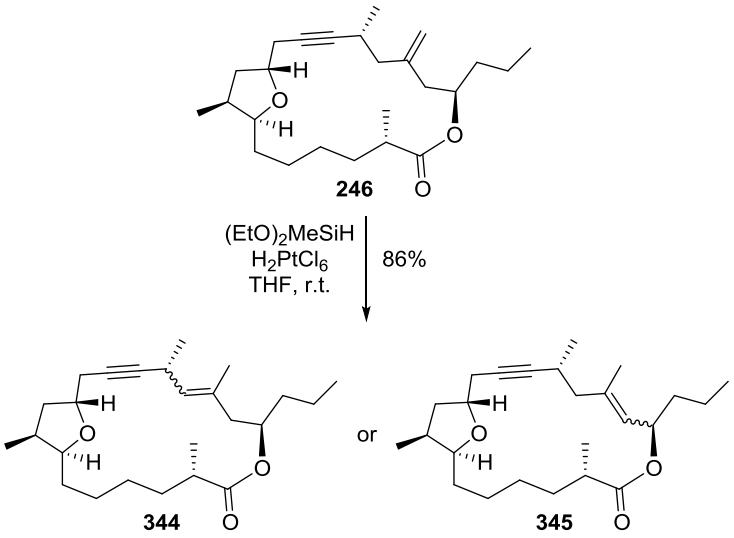
Control of the regioselectivity of the hydrosilylation reaction would further improve the efficiency of the synthesis. This task represents a major challenge because there are no examples of selective hydrosilylation of internal alkynes without the assistance of a propargylic or homopropargylic hydroxyl group that can coordinate or form hydrogen bond with the catalyst. Despite this, some attempts to improve the regiocontrol of the hydrosilylation were made by screening various catalysts.

The well-known hydrosilylation reaction using chloroplatinic acid as a catalyst was tested first.[110] Platinum-catalysed hydrosilylation of alkynes fits the original Chalk–Harrod mechanism and follows a pathway that is based on sequential oxidative addition, migratory insertion, and reductive elimination to deliver the corresponding *E*-vinylsilane (Scheme 98).[107]



Scheme 98

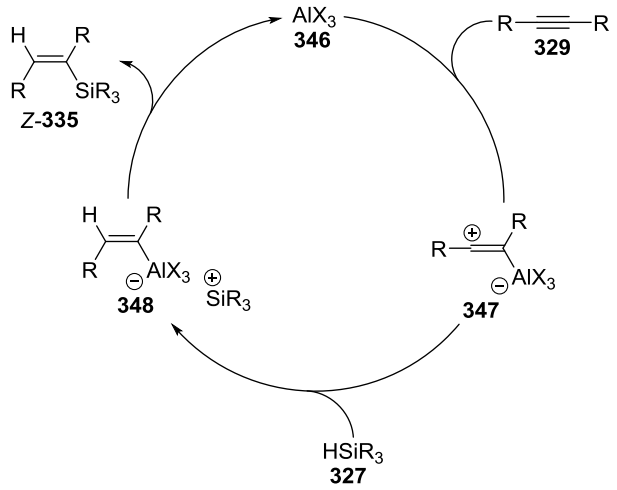
Unfortunately, treatment of the alkyne **246** with 5 mol% of chloroplatinic acid in the presence of methyldiethoxysilane did not afford either of the desired products and a 2:1 mixture of isomers resulting from the migration of the exocyclic double bond was observed instead (Scheme 99).



Scheme 99

Chloroplatinic acid is known to be able to catalyse the hydrosilylation of terminal alkenes, thus some issues about the chemoselectivity of the reaction could have been anticipated, although the higher rate of silane addition to alkynes *vs* olefins is well documented.[111] On the other hand, migration of the alkene was totally unexpected.

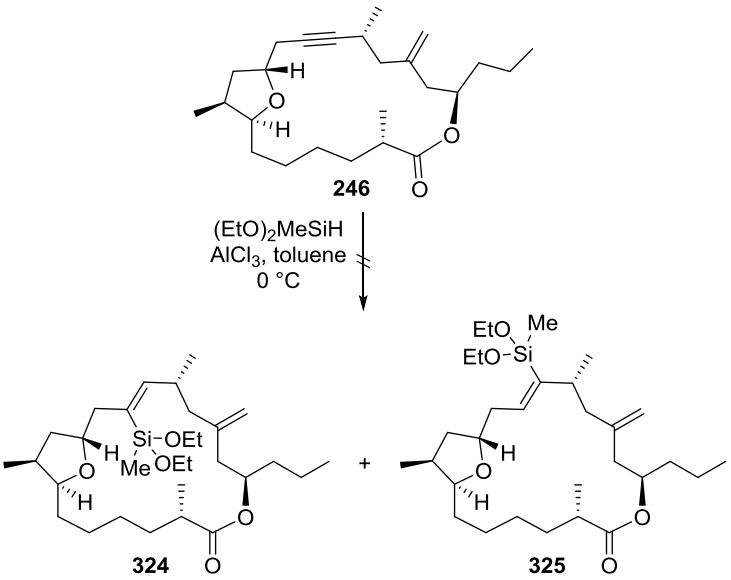
Hydrosilylation of internal alkynes is also possible employing a strong Lewis acid catalyst, which gives products of *trans* addition. Some particularly interesting examples of this process come from work performed by Yamamoto and co-workers, who showed that $AlCl_3$ and $EtAlCl_2$ can be used to promote the hydrosilylation of alkynes and allenes (Scheme 100).[112]



Scheme 100

The mechanism proposed by Yamamoto involves the coordination of $AlCl_3$ or $EtAlCl_2$ (AlX_3) to the acetylenic bond of alkyne **329** to produce the zwitterionic intermediate **347** *via* a π-complex. Next, the hydride from silane **327** attacks the electron-deficient carbon from the opposite side with respect to AlX_3 to produce an aluminium ate-complex **348**. Finally, vinyl-aluminium intermediate **348** undergoes coupling with the trialkylsilyl cation with retention of geometry to give *Z*-vinylsilane **335** and regenerate aluminium catalyst **346**. The main issue related to the use of this method is the incompatibility of several functional groups with the strong Lewis acid catalyst.

Disappointingly, when the hydrosilylation conditions developed by Yamamoto and co-workers were applied to compound **246**, only decomposition of the starting material was observed (Scheme 101).



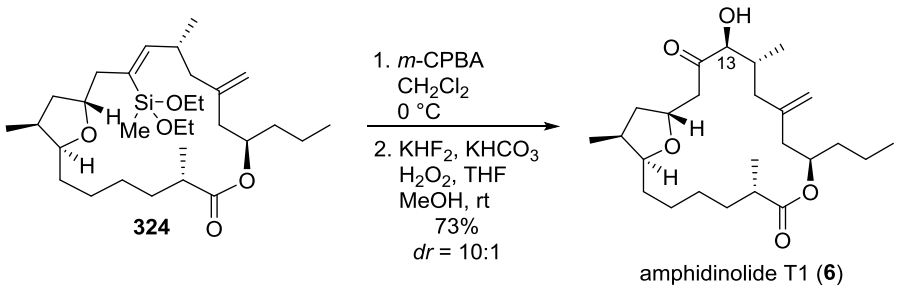
Scheme 101

In conclusion, the $[Cp^*Ru(CH_3CN)_3]PF_6$ complex proved to be the only suitable catalyst for the hydrosilylation of late-stage intermediate **246**. The desired vinylsilanes **324** and **325** were obtained in excellent combined yield as a separable 1:1 mixture. Attempts to improve the regioselectivity of the reaction using various metal catalysts were unsuccessful.

2.3.8 Completion of Amphidinolides T1, T3 and T4

With the two vinylic silanes in hand, the stage was set for the epoxidation/Tamao-Fleming oxidation sequence to complete the synthesis of the natural product targets.

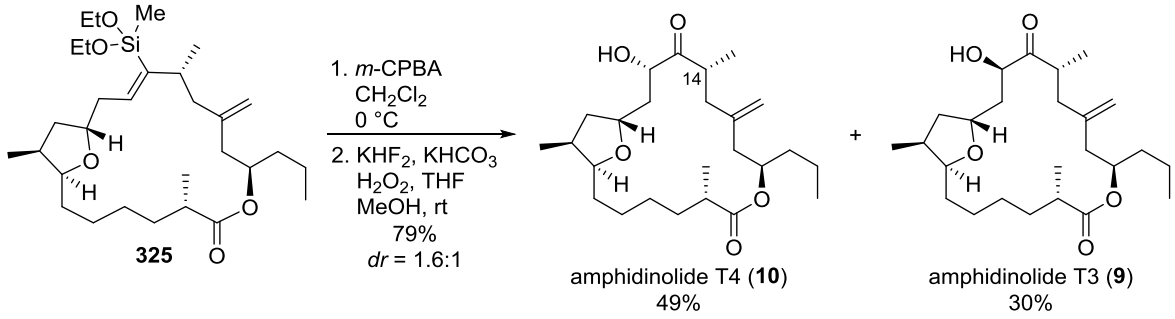
Regioselective epoxidation of *Z*-vinylsilane **324** using *m*-CPBA followed by Tamao-Fleming oxidation of the resulting epoxide proceeded according to plan. Under standard conditions, amphidinolide T1 was obtained in 73% yield over 2 steps, along with 7% of another product, the data for which are consistent with it being C13-*epi*-amphidinolide T1 (Scheme 102). Spectroscopic and other data for synthetic compound **6** are identical to those reported for amphidinolide T1.[5]



Scheme 102

Pleasingly, use of *m*-CPBA as the oxidant and reliance on substrate control resulted in a highly diastereoselective epoxidation reaction to deliver natural amphidinolide T1 selectively over its C13-epimer. Applying this synthetic strategy, the synthesis of amphidinolide T1 was completed in 17 steps from the alcohol **253** with an overall yield of 6.9%.

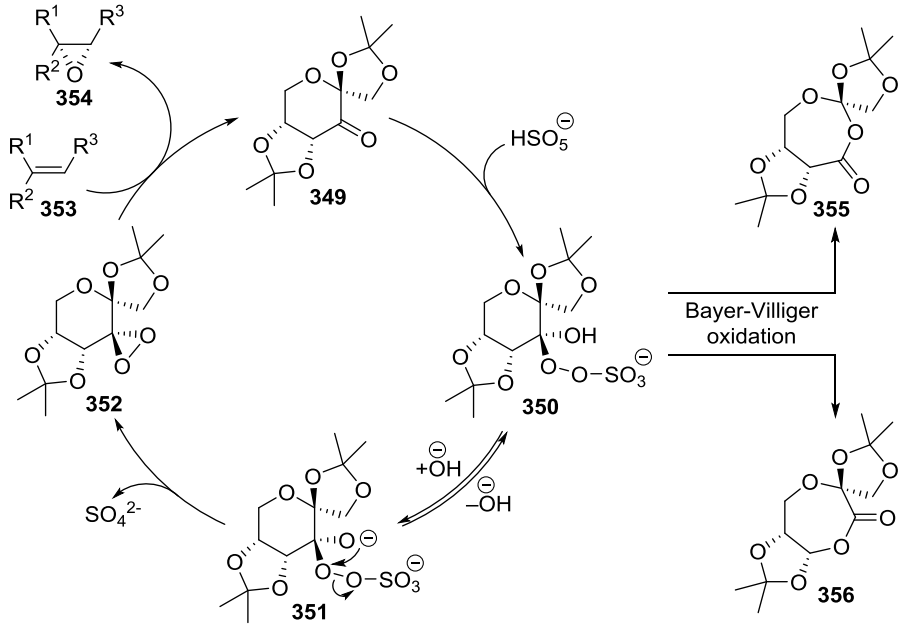
Treatment of *Z*-vinylsilane **325** under the same conditions as its regioisomer **324** provided amphidinolides T4 and T3 as a separable 1.6:1 diastereomeric mixture and in a combined yield of 79% over 2 steps (Scheme 103). Spectroscopic and other data of the synthetic samples of **9** and **10** are in agreement with those reported for the natural amphidinolide T4 and T3.[8] Using this synthetic route, amphidinolide T3 was synthesised in 17 steps with an overall yield of 2.9%, and the synthesis of amphidinolide T4 was completed in 17 steps with an overall yield of 4.8%.



Scheme 103

It is worth noting that the silane **324** could be converted into amphidinolide T1 selectively over its C13 epimer (*dr* = 10:1), whereas oxidation of the silane **325** resulted in a mixture of amphidinolides T4 and T3 (*dr* = 1.6:1). This strategy allowed the synthesis of all the natural product targets, but the efficiency of the route would be improved by stereoselective formation of amphidinolides T4 and T3. To achieve this objective, it would be necessary to enhance the diastereoselectivity of the epoxidation reaction of the silane **325**, the precursor to the natural products.

The Shi asymmetric epoxidation reaction[113] was the protocol chosen to accomplish this goal. This method was chosen because it had already been shown to be a suitable one for the asymmetric epoxidation of vinylic silanes with excellent levels of enantioselectivity.[114]



Scheme 104

The Shi asymmetric epoxidation reaction involves the *in situ* generation of the chiral dioxirane **352** formed from the oxidation of the sugar-derived ketone **349** with Oxone (Scheme 104). The dioxirane that is produced is capable of transferring an oxygen atom to a wide variety of olefinic substrates, and the ketone is regenerated after the oxygen-transfer. The pH of the reaction medium plays a crucial role in dictating the outcome of the reaction: at high pH, Oxone decomposes rapidly, while at lower pH values the catalyst decomposes by Baeyer-Villiger oxidation. For this reason, it is important to maintain the pH of the reaction medium at an optimum level (~10.5); under these conditions the epoxidation usually takes place with high enantioselectivity at low catalyst loadings without the need to use a large excess of Oxone. Furthermore, the epoxide products are more stable at the optimum pH than at lower pH values.

Two possible transition states have been proposed for the Shi epoxidation reaction: spiro and planar (Figure 8). For nearly every example involving epoxidation of a *trans*-disubstituted or a trisubstituted olefin using Shi's catalyst, the outcome is consistent with the spiro transition state **357a**. The extent of the involvement of the competing planar transition state **357b** depends on the nature of the substituents on the olefin substrate.

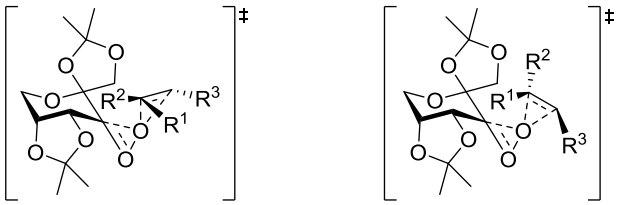
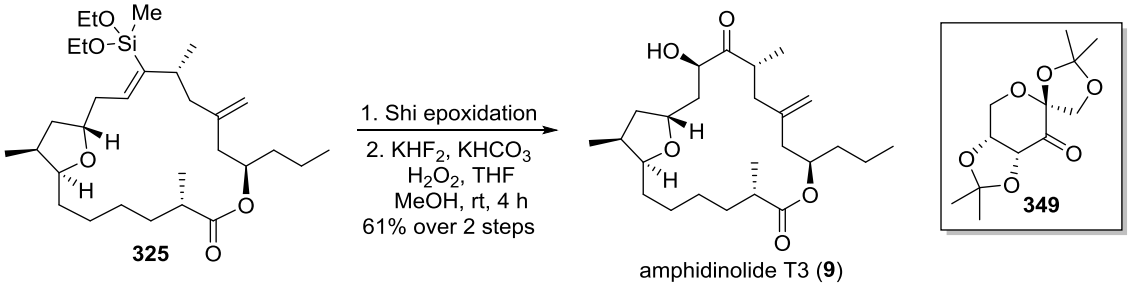


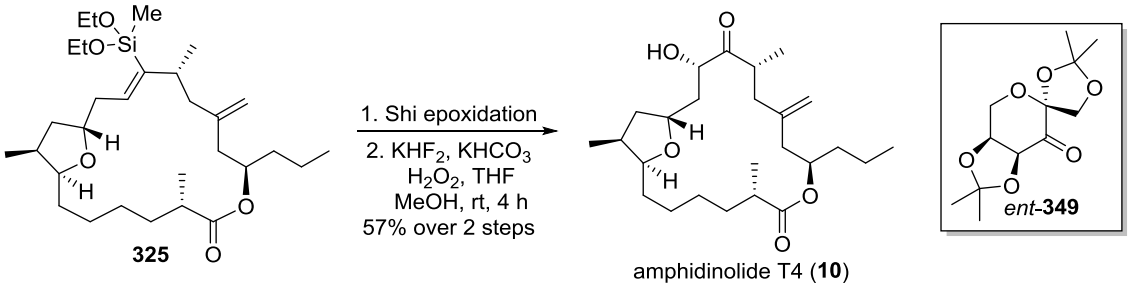
Figure 8

Pleasingly, treatment of vinylic silane **325** under Shi epoxidation conditions using the D-fructose-derived ketone **349**, followed by Tamao-Fleming oxidation afforded amphidinolide T3 in 61% yield over 2 steps; amphidinolide T4 was not detected (Scheme 105). In this way, the overall yield for amphidinolide T3 was increased from 2.9 % to 5.9%.



Scheme 105

Furthermore, when vinylic silane **325** was subjected to the same conditions, but using L-fructose-derived ketone *ent*-**349** as source of chirality for the asymmetric epoxidation step, amphidinolide T4 was formed selectively in 57% yield over 2 steps, and amphidinolide T3 was not detected (Scheme 106). This method allowed the overall yield of amphidinolide T4 to be increased from 4.8% to 5.5%.



Scheme 106

In conclusion the Shi asymmetric epoxidation reaction enabled amphidinolide T3 or T4 to be prepared selectively from the vinylic silane **325** in good yield, thus improving the efficiency of the syntheses of these natural products.

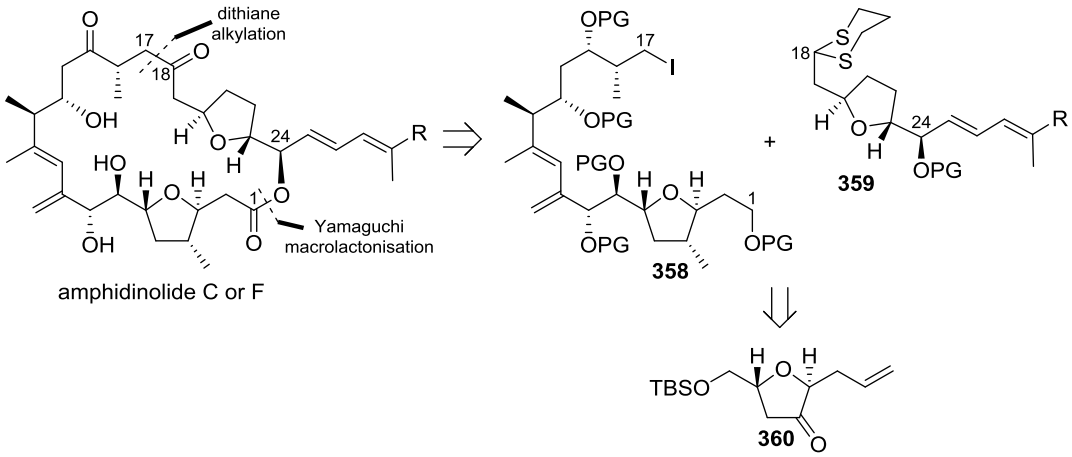
Kobayashi and co-workers have shown that amphidinolide T4 undergoes epimerization at C14 upon treatment with K_2CO_3 in MeOH to give amphidinolide T5 (**11**), and so a formal total synthesis of a fourth member of the family has also been achieved.[7]

2.3.9 Conclusions

A concise, efficient and high yielding route for the synthesis of four members of the amphidinolide T family of natural products from a common late-stage intermediate has been described. The syntheses of amphidinolides T1, T3 and T4 were completed in 17 steps from alcohol **253** with an overall yield of 6.9%, 5.9% and 5.5% respectively. Since amphidinolide T5 can be prepared by simple epimerization of amphidinolide T4, as described by Kobayashi, a formal total synthesis of this natural product has also been achieved.[7] The pivotal *trans* trisubstituted tetrahydrofuran ring moiety was assembled employing the [2,3]-sigmatropic rearrangement of an oxonium ylide generated by decomposition of a diazo ketone, proving once more the utility of this methodology for the synthesis of complex natural products. The key connection between the two main fragments was realized by chemoselective triflate displacement with a lithium acetylide in the presence of a potentially reactive methyl ester. The common late stage intermediate was converted into the amphidinolides T installing the α-hydroxy ketone functionality by a hydrosilylation, stereoselective epoxidation, and Tamao-Fleming oxidation sequence.

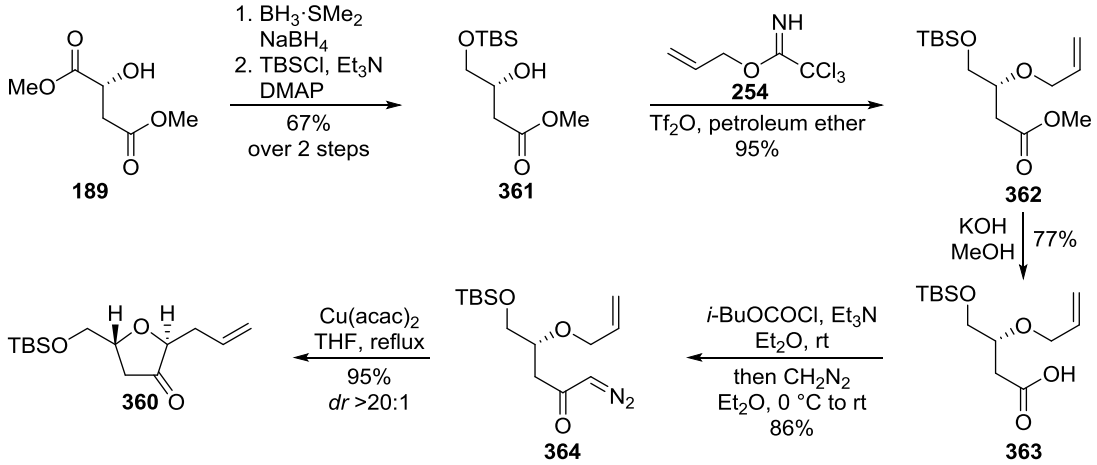
2.4 Clark Synthesis of Fragments of Amphidinolides C and F

The initial retrosynthetic plan, in analogy with Carter (Section 1.5.1), relied on the symmetry within the two tetrahydrofuran ring segments within the macrocyclic core of amphidinolide C and F.[36m,n] Disconnections at the C—O macrolactone bond and at the C17—C18 bond revealed two main fragments, the iodide **358** and dithiane **359**, which can both be accessed from the common intermediate dihydrofuranone **360** (Scheme 107). The *trans*-2,5-disubstituted dihydrofuranone **360** can be readily prepared as a single diastereoisomer using Clark's oxonium ylide rearrangement methodology (Section 1.6.3).[62]



Scheme 107

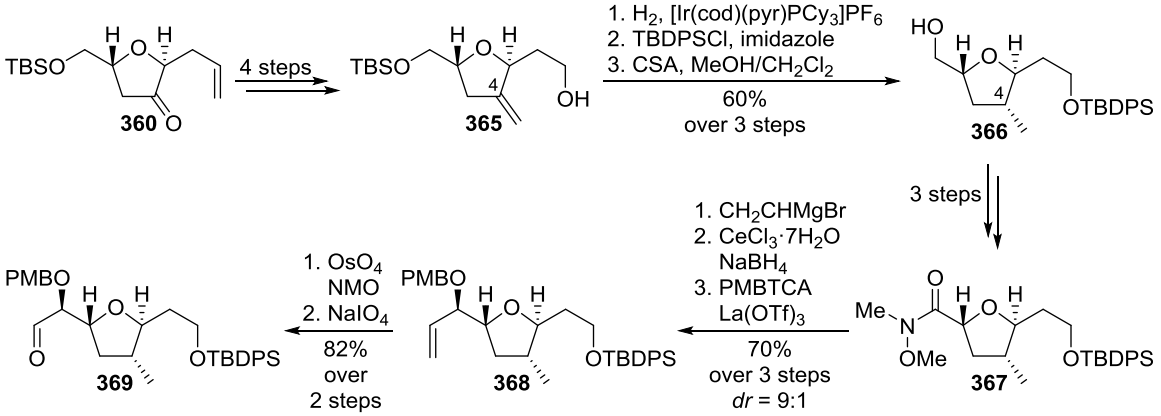
The synthesis of the dihydrofuranone **360** started from dimethyl D-malate **189**, which was easily transformed into the alcohol **361** in two steps (Scheme 108).



Scheme 108

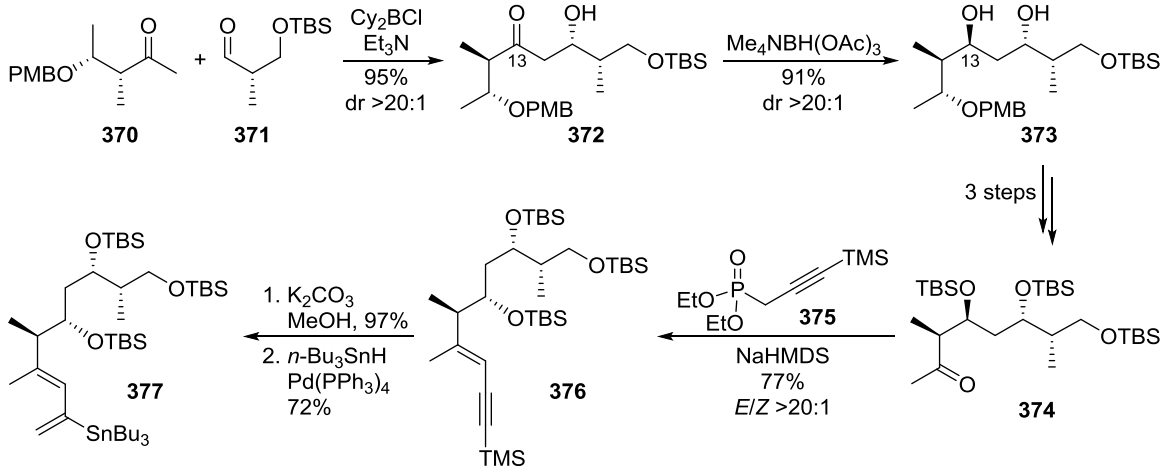
Allylation of the free hydroxyl group followed by saponification of the ester moiety delivered the acid **363** and this was then converted into the key α-diazo ketone **364**. The pivotal *trans*-dihydrofuranone **360** was formed by diastereoselective copper catalysed decomposition of diazo ketone **364**, with consequent formation and [2,3]-sigmatropic rearrangement of the corresponding putative oxonium ylide. This transformation provided the ketone **360** as a single diastereoisomer in 95% yield.

For the synthesis of iodide fragment **358**, the dihydrofuranone **360** was converted into the alcohol **365**, and directed hydrogenation, employing Crabtree's catalyst, was used to install the desired stereochemistry at C4 (Scheme 109). The alcohol **366** was then converted into the corresponding Weinreb amide **367**. Addition of vinylmagnesium bromide to the Weinreb amide, followed by diastereoselective reduction of the resulting ketone and subsequent PMB protection provided alkene **368** in 70% yield over 3 steps. Finally, oxidative cleavage of the double bond delivered aldehyde **369**.



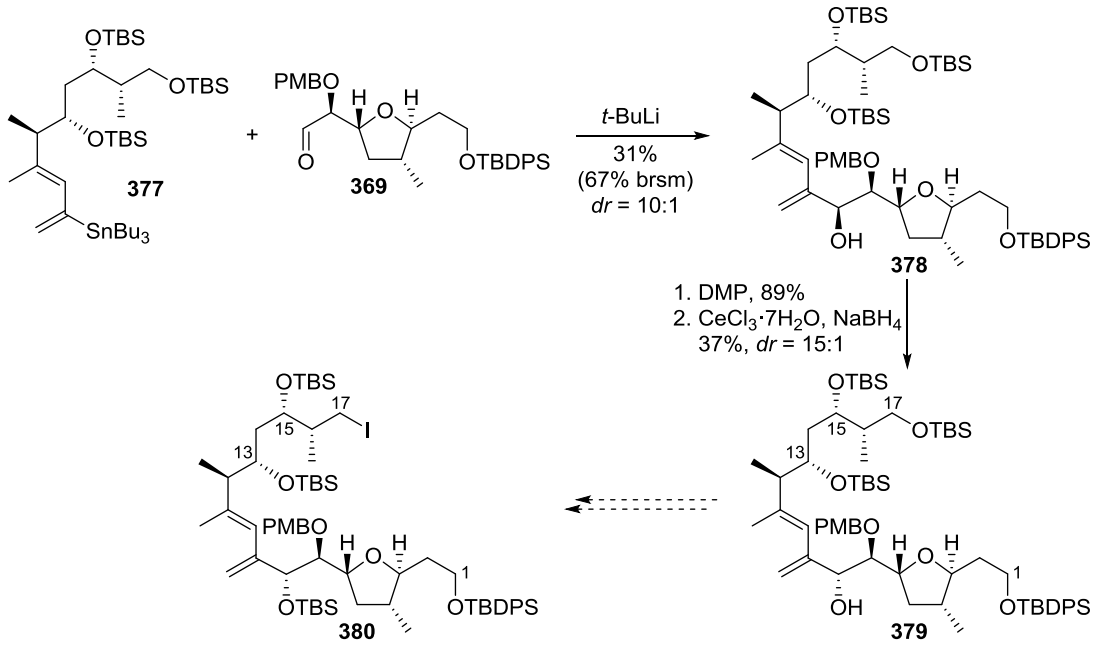
Scheme 109

The other segment of the iodide fragment **358** was prepared using a Paterson aldol reaction of the methyl ketone **370** and the aldehyde **371** followed by alcohol-directed reduction of the resulting ß-hydroxy ketone **372** to set the required stereochemistry at C13 (Scheme 110).[115,116] The diol **373** was then converted into ketone **374**, which was subjected to a Horner-Wadsworth-Emmons olefination reaction using the phosphonate **375** to give enyne **376** in good yield and with excellent control of the geometry of the newly formed double bond. The enyne **376** was then converted into the final stannane **377** in two steps.



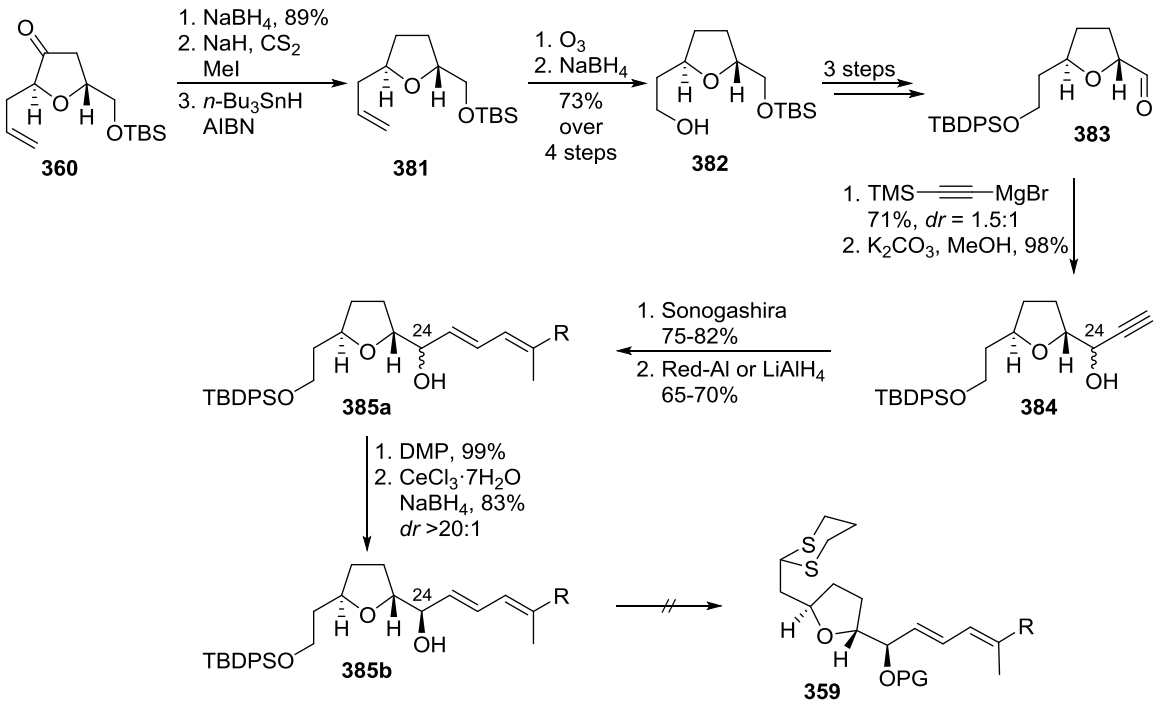
Scheme 110

Coupling of the segments was achieved by addition of the organolithium species formed from the stannane **377** to the aldehyde **369** (Scheme 111). The reaction proceeded with low conversion and the alcohol **378** was isolated in a modest 31% yield. Furthermore, the stereochemistry at C8 required inversion by an oxidation/reduction sequence, resulting in the addition of two extra steps to the synthetic route. Conversion of the TBS-ether **379** into the iodide **380** was never performed. The reason behind this decision is that compound **379** features a pattern of protecting groups that is unsuitable for completion of the syntheses of the natural targets because it does not allow differentiation between the hydroxyl groups at C13 and C15 to be accomplished very readily.



Scheme 111

The key dihydrofuranone **360** was also employed in the synthesis of the dithiane fragment **359** (Scheme 112). For this purpose, the ketone group was removed by deoxygenation. The tetrahydrofuran **381** was transformed smoothly into the aldehyde **383**. Various reaction conditions, exploiting either substrate or reagent control, were screened in order to achieve a stereocontrolled addition of an alkyne nucleophile to the aldehyde **383**. Unfortunately, none of the conditions tested allowed good levels of diastereocontrol to be achieved. The best result was obtained from the addition of magnesium trimethylsilylacetylide in the presence of $MgBr_2 \cdot OEt_2$ to the aldehyde. The reaction delivered the propargylic alcohol **384** in 71% yield as a 1.5:1 mixture of diastereoisomers at C24.



Scheme 112

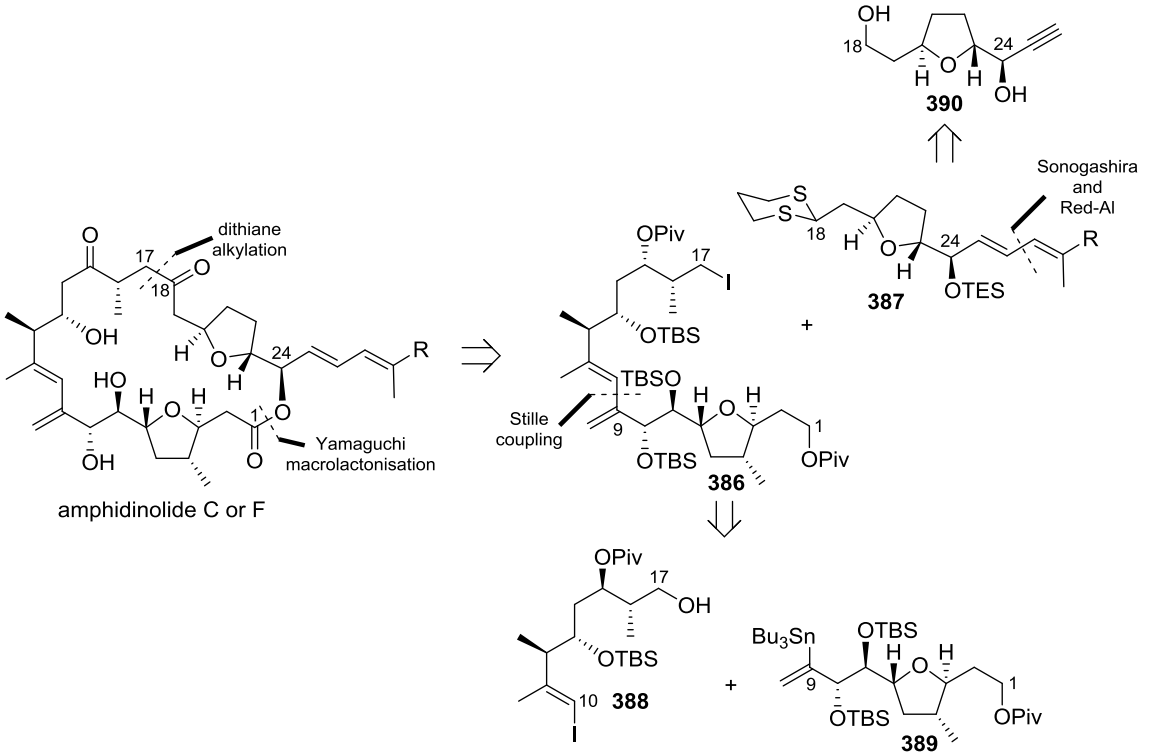
The various side chains were introduced by Sonogashira cross-coupling and the alkyne was reduced stereoselectively into the corresponding *E*-alkene using either Red-Al or $LiAlH_4$ and exploiting the anchimeric assistance of the free hydroxyl group. An oxidation/reduction sequence was required to install the desired stereochemistry at C24, with an addition of two extra steps to the synthetic route. Unfortunately, alcohol **385b** could not be converted into the required dithiane **370**.

The first problem of this strategy was that the protecting groups used during the synthesis of intermediate **379** were not suitable to complete the natural

products because they did not allow differentiation between the hydroxyl groups at C13 and C15. It is important to note that amphidinolides C and F feature an alcohol at C13 and a ketone at C15. The relatively high number of steps necessary to convert the dihydrofuranone **360** into the dithiane **359** suggested that the use of ketone **360** as common intermediate for both portions of the molecule is inefficient. Furthermore, an approach that relied on the latent symmetry within the macrocyclic core of amphidinolides C and F has been already reported by Carter (Section 1.5.1).[35,38] As a consequence of these considerations, a new strategy was designed.

2.5 Evolution of the Strategy towards Amphidinolides C and F

The new strategy involves the same primary disconnections as the previous one, revealing the iodide **386** and the dithiane **387** (Scheme 113). However, in this case the two main fragments were further disconnected in two segments and the THF rings were envisioned to originate from different precursors.



Scheme 113

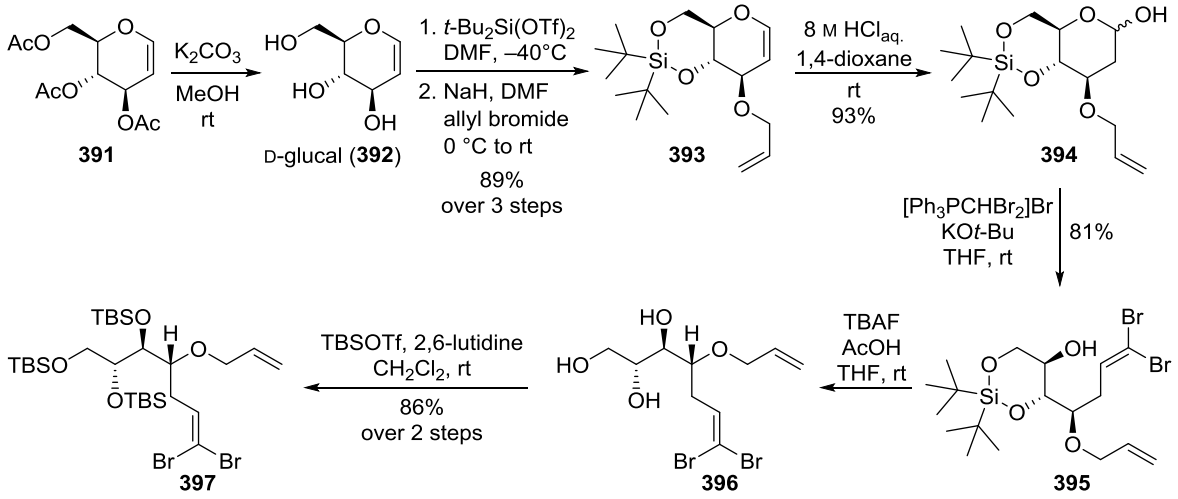
Disconnection of the C1-C17 fragment **386** through the C9—C10 bond revealed the vinylic iodide **388** and the stannane **389**. The *trans*-2,5-trisubstituted tetrahydrofuran ring within the stannane fragment **389** can be prepared by [2,3]-sigmatropic rearrangement of an oxonium ylide generated by denitrogenation of a tosyl-triazole (Section 1.6.4).[77] On the other hand, the dithiane **387** could be obtained from the *trans*-tetrahydrofuran **390** and the side chain can be introduced by Sonogashira cross-coupling. This revised strategy should allow the preparation of the two main fragments bearing suitable protective groups and to avoid extra steps to adjust the stereochemistry.

My work, which will be discussed in the next section, focused on the synthesis of the C1-C17 fragment **386** as well as exploration of the coupling of the main fragments.

2.6 Amphidinolides C and F: Synthesis

2.6.1 Synthesis of the C1-C9 Fragment

The synthesis of the C1-C9 fragment commenced with deacetylation of commercially available tri-*O*-acetyl-D-glucal (**391**) by treatment with a catalytic amount of potassium carbonate in methanol (Scheme 114). Protection of the primary and proximal secondary hydroxy groups of the resulting D-glucal **392** with a di-*tert*-butylsilylene group followed by allylation of the remaining hydroxy group delivered the enol ether **393** in 89% yield over 3 steps.[117] Hydration of the enol ether **393** by treatment with aqueous HCl afforded 2-deoxysugar **394** in excellent yield without affecting the di-*tert*-butylsilylene protecting group.

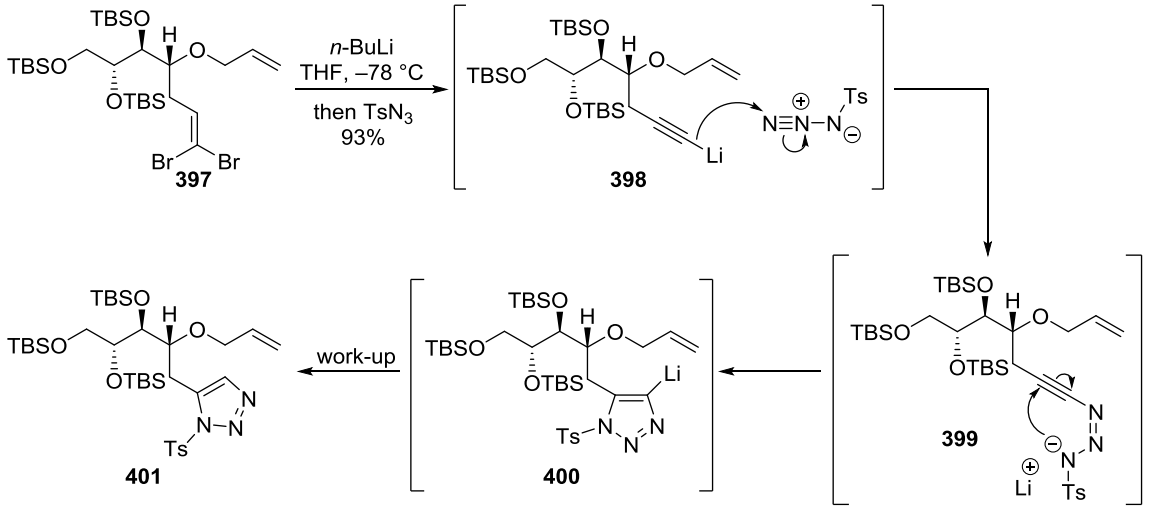


Scheme 114

The lactol **394** was subjected to Ramirez olefination to give the dibromoalkene **395** in 81% yield. Cleavage of the di-*tert*-butylsilylene protecting group was achieved by treatment of **395** with tetra-*n*-butylammonium fluoride in the presence of acetic acid buffer. The addition of acetic acid to the reaction mixture proved to be crucial to avoid decomposition of compound **395**. The resulting triol **396** was immediately protected by treatment with TBSOTf in the presence of 2,6-lutidine to give the dibromoalkene **397** in 86% yield over 2 steps.

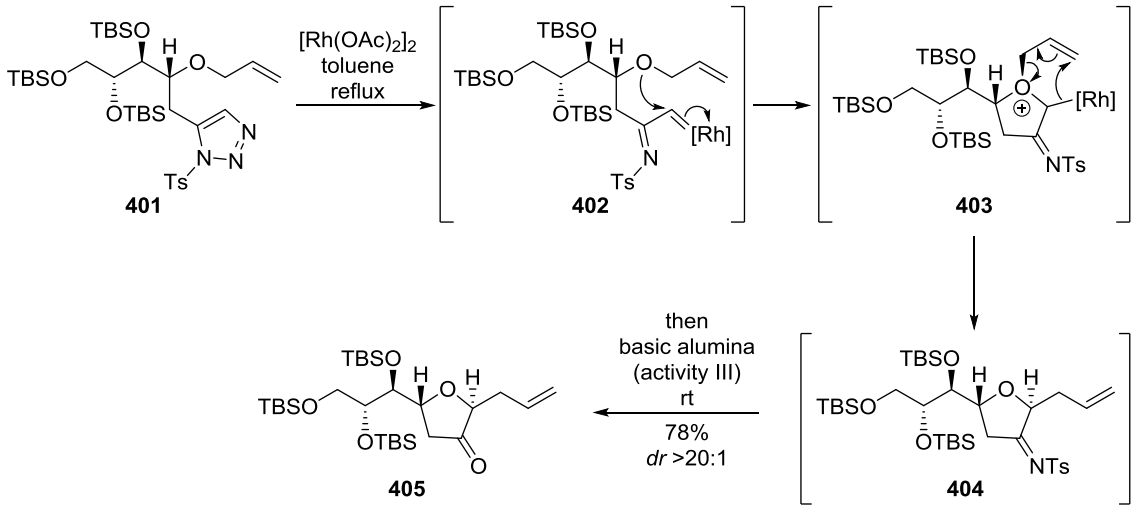
The dibromoalkene **397** was then converted into key sulfonyl triazole **401** (Scheme 115).[118] This transformation was achieved by treatment of dibromoalkene **397** with 2 equivalents of *n*-BuLi to generate the lithium acetylide species **398**, which was then reacted with tosyl azide to give the

lithiated triazole **400**. Quenching of the reaction with a saturated aqueous solution of ammonium chloride delivered the 1-sulfonyl-1,2,3-triazole **401** in excellent yield. The sulfonyl triazole **401** is prone to isomerisation, particularly when solvent free and for this reason, compound **401** had to be purified rapidly by column chromatography on silica gel and stored as solution in toluene.



Scheme 115

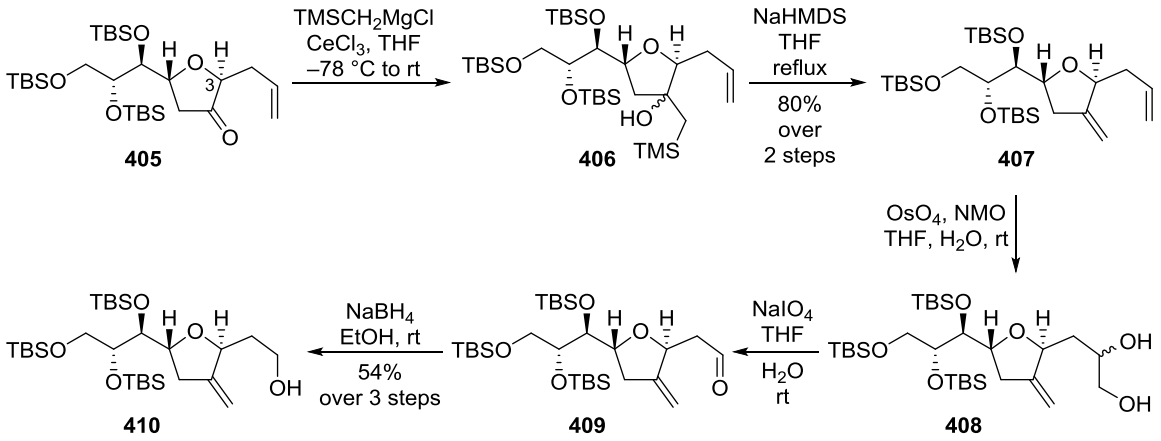
With triazole **401** in hand, the stage was set for the pivotal [2,3]-sigmatropic rearrangement to generate dihydrofuranone **405** (Section 1.6.4).[77] Treatment of the triazole **401** with 1 mol% of $[Rh(OAc)_2]_2$ in refluxing toluene for 1 h resulted in formation of the corresponding metal carbenoid **402** with loss of dinitrogen (Scheme 116).



Scheme 116

Subsequent selective attack of one of the diastereotopic lone pairs of the ether oxygen onto the metal carbenoid generates metal-bound oxonium ylide **403**, which undergoes [2,3]-sigmatropic rearrangement to generate imine **404**. The reaction mixture was then cooled to rt and stirred in the presence of basic alumina (Brockmann activity III) for a further 30 min in order to promote the hydrolysis of imine **404** to give the corresponding *trans*-dihydrofuranone **405** as a single diastereoisomer in 78% yield.

Methylenation of the ketone **405** was performed using a 2-step Peterson olefination procedure to avoid epimerisation of the C3 stereocentre, a problem that was observed when standard Wittig olefination conditions were employed (Scheme 117). Treatment of the dihydrofuranone **405** with an excess of the organocerium reagent generated by reaction of trimethylsilylmethylmagnesium chloride with anhydrous cerium(III) chloride[95] resulted in the formation of the sterically hindered tertiary alcohol **406**. Workup and exposure of the crude tertiary alcohol **406** to NaHMDS in refluxing THF facilitated Peterson elimination and delivered the diene **407** in excellent yield.

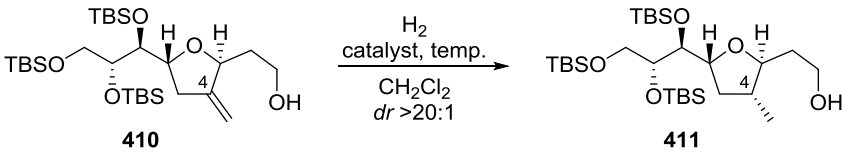


Scheme 117

Selective dihydroxylation of the less hindered monosubstituted alkene within diene **407** was achieved using a catalytic amount of osmium tetroxide in the presence of NMO as co-oxidant.[119] It was extremely important to employ no more than 1.2 equivalents of co-oxidant in this reaction in order to avoid double dihydroxylation. The resulting diol **408** was then subjected to oxidative cleavage to give the intermediate aldehyde **409** which was reduced with $NaBH_4$ to provide the alcohol **410** in 54% yield over 3 steps.

The next challenge was the hydrogenation of the methylene group to install the C4 methyl substituent with the required stereochemistry. The idea, in analogy to what has been done in the synthesis of the amphidinolides T, was to use Crabtree's catalyst in order to exploit coordination of the C1 hydroxyl group to the iridium centre of the catalyst in order to direct the hydrogenation reaction to the desired face (Table 11).

Table 11



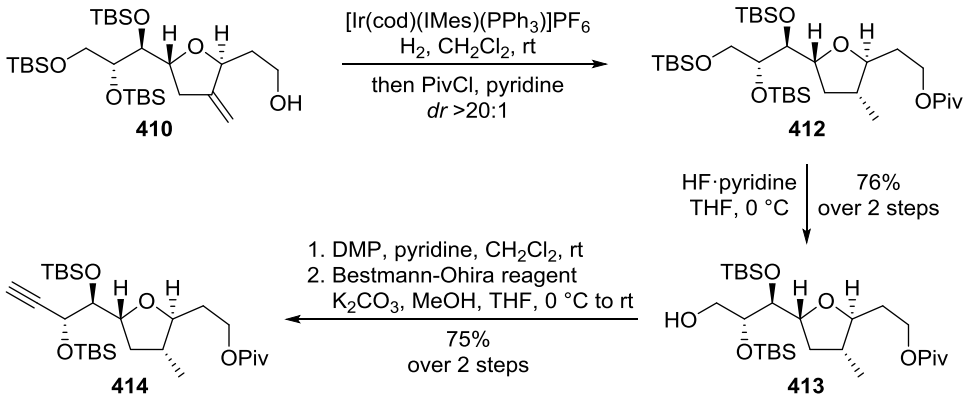
entry	catalyst	equiv. of catalyst	temp.	time	yield
1	$[Ir(cod)(pyr)(PCy_3)]PF_6$	0.10	rt	24 h	0%
2	$[Ir(cod)(pyr)(PCy_3)]PF_6$	0.20	rt	24 h	0%
3	$[Ir(cod)(pyr)(PCy_3)]PF_6$	0.50	rt	24 h	14%
4	$[Ir(cod)(pyr)(PCy_3)]PF_6$	1.00	rt	24 h	24%
5	$[Ir(cod)(IMes)(PPh_3)]PF_6$	0.10	−78 °C to rt	30 min	97%
6	$[Ir(cod)(IMes)(PPh_3)]PF_6$	0.05	−78 °C to rt	30 min	96%
7	$[Ir(cod)(IMes)(PPh_3)]PF_6$	0.01	−78 °C to rt	1 h	96%

The use of 10 or 20 mol% of Crabtree's catalyst did not result in hydrogenation and most of the starting material was recovered at the end of the reaction (entries 1 and 2). Increasing the amount of catalyst to 50 mol % resulted in the formation of a small amount of the desired product **411** (entry 3). However, even when a stoichiometric amount of Crabtree's catalyst was employed, the product **411** could be isolated in only 24% yield (entry 4). Prolonging the reaction time did not provide any improvement and heating the reaction mixture to higher temperatures was not considered to be a viable option. In fact, Crabtree's iridium-based species is known to be thermally unstable and is prone to deactivation *via* the irreversible formation of inactive clusters.[120]

Recently, Kerr and co-workers developed a series of novel iridium(I) complexes containing bulky N-heterocyclic carbene ligands and encumbered phosphine ligands which showed higher activity and increase stability with respect to the

Crabtree's catalyst.[121] Pleasingly, performing the hydrogenation reaction in the presence of 10 mol% of $[Ir(cod)(IMes)(PPh_3)]PF_6$ resulted in the formation of the desired product as a single diastereoisomer in almost quantitative yield after only 30 min (entry 5). This represents the first example of the use of Kerr's catalyst to perform a directed diastereoselective hydrogenation. More importantly, reduction of the catalyst loading to 1 mol% did not affect the yield or the diastereoselectivity (entry 7).

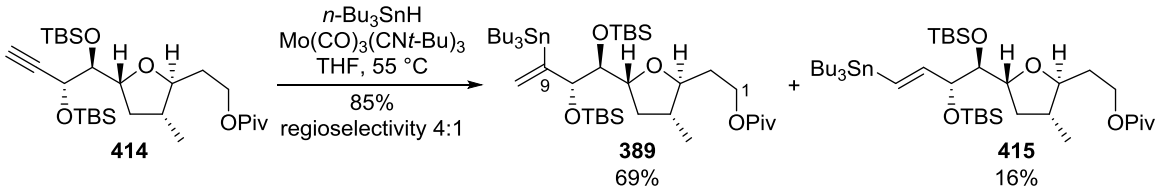
Directed hydrogenation of alkene **410** using 1 mol% of $[Ir(cod)(IMes)(PPh_3)]PF_6$ as the catalyst followed by one-pot Piv protection of the free hydroxyl group provided the intermediate THF **412** as a single diastereoisomer (Scheme 118). Subsequent selective cleavage of the primary TBS-ether by exposure to HF·pyridine at 0 °C afforded the alcohol **413** in good yield. The alcohol **413** was then oxidised to the corresponding aldehyde and this was converted into the terminal alkyne **414** in 75% yield over 2 steps using the Bestmann-Ohira protocol.[94]



Scheme 118

The last step to complete the C1-C9 fragment was the challenging regioselective hydrostannation of hindered terminal alkyne **414** (Scheme119). Two related compounds had been shown[36i,l] to undergo regioselective hydrostannation using the protocol developed by Kazmaier,[122] which involves the use of a molybdenum-based catalyst prepared by Coville and co-workers.[123] With this in mind, alkyne **414** was treated with an excess of *n*-Bu_3SnH in the presence of catalytic amount of molybdenum complex $Mo(CO)_3(CN\textit{t}\text{-}Bu)_3$ in THF at 55 °C. As a consequence of the extreme steric hindrance caused by the TBS groups, the hydrostannation

reaction proceeded slowly in 48 h. Using these conditions, the desired 1,1-disubstituted olefin **389** was obtained as the major product (68% yield) and the *E*-disubstituted olefin **415** as the minor product (16% yield). Pleasingly, these two regioisomers were separable by column chromatography on silica gel and pure C1-C9 fragment **389** could be obtained.



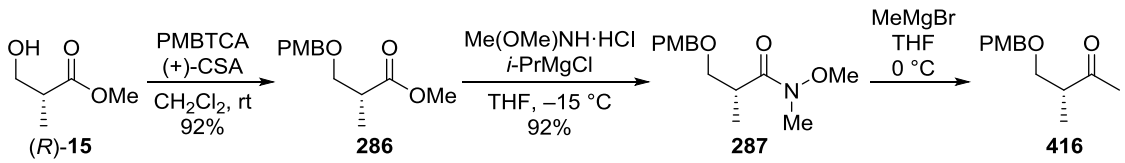
Scheme119

It is worth noting that when hydrostannation of the alkyne **414** was performed using $Pd(PPh_3)_4$ as catalyst a reversal of regioselectivity was observed and a 1:4 mixture of products was obtained favouring the *E*-disubstituted olefin **415**.

In conclusion C1-C9 fragment **389** was prepared from tri-*O*-acetyl-D-glucal **391** in 20 steps with an overall yield of 7.1%.

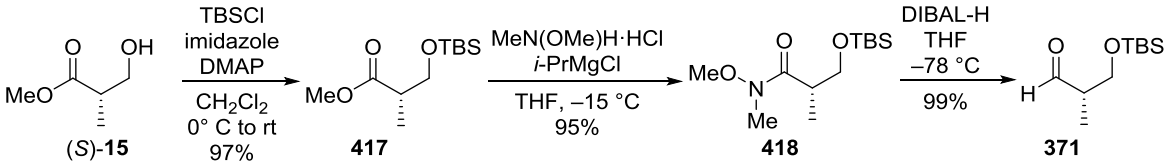
2.6.2 Preparation of the C10-C17 Fragment

The synthesis of the C10-C17 fragment commenced from the commercially available ester (*R*)-**15** as a chiral pool starting material. The alcohol was converted into the corresponding PMB-ether **286** by reaction with PMBTCA in the presence of a catalytic amount of (+)-CSA (Scheme 120). Subsequent treatment of ester **286** with *N,O*-dimethylhydroxylamine hydrochloride in the presence of isopropylmagnesium chloride as base furnished the Weinreb amide **287** in 92% yield. Reaction of the amide **287** with methylmagnesium bromide afforded the target methyl ketone **416** in high yield.



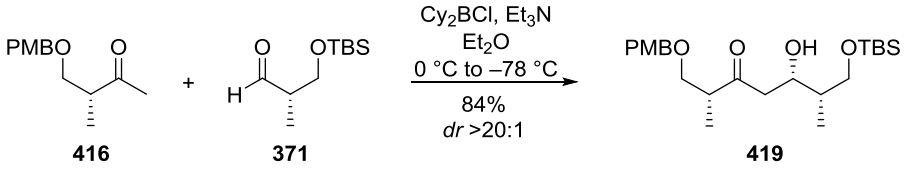
Scheme 120

Aldehyde **371**, the requisite aldol coupling partner, was prepared from the commercially available ester (*S*)-**15** in a 3-step sequence (Scheme 121). The hydroxyl group was protected as a TBS ether to give the ester **417**, which was then converted into the corresponding Weinreb amide **418** in excellent yield. Reduction of the Weinreb amide **418** with DIBAL-H at low temperature afforded the aldehyde **371** in almost quantitative yield.



Scheme 121

Aldol condensation of the aldehyde **371** with the boron enolate generated from the methyl ketone **416** proceeded in good yield and afforded the ß-hydroxy ketone **419** as a single diastereoisomer, presumably as a consequence of 1,4-stereoinduction (Scheme 122).[115]



Scheme 122

The remarkably high level of diastereoselectivity operating in the Cy_2BCl-mediated aldol reaction can be traced to the relative steric and electronic properties of the three substituents at the α stereogenic centre of the boron enolate generated from the methyl ketone **416**.[124,125] The boron aldol reaction proceed *via* a boat-shaped transition state in which it is most favourable to orient the alkoxy group toward the formyl hydrogen to form a stabilising hydrogen bond between the alkoxy oxygen and the aldehyde proton (Scheme 123).[125] The diastereomeric differentiation derives from a steric interaction between the methyl group at the α stereogenic centre of the boron enolate and the enolate double bond. In the favoured transition state **420a**, leading to the attack on the *si*-face of the aldehyde, there is a *gauche* interaction between the enolate double bond and a hydrogen. The competing transition state **420b**, leading to the attack on the *re*-face of the aldehyde, experiences an

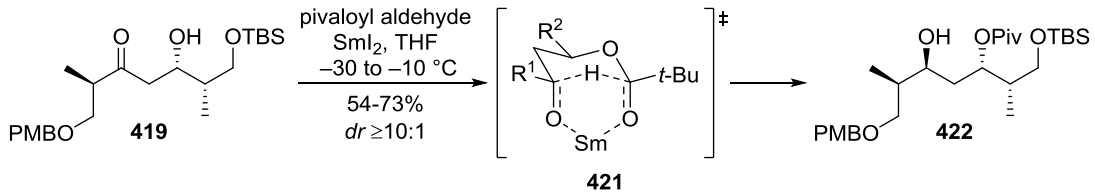
unfavourable *gauche* interaction between the methyl group and the enolate double bond.

420a
si-face attack
favoured

420b
re-face attack

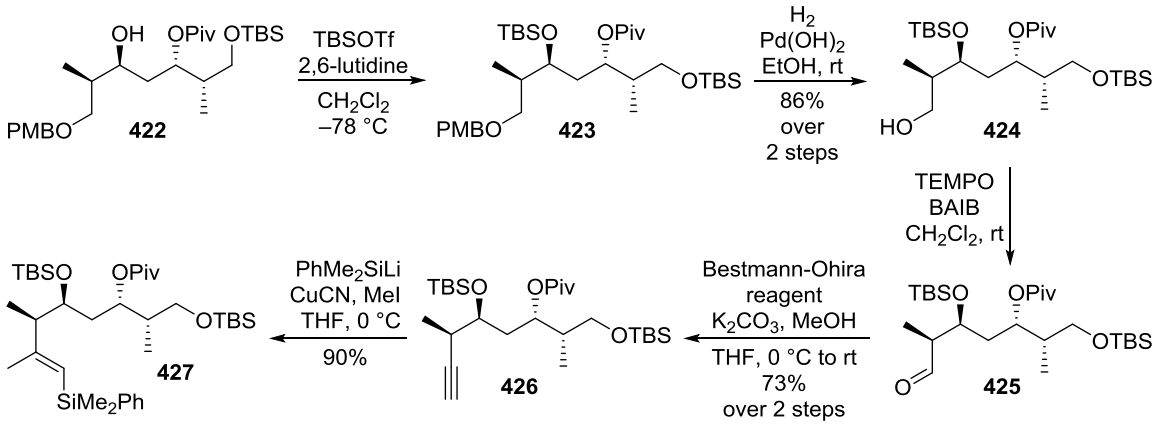
Scheme 123

The desired stereochemistry at C13 was set by Evans-Tishchenko reduction of the ß-hydroxy ketone **419** using pivaloyl aldehyde as hydride donor (Scheme 124).[126] The reaction proved to be quite capricious and the diol monoester **422** was obtained in yields ranging between 54% and 73%, with *dr* ranging between 10:1 and >20:1. The *anti*-selectivity of the Evans-Tishchenko reduction can be explained with chelated transition state **421**.



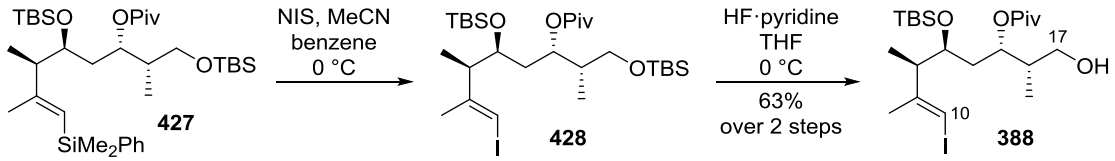
Scheme 124

The alcohol **422** was protected as TBS ether and the resulting intermediate **423** was subjected to hydrogenation in the presence of the Pearlman's catalyst to cleave the PMB protecting group and give the primary alcohol **424** in 86% yield over 2 steps (Scheme 125). The alcohol **424** was then oxidised to give the corresponding aldehyde **425** using a catalytic amount of TEMPO in the presence of $PhI(OAc)_2$ as co-oxidant. The intermediate aldehyde **425** was then converted into the terminal alkyne **426** using the Bestmann-Ohira protocol in 73% yield over 2 steps.[94] The terminal alkyne **426** was subjected to silylcupration followed by methyl iodide quench, affording the vinylic silane **427** in excellent yield as a single isomer.[127]



Scheme 125

The requisite iodide functionality necessary for the Stille coupling reaction was installed by iodine-for-silicon exchange by treatment of the vinylic silane **427** with *N*-iodosuccinimide to give the iodide **428** (Scheme 126). Completion of the C10-C17 fragment was accomplished by selective cleavage of the primary TBS ether by exposure to HF·pyridine in THF at 0 °C and the alcohol **388** was obtained in 63% yield over 2 steps.



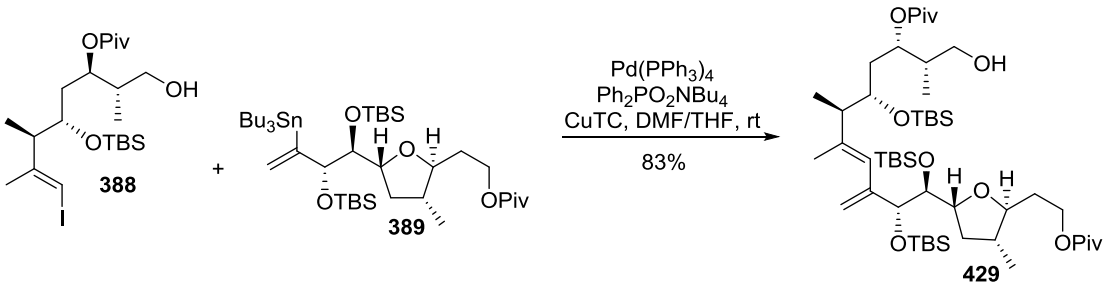
Scheme 126

The C10-C17 fragment **388** was prepared from commercially available Roche ester **15** in 12 steps with an overall yield of 22%. Having completed the synthesis of both segments, efforts were then focused on the coupling of the two fragments and the preparation of the final iodide fragment **386**.

2.6.3 Completion of the C1-C17 Fragment

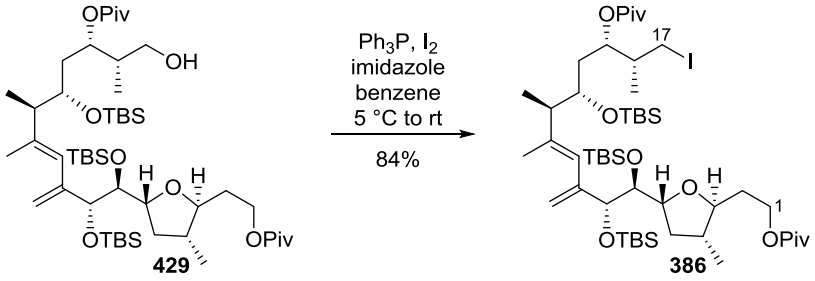
Coupling of the iodide **388** and the stannane **389** was performed by Stille cross-coupling. This reaction allowed the isomerization-prone 1,3-diene unit of compound **429** to be assembled (Scheme 127). The Stille coupling reaction was carried out using the very mild conditions developed by Fürstner and co-workers.[128] Fürstner protocol involves the use of copper(I) thiophene-2-carboxylate (CuTC) to favour transmetallation of the tin reagents with formation

of an organocopper species, which is more nucleophilic ensuing a positive effect on the rate and efficiency of the reaction.[129] As the tin/copper exchange is likely reversible, and the phosphinate salt $[Ph_2PO_2][NBu_4]$ is added to the reaction mixture as an essentially neutral tin scavenger driving the equilibrium towards the formation of the organocopper species.[130] Under these conditions the desired alcohol **429** was obtained in a remarkable 83% yield.



Scheme 127

Transformation of the alcohol **429** into the corresponding iodide **386** by treatment with iodine in the presence of PPh_3 and imidazole completed the synthesis of the C1-C17 fragment of amphidinolides C and F (Scheme 128).



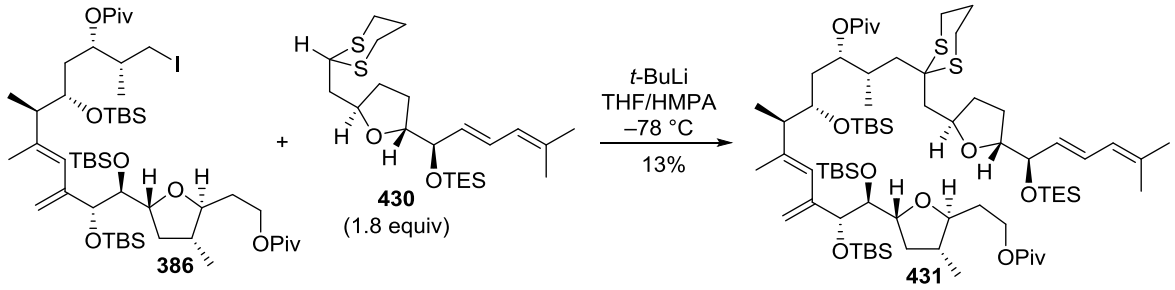
Scheme 128

The C1-C17 fragment of amphidinolides C and F **386** was synthetized from tri-*O*-acetyl-D-glucal **391** in 22 steps with an overall yield of 5%. With the iodide **386** in hand, the stage was set to couple the two main fragments.

2.6.4 Attemped Fragment Coupling

Amphidinolide F was chosen as first target to test the conditions for the fragment coupling and eventually develop the end game of the synthesis because it features a simpler side chain.

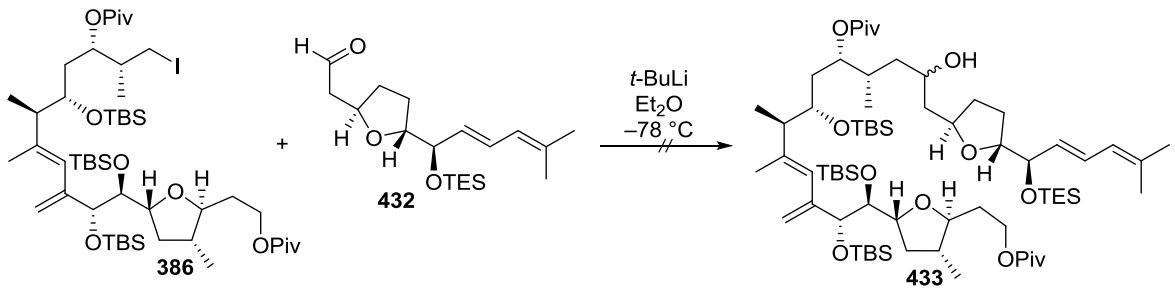
According to the initial plan, fragment coupling was attempted by displacement of iodide within fragment **386** using the anion generated by deprotonation of dithiane **430**, prepared in our group by Ludovic Decultot, with *t*-BuLi in the presence of HMPA (Scheme 129).



Scheme 129

The reaction was quenched after 1 h and delivered the desired dithiane **431** in only 13% yield. Amounts of both the iodide **386** and the dithiane **430** were partially recovered - 50% and 42% respectively. Prolonging the reaction time was not beneficial with formation of the product in similar yields, but with increased decomposition and lower recovery of the two starting materials.

As a consequence of the poor yield obtained from the umpolung coupling reaction, a different approach involving the addition of the organolithium species, prepared from iodide **386**, to the aldehyde **432** was investigated (Scheme 130). Unfortunately, treatment of the iodide **386** with *t*-BuLi followed by addition of the aldehyde **432** resulted in rapid decomposition of the iodide **386** and formation of the desired alcohol **433** was not observed. The same result was obtained when *t*-BuLi was added to a mixture of the iodide **386** and the aldehyde **432** in Et_2O at −78°C.

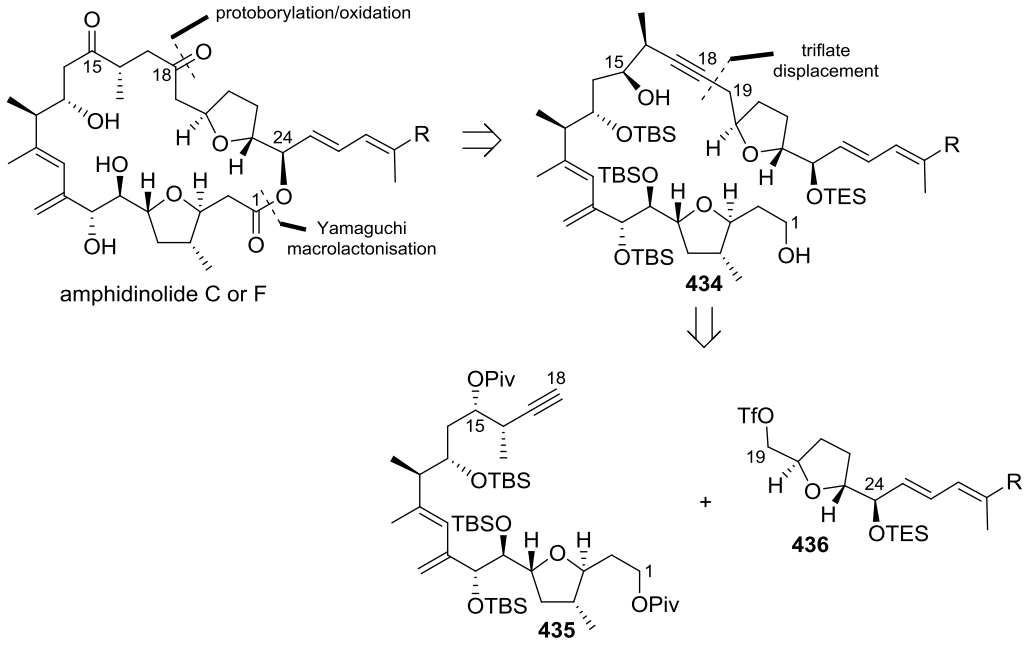


Scheme 130

2.6.5 Revised Strategy towards the Amphidinolides C and F

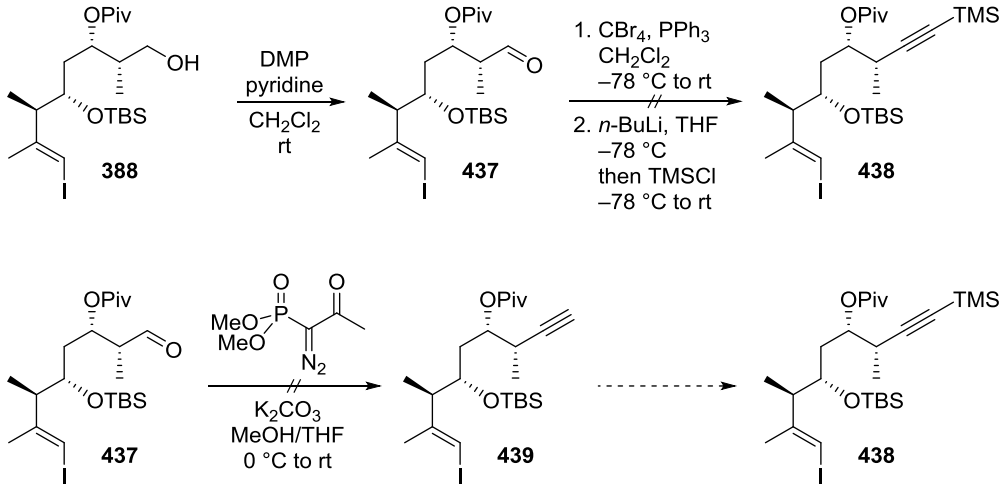
The results obtained from attempted of fragment coupling suggested that a new strategy was required.

The new strategy relies on the possibility of installing the 1,4-diketone moiety at C15 and C18 by a protoborylation/oxidation sequence and the homopropargylic alcohol **434** was identified as an advanced intermediate (Scheme 131).[131] Disconnection of the C18—C12 bond in the intermediate **434** reveals the C1-C18 alkyne fragment **435** and the triflate fragment **436**. My work focused on the preparation of the C1-C18 alkyne fragment **435**.



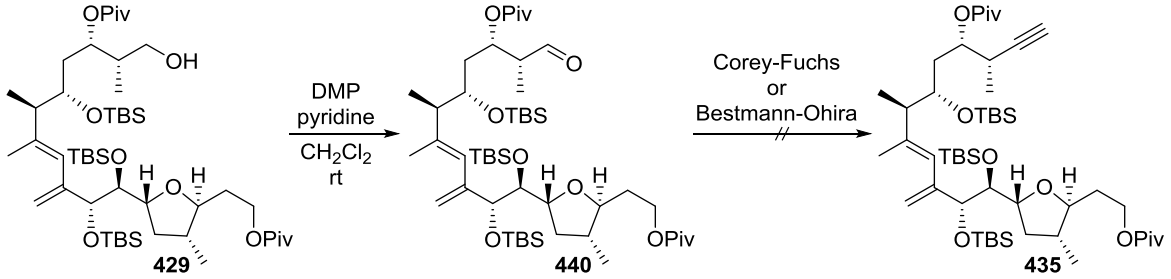
Scheme 131

The initial idea involved the transformation of the previously prepared alcohol **388** (Section 2.6.2) into the corresponding terminal TMS-alkyne **438**, which would then be coupled with stannane **389** by Stille reaction. According to this plan alcohol **388** was oxidised to the corresponding aldehyde **437** using DMP (Scheme 132). Unfortunately, when the intermediate aldehyde **437** was subjected to Corey-Fuchs[93] or Bestmann-Ohira[94] conditions formation of the desired alkyne was not observed and only decomposition occurred.



Scheme 132

Due to the failure of this approach, the possibility of converting the alcohol **429** into the alkyne **435** was investigated (Scheme 133). Oxidation of the alcohol **429** into the intermediate aldehyde **440** by treatment with DMP occurred without any problem. Once again, when the intermediate aldehyde **440** was subjected to Corey-Fuchs[93] or Bestmann-Ohira[94] conditions the desired alkyne **435** was not produced and only decomposition occurred.



Scheme 133

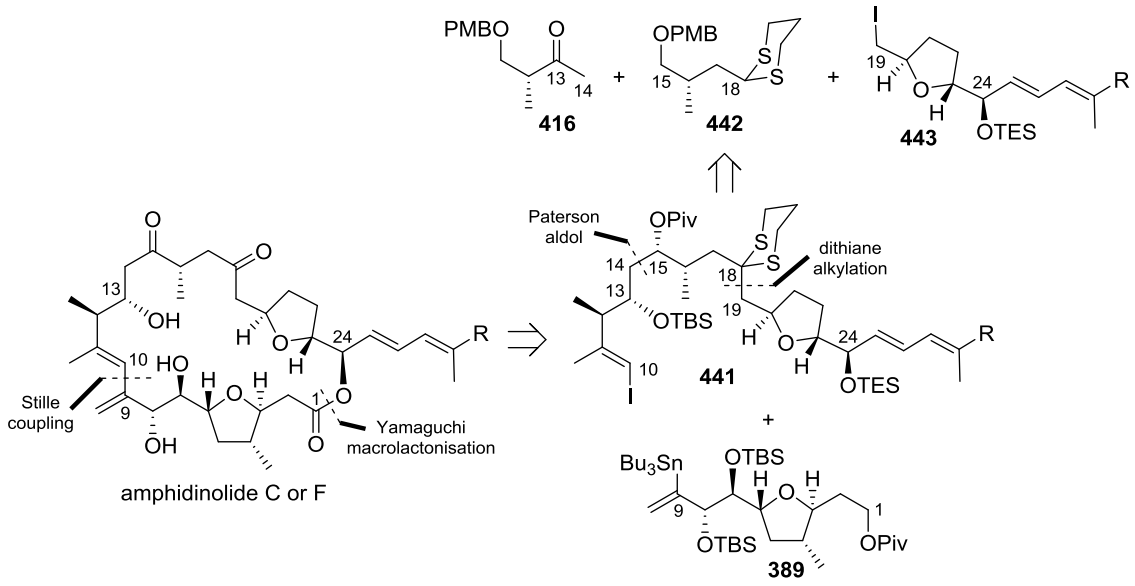
In the light of these results, a new route towards vinylic iodide **437**, in which the TMS-alkyne functionality is introduced in an early stage of the synthesis, is required.

2.6.6 Conclusions and Future Work

The synthesis of the C1-C17 iodide fragment of amphidinolides C and F **386** was successfully completed in 22 steps from commercially available tri-*O*-acetyl-D-glucal **391** with an overall yield of 5%. The pivotal *trans* trisubstituted

tetrahydrofuran ring moiety was assembled employing the [2,3]-sigmatropic rearrangement of an oxonium ylide generated by decomposition of a 1-sulfonyl-1,2,3-triazoles.[77] The key connection between the two segments was achieved by Stille cross-coupling under very mild conditions, resulting in assembly of the isomerization-prone 1,3-diene unit in high yield. The umpolung coupling between the iodide **386** and C18-C29 dithiane fragment of amphidinolide F **430** afforded the desired product in a poor 13% yield, and so a revision of the strategy towards amphidinolides C and F is required.

The new approach could rely on the robust Stille cross-coupling for assembling the two main fragments and the use of a Paterson aldol/Evans-Tishchenko reduction sequence in a late stage of the synthesis to set the desired stereochemistry at C13 (Sheme 134).



Scheme 134

Disconnections at the C—O macrolactone bond and at the C9—C10 bond would reveal two main fragments, the vinylic iodide **441** and the previously prepared stannane **389** (Section 2.6.1). The C14—C15 bond could be formed by a boron aldol reaction and the so formed stereocentre at C15 can be used to direct the installation of the desired stereochemistry at C13 by means of an Evans-Tishchenko reduction. The C18—C19 bond could be formed by alkylation of dithiane **442** with iodide **443**.

3 Experimental Section

General Experimental

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

All reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 covered aluminium backed plates F_{254}. TLC plates were visualised under UV light and stained using potassium permanganate solution, acidic ethanolic anisaldehyde solution or phosphomolybdic acid solution. Flash column chromatography was performed with silica gel (Fluorochem LC60A 35-70 μm, or Geduran Si 60 35-70 μm) as solid support.

IR spectra were recorded using a Shimadzu FT IR-8400S ATR instrument. The IR spectrum of each compound (solid or liquid) was acquired directly on a thin layer at ambient temperature.

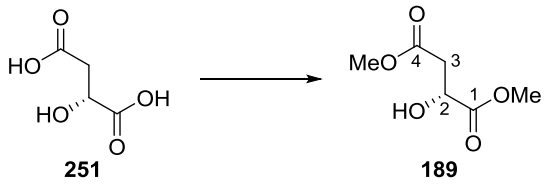
All ^{1}H NMR spectra were recorded on Bruker Avance III 400 MHz and 500 MHz spectrometers at ambient temperature. Data are reported as follows; chemical shifts in ppm relative to $CHCl_3$ (7.26) or C_6H_6 (7.16) on the δ scale, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, app. = apparent or a combination of these), coupling constant(s) *J* (Hz) and assignment. All ^{13}C NMR spectra were recorded on Bruker Avance III 400 MHz and 500 MHz spectrometers at 101 MHz and 126 MHz at ambient temperature and multiplicities were obtained using a DEPT sequence. Data are reported as follow; chemical shifts in ppm relative to $CDCl_3$ (77.16) or C_6D_6 (128.1) on the δ scale and assignment.

Optical rotations were recorded with an error of $\leq\pm0.1$ using an automatic polarimeter Autopol V.

High resolution mass spectra (HRMS) were recorded using positive chemical ionization (CI+) or positive ion impact (EI+) ionisation on a Jeol MStation JMS-700 instrument, or using positive or negative ion electrospray (ESI+/ESI-) techniques

on a Bruker micrOTOF-Q instrument. Low resolution mass spectra (LRMS) were obtained using the same instruments and the intensity of each peak is quoted as a percentage of the largest, where this information was available.
Elemental analyses were carried out on an Exeter Analytical Elemental Analyser EA 440.
Melting points were recorded with an Electrothermal IA 9100 apparatus.
Compounds were named according to the IUPAC rules, whereas numbering of the carbons has been done independently to these rules to help at their identification.

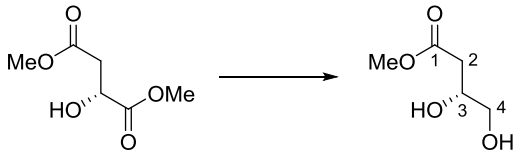
Dimethyl D-malate 189[83]



$SOCl_2$ (29.9 mL, 410 mmol) was added over 30 minutes to a solution of D-malic acid **251** (25.0 g, 190 mmol) in MeOH (450 mL) at 0 °C and upon complete addition the mixture was stirred at rt for a further 18 h. The reaction mixture was concentrated under reduced pressure 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 phase was back extracted with CH_2Cl_2 (100 mL). The combined organic phases were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentred under reduced pressure to provide the diester **189** (28.5 g, 92%) as a pale yellow oil. R_f = 0.48 (EtOAc); $[\alpha]_D^{22}$ +16.7 (c = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.46 (1H, m, CH-C2), 3.74 (3H, s, CH_3-OMe), 3.64 (3H, s, CH_3-OMe), 3.45 (1H, m, OH), 2.80 (1H, ddd, *J* = 16.4, 4.4, 1.2 Hz, CH_2-C3) 2.80 (1H, ddd, *J* = 16.4, 6.1, 1.1 Hz, CH_2-C3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7 (C-C1), 171.0 (C-C4), 67.2 (CH-C2), 52.8 (CH_3-OMe), 52.0 (CH_3-OMe), 38.5 (CH_2-C3); ν_{max} 3493, 2957, 1730, 1438, 1167, 1103 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 163.2 $[M+H]^+$ (100), 131.2 (30), 103.17 (25), 97.2 (10), 71.1 (23); HRMS (CI, *iso*-butane) calcd for $C_6H_{11}O_5$ $[M+H]^+$ 163.0633, found

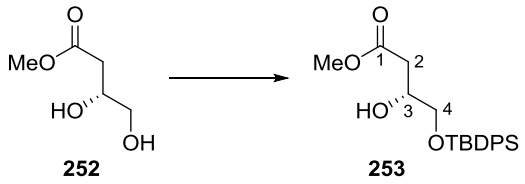
163.0631; Anal. calcd for $C_6H_{10}O_5$: C, 44.45%; H, 6.22%, found: C, 44.27%; H, 6.29%.

(*R*)-Methyl 3,4-dihydroxybutanoate 252[84]



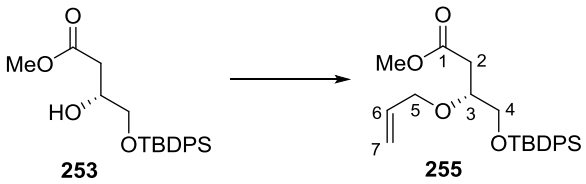
BH_3·DMS complex (16.6 mL, 180 mmol) was added dropwise to a stirring solution of α-hydroxy ester **189** (28.4 g, 180 mmol) in THF (336 mL) at rt. Upon complete addition and cessation of gas evolution the reaction mixture was stirred for 30 minutes. $NaBH_4$ (662 mg, 17.5 mmol) was added to the solution in two equal portions over 5 min and the reaction stirred for 3 h at rt. The reaction was quenched by addition of MeOH (200 mL) followed by stirring for 10 min. The resulting solution was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc) to provide the diol **252** (20.0 g, 85%) as a colourless oil. R_f = 0.23 (EtOAc); $[\alpha]_D^{22}$ +53.8 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18—4.09 (1H, m, CH-C3), 3.72 (3H, s, CH_3-OMe), 3.71—3.64 (1H, m, CH_2-C4), 3.52 (1H, dt, *J* = 11.2, 5.5 Hz, CH_2-C4), 3.40—3.34 (1H, m, OH), 2.57 (1H, dd, J = 16.5, 8.5 Hz, CH_2-C2), 2.50 (1H, dd, J = 16.5, 4.1 Hz, CH_2-C2), 2.45—2.34 (1H, m, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9 (C-C1), 68.7 (CH-C3), 65.8 (CH_2-C4), 52.0 (CH_3-OMe), 37.8 (CH_2-C2); ν_{max} 3379, 2955, 2886, 1720, 1442, 1165, 1034 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 135.2 $[M+H]^+$ (82), 103.2 (100); HRMS (CI, *iso*-butane) calcd for $C_5H_{11}O_4$ $[M+H]^+$ 135.0657, found 135.0656; Anal. calcd for $C_5H_{10}O_4$: C, 44.77%; H, 7.61%, found: C, 44.45%; H, 7.61%.

(*R*)-Methyl 4-[(*tert*-butyldiphenylsilyl)oxy]-3-hydroxybutanoate 253



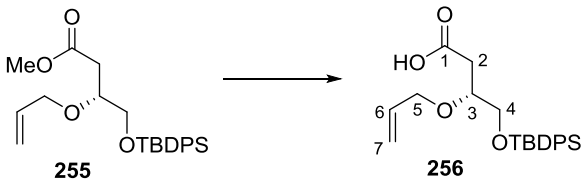
TBDPSCl (38.7 mL, 149 mmol) and Et_3N (39.5 mL, 283 mmol) were added sequentially to a solution of diol **252** (19.0 g, 141 mmol) in CH_2Cl_2 (150 mL) at 0 °C. The solution was stirred for 15 min at 0 °C, then a single portion of DMAP (3.46 g, 28.3 mmol) was added and the mixture was stirred at rt for 63 h. The reaction was quenched by addition of 1 M aqueous HCl (300 mL) and extracted with CH_2Cl_2 (3 × 250 mL). The combined organic phases were washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 9:1 to 4:1) to provide the silyl ether **253** (47.5 g, 90%) as a pale yellow oil. R_f = 0.16 (petroleum ether–EtOAc, 9:1); $[\alpha]_D^{26}$ +7.85 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69—7.63 (4H, m, Ph-TBDPS), 7.51—7.30 (6H, m, Ph-TBDPS), 4.22—4.10 (1H, m, CH-C3), 3.69 (3H, s, CH_3-OMe), 3.65 (1H, dd, *J* = 10.1, 5.8 Hz, CH_2-C4), 3.63 (1H, dd, *J* = 10.1, 5.8 Hz, CH_2-C4), 2.88 (1H, dd, *J* = 7.8, 4.8 Hz, OH), 2.62—2.48 (2H, m, CH_2-C2). 1.07 (9H, s, CH_3-*t*-Bu-TBDPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (C-C1), 135.7 (4C, *o*-CH-Ph-TBDPS), 133.2 (C-Ph-TBDPS), 133.1 (C-Ph-TBDPS), 130.0 (2C, *p*-CH-Ph-TBDPS), 128.0 (4C, *m*-CH-Ph-TBDPS), 68.8 (CH-C3), 67.0 (CH_2-C4), 51.9 (CH_3-OMe), 38.0 (CH_2-C2), 27.0 (3C, CH_3-*t*-Bu-TBDPS) 19.4 (C-*t*-Bu-TBDPS); ν_{max} 3496, 2932, 2859, 1736, 1428, 1108, 1067, 701 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 373.4 $[M+H]^+$ (10), 295.3 (100), 257.3 (22), 237.2 (16), 217.3 (86); HRMS (CI, *iso*-butane) calcd for $C_{21}H_{29}O_4Si$ $[M+H]^+$ 373.1835, found 373.1831; Anal. calcd for $C_{21}H_{28}O_4Si$: C, 67.71%; H, 7.58%, found: C, 67.55%; H, 7.58%.

(*R*)-Methyl 3-(allyloxy)-4-[(*tert*-butyldiphenylsilyl)oxy]butanoate 255



To a solution of alcohol **253** (20.0 g, 53.7 mmol) and allyl tricholoacetimidate **254** (21.7 g, 105 mmol) in petroleum ether (50 mL) was added TfOH (354 µL, 4.03 mmol) at rt. The mixture was stirred at rt for 18 h, then filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 50:1 to 19:1) to provide the allyl ether **255** (19.3 g, 87%) as a pale yellow oil. R_f = 0.45 (petroleum ether–EtOAc, 9:1); $[\alpha]_D^{26}$ +22.8 (c = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73—7.66 (4H, m, Ph-TBDPS), 7.48—7.38 (6H, m, Ph-TBDPS), 5.86 (1H, ddt, *J* = 17.2, 10.4, 5.7 Hz, CH-C6), 5.23 (1H, ddd, *J* = 17.2, 1.6, 0.7 Hz, CH_2-C7), 5.14 (1H, ddd, *J* = 10.4, 1.2, 0.6 Hz, CH_2-C7), 4.09 (1H, ddd, *J* = 12.7, 5.7, 0.6 Hz, CH_2-C5), 4.02 (1H, ddd, *J* = 12.7, 5.7, 0.7 Hz, CH_2-C5), 3.96 (1H, dtd, *J* = 9.5, 5.2, 4.6 Hz, CH-C3), 3.76 (1H, ddd, *J* = 10.6, 5.2, 0.9 Hz, CH_2-C4), 3.70 (3H, s, CH_3-OMe), 3.64 (1H, ddd, *J* = 10.6, 5.2, 1.0 Hz, CH_2-C4), 2.71 (1H, ddd, *J* = 15.7, 4.6, 0.9 Hz, CH_2-C2), 2.58 (1H, ddd, *J* = 15.7, 9.5, 1.0 Hz, CH_2-C2), 1.08 (9H, s, CH_3-*t*-Bu-TBDPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (C-C1), 135.7 (2C, *o*-CH-Ph-TBDPS), 135.7 (2C, *o*-CH-Ph-TBDPS), 135.1 (CH-C6), 133.4 (C-Ph-TBDPS), 133.4 (C-Ph-TBDPS), 129.8 (2C, *p*-CH-Ph-TBDPS), 127.8 (4C, *m*-CH-Ph-TBDPS), 116.9 (CH_2-C7), 76.4 (CH-C3), 71.5 (CH_2-C5), 65.3 (CH_2-C4), 51.7 (CH_3-OMe), 37.5 (CH_2-C2), 26.9 (3C, CH_3-*t*-Bu-TBDPS) 19.3 (C-*t*-Bu-TBDPS); ν_{max} 3072, 2931, 2859, 1739, 1428, 1110, 1074, 701 cm^{-1}; LRMS (CI, *iso*-butane) *m*/*z* (intensity) 413.3 $[M+H]^+$ (85), 335.3 (100), 217.2 (41), 172.2 (15), 73.1 (24); HRMS (CI, *iso*-butane) calcd for $C_{24}H_{33}O_4Si$ $[M+H]^+$ 413.2148, found 413.2150; Anal. calcd for $C_{24}H_{32}O_4Si$: C, 69.86%; H, 7.82%, found: C, 69.18%; H, 7.85%.

(*R*)-3-(Allyloxy)-4-[(*tert*-butyldiphenylsilyl)oxy]butanoic acid 256



To a solution of ester **255** (20.0 g, 48.5 mmol) in MeOH (260 mL) at rt was added an aqueous 1 M solution of KOH (58.2 mL, 58.2 mmol). The resultant mixture was stirred for 5 h at rt and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 mL) and 1 M aqueous HCl was added until pH 2 was reached. The organic phase was isolated and the aqueous phase back extracted with CH_2Cl_2 (2 × 150 mL). The combined organic phases were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 3:1) to provide the acid **256** (16.0 g, 83%) as a pale yellow oil. R_f = 0.23 (petroleum ether–EtOAc, 3:1); $[\alpha]_D^{25}$ +22.7 (c = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.60 (1H, bs, OH-acid), 7.70—7.64 (4H, m, Ph-TBDPS), 7.47—7.35 (6H, m, Ph-TBDPS), 5.84 (1H, ddt, *J* = 17.1, 10.4, 5.7 Hz, CH-C6), 5.21 (1H, ddt, *J* = 17.1, 1.7, 1.3 Hz, CH_2-C7), 5.14 (1H, ddt, *J* = 10.4, 1.7, 1.3 Hz, CH_2-C7), 4.07 (1H, ddt, *J* = 12.5, 5.7, 1.3 Hz, CH_2-C5), 4.00 (1H, ddt, *J* = 12.5, 5.7, 1.3 Hz, CH_2-C5), 3.90 (1H, ddt, *J* = 7.9, 5.6, 4.7 Hz, CH-C3), 3.73 (1H, dd, *J* = 10.6, 4.7 Hz, CH_2-C4), 3.63 (1H, dd, *J* = 10.6, 5.6 Hz, CH_2-C4), 2.74 (1H, dd, *J* = 16.0, 4.7 Hz, CH_2-C2), 2.62 (1H, dd, *J* = 16.0, 7.9 Hz, CH_2-C2), 1.05 (9H, s, CH_3-*t*-Bu-TBDPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9 (C-C1), 135.8 (2C, *o*-CH-Ph-TBDPS), 135.7 (2C, *o*-CH-Ph-TBDPS), 134.6 (CH-C6), 133.3 (C-Ph-TBDPS), 133.2 (C-Ph-TBDPS), 130.0 (2C, *p*-CH-Ph-TBDPS), 127.9 (2C, *m*-CH-Ph-TBDPS), 127.9 (2C, *m*-CH-Ph-TBDPS), 117.5 (CH_2-C7), 76.0 (CH-C3), 71.5 (CH_2-C5), 65.0 (CH_2-C4), 37.3 (CH_2-C2), 26.9 (3C, CH_3-*t*-Bu-TBDPS) 19.3 (C-*t*-Bu-TBDPS); ν_{max} 2960, 2935, 2860, 2362, 2339, 1711, 1428, 1113, 1073, 910, 736, 702 cm^{-1}; LRMS (CI, *iso*-butane) *m*/*z* (intensity) 399.3 $[M+H]^+$ (22), 341.3 (20), 321.3 (100), 243.2 (45), 203.2 (37); HRMS (ESI+) calcd for $C_{23}H_{31}O_4Si$ $[M+H]^+$ 399.1992, found 399.1991.

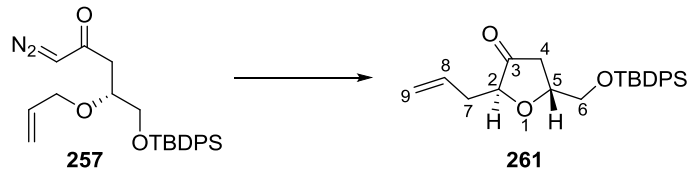
(*R*)-4-(Allyloxy)-5-[(*tert*-butyldiphenylsilyl)oxy]-1-diazopentan-2-one 257

The reaction sequence was carried out in duplicate and material was combined for work up and purification.

To a solution of carboxylic acid **256** (3.98 g, 9.99 mmol) in Et_2O (110 mL) at rt, were added sequentially Et_3N (1.39 mL, 9.99 mmol) and isobutyl chloroformate (1.44 mL, 11.0 mmol). The reaction mixture was stirred vigorously at rt for 2 h and then filtered to remove the precipitates. The solution of the anhydride was then added to a freshly distilled ethereal solution of diazomethane (99.9 mmol) at 0 °C. The resultant solution was allowed to warm to rt and stirred at that temperature for 16 h. The reaction was quenched by careful addition of AcOH (4.4 mL). The resultant acidic solutions were added carefully to saturated aqueous $NaHCO_3$ (250 mL). The ethereal phase was isolated and the aqueous phase was extracted with Et_2O (100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 19:1 to 9:1) to provide the diazo ketone **257** (7.43 g, 88%) as a yellow oil. R_f = 0.14 (petroleum ether–EtOAc, 9:1); $[\alpha]_D^{26}$ +78.2 (c = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69—7.64 (4H, m, Ph-TBDPS), 7.46—7.36 (6H, m, Ph-TBDPS), 5.84 (1H, ddt, *J* = 17.2, 10.4, 5.6 Hz, CH-C7), 5.31 (1H, bs, CH-C1), 5.21 (1H, ddt, *J* = 17.2, 1.6, 1.5 Hz, CH_2-C8), 5.12 (1H, ddt, *J* = 10.4, 1.5, 1.3 Hz, CH_2-C8), 4.05 (1H, dddd, *J* = 12.6, 5.6, 1.6, 1.3 Hz, CH_2-C6), 3.97 (1H, dddd, *J* = 12.6, 5.6, 1.5, 1.3 Hz, CH_2-C6) 3.97—3.90 (1H, m, CH-C4), 3.71 (1H, dd, *J* = 10.7, 5.0 Hz, CH_2-C5), 3.63 (1H, dd, *J* = 10.7, 5.3 Hz, CH_2-C5), 2.61 (1H, dd, *J* = 14.6, 4.1 Hz, CH_2-C3), 2.53 (1H, dd, *J* = 14.6, 6.2 Hz, CH_2-C3), 1.0 (9H, s, CH_3-*t*-Bu-TBDPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2 (C-C2), 135.8 (2C, *o*-CH-Ph-TBDPS), 135.7 (2C, *o*-CH-Ph-TBDPS), 135.0 (CH-C7), 133.4 (C-Ph-TBDPS), 133.4 (C-Ph-TBDPS), 129.9 (2C, *p*-CH-Ph-TBDPS), 127.9 (2C, *m*-CH-Ph-TBDPS), 127.9 (2C, *m*-CH-Ph-TBDPS), 117.0 (CH_2-C8), 76.6 (CH-C4), 71.5 (CH_2-C6), 65.4 (CH_2-C5), 55.5 (CH-C1), 43.8 (CH_2-C3), 26.9 (3C, CH_3-*t*-Bu-TBDPS) 19.3 (C-*t*-Bu-TBDPS); ν_{max}

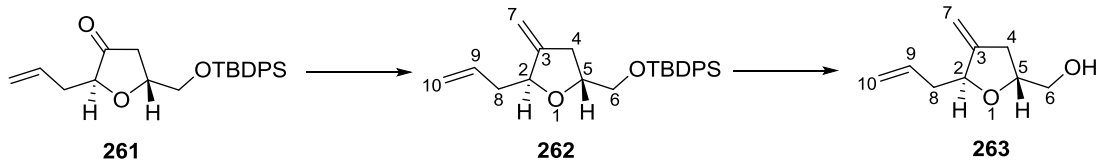
2930, 2858, 2100, 1638, 1427, 1362, 1345, 1111, 1105, 1072, 700 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 423.2$[M+H]^+$ (3), 395.3 (17), 317.2 (55), 277.2 (46), 202.2 (18), 165.2 (21), 149.1 (100), 135.1 (35), 101.1 (100), 89.1 (100), 73.1 (100); HRMS (ESI+) calcd for $C_{24}H_{30}N_2O_3SiNa$ $[M+Na]^+$ 445.1918, found 445.1903.

(2*S*,5*R*)-2-Allyl-5-{[(*tert*-butyldiphenylsilyl)oxy]methyl}dihydrofuran-3(2*H*)-one 261



A solution of diazo ketone **257** (5.00 g, 11.8 mmol) in THF (180 mL) was added over 30 min to a stirred solution of $Cu(acac)_2$ (310 mg, 1.18 mmol) in THF (180 mL) at reflux. Upon complete addition, the mixture was heated for a further 40 min and then cooled to rt. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatogrphy on silica gel (petroleum ether–Et_2O, 19:1 to 9:1) to afford the ketone **261** (4.25 g, 91%, *dr* >20:1) as a colourless solid. R_f = 0.43 (petroleum ether–EtOAc, 9:1); mp = 62–63 °C; $[\alpha]_D^{25}$ –67.1 (c = 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69—7.61 (4H, m, Ph-TBDPS), 7.48—7.35 (6H, m, Ph-TBDPS), 5.83 (1H, dddd, *J* = 17.1, 10.2, 7.2, 6.7 Hz, CH-C8), 5.20—5.13 (1H, m, CH_2-C9), 5.16—5.11 (1H, m, CH_2-C9), 4.49 (1H, tdd, *J* = 6.2, 3.1, 2.8 Hz, CH-C5), 4.23 (1H, dd, *J* = 7.2, 4.4 Hz, CH-C2), 3.96 (1H, dd, *J* = 11.0, 3.1 Hz, CH_2-C6), 3.64 (1H, dd, *J* = 11.0, 2.8 Hz, CH_2-C6), 2.56 (2H, d, *J* = 6.2 Hz, CH_2-C4), 2.55—2.47 (1H, m, CH_2-C7), 2.31 (1H, dt, *J* = 14.6, 7.2 Hz, CH_2-C7) 1.03 (9H, s, CH_3-*t*-Bu-TBDPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.7 (C-C3), 135.7 (2C, *o*-CH-Ph-TBDPS), 135.6 (2C, *o*-CH-Ph-TBDPS), 133.2 (CH-C8), 132.9 (C-Ph-TBDPS), 132.8 (C-Ph-TBDPS), 130.0 (*p*-CH-Ph-TBDPS), 129.9 (*p*-CH-Ph-TBDPS), 127.9 (4C, *m*-CH-Ph-TBDPS), 118.2 (CH_2-C9), 79.7 (CH-C2), 75.7 (CH-C5), 67.4 (CH_2-C6), 38.4 (CH_2-C4), 36.4 (CH_2-C7), 26.8 (3C, CH_3-*t*-Bu-TBDPS) 19.2 (C-*t*-Bu-TBDPS); ν_{max} 2957, 2932, 2859, 1757, 1427, 1111, 1086, 739, 700 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 395.3 $[M+H]^+$ (52), 317.3 (100), 289.3 (12), 239.2 (9); HRMS (CI, *iso*-butane) calcd for $C_{24}H_{31}O_3Si$ $[M+H]^+$ 395.2042, found 395.2039.

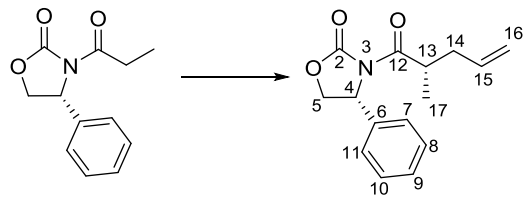
[(2*R*,5*S*)-5-Allyl-4-methylenetetrahydrofuran-2-yl]methanol 263



A solution of *t*-BuOK (7.85 g, 45.6 mmol) in THF (60 mL) was added dropwise to a suspension of methyltriphenylphosphonium bromide (16.3 g, 45.6 mmol) in THF (80 mL) at rt. Upon complete addition, the resultant yellow mixture was stirred at rt for a further 1 h before dropwise addition of a solution of ketone **261** (6.00 g, 15.2 mmol) in THF (100 mL). The mixture was stirred at rt for 1h and the reaction was quenched by addition of H_2O (100 mL). The mixture was extracted with EtOAc (3 × 160 mL) and the combined organic phases were washed with brine (160 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a short pad of silica gel (petroleum ether–EtOAc, 19:1) to afford the crude diene **262** as a pale yellow oil. R_f = 0.83 (petroleum ether–EtOAc, 9:1); $[\alpha]_D^{25}$ −57.2 (c = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70—7.64 (4H, m, Ph-TBDPS), 7.44—7.33 (6H, m, Ph-TBDPS), 5.86 (1H, ddt, *J* = 17.1, 10.2, 7.0 Hz, CH-C9), 5.16—5.05 (2H, m, CH_2-C10), 5.01 (1H, dd, *J* = 4.3, 2.2 Hz, CH_2-C7), 4.86 (1H, dd, *J* = 4.3, 2.2 Hz, CH_2-C7), 4.47 (1H, ddd, *J* = 6.2, 4.3, 1.7 Hz, CH-C2), 4.23 (1H, ddt, *J* = 7.4, 5.7, 4.6 Hz, CH-C5), 3.67 (1H, dd, *J* = 10.4, 4.6 Hz, CH_2-C6), 3.62 (1H, dd, *J* = 10.4, 5.7 Hz, CH_2-C6), 2.69 (1H, dddd, *J* = 15.8, 7.4, 4.3, 2.2 Hz, CH_2-C4), 2.63—2.56 (1H, m, CH_2-C4), 2.43—2.35 (1H, m, CH_2-C8), 2.33—2.25 (1H, m, CH_2-C8), 1.05 (9H, s, CH_3-*t*-Bu-TBDPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9 (C-C3), 135.8 (4C, *o*-CH-Ph-TBDPS), 134.9 (CH-C9), 133.8 (C-Ph-TBDPS), 133.7 (C-Ph-TBDPS), 129.8 (*p*-CH-Ph-TBDPS), 129.7 (*p*-CH-Ph-TBDPS), 127.8 (4C, *m*-CH-Ph-TBDPS), 117.1 (CH_2-C10), 105.1 (CH_2-C7), 80.1 (CH-C2), 78.0 (CH-C5), 66.3 (CH_2-C6), 40.3 (CH_2-C8), 35.2 (CH_2-C4), 27.0 (3C, CH_3-*t*-Bu-TBDPS) 19.4 (C-*t*-Bu-TBDPS); ν_{max} 2957, 2931, 2858, 1427, 1110, 1075, 700 cm^{-1}; LRMS (CI, *iso*-butane) *m*/*z* (intensity) 393.2 $[M+H]^+$ (3), 335.2 (25), 315.2 (19), 241.1 (100), 221.1 (90); HRMS (CI, *iso*-butane) calcd for $C_{25}H_{33}O_2Si$ $[M+H]^+$ 393.2250, found 393.2250.

TBAF (16.7 mL of a 1.0 M solution in THF, 16.7 mmol) was added dropwise to a solution of crude diene **262** in THF (300 mL) and the resultant mixture was stirred at rt for 45 min. The reaction was quenched by addition of H_2O (200 mL) and extracted with EtOAc (3 × 300 mL). The combined organic phases were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 50:1 to 19:1) to provide the alcohol **263** (2.32 g, 99%) as a colourless oil. R_f = 0.21 (petroleum ether–EtOAc, 3:1); $[\alpha]_D^{23}$ −90.2 (c = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, CH-C9), 5.12 (1H, dq, *J* = 17.1, 1.6 Hz, CH_2-C10), 5.11—5.07 (1H, m, CH_2-C10), 5.03 (1H, q, *J* = 2.2 Hz, CH_2-C7), 4.89 (1H, q, *J* = 2.2 Hz, CH_2-C7), 4.49 (1H, ddt, *J* = 6.5, 4.3, 2.2 Hz, CH-C2), 4.21 (1H, dddd, *J* = 7.5, 7.0, 6.0, 3.5 Hz, CH-C5), 3.64 (1H, ddd, *J* = 11.5, 7.0, 3.5 Hz, CH_2-C6), 3.52 (1H, dt, *J* = 11.5, 6.0 Hz, CH_2-C6), 2.63 (1H, ddq, *J* = 16.0, 7.0, 2.2 Hz, CH_2-C4), 2.45 (1H, ddtd, *J* = 16.0, 7.5, 2.2, 0.5 Hz, CH_2-C4), 2.41—2.28 (2H, m, CH_2-C8), 2.06—2.00 (1H, m, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3 (C-C3), 134.6 (CH-C9), 117.5 (CH_2-C10), 105.8 (CH_2-C7), 79.9 (CH-C2), 77.8 (CH-C5), 64.4 (CH_2-C6), 40.1 (CH_2-C8), 34.3 (CH_2-C4); ν_{max} 3427, 2932, 2907, 2875, 1433, 1046, 999, 887, 735 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 155.2 $[M+H]^+$ (100), 113.2 (63); HRMS (ESI+) calcd for $C_9H_{14}NaO_2$ $[M+Na]^+$ 177.0886, found 177.0887; Anal. calcd for $C_9H_{14}O_2$: C, 70.10%; H, 9.15%, found: C, 69.72%; H, 9.27%.

(*R*)-3-[(*S*)-2-Methylpent-4-enoyl]-4-phenyloxazolidin-2-one 268

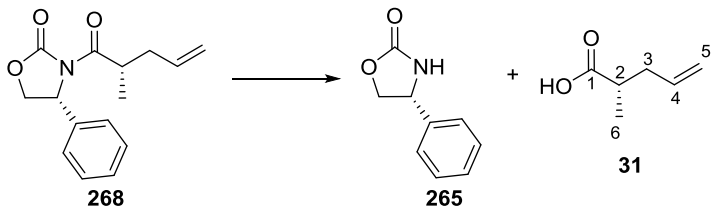


266 **268**

Oxazolidinone **266** (5.00 g, 22.8 mmol) was dissolved in THF (75 mL) and the solution was cooled to −78 °C. NaHMDS (12.0 mL of a 2.0 M solution in THF, 23.9 mmol) was added dropwise and the mixture was stirred at −78 °C for 1 h. Freshly distilled allyl iodide (6.30 mL, 68.4 mmol) was added dropwise and the mixture was stirred at −78 °C for 4 h. The resultant mixture was then allowed to

warmed to rt over 14 h. The reaction mixture was then diluted with saturated aqueous $Na_2S_2O_3$ (50 mL) and CH_2Cl_2 (80 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 80 mL). The combined organic phases were washed with brine (70 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 9:1 to 4:1) and subsequent recrystallisation (40 °C then −18 °C for two days, petroleum ether–EtOAc, 40:1) to give the oxazolidinone **268** (4.97 g, 84%, *dr* >20:1) as a colourless crystalline solid. R_f = 0.25; (petroleum ether–Et_2O, 2:1); $[\alpha]_D^{25}$ −61.9 (c = 1.2, $CHCl_3$); mp = 61.2–62.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41—7.27 (5H, m, CH-C7, CH-C8, CH-C9, CH-C10, CH-C11), 5.61 (1H, ddt, *J* = 17.0, 10.0, 6.8 Hz, CH-C15), 5.44 (1H, dd, *J* = 8.9, 4.0 Hz, CH-C4), 4.93—4.87 (2H, m, CH_2-C16), 4.68 (1H, t, *J* = 8.9 Hz, CH_2-C5), 4.26 (1H, dd, *J* = 8.9, 4.0 Hz, CH_2-C5), 3.85 (1H, app. sextet, *J* = 6.8 Hz, CH-C13), 2.40 (1H, dt, *J* = 13.8, 6.8 Hz, CH_2-C14), 2.09 (1H, dt, *J* = 13.8, 6.8 Hz, CH_2-C14), 1.13 (3H, d, *J* = 6.8 Hz, CH_3-C17); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1 (C-C12), 153.5 (C-C2), 139.2 (C-C6), 135.0 (CH-C15), 129.2 (CH-C8, CH-C10), 128.8 (CH-C9), 126.1 (CH-C7, CH-C11), 117.4 (CH_2-C16), 69.8 (CH_2-C5), 57.9 (CH-C4), 38.0 (CH_2-C14), 37.4 (CH-C13), 16.1 (CH_3-C17); ν_{max} 2983, 1776, 1713, 1331, 1217, 1084, 1063, 995, 928, 766, 700 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 260.1 $[M+H]^+$ (100); HRMS (CI; *iso*-butane) calcd for $C_{15}H_{18}NO_3$ $[M+H]^+$ 260.1287, found 260.1288; Anal. calcd for $C_{15}H_{17}O_3N$: C, 69.48%; H, 6.61%; N, 5.40%, found: C, 69.23%; H, 6.55%; N, 5.44%.

(*S*)-2-Methylpent-4-enoic acid 31



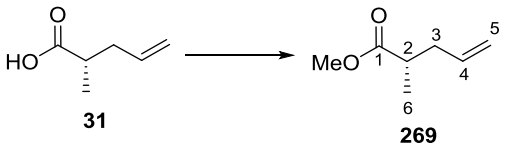
268 **265** **31**

To a solution of oxazolidinone **268** (3.00 g, 11.6 mmol) in a 4:1 mixture of THF and H_2O (45 mL) at 0 °C, was slowly added H_2O_2 (5.25 mL of a 30% w/w solution in H_2O, *ca.* 46.3 mmol) followed by a solution of LiOH (390 mg, 16.2 mmol) in H_2O (6 mL). The resultant mixture was stirred at 0 °C for 1 h and the reaction

was quenched by addition of saturated aqueous Na_2SO_3 (15.0 mL). The pH was adjusted to 12–13 by the addition of 1 M aqueous NaOH and the solution was extracted with CH_2Cl_2 (3 × 60 mL) to recover the oxazolidinone **265** (1.85 g, 98%) as a colourless crystalline solid.

The aqueous phase was acidified (pH 1-2) by addition of 2 M aqueous HCl and the solution was extracted with EtOAc (3 × 60 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the carboxylic acid **31** (1.32 g, 99%) as a pale yellow oil. The acid was used without further purification. R_f = 0.22; (petroleum ether–Et_2O, 1:3); $[\alpha]_D^{24}$ +10.3 (c = 1.1, $CHCl_3$) {Lit.[10b] $[\alpha]_D^{20}$ +9.2 (c = 1.4, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.51 (1H, bs, OH acid), 5.77 (1H, ddt, *J* = 17.1, 10.2, 7.0 Hz, CH-C4), 5.10 (1H, dtd, *J* = 17.1, 1.6, 1.2 Hz, CH_2-C5 *trans*), 5.05 (1H, dtd, *J* = 10.2, 1.6, 1.2 Hz, CH_2-C5 *cis*), 2.56 (1H, app. sextet, *J* = 7.0 Hz, CH-C2), 2.44 (1H, dtt, *J* = 14.0, 7.0, 1.2 Hz, CH_2-C3), 2.21 (1H, dtt, *J* = 14.0, 7.0, 1.6 Hz, CH_2-C3), 1.19 (3H, d, *J* = 7.0 Hz, CH_3-C6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.4 (C-C1), 135.2 (CH-C4), 117.3 (CH_2-C5), 39.2 (CH-C2), 37.6 (CH_2-C3), 16.4 (CH_3-C6); ν_{max} 3078, 2980, 1701, 1643, 1417, 1285, 1244, 1213, 914 cm^{-1}; LRMS (CI, *iso*-butane at 100 °C) *m*/*z* (intensity) 115.1 $[M+H]^+$ (81), 105.1 (100), 87.1 (25); HRMS (CI, *iso*-butane at 100 °C) calcd for $C_6H_{11}O_2$ $[M+H]^+$ 115.0759, found 115.0758.

(*S*)-Methyl 2-methylpent-4-enoate 269[132]

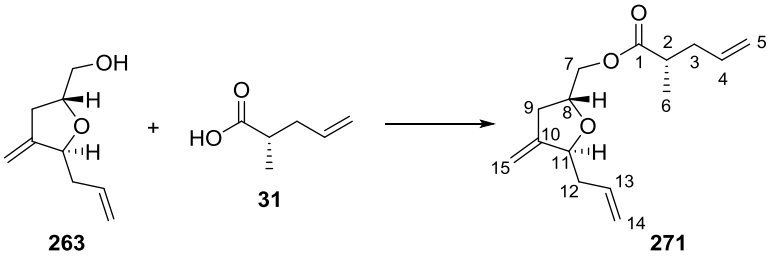


31 **269**

$TMSCHN_2$ (2.10 mL of a 2.0 M solution in hexanes, 4.21 mmol) was added to a solution of acid **31** (400 mg, 3.51 mmol) in a 10:1 mixture of Et_2O and MeOH (66 mL) at 0 °C. Upon complete addition, the mixture was warmed to rt and stirred at this temperature for 20 h. The reaction was quenched by the addition of AcOH (1 mL) and the resulting mixture was added carefully to saturated aqueous $NaHCO_3$ (20 mL). The ethereal layer was isolated and the aqueous layer was back extracted with Et_2O (10 mL). The combined organic phases were dried over

$MgSO_4$, filtered and the solvent was distilled off under 1 atm. The residue was purified by flash chromatography on silica gel (pentane–Et_2O, 500:1) followed by Kugelrohr distillation (1 atm) to afford the methyl ester **269** (274 mg, 61%) as a colourless oil. R_f = 0.60; (petroleum ether–Et_2O, 19:1); $[\alpha]_D^{31}$ +19.7 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (1H, dddd, *J* = 17.3, 10.2, 7.0, 3.3 Hz, CH-C4), 5.11—4.99 (2H, m, CH_2-C5), 3.67 (3H, s, CH_3-MeO), 2.53 (1H, app. sextet, *J* = 7.0 Hz, CH-C2), 2.45—2.36 (1H, m, CH_2-C3), 2.22—2.14 (1H, m, CH_2-C3), 1.15 (3H, d, *J* = 7.0 Hz, CH_3-C6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7 (C-C1), 135.6 (CH-C4), 117.0 (CH_2-C5), 51.6 (CH_3-MeO), 39.4 (CH-C2), 37.9 (CH_2-C3), 16.7 (CH_3-C6); ν_{max} 2960, 2923, 2855, 1735, 1260, 1250, 1174, 1099, 1016, 843, 803 cm^{-1}.

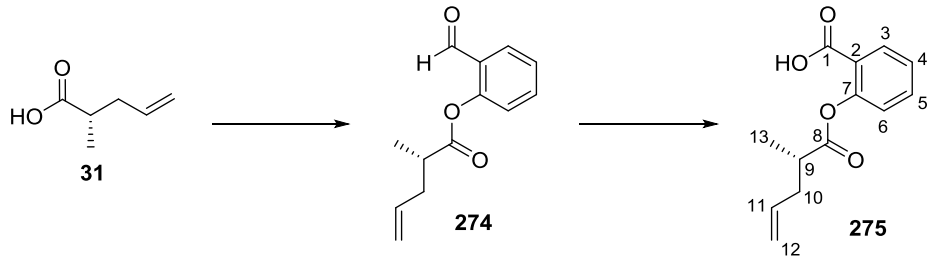
(*S*)-[(2*R*,5*S*)-5-Allyl-4-methylenetetrahydrofuran-2-yl]methyl 2-methylpent-4-enoate 271



EDC (460 mg, 2.40 mmol) and DMAP (238 g, 1.94 mmol) were added to a solution of the carboxylic acid **31** (92.5 g, 0.81 mmol) and the alcohol **263** (100 mg, 0.65 mmol) in CH_2Cl_2 (6 mL). The resultant mixture was stirred at rt for 1.5 h. The reaction was quenched with H_2O (3 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were washed with brine (3 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 19:1) to afford the ester **271** (137 mg, 85% yield) as a colourless oil. R_f = 0.31 (petroleum ether–Et_2O, 9:1); $[\alpha]_D^{24}$ −69.1 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (1H, dddd, *J* = 17.1, 10.2, 6.9, 3.3 Hz, CH-C13), 5.73 (1H, dddd, *J* = 17.0, 10.1, 7.0, 3.2 Hz, CH-C4), 5.13—4.98 (4H, m, CH_2-C5, CH_2-C14, 1 × CH_2-C15), 4.89 (1H, dd, *J* = 4.3, 2.2 Hz, CH_2-C15), 4.49 (1H, ddd, J = 6.5, 4.7, 2.2 Hz, CH-C11), 4.30 (1H, dddd, *J* = 7.4, 5.9, 4.6, 4.2 Hz, CH-C8), 4.10 (1H, dd, *J* = 11.5, 5.9 Hz, CH_2-C7),

4.04 (1H, dd, *J* = 11.5, 4.6 Hz, CH_2-C7), 2.69 (1H, dddd, *J* = 15.9, 7.4, 4.2, 2.2 Hz, CH_2-C9), 2.55 (1H, app. sextet, *J* = 7.0 Hz, CH-C2), 2.44—2.25 (4H, m, 1 × CH_2-C3, 1 × CH_2-C9, CH_2-C12), 2.17 (1H, dtt, *J* = 14.1, 7.0, 1.1 Hz, CH_2-C3), 1.14 (3H, d, *J* = 7.0 Hz, CH_3-C6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0 (C-C1), 149.7 (C-C10), 135.5 (CH-C4), 134.4 (CH-C13), 117.4 (CH_2-C14), 117.0 (CH_2-C5), 105.8 (CH_2-C15), 80.0 (CH-C11), 75.3 (CH-C8), 65.9 (CH_2-C7), 40.1 (CH_2-C9), 39.3 (CH-C2), 37.9 (CH_2-C3), 35.2 (CH_2-C12), 16.6 (CH_3-C6); ν_{max}, 2978, 2936, 2851, 1734, 1641, 1437, 1174, 1080, 994, 912, 889 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 251.2 $[M+H]^+$ (100), 129.1 (30); HRMS (CI, *iso*-butane) calcd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1647, found 251.1645; Anal. calcd for $C_{15}H_{22}O_3$: C, 71.97%; H, 8.86%, found: C, 71.61%; 9.15%.

(*S*)-2-[(2-Methylpent-4-enoyl)oxy]benzoic acid 275

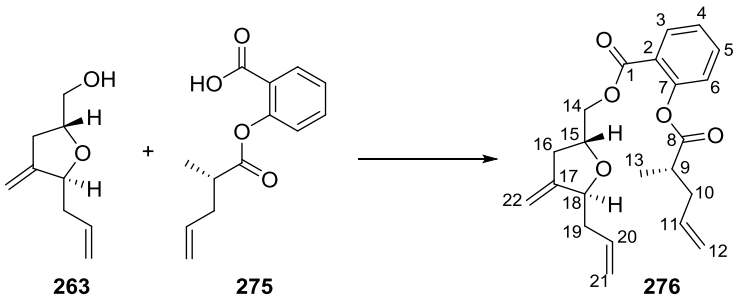


EDC (7.45 g, 38.9 mmol) and DMAP (3.85 g, 31.5 mmol) were added to a solution of the carboxylic acid **31** (1.50 g, 13.1 mmol) and salicylaldehyde (1.12 mL, 10.5 mmol) in CH_2Cl_2 (150 mL). The resultant mixture was stirred at rt for 3 h. The reaction was quenched with H_2O (80 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a short pad of silica gel (petroleum ether–Et_2O, 19:1) to afford the crude aldehyde **274** which was used in the next step without any further purification.

2-Methyl-2-butene (8.93 mL, 84.0 mmol) was added to a solution of the crude aldehyde **274** in *t*-BuOH (50 mL). A solution of $NaClO_2$ (5.7 g, 63.0 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (10.6 g, 68.2 mmol) in H_2O (30 mL) was added dropwise and the resultant mixture was stirred vigorously at rt for 45 min. The mixture was diluted with CH_2Cl_2 (100 mL) and the phases were separated. The aqueous phase

was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 3:1) to provide the carboxylic acid **275** (2.34 g, 76% over 2 steps) as a colourless solid. R_f = 0.21; (petroleum ether–Et_2O, 3:1); $[\alpha]_D^{22}$ +25.2 (c = 1.4, $CHCl_3$); mp = 43.6–44.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (1H, dd, *J* = 7.8, 1.7 Hz, CH-C3), 7.61 (1H, ddd, *J* = 8.1, 7.8, 1.7 Hz, CH-C5), 7.34 (1H, td, *J* = 7.8, 1.2 Hz, CH-C4), 7.10 (1H, dd, *J* = 8.1, 1.2 Hz, CH-C6), 5.87 (1H, ddt, *J* = 17.1, 10.2, 7.0 Hz, CH-C11), 5.20—5.09 (2H, m, CH_2-C12), 2.84 (1H, app. sextet, *J* = 7.0 Hz, CH-C9), 2.62 (1H, dtt, *J* = 14.2, 7.0, 1.2 Hz, CH_2-C10), 2.35 (1H, dtt, *J* = 14.2, 7.0, 1.2 Hz, CH_2-C10), 1.26 (3H, d, *J* = 7.0 Hz, CH_3-C13); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5 (C-C8), 169.6 (C-C1), 151.4 (C-C7), 135.5 (CH-C11), 134.9 (CH-C5), 132.6 (CH-C3), 126.2 (CH-C4), 124.2 (CH-C6), 122.6 (C-C2), 117.4 (CH_2-C12), 39.4 (CH-C9), 37.7 (CH_2-C10), 16.4 (CH_3-C13); ν_{max} 3078, 2978, 1759, 1697, 1204, 1084, 914, 752 cm^{-1}; LRMS (EI) *m/z* (intensity) 234.0 $[M]^+$ (10), 69.0 (100), 120.0 (97), 40.9 (60), 84.9 (55), 97.0 (52), 138.0 (40); HRMS (EI) calcd for $C_{13}H_{14}O_4$ $[M]^+$ 234.0892, found 234.0889; Anal. calcd for $C_{13}H_{14}O_4$: C, 66.66%; H, 6.02%; found: C, 66.23%; H, 6.06%.

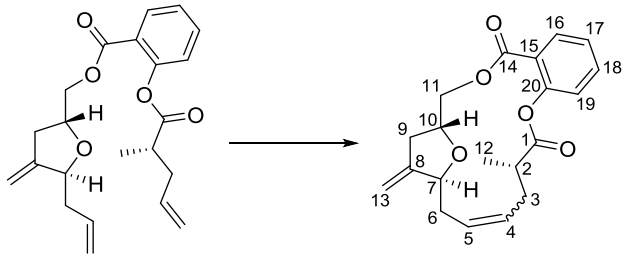
[(2*R*,5*S*)-5-Allyl-4-methylenetetrahydrofuran-2-yl]methyl 2-{[(*S*)-2-methylpent-4-enoyl]oxy}benzoate 276



Alcohol **263** (1.08 g, 7.00 mmol), carboxylic acid **275** (1.94 g, 8.40 mmol) and triphenylphosphine (2.76 g, 10.5 mmol) were dissolved in THF (150 mL) and the resulting solution was cooled to 0 °C. DIAD (2.44 mL, 12.6 mmol) was added dropwise and the mixture was stirred at rt for 45 min. The reaction mixture was then concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 49:1 to 9:1) to afford the

ester **276** (2.57 g, 99%) as a colourless oil. R_f = 0.48; (petroleum ether–Et_2O, 3:1); $[\alpha]_D^{26}$ −51.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (1H, dd, *J* = 7.9, 1.6 Hz, CH-C3), 7.53 (1H, td, *J* = 7.9, 1.6 Hz, CH-C5), 7.28 (1H, td, *J* = 7.9, 1.0 Hz, CH-C4), 7.06 (1H, dd, *J* = 7.9, 1.0 Hz, CH-C6), 5.91—5.81 (2H, m, CH-C11, CH-C20), 5.18—5.06 (4H, m, CH_2-C12, CH_2-C21), 5.05 (1H, dd, *J* = 4.1, 2.0 Hz, CH_2-C22), 4.92 (1H, dd, *J* = 4.1, 2.0 Hz, CH_2-C22), 4.57—4.50 (1H, m, CH-C15), 4.43 (1H, dq, *J* = 7.5, 5.2 Hz, CH-C18), 4.28 (1H, dd, *J* = 11.5, 5.8 Hz, CH_2-C14), 4.23 (1H, dd, *J* = 11.5, 4.6 Hz, CH_2-C14), 2.86 (1H, app. sextet, J = 7.0 Hz, CH-C9), 2.75 (1H, ddq, *J* = 15.6, 7.5, 2.0 Hz, CH_2-C19), 2.68—2.57 (1H, m, CH_2-C10), 2.48 (1H, ddd, *J* = 15.6, 5.2, 2.0 Hz, CH_2-C19), 2.43—2.30 (3H, m, CH_2-C16, 1 × CH_2-C10), 1.33 (3H, d, *J* = 7.0 Hz, CH_3-C13); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5 (C-C8), 164.2 (C-C1), 150.9 (C-C7), 149.6 (C-C2), 135.5 (CH-C11 or CH-C20), 134.4 (CH-C11 or CH-C20), 133.8 (CH-C5), 131.7 (CH-C3), 125.9 (CH-C4), 123.9 (CH-C6), 123.4 (C-C17), 117.4 (CH_2-C12 or CH_2-C21), 117.2 (CH_2-C12 or CH_2-C21), 105.9 (CH_2-C22), 80.0 (CH-C15), 75.2 (CH-C18), 66.5 (CH_2-C14), 40.1 (CH_2-C16), 39.1 (CH-C9), 37.6 (CH_2-C10), 35.3 (CH_2-C19), 16.2 (CH_3-C13); ν_{max} 3077, 2970, 2938, 2359, 2330 1757, 1724, 1252, 1136, 1071, 910, 795, 700 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 371.2 $[M+H]^+$ (100), 329.2 (14), 217.2 (14); HRMS (CI, *iso*-butane) calcd for $C_{22}H_{27}O_5$ $[M+H]^+$ 371.1858, found 371.1860; Anal. calcd for $C_{22}H_{26}O_5$: C, 71.33%; H, 7.07%, found: C, 71.45%; 7.17%.

(1R, 13S, 15Z, 18S)-13-methyl-19-methylidene-3,11,21-trioxatricyclo [16.2.1.0,^{1}]henicosa-5-(10),6,8,15-tetraene-4,12-dione 277



276 **277**

A solution of triene **276** (2.00 g, 5.40 mmol) in CH_2Cl_2 (50 mL) was added slowly to a solution of the Grubbs second generation catalyst (138 mg, 0.16 mmol) in CH_2Cl_2 (950 mL) at rt. The mixture was heated to reflux and stirred at this temperature. Three further portions of the Grubbs second generation catalyst (3

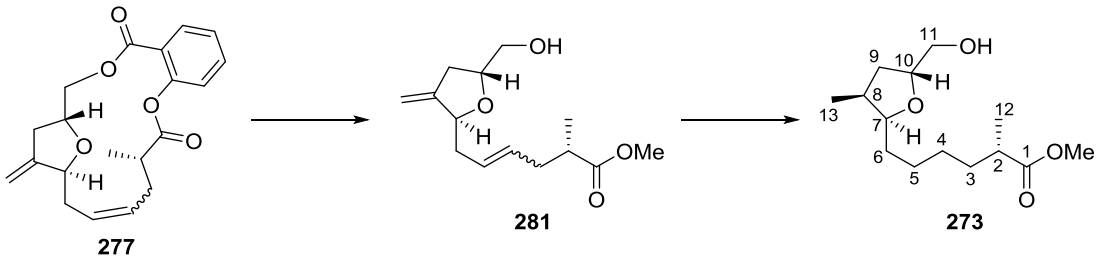
× 138 mg, 3 × 0.16 mmol) were added at 2 h intervals and the resulting mixture was stirred at reflux for 14 h. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel (petroleum ether–Et_2O, 19:1 to 4:1) to provide the macrolactone **277** (1.78 g, 96%) as a mixture of isomers (*E*:*Z* = 1.2:1) as a colourless resin: LRMS (CI, *iso*-butane) *m*/*z* (intensity) 343.1 $[M+H]^+$ (100); HRMS (CI, *iso*-butane) calcd for $C_{20}H_{23}O_5$ $[M+H]^+$ 343.1545, found 343.1541; Anal. calcd for $C_{20}H_{22}O_5$: C, 70.16%; H, 6.48%, found: C, 70.24%; 6.53%.

Z isomer: colourless oil/foam, R_f = 0.25; (petroleum ether–Et_2O, 4:1); $[\alpha]_D^{25}$ −88.3 (c = 1.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (1H, dd, *J* = 7.8, 1.7 Hz, CH-C16), 7.55 (1H, td, *J* = 7.8, 1.7 Hz, CH-C18), 7.32 (1H, td, *J* = 7.8, 0.9 Hz, CH-C17), 7.05 (1H, dd, *J* = 7.8, 0.9 Hz, CH-C19), 5.83 (1H, td, *J* = 10.6, 5.4 Hz, CH-C4), 5.64 (1H, dt, *J* = 10.6, 8.1 Hz, CH-C5), 5.08 (1H, q, *J* = 2.4 Hz, CH_2-C13), 4.94 (1H, td, *J* = 2.4, 1.4 Hz, CH_2-C13), 4.68 (1H, d, *J* = 12.1 Hz, CH_2-C11), 4.61—4.55 (1H, m, CH-C7), 4.24 (1H, ddd, *J* = 11.5, 8.8, 5.6 Hz, CH-C10), 4.01 (1H, dd, *J* = 12.1, 8.8 Hz, CH_2-C11), 3.14 (1H, dqd, *J* = 8.9, 7.4, 5.1 Hz, CH-C2), 2.71 (1H, ddd, *J* = 13.5, 10.6, 5.1 Hz, CH_2-C3), 2.61 (1H, ddd, *J* = 15.3, 5.6, 1.4 Hz, CH_2-C9), 2.46 (1H, dt, *J* = 14.0, 8.1 Hz, CH_2-C6), 2.33 (1H, ddt, *J* = 15.3, 11.5, 2.4 Hz, CH_2-C9), 2.21 (1H, ddd, *J* = 14.0, 8.1, 2.1 Hz, CH_2-C6), 1.99 (1H, ddd, *J* = 13.5, 8.9, 5.4 Hz, CH_2-C3), 1.46 (3H, d, *J* = 7.4 Hz, CH_3-C12); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5 (C-C1), 166.2 (C-C14), 150.1 (C-C20), 149.8 (C-C16), 133.8 (CH-C18), 132.7 (CH-C16), 130.6 (CH-C4), 127.3 (CH-C5), 126.0 (CH-C17), 124.1 (CH-C19), 124.0 (C-C8), 106.0 (CH_2-C13), 81.4 (CH-C7), 75.5 (CH-C10), 68.4 (CH_2-C11), 40.4 (CH-C2), 36.2 (CH_2-C9), 33.8 (CH_2-C6), 29.7 (CH_2-C3), 17.3 (CH_3-C12); ν_{max} 2972, 2940, 2901, 1757, 1709, 1290, 1248, 1148, 1124, 1098, 732 cm^{-1}.

E isomer: colourless solid; R_f (*E*)= 0.15; (petroleum ether–Et_2O, 4:1); $[\alpha]_D^{28}$ −174.7 (c = 1.2, $CHCl_3$); mp = 128−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, dd, *J* = 7.8, 1.7 Hz, CH-C16), 7.51 (1H, td, *J* = 7.8, 1.7 Hz, CH-C18), 7.27 (1H, td, *J* = 7.8, 1.1 Hz, CH-C17), 7.02 (1H, dd, *J* = 7.8, 1.1 Hz, CH-C19), 5.73—5.65 (1H, m, CH-C4), 5.65–5.56 (1H, m, CH-C5), 5.00 (1H, q, *J* = 2.1 Hz, CH_2-C13), 4.89 (1H, q, *J* = 2.1 Hz, CH_2-C13), 4.67 (1H, dd, *J* = 11.7, 10.2 Hz, CH_2-C11), 4.56—4.50 (1H, m, CH-C7), 4.30 (1H, dtd, *J* = 10.2, 6.8, 2.4 Hz, CH-C10), 3.95 (1H, dd, *J* = 11.7, 2.4 Hz, CH_2-C11), 2.88 (1H, dqd, *J* = 14.5, 7.3, 2.8 Hz, CH-C2), 2.71 (1H, ddq, *J* = 16.2, 6.8, 2.1 Hz, CH_2-C9), 2.48 (1H, ddd, *J* = 14.5, 12.1, 6.2

Hz, CH_2-C3), 2.35—2.24 (2H, m, 1 × CH_2-C9, 1 × CH_2-C6), 2.13—2.04 (2H, m, 1 × CH_2-C3, 1 × CH_2-C6), 1.41 (3H, d, *J* = 7.3 Hz, CH_3-C12); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0 (C-C1), 165.1 (C-C14), 150.4 (C-C20), 150.3 (C-C16), 133.2 (CH-C18), 131.5 (CH-C16), 130.7 (CH-C4), 128.3 (CH-C5), 125.8 (CH-C17), 125.1 (C-C8), 123.8 (CH-C19), 104.9 (CH_2-C13), 78.8 (CH-C7), 74.7 (CH-C10), 65.5 (CH_2-C11), 41.1 (CH-C2), 36.8 (CH_2-C6), 35.6 (CH_2-C3), 34.7 (CH_2-C9), 19.2 (CH_3-C12); ν_{max} 2969, 2940, 2911, 1757, 1728, 1250, 1140, 1091, 1078, 729, 702 cm^{-1}.

(*S*)-Methyl 6-[(2*S*,3*S*,5*R*)-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl]-2-methylhexanoate 273

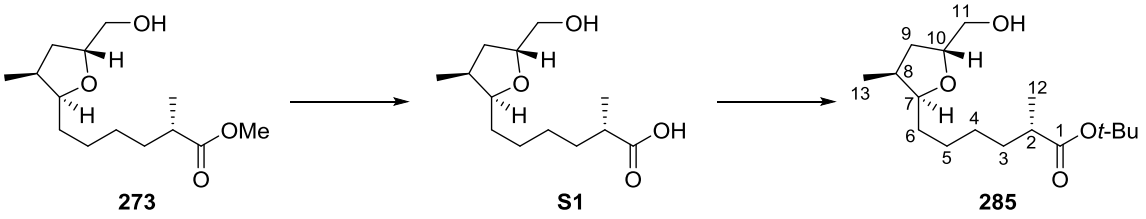


A solution of KOH (583 mg, 10.4 mmol) in H_2O (6 mL) was added to a solution of ester **277** (1.78 g, 5.20 mmol) in MeOH (140 mL). The resulting mixture was stirred at rt for 2 h. The reaction was quenched by addition of 1 M aqueous HCl (60 mL) and extracted with EtOAc (3 × 140 mL). The combined organic extracts were washed with brine (120 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was filtered through a short pad of silica gel (petroleum ether–Et_2O, 2:3) to afford the crude diene **281** (*ca.* 1.2:1 mixture of *E*:*Z* isomers) which was used in the next step without any further purification.

Crabtree's catalyst (416 mg, 0.52 mmol) was dissolved in CH_2Cl_2 (250 mL) under atmosphere of argon at rt. The mixture was purged three times with H_2 and then was stirred under atmosphere of H_2 for 10 min until decolouration occurred (from orange to yellow). A solution of crude diene **281** in CH_2Cl_2 (8 mL) was added dropwise and the mixture stirred at rt under atmosphere of H_2 until the reaction was judged complete by TLC (3–4 h). The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 1:1 to 1:3) to afford

the methyl ester **273** (1.14 g, 85% over 2 steps) as a pale yellow resin with *dr* >20:1.[133] R_f = 0.25 (petroleum ether–Et_2O, 2:3); $[\alpha]_D^{24}$ +13.9 (c = 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.12 (1H, qd, *J* = 7.3, 3.3 Hz, CH-C10), 3.81 (1H, dt, *J* = 7.9, 5.1 Hz, CH-C7), 3.63 (3H, s, CH_3-OMe), 3.56 (1H, bdd, *J* = 11.0, 7.3 Hz, CH_2-C11), 3.43 (1H, bdd, *J* = 11.0, 7.3 Hz, CH_2-C11), 2.41 (1H, app. sextet, *J* = 7.0 Hz, CH-C2), 2.28 (1H, bs, OH), 2.24—2.18 (1H, m, CH-C8), 1.81 (1H, dt, *J* = 12.5, 7.3 Hz, CH_2-C9), 1.63 (1H, ddd, *J* = 12.5, 7.3, 3.3 Hz, CH_2-C9), 1.61 (1H, dtd, *J* = 12.3, 7.9, 7.0 Hz, CH_2-C3), 1.49—1.22 (7H, m, CH_2-C4, CH_2-C5, CH_2-C6, 1 × CH_2-C3), 1.11 (3H, d, *J* = 7.0 Hz, CH_3-C13), 0.88 (3H, d, *J* = 7.0 Hz, CH_3-C12); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4 (C-C1), 81.8 (CH-C7), 77.2 (CH-C10), 65.7 (CH_2-C11), 51.5 (CH_3-OMe), 39.5 (CH-C2), 36.0 (CH-C8), 35.6 (CH_2-C9), 33.8 (CH_2-C3), 30.3 (CH_2-C6), 27.5 (CH_2-C4), 26.6 (CH_2-C5), 17.1 (CH_3-C12), 14.1 (CH_3-C13); ν_{max} 2927, 2861, 1729, 1265, 734, 704 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 259.3 $[M+H]^+$ (100); HRMS (CI, *iso*-butane) calcd for $C_{14}H_{27}O_4$ $[M+H]^+$ 259.1904, found 259.1909.

(S)-tert-Butyl 6-[(2*S*,3*S*,5*R*)-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl]-2-methylhexanoate 285

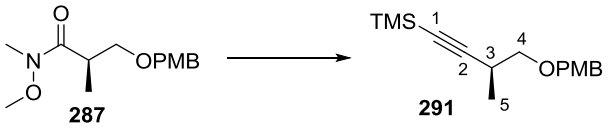


To a solution of the methyl ester **273** (500 mg, 1.94 mmol) in a 3:2 mixture of THF and MeOH (40 mL), was added dropwise a solution of LiOH (1.82 g, 77.4 mmol) in H_2O (7 mL) and the resultant mixture was stirred at rt for 4 h. The reaction was quenched by addition of 1 M aqueous HCl until pH 2–3 was reached and the mixture was extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude carboxylic acid **S1** which was used in the next step without any further purification.

The crude carboxylic acid **S1** was dissolved in a 1:1 mixture of CH_2Cl_2 and *t*-BuOH (50 mL) and the mixture was cooled to 0 °C. *N,N'*-diisopropyl-*O*-*tert*-

butylisourea **284** (3.88 g, 19.4 mmol) was added dropwise and the mixture was stirred at 0 °C for 15 min. The mixture was warmed to rt, stirred at this temperature for 18 h and the reaction was then quenched by addition of H_2O (50 mL). The phases were separated and the aqueous phase was back extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 1:1 to 2:3) to provide the *tert*-butyl ester **285** (547 mg, 94% over 2 steps) as a colourless oil. R_f = 0.22; (petroleum ether–Et_2O, 1:1); $[\alpha]_D^{23}$ +19.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (1H, qd, *J* = 7.4, 3.3 Hz, CH-C10), 3.83 (1H, dt, *J* = 7.8, 5.1 Hz, CH-C7), 3.59 (1H, bdd, *J* = 11.2, 7.4 Hz, CH_2-C11), 3.45 (1H, bdd, *J* = 11.2, 7.4 Hz, CH_2-C11), 2.29 (1H, app. sextet, *J* = 7.0 Hz, CH-C2), 2.25—2.20 (1H, m, CH-C8), 2.13 (1H, bs, OH), 1.82 (1H, dt, *J* = 12.5, 7.4 Hz, CH_2-C9), 1.64 (1H, ddd, *J* = 12.5, 7.3, 3.3 Hz, CH_2-C9), 1.61 (1H, ddd, *J* = 12.5, 7.8, 3.3 Hz, CH_2-C6), 1.50—1.23 (7H, m, CH_2-C3, CH_2-C4, CH_2-C5, 1 × CH_2-C6), 1.42 (9H, s, CH_3-*t*-Bu), 1.08 (3H, d, *J* = 7.0 Hz, CH_3-C13), 0.90 (3H, d, *J* = 7.0 Hz, CH_3-C12); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4 (C-C1), 81.8 (CH-C7), 79.9 (C-*t*-Bu) 74.4 (CH-C10) 65.7 (CH_2-C11), 40.5 (CH-C2), 36.1 (CH-C8), 35.6 (CH_2-C9), 33.9 (CH_2-C6), 30.3 (CH_2-C3), 28.2 (3C, CH_3-*t*-Bu) 27.5 (CH_2-C4), 26.7 (CH_2-C5), 17.3 (CH_3-C12), 14.1 (CH_3-C13); ν_{max} 3433, 2967, 2934, 2862, 1726, 1460, 1152, 736 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 301.5 $[M+H]^+$ (23), 245.4 (100); HRMS (CI, *iso*-butane) calcd for $C_{17}H_{33}O_4$ $[M+H]^+$ 301.2379, found 301.2375.

(*S*)-{4-[(4-Methoxybenzyl)oxy]-3-methylbut-1-yn-1-yl}trimethylsilane 291



DIBAL-H (18.7 mL of a 1.0 M solution in CH_2Cl_2, 18.7 mmol) was added over 20 min to a solution of the Weinreb amide **287**[80b] (2.0 g, 7.5 mmol) in THF (20 mL) at −78 °C and the mixture was stirred for 1 h at −78 °C. The reaction was quenched carefully with MeOH (8 mL) and the mixture stirred for 15 min before warming to 0 °C. Et_2O (50 ml) and saturated aqueous potassium sodium tartrate (50 mL) were added and the mixture was stirred vigorously at rt until two clear

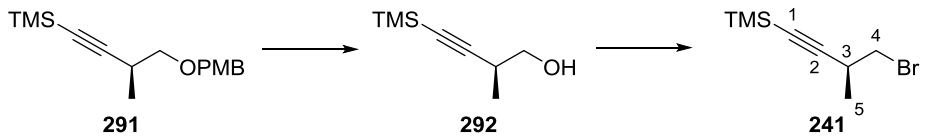
phases were obtained (2 h). The phases were separated and the aqueous phase was back extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude aldehyde as **288** a colourless oil which was used without further purification.

K_2CO_3 anhydrous (3.10 g, 22.4 mmol) was added to a solution of the Bestmann-Ohira reagent (5.74 g, 28.7 mmol) in MeOH (34 mL) at 0 °C. After stirring for 1 h at 0 °C, a solution of the crude aldehyde **288** in THF (19 mL) was added over 30 min. Stirring was continued for 1 h at 0 °C, then the mixture was warmed to rt and stirred at this temperature for 16 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (12 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 19:1) to give the alkyne **290** (1.19 g, 78% over 2 steps) as a colourless oil. R_f = 0.37 (petroleum ether–Et_2O, 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30—7.25 (2H, m, *m*-CH-PhPMB), 6.91–6.86 (2H, m, *o*-CH-PhPMB), 4.52 (1H, bd, *J* = 11.8 Hz, CH_2-PMB), 4.48 (1H, bd, *J* = 11.8 Hz, CH_2-PMB), 3.81 (3H, s, CH_3-MeO-PMB), 3.50 (1H, dd, *J* = 9.1, 6.3 Hz, CH_2-C4), 3.36 (1H, dd, *J* = 9.1, 7.3 Hz, CH_2-C4), 2.79—2.69 (1H, m, CH-C3), 2.08 (1H, d, *J* = 2.4 Hz, CH-C1), 1.22 (3H, d, *J* = 6.9 Hz, CH_3-C5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (*p*-C-PhPMB), 130.3 (C-PhPMB), 129.4 (2C, *m*-CH-PhPMB), 113.9 (2C, *o*-CH-PhPMB), 86.6 (C-C2), 73.9 (CH_2-PMB), 72.8 (CH_2-C4), 69.1 (CH-C1), 55.3 (CH_3-MeO-PMB), 26.6 (CH-C3), 17.7 (CH_3-C5).

n-BuLi (2.57 mL of a 2.5 M solution in hexanes, 6.42 mmol) was added over 10 min to a solution of alkyne **290** (1.19 g, 5.83 mmol) in THF (7 mL) at −78 °C. After 30 min, TMSCl (815 µL, 6.42 mmol) was added over 5 min to the reaction mixture. The mixture was stirred at −78 °C for 30 min and at rt for 1.5 h and the reaction was quenched by the addition of H_2O (10 mL). The reaction mixture was extracted with petroleum ether (3 × 7 mL) and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 49:1) to give the TMS-alkyne **291** (1.47 g, 91%) as a colourless oil. R_f = 0.50 (petroleum ether–Et_2O, 9:1); $[\alpha]_D^{23}$ −4.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.6 Hz, *m*-CH-PhPMB), 6.88

(2H, d, *J* = 8.6 Hz, *o*-CH-PhPMB), 4.49 (2H, s, CH_2-PMB), 3.81 (3H, s, CH_3-MeO-PMB), 3.51 (1H, dd, *J* = 9.2, 5.9 Hz, CH_2-C4), 3.33 (1H, dd, *J* = 9.2, 7.8 Hz, CH_2-C4), 2.75 (1H, dqd, *J* = 7.8, 6.9, 5.9 Hz, CH-C3), 1.19 (3H, d, *J* = 6.9 Hz, CH_3-C5), 0.15 (9H, s, CH_3-TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (*p*-C-PhPMB), 130.6 (C-PhPMB), 129.3 (2C, *m*-CH-PhPMB), 113.9 (2C, *o*-CH-PhPMB), 109.2 (C-C1), 85.1 (C-C2), 73.9 (CH_2-PMB), 72.8 (CH_2-C4), 55.4 (CH_3-MeOPMB), 27.8 (CH-C3), 18.0 (CH_3-C5), 0.32 (3C, CH_3-TMS); ν_{max} 2959, 2872, 2170, 1612, 1514, 1248, 1092, 1037, 841 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 277.4 $[M+H]^+$ (11), 261.3 (12), 121.2 (100), 75.2 (24); HRMS (CI, *iso*-butane) calcd for $C_{16}H_{25}O_2Si$ $[M+H]^+$ 277.1624, found 277.1620.

(*S*)-(4-Bromo-3-methylbut-1-yn-1-yl)trimethylsilane 241

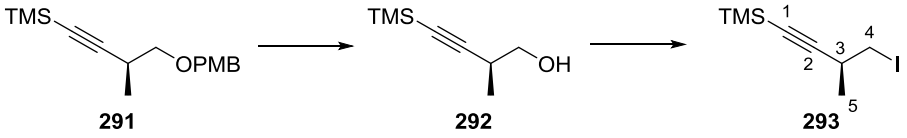


To a solution of DDQ (540 mg, 2.39 mmol) in a 10:1 mixture of CH_2Cl_2 and H_2O (44 mL) at 0 °C, was added a solution of the alkyne **291** (600 mg, 2.17 mmol) in CH_2Cl_2 (5.0 mL). The reaction mixture was stirred at rt for 2 h and then washed sequentially with saturated aqueous Na_2CO_3 (50 mL), H_2O (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a short pad of silica gel (petroleum ether–Et_2O, 9:1) to give the crude alcohol **292**, which was used in the next step without any further purification.

To a solution of the crude alcohol **292**, 2,6-lutidine (404 µL, 3.47 mmol) and triphenylphosphine (1.42 g, 5.43 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added dropwise a solution of carbon tetrabromide (1.80 g, 5.43 mmol) in CH_2Cl_2 (2 mL) and the resulting mixture stirred at rt for 2 h. The reaction was quenched by careful addition of H_2O (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether) to give the bromide **241** (404 mg, 85% over 2 steps) as a colourless oil. R_f = 0.82 (petroleum ether–Et_2O,

9:1); $[\alpha]_D^{25}$ +3.6 (c = 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (1H, dd, *J* = 9.8, 5.3 Hz, CH_2-C4), 3.30 (1H, dd, *J* = 9.8, 7.9 Hz, CH_2-C4), 2.83 (1H, dqd, *J* = 7.9, 6.8, 5.3 Hz, CH-C3), 1.30 (3H, d, *J* = 6.8 Hz, CH_3-C5), 0.15 (9H, s, CH_3-TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 107.6 (C-C1), 86.7 (C-C2), 37.3 (CH_2-C4), 29.8 (CH-C3), 19.7 (CH_3-C5), 0.2 (3C, CH_3-TMS); ν_{max} 2924, 1427, 1250, 1026, 841 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 221.2 $[M+H]^+$ (46), 219.2 $[M+H]^+$ (43), 165.3 (58), 123.3 (95), 75.1 (100); HRMS (CI, *iso*-butane) calcd for $C_8H_{16}Si^{81}Br$ $[M+H]^+$ 221.0184, $C_8H_{16}Si^{79}Br$ $[M+H]^+$ 219.0205, found 221.0171, 219.0206.

(*S*)-(4-Iodo-3-methylbut-1-yn-1-yl)trimethylsilane 293

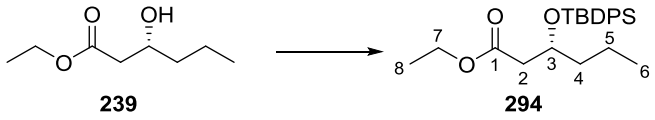


To a solution of DDQ (126 mg, 0.58 mmol) in a 10:1 mixture of CH_2Cl_2 and H_2O (11 mL) at 0 °C, was added a solution of the alkyne **291** (140 mg, 0.51 mmol) in CH_2Cl_2 (0.8 mL). The reaction mixture was stirred at rt for 2 h and then washed sequentially with saturated aqueous Na_2CO_3 (12 mL), H_2O (12 mL) and brine (12 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was filtered through a short pad of silica gel (petroleum ether–Et_2O, 9:1) to give the crude alcohol **292**, which was used in the next step without any further purification.

Triphenylphosphine (358 mg, 1.52 mmol) and imidazole (208 mg, 3.06 mmol) were added sequentially to a solution of the crude alcohol **292** in THF (7 mL) at 0 °C. After the solution was stirred for 10 min, I_2 (386 mg, 1.52 mmol) was added in three portions and the mixture stirred at 0 °C for a further 10 min. The mixture was then allowed to warm to rt and stirred at this temperature for 2 h. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (7 mL) and the resulting mixture was extracted with Et_2O (3 × 7 mL). The combined organic extracts were washed with brine (4 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether) to give the iodide **293** (98.3 mg, 73% over 2 steps) as a colourless oil. R_f = 0.82 (petroleum ether–Et_2O, 9:1); ^1H

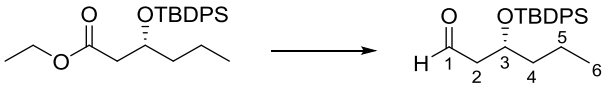
NMR (400 MHz, $CDCl_3$) δ 3.29 (1H, dd, *J* = 9.6, 5.5 Hz, CH_2-C4), 3.16 (1H, dd, *J* = 9.6, 7.4 Hz, CH_2-C4), 2.75—2.65 (1H, m, CH-C3), 1.27 (3H, d, *J* = 6.8 Hz, CH_3-C5), 0.16 (9H, s, CH_3-TMS).

(*R*)-Ethyl 3-[(*tert*-butyldiphenylsilyl)oxy]hexanoate 294



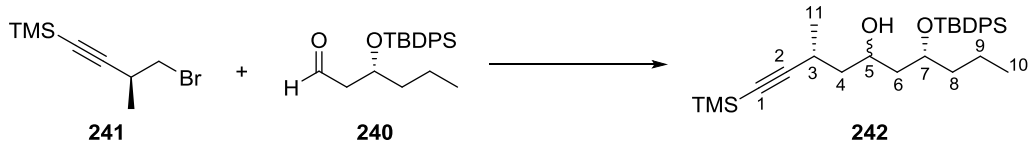
DMAP (1.14 g, 9.36 mmol), imidazole (9.79 g, 93.6 mmol) and TBDPSCl (14.6 mL, 56.2 mmol) were sequentially added to a solution of ß-hydroxy ester **239**[80b] (7.5 g, 46.8 mmol) in DMF (48 mL) at 0 °C and the resulting mixture was allowed to warm up to rt over 14 h. The reaction mixture was quenched by the addition 1 M aqueous HCl (30 mL), diluted with Et_2O (80 mL) and the phases were separated. The organic phase was washed with a saturated aqueous $NaHCO_3$ (3 × 80 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (from pure petroleum ether to petroleum ether–EtOAc, 19:1) to yield the TBDPS-ether **294** (18.3 g, 98%) as a colourless oil. R_f = 0.52 (petroleum ether–EtOAc, 19:1); $[\alpha]_D^{25}$ −8.4 (c = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71—7.65 (4H, m, Ph-TBDPS), 7.44—7.34 (6H, m, Ph-TBDPS), 4.23—4.17 (1H, m, CH-C3), 4.01 (2H, qd, *J* = 7.1, 4.2 Hz, CH_2-C7), 2.48 (1H, dd, *J* = 14.7, 6.8 Hz, CH_2-C2), 2.41 (1H, dd, *J* = 14.7, 5.8 Hz, CH_2-C2), 1.46—1.40 (2H, m, CH_2-C4), 1.30—1.21 (2H, m, CH_2-C5), 1.85 (3H, t, *J* = 7.1 Hz, CH_3-C8), 1.03 (9H, s, CH_3-*t*-Bu-TBDPS), 0.71 (3H, t, *J* = 7.3 Hz, CH_3-C6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8 (C-C1), 136.1 (4C, *o*-CH-Ph-TBDPS), 134.4 (2C, C-Ph-TBDPS), 129.7 (2C, *p*-CH-Ph-TBDPS), 127.6 (4C, *m*-CH-Ph-TBDPS), 70.4 (CH-C3), 60.4 (CH_2-C7), 42.3 (CH_2-C2), 36.4 (CH_2-C4), 27.1 (3C, CH_3-*t*-Bu-TBDPS), 19.5 (C-*t*-Bu-TBDPS), 18.1 (CH_2-C5), 14.2 (CH_3-C8), 14.0 (CH_3-C6); ν_{max} 2931, 1736, 1466, 1427, 1312, 1258, 1103, 1034, 702 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 399.3 $[M+H]^+$ (9), 321.3 (100), 75.1 (55); HRMS (CI, *iso*-butane) calcd for $C_{24}H_{35}O_3Si$ $[M+H]^+$ 399.2355, found 399.2357; Anal. calcd for $C_{24}H_{34}O_3Si$: C, 72.32%; H, 8.60%, found: C, 71.98%; H, 8.32%.

(*R*)-3-[(*tert*-butyldiphenylsilyl)oxy]hexanal 240



DIBAL-H (1.5 mL of a 1 M solution in CH_2Cl_2, 1.50 mmol) was added over 30 min to a solution of the ester **294** (500 mg, 1.25 mmol) in CH_2Cl_2 (6 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 2 h then quenched by careful addition of saturated aqueous NH_4Cl (1.2 mL). The resulting mixture was allowed to warm to rt and stirred vigorously to form precipitate (1 h). After filtration to remove the precipitate, the organic phase was separated and the aqueous phase was back extracted with CH_2Cl_2 (2 × 1 mL). The combined organic extracts were washed with brine (3 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 19:1) to afford the aldehyde **240** (410 mg, 92%) as a colourless oil. R_f = 0.30 (petroleum ether–Et_2O, 19:1); $[\alpha]_D^{23}$ −2.6 (c = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (1H, t, J = 2.5 Hz, CH-C1), 7.68—7.65 (4H, m, Ph-TBDPS), 7.46—7.36 (6H, m, Ph-TBDPS), 4.23—4.18 (1H, m, CH-C3), 2.47 (2H, dd, J = 5.7, 2.5 Hz, CH_2-C2), 1.53—1.47 (2H, m, CH_2-C4), 1.31—1.17 (2H, m, CH_2-C5), 1.04 (9H, s, CH_3-*t*-Bu-TBDPS), 0.74 (3H, t, J = 7.3 Hz, CH_3-C6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.5 (CH-C1), 136.0 (4C, *o*-CH-Ph-TBDPS), 133.8 (2C, C-Ph-TBDPS), 129.9 (2C, *p*-CH-Ph-TBDPS), 127.7 (4C, *m*-CH-Ph-TBDPS), 69.2 (CH_2-C2), 50.3 (CH-C3), 39.7 (CH_2-C4), 27.1 (3C, CH_3-*t*-Bu-TBDPS), 19.4 (C-*t*-Bu-TBDPS), 18.3 (CH_2-C5), 14.0 (CH_3-C6); ν_{max} 2955, 2931, 2862, 1728, 1465, 1427, 1111, 1042, 702 cm^{-1}; LRMS (CI, iso-butane) m/z (intensity) 355.4 $[M+H]^+$ (16), 311.4 (100), 277.4 (72), 251.3 (20); HRMS (CI, iso-butane) calcd for $C_{22}H_{31}O_2Si$ $[M+H]^+$ 355.2093, found 355.2094; Anal. calcd for $C_{22}H_{30}O_2Si$: C, 74.53%; H, 8.53%, found: C, 74.38%; H, 8.62%.

(3*R*,7*R*)-7-[(*tert*-Butyldiphenylsilyl)oxy]-3-methyl-1-(trimethylsilyl)dec-1-yn-5-ol 242



To a suspension of magnesium turnings (102 mg, 4.00 mmol) in a 3:1 mixture of Et_2O and benzene (4 mL) was added dropwise 1,2-dibromoethane (0.35 mL, 4.00 mmol) and the suspension was stirred at rt until gas evolution ceased. The mixture was then heated to 50 °C for 1 h. The resulting 1 M solution of $MgBr_2{\cdot}OEt_2$ was then cooled to rt.

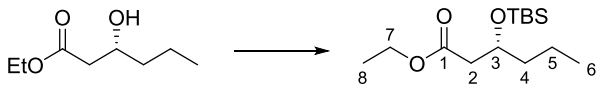
To a solution of bromide **241** (340 mg, 1.56 mmol) in Et_2O (8 mL) at −78 °C was added dropwise *t*-BuLi (1.95 mL of a 1.6 M solution in hexanes, 3.12 mmol). The mixture was stirred at −78 °C for 30 min then allowed to warm to −40 °C over 30 min. The resulting yellow mixture was then cooled to −78 °C and the freshly prepared 1 M solution of $MgBr_2{\cdot}OEt_2$ (2.00 mL, 2.00 mmol) was added. The mixture was stirred at −78 °C for 30 min then allowed to warm to −40 °C over 30 min. The resulting cloudy mixture was cooled to −40 °C and a solution of the aldehyde **240** (226 mg, 0.63 mmol) in Et_2O (1.6 mL) was added. The mixture was stirred at −40 °C for 30 min then allowed to warm to rt over 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and the resulting mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 49:1 to 19:1) to provide the alcohol **242** (220 mg, 71%, *dr* = 1:1) as a colourless oil. R_f = 0.43 (petroleum ether–Et_2O, 4:1); ν_{max} 3389, 2916, 2166, 1719, 1464, 1427, 1250, 1113, 1040, 843 cm^{-1}; LRMS (CI, *iso*-butane) *m*/*z* (intensity) 495.5 $[M+H]^+$ (8), 257.3 (20), 85.2 (67), 75.1 (100); HRMS (CI, *iso*-butane) calcd for $C_{30}H_{47}O_2Si_2$ $[M+H]^+$ 495.3115, found 495.3115.

242a: ^1H NMR (400 MHz, $CDCl_3$) δ 7.72—7.69 (4H, m, Ph-TBDPS), 7.43—7.37 (6H, m, Ph-TBDPS), 4.07—4.01 (1H, m, CH-C5), 4.00—3.96 (1H, m, CH-C7), 2.70 (1H, qt, *J* = 7.1, 7.0 Hz, CH-C3), 2.65 (1H, bs, OH), 1.65—1.61 (2H, m, CH_2-C6), 1.45—

1.41 (2H, m, CH_2-C4), 1.40—1.18 (4H, m, CH_2-C8, CH_2-C9), 1.15 (3H, d, *J* = 7.0 Hz, CH_3-C11), 1.05 (9H, s, CH_3-*t*-Bu-TBDPS), 0.62 (3H, t, *J* = 7.3 Hz, CH_3-C10), 0.14 (9H, s, CH_3-TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0 (4C, *o*-CH-Ph-TBDPS), 133.9 (2C, C-Ph-TBDPS), 129.7 (2C, *p*-CH-Ph-TBDPS), 127.6 (4C, *m*-CH-Ph-TBDPS), 111.6 (C-C1), 84.9 (C-C2), 73.4 (CH-C7), 68.6 (CH-C5), 45.0 (CH_2-C4), 43.8 (CH_2-C6), 39.4 (CH_2-C8), 27.2 (3C, CH_3-*t*-Bu-TBDPS), 23.6 (CH-C3), 21.6 (CH_3-C11), 19.5 (C-*t*-Bu-TBDPS), 18.1 (CH_2-C9), 14.0 (CH_3-C10), 0.4 (3C, CH_3-TMS).

242b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72—7.69 (4H, m, Ph-TBDPS), 7.43—7.37 (6H, m, Ph-TBDPS), 4.07—4.01 (1H, m, CH-C5), 4.00—3.96 (1H, m, CH-C7), 2.70 (1H, qt, *J* = 7.1, 7.0 Hz, CH-C3), 2.66 (1H, bs, OH), 1.65—1.61 (2H, m, CH_2-C6), 1.45—1.41 (2H, m, CH_2-C4), 1.40—1.18 (4H, m, CH_2-C8, CH_2-C9), 1.15 (3H, d, *J* = 7.0 Hz, CH_3-C11), 1.05 (9H, s, CH_3-*t*-Bu-TBDPS), 0.62 (3H, t, *J* = 7.3 Hz, CH_3-C10), 0.14 (9H, s, CH_3-TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1 (4C, *o*-CH-Ph-TBDPS), 134.6 (2C, C-Ph-TBDPS), 129.8 (2C, *p*-CH-Ph-TBDPS), 127.8 (4C, *m*-CH-Ph-TBDPS), 111.6 (C-C1), 84.9 (C-C2), 73.4 (CH-C7), 68.6 (CH-C5), 45.0 (CH_2-C4), 43.8 (CH_2-C6), 39.4 (CH_2-C8), 27.2 (3C, CH_3-*t*-Bu-TBDPS), 23.6 (CH-C3), 21.6 (CH_3-C11), 19.5 (C-*t*-Bu-TBDPS), 18.1 (CH_2-C9), 14.0 (CH_3-C10), 0.4 (3C, CH_3-TMS).

(*R*)-Ethyl 3-[(*tert*-butyldimethylsilyl)oxy]hexanoate 295

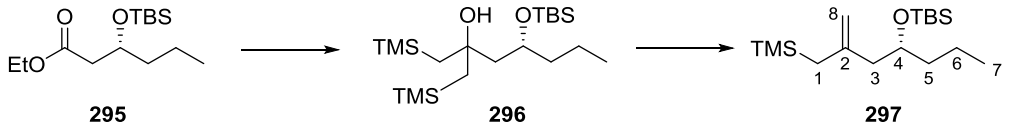


239 **295**

To a stirred solution of **239** (4.80 g, 30.0 mmol) in DMF (40 mL) cooled at 0 °C were added imidazole (5.40 g, 36.0 mmol) and TBDPSCl (6.28 g, 60 mmol). After 5 min at 0 °C, the solution was warmed to rt and stirred at this temperature for 8 h. The reaction was then quenched by addition of H_2O (25 mL), and the resulting mixture was stirred at rt for 30 min then extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by

flash chromatography on silica gel (from pure petroleum ether to petroleum ether–Et_2O, 49:1) to afford silyl ether **295** (8.06 g, 98%) as a colourless oil. R_f = 0.72 (petroleum ether–Et_2O, 19:1); $[\alpha]_D^{23}$ −16.8 (c = 0.85, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.16—4.04 (3H, m, CH-C3, CH_2-C7), 2.41 (1H, dd, *J* = 13.5, 5.9 Hz, CH_2-C2), 2.36 (1H, dd, *J* = 13.5, 4.4 Hz, CH_2-C2), 1.50—1.39 (2H, m, CH_2-C4), 1.32 (2H, dt, *J* = 13.8, 7.2 Hz, CH_2-C5), 1.23 (3H, t, *J* = 7.1 Hz, CH_3-C8), 0.88 (3H, t, *J* = 7.2 Hz, CH_3-C6), 0.84 (9H, s, CH_3-*t*-Bu-TBS), 0.03 (3H, s, CH_3-TBS), 0.01 (3H, s, CH_3-TBS);^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C-C1), 69.4 (CH-C3), 60.3 (CH_2-C7), 42.9 (CH_2-C2), 40.0 (CH_2-C4), 25.9 (3C, CH_3-*t*-Bu-TBS), 18.4 (CH_2-C5), 18.1 (C-*t*-Bu-TBS), 14.3 (CH_3-C8), 14.3 (CH_3-C6), −4.4 (CH_3-TBS), −4.7 (CH_3-TBS); ν_{max} 2959, 2930, 2859, 1736, 1375, 1254, 1177, 1090, 1040, 829, 775 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 275.4 $[M+H]^+$ (80), 113.2 (44), 85.2 (50), 73.1 (100), 71.1 (64); HRMS (CI, *iso*-butane) calcd for $C_{14}H_{31}O_3Si$ $[M+H]^+$ 275.2037, found 275.2039; Anal. calcd for $C_{14}H_{30}O_3Si$: C, 61.26%; H, 11.02%, found: C, 61.12%; H, 11.25%.

(*R*)-*tert*-Butyldimethyl({2-[(trimethylsilyl)methyl]hept-1-en-4-yl}oxy)silane 297



295 **296** **297**

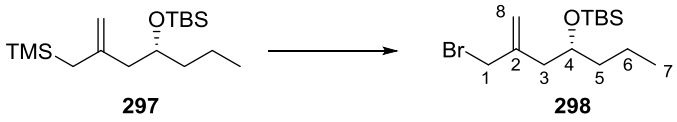
$CeCl_3 \cdot 7H_2O$ (22.4 g, 60.1 mmol) was placed in a 500 mL round-bottomed flask and dried under *vacuum* at 120 °C (temperature reached gradually) for 2h, then at 140 °C for 2h and at 160 °C for another 2h. The flask was allowed to cool to rt and was purged with argon for 10 min. THF (90 mL) was added and the mixture was stirred for 2 h at rt under argon to give the cerium(III) chloride-THF complex as a white precipitate.

A solution of $TMSCH_2Cl$ (8.40 mL, 60.1 mmol) in THF (44.6 mL) was added dropwise to a stirred suspension of magnesium turnings (1.33 g, 54.6 mmol) and 1,2-dibromoethane (2 drops) in THF (10 mL). Formation of the Grignard reagent was accomplished by heating the mixture to reflux, followed by slow addition of the halide to maintain reflux. The Grignard reagent was stirred at rt for 2 h and then added to the cerium(III) chloride-THF complex at −78 °C. The resulting grey

mixture was stirred at −78 °C for 30 min, then a solution of the ester **295** (5.00 g, 18.2 mmol) in THF (10 mL) was added. The reaction mixture was stirred at −78 °C for 2 h and the flask was then removed from the cold bath. The mixture was stirred at rt for a further period of 12 h and then cooled to 0 °C. Saturated aqueous NH_4Cl (80 mL) was added at 0 °C and the mixture was stirred for 20 min. H_2O (200 mL) was added and the mixture was extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude tertiary alcohol **296** as a pale yellow oil.

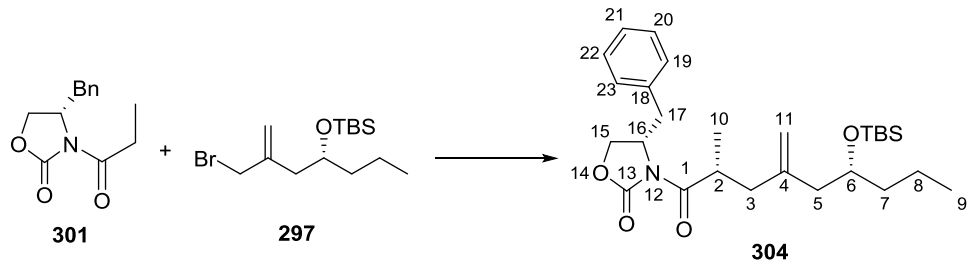
Crude tertiary alcohol **296** was dissolved in THF (350 mL) and the solution was cooled in an ice–water bath. Once cold (*ca*. 10 min), NaHMDS (10.0 mL of a 2.0 M solution in THF, 20.0 mmol) was added over 30 s. The mixture was stirred at 0 °C for 40 min and then the reaction was quenched with saturated aqueous NH_4Cl (250 mL). The biphasic mixture was diluted with Et_2O (400 mL) and H_2O (200 mL) and the phases were separated. The aqueous phase was back extracted with Et_2O (2 × 200 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 400:1) to give allylic silane **297** (5.33 g, 93% over two steps) as a colourless oil. R_f = 0.63 (petroleum ether); $[\alpha]_D^{23}$ +12.4 (c = 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (1H, d, *J* = 0.8 Hz, CH_2-C8), 4.55 (1H, s, CH_2-C8), 3.82—3.74 (1H, m, CH-C4), 2.13 (1H, dd, *J* = 13.5, 6.0 Hz, CH_2-C3), 2.05 (1H, dd, *J* = 13.5, 6.8 Hz, CH_2-C3), 1.52 (2H, s, CH_2-C1), 1.50—1.24 (4H, m, CH_2-C5, CH_2-C6), 0.92—0.86 (3H, m, CH_3-C7), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.05 (6H, s, CH_3-TBS), 0.02 (9H, s, CH_3-TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (C-C2), 109.9 (CH_2-C8), 71.4 (CH-C4), 46.7 (CH_2-C3), 39.5 (CH_2-C5), 27.3(CH_2-C1), 26.1 (3C, CH_3-*t*-Bu-TBS), 18.7 (CH_2-C6), 18.3 (C-*t*-Bu-TBS), 14.4 (CH_3-C7), −1.2 (3C, CH_3-TMS) −4.2 (CH_3-TBS), −4.3 (CH_3-TBS); ν_{max} 2957, 2930, 2859, 1249, 1040, 835, 772 cm^{-1}; Anal. calcd for $C_{17}H_{38}OSi_2$: C, 64.89%; H, 12.17%, found: C, 64.48%; H, 12.30%.

(*R*)-{[2-(Bromomethyl)hept-1-en-4-yl]oxy}(*tert*-butyl)dimethylsilane 298



Pyrrolidone hydrotribromide (8.82 g, 17.8 mmol) was added to a stirred solution of the allylic silane **297** (5.33 g, 16.9 mmol) and pyridine (8.76 mL) in THF (500 mL) at −10 °C. The mixture was stirred for 2 h and allowed to warm to rt during this period. The reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (150 mL) and the mixture was extracted with Et_2O (3 × 250 mL). The combined organic layers were washed with H_2O (500 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 400:1) to afford the bromide **298** (5.23 g, 96%) as a colourless oil. R_f = 0.51 (petroleum ether); $[\alpha]_D^{26}$ +15.3 (c = 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24—5.14 (1H, m, CH_2-C8), 4.98 (1H, dd, *J* = 2.3, 1.0 Hz, CH_2-C8), 4.05 (1H, dd, *J* = 9.9, 0.8 Hz, CH_2-C1), 3.98 (1H, dd, *J* = 9.9, 0.7 Hz, CH_2-C1), 3.83 (1H, p, *J* = 5.8 Hz, CH-C4), 2.41 (1H, ddd, *J* = 14.1, 5.8, 1.0 Hz, CH_2-C3), 2.33 (1H, ddd, *J* = 14.1, 5.8, 1.0 Hz, CH_2-C3), 1.45—1.27 (4H, m, CH_2-C5, CH_2-C6), 0.92—0.87 (3H, m, CH_3-C7), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.05 (6H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2 (C-C2), 118.0 (CH_2-C8), 71.0 (CH-C4), 41.1 (CH_2-C3), 39.4 (CH_2-C5), 37.6 (CH_2-C1), 26.0 (3C, CH_3-*t*-Bu-TBS), 18.7 (CH_2-C6), 18.2 (C-*t*-Bu-TBS), 14.4 (CH_3-C7), −4.2 (CH_3-TBS), −4.4 (CH_3-TBS); ν_{max} 2956, 2929, 2857, 1253, 1039, 906, 833, 772 cm^{-1}; Anal. calcd for $C_{14}H_{29}BrOSi$: C, 52.32%; H, 9.10%, found: C, 52.36%; H, 9.23%.

(*S*)-4-Benzyl-3-{(2*R*,6*R*)-6-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-4-methylenenonanoyl}oxazolidin-2-one 304



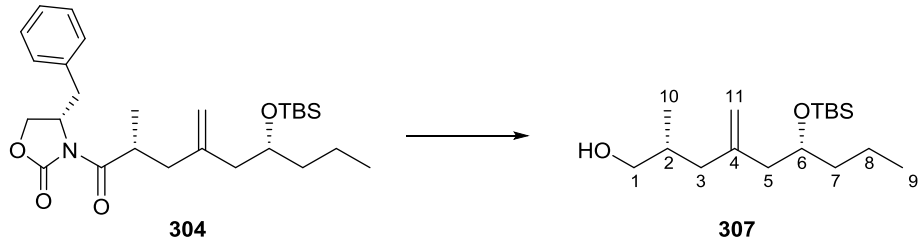
To a solution of the *N*-propionyloxazolidinone **301** (5.81 g, 24.9 mmol) in THF (80 mL) at −78 °C, was added NaHMDS (13.7 mL of a 2.0 M solution in THF, 27.4 mmol) over 15 min. The resulting solution was stirred at −78 °C for 45 min before a solution of allylic bromide **297** (4.00 g, 12.4 mmol) in THF (15 mL) was added dropwise immediately followed by addition of TBAI (460 mg, 1.24 mmol). The reaction mixture was allowed to reach −30 °C, stirred at this temperature for 18 h and then warmed to 0 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL) and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 40:1 to 10:1) to yield the desired acyloxazolidinone **304** (3.54 g, 60%) as a colourless solid. The C2 epimer (236 mg, 4%) was also isolated as a colourless resin along with unconsumed **297** (840 mg, 21%).

304: R_f = 0.24 (petroleum ether–Et_2O, 4:1); $[\alpha]_D^{27}$ +36.5 (c = 1.0, $CHCl_3$); mp = 55−56 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (2H, t, J = 7.3 Hz, CH-C20, CH-C22), 7.27 (1H, t, J = 7.3 Hz, CH-C21), 7.21 (2H, d, *J* = 7.3 Hz, CH-C19, CH-C23), 4.85 (2H, s, CH_2-C11), 4.68 (1H, dddd, *J* = 9.9, 7.7, 3.2, 3.1 Hz, CH-C16), 4.18 (1H, dd, *J* = 9.1, 7.7 Hz, CH_2-C15), 4.14 (1H, dd, *J* = 9.1, 3.1 Hz, CH_2-C15), 4.05 (1H, app. sextet, *J* = 7.0 Hz, CH-C2), 3.85—3.80 (1H, m, CH-C6), 3.28 (1H, dd, *J* = 13.3, 3.2 Hz, CH_2-C17), 2.68 (1H, dd, *J* = 13.3, 9.9 Hz, CH_2-C17), 2.57 (1H, dd, J = 14.3, 7.0 Hz, CH_2-C3), 2.27—2.17 (2H, m, CH_2-C5), 2.12 (1H, dd, *J* = 14.3, 7.0 Hz, CH_2-C3), 1.46—1.27 (4H, m, CH_2-C7, CH_2-C8), 1.17 (3H, d, *J* = 7.0 Hz, CH_3-C10), 0.91—0.87 (3H, m, CH_3-C9), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.06 (6H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.1 (C-C1), 153.2 (C-C13), 144.3 (C-C4),

135.6 (C-C18), 129.6 (2C, CH-C19, CH-C23), 129.1 (2C, CH-C20, CH-C22), 127.4 (CH-C21), 114.2 (CH_2-C11), 71.1 (CH-C6), 66.1 (CH_2-C15), 55.6 (CH-C16), 44.2 (CH_2-C5), 40.5 (CH_2-C3), 39.3 (CH_2-C7), 38.2 (CH_2-C17), 35.9 (CH-C2), 26.1 (3C, CH_3-*t*-Bu-TBS), 18.7 (CH_2-C8), 18.2 (C-*t*-Bu-TBS), 17.4 (CH_3-C10), 14.4 (CH_3-C9), −4.2 (CH_3-TBS), −4.4 (CH_3-TBS); ν_{max} 2955, 2930, 2857, 1780, 1697, 1383, 1207, 1040, 833, 773, 700 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 474.4 $[M+H]^+$ (9), 234.2 (15), 187.2 (12), 113.2 (19), 89.1 (100); HRMS (CI, *iso*-butane) calcd for $C_{27}H_{44}NO_4Si$ $[M+H]^+$ 474.3040, found 474.3038; Anal. calcd for $C_{27}H_{43}NO_4Si$: C, 68.46%; H, 9.15%, N, 2.96%, found: C, 68.35%; H, 9.30%, N, 2.93%.

C2 epimer: R_f = 0.34 (petroleum ether–Et_2O, 4:1); $[\alpha]_D^{25}$ +84.5 (c = 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36—7.25 (3H, m, CH-C20, CH-C21, CH-C22), 7.23—7.19 (2H, m, CH-C19, CH-C23), 4.81 (1H, bs, CH_2-C11), 4.79 (1H, bs, CH_2-C11), 4.66 (1H, dddd, *J* = 9.6, 6.8, 3.8, 3.2 Hz, CH-C16), 4.19 (1H, dd, *J* = 9.2, 6.8 Hz, CH_2-C15), 4.16 (1H, dd, *J* = 9.2, 3.8 Hz, CH_2-C15), 3.97 (1H, app. sextet, *J* = 6.8 Hz, CH-C2), 3.83—3.75 (1H, m, CH-C6), 3.26 (1H, dd, *J* = 13.3, 3.2 Hz, CH_2-C17), 2.77 (1H, dd, *J* = 13.3, 9.6 Hz, CH_2-C17), 2.51 (1H, dd, J = 14.4, 7.7 Hz, CH_2-C3), 2.22—2.12 (2H, m, CH_2-C5), 2.12 (1H, dd, *J* = 14.4, 6.2 Hz, CH_2-C3), 1.46—1.29 (4H, m, CH_2-C7, CH_2-C8), 1.23 (3H, d, *J* = 6.8 Hz, CH_3-C10), 0.91—0.86 (3H, m, CH_3-C9), 0.87 (9H, s, CH_3-*t*-Bu-TBS), 0.04 (3H, s, CH_3-TBS), 0.03 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0 (C-C1), 153.2 (C-C13), 144.4 (C-C4), 135.4 (C-C18), 129.6 (2C, CH-C19, CH-C23), 129.1 (2C, CH-C20, CH-C22), 127.5 (CH-C21), 113.9 (CH_2-C11), 71.1 (CH-C6), 66.2 (CH_2-C15), 55.4 (CH-C16), 44.3 (CH_2-C5), 40.0 (CH_2-C3), 39.5 (CH_2-C7), 38.1 (CH_2-C17), 36.1 (CH-C2), 26.0 (3C, CH_3-*t*-Bu-TBS), 18.6 (CH_2-C8), 18.2 (C-*t*-Bu-TBS), 17.7 (CH_3-C10), 14.4 (CH_3-C9), −4.2 (CH_3-TBS), −4.4 (CH_3-TBS).

(2*R*,6*R*)-6-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-4-methylenenonan-1-ol 307

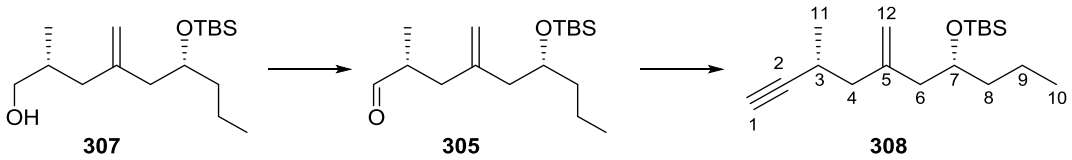


Method A: To a suspension of $LiAlH_4$ (577 mg, 15.2 mmol) in THF (100 mL) at 0 °C, was added a solution of compound **304** (2.40 g, 5.06 mmol) in THF (10 mL). The resulting mixture was stirred at 0° C for 45 min and the reaction was quenched by the addition of H_2O (600 µL) and 1 M aqueous NaOH (600 µL). The mixture was stirred at 0 °C for 5 min and additional H_2O (1.8 mL) was added. The reaction was stirred at 0 °C for additional 5 min before $MgSO_4$ was added. The mixture was stirred at rt for 15 min, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 7:1 to 6:1) to afford the alcohol **307** (1.50 g, 99%) as a colourless oil.

Method B: Compound **304** (2.80 g, 5.91 mmol) was dissolved in Et_2O (75 mL) and H_2O (106 µL, 5.91 mmol) was added. The mixture was cooled to 0 °C, $LiBH_4$ (167 mg, 7.68 mmol) was added portionwise over 10 min and the reaction was stirred at the same temperature for another 5 h. The reaction was quenched by the addition of 0.1 M aqueous NaOH (75 mL) and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 7:1 to 6:1) to yield the alcohol **307** (1.76 g, 99%) as a colourless oil. R_f = 0.52 (petroleum ether–Et_2O, 3:2); $[\alpha]_D^{22}$ +15.2 (c = 0.8, $CHCl_3$) {Lit.[13] $[\alpha]_D^{20}$ +14.9 (c = 1.00, $CHCl_3$)}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.81 (2H, s, CH_2-C11), 3.79 (1H, ddd, *J* = 12.3, 6.2, 4.8 Hz, CH-C6), 3.51 (1H, bdd, *J* = 9.9, 2.7 Hz, CH_2-C1), 3.46 (1H, bdd, *J* = 9.9, 3.6 Hz, CH_2-C1), 2.22—2.10 (2H, m, CH_2-C5), 2.14 (1H, dd, *J* = 16.7, 9.4 Hz, CH_2-C3), 1.88—1.81 (1H, m, CH-C2), 1.85 (1H, dd, *J* = 16.7, 7.7 Hz, CH_2-C3), 1.47—1.24 (4H, m, CH_2-C7, CH_2-C8), 1.44—1.40 (1H, m, OH), 0.91—0.86 (6H, m, CH_3-C9, CH_3-C10), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.04

(3H, s, CH_3-TBS), 0.04 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.4 (C-C4), 113.7 (CH_2-C11), 71.1 (CH-C6), 68.4 (CH_2-C1), 43.9 (CH_2-C5), 40.9 (CH_2-C3), 39.3 (CH_2-C7), 34.0 (CH-C2), 26.1 (3C, CH_3-*t*-Bu-TBS), 18.7 (CH_2-C8), 18.3 (C-*t*-Bu-TBS), 16.9 (CH_3-C10), 14.4 (CH_3-C9), −4.2 (CH_3-TBS), −4.4 (CH_3-TBS); ν_{max} 2957, 2928, 2857, 1462, 1253, 1037, 833, 771 cm^{-1}; LRMS (CI, *iso*-butane) *m*/*z* (intensity) 301.3 $[M+H]^+$ (100), 187.2 (96), 169.2 (42), 69.1 (81); HRMS (CI, *iso*-butane) calcd for $C_{17}H_{37}O_2Si$ $[M+H]^+$ 301.2563, found 301.2562.

tert-Butyldimethyl{[(4*R*,8*R*)-8-methyl-6-methylenedec-9-yn-4-yl]oxy}silane 308

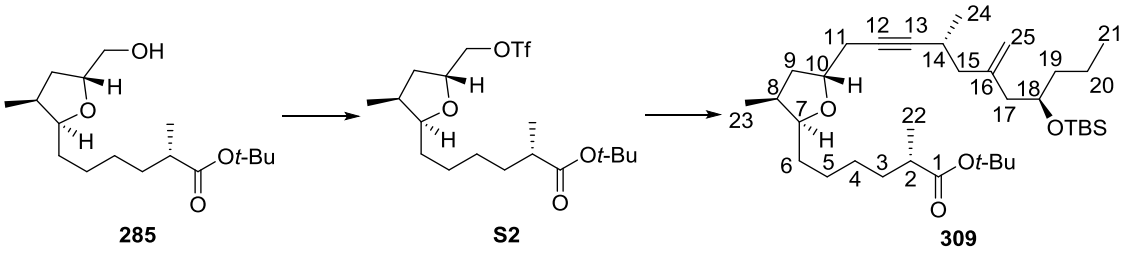


To a solution of alcohol **307** (1.41 g, 4.69 mmol) in CH_2Cl_2 (40 mL) at rt was added DMP (3.18 g, 7.51 mmol) in one portion and the mixture was stirred for 30 min. The reaction was quenched by sequential addition of Et_2O (40 mL), saturated aqueous $Na_2S_2O_3$ (40 mL) and saturated aqueous $NaHCO_3$ (20 mL). The phases were separated and the aqueous phase was back extracted with Et_2O (3 × 30 mL). The combined extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude aldehyde **305** as a pale yellow oil which was used in the next step without further purification.

K_2CO_3 anhydrous (1.94 g, 14.1 mmol) was added to a solution of the Ohira-Bestmann reagent[134] (3.60 g, 18.8 mmol) in MeOH (24 mL) at 0 °C. After stirring the mixture at this temperature for 1 h, a solution of the crude aldehyde **305** in THF (12 mL) was added over 30 min and the mixture was stirred at 0 °C for 1 h. The mixture was then warmed to rt and stirred for an additional 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (25 mL) and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 500:1 to 200:1) to

yield the alkyne **308** (1.13 g, 82% over 2 steps) as a colourless oil. R_f = 0.36 (petroleum ether); $[\alpha]_D^{28}$ +10.5 (c = 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.87 (1H, s, CH_2-C12), 4.85 (1H, s, CH_2-C12), 3.81—3.74 (1H, m, CH-C7), 2.60 (1H, dpd, *J* = 7.9, 6.9, 2.4 Hz, CH-C3), 2.27—2.10 (4H, m, CH_2-C4, CH_2-C6), 2.04 (1H, d, *J* = 2.4 Hz, CH-C1), 1.47—1.25 (4H, m, CH_2-C8, CH_2-C9), 1.18 (1H, d, *J* = 6.9 Hz, CH_3-C11), 0.91—0.87 (3H, m, CH_3-C10), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.05 (3H, s, CH_3-TBS), 0.04 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.1 (C-C5), 114.4 (CH_2-C12), 89.0 (C-C2), 71.2 (CH-C7), 68.5 (CH-C1), 44.0 (CH_2-C4 or CH_2-C6), 43.8 (CH_2-C4 or CH_2-C6), 39.3 (CH_2-C8), 26.7 (3C, CH_3-*t*-Bu-TBS), 24.4 (CH-C3), 20.9 (CH_3-C11), 18.7 (CH_2-C9), 18.3 (C-*t*-Bu-TBS), 14.4 (CH_3-C10), −4.2 (CH_3-TBS), −4.4 (CH_3-TBS); ν_{max} 2958, 2931, 2858, 1265, 1038, 835, 774, 741 cm^{-1}; HRMS (ESI+) calcd for $C_{18}H_{34}NaOSi$ $[M+Na]^+$ 301.2271, found 317.2262; Anal. calcd for $C_{18}H_{34}OSi$: C, 73.40%; H, 11.63%, found: C, 73.11%; H, 11.92%.

(*S*)-*tert*-Butyl 6-{(2*S*,3*S*,5*R*)-5-{(4*R*,8*R*)-8-[(*tert*-butyldimethylsilyl)oxy]-4-methyl-6-methyleneundec-2-yn-1-yl}-3-methyltetrahydrofuran-2-yl}-2-methylhexanoate 309

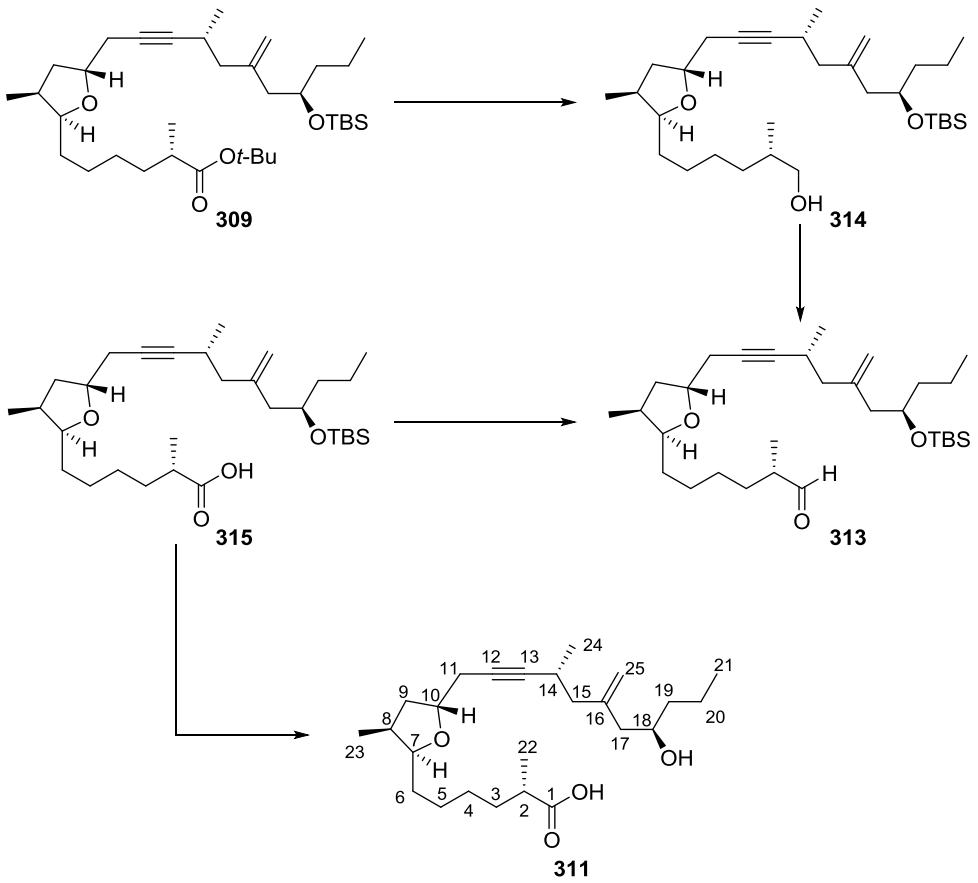


2,6-Lutidine (155 µL, 1.33 mmol) and Tf_2O (168 µL, 1.00 mmol) were sequentially added to a solution of alcohol **285** (100 mg, 0.33 mmol) in CH_2Cl_2 (4 mL) at −78 °C and the resulting mixture was stirred at this temperature for 30 min. The reaction was quenched by addition of H_2O (4 mL) and saturated aqueous $CuSO_4$ (1 mL), then extracted with Et_2O (3 × 7 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was filtered through a short pad of silica gel (petroleum ether–Et_2O, 9:1) to afford the crude triflate **S2** as a yellow oil which was used in the next step without further purification.

n-BuLi (320 µL of a 2.5 M solution in hexanes, 0.80 mmol) was added to a solution of alkyne **308** (196 mg, 0.67 mmol) in THF (1 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 15 min, 0 °C for 5 min and then at −78 °C for another 5 min before addition of a solution of crude triflate **S2** in a 3:2 mixture of THF and HMPA (500 µL). The resulting mixture was stirred at −78 °C for 15 min and the reaction was quenched by addition of saturated aqueous NH_4Cl (1 mL). The mixture was extracted with Et_2O (3 × 2 mL) and the combined organic phases were washed with brine (1 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 100:1 to 19:1) to yield the *tert*-butyl ester **309** (117 mg, 61% over 2 steps) as a colourless oil. R_f = 0.30 (petroleum ether–Et_2O, 9:1); $[\alpha]_D^{25}$ +45.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 (1H, s, CH_2-C25), 4.81 (1H, s, CH_2-C25), 4.14 (1H, qd, *J* = 7.2, 4.5 Hz, CH-C10), 3.89 (1H, dt, *J* = 7.9, 5.3 Hz, CH-C7), 3.78—3.73 (1H, m, CH-C18), 2.60—2.52 (1H, m, CH-C14), 2.41 (1H, ddd, *J* = 16.3, 4.5, 2.2 Hz, CH_2-C11), 2.29 (1H, ddd, *J* = 16.3, 7.2, 2.2 Hz, CH_2-C11), 2.33—2.22 (2H, m, CH-C2, CH-C8), 2.19 (1H, dd, *J* = 14.0, 7.9 Hz, CH_2-C17), 2.17 (1H, dd, *J* = 14.1, 6.1 Hz, CH_2-C15), 2.13 (1H, dd, *J* = 14.0, 6.8 Hz, CH_2-C17), 2.07 (1H, dd, *J* = 14.1, 6.9 Hz, CH_2-C15), 1.96 (1H, dt, *J* = 12.6, 7.2 Hz, CH_2-C9), 1.76 (1H, ddd, *J* = 12.6, 7.2, 3.6 Hz, CH_2-C9), 1.65 (1H, dddd, *J* = 12.0, 7.6, 7.0 4.3 Hz, CH_2-C3), 1.48—1.25 (11H, m, 1 × CH_2-C3, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C19, CH_2-C20), 1.43 (9H, s, CH_3-*t*-Bu), 1.12 (1H, d, *J* = 6.8 Hz, CH_3-C24), 1.08 (3H, d, *J* = 7.0 Hz, CH_3-C22), 0.91—087 (6H, m, CH_3-C23, CH_3-C21), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.04 (3H, s, CH_3-TBS), 0.04 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5 (C-C1), 144.4 (C-C16), 114.1 (CH_2-C25), 86.1 (C-C12 or C-C13), 82.1 (CH-C7), 79.9 (C-*t*-Bu), 77.7 (C-C12 or C-C13), 75.4 (CH-C10), 71.2 (CH-C18), 44.3 (CH_2-C15), 44.1 (CH_2-C17), 40.5 (CH-C2), 39.3 (CH_2-C19), 39.2 (CH_2-C9), 36.0 (CH-C8), 33.9 (CH_2-C3), 30.5 (CH_2-C6), 28.2 (3C, CH_3-*t*-Bu), 27.6 (CH_2-C4), 26.6 (CH_2-C5), 26.5 (CH_2-C11), 26.1 (3C, CH_3-*t*-Bu-TBS), 24.6 (CH-C14), 21.3 (CH_3-C24), 18.7 (CH_2-C20), 18.3 (C-*t*-Bu-TBS), 17.3 (CH_3-C22), 14.4 (CH_3-C21), 14.1 (CH_3-C23), −4.2 (CH_3-TBS), −4.4 (CH_3-TBS); ν_{max} 2960, 2931, 2858, 1729, 1367, 1256, 1149, 1039, 835, 773, 736 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 577.5 $[M+H]^+$ (15), 521.5 (15), 449.5 (25), 391.4 (24), 389.4 (23), 335.3 (10), 285.3 (13), 187.2 (100), 145.2 (65),

133.2 (28), 73.1 (42); HRMS (CI, *iso*-butane) calcd for $C_{35}H_{65}O_4Si$ $[M+H]^+$ 577.4652, found 577.4644.

(*S*)-6-{(2*S*,3*S*,5*R*)-5-[(4*R*,8*R*)-8-Hydroxy-4-methyl-6-methyleneundec-2-yn-1-yl]-3-methyltetrahydrofuran-2-yl}-2-methylhexanoic acid 311



To a suspension of $LiAlH_4$ (5.90 mg, 0.156 mmol) in THF (1 mL) at 0 °C, was added a solution of ester **309** (30 mg, 0.052 mmol) in THF (100 µL). The resulting mixture was stirred at 0 °C for 1 h and then the reaction was quenched by addition of H_2O (6 µL) and 1 M aqueous NaOH (6 µL). The reaction mixture was stirred at 0 °C for further 5 min before addition of H_2O (18 µL). The mixture was stirred at rt for 5 min, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude alcohol **314** which was used in the next step without further purification.

To a solution of crude alcohol **314** in CH_2Cl_2 (5 mL) were added 4 Å MS (25 mg) and NaOAc (4.30 mg, 0.052 mmol). The mixture was cooled to 0 °C and PCC (33.6 mg, 0.104 mmol) was added; the reaction was then stirred at this temperature for 24 h. The reaction mixture was diluted with petroleum ether

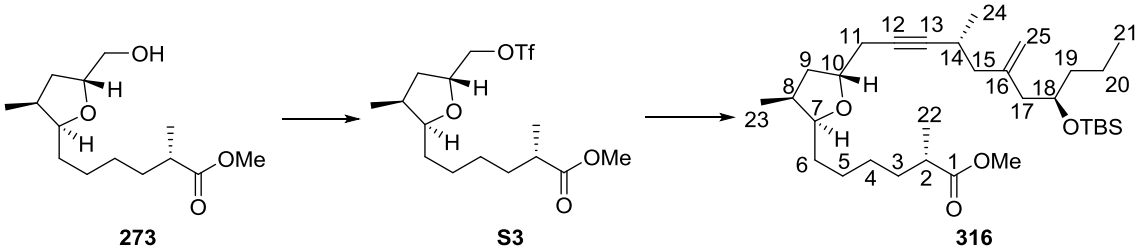
(10 mL) and the precipitate was removed by filtration. The filtrate was concentrated under reduced pressure to afford the crude aldehyde **313** which was used in the next step without further purification.

To a solution of $AgNO_3$ (21.2 mg, 0.125 mmol) in H_2O (809 μL) cooled to 0 °C was added a solution of crude aldehyde **313** in THF (1.6 mL) followed by slow addition of a 0.3 M aqueous NaOH (809 μL). The mixture was stirred vigorously at 0 °C for 1.5 h and the deposited Ag was filtered off and washed with H_2O. The filtrate was cooled to 0 °C, acidified with 1 M aqueous HCl until pH 5 was reached and the resulting mixture was extracted with Et_2O (3 × 4 mL). The combined organic extracts were washed with brine (3 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish the crude acid **315** which was used in the next step without further purification.

To a solution of crude acid **315** in CH_2Cl_2 (600 μL) at 0 °C, was added TFA (40 μL, 0.52 mmol). The mixture was stirred at rt for 1 h and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 3:1 to 1:1) to afford the seco acid **311** (15.6 mg, 74% over 4 steps) as a colourless oil. R_f = 0.20 (petroleum ether–Et_2O, 1:2); $[\alpha]_D^{25}$ +18.2 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94 (1H, s, CH_2-C25), 4.92 (1H, s, CH_2-C25), 4.14 (1H, qd, *J* = 7.0, 4.9 Hz, CH-C10), 3.88 (1H, dt, *J* = 7.7, 5.1 Hz, CH-C7), 3.76—3.70 (1H, m, CH-C18), 2.63—2.55 (1H, m, CH-C14), 2.44 (1H, app. sextet, *J* = 6.9 Hz, CH-C2), 2.38 (1H, ddd, *J* = 16.3, 4.9, 2.1 Hz, CH_2-C11), 2.30 (1H, ddd, *J* = 16.3, 7.0, 2.0 Hz, CH_2-C11), 2.25 (1H, dd, *J* = 13.7, 3.2 Hz, CH_2-C17), 2.27—2.20 (1H, m, CH-C8), 2.16—2.06 (2H, m, CH_2-C15), 2.09 (1H, dd, *J* = 13.7, 4.6 Hz, CH_2-C17), 1.92 (1H, dt, *J* = 12.7, 7.0 Hz, CH_2-C9), 1.74 (1H, ddd, *J* = 12.7, 7.0, 3.7 Hz, CH_2-C9), 1.65 (1H, dddd, *J* = 12.3, 7.2, 6.9, 5.2 Hz, CH_2-C3), 1.50—1.23 (12H, m, 1 × CH_2-C3, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C19, CH_2-C20, OH), 1.16 (3H, d, *J* = 6.9 Hz, CH_3-C22), 1.15 (3H, d, *J* = 6.8 Hz, CH_3-C24), 0.92 (3H, t, *J* = 7.0 Hz, CH_3-C21), 0.89 (3H, d, *J* = 7.0 Hz, CH_3-C23); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.4 (C-C1), 144.4 (C-C16), 114.6 (CH_2-C25), 85.7 (C-C12 or C-C13), 82.0 (CH-C7), 77.7 (C-C12 or C-C13), 75.4 (CH-C10), 68.8 (CH-C18), 44.5 (CH_2-C17), 43.5 (CH_2-C15), 39.4 (CH-C2), 39.2 (CH_2-C19), 39.1 (CH_2-C9), 36.0 (CH-C8), 33.6 (CH_2-C3), 30.3 (CH_2-C6), 27.5 (CH_2-C4), 26.5 (CH_2-C5), 26.4 (CH_2-C11), 24.9 (CH-C14), 21.5 (CH_3-C22), 19.1 (CH_2-C20), 17.0 (CH_3-C24), 14.3 (CH_3-C21), 14.1 (CH_3-C23); ν_{max} 2961, 2930, 2874, 1707, 1458, 1088, 1072,

908, 731 cm^{-1}; LRMS (EI+) *m/z* (intensity) 460.3 $[M]^+$ (1), 279.2 (12), 213.1 (46), 195.1 (100), 149.1 (15), 82.9 (18); HRMS (EI+) calcd for $C_{25}H_{42}O_4$ $[M]^+$ 406.3083, found 406.3088.

(*S*)-Methyl 6-{(2*S*,3*S*,5*R*)-5-{(4*R*,8*R*)-8-[(*tert*-butyldimethylsilyl)oxy]-4-methyl-6-methyleneundec-2-yn-1-yl}-3-methyltetrahydrofuran-2-yl}-2-methylhexanoate 316

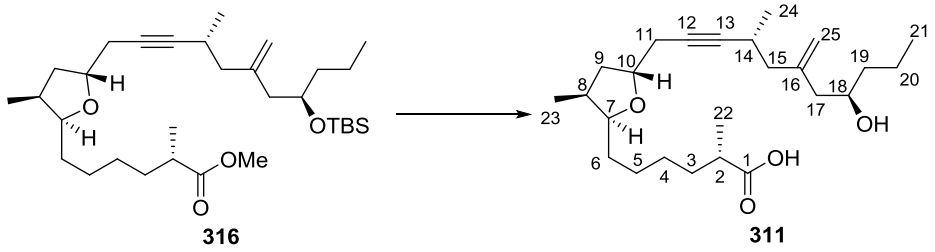


2,6-Lutidine (721 µL, 6.19 mmol) and Tf_2O (787 µL, 4.64 mmol) were added sequentially to a solution of alcohol **273** (400 mg, 1.55 mmol) in CH_2Cl_2 (22 mL) at −78 °C and the resulting mixture was stirred at this temperature for 30 min. The reaction was quenched by addition of H_2O (20 mL) and saturated aqueous $CuSO_4$ (5 mL) and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was filtered through a short pad of silica gel (petroleum ether–Et_2O, 4:1) to afford the crude triflate **S3** as a yellow oil which was used in the next step without further purification.

n-BuLi (681 µL of a 2.5 M solution in hexanes, 1.70 mmol) was added to a solution of alkyne **308** (456 mg, 1.55 mmol) in Et_2O (7 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 15 min, 0 °C for 5 min and then at −78 °C for another 5 min before addition of a solution of crude triflate **S3** in a 3:2 mixture of Et_2O and HMPA (3.6 mL). The resulting yellow mixture was stirred at −78 °C for 15 min, then the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 100:1 to 19:1) to yield the methyl ester **316** (563 mg, 68% over 2 steps) as a colourless

oil. R_f = 0.29 (petroleum ether–Et_2O, 4:1); $[\alpha]_D^{25}$ +33.5 (c = 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.83 (1H, s, CH_2-C25), 4.80 (1H, s, CH_2-C25), 4.13 (1H, qd, *J* = 7.2, 4.6 Hz, CH-C10), 3.88 (1H, dt, *J* = 7.8, 5.1 Hz, CH-C7), 3.79—3.71 (1H, m, CH-C18), 3.65 (3H, s, CH_3-OMe), 2.59—2.50 (1H, m, CH-C14), 2.42 (1H, app. sextet, *J* = 7.0 Hz, CH-C2), 2.40 (1H, ddd, *J* = 16.3, 4.6, 2.3 Hz, CH_2-C11), 2.29 (1H, ddd, *J* = 16.3, 7.2, 2.2 Hz, CH_2-C11), 2.26—2.13 (3H, m, CH-C8, CH_2-C17), 2.13 (1H, dd, *J* = 14.1, 6.3 Hz, CH_2-C15), 2.06 (1H, dd, *J* = 14.1, 7.0 Hz, CH_2-C15), 1.95 (1H, dt, *J* = 12.6, 7.2 Hz, CH_2-C9), 1.74 (1H, ddd, *J* = 12.6, 7.2, 3.7 Hz, CH_2-C9), 1.65 (1H, dddd, *J* = 12.3, 7.2, 7.0, 5.2 Hz, CH_2-C3), 1.47—1.23 (11H, m, 1 × CH_2-C3, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C19, CH_2-C20), 1.12 (3H, d, *J* = 7.0 Hz, CH_3-C22), 1.11 (3H, d, *J* = 6.8 Hz, CH_3-C24), 0.90—084 (6H, m, CH_3-C23, CH_3-C21), 0.87 (9H, s, CH_3-*t*-Bu-TBS), 0.03 (3H, s, CH_3-TBS), 0.02 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4 (C-C1), 144.4 (C-C16), 114.1 (CH_2-C25), 86.0 (C-C12 or C-C13), 82.0 (CH-C7), 77.1 (C-C12 or C-C13), 75.4 (CH-C10), 71.2 (CH-C18), 51.6 (CH_3-OMe), 44.2 (CH_2-C17), 44.0 (CH_2-C15), 39.5 (CH-C2), 39.3 (CH_2-C19), 39.1 (CH_2-C9), 36.0 (CH-C8), 33.9 (CH_2-C3), 30.4 (CH_2-C6), 27.6 (CH_2-C4), 26.6 (CH_2-C5), 26.4 (CH_2-C11), 26.0 (3C, CH_3-*t*-Bu-TBS), 24.6 (CH-C14), 21.3 (CH_3-C24), 18.7 (CH_2-C20), 18.2 (C-*t*-Bu-TBS), 17.2 (CH_3-C22), 14.4 (CH_3-C21), 14.1 (CH_3-C23), −4.2 (CH_3-TBS), −4.4 (CH_3-TBS); ν_{max} 2955, 2932, 2858, 1740, 1463, 1255, 1090, 1040, 835, 773 cm^{-1}; LRMS (CI, *iso*-butane) *m*/*z* (intensity) 535.3 $[M+H]^+$ (7), 463.3 (62), 403.3 (63), 349.2 (33), 227.1 (40), 187.1 (100); HRMS (CI, *iso*-butane) calcd for $C_{32}H_{59}O_4Si$ $[M+H]^+$ 535.4183, found 535.4178.

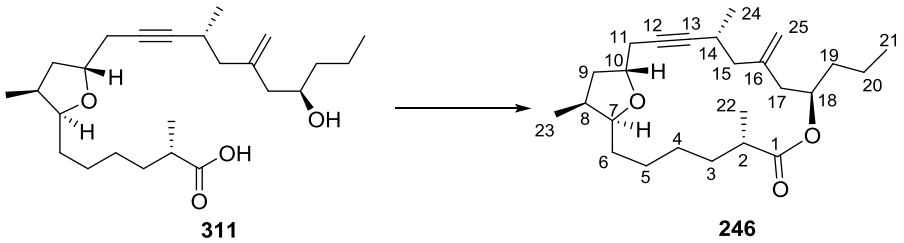
(*S*)-6-{(2*S*,3*S*,5*R*)-5-[(4*R*,8*R*)-8-Hydroxy-4-methyl-6-methyleneundec-2-yn-1-yl]-3-methyltetrahydrofuran-2-yl}-2-methylhexanoic acid 311



To a solution of ester **316** (400 mg, 0.75 mmol) in THF (40 mL) at rt was added TMSOK (90%, 1.07 g, 7.48 mmol). The reaction was stirred at rt for 24 h before addition of conc. HCl (6.23 mL, 74.8 mmol). The resulting mixture was stirred at rt for 1 h, then diluted with H_2O (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 3:2 to 1:1) to afford the *seco* acid **311** (262 mg, 86%) as a colourless oil. R_f = 0.20 (petroleum ether–Et_2O, 1:2); $[\alpha]_D^{25}$ +18.2 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94 (1H, s, CH_2-C25), 4.92 (1H, s, CH_2-C25), 4.14 (1H, qd, *J* = 7.0, 4.9 Hz, CH-C10), 3.88 (1H, dt, *J* = 7.7, 5.1 Hz, CH-C7), 3.76—3.70 (1H, m, CH-C18), 2.63–2.55 (1H, m, CH-C14), 2.44 (1H, app. sextet, *J* = 6.9 Hz, CH-C2), 2.38 (1H, ddd, *J* = 16.3, 4.9, 2.1 Hz, CH_2-C11), 2.30 (1H, ddd, *J* = 16.3, 7.0, 2.0 Hz, CH_2-C11), 2.25 (1H, dd, *J* = 13.7, 3.2 Hz, CH_2-C17), 2.27—2.20 (1H, m, CH-C8), 2.16—2.06 (2H, m, CH_2-C15), 2.09 (1H, dd, *J* = 13.7, 4.6 Hz, CH_2-C17), 1.92 (1H, dt, *J* = 12.7, 7.0 Hz, CH_2-C9), 1.74 (1H, ddd, *J* = 12.7, 7.0, 3.7 Hz, CH_2-C9), 1.65 (1H, dddd, *J* = 12.3, 7.2, 6.9, 5.2 Hz, CH_2-C3), 1.50—1.23 (12H, m, 1 × CH_2-C3, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C19, CH_2-C20, OH), 1.16 (3H, d, *J* = 6.9 Hz, CH_3-C22), 1.15 (3H, d, *J* = 6.8 Hz, CH_3-C24), 0.92 (3H, t, *J* = 7.0 Hz, CH_3-C21), 0.89 (3H, d, *J* = 7.0 Hz, CH_3-C23); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.4 (C-C1), 144.4 (C-C16), 114.6 (CH_2-C25), 85.7 (C-C12 or C-C13), 82.0 (CH-C7), 77.7 (C-C12 or C-C13), 75.4 (CH-C10), 68.8 (CH-C18), 44.5 (CH_2-C17), 43.5 (CH_2-C15), 39.4 (CH-C2), 39.2 (CH_2-C19), 39.1 (CH_2-C9), 36.0 (CH-C8), 33.6 (CH_2-C3), 30.3 (CH_2-C6), 27.5 (CH_2-C4), 26.5 (CH_2-C5), 26.4 (CH_2-C11), 24.9 (CH-C14), 21.5 (CH_3-C22), 19.1 (CH_2-C20), 17.0 (CH_3–C24), 14.3 (CH_3-C21), 14.1 (CH_3–C23); ν_{max} 2961, 2930, 2874, 1707, 1458, 1088, 1072,

908, 731 cm^{-1}; LRMS (EI+) *m/z* (intensity) 460.3 $[M]^+$ (1), 279.2 (12), 213.1 (46), 195.1 (100), 149.1 (15), 82.9 (18); HRMS (EI+) calcd for $C_{25}H_{42}O_4$ $[M]^+$ 406.3083, found 406.3088.

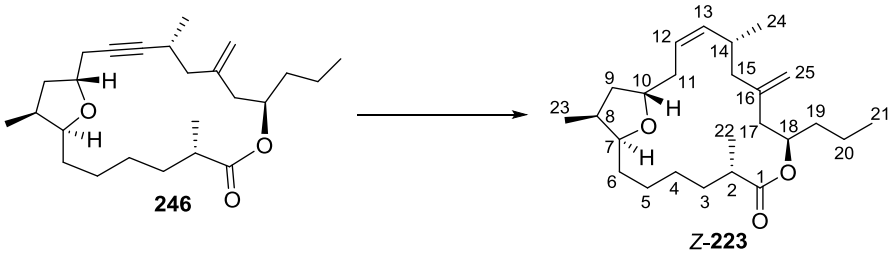
(1*S*,6*S*,9*R*,13*R*,17*R*,19*S*)-6,13,19-Trimethyl-11-methylene-9-propyl-8,20-dioxabicyclo[15.2.1]icos-14-yn-7-one 246



To a solution of *seco* acid **311** (61.0 mg, 0.15 mmol) in toluene (18 mL) at rt were added 2,4,6-trichlorobenzoyl chloride (820 µL, 5.25 mmol) and DIPEA (1.83 mL, 10.5 mmol). The mixture was stirred at rt for 12 h, then diluted with toluene (18 mL) and added *via* syringe pump to a solution of DMAP (733 mg, 6.00 mmol) in toluene (410 mL) at 45 °C over 12 h. The reaction was stirred at 45 °C for an additional 10 h and quenched by the addition of saturated aqueous NH_4Cl (200 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 49:1 to 19:1) to afford the macrolactone **246** (46.6 mg, 80%) as a colourless solid. R_f = 0.50 (petroleum ether–Et_2O, 4:1); $[\alpha]_D^{24}$ +20.4 (c = 0.8, $CHCl_3$); mp = 36.5–37.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.07—4.99 (1H, m, CH-C18), 5.03 (1H, d, *J* = 1.0 Hz, CH_2-C25), 4.92 (1H, d, *J* = 1.0 Hz, CH_2-C25), 4.18 (1H, qd, *J* = 7.0, 3.9 Hz, CH-C10), 4.06 (1H, dt, *J* = 8.2, 4.6 Hz, CH-C7), 2.61 (1H, ddd, J = 16.7, 3.9, 2.0 Hz, CH_2-C11), 2.60—2.52 (1H, m, CH-C14), 2.46 (1H, app. sextet, *J* = 6.8 Hz, CH-C2), 2.34 (1H, dd, *J* = 14.2, 7.2 Hz, CH_2-C17), 2.26—2.10 (5H, m, CH-C8, 1 × CH_2-C9, 1 × CH_2-C11, 1 × CH_2-C15, 1 × CH_2-C17), 2.05 (1H, dd, *J* = 13.8, 5.9 Hz, CH_2-C15), 1.68—1.50 (4H, m, CH_2-C3, 1H CH_2-C6, CH_2-C19), 1.63 (1H, ddd, *J* = 12.0, 7.0, 1.3 Hz, CH_2-C9),1.50—1.23 (8H, m, CH_2-C4, CH_2-C5, 1 × CH_2-C6, 1 × CH_2-C19, CH_2-C20), 1.15 (3H, d, *J* = 6.3 Hz, CH_3-C24),

1.14 (3H, d, *J* = 6.8 Hz, CH_3-C22), 0.90 (3H, t, *J* = 7.2 Hz, CH_3-C21), 0.87 (3H, d, *J* = 6.9 Hz, CH_3-C23); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9 (C-C1), 143.7 (C-C16), 114.4 (CH_2-C25), 86.3 (C-C12 or C-C13), 80.8 (CH-C7), 77.7 (C-C12 or C-C13), 74.6 (CH-C10), 72.4 (CH-C18), 44.0 (CH_2-C15), 41.6 (CH_2-C17), 40.8 (CH-C2), 38.4 (CH_2-C9), 36.5 (CH-C8), 36.5 (CH_2-C3), 34.4 (CH_2-C19), 29.8 (CH_2-C6), 26.8 (CH_2-C4), 25.9 (CH_2-C11), 25.7 (CH_2-C5), 25.5 (CH-C14), 21.7 (CH_3-C24), 18.7 (CH_2-C20), 17.6 (CH_3-C22), 14.3 (CH_3-C21), 14.1 (CH_3-C23); ν_{max} 2961, 2934, 2874, 1724, 1458, 1252, 1086, 1065, 912, 733 cm^{-1}; LRMS (EI+) *m*/*z* (intensity) 388.4 [M]$^+$ (77), 277.2 (17), 195.2 (100), 177.2 (55), 162.2 (89), 119.1 (95), 105.1 (100); HRMS (EI+) calcd for $C_{25}H_{40}O_3$ [M]$^+$ 388.2977, found 388.2982.

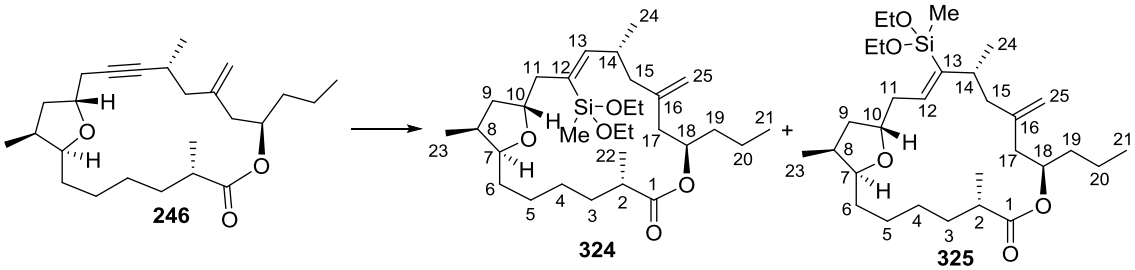
(1*S*,6*S*,9*R*,13*R*,17*S*,19*S*,*Z*)-6,13,19-Trimethyl-11-methylene-9-propyl-8,20-dioxabicyclo[15.2.1]icos-14-en-7-one *Z*-223



A mixture containing alkyne **246** (25.0 mg, 64.0 μmol), Lindlar catalyst (25.0 mg) and quinolone (18 μL) in toluene (5 mL) was purged three times with H_2 and then stirred under atmosphere of H_2 at rt for 3 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 49:1) to yield macrolactone *Z*-**223** (24.0 mg, 96%) as a colourless oil. R_f = 0.35 (petroleum ether–Et_2O, 9:1); $[\alpha]_D^{24}$ −17.3 (c = 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (1H, ddd, *J* = 10.8, 9.0, 5.8 Hz, CH-C12), 5.29 (1H, dd, *J* = 10.8, 9.8 Hz, CH-C13), 5.02 (1H, dddd, *J* = 7.9, 6.6, 6.5, 5.2 Hz, CH-C18), 4.83 (1H, s, CH_2-C25), 4.80 (1H, s, CH_2-C25), 4.16 (1H, qd, *J* = 7.3, 5.4 Hz, CH-C10), 3.85 (1H, dt, *J* = 9.7, 4.5 Hz, CH-C7), 2.60—2.52 (1H, m, CH-C14), 2.45 (1H, ddd, J = 14.1, 9.0, 5.4 Hz, CH_2-C11), 2.44—2.36 (2H, m, CH-C2, 1 × CH_2-C17), 2.19—2.11 (3H, m, CH-C8, 1 × CH_2-C11, 1 × CH_2-C17), 2.06 (1H, dd, *J* = 13.7, 6.5 Hz, CH_2-C15), 1.90 (1H, dd, *J* = 13.7, 7.9 Hz, CH_2-C15), 1.83 (1H, dt, *J* = 12.5, 7.3 Hz,

CH_2-C9), 1.70—1.58 (2H, m, 1 × CH_2-C3, 1 × CH_2-C9), 1.57—1.47 (3H, m, 1 × CH_2-C6, CH_2-C19), 1.42—1.23 (8H, m, 1 × CH_2-C3, CH_2-C4, CH_2-C5, 1 × CH_2-C6, CH_2-C20), 1.14 (3H, d, *J* = 6.9 Hz, CH_3-C22), 0.93 (3H, d, *J* = 6.6 Hz, CH_3-C24), 0.90 (3H, t, *J* = 7.4 Hz, CH_3-C21), 0.86 (3H, d, *J* = 7.0 Hz, CH_3-C23); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3 (C-C1), 144.2 (C-C16), 138.8 (CH-C13), 123.3 (CH-C12), 113.9 (CH_2-C25), 78.9 (CH-C7), 76.0 (CH-C10), 72.2 (CH-C18), 44.4 (CH_2-C15), 41.3 (CH-C2), 40.6 (CH_2-C17), 38.5 (CH_2-C9), 36.5 (CH-C8), 36.0 (CH_2-C19), 34.2 (CH_2-C3), 33.8 (CH_2-C11), 30.5 (CH-C14), 28.6 (CH_2-C6), 26.6 (CH_2-C4), 25.2 (CH_2-C5), 20.8 (CH_3-C24), 18.7 (CH_2-C20), 18.0 (CH_3-C22), 14.5 (CH_3-C23), 14.1 (CH_3-C21); ν_{max} 2957, 2934, 2872, 1726, 1458, 1250, 1070, 897, 735 cm^{-1}; LRMS (EI+) *m/z* (intensity) 390.4 $[M]^+$ (15), 206.2 (33), 191.2 (100); HRMS (EI+) calcd for $C_{25}H_{42}O_3$ $[M]^+$ 390.3134, found 390.3133.

(1*S*,6*S*,9*R*,13*R*,17*R*,19*S*,*Z*)-15-[Diethoxy(methyl)silyl]-6,13,19-trimethyl-11-methylene-9-propyl-8,20-dioxabicyclo[15.2.1]icos-14-en-7-one 324 and (1*S*,6*S*,9*R*,13*R*,17*R*,19*S*,*Z*)-14-[diethoxy(methyl)silyl]-6,13,19-trimethyl-11-methylene-9-propyl-8,20-dioxabicyclo[15.2.1]icos-14-en-7-one 325



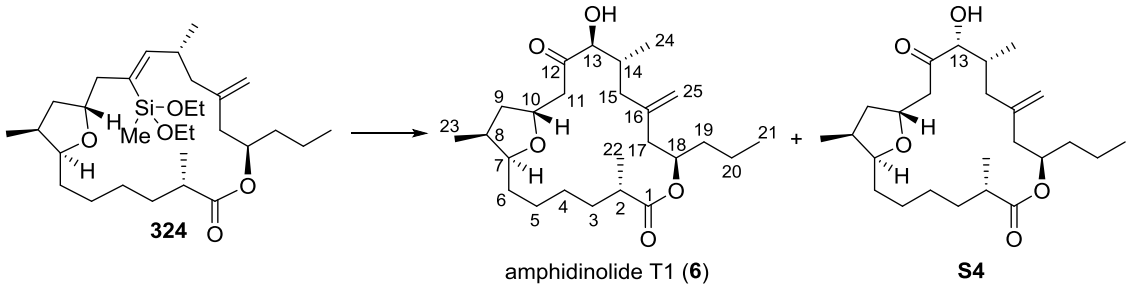
$[Cp^*Ru(MeCN)_3]PF_6$ (3.9 mg, 7.72 μmol) and $(EtO)_2MeSiH$ (37 μL, 232 μmol) were added sequentially to a solution of alkyne **246** (30.0 mg, 77.2 μmol) in CH_2Cl_2 (300 μL) at 0 °C. The mixture was stirred at this temperature for 20 min until the catalyst fully dissolved and then at rt for a further 1 h. The solvent was then evaporated by a stream of argon and the resulting residue was purified by quick flash chromatography on silica gel (petroleum ether–Et_2O, 19:1 to 9:1) to afford the vinylic silane **324** (17.8 mg, 44%) and the vinylic silane **325** (*ca*. 5:1 *Z*:*E* mixture, 18.2 mg, 45%) as colourless oils. The silanes were unstable and so were used in the next step immediately after purification. One batch of the vinylic silanes was used for characterisation purpose.

Vinylic silane **324**. R_f = 0.57 (petroleum ether–Et_2O, 4:1); $[\alpha]_D^{26}$ −8.8 (c = 0.8, benzene); ^{1}H NMR (500 MHz, C_6D_6) δ 6.09 (1H, d, *J* = 10.4 Hz, CH-C13), 5.22 (1H, tdd, *J* = 7.5, 5.8, 4.2 Hz, CH-C18), 5.13 (1H, s, CH_2-C25), 4.94 (1H, s, CH_2-C25), 4.39 (1H, dtd, *J* = 10.0, 6.7, 2.7 Hz, CH-C10), 3.86—3.80 (2H, m, CH_2-EtO), 3.79—3.72 (3H, m, CH-C7, CH_2-EtO), 3.12—3.03 (1H, m, CH-C14), 2.62 (1H, ddd, *J* = 13.0, 2.7, 1.1 Hz, CH_2-C11), 2.52 (1H, app. sextet, *J* = 6.8 Hz, CH-C2), 2.48 (1H, dd, *J* = 14.3, 5.1 Hz, CH_2-C15), 2.36 (1H, dd, *J* = 13.9, 7.5 Hz, CH_2-C17), 2.21 (1H, dd, *J* = 13.9, 4.2 Hz, CH_2-C17), 2.13 (1H, dd, *J* = 13.0, 10.0 Hz, CH_2-C11), 2.08—2.02 (1H, m, CH-C8), 1.98 (1H, dd, *J* = 14.3, 8.4 Hz, CH_2-C15), 1.90—1.82 (1H, m, CH_2-C3), 1.68—1.57 (3H, m, CH_2-C9, 1 × CH_2-C19), 1.57—1.51 (1H, m, CH_2-C5), 1.50—1.26 (9H, m, 1 × CH_2-C3, CH_2-C4, 1 × CH_2-C5, CH_2-C6, 1 × CH_2-C19, CH_2-C20), 1.22 (3H, t, *J* = 7.0 Hz, CH_3-EtO), 1.19 (3H, t, *J* = 7.0 Hz, CH_3-EtO), 1.18 (3H, d, *J* = 6.8 Hz, CH_3-C22), 1.13 (3H, d, *J* = 6.5 Hz, CH_3-C24), 0.86 (3H, t, *J* = 7.3 Hz, CH_3-C21), 0.81 (3H, d, *J* = 7.1 Hz, CH_3-C23), 0.41 (3H, s, CH_3-MeSi); ^{13}C NMR (126 MHz, C_6D_6) δ 175.4 (C-C1), 154.7 (CH-C13), 145.3 (C-C16), 131.0 (C-C12), 114.4 (CH_2-C25), 79.1 (CH-C7), 75.5 (CH-C10), 73.7 (CH-C18), 58.3 (CH_2-EtO), 58.2 (CH_2-EtO), 45.6 (CH_2-C11), 44.3 (CH_2-C15), 42.4 (CH_2-C17), 40.9 (CH_2-C9), 39.6 (CH-C2), 36.5 (CH_2-C19), 36.2 (CH-C8), 36.2 (CH-C14), 34.8 (CH_2-C3), 30.4 (CH_2-C6), 27.0 (CH_2-C4), 26.6 (CH_2-C5), 21.1 (CH_3-C24), 19.1 (CH_2-C20), 18.7 (CH_3-EtO), 18.6 (CH_3-EtO), 16.9 (CH_3-C22), 15.0 (CH_3-C23), 14.2 (CH_3-C21), −1.9 (CH_3-MeSi); ν_{max} 2961, 2926, 2874, 1732, 1458, 1256, 1170, 1103, 1078, 951, 793 cm^{-1}; LRMS (EI+) *m/z* (intensity) 522 $[M]^+$ (10), 476 (24), 266 (58), 264 (49), 209 (100), 207 (76), 133 (41); HRMS (EI+) calcd for $C_{30}H_{54}O_5Si$ $[M]^+$ 522.3741, found 522.3736.

Vinylic silane **325**. R_f = 0.51 (petroleum ether–Et_2O, 4:1); $[\alpha]_D^{26}$ +17.5 (c = 0.9, benzene); ^{1}H NMR (500 MHz, C_6D_6) major isomer δ 6.60 (1H, dd, *J* = 7.6, 6.8 Hz, CH-C12), 5.32—5.26 (1H, m, CH-C18), 5.06 (1H, s, CH_2-C25), 4.95 (1H, s, CH_2-C25), 4.15 (1H, qd, *J* = 7.3, 3.6 Hz, CH-C10), 3.89 (1H, dt, *J* = 9.3, 4.7 Hz, CH-C7), 3.81—3.69 (4H, m, 2 × CH_2-EtO), 2.90—2.81 (1H, m, CH-C14), 2.72 (1H, dd, *J* = 14.0, 8.7 Hz, CH_2-C15), 2.66—2.58 (2H, m, 1 × CH_2-C11, 1 × CH_2-C17), 2.55—2.44 (2H, m, CH-C2, 1 × CH_2-C11), 2.34 (1H, dd, *J* = 14.0, 6.6 Hz, CH_2-C15), 2.15 (1H, dd, *J* = 13.9, 8.8 Hz, CH_2-C17), 2.07—2.01 (1H, m, CH-C8), 1.78—1.66 (2H, m, 1 × CH_2-C3, 1 × CH_2-C9), 1.64—1.51 (4H, m, 1 × CH_2-C5, 1 × CH_2-C6, CH_2-C19),

1.51—1.30 (8H, m, 1 × CH_2-C3, CH_2-C4, 1 × CH_2-C5, 1 × CH_2-C6, 1 × CH_2-C9, CH_2-C20), 1.30 (3H, d, *J* = 6.8 Hz, CH_3-C24), 1.20 (3H, t, *J* = 7.0 Hz, CH_3-EtO), 1.18 (3H, t, *J* = 7.0 Hz, CH_3-EtO), 1.14 (3H, d, *J* = 6.9 Hz, CH_3-C22), 0.87 (3H, t, *J* = 7.4 Hz, CH_3-C21), 0.79 (3H, d, *J* = 7.0 Hz, CH_3-C23), 0.35 (3H, s, CH_3-MeSi); ^{13}C NMR (126 MHz, C_6D_6) δ 175.5 (C-C1), 145.8 (CH-C16), 142.4 (C-C13),142.4 (CH-C12), 113.5 (CH_2-C25), 79.9 (CH-C7), 75.9 (CH-C10), 73.0 (CH-C18), 58.0 (CH_2-EtO), 58.0 (CH_2-EtO), 44.5 (CH_2-C15), 42.5 (CH-C14), 40.7 (CH_2-C17), 40.6 (CH-C2), 39.4 (CH_2-C9), 37.9 (CH_2-C11), 36.6 (CH-C8), 35.9 (CH_2-C19), 34.5 (CH_2-C3), 29.5 (CH_2-C6), 26.6 (CH_2-C4), 26.1 (CH_2-C5), 21.9 (CH_3-C24), 19.1 (CH_2-C20), 18.6 (CH_3-EtO), 18.6 (CH_3-EtO), 17.8 (CH_3-C22), 14.3 (CH_3-C23), 14.1 (CH_3-C21), −1.5 (CH_3-MeSi); ν_{max} 2959, 2926, 2872, 1728, 1458, 1254, 1167, 1103, 1080, 951, 793 cm^{-1}; LRMS (EI+) *m/z* (intensity) 522.3 [M]$^+$ (10), 476.3 (24), 294.1 (17), 195.1 (20), 185.1 (77), 133.1 (100); HRMS (EI+) calcd for $C_{30}H_{54}O_5Si$ [M]$^+$ 522.3741, found 522.3738.

Amphidinolide T1 (6)



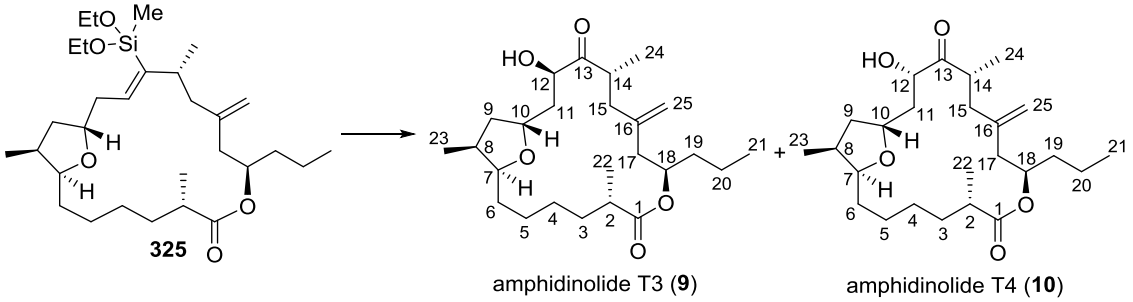
To a solution of vinylic silane **324** (17.8 mg, 34.0 μmol) in CH_2Cl_2 (340 μL) at 0 °C was added *m*-CPBA (75% purity, 8.6 mg, 37.4 μmol). The mixture was stirred at 0 °C for 14 h and then diluted with petroleum ether (500 μL) and saturated aqueous $NaHCO_3$ (1.5 mL). The mixture was extracted with petroleum ether (3 × 1 mL). The combined organic extracts were washed with brine (1.5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to deliver the crude epoxide which was used in the next step without further purification.

To a solution of crude epoxide, KHF_2 (5.3 mg, 68.1 μmol) and $KHCO_3$ (10.2 mg, 102 μmol) in a 1:1 mixture of THF and MeOH (780 μL) was added H_2O_2 (30% solution in H_2O, 19 μL, *ca.* 170 μmol). The mixture was stirred at rt for 4 h and

then the reaction was quenched by addition of saturated aqueous Na_2SO_3 (1 mL). The mixture was extracted with EtOAc (3 × 1 mL) and the combined organic extracts were washed with brine (1 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 4:1 to 3:1) to afford amphidinolide T1 **6** (10.5 mg, 73% over 2 steps) and C13-*epi*-amphidinolide T1 **S4** (1 mg, 7% over 2 steps) as colourless oils.

Amphidinolide T1. R_f = 0.25 (petroleum ether–Et_2O, 2:1); $[\alpha]_D^{23}$ +20.1 (c = 0.3, $CHCl_3$) {Lit.[5] $[\alpha]_D^{24}$ +18.0 (c = 0.3, $CHCl_3$)}; the ^1H and ^{13}C NMR data were identical to those reported in the literature;[5] ^1H NMR (400 MHz, C_6D_6) δ 5.37—5.30 (1H, m, CH-C18), 5.13 (1H, s, CH_2-C25), 4.91 (1H, s, CH_2-C25), 4.47 (1H, qd, *J* = 7.6, 2.7 Hz, CH-C10), 4.30 (1H, bs, CH-C13), 3.64 (1H, ddd, *J* = 10.7, 4.6, 2.5 Hz, CH-C7), 3.63 (1H, d, *J* = 4.6 Hz, OH), 2.53 (1H, dd, *J* = 13.3, 10.2 Hz, CH_2-C15), 2.49—2.37 (3H, m, CH-C2, CH-C14, 1 × CH_2-C11), 2.34—2.21 (3H, m, 1 × CH_2-C15, CH_2-C17), 1.90 (1H, dd, *J* = 14.3, 2.7 Hz, CH_2-C11), 1.73—1.66 (1H, m, CH-C8), 1.63—1.47 (5H, m, 1 × CH_2-C3, 1 × CH_2-C4, 1 × CH_2-C5, 1 × CH_2-C6, 1 × CH_2-C19), 1.46—1.20 (7H, m, 1 × CH_2-C3, 1 × CH_2-C5, CH_2-C9, 1 × CH_2-C19, CH_2-C20), 1.18—1.11 (1H, m, CH_2-C4), 1.07 (3H, d, *J* = 7.0 Hz, CH_3-C22), 1.07—1.01 (1H, m, CH_2-C6), 0.93 (3H, d, *J* = 6.5 Hz, CH_3-C24), 0.86 (3H, t, *J* = 7.2 Hz, CH_3-C21), 0.62 (3H, d, *J* = 7.1 Hz, CH_3-C23); ^{13}C NMR (101 MHz, C_6D_6) δ 212.2 (C-C12), 175.1 (C-C1), 143.6 (C-C16), 116.2 (CH_2-C25), 78.7 (CH-C7), 78.3 (CH-C13), 73.8 (CH-C10), 71.9 (CH-C18), 45.1 (CH_2-C11), 41.9 (CH-C2), 41.3 (CH_2-C15), 40.2 (CH_2-C17), 39.8 (CH_2-C9), 36.6 (CH-C8), 35.8 (CH_2-C19), 35.2 (CH_2-C3), 32.1 (CH-C14), 29.8 (CH_2-C6), 26.9 (CH_2-C4), 26.4 (CH_2-C5), 19.2 (CH_2-C20), 18.2 (CH_3-C22), 14.1 (CH_3-C23), 14.1 (CH_3-C21), 13.9 (CH_3-C24); ν_{max} 3495, 2961, 2934, 2874, 1724, 1462, 1252, 1059, 1004 cm^{-1}; LRMS (EI+) *m/z* (intensity) 422.3 $[M]^+$ (21), 394.4 (35), 325.3 (100), 312.2 (39), 257.2 (50), 221.2 (100), 220.2 (85), 149.2 (48), 109.1 (38); HRMS (EI+) calcd for $C_{25}H_{42}O_5$ $[M]^+$ 422.3032, found 422.3029.

Amphidinolides T3 (9) and T4 (10)



To a solution of vinylic silane **325** (18.2 mg, 34.8 μmol) in CH_2Cl_2 (350 μL) at 0 °C was added *m*-CPBA (75% purity, 8.8 mg, 38.3 μmol). The mixture was stirred at 0 °C for 14 h and then diluted with petroleum ether (500 μL) and saturated aqueous $NaHCO_3$ (1.5 mL). The mixture was extracted with petroleum ether (3 × 1 mL). The combined organic extracts were washed with brine (1.5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to deliver the crude epoxide which was used in the next step without further purification.

To a solution of crude epoxide, KHF_2 (10.9 mg, 139 μmol) and $KHCO_3$ (13.9 mg, 139 μmol) in a 1:1 mixture of THF and MeOH (800 μL) was added H_2O_2 (30% solution in H_2O, 20 μL, *ca.* 174 μmol). The mixture was stirred at rt for 4 h and then the reaction was quenched by addition of saturated aqueous Na_2SO_3 (1 mL). The mixture was extracted with EtOAc (3 × 1 mL) and the combined organic extracts were then washed with brine (1 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 4:1 to 3:1) to afford amphidinolide T3 **9** (4.4 mg, 30% over 2 steps) and amphidinolide T4 **10** (7.2 mg, 49% over 2 steps) as colourless oils.

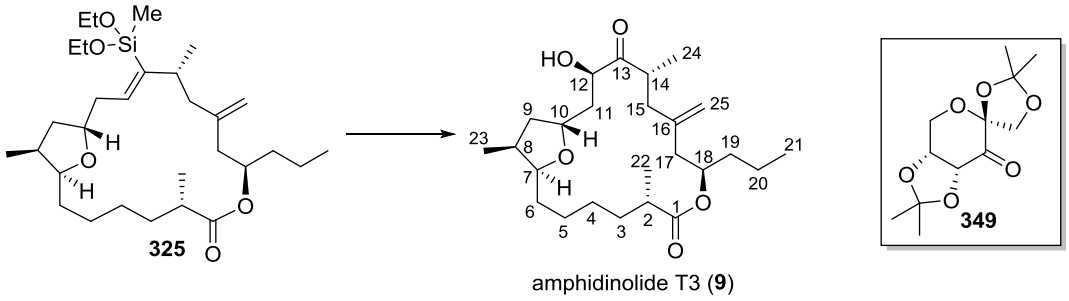
Amphidinolide T3. R_f = 0.28 (petroleum ether–Et_2O, 2:1); $[\alpha]_D^{22}$ −40.1 (c = 0.3, $CHCl_3$) {Lit.[10b] $[\alpha]_D^{20}$ −40.0 (c = 0.075, $CHCl_3$)}; the ^1H and ^{13}C NMR data were identical to those reported in the literature;[8] ^1H NMR (500 MHz, C_6D_6) δ 5.23—5.16 (1H, m, CH-C18), 4.88 (1H, s, CH_2-C25), 4.85 (1H, s, CH_2-C25), 4.56 (1H, bs, OH), 4.37 (1H, dd, *J* = 9.2, 2.9 Hz, CH-C12), 4.02 (1H, ddd, *J* = 10.6, 8.2, 2.9 Hz, CH-C10), 3.76 (1H, ddd, *J* = 9.9, 4.2, 3.1 Hz, CH-C7), 3.56—52 (1H, m, CH-C14), 2.61 (1H, dd, *J* = 13.5, 5.5 Hz, CH_2-C15), 2.54 (1H, dd, *J* = 13.5, 5.5 Hz, CH_2-C17), 2.46—2.40 (1H, m, CH-C2), 2.14 (1H, dd, *J* = 13.5, 8.5 Hz, CH_2-C17), 1.96 (1H, dt, *J* = 14.5, 2.9 Hz, CH_2-C11), 1.85 (1H, dd, *J* = 13.5, 8.6 Hz, CH_2-C15),

1.79—1.20 (16H, m, CH_2-C3, CH_2-C4, CH_2-C5, CH_2-C6, CH-C8, CH_2-C9, 1 × CH_2-C11, CH_2-C19, CH_2-C20), 1.13 (3H, d, *J* = 6.6 Hz, CH_3-C24), 1.12 (3H, d, *J* = 7.0 Hz, CH_3-C22), 0.84 (3H, t, *J* = 7.3 Hz, CH_3-C21), 0.69 (3H, d, *J* = 7.0 Hz, CH_3-C23); ^{13}C NMR (126 MHz, C_6D_6) δ 215.8 (C-C13), 174.9 (C-C1), 143.3 (C-C16), 114.7 (CH_2-C25), 79.2 (CH-C7), 76.3 (CH-C12), 76.2 (CH-C10), 72.2 (CH-C18), 41.5 (CH_2-C15), 41.2 (CH-C2), 40.6 (CH_2-C17), 39.9 (CH_2-C9), 39.3 (CH_2-C11), 38.5 (CH-C14), 36.4 (CH-C8), 35.9 (CH_2-C19), 34.6 (CH_2-C3), 29.7 (CH_2-C6), 26.6 (CH_2-C4), 26.5 (CH_2-C5), 18.8 (CH_2-C20), 17.8 (CH_3-C22), 15.6 (CH_3-C24), 14.2 (CH_3-C23), 14.1 (CH_3-C21); ν_{max} 3451, 2956, 2926, 2874, 1722, 1460, 1252, 1072, 1005 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 423.3 $[M+H]^+$ (62), 405.4 (100), 394.4 (59), 325.3 (45), 279.2 (37), 257.2 (56), 213.2 (50), 195.2 (58), 165.2 (50), 125.2 (53), 95.1 (79); HRMS (CI, *iso*-butane) calcd for $C_{25}H_{43}O_5$ $[M+H]^+$ 423.3110, found 423.3105.

Amphidinolide T4. R_f = 0.21 (petroleum ether–Et_2O, 2:1); $[\alpha]_D^{22}$ −6.5 (c = 0.5, $CHCl_3$) {Lit.[10b] $[\alpha]_D^{20}$ −3.0 (c = 0.12, $CHCl_3$)}; the ^{1}H and ^{13}C NMR data were identical to those reported in the literature;[8] ^{1}H NMR (500 MHz, C_6D_6) δ 5.24—5.17 (1H, m, CH-C18), 4.82 (2H, s, CH_2-C25), 4.55—4.52 (1H, m, CH-C12), 4.32—4.28 (1H, m, CH-C10), 4.07 (1H, bs, OH), 3.80—3.75 (1H, m, CH-C7), 3.38—3.29 (1H, m, CH-C14), 2.71 (1H, dd, *J* = 14.1, 4.4, Hz, CH_2-C15), 2.53 (1H, dd, *J* = 13.6, 5.1 Hz, CH_2-C17), 2.46—2.38 (1H, m, CH-C2), 2.10 (1H, dd, *J* = 13.6, 8.6 Hz, CH_2-C17), 2.02 (1H, dd, *J* = 14.1, 9.9 Hz, CH_2-C15), 1.97 (1H, ddd, *J* = 14.1, 7.8, 3.2 Hz, CH_2-C11), 1.90—1.84 (1H, m, CH-C8), 1.71—1.65 (1H, m, CH_2-C3), 1.64—1.25 (13H, m, 1 × CH_2-C3, CH_2-C4, CH_2-C5, 1 × CH_2-C6, CH_2-C9, 1 × CH_2-C11, CH_2-C19, CH_2-C20), 1.21—1.14 (1H, m, CH_2-C6), 1.10 (3H, d, *J* = 7.0 Hz, CH_3-C22), 0.97 (3H, d, *J* = 6.9 Hz, CH_3-C24), 0.85 (3H, t, *J* = 7.3 Hz, CH_3-C21), 0.70 (3H, d, *J* = 7.1 Hz, CH_3-C23); ^{13}C NMR (126 MHz, C_6D_6) δ 215.7 (C-C13), 175.5 (C-C1), 143.0 (C-C16), 115.5 (CH_2-C25), 79.3 (CH-C7), 74.9 (CH-C12), 74.6 (CH-C10), 71.9 (CH-C18), 41.0 (CH-C2), 40.8 (CH_2-C17), 40.2 (CH_2-C9), 40.1 (CH_2-C11), 39.5 (CH-C14), 38.3 (CH_2-C15), 36.0 (CH-C8), 35.5 (CH_2-C19), 33.8 (CH_2-C3), 28.6 (CH_2-C6), 26.6 (CH_2-C4), 26.0 (CH_2-C5), 18.7 (CH_2-C20), 18.0 (CH_3-C22), 15.9 (CH_3-C24), 14.1 (CH_3-C23), 13.9 (CH_3-C21); ν_{max} 3458, 2960, 2931, 2874, 1722, 1458, 1252, 1069, 1005 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 423.3

$[M+H]^+$ (56), 391.3 (100), 282.3 (19), 257.3 (36); HRMS (CI, *iso*-butane) calcd for $C_{25}H_{43}O_5$ $[M+H]^+$ 423.3110, found 423.3103.

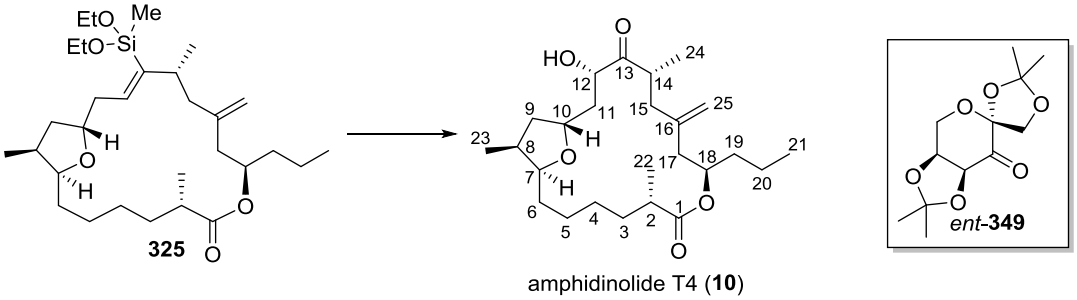
Amphidinolide T3 (9)



To a solution of vinylic silane **325** (12.1 mg, 23.1 μmol) in a 1:2 mixture of MeCN and DMM (8.4 mL) and a 0.05 M solution of $Na_2B_4O_7{\cdot}10H_2O$ in $4{\cdot}\times 10^{-4}$ M aqueous Na_2EDTA (552 μL) at 0 °C were added *n*-Bu_4NHSO_4 (1.9 mg, 5.55 μmol) and ketone **349**[135] (14.2 mg, 55.5 μmol). To this rapidly stirring solution was added, simultaneously over 1 h *via* syringe pump, a solution of Oxone® (67.6 mg, 110 μmol) in 4×10^{-4} M aqueous Na_2EDTA (460 μL) and a 0.89 M solution of K_2CO_3 (460 μL). After the additions of Oxone® and K_2CO_3 solutions, the resulting mixture was stirred at 0 °C for further 1 h and H_2O (4 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to deliver the crude epoxide, which was used in the next step without further purification.

To a solution of crude epoxide, KHF_2 (7.2 mg, 92.5 μmol) and $KHCO_3$ (9.3 mg, 92.5 μmol) in a 1:1 mixture of THF and MeOH (500 μL) was added H_2O_2 (30% solution in H_2O, 14 μL, *ca.* 115 μmol). The mixture was stirred at rt for 4 h and then the reaction was quenched by addition of saturated aqueous Na_2SO_3 (1 mL). The mixture was extracted with EtOAc (3 × 1 mL) and the combined organic layers were washed with brine (1 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 4:1 to 3:1) to yield amphidinolide T3 **9** (6.0 mg, 61% over 2 steps) as a colourless oil.

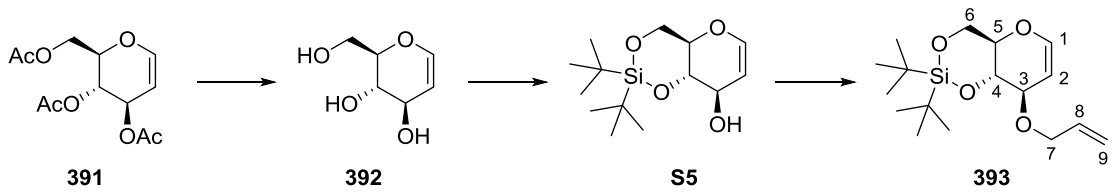
Amphidinolide T4 (10)



To a solution of vinylic silane **325** (11.8 mg, 22.5 μmol) in a 1:2 mixture of MeCN and DMM (8.1 mL) and a 0.05 M solution of $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M aqueous Na_2EDTA (540 μL) at 0 °C were added *n*-Bu_4NHSO_4 (1.8 mg, 5.42 μmol) ketone *ent*-**349**[135,136] (13.9 mg, 54.2 μmol). To this rapidly stirring solution was added, simultaneously over 1 h *via* syringe pump, a solution of Oxone® (66.4 mg, 108 μmol) in 4×10^{-4} M aqueous Na_2EDTA (450 μL) and a 0.89 M solution of K_2CO_3 (450 μL). After the additions of Oxone® and K_2CO_3 solutions, the resulting mixture was stirred at 0 °C for further 1 h and H_2O (4 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure to deliver the crude epoxide, which was used in the next step without further purification.

To a solution of crude epoxide, KHF_2 (7.0 mg, 90.0 μmol), $KHCO_3$ (9.0 mg, 90.0 μmol) in a 1:1 mixture of THF and MeOH (500 μL) was added H_2O_2 (30% solution in H_2O, 13 μL, *ca.* 112 μmol). The mixture was stirred at rt for 4 h, then quenched by addition of saturated aqueous Na_2SO_3 (1 mL) and extracted with EtOAc (3 × 1 mL). The combined organic layers were washed with brine (1 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 4:1 to 3:1) to yield amphidinolide T4 **10** (5.4 mg, 57% over 2 steps) as a colourless oil.

(4a*R*,8*R*,8a*S*)-8-(Allyloxy)-2,2-di-*tert*-butyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline 393



391 **392** **S5** **393**

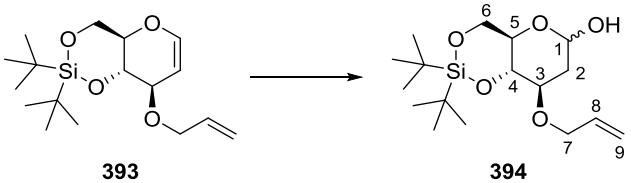
To a solution of tri-*O*-acetyl-D-glucal **391** (10.0 g, 36.7 mmol) in MeOH (80 mL) at rt was added K_2CO_3 (51 mg, 0.37 mmol). The reaction mixture was stirred at rt for 16 h before being concentrated under reduced pressure to give the crude D-glucal **392** which was used in the next step without further purification.

To a solution of D-glucal **392** in DMF (88 mL) at −40 °C was added di-*tert*-butylsiyl-bis(trifluoromethanesulfonate) (13.1 mL, 40.4 mmol) *via* syringe pump over 1 h. After complete addition of the silylating agent, the reaction mixture was stirred at −40 °C for 2 h. The reaction was quenched by addition of pyridine (8 mL) and the mixture was diluted with Et_2O (100 mL) and H_2O (100 mL). The phases were separated and the aqueous phase was back extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to deliver the crude allylic alcohol **S5** which was used in the next step without further purification.

To a solution of alcohol **S5** in DMF (100 mL) at 0 °C was added NaH (2.20 g of a 60% dispersion in mineral oil, 55.1 mmol) portionwise and the resulting mixture was stirred at 0 °C for 10 min during which time evolution of H_2 ceased. Allyl bromide (16.0 mL, 184 mmol) was added followed by addition of TBAI (1.36 g, 3.67 mmol). The mixture was then allowed to warm to rt and stirred at this temperature for 18 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (100 mL) and extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with saturated aqueous LiCl (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–Et_2O, 100:1) to afford the allyl ether **393** (10.7 g, 89% over 3 steps) as a colourless oil. R_f = 0.24 (petroleum ether–Et_2O, 50:1); $[\alpha]_D^{31}$ −28.2 (c = 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (1H, ddd, *J* = 6.1, 1.8, 0.4 Hz, CH-C1), 5.94 (1H, ddt, *J* = 17.2,

10.4, 5.5 Hz, CH-C8), 5.31 (1H, dq, *J* = 17.2, 1.5 Hz, CH_2-C9), 5.17 (1H, dq, *J* = 10.4, 1.5 Hz, CH_2-C9), 4.71 (1H, dd, *J* = 6.1, 1.8 Hz, CH-C2), 4.36 (1H, ddt, *J* = 13.1, 5.5, 1.5 Hz, CH_2-C7), 4.23 (1H, ddt, *J* = 13.1, 5.5, 1.5 Hz, CH_2-C7), 4.15 (1H, dd, *J* = 10.4, 5.0 Hz, CH_2-C6), 4.12 (1H, dd, *J* = 10.4, 7.0 Hz, CH-C4), 4.08 (1H, dt, *J* = 7.0, 1.8 Hz, CH-C3), 3.96 (1H, t, *J* = 10.4 Hz, CH_2-C6), 3.81 (1H, td, *J* = 10.4, 5.0 Hz, CH-C5), 1.07 (9H, s, CH_3-*t*-Bu-Si), 1.00 (9H, s, CH_3-*t*-Bu-Si); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.2 (C-C1), 135.6 (CH-C8), 116.6 (CH_2-C9), 102.8 (CH-C2), 77.5 (CH-C4), 76.7 (CH-C3), 72.9 (CH-C5), 71.5 (CH_2-C7), 66.2 (CH_2-C6), 27.7 (3C, CH_3-*t*-Bu-Si), 27.2 (3C, CH_3-*t*-Bu-Si), 22.9 (C-*t*-Bu-Si), 20.1 (C-*t*-Bu-Si); ν_{max} 2963, 2934, 2889, 2860, 1647, 1473, 1233, 1158, 1119, 1102, 869, 826, 768, 653 cm^{-1}; LRMS (CI, *iso*-butane) *m*/*z* (intensity) 326.9 $[M+H]^+$ (86), 268.9 (100); HRMS (ESI+) calcd for $C_{17}H_{30}NaO_4Si$ $[M+Na]^+$ 349.1806, found 349.1801; Anal. calcd for $C_{17}H_{30}O_4Si$: C, 62.54%; H, 9.26%, found: C, 62.51%; H, 9.39%.

(4a*R*,8*R*,8a*S*)-8-(Allyloxy)-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*] [1,3,2]dioxasilin-6-ol 394

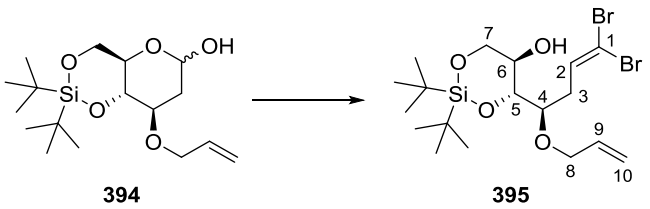


393 **394**

To a solution of enol **393** (13 g, 39.8 mmol) in 1,4-dioxane (470 mL) at rt was added 8 M aqueous HCl (99.5 mL, 796 mmol) and the reaction mixture was stirred at rt for 3 h. The reaction was diluted with CH_2Cl_2 (650 mL) and saturated aqueous $NaHCO_3$ (650 mL), the phases were separated and the aqueous phase was back extracted with CH_2Cl_2 (2 × 500 mL). The combined organic extracts were washed with brine (500 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 9:1) to give the lactol **394** (3:1 mixture of anomers, 12.8 g, 93%,) as a colourless solid. R_f = 0.11 (petroleum ether–EtOAc, 9:1); $[\alpha]_D^{30}$ +21.6 (c = 1.0, $CHCl_3$); mp = 85–86 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.99—5.87 (1H, m, CH-C8 two anomers), 5.99—5.87 (3H, m, CH-C1 major anomer, 1 × CH_2-C9 two anomers), 5.16 (1H, ddt, *J* = 10.4, 1.6, 1.4 Hz, CH_2-C9

minor anomer), 5.15 (1H, ddt, *J* = 10.4, 1.8, 1.3 Hz, CH_2-C9 major anomer), 4.85 (1H, ddd, *J* = 9.5, 6.8, 2.1 Hz, CH-C1 minor anomer), 4.40 (1H, ddt, *J* = 13.0, 5.7, 1.4 Hz, CH_2-C7 major anomer), 4.40 (1H, ddt, *J* = 12.9, 5.4, 1.4 Hz, CH_2-C7 minor anomer), 4.23 (1H, ddt, *J* = 13.0, 5.7, 1.4 Hz, CH_2-C7 major anomer), 4.13 (1H, dd, *J* = 10.2, 5.0 Hz, CH_2-C6 minor anomer), 4.04 (1H, dd, *J* = 9.5, 4.5 Hz, CH_2-C6 major anomer), 3.98—3.91 (2H, m, CH-C4 two anomers), 3.90—3.68 (4H, m, CH-C3 major anomer, CH-C5 major anomer, 1 × CH_2-C6 two anomers), 3.44 (1H, ddd, *J* = 11.6, 8.4, 5.0 Hz, CH-C3 minor anomer), 3.38—3.31 (2H, m, CH-C5 minor anomer, OH minor anomer), 2.86 (1H, dd, *J* = 2.9, 2.4 Hz, OH major anomer) 2.27 (1H, ddd, *J* = 12.9, 5.0, 2.1 Hz, CH_2-C2 minor anomer), 2.14 (1H, ddd, *J* = 13.3, 4.6, 1.2 Hz, CH_2-C2 major anomer), 1.71—1.61 (1H, m, CH_2-C2 major anomer), 1.59—1.49 (1H, m, CH_2-C2 minor anomer), 1.06 (9H, s, CH_3-*t*-Bu-Si major anomer), 1.06 (9H, s, CH_3-*t*-Bu-Si minor anomer), 1.01 (9H, s, CH_3-*t*-Bu-Si major anomer), 0.99 (9H, s, CH_3-*t*-Bu-Si); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7 (CH-C8 major anomer), 135.5 (CH-C8 minor anomer), 116.7 (CH_2-C9 minor anomer), 116.6 (CH_2-C9 major anomer), 94.7 (CH-C1 minor anomer), 92.6 (CH-C1 major anomer), 80.4 (CH-C3 major anomer), 79.3 (CH-C3 minor anomer), 75.1 (CH-C5 major anomer), 72.8 (CH_2-C7 major anomer), 72.4 (CH_2-C7 minor anomer), 71.1 (CH-C5 minor anomer), 67.2 (CH-C4 minor anomer), 67.2 (CH-C4 major anomer), 67.1 (CH_2-C6 major anomer), 66.7 (CH_2-C6 minor anomer), 39.2 (CH_2-C2 minor anomer), 36.5 (CH_2-C2 major anomer), 27.6 (3C, CH_3-*t*-Bu-Si major anomer), 27.6 (3C, CH_3-*t*-Bu-Si minor anomer), 27.2 (3C, CH_3-*t*-Bu-Si major anomer), 27.2 (3C, CH_3-*t*-Bu-Si minor anomer), 22.8 (C-*t*-Bu-Si major anomer), 22.8 (C-*t*-Bu-Si minor anomer), 20.1 (C-*t*-Bu-Si major anomer), 20.1 (C-*t*-Bu-Si minor anomer); ν_{max} 3407, 2963, 2934, 2888, 2860, 1473, 1160, 1095, 1024, 978, 919, 858, 826, 769, 735, 652 cm^{-1}; LRMS (EI+) *m/z* (intensity) 344.0 $[M]^+$ (12), 287.0 (44), 257.0 (76), 215.0 (100), 173 (86), 161.0 (42); HRMS (EI+) calcd for $C_{17}H_{32}O_5Si$ $[M]^+$ 344.2019, found 344.2018; Anal. calcd for $C_{17}H_{32}O_5Si$: C, 59.27%; H, 9.36%, found: C, 59.17%; H, 9.62%.

(4*R*,5*R*)-4-[(*R*)-1-(Allyloxy)-4,4-dibromobut-3-en-1-yl]-2,2-di-*tert*-butyl-1,3,2-dioxasilinan-5-ol 395

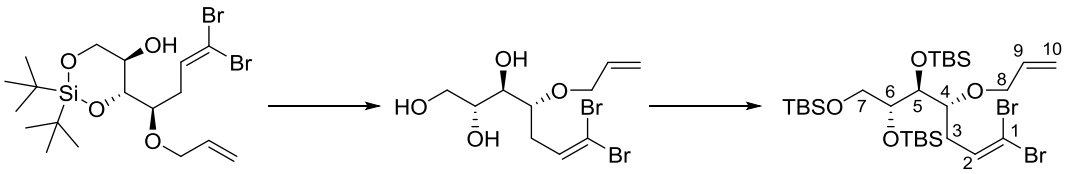


394 **395**

A solution of KO*t*-Bu (7.30 g, 65.0 mmol) in THF (400 mL) was added to a suspension of $[Ph_3PCHBr_2]Br$[137] (35.9 g, 69.7 mmol) in THF (300 mL) at rt. The resulting mixture was stirred at rt for 30 min during which time the colour turned from yellow to brown. A solution of lactol **394** (8.00 g, 23.2 mmol) in THF (100 mL) was added and the reaction was stirred at rt for 16 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (800 mL) and extracted with Et_2O (3 × 500 mL). The combined organic layers were washed with brine (500 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 19:1) to yield the dibromo alkene **395** (9.41 g, 81%) as a colourless oil. R_f = 0.31 (petroleum ether–EtOAc, 9:1); $[\alpha]_D^{28}$ −13.2 (c = 1.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (1H, t, *J* = 7.2 Hz, CH-C2), 5.89 (1H, ddt, *J* = 17.2, 10.5, 5.7 Hz, CH-C9), 5.30 (1H, dq, *J* = 17.2, 1.4 Hz, CH_2-C10), 5.22 (1H, dq, *J* = 10.5, 1.4 Hz, CH_2-C10), 4.14 (1H, ddt, *J* = 12.7, 5.7, 1.4 Hz, CH_2-C8), 4.11 (1H, dd, *J* = 10.5, 4.2 Hz, CH_2-C7), 4.07 (1H, ddt, *J* = 12.7, 5.7, 1.4 Hz, CH_2-C8), 3.98—3.90 (2H, m, CH-C5, CH-C6), 3.79 (1H, t, *J* = 10.5 Hz, CH_2-C7), 3.73 (1H, ddd, *J* = 7.7, 5.0, 2.6 Hz, CH-C4), 2.92 (1H, s, OH), 2.61 (1H, ddd, *J* = 15.0, 7.2, 5.0 Hz, CH_2-C3), 2.43 (1H, ddd, *J* = 15.0, 7.7, 7.2 Hz, CH_2-C3), 1.04 (9H, s, CH_3-*t*-Bu-Si), 0.99 (9H, s, CH_3-*t*-Bu-Si); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.4 (CH-C2), 134.3 (CH-C9), 117.9 (CH_2-C10), 90.3 (C-C1), 78.8 (CH-C4), 76.8 (CH-C5), 71.9 (CH_2-C8), 68.7 (CH_2-C7), 67.1 (CH-C6), 33.4 (CH_2-C3), 27.7 (3C, CH_3-*t*-Bu-Si), 27.2 (3C, CH_3-*t*-Bu-Si), 22.9 (C-*t*-Bu-Si), 20.3 (C-*t*-Bu-Si); ν_{max} 3429, 2961, 2933, 2891, 2860, 1474, 1146, 1133, 1060, 1011, 856, 826, 773, 652 cm^{-1}; LRMS (CI, *iso*-butane) *m*/*z* (intensity) 501.0 $[M+H]^+$ (100), 443.0 (30), 421.0 (33), 341.0 (25), 201.0 (15), 177.0 (13); HRMS (ESI+) calcd for $C_{18}H_{32}NaO_4SiBr_2$ $[M+Na]^+$ 521.0329, found

521.0315; Anal. calcd for $C_{18}H_{32}O_4SiBr_2$: C, 43.21%; H, 6.45%, found: C, 42.66%; H, 6.50%.

(5*S*,6*R*)-5-[(*R*)-1-(Allyloxy)-4,4-dibromobut-3-en-1-yl]-6-[(*tert*-butyldimethylsilyl)oxy]-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane 397



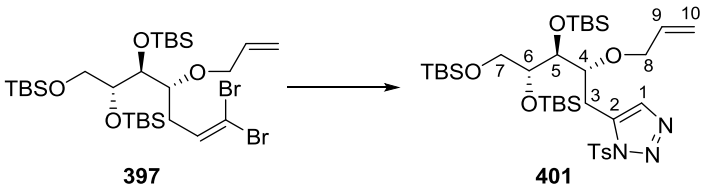
395 **396** **397**

To a solution of silyl ether **395** (9.01 g, 18.0 mmol) in THF (280 mL) at rt, were added sequentially AcOH (2.06 mL, 36.0 mmol) and TBAF (72.0 mL of a 1.0 M solution in THF, 72.0 mmol). The reaction mixture was stirred at rt for 14 h and then concentrated under reduced pressure. The residue was filtered through a short pad of silica gel (petroleum ether–EtOAc, 1:2) to afford the crude triol **396** as a pale yellow solid.

TBSOTf (20.7 mL, 90.0 mmol) and 2,6-lutidine (16.8 mL, 144 mmol) were sequentially added to a solution of the crude triol **396** in CH_2Cl_2 (280 mL) at rt. The mixture was stirred at rt for 3 h and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (280 mL). The mixture was extracted with Et_2O (3 × 400 mL) and the combined organic extracts were washed with saturated aqueous $CuSO_4$ (400 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 200:1) to give the silyl ether **397** (1.40 g, 86% over 2 steps) as a colourless oil. R_f = 0.90 (petroleum ether–EtOAc, 19:1); $[\alpha]_D^{26}$ −3.4 (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (1H, dd, *J* = 7.2, 6.4 Hz, CH-C2), 5.89 (1H, ddt, *J* = 17.2, 10.4, 5.7 Hz, CH-C9), 5.25 (1H, dq, *J* = 17.2, 1.5 Hz, CH_2-C10), 5.16 (1H, dq, *J* = 10.4, 1.5 Hz, CH_2-C10), 4.08 (1H, ddt, *J* = 12.5, 5.7, 1.5 Hz, CH_2-C8), 3.96 (1H, ddt, *J* = 12.5, 5.7, 1.5 Hz, CH_2-C8), 3.82—3.76 (3H, m, CH-C5, CH-C6, 1 × CH_2-C7), 3.49—3.42 (2H, m, CH-C4, 1 × CH_2-C7), 2.46 (1H, ddd, *J* = 16.0, 6.4, 4.2 Hz, CH_2-C3), 2.37 (1H, dt, *J* = 16.0, 7.2 Hz, CH_2-C3), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.89 (9H, s, CH_3-*t*-Bu-

TBS), 0.09 (3H, s, CH_3-TBS), 0.09 (3H, s, CH_3-TBS), 0.08 (3H, s, CH_3-TBS), 0.07 (3H, s, CH_3-TBS), 0.05 (6H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0 (CH-C2), 135.2 (CH-C9), 117.1 (CH_2-C10), 89.5 (C-C1), 79.4 (CH-C4), 76.5 (CH-C5), 75.4 (CH-C6), 71.6 (CH_2-C8), 64.7 (CH_2-C7), 34.8 (CH_2-C3), 26.2 (3C, CH_3-*t*-Bu-TBS), 26.2 (3C, CH_3-*t*-Bu-TBS), 26.2 (3C, CH_3-*t*-Bu-TBS), 18.5 (C-*t*-Bu-TBS), 18.5 (C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), −4.2 (CH_3-TBS), −4.4 (CH_3-TBS), −4.5 (CH_3-TBS), −4.5 (CH_3-TBS), −5.3 (CH_3-TBS), −5.3 (CH_3-TBS); ν_{max} 2954, 2929, 2886, 2857, 2360, 2341, 1252, 1078, 831, 774 cm^{-1}; LRMS (CI, *iso*-butane) *m*/*z* (intensity) 703.0 $[M+H]^+$ (100), 289.0 (64); HRMS (ESI+) calcd for $C_{28}H_{58}NaO_4Si_3Br_2$ $[M+Na]^+$ 723.1902, found 723.1876; Anal. calcd for $C_{28}H_{58}O_4Si_3Br_2$: C, 47.85%; H, 8.32%, found: C, 48.24%; H, 8.49%.

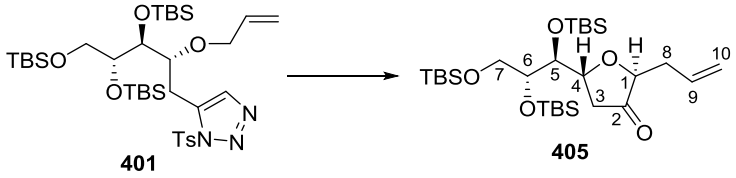
5-{(2*R*,3*S*,4*R*)-2-(Allyloxy)-3,4,5-tris[(*tert*-butyldimethylsilyl)oxy]pentyl}-1-tosyl-1*H*-1,2,3-triazole 401



n-BuLi (6.83 mL of a 2.5 M solution in hexanes, 17.1 mmol) was added dropwise to a solution of dibromo alkene **397** (6.00 g, 8.54 mmol) in THF (42 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 20 min and then TsN_3 (2.0 M in THF, 4.48 mL, 8.96 mmol) was added. The resulting solution was stirred at −78 °C for further 30 min and the reaction was quenched by the addition of saturated aqueous NH_4Cl (40 mL). The mixture was warmed to rt and then extracted with Et_2O (3 × 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by rapid flash chromatography on silica gel (petroleum ether–EtOAc, 10:1) to give the triazole **401** (5.89 g, 93%) as a colourless oil. R_f = 0.28 (petroleum ether–EtOAc, 9:1); $[\alpha]_D^{27}$ +20.3 (c = 2.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (2H, d, *J* = 8.3 Hz, Ar-Ts), 7.54 (1H, s, CH-C1), 7.35 (2H, d, *J* = 8.3 Hz, Ar-Ts), 5.56 (1H, ddt, *J* = 17.2, 10.5, 5.7 Hz, CH-C9), 5.08 (1H, dq, *J* = 17.2, 1.4 Hz, CH_2-C10), 5.03 (1H, dq, *J* = 10.5, 1.4 Hz, CH_2-C10), 4.01 (1H, dd, *J* = 5.7,

1.3 Hz, CH-C5), 3.98 (1H, ddt, *J* = 12.5, 5.7, 1.4 Hz, CH_2-C8), 3.88 (1H, td, *J* = 6.2, 1.3 Hz, CH-C6), 3.82 (1H, dd, *J* = 10.0, 6.2 Hz, CH_2-C7), 3.73 (1H, ddt, *J* = 12.5, 5.7, 1.5 Hz, CH_2-C8), 3.68 (1H, dt, *J* = 12.2, 5.7 Hz, CH-C4), 3.52 (1H, dd, *J* = 10.0, 6.2 Hz, CH_2-C7), 3.38—3.30 (2H, m, CH_2-C3), 2.44 (3H, s, CH_3-Ts), 0.92 (9H, s, CH_3-*t*-Bu-TBS), 0.91 (9H, s, CH_3-*t*-Bu-TBS), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.13 (3H, s, CH_3-TBS), 0.10 (3H, s, CH_3-TBS), 0.07 (3H, s, CH_3-TBS), 0.06 (3H, s, CH_3-TBS), 0.06 (3H, s, CH_3-TBS), 0.05 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.9 (C-C2), 138.2 (C-Ts), 134.4 (CH-C9), 134.2 (C-Ts), 134.0 (CH-C1), 130.3 (2C, CH-Ts), 128.8 (2C, CH-Ts), 117.3 (CH_2-C10), 79.7 (CH-C4), 76.2 (CH-C6), 74.7 (CH-C5), 71.8 (CH_2-C8), 65.0 (CH_2-C7), 26.2 (3C, CH_3-*t*-Bu-TBS), 26.1 (3C, CH_3-*t*-Bu-TBS), 26.1 (3C, CH_3-*t*-Bu-TBS), 25.8 (CH_2-C3), 21.9 (CH_3-Ts), 18.5 (C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), 18.3 (C-*t*-Bu-TBS), −4.2 (CH_3-TBS), −4.5 (CH_3-TBS), −4.6 (CH_3-TBS), −4.6 (CH_3-TBS), −5.3 (CH_3-TBS), −5.3 (CH_3-TBS); ν_{max} 2955, 2929, 2885, 2857, 1390, 1253, 1197, 1087, 834, 777, 668 cm^{-1}; HRMS (ESI+) calcd for $C_{35}H_{65}N_3NaO_6Si_3S$ $[M+Na]^+$ 762.3794, found 762.3774.

(2*S*,5*R*)-2-Allyl-5-{(5*S*,6*R*)-6-[(*tert*-butyldimethylsilyl)oxy]-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-5-yl}dihydrofuran-3(2*H*)-one 405

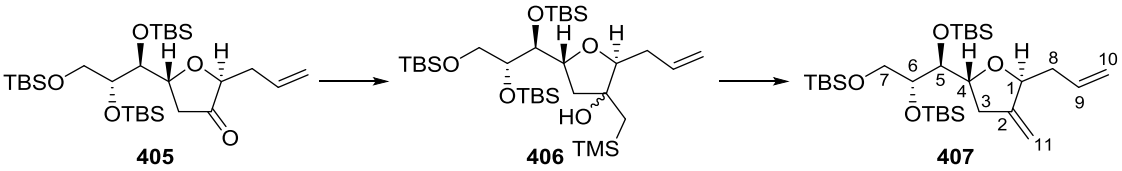


*Note: ketone **405** was prone to epimerisation and decomposition, therefore was kept in the freezer and used in the next step as soon as possible.*

$[Rh(OAc)_2]_2$ (42.0 mg, 94.6 μmol) was added to a solution of triazole **401** (7.00 g, 9.46 mmol) in toluene (400 mL). The resulting mixture was heated to reflux and stirred at this temperature for 1 h. The mixture was then cooled to rt and basic alumina (Brockmann activity III, 95 g) was added. The resulting mixture was stirred at rt for further 30 min then filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 50:1) to afford the dihydrofuranone **405** (4.13 g, 78%, *dr* >20:1) as a colourless oil. R_f = 0.78 (petroleum ether–EtOAc, 9:1); $[\alpha]_D^{19}$ −36.2 (c = 2.5, $CHCl_3$); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 5.80 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz, CH-C9), 5.12 (1H, dq, *J* = 17.2, 1.5 Hz, CH_2-C10), 5.07 (1H, dq, *J* = 10.2, 1.5 Hz, CH_2-C10), 4.49 (1H, dt, *J* = 7.5, 6.3 Hz, CH-C4), 4.03 (1H, dd, *J* = 7.5, 4.5 Hz, CH-C1), 3.83 (1H, dd, *J* = 9.5, 5.5 Hz, CH_2-C7), 3.79 (1H, td, *J* = 5.5, 2.0 Hz, CH-C6), 3.74 (1H, dd, *J* = 6.3, 2.0 Hz, CH-C5), 3.46 (1H, dd, *J* = 9.5, 5.5 Hz, CH_2-C7), 2.48 (1H, dd, *J* = 18.2, 7.5 Hz, CH_2-C3), 2.45—2.38 (1H, m, CH_2-C8), 2.34 (1H, dd, *J* = 18.2, 6.3 Hz, CH_2-C3), 2.34—2.21 (1H, m, CH_2-C8), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.87 (9H, s, CH_3-*t*-Bu-TBS), 0.10 (3H, s, CH_3-TBS), 0.08 (3H, s, CH_3-TBS), 0.07 (6H, s, CH_3-TBS), 0.05 (3H, s, CH_3-TBS), 0.04 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.9 (C-C2), 133.4 (CH-C9), 118.2 (CH_2-C10), 79.5 (CH-C1), 78.9 (CH-C6), 76.8 (CH-C4), 76.1 (CH-C5), 64.6 (CH_2-C7), 39.5 (CH_2-C3), 35.9 (CH_2-C8), 26.2 (3C, CH_3-*t*-Bu-TBS), 26.1 (3C, CH_3-*t*-Bu-TBS), 26.1 (3C, CH_3-*t*-Bu-TBS), 18.5 (C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), −4.1 (CH_3-TBS), −4.3 (CH_3-TBS), −4.4 (CH_3-TBS), −4.6 (CH_3-TBS), −5.2 (CH_3-TBS), −5.2 (CH_3-TBS); ν_{max} 2953, 2929, 2886, 2858, 1761, 1473, 1253, 1085, 832, 776 cm^{-1}; HRMS (ESI+) calcd for $C_{28}H_{58}NaO_5Si_3$ $[M+Na]^+$ 581.3484, found 581.3467.

(5*S*,6*R*)-5-[(2*R*,5*S*)-5-Allyl-4-methylenetetrahydrofuran-2-yl]-6-[(*tert*-butyldimethylsilyl)oxy]-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane 407



$CeCl_3 \cdot 7H_2O$ (6.74 g, 18.1 mmol) was added to a 100 mL round-bottomed flask and dried under *vacuum* at 120 °C (temperature reached gradually) for 2 h, then at 140 °C for 2 h and at 160 °C for another 2 h. The flask was allowed to cool to rt and was purged with argon for 10 min. THF (23 mL) was added and the mixture was stirred at rt for 2 h under argon to give the cerium(III) chloride-THF complex as a white precipitate.

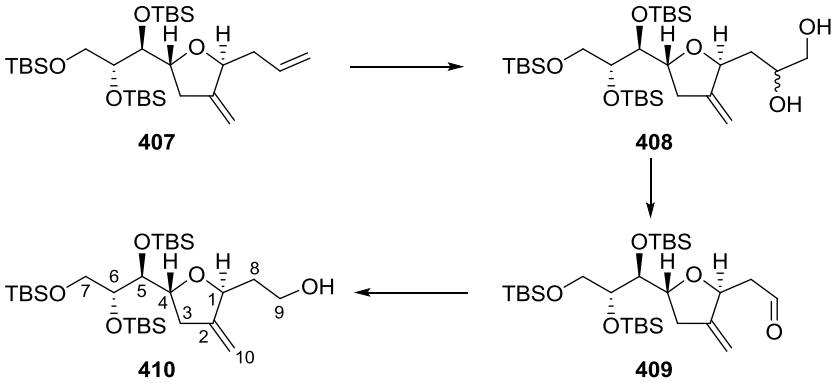
A solution of $TMSCH_2Cl$ (2.53 mL, 18.2 mmol) in THF (10 mL) was added dropwise to a stirred suspension of magnesium turnings (401 mg, 16.5 mmol) and 1,2-dibromoethane (2 drops) in THF (4 mL). Formation of the Grignard reagent was

accomplished by heating the mixture to reflux, followed by slow addition of the halide to maintain reflux. The Grignard reagent was stirred at rt for 2 h and then added to the cerium(III) chloride-THF complex at −78 °C. The resulting grey mixture was stirred at −78 °C for 30 min and then a solution of the ketone **405** (2.30 g, 4.11 mmol) in THF (4 mL) was added. The reaction mixture was stirred at −78 °C for 1 h and the flask was then removed from the cold bath. The mixture was stirred at rt for a further period of 18 h and then cooled to 0 °C. Saturated aqueous NH_4Cl (10 mL) was added at 0 °C and the mixture was stirred for 20 min. H_2O (40 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude tertiary alcohol **406** as a pale yellow oil.

The crude rude tertiary alcohol **406** was dissolved in THF (45 mL) at rt and NaHMDS (8.25 mL of a 2.0 M solution in THF, 16.5 mmol) was added over 30 s. The solution was stirred at rt for 5 min and then heated to reflux for 1.5 h. The mixture was then cooled to rt and quenched by the addition of saturated aqueous NH_4Cl (50 mL). The biphasic mixture was diluted with Et_2O (50 mL) and H_2O (20 mL), the layers were separated and the aqueous layer was back extracted with Et_2O (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 200:1) to afford the diene **407** (1.83 g, 80% over 2 steps) as a colourless oil. R_f = 0.82 (petroleum ether–EtOAc, 40:1); $[\alpha]_D^{24}$ −38.9 (c = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (1H, ddt, *J* = 17.2, 10.2, 5.9 Hz, CH-C9), 5.08 (1H, dq, *J* = 17.2, 1.6 Hz, CH_2-C10), 5.05 (1H, dq, *J* = 10.2, 1.6 Hz, CH_2-C10), 4.97 (1H, q, *J* = 2.1 Hz, CH_2-C11), 4.83 (1H, q, *J* = 2.1 Hz, CH_2-C11), 4.44—4.39 (1H, m, CH-C1), 4.07 (1H, q, *J* = 7.2 Hz, CH-C4), 3.82 (1H, dd, *J* = 9.9, 5.9 Hz, CH_2-C7), 3.69 (1H, td, *J* = 5.9, 1.5 Hz, CH-C6), 3.63 (1H, dd, *J* = 7.2, 1.5 Hz, CH-C5), 3.44 (1H, dd, *J* = 9.9, 5.9 Hz, CH_2-C7), 2.60 (1H, ddt, *J* = 15.5, 7.2, 2.1 Hz, CH_2-C3), 2.40—2.32 (1H, m, CH_2-C3), 2.32—2.22 (2H, m, CH_2-C8), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.08 (3H, s, CH_3-TBS), 0.07 (3H, s, CH_3-TBS), 0.07 (3H, s, CH_3-TBS), 0.06 (3H, s, CH_3-TBS), 0.04 (6H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5 (C-C2), 135.3 (CH-C9), 116.9 (CH_2-C10), 104.8 (CH_2-C11), 79.4 (CH-C5), 79.3 (CH-C1), 79.0 (CH-C4), 75.7 (CH-C6), 64.3

(CH_2-C7), 40.0 (CH_2-C8), 36.0 (CH_2-C3), 26.2 (3C, CH_3-*t*-Bu-TBS), 26.2 (3C, CH_3-*t*-Bu-TBS), 26.2 (3C, CH_3-*t*-Bu-TBS), 18.6 (C-*t*-Bu-TBS), 18.5 (C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), −4.3 (CH_3-TBS), −4.4 (CH_3-TBS), −4.5 (CH_3-TBS), −4.5 (CH_3-TBS), −5.3 (CH_3-TBS), −5.3 (CH_3-TBS); ν_{max} 2953, 2929, 2886, 2857, 1252, 1086, 831, 774 cm^{-1}; HRMS (ESI+) calcd for $C_{29}H_{60}NaO_4Si_3$ $[M+Na]^+$ 579.3692, found 579.3666.

2-{(2*S*,5*R*)-5-{(5*S*,6*R*)-6-[(*tert*-Butyldimethylsilyl)oxy]-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-5-yl}-3-methylenetetrahydrofuran-2-yl}ethanol 410

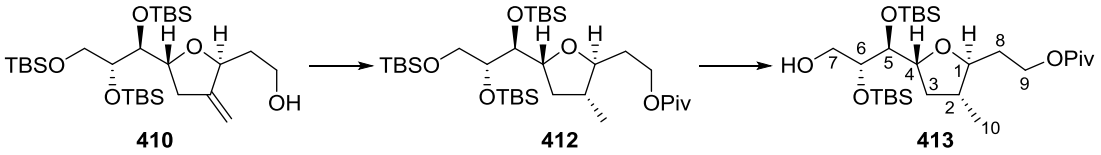


OsO_4 (730 μL of a 2.5% solution in *t*-BuOH, *ca*. 0.07 mmol) was added to a solution of diene **407** (2.00 g, 3.59 mmol) and NMO (505 mg, 4.31 mmol) in a 10:1 mixture of THF and H_2O (49.5 mL) at rt. The solution was stirred at rt for 16 h and then the reaction was quenched by the addition of solid Na_2SO_3 (1.8 g). The mixture was stirred at rt for 30 min before CH_2Cl_2 (80 mL) and H_2O (50 mL) were added. The phases were separated and the aqueous phase was back extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude diol **408** which was used in the next step without further purification.

$NaIO_4$ (1.54 g, 7.18 mmol) was added to a stirred solution of the crude diol **408** in a 4:1 mixture of THF and H_2O (50 mL) at rt. The mixture was stirred at rt for 1.5 h, diluted with H_2O (40 mL) and extracted with Et_2O (3 × 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to deliver the crude aldehyde **409** which was used in the next step without further purification.

The crude aldehyde **409** was dissolved in EtOH (36 mL) at rt and $NaBH_4$ (143 mg, 3.77 mmol) was added. The mixture was stirred at rt for 1 h and then concentrated under reduced pressure. CH_2Cl_2 (20 mL) and H_2O (20 mL) were added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 19:1) to yield the alcohol **410** (1.09 g, 54% over 3 steps) as a colourless oil. R_f = 0.14 (petroleum ether–EtOAc, 19:1); $[\alpha]_D^{24}$ −23.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.98 (1H, q, *J* = 2.0 Hz, CH_2-C10), 4.81 (1H, q, *J* = 2.0 Hz, CH_2-C10), 4.58 (1H, bdd, *J* = 5.7, 2.0 Hz, CH-C1), 4.13 (1H, dt, *J* = 14.5, 7.4 Hz, CH-C4), 3.84—3.76 (2H, m, CH_2-C9), 3.77 (1H, dd, *J* = 9.9, 6.3 Hz, CH_2-C7), 3.68 (1H, td, *J* = 6.3, 1.1 Hz, CH-C6), 3.65 (1H, dd, *J* = 7.4, 1.1 Hz, CH-C5), 3.43 (1H, dd, *J* = 9.9, 6.3 Hz, CH_2-C7), 2.74 (1H, dd, *J* = 6.6, 4.1 Hz, OH), 2.63 (1H, ddq, *J* = 15.6, 7.4, 2.0 Hz, CH_2-C3), 2.37 (1H, ddt, *J* = 15.6, 7.4, 2.0 Hz, CH_2-C3), 1.83—1.72 (2H, m, CH_2-C8), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.88 (18H, s, CH_3-*t*-Bu-TBS), 0.07 (3H, s, CH_3-TBS), 0.07 (3H, s, CH_3-TBS), 0.07 (3H, s, CH_3-TBS), 0.05 (3H, s, CH_3-TBS), 0.03 (6H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.4 (C-C2), 104.9 (CH_2-C10), 79.9 (CH-C1), 79.0 (CH-C4), 78.8 (CH-C5), 75.8 (CH-C6), 64.2 (CH_2-C7), 61.6 (CH_2-C9), 37.0 (CH_2-C8), 35.9 (CH_2-C3), 26.2 (3C, CH_3-*t*-Bu-TBS), 26.2 (3C, CH_3-*t*-Bu-TBS), 26.1 (3C, CH_3-*t*-Bu-TBS), 18.5 (C-*t*-Bu-TBS), 18.5 (C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), −4.2 (CH_3-TBS), −4.4 (CH_3-TBS), −4.4 (CH_3-TBS), −4.4 (CH_3-TBS), −5.3 (CH_3-TBS), −5.3 (CH_3-TBS); ν_{max} 3409, 2953, 2929, 2886, 2857, 1473, 1253, 1085, 1005, 831, 774, 668 cm^{-1}; LRMS (CI, *iso*-butane) *m*/*z* (intensity) 561.4 $[M+H]^+$ (100); HRMS (CI, *iso*-butane) calcd for $C_{28}H_{61}O_5Si_3$ $[M+H]^+$ 561.3827, found 561.3831.

2-{(2*S*,3*R*,5*R*)-5-[(5*S*,6*R*)-6-(Hydroxymethyl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl]-3-methyltetrahydrofuran-2-yl}ethyl pivalate 412

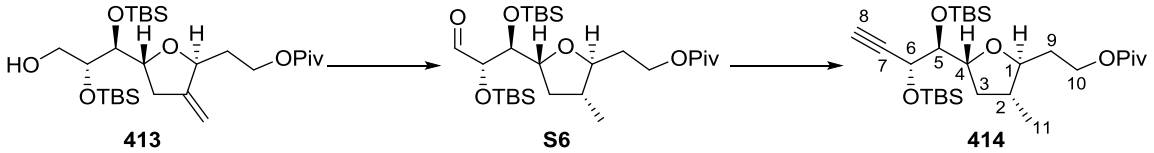


A solution of alcohol **410** (1.09 g, 1.94 mmol) and $[Ir(cod)(IMes)(PPh_3)]PF_6$ catalyst (19.7 mg, 19.4 μmol) in CH_2Cl_2 (40 mL) was cooled to −78 °C. The flask was purged three times with H_2 and the cooling bath was removed. The solution was stirred under atmosphere of H_2 at rt for 1 h and then the atmosphere of H_2 was replaced with argon. Pyridine (629 μL, 7.77 mmol) and PivCl (718 μL, 5.83 mmol) were added sequentially and the mixture was stirred at rt for further 22 h. The reaction was quenched by addition of 1 M aqueous HCl (40 mL) and the mixture was extracted with Et_2O (3 × 60 mL). The combined organic extracts were washed with 1 M aqueous NaOH (40 mL) and saturated aqueous $CuSO_4$ (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude pivaloyl ester **412** which was used in the next step without further purification.

To a solution of crude tri-TBS ether **412** in THF (200 mL) at 0 °C, was added a stock solution of HF·pyridine (11.5 mL).[138] The mixture was stirred at 0 °C for 24 h and the reaction was then quenched by addition of saturated aqueous $NaHCO_3$ (250 mL). The mixture was extracted with Et_2O (3 × 100 mL) and the combined organic layers were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 19:1 to 10:1) to give the alcohol **413** (787 mg, 76% over 2 steps) as a colourless oil. R_f = 0.31 (petroleum ether–EtOAc, 9:1); $[\alpha]_D^{23}$ −17.0 (c = 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.18 (1H, ddd, *J* = 11.1, 6.9, 5.6 Hz, CH_2-C9), 4.14—4.05 (2H, m, CH-C4, 1 × CH_2-C9), 4.02 (1H, dt, *J* = 8.3, 5.0 Hz, CH-C1), 3.80—3.73 (2H, m, CH-C6, 1 × CH_2-C7), 3.63 (1H, dd, *J* = 3.6, 1.8 Hz, CH-C5), 3.54—3.47 (1H, m, CH_2-C7), 3.28—3.24 (1H, m, OH), 2.31—2.24 (1H, m, CH-C2), 2.08 (1H, ddd, *J* = 12.3, 8.8, 7.0 Hz, CH_2-C3), 1.82—1.70 (2H, m, CH_2-C8), 1.64 (1H, ddd, *J* = 12.3, 7.0, 2.0 Hz, CH_2-C3), 1.19 (9H, s, CH_3-*t*-Bu-Piv), 0.91 (3H, d, *J* = 7.0 Hz, CH_3-C10), 0.90 (9H, s,

CH_3-*t*-Bu-TBS), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.12 (3H, s, CH_3-TBS), 0.09 (3H, s, CH_3-TBS), 0.08 (3H, s, CH_3-TBS), 0.08 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6 (C-Piv), 79.1 (CH-C1), 79.0 (CH-C5), 78.2 (CH-C4), 75.7 (CH-C6), 62.9 (CH_2-C7), 62.3 (CH_2-C9), 38.8 (C-*t*-Bu-Piv), 36.5 (CH_2-C3), 36.3 (CH-C2), 30.1 (CH_2-C8), 27.3 (3C, CH_3- *t*-Bu-Piv), 26.2 (3C, CH_3-*t*-Bu-TBS), 26.1 (3C, CH_3-*t*-Bu-TBS), 18.6 (C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), 14.3 (CH_3-C10), −4.0 (CH_3-TBS), −4.5 (CH_3-TBS), −4.5 (CH_3-TBS), −4.8 (CH_3-TBS); ν_{max} 3445, 2958, 2930, 2884, 2857, 1730, 1472, 1253, 1156, 1090, 1055, 1004, 835, 777 cm^{-1}; HRMS (ESI+) calcd for $C_{27}H_{56}NaO_6Si_2$ $[M+Na]^+$ 555.3508, found 555.3484.

2-{(2*S*,3*R*,5*R*)-5-[(5*S*,6*R*)-6-Ethynyl-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl]-3-methyltetrahydrofuran-2-yl}ethyl pivalate 414

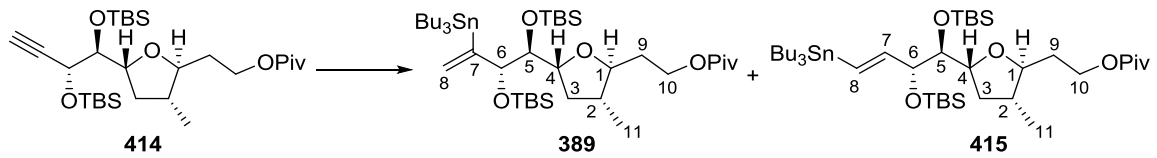


Pyridine (1.09 mL, 13.4 mmol) and DMP (1.90 g, 4.48 mmol) were added sequentially to a solution of alcohol **413** (597 mg, 1.12 mmol) in CH_2Cl_2 (18 mL) at rt. The solution was stirred at rt for 3 h and the reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (40 mL) and saturated aqueous $NaHCO_3$ (40 mL). The mixture was extracted with Et_2O (3 × 40 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (40 mL) and saturated aqueous $CuSO_4$ (80 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude aldehyde **S6**, which was used directly in the next step without further purification.

K_2CO_3 anhydrous (464 mg, 3.36 mmol) was added to a solution of the Ohira-Bestmann reagent[134] (861 mg, 4.48 mmol) in MeOH (18 mL) at 0 °C. The mixture was stirred at this temperature for 1 h and then a solution of the crude aldehyde **S6** in THF (9 mL) was added dropwise. Stirring was continued at 0 °C for 1 h and the mixture was then warmed to rt and stirred for an additional 15 min. The reaction was quenched with saturated aqueous NH_4Cl (40 mL) and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under

reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 50:1) to yield the alkyne **414** (443 mg, 75% over 2 steps) as a colourless oil. R_f = 0.50 (petroleum ether–EtOAc, 20:1); $[\alpha]_D^{22}$ −29.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (1H, dd, *J* = 4.2, 2.2 Hz, CH-C6), 4.20 (1H, ddd, *J* = 11.2, 7.0, 5.7 Hz, CH_2-C10), 4.15 (1H, ddd, *J* = 8.2, 7.1, 5.6 Hz, CH-C4), 4.11 (1H, ddd, *J* = 11.2, 7.7, 6.8 Hz, CH_2-C10), 3.94 (1H, dt, *J* = 8.4, 5.0 Hz, CH-C1), 3.57 (1H, dd, *J* = 5.6, 4.2 Hz, CH-C5), 2.36 (1H, d, *J* = 2.2 Hz, CH-C8), 2.29—2.21 (1H, m, CH-C2), 2.11 (1H, ddd, *J* = 12.3, 8.2, 7.2 Hz, CH_2-C3), 1.78—1.67 (2H, m, CH_2-C9), 1.63 (1H, ddd, *J* = 12.3, 7.1, 2.6 Hz, CH_2-C3), 1.19 (9H, s, CH_3-*t*-Bu-Piv), 0.91 (3H, d, *J* = 7.0 Hz, CH_3-C11), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.13 (3H, s, CH_3-TBS), 0.12 (3H, s, CH_3-TBS), 0.11 (3H, s, CH_3-TBS), 0.09 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7 (C-Piv), 84.4 (C-C7), 78.9 (CH-C5), 78.0 (CH-C1), 77.3 (CH-C4), 74.0 (CH-C8), 65.7 (CH-C6), 62.7 (CH_2-C10), 38.8 (C-*t*-Bu-Piv), 36.4 (CH-C2), 36.0 (CH_2-C3), 30.5 (CH_2-C9), 27.4 (3C, CH_3- *t*-Bu-Piv), 26.3 (3C, CH_3-*t*-Bu-TBS), 25.9 (3C, CH_3-*t*-Bu-TBS), 18.6 (C-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), 14.3 (CH_3-C11), −3.9 (CH_3-TBS), −4.0 (CH_3-TBS), −4.5 (CH_3-TBS), −5.0 (CH_3-TBS); ν_{max} 2958, 2929, 2886, 2858, 1730, 1473, 1252, 1155, 1084, 832, 776 cm^{-1}; HRMS (ESI+) calcd for $C_{28}H_{54}NaO_5Si_2$ $[M+Na]^+$ 549.3402, found 549.3390.

2-{(2*S*,3*R*,5*R*)-3-Methyl-5-{(5*S*,6*S*)-2,2,3,3,8,8,9,9-octamethyl-6-[1-(tributylstannyl)vinyl]-4,7-dioxa-3,8-disiladecan-5-yl}tetrahydrofuran-2-yl}ethyl pivalate 389 and 2-{(2*S*,3*R*,5*R*)-3-Methyl-5-{(5*S*,6*R*)-2,2,3,3,8,8,9,9-octamethyl-6-[(*E*)-2-(tributylstannyl)vinyl]-4,7-dioxa-3,8-disiladecan-5-yl}tetrahydrofuran-2-yl}ethyl pivalate 415



To a solution of alkyne **414** (216 mg, 0.410 mmol), 2,6-*tert*-butyl-4-methylphenol (9 mg) and $Mo(CO)_3(CN$*t*$-Bu)_3$ (17.6 mg, 0.041 mmol) in THF (1.8 mL)at rt was added *n*-Bu_3SnH (551 µL, 2.050 mmol). The mixture was heated to 55 °C and stirred at this temperature for 24 h. Additional $Mo(CO)_3(CN$*t*$-Bu)_3$ (17.6

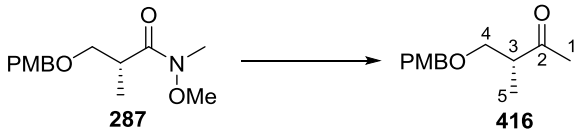
mg, 0.041 mmol) and *n*-Bu_3SnH (331 μL, 1.230 mmol) were added and the solution was stirred at 55 °C for an additional 24 h. The reaction was then concentrated under reduced pressure and the residue was purified directly by flash chromatography on silica gel (petroleum ether–EtOAc, 200:1) to afford in the order of elution 1,1-disubstituted vinyl stannane **389** (231.5 mg, 69%) and (*E*)-disubstituted vinyl stannane **415** (53.7 mg, 16%).

1,1-Disubstituted vinyl stannane **389**: R_f = 0.87 (petroleum ether–EtOAc, 20:1); $[\alpha]_D^{22}$ −19.7 (c = 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (1H, dd, *J* = 2.7, 1.9 Hz, $^3J_{SnH}$ = 132.4 Hz, CH_2-C8), 5.23 (1H, dd, *J* = 2.7, 1.9 Hz, $^3J_{SnH}$ = 63.8 Hz, CH_2-C8), 4.34 (1H, q, *J* = 1.9 Hz, $^3J_{SnH}$ = 28.3 Hz, CH-C6), 4.19 (1H, dt, *J* = 11.8, 6.1 Hz, CH_2-C10), 4.12—4.05 (2H, m, CH-C4, 1 × CH_2-C10), 3.84 (1H, dt, *J* = 7.9, 5.2 Hz, CH-C1), 3.53 (1H, dd, *J* = 7.6, 1.9 Hz, CH-C5), 2.17—2.09 (1H, m, CH-C2), 1.76—1.68 (3H, m, CH_2-C3, 1 × CH_2-C9), 1.56—1.40 (7H, m, 1 × CH_2-C9, 3 × CH_2-Bu_3Sn), 1.36—1.27 (6H, m, 3 × CH_2-Bu_3Sn), 1.19 (9H, s, CH_3-*t*-Bu-Piv), 0.96—0.85 (18H, m, CH_3-C11, 3 × CH_2-Bu_3Sn, 3 × CH_3-Bu_3Sn), 0.91 (9H, s, CH_3-*t*-Bu-TBS), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.11 (3H, s, CH_3-TBS), 0.09 (3H, s, CH_3-TBS), 0.06 (3H, s, CH_3-TBS), −0.01 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6 (C-Piv), 154.0 (C-C7), 125.5 (CH_2-C8), 82.7 (CH-C6), 79.3 (CH-C5), 78.8 (CH-C4), 76.9 (CH-C1), 62.6 (CH_2-C10), 38.8 (C-*t*-Bu-Piv), 37.8 (CH_2-C3), 36.4 (CH-C2), 30.3 (CH_2-C9), 29.3 (3C, CH_2-Bu_3Sn), 27.6 (3C, CH_2-Bu_3Sn), 27.4 (3C, CH_3- *t*-Bu-Piv), 26.5 (3C, CH_3-*t*-Bu-TBS), 26.3 (3C, CH_3-*t*-Bu-TBS), 18.7 (C-*t*-Bu-TBS), 18.6 (C-*t*-Bu-TBS), 14.1 (CH_3-C11), 13.8 (3C, CH_3-Bu_3Sn), 10.2 (3C, CH_2-Bu_3Sn), −3.7 (CH_3-TBS), −4.1 (CH_3-TBS), −4.2 (CH_3-TBS), −4.3 (CH_3-TBS); ν_{max} 2956, 2928, 2856, 1733, 1463, 1251, 1155, 1089, 1071, 832, 776 cm^{-1}; HRMS (ESI+) calcd for $C_{40}H_{82}NaO_5Si_2Sn$ $[M+Na]^+$ 841.4615, found 841.4600.

(*E*)-Disubstituted vinyl stannane **415**: R_f = 0.83 (petroleum ether–EtOAc, 20:1); $[\alpha]_D^{25}$ −23.0 (c = 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (1H, d, *J* = 5.3 Hz, $^2J_{SnH}$ = 39.0 Hz, CH-C8), 6.03 (1H, bs, $^3J_{SnH}$ = 73.2 Hz, CH-C7), 4.20 (1H, ddd, *J* = 11.0, 6.8, 5.4 Hz, CH_2-C10), 4.11 (1H, ddd, *J* = 11.0, 7.7, 6.8 Hz, CH_2-C10), 4.00 (1H, dd, *J* = 5.3, 2.7 Hz, CH-C6), 3.95 (1H, dt, *J* = 8.4, 7.1 Hz, CH-C4), 3.90 (1H, dt, *J* = 8.4, 5.0 Hz, CH-C1), 3.49 (1H, dd, *J* = 7.1, 2.7 Hz, CH-C5), 2.24—2.17 (1H, m, CH-C2), 1.85 (1H, ddd, *J* = 12.4, 8.7, 7.1 Hz, CH_2-C3), 1.79—1.70 (2H, m, CH_2-C9), 1.59 (1H, ddd, *J* = 12.4, 8.4, 1.9 Hz, CH_2-C3), 1.52—1.40 (6H, m, 3 × CH_2-Bu_3Sn), 1.30 (6H, dq, *J* = 14.7, 7.4 Hz, 3 × CH_2-Bu_3Sn), 1.19 (9H, s, CH_3-*t*-Bu-

Piv), 0.90—0.85 (18H, m, CH_3-C11, 3 × CH_2-Bu_3Sn, 3 × CH_3-Bu_3Sn), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.06 (3H, s, CH_3-TBS), 0.06 (3H, s, CH_3-TBS), 0.04 (3H, s, CH_3-TBS), 0.01 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6 (C-Piv), 148.9 (CH-C8), 129.3 (CH-C7), 80.2 (CH-C5), 78.9 (CH-C6), 78.2 (CH-C4), 77.5 (CH-C1), 62.6 (CH_2-C10), 38.9 (C-*t*-Bu-Piv), 36.8 (CH_2-C3), 36.4 (CH-C2), 30.2 (CH_2-C9), 29.3 (3C, CH_2-Bu_3Sn), 27.4 (3C, CH_2-Bu_3Sn), 27.4 (3C, CH_3- *t*-Bu-Piv), 26.3 (3C, CH_3-*t*-Bu-TBS), 26.2 (3C, CH_3-*t*-Bu-TBS), 18.6 (C-*t*-Bu-TBS), 18.5 (C-*t*-Bu-TBS), 14.3 (CH_3-C11), 13.8 (3C, CH_3-Bu_3Sn), 9.6 (3C, CH_2-Bu_3Sn), −4.1 (CH_3-TBS), −4.1 (CH_3-TBS), −4.2 (CH_3-TBS), −4.5 (CH_3-TBS); ν_{max} 2957, 2928, 2856, 1731, 1463, 1251, 1153, 1076, 834, 776 cm^{-1}; HRMS (ESI+) calcd for $C_{40}H_{82}NaO_5Si_2Sn$ $[M+Na]^+$ 841.4622, found 841.4584.

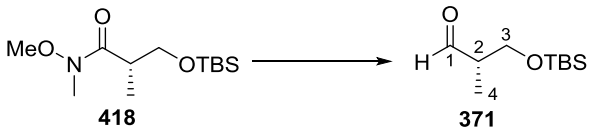
(*R*)-4-[(4-Methoxybenzyl)oxy]-3-methylbutan-2-one 416



To a solution of the Weinreb amide **287**[80b] (19.2 g, 71.8 mmol) in THF (190 mL) at 0 °C was added MeMgBr (47.9 mL of a 3.0 M solution in Et_2O, 144 mmol) over 10 min. Upon complete addition, the reaction was stirred at 0 °C for 30 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (250 mL) and the mixture was extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 10:1) to provide the methyl ketone **416** (14.4 g, 90%) as a colourless oil. R_f = 0.34 (petroleum ether–EtOAc, 4:1); $[\alpha]_D^{25}$ −16.0 (c = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24—7.19 (2H, m, *m*-CH-PhPMB), 6.89—6.84 (2H, m, *o*-CH-PhPMB), 4.43 (1H, d, *J* = 11.8 Hz, CH_2-PMB), 4.40 (1H, d, *J* = 11.8 Hz, CH_2-PMB), 3.79 (3H, s, CH_3-OMePMB), 3.59 (1H, dd, *J* = 9.2, 7.5 Hz, CH_2-C4), 3.45 (1H, dd, *J* = 9.2, 5.5 Hz, CH_2-C4), 2.83 (1H, dqd, *J* = 7.5, 7.1, 5.5 Hz, CH-C3), 2.16 (3H, s, CH_3-C1), 1.08 (3H, d, *J* = 7.1 Hz, CH_3-C5); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.1 (C-C2), 159.3 (*p*-C-PhPMB), 130.3 (C-PhPMB), 129.3 (2C, *m*-CH-PhPMB), 113.9 (2C, *o*-CH-PhPMB), 73.0 (CH_2-PMB), 71.9 (CH_2-C4), 55.3

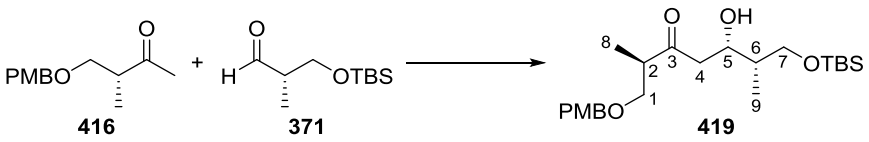
(CH_3-OMePMB), 47.3 (CH-C3), 29.0 (CH_3-C1), 13.5 (CH_3-C5); ν_{max} 2969, 2935, 2858, 2838, 1713, 1613, 1512, 1358, 1245, 1174, 1087, 1033, 819 cm^{-1}; LRMS (EI) *m/z* (intensity) 222.1 $[M]^+$ (24), 137.0 (100), 121.0 (81), 109.0 (34); HRMS (EI) calcd for $C_{13}H_{18}O_3$ $[M]^+$ 222.1256, found 222.1265; Anal. calcd for $C_{13}H_{18}O_3$: C, 70.24%; H, 8.16%, found: C, 70.26%; H, 8.30%.

(*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpropanal 371



DIBAL-H (8.42 mL of a 1 M solution in CH_2Cl_2, 8.42 mmol) was added dropwise to a solution of the Weinreb amide **418**[36m] (2.00 g, 7.65 mmol) in THF (10 mL) at −78 °C. The reaction was stirred at −78 °C for 1.5 h and then poured into a mixture of saturated aqueous sodium,potassium tartrate (60 mL) and Et_2O (40 mL). The resulting mixture was stirred vigorously at rt for until two clear phases were obtained (*ca.* 4 h). The phases were separated and the aqueous phase was back extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by rapid flash chromatography on silica gel (petroleum ether–EtOAc, 20:1) to afford the aldehyde **371** (1.53 g, 99%) as a colourless oil. R_f = 0.84 (petroleum ether–EtOAc, 4:1); $[\alpha]_D^{25}$ +34.8 (c = 1.0, $CHCl_3$), {Lit.[139] $[\alpha]_D$ +32.5 (c = 1.0, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (1H, d, *J* = 1.6 Hz, CH-C1), 3.84 (1H, dd, *J* = 10.2, 5.2 Hz, CH_2-C3), 3.79 (1H, dd, *J* = 10.2, 6.3 Hz, CH_2-C3), 2.56—2.46 (1H, m, CH-C2), 1.07 (3H, d, *J* = 7.0 Hz, CH_3-C4), 0.86 (9H, s, CH_3-*t*-Bu-TBS), 0.04 (6H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.7 (C-C1), 63.6 (CH_2-C3), 48.9 (CH-C2), 25.9 (3C, CH_3-*t*-Bu-TBS), 18.3 (C-*t*-Bu-TBS), 10.4 (CH_3-C4), −5.4 (CH_3-TBS), −5.4 (CH_3-TBS); ν_{max} 2956, 2929, 2858, 1735, 1473, 1253, 1097, 1032, 835, 776 cm^{-1}; HRMS (ESI+) calcd for $C_{10}H_{22}NaO_2Si$ $[M+Na]^+$ 225.1281, found 225.1281.

(2*R*,5*S*,6*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-1-[(4-methoxybenzyl)oxy]-2,6-dimethylheptan-3-one 419

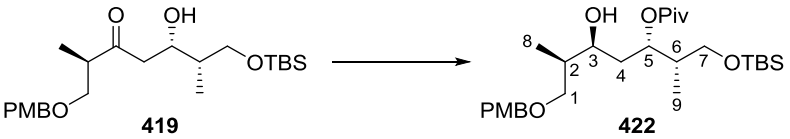


*Note: methyl ketone **416** and aldehyde **371** were dried prior to use by dissolving them in toluene and concentration under vacuum.*

A solution of methyl ketone **416** (1.40 g, 6.30 mmol) in Et_2O (4 mL) was added to a solution Cy_2BCl (3.35 g, 15.8 mmol) in Et_2O (24 mL) at 0 °C. Et_3N was added dropwise and the resulting suspension was stirred at 0 °C for 1 h. The mixture was cooled to −78 °C, then a solution of aldehyde **371** (1.53 g, 7.56 mmol) in Et_2O (4 mL) was added and the resulting mixture was stirred at −78 °C for 2 h. The mixture was then warmed to 0 °C and the reaction was quenched by sequential addition of MeOH (12 mL), aqueous pH 7 buffer (24 mL) and H_2O_2 (30% in H_2O, 24 mL). The resulting mixture was stirred vigorously at rt for 1 h. The phases were separated and the aqueous phase was back extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 19:1 to 9:1) to afford the hydroxyketone **419** (2.17 g, 84%, *dr* >20:1) as a colourless oil. R_f = 0.35 (petroleum ether–EtOAc, 4:1); $[\alpha]_D^{23}$ −15.3 (c = 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (2H, d, *J* = 8.6 Hz, *m*-CH-PhPMB), 6.86 (2H, d, *J* = 8.6 Hz, *o*-CH-PhPMB), 4.42 (1H, d, *J* = 11.7 Hz, CH_2-PMB), 4.38 (1H, d, *J* = 11.7 Hz, CH_2-PMB), 4.30—4.23 (1H, m, CH-C5), 3.79 (3H, s, CH_3-OMePMB), 3.67 (1H, dd, *J* = 9.9, 4.6 Hz, CH_2-C7), 3.61 (1H, dd, *J* = 9.9, 5.9 Hz, CH_2-C7), 3.58 (1H, dd, *J* = 9.0, 8.0 Hz, CH_2-C1), 3.45 (1H, dd, *J* = 9.0, 5.3 Hz, CH_2-C1), 3.29 (1H, d, *J* = 2.7 Hz, OH), 2.93—2.85 (1H, m, CH-C2), 2.70 (1H, dd, *J* = 17.0, 9.1 Hz, CH_2-C4), 2.58 (1H, dd, *J* = 17.0, 3.4 Hz, CH_2-C4), 1.73—1.64 (1H, m, CH-C6), 1.06 (3H, d, *J* = 7.1 Hz, CH_3-C8), 0.89 (3H, d, *J* = 6.9 Hz, CH_3-C9), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.05 (6H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.7 (C-C3), 159.4 (*p*-C-PhPMB), 130.1 (C-PhPMB), 129.4 (2C, *m*-CH-PhPMB), 113.9 (2C, *o*-CH-PhPMB), 73.1 (CH_2-PMB), 72.0 (CH_2-C1), 69.3 (CH-C5), 66.9 (CH_2-C7), 55.4 (CH_3-OMePMB),

47.0 (CH-C2), 46.9 (CH_2-C4), 39.5 (CH-C6), 26.0 (3C, CH_3-*t*-Bu-TBS), 18.3 (C-*t*-Bu-TBS), 13.3 (CH_3-C8), 10.9 (CH_3-C9), −5.4 (CH_3-TBS), −5.4 (CH_3-TBS); ν_{max} 3510, 2955, 2930, 2857, 1708, 1513, 1463, 1247, 1092, 1035, 834, 775 cm^{-1}; HRMS (ESI+) calcd for $C_{23}H_{40}NaO_5Si$ $[M+Na]^+$ 447.2537, found 447.2548.

(2*S*,3*S*,5*S*,6*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-hydroxy-7-[(4-methoxybenzyl)oxy]-2,6-dimethylheptan-3-yl pivalate 422

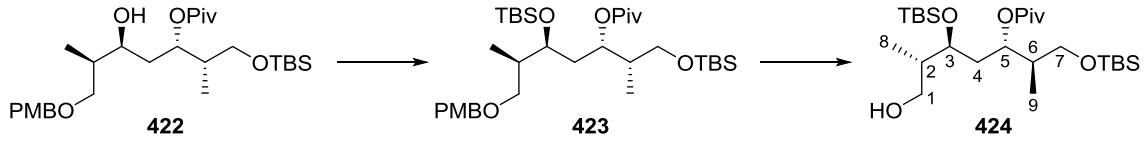


Samarium powder (451 mg, 3.00 mmol) was added to a flame dried round-bottomed flask. The flask was evacuated and refilled with argon three times before THF (20 mL) was added. Iodine (508 mg, 2.00 mmol) was added and the resulting brown slurry was heated at 50 °C for 18 h giving a dark blue solution of SmI_2 (approximate 0.1 M). The solution was allowed to cool and settle to rt over 1 h and then used directly in the Evans-Tischenko reaction.[140]

To a solution of freshly distilled pivaloyl aldehyde (3.81 mL, 35.1 mmol) in THF (8.2 mL) at −30 °C was added SmI_2 (11.7 mL of a 0.1 M solution in THF, 1.17 mmol). The resulting mixture was stirred at −30 °C for 10 min. A solution of hydroxyketone **419** (2.40 g, 5.84 mmol) in THF (8.2 mL) was added and the reaction mixture stirred for 3 h maintaining the temperature between −10 and −20 °C. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (20 mL) and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 20:1) to yield the alcohol **419** (2.18 g, 73%, *dr* ≥10:1) as a colourless oil. R_f = 0.21 (petroleum ether–EtOAc, 19:1); $[\alpha]_D^{23}$ −10.0 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25—7.21 (2H, m, *m*-CH-PhPMB), 6.88—6.84 (2H, m, *o*-CH-PhPMB), 5.22 (1H, ddd, *J* = 10.7, 3.3, 2.7 Hz, CH-C5), 4.43 (1H, d, *J* = 11.8 Hz, CH_2-PMB), 4.40 (1H, d, *J* = 11.8 Hz, CH_2-PMB), 3.80 (3H, s, CH_3-OMePMB), 3.51—3.38 (5H, m, CH_2-C7, CH_2-C1, OH), 3.38—3.30 (1H, m, CH-C3), 1.89—1.80 (2H, m, CH-C2, CH-C6), 1.74 (1H, ddd, *J* = 14.0, 10.7, 2.3 Hz, CH_2-C4), 1.52 (1H, ddd, *J* = 14.0, 10.7, 2.7 Hz, CH_2-C4), 1.20 (9H,

s, CH_3-*t*-Bu-Piv), 0.93 (3H, d, *J* = 6.9 Hz, CH_3-C9), 0.92 (3H, d, *J* = 6.9 Hz, CH_3-C8), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.02 (3H, s, CH_3-TBS), 0.01 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4 (C-Piv), 159.3 (*p*-C-PhPMB), 130.7 (C-PhPMB), 129.3 (2C, *m*-CH-PhPMB), 113.9 (2C, *o*-CH-PhPMB), 73.2 (CH_2-C1), 73.0 (CH_2-PMB), 71.2 (CH-C5), 69.9 (CH-C3), 65.1 (CH_2-C7), 55.4 (CH_3-OMePMB), 40.3 (CH-C2 or CH-C6), 39.2 (C-*t*-Bu-Piv), 38.9 (CH-C2 or CH-C6), 37.5 (CH_2-C4), 27.4 (3C, CH_3-*t*-Bu-Piv), 26.0 (3C, CH_3-*t*-Bu-TBS), 18.3 (C-*t*-Bu-TBS), 14.0 (CH_3-C8), 11.5 (CH_3-C9), −5.3 (2C, CH_3-TBS); ν_{max} 3517, 2957, 2929, 2858, 1707, 1513, 1463, 1286, 1248, 1172, 1093, 1036, 836, 775 cm^{-1}; HRMS (ESI+) calcd for $C_{28}H_{50}NaO_6Si$ $[M+Na]^+$ 533.3269, found 533.3271.

(5*S*,7*S*,8*R*)-5-[(*S*)-1-Hydroxypropan-2-yl]-2,2,3,3,8,11,11,12,12-nonamethyl-4,10-dioxa-3,11-disilatridecan-7-yl pivalate 424

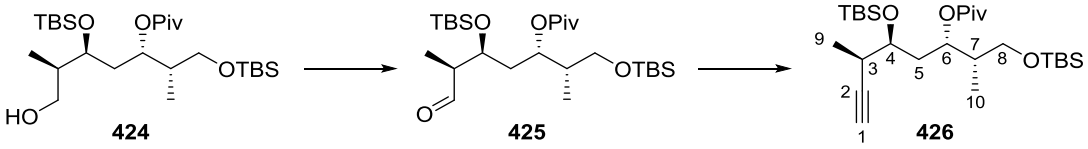


To a solution of alcohol **422** (2.18 g, 4.27 mmol) in CH_2Cl_2 (21 mL) at −78 °C were sequentially added 2,6-lutidine (1.49 mL, 12.8 mmol) and TBSOTf (1.47 mL, 6.40 mmol). The mixture was stirred at −78 °C for 1.5 h and the reaction was then quenched by addition of saturated aqueous $NaHCO_3$ (20 mL). The resulting mixture was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were washed with saturated aqueous $CuSO_4$ (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a short pad of silica gel (petroleum ether–EtOAc, 20:1) to deliver the crude silyl ether **423** which was used directly in the next step without further purification.

A mixture of PMB ether **423** and $Pd(OH)_2/C$ (20 wt. %, 599 mg, 0.85 mmol) in EtOH at rt was purged three times with H_2 and the reaction was stirred under atmosphere of H_2 at rt for 2 h. The mixture was filtered to remove the catalyst and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 20:1) to afford the primary alcohol **424** (1.85 g, 86% over 2 steps) as a colourless oil. R_f = 0.42 (petroleum ether–EtOAc, 9:1); $[\alpha]_D^{22}$ −10.1 (c = 0.9, $CHCl_3$); ^1H NMR (400 MHz,

$CDCl_3$) δ 4.99 (1H, ddd, *J* = 7.8, 5.5, 3.0 Hz, CH-C5), 3.84 (1H, dt, *J* = 11.1, 3.5 Hz, CH_2-C1), 3.75 (1H, td, *J* = 6.3, 2.7 Hz, CH-C3), 3.55—3.49 (1H, m, CH_2-C1), 3.46 (1H, dd, *J* = 9.4, 6.9 Hz, CH_2-C7), 3.39 (1H, dd, *J* = 9.4, 6.5 Hz, CH_2-C7), 2.37 (1H, dd, *J* = 7.4, 3.5 Hz, OH), 1.89—1.79 (2H, m, 1 × CH_2-C4, CH-C6), 1.79—1.68 (2H, m, CH-C2, 1 × CH_2-C4), 1.18 (9H, s, CH_3-*t*-Bu-Piv), 1.01 (3H, d, *J* = 7.1 Hz, CH_3-C8), 0.93 (3H, d, *J* = 7.0 Hz, CH_3-C9), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.87 (9H, s, CH_3-*t*-Bu-TBS), 0.09 (3H, s, CH_3-TBS), 0.07 (3H, s, CH_3-TBS), 0.01 (3H, s, CH_3-TBS), 0.01 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.0 (C-Piv), 73.7 (CH-C3), 71.9 (CH-C5), 64.8 (CH_2-C1 or CH_2-C7), 64.7 (CH_2-C1 or CH_2-C7), 39.6 (CH-C6), 39.4 (C-*t*-Bu-Piv), 39.1 (CH-C2), 36.7 (CH_2-C4), 27.4 (3C, CH_3-*t*-Bu-Piv), 26.0 (6C, CH_3-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), 18.1 (C-*t*-Bu-TBS), 13.9 (CH_3-C8), 11.2 (CH_3-C9), −4.3 (CH_3-TBS), −4.5 (CH_3-TBS), −5.3 (CH_3-TBS), −5.4 (CH_3-TBS); ν_{max} 3510, 2956, 2929, 2858, 1728, 1472, 1283, 1253, 1163, 1082, 1032, 835, 774 cm^{-1}; HRMS (ESI+) calcd for $C_{26}H_{56}NaO_5Si_2$ $[M+Na]^+$ 527.3558, found 527.3539.

(5*S*,7*S*,8*S*)-5-[(*R*)-But-3-yn-2-yl]-2,2,3,3,8,11,11,12,12-nonamethyl-4,10-dioxa-3,11-disilatridecan-7-yl pivalate 426

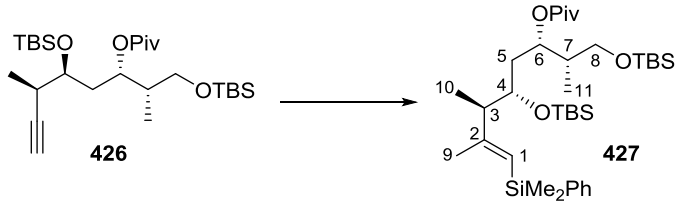


TEMPO (50 mg, 0.32 mmol) and $PhI(OAc)_2$ (1.13 g, 3.51 mmol) were added sequentially to a solution of alcohol **424** (1.61 g, 3.19 mmol) in CH_2Cl_2 (16 mL) at rt. The mixture was stirred at rt for 5 h and the reaction was quenched by addition of H_2O (20 mL). The resulting mixture was extracted with Et_2O (3 × 25 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was rapidly filtered on a short pad of silica gel (petroleum ether–EtOAc, 30:1) to give the crude aldehyde **425** which was used directly in the next step without further purification.

Anhydrous K_2CO_3 (1.32 g, 9.57 mmol) was added to a solution of the Ohira-Bestmann reagent[134] (2.45 g, 12.8 mmol) in MeOH (15 mL) at 0 °C. The mixture was stirred for 1 h at this temperature and then a solution of the crude aldehyde

425 in THF (7.5 mL) was added dropwise. Stirring was continued at 0 °C for 1 h and the mixture was then warmed to rt and stirred for an additional 15 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (40 mL) and the resulting mixture was extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 100:1) to yield the alkyne **426** (1.16 g, 73% over 2 steps) as a colourless oil. R_f = 0.72 (petroleum ether–EtOAc, 20:1); $[\alpha]_D^{25}$ −11.1 (c = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (1H, ddd, *J* = 9.9, 3.7, 2.2 Hz, CH-C6), 3.71 (1H, ddd, *J* = 9.2, 3.7, 2.0 Hz, CH-C4), 3.55 (1H, dd, *J* = 9.9, 5.5 Hz, CH_2-C8), 3.40 (1H, dd, *J* = 9.9, 6.9 Hz, CH_2-C8), 2.63—2.56 (1H, m, CH-C3), 2.05 (1H, d, *J* = 2.5 Hz, CH-C1), 2.03—1.93 (1H, m, CH_2-C5), 1.92—1.82 (1H, m, CH-C7), 1.59 (1H, ddd, *J* = 14.3, 9.2, 2.2 Hz, CH_2-C5), 1.20 (9H, s, CH_3-*t*-Bu-Piv), 1.13 (3H, d, *J* = 7.1 Hz, CH_3-C9), 0.93 (3H, d, *J* = 7.0 Hz, CH_3-C10), 0.88 (18H, s, CH_3-*t*-Bu-TBS), 0.09 (3H, s, CH_3-TBS), 0.03 (3H, s, CH_3-TBS), 0.02 (3H, s, CH_3-TBS), 0.02 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9 (C-Piv), 86.2 (C-C2), 72.4 (CH-C6), 71.3 (CH-C4), 70.1 (CH-C1), 64.9 (CH_2-C8), 40.4 (CH-C7), 39.1 (C-*t*-Bu-Piv), 35.3 (CH_2-C5), 32.6 (CH-C3), 27.5 (3C, CH_3-*t*-Bu-Piv), 26.1 (3C, CH_3-*t*-Bu-TBS), 26.0 (3C, CH_3-*t*-Bu-TBS), 18.4 (C-*t*-Bu-TBS), 18.2 (C-*t*-Bu-TBS), 13.6 (CH_3-C9), 12.0 (CH_3-C10), −4.5 (CH_3-TBS), −4.5 (CH_3-TBS), −5.3 (CH_3-TBS), −5.3 (CH_3-TBS); ν_{max} 3315, 2957, 2930, 2886, 2859, 1727, 1473, 1282, 1253, 1164, 1089, 1032, 836, 775 cm^{-1}; HRMS (ESI+) calcd for $C_{27}H_{54}NaO_4Si_2$ $[M+Na]^+$ 521.3453, found 521.3427.

(5*S*,7*S*,8*S*)-5-{(*R*,*E*)-4-[Dimethyl(phenyl)silyl]-3-methylbut-3-en-2-yl}-2,2,3,3,8,11,11,12,12-nonamethyl-4,10-dioxa-3,11-disilatridecan-7-yl pivalate 427

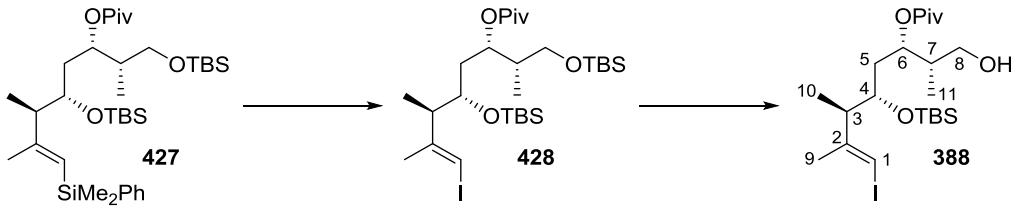


Lithium metal (312 mg, 45.0 mmol) was added to a flame dried round-bottomed flask. The flask was evacuated and refilled with argon before THF (20 mL) was added. The mixture was cooled to 0 °C and freshly distilled $PhMe_2SiCl$ (1.66 mL, 10.00 mmol) was added. The resulting mixture was stirred at 0 °C for 6 h giving a dark red solution of $PhMe_2SiLi$ (approximate concentration 0.5 M) and the solution was used immediately for the reaction.

CuCN (270 mg, 3.01 mmol) was added to a flame dried round-bottomed flask and dried at 55 °C under high *vacuum* overnight. The flask was cooled to 0 °C and refilled with argon before THF (6.5 mL) was added. A solution of $PhMe_2SiCl$ (12.0 mL of a 0.5 M solution in THF, 6.01 mmol) was then added in one portion. The resulting blood red solution was stirred at 0 °C for 30 min during which time the colour changed from red to purple. A solution of alkyne **426** (1.00 g, 2.00) in THF (17 mL) was added and the reaction stirred at 0 °C for 1 h. MeI (1.25 mL, 20.0 mmol) was added and stirring continued at 0 °C for an additional 1 h. The reaction was quenched by addition of NH_4OH (30% v/v in H_2O, 40 mL) and Et_2O (25 mL) under vigorous stirring. The biphasic mixture was transferred into a separatory funnel containing H_2O (80 mL) and Et_2O (40 mL), and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with H_2O (3 × 40 mL) and brine (65 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 200:1) to give the vinylic silane **427** (1.17 g, 90%) as a colourless oil. R_f = 0.74 (petroleum ether–EtOAc, 20:1); $[\alpha]_D^{25}$ −4.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55—7.52 (2H, m, CH-Ph), 7.35—7.32 (3H, m, CH-Ph), 5.45 (1H, bs, CH-C1), 5.03 (1H, dt, *J* = 9.7, 2.8 Hz, CH-C6), 3.80 (1H, ddd, *J* = 9.4, 3.6, 2.0 Hz, CH-C4), 3.57 (1H, dd, *J* =

9.9, 5.3 Hz, CH_2-C8), 3.36 (1H, dd, *J* = 9.9, 7.5 Hz, CH_2-C8), 2.39 (1H, bqd, *J* = 7.0, 3.4 Hz, CH-C3), 1.90—1.84 (1H, m, CH-C7), 1.73 (3H, s, CH_3-C9), 1.58 (1H, ddd, *J* = 14.4, 9.7, 2.0 Hz, CH_2-C5), 1.49 (1H, ddd, *J* = 14.4, 9.4, 2.8 Hz, CH_2-C5), 1.15 (9H, s, CH_3-*t*-Bu-Piv), 1.04 (3H, d, *J* = 7.0 Hz, CH_3-C10), 0.93 (3H, d, *J* = 7.0 Hz, CH_3-C11), 0.91 (9H, s, CH_3-*t*-Bu-TBS), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.37 (3H, s, CH_3-$SiMe_2Ph$), 0.36 (3H, s, CH_3-$SiMe_2Ph$), 0.09 (3H, s, CH_3-TBS), 0.06 (3H, s, CH_3-TBS), 0.03 (3H, s, CH_3-TBS), 0.03 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7 (C-Piv), 157.9 (C-C2), 140.2 (C-Ph), 133.9 (2C, CH-Ph), 128.8 (CH-Ph), 127.9 (2C, CH-Ph), 121.6 (CH-C1), 72.5 (CH-C6), 70.4 (CH-C4), 65.0 (CH_2-C8), 50.0 (CH-C3), 40.5 (CH-C7), 39.0 (C-*t*-Bu-Piv), 33.8 (CH_2-C5), 27.5 (3C, CH_3-*t*-Bu-Piv), 26.1 (6C, CH_3-*t*-Bu-TBS), 22.8 (CH_3-C9), 18.4 (C-*t*-Bu-TBS), 18.2 (C-*t*-Bu-TBS), 12.0 (CH_3-C11), 11.7 (CH_3-C10), −0.7 (CH_3-$SiMe_2Ph$), −0.8 (CH_3-$SiMe_2Ph$), −4.2 (CH_3-TBS), −4.5 (CH_3-TBS),−5.3 (2C, CH_3-TBS); ν_{max} 2956, 2929, 2885, 2857, 2360, 2337, 1727, 1473, 1282, 1250, 1162, 1112, 1080, 1044, 834, 774 cm^{-1}; HRMS (ESI+) calcd for $C_{36}H_{68}NaO_4Si_3$ $[M+Na]^+$ 671.4318, found 671.4292.

(2*S*,3*S*,5*S*,6*R*,*E*)-5-[(*tert*-Butyldimethylsilyl)oxy]-1-hydroxy-8-iodo-2,6,7-trimethyloct-7-en-3-yl pivalate 388



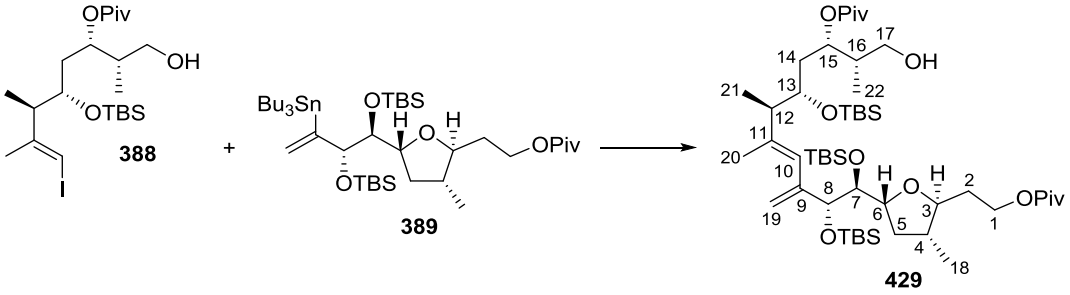
Note: the vinyl iodides are light-sensitive and all manipulations were performed in the dark.

A solution of freshly recrystallised NIS (700 mg, 3.10 mmol) in MeCN (3.6 mL) was added dropwise to a solution of vinylic silane **427** (400 mg, 0.62 mmol) in a 2.5:1 mixture of MeCN and benzene (5 mL) at 0 °C. The bright red mixture was stirred at 0 °C for 4 h and the reaction was then quenched with saturated aqueous $Na_2S_2O_3$ (8 mL) under vigorous stirring. The resulting colourless mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was filtered rapidly

through a short pad (*ca*. 5 cm) of silica gel (from pure pentane to pentane–Et_2O, 200:1) to afford crude vinylic iodide **428** which was immediately used in the next step without further purification.

Pyridine (4 mL) and HF·pyridine (70% HF, 4 mL) were added sequentially to a solution of crude *bis*-TBS-ether **428** in THF (60 mL) at 0 °C. The resulting solution was stirred at 0 °C until TLC indicated complete consumption of the starting material (24-36 h). The reaction was quenched by addition of saturated aqueous $NaHCO_3$ until gas evolution ceased and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 20:1 to 10:1) to give vinylic iodide **388** (206 mg, 63% over 2 steps) as a colourless oil. R_f = 0.11 (petroleum ether–EtOAc, 19:1); $[\alpha]_D^{21}$ +14.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03—6.01 (1H, m, CH-C1), 5.21 (1H, dt, *J* = 9.8, 2.3 Hz, CH-C6), 3.73 (1H, ddd, *J* = 9.3, 3.9, 2.3 Hz, CH-C4), 3.40 (1H, ddd, *J* = 13.0, 11.1, 5.4 Hz, CH_2-C8), 3.13—3.06 (2H, m, 1 × CH_2-C8, OH), 2.54—2.47 (1H, m, CH-C3), 1.85 (3H, d, *J* = 0.8 Hz, CH_3-C9), 1.84—1.77 (1H, m, CH-C7), 1.65 (1H, ddd, *J* = 14.4, 9.8, 2.3 Hz, CH_2-C5), 1.40 (1H, ddd, *J* = 14.4, 9.3, 2.3 Hz, CH_2-C5), 1.21 (9H, s, CH_3-*t*-Bu-Piv), 1.05 (3H, d, *J* = 7.0 Hz, CH_3-C10), 0.89 (9H, s, CH_3-*t*-Bu-TBS), 0.77 (3H, d, *J* = 7.0 Hz, CH_3-C11), 0.07 (3H, s, CH_3-TBS), 0.05 (3H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9 (C-Piv), 148.8 (C-C2), 77.6 (CH-C1), 70.6 (CH-C4), 70.4 (CH-C6), 64.5 (CH_2-C8), 48.7 (CH-C3), 40.7 (CH-C7), 39.3 (C-*t*-Bu-Piv), 35.6 (CH_2-C5), 27.5 (3C, CH_3-*t*-Bu-Piv), 26.0 (3C, CH_3-*t*-Bu-TBS), 24.6 (CH_3-C9), 18.2 (C-*t*-Bu-TBS), 12.4 (CH_3-C10), 9.8 (CH_3-C11), −4.0 (CH_3-TBS),−4.6 (2C, CH_3-TBS); ν_{max} 3491, 2957, 2930, 2883, 2858, 1725, 1708, 1473, 1283, 1253, 1167, 1116, 1079, 1046, 836, 806, 775 cm^{-1}; LRMS (CI, *iso*-butane) *m/z* (intensity) 527.0 $[M+H]^+$ (15), 395.0 (15), 113.1 (38), 73.1 (100); HRMS (CI, *iso*-butane) calcd for $C_{22}H_{44}O_4SiI$ $[M+H]^+$ 527.2054, found 527.2052.

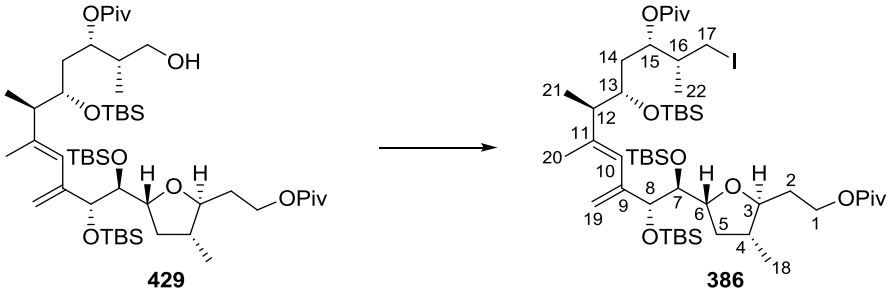
2-{(2*S*,3*R*,5*R*)-5-{(5*S*,6*R*,10*R*,11*S*,*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-11-[(2*S*,3*S*)-4-hydroxy-3-methyl-2-(pivaloyloxy)butyl]-2,2,3,3,9,10,13,13,14,14-decamethyl-7-methylene-4,12-dioxa-3,13-disilapentadec-8-en-5-yl}-3-methyltetrahydrofuran-2-yl}ethyl pivalate 429



Tetrabutylammonium diphenylphosphinate (243 mg, 0.528 mmol) was dried by azeotropic distillation with benzene (1 mL) and drying under high *vacuum*. The flask was then filled with argon and DMF (450 µL) was added at rt. A solution of the stannane **389** (108 mg, 0.132 mmol) in a 4:1 mixture of DMF and THF (1 mL) was added followed by addition of a solution of the iodide **388** (69.5 mg, 0.132 mmol) in a 4:1 mixture of DMF and THF (1 mL). $Pd(PPh_3)_4$ (46 mg, 39.6 µmol) and CuTC (75.5 mg, 0.396 mmol) were introduced quickly in solid form and the resulting mixture was stirred at rt for 2 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 20:1 to 10:1) to deliver 1,3-diene **429** (100 mg, 83%) as a colourless oil. R_f = 0.32 (petroleum ether–EtOAc, 9:1); $[\alpha]_D^{24}$ +4.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (1H, bs, CH-C10), 5.29 (1H, dd, *J* = 1.9, 1.2 Hz, CH_2-C19), 5.24 (1H, dt, *J* = 10.0, 1.7 Hz, CH-C15), 4.91 (1H, bs, CH_2-C19), 4.19 (1H, ddd, *J* = 11.1, 6.7, 5.6 Hz, CH_2-C1), 4.13—4.04 (3H, m, 1 × CH_2-C1, CH-C6, CH-C8), 3.86 (1H, dt, *J* = 8.1, 5.1 Hz, CH-C3), 3.79 (1H, ddd, *J* = 9.6, 3.6, 1.7 Hz, CH-C13), 3.51 (1H, dd, *J* = 7.0, 3.2 Hz, CH-C7), 3.39 (1H, ddd, *J* = 11.6, 9.7, 5.5 Hz, CH_2-C17), 3.18 (1H, dd, *J* = 9.7, 3.6 Hz, OH), 3.08 (1H, td, *J* = 11.6, 3.6 Hz, CH_2-C17), 2.43—2.33 (1H, m, CH-C12), 2.22—2.12 (1H, m, CH-C4), 1.87—1.77 (2H, m, 1 × CH_2-C5, CH-C16), 1.79 (3H, d, *J* = 0.6 Hz, CH_3-C20), 1.75—1.68 (3H, m, CH_2-C2, 1 × CH_2-C14), 1.61 (1H, ddd, *J* = 12.4, 6.7, 2.1 Hz, CH_2-C5), 1.41—1.33 (1H, m, CH_2-C14), 1.20 (9H, s, CH_3-*t*-Bu-

Piv), 1.18 (9H, s, CH_3-*t*-Bu-Piv), 1.04 (3H, d, *J* = 7.0 Hz, CH_3-C21), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.89 (3H, d, *J* = 7.1 Hz, CH_3-C18), 0.87 (9H, s, CH_3-*t*-Bu-TBS), 0.75 (3H, d, *J* = 6.9 Hz, CH_3-C22), 0.08 (3H, s, CH_3-TBS), 0.06 (6H, s, CH_3-TBS), 0.04 (3H, s, CH_3-TBS), 0.01 (6H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9 (C-Piv), 178.6 (C-Piv), 145.8 (C-C9), 139.9 (C-C11), 124.9 (CH-C10), 115.1 (CH_2-C19), 79.0 (CH-C7), 78.8 (CH-C8), 78.2 (CH-C6), 77.2 (CH-C3), 71.3 (CH-C13), 70.6 (CH-C15), 64.5 (CH_2-C17), 62.6 (CH_2-C1), 48.7 (CH-C12), 40.8 (CH-C16), 39.2 (C-*t*-Bu-Piv), 38.8 (C-*t*-Bu-Piv), 37.0 (CH_2-C5), 36.4 (CH-C4), 35.4 (CH_2-C14), 30.2 (CH_2-C2), 27.5 (3C, CH_3-*t*-Bu-Piv), 27.3 (3C, CH_3-*t*-Bu-Piv), 26.3 (3C, CH_3-*t*-Bu-TBS), 26.1 (3C, CH_3-*t*-Bu-TBS), 26.1 (3C, CH_3-*t*-Bu-TBS), 18.6 (C-*t*-Bu-TBS), 18.5 (C-*t*-Bu-TBS), 18.2 (C-*t*-Bu-TBS), 18.2 (CH_3-C20), 14.3 (CH_3-C18), 11.8 (CH_3-C21), 9.9 (CH_3-C22), −3.9 (CH_3-TBS), −4.0 (2C, CH_3-TBS), −4.1 (CH_3-TBS), −4.6 (CH_3-TBS), −4.6 (CH_3-TBS), −4.6 (CH_3-TBS); ν_{max} 2956, 2929, 2857, 1728, 1462, 1284, 1251, 1161, 1077, 1051, 834, 775 cm^{-1}; HRMS (ESI+) calcd for $C_{50}H_{98}NaO_9Si_3$ $[M+Na]^+$ 949.6411, found 949.6366.

2-{(2*S*,3*R*,5*R*)-5-{(5*S*,6*R*,10*R*,11*S*,*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-11-[(2*S*,3*R*)-4-iodo-3-methyl-2-(pivaloyloxy)butyl]-2,2,3,3,9,10,13,13,14,14-decamethyl-7-methylene-4,12-dioxa-3,13-disilapentadec-8-en-5-yl}-3-methyltetrahydrofuran-2-yl}ethyl pivalate 386

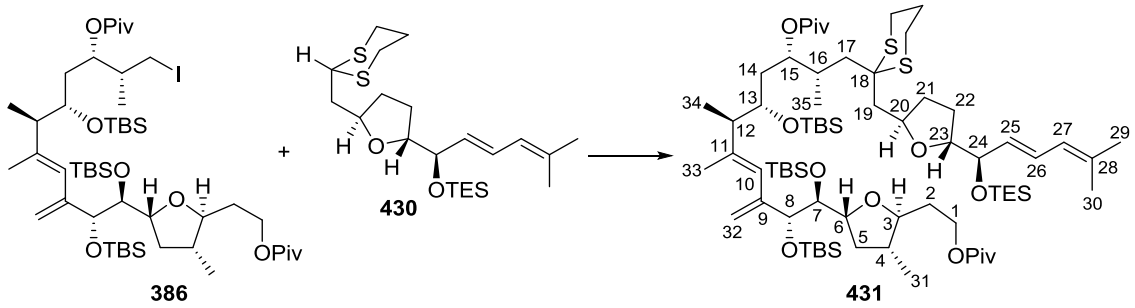


Note: the product is light-sensitive and all manipulations were performed in the dark.

Alcohol **429** (78 mg, 0.084 mmol) was dissolved in benzene (2 mL) and the resulting solution was cooled to 5 °C. PPh_3 (66 mg, 0.252 mmol), imidazole (34 mg, 0.504 mmol) and I_2 (64 mg, 0.252 mmol) were added sequentially and the resulting mixture was stirred at 5 °C for 10 min. The reaction mixture was warmed to rt, wrapped in aluminium foil and stirred at this temperature for

further 2 h. The reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (5 mL) and the mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified quickly by flash chromatography on silica gel (petroleum ether–EtOAc, 50:1) to afford iodide **386** (81 mg, 93%) as a colourless oil. R_f = 0.86 (petroleum ether–EtOAc, 9:1); $[\alpha]_D^{24}$ +5.2 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (1H, bs, CH-C10), 5.29 (1H, bs, CH_2-C19), 5.00 (1H, dt, *J* = 9.7, 2.6 Hz, CH-C15), 4.92 (1H, bs, CH_2-C19), 4.22—4.17 (1H, m, CH_2-C1), 4.21—4.06 (3H, m, 1 × CH_2-C1, CH-C6, CH-C8), 3.89—3.85 (1H, m, CH-C3), 3.84 (1H, ddd, *J* = 9.6, 3.5, 1.5 Hz, CH-C13), 3.50 (1H, dd, *J* = 6.8, 3.3 Hz, CH-C7), 3.25 (1H, dd, *J* = 9.7, 4.4 Hz, CH_2-C17), 2.85 (1H, t, *J* = 9.7 Hz, CH_2-C17), 2.43—2.34 (1H, m, CH-C12), 2.21—2.16 (1H, m, CH-C4), 2.08—2.00 (1H, m, CH-C16), 1.87—1.68 (3H, m, CH_2-C2, 1 × CH_2-C5), 1.79 (3H, bs, CH_3-C20), 1.62 (1H, ddd, *J* = 12.2, 6.4, 1.7 Hz, CH_2-C5), 1.53 (1H, ddd, *J* = 13.8, 9.7, 1.5 Hz, CH_2-C14), 1.47—1.40 (1H, m, CH_2-C14), 1.19 (18H, s, CH_3-*t*-Bu-Piv), 1.04 (3H, d, *J* = 6.7 Hz, CH_3-C21), 1.03 (3H, d, *J* = 6.7 Hz, CH_3-C22), 0.91 (9H, s, CH_3-*t*-Bu-TBS), 0.90 (9H, s, CH_3-*t*-Bu-TBS), 0.90 (3H, d, *J* = 7.0 Hz, CH_3-C18), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.09 (3H, s, CH_3-TBS), 0.08 (3H, s, CH_3-TBS), 0.07 (3H, s, CH_3-TBS), 0.05 (3H, s, CH_3-TBS), 0.01 (3H, s, CH_3-TBS), 0.01 (3H, s, CH_3-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6 (C-Piv), 177.8 (C-Piv), 145.8 (C-C9), 139.9 (C-C11), 124.8 (CH-C10), 115.2 (CH_2-C19), 79.0 (CH-C7), 78.9 (CH-C8), 78.2 (CH-C6), 77.2 (CH-C3), 73.8 (CH-C15), 71.0 (CH-C13), 62.6 (CH_2-C1), 48.7 (CH-C12), 41.2 (CH-C16), 39.1 (C-*t*-Bu-Piv), 38.8 (C-*t*-Bu-Piv), 37.0 (CH_2-C5), 36.4 (CH-C4), 33.8 (CH_2-C14), 30.3 (CH_2-C2), 27.4 (3C, CH_3-*t*-Bu-Piv), 27.4 (3C, CH_3-*t*-Bu-Piv), 26.3 (3C, CH_3-*t*-Bu-TBS), 26.1 (3C, CH_3-*t*-Bu-TBS), 26.1 (3C, CH_3-*t*-Bu-TBS), 18.6 (C-*t*-Bu-TBS), 18.5 (C-*t*-Bu-TBS), 18.4 (CH_3-C20), 18.2 (C-*t*-Bu-TBS), 15.8 (CH_3-C22), 14.3 (CH_3-C18), 11.6 (CH_3-C21), 9.8 (CH_2-C17), −4.0 (CH_3-TBS), −4.0 (2C, CH_3-TBS), −4.1 (CH_3-TBS), −4.5 (CH_3-TBS), −4.5 (CH_3-TBS), −4.6 (CH_3-TBS); HRMS (ESI+) calcd for $C_{50}H_{98}IO_8Si_3$ $[M+H]^+$ 1037.5609, found 1037.5586.

(2*S*, 3*S*, 5*S*, 6*R*, 7*E*, 10*R*, 11*R*)-5-,11-*bis*[(*tert*-Butyldimethylsilyl)oxy]-11-[(2*R*, 4*R*, 5*S*)-5-{2-[(2,2-dimethylpropanoyl)oxy]ethyl}-4-methyloxolan-2-yl]-6,7,10-trimethyl-2-[(2-{[(2*R*,5*R*)-5-[(1*R*,2*E*)-5-methyl-1-[(triethylsilyl)oxy]dien-1-yl]oxolan-2-yl]methyl}-1,3-dithian-2-yl)methyl]-9-methylideneundec-7-en-3-yl pivalate 431



Dithiane **430** (50 mg, 0.117 mmol) was dissolved in a 4.5:1 mixture of THF and HMPA (430 µL) and the resulting solution was cooled to −78 °C. *t*-BuLi (47 µL of a 2.5 M solution in hexanes, 0.117 mmol) was added and the resulting orange/red mixture was stirred at −78 °C for 10 min. A solution of iodide **386** (81 mg, 0.078 mmol) in THF (350 µL) was added and the reaction was stirred at −78 °C for 1 h. The reaction was quenched by addition of aqueous pH 7 buffer (2 mL) and extracted with Et_2O (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc, 50:1 to 20:1) to afford recovered dithiane **430** (21 mg, 42%), recovered iodide **386** (41 mg, 50%) and desired dithiane **431** (14 mg, 13%) as a colourless oil. R_f = 0.31 (petroleum ether–EtOAc, 19:1); $[\alpha]_D^{28}$ +8.7 (c = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (1H, ddd, *J* = 15.3, 10.9, 0.9 Hz, CH-C26), 5.86—5.80 (1H, m, CH-C27), 5.72 (1H, bs, CH-C10), 5.55 (1H, dd, *J* = 15.3, 5.8 Hz, CH-C25), 5.28 (1H, dd, *J* = 2.2, 1.3 Hz, CH_2-C32), 5.03 (1H, dt, *J* = 9.6, 2.5 Hz, CH-C15), 4.91—4.89 (1H, m, CH_2-C32), 4.23—4.16 (2H, m, 1 × CH_2-C1, CH-C24), 4.16—4.04 (4H, m, 1 × CH_2-C1, CH-C6, CH-C8, CH-C20), 3.94 (1H, dd, *J* = 13.3, 7.1 Hz, CH-C23), 3.86 (1H, dt, *J* = 8.2, 5.1 Hz, CH-C3), 3.79—3.73 (1H, m, CH-C13), 3.50 (1H, dd, *J* = 7.0, 3.0 Hz, CH-C7), 2.93—2.84 (1H, m, CH_2-dithiane), 2.81—2.71 (3H, m, CH_2-dithiane), 2.40—2.33 (1H, m, CH-C12), 2.27 (1H, dd, *J* = 15.0, 4.5 Hz, CH_2-C19), 2.22—2.08 (3H, m, CH-C4, CH_2-C17), 2.06—1.45 (13H, m, CH_2-C2, CH_2-C5, CH_2-

C14, CH-C16, CH_2-C21, CH_2-C22, CH_2-dithiane), 1.77 (6H, bs, CH_3-C29, CH_3-C30), 1.75 (3H, d, *J* = 0.6 Hz, CH_3-C33), 1.19 (9H, s, CH_3-*t*-Bu-Piv), 1.19 (9H, s, CH_3-*t*-Bu-Piv), 1.04 (3H, d, *J* = 6.9 Hz, CH_3-C34), 1.03 (3H, d, *J* = 6.9 Hz, CH_3-C35), 0.95 (9H, t, *J* = 7.9 Hz, CH_3-TES), 0.91 (18H, s, CH_3-*t*-Bu-TBS), 0.90 (3H, d, *J* = 6.2 Hz, CH_3-C31), 0.88 (9H, s, CH_3-*t*-Bu-TBS), 0.60 (6H, q, *J* = 7.9 Hz, CH_2-TES), 0.11 (3H, s, CH_3-TBS), 0.08 (3H, s, CH_3-TBS), 0.07 (3H, s, CH_3-TBS), 0.05 (3H, s, CH_3-TBS), 0.01 (6H, s, CH_3-TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7 (C-Piv), 178.2 (C-Piv), 145.8 (C-C9), 140.2 (C-C11), 134.8 (C-C28), 130.0 (CH-C25), 127.6 (CH-C26), 125.0 (CH-C10), 124.7 (CH-C27), 114.8 (CH_2-C32), 81.7 (CH-C23), 79.0 (CH-C7), 78.9 (CH-C8), 78.3 (CH-C6), 77.0 (CH-C3), 76.4 (CH-C20), 76.2 (CH-C15), 75.3 (CH-C24), 71.8 (CH-C13), 65.3 (CH_2-C18), 62.7 (CH_2-C1), 48.3 (CH-C12), 46.5 (CH_2-C19), 44.2 (C-C18), 42.4 (CH_2-C17), 41.2 (CH-C16), 39.1 (C-*t*-Bu-Piv), 38.9 (C-*t*-Bu-Piv), 37.6 (CH_2-C5), 36.4 (CH-C4), 34.5 (CH_2-C14), 34.2 (CH_2-C21), 31.0 (CH_2-dithiane), 30.5 (CH_2-dithiane), 30.3 (CH_2-C2), 27.6 (3C, CH_3-*t*-Bu-Piv), 27.4 (CH_2-C22), 27.4 (3C, CH_3-*t*-Bu-Piv), 26.4 (CH_2-dithiane), 26.3 (3C, CH_3-*t*-Bu-TBS), 26.2 (CH_3-C30), 26.2 (3C, CH_3-*t*-Bu-TBS), 26.1 (3C, CH_3-*t*-Bu-TBS), 18.6 (C-*t*-Bu-TBS), 18.5 (C-*t*-Bu-TBS), 18.4 (CH_3-C33), 18.3 (C-*t*-Bu-TBS), 18.0 (CH_3-C29), 16.8 (CH_3-C34), 14.3 (CH_3-C31), 12.9 (CH_3-C35), 7.1 (3C, CH_3−TES), 5.1 (3C, CH_2−TES), −4.1 (2C, CH_3-TBS), −4.2 (CH_3-TBS), −4.3 (2C, CH_3-TBS), −4.5 (CH_3-TBS), −4.6 (CH_3-TBS); ν_{max} 2956, 2930, 2878, 2857, 1728, 1462, 1283, 1252, 1160, 1079, 1005, 835, 776 cm^{-1}; HRMS (ESI+) calcd for $C_{72}H_{136}O_{10}S_2Si_4$ $[M+H]^+$ 1359.8544, found 1359.8398.

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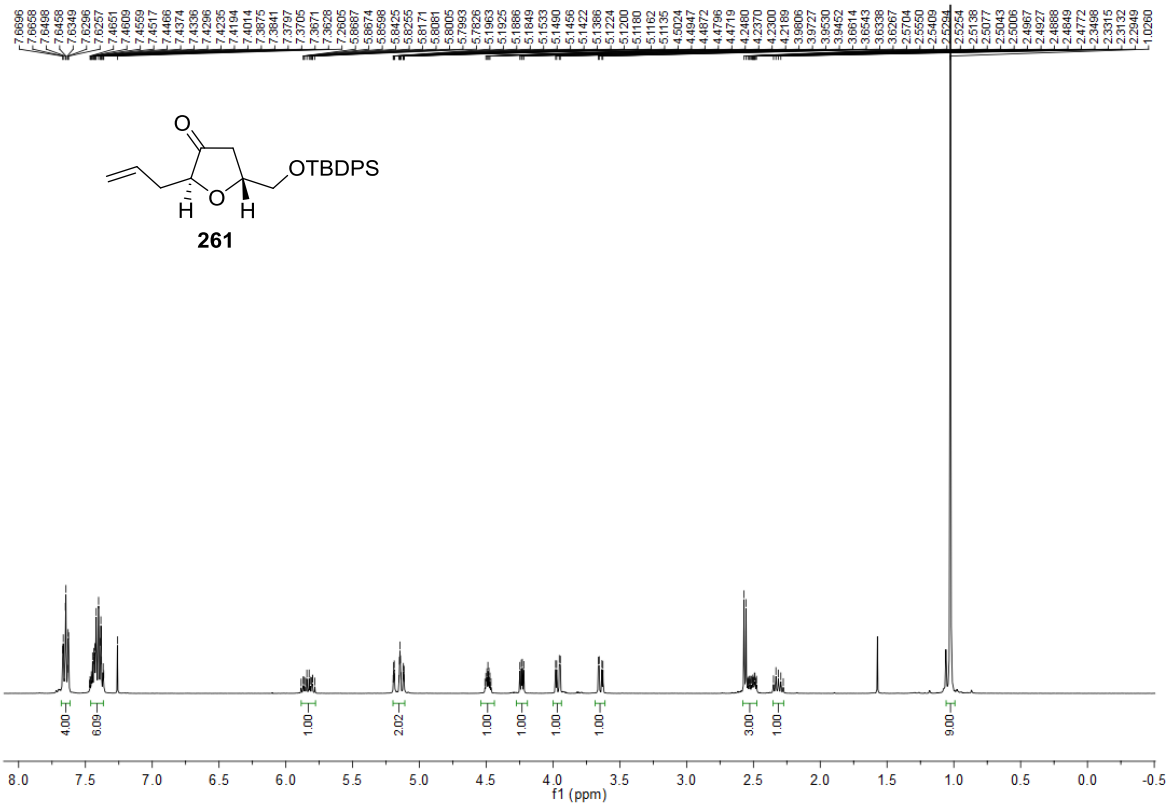
(132) Ställberg, G. *Acta Chem. Scand.* **1956**, *10*, 1360–1361.
(133) The *dr* varied from 10:1 to >20:1 depending on the batch of catalyst used. The mixture of diastereoisomer at C8 could not be separated by column chromatography on silica gel.
(134) For the preparation see: (a) Dirat, O.; Clipson, A.; Elliott, J. M.; Garrett, S.; Jones, A. B.; Reader, M.; Shaw, D. *Tetrahedron Lett.* **2006**, *47*, 1729–1731. (b) Pietruszka, J.; Witt, A. *Synthesis* **2006**, 4266–4268.
(135) For the preparation see: (a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235. (b) Mio, S.; Kumagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133-2144.
(136) For the synthesis of l-fructose see: Chen, C. C.; Whistler, R. L. *Carbohydr. Res.* **1988**, 175, 265–271.
(137) For the preparation see: Dolhem, F.; Lièvre, C.; Demailly, G. *Tetrahedron Lett.* **2002**, *43*, 1847–1849.
(138) The stock solution was prepared by mixing HF·pyridine (70% HF in pyridine, 1.0 mL), pyridine (2.0 mL) and THF (5.0 mL).
(139) Izgu, E. C.; Burns, A. C.; Hoye, T. R. *Org. Lett.* **2011**, *13*, 703–705.
(140) Szostak, M.; Spain, M.; Procter, D. J. *J. Org. Chem.* **2012**, *77*, 3049-3059.

Appendices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1.00
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3.00
1.00
9.00
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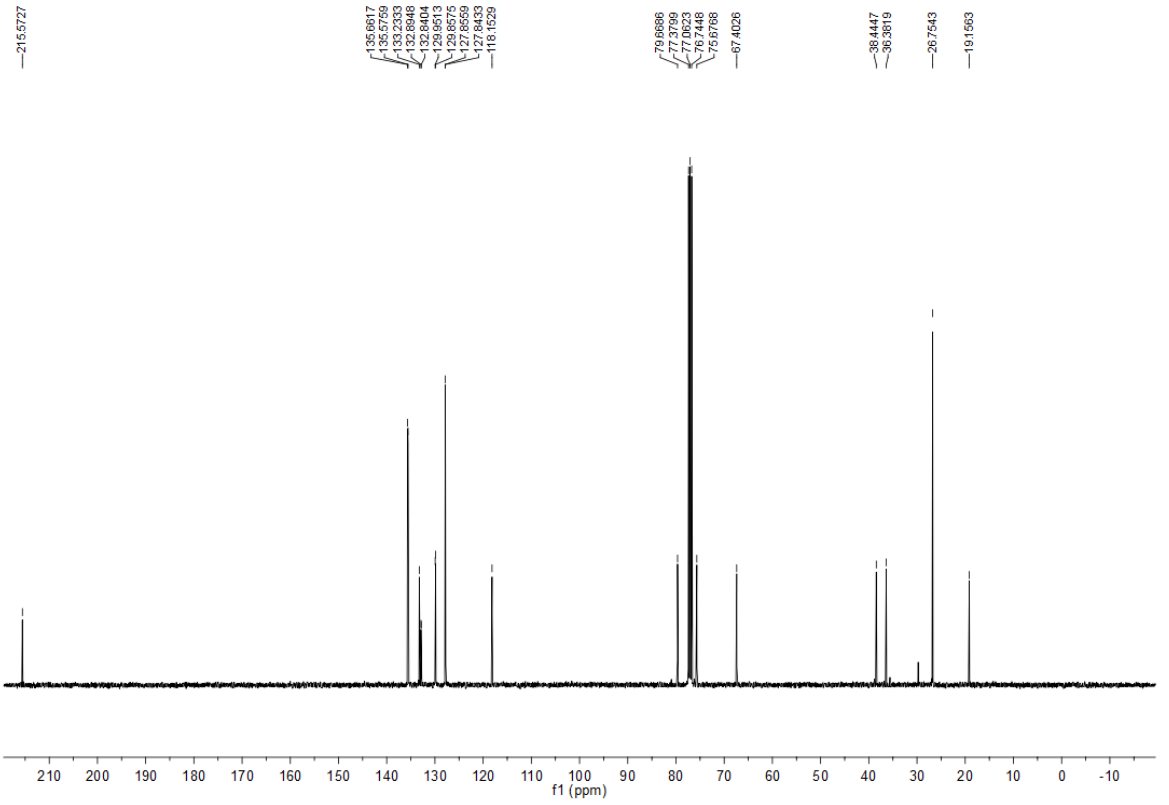
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79.9686
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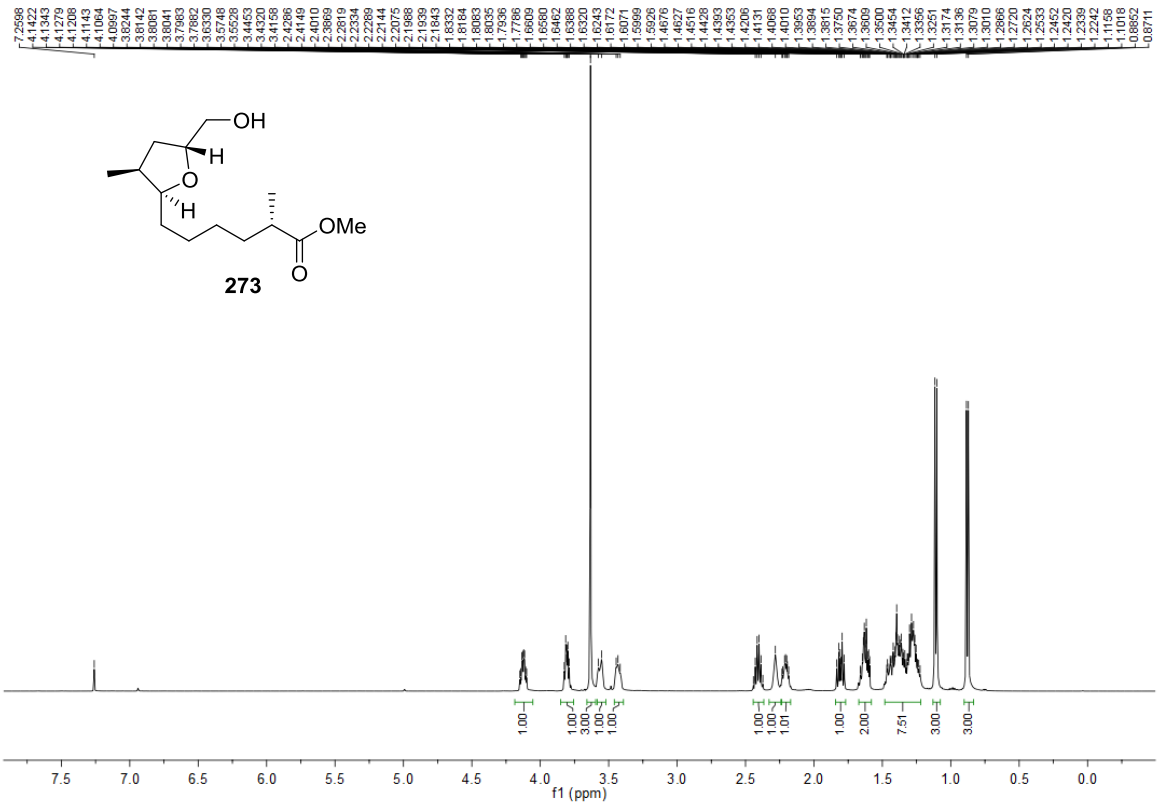
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H
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O
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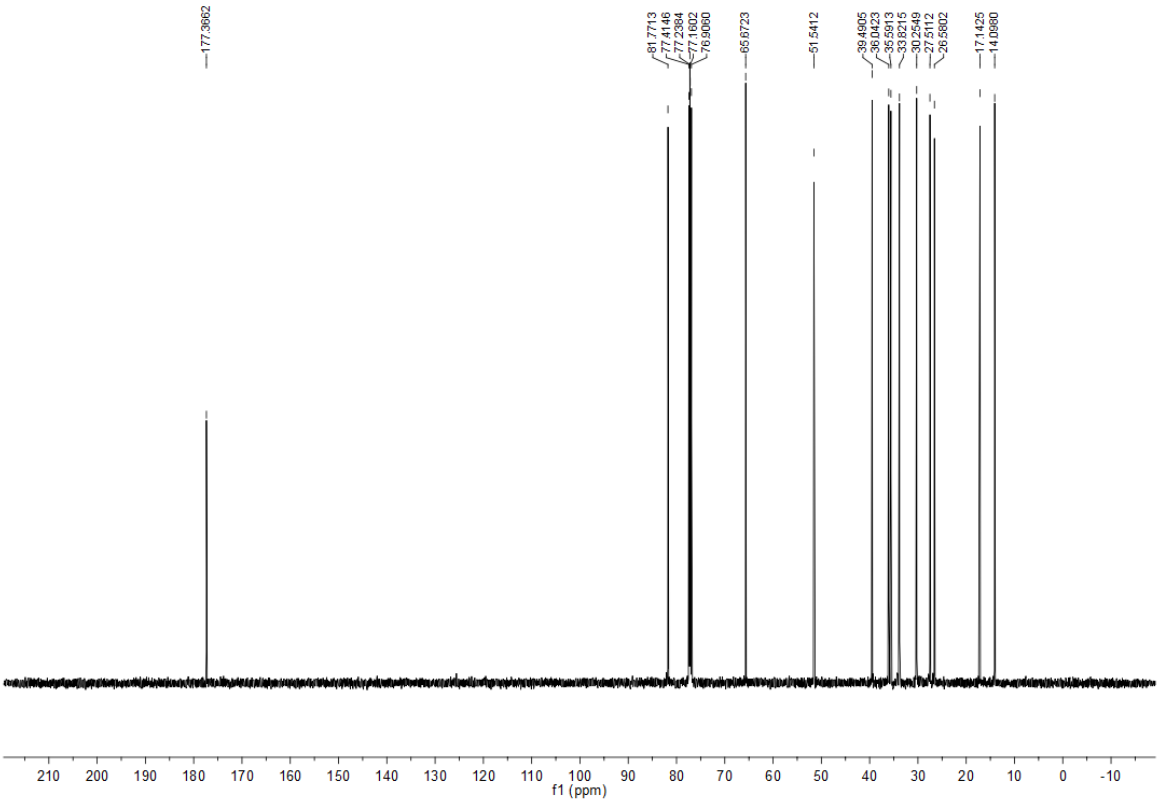
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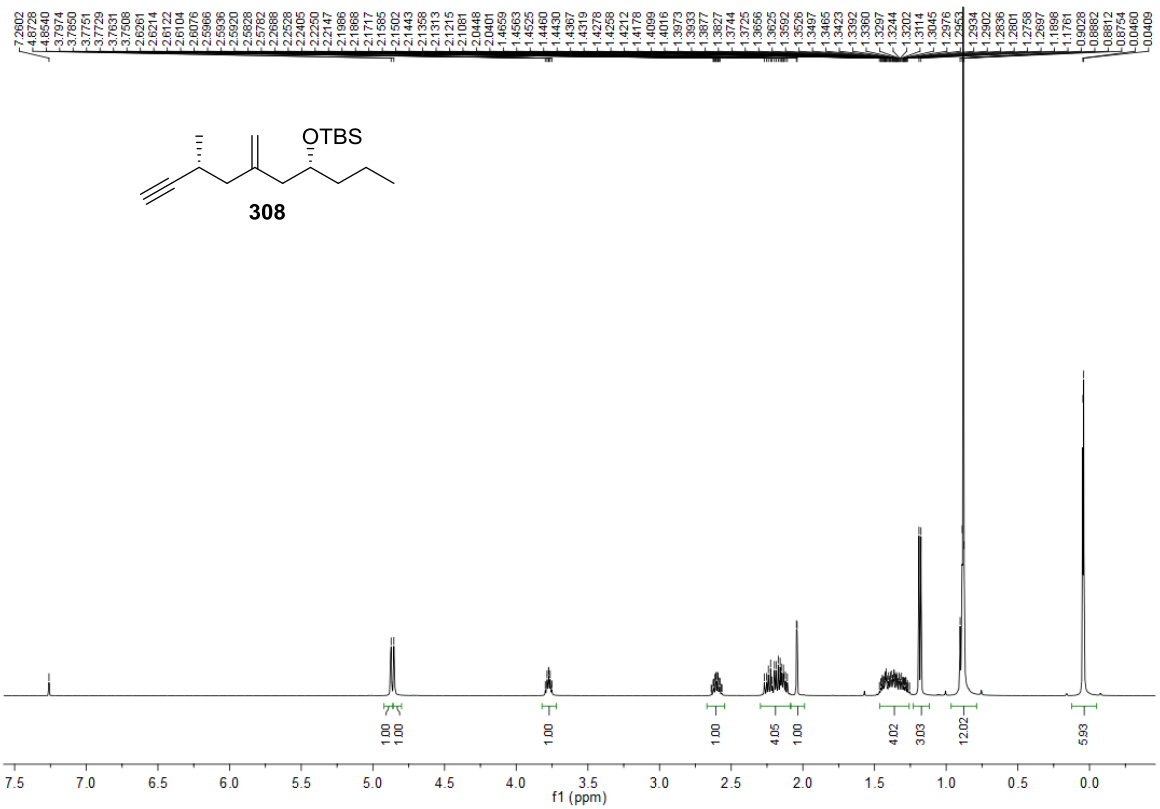
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308
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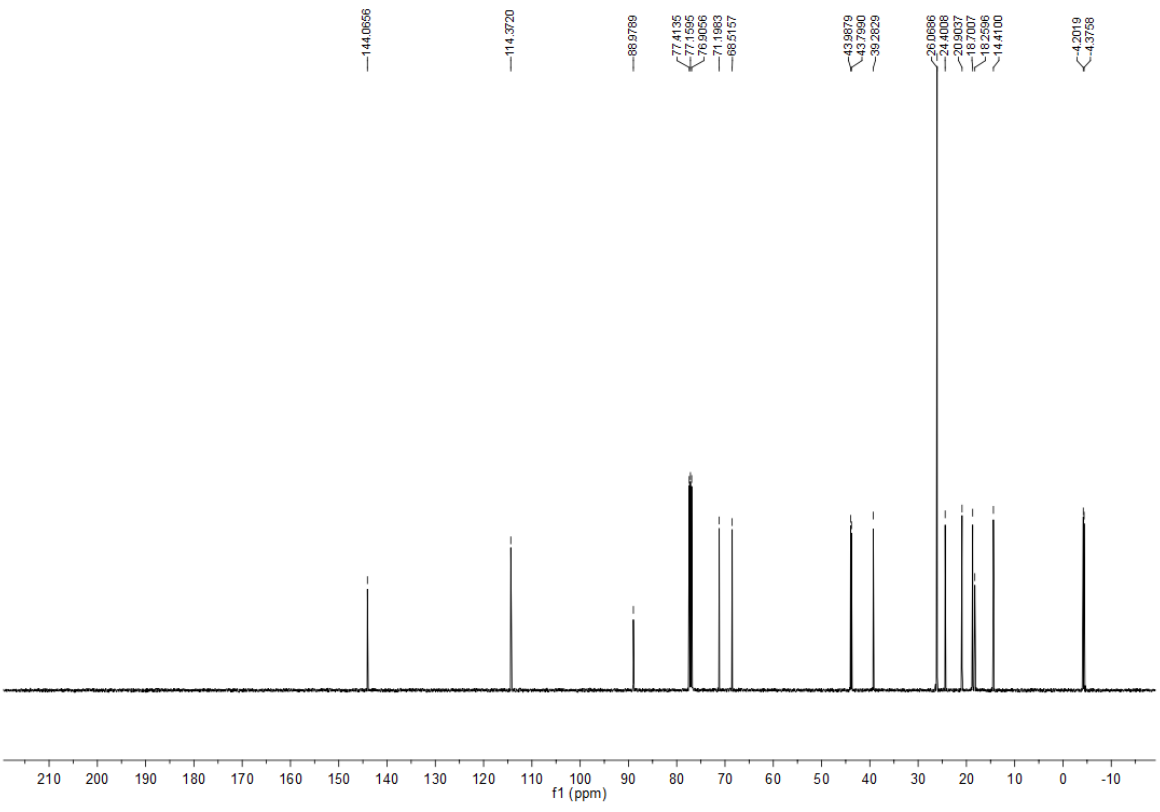
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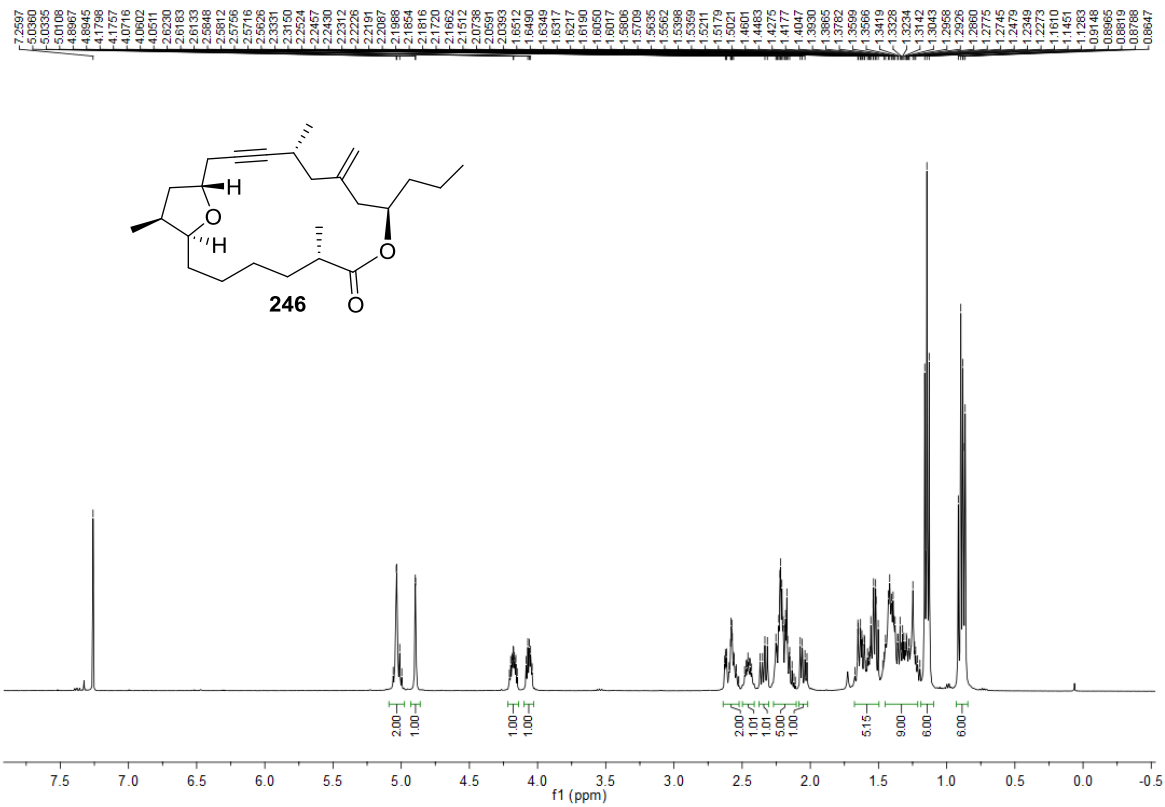
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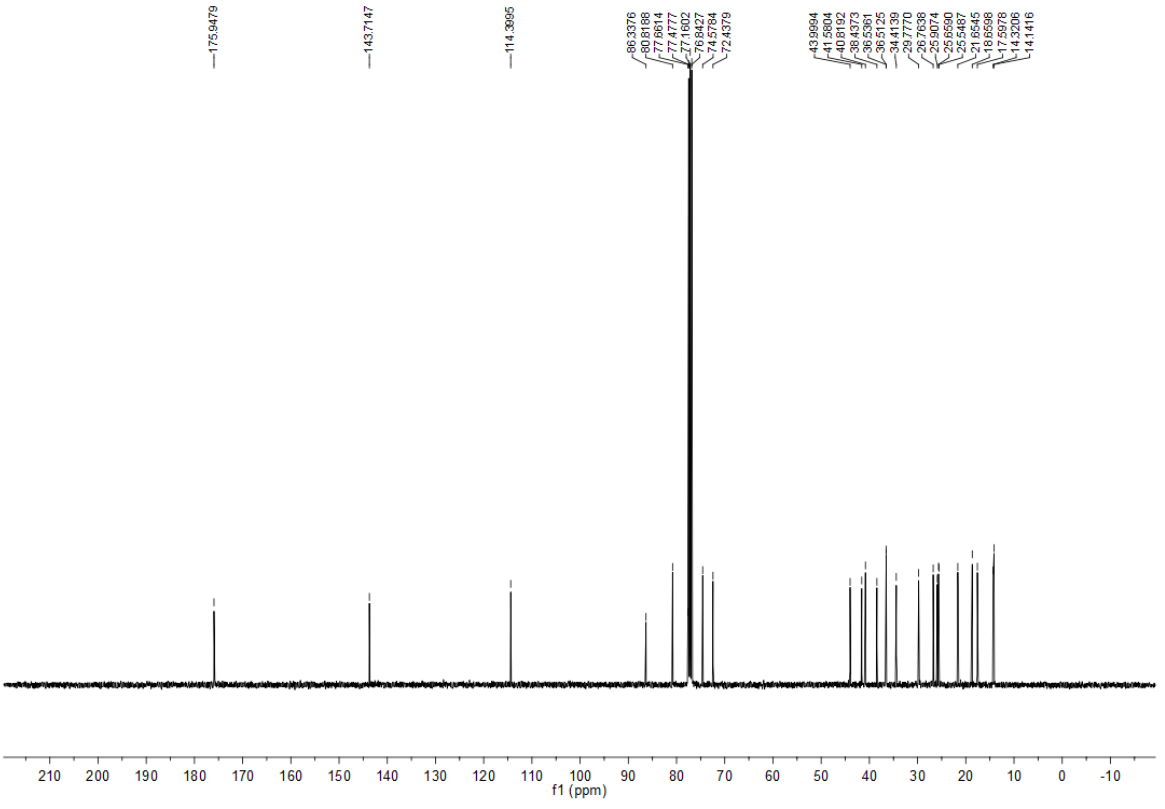
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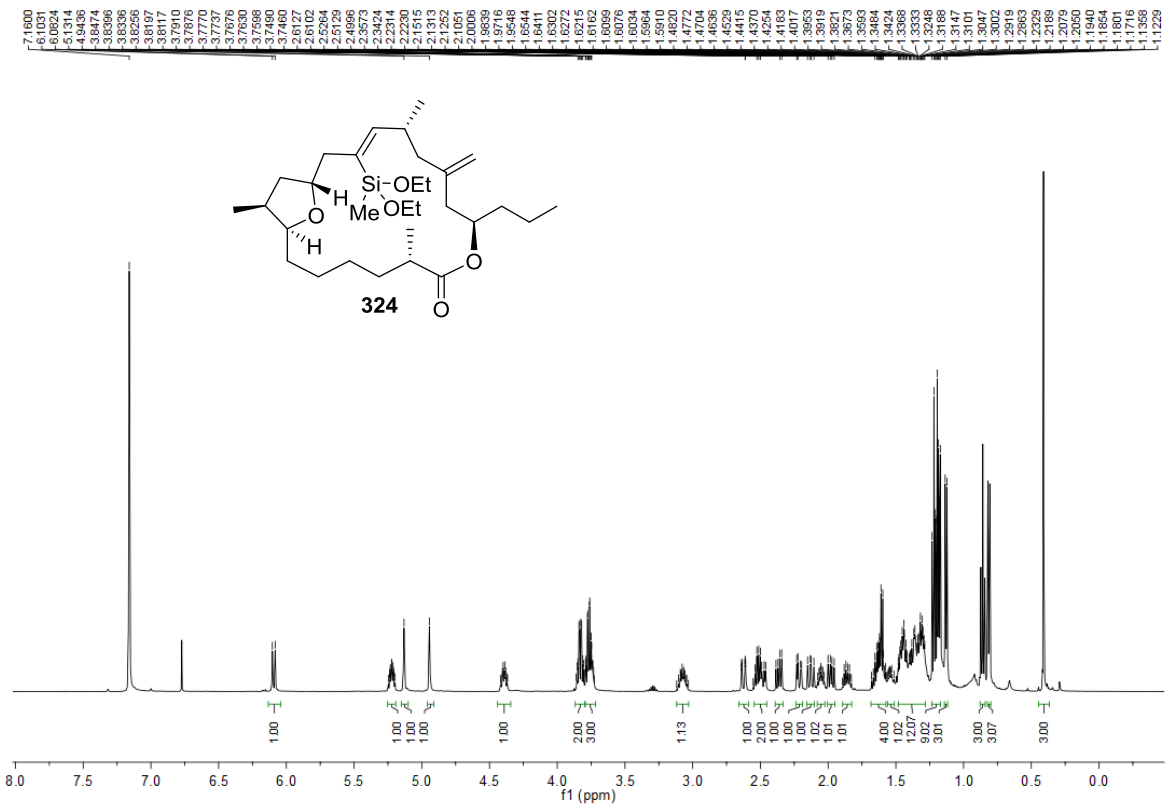
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O
H
O
O
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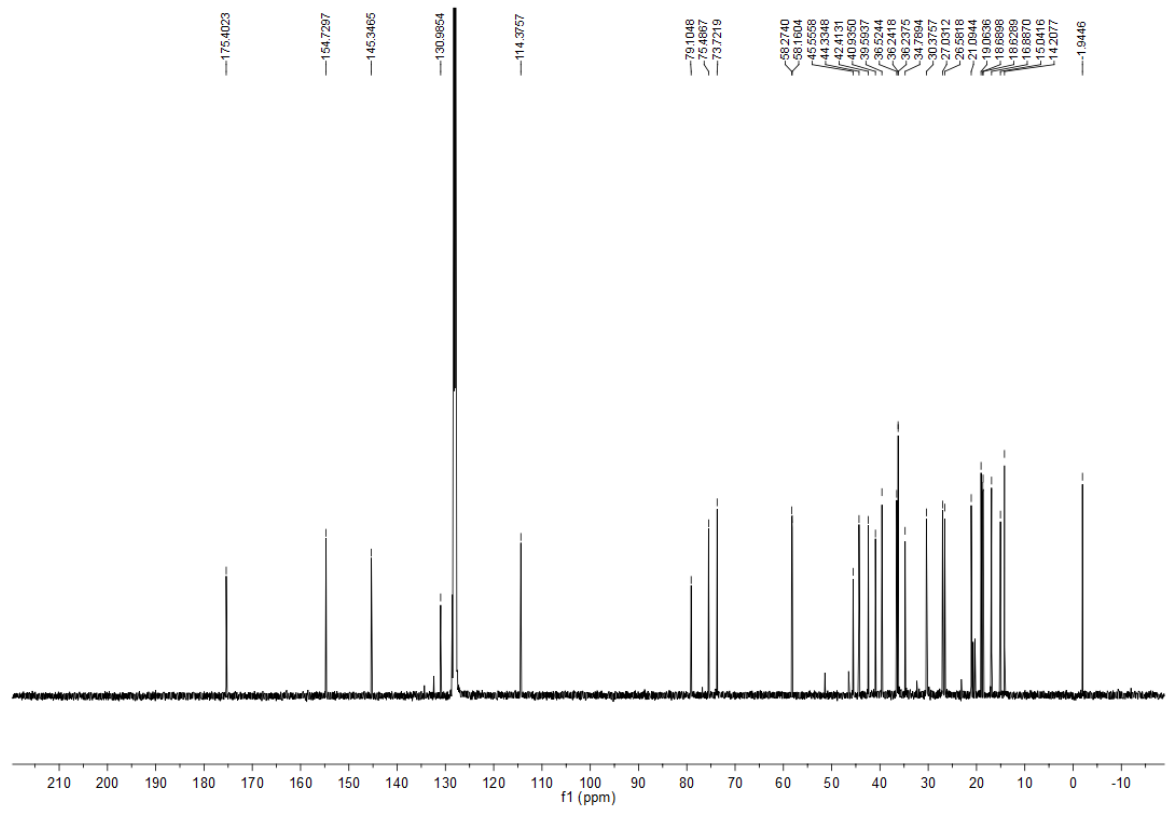
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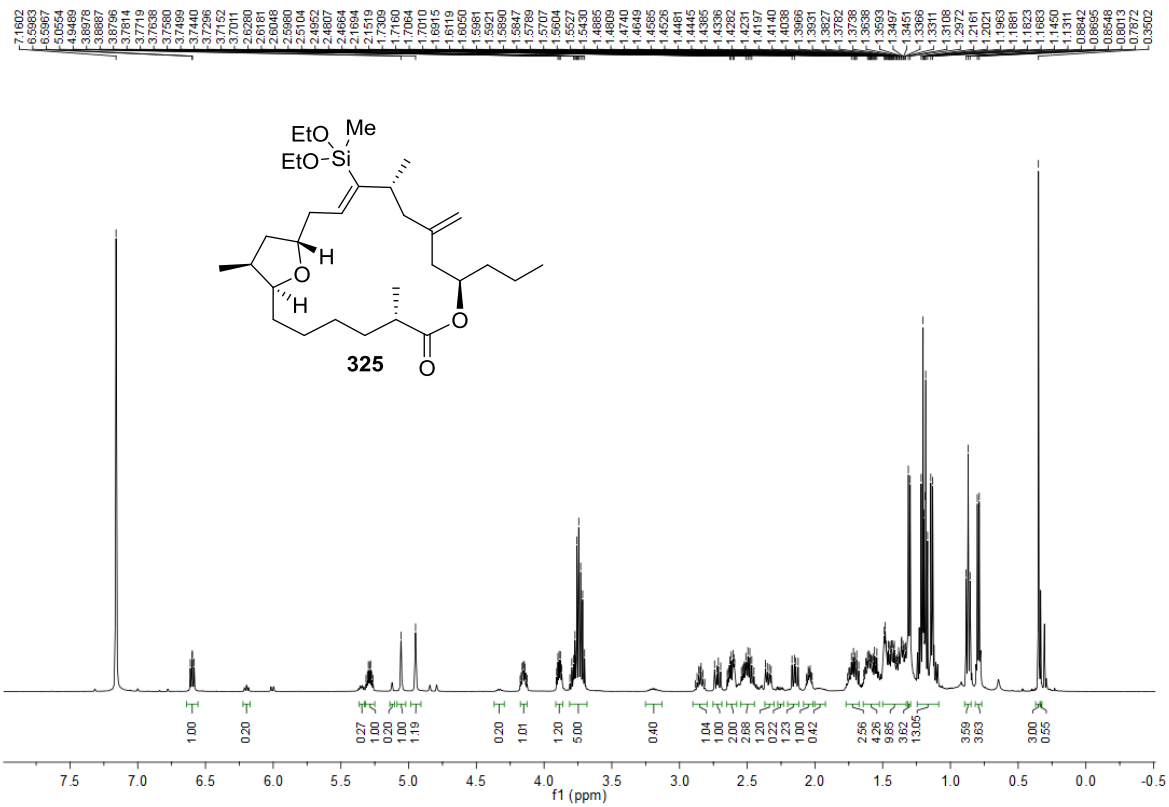
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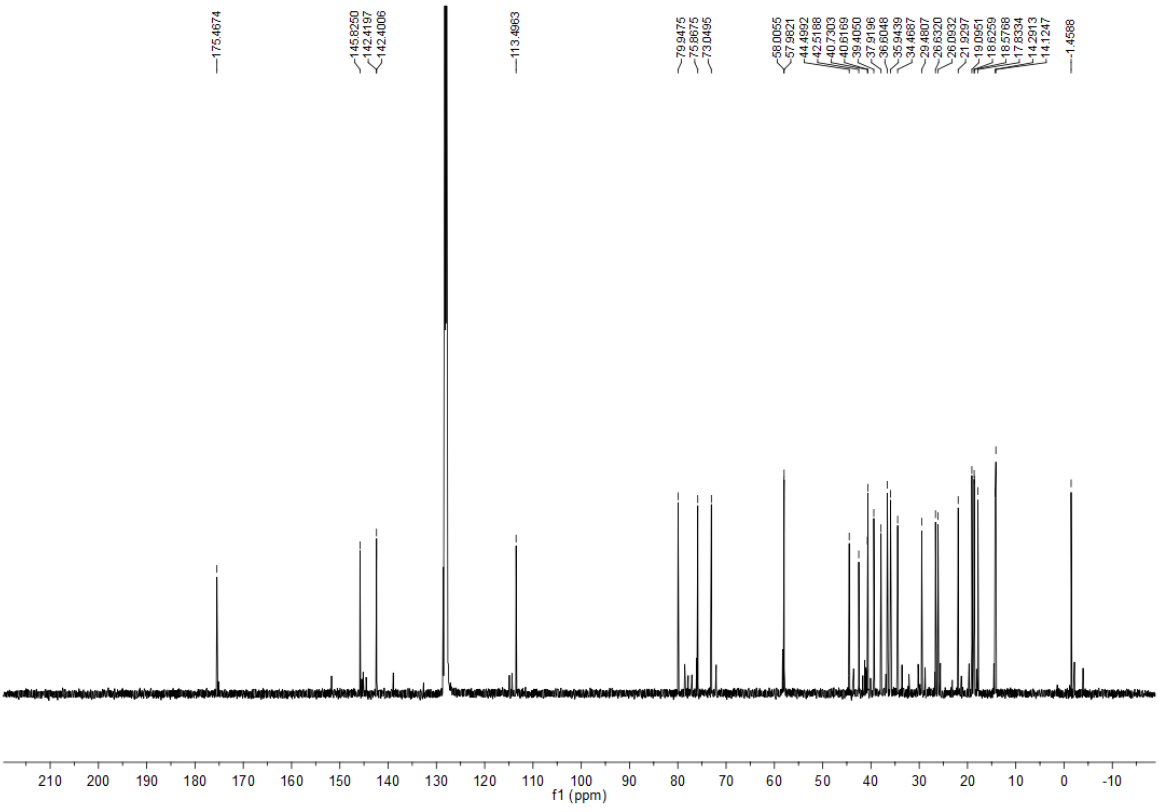
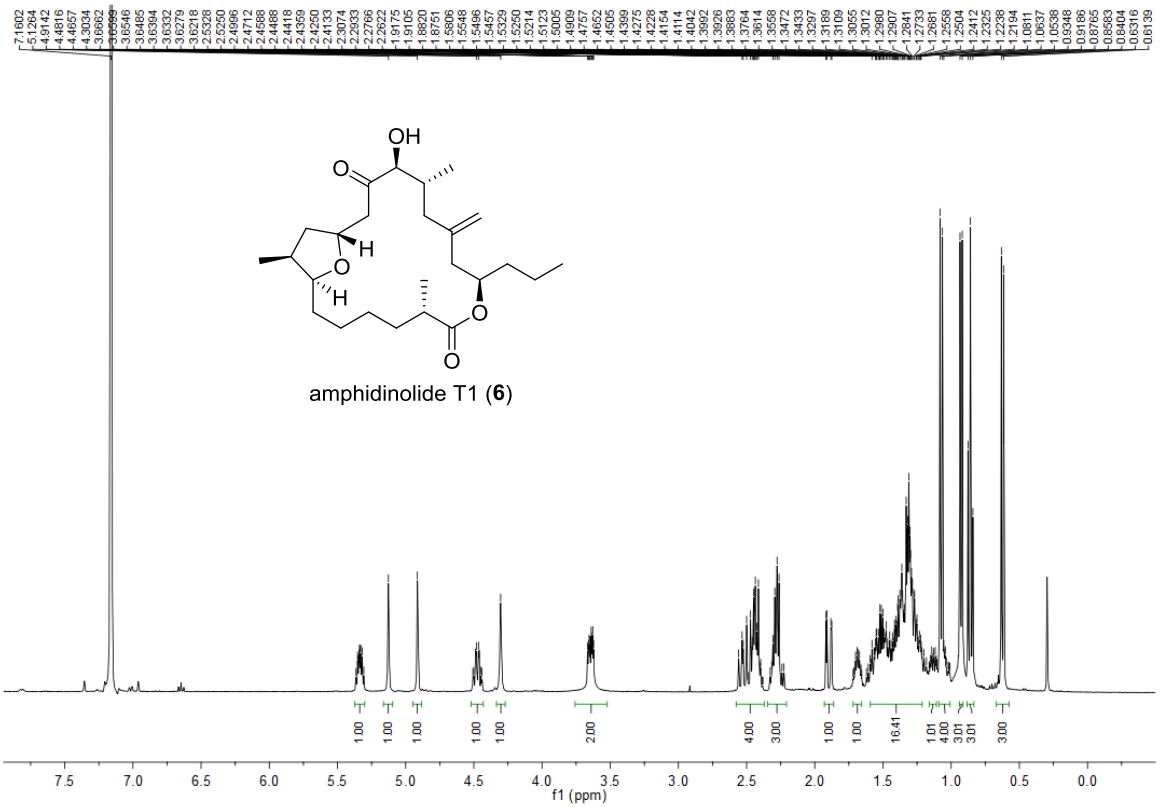
O
H
O
O
325

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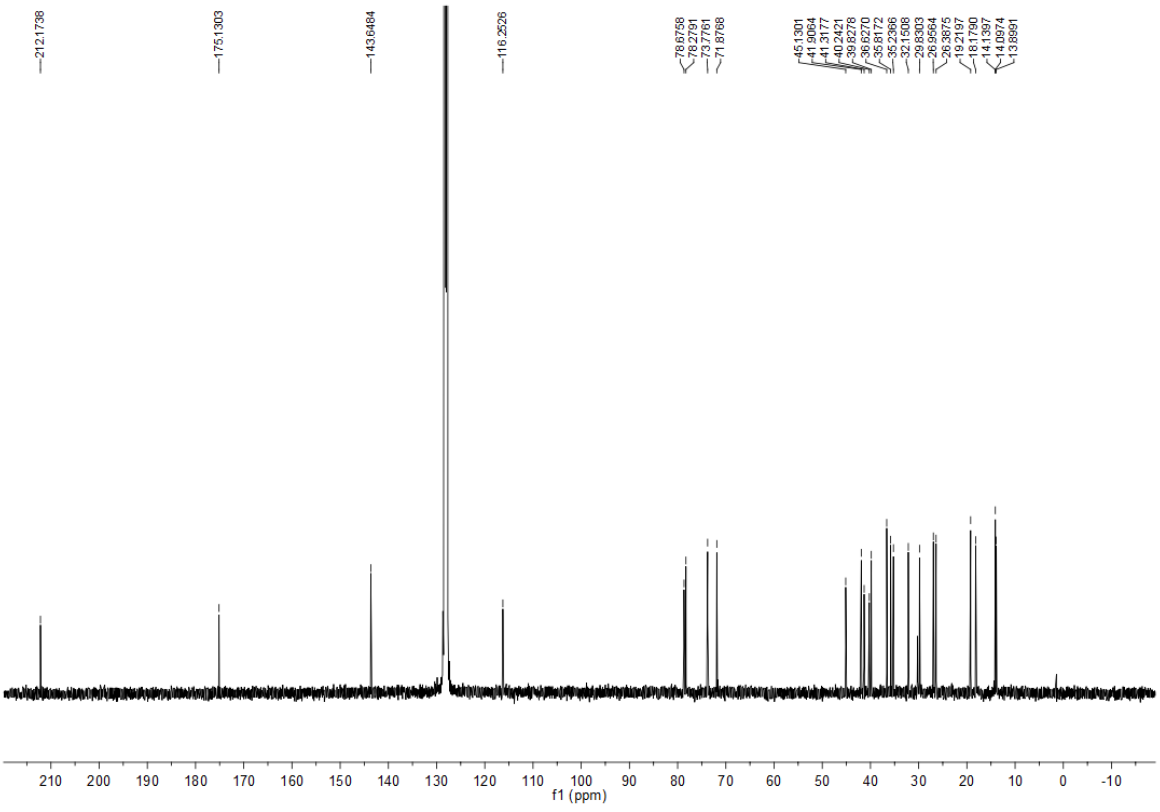
H
O
H
O
O
amphidinolide T1 (6)
f1 (ppm)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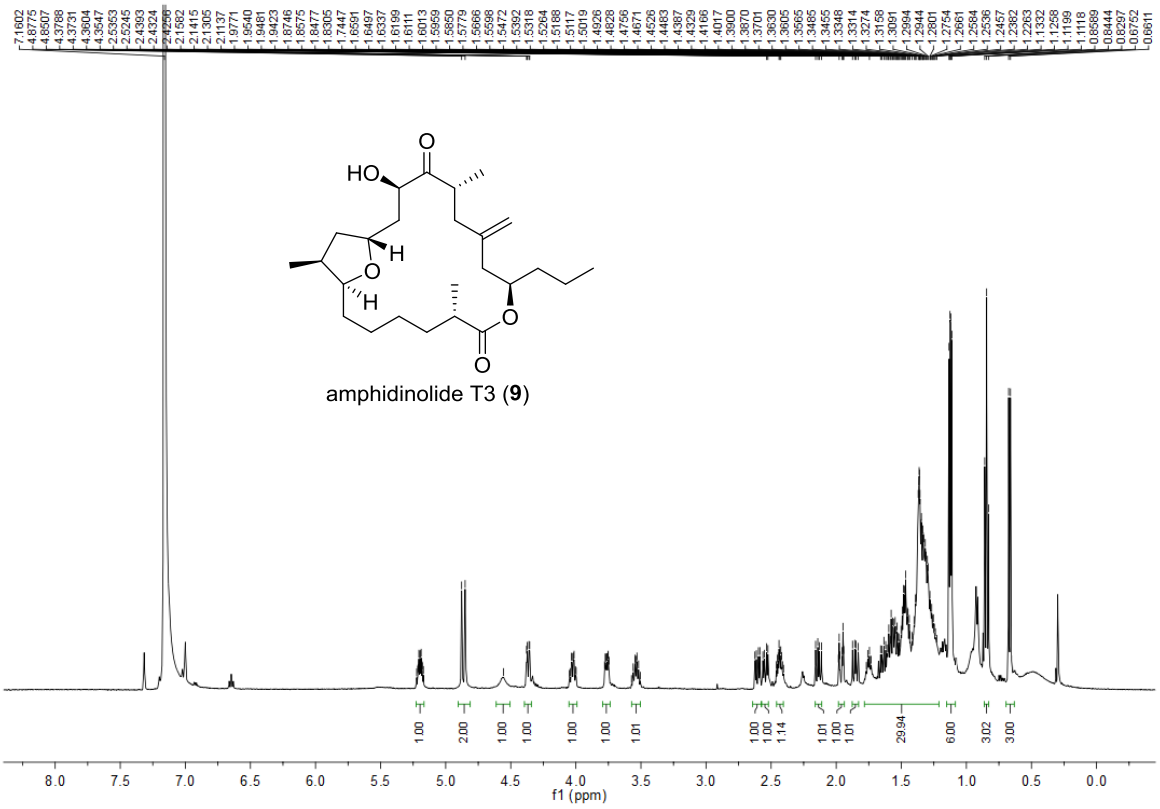

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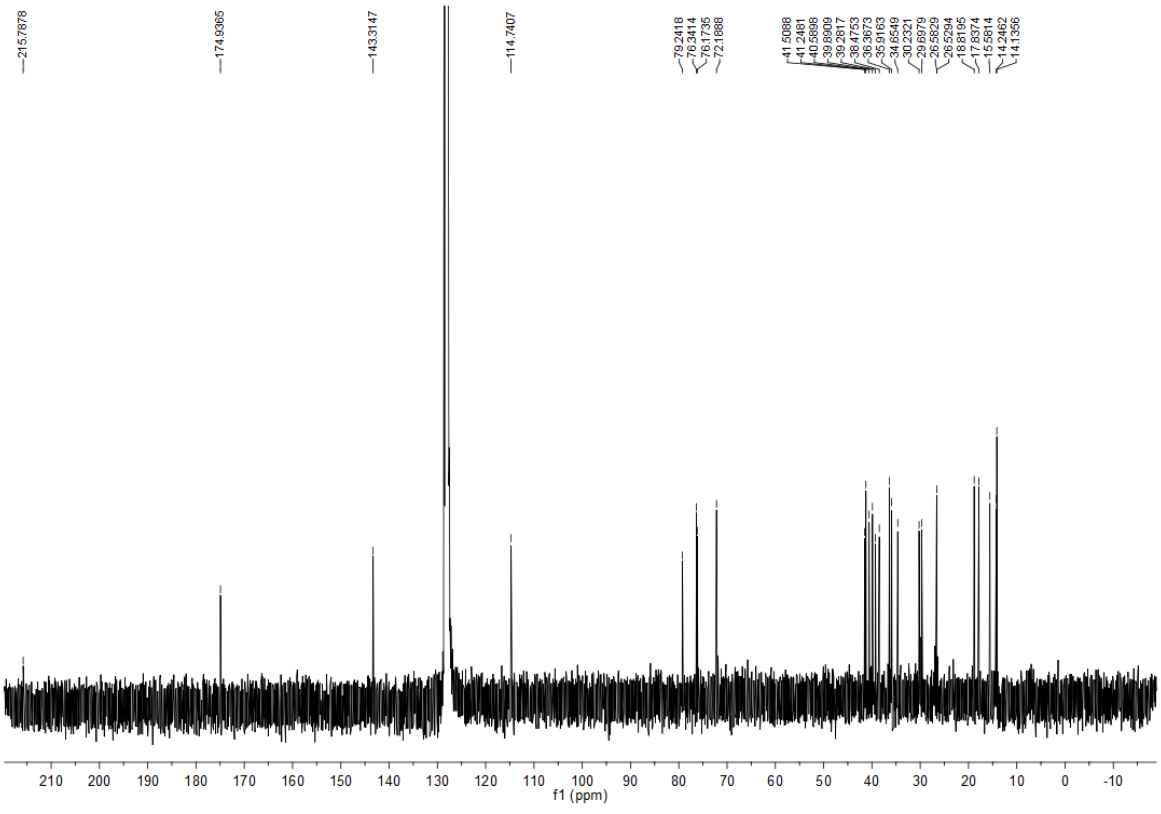

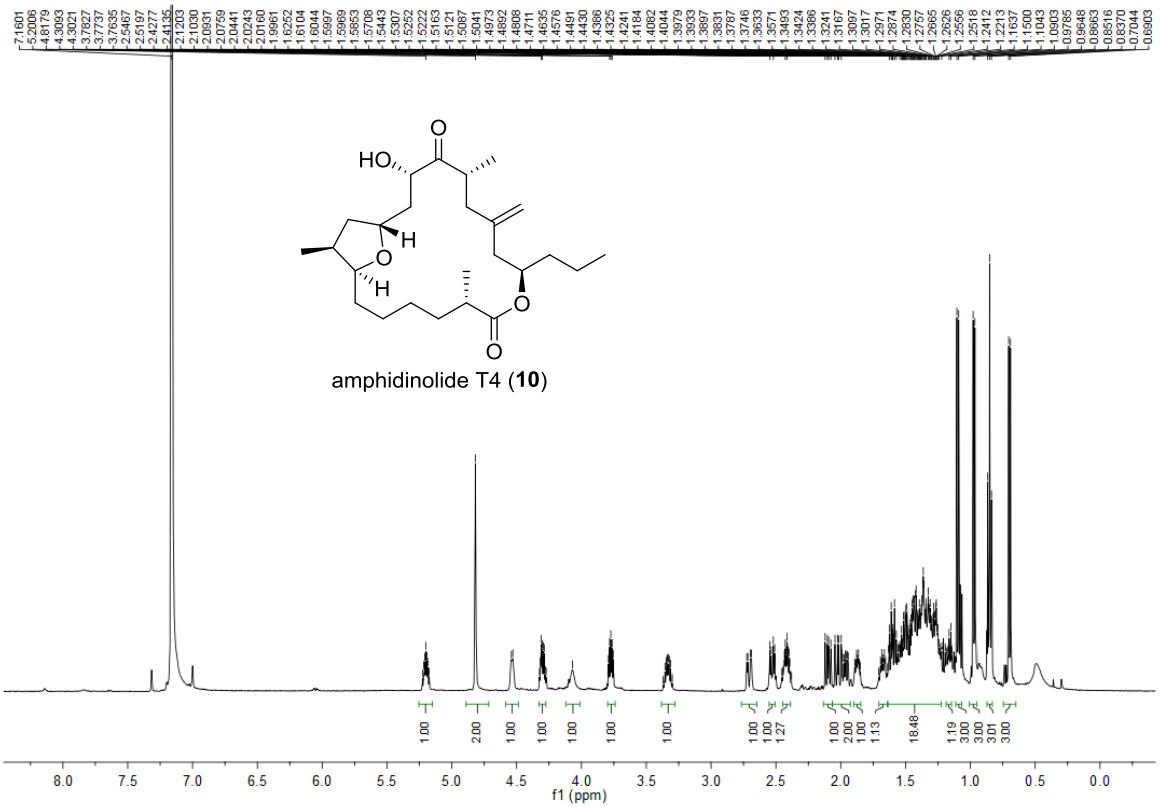
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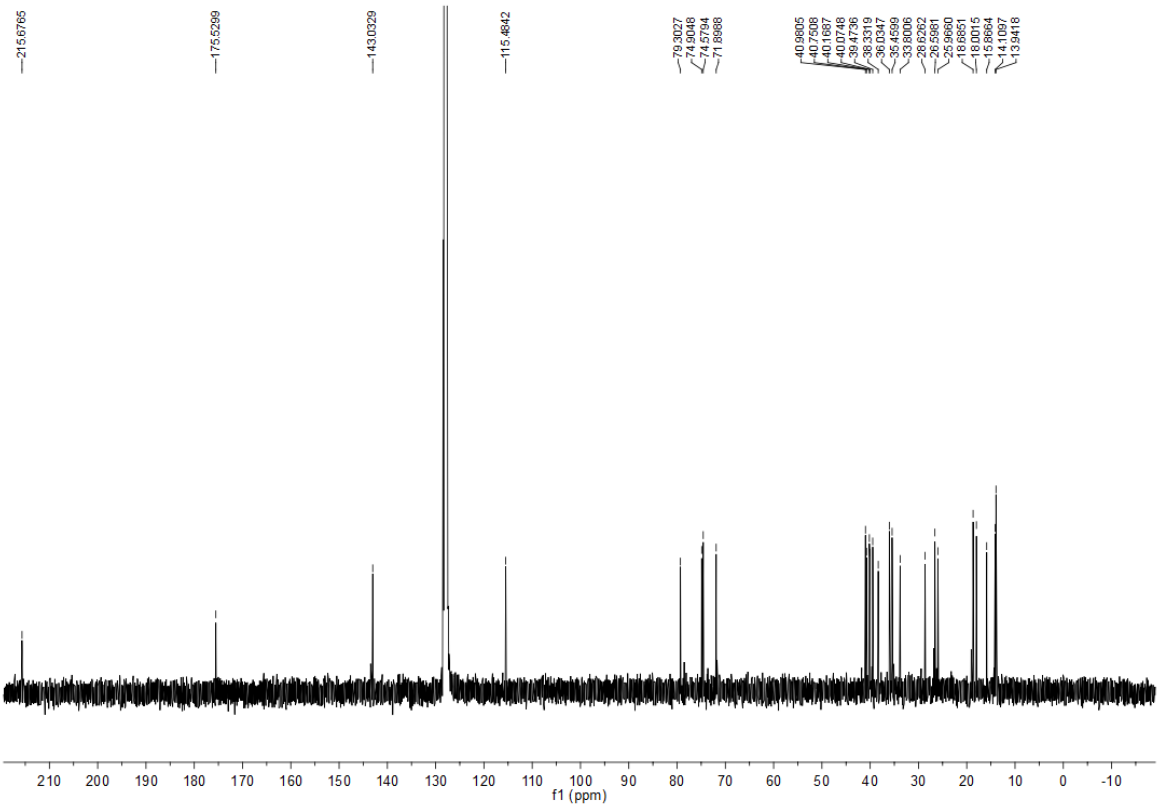
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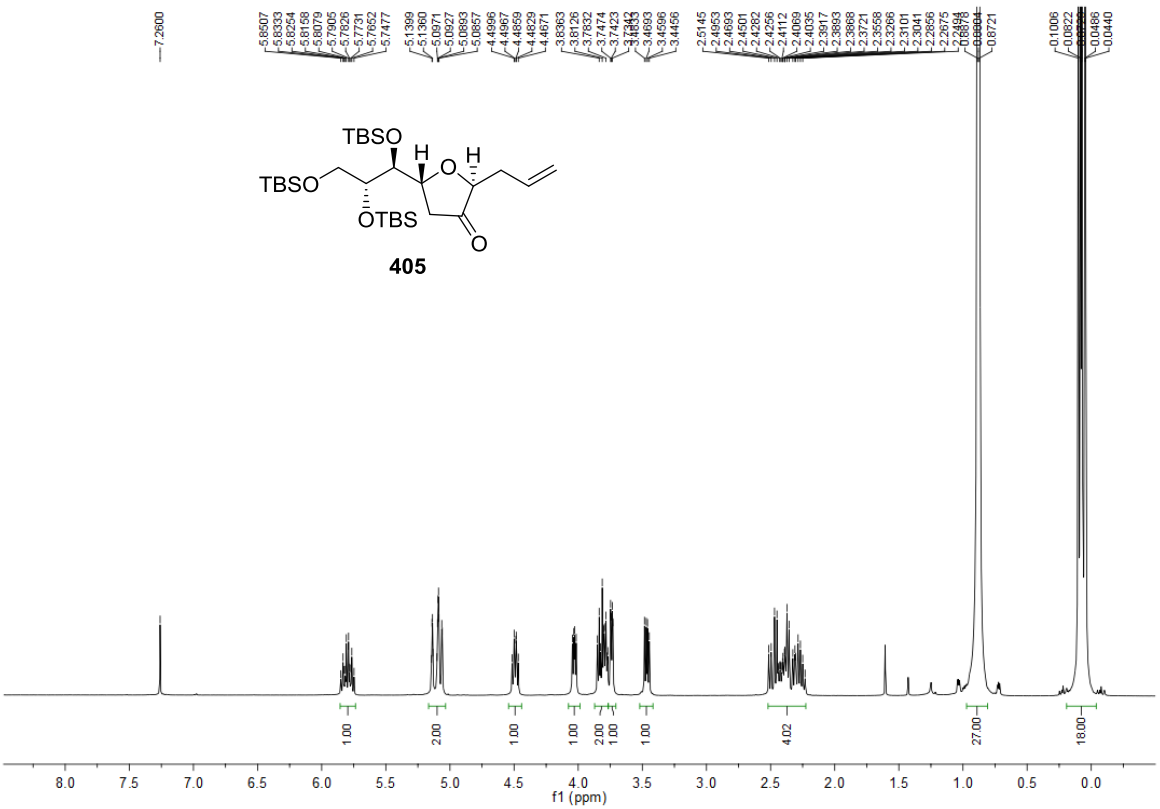
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O
H
TBSO
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O
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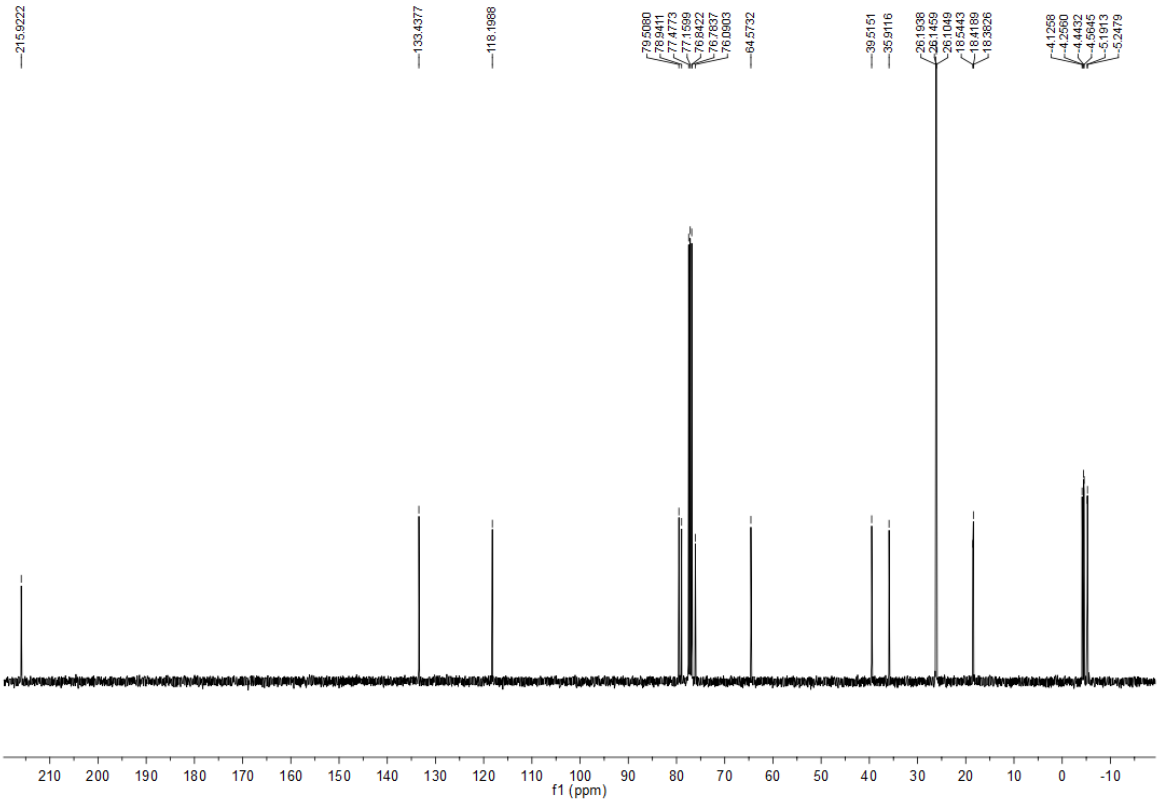
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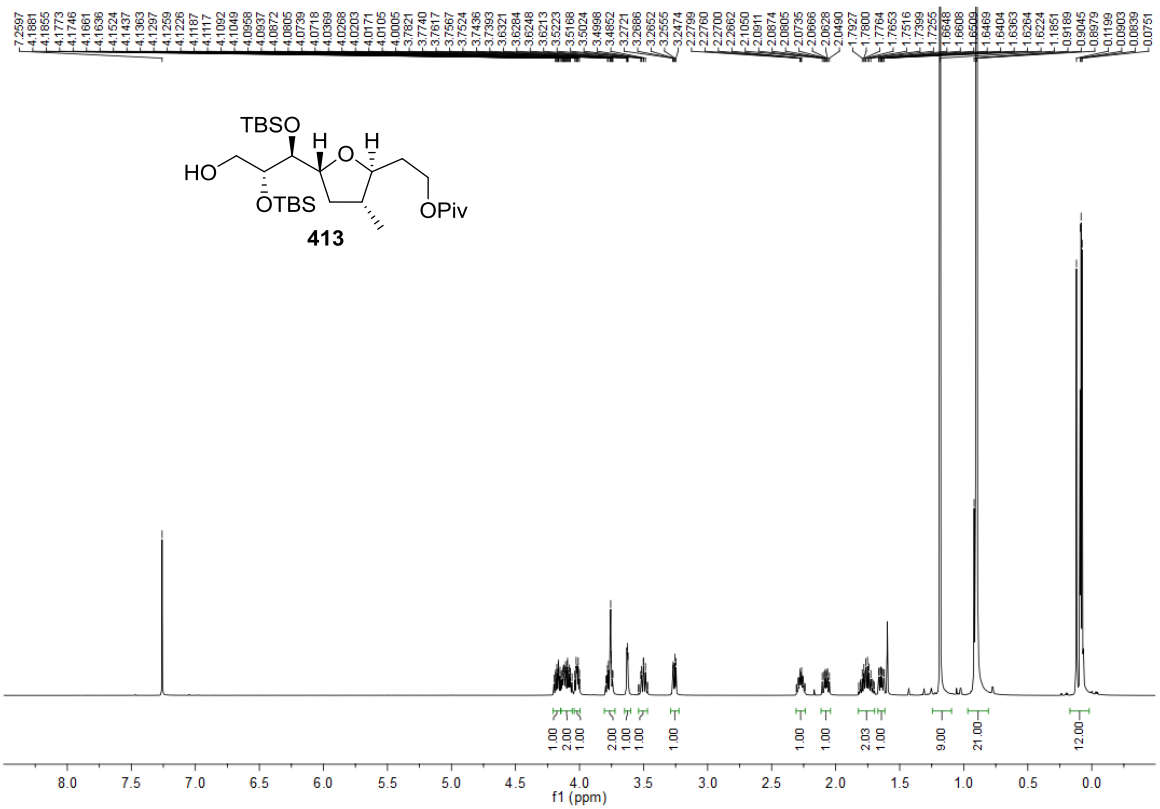
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O
H
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OPiv
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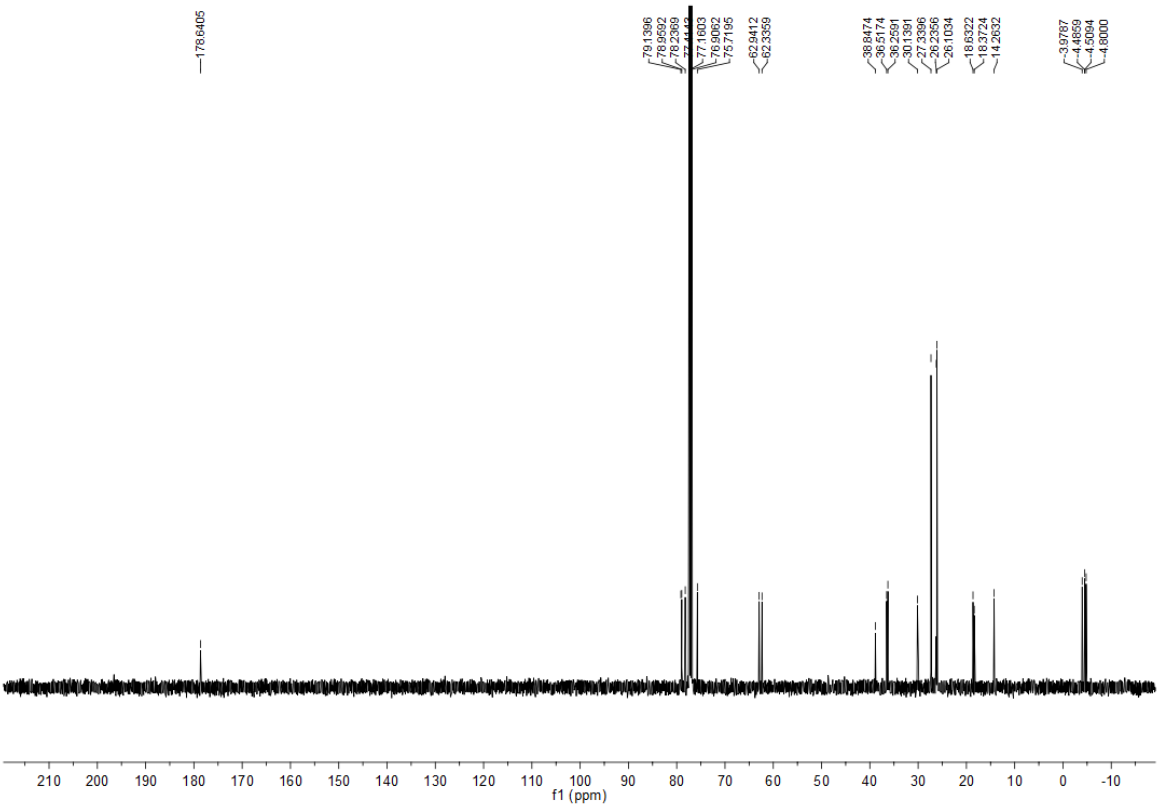
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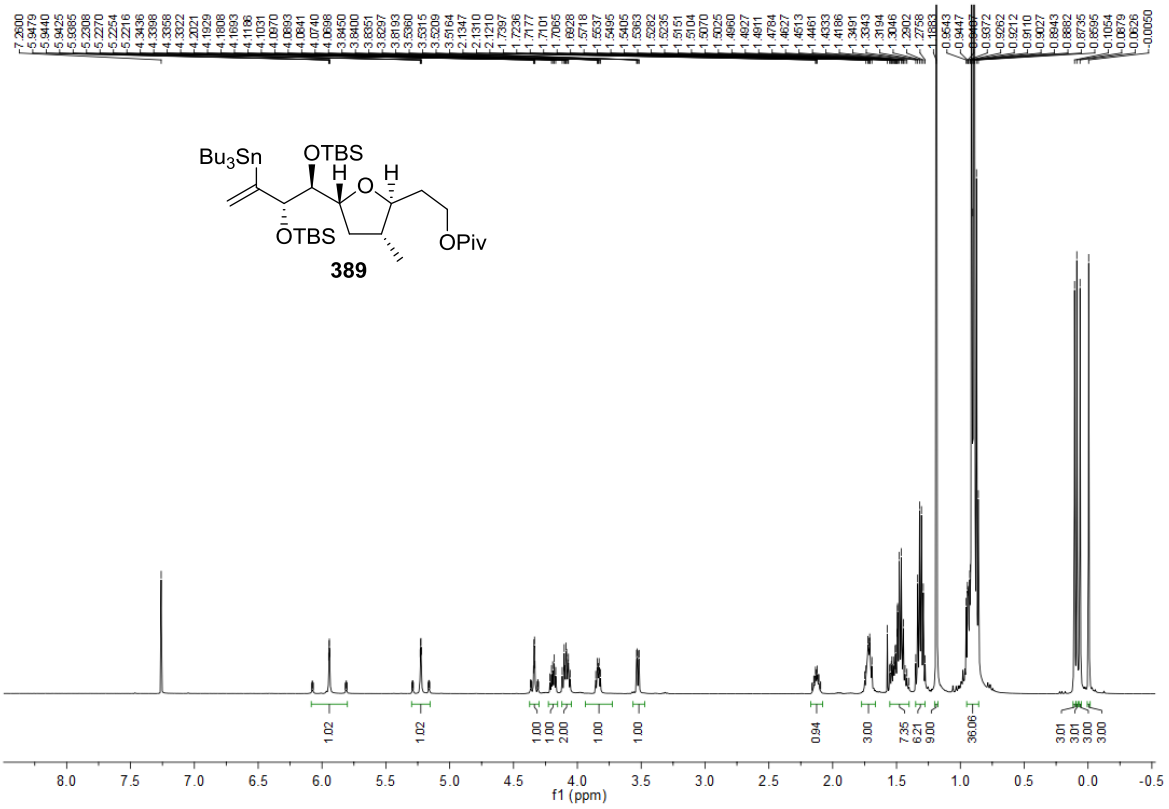
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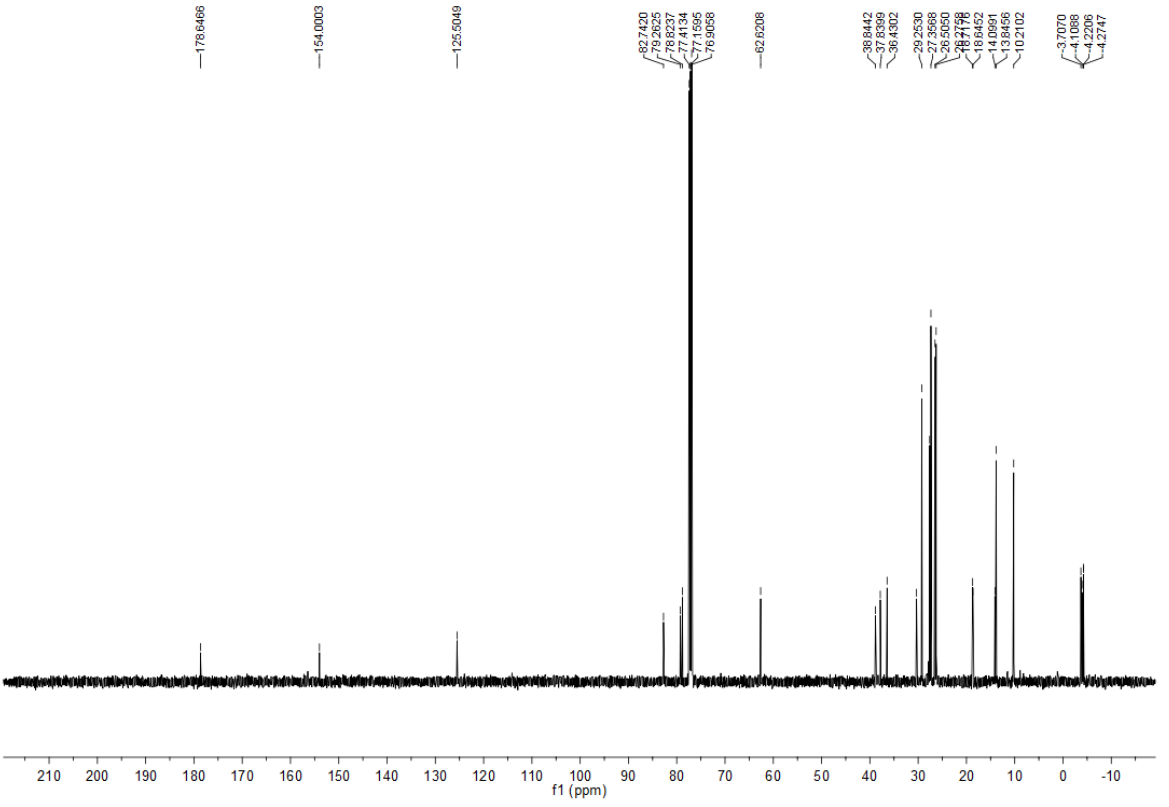
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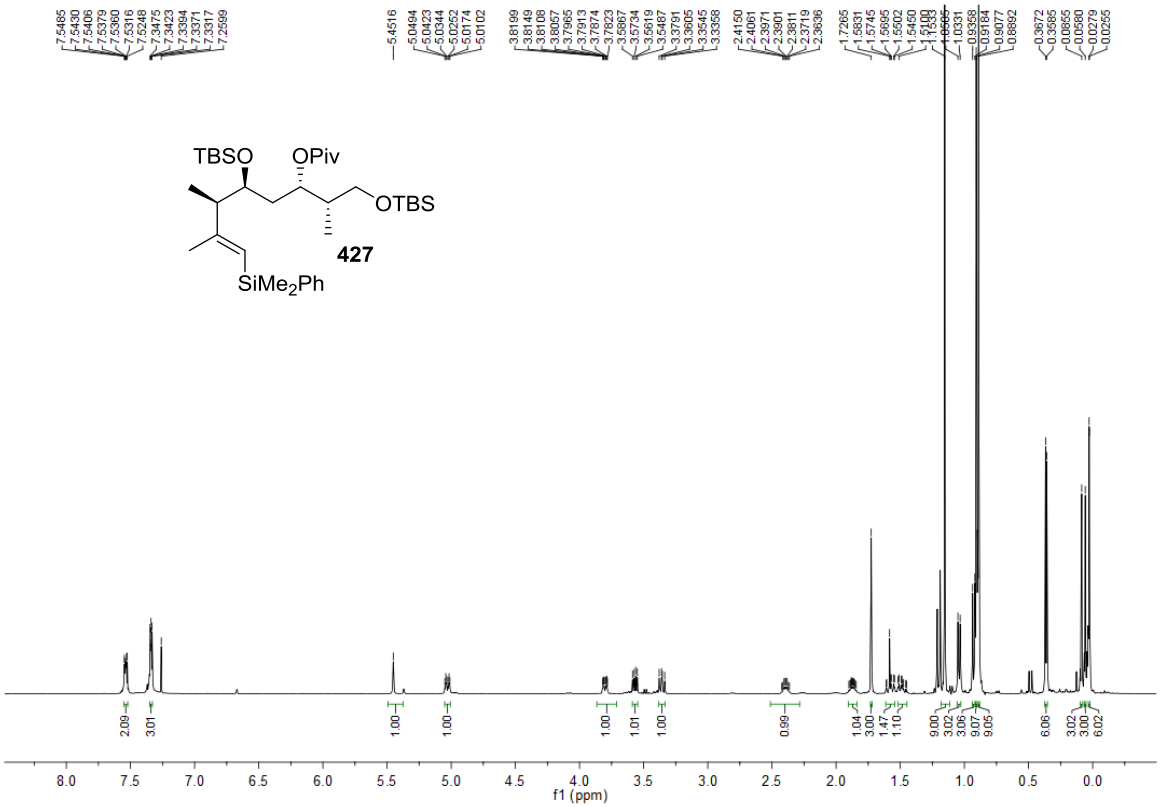
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OPiv
OTBS
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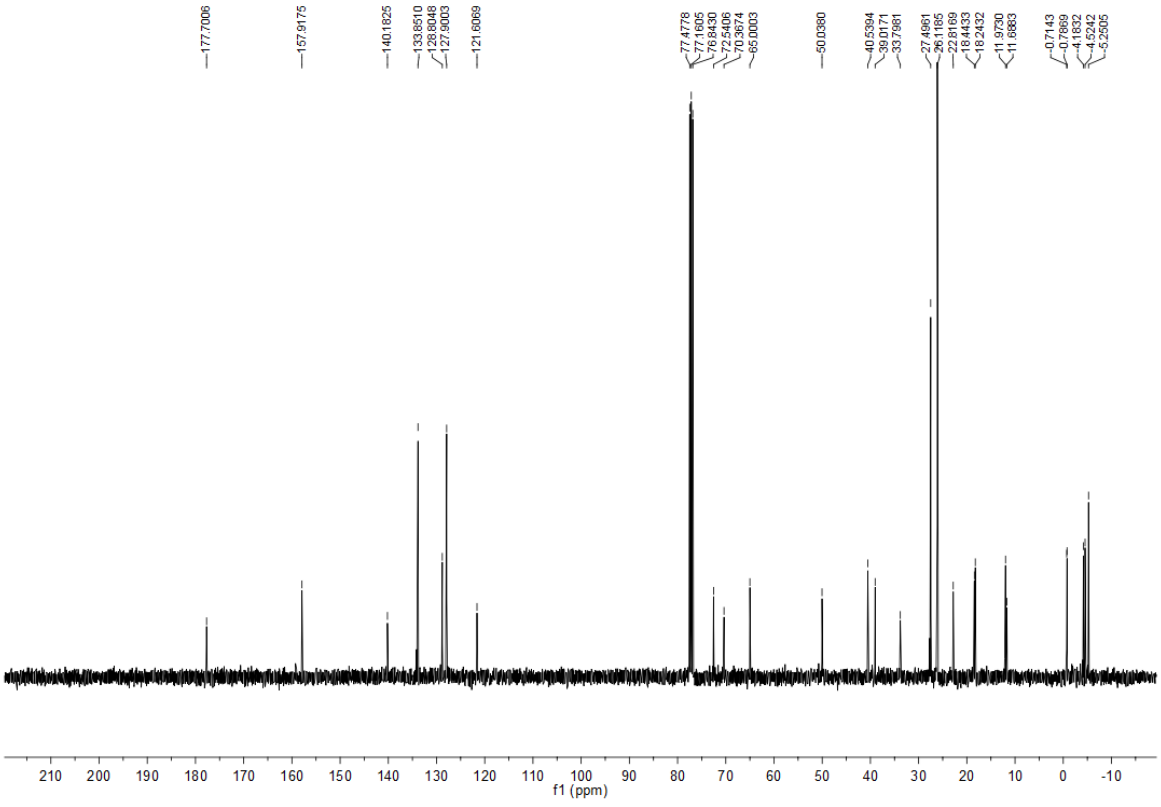
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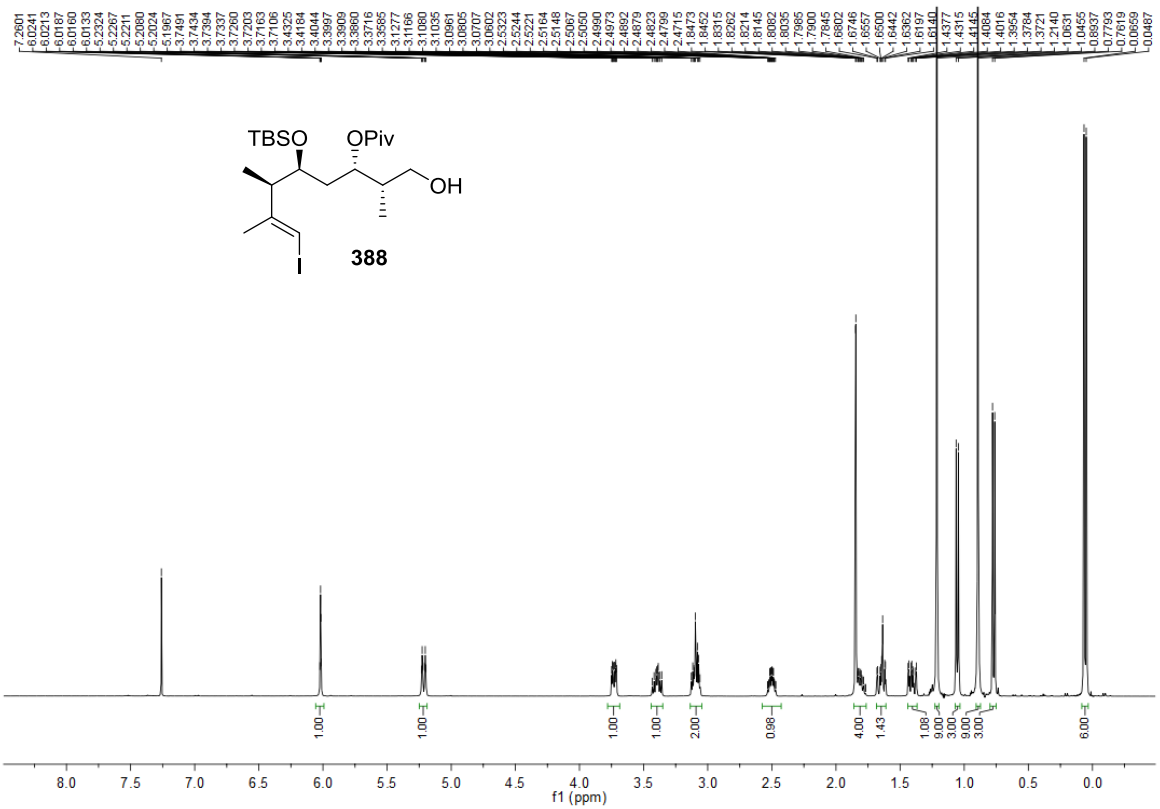
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OPiv
OH
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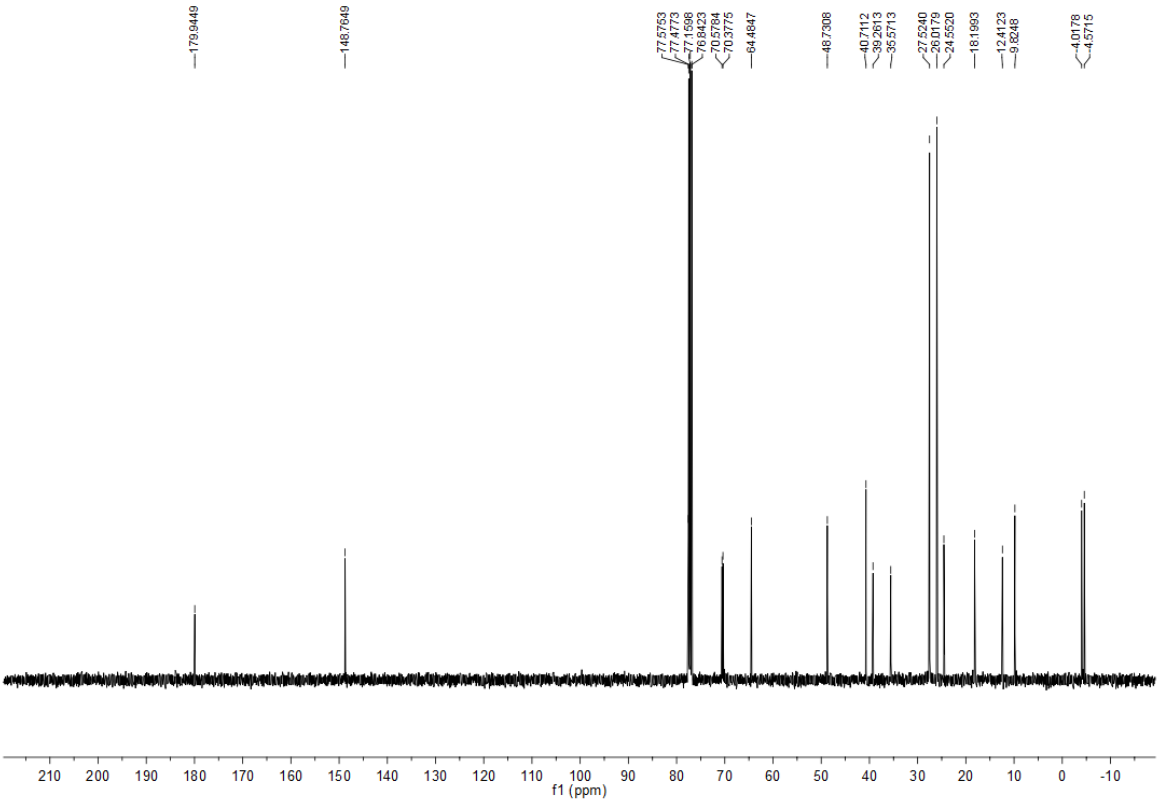
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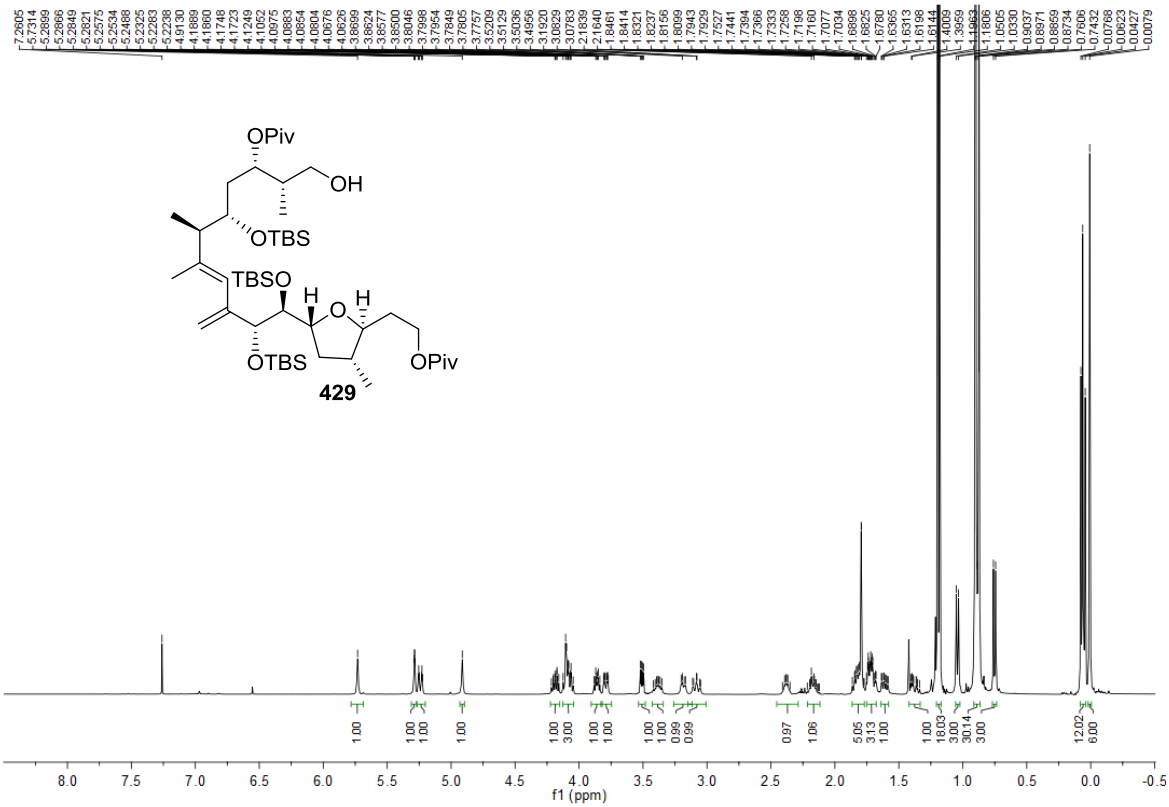
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H
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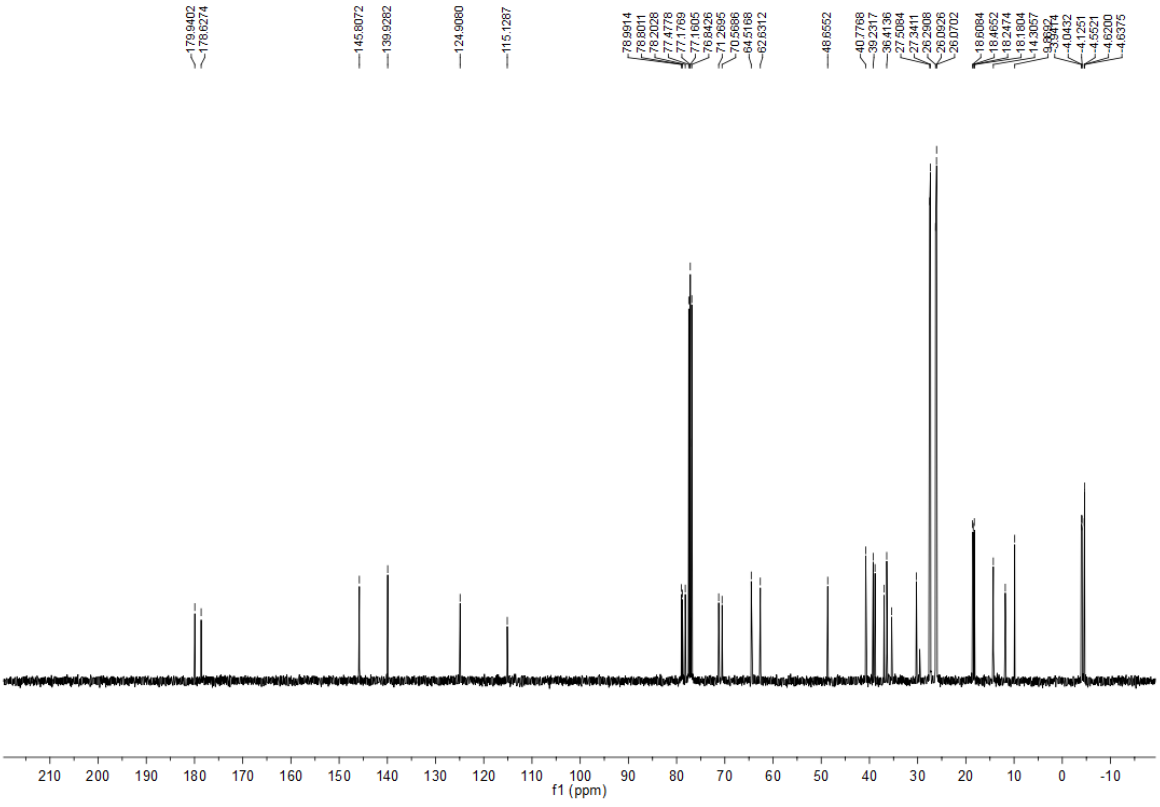
OPiv
429
f1 (ppm)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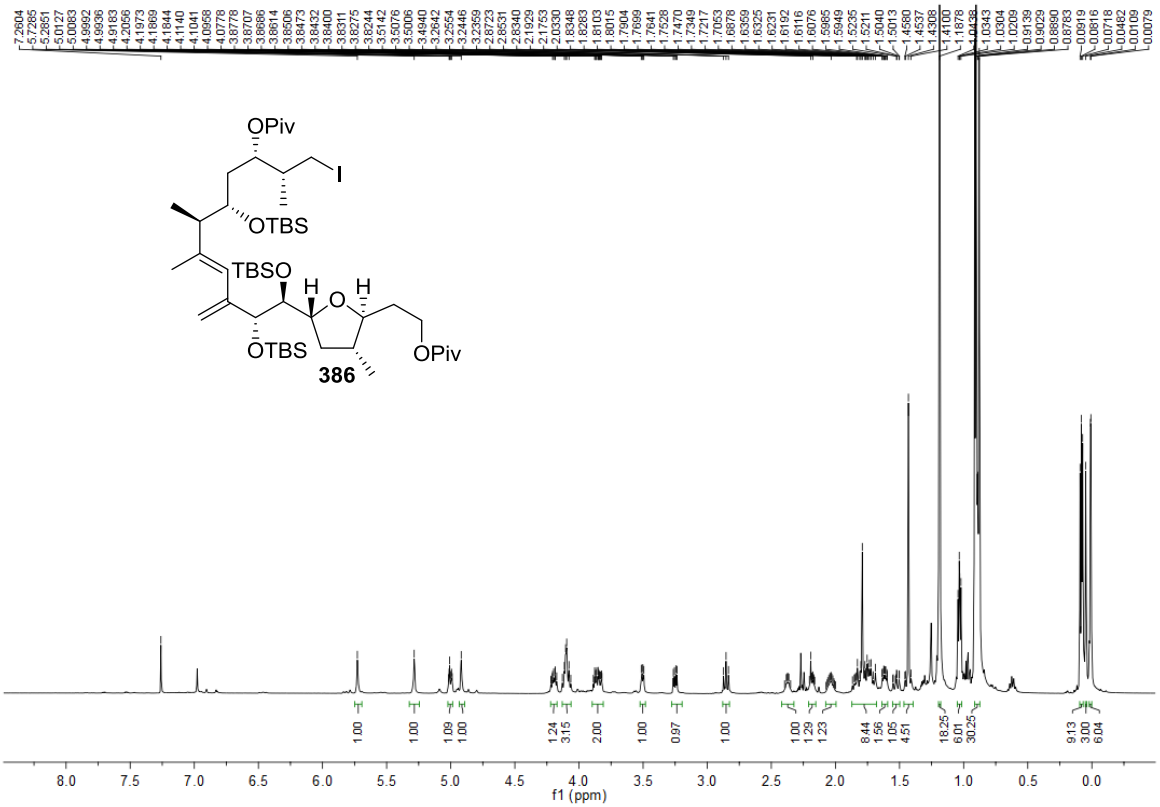
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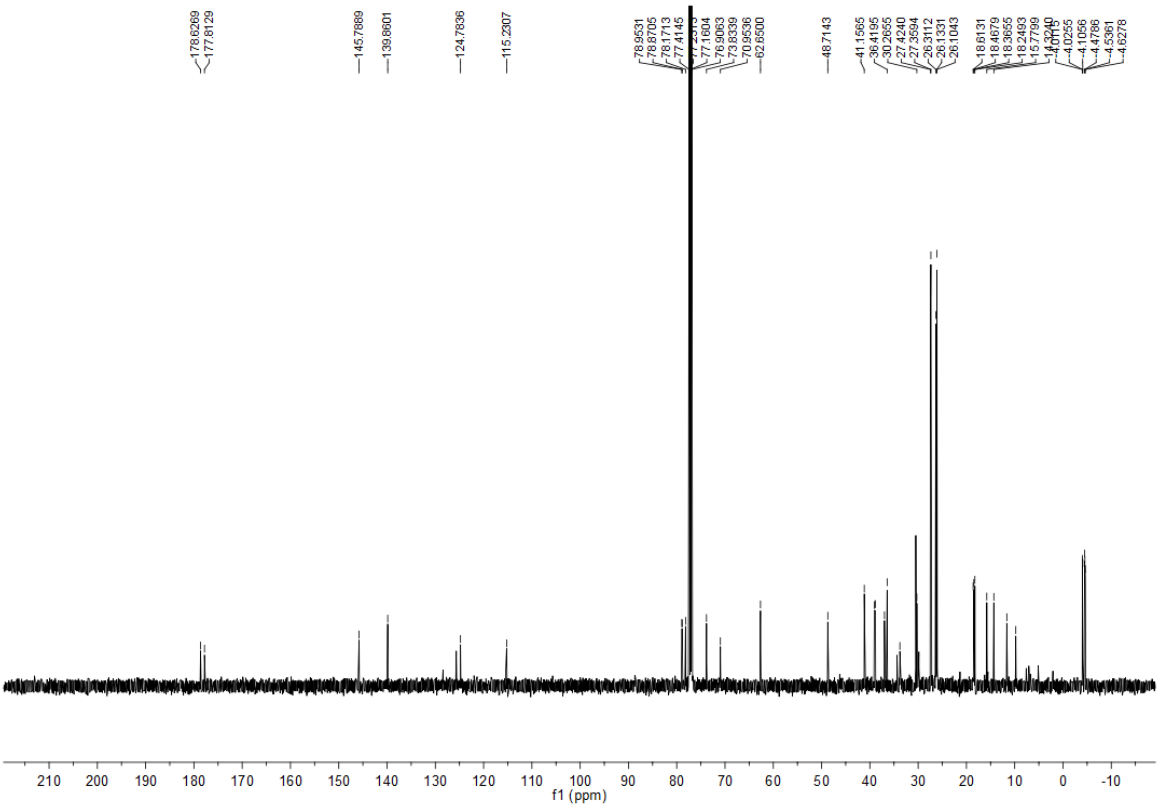
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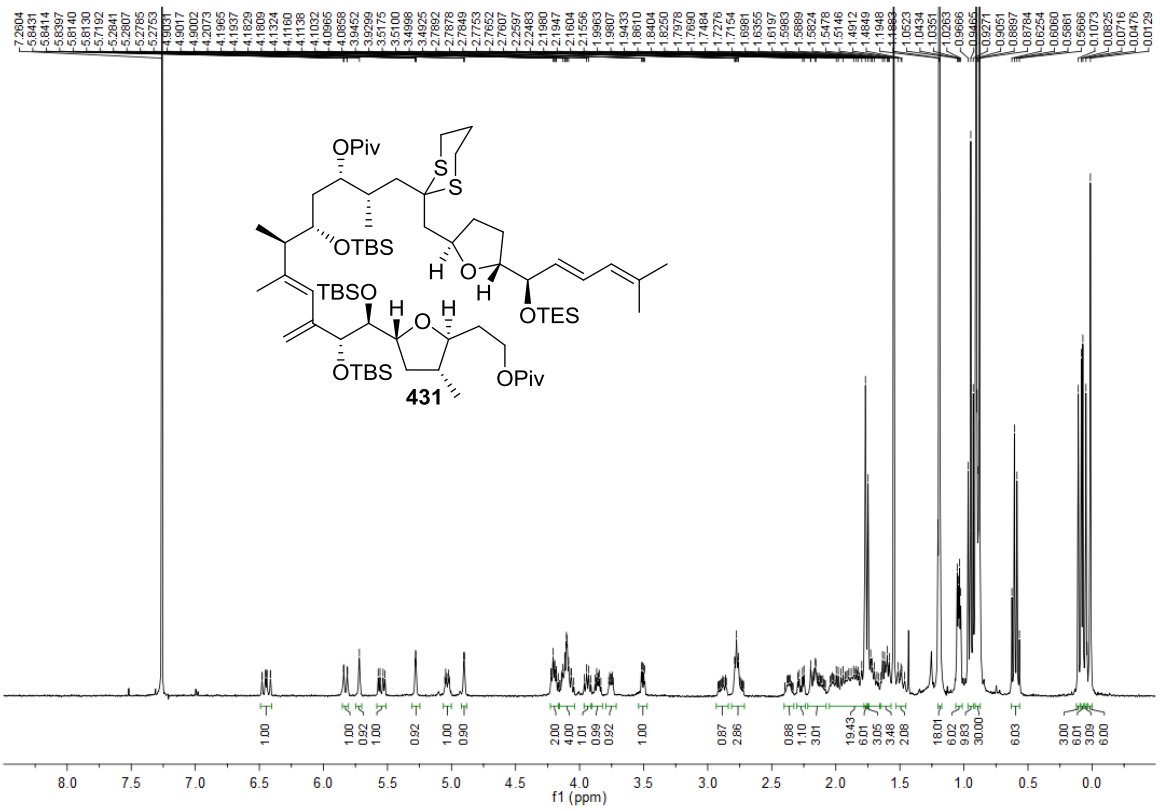
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OPiv
431
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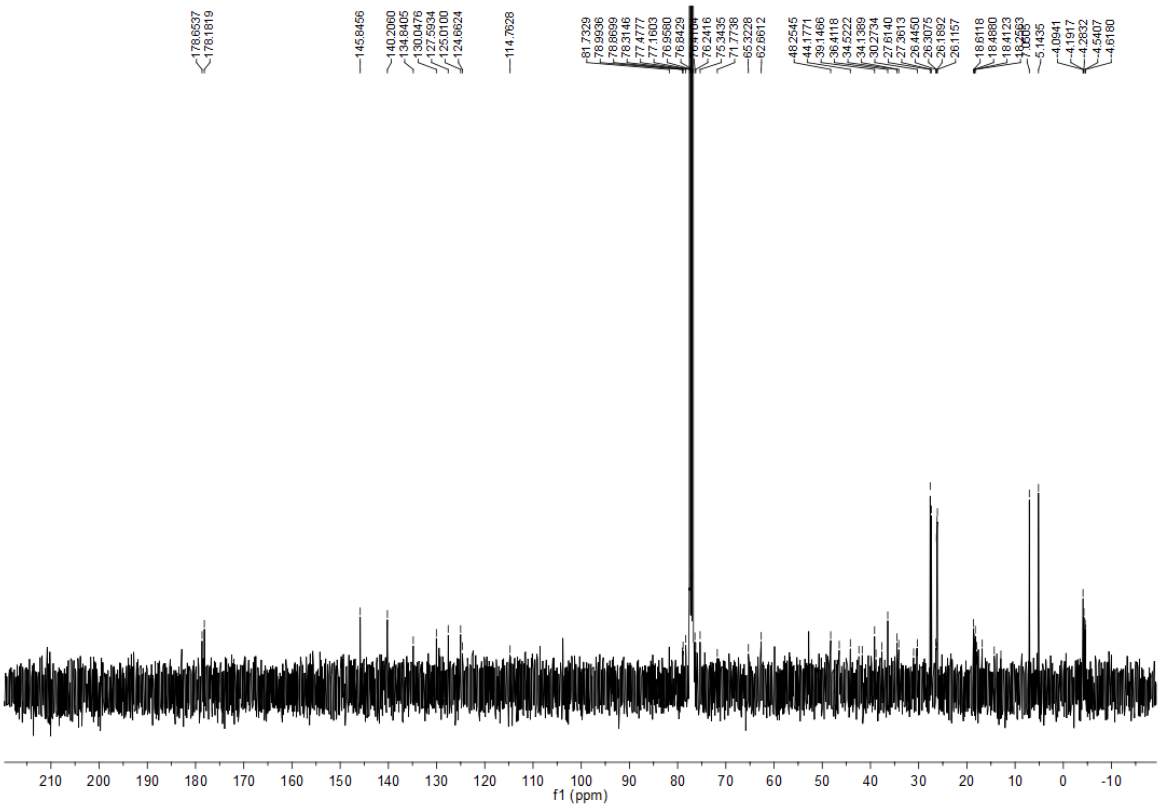
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Angewandte Communications

Natural Products

DOI: 10.1002/anie.201305467

Total Syntheses of Amphidinolides T1, T3, and T4**

J. Stephen Clark and Filippo Romiti*

The amphidinolides are macrolides isolated from marine dinoflagellates of the genus *Amphidinium sp.*, which are symbionts found on acoel flatworms of the *Amphiscolops* species.[1] More than 30 amphidinolides have been isolated and most of them display cytotoxic activities.[1,2] Some of the amphidinolides possess other biological activities, but insufficient quantities of material are available to fully establish their therapeutic potential in most cases.

The amphidinolide T subgroup comprises five compounds (T1–T5), which exhibit cytotoxic activities against L1210 murine lymphoma cells and KB human epidermoid carcinoma cells.[1c] These compounds, first isolated and characterized by the Kobayashi group,[3] are 19-membered lactones possessing seven or eight stereogenic centers, an exocyclic alkene, an α-hydroxy ketone motif, and a trisubstituted tetrahydrofuran (Figure 1). Amphidinolides of the T series

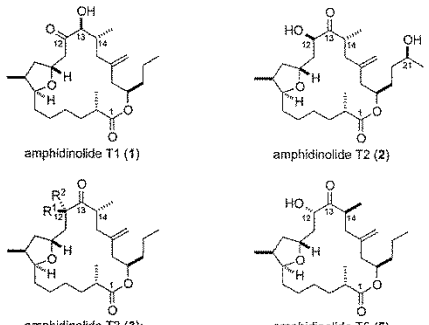


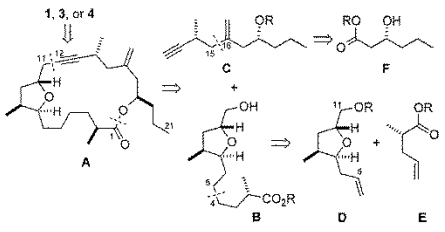
Figure 1. Amphidinolides T1–T5.

differ only in their oxygenation pattern and stereochemistry in the C12–C14 region with the exception of amphidinolide T2 (**2**), which possesses a longer, C21-hydroxylated side chain. Amphidinolide T1 (**1**) features a ketone at C12 flanked by a hydroxy group at C13. Amphidinolides T3–T5 are isomers of T1, displaying a reversal of the hydroxy ketone pattern and have diastereomeric relationships at C12 and C14.

The challenging structures and bioactivities of amphidinolides T1–T5 make them attractive synthetic targets.[2,4] Fürstner and co-workers completed the synthesis of amphidinolide T4 in 2002 and then used their elegant strategy to synthesize amphidinolides T1, T3, and T5.[5] The groups of Ghosh (T1),[6] Jamison (T1, T4),[7] Zhao (T3),[8] Yadav (T1),[9] and Dai (T1–T4)[10] have also completed syntheses of members of the family. In many of these syntheses, substituents and stereocenters in the C12–C14 region have been introduced before or during formation of the macrocycle, which has meant that the route to each member is differentiated at an early stage or that several steps are required to change oxidation states or invert stereocenters in order to access more than one natural product. The exception is the route of Dai and co-workers in which ring-closing metathesis (RCM) was used to close the macrocycle with C12–C13 bond formation and the resulting alkene was dihydroxylated.[10] In this case, however, the RCM and dihydroxylation reactions were not stereoselective and several steps were required to convert mixtures of isomeric products into each natural product.

As part of our programme concerning the synthesis of marine natural products, we became interested in synthesizing amphidinolides T1 and T3–T5 from a single macrocycle. Because of the similarities between targets **1** and **3**–**5**, we proposed that they could be accessed from the common intermediate **A**. The desired α-hydroxy ketone motif could be installed thereafter by sequential hydrosilylation of the alkyne, epoxidation of the resulting vinyl silane, and Fleming–Tamao oxidation[11] (Scheme 1).

Disconnection of the intermediate **A** through the lactone C–O bond and the C11–C12 bond gave the western and eastern fragments **B** and **C**, respectively (Scheme 1). Fragment **B** could be prepared from the alkene **E**[5] and the *trans*



Scheme 1. Retrosynthetic analysis of amphidinolides T1, T3, and T4.

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Homepage: http://www.chem.gla.ac.uk/staff/stephenc/

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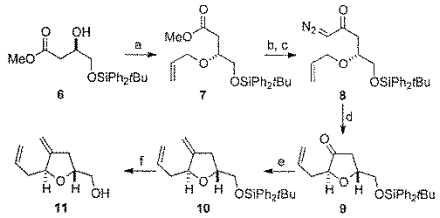
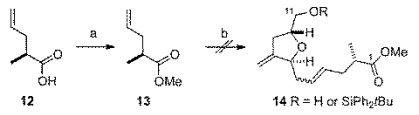
2,5-disubstituted dihydrofuranone **D**, which should be readily accessible by rearrangement of an oxonium ylide or a metal-bound ylide equivalent generated from a metal carbenoid.[12] Fragment **C** could be synthesized from protected β-hydroxy ester **F** (Scheme 1).

The tetrahydrofuran-containing fragment **11** was prepared from the commercially available alcohol **6**, which can be obtained from dimethyl D-malate in two steps (Scheme 2).[13] The alcohol **6** was converted into the corresponding allyl ether **7** under acidic conditions. Sequential ester saponification, activation of the acid as a mixed anhydride, and treatment with diazomethane afforded the α-diazo ketone **8**. Treatment of **8** with $[Cu(acac)_2]$ in THF at reflux delivered the required trans dihydrofuranone **9** in 91% yield with excellent diastereocontrol (d.r. ≥ 98:2).[12d,f,i–k] Ketone methylenation gave the diene **10** and subsequent cleavage of the silyl ether provided the alcohol **11**.



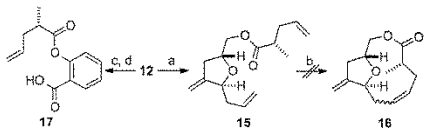
Scheme 2. a) $CH_2CHCH_2OC(NH)CCl_3$, CF_3SO_3H, petroleum ether, RT, 87%; b) KOH, MeOH, RT, 83%; c) $iBuO_2CCl$, Et_3N, Et_2O, RT, then CH_2N_2, 88%; d) $[Cu(acac)_2]$ (10 mol%), THF, reflux, 91%; e) $[Ph_3PCH_3]^+Br^-$, $tBuOK$, THF, RT; f) nBu_4NF, THF, RT, 99% over two steps. acac = acetylacetonate.

Assembly of the C1–C11 fragment by cross-metathesis (CM) of the dienes **10** or **11** with the alkene **13** was attempted (Scheme 3). The carboxylic acid **12**, which can be accessed by using Evans' methodology[14,15] and has been prepared by us and others,[5,12i] was methylated to give ester **13**. Unfortunately, it was not possible to effect cross-metathesis of dienes **10** or **11** with the alkene **13** to give **14**, a finding that contrasts with the outcome of the cross-metathesis reaction of closely related substrates.[6]



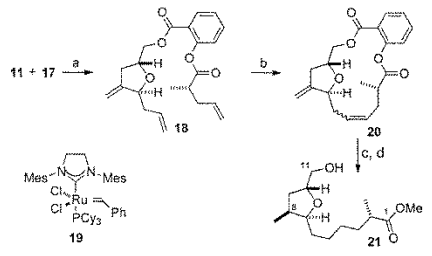
Scheme 3. a) Me_3SiCHN_2, Et_2O, MeOH, 0 °C, 61%; b) CM with **10** or **11**.

To avoid using cross-metathesis, we decided to couple the acid **12** to the alcohol **11** to give the ester **15** and then perform RCM (Scheme 4). However, attempted formation of the 11-membered lactone **16** by RCM of the diene **15** failed.[16] In order to circumvent this problem, the use of a salicylate spacer group to facilitate RCM was explored.



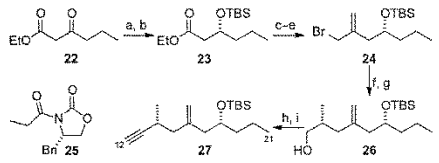
Scheme 4. a) **11**, EDC, DMAP, CH_2Cl_2, RT, 85%; b) RCM; c) EDC, DMAP, salicylaldehyde, CH_2Cl_2, RT; d) $NaClO_2$, $NaH_2PO_4 \cdot 2H_2O$, 2-methyl-2-butene, $tBuOH/H_2O$, RT, 76% over two steps. EDC = *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride.

Esterification of carboxylic acid **12** with salicylaldehyde and subsequent oxidation of the aldehyde gave carboxylic acid **17** (Scheme 4). Coupling of the alcohol **11** to acid **17** proceeded under Mitsunobu conditions[17] and delivered triene **18** (Scheme 5). The RCM reaction of **18**, promoted by catalyst **19**, afforded an inconsequential isomeric mixture (E/Z = 1.2:1) of the lactone **20**.[18] Base-mediated excision of the spacer group and directed hydrogenation of the resulting diene provided the complete western (C1–C11) fragment **21** as a single diastereomer with the required configuration at C8.[19]



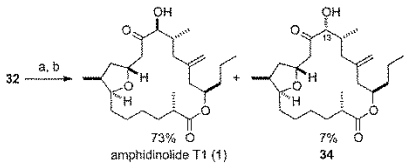
Scheme 5. a) Ph_3P, DIAD, THF, 0 °C → RT, 99%; b) **19** (12 mol%), CH_2Cl_2, reflux, 96% (E/Z = 1.2:1); c) KOH, MeOH, RT; d) $[Ir(cod)(PCy_3)(py)]PF_6$, H_2, CH_2Cl_2, RT, 85% over two steps. DIAD = diisopropyl azodicarboxylate.

Synthesis of the eastern fragment commenced with asymmetric reduction[20] of ethyl 3-oxohexanoate (**22**) and protection of the resulting alcohol to give **23** (Scheme 6). Treatment of the ester **23** with an excess of the organocerium reagent prepared from trimethylsilylmethylmagnesium chloride resulted in double Grignard addition.[21,22] Base-mediated Peterson elimination of the intermediate tertiary alcohol delivered an allylic silane, which was then converted into the bromide **24** by treatment with pyrrolidone hydrotribromide (PHT).[23] Deprotonation of *N*-propionyloxazolidinone (**25**) with NaHMDS and enolate alkylation with bromide **24** followed by reductive cleavage of the oxazolidinone auxiliary provided alcohol **26**.[24] Oxidation of the alcohol **26** and conversion of the resulting aldehyde into the corresponding



Scheme 6. a) [{(*R*)-Tol-BINAP}RuCl$_2$], H_2 (5 bar), EtOH, 95 °C, 97% (98% *ee*); b) TBSCl, imidazole, DMF, 0 °C → RT, 98%; c) $CeCl_3$, Me_3SiCH_2MgCl, THF, −78 °C → RT; d) NaHMDS, THF, 0 °C, 93% over two steps; e) PHT, pyridine, THF, −10 °C → RT, 96%; f) **25**, NaHMDS, −78 °C, THF, then **24**, nBu_4NI, −30 °C, 60% (76% brsm), d.r. = 15:1; g) $LiBH_4$, H_2O, Et_2O, 0 °C, 99%; h) DMP, CH_2Cl_2, RT; i) dimethyl 1-diazo-2-oxopropylphosphonate, K_2CO_3, THF/MeOH, 0 °C → RT, 82% over two steps. TBS = *tert*-butyldimethylsilyl; NaHMDS = sodium hexamethyldisilazide; PHT = pyrrolidone hydrotribromide; DMP = Dess–Martin periodinane.

using [Cp*Ru(CH$_3$CN)$_3$]PF$_6$ delivered a separable mixture (1:1) of the isomeric *Z*-vinylsilanes **32** and **33** in a combined yield of 89% (Scheme 7).[28,29] Pleasingly, treatment of **32** with *m*-CPBA resulted in selective epoxidation of the vinylic silane, rather than the exocyclic alkene (Scheme 8). Fleming–Tamao oxidation[11] of the resulting silyl-substituted epoxide

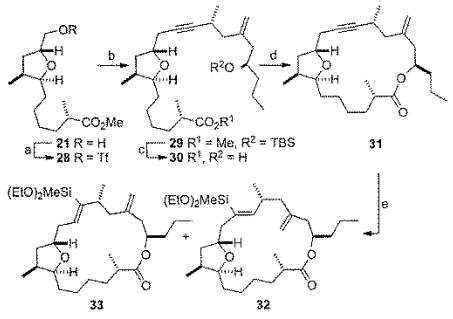


Scheme 8. a) *m*-CPBA, CH_2Cl_2, 0 °C; b) KHF_2, $KHCO_3$, 30% H_2O_2, THF, MeOH, RT. *m*-CPBA = 3-Cl$C_6H_4CO_3H$.

alkyne using the Ohira–Bestmann reagent[25] afforded the eastern (C12–C21) fragment **27**.

Coupling of the eastern and western fragments was accomplished by conversion of the alcohol **21** into the triflate **28** and subsequent displacement of triflate by the alkynyl lithium species generated by deprotonation of fragment **27** (Scheme 7). The coupled product **29** was obtained in 68% yield and competitive addition of the alkynyl lithium intermediate to the ester was not observed. The seco acid **30**, which was required for lactonization, was produced in a one-pot fashion by ester cleavage using potassium trimethylsilanolate[26] and quenching the reaction with concentrated HCl. Macrolactonization of **30** under Yamaguchi conditions[27] gave the common late-stage intermediate **31**, corresponding to **A** in our retrosynthetic analysis (Scheme 1).

Following the preparation of lactone **31**, installation of the various oxygenation patterns found in amphidinolides T1, T3, and T4 was explored. Catalytic hydrosilylation of the alkyne

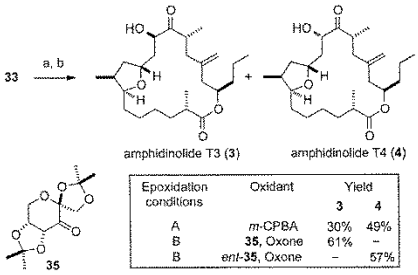


Scheme 7. a) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; b) **27**, *n*BuLi, HMPA, Et_2O, −78 °C, 68% over two steps; c) Me_3SiOK, THF, RT, then conc. HCl, 86%; d) 2,4,6-$Cl_3PhCOCl$, iPr_2NEt, toluene, RT, then DMAP, 45 °C, 80%; e) [Cp*Ru(MeCN)$_3$]PF$_6$, $(EtO)_2MeSiH$, CH_2Cl_2, 0 °C → RT, 44% of **32** and 45% of **33**. Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl; Tf = SO_2CF_3. HMPA = hexamethylphosphoramide.

afforded amphidinolide T1 in 73% yield over two steps, along with a minor product, the data for which are consistent with 13-*epi*-amphidinolide T1 (**34**). Spectroscopic and other data for synthetic **1** are identical to those reported for amphidinolide T1.[3a]

Treatment of **33** under the same conditions as **32** delivered amphidinolides T4 (**4**) and T3 (**3**) as a separable mixture (d.r. = 1.6:1) of diastereomers in 79% yield (Scheme 9). Spectroscopic and other data for synthetic **3** and **4** are identical to those reported in the literature.[3b,5]

The efficiency of the route to **3** and **4** could be improved by increasing the diastereoselectivity of the epoxidation reaction. Epoxidation of the vinylic silane **33** under Shi conditions,[30,31] employing the D-fructose-derived ketone **35**, followed by Fleming–Tamao oxidation afforded amphidinolide T3 in 61% yield over two steps (Scheme 9). Furthermore, when the vinylic silane **33** was subjected to the same conditions, but using the L-fructose-derived ketone *ent*-**35** to perform epoxidation, amphidinolide T4 was formed in 57% yield over two steps. In each case, a high degree of reagent control was observed and the other diastereomer was not obtained. Amphidinolide T4 can be epimerized at C14 to give



Epoxidation conditions	Oxidant	Yield 3	Yield 4
A	*m*-CPBA	30%	49%
B	**35**, Oxone	61%	–
B	*ent*-**35**, Oxone	–	57%

Scheme 9. a) Epoxidation conditions A: oxidant, CH_2Cl_2, 0 °C; conditions B: oxidant, $Na_2B_4O_7{\cdot}10H_2O$, nBu_4NHSO_4, $KHCO_3$, Na_2EDTA, H_2O, MeCN, DMM, 0 °C; b) KHF_2, $KHCO_3$, 30% H_2O_2, THF, MeOH, RT.

amphidinolide T5,[3c] so a formal synthesis of this natural product has also been achieved.

In conclusion, efficient and high-yielding synthetic routes to members of the amphidinolide T family of natural products via a single late-stage intermediate (**31**) have been established. The syntheses of amphidinolides T1, T3, and T4 were completed in 17 steps from the alcohol **6**. The macrolactone **31** was prepared from **6** in 14 steps and 21.6% yield; the overall yields of amphidinolides T1, T3, and T4 were 6.9%, 5.9%, and 5.5%, respectively. The key tetrahydrofuran unit was assembled by rearrangement of an oxonium ylide, or its metal-bound equivalent, generated from a copper carbenoid, further demonstrating the utility of this methodology for the synthesis of complex natural products.[12f,j–k,32]

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Keywords: diazo ketone · natural products · oxidation · rearrangement · total synthesis

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Cascade Reactions

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Synthesis of Cyclopropyl-Substituted Furans by Brønsted Acid Promoted Cascade Reactions**

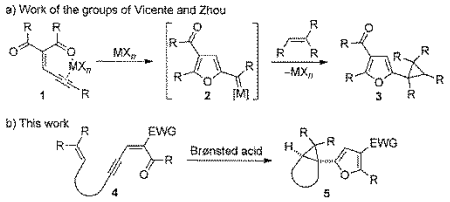
J. Stephen Clark, Filippo Romiti, Kirsten F. Hogg, Malai Haniti S. A. Hamid, Sven C. Richter, Alistair Boyer, Joanna C. Redman, and Louis J. Farrugia*

Abstract: *Chloroacetic acid promotes an efficient and diastereoselective intramolecular cascade reaction of electron-deficient ynenones to deliver products featuring a 2,3,5-trisubstituted furan bearing a fused cyclopropyl substituent at the 5-position. Synthetically relevant polycyclic building blocks featuring rings of various sizes and heteroatoms have been synthesized in high yield using this mild acid-catalyzed reaction.*

Furans occur frequently as subunits of natural products,[1] bioactive compounds,[2] and functional materials,[3] and they are also valuable synthetic building blocks that can be transformed into many other functional groups.[4] The importance of furans has led to the development of a wide range of methods for their synthesis.[5] In addition to traditional methods,[6] the metal-mediated synthesis of furans using copper,[7] zinc,[8] palladium,[9] and gold[10] catalysts has become popular. A few organocatalytic processes for the synthesis of furans have also been described,[11] including the tetrahydrothiophene-catalyzed synthesis of highly substituted furfuryl alcohols and amines developed by our group recently.[12]

Cyclopropanes, despite their ring strain, are found in many natural products including terpenes, pheromones, pyrethroid insecticides, fatty acid metabolites, and unusual amino acids.[13] The cyclopropane group is also prevalent in pharmaceuticals and features in members of the fluoroquinolone family of antibiotics, the antidepressant tranylcypromine,[14] antipsychotic substances,[15] and anti-HIV agents.[16] In medicinal chemistry, a cyclopropane is often used as a bioisostere of an alkene because of its superior metabolic stability.[17] The significant strain present in cyclopropanes makes them challenging to synthesize and they are usually prepared from highly reactive species such as carbenoids, free carbenes,[18] and ylides.[19]

The groups of Vicente[8b] and Zhu[10a] recently reported two methods for the synthesis of cyclopropyl furans **3** in which the metal carbenoid **2** is produced directly from an ynenedione **1** (Scheme 1 a). On the basis of these reports and results



Scheme 1. Cyclopropyl-substituted furan synthesis from carbonyl-conjugated enynes.

of earlier studies concerning the acid-promoted synthesis of furans from ynenones,[20] we postulated that treatment of the electron-deficient enyne **4** with a Brønsted acid would trigger an intramolecular cascade reaction to produce a highly functionalized cyclopropylfuran **5** (Scheme 1 b).

The initial experiment in our study involved reaction of the ynenedione **6a** with a stoichiometric amount of benzoic acid in CH_2Cl_2 at reflux (Table 1, entry 1). Under these conditions, starting material was converted into the furan-containing tetracyclic ketone **7a** (single diastereoisomer)[21] in 72 h. Several carboxylic acids were screened and it was found that chloroacetic acid ($pK_a = 2.9$) is optimal (entry 3) and weaker acids, such as acetic ($pK_a = 4.8$) or benzoic acid ($pK_a = 4.2$), deliver reduced reaction rates (entries 1 and 2). 1,1,1,3,3,3-Hexafluoro-2-propanol ($pK_a \approx 11$) is also sufficiently acidic to promote the transformation, but it took five days for complete reaction of ynenedione **6a** (entry 4). The use of trifluoroacetic acid ($pK_a = 0.2$) resulted in the formation of the highly unsaturated by-product **8** instead of the product **7a** (entry 5).

The reaction can be performed in CH_2Cl_2 or toluene (entries 3 and 7, Table 1). Furthermore, a substoichiometric amount of acid can be employed to promote the transformation without a significant decrease in reaction rate (entries 8 and 9). However, the reaction rate drops substan-

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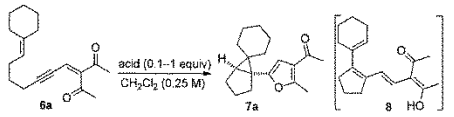
Table 1: Summary of optimization studies.



Entry	Acid	Loading [equiv]	Solvent	Temperature	Time [h][a]
1	$PhCO_2H$	1.0	CH_2Cl_2	reflux	72
2	$MeCO_2H$	1.0	CH_2Cl_2	reflux	72
3	$ClCH_2CO_2H$	1.0	CH_2Cl_2	reflux	20
4	$(CF_3)_2CHOH$	1.0	CH_2Cl_2	reflux	120
5	CF_3CO_2H	1.0	CH_2Cl_2	reflux	–[b]
6	$ClCH_2CO_2H$	1.0	THF	40 °C	–[c]
7	$ClCH_2CO_2H$	1.0	PhMe	40 °C	20
8	$ClCH_2CO_2H$	0.5	CH_2Cl_2	reflux	24
9	$ClCH_2CO_2H$	0.25	CH_2Cl_2	reflux	24
10	$ClCH_2CO_2H$	0.1	CH_2Cl_2	reflux	–[d]
11	–	–	CH_2Cl_2	reflux	–[e]

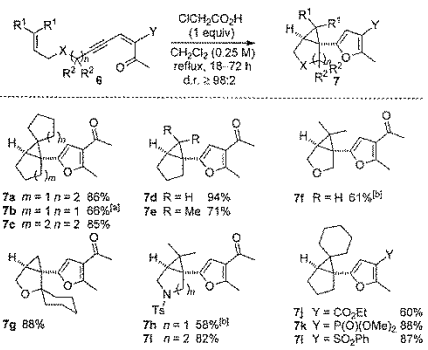
[a] Time taken to reach 100% conversion as determined by ^1H NMR analysis. [b] The substrate **6a** was consumed after 20 h but only product **8** observed. [c] The substrate **6a** decomposed. [d] Conversion of 33% was observed when the reaction was stopped after 48 h. [e] No reaction observed after 72 h.

tially when the amount of acid is reduced to 0.1 equivalents (entry 10). Finally, the crucial role played by the acid is clear because there is no reaction in its absence (entry 11).

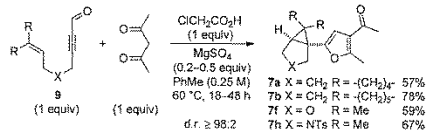
Optimization experiments showed that the reaction is robust and so the scope was expanded to the preparation of a range of furans bearing a cyclopropyl substituent at the 5-position (Scheme 2). Various substituents on the pendent alkene tethered to the electron-deficient enyne substrate were tolerated. For example, cyclopentylidene and cyclohexylidene substrates underwent cyclization to give the novel spirocyclic products **7a–c** and **7j–l**; the structures of the products **7a** and **7c** were confirmed by single-crystal X-ray analysis.[21] The tether length between the alkene functionality and the electron-deficient enyne was varied to deliver cyclopropanes fused to five- or six-membered rings. The formation of polycyclic products incorporating oxygen or nitrogen was also shown to be possible and the synthetically relevant 3-oxa- and 3-aza-bicyclo[*n*.1.0]alkane derivatives **7f–i** were obtained in good yields. These products are particularly valuable because the bicyclo[*n*.1.0]alkane motif is present in several natural products and other bioactive compounds.[22] The reaction was also performed on substrates in which one of the carbonyl groups of the diketone was replaced with an alternative electron-withdrawing substituent. When the ketone was replaced with an ester, a phosphonate, or a sulfone group, the reaction afforded the corresponding cyclopropyl furans **7j–l** with good to excellent yields. The ynenediones **6f** and **6h** underwent spontaneous partial cyclization to deliver the desired cyclopropyl furans **7f** and **7h** immediately after Knoevenagel condensation. Furthermore, the ynenedione **6b** underwent partial cyclization to give the desired furan **7b** during purification, even though formation of the cyclopropyl furan **7b** was not observed immediately following Knoevenagel condensation.

The substrates **6** were accessed by Knoevenagel condensation reactions of a 2-alkynal **9**. As a consequence of the instability of some substrates and the ability of Brønsted acids to catalyze the Knoevenagel condensation reaction, we investigated the viability of performing condensation and cyclization in one pot. Pleasingly, when a mixture of the 2-alkynal **9**, acetylacetone, chloroacetic acid, and $MgSO_4$ in toluene was heated at 60 °C for 18 h, the cyclopropyl furans **7a**, **7b**, **7f**, and **7h** were obtained in good yield (Scheme 3).

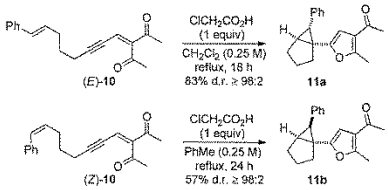
The influence of the alkene geometry on the outcome of the reaction was explored using substrates (*E*)-**10** and (*Z*)-**10** (Scheme 4). When a mixture of the substrate (*E*)-**10** and chloroacetic acid was heated at reflux in CH_2Cl_2 for 18–48 h,



Scheme 2. Scope of the reaction. [a] Yield calculated over two steps because of cyclization of the substrate **6b** on silica gel. [b] Yield calculated over three steps because of the spontaneous cyclization of substrates **6f** and **6h**.



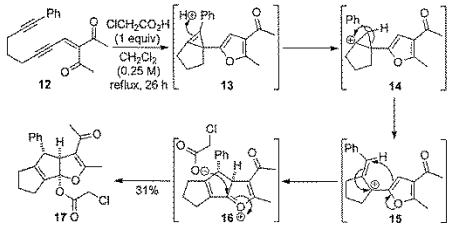
Scheme 3. One-pot synthesis of cyclopropyl furans **7a**, **7b**, **7f**, and **7h**.



Scheme 4. Influence of the alkene geometry on the stereochemical outcome of the cascade reaction.

the cyclopropane **11a** was obtained in 83% yield as a single diastereoisomer. The reaction of the isomeric compound (*Z*)-**10** under the same conditions was much slower; incomplete conversion (76%) into furan **11b** was observed after 7 days.[23] However, when a mixture of the ynenedione (*Z*)-**10** and chloroacetic acid was heated in toluene at reflux for 24 h there was complete consumption of starting material and the product **11b** was obtained in 57% yield as a single diastereoisomer.[24] The configuration of the alkene has a dramatic influence on the rate of the reaction and, more importantly, is translated directly into the stereochemistry of product. Thus, either diastereomer of the tricyclic compound **11** can be obtained simply by choosing the substrate with appropriate alkene configuration.

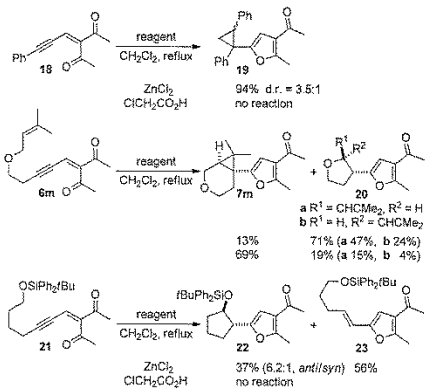
Expansion of the reaction scope to include substrates bearing a pendant alkyne was also investigated. Treatment of the substrate **12** with a stoichiometric amount of chloroacetic acid in CH_2Cl_2 at reflux for 26 h afforded the tricyclic acetal **17** in 31% yield, the structure of which was confirmed by single-crystal X-ray analysis (Scheme 5).[21] The reaction is believed to proceed by generation of the cyclopropene **13** followed by protonation to give the cation **14** and then ring opening to give the stabilized cation **15**. Subsequent thermal conrotatory Nazarov-type ring closure of **15** affords oxocarbenium ion **16**, which is trapped by the carboxylate to give the tricyclic acetal **17**.



Scheme 5. Synthesis of tricyclic acetal **17**.

Our results pose interesting questions with regard to the reaction mechanism. One potential mechanism would involve nucleophilic attack of the pendent alkene onto an activated form of the ynenone to generate a cationic center followed by closure of the three-membered ring. However, results of the reactions presented in Scheme 4 show that cyclopropane C–C bond formation cannot occur in a stepwise fashion through an intermediate benzylic carbocation, because alkene configuration is translated into product stereochemistry. The fact that the highest yields are obtained for the reactions of **6d** and **6g** to give the furans **7d** and **7g** also rules out a cationic intermediate because it would be primary and therefore very unstable.

An intriguing possibility is the involvement of a free carbene during the acid-catalyzed process. To clarify matters, a series of experiments was performed in which the Brønsted acid and Lewis acid catalyzed reactions were compared



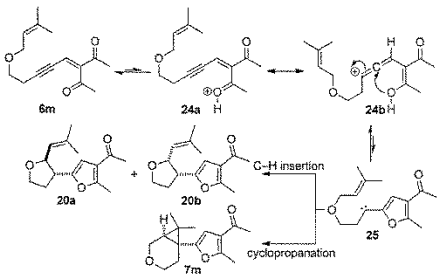
Scheme 6. Comparison of reactions mediated by zinc(II) chloride and those catalyzed by chloroacetic acid.

(Scheme 6). In the first set of experiments, the Lewis acid catalyzed reaction was performed with intermolecular trapping of the intermediate carbenoid with styrene, as reported by Vicente and co-workers,[8] and results compared to those of the corresponding acid-catalyzed process. Exposure of the substrate **18** to zinc(II) chloride in the presence of styrene afforded the cyclopropane **19** as expected. In contrast, the acid-catalyzed reaction failed to deliver the cyclopropane **19** and starting material was recovered.

In the second set of experiments, the substrate **6m** was treated with zinc(II) chloride to give a mixture of the expected cyclopropane **7m** along with the diastereomeric tetrahydrofurans **20a** and **20b** resulting from an unprecedented intramolecular C–H insertion reaction of the putative zinc carbenoid (Scheme 6). The corresponding acid-mediated reaction delivered all three products, but the cyclopropane **7m** was now the major product.

In the final set of experiments, the reactions of the substrate **21** were investigated (Scheme 6). The zinc-catalyzed reaction afforded a diastereomeric mixture (6.2:1, *anti*:*syn*) of the cyclopentane **22**, arising from intramolecular C–H insertion of the putative zinc carbenoid at the position adjacent to the silyl ether, along with the *E* alkene **23** produced by elimination of the presumed carbenoid intermediate. In contrast, the acid-catalyzed reaction afforded neither of these products and starting material was recovered.

Results from the experiments shown in Scheme 4 and Scheme 6 suggest that the acid-catalyzed reaction proceeds via a free carbene that can undergo competitive intramolecular cyclopropanation and C–H insertion with allylic ethers such as **6m**, but does not participate in intermolecular cyclopropanation reactions or intramolecular C–H insertion reactions with less reactive substrates. The proposed reaction mechanism accounting for the formation of **7m** and **20a/b** is shown in Scheme 7. Protonation of one of the carbonyl groups of **6m** results in the formation of **24a** which, when considered as resonance form **24b**, can undergo cyclization by intra-



Scheme 7. Proposed mechanism for the acid-catalyzed reaction of **6m**.

molecular nucleophilic attack of the allenic carbon by the enol to give carbene **25**. Carbene **25** then reacts with the alkene or undergoes allylic C–H insertion to give the products **7m** and **20a/b**. The fact that intermolecular cyclopropanation and intramolecular C–H insertion reactions of less activated substrates are disfavored suggests that cyclization to give the furan and carbene is reversible in the absence of a reactive group that can trap the carbene and that a low concentration of the carbene intermediate is generated from the protonated substrate.

In summary, a high-yielding and highly stereoselective Brønsted acid catalyzed synthesis of trisubstituted furans bearing a ring-fused cyclopropyl substituent has been developed in which three bonds are created in a single step. Data suggest that the reaction proceeds by an unusual mechanism in which a free carbene is generated under acidic conditions. Studies are underway to expand this method, confirm the reaction mechanism, and apply it to the synthesis of bioactive targets.

Keywords: cascade reactions · cyclopropanes · enynes · furans · polycyclic compounds

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[21] Structures of compounds **7a** (CCDC 1043529), **7c** (CCDC 1043528), and **17** (CCDC 1043527) were confirmed by X-ray crystallography. Data have been lodged with the Cambridge Crystallographic Data Centre (CCDC). Details can be found in the Supporting Information and data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[23] See the Supporting Information for further details.

[24] The relative stereochemistry of products **11a** and **11b** was assigned by comparison of the coupling constants between the cyclopropyl protons in the ^{1}H NMR spectrum of each compound. Values of $J = 4.7$ Hz (**11a**) and $J = 8.4$ Hz (**11b**) were obtained, which are similar to those reported for related fused cyclopropanes. For examples, see: H. E. Zimmerman, L. C. Roberts, R. Arnold, *J. Org. Chem.* **1977**, *42*, 621–629.

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