Towards the Total Synthesis of Amphidinolides C and F

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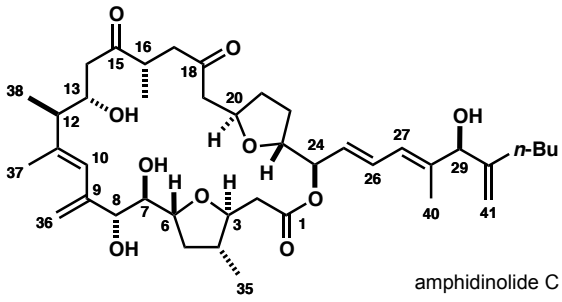
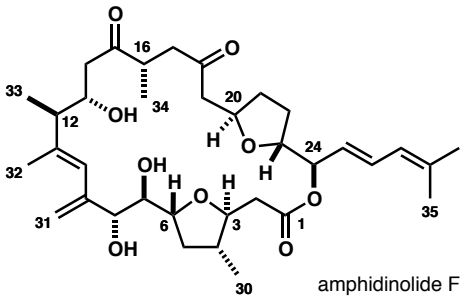
Abstract

The amphidinolides are marine macrolides extracted from dinoflagellates of the genus *Amphidinium*. To date, 37 amphidinolides have been isolated and identified, most of them possessing cytotoxicity against human cancer cell lines. Among these, amphidinolides C, F, C2 and C3 represent synthetic targets of interest owing to their scarcity, structural complexity and promising biological activities.



amphidinolide C



amphidinolide F

This thesis describes the work realised towards the total synthesis of amphidinolides C and F, with a focus on the different strategies investigated and the key fragments synthesised.

In the first approach, the C18−C29 fragment of amphidinolide F was prepared using an intramolecular etherification of an epoxide under acidic catalysis to produce the 2,5-*trans*-disubstituted tetrahydrofuran ring featured in the natural product. Unfortunately, dithiane alkylation with the C1−C17 iodide counterpart generated the desired coupling product in low yield. A second approach proposing to build the C17−C18 bond by a silicon-tethered RCM proved unsuccessful, because the requisite diene could not be obtained. It was then envisioned to form the C18−C19 bond by displacement of a triflate with an alkyne and install the ketone at C18 by a protoborylation/oxidation sequence. To this end, the C19−C29 triflate precursor was synthesised. Displeasingly, the C1−C18 alkyne counterpart (work by Dr Filippo Romiti) could not be prepared and coupling of the two fragments was not attempted. In the latest approach, the C10−C29 fragment of amphidinolide F was obtained employing a boron-mediated aldol condensation and a dithiane alkylation to form the C13−C14 and C18−C19 bonds. Several end-game strategies were examined including the successful Yamaguchi esterification of the C13-*epi* C10−C29 fragment and the C1−C9 acid. A challenging Stille cross-coupling was then effected to close the macrocycle but only yielded the desired macrolactone in trace amounts after global desilylation.

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.

Ludovic Decultot

Prof J. Stephen Clark

Acknowledgements

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The most significant acknowledgment of all is left for my parents, Laura and Jean-François, for their unconditional love and unwavering support, for believing in me and for being the models a son can look up to.

Abbreviations

ABSA	acetamidobenzenesulfonyl azide
acac	acetylacetonate
AIBN	azobisisobutyronitrile
Bz	benzoate
CBS	Corey-Bakshi-Shibata
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cp^*	1,2,3,4,5-pentamethylcyclopentadienyl
CSA	camphorsulfonic acid
CuTC	copper(I) thiophene-2-carboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DET	diethyl tartrate
$(DHQD)_2PHAL$	*bis*(dihydroquinidino)phtalazine
DIAD	diisopropyl azodicarboxylate
DIPT	diisopropyl tartrate
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N*,*N*'-dimethylpropylene urea
DMSO	dimethyl sulfoxide
dppf	1,1'-*bis*(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
EE	ethoxyethyl
equiv.	equivalent
FDA	U.S. Food and Drug Administration
Grubbs II	Grubbs second-generation catalyst
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide

HOMO	highest occupied molecular orbital
HWE	Horner-Wadsworth-Emmons
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
imid. (Im)	imidazole
Ipc	isopinocampheyl
IR	infrared
L	ligand
LA	Lewis acid
LDA	lithium diisopropylamide
L-Selectride	lithium tri-*sec*-butylborohydride
LUMO	lowest unoccupied molecular orbital
lut.	lutidine
M	metal
Mes	mesityl (2,4,6-trimethylphenyl)
MIB	morpholinoisoborneol
MOM	methoxymethyl
mp	melting point
Ms	mesyl (methanesulfonyl)
MTPA	*α*-methoxy-*α*-trifluoromethylphenylacetate
NBS	*N*-bromosuccinimide
NHK	Nozaki-Hiyama-Kishi
NMO	*N*-methylmorpholine-*N*-oxide
nmp	5,5-dimethyl-1-(4-methylpiperazin-1-yl)hexane-1,2,4-trione
Nu	nucleophile
pet.	petroleum
Piv	pivalate
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
Pyr	pyridine
quant.	quantitative
R	generalised group
RCAM	ring-closing alkyne metathesis
RCM	ring-closing metathesis
Red-Al	sodium *bis*(2-methoxyethoxy)aluminium hydride

R_f	retention factor in chromatography
RT	room temperature
SAR	structure-activity relationship
S_E	electrophilic substitution
S_N	nucleophilic substitution
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TES	triethylsilyl
tet	tetrahedral
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
TS	transition state
TSA	toluenesulfonic acid

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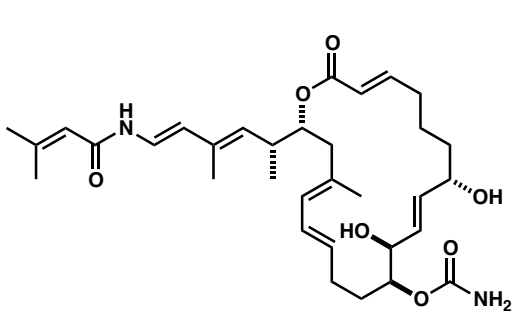
1. Introduction

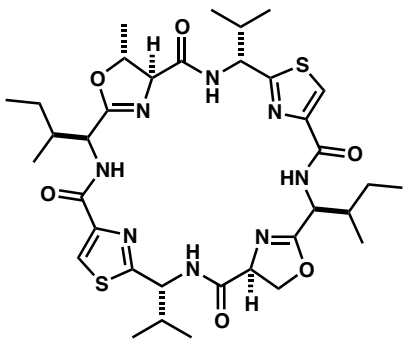
1.1. Drug Discovery from the Marine World

Natural products can be defined as substances produced by living organisms found in nature and are characterised by a high structural diversity and complexity. The latter feature means that natural products cover a wide area of biologically relevant chemical space.[1] In fact, the elaborate geometry of these molecules enables an efficient interaction with their biological targets by complementing precisely their spatial environment. In this regard, nature represents a unique source and an inspiration for drug discovery. To this day, many of the world's best selling pharmaceutical products are derived from natural products or have been inspired by them.

Even though most of the currently available treatments derived from nature are based of terrestrial natural products, the marine world has proven to be an incredibly rich source of chemical and biological diversity.[2] In this mostly unexplored environment, which represents 70% of the planet's surface and 90% of the biosphere, marine organisms produce a fascinating range of structurally elaborate and diverse secondary metabolites as protection against aggressive conditions such as elevated pressures, extreme temperatures and the absence of light, or for defense against predators (**Figure 1**). These secondary metabolites, which are not essential to the survival of the organism but provide it with an evolutionary advantage, often possess interesting biological activities and can involve unprecedented mechanisms of action.[3]



palmerolide A



patellamide A

Figure 1. Examples of Marine Secondary Metabolites

The structural diversity and novelty of marine natural products make them excellent candidates for the investigation of new bioactive molecules with a high pharmacological potential.

Nevertheless, the transition from drug discovery to a pharmaceutical product is paved with challenges. The determination of full bioactivity, elucidation of the mechanism of action, and the undertaking of preclinical and clinical studies are generally unfeasible because low yields of natural products are usually obtained from natural sources and access to the marine environment is technically difficult. This supply problem has stimulated tremendous interest in the synthesis of such compounds. To this end, a viable total synthetic approach is often necessary, to provide reasonable amounts of the bioactive molecule, as well as allowing further structure-activity relationship (SAR) studies to be conducted to identify simpler potent analogues which are easier to access by means of synthesis.[3]

A striking example is halichondrin B (**1**), a marine macrolide isolated from the sea sponge *Halichondria okadai* in Japan, which displays potent cytotoxicity (**Figure 2**)[4]. This complex product, bearing 32 stereocentres, was first synthesised by Kishi and co-workers in 1992.[5] Further to the understanding of its mechanism of action, which involves the inhibition of tubulin, SAR studies led to the more potent, more stable and structurally simpler analogue eribulin (**2**). Its mesylate form was approved by the FDA in 2010 for metastatic breast cancer under the name Halaven.

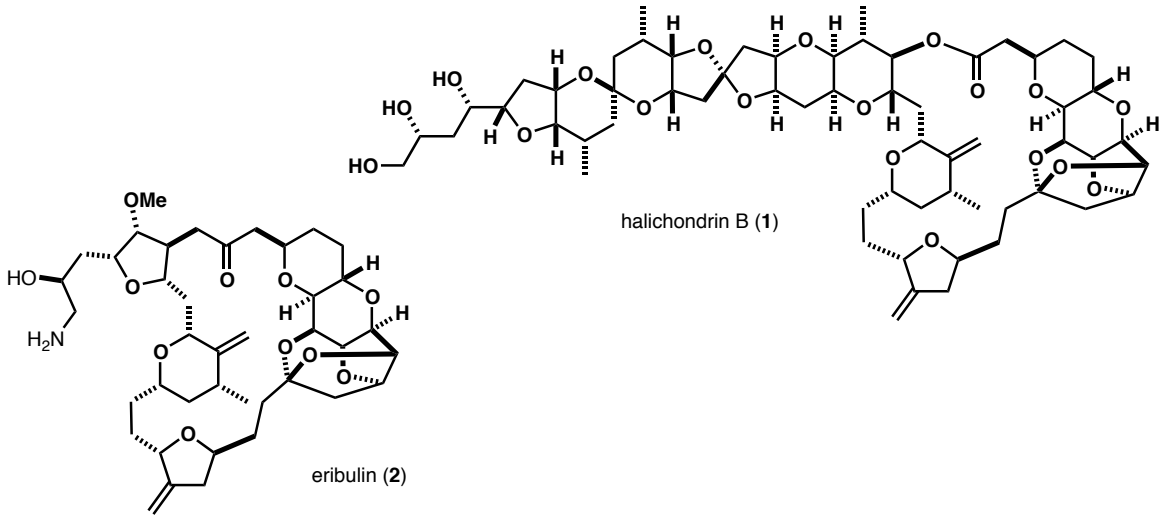
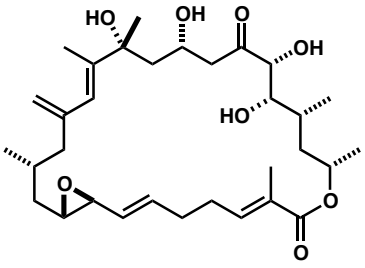


Figure 2. From Halichondrin B to Eribulin

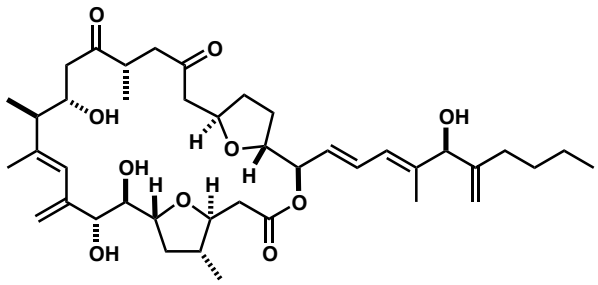
Consequently, total synthesis is one of the key activities required to provide answers to the challenges of drug discovery and to pave the way from marine natural products to pharmaceutical products used in the clinic.

1.2. The Amphidinolide Family of Natural Products

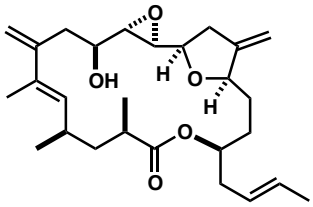
The amphidinolides are structurally complex marine macrolides extracted from dinoflagellates of the genus *Amphidinium*, endosymbionts naturally found in the inner wall cells of Okinawan acoel flatworms from the *Amphiscolops* species.[6] These microorganisms are a rich source of secondary metabolites and are also amenable to laboratory culture, which make them readily available for further studies. To date, 37 amphidinolides have been isolated and identified by Kobayashi and co-workers; most of them possess cytotoxicity against human cancer cell lines (**Figure 3**).[7]



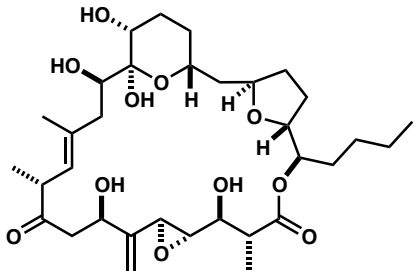
amphidinolide B_1 (**3**)



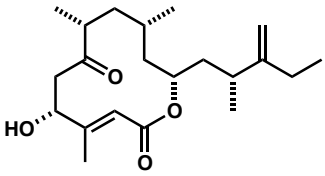
amphidinolide C (**4**)



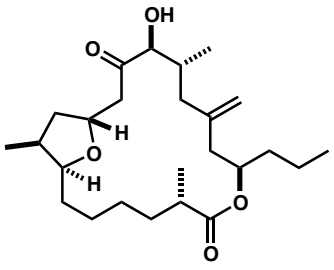
amphidinolide K



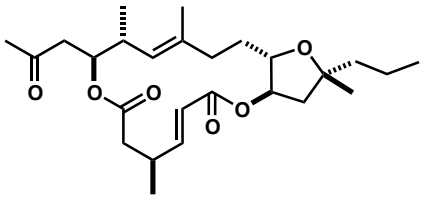
Amphidinolide N (**5**)



amphidinolide Q (**6**)



amphidinolide T1



amphidinolide X

Figure 3. Various Examples of Amphidinolides

This family of natural products is characterised by the wide structural diversity of the compounds in it, with a particular prevalence of the macrolactone compounds with ring size varying from 12 (e.g. amphidinolides Q, **6**) to 29 (e.g. amphidinolide M). However, common general features such as *exo*-methylene groups, 1,3-diene units, multiple sites of unsaturation and the inclusion of oxacycles (epoxides, tetrahydrofurans and tetrahydropyrans) within the macrocycle are evident across the entire series.

Almost all amphidinolides display encouraging levels of cytotoxic activity against two cancer cell lines: KB human epidermoid carcinoma cells and L1210 murine lymphoma cells.[8] Among those macrolides, amphidinolides B (**3**), C (**4**) and N (**5**) exhibit truly remarkable potencies (**Table 1**).

Amphidinolide	**Macrolactone Size**	**Cytotoxicity** (IC_{50}, ng/mL)	
		L1210	KB
B (**3**)	26	0.14	4.2
C (**4**)	25	5.8	4.6
N (**5**)	26	0.05	0.06

Table 1. Cytotoxicity of Amphidinolides B, C and N

The unprecedented and unique molecular architecture of this set of molecules, their scarcity and their biological properties make them attractive targets for total synthesis,[9] because this is the most viable method of providing sufficient material to allow the determination of the full bioactivity and mechanism of action and to pave the way for further SAR development. To this end, the Clark group has a particular interest in those amphidinolides that bear one or more tetrahydrofuran units, with the intention of applying its expertise in the synthesis of such heterocycles and their incorporation in complex structures.[10]

1.3. Amphidinolides C and F: Structure, Isolation and Bioactivity

Amphidinolides C (**4**), F (**7**), C2 (**8**) and C3 (**9**) are 25-membered lactones possessing a common macrocyclic core and feature eleven or twelve stereogenic centres, two 2,5-*trans* substituted tetrahydrofurans, a 1,4-diketone and two 1,3-diene units, one of which contains an exocyclic alkene (**Figure 4**).

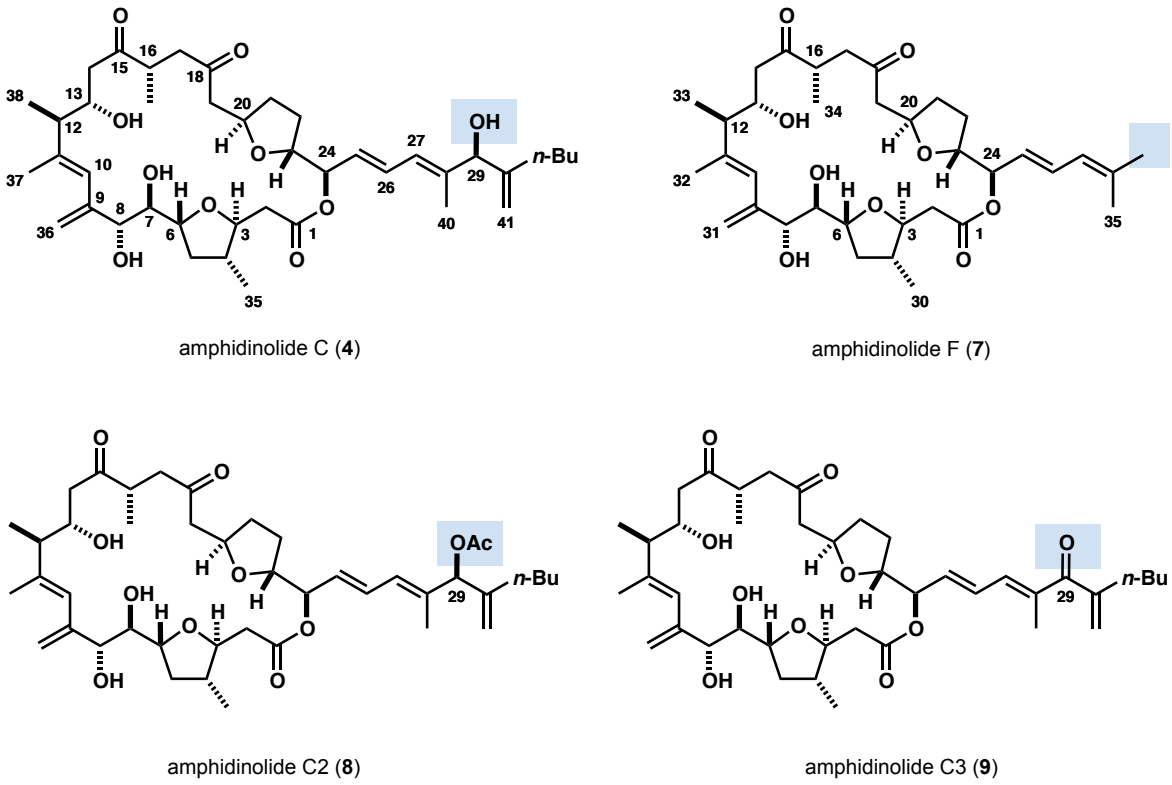


Figure 4. Structures of Amphidinolides C, F, C2 and C3

Amphidinolide C (**4**) was isolated in 1988 by Kobayashi and co-workers. It was the first 25-membered macrolactone extracted from a natural source and immediately aroused interest because of its potent antitumor activity in vitro.[11] The gross structure of amphidinolide C was elucidated by extensive 2D NMR studies. Further NMR experiments combined with Mosher ester analyses of amphidinolide derivatives,[12] as well as comparison between synthetic fragments and degradation products,[13] allowed a full determination of the absolute configuration for the 12 stereocentres featured in the natural product.[14] Later, closely related macrocycles were isolated by the Kobayashi group: amphidinolide F [15] (**7**) in 1991, amphidinolide C2[16] (**8**) in 2004 and amphidinolide C3[17] (**9**) in 2010. Even though the structures of amphidinolides C2 and C3 were established at the time, the low

isolated yield of amphidinolide F prevented the structure of this natural product to be determined with a high degree of certainty. It was only after the first total synthesis of amphidinolide F by Carter and co-workers[18] in 2012 that the structure elucidation and stereochemical assignment of this macrolactone was confirmed.

Among the subgroup, amphidinolide C displays the highest potency with a remarkable IC_{50} = 4.6 ng/mL against KB human epidermoid carcinoma cells and an IC_{50} = 5.8 ng/mL against L1210 murine lymphoma cells (**Table 2**). Interestingly, amphidinolides C2, C3 and F, whose only structural difference is located at the C29 position of the side chain, exhibit lower biological activity towards the previously mentioned cancer cells than amphidinolide C. This observation underlines the likely importance of this area in terms of establishing a SAR.

Amphidinolide	**Isolation Yield**	**Cytotoxicity** (IC_{50}, µg/mL)	
	(%)	L1210	KB
C (**4**)	0.0015	0.0058	0.0046
F (**7**)	0.00001	1.5	3.2
C2 (**8**)	0.00015	0.8	3.0
C3 (**9**)	0.00006	7.6	10.0

Table 2. Bioactivity and Isolation Yields of Amphidinolides C, C2, C3 and F

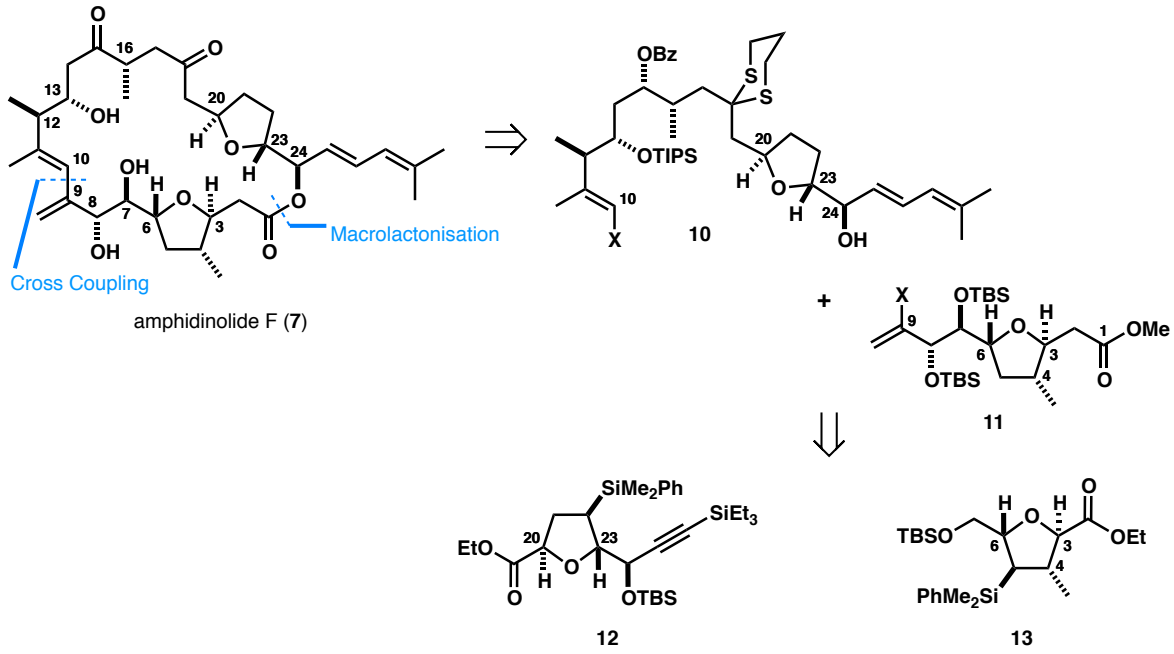
1.4. Previous Syntheses of Amphidinolides C and F

The rarity of amphidinolides C, F, C2 and C3, their structural complexity and promising biological activities predestined these molecules for synthetic investigations. Fragment syntheses have been reported by the research groups of Roush,[19] Armstrong,[20] Spilling,[21] Mohapatra,[22] Pagenkopf,[23] Figadère,[24] Forsyth[25] and Clark[26]. The first total synthesis of amphidinolide F was completed by the Carter group,[18] which later employed a similar strategy to produce amphidinolide C.[27] Finally, Fürstner and co-workers reported concise and efficient syntheses of amphidinolides C and F.[28] This work will be discussed in detail in this section.

1.4.1. Roush: Diastereoselective [3+2]-Annulation Reaction

In 2004, Roush and co-workers reported the synthesis of the C11−C29 fragment of amphidinolide F, followed by the C1−C9 fragment of amphidinolides C and F four years later.[19] Their approach relied on a diastereoselective [3+2]-annulation reaction between a functionalised allylsilane and ethyl glyoxylate to prepare the key *trans*-tetrahydrofurans, a methodology developed within the group.[29]

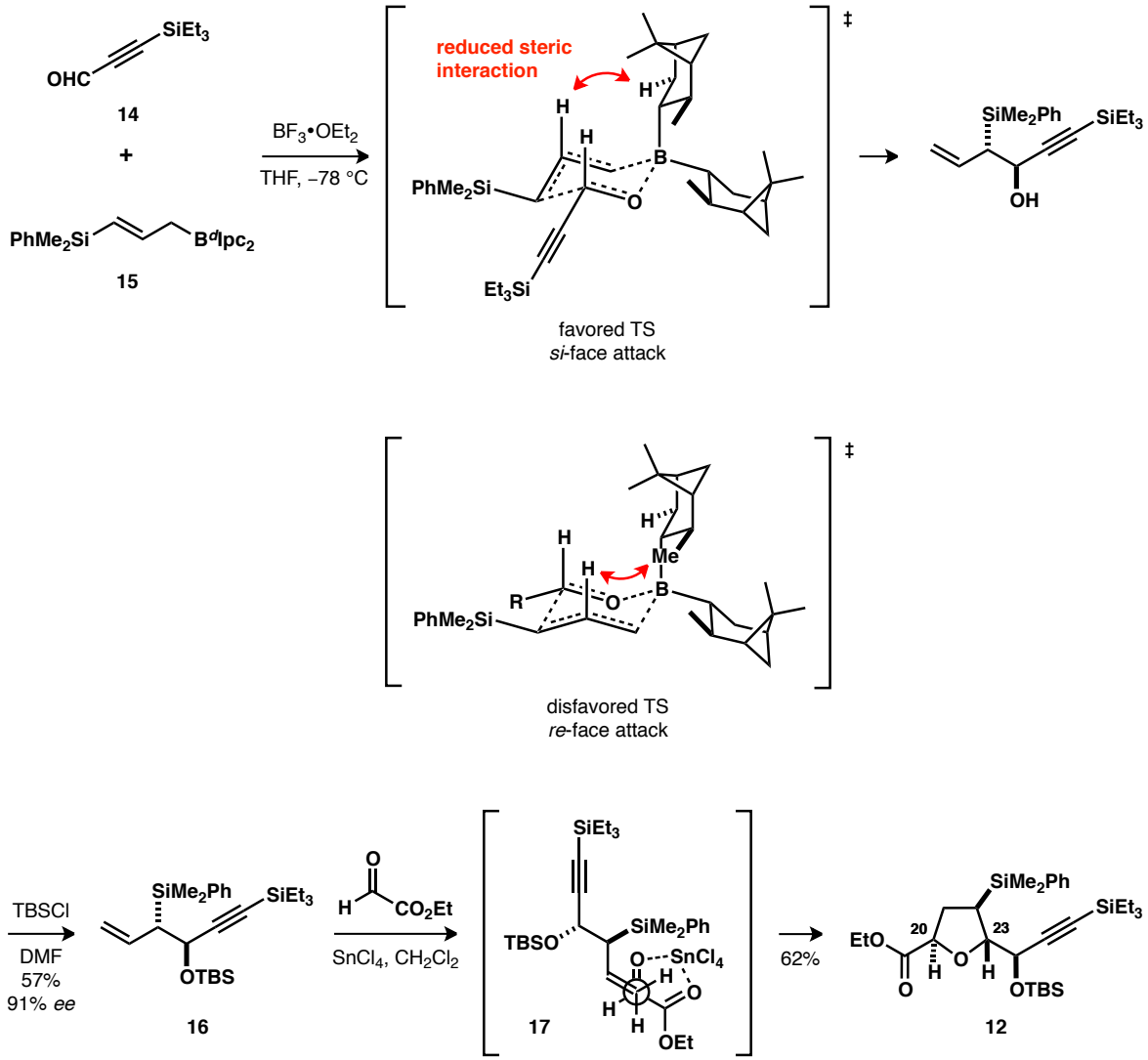
The retrosynthetic analysis proposed the assembly of amphidinolide F (**7**) through two major fragments **10** and **11** *via* a late-stage cross coupling and macrolactonisation sequence (**Scheme 1**). Fragments **10** and **11** were to be derived from tetrahydrofurans **12** and **13**.



Scheme 1. Roush's Retrosynthetic Analysis

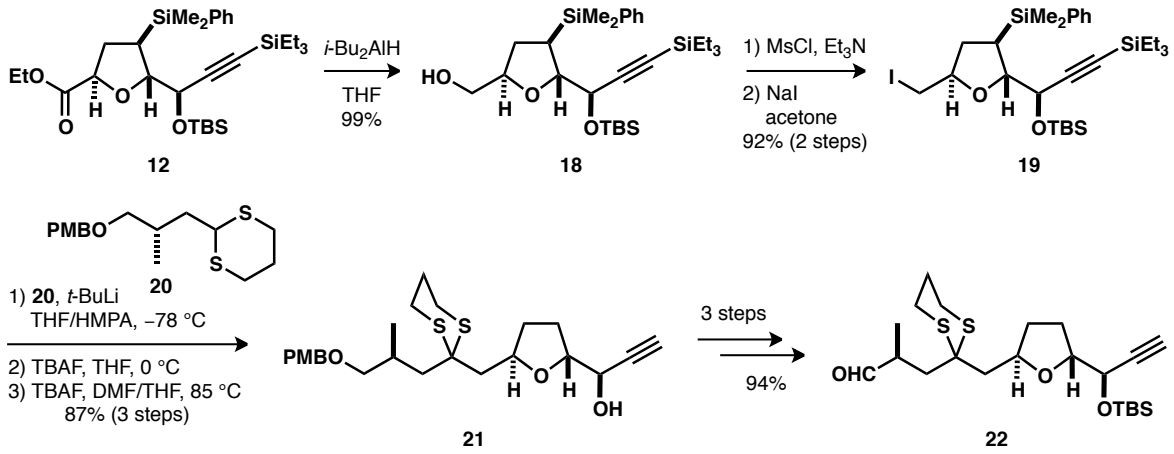
The synthesis of the C11−C29 fragment was commenced with the silylboration of aldehyde **14** with (+)-pinene-derived silylallylborane **15** (**Scheme 2**). The observed selectivity is thought to arise from minimisation of steric interactions between the axial Ipc ligand and the allyl group.[30] Subsequent silyl protection afforded α-hydroxyallylsilane **16** in 57% yield and with 91% *ee*. Treatment with ethyl glyoxylate and $SnCl_4$ delivered *trans*-tetrahydrofuran **12** in good yield as a single diastereomer (*dr* > 20:1). This [3+2]-annulation reaction proceeds *via* a stepwise *anti* S_E' addition of the allylsilane to the Lewis acid-complexed aldehyde followed by a suprafacial 1,2-silyl migration and intramolecular etherification.[29] Reacting

arrangement **17** features a *syn*-synclinal arrangement of the π reacting system, where the alkene lies *syn* to the carbonyl oxygen, providing the lowest energy pathway due to favourable HOMO-LUMO interactions.[31]



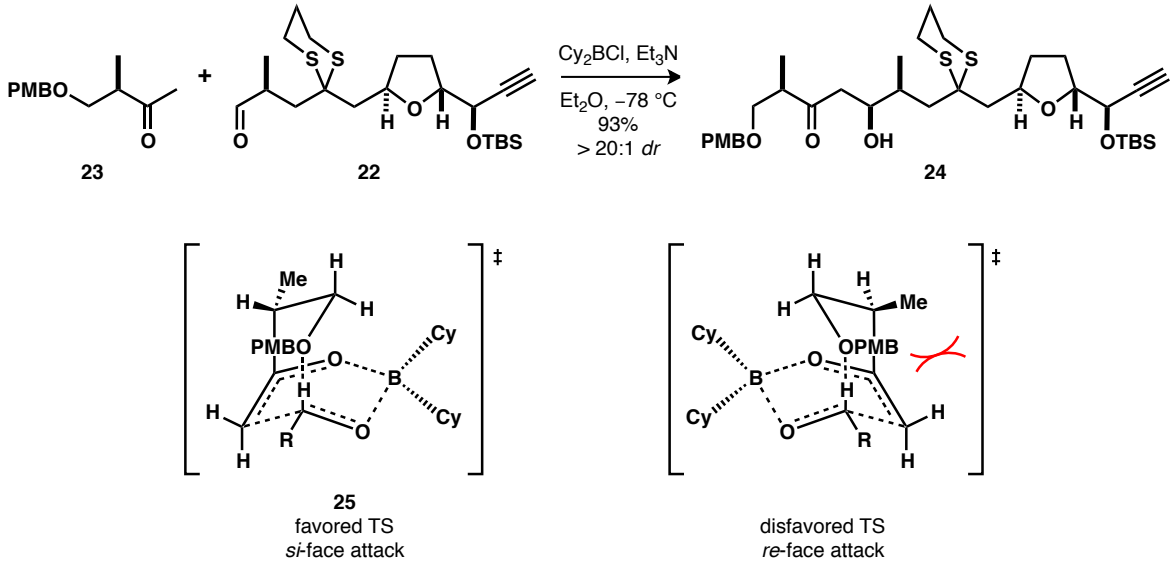
Scheme 2. *trans*-Tetrahydrofuran **12** Elaboration

Reduction of the ethyl ester followed by conversion of alcohol **18** to alkyl iodide **19** was achieved in a three-step sequence and high yields (**Scheme 3**). Deprotonation of mono-substituted 1,3-dithiane **20** with *t*-BuLi in a THF/HMPA mixture and addition of this lithiated species to iodide **19** afforded the propargylic alcohol **21**. Further standard manipulation led to the formation of aldehyde **22** in excellent yields.



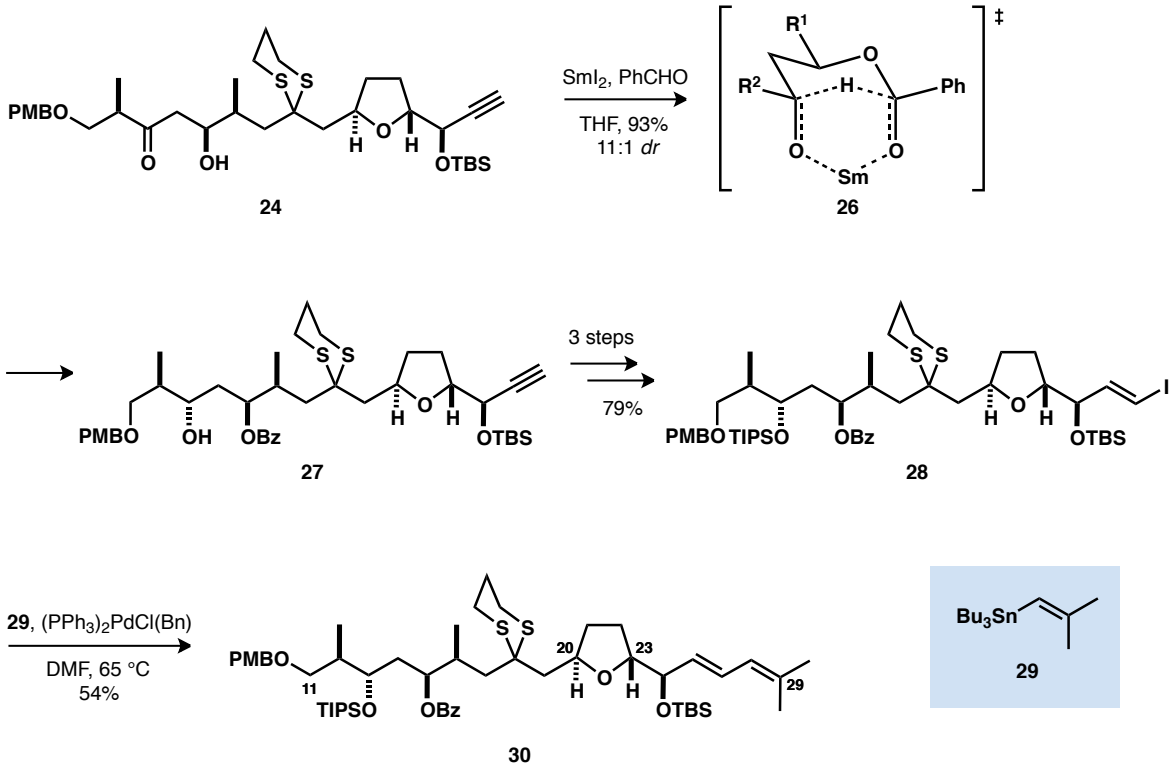
Scheme 3. Aldehyde **22** Synthesis

After formation of the dicyclohexylboron enolate of methyl ketone **23** and its addition to aldehyde **22**, *β*-hydroxy ketone **24** was obtained in 93% yield as a single diastereomer (*dr* > 20:1), as a consequence of 1,4-stereoinduction (**Scheme 4**). The high diastereoselectivity observed in this Cy_2BCl-mediated aldol reaction is to be linked to the relative steric and electronic properties of the three substituents at the α stereocentre of the boron enolate intermediate.[32] It is postulated that the 1,4-*syn* aldol addition proceeds *via* the favoured boat-shaped transition state **25**, which involves a stabilising formyl hydrogen bond with the PMB ether oxygen. The diastereomeric differentiation originates from A(1,3) allylic strain within the enolate. In the preferred transition state **25**, this strain is minimised due to a *gauche* interaction between a hydrogen and the enolate double bond, and *si*-face attack of the aldehyde is observed.



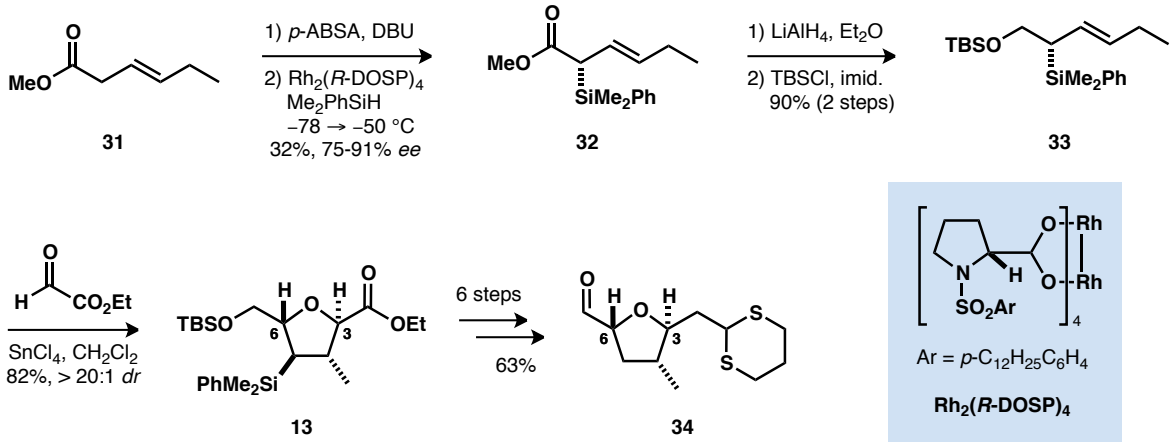
Scheme 4. Cy_2BCl-Mediated Aldol Reaction and Transition States

Further Evans-Tishchenko reduction of *β*-hydroxy ketone **24** afforded *anti*-1,3-benzoate **27** as the major product in a 11:1 *dr* (**Scheme 5**). The stereochemical outcome of this reaction can be rationalised by consideration of the chelated transition state **26**. The C11−C29 fragment **30** was completed through a two-step stannylation/iododestannylation to give vinyl iodide **28** followed by a Stille cross-coupling with vinylstannane **29**. Vinyl iodide **28** was completed in 18 steps and with an overall yield of 10%. The authors envisioned using vinyl iodide **28** as the key handle to install a range of multiple side chains in order to prepare analogues.



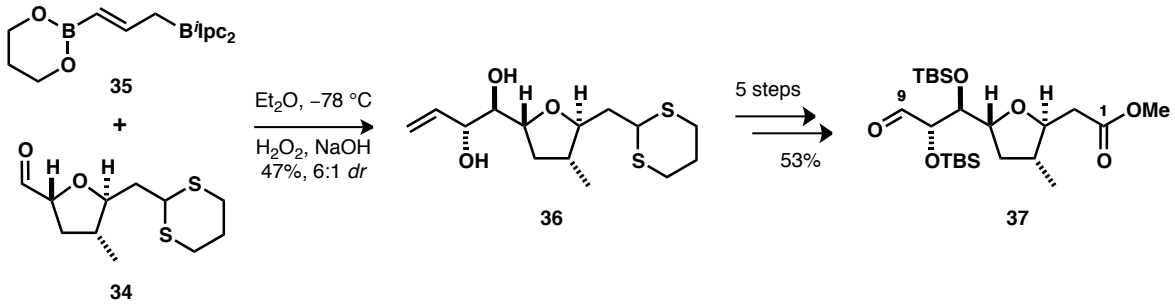
Scheme 5. Completion of Fragment C11−C29

Following the successful synthesis of the C11−C29 fragment, the preparation of the C1−C9 fragment was reported, including two different approaches to the synthesis of the tetrahydrofuran ring.[19b] First, allylsilane **32** was synthesised in two steps from methyl ester **31** using an enantioselective insertion of a rhodium carbenoid, generated from the corresponding diazoester intermediate, into the Si−H bond of phenyldimethylsilane (**Scheme 6**).[33] Conversion of the methyl ester into a silyl ether gave allylsilane **33** in good yield. The key *trans*-tetrahydrofuran **13** was obtained as a single diastereomer in 82% yield using a $SnCl_4$-promoted [3+2]-annulation reaction and was further converted into aldehyde **34** in six steps.



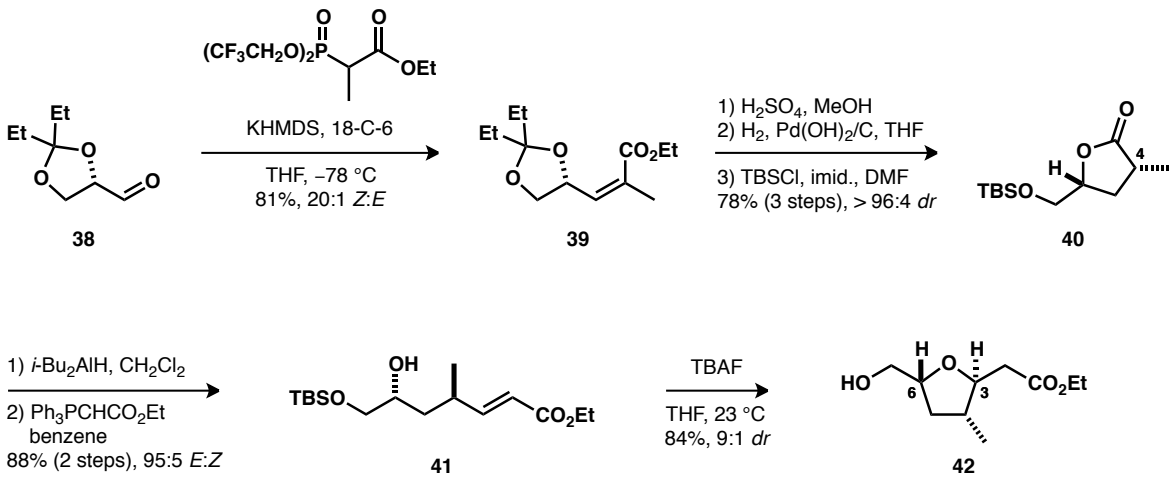
Scheme 6. Aldehyde **34** Formation

Using *γ*-borylallylborane **35**, *anti*-diol **36** was obtained from aldehyde **34** in 47% yield and with a 6:1 *dr* (**Scheme 7**). The final C1−C9 fragment **37** was obtained in five steps, including conversion of the dithiane moiety into the corresponding methyl ester and ozonolysis of the alkene to produce its aldehyde counterpart. The total sequence involved 17 steps and was accomplished with a 4% overall yield.



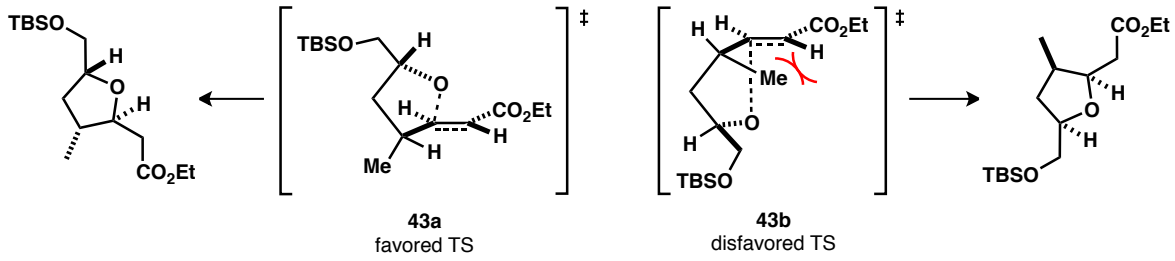
Scheme 7. C1−C9 Fragment Completion

To improve the step-count of this synthetic sequence, an alternative method to provide the *trans*-tetrahydrofuran was implemented (**Scheme 8**). Using the Still-Gennari modification of the Horner-Wadsworth-Emmons (HWE) olefination, glyceraldehyde isopentylidene acetal **38** was converted into *Z*-enoate **39** in excellent yield and high selectivity (20:1, *Z*:*E*). Subsequent acid-catalysed deprotection of the ketal triggered an *in situ* lactonisation of the *γ*-hydroxy ester. Hydrogenation of the butenolide installed the C4 stereocentre in a diastereoselective fashion. Further protection of the alcohol gave lactone **40** in 78% yield over three steps and with an excellent *dr*. Reduction and olefination using a stabilised phosphonium ylide provided alkene **41**.



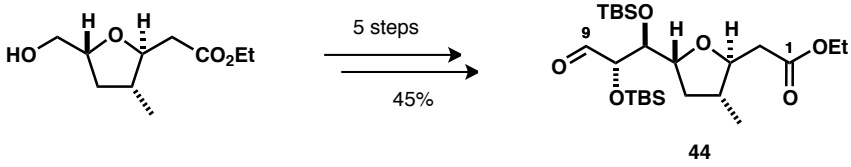
Scheme 8. Second Generation Elaboration of the *trans*-Tetrahydrofuran

Finally, tetrahydrofuran **42** was formed by treatment of enoate **41** with TBAF in THF *via* an intramolecular Michael cyclisation reaction. The diastereoselectivity of this kinetically controlled process can be explained by a reduction of the A(1,3) strain as can be seen in transition state **43a**, which is favoured over the more sterically demanding transition state **43b** (**Scheme 9**).



Scheme 9. Rationalisation of the Observed Diastereoselectivity

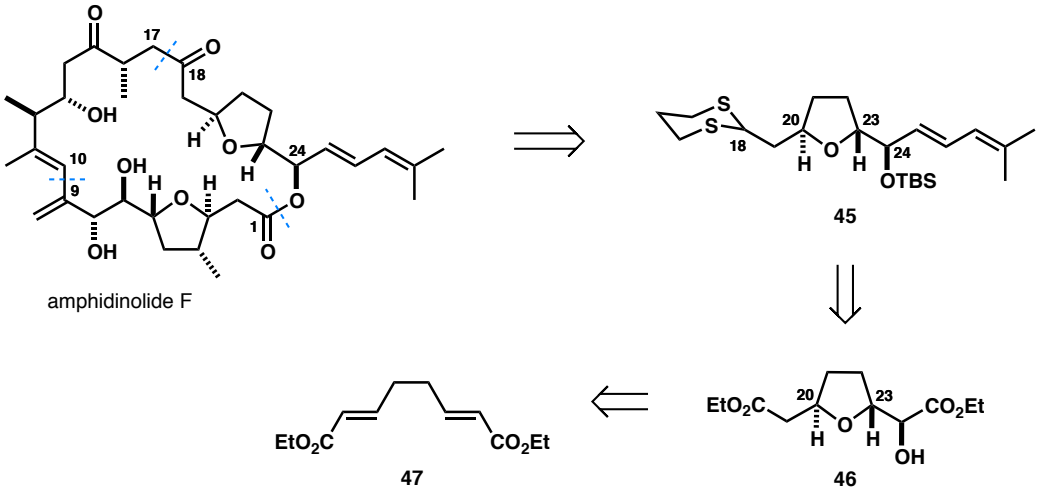
The target fragment was completed using similar transformations as the ones outlined in the first-generation route, leading to aldehyde **44** in 12 steps and with 21% overall yield (**Scheme 10**).



Scheme 10. Second Generation C1−C9 Fragment Completion

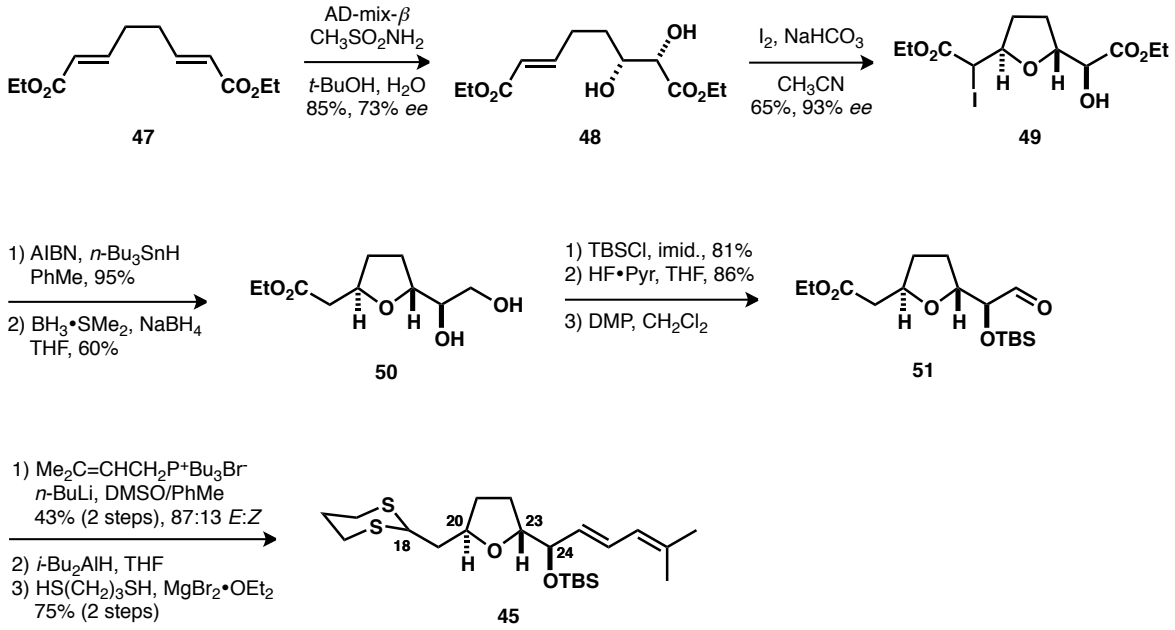
1.4.2. Armstrong: Sharpless Dihydroxylation / Iodocyclisation

Armstrong and co-workers reported the synthesis of the C18−C29 fragment of amphidinolide F, relying on a Sharpless asymmetric dihydroxylation reaction followed by iodo-etherification to build the desired 2,5-*trans*-disubstituted tetrahydrofuran.[20] The proposed retrosynthesis disconnected the macrolactone at the C17−C18 bond, the C9−C10 diene bond, and the ester bond, revealing dithiane **45** as the targeted fragment of their work (**Scheme 11**). Diester **46** was obtained by a desymmetrisation of dienoate **47** using a mono-Sharpless dihydroxylation/iodocyclisation sequence.



Scheme 11. Armstrong's Retrosynthesis

Sharpless asymmetric dihydroxylation of dienoate **47**, using AD-mix-*β* (K_2OsO_4•$2H_2O$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$) and methanesulfonamide, delivered diol **48** in 85% yield and a moderate 73% *ee*. (**Scheme 12**). Further iodocyclisation generated *trans*-tetrahydrofuran **49** with an improved 93% *ee*, upon recrystallisation. A standard deiodination protocol followed by a selective reduction of the α-hydroxy ester led to diol **50**. Aldehyde **51** was obtained by a simple protection/deprotection sequence and subsequent oxidation of the primary alcohol. The aldehyde was readily subjected to an *E*-selective olefination to provide the corresponding alkene in a 87:13 *E*:*Z* ratio. Finally, the dithiane moiety was installed by reduction of the ethyl ester and subsequent treatment of the aldehyde with 1,3-propanedithiol in the presence of a mild Lewis acid. Formation of the C18−C29 fragment **45** was completed in a total of 12 steps and 4% overall yield.



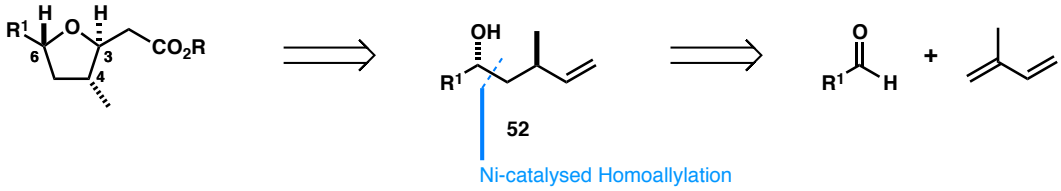
47 48 49 50 51 45

Scheme 12. Fragment C18−C29 Synthesis

1.4.3. Spilling: Nickel-catalysed Homoallylation

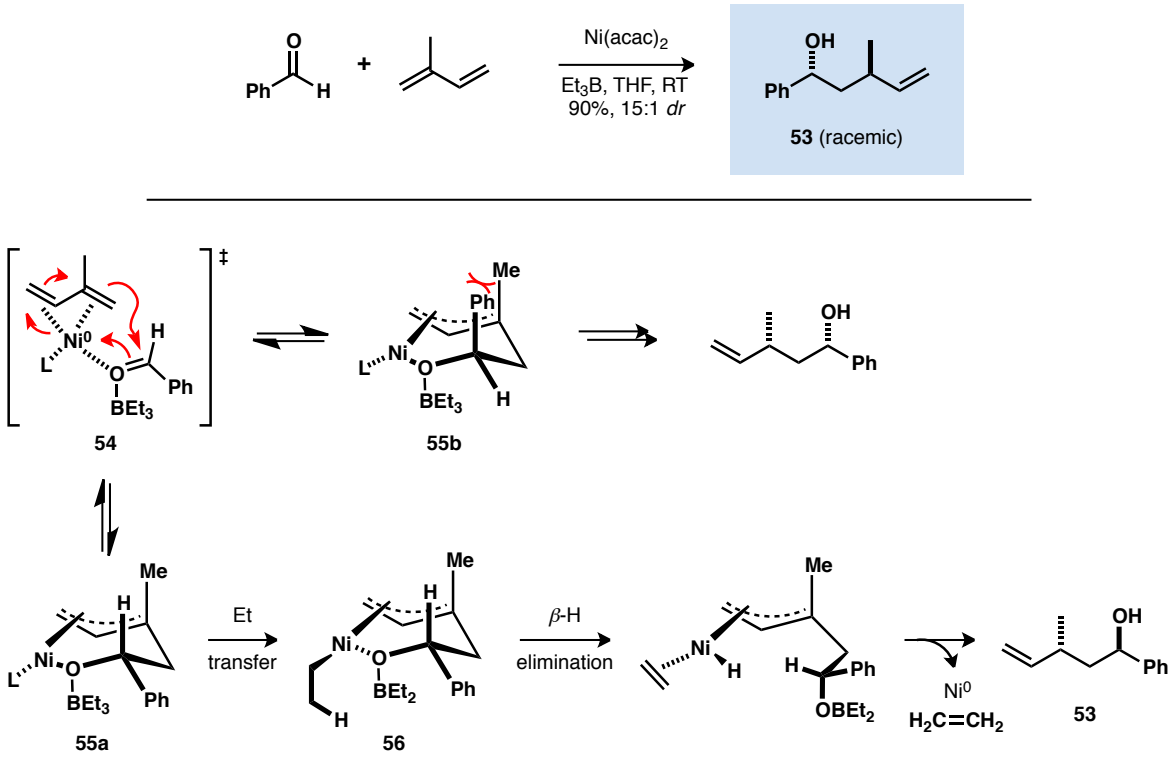
The Spilling group reported their efforts towards the synthesis and elaboration of a variety of tetrahydrofuran-containing fragments that are potentially useful for the synthesis of amphidinolide C or F.[21]

First, their attention focused on preparing trisubstituted tetrahydrofuran rings with the correct 3,6-*trans* and 3,4-*syn* relationships, as featured in the amphidinolide C series (**Scheme 13**).[21a] Their strategy relied on a nickel-catalysed homoallylation methodology developed by Tamaru and co-workers to access 1,3-*anti* unsaturated alcohols (**52**) with high diastereoselectivity.[34]



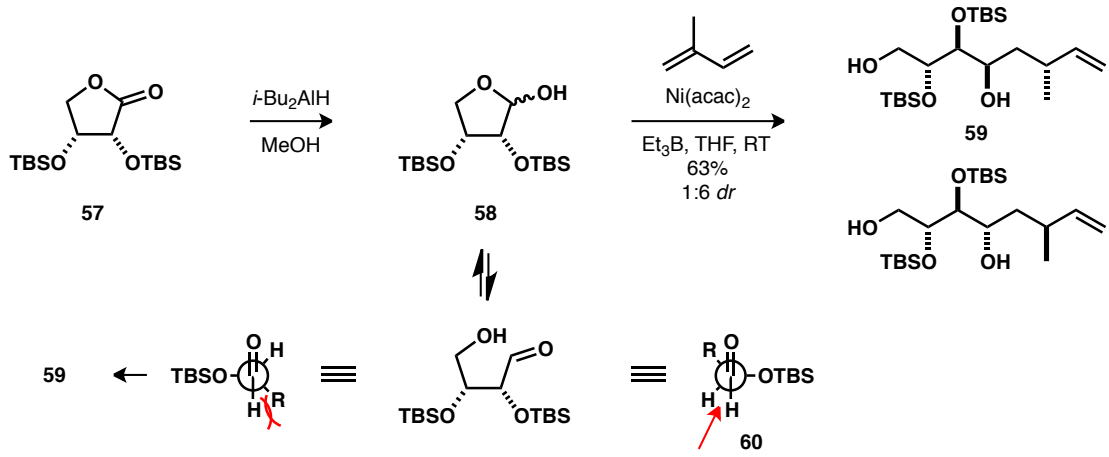
Scheme 13. General Retrosynthetic Outline

The Tamaru reaction was first illustrated in an example for which mechanistic considerations accounting for the regioselectivity and stereoselectivity have been proposed (**Scheme 14**). The regioselectivity of the reaction is likely to be determined by the electronic densities of the diene extremities, the terminal with the highest electron density reacting with the aldehyde. First, oxidative cyclisation of a Ni^0 species across isoprene and the aldehyde is believed to lead from transition state **54** to two diastereomeric intermediates **55a** and **55b**. In this transition, the diene acts as a nucleophile towards the aldehyde and as an electrophile towards the Ni^0 species, with electron donation from the Ni^0. The oxidative cyclisation reaction is accelerated by coordination of Et_3B to the aldehyde. Intermediate **55b** suffers from a 1,3-diaxial repulsion between the methyl of the isoprene and the substituent of the aldehyde and so the reaction proceeds through the more favourable intermediate **55a**. Ethyl transfer from the boron to the nickel follows, concomitant to an ionic Ni−O bond cleavage, to form intermediate **56**, which readily undergoes *β*-H elimination. Finally, reductive elimination provides the *anti* homoallylation product **53**.



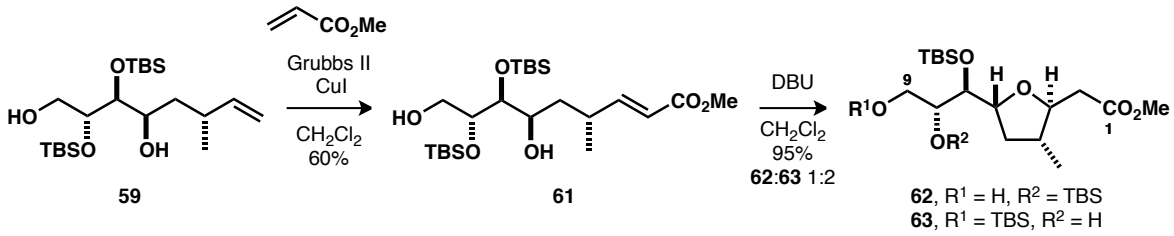
Scheme 14. Ni-catalysed Homoallylation Example and Rationalisation

Hemiacetal **58**, derived from silyl protected erythronolactone **57**, was identified as a suitable substituted aldehyde partner for the aforementioned strategy, as it possesses the 1,2-*anti* relationship found at the C7 and C8 positions of the targeted amphidinolides (**Scheme 15**). Unfortunately, the nickel-catalysed homoallylation reaction yielded the desired 1,3-*anti* product **59** with an unsatisfactory 1:6 *dr*. Even though the authors did not propose a rationalisation for this result, consideration of the Felkin-Ahn model can help explain this outcome, where the transition state corresponding to the Newman projection **60** is favoured due to reduced steric interactions.



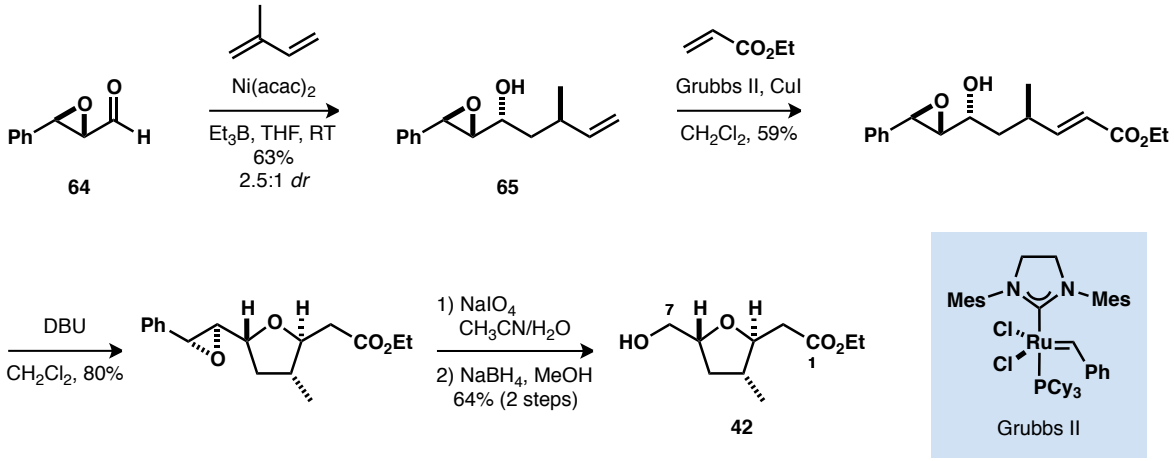
Scheme 15. Ni-catalysed Homoallylation of Hemiacetal **58**

After separation, minor diastereomer **59** was subjected to a cross-metathesis reaction with methyl acrylate using Grubbs second-generation ruthenium catalyst, yielding *α*,*β*-unsaturated ester **61** in decent yield. Oxa-Michael cyclisation using DBU provided a mixture of tetrahydrofurans **62** and **63**, as a result of partial silyl migration (**Scheme 16**).



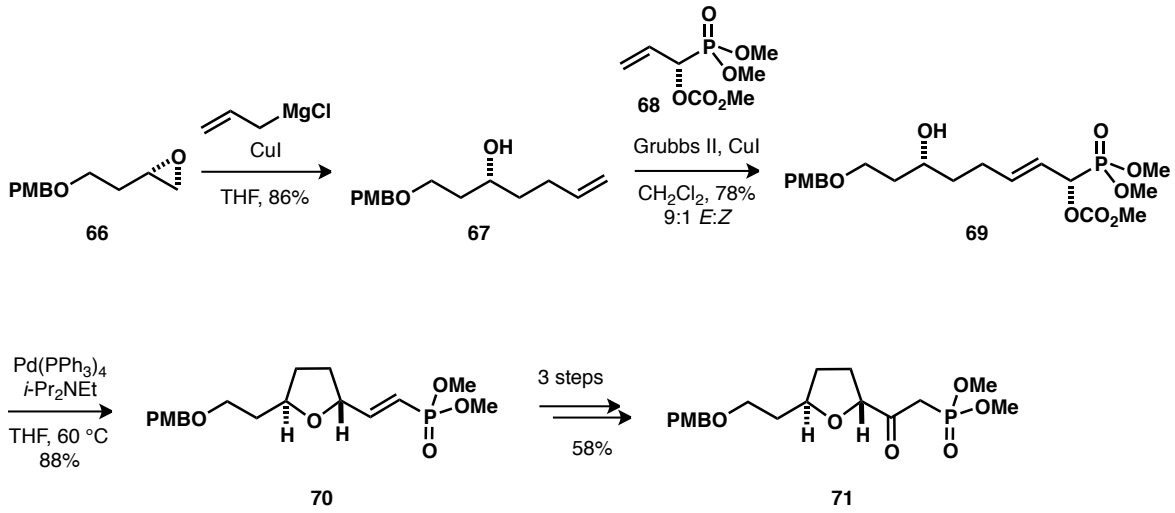
Scheme 16. C1−C9 Fragment Completion Attempt

A moderate improvement of the stereochemical outcome was obtained when using phenylglycidal **64** as a partner for the homoallylation reaction. In this case, alcohol **65** was obtained as the major diastereomer with low selectivity (2.5:1 *dr*) (**Scheme 17**). Tetrahydrofuran **42** was completed in four additional steps.



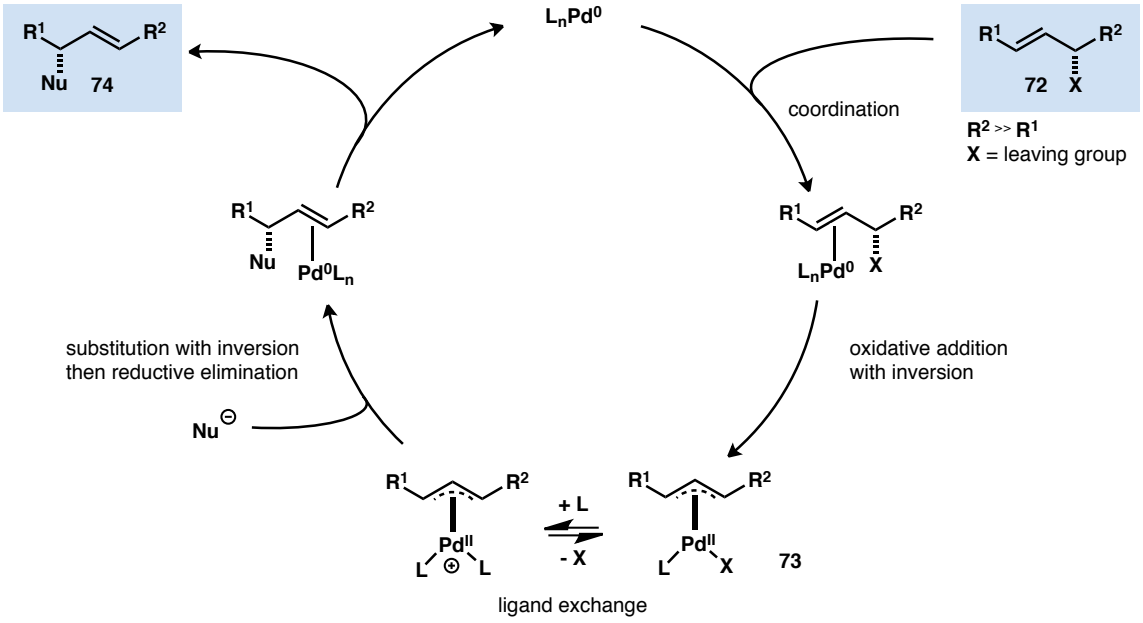
Scheme 17. C1−C7 Fragment Synthesis

Further to these results, elaboration of a C18−C29 fragment of amphidinolide F was also reported.[21b] First, (*S*)-epoxide **66** was treated with allylmagnesium chloride and copper iodide to furnish alcohol **67** in good yield (**Scheme 18**). Subsequent cross-metathesis with (*S*)-carbonate **68** gave phosphonoallylic carbonate **69** in 78% yield as an inseparable 9:1 mixture of *E* and *Z* isomers. Tsuji-Trost palladium-catalysed allylation led to tetrahydrofuran **70** in excellent yield. Vinylphosphonate **70** was then converted into *β*-ketophosphonate **71** using a three-step sequence that included hydroboration and oxidation.



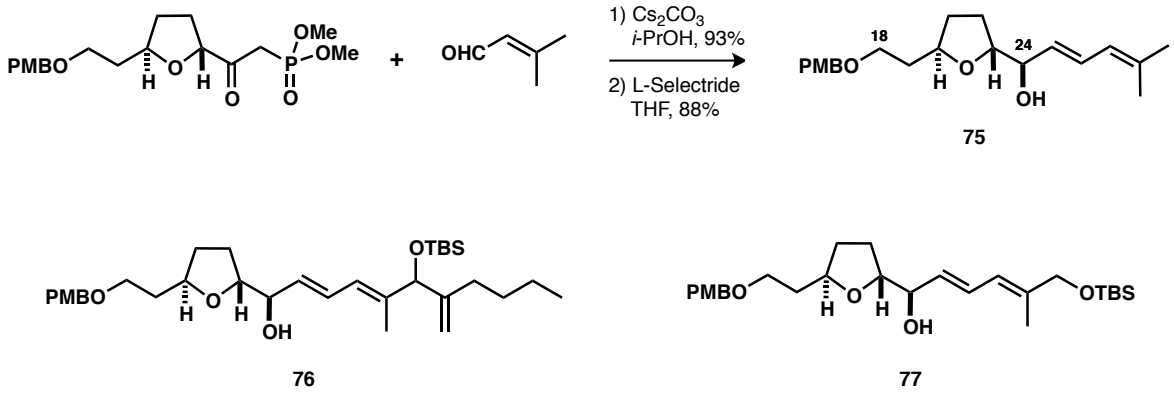
Scheme 18. Synthesis of *β*-Ketophosphonate **71**

The mechanism of the Tsuji-Trost allylation reaction is outlined below (**Scheme 19**). The catalytic cycle begins with the coordination of the Pd^0 species to alkene **72**. Oxidative addition then proceeds with inversion of configuration leading to Pd^{II} species **73** and the leaving group is expelled. The nucleophile adds to the π-allylpalladium complex with inversion of configuration. In the case of an unsymmetrical π-allylpalladium complex, this addition is also regioselective, as it favours the least substituted allyl terminus, regardless of the initial position of the leaving group. Finally, reductive elimination provides alkene product **74**.



Scheme 19. Tsuji-Trost Allylation Reaction

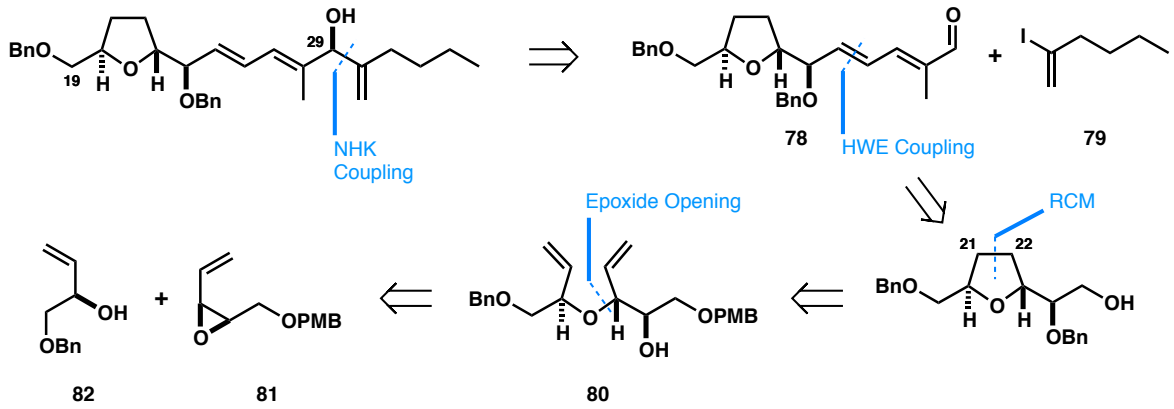
Synthesis of the C18−C29 fragment was completed by HWE olefination and subsequent reduction of the dienone under Felkin-Ahn control, to afford alcohol **75** as a single diastereomer in excellent yield (**Scheme 20**). Two related fragments - **76** and **77** - were prepared in a similar fashion.



Scheme 20. C18−C29 Fragment Completion

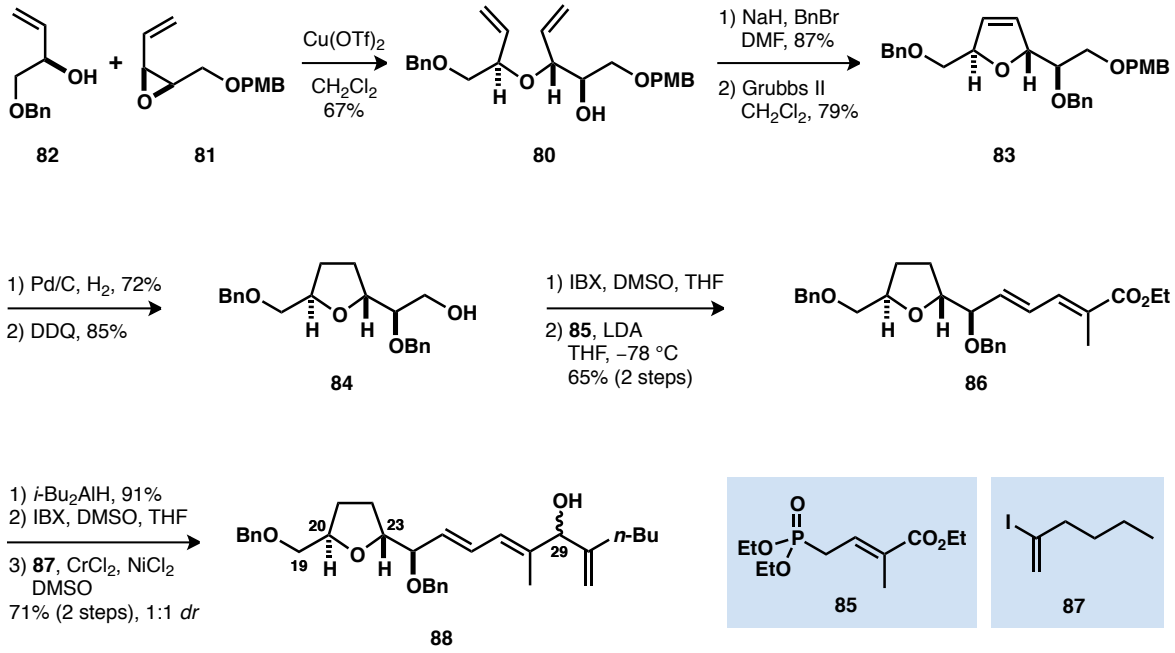
1.4.4. Mohapatra: Ring-Closing Metathesis / Nozaki-Hiyama-Kishi Coupling

In 2007, Mohapatra and co-workers reported the synthesis of the C19−C34 fragment of amphidinolide C.[22] First, the retrosynthetic analysis proposed to install the C29 stereocentre through a Nozaki-Hiyama-Kishi (NHK) coupling between aldehyde **78** and vinyl iodide **79** (**Scheme 21**). The C25−C26 alkene could be obtained by an olefination reaction. Further formation of the tetrahydrofuran ring was to be completed by a ring-closing metathesis (RCM) reaction to form the C21−C22 bond. Finally, regioselective opening of epoxide **81** with alcohol **82** would provide diene **80**, bearing three out of the four required stereocentres with the appropriate configuration.



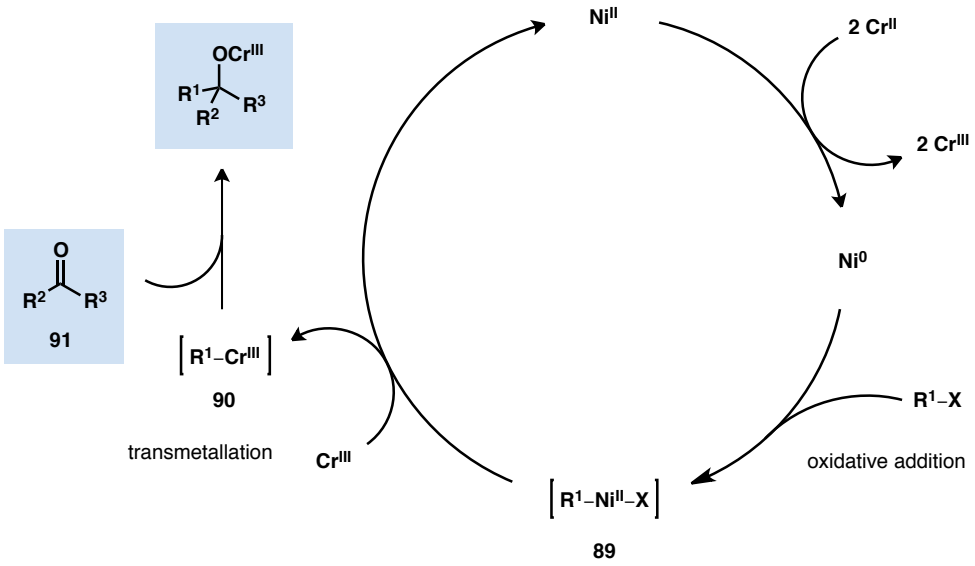
Scheme 21. Retrosynthetic Proposal

The synthesis started by the treatment of alcohol **82** and epoxide **81** with a catalytic amount of $Cu(OTf)_2$ to yield diene **80** in 67% yield (**Scheme 22**).[35] RCM using Grubbs second-generation catalyst delivered the corresponding dihydrofuran derivative **83** in good yield. Submission of the alkene to hydrogenation conditions and PMB cleavage led to key tetrahydrofuran **84**. Oxidation of the primary alcohol and subsequent HWE olefination using phosphonate **85** gave ethyl ester **86** bearing the required diene moiety. Unsurprisingly, attempts to perform NHK coupling between the corresponding C29 aldehyde and vinyl iodide **87** produced alcohol **88** as a 1:1 mixture of separable diastereomers. The required C19−C34 fragment was obtained in 14 steps and with 2% overall yield.



Scheme 22. Elaboration of the C19−C34 Fragment

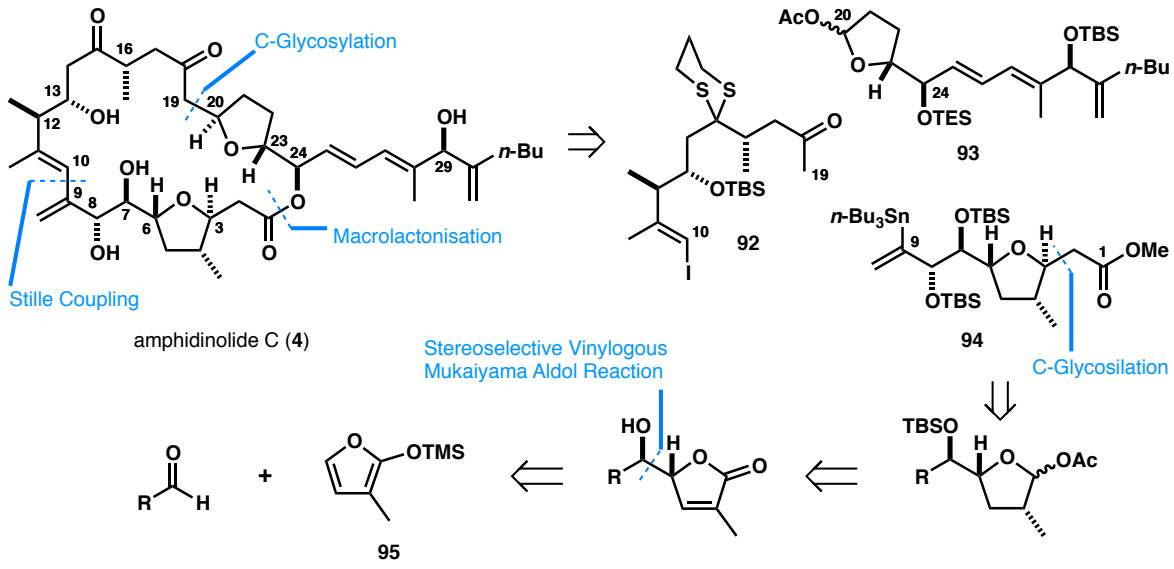
The mechanism involved in the Ni^{II}-catalysed NHK reaction is outlined below (**Scheme 23**).[36] The first step is the reduction of Ni^{II} to Ni^0, which then undergoes an oxidative addition and inserts into the C−halogen bond. Because Cr^{II} is a one-electron donor, two equivalents are required for the reduction process. Further transmetallation of the organonickel species **89** with Cr^{III} forms the organochromium nucleophile **90**. Finally, this species reacts with the carbonyl partner **91**. In this reaction, aldehydes react noticeably faster than ketones and high chemoselectivity can be achieved when both functionalities are present. A significant drawback of this transformation is the toxicity of the nickel and chromium salts used.



Scheme 23. NHK Reaction Mechanism

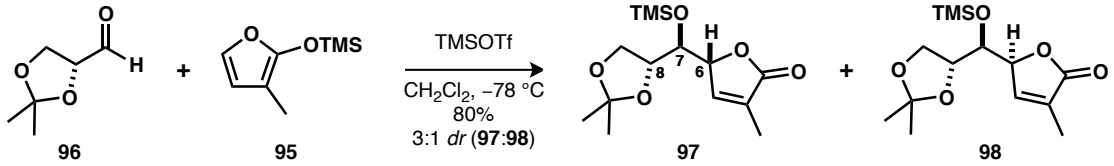
1.4.5. Ferrié: Mukaiyama Aldol Reaction / C-Glycosylation

Ferrié and co-workers developed a synthetic approach towards the C1−C9 fragment of amphidinolides C and F.[24] Their strategy relied on disconnection of the macrolactone in three main fragments: vinyl iodide **92**, lactol derivative **93** and stannane **94** (**Scheme 24**). Completion of the fragment **94** included a key stereoselective vinylogous Mukaiyama aldol reaction with silyloxyfuran **95** and a C-glycosylation to install the methyl ester with the required *trans* configuration.

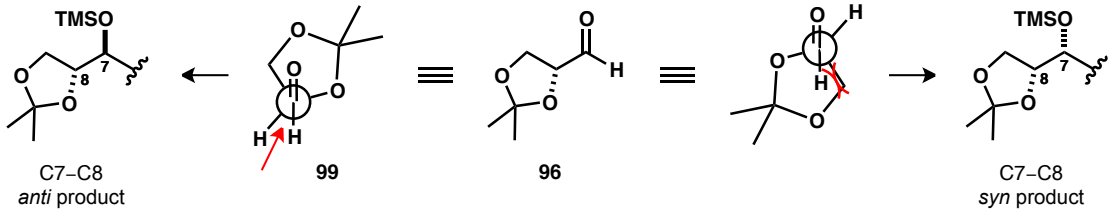


Scheme 24. General Retrosynthetic Analysis

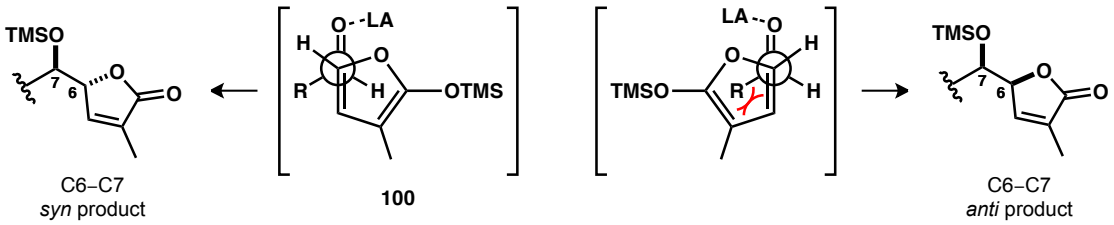
The synthesis began by the vinylogous addition of furan **95** on aldehyde **96** in the presence of TMS triflate (**Scheme 25**) to give a 3:1 mixture of the TMS ethers **97** and **98** in 80% yield. The exclusive C7−C8 *anti* relationship can be rationalised by a Felkin-Ahn control favouring an attack on the *si*-face of the aldehyde, as shown with Newman projection **99**. On the other hand, the sterically less demanding open transition state **100**, with *anti*-periplanar attack of the aldehyde, can account for the preferential formation of the C6−C7 *syn* adduct.



- C7−C8 *anti* relationship: Felkin-Ahn control



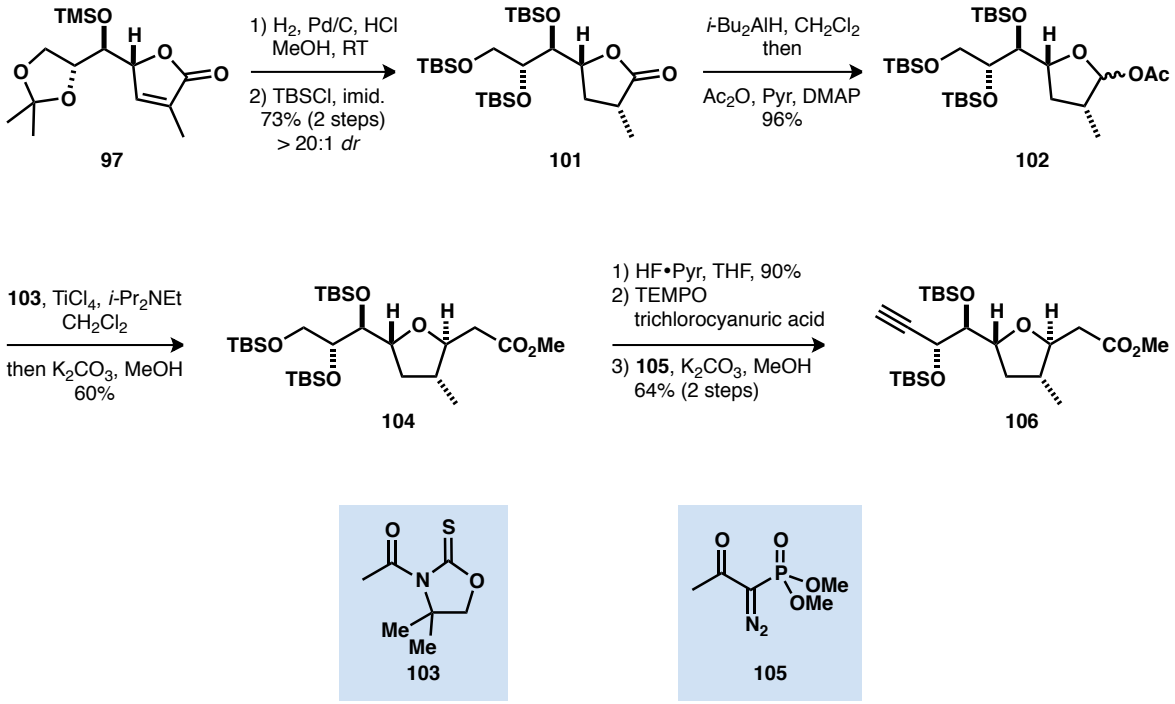
- C6−C7 *syn* relationship: open transition state



Scheme 25. Vinylogous Mukaiyama Aldol Reaction

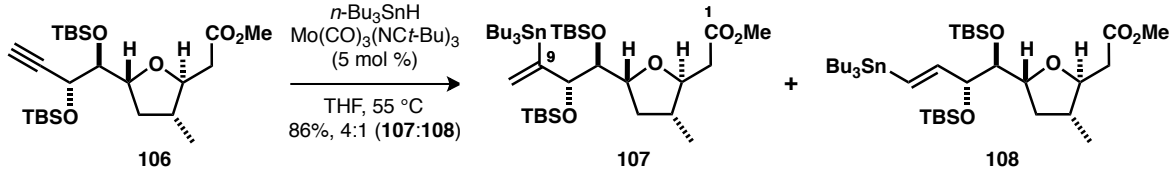
Further hydrogenation of the double bond in lactone **97** under acidic conditions in MeOH proceeded only on the less hindered face of the lactone to deliver the corresponding triol as a single diastereomer (**Scheme 26**). This triol was readily converted into *tris*-TBS ether **101** in excellent yield. Subsequent partial reduction of the lactone and acetylation of the lactol produced the acetate derivative **102** in 96% yield. The C-glycosylation product was obtained by treatment of the acetate with the titanium enolate generated from the achiral acetyloxazolidinethione **103**,[37]

followed by methanolysis. This reaction proceeded with excellent control of the diastereoselectivity to deliver the 2,5-*trans*-tetrahydrofuran **104**. Selective cleavage of the primary TBS ether, oxidation with TEMPO and trichloroisocyanuric acid as co-oxidant,[38] followed by Seyferth-Gilbert homologation using the Ohira-Bestmann reagent **105** furnished terminal alkyne **106**.



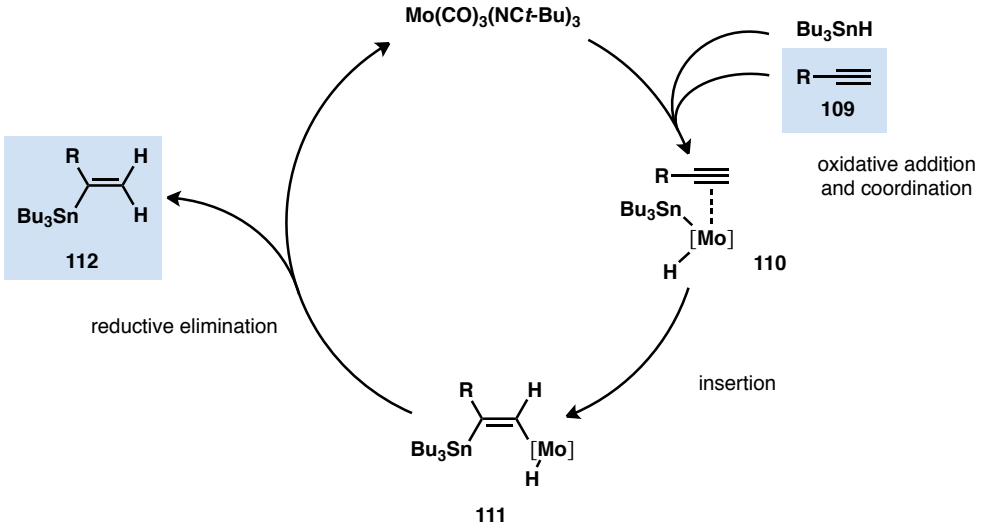
Scheme 26. C4 Methyl Installation and C-Glycosylation

The final step towards the completion of the C1−C9 fragment was regioselective hydrostannylation of hindered terminal alkyne **106** (**Scheme 27**). Using a protocol developed by Kazmaier,[39] which involved the use of an excess of *n*-Bu_3SnH and a catalytic amount of molybdenum complex $Mo(CO)_3(CN\textit{t}\text{-}Bu)_3$,[40] 1,1-disubstituted olefin **107** was obtained as the major product alongside *E*-substituted olefin **108**, as a minor component, in a 4:1 ratio. The two regioisomers were separated by silica gel chromatography to afford pure C1−C9 fragment **107** in 70% yield. In conclusion, a short and elegant synthesis of highly functionalised fragment **107** was completed in nine steps and with 16% overall yield.



Scheme 27. Metal Catalysed Hydrostannylation of Alkyne **106**

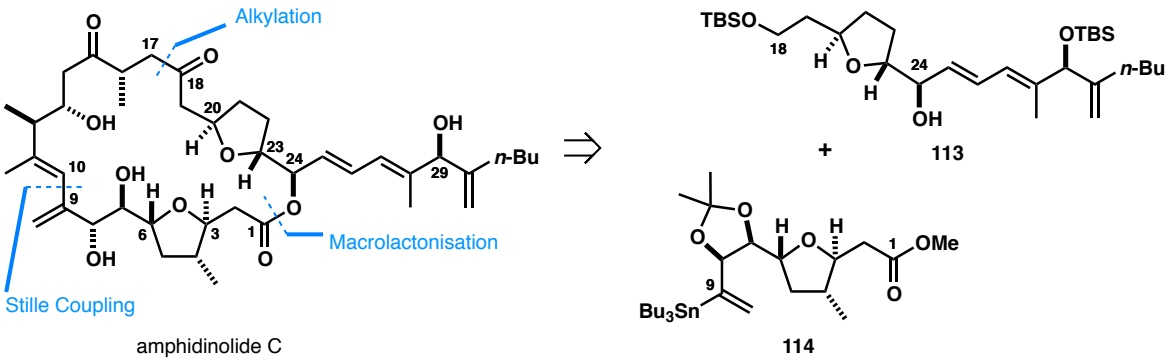
The regioselectivity observed in the molybdenum-catalysed hydrostannylation reaction can be rationalised by steric considerations (**Scheme 28**).[39] After oxidative addition into the tin hydride bond and coordination of alkyne **109** to give the intermediate **110**, insertion of the alkyne into the molybdenum tin bond occurs so that the sterically more demanding molybdenum fragment is added to the less hindered terminus of the alkyne, leading to intermediate **111**. Finally, reductive elimination completes the catalytic cycle to form **112**.



Scheme 28. Mechanistic Rationale for the Mo-catalysed Hydrostannylation

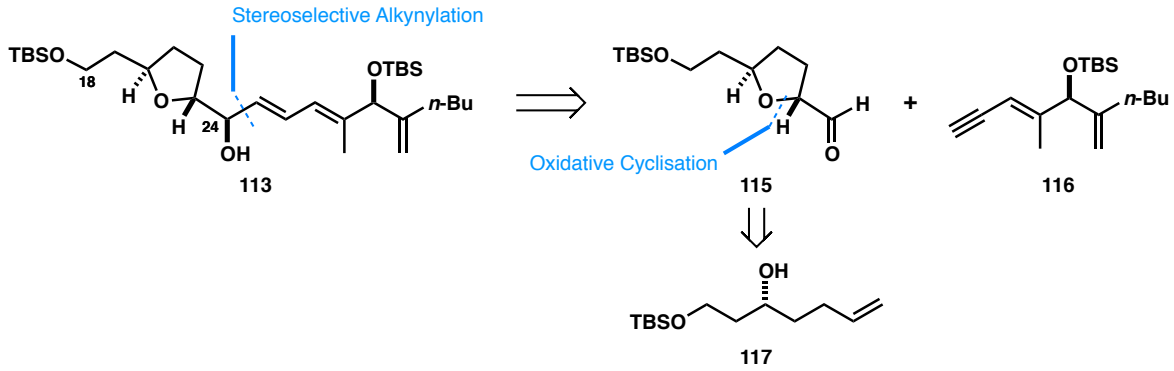
1.4.6. Pagenkopf: Cobalt Catalysed Mukaiyama Oxidative Cyclisation

The general approach of the Pagenkopf group to the synthesis of this series of macrolactones featured general disconnections that are similar to those highlighted previously, revealing the tetrahydrofuran-containing fragments **113**[23a] and **114**[23b] as the focus of their work (**Scheme 29**).



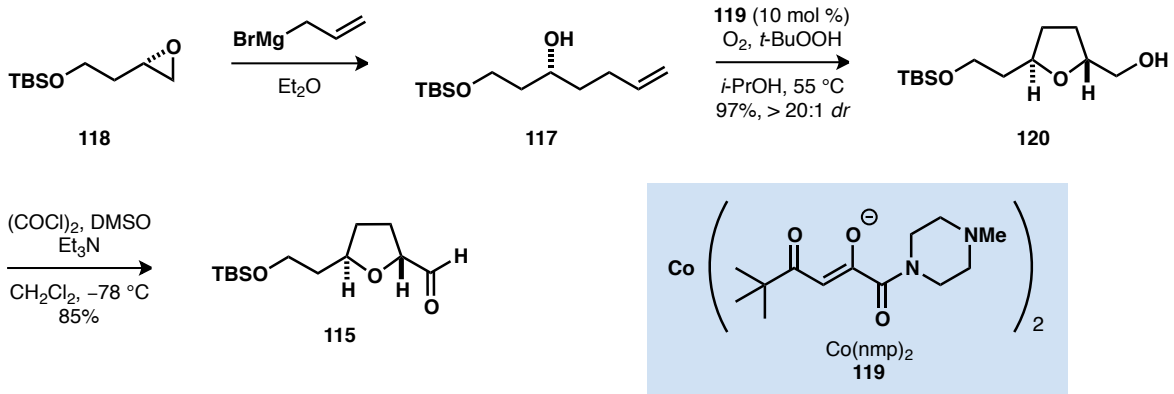
Scheme 29. General Disconnections of the Macrocycle

The strategy that was adopted by Pagenkopf and co-workers to access the C18−C34 fragment **113** of amphidinolide C relied on the Mukaiyama oxidative cyclisation of alkenol **117** using a cobalt catalyst developed within their group (**Scheme 30**). The diene side chain was to be installed by the diastereoselective alkynylation of aldehyde **115** by enyne **116**.



Scheme 30. Approach Towards the C18−C34 Fragment

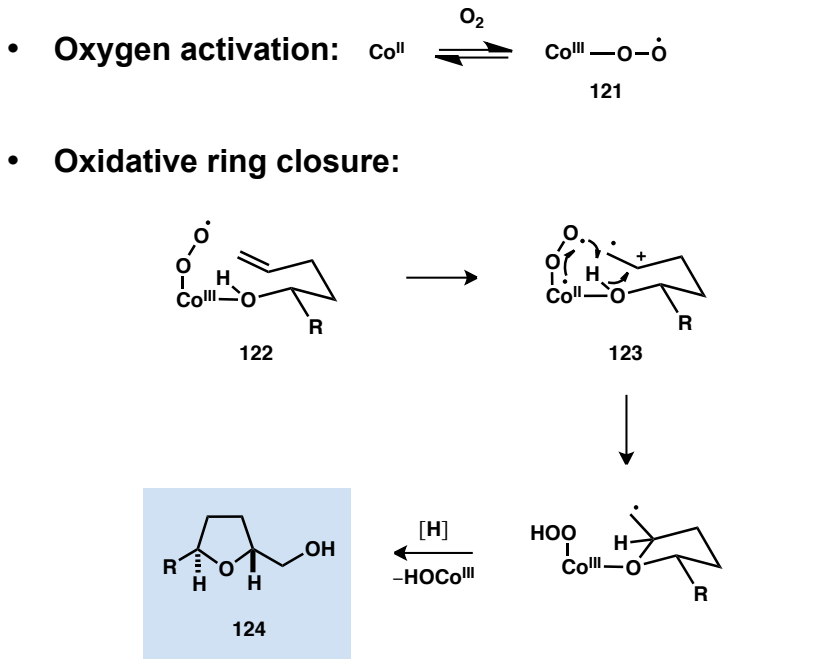
The tetrahydrofuran segment was assembled from chiral non-racemic epoxide **118** in only four steps (**Scheme 31**). *γ*,*δ*-Unsatured alcohol **117** was converted into *trans*-tetrahydrofuran **120** by means of an oxidative Mukaiyama cyclisation reaction, a transformation in which molecular oxygen acts as the stoichiometric oxidant. Cobalt catalyst **119** had been developed by the Pagenkopf group to promote this reaction.[41] Subsequent Swern oxidation provided aldehyde **115**.



Scheme 31. Elaboration of the *trans*-Tetrahydrofuran Segment

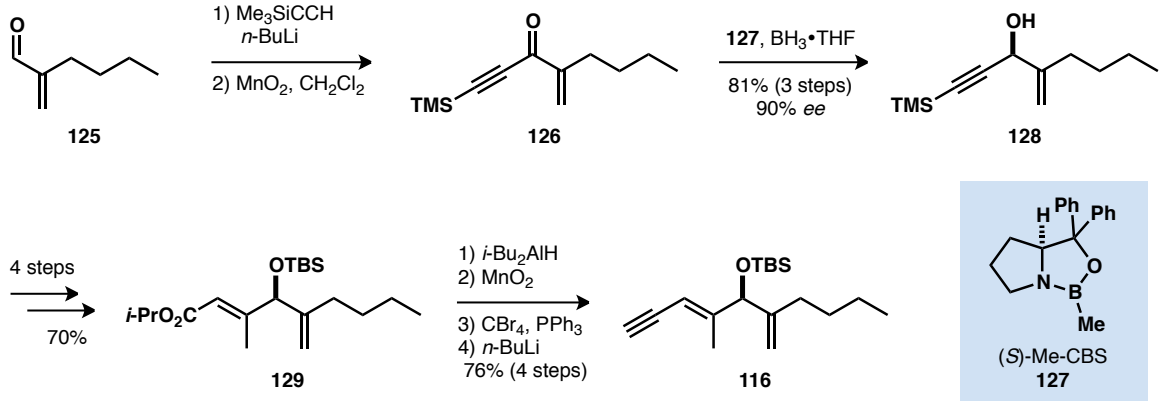
In order to explain the 5-*exo*-ring closure and the preferred formation of the 2,5-*trans*-tetrahydrofuran, Hartung and co-workers have proposed a mechanistic interpretation of the outcome (**Scheme 32**).[42] First, oxygen activation would occur by binding to Co^{II} leading to adduct **121**. Intermediate **122** would furnish radical

cation **123**, followed by 5-*exo* attack of the hydroxyl oxygen atom. A stereochemical model where the alkenol chain in **122** and **123** would adopt a chair-like conformation to direct substituents in the equatorial positions is thought to account for the 2,5-*trans* relationship observed. Finally, in the presence of a suitable hydrogen donor, alcohol **124** and $HOCo^{III}$ would be obtained. Co^{II} regeneration would occur *via* a hydride shift from coordinated isopropanol.



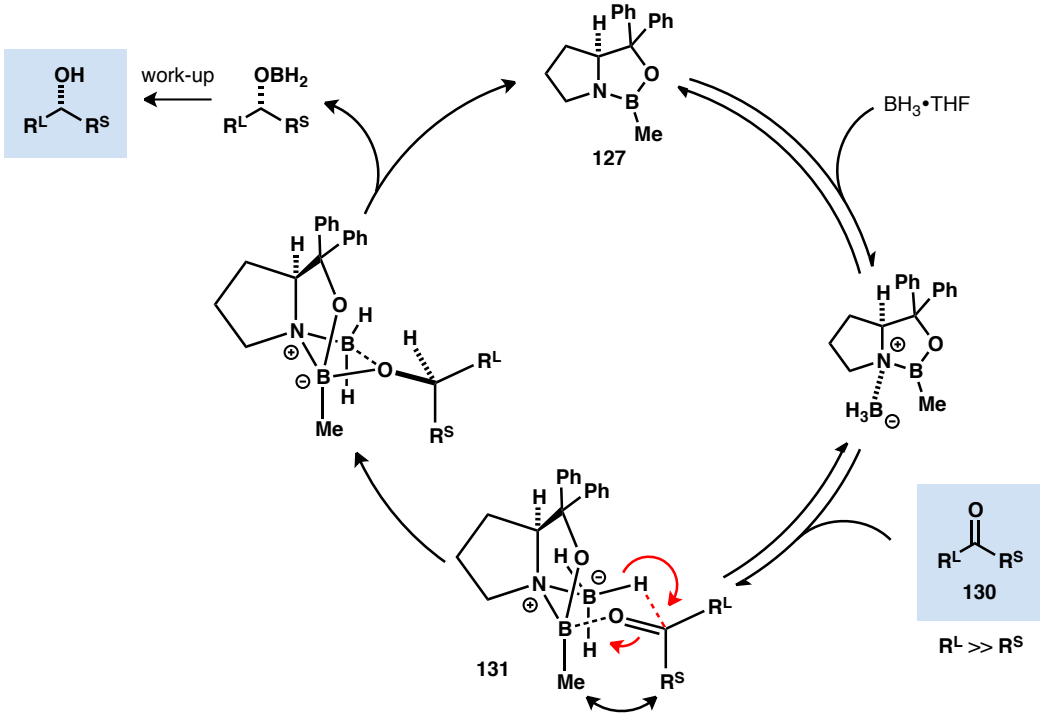
Scheme 32. Mechanistic Interpretation of the Oxidative Cyclisation Reaction

The required enyne counterpart was then prepared (**Scheme 33**). Starting from known 2-methylenehexanal (**125**), acetylide addition and manganese mediated oxidation delivered ketone **126**. Subsequent enantioselective Corey-Bakshi-Shibata (CBS) reduction using (*S*)-methyl-oxazaborolidine **127** yielded alcohol **128** with 90% *ee* and in 81% yield over three steps. Further protecting group manipulation and installation of the required methyl group *via* Michael addition on a propargylic ester intermediate furnished enoate **129**. Finally the ester functionality was converted into alkyne **116** by the use of a four-step protocol.



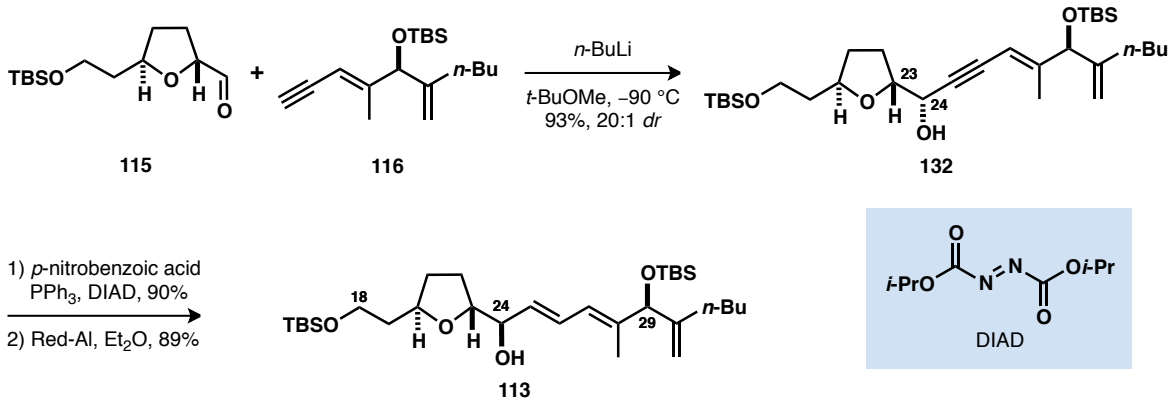
Scheme 33. Enyne Side Chain **116** Formation

The CBS reduction of ketones is thought to proceed as follows (**Sceme 34**).[43] First, complexation of the borane to the nitrogen atom of oxazaborolidine **127** occurs. Ketone **130** then coordinates to the endocyclic boron and then hydrogen transfer from the NBH_3^- unit to the carbonyl takes place *via* a six-membered transition state, as shown in intermediate **131**. Finally, the catalytic species is regenerated. As proposed by Liotta,[44] the enantioselective outcome can be explained by a chair arrangement in **131**, in which the 1,3-diaxial interaction between the oxazaborolidine methyl group and the large or small substituents of the ketone dictates the face of the aldehyde that will undergo the hydride transfer.



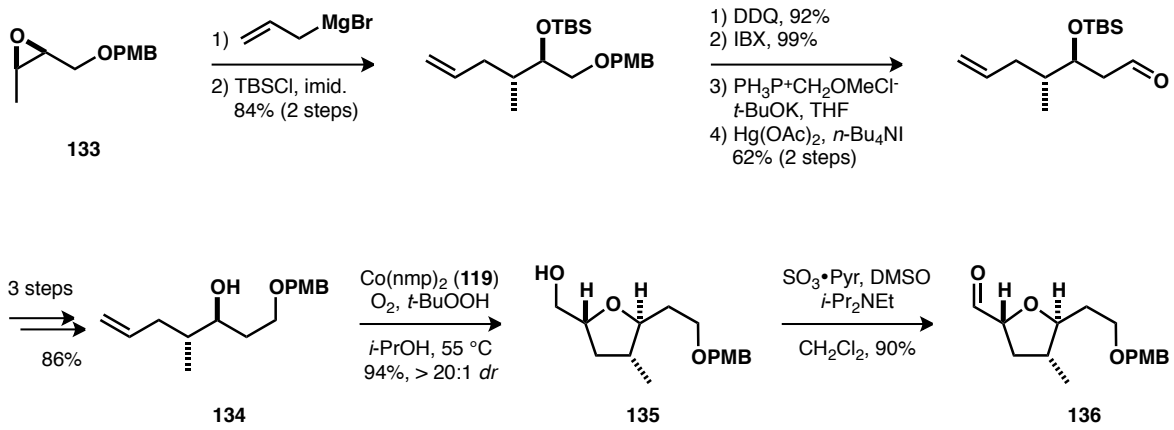
Scheme 34. CBS Reduction Mechanism

Finally, treatment of the lithium acetylide of alkyne **116** with aldehyde **115** in methyl *t*-butyl ether at −90 °C furnished propargylic alcohol **132** with a C23−C24 *anti* relationship with high diastereoselectivity (20:1 *dr*) under Felkin-Ahn control (**Scheme 35**). Further inversion of configuration at the C23 alcohol under Mitsunobu conditions followed by reduction with Red-Al provided the C18−C34 fragment **113** in a total of 17 steps and in 26% overall yield.



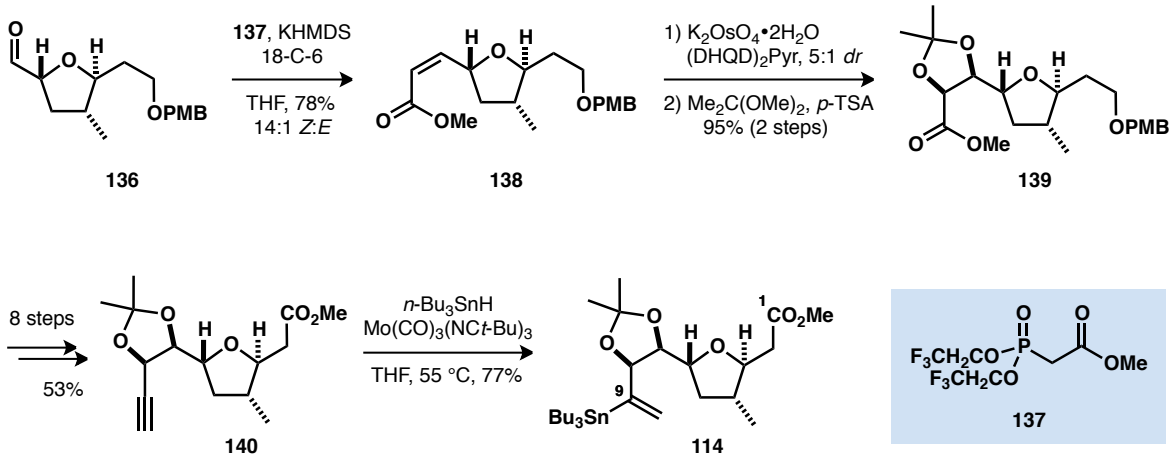
Scheme 35. Completion of C18−C34 Fragment **113**

Following completion of the synthesis of the C18−C34 fragment, efforts were directed towards the preparation of its C1−C9 counterpart (**Scheme 36**).[23b] Starting from chiral non-racemic epoxide **133**, the alkenol cyclisation precursor **134** was prepared in nine steps. The sequence included homologation *via* formation of an enol ether by Schlosser modification of the Wittig olefination and subsequent hydrolysis. The key cobalt-catalysed oxidative cyclisation reaction furnished 2,5-*trans*-tetrahydrofuran **135** in excellent yield and with high *dr*. Aldehyde **136** was obtained using a standard Parrikh-Doering oxidation reaction.



Scheme 36. C3−C6 Tetrahydrofuran Preparation

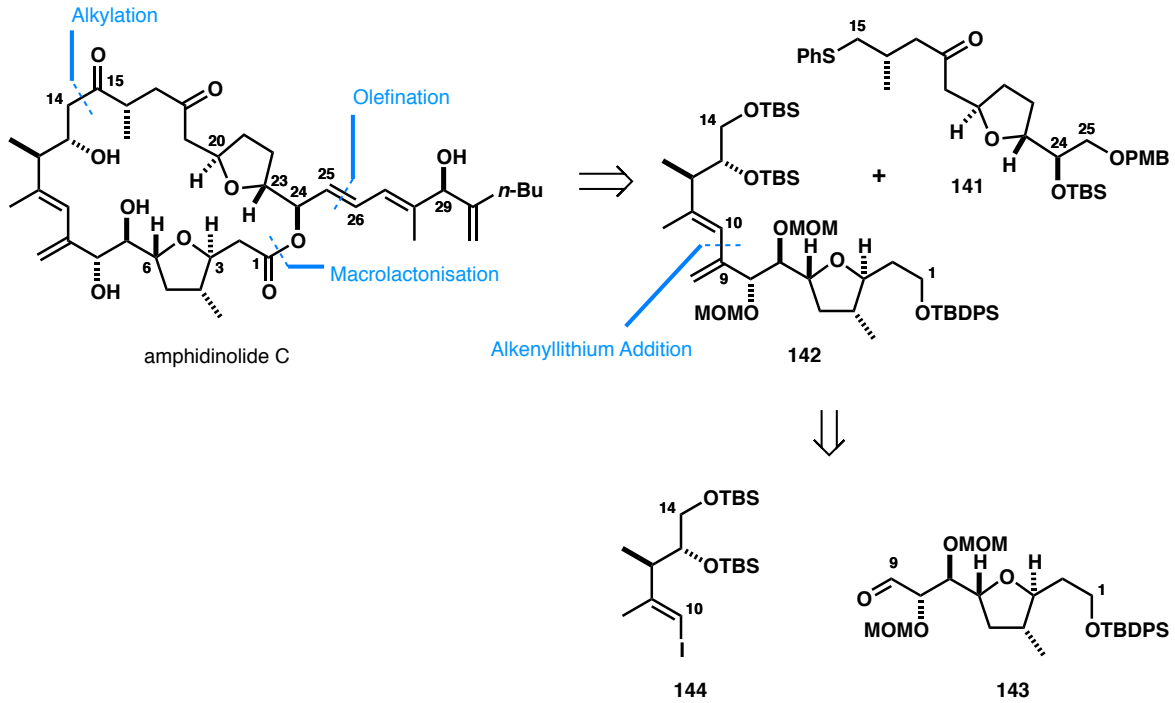
Aldehyde **136** was converted into *α*,*β*-unsaturated ester **138** by a Still-Gennari olefination with phosphonate **137** to provide the desired alkene as a mixture of isomers (14:1, *Z*:*E*) (**Scheme 37**). Installation of the appropriate stereocentres at the C7 and C8 positions was effected by a Sharpless asymmetric dihydroxylation. The resulting diol was obtained as a 5:1 mixture of inseparable diastereomers which were readily protected to acetonide **139**. Further transformations installed the methyl ester functionality as well as the terminal alkyne featured in adduct **140**. Finally, hydrostannylation under the conditions used by Ferrié and Figadère in their synthesis of a similar fragment[24] provided 1,1-disubstituted vinyl stannane **114**, and the lengthy 23-step sequence was completed in 10% overall yield.



Scheme 37. Elaboration of C1−C9 Fragment **114**

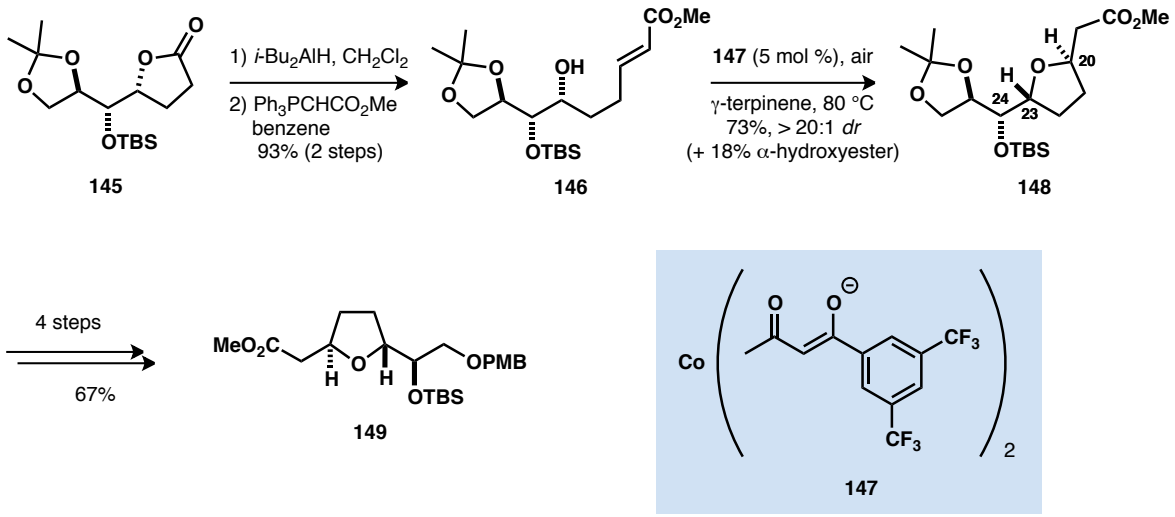
1.4.7. Forsyth: Alkenyllithium Addition / Peterson Olefination

In 2013, the Forsyth group reported the syntheses of both the C1−C14 (**142**) and C15−C25 (**141**) fragments of amphidinolides C and F (**Scheme 38**).[25] The retrosynthetic approach that was adopted involved the usual macrolactone disconnection at the C1 ester bond and the use of a sulfone alkylation reaction, similar to the one employed by Carter and co-workers,[18,27] to form the C14−C15 bond. Finally, the C9−C10 bond was to be constructed by addition of an alkenyllithium species, generated from vinyl iodide **144**, to aldehyde **143**. The originality of this strategy relied on a potential late-stage installation of the C26−C34 polyene side chain after elaboration of the macrocycle, in order to facilitate the generation of analogues, a goal that has not been accomplished yet.



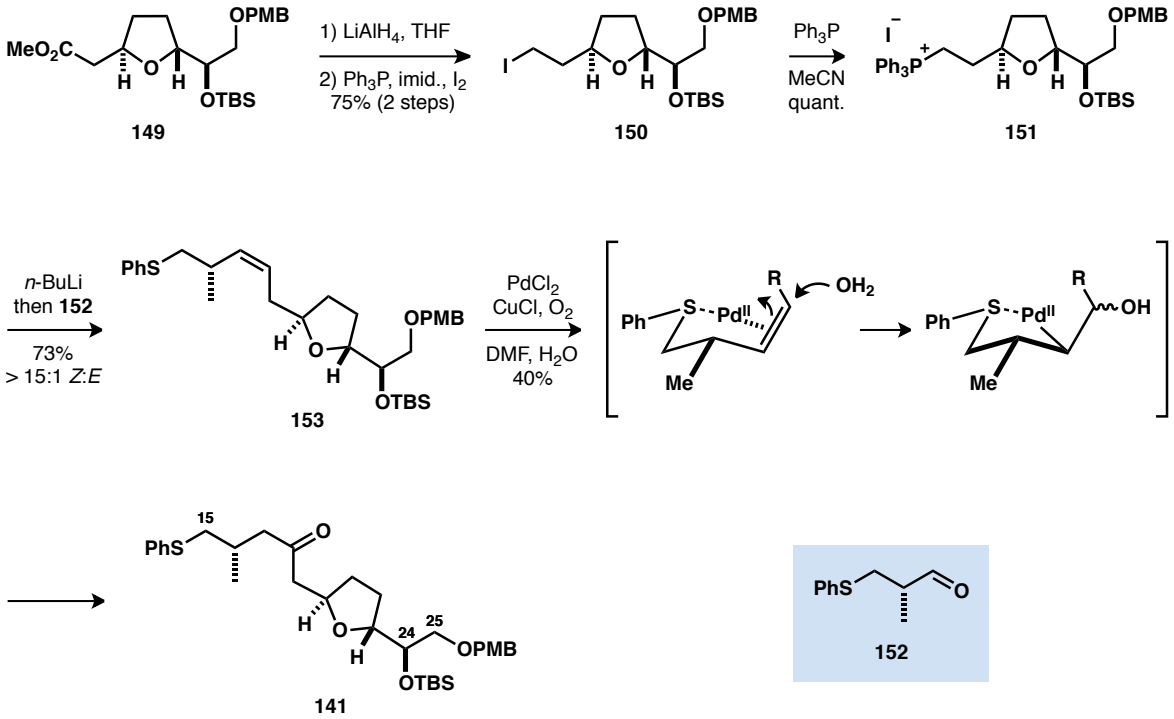
Scheme 38. Main Retrosynthetic Disconnections

The synthesis of thioether **141** started with reduction of lactone **145** and Wittig olefination of the lactol intermediate to provide *α*,*β*-unsaturated ester **146** in excellent yield (**Scheme 39**). Further Mukaiyama aerobic alkenol cyclisation using cobalt complex **147** developed by Hartung[45] yielded *trans*-tetrahydrofuran **148** as a single diastereomer in which the C20, C23 and C24 stereocentres were introduced with the appropriate configuration. In four additional steps, the acetonide segment was converted into the corresponding PMB ether **149**.



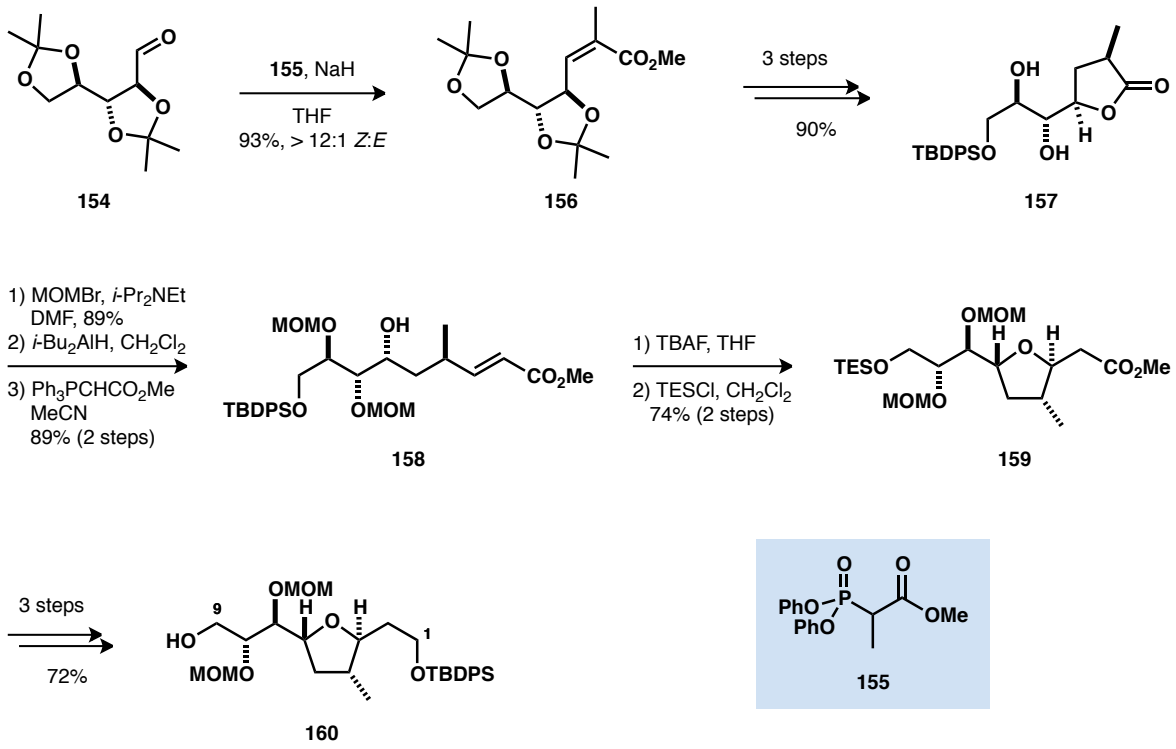
Scheme 39. C20−C23 Tetrahydrofuran **149** Preparation

The ester segment of tetrahdyrofuran **149** was converted into phosphonium iodide **151** *via* iodide **150** (**Scheme 40**). Coupling of the anion of phosphonium **151** with aldehyde **152** under Wittig conditions furnished alkene **153** (15:1, *Z*:*E*) in 73% yield. Finally, ketone **141** was prepared in moderate yield by a sulfur-directed regioselective Wacker oxidation, under conditions initially proposed by Raghavan for the oxidation of internal alkenes.[46] In this case, the sulfide moiety directs palladium to the proximal terminus of the tethered olefin and water attacks the distal carbon preferentially affording regioselectively the keto-sulfide product after reductive elimination. The C15−C25 thioether **141** was obtained in 12 steps from known lactone **145** in 13% overall yield.



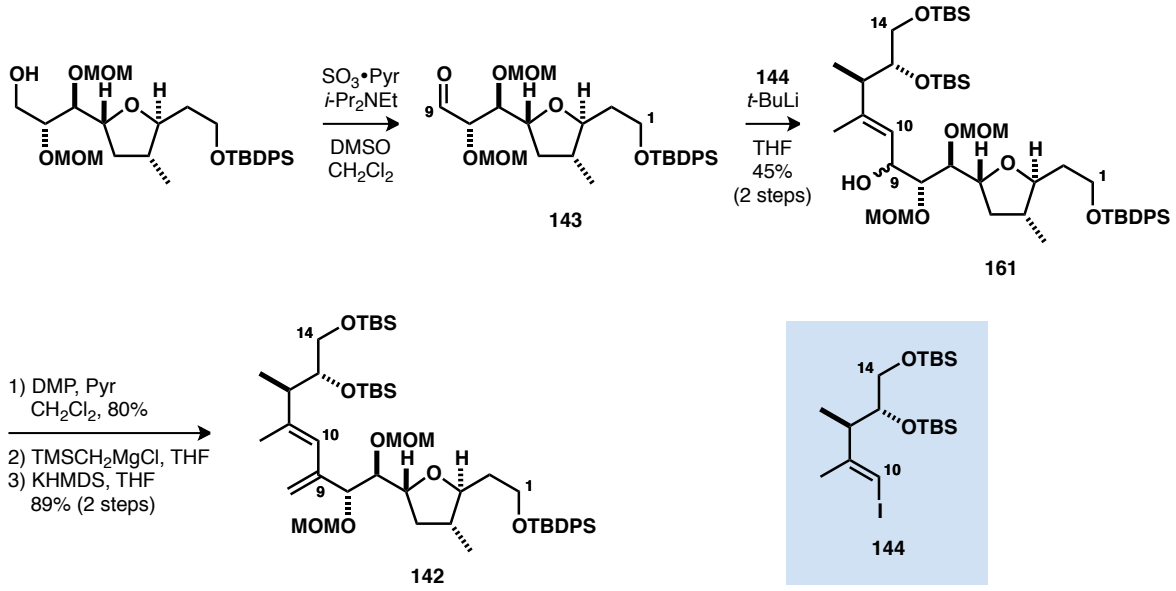
Scheme 40. Regiocontrolled Wacker Oxidation to Thioether **141**

Elaboration of the C1−C9 fragment started from known aldehyde **154** as the source of the C7−C8 stereochemistry (**Scheme 41**). The general synthetic approach was derived from Roush's precedent.[19b] Ando olefination using phosphonate **155** furnished *Z*-olefin **156** in excellent yield. Further formation of a butenolide and diastereoselective hydrogenation to install the C4 stereocentre provided lactone **157**. After reduction to the lactol and incorporation of the *α*,*β*-unsaturated ester segment, enoate **158** was cyclised by treatment with TBAF to provide *trans*-tetrahydrofuran **159**, which was readily converted into alcohol **160** in three additional steps.



Scheme 41. Preparation of C1−C9 Alcohol **160**

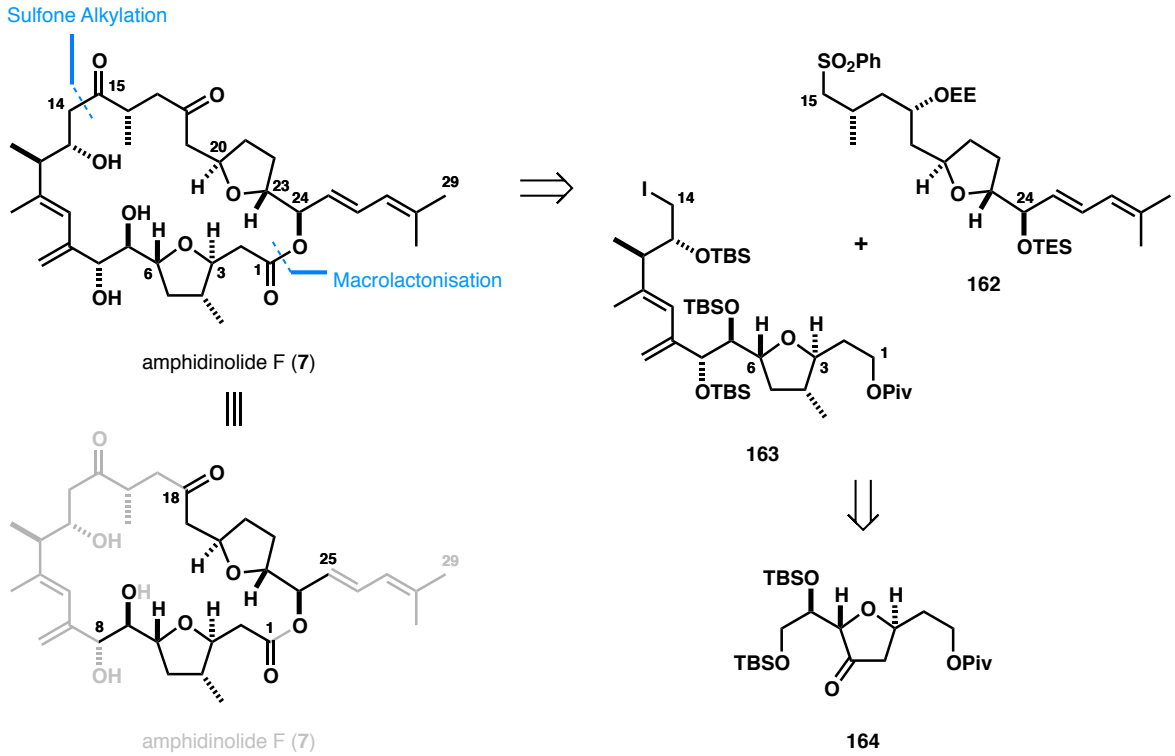
Installation of the C10−C14 side chain was effected by lithium-halogen exchange of Carter's iodide **144**[47] and subsequent addition to aldehyde **143**, to give alcohol **161** as a 1:1 diastereomeric mixture (**Scheme 42**). Finally, oxidation and Peterson olefination of the resulting ketone formed the C9 exocyclic methylene. The synthesis of fragment **142** was completed in a total of 17 steps from aldehyde **154** and with 11% overall yield.



Scheme 42. Completion of C1−C14 Fragment **142**

1.4.8. Carter: First Total Synthesis by Use of Hidden Symmetry

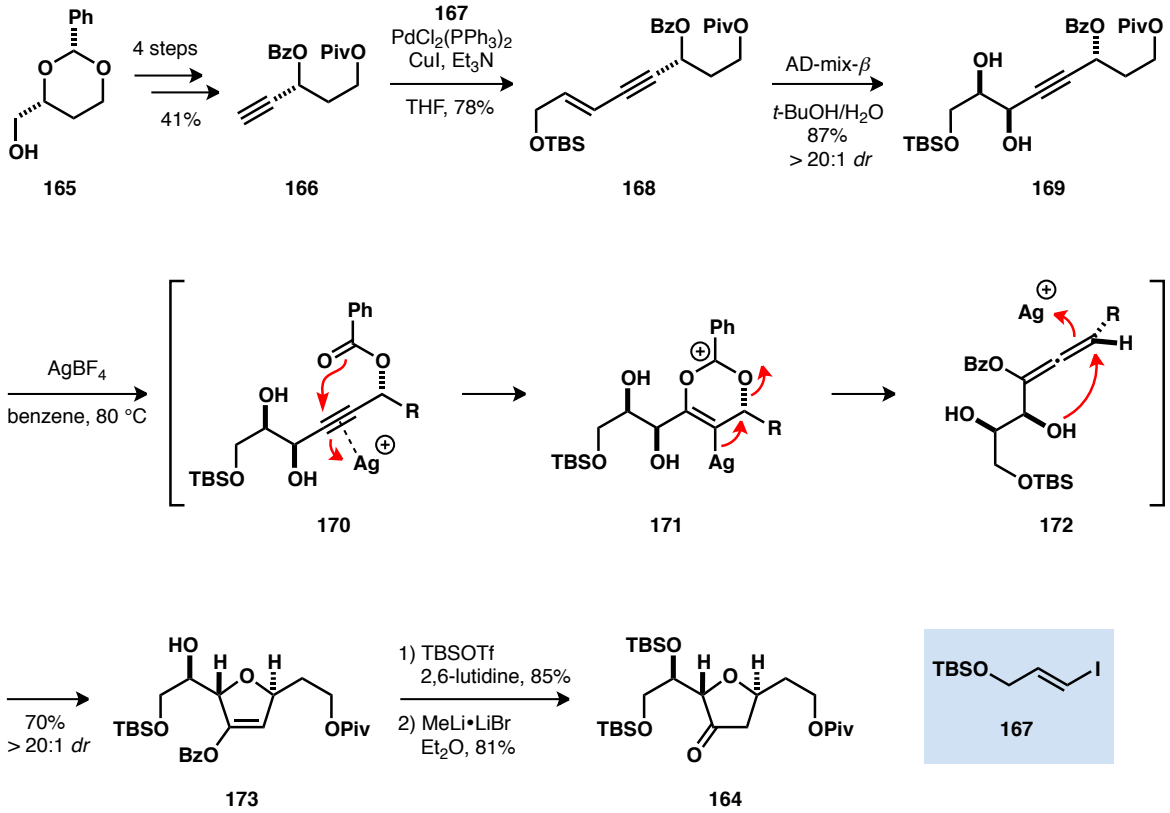
In 2012, Carter and co-workers reported the preparation of amphidinolide F. This work was the first total synthesis of a member of the amphidinolide C series (**Scheme 43**).[18] The Carter group approach relied on the identification of hidden symmetry within the two *trans*-tetrahydrofuran rings present in macrolactone **7**, with the C1−C8 and C18−C25 segments bearing similar stereochemistry, oxidation states and functionalisation. The retrosynthetic analysis proposed disconnections of the ester bond of the macrolactone and the C14−C15 bond through an umpolung strategy, revealing two main fragments: sulfone **162** and alkyl iodide **163**, which could be accessed from the common intermediate **164**.



Scheme 43. Retrosynthesis and Hidden Symmetry

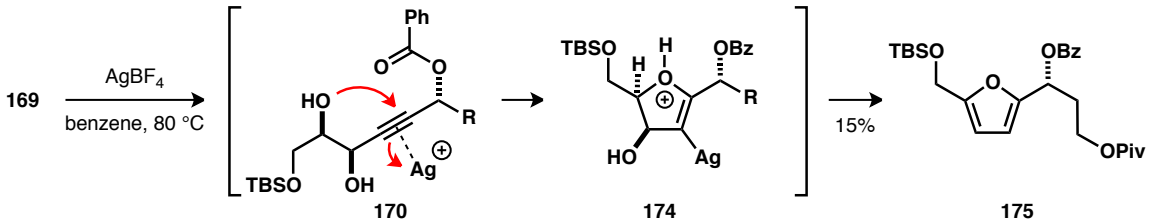
The synthesis of the common dihydrofuranone **164** started from known alcohol **165** (**Scheme 44**). Following the preparation of alcohol **165** in just two steps from D-malic acid, the hydroxyl group was converted into alkyne **166** by means of sequential oxidation and Ohira-Bestmann homologation followed by protecting group manipulation. Sonogashira cross-coupling of alkyne **166** to vinyl iodide **167** afforded enyne **168** in good yield. 1,2-Diol **169** was then obtained as a single diastereomer by Sharpless asymmetric dihydroxylation of the alkene. Subsequent

silver-catalysed cyclisation of diol **169** furnished dihydrofuran **173** in excellent yield and with complete diastereoselectivity. It was hypothesised that the benzoate oxygen undergoes nucleophilic addition to the activated alkyne **170** leading to chiral allene **172** *via* stabilised carbocation **171**. A second silver-mediated activation of the allene species promotes nucleophilic attack by the nearby alcohol to deliver dihydrofuran **173** after protodemetalation. Finally, silyl protection and removal of the enol benzoate produced dihydrofuranone **164**.



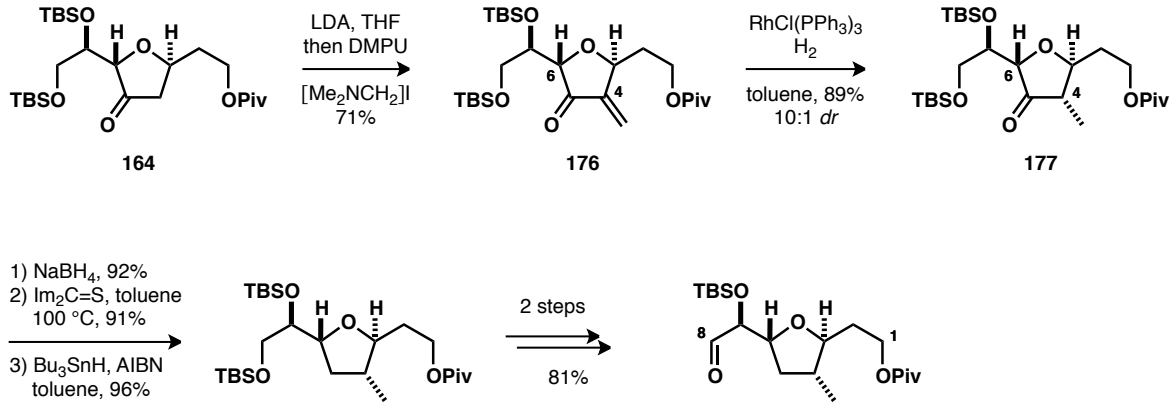
Scheme 44. Ag-catalysed Cyclisation Towards Dihydrofuranone **164**

To account for the formation of furan **175** as a minor byproduct during the silver-catalysed cyclisation of diol **169**, it was proposed that competitive nucleophilic attack onto the activated alkyne **170** by the nearby alcohol produces vinyl silver intermediate **174**, followed by protodemetalation and acid-catalysed aromatisation to give furan **175** (**Scheme 45**).



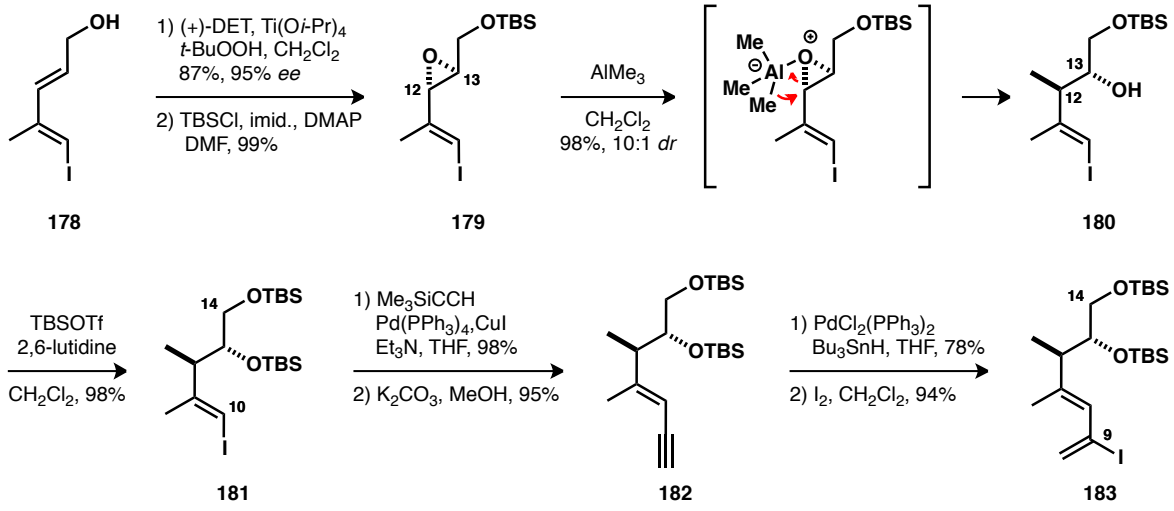
Scheme 45. Competitive Formation of Furan **175**

First diversification of common dihydrofuranone **164** was achieved with the installation of the C4 methyl group by trapping the enolate intermediate using Eschenmoser's salt to give enone **176** (**Scheme 46**). Subsequent hydrogenation of the double bond using Wilkinson's catalyst then produced ketone **177**. The stereocontrol observed during the hydrogenation reaction was linked to the stereochemistry at the C6 position because this was the dominant element in the direct alkylation process. This observation was made during previous attempts to perform direct enolate alkylation, which gave the undesired C4 stereochemistry.



Scheme 46. Synthesis of the C1−C8 Aldehyde

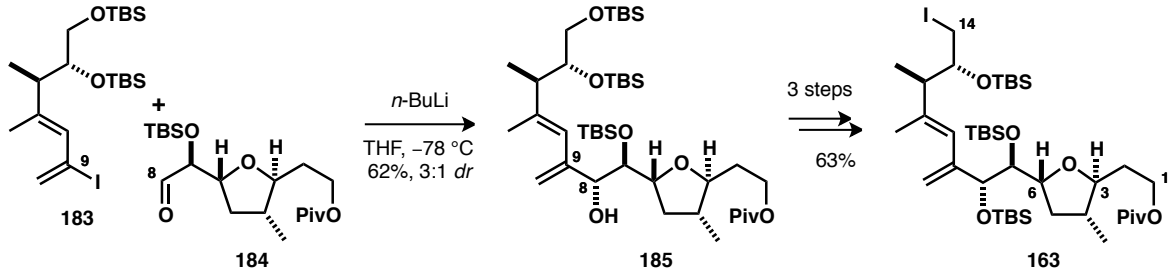
In order to complete the elaboration of fragment C1−C14, the required vinyl iodide **183** was prepared (**Scheme 47**). Known vinyl iodide **178** was subjected to Sharpless asymmetric epoxidation to provide, after silyl protection, epoxide **179** in high yield and with good diastereoselectivity. Treatment of the allyl epoxide with trimethylaluminium yielded alcohol **180** with preferential S_N2 opening at C12.



Scheme 47. Preparation of Vinyl Iodide **183**

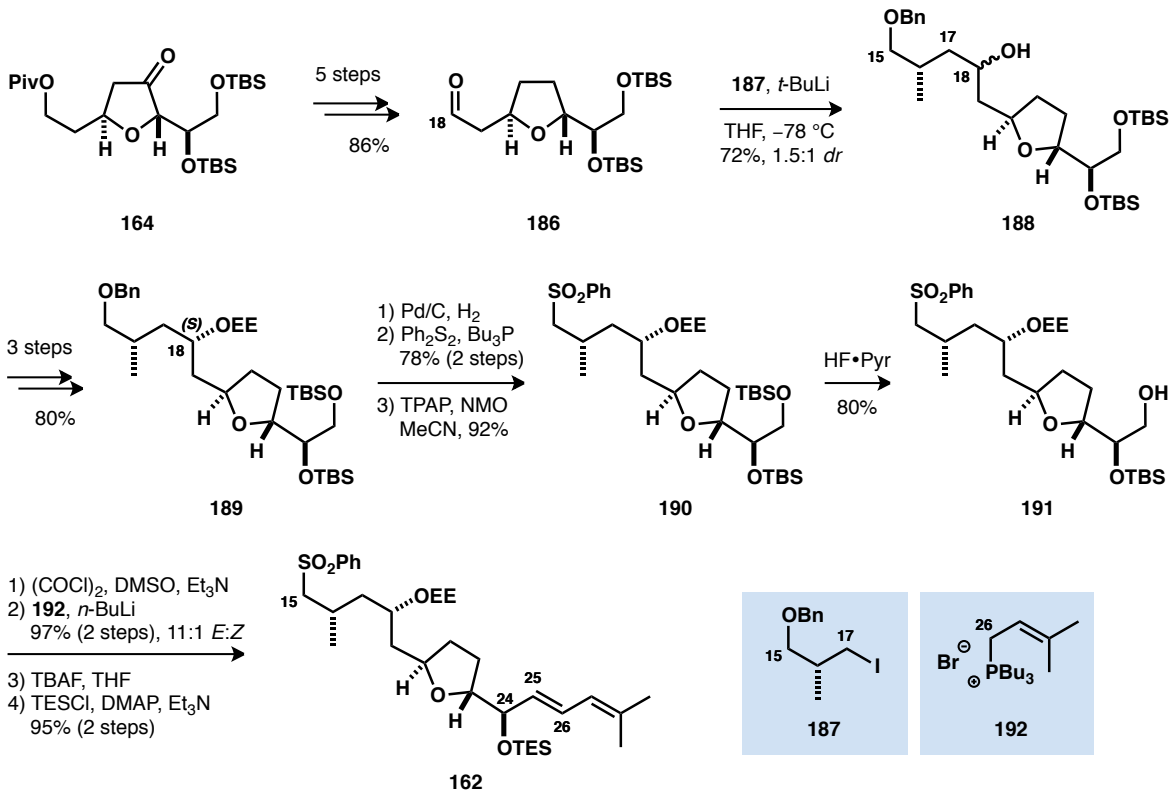
Further Sonogashira coupling of vinyl iodide **181** with TMS-acetylene provided enyne **182** in excellent yield. Finally, regioselective hydrostannylation of the alkyne and subsequent iodination furnished 2-iodo-1,3-diene **183**.

To complete the targeted alkyl iodide fragment **163**, metal-halogen exchange was performed by treatment of vinyl iodide **183** with *n*-butyllithium, and addition of aldehyde **184** to the resulting vinyl lithium species produced allylic alcohol **185** in reasonable yield and with modest diastereoselectivity (**Scheme 48**). The required iodide fragment **163** was obtained after three additional steps.



Scheme 48. Completion of the C1−C14 Fragment

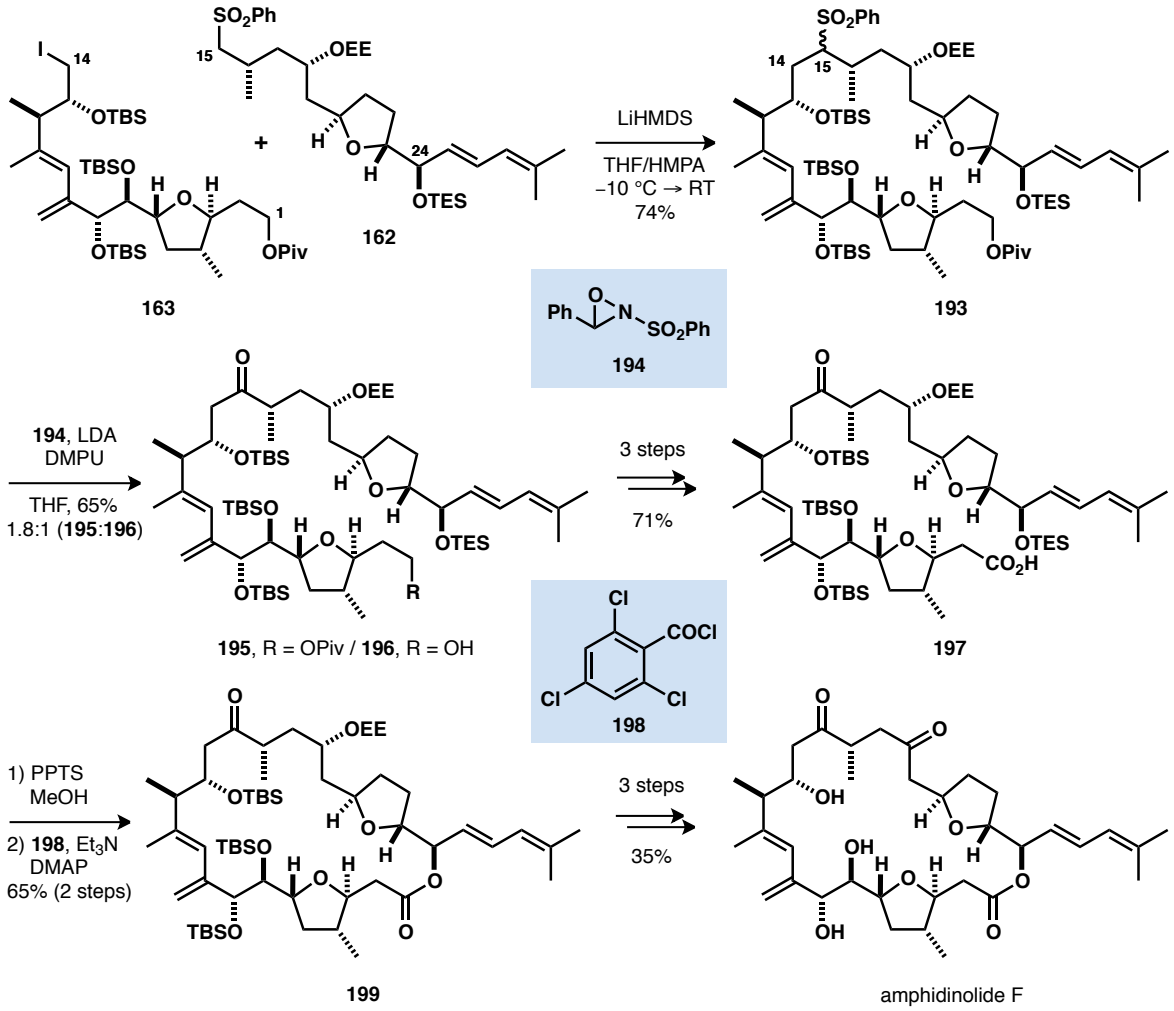
Diversification of dihydrofuranone **164** en route to sulfone **162** began with deoxygenation at C22 and formation of aldehyde **186** (**Scheme 49**).



Scheme 49. Elaboration of Final Sulfone **162**

Addition of the organolithium species obtained from known iodide **187** generated a 1.5:1 mixture of inseparable diastereomeric secondary alcohols **188** in 72% yield. Even though it would have been possible for both diastereomers to have been used to complete the synthesis, a two-step oxidation/reduction sequence was applied to convert the mixture into the single isomer **189** bearing the C18-(*S*) configuration. Cleavage of the benzyl protecting group and installation of the key sulfone moiety gave adduct **190** in excellent yield over three steps. Finally, oxidation of primary alcohol **191** and subsequent olefination using the Vedejs-type phosphonium salt **192**[48] formed the C25−C26 *E*-alkene in excellent yield and with high selectivity. Protecting group manipulation completed the synthesis of sulfone **162**.

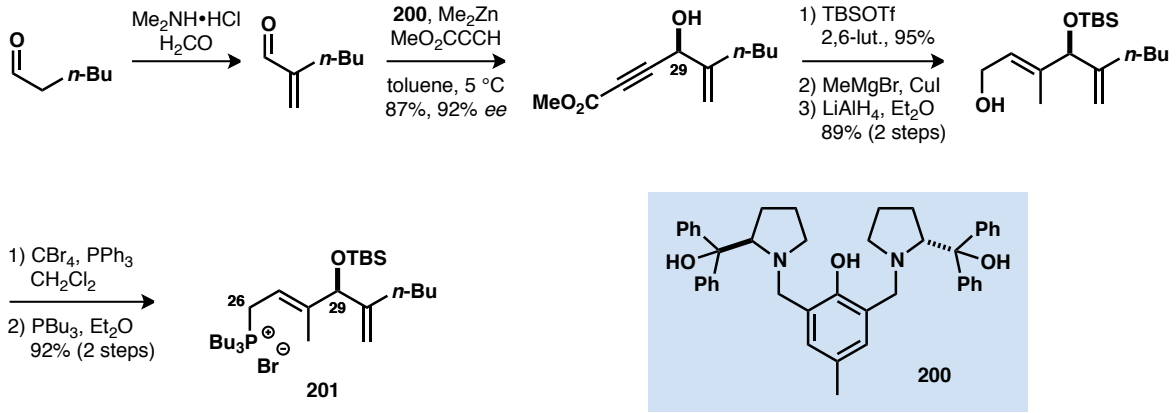
The endgame of the synthesis was initiated by deprotonation of sulfone **162** using LiHMDS in the presence of HMPA and subsequent addition of the anion to iodide **163**, forming the C14−C15 bond in 74% yield (**Scheme 50**).



Scheme 50. Total Synthesis of Amphidinolide F

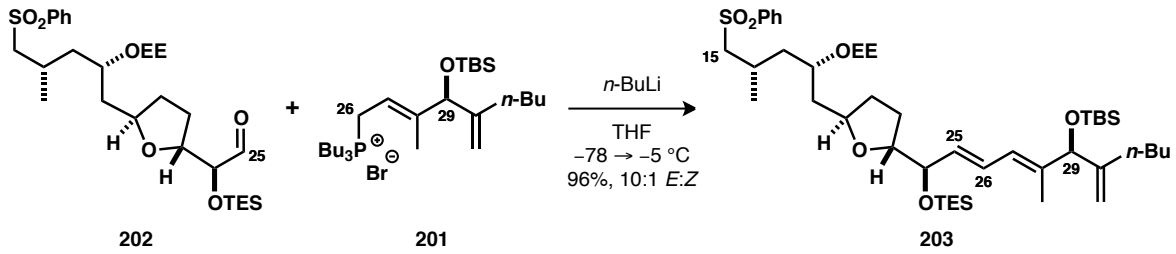
Oxidative desulfurisation of sulfone **193** upon treatment with Davis' oxaziridine (**194**) yielded a 1.8:1 mixture of the desired ketone **195** alongside the pivalate-deprotected hydroxy ketone **196**. Both ketones were converted into acid **197** in good yield using standard reactions. Formation of the seco acid and Yamaguchi macrolactonisation using acyl chloride **198** provided macrolactone **199** in 65% yield over two steps. Finally, selective removal of the EE protecting group under aqueous acidic conditions, oxidation of the resulting alcohol and global desilylation afforded amphidinolide F. The synthesis was completed in a total of 34 steps and with an overall yield of 0.3%.

In 2013, Carter used the same strategy to synthesise amphidinolide C.[27] In order to install the appropriate side chain, phosphonium salt **201** was prepared (**Scheme 51**). The key feature of this seven-step sequence was the use of a Trost asymmetric alkynylation with ligand **200** to install the C29 stereocentre.[49]



Scheme 51. Synthesis of Phosphonium Salt **201**

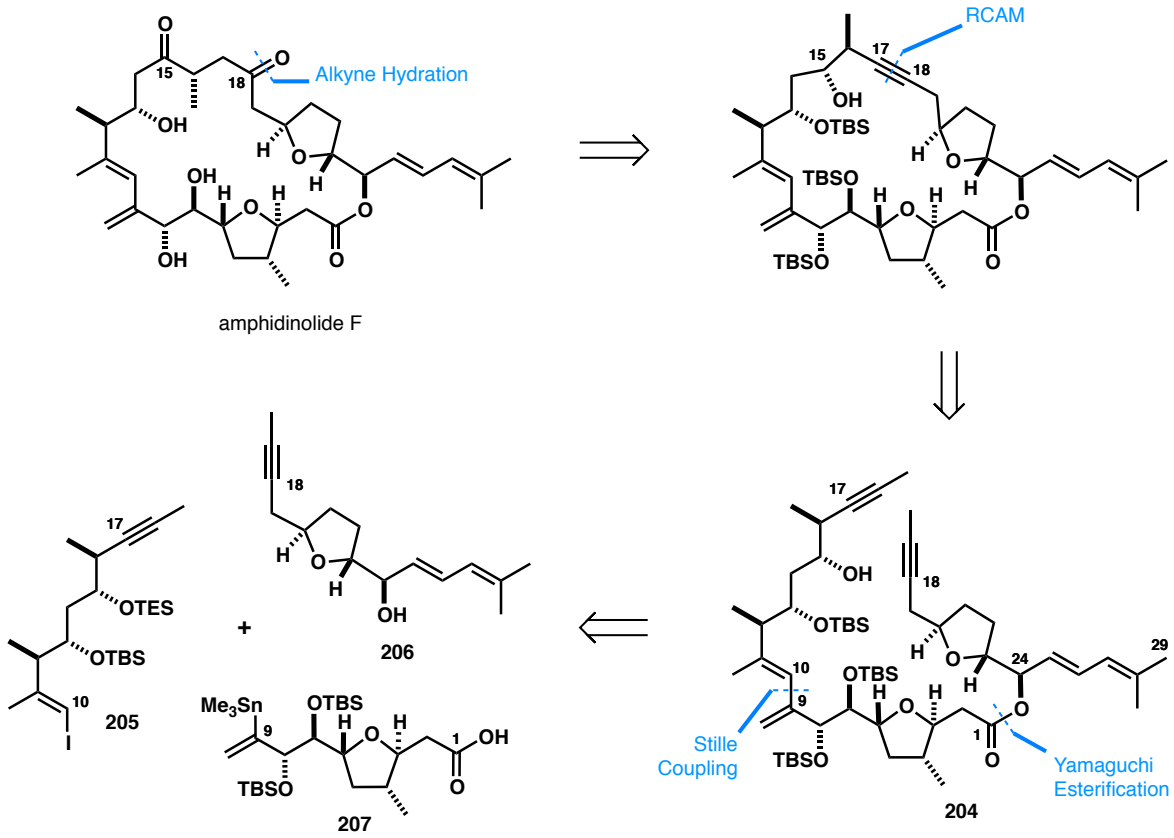
The side chain was installed by olefination of aldehyde **202** under Vedejs conditions using phosphonium salt **201**, which provided *E*-alkene **203** selectively (**Scheme 52**). Sulfone **203** was employed in the same synthetic sequence as described previously to yield amphidinolide C, in 33 steps and 0.2% overall yield.



Scheme 52. Completion of C15−C34 Sulfone **203**

1.4.9. Fürstner: Ring-Closing Alkyne Metathesis / Alkyne Hydration

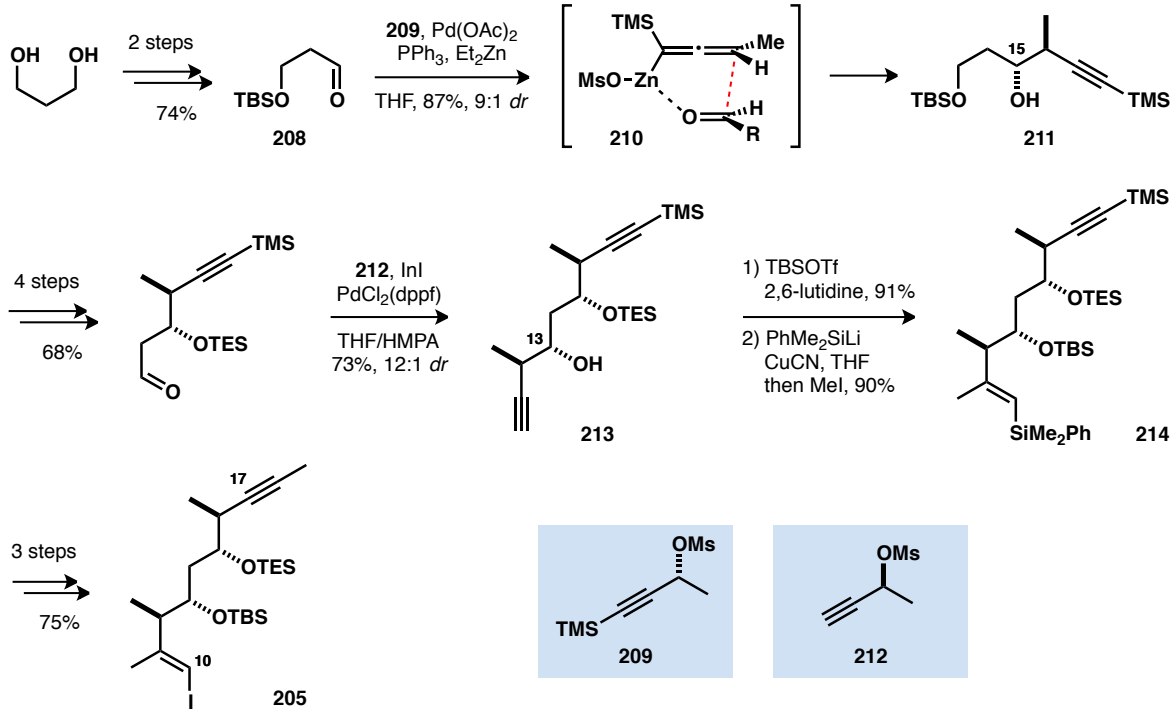
In 2013, the Fürstner group reported the second total synthesis of amphidinolide F.[28a] Their original and concise approach relied on the use of a ring-closing alkyne metathesis (RCAM) to close the macrocycle followed by a directed transannular alkyne hydration reaction to access the 1,4-diketone functionality (**Scheme 53**). Further disconnections revealed three main fragments of comparable size and complexity: vinyl iodide **205**, allylic alcohol **206** and vinyl stannane **207**, which could be coupled by Yamaguchi esterification and Stille cross-coupling to give diyne **204**.



Scheme 53. Retrosynthetic Analysis and Main Fragments

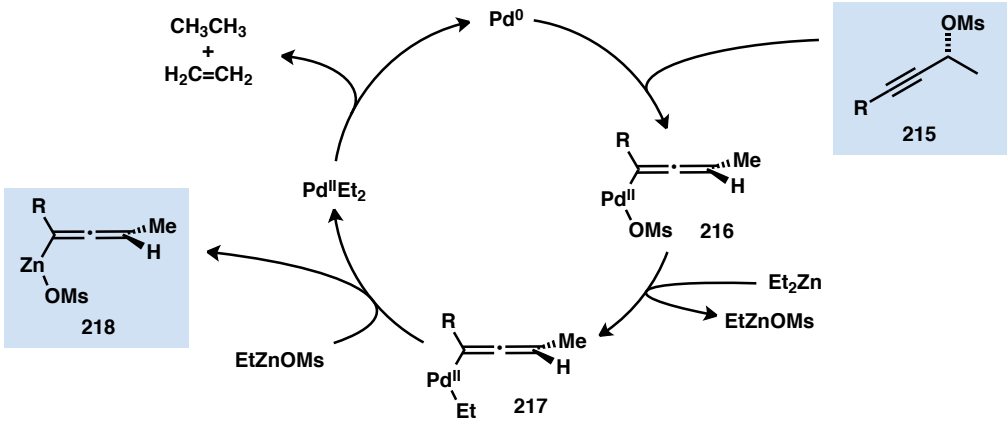
The synthesis of vinyl iodide **205** exploited the latent symmetry of this building block. Starting from 1,3-propanediol, an *anti*-propargylation methodology developed by Marshall[50] was implemented to set the C13 and C15 stereocentres (**Scheme 54**). First, zinc-mediated palladium catalysed propargylation of aldehyde **208** with chiral mesylate **209** gave alcohol **211** in excellent yield and with a 9:1 *dr*, through the less sterically demanding orientation (**210**) of the complexed aldehyde and the allenylzinc partner. A similar oxidation/propargylation sequence using the

indium(I) iodide variant of Marshall protocol with alkyne **212** completed this two-directional approach and delivered alcohol **213** with high diastereoselectivity. Regioselective silylcupration of the terminal alkyne followed by a methyl iodide quench provided vinyl silane **214** in 90% yield. Methylation of the remaining alkyne and iodine-silicon exchange completed the elaboration of vinyl iodide **205**.



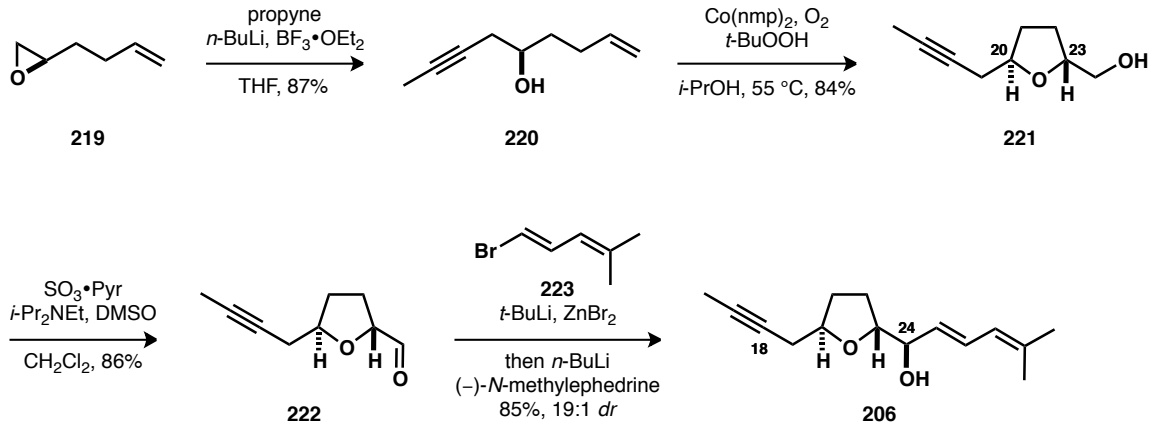
Scheme 54. *anti* Propargylation Methodology Towards Iodide **205**

A possible catalytic cycle for the zincation of propargylic mesylates (**215**) was proposed (**Scheme 55**).[50] First, a S_N2' palladium insertion gives Pd^{II} species **216**. Reaction with diethylzinc then leads to alkylpalladium **217**. Further exchange of ligands with remaining EtZnOMs provides allenylzinc mesylate **218** and a Pd^{II} species. The latter decomposes rapidly to form ethylene and ethane, thereby regenerating the active Pd^0 catalyst.



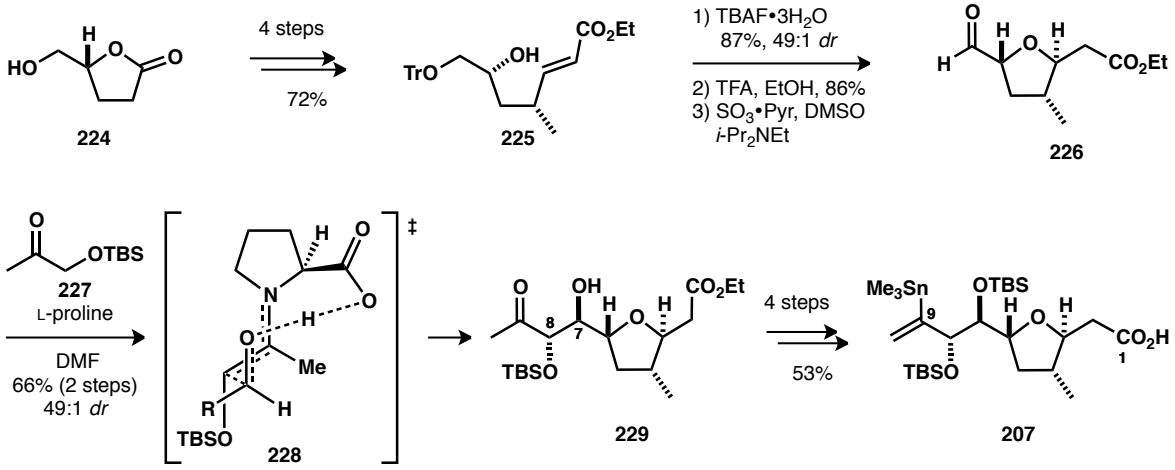
Scheme 55. Proposed Catalytic Cycle to Allenylzinc Reagent **218**

Preparation of the tetrahydrofuran building block **206** from chiral epoxide **219** was achieved in just four steps (**Scheme 56**). After nucleophilic opening of the epoxide with lithiated propyne, Mukaiyama cyclisation of alkenol **220** using the cobalt catalyst developed by Pagenkopf[41] afforded *trans*-tetrahydrofuran **221** as a single diastereomer. Finally, a reagent-controlled *N*-methylephedrine-assisted reaction of an organozinc reagent,[51] generated from vinyl bromide **223**, with aldehyde **222** furnished allylic alcohol **206** in excellent yield and with high diastereoselectivity, and completed the installation of the diene side chain.



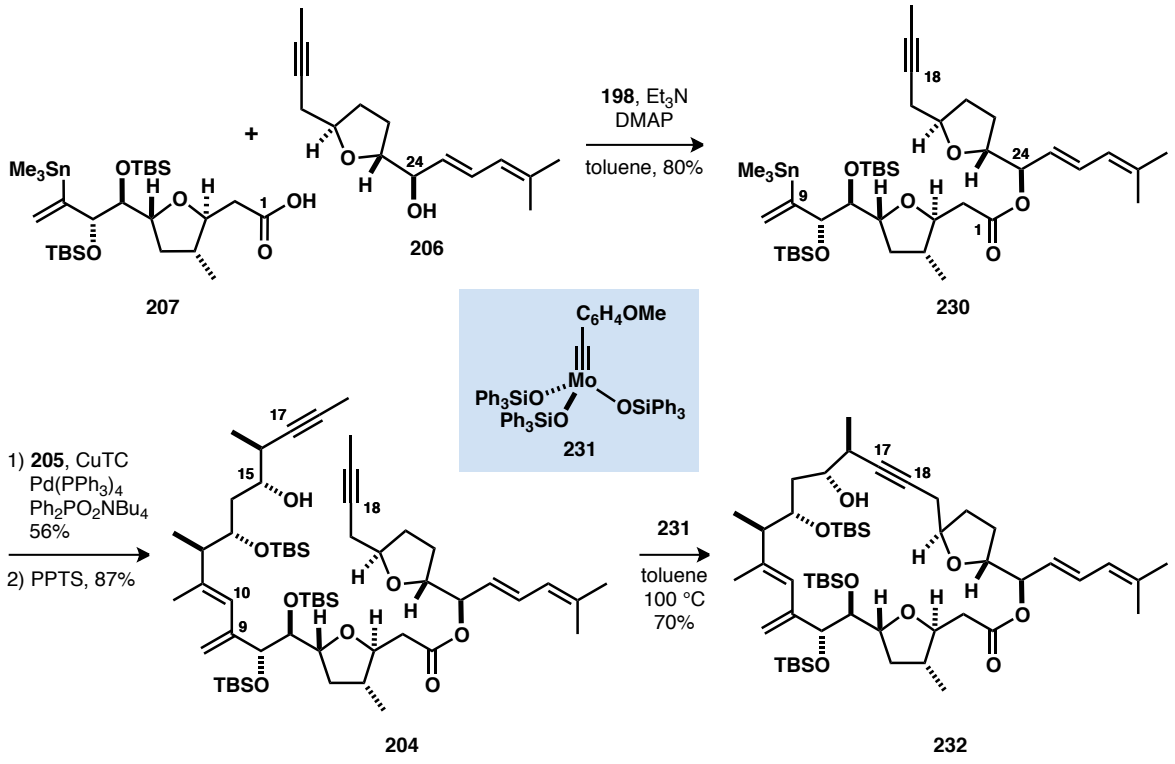
Scheme 56. Elaboration of *trans*-Tetrahydrofuran **206**

Vinyl stannane fragment **207** was assembled from commercially available furanone **224** (**Scheme 57**). The lactone was converted into the enoate **225** in four steps. The unsaturated ester underwent oxa-Michael addition upon treatment with TBAF to obtain the corresponding *trans*-tetrahydrofuran in excellent yield and as a single diastereomer. Removal of the trityl group and subsequent oxidation of the resulting alcohol delivered aldehyde **226**. The key proline-catalysed aldol reaction between aldehyde **226** and hydroxyacetone derivative **227** yielded alcohol **229** in decent yield and installed the required C7−C8 *anti* relationship. In transition state **228**, accounting for the C−C bond formation, proline is employed as a bifunctional entity, with the enamine catalytic role and the carboxylic acid cocatalyst used to protonate the acceptor carbonyl group.[52] Finally, the ketone segment was converted into the vinyl stannane and the ester was saponified to complete carboxylic acid **207**.



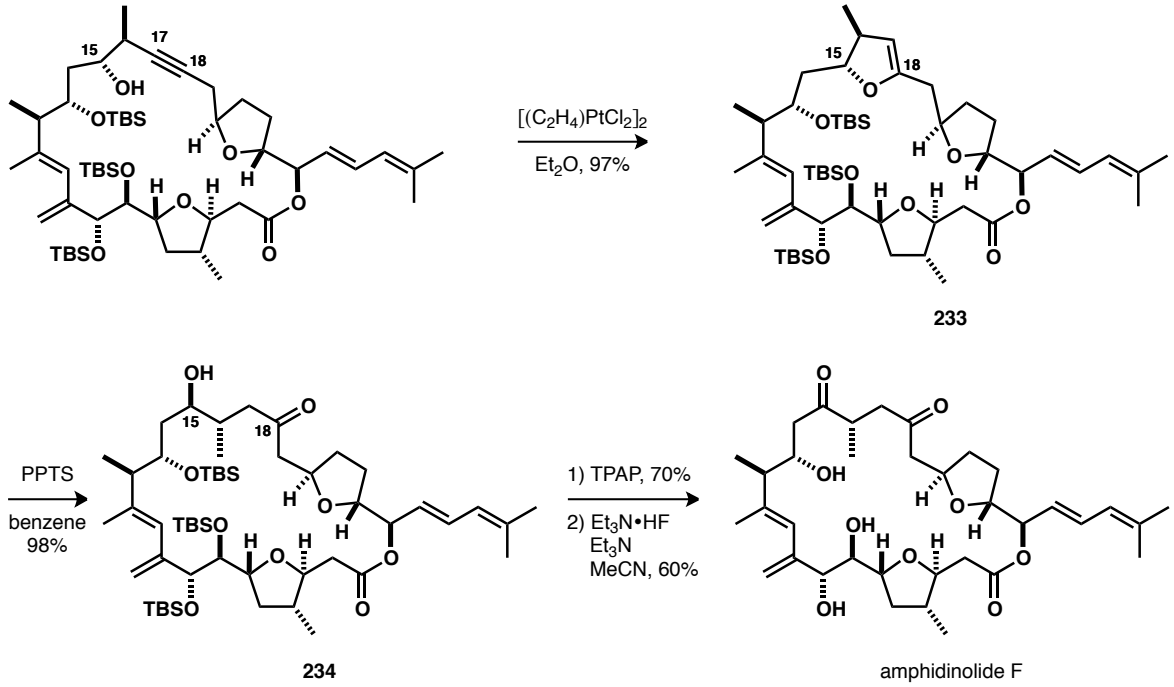
Scheme 57. Proline-catalysed Aldol Reaction Towards Stannane **207**

With the three key fragments in hand, Fürstner and co-workers commenced the fragment coupling sequence by using a Yamaguchi esterification to join alcohol **206** and carboxylic acid **207** (**Scheme 58**). Stille coupling of the resulting vinyl stannane **230** and vinyl iodide **205** under mild conditions [53] produced the corresponding diene unit in 56% yield. Selective silyl deprotection at C15 then provided diyne **204** required for the key macrolactonisation reaction and subsequent ring-closing diyne metathesis of this substrate, mediated by the molybdenum complex **231**, afforded macrolactone **232** in 70% yield.



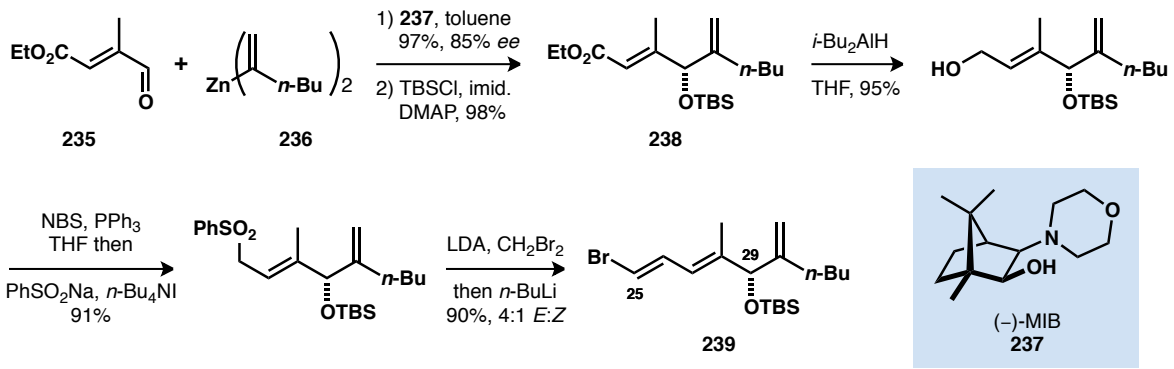
Scheme 58. Endgame RCAM Towards Macroclycle **232**

Platinum-catalysed transannular alkyne hydration provided enol ether **233** in 97% yield (**Scheme 59**). Hydration of the cyclic enol ether delivered hydroxy ketone **234**, in equilibrium with the corresponding hemiketal. Finally, oxidation and global deprotection furnished amphidinolide F, in a total of 21 steps and 2.2% overall yield.



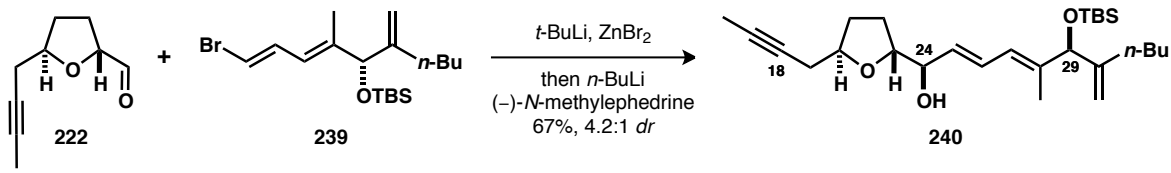
Scheme 59. Transannular Alkyne Hydration Towards amphidinolide F

The Fürstner group applied an identical strategy to the synthesis of amphidinolide C,[28b] for which the extended side chain **239** was prepared (**Scheme 60**). The side chain synthesis featured asymmetric addition of *bis*-alkenylzinc **236** to aldehyde **235** in the presence of (−)-3-*exo*-morpholinoisoborneol (MIB, **237**) as the chiral ligand.[54] This reaction delivered the required alcohol in excellent yield and with 85% *ee*, and the compound was then silylated to give the fragment **238**.



Scheme 60. Synthesis of the Extended 1-Bromo-1,3-diene **239**

In the final step in the synthetic sequence, asymmetric addition of the organozinc species generated from 1-bromo-1,3-diene **239** to aldehyde **222** produced alcohol **240**, bearing the extended side chain, in decent yield and with reasonable diastereoselectivity (**Scheme 61**).



222 239 240

Scheme 61. Analogous Building Block **240** Completion

1.4.10. Conclusion on Fragment / Total Syntheses of Amphidinolides C and F

The syntheses of fragments and the total syntheses discussed in this review showcase a wide range of innovative synthetic strategies and transformations, but also highlight the problems and challenges that need to be faced when attempting to complete such natural products.

It is particularly important to note the efforts that are required to install the large number of stereocentres present as well as the 2,5-*trans*-tetrahydrofuran sub-units, and to appreciate the numerous approaches that have been developed. On the one hand, the cobalt-catalysed Mukaiyama oxidative cyclisation appears to be a powerful tool for the concise assembly of the C20−C23 disubstituted tetrahydrofuran but this approach requires the subsequent installation of the C24 stereocentre in a diastereoselective fashion (**Schemes 31**, **35**, **56**). On the other hand, an oxa-Michael addition on an *α*,*β*-unsaturated ester proves to be a reliable and highly diastereoselective method to assemble the C4−C6 trisubstituted tetrahydrofuran (**Schemes 16**, **17**, **41**, **57**).

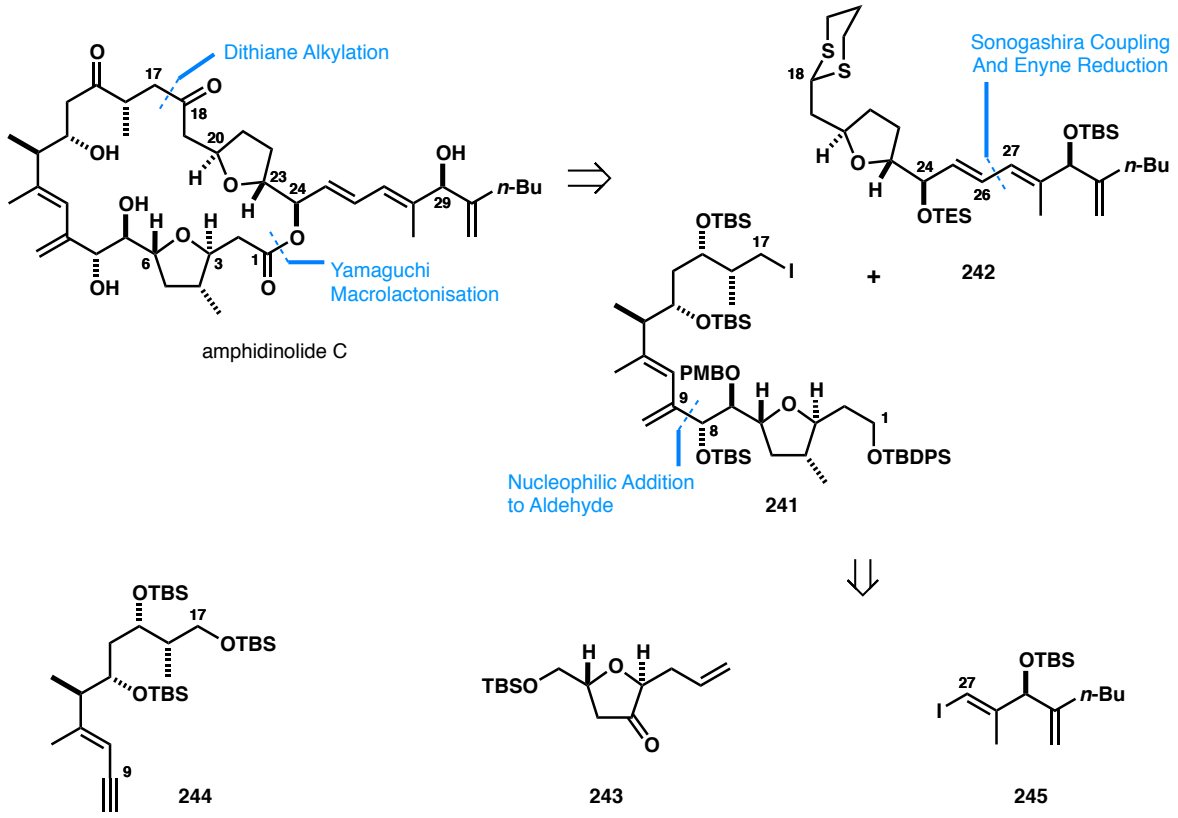
To date, two total syntheses of amphidinolides C and F have been reported. Carter's approach relied on the synthesis of common dihydrofuranone **164** to exploit the hidden symmetry around the tetrahydrofuran units. This is an interesting strategy but differentiation of the common precursor accounted for a higher number of steps. Fürstner and co-workers proposed a highly convergent

strategy with the elaboration of three major fragments of high complexity. Fragment coupling was performed at a late stage using sequential Yamaguchi esterification, a challenging Stille coupling and a RCAM to complete syntheses of both macrolide natural products in just 21 steps.

2. Results and Discussion

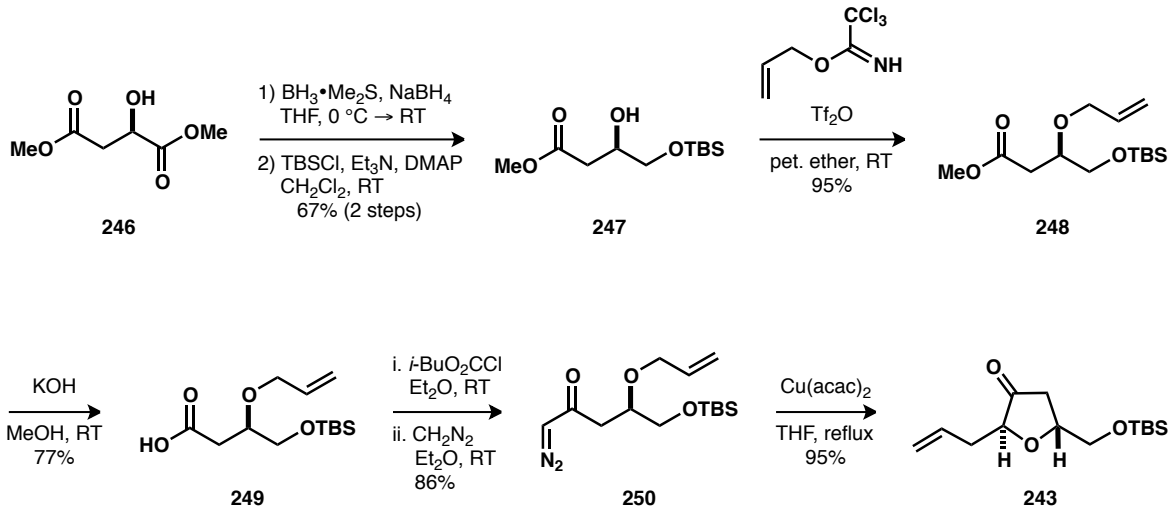
2.1. Previous Work in the Clark Group

The Clark group approach for the synthesis of the amphidinolide C series of macrolides initially relied on the hidden symmetry within the two *trans*-tetrahydrofuran rings.[26] Since the project was commenced in our group, the recognition of hidden symmetry has proven valuable with regard to the strategy employed in the first total synthesis of amphidinolide F reported by Carter and co-workers.[18] Disconnection of the macrocycle at the C17−C18 bond, implying a dithiane alkylation reaction in the forward direction, and at the ester bond, implying a macrolactonisation reaction in the forward direction, revealed two building blocks: alkyl iodide **241** and dithiane **242** (**Scheme 62**). Both these fragments were to be prepared from a common intermediate, dihydrofuranone **243**, which could be readily accessed using the Clark group oxonium ylide rearrangement methodology.[55] This common precursor was to be employed twice and further functionalised before reaction with enyne **244** to form the C8−C9 bond and coupling with vinyl iodide **245** to install the side chain.



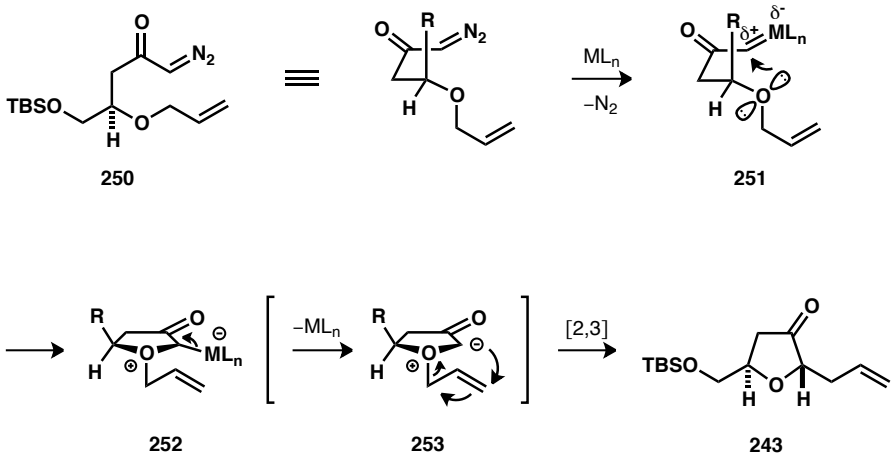
Scheme 62. Clark Group Initial Retrosynthesis

The common dihydrofuranone building block **243** was prepared in six steps from dimethyl D-malate (**246**) (**Scheme 63**). Selective reduction of the *α*-hydroxy ester and subsequent silyl protection of the primary alcohol afforded TBS ether **247**. Further acid-catalysed allylation of the remaining alcohol delivered allyl ether **248** in excellent yield. The methyl ester functionality was saponified and the resulting carboxylic acid **249** was converted into *α*-diazoketone **250**. Finally, ketone **243** was produced as a single diastereomer in 95% yield upon treatment with $Cu(acac)_2$.[55]



Scheme 63. Synthesis of Common Dihydrofuranone **243**

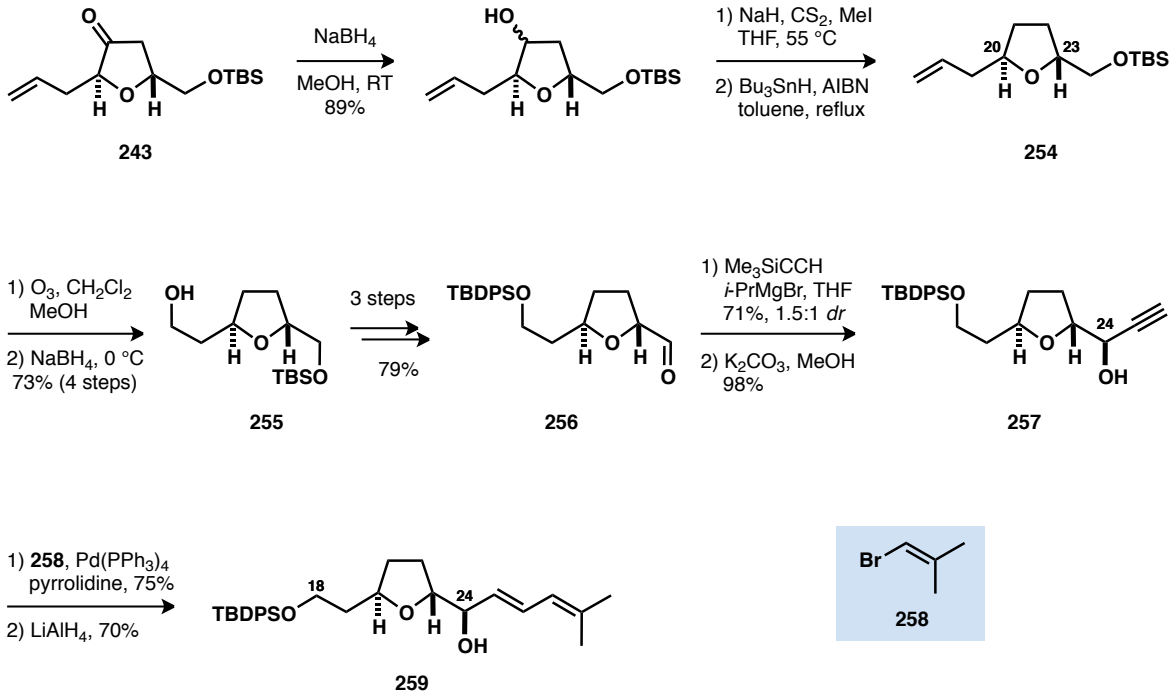
According to the proposed reaction mechanism, the electrophilic metal carbenoid **251** is formed by treatment of diazoketone **250** with a transition metal catalyst (**Scheme 64**).



Scheme 64. Proposed Mechanism

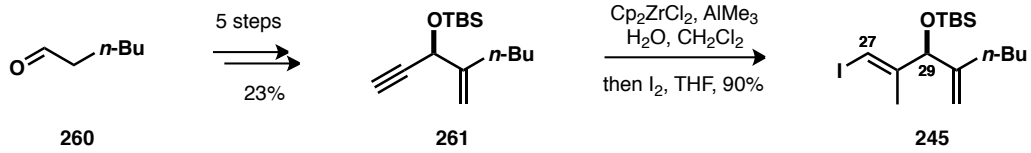
One of the two diastereotopic lone pairs of the ether oxygen then attacks the metal carbenoid to give metal-bound ylide **252** possessing an *anti* relationship between the allyl group and the R substituent. Finally, the metal-bound intermediate either undergoes direct rearrangement to yield dihydrofuranone **243**, or dissociates to deliver the highly reactive free oxonium ylide **253**, which then undergoes [2,3]-sigmatropic rearrangement with efficient transfer of chirality.

Dihydrofuranone **243** was then used to prepare the C18−C29 fragment of amphidinolide F (**Scheme 65**). A three-step deoxygenation protocol afforded disubstituted tetrahydrofuran **254**. The alkene segment was converted into alcohol **255** in good yield. Protecting group manipulation and oxidation afforded aldehyde **256** in three steps. Stereoselective nucleophilic addition to aldehyde **256** was then attempted using a range of alkyne nucleophiles and reaction conditions and relying on either reagent control or substrate control to dictate the stereochemical outcome of the reaction. Unfortunately, low levels of diastereocontrol were observed and propargylic alcohol **257** was obtained along with its C24 diastereomer (1.5:1 *dr*) in 71% yield from the addition of magnesium (trimethylsilyl)acetylide. The mixture of isomers was separated and a copper-free Sonogashira coupling reaction with 1-bromo-2-methylpropene (**258**) followed by reduction provided *E*-allyl alcohol **259**.



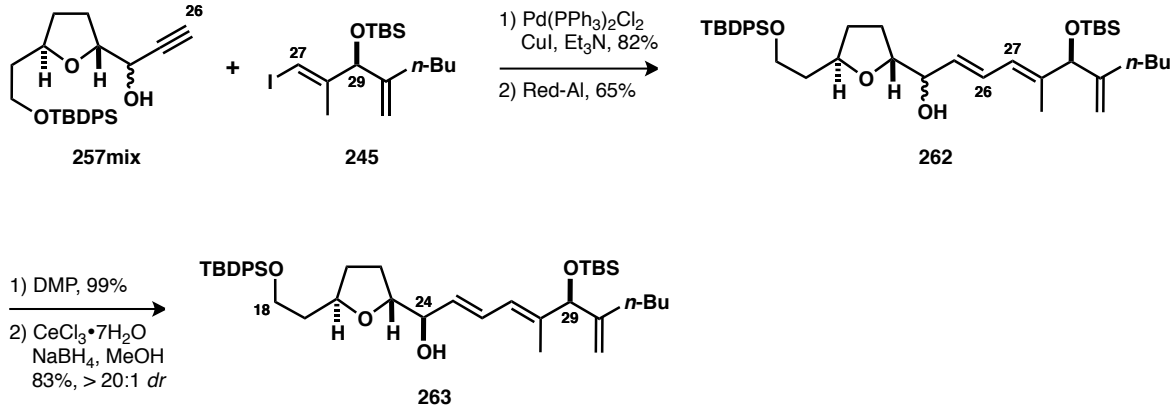
Scheme 65. Construction of the C18−C29 Fragment

In order to access the more complex side chain of amphidinolide C, vinyl iodide **245** was prepared (**Scheme 66**). Alkyne **261** was obtained in five steps from hexanal (**260**), using a similar sequence as the one employed by Pagenkopf.[23a] The terminal alkyne was submitted to modified Negishi carboalumination and iodination conditions[56] to provide *E*-vinyl iodide **245**.



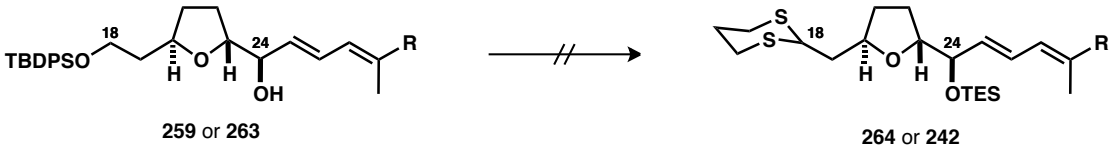
Scheme 66. Elaboration of Coupling Partner **245**

Side chain **245** was then introduced by means of a Sonogashira coupling with alkyne **257mix**, which was used as a diastereomeric mixture. Subsequent stereoselective reduction of the alkyne moiety to give the corresponding *E*-olefin **262** was performed using Red-Al (**Scheme 67**). Finally, sequential oxidation of the C24 alcohol and ketone reduction under Luche conditions completed the assembly of the C18−C34 fragment **263** as a single diastereomer and in excellent yield.



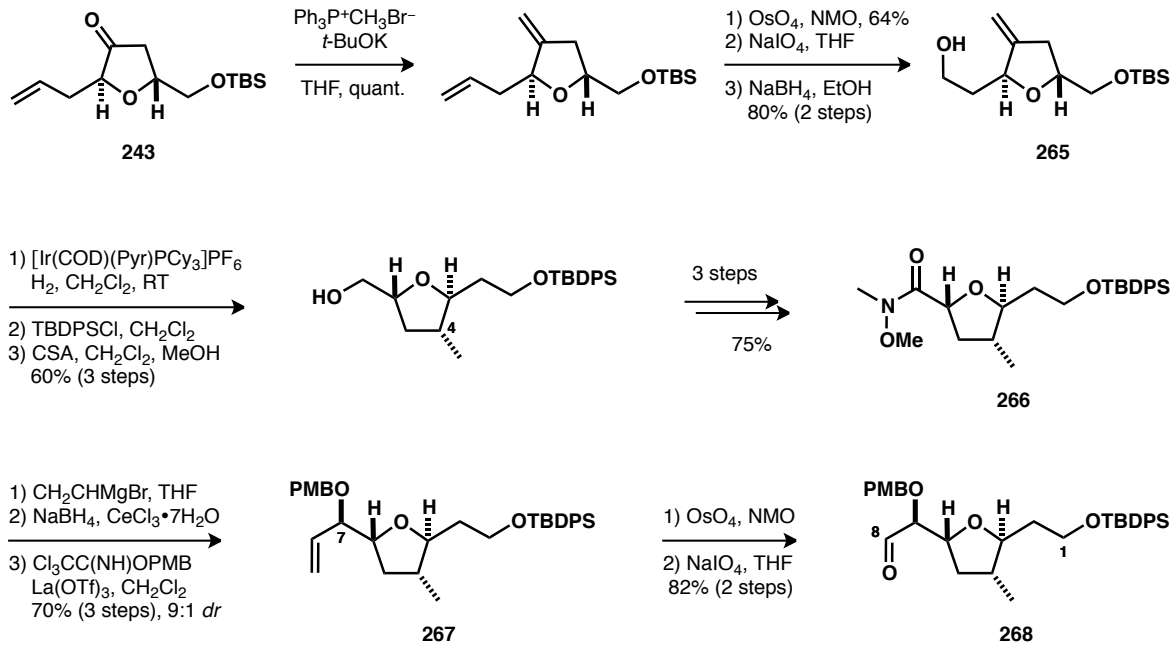
Scheme 67. Completion of the C18−C34 Fragment of Amphidinolide C

Unfortunately, efforts to convert both fragments **259** and **263** into the corresponding dithianes **264** and **242** were unsuccessful (**Scheme 68**). Consequently, a new approach had to be adopted.



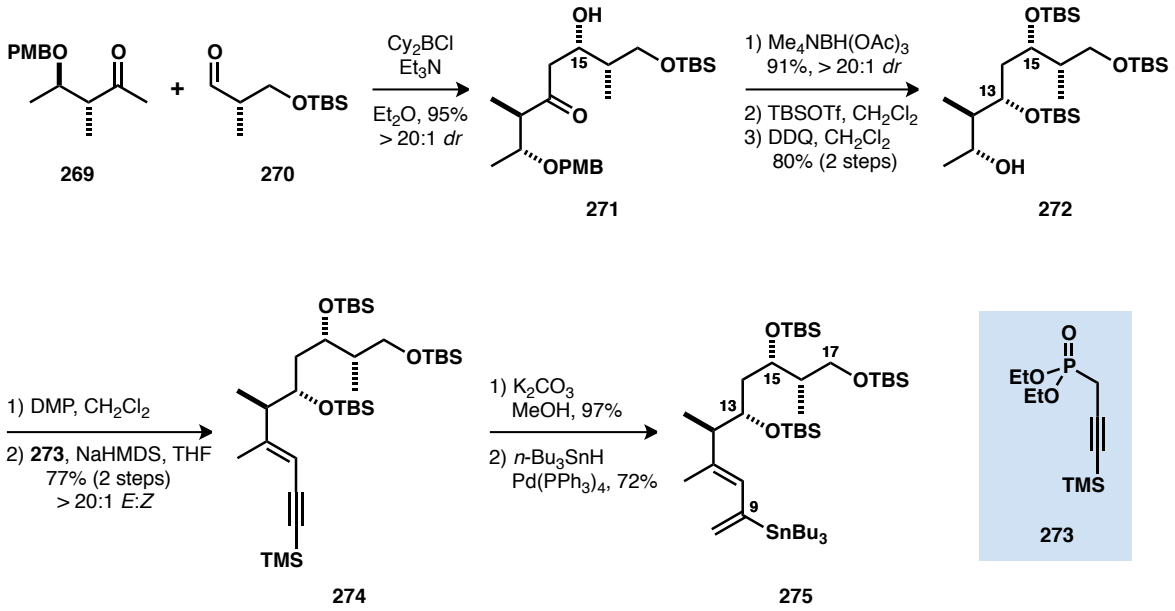
Scheme 68. C18−C29 and C18−C34 Dithiane Fragments

Dihydrofuranone **243** was also employed for construction of the C1−C17 fragment of amphidinolides C and F. Methylenation of the ketone functionality and conversion of the monosubstituted olefin into the corresponding primary alcohol was accomplished in three steps and afforded alkene **265** (**Scheme 69**). Further directed hydrogenation of this alkene using Crabtree's catalyst[57] installed the C4 methyl substituent with the desired stereochemistry. Weinreb amide **266** was then produced in good yield using a three-step sequence. Addition of vinylmagnesium bromide to Weinreb amide **266** and subsequent diastereoselective reduction of the enone intermediate under Luche conditions furnished alkene **267** in 70% yield over three steps and with a 9:1 *dr*. Finally, aldehyde **268** was obtained by sequential dihydroxylation of the alkene and cleavage of the 1,2-diol.



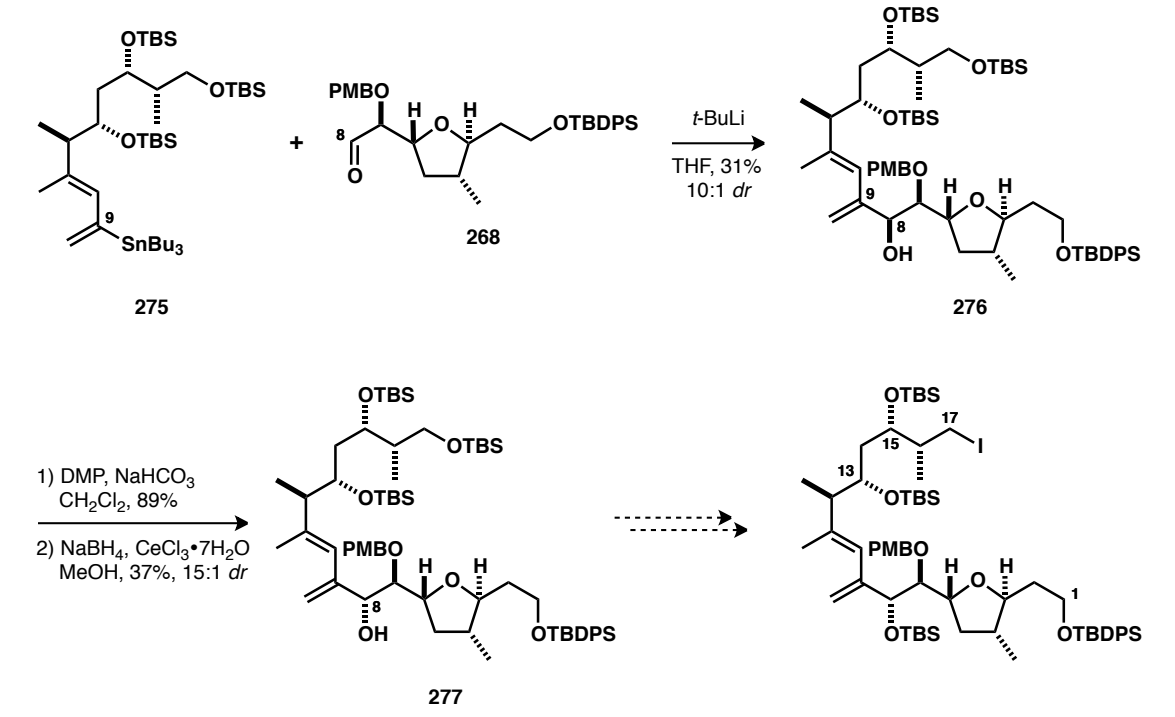
Scheme 69. Construction of the C1−C8 Aldehyde **268**

To complete the synthesis of the C1−C17 fragment, vinyl stannane **275** was prepared (**Scheme 70**). A Paterson aldol reaction between aldehyde **270** and the boron enolate generated from methyl ketone **269** produced *β*-hydroxy ketone **271** in excellent yield and as a single diastereomer at C15. Alcohol-directed reduction of the ketone functionality yielded the corresponding *anti*-1,3-diol with a high level of diastereocontrol; alcohol **272** was obtained after protecting group manipulation. Further oxidation to the corresponding methyl ketone and HWE olefination using phosphonate **273** gave enyne **274** in good yield and as a single isomer. Finally, palladium-catalysed hydrostannylation provided stannane **275**.



Scheme 70. Completion of the C9−C17 Vinyl Stannane **275**

The C1−C17 alcohol **277** was assembled by reaction of aldehyde **268** with the organolithium species generated from vinyl stannane **275** (**Scheme 71**). Alcohol **276** was obtained in a modest 31% yield and with the undesired stereochemical outcome. Consequently, an oxidation/reduction sequence was required to install the C8 stereocentre with the appropriate configuration.



Scheme 71. Coupling of Aldehyde **268** and Stannane **275**

Unfortunately, the protecting group strategy adopted during elaboration of this fragment was judged to be unsuitable for the completion of the natural product because differentiation between the C13 and C15 hydroxyl groups was not possible and removal of the PMB protecting group proved challenging. Therefore, fragment **277** was not elaborated further.

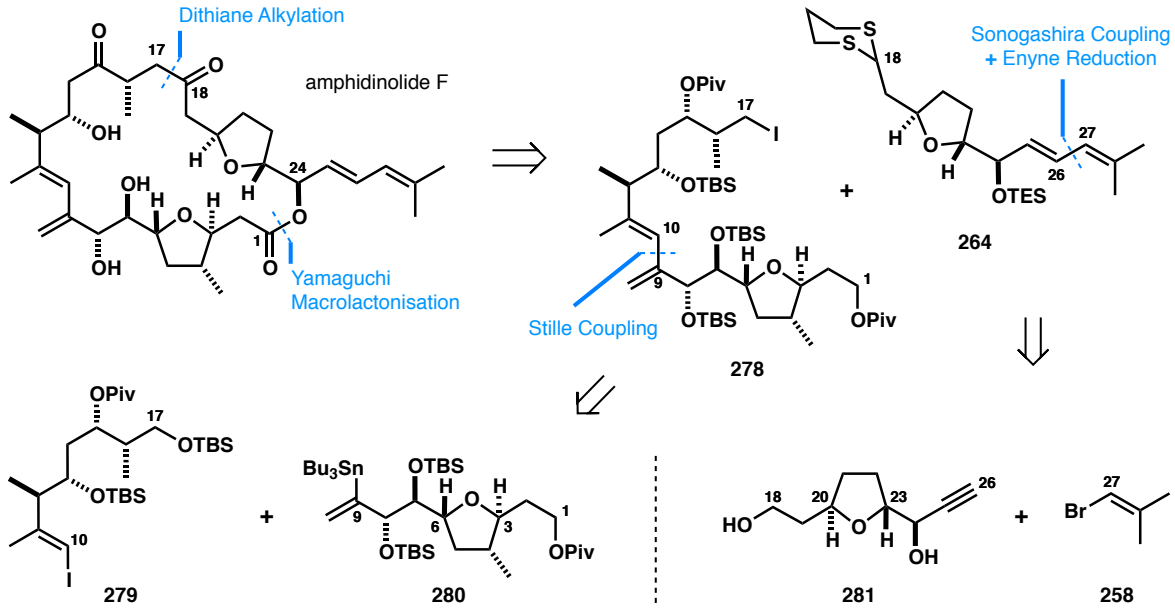
In the light of these results, it is important to note that the entire carbon framework required to complete the natural target had been introduced. However, the general protecting group strategy did not allow fragments **259**/**263** and **277** to be elaborated further and then coupled. In addition, the number of steps needed to convert common dihydrofuranone **243** to each of the tetrahydrofuran-containing sub-units highlighted the inefficiency of a synthetic approach based on a common precursor, an observation that was apparent in the total synthesis of amphidinolides C and F by Carter.[27] These considerations invited us to revisit our original approach to this series of macrolides.

2.2. Evolution of the Strategy Towards Amphidinolides C and F

2.2.1. Retrosynthetic Analysis

In an effort to complete amphidinolides C and F, it was proposed to use a dithiane alkylation reaction as a key C−C bond-forming step, which has been known to be amenable to the construction of these macrocycles.[58]

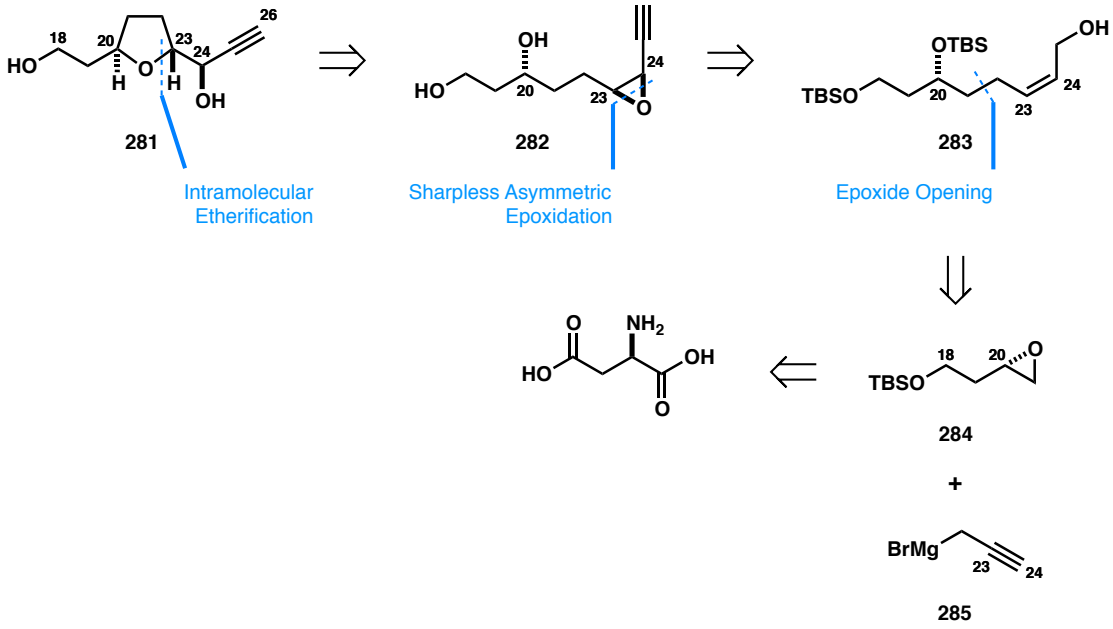
Main disconnections of the macrocycle recognised a dithiane alkylation reaction to form the C17−C18 bond and a macrolactonisation reaction to reveal iodide **278** and dithiane **264** (**Scheme 72**). Dithiane **264** was further disconnected through the C26−C27 bond leading to alkyne **281** and vinyl bromide **258**. This disconnection implied a Sonogashira coupling and subsequent enyne reduction in the forward direction. Additionally, disconnection of alkyl iodide **278** through the C9−C10 bond revealed the Stille coupling of vinyl iodide **279** and stannane **280** in the forward direction. The tetrahydrofuran-containing stannane **280** and alkyne **281** were to be accessed through different synthetic sequences rather than by differentiation of a common precursor. The revisions proposed in this synthetic approach were expected to allow the concise elaboration of fragments bearing suitable protecting groups and lead to the completion of the natural product in a highly convergent fashion. The work discussed in this section will focus on the synthesis of C18−C29 dithiane **264** and coupling attempts to unite the main fragments.



Scheme 72. Revised Retrosynthetic Approach

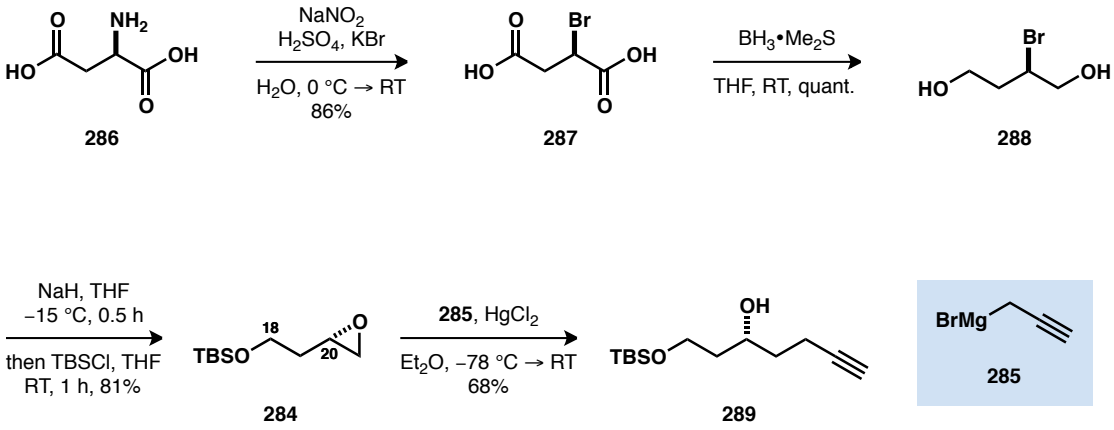
2.2.2. Synthesis of the C18−C26 Alkyne

It was expected that *trans*-tetrahydrofuran **281** could be prepared by acid-catalysed intramolecular nucleophilic opening of *cis*-epoxide **282** (**Scheme 73**). Previous work by Nicolaou[59] and Braddock[60] had shown that intramolecular etherification of *α*-epoxy alkynes led to exclusive formation of the 5-*exo*-tet cyclisation product, which supported our approach. Epoxide **282** was to be accessed by Sharpless asymmetric epoxidation of allylic alcohol **283**, which would be prepared from the opening of chiral epoxide **284** using Grignard reagent **285**.



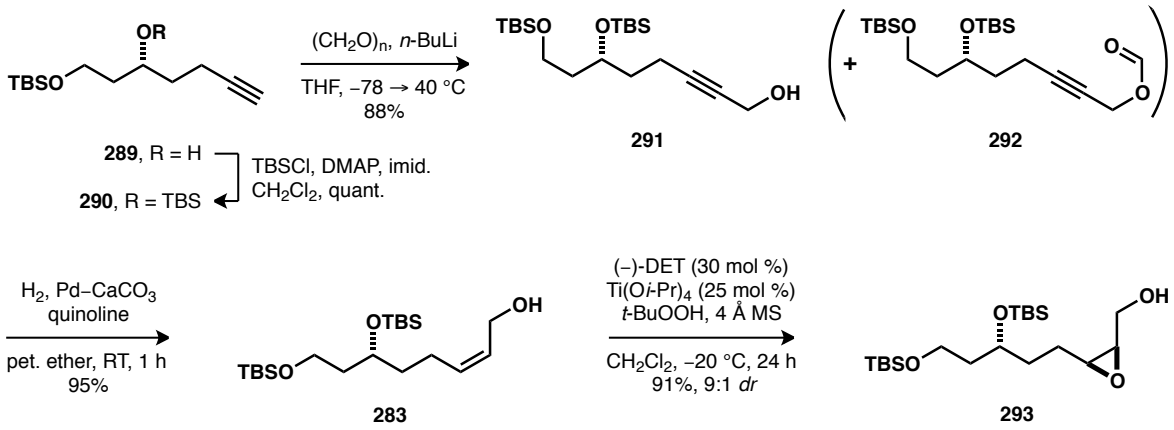
Scheme 73. Synthetic Plan for Tetrahydrofuran **281**

The synthesis of alkyne **281** started by the bromination of D-aspartic acid (**286**) using sodium nitrite and potassium bromide in an acidic aqueous medium to deliver (*R*)-2-bromosuccinic acid (**287**) in good yield and with retention of configuration (**Scheme 74**).[61] The diacid was then reduced to bromodiol **288** in excellent yield. Further treatment of diol **288** with sodium hydride in THF, to effect epoxide formation, followed by addition of *t*-butyldimethylsilyl chloride, after complete consumption of the diol, afforded epoxide **284** in 81% yield as a single enantiomer. Finally, epoxide ring-opening with propargylmagnesium bromide **285**,[62] prepared from propargyl bromide and magnesium turnings in the presence of mercury(II) chloride, generated terminal alkyne **289** in decent yield.



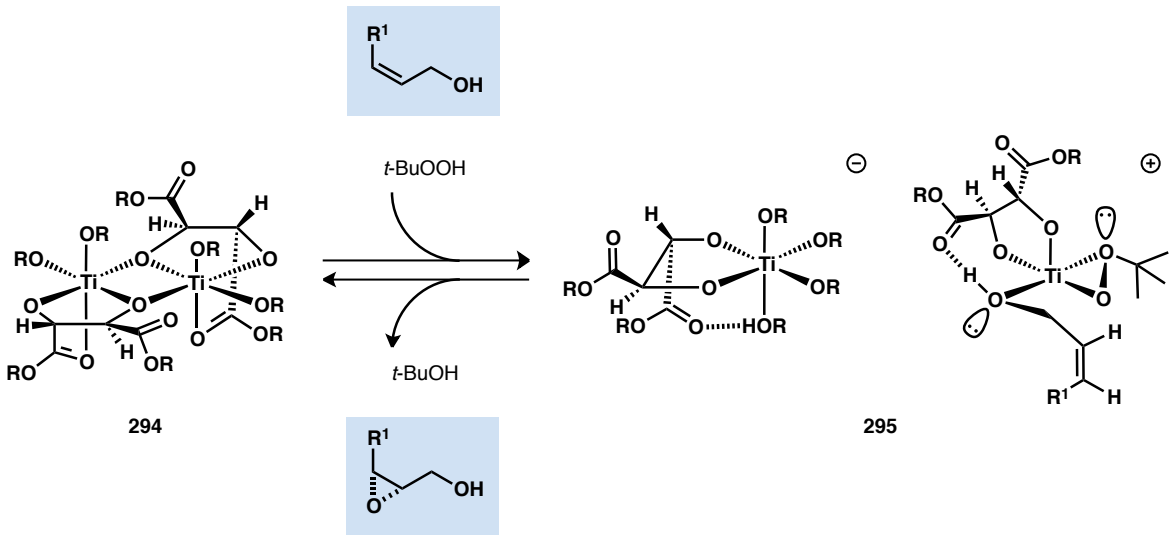
Scheme 74. Completion of Alkyne **289** by Epoxide Opening

Silyl protection of alcohol **289** to give *bis*-TBS ether **290** was followed by addition of paraformaldehyde to the lithium acetylide generated from the terminal alkyne to produce propargylic alcohol **291** in high yield (**Scheme 75**). Along with the desired product **291**, formate **292** was obtained initially (*ca*. 20% yield). However, formation of this by-product could be avoided by use of a simple basic work-up procedure (addition of a 1 M NaOH aq. solution to the reaction mixture) to convert formate **292** into the desired alcohol. Subsequent reduction of the alkyne moiety under Lindlar conditions delivered *Z*-alkene **283** in 95% yield, with no over reduction observed. Finally, Sharpless asymmetric epoxidation[63] of allylic alcohol **283** using (−)-diethyl D-tartrate (30 mol %) and titanium isopropoxide (25 mol %) yielded *cis*-epoxide **293** in 91% yield and with a 9:1 *dr*.



Scheme 75. Formation of Epoxide **293** by Asymmetric Epoxidation

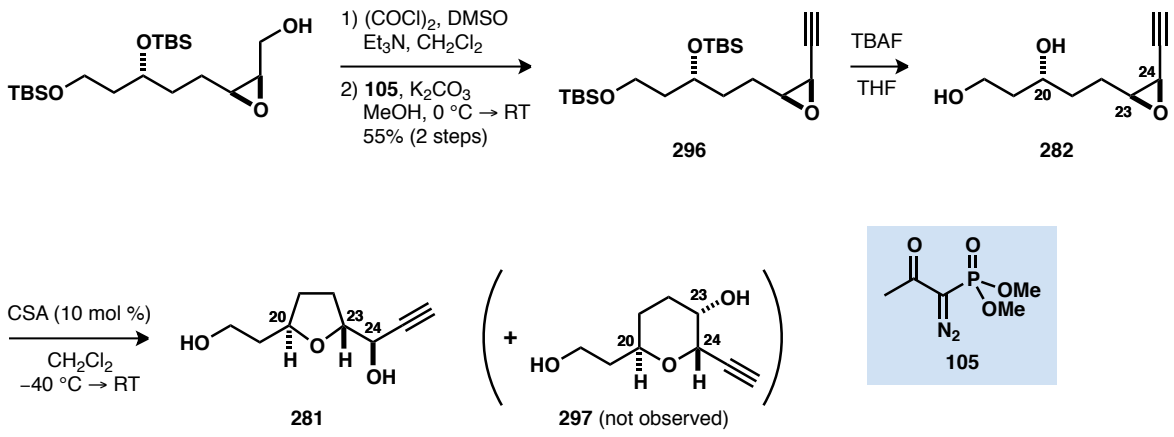
The exact structure of the active catalyst involved in the Sharpless epoxidation remains uncertain but studies have shown that it is likely to have a dimeric structure.[64] The ion pair **295** is potentially formed from the binuclear reagent **294** (**Scheme 76**). In this assembly, the arrangement of the ligands around the titanium centre of the cationic moiety creates a stereogenic centre, the absolute configuration of which is dictated by the tartrate ligand. Other arrangements of ligands around titanium would create additional steric repulsion with the *t*-butyl group. In addition, the *t*-butylperoxy group is chelated to the titanium with the terminal oxygen *cis* to the coordinated allylic hydroxyl group. This chirality and the fixed hydrogen bond between the hydroxyl group of the allylic alcohol and the carbonyl of the tartrate ester favour internal epoxidation at only one face of the olefin in which the π-system approaches the peroxy O−O bond with an optimal stereoelectronic arrangement. The formation of the epoxy alcohol from ion pair **295** then allows regeneration of reagent **294** by dissociation of the epoxide from the catalytic site.



Scheme 76. Catalyst Structure in the Sharpless Epoxidation

Attempts to improve the diastereoselectivity of the Sharpless epoxidation reaction to form epoxide **293** by replacing (−)-diethyl D-tartrate with the more bulky (−)-diisopropyl D-tartrate failed to provide a better outcome and identical yields and levels of diastereoselectivity were obtained.

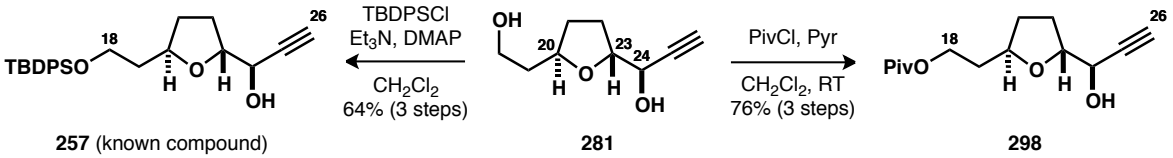
The alcohol segment was then oxidised under Swern conditions and the unstable aldehyde product was subjected to Seyferth-Gilbert homologation using Ohira-Bestmann reagent (**105**)[65] to yield *α*-epoxy alkyne **296** in 55% yield over two steps (**Scheme 77**). The instability of the aldehyde intermediate over time limited the scale of this two-step sequence to *ca*. 3 g of starting alcohol due to practical considerations. Subsequent global silyl deprotection of alkyne **296** using TBAF in THF afforded diol **282**, the key substrate required for the intramolecular etherification reaction envisioned in this approach. After a rapid filtration of diol **282** through silica gel, it was submitted to Nicolaou's cyclisation conditions[59] − a sub-stoichiometric amount of CSA (10 mol %) in CH_2Cl_2 − to promote the stereospecific ring-opening of the epoxide functionality. Pleasingly, full conversion of the epoxide into the tetrahydrofuran product was observed and *trans*-tetrahydrofuran **281** was obtained as a single diastereomer.



Scheme 77. Elaboration of *trans*-Tetrahydrofuran **281**

The reaction proceeded with complete inversion of configuration at C23 and formation of tetrahydropyran **297** derived from the 6-*endo*-tet cyclisation pathway was not observed. Exclusive production of the smaller ring during this cyclisation process could be explain by a better antiparallel alignment of the bond being formed and the bond being broken, in agreement with Baldwin's rules for ring closure.[66] In addition, attempts at a direct cyclisation of crude diol **282** without any purification resulted in an incomplete conversion into tetrahydrofuran **281**, even after an extended reaction time. Finally, selective protection of the primary alcohol using pivaloyl chloride and pyridine in CH_2Cl_2 completed the C18−C26 fragment **298** in 76% yield over three steps (**Scheme 78**). Alternatively, the stereochemistry of tetrahydrofuran **281** was confirmed by selective protection of the primary alcohol

to provide silyl ether **257**, a compound that had been synthesised within the group already, and comparison of NMR data.[26b]

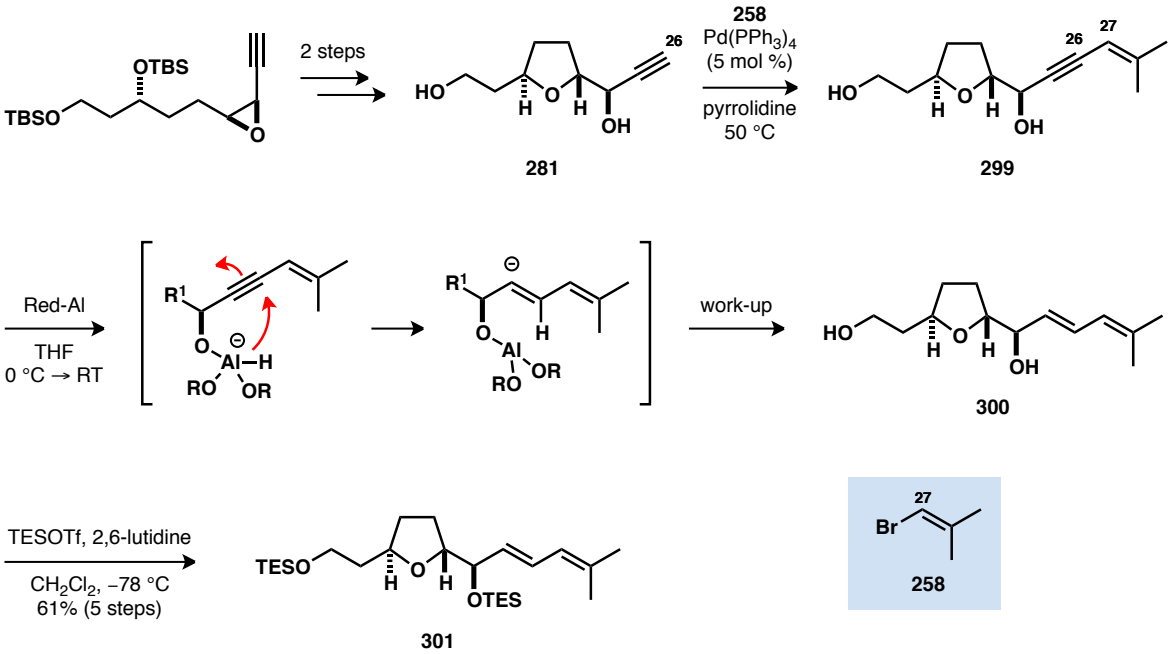


257 (known compound) **281** **298**

Scheme 78. C18−C26 Fragment Completion and Confirmation of Stereochemistry

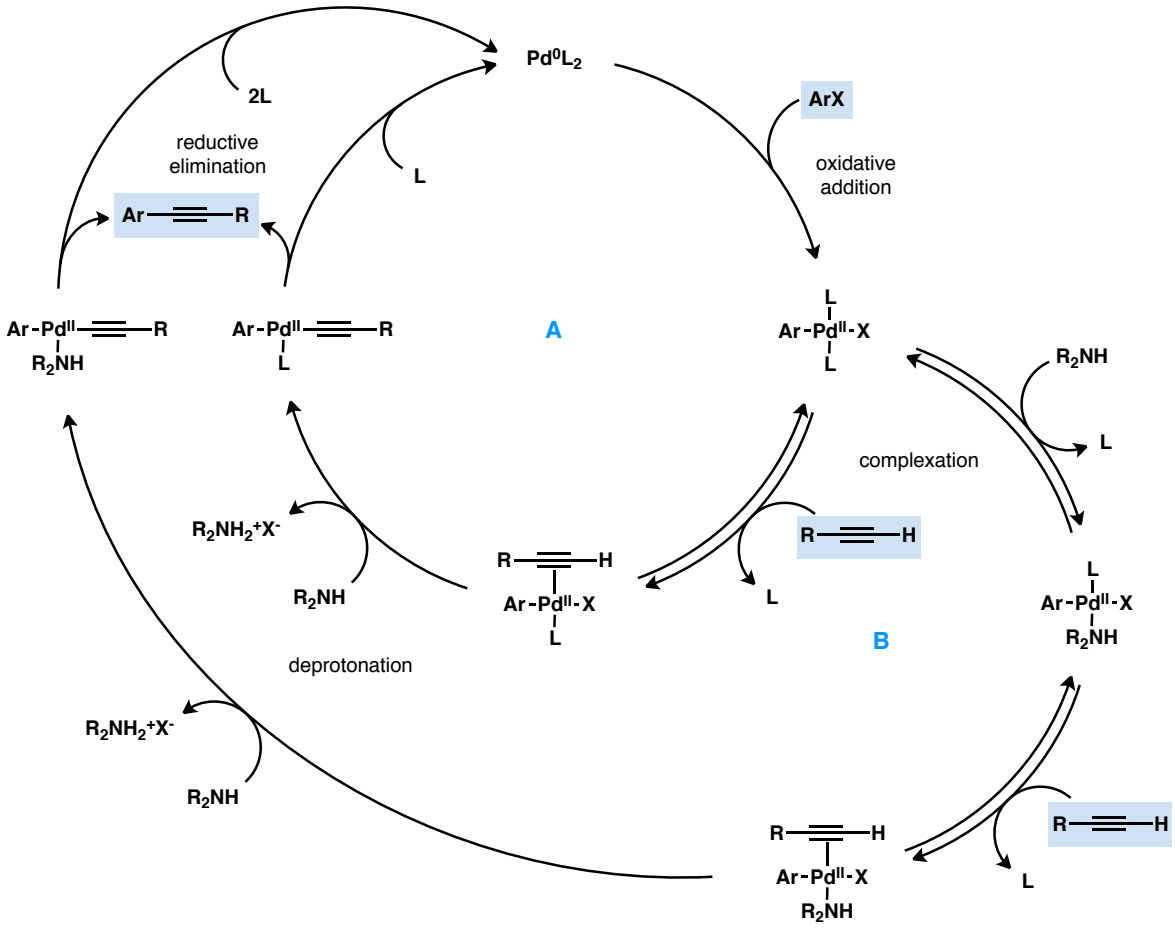
2.2.3. Side Chain Installation and C18−C29 Fragment Completion

Preparation of the diene side chain found in amphidinolide F started by use of the copper-free variant[67] of the Sonogashira cross-coupling reaction between alkyne **281** and commercially available vinyl bromide **258** to provide enyne **299** (**Scheme 79**). Standard Sonogashira conditions performed in the presence of copper iodide had been shown to be unsuitable for the coupling of similar substrates because they resulted in the generation of a significant amount of alkyne homocoupling product.[26b] The alkyne was then reduced stereoselectively to the corresponding *E*-alkene **300** using Red-Al by exploiting the anchimeric assistance of the neighbouring hydroxyl group. Finally, double silyl protection afforded *bis*-TES ether **301** in 61% yield over five steps.



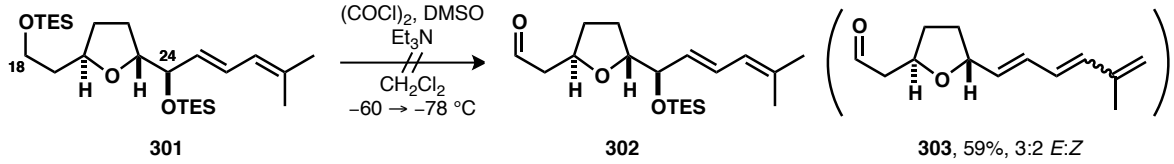
Scheme 79. Diene Side Chain Assembly

The mechanism of the copper-free Sonogashira reaction remains unclear, but two possible reaction mechanisms (A and B) have been proposed, depending on the ligand, the amine used as well as the rate of the competition between the amine and the alkyne in the substitution of a ligand (**Scheme 80**).[68] In pathway A, substitution of a ligand after oxidative addition by the amine is less favored than substitution by the alkyne, and so prior coordination of the alkyne is suggested, followed by deprotonation of the ligated alkyne by the amine, the ligated alkyne being more acidic than the free alkyne. A more basic amine is then more efficient in this process as it is more reactive during the deprotonation step. In contrast, pathway B operates when the amine is a better ligand than the alkyne for the Pd^{II} centre. In this case, substitution of a ligand by the amine happens first and is followed by substitution of the second ligand by the alkyne. Deprotonation of the alkyne by an external amine furnishes the product after reductive elimination. Pathways A and B are branched at the Pd^{II} species obtained after the initial oxidative addition. It has been suggested that altering the relative concentrations of the alkyne and the amine might allow switching from one pathway to the other.



Scheme 80. Proposed Mechanisms for Copper-free Sonogoshira Coupling

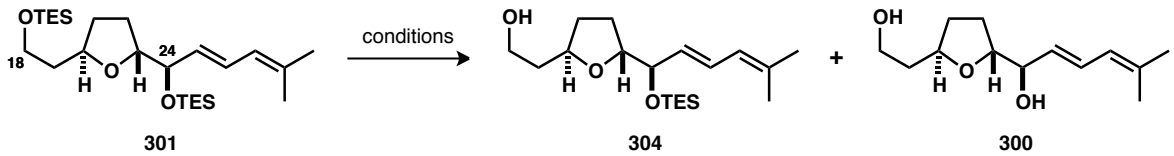
With *bis*-TES ether **301** in hand, formation of the requisite dithiane segment was then investigated. In order to access the key aldehyde **302**, direct chemoselective Swern oxidation was first attempted (**Scheme 81**). The acidic conditions of the Swern oxidation were expected to trigger selective deprotection of the primary alcohol, which could then be oxidised *in situ* to provide aldehyde **302**.[69] Unfortunately, this approach proved to be unsuccessful and not only was the C18 silyl ether converted to the corresponding aldehyde but the C24 silyl ether was also eliminated to form the highly conjugated adduct **303** as a mixture of *E* and *Z* isomers in 59% yield.



301 **302** **303**, 59%, 3:2 *E*:*Z*

Scheme 81. Attempt at Chemoselective Oxidation of Silyl Ether **301**

In order to obtain aldehyde **302**, attention was focused on achieving selective deprotection of the C18 alcohol (**Table 3**) and subsequent oxidation as two distinct transformations. Aqueous acidic conditions, using a 8:8:1 mixture of AcOH, THF and water at −20 °C, resulted in full conversion of the *bis*-TES ether to give a 3:1 mixture of alcohol **304** and diol **300** (**Entry 1**). Decreasing the reaction temperature resulted in a longer reaction time over which more complete deprotection was observed (**Entry 2**). Desilylation using HF•Pyr and an excess of pyridine in THF at 0 °C resulted in a similar outcome and products **304** and **300** were formed in a 2:3 ratio (**Entry 3**). Pleasingly, decreasing the reaction temperature to −20 °C prevented formation of diol **300** and adduct **304** was obtained in 79% yield (**Entry 4**).



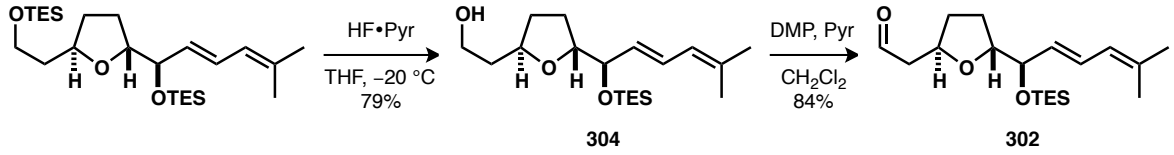
301 304 300

Entry	Conditions	T (° C)	Time (h)	304:300[a]	304[b]
1	AcOH/THF/H_2O (8:8:1)	−20	5	3:1	53%
2	AcOH/THF/H_2O (8:8:1)	−30	12	2:3	−
3	HF•Pyr, THF	0	6	2:3	−
4	HF•Pyr, THF	−20	15	1:0	79%

(a) Ratio observed by ^{1}H NMR analysis of the crude mixture.
(b) Isolated yield.

Table 3. Selective Deprotection of the C18 Alcohol in **301**

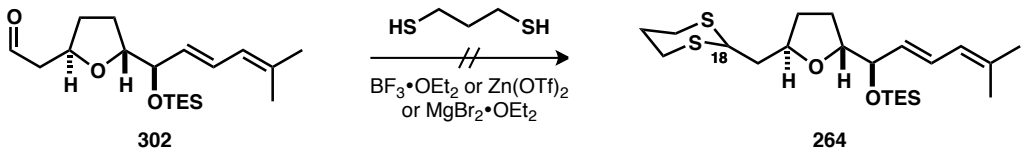
Further treatment of alcohol **304** with Dess-Martin periodinane and pyridine in CH_2Cl_2 afforded key aldehyde **302** in 84% yield (**Scheme 82**).



304 302

Scheme 82. Two-step Formation of Aldehyde **302**

Conversion of aldehyde **302** into the final C18−C29 dithiane fragment **264** was attempted by treatment with 1,3-propanedithiol and a Lewis acid (**Scheme 83**). A variety of Lewis acids were used for this reaction but unfortunately decomposition of the starting material occurred in all cases.

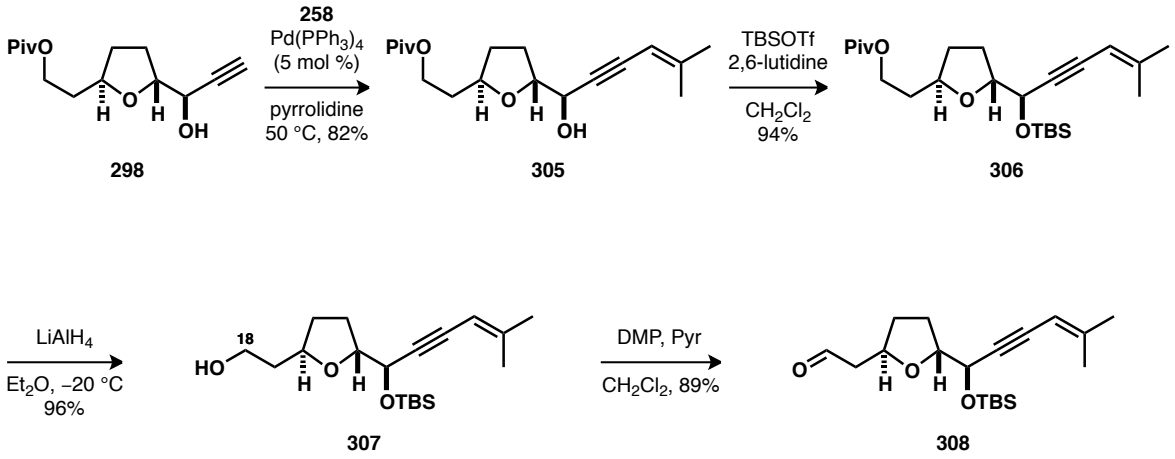


302 264

Scheme 83. Attempt at Formation of the Dithiane Segment

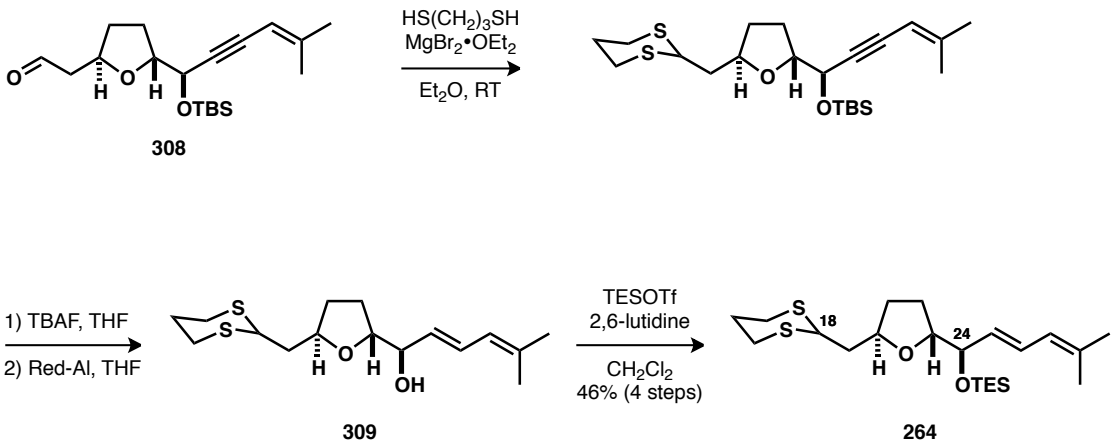
Although the complex mixtures obtained did not allow characterisation of side products, it appeared that the Lewis acid, including $MgBr_2 \bullet OEt_2$, triggered cleavage of the silyl protecting group and further decomposition, including opening of the tetrahydrofuran ring or loss of the diene side chain, then followed, as suggested by analysis of the ^1H NMR spectra of the crude mixture.

With these unsatisfying results in mind, it was envisioned that the dithiane functionality could be installed at an earlier stage in the synthesis, on an aldehyde that would be more tolerant of the reaction conditions required for the formation of the dithiane. Starting from the C18−C26 tetrahydrofuran **298**, enyne **305** was obtained in 82% yield by Sonogashira cross-coupling with vinyl bromide **258** under the conditions described previously (**Scheme 84**). The propargylic alcohol was protected and silyl ether **306** was obtained in excellent yield. Cleavage of the pivalate ester using lithium aluminium hydride in Et_2O at −20 °C delivered the C18 primary alcohol **307** in high yield. Finally, treatment of the alcohol with Dess-Martin periodinane and pyridine in CH_2Cl_2 produced aldehyde **308** in 89% yield.



Scheme 84. Elaboration of Aldehdye **308**

To install the dithiane segment, aldehyde **308** was treated with 1,3-propanedithiol and $MgBr_2 \bullet OEt_2$ in Et_2O (**Scheme 85**). Full conversion of the starting material was achieved within 1.5 h. No decomposition was observed due to the use of the more resistant TBS protecting group. Further deprotection and stereoselective reduction of the enyne moiety using Red-Al yielded *E*-alkene **309**. Finally, protection of the free alcohol to give the corresponding TES ether proceeded smoothly and dithiane **264** was obtained in 46% yield over four steps after chromatographic purification.



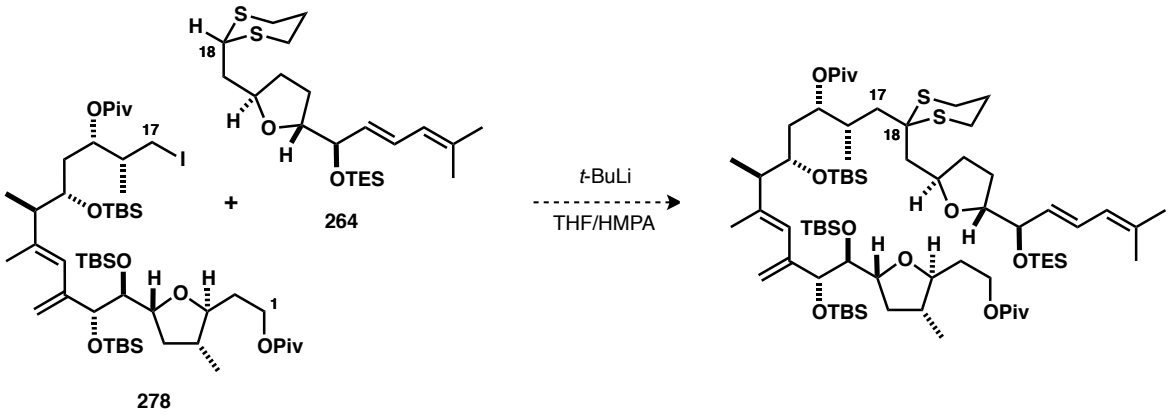
Scheme 85. Completion of the C18−C29 Dithiane Fragment **264**

In conclusion, the C18−C29 fragment **264** was prepared in 18 steps from known epoxide **284** and with 6.6% overall yield. Failure to form the dithiane segment directly from aldehyde **302** required the implementation of a more robust synthetic sequence but added several steps. This drawback would be addressed upon success of the coupling strategy. Nevertheless, having dithiane **264** in hand allowed for coupling attempts with iodide **278** to be carried out.

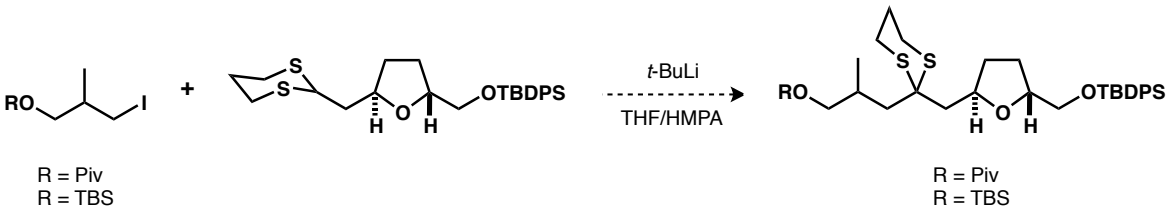
2.2.4. Coupling Attempts of the C1−C17 and C18−C29 Fragments

According to the revised strategy, coupling was expected to proceed by nucleophilic displacement of iodide in fragment **278** by the anion generated from deprotonation of dithiane **264** with *t*-BuLi in the presence of HMPA. In order to identify suitable reaction conditions, two simple model compounds were proposed that mimic the steric environments within the nucleophilic and electrophilic sites of the two building blocks (**Scheme 86**).

- Fragment coupling envisioned

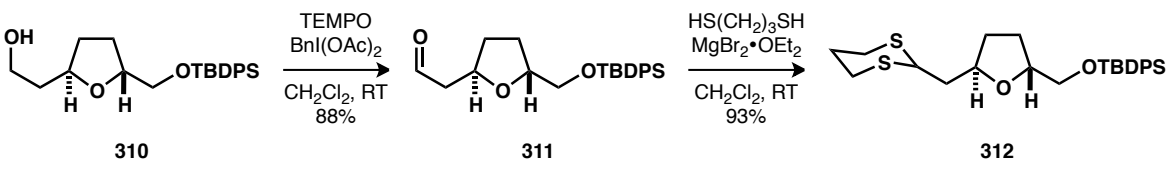


- Model system proposed



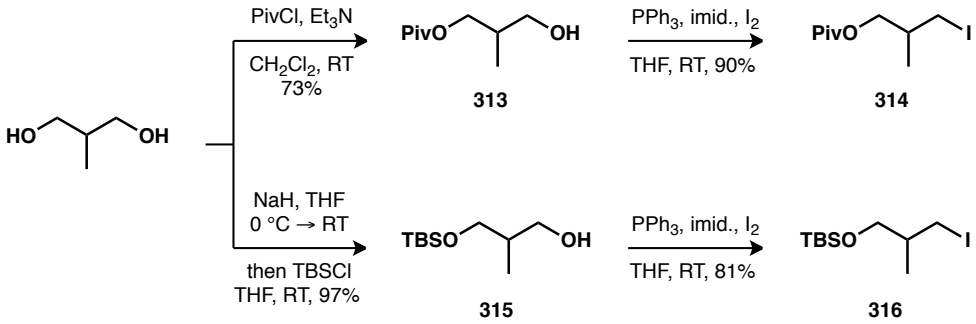
Scheme 86. Model System Proposed for Coupling Conditions

The simplified dithiane **312** was prepared from alcohol **310**[70] by oxidation, to give aldehyde **311**, followed by formation of the dithiane ring in high yield (**Scheme 87**).



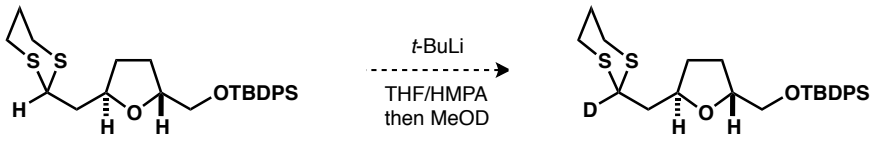
Scheme 87. Synthesis of Model Dithiane Coupling Partner **312**

Two iodide substrates were easily synthesised from 2-methyl-1,3-propanediol (**Scheme 88**). Monoprotection using either PivCl or TBSCl afforded alcohols **313** and **315**. Iodides **314** and **316** were then prepared by treatment of alcohols **313** and **315** with triphenylphosphine and iodine in the presence of imidazole.



Scheme 88. Model Alkyl Iodides **314** and **316**

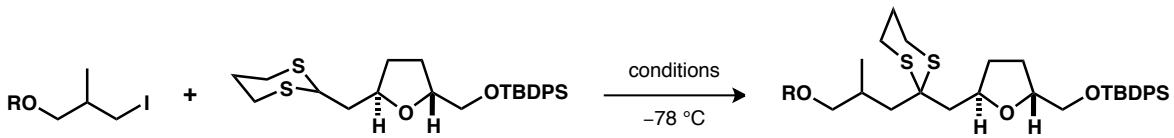
A rapid study concerning the deprotonation of dithiane **312** was carried out first (**Table 4**). Solutions of dithiane in a 4.5:1 mixture of THF and HMPA at −78 °C were treated with *t*-BuLi (1.0 equiv.) and stirred for 5, 10, 20 and 30 min, before addition of deuterated methanol. After five minutes, incomplete deprotonation (*ca*. 30%) was observed by ^{1}H NMR of the crude reaction mixture (**Entry 1**), whereas full deprotonation was reached after only ten minutes (**Entry 2**). Longer reaction times resulted in partial reprotonation of the substrate, potentially from the THF itself (**Entry 3** and **4**). Therefore, ten minutes appeared to be the optimum time for lithiation of the dithiane prior to addition of the iodide.



Entry	Base	Additive	T (°C)	Time (min)	^{2}H Incorporation
1	*t*-BuLi	HMPA	−78	5	30%
2	*t*-BuLi	HMPA	−78	10	100%
3	*t*-BuLi	HMPA	−78	20	90%
4	*t*-BuLi	HMPA	−78	30	60%

Table 4. Optimised Conditions for Dithiane **312** Deprotonation

Coupling reactions on the model system were then attempted (**Table 5**). Deprotonation of an excess of dithiane **312** (1.8 equiv.) with an equimolar amount of *t*-BuLi (1.8 equiv.) for ten minutes at −78 °C followed by addition of iodide **314** (1.0 equiv.) and stirring for one hour at −78 °C afforded coupling product **317** in 54% yield; almost complete recovery of unreacted **312** was possible (**Entry 1**). In the presence of silver triflate, an efficient halide activating reagent,[71] both the yield and the amount of unreacted **312** recovered decreased significantly, probably as a consequence of the ability of silver salts to react with dithianes (**Entry 2**).[72] Reduced solubility of dithiane **312** was observed in Et_2O, resulting in incomplete deprotonation and a lower yield (**Entry 3**). Finally, to assess the compatibility of the pivalate ester with the proposed conditions, TBS ether **316** was submitted to the coupling reaction (**Entry 4**). Coupling product **318** was obtained in a 63% yield, demonstrating the small deleterious effect that the pivalate ester has on the reaction outcome. It is important to note that removal of traces of water present in the starting materials by azeotropic distillation with benzene proved to be critical in all cases.



314, R = Piv
316, R = TBS

312

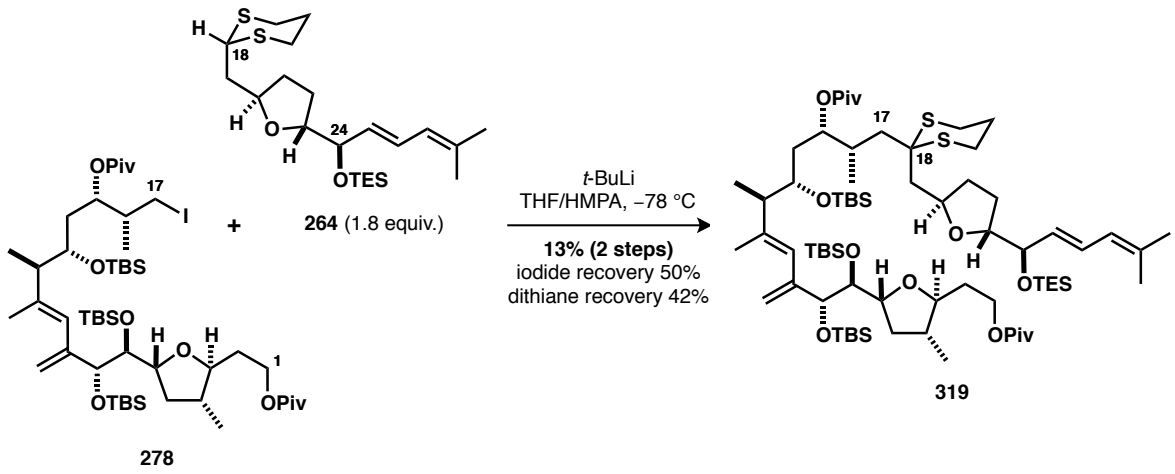
317, R = Piv
318, R = TBS

Entry	R	Solvent	Additive	317/318	Recovered 312[a]
1	Piv	THF	−	54%	94%
2	Piv	THF	AgOTf [b]	8%	67%
3	Piv	Et_2O	−	38%	87%
4	TBS	THF	−	63%	87%

(a) Percentage calculated based on the theoretical amount of **312** remaining.
(b) 1.0 equiv. used.

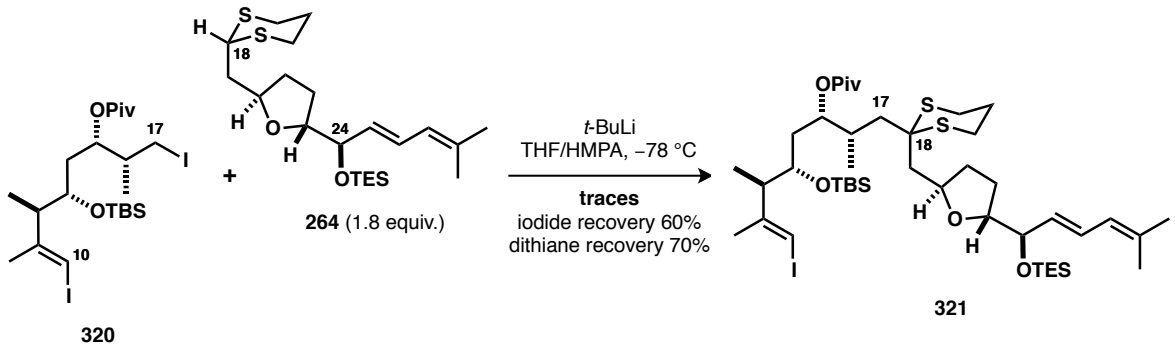
Table 5. Model Study: Conditions and Results

Following the identification of the optimum experimental procedure, fragment coupling was attempted. An excess of dithiane **264** was treated with an equimolar amount of *t*-BuLi in the presence of HMPA and after ten minutes iodide **278**[73] was added (**Scheme 89**). After one hour, the reaction was quenched and the desired 1,1-disubstituted dithiane product **319** was obtained in just 13% yield. Unreacted iodide **278** and dithiane **264** were recovered in 50% yield and 42% yield respectively. Extending the reaction time did not improve the yield of coupling product and only resulted in more decomposition of the starting materials.



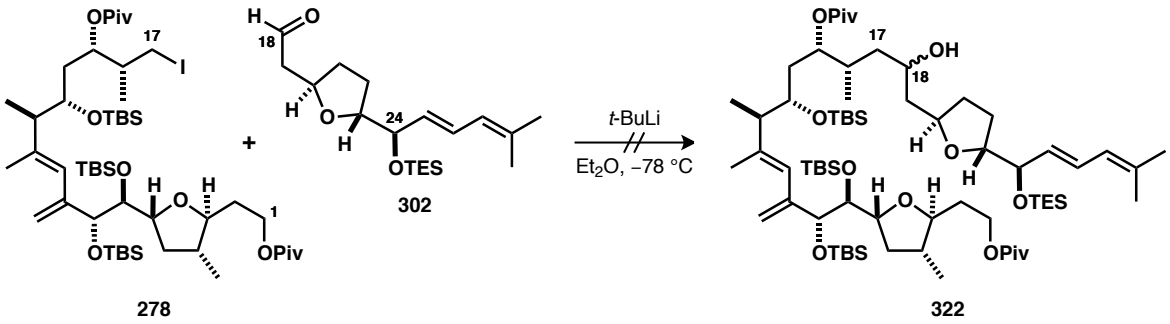
Scheme 89. Coupling Attempt of Iodide **278** and Dithiane **264**

Coupling with truncated iodide fragment **320**[73] was also investigated (**Scheme 90**). Unfortunately, the use of this sterically less demanding fragment did not result in any improvement and only a trace amount of coupled product **321** was observed along with significant amounts of recovered starting materials.



Scheme 90. Coupling Attempt of Iodide **320** and Dithiane **264**

The poor results obtained following an umpolung strategy for the coupling of fragments **264** and **278** meant that a different approach was necessary in which the original building blocks could be used. Formation of alcohol **322** by generation of the organolithium species from iodide **278** using *t*-BuLi and subsequent addition of this lithiated compound to aldehyde **302** was attempted (**Scheme 91**). Unfortunately, significant decomposition of the aldehyde was observed under these reaction conditions and the required alcohol product was not formed. Addition of *t*-BuLi to a mixture of iodide **278** and aldehyde **302** in Et_2O at −78 °C resulted in an identical outcome.



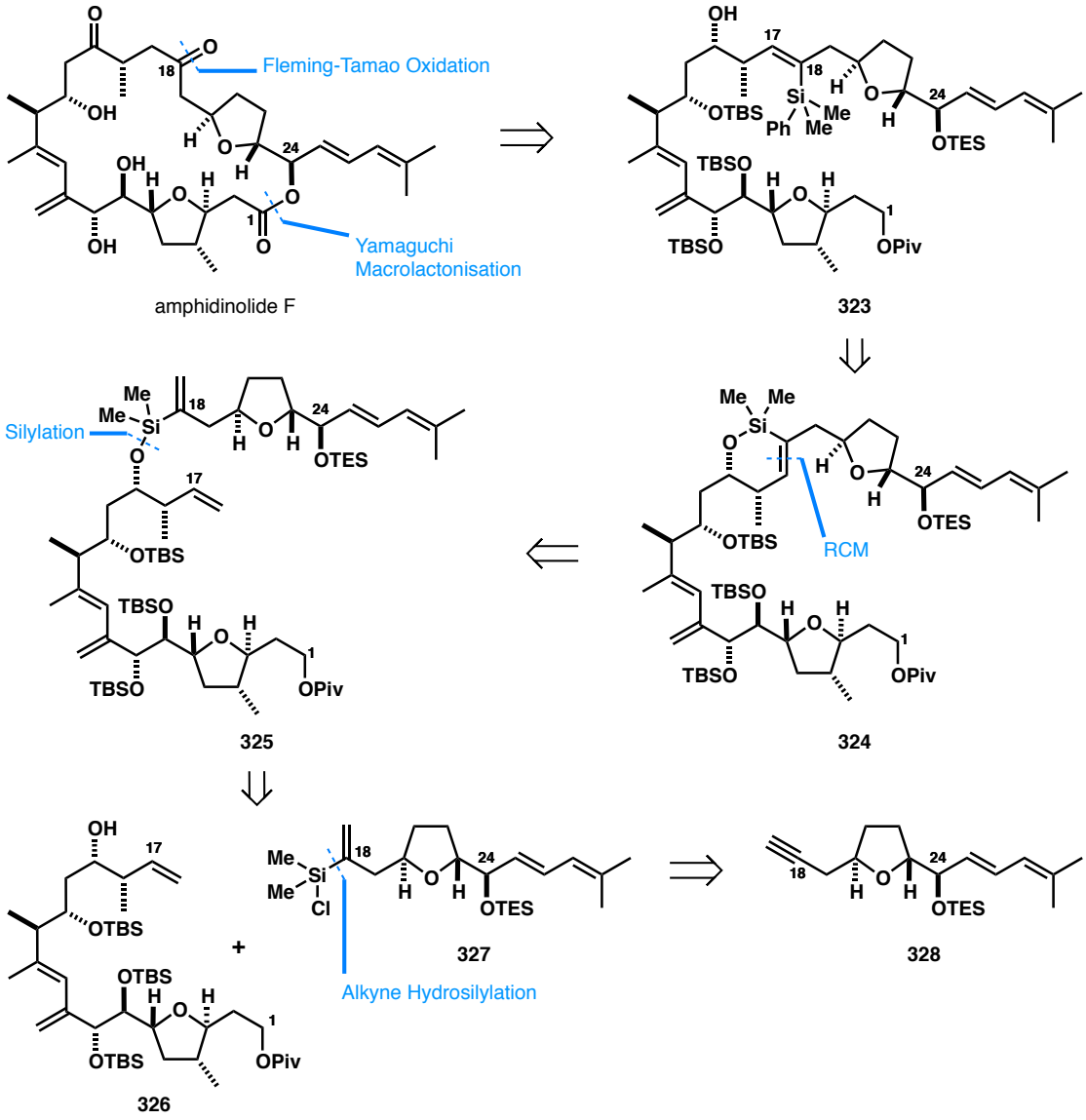
Scheme 91. Coupling Attempt of Iodide **278** and Aldehyde **302**

In conclusion, formation of the C17−C18 bond by coupling of two main fragments using either of the two approaches outlined above proved to be unsuccessful. The proposed strategy was not investigated further because the synthesis of dithiane **264** suffered from an unsatisfying step-count and because the stocks of both building blocks were depleted. A revision of the synthetic strategy was therefore considered in order to access the targeted macrolactone.

2.3. Revised Strategy: Silicon-Tethered RCM

2.3.1. Retrosynthetic Analysis

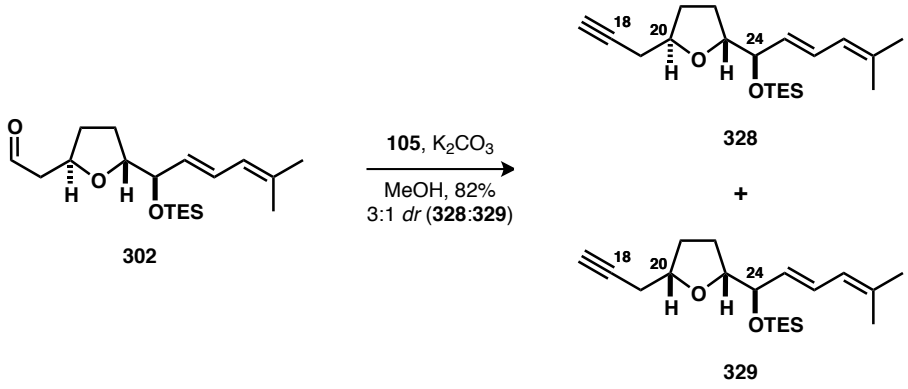
Attention was directed at employing a silicon-tethered RCM[74] to assemble the C17−C18 bond. Disconnection of the macrolactone at the ester bond and formation of the C18 ketone by Fleming-Tamao oxidation in the forward direction revealed vinylsilane **323** (**Scheme 92**). This fragment was to be generated by treatment of siloxacycle **324** with phenyllithium. Disconnection across the C17−C18 olefin led to diene **325** and suggested a challenging RCM reaction in the forward direction. Finally, cleavage of the silicon-oxygen bond revealed alcohol **326** and chlorosilane **327**. In the forward direction, alkyne **328** would be converted into chloro(dimethyl)vinylsilane **327** by ruthenium-catalysed hydrosilylation.



Scheme 92. Silicon-tethered Approach Towards Amphidinolide F

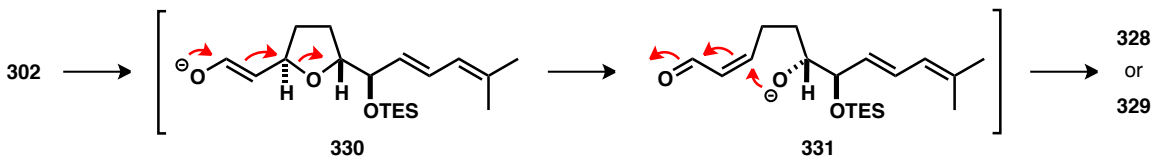
2.3.2. Synthesis of the C18−C29 Alkyne

The terminal alkyne of the C18−C29 fragment required for the hydrosilylation reaction was prepared in one step from previously synthesised aldehyde **302** (**Scheme 93**). A Seyferth-Gilbert homologation reaction using Ohira-Bestmann reagent **105** produced a 3:1 mixture of *trans*-tetrahydrofuran **328** and *cis*-tetrahydrofuran **329** in 82% yield. Pure alkyne **328** could be obtained following chromatographic isomer separation.



Scheme 93. Homologation of Aldehyde **302**

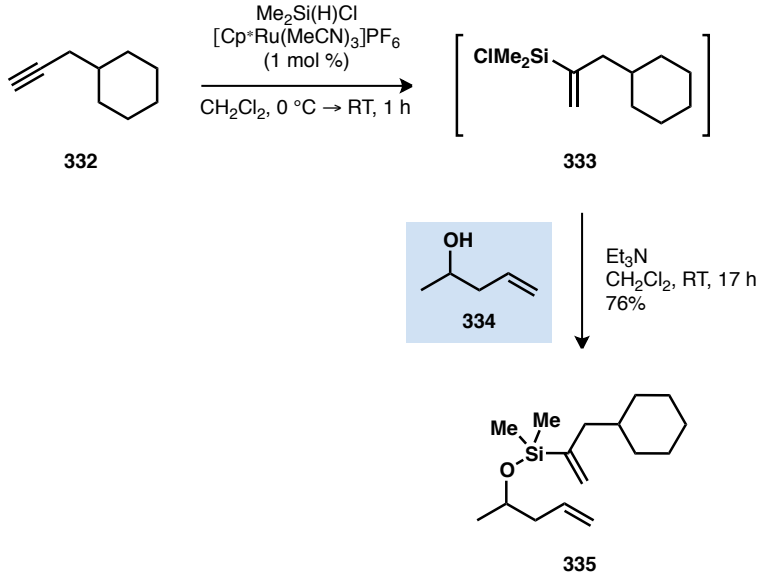
Basic conditions are used in the homologation reaction and so formation of *cis*-tetrahydrofuran **329** can be explained by deprotonotion of aldehyde **302** to produce enolate **330** which then undergoes retro oxa-Michael addition to provide alcoholate species **331** (**Scheme 94**). Finally, an oxa-Michael addition on the enal segment regenerates the tetrahydrofuran moiety with potential formation of both diastereomers.[75]



Scheme 94. Proposed Mechanism for the Formation of Diastereomer **329**

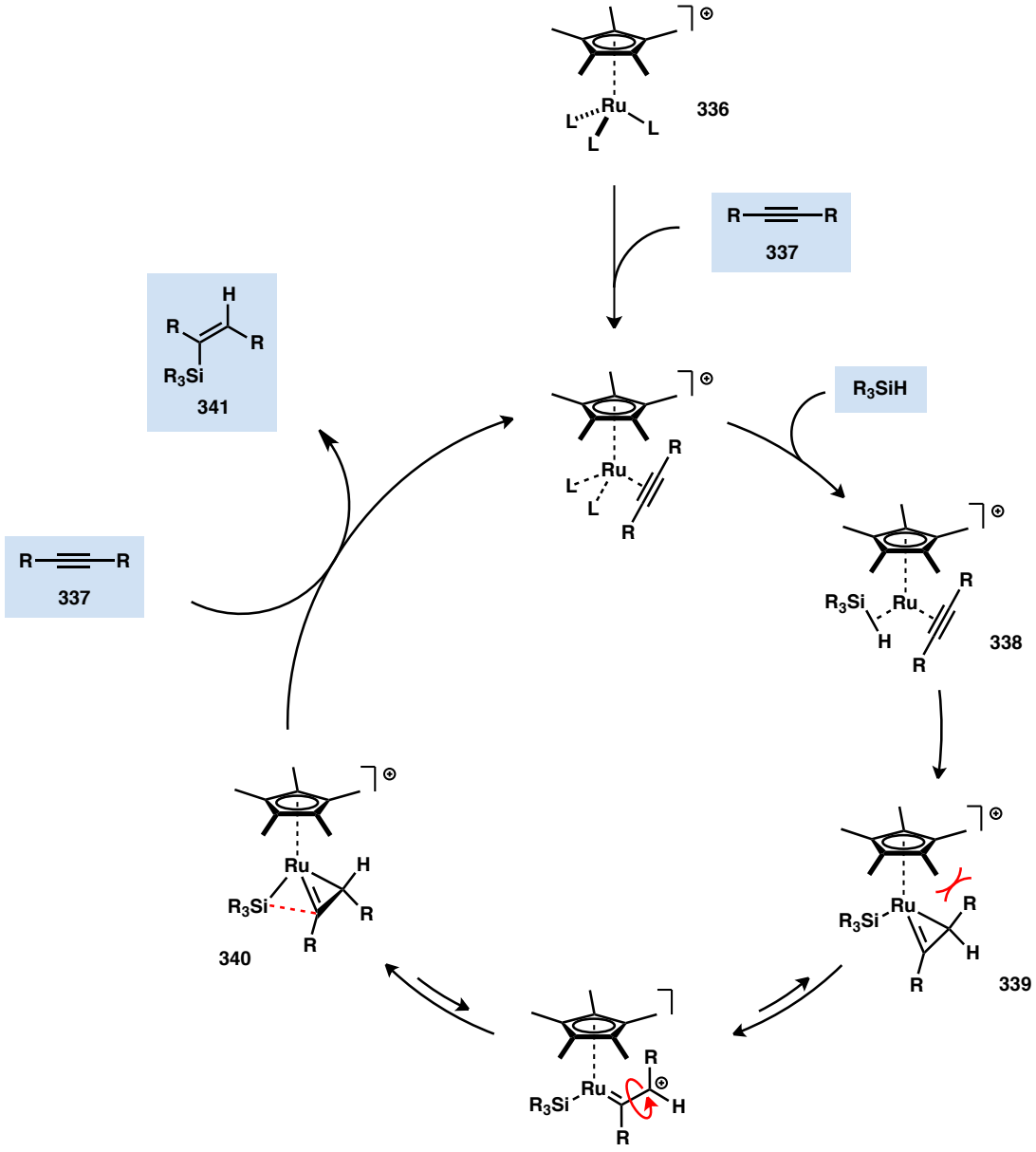
2.3.3. Coupling Attempts of the C1−C17 and C18−C29 Fragments

The proposed two-step one-pot silylation reaction was first attempted on simple homoallylic alcohol **334** (**Scheme 95**). Using conditions developed by Trost,[76] 3-cyclohexyl-1-propyne (**332**) was treated with 1 mol % of ruthenium complex $[Cp^*Ru(MeCN)_3]PF_6$ in the presence of chlorodimethylsilane. Formation of the required 1,1-disubstituted vinylsilane **333** was then directly followed by the addition of a solution of alcohol **334** and Et_3N in CH_2Cl_2 to provide diene **335** in 76% yield.



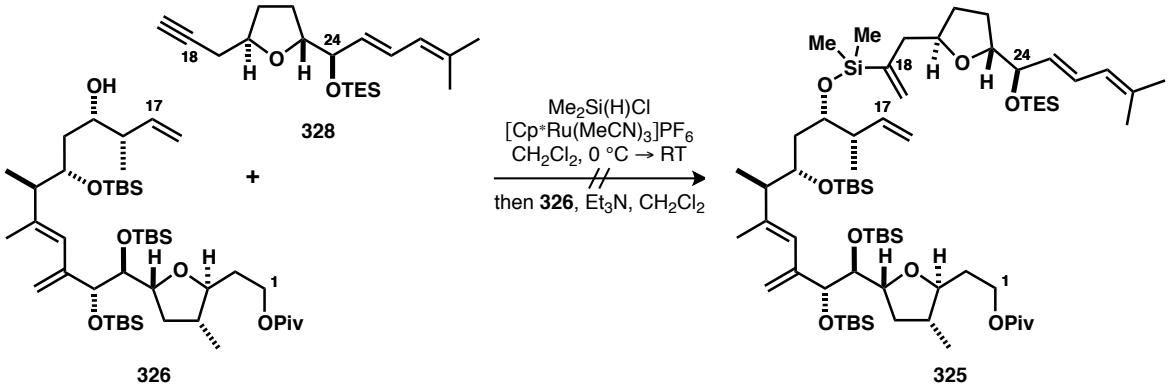
Scheme 95. Model System for the Silylation of Alcohol **334**

Mechanistic hypotheses have been proposed for this hydrosilylation reaction of alkynes (**Scheme 96**).[77] *trans* Addition of silane reagents across acetylene derivatives in the presence of cationic [Cp*Ru]-based catalysts (**336**) is thought to involve complex **338** that is produced by binding of alkyne **337** to the electrophilic metal centre followed by coordination of the silane. Inner-sphere delivery of the hydride to the bound alkyne then generates metallacyclopropene **339** without prior formation of a discrete metal hydride species. The *β*-carbon atoms of such η^2-vinyl complexes are configurationally labile and can swap places by reversible hapticity change. Consequently, isomer **340**, in which the hydrogen rather than the larger substituent R is oriented towards the bulky Cp* ligand, is favored over isomer **339**. The presence of the Cp* ligand appears to have a decisive steric influence. Finally, reductive elimination from intermediate **340**, in which the silicon entity is *anti* to the hydrogen, provides *E*-alkenylsilane product **341**.



Scheme 96. Possible Mechanism for the *trans* Hydrosilylation

The key coupling sequence, which was shown to be viable on the simplified system, was then applied to homoallylic alcohol **326**[78] and terminal alkyne **328** (**Scheme 97**). Unfortunately, the desired Si−O bond in diene **325** was not formed under the reaction conditions and homoallylic alcohol **326** was recovered fully. As an alternative, it should have been possible to convert the silyl chloride intermediate into the more reactive silyl triflate *in situ* using silver triflate prior to addition of a solution of alcohol and 2,6-lutidine.[74b] Unfortunately, significant difficulties were encountered when attempting to prepare the homoallylic alcohol (work by Dr Filippo Romiti) and so a revised synthetic approach for the coupling of two major fragments was required.

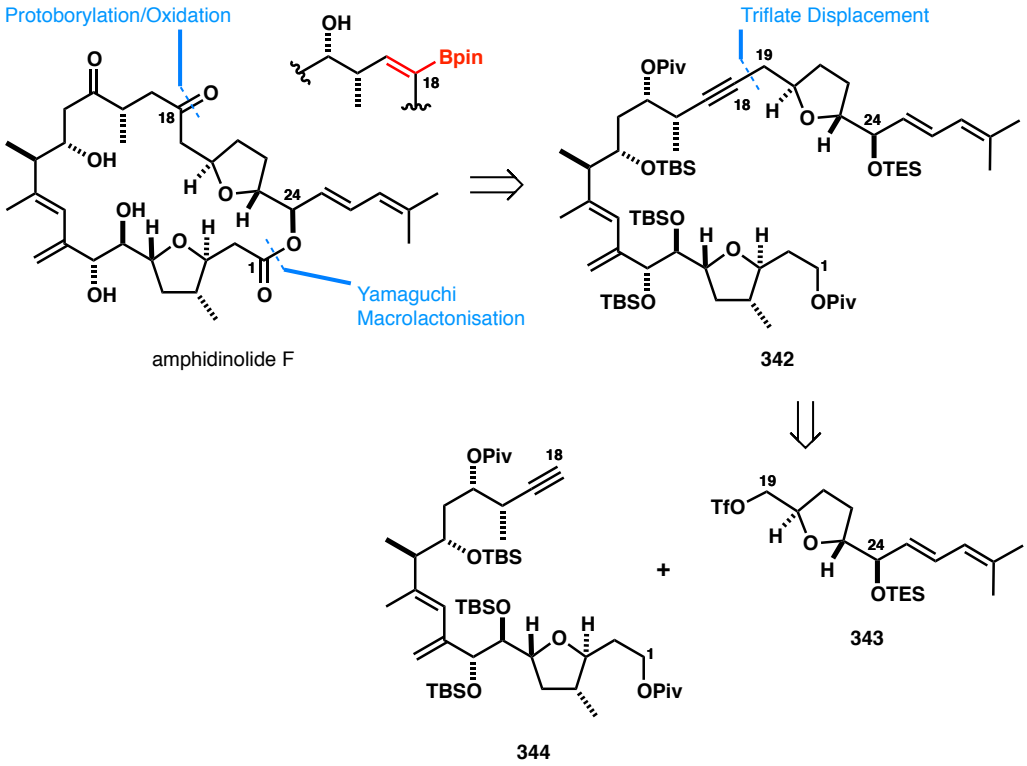


Scheme 97. Silylation Attempt of Alcohol **326**

2.4. Alkylation and Protoborylation Approach

2.4.1. Retrosynthetic Analysis

In order to access the challenging 1,4-diketone functionality at C15 and C18, an alkyne protoborylation to give a vinyl boronic ester and subsequent oxidation, unprecedented on such a complex substrate, were envisioned (**Scheme 98**).[79] Disconnection of the macrolactone and functional group interconversion revealed alkyne **342**. Further disconnection at the propargylic C18−C19 bond led to the terminal alkyne **344** and triflate **343** as the main advanced fragments in this approach.

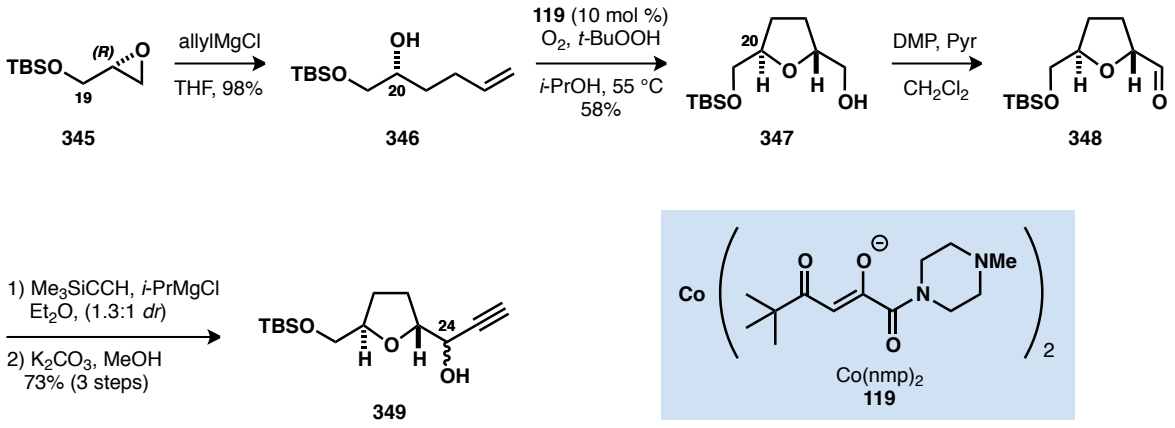


Scheme 98. Alkylation and Alkyne Protoborylation Approach

2.4.2. Synthesis of the C19−C29 Triflate Precursor

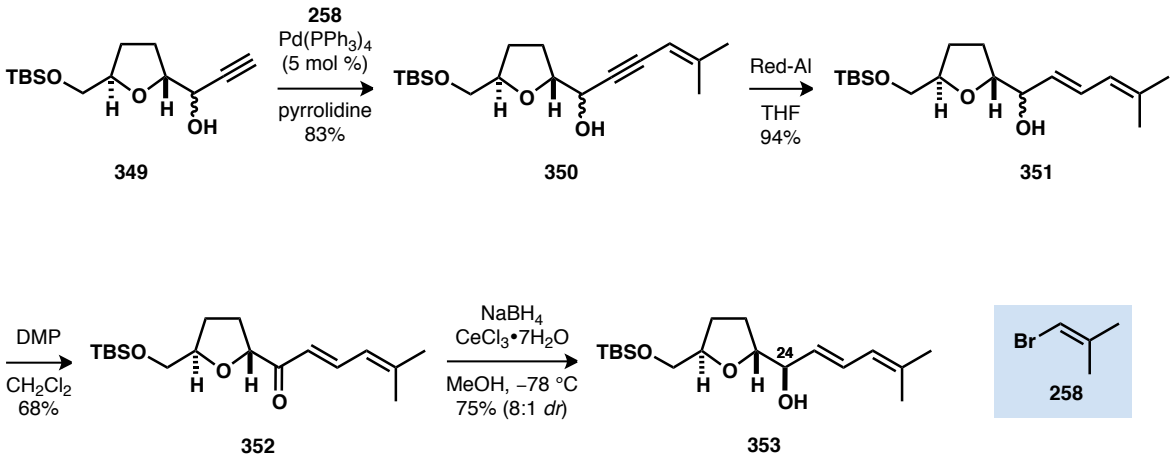
The synthesis of triflate **343** started from the commercially available glycidyl ether **345** (**Scheme 99**). Epoxide opening using allylmagnesium chloride yielded known pentenol **346** in excellent yield.[80] Tetrahydrofuran **347** was prepared as a single diastereomer by Mukaiyama aerobic oxidative cyclisation using the cobalt catalyst

119. Oxidation of the resulting alcohol with Dess-Martin periodinane afforded unstable aldehyde **348** and this was treated directly with magnesium (trimethylsilyl)acetylide. Finally, cleavage of the silyl group under basic conditions gave propargylic alcohol **349** as a 1.3:1 mixture of diastereomers at C24 in 73% yield over three steps.



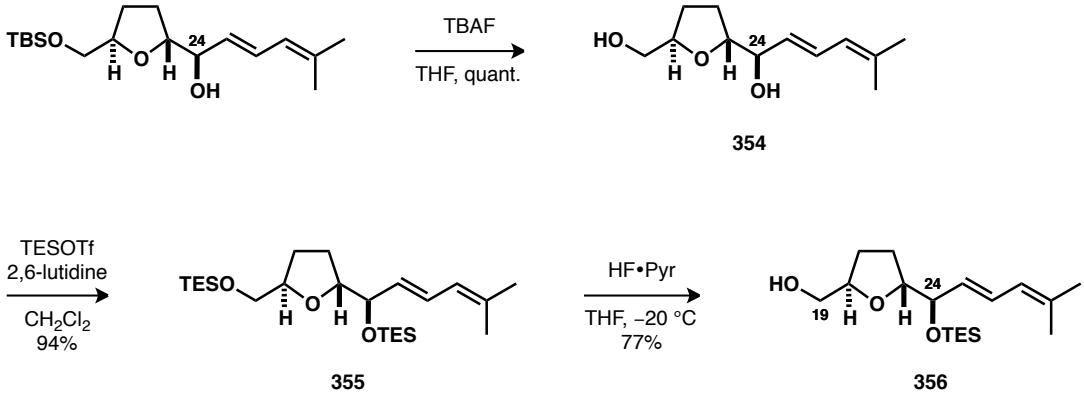
Scheme 99. Mukaiyama Oxidative Cyclisation Towards Alkyne **349**

The mixture **349** was submitted to a copper-free Sonogashira cross-coupling with vinyl bromide **258** in pyrrolidine to provide enyne **350** in 83% yield (**Scheme 100**). Stereoselective reduction of the diastereomeric mixture using Red-Al yielded *E*-alkene **351**. Formation of the key C24 stereocentre was achieved by oxidation of the allylic alcohol and subsequent reduction of enone **352** under Luche conditions,[81] providing (*R*)-alcohol **353** in 75% yield and with an 8:1 *dr*. Pure alcohol **353** was obtained in 60% yield after separation from the minor diastereomer by silica gel chromatography.



Scheme 100. Elaboration of Allylic Alcohol **353**

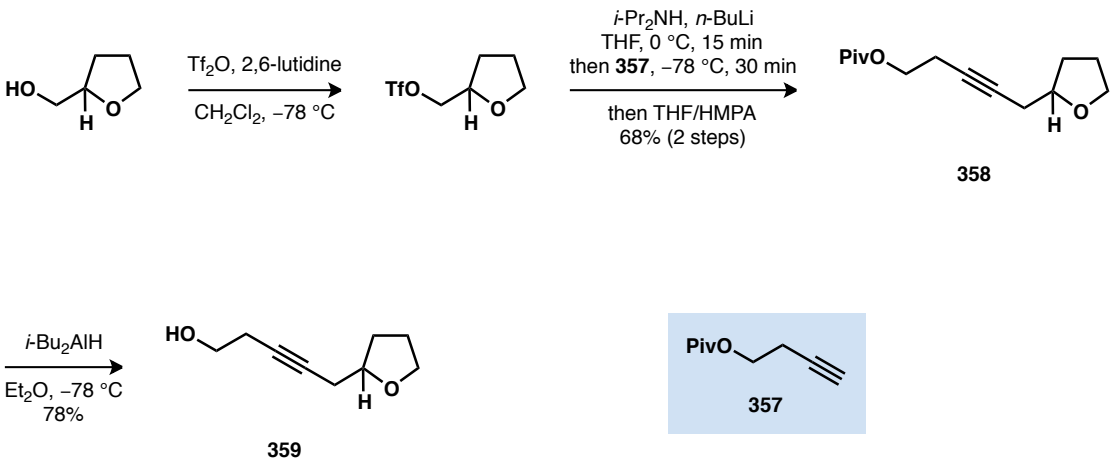
Finally, protecting group manipulation, including selective cleavage of the C19 silyl group of **355**, delivered alcohol **356**. The synthesis of the C19−C24 fragment was completed in a total of 12 steps and with an overall yield of 10% (**Scheme 101**).



Scheme 101. Completion of Triflate Precursor **356**

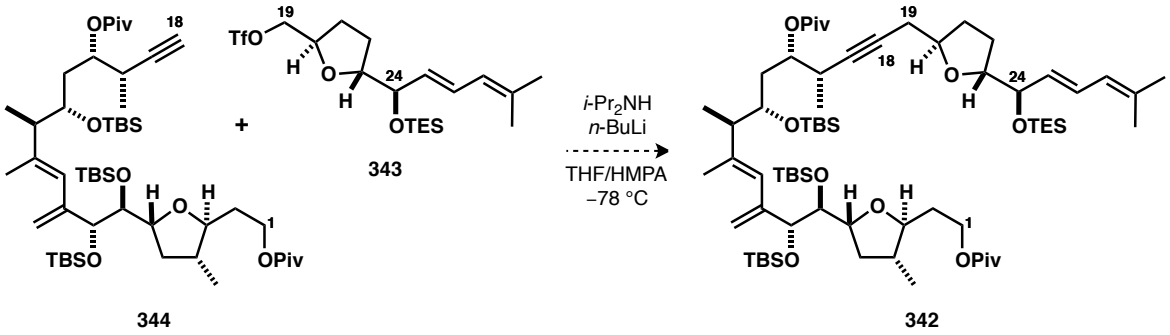
2.4.3. Alkylation by Displacement of a Simple Triflate

A model system was chosen in order to perform a rapid investigation of the coupling conditions. First, racemic tetrahydrofurfuryl alcohol was converted to the corresponding unstable triflate (**Scheme 102**). Deprotonation of known alkyne **357**[82] using LDA and subsequent addition of the lithium acetylide to the triflate produced alkyne **358** with creation of a new C−C bond in 68% yield over two steps. Cleavage of the pivalate ester afforded alcohol **359** and completed a three-step sequence that would be potentially suitable to join the main fragments.



Scheme 102. Simple Model System for Coupling Conditions

Unfortunately, alkyne **344** required for the coupling strategy outlined above could not be obtained, owing to the unexpected difficulty of forming the C17−C18 triple bond, either on the full fragment or at an earlier stage in its synthesis (work by Dr Filippo Romiti). Therefore, alcohol **356** was not converted into the triflate **343** and the coupling reaction developed in the context of the aforementioned model system was not applied to the fully functionalised fragments (**Scheme 103**).

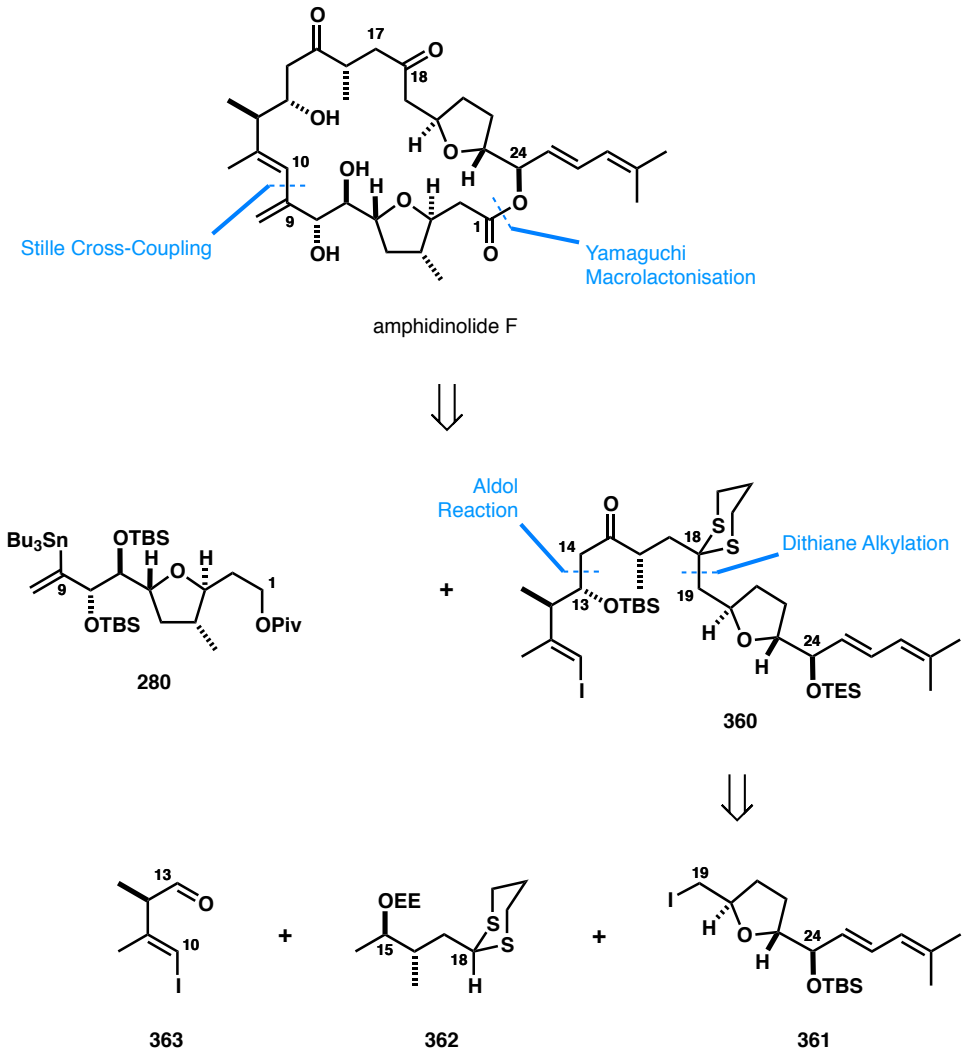


Scheme 103. Envisioned Coupling Towards Alkyne **342**

2.5. Umpolung and Aldol Strategy

2.5.1. Retrosynthetic Analysis

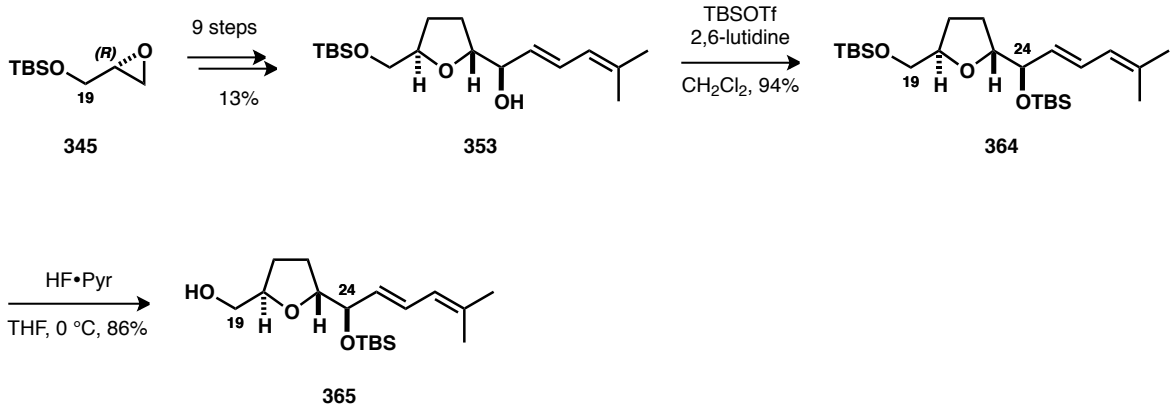
Current efforts focus on implementing an umpolung and aldol approach to the synthesis of the amphidinolide C series (**Scheme 104**). This strategy relies on a Stille cross-coupling reaction to unite the two main fragments. Disconnection of the macrolactone at the ester bond and the C9−C10 diene then reveals vinyl iodide **360** and vinyl stannane **280**. Iodide **360** could be prepared from alkyl iodide **361**, dithiane **362** and aldehyde **363**. These three fragments were to be joined by a boron-mediated aldol reaction to form the C13−C14 bond and a dithiane alkylation to construct the C18−C19 bond.



Scheme 104. Umpolung and Aldol Strategy

2.5.2. Synthesis of the C19−C29 Iodide Precursor

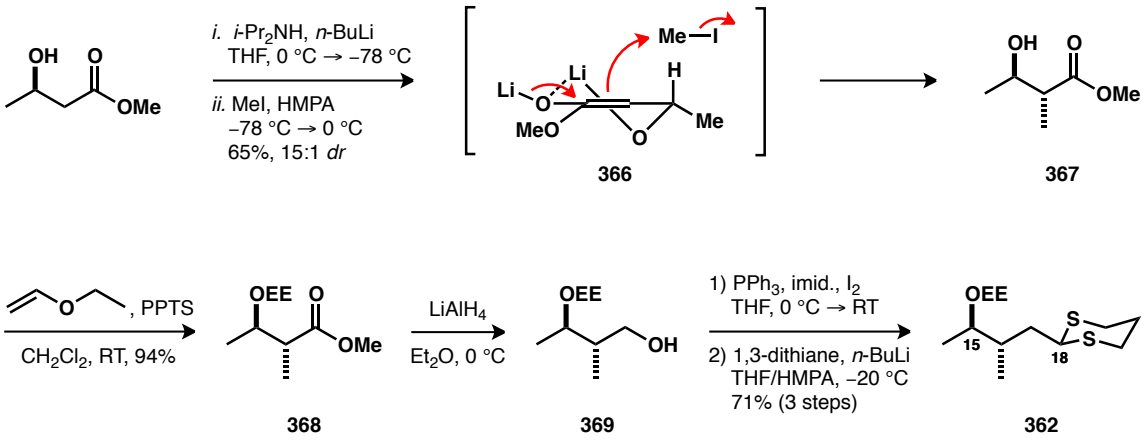
The synthesis of alcohol **365**, a stable precursor to alkyl iodide **361**, started from allylic alcohol **353**, previously synthesised in nine steps and with 13% overall yield from commercially available glycidyl ether **345** (**Scheme 105**). Silyl protection and selective deprotection of the C19 alcohol of **364** using HF•Pyr complex, provided the desired C19−C29 alcohol in a total of 11 steps and with 11% overall yield.



Scheme 105. Synthesis of Precursor to Iodide **361**

2.5.3. Preparation of the C14−C18 Dithiane

The synthesis of the C14−C18 dithiane fragment **362** commenced from the commercially available (*R*)-methyl-3-hydroxybutanoate as a chiral pool starting material (**Scheme 106**). Diastereoselective *α*-methylation produced (*R*,*R*)-ester **367** in 65% yield and with an excellent 15:1 *dr*.[83]

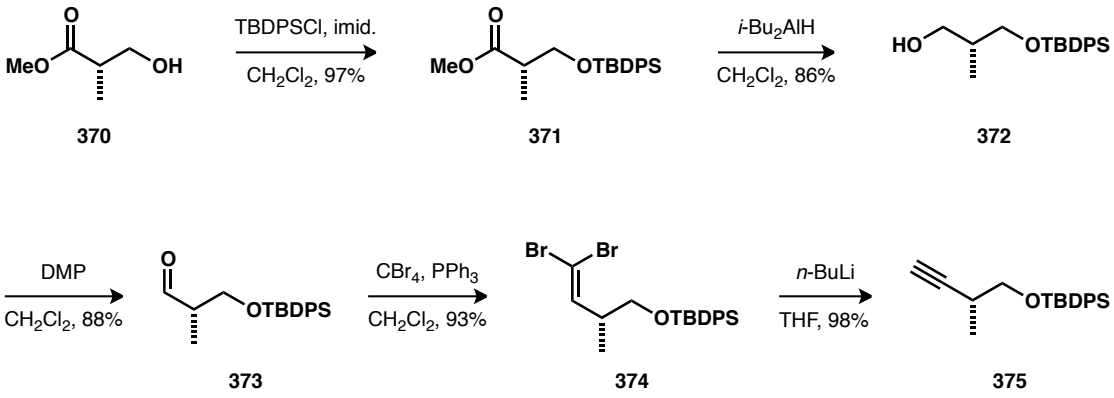


Scheme 106. Preparation of Dithiane **362**

The high diastereoselectivity obtained during the Fráter-Seebach alkylation can be rationalised by six-membered intermediate **366**, in which the reaction with the electrophile proceeds on the less hindered face of the chelated adduct.[84] Acid-catalysed protection of the hydroxyl group using ethyl vinyl ether provided methyl ester **368** as a 1.1:1 diastereomeric mixture in excellent yield. The choice of an EE acetal for the protection of the C15 alcohol resulted from the difficulties encountered previously within our group when using various acetal protecting groups such as the MOM protecting group,[70] and was influenced by the successful use of an EE acetal by Carter and co-workers in their synthesis of amphidinolides C and F.[27] Subsequent reduction of the methyl ester using lithium aluminium hydride in Et_2O at 0 °C afforded primary alcohol **369**. Finally, iodination and addition of the anion generated by treatment of 1,3-dithiane with *n*-BuLi installed the dithiane moiety in 71% yield over three steps. Overall, the C14−C18 dithiane **362** was completed in five steps and with 43% overall yield.

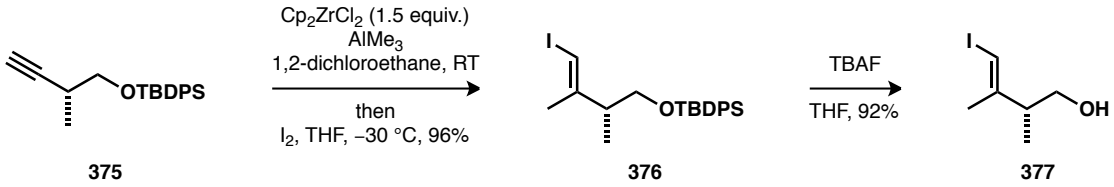
2.5.4. Elaboration of the C10−C13 Aldehyde Precursor

The final small C10−C13 fragment required for the elaboration of vinyl iodide **360** was prepared from commercially available (*S*)-Roche ester (**370**) (**Scheme 107**). First, the primary alcohol was protected and silyl ether **371** was obtained in excellent yield.[85] Reduction of the methyl ester moiety using *i*-Bu_2AlH gave alcohol **372** and subsequent oxidation afforded aldehyde **373** in good yield. Finally, conversion of the aldehyde into terminal alkyne **375**[86] was achieved in two high-yielding steps *via* dibromo olefin **374** using the Corey-Fuchs protocol.[87]



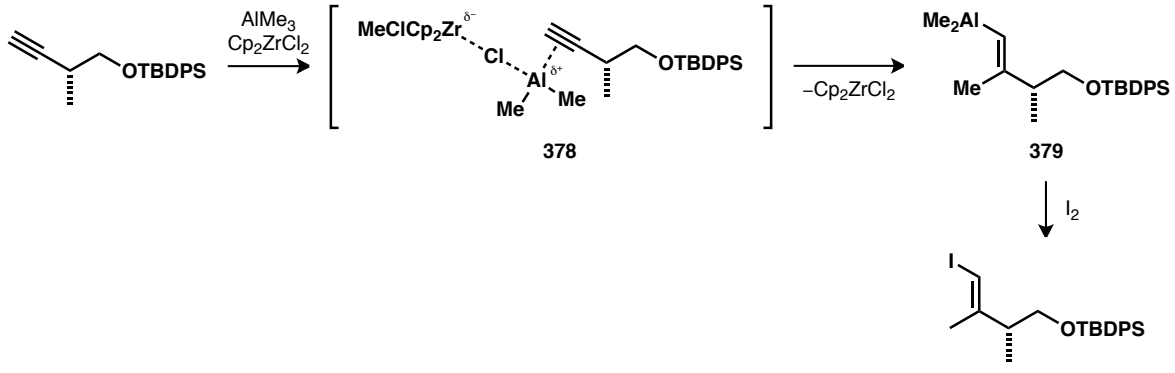
Scheme 107. Preparation of Alkyne **375**

The synthesis of alcohol **377**, the stable precursor to aldehyde **363**, was completed in two additional steps (**Scheme 108**). First, terminal alkyne **375** was subjected to a carboalumination reaction under Negishi's conditions.[88] Treatment with a solution of $AlMe_3$ (4.0 equiv.) and Cp_2ZrCl_2 (1.5 equiv.) in 1,2-dichloroethane at room temperature produced the corresponding alkenylmetal species; the desired *syn* addition product **376** was obtained in excellent yield and with high regioselectivity and stereoselectivity following an iodine quench. Finally, deprotection of the alcohol using TBAF provided vinyl iodide **377** in 92% yield, completing a seven-step synthetic sequence with an overall yield of 59%.



Scheme 108. Completion of Aldehyde Precursor **377**

The carboalumination of alkynes with a methylalane species and a zirconocene derivative represents a convenient tool to access (*E*)-2-methyl-1-alkenylalanes. This transformation is generally catalytic in zirconium. Although the mechanism has not been fully elucidated,[89] it is likely to involve a zirconium-assisted direct Al−C bond *syn* addition to the triple bond (**Scheme 109**). The zirconium catalyst is thought to activate the aluminium centre towards the alkyne by polarisation between these two metals *via* three-centre two-electron bonding, as can be seen in intermediate **378**. *E*-alkenylalane **379** is then obtained alongside the catalytic species. The regioselectivity of this process is dictated by the steric requirements of the Al−Me system.

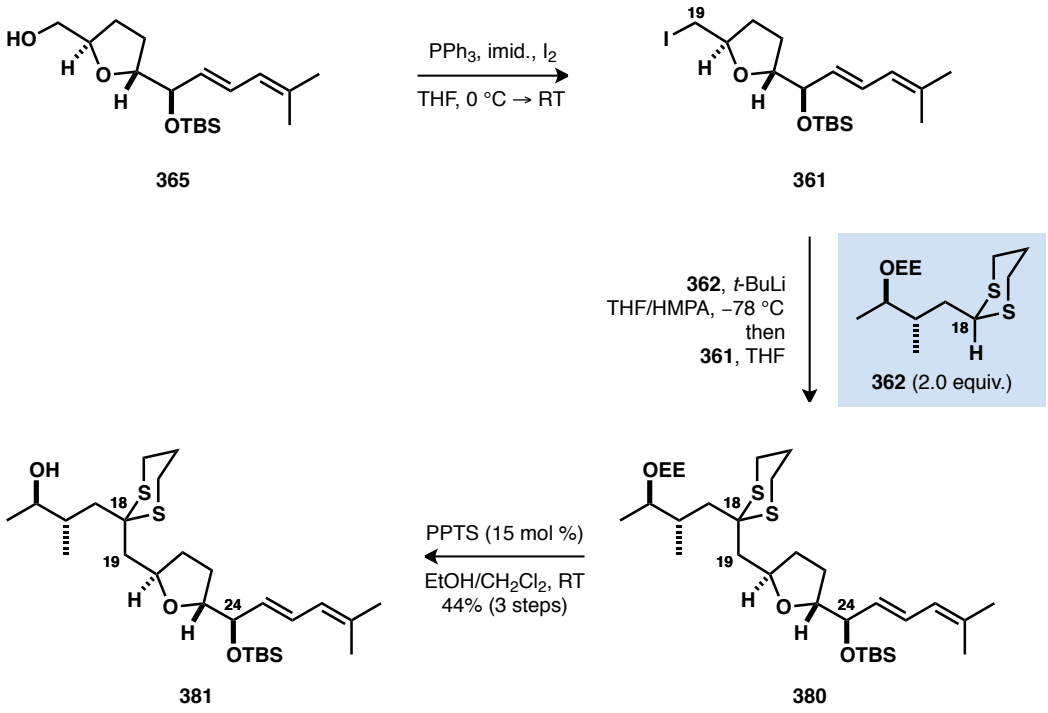


Scheme 109. Mechanistic Rationale for the Carboalumination Reaction

2.5.5. Completion of the C10−C29 Vinyl Iodide Fragment

With alcohol **365**, dithiane **362** and vinyl iodide **377** now available, efforts to complete fragment **360** were initiated.

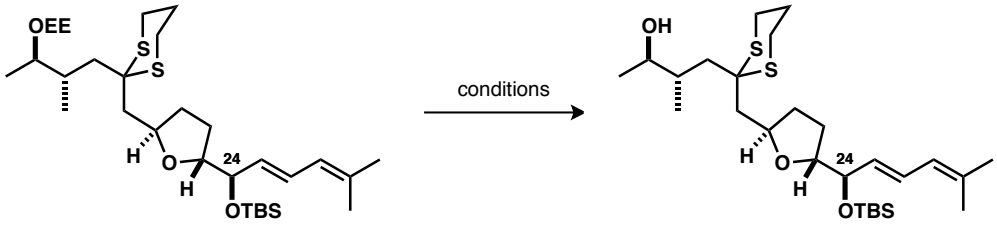
First, alcohol **365** was converted cleanly into the unstable alkyl iodide **361** using triphenylphosphine, imidazole and iodine in THF (**Scheme 110**). Displacement of iodide from fragment **361** using the anion obtained by deprotonation of dithiane **362** with *t*-BuLi in the presence of HMPA forged the C18−C19 bond, yielding a 1:2 mixture of 1,1-disubstituted dithiane **380** and excess dithiane **362**. Finally, cleavage of the ethoxyethyl acetal (*vide infra*) delivered secondary alcohol **381** in a satisfying 44% yield over three steps. Practically, this also allowed complete separation of the alcohol produced by deprotection of excess acetal **362**, which could not be separated from dithiane **380** by chromatography.



Scheme 110. Construction of the C18−C19 Bond of Alcohol **381**

Reaction conditions required for the cleavage of the ethoxyethyl acetal were investigated (**Table 6**). For this purpose, a small amount of pure dithiane **380** was obtained by treatment of the mixture of **380** and **362** with TBAF in THF and subsequent separation of dithiane **362**, followed by silyl reprotection of the alcohol

derived from **380** using TBSOTf and 2,6-lutidine in CH_2Cl_2. Treatment of the ethoxyethyl acetal **380** with PPTS in a mixture of EtOH and CH_2Cl_2[90] (**Entry 1**) provided alcohol **381** in 86% yield after nine hours. Deprotection of the same substrate under aqueous acidic conditions (**Entry 2**) afforded the desired product after an extended reaction time and in a lower 75% yield.



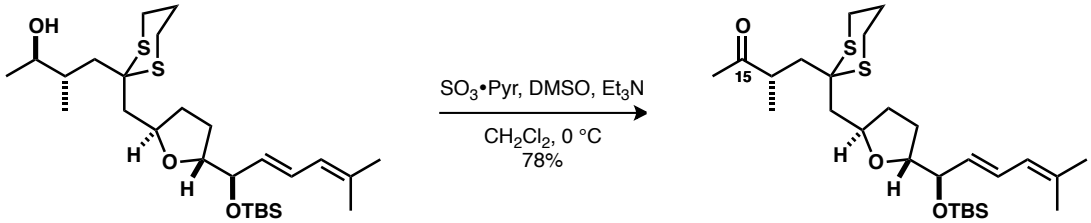
380 381

Entry	Conditions[a]	T (°C)	Time (h)	381
1	PPTS[b] in EtOH/CH_2Cl_2 (3:1)	23	9	86%
2	THF/AcOH/H_2O (4:4:1)	23	17	75%

(a) All reactions were performed on a 10 mg scale.
(b) 10 mol % used.

Table 6. Ethoxyethyl Acetal Cleavage Conditions

The successful synthesis of alcohol **381** was followed by oxidation under mild conditions using the Parikh-Doering protocol.[91] This reaction delivered the *α*-substituted ketone **382** in 78% yield after 48 h (**Scheme 111**).

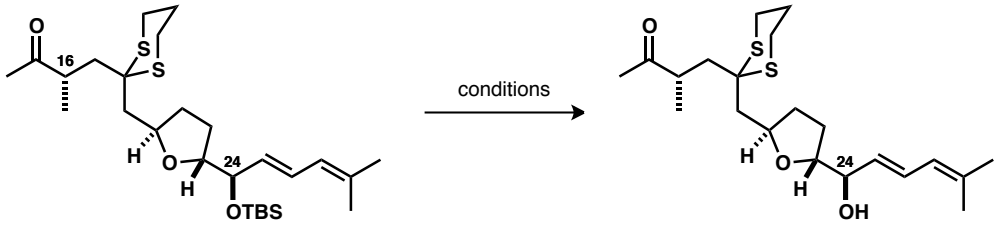


381 382

Scheme 111. Preparation of the C15 Ketone **382**

With ketone **382** in hand, installation of the requisite TES ether at the C24 position was now required. Introduction of this more labile silyl ether would allow selective deprotection of the C24 alcohol at a later stage in the synthesis prior to the envisioned Yamaguchi macrolactonisation reaction.

Deprotection of the C24 alcohol appeared to be a difficult transformation because of the potential for epimerisation of the C16 stereocentre. Attempts to perform an acid-mediated cleavage of the silyl protecting group by a slow *in situ* generation of HCl (**Table 7**, **Entry 1**) resulted in the complete decomposition of ketone **382** to give a complex mixture of products. Treatment of the silyl ether with a solution of TBAF in THF buffered with acetic acid provided allylic alcohol **383** as a single diastereromer in quantitative yield, but only after an impractically long reaction time (**Entry 2**). Finally, exposure of ketone **382** to a solution of TBAF in THF afforded the desired product in quantitative yield and in only five hours; no epimerisation was observed under these basic conditions[92] (**Entry 3**).



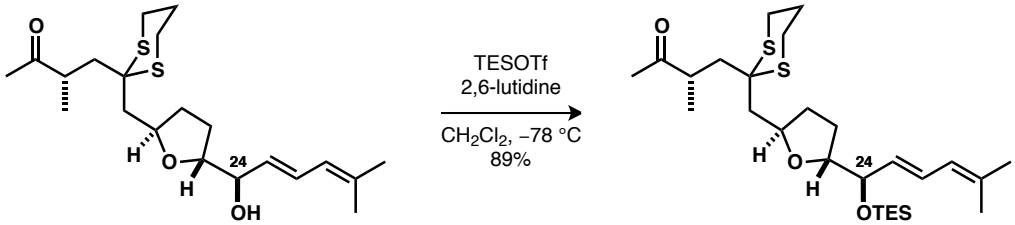
382 383

Entry	Conditions	T (°C)	Time (h)	*dr*	383
1	AcCl, EtOH	23	4	–	0%[a]
2	TBAF, AcOH, THF	23	92	> 20:1[b]	quant.
3	TBAF, THF	23	5	> 20:1[b]	quant.

(a) Complete decomposition of the material observed.
(b) No epimerisation observed by ^{1}H NMR of the crude mixture.

Table 7. C24 Alcohol Deprotection Conditions

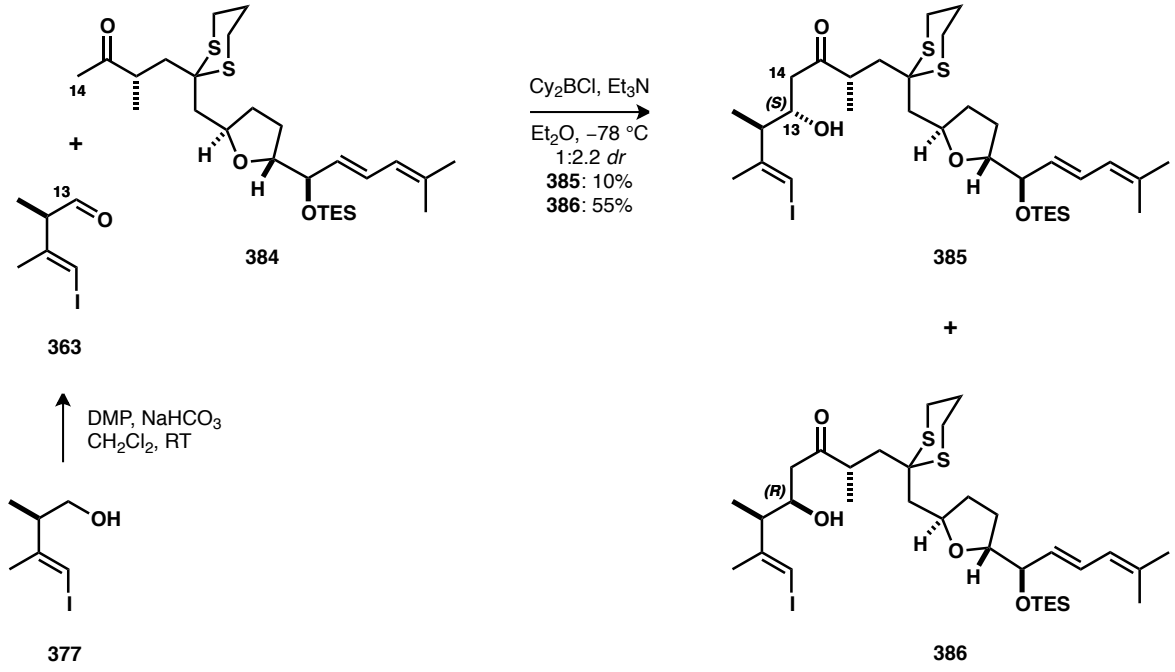
Finally, methyl ketone **384** was completed by silyl protection of allylic alcohol **383** to furnish the corresponding TES ether in 89% yield (**Scheme 112**).



383 384

Scheme 112. Completion of Ketone Partner **384**

Successful synthesis of ketone **384** allowed the key boron-mediated aldol reaction to be investigated. First, alcohol **377** was converted to unstable aldehyde **363** using Dess-Martin periodinane buffered with sodium bicarbonate (**Scheme 113**). Purification of the aldehyde product by silica gel chromatography resulted in complete decomposition of the material and so crude aldehyde **363** was used in the subsequent reaction. Aldol condensation of aldehyde **363** with the boron enolate generated by treatment of ketone **384** with Cy_2BCl proceeded with full conversion to afford a 1:2.2 diastereomeric mixture of (*S*)-*β*-hydroxy ketone **385** and (*R*)-aldol product **386**. Unfortunately, following tedious separation of the two diastereomers by silica gel chromatography, the desired fragment **385** was only isolated in 10% yield and the undesired (*R*)-*β*-hydroxy ketone **386** was obtained in 55% yield. A third fraction that contained a mixture of both diastereomers and boron residues was also isolated. Attempts to remove the boron residues during the reaction work-up by treatment with aqueous hydrogen peroxide produced a complex mixture of unidentifiable side products.



Scheme 113. Key Boron-mediated Aldol Reaction

The low diastereoselectivity obtained during the Cy_2BCl-mediated condensation reaction can presumably be related to the steric properties of the three substituents at the *α* stereogenic centre of the boron enolate generated from methyl ketone **384**. The boron aldol reaction may proceed *via* chair-like transition

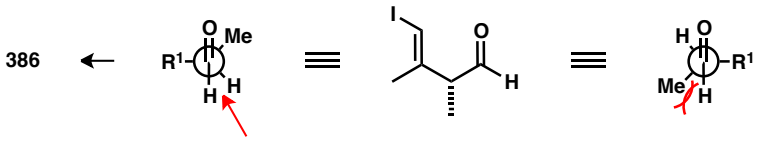
state **387**[93] in which the aldehyde attacks from the face away from the R^2 group, with the hydrogen pointing towards the incoming aldehyde and the R^2 group directed away from it (**Scheme 114**). Therefore, the low level of diastereocontrol could arise from similar steric demands of the R^2 and Me groups, as well as other more complex competing effects.

387
favored TS
re-face attack

disfavored TS
si-face attack

Scheme 114. Aldol Condensation Transition States

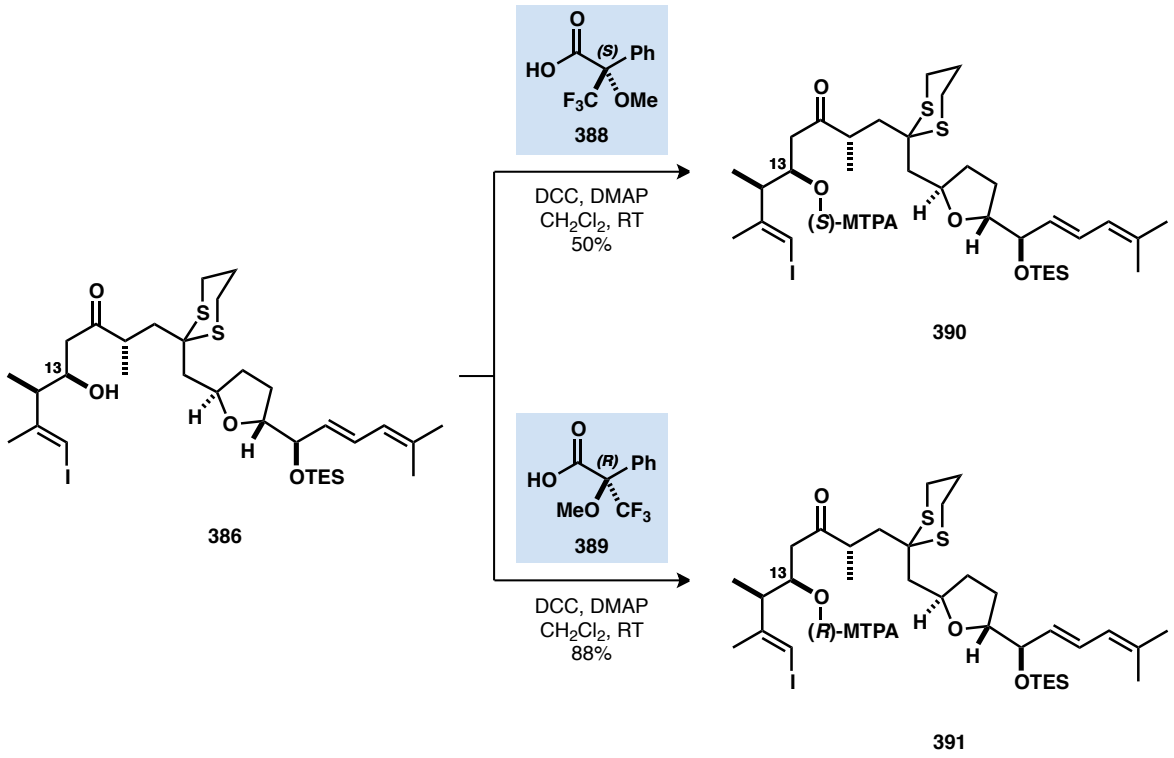
The low diastereoselectivity is also consistent with a Felkin-type addition to the aldehyde (**Scheme 115**). The size discrepancy between the methyl group at the *α* stereogenic centre of the aldehyde and the larger R^1 substituent may also be insufficient to generate significant facial discrimination on the aldehyde.



Scheme 115. Facial Selectivity of the Aldehyde

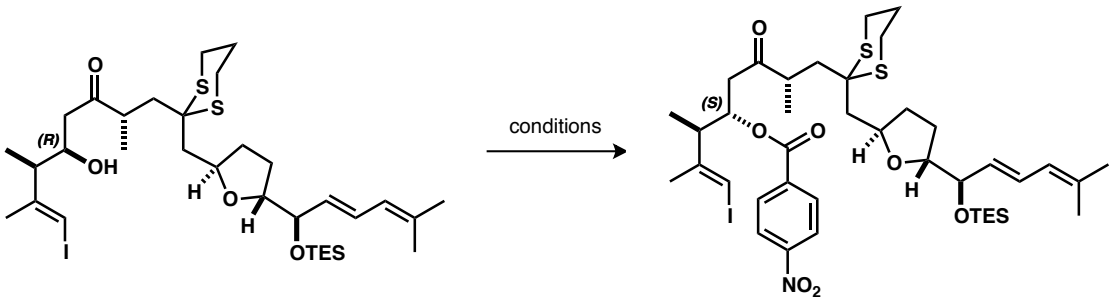
In order to establish the stereochemistry at C13 conclusively for each diastereomer obtained from the aldol condensation reaction, Mosher ester analysis was conducted on the predominating *β*-hydroxy ketone isomer **386** (**Scheme 116**).[94] This NMR-based method relies on the fact that the protons in diastereomeric Mosher esters **390** and **391** display predictable changes in chemical shifts in their ^{1}H NMR spectra. To this end, *β*-hydroxy ketone **386** was treated with either (*S*)-*α*-methoxy-*α*-trifluoromethylphenylacetic acid **388** or its (*R*) equivalent **389**, DCC and DMAP in CH_2Cl_2 at room temperature for 24 h to provide analytical samples of both Mosher esters **390** and **391**. Subsequent analysis of

their ^{1}H NMR spectra revealed the C13 stereocentre of fragment **386** to be of (*R*) configuration and therefore the undesired diastereomer.



Scheme 116. Advanced Mosher Analysis

In an attempt to convert *β*-hydroxy ketone **386** into the desired diastereomer **385**, Mitsunobu conditions were employed (**Table 8**). Not unexpectedly,[95] the system proved to be unreactive, most likely due to the sterically hindered environment of the hydroxyl group. Treatment of adduct **386** with 4-nitrobenzoic acid (4 equiv.), DEAD (4 equiv.) and triphenylphosphine (4 equiv.) in benzene at room temperature resulted in partial recovery of the starting material and decomposition products after an extended reaction time and the ester **392** was not observed (**Entry 1**). Increasing the reaction temperature and the amount of reagents did not bring any improvement and even more decomposition was observed (**Entry 2** and **Entry 3**).



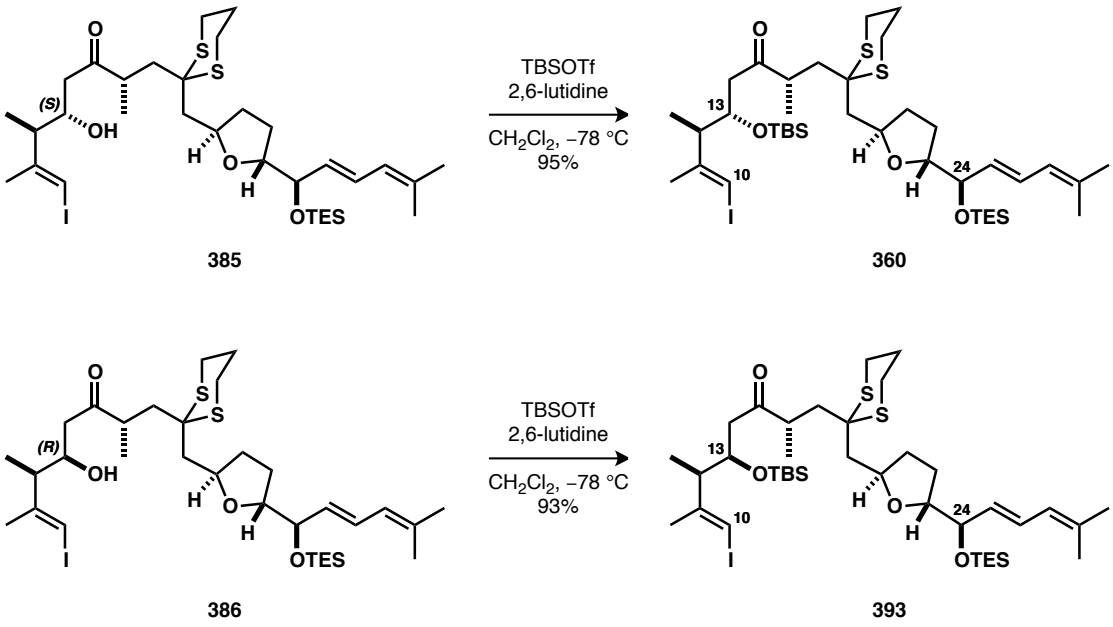
386 392

Entry	Acid[a] (equiv.)	DEAD (equiv.)	PPh_3 (equiv.)	T (°C)	Time (h)	392	386
1	4	4	4	23	44	0%	48%
2	6	6	6	40	20	0%	–
3	6	6	6	70	20	0%	–

(a) 4-nitrobenzoic acid used.

Table 8. Mitsunobu Inversion of *β*-Hydroxy Ketone **386**

Instead, both (*S*)-*β*-hydroxy ketone **385** and (*R*)-*β*-hydroxy ketone **386** were converted to silyl ethers **360** and **393** in excellent yield (**Scheme 117**). The required vinyl iodide **360** was therefore synthesised in 19 steps and with 0.31% overall yield.



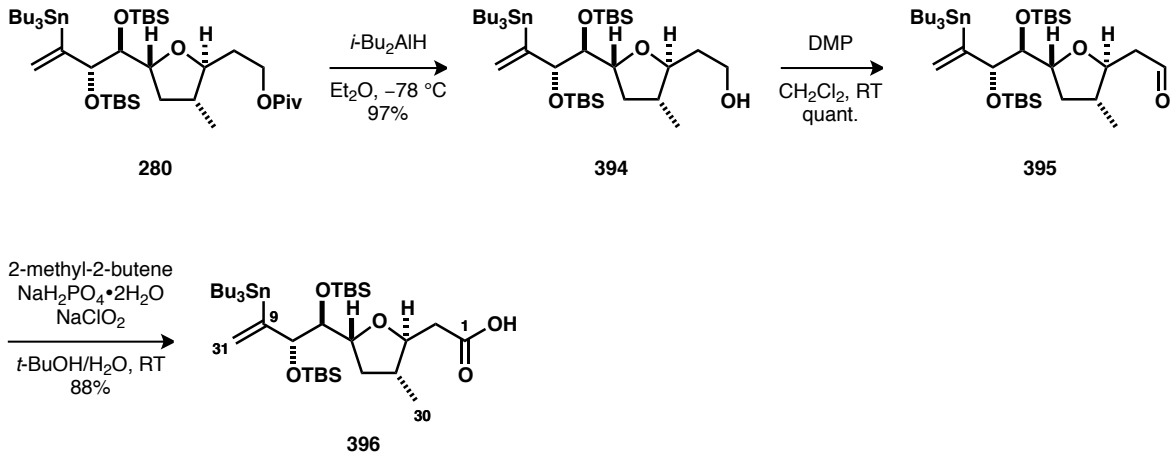
385 360

386 393

Scheme 117. C10−C29 Vinyl Iodide Fragment Completion

2.5.6. Synthesis of the C1−C9 Carboxylic Acid

Following the synthesis of vinyl iodides **360** and **393**, the stannane partner required for the envisioned Stille cross-coupling was prepared (**Scheme 118**). Cleavage of the pivalate ester by treatment of fragment **280**[73] with *i*-Bu_2AlH in Et_2O at −78 °C afforded primary alcohol **394** in excellent yield. Subsequent oxidation using Dess-Martin periodinane provided aldehyde **395** quantitatively. Finally, carboxylic acid **396** was obtained in 88% yield by Pinnick oxidation, completing the desired C1−C9 stannane fragment.

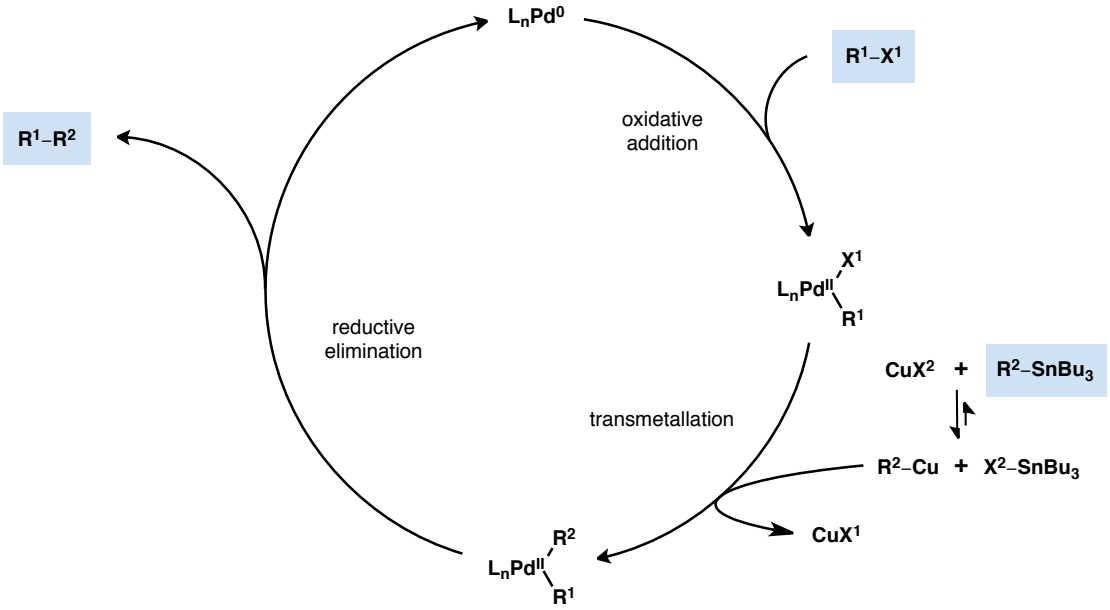


Scheme 118. Formation of Acid **396** by Reduction/Oxidation Sequence

2.5.7. Coupling Attempts of the C1−C9 and C10−C29 Fragments

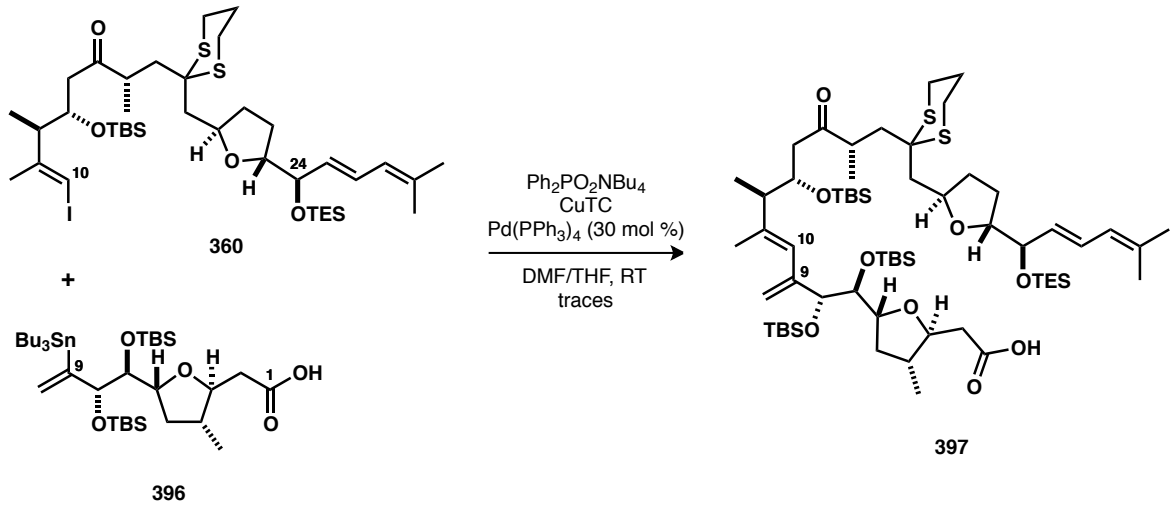
It was expected that coupling of vinyl iodide **360** and stannane **396** by formation of the C9−C10 bond would be performed by a Stille cross-coupling. The protocol selected for this reaction was that developed by Fürstner and co-workers because of the mild conditions.[53] These conditions rely on the co-catalytic effect exerted by copper(I), in this case copper(I) thiophene-2-carboxylate (CuTC), which transmetallates with tin species to form the corresponding organocopper species (**Scheme 119**). The more nucleophilic organocopper reagent then has a positive impact on the rate and the efficiency of the reaction.[96] Because the tin/copper exchange is likely reversible, the phosphinate salt $[Ph_2PO_2][NBu_4]$ is employed as an essentially neutral tin scavenger[97] driving the equilibrium towards the formation of the organocopper species. The use of this procedure circumvents problems

encountered with fluoride additives such as their basicity and incompatibility with silyl protecting groups.



Scheme 119. Stille-Migita Cross-coupling Proposed Mechanism

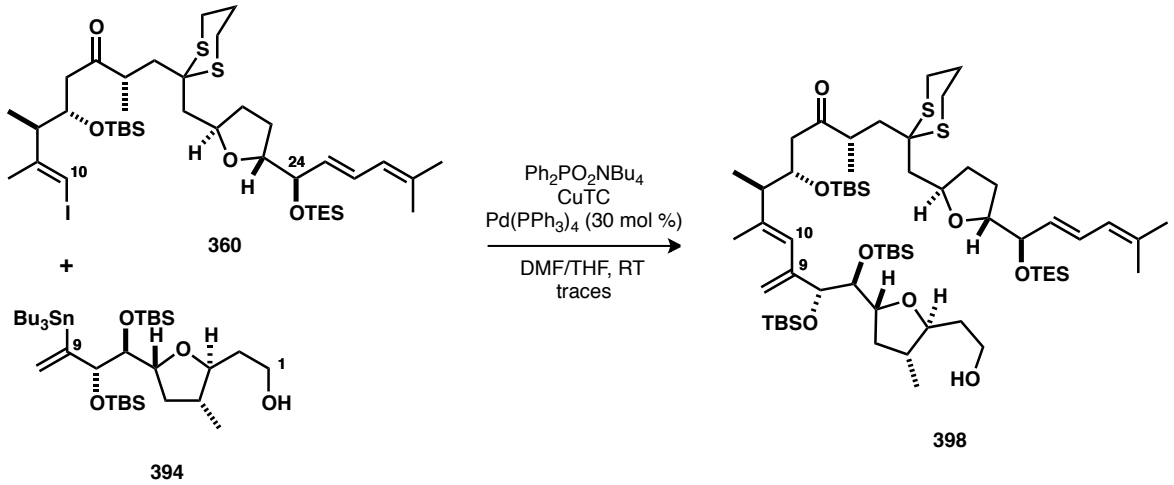
Unfortunately, under these mild Stille coupling conditions, iodide **360** and stannane **396** were both consumed but only trace amounts of coupled carboxylic acid **397** could be detected within the complex mixture (**Scheme 120**).



Scheme 120. Stille Coupling: Iodide **360** and Carboxylic Acid **396**

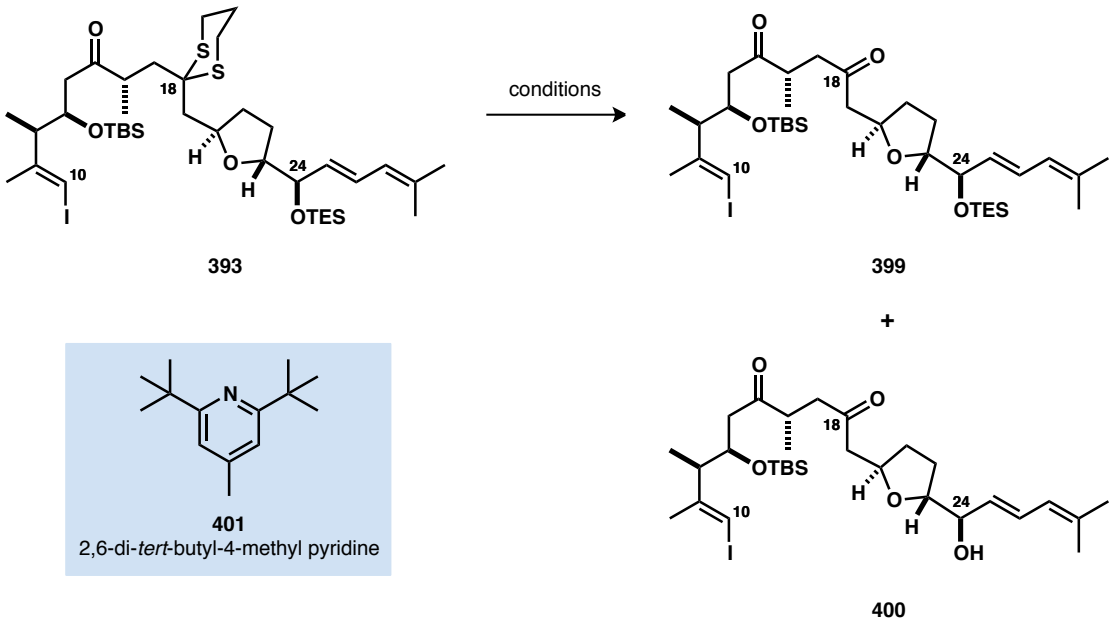
As an alternative, a similar coupling was attempted between vinyl iodide **360** and alcohol **394**, using identical conditions (**Scheme 121**). The outcome was equally

unsatisfying because alcohol **398** was also obtained in trace amounts and the starting compounds were only partially recovered. At this point, it was thought that the dithiane in iodide **360** might be problematic because it could inhibit the oxidative addition of the vinyl iodide to the palladium by ligation to the metal.[98]



Scheme 121. Stille Coupling: Iodide **360** and Alcohol **394**

It was therefore proposed to convert the dithiane moiety to the corresponding ketone prior to the Stille coupling reaction. Conditions for this transformation were investigated on vinyl iodide **393**, the C13 epimer of fragment **360** (**Table 9**). Hydrolysis of the dithiane segment on this complex fragment proved to be challenging. Common methods involving mercury salts were attempted first. Treatment of the substrate with $HgCl_2$ resulted in either no conversion (**Entry 1**) or partial decomposition of the starting material and the desired ketone **399** was obtained in just 20% yield (**Entry 2**). Similarly, the use of $Hg(ClO_4)_2$ in THF and MeOH, buffered with 2,6-lutidine, resulted in rapid decomposition of the dithiane fragment (**Entry 3**). Unexpectedly, the use of $Hg(ClO_4)_2$ and $CaCO_3$ in a mixture of MeCN, THF and water at 0 °C produced ketone **400**, which is *O*-desilylated at the C24 position, in 77% yield along with a small amount of the required ketone **399** (**Entry 4**). An increase in the reaction time resulted in significant decomposition and ketone **400** was isolated in 39% yield (**Entry 5**). Finally, Stork's reagent buffered with 2,6-di-*tert*-butyl-4-methyl pyridine (**401**) was tested and this reaction produced a 1:1.5 mixture of ketones **399** and **400** (**Entry 6**). Reduction of the reaction temperature, limited by the presence of water in the solvent mixture, slowed the conversion rate (*ca*. 50% after two hours) and formation of both diketones **399** and **400** was observed from the start (**Entry 7**).



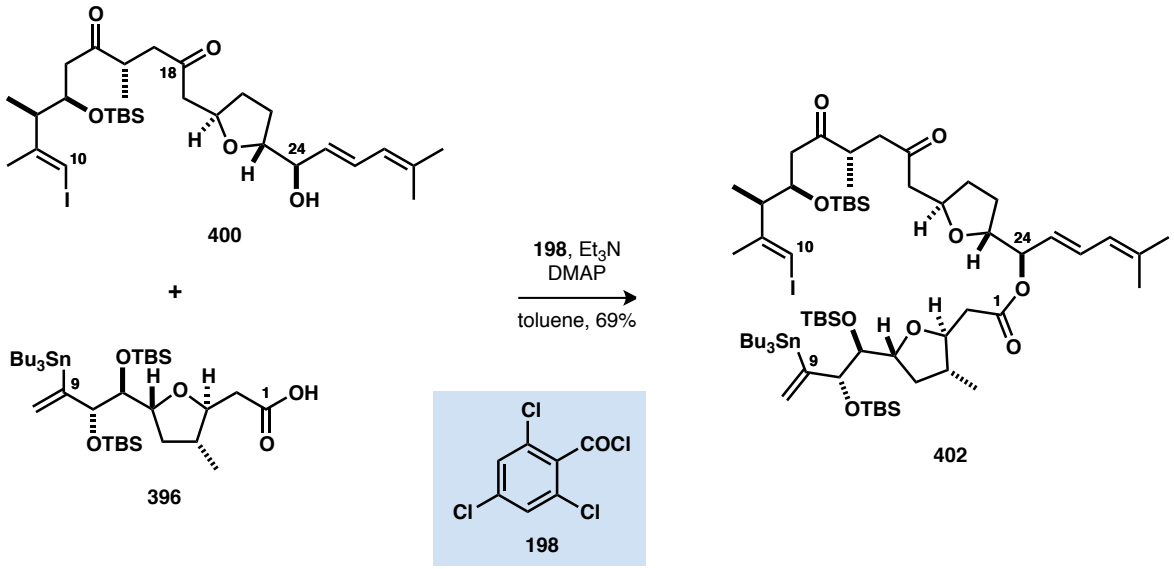
401
2,6-di-*tert*-butyl-4-methyl pyridine

Entry	Conditions[a]	Solvent	T (°C)	t (h)	399[b]	400[b]
1	$HgCl_2$, $CaCO_3$	THF	23	2	–	–
2	$HgCl_2$, $CaCO_3$	MeCN/H_2O	23	2	20%	–
3	$Hg(ClO_4)_2$, 2,6-lutidine	THF/MeOH	0	0.5	–	–
4	$Hg(ClO_4)_2$, $CaCO_3$	MeCN/THF/H_2O	0	0.3	8%	77%
5	$Hg(ClO_4)_2$, $CaCO_3$	MeCN/THF/H_2O	0	0.5	–	39%
6	$PhI(OCOCF_3)_2$, **401**	MeCN/THF/H_2O	0	0.8	41%	25%
7	$PhI(OCOCF_3)_2$, **401**	MeCN/THF/H_2O	−15	2	31%	15%

(a) All reactions were performed on a 5 mg scale.
(b) Isolated yield.

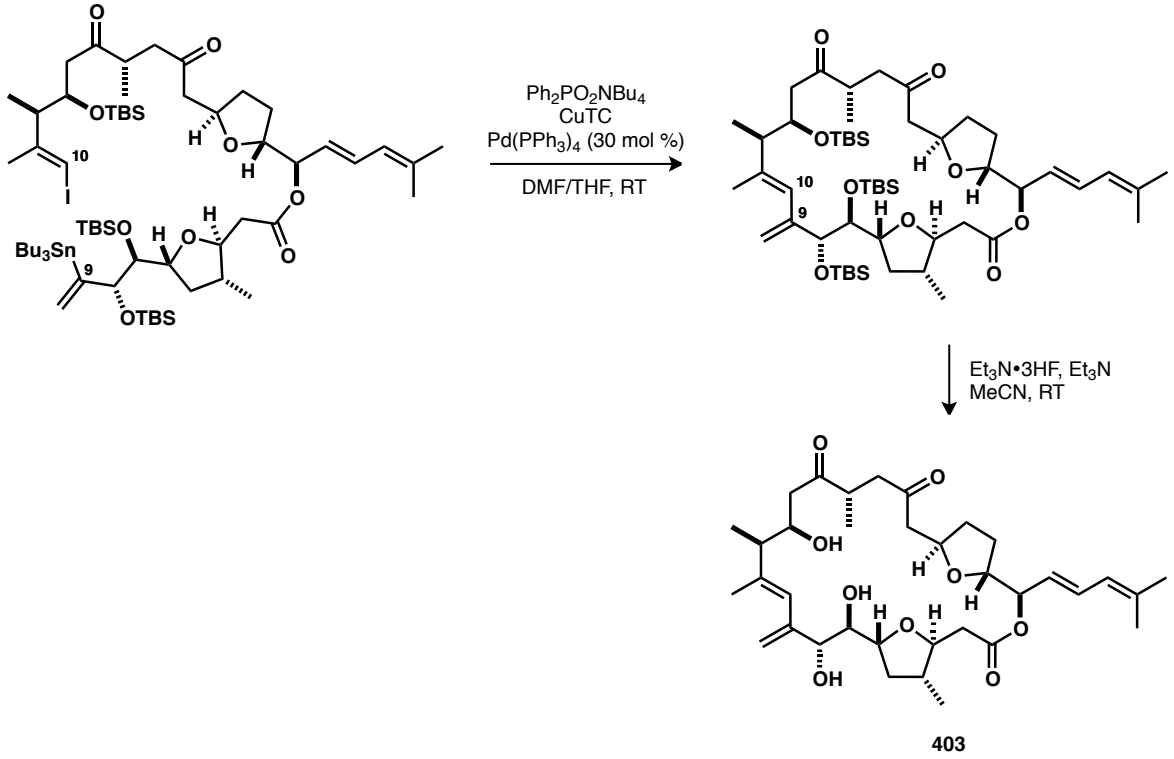
Table 9. Conditions for Hydrolysis of Dithiane **393**

In the light of these results, it was decided to take advantage of the formation of ketone **400**, bearing a free allylic alcohol at C24, and join the two main fragments employing a Yamaguchi esterification reaction before undertaking a macrocyclisation reaction using the aforementioned Stille coupling.[28, 32d] Pleasingly, addition of alcohol **400** and DMAP to the Yamaguchi[99] mixed anhydride generated by treatment of carboxylic acid **396** with acyl chloride **198** and triethylamine produced the ester **402** in 69% yield (**Scheme 122**).



Scheme 122. Fragment Coupling by Yamaguchi Esterification

Ring closure was then attempted using aforementioned conditions for the Stille coupling reaction (**Scheme 123**). This approach appeared challenging due to the steric constrains involved in the formation of this congested ring.[32d, 100]



Scheme 123. Completion Attempt of Amphidinolide F C13-Epimer

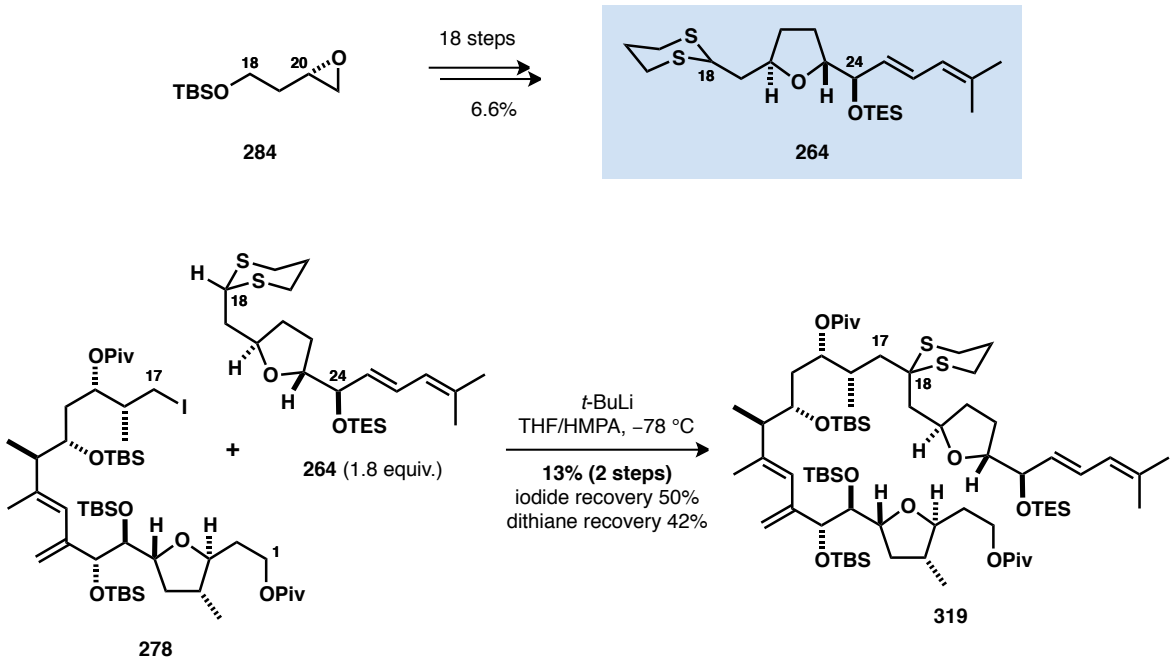
The intramolecular Stille cross-coupling resulted in full conversion of the starting material to a mixture of three inseparable products. NMR analysis of this material proved difficult probably due to the presence of conformational isomers. It was therefore decided to submit this mixture to global desilylation conditions using $Et_3N•3HF$ complex and triethylamine in MeCN at room temperature for seven days. Formation of the desired triol **403** was observed by mass spectrometry but attempts to isolate the pure macrolactone were unsuccessful.

To conclude, successful syntheses of vinyl iodides **360** and **393** were completed from alkyl iodide **361**, dithiane **362** and aldehyde **363** using a dithiane alkylation reaction and a boron-mediated aldol condensation reaction. Subsequent hydrolysis of the dithiane moiety provided 1,4-diketone **400** bearing a free allylic alcohol at C24. Coupling of the two main fragments was achieved by means of a Yamaguchi esterification reaction between carboxylic acid **396** and allylic alcohol **400**. However, closure of the macrocyclic core proved to be challenging and although there was mass spectrometry evidence to support formation of the desired product, no other data could be collected due to the minuscule amount of material available.

2.6. Conclusions and Future Work

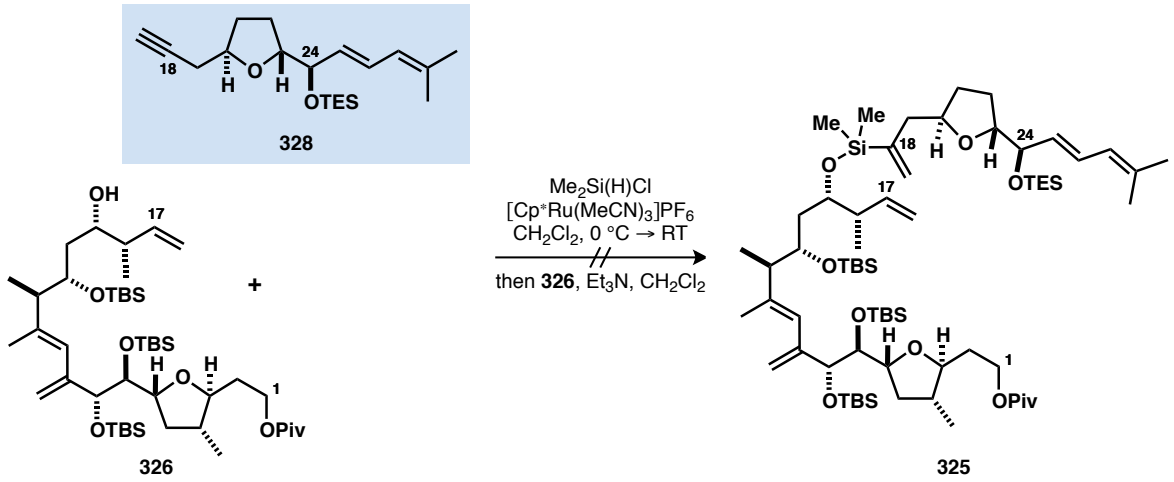
In conclusion, efforts to complete the total synthesis of members of the amphidinolide C series proved challenging but have provided valuable insights. During the course of this work, several synthetic strategies were investigated and significant progress was accomplished.

First, dithiane **264** was prepared in 18 steps and with an overall yield of 6.6%, starting from known epoxide **284** (**Scheme 124**). Despite the optimisation of coupling conditions by use of a model system, attempts to perform the coupling between alkyl iodide **278** and dithiane **264** did not lead to efficient construction of the C17−C18 bond, and gave the disubstituted dithiane **319** in only 13% yield over two steps while allowing for partial recovery of both starting materials.



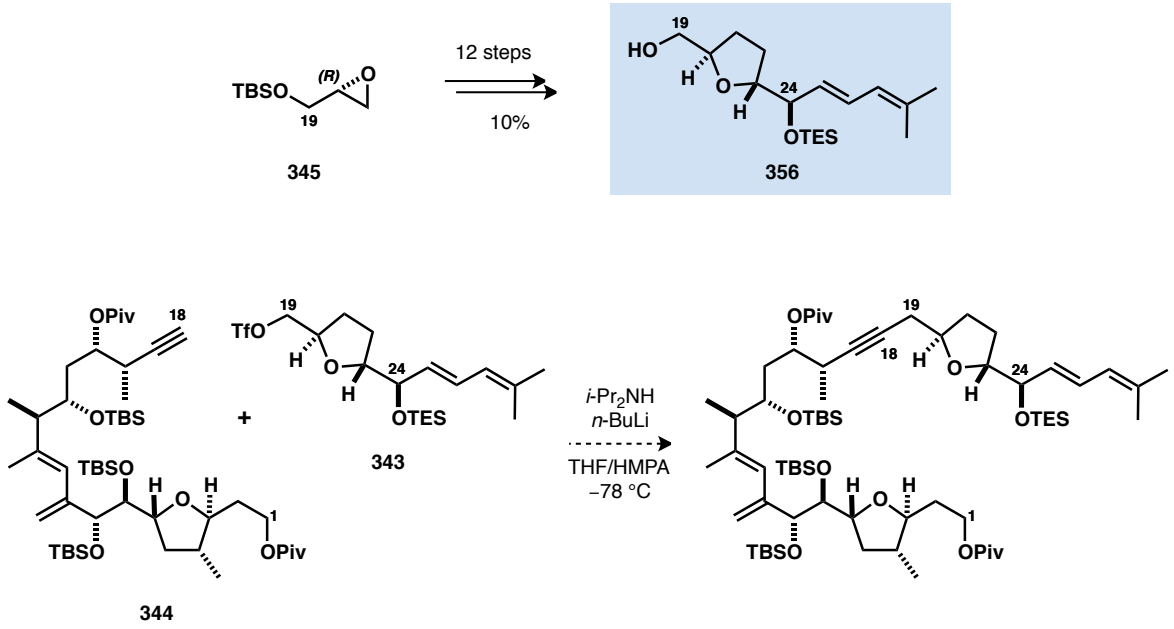
Scheme 124. C17−C18 Bond Formation by Dithiane Alkylation

Alternatively, terminal alkyne **328** could be prepared (**Scheme 125**). Nevertheless, conversion of the triple bond to the corresponding chloro(dimethyl)vinylsilane employing a ruthenium-catalysed hydrosilylation reaction and subsequent silylation of homoallylic alcohol **326** failed to form the desired Si−O bond and generate diene **325**. Therefore, RCM could not be investigated and alcohol **326** was entirely recovered in the process.



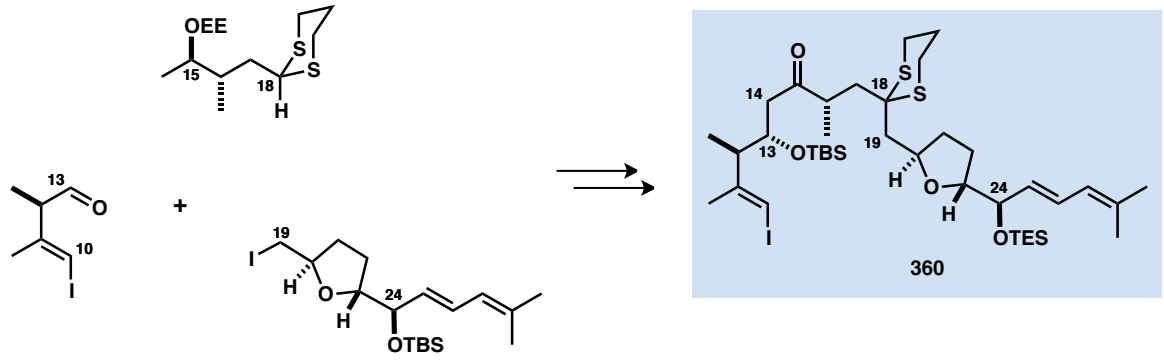
Scheme 125. Si−O Bond Formation by Silylation of Alcohol **326**

In a third approach, it was proposed that the challenging 1,4-diketone moiety at C15 and C18 would be installed by an alkyne protoborylation/oxidation sequence for which alkyne **344** and triflate **343** were identified as key fragments. To this end, alcohol adduct **356** was synthesised from commercially available glycidyl ether **345** in 12 steps and in 10% overall yield (**Scheme 126**). Unfortunately, the alkyne counterpart **344** could not be obtained (work by Dr Filippo Romiti) and therefore alcohol **356** was not converted into triflate **343**.



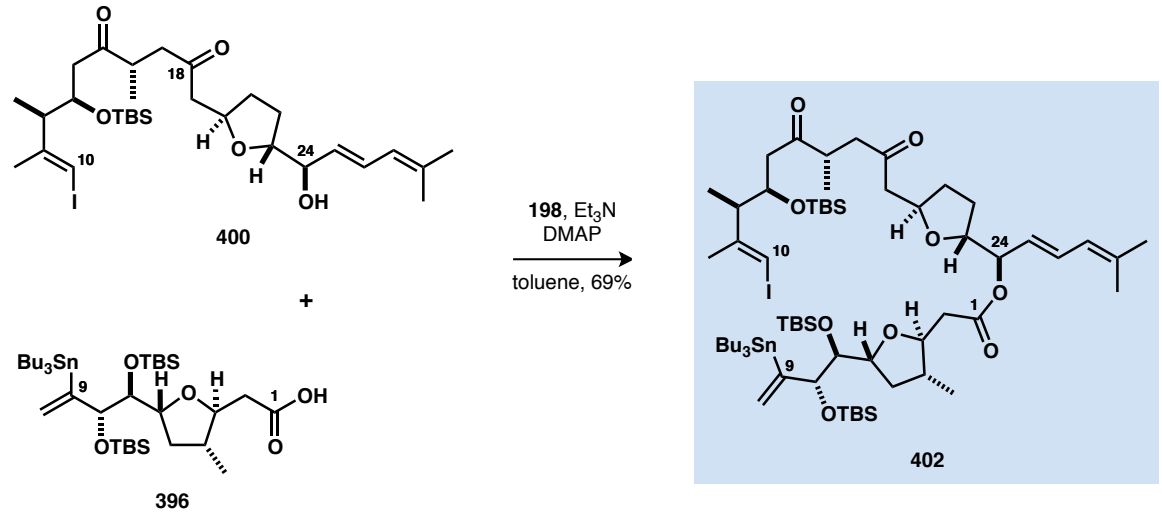
Scheme 126. Fragment Coupling by Triflate Displacement

Finally, the most recent strategy implemented involves an umpolung and aldol approach for the completion of vinyl iodide **360**. This fragment was synthesised in 19 steps and with an overall yield of 0.31% (**Scheme 127**).



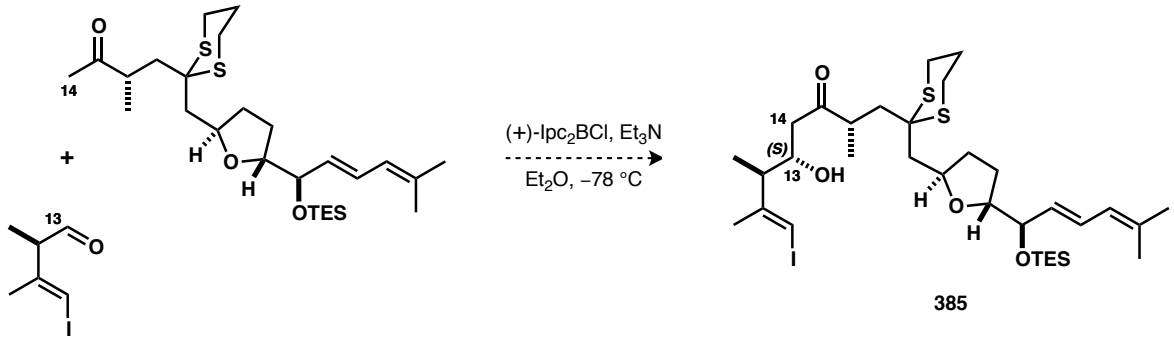
Scheme 127. Completion of Iodide **360**

Subsequent Yamaguchi esterification between 1,4-diketone **400** and carboxylic acid **396** then delivered ester **402** in good yield (**Scheme 128**). Closure of the macrolactone under Stille coupling conditions proved difficult, probably due to steric factors. Formation of the desired C13 epimer of amphidinolide F could only be supported by mass spectrometry evidence.



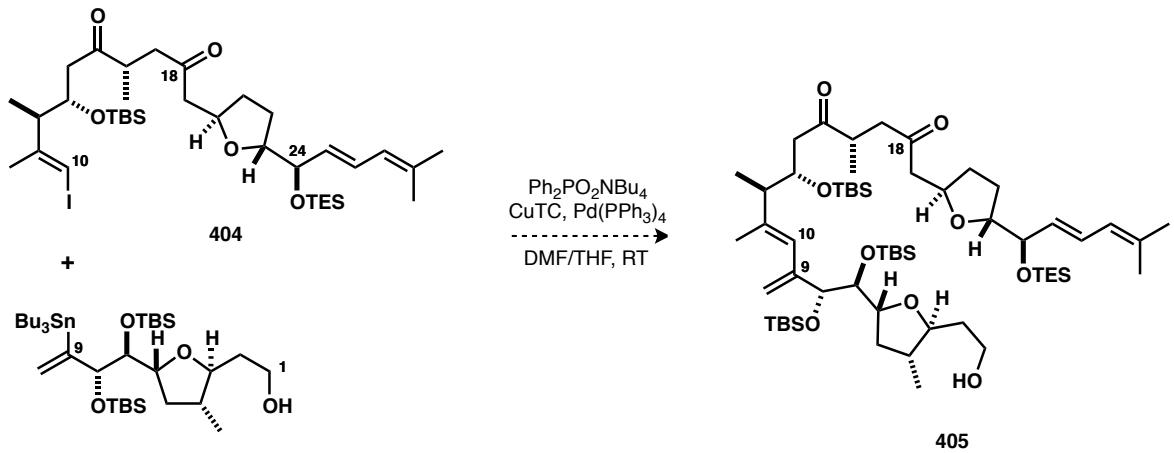
Scheme 128. Formation of Ester **402** by Yamaguchi Macrolactonisation

Future work will focus on improving the diastereoselectivity of the aldol condensation reaction used to build the C13−C14 bond, in order to ensure the viability of this strategy and provide a reliable synthesis of the vinyl iodide fragment. A chiral boron auxiliary such as (+)-Ipc_2BCl could potentially overturn the dominating substrate selectivity, as suggested by the literature,[101] and deliver the *β*-hydroxy ketone **385** in higher yield (**Scheme 129**).



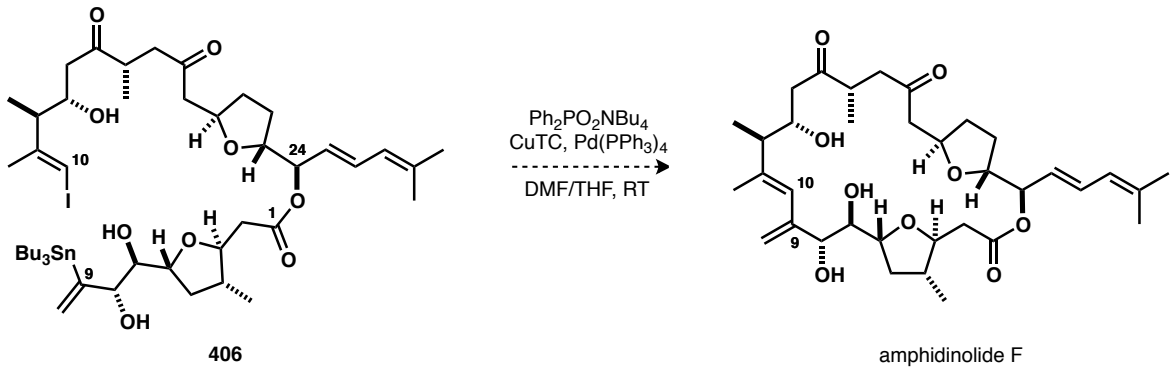
Scheme 129. Reagent-controlled Aldol Condensation

In order to rule out the potential influence of the dithiane moiety on the Stille reaction and avoid the steric congestion of an intramolecular cross-coupling, 1,4-diketone **404** bearing a TES ether at the C24 position could be prepared by careful optimisation of the dithiane hydrolysis conditions. The Stille coupling reaction would then be performed in an intermolecular fashion using the aforementioned diketone (**Scheme 130**).



Scheme 130. Revised Stille Coupling Towards Alcohol **405**

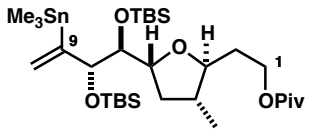
Coupling of the vinyl iodide and stannane fragments through a Yamaguchi esterification reaction was successful and so global desilylation of the resulting ester to provide triol **406** could be performed prior to closure of the macrocycle by Stille coupling to reduce the steric congestion during this transformation (**Scheme 131**).



406 amphidinolide F

Scheme 131. Revised Stille Coupling Towards Amphidinolide F

Finally, the outcome of the several Stille cross-coupling reactions mentioned above could be improved by use of the stannane **407**, which is a more reactive trimethylstannane equivalent[102] of fragment **280** (**Figure 5**).



407

Figure 5. Trimethylstannane **407**

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 specified otherwise. Petroleum ether (pet. ether) used for reactions and column chromatography was the 40-60 °C fraction.

Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 covered aluminium backed plates F_{524}. TLC plates were visualised under UV light and stained using either a potassium permanganate solution or an acidic ethanolic anisaldehyde solution. Flash column chromatography was performed with silica gel (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.

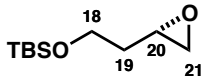
All ^{1}H NMR spectra were recorded on Bruker Avance III 400 MHz and 500 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift in ppm relative to $CHCl_3$ (7.26) on the δ scale, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, m = multiplet, br = 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 follows: chemical shift in ppm relative to $CDCl_3$ (77.16) on the δ scale and assignment.

Optical rotations were recorded using an automatic polarimeter Autopol V.

High resolution mass spectra (HRMS) were recorded using positive chemical ionisation (CI+) or positive ion impact ionisation (EI+) on a Jeol MStation JMS-700 instrument, or using positive ion electrospray (ESI+) technique on a Bruker micrOTOF-Q instrument. Low resolution mass spectra (LRMS) were obtained using the same instruments and the intensity of each peak was quoted as a percentage of the largest, where this information was available.

Melting points were recorded with an Electrothermal IA 9100 apparatus.

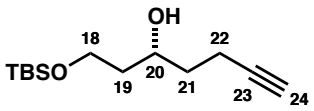
(*S*)-*tert*-Butyldimethyl(2-(oxiran-2-yl)ethoxy)silane 284[103]



Chemical Formula: $C_{10}H_{22}O_2Si$
Molecular Weight: 202,37

To a suspension of NaH (1.4 g, 36 mmol, 3.0 equiv.) in THF (100 mL) at −15 °C, was added a solution of (*R*)-2-bromobutane-1,4-diol (**288**)[61b] (2.0 g, 12 mmol) in THF (20 mL) dropwise. The resulting mixture was stirred at −15 °C for 30 min, followed by the dropwise addition of a solution of TBSCl (2.1 g, 14 mmol, 1.2 equiv.) in THF (14 mL). The resulting mixture was stirred at −15 °C for 5 min and at RT for 1 h. The reaction was quenched by the slow addition of a sat. aq. NH_4Cl solution (100 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/Et_2O, 95:5) to afford epoxide **284** (1.9 g, 9.6 mmol, 81%) as a colourless oil. R_f = 0.38 (pet. ether/Et_2O, 95:5); $[\alpha]_D^{25}$ −13.0 (*c* = 1.04, $CHCl_3$) [lit[103] $[\alpha]_D^{27}$ −13.7 (*c* = 2.31, $CHCl_3$)]; ν_{max} 2930, 2859, 1472, 1412, 1254, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80−3.75 (2H, m, CH_2−C18), 3.05 (1H, dddd, *J* = 6.5, 5.0, 4.0, 2.8 Hz, CH−C20), 2.78 (1H, ddd, *J* = 5.1, 4.0, 0.3 Hz, CH−C21), 2.52 (1H, dd, *J* = 5.1, 2.8 Hz, CH−C21), 1.78 (1H, dddd, *J* = 14.0, 7.2, 6.4, 5.0 Hz, CH−C19), 1.69 (1H, app ddtd, *J* = 14.0, 6.5, 5.5, 0.3 Hz, CH−C19), 0.90 (9H, s, CH_3−*t*-Bu TBS), 0.07 (3H, s, CH_3−TBS), 0.06 (3H, s, CH_3−TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 60.2 (CH_2−C18), 50.2 (CH−C20), 47.3 (CH_2−C21), 36.1 (CH_2−C19), 26.0 (CH_3−*t*-Bu TBS), 18.4 (C−*t*-Bu TBS), −5.2 (CH_3−TBS), −5.3 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{10}H_{22}O_2SiNa$ 225.1281, found 225.1280, Δ 0.6 ppm.

(*R*)-1-((*tert*-Butyldimethylsilyl)oxy)hept-6-yn-3-ol 289

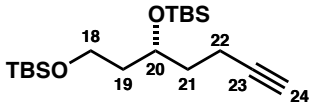


Chemical Formula: $C_{13}H_{26}O_2Si$
Molecular Weight: 242,43

To a suspension of magnesium turnings (2.2 g, 90 mmol, 2.0 equiv.) in Et_2O (45 mL) at RT, were added $HgCl_2$ (0.12 g, 0.45 mmol, 1 mol %) and crystals of iodine (2 crystals). The mixture was cooled to 0 °C and propargyl bromide (80 wt % in toluene, 5.0 mL, 45 mmol) was added dropwise. The mixture was cooled down until reflux stabilised. The reaction mixture was then heated at reflux, stirred for 1 h, and the resulting yellow solution was then allowed to cool to RT.

To a solution of epoxide **284** (1.9 g, 9.6 mmol) in Et_2O (200 mL) at −78 °C, was added a freshly prepared solution of propargylmagnesium bromide (1.0 M in Et_2O, 29 mL, 29 mmol, 3.0 equiv.) dropwise. The resulting mixture was stirred at −78 °C for 30 min and at RT for 1.5 h. The reaction mixture was cooled to 0 °C and a sat. aq. NH_4Cl solution (200 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 160 mL). The combined organic extracts were washed with brine (400 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/Et_2O, 80:20) to deliver alcohol **289** (1.6 g, 6.5 mmol, 68%) as a yellow oil. R_f = 0.37 (pet. ether/Et_2O, 80:20); $[\alpha]_D^{24}$ +26.9 (*c* = 1.11, $CHCl_3$); ν_{max} 3444, 3315, 2929, 2858, 1473, 1362, 1255, 1084 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00−3.93 (1H, m, CH−C20), 3.91 (1H, app dt, *J* = 9.9, 4.7 Hz, CH−C18), 3.87−3.80 (1H, m, CH−C18), 3.51 (1H, d, *J* = 2.3 Hz, OH−C20), 2.34 (2H, ddd, *J* = 7.7, 6.9, 2.7 Hz, CH_2−C22), 1.95 (1H, t, *J* = 2.7 Hz, CH−C24), 1.76−1.60 (4H, m, CH_2−C19, CH_2−C21), 0.90 (9H, s, CH_3−*t*-Bu TBS), 0.08 (3H, s, CH_3−TBS), 0.08 (3H, s, CH_3−TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 84.6 (C−C23), 71.0 (CH−C20), 68.5 (CH−C24), 62.9 (CH_2−C18), 38.3 (CH_2−C19), 36.2 (CH_2−C21), 26.0 (CH_3−*t*-Bu TBS), 18.3 (C−*t*-Bu TBS), 14.9 (CH_2−C22), −5.4 (CH_3−TBS), −5.4 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{13}H_{26}O_2SiNa$ 265.1594, found 265.1588, Δ 2.3 ppm.

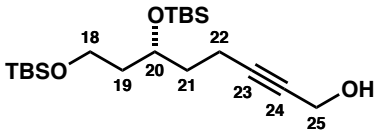
(*R*)-1,3-Bis((*tert*-butyldimethylsilyl)oxy)hept-6-yne 290



Chemical Formula: $C_{19}H_{40}O_2Si_2$
Molecular Weight: 356,69

To a solution of alcohol **289** (1.6 g, 6.5 mmol) in CH_2Cl_2 (30 mL) at 0 °C, were added imidazole (1.3 g, 19 mmol, 3.0 equiv.), DMAP (0.24 g, 1.9 mmol, 0.3 equiv.) and TBSCl (2.0 g, 13 mmol, 2.0 equiv.). The reaction mixture was stirred at RT for 36 h, before the addition of a sat. aq. NH_4Cl solution (30 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/Et_2O, 98:2) to afford alkyne **290** (2.2 g, 6.2 mmol, 96%) as a colourless oil. R_f = 0.34 (pet. ether/Et_2O, 98:2); $[\alpha]_D^{26}$ +6.1 (*c* = 1.0, $CHCl_3$); ν_{max} 3316, 2929, 2858, 1473, 1361, 1253, 1094, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.97−3.91 (1H, m, CH−C20), 3.66 (2H, t, *J* = 6.6 Hz, CH_2−C18), 2.24 (2H, td, *J* = 7.4, 2.7 Hz, CH_2−C22), 1.92 (1H, t, *J* = 2.7 Hz, CH−C24), 1.75−1.59 (4H, m, CH_2−C19, CH_2−C21), 0.89 (9H, s, CH_3−*t*-Bu TBS), 0.88 (9H, s, CH_3−*t*-Bu TBS), 0.07 (3H, s, CH_3−TBS), 0.06 (3H, s, CH_3−TBS), 0.04 (6H, s, 2 × CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 84.7 (C−C23), 68.4 (CH−C24), 68.2 (CH−C20), 59.8 (CH_2−C18), 40.1 (CH_2−C19), 36.1 (CH_2−C21), 26.1 (CH_3−*t*-Bu TBS), 26.0 (CH_3−*t*-Bu TBS), 18.4 (C−*t*-Bu TBS), 18.2 (C−*t*-Bu TBS), 14.6 (CH_2−C22), −4.4 (CH_3−TBS), −4.4 (CH_3−TBS), −5.2 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{19}H_{40}O_2Si_2Na$ 379.2459, found 379.2441, Δ 4.8 ppm.

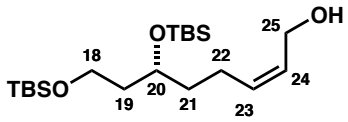
(*R*)-6,8-Bis((*tert*-butyldimethylsilyl)oxy)oct-2-yn-1-ol 291



Chemical Formula: $C_{20}H_{42}O_3Si_2$
Molecular Weight: 386,72

To a solution of alkyne **290** (3.9 g, 11 mmol) in THF (54 mL) at −78 °C, was added *n*-BuLi (2.1 M in hexanes, 5.7 mL, 12 mmol, 1.1 equiv.) dropwise. The resulting solution was stirred at −78 °C for 1 h, before the addition of paraformaldehyde (1.1 g, 12 mmol, 1.2 equiv.) in one portion. The reaction mixture was allowed to warm to RT for 10 min and stirred at 40 °C for 45 min. The solution was allowed to cool to RT and a 1 M NaOH aq. solution (50 mL) was added. The biphasic mixture was stirred vigorously at RT for 45 min and the layers were separated. The organic layer was washed with a sat. aq. NH_4Cl solution (50 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/Et_2O, 80:20) to provide propargylic alcohol **291** (3.7 g, 9.5 mmol, 88%) as a yellow oil. R_f = 0.33 (pet. ether/Et_2O, 80:20); $[\alpha]_D^{22}$ +5.5 (*c* = 1.1, $CHCl_3$); ν_{max} 3353, 2929, 2857, 1473, 1361, 1254, 1093, 1005 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.24 (2H, dt, *J* = 6.1, 2.1 Hz, CH_2−C25), 3.94−3.88 (1H, m, CH−C20), 3.66 (2H, t, *J* = 6.6 Hz, CH_2−C18), 2.27 (2H, tt, *J* = 7.3, 2.1 Hz, CH_2−C22), 1.74−1.59 (4H, m, CH_2−C19 and CH_2−C21), 1.49 (1H, t, *J* = 6.1 Hz, OH−C25), 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 (6H, s, 2 × CH_3−TBS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 86.7 (C−C23), 78.5 (C−C24), 68.3 (CH−C20), 59.8 (CH_2−C18), 51.6 (CH_2−C25), 40.1 (CH_2−C19), 36.1 (CH_2−C21), 26.1 (CH_3−*t*-Bu TBS), 26.0 (CH_3−*t*-Bu TBS), 18.4 (C−*t*-Bu TBS), 18.2 (C−*t*-Bu TBS), 14.8 (CH_2−C22), −4.4 (CH_3−TBS), −4.4 (CH_3−TBS), −5.2 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{20}H_{42}O_3Si_2Na$ 409.2565, found 409.2566, Δ 0.4 ppm.

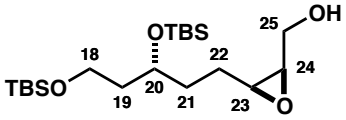
(*R*,*Z*)-6,8-Bis((*tert*-butyldimethylsilyl)oxy)oct-2-en-1-ol 283



Chemical Formula: $C_{20}H_{44}O_3Si_2$
Molecular Weight: 388,73

To a solution of propargylic alcohol **291** (4.5 g, 12 mmol) in pet. ether (58 mL) at RT, was added quinoline (1.7 mL, 14 mmol, 1.2 equiv.) slowly, followed by palladium on calcium carbonate (5 wt %, poisoned with lead, 0.50 g, 0.23 mmol, 2 mol %). The reaction mixture was purged with hydrogen (3 ×), stirred at RT under a hydrogen atmosphere for 1.5 h and filtered through a celite pad. The solids were washed with Et_2O (5 × 50 mL) and the filtrates concentrated. Crude material was purified by silica gel chromatography (pet. ether/Et_2O, 80:20) to provide allylic alcohol **283** (4.3 g, 11 mmol, 95%) as a light yellow oil. R_f = 0.28 (pet. ether/Et_2O, 80:20); $[\alpha]_D^{20}$ −5.4 (*c* = 1.0, $CHCl_3$); ν_{max} 3327, 2929, 2858, 1473, 1361, 1255, 1092, 1051, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.64−5.57 (1H, m, CH−C24), 5.57−5.49 (1H, m, CH−C23), 4.25−4.14 (2H, m, CH_2−C25), 3.84 (1H, app p, *J* = 5.7 Hz, CH−C20), 3.66 (2H, t, *J* = 6.5 Hz, CH_2−C18), 2.22−2.03 (2H, m, CH_2−C22), 1.69−1.62 (2H, m, CH_2−C19), 1.58−1.47 (2H, m, CH_2−C21), 1.31 (1H, t, *J* = 5.7 Hz, OH−C25), 0.89 (18H, s, 2 × CH_3−*t*-Bu TBS), 0.05 (3H, s, CH_3−TBS), 0.05 (3H, s, CH_3−TBS), 0.04 (6H, s, 2 × CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.0 (CH−C23), 128.6 (CH−C24), 69.0 (CH−C20), 60.0 (CH_2−C18), 58.7 (CH_2−C25), 40.0 (CH_2−C19), 37.3 (CH_2−C21), 26.1 (CH_3−*t*-Bu TBS), 26.0 (CH_3−*t*-Bu TBS), 23.3 (CH_2−C22), 18.4 (C−*t*-Bu TBS), 18.2 (C−*t*-Bu TBS), −4.3 (CH_3−TBS), −4.4 (CH_3−TBS), −5.2 (CH_3−TBS), −5.2 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{20}H_{44}O_3Si_2Na$ 411.2721, found 411.2714, Δ 1.7 ppm.

(*R*)-1,3-Bis((*tert*-butyldimethylsilyl)oxy)-5-((2*S*,3*R*)-3-(hydroxymethyl)oxiran-2-yl)pentane 293

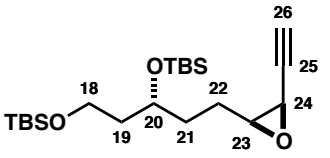


Chemical Formula: $C_{20}H_{44}O_4Si_2$
Molecular Weight: 404,73

To a suspension of 4 Å MS (1.0 g) in CH_2Cl_2 (21 mL) at −20 °C, were added D-(−)-diethyltartrate (0.26 mL, 1.5 mmol, 30 mol %), Ti(O*i*-Pr)$_4$ (0.38 mL, 1.3 mmol, 25 mol %) and *t*-BuOOH (1.9 M in CH_2Cl_2, 8.1 mL, 15 mmol, 3.0 equiv.) sequentially. The resulting mixture was stirred at −20 °C for 30 min, before the dropwise addition of allylic alcohol **283** (2.0 g, 5.1 mmol) in CH_2Cl_2 (6 mL) over 10 min. The reaction mixture was stirred at −20 °C for 24 h. The reaction was quenched by the addition of water (7.3 mL) at 0 °C and the mixture was stirred for 45 min while warming to RT. Hydrolysis of the tartrate was then effected by adding a 30% NaOH aq. solution saturated with NaCl (1.6 mL) and the mixture was stirred vigorously for 45 min. The layers were separated and the milky, aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (90 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 80:20) to afford epoxide **293** (1.9 g, 4.7 mmol, 91%) as a colourless oil. R_f = 0.33 (pet. ether/EtOAc, 80:20); $[\alpha]_D^{25}$ −5.1 (*c* = 1.1, $CHCl_3$); ν_{max} 3407, 2929, 2857, 1473, 1254, 1093, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.92−3.85 (1H, m, CH−C20), 3.82 (1H, ddd, *J* = 12.0, 7.2, 4.6 Hz, CH−C25), 3.70 (1H, ddd, *J* = 12.0, 6.6, 5.3 Hz, CH−C25), 3.66 (2H, t, *J* = 6.4 Hz, CH_2−C18), 3.16 (1H, ddd, *J* = 6.6, 4.6, 4.4 Hz, CH−C24), 3.02 (1H, app td, *J* = 6.3, 4.4 Hz, CH−C23), 1.81 (1H, dd, *J* = 7.2, 5.3 Hz, OH−C25), 1.78−1.47 (6H, m, CH_2−C19, CH_2−C21, CH_2−C22), 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), 0.05 (3H, s, CH_3−TBS), 0.04 (6H, s, 2 × CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 68.9 (CH−C20), 60.9 (CH_2−C25), 59.9 (CH_2−C18), 57.4 (CH−C23), 56.9 (CH−C24), 40.3 (CH_2−C19), 33.9 (CH_2−C21), 26.1 (CH_3−*t*-Bu TBS), 26.0 (CH_3−*t*-Bu TBS), 23.8 (CH_2−C22), 18.4 (C−*t*-Bu TBS), 18.2 (C−*t*-Bu TBS), −4.3 (CH_3−TBS), −4.4 (CH_3−TBS), −5.2 (CH_3−TBS), −5.2 (CH_3−TBS); HRMS (CI+, isobutane) $[M+H]^+$ calcd for $C_{20}H_{45}O_4Si_2$ 405.2856, found 405.2851, Δ 1.3 ppm; LRMS (CI+,

isobutane) *m/z* (intensity) 405.3 (100%), 273.2 (34%).

(*R*)-1,3-Bis((*tert*-butyldimethylsilyl)oxy)-5-((2*S*,3*R*)-3-ethynyloxiran-2-yl)pentane 296



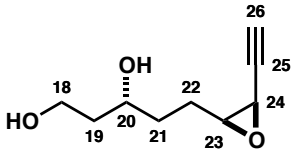
Chemical Formula: $C_{21}H_{42}O_3Si_2$
Molecular Weight: 398,73

To a solution of oxalyl chloride (1.6 mL, 19 mmol, 2.2 equiv.) in CH_2Cl_2 (25 mL) at −78 °C was added a solution of DMSO (2.9 mL, 41 mmol, 4.8 equiv.) in CH_2Cl_2 (4 mL) dropwise. The resulting solution was stirred at −78 °C for 20 min, before the slow addition of alcohol **293** (3.4 g, 8.5 mmol) in CH_2Cl_2 (13 mL). The reaction mixture was stirred at −78 °C for 1.5 h, before the addition of Et_3N (5.9 mL, 42 mmol, 5.0 equiv.) and the mixture was stirred at RT for 1 h. The reaction was quenched by the addition of a sat. aq. NH_4Cl solution (40 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic extracts were washed with brine (120 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was directly used in the next step without further purification.

To a solution of dimethyl-1-diazo-2-oxopropyl phosphonate (1.8 g, 9.3 mmol, 1.1 equiv.) in MeOH (38 mL) at 0 °C, was added K_2CO_3 (1.6 g, 12 mmol, 1.4 equiv.) in one portion. The mixture was stirred at 0 °C for 1.5 h, before dropwise addition of the crude aldehyde in THF (19 mL). The resulting yellow suspension was stirred at 0 °C for 2 h and at RT for 45 min. The reaction was quenched by the addition of a sat. aq. NH_4Cl solution (50 mL). The white solids were filtered through a cotton plug and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/Et_2O, 95:5) to provide alkyne **296** (1.9 g, 4.6 mmol, 55% over 2 steps) as a colourless oil. R_f = 0.28 (pet. ether/Et_2O, 95:5); $[\alpha]_D^{24}$ −15.6 (*c* = 1.00, $CHCl_3$); ν_{max} 3314, 2929, 2857, 1473, 1361, 1253, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.92−3.85 (1H, m, CH−C20), 3.70−3.64 (2H, m, CH_2−C18), 3.42 (1H, dd, *J* = 4.0, 1.7 Hz, CH−C24), 3.07−3.02 (1H, m, CH−C23),

2.33 (1H, d, *J* = 1.7 Hz, CH−C26), 1.84−1.56 (6H, m, CH_2−C19, CH_2−C21, CH_2−C22), 0.89 (9H, s, CH_3−*t*-Bu TBS), 0.88 (9H, s, CH_3−*t*-Bu TBS), 0.06 (6H, s, 2 × CH_3−TBS), 0.04 (6H, s, 2 × CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 79.0 (C−C25), 73.6 (CH−C26), 69.0 (CH−C20), 60.0 (CH_2−C18), 58.0 (CH−C23), 45.0 (CH−C24), 40.2 (CH_2−C19), 33.3 (CH_2−C21), 26.1 (CH_3−*t*-Bu TBS), 26.0 (CH_3−*t*-Bu TBS), 25.4 (CH_2−C22), 18.4 (C−*t*-Bu TBS), 18.2 (C−*t*-Bu TBS), −4.3 (CH_3−TBS), −4.4 (CH_3−TBS), −5.2 (CH_3−TBS); HRMS (CI+, isobutane) $[M+H]^+$ calcd for $C_{21}H_{43}O_3Si_2$ 399.2751, found 399.2756, Δ 1.2 ppm; LRMS (CI+, isobutane) *m/z* (intensity) 399.3 (100%), 267.2 (34%).

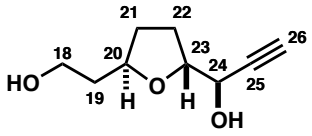
(*R*)-5-((2*S*,3*R*)-3-Ethynyloxiran-2-yl)pentane-1,3-diol 282



Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170,21

To a solution of *bis*-TBS ether **296** (0.89 g, 2.2 mmol) in THF (11 mL) at 0 °C, was added TBAF (1.0 M in THF, 6.7 mL, 6.7 mmol, 3.0 equiv.) dropwise. The resulting solution was stirred at RT for 2.5 h. The reaction was quenched by the addition of a sat. aq. NH_4Cl solution (10 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue was filtered rapidly through a short pad of silica gel (EtOAc) to give the crude diol **282**, which was used directly in the next step without further purification. R_f = 0.41 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02−3.95 (1H, m, CH−C20), 3.94−3.82 (2H, m, CH_2−C18), 3.46 (1H, dd, *J* = 4.0, 1.7 Hz, CH−C24), 3.12−3.07 (1H, m, CH−C23), 2.37 (1H, d, *J* = 1.7 Hz, CH−C26), 1.95−1.86 (1H, m, CH−C22), 1.85−1.78 (1H, m, CH−C22), 1.78−1.67 (4H, m, CH_2−C19, CH_2−C21); ^{13}C NMR (126 MHz, $CDCl_3$) δ 78.8 (C−C25), 74.0 (CH−C26), 71.6 (CH−C20), 62.0 (CH_2−C18), 57.9 (CH−C23), 45.0 (CH−C24), 38.5 (CH_2−C19), 34.0 (CH_2−C21), 25.6 (CH_2−C22); HRMS (ESI+) $[M+Na]^+$ calcd for $C_9H_{14}O_3Na$ 193.0835, found 193.0830, Δ 2.7 ppm.

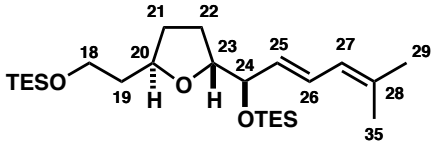
(*R*)-1-((2*R*,5*R*)-5-(2-Hydroxyethyl)tetrahydrofuran-2-yl)prop-2-yn-1-ol 281



Chemical Formula: $C_9H_{14}O_3$
Molecular Weight: 170,21

To a solution of crude diol **282** in CH_2Cl_2 (22 mL) at −40 °C, was added (1*S*)-(+)-camphorsulfonic acid (52 mg, 0.22 mmol, 10 mol %). The resulting mixture was stirred at −40 °C for 10 min and at RT for 30 min. The reaction was quenched by the addition of Et_3N (0.10 mL, 0.66 mmol) and the solution was concentrated. The residue was filtered rapidly through a short pad of silica gel (EtOAc) to give the crude tetrahydrofuran **281** which was used directly in the next step without further purification. R_f = 0.38 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25−4.17 (2H, m, CH−C20, CH−C24), 4.16−4.09 (1H, m, CH−C23), 3.79 (2H, app t, *J* = 5.7 Hz, CH_2−C18), 2.69 (1H, br s, OH−C24), 2.56 (1H, br s, OH−C18), 2.44 (1H, d, *J* = 2.2 Hz, CH−C26), 2.16−2.06 (2H, m, CH−C21, CH−C22), 1.91−1.82 (1H, m, CH−C22), 1.81−1.76 (2H, m, CH_2−C19), 1.70−1.59 (1H, m, CH−C21); ^{13}C NMR (126 MHz, $CDCl_3$) δ 82.1 (C−C25), 81.8 (CH−C23), 79.7 (CH−C20), 73.9 (CH−C26), 65.1 (CH−C24), 61.3 (CH_2−C18), 37.5 (CH_2−C19), 32.3 (CH_2−C21), 27.9 (CH_2−C22).

Triethyl(((*R*,*E*)-5-methyl-1-((2*R*,5*R*)-5-(2-((triethylsilyl)oxy)ethyl)tetrahydrofuran-2-yl)hexa-2,4-dien-1-yl)oxy)silane 301



Chemical Formula: $C_{25}H_{50}O_3Si_2$
Molecular Weight: 454,83

To a suspension of $Pd(PPh_3)_4$ (0.13 g, 0.11 mmol, 5 mol %) in pyrrolidine (2.5 mL) at RT, was added 1-bromo-2-methyl-1-propene (0.68 mL, 6.7 mmol, 3.0 equiv.) followed, after 5 min, by the dropwise addition of crude alkyne **281** in pyrrolidine (2.5 mL). The resulting yellow solution was stirred at 50 °C for 16 h. The reaction mixture was allowed to cool to RT, followed by the addition of a sat. aq. NH_4Cl

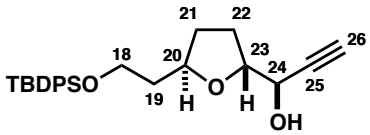
solution (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Crude enyne **299** was used directly in the next step without further purification.

To a solution of crude enyne **299** in THF (40 mL) at 0 °C, was added sodium bis(2-methoxyethoxy)aluminium hydride (≥ 65 wt % in toluene, 2.6 mL, 8.9 mmol, 4.0 equiv.) dropwise. The resulting cloudy mixture was stirred at RT for 30 min and cooled to 0 °C, before the dropwise addition of a sat. aq. potassium sodium tartrate solution (50 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated. Crude diene **300** was used directly in the next step without further purification.

To a solution of crude diol **300** in CH_2Cl_2 (15 mL) at −78 °C, were added 2,6-lutidine (1.1 mL, 9.4 mmol, 6.0 equiv.) and TESOTf (1.1 mL, 4.7 mmol, 3.0 equiv.) sequentially. The resulting solution was stirred at −78 °C for 45 min. Water (15 mL) was added and the biphasic mixture was allowed to warm to RT. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 98:2) to deliver *bis*-TES ether **301** (0.61 g, 1.4 mmol, 61% over 5 steps) as a colourless oil. R_f = 0.28 (pet. ether/EtOAc, 98:2); $[\alpha]_D^{24}$ +13.5 (*c* = 2.13, $CHCl_3$); ν_{max} 2955, 2911, 2876, 1460, 1414, 1379, 1238, 1086, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.45 (1H, ddd, *J* = 15.2, 11.0, 1.4 Hz, CH−C26), 5.82 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.54 (1H, dd, *J* = 15.2, 5.9 Hz, CH−C25), 4.18 (1H, app td, *J* = 5.9, 1.4 Hz, CH−C24), 3.97 (1H, app ddt, *J* = 8.2, 7.7, 5.5 Hz, CH−C20), 3.92 (1H, app td, *J* = 7.3, 5.9 Hz, CH−C23), 3.78−3.62 (2H, m, CH_2−C18), 1.96 (1H, dddd, *J* = 11.7, 8.3, 5.5, 3.2 Hz, CH−C21), 1.91−1.79 (2H, m, CH−C19, CH−C22), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.73−1.61 (2H, m, CH−C19, CH−C22), 1.46 (1H, app ddt, *J* = 11.7, 9.8, 8.2 Hz, CH−C21), 0.96 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.95 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.64−0.56 (12H, m, CH_2−TES); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.0 (C−C28), 130.1 (CH−C25), 127.6 (CH−C26), 124.9 (CH−C27), 82.2 (CH−C23), 76.8 (CH−C20), 75.6 (CH−C24), 60.6 (CH_2−C18), 39.2 (CH_2−C19), 32.5 (CH_2−C21), 27.5 (CH_2−C22), 26.1 (CH_3−C35), 18.4 (CH_3−C29), 7.0 (CH_3−TES), 6.9 (CH_3−TES), 5.2 (CH_2−TES), 4.6 (CH_2−TES); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{25}H_{50}O_3Si_2Na$ 477.3191, found 477.3198, Δ 1.5

ppm.

(*R*)-1-((2*R*,5*R*)-5-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)tetrahydrofuran-2-yl)prop-2-yn-1-ol 257[26b]



Chemical Formula: $C_{25}H_{32}O_3Si$
Molecular Weight: 408,61

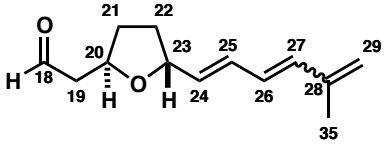
To a solution of *bis*-TBS ether **296** (0.12 g, 0.30 mmol) in THF (2 mL) at 0 °C, was added TBAF (1.0 M in THF, 0.89 mL, 0.89 mmol, 3.0 equiv.) dropwise. The resulting solution was stirred at RT for 2.5 h. The reaction was quenched by the addition of a sat. aq. NH_4Cl solution (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (6 mL), dried over $MgSO_4$, filtered and concentrated. The residue was filtered rapidly through a short pad of silica gel (EtOAc) to give the crude diol **282** which was used directly in the next step without further purification.

To a solution of crude diol **282** in CH_2Cl_2 (3 mL) at −40 °C, was added (1*S*)-(+)-camphorsulfonic acid (7 mg, 0.03 mmol, 10 mol %). The resulting mixture was stirred at −40 °C for 10 min and at RT for 30 min. The reaction was quenched by the addition of Et_3N (12 µL, 89 µmol) and the solution was concentrated. The residue was filtered rapidly through a short pad of silica gel (EtOAc) to give the crude tetrahydrofuran **281** which was used directly in the next step without further purification.

To a solution of crude tetrahydrofuran **281** in CH_2Cl_2 (3 mL) at 0 °C, were added Et_3N (40 µL, 0.31 mmol, 1.1 equiv.), TBDPSCl (80 µL, 0.31 mmol, 1.1 equiv.) and DMAP (4 mg, 0.03 mmol, 0.1 equiv.). The resulting solution was stirred at RT for 15 h. The reaction was quenched by the addition of water (2 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 3 mL) and the combined organic extracts were washed with brine (9 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 85:15) to afford silyl ether **257** (77 mg, 0.19 mmol, 64% over 3 steps) as a colourless oil. R_f = 0.47 (pet. ether/EtOAc, 80:20);

$[\alpha]_D^{26}$ −0.74 (*c* = 1.3, $CHCl_3$) [lit[26b] $[\alpha]_D^{26}$ −0.73 (*c* = 2.2, $CHCl_3$)]; ν_{max} 3408, 3306, 2932, 2857, 1472, 1427, 1389, 1111, 1080 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69−7.64 (4H, m, CH−Ar TBDPS), 7.45−7.36 (6H, m, CH−Ar TBDPS), 4.20−4.11 (2H, m, CH−C20, CH−C24), 4.03 (1H, app q, *J* = 6.9 Hz, CH−C23), 3.81−3.71 (2H, m, CH_2−C18), 2.42 (1H, d, *J* = 4.5 Hz, OH−C24), 2.42 (1H, d, *J* = 2.0 Hz, CH−C26), 2.13−2.01 (2H, m, CH−C21, CH−C22), 1.89−1.77 (2H, m, CH−C19, CH−C22), 1.73 (1H, app ddt, *J* = 13.5, 7.4, 5.9 Hz, CH−C19), 1.62−1.53 (1H, m, CH−C21), 1.05 (9H, s, CH_3−*t*-Bu TBDPS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.7 (CH−Ar TBDPS), 134.0 (C−Ar TBDPS), 134.0 (C−Ar TBDPS), 129.8 (CH−Ar TBDPS), 127.8 (CH−Ar TBDPS), 82.1 (C−C25), 81.5 (CH−C23), 77.2 (CH−C20), 73.8 (CH−C26), 65.4 (CH−C24), 61.2 (CH_2−C18), 38.5 (CH_2−C19), 32.1 (CH_2−C21), 28.2 (CH_2−C22), 27.0 (CH_3−*t*-Bu TBDPS), 19.4 (C−*t*-Bu TBDPS); HRMS (CI+, isobutane) $[M+H]^+$ calcd for $C_{25}H_{33}O_3Si$ 409.2199, found 409.2202, Δ 0.8 ppm; LRMS (CI+, isobutane) *m/z* (intensity) 409.2 (86%), 383.2 (89%), 331.2 (89%), 305.1 (100%), 253.1 (44%).

2-((2*R*,5*R*)-5-((1*E*)-5-Methylhexa-1,3,5-trien-1-yl)tetrahydrofuran-2-yl)acetaldehyde 303

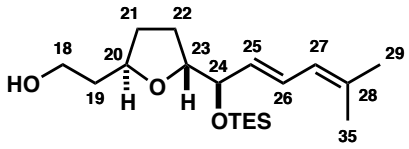


Chemical Formula: $C_{13}H_{18}O_2$
Molecular Weight: 206,28

To a solution of DMSO (40 µL, 0.53 mmol, 8.0 equiv.) in CH_2Cl_2 (1.1 mL) at −78 °C, was added oxalyl chloride (2.0 M in CH_2Cl_2, 0.13 mL, 0.26 mmol, 4.0 equiv.) dropwise. The solution was stirred at −78 °C for 15 min, before the addition of silyl ether **301** (30 mg, 66 mmol) in CH_2Cl_2 (0.2 mL) over 15 min. The reaction mixture was stirred at −60 °C for 8 h and cooled to −78 °C, before the dropwise addition of Et_3N (0.15 mL, 1.1 mmol, 16.0 equiv.). The reaction mixture was stirred at 0 °C for 30 min, followed by the addition of water (2.2 mL) and CH_2Cl_2 (2.2 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 2.2 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 85:15) to provide a 2:3 mixture of *Z* and *E*

isomers **303** (8 mg, 0.04 mmol, 59%) as a colourless oil. R_f = 0.28 (pet. ether/EtOAc, 85:15); ν_{max} 2923, 2857, 1723, 1620, 1457, 1374, 1261, 1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.82 (2.5H, app t, *J* = 2.1 Hz, CH−C18, CH−C18'), 6.34−6.15 (7.5H, m, CH−C25, CH−C25', CH−C26, CH−C26', CH−C27, CH−C27'), 5.72 (1H, dd, *J* = 14.9, 6.9 Hz, CH−C24'), 5.71 (1.5H, dd, *J* = 14.8, 6.9 Hz, CH−C24), 4.99 (5H, m, CH_2−C29, CH_2−C29'), 4.54−4.45 (3H, m, CH−C20, CH−C23), 4.42−4.34 (2H, m, CH−C20', CH−C23'), 2.75 (1H, ddd, *J* = 14.9, 7.2, 2.1 Hz, CH−C19'), 2.71 (1.5H, ddd, *J* = 13.4, 7.2, 2.1 Hz, CH−C19), 2.63 (1H, ddd, *J* = 14.9, 5.5, 2.1 Hz, CH−C19'), 2.59 (1.5H, ddd, *J* = 13.4, 5.4, 2.1 Hz, CH−C19), 2.25−2.06 (5H, m, CH−C21, CH−C21', CH−C22, CH−C22'), 1.87−1.84 (7.5H, m, CH_3−C35, CH_3−C35'), 1.77−1.59 (5H, m, CH−C21, CH−C21', CH−C22, CH−C22'); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3 (CH−C18), 201.2 (CH−C18'), 142.1 (C−C28), 142.1 (C−C28'), 136.0 (CH−C27'), 136.0 (CH−C27), 134.1 (CH−C24), 134.1 (CH−C24'), 131.6 (CH−C25'), 131.3 (CH−C25), 128.4 (CH−C26'), 128.4 (CH−C26), 117.2 (CH_2−C29'), 117.2 (CH_2−C29), 80.1 (CH−C23'), 79.6 (CH−C23), 74.4 (CH−C20'), 74.0 (CH−C20), 50.0 (CH_2−C19'), 49.9 (CH_2−C19), 32.9 (CH_2−C21), 32.4 (CH_2−C22), 32.1 (CH_2−C21'), 31.5 (CH_2−C22'), 18.6 (CH_3−C35, CH_3−C35'); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{13}H_{18}O_2Na$ 229.1199, found 229.1192, Δ 3.0 ppm.

2-((2*R*,5*R*)-5-((*R*,*E*)-5-Methyl-1-((triethylsilyl)oxy)hexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)ethanol 304



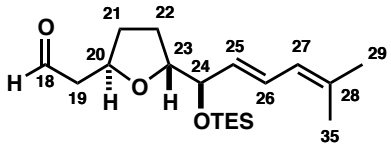
Chemical Formula: $C_{19}H_{36}O_3Si$
Molecular Weight: 340,57

Note: The HF•Pyr stock solution was prepared by mixing HF•Pyr (1.0 mL, 70% HF in pyridine), pyridine (2.0 mL) and THF (5.0 mL).

To a solution of *bis*-TES ether **301** (0.22 g, 0.48 mmol) in THF (48 mL) at −20 °C, was added a stock solution of HF•Pyr (1.8 mL) and the resulting mixture was stirred for 15 h. The reaction was quenched by the dropwise addition of a sat. aq. $NaHCO_3$ solution (150 mL). The biphasic mixture was allowed to warm to RT and

the layers were separated. The aqueous phase was extracted with Et_2O (3 × 150 mL) and the combined organic extracts were washed with brine (400 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 85:15) to afford alcohol **304** (0.13 g, 0.38 mmol, 79%) as a colourless oil. R_f = 0.21 (pet. ether/EtOAc, 85:15); $[\alpha]_D^{24}$ +11.4 (*c* = 2.08, $CHCl_3$); ν_{max} 3410, 2955, 2876, 1659, 1460, 1377, 1238, 1069, 1005 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.44 (1H, ddd, *J* = 15.2, 11.1, 1.3 Hz, CH−C26), 5.81 (1H, dm, *J* = 11.1 Hz, CH−C27), 5.51 (1H, dd, *J* = 15.2, 6.2 Hz, CH−C25), 4.19−4.06 (2H, m, CH−C20, CH−C24), 3.96 (1H, app dt, *J* = 8.0, 6.3 Hz, CH−C23), 3.84−3.71 (2H, m, CH_2−C18), 3.00 (1H, dd, *J* = 7.0, 4.2 Hz, OH−C18), 2.00 (1H, dddd, *J* = 11.9, 8.3, 5.7, 3.0 Hz, CH−C21), 1.92−1.84 (1H, m, CH−C22), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.79−1.62 (3H, m, CH_2−C19, CH−C22), 1.54 (1H, app ddt, *J* = 11.9, 9.9, 8.2 Hz, CH−C21), 0.95 (9H, t, *J* = 8.0 Hz, CH_3−TES), 0.60 (6H, q, *J* = 8.0 Hz, CH_2−TES); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.5 (C−C28), 129.9 (CH−C25), 127.9 (CH−C26), 124.7 (CH−C27), 82.7 (CH−C23), 80.0 (CH−C20), 75.7 (CH−C24), 62.0 (CH_2−C18), 37.4 (CH_2−C19), 32.6 (CH_2−C21), 27.4 (CH_2−C22), 26.2 (CH_3−C35), 18.4 (CH_3−C29), 7.0 (CH_3−TES), 5.2 (CH_2−TES); HRMS (EI+) $[M]^+$ calcd for $C_{19}H_{36}O_3Si$ 340.2434, found 340.2431, Δ 0.9 ppm; LRMS (EI+) *m/z* (intensity) 340.2 (2%), 225.1 (100%), 115.1 (18%), 87.1 (12%).

2-((2*R*,5*R*)-5-((*R*,*E*)-5-Methyl-1-((triethylsilyl)oxy)hexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)acetaldehyde 302

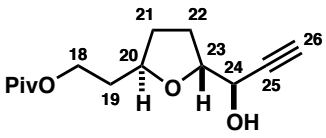


Chemical Formula: $C_{19}H_{34}O_3Si$
Molecular Weight: 338,56

To a solution of alcohol **304** (0.13 g, 0.38 mmol) in CH_2Cl_2 (4 mL) at RT, were added pyridine (0.14 mL, 1.7 mmol, 4.5 equiv.) and DMP (0.24 g, 0.57 mmol, 1.5 equiv.) sequentially. The resulting solution was stirred at RT for 1 h, before the addition of a sat. aq. $Na_2S_2O_3$ solution (4 mL). The layers were separated and the organic layer was washed with a sat. aq. $NaHCO_3$ solution (4 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL) and the combined organic extracts

were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 90:10) to deliver aldehyde **302** (0.11 g, 0.32 mmol, 84%) as a colourless oil. R_f = 0.37 (pet. ether/EtOAc, 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (1H, app t, *J* = 2.2 Hz, CH−C18), 6.45 (1H, ddd, *J* = 15.2, 11.0, 1.3 Hz, CH−C26), 5.82 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.53 (1H, dd, *J* = 15.2, 6.0 Hz, CH−C25), 4.35 (1H, app ddt, *J* = 8.4, 7.3, 5.5 Hz, CH−C20), 4.17 (1H, ddd, *J* = 6.0, 5.8, 1.3 Hz, CH−C24), 3.98 (1H, app td, *J* = 7.3, 5.8 Hz, CH−C23), 2.66 (1H, ddd, *J* = 16.2, 7.3, 2.2 Hz, CH−C19), 2.54 (1H, ddd, *J* = 16.2, 5.5, 2.2 Hz, CH−C19), 2.13−2.05 (1H, m, CH−C22), 1.96−1.86 (1H, m, CH−C21), 1.77 (3H, br s, CH_3−C35), 1.83−1.73 (1H, m, CH−C22), 1.75 (3H, br s, CH_3−C29), 1.51 (1H, app ddt, *J* = 12.0, 9.6, 8.4 Hz, CH−C21), 0.94 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.59 (6H, q, *J* = 7.9 Hz, CH_2−TES).

2-((2*R*,5*R*)-5-((*R*)-1-Hydroxyprop-2-yn-1-yl)tetrahydrofuran-2-yl)ethyl pivalate 298



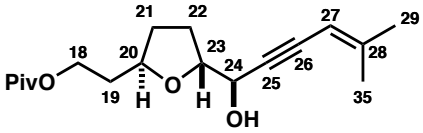
Chemical Formula: $C_{14}H_{22}O_4$
Molecular Weight: 254,32

To a solution of *bis*-TBS ether **296** (0.92 g, 2.3 mmol) in THF (15 mL) at 0 °C, was added TBAF (1.0 M in THF, 6.9 mL, 6.9 mmol, 3.0 equiv.) dropwise. The resulting solution was stirred at RT for 2.5 h. The reaction was quenched by the addition of a sat. aq. NH_4Cl solution (15 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (45 mL), dried over $MgSO_4$, filtered and concentrated. The residue was filtered rapidly through a short pad of silica gel (EtOAc) to give the crude diol **282** which was used directly in the next step without further purification.
To a solution of crude diol **282** in CH_2Cl_2 (23 mL) at −40 °C, was added (1*S*)-(+)-camphorsulfonic acid (53 mg, 0.23 mmol, 10 mol %). The resulting mixture was stirred at −40 °C for 10 min and at RT for 30 min. The reaction was quenched by the addition of Et_3N (0.10 mL, 0.69 mmol) and the solution was concentrated. The residue was filtered rapidly through a short pad of silica gel (EtOAc) to give the

crude tetrahydrofuran **281** which was used directly in the next step without further purification.

To a solution of crude tetrahydrofuran **281** in CH_2Cl_2 (12 mL) at 0 °C, were added pyridine (0.28 mL, 3.5 mmol, 1.5 equiv.) and, after 5 min, PivCl (0.31 mL, 2.5 mmol, 1.1 equiv.). The resulting solution was stirred at 0 °C for 10 min and at RT for 22 h. The reaction was quenched by the addition of a sat. aq. $NaHCO_3$ solution (9 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 70:30) to provide pivalate **298** (0.44 g, 1.7 mmol, 76% over 3 steps) as a colourless oil. R_f = 0.49 (pet. ether/EtOAc, 70:30); $[\alpha]_D^{24}$ −12.6 (*c* = 1.04, $CHCl_3$); ν_{max} 3447, 3284, 2972, 1724, 1481, 1398, 1367, 1286, 1156, 1038 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.23−4.12 (3H, m, CH_2−C18, CH−C24), 4.09 (1H, app q, *J* = 7.0 Hz, CH−C23), 4.07−4.00 (1H, m, CH−C20), 2.53 (1H, d, *J* = 4.3 Hz, OH−C24), 2.43 (1H, d, *J* = 2.2 Hz, CH−C26), 2.16−2.00 (2H, m, CH−C21, CH−C22), 1.95−1.87 (1H, m, CH−C19), 1.86−1.77 (2H, m, CH−C19, CH−C22), 1.65−1.56 (1H, m, CH−C21), 1.19 (9H, s, CH_3−*t*-Bu Piv); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6 (C−Piv), 81.9 (C−C25), 81.5 (CH−C23), 77.0 (CH−C20), 73.7 (CH−C26), 65.1 (CH−C24), 61.7 (CH_2−C18), 38.7 (C−*t*-Bu Piv), 34.5 (CH_2−C19), 32.0 (CH_2−C21), 28.0 (CH_2−C22), 27.2 (CH_3−*t*-Bu Piv); HRMS (CI+, isobutane) $[M+H]^+$ calcd for $C_{14}H_{23}O_4$ 255.1596, found 255.1593, Δ 1.3 ppm; LRMS (CI+, isobutane) *m/z* (intensity) 255.19 (100%), 229.18 (17%).

2-((2*R*,5*R*)-5-((*R*)-1-Hydroxy-5-methylhex-4-en-2-yn-1-yl)tetrahydrofuran-2-yl)ethyl pivalate 305

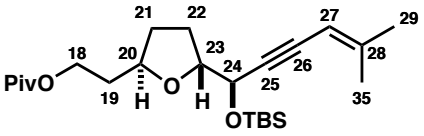


Chemical Formula: $C_{18}H_{28}O_4$
Molecular Weight: 308,41

To a suspension of $Pd(PPh_3)_4$ (10 mg, 10 µmol, 5 mol %) in pyrrolidine (300 µL) at RT, was added 1-bromo-2-methyl-1-propene (60 µL, 0.60 mmol, 3.0 equiv.) followed, after 5 min, by the dropwise addition of alkyne **298** (50 mg, 0.20 mmol) in pyrrolidine (300 µL). The resulting yellow solution was stirred at 50 °C for 16 h.

The reaction mixture was allowed to cool to RT, before the addition of a sat. aq. NH_4Cl solution (2 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 80:20) to afford enyne **305** (50 mg, 0.16 mmol, 82%) as a light yellow oil. R_f = 0.26 (pet. ether/EtOAc, 80:20); $[\alpha]_D^{27}$ +12.6 (*c* = 2.32, $CHCl_3$); ν_{max} 3443, 2969, 1726, 1481, 1397, 1285, 1155, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.28−5.25 (1H, m, CH−C27), 4.37−4.32 (1H, m, CH−C24), 4.22−4.12 (2H, m, CH_2−C18), 4.12−4.00 (2H, m, CH−C20, CH−C23), 2.49 (1H, d, *J* = 4.0 Hz, OH−C24), 2.18−1.99 (2H, m, CH−C21, CH−C22), 1.96−1.87 (1H, m, CH−C19), 1.88 (3H, br s, CH_3−C35), 1.87−1.78 (2H, m, CH−C19, CH−C22), 1.80 (3H, br s, CH_3−C29), 1.65−1.54 (1H, m, CH−C21), 1.19 (9H, s, CH_3−*t*-Bu Piv); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7 (C−Piv), 149.7 (C−C28), 104.7 (CH−C27), 89.0 (C−C25), 83.9 (C−C26), 82.1 (CH−C23), 76.9 (CH−C20), 66.2 (CH−C24), 61.9 (CH_2−C18), 38.9 (C−*t*-Bu Piv), 34.7 (CH_2−C19), 32.2 (CH_2−C21), 28.3 (CH_2−C22), 27.3 (CH_3−*t*-Bu Piv), 24.9 (CH_3−C29), 21.2 (CH_3−C35); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{18}H_{28}O_4Na$ 331.1880, found 331.1870, Δ 3.0 ppm.

2-((2*R*,5*R*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-methylhex-4-en-2-yn-1-yl)tetrahydrofuran-2-yl)ethyl pivalate 306

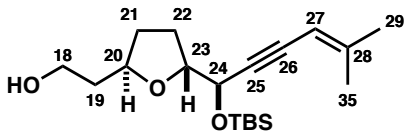


Chemical Formula: $C_{24}H_{42}O_4Si$
Molecular Weight: 422,67

To a solution of alcohol **305** (0.17 g, 0.56 mmol) in CH_2Cl_2 (6 mL) at −78 °C, were added 2,6-lutidine (0.17 mL, 1.5 mmol, 2.6 equiv.) and TBSOTf (0.17 mL, 0.73 mmol, 1.3 equiv.) sequentially. The resulting solution was stirred at −78 °C for 30 min and water (2 mL) was added. The biphasic mixture was allowed to warm to RT and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 95:5) to give TBS ether **306** (0.23 g, 0.53 mmol, 94%) as a colourless oil. R_f = 0.26 (pet. ether/EtOAc, 95:5); $[\alpha]_D^{25}$ −13.1 (*c*

= 2.40, $CHCl_3$); ν_{max} 2930, 2857, 1730, 1479, 1285, 1252, 1155, 1071 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.27−5.23 (1H, m, CH−C27), 4.51 (1H, dd, *J* = 5.8, 1.4 Hz, CH−C24), 4.20−4.04 (4H, m, CH_2−C18, CH−C20, CH−C23), 2.11−2.03 (2H, m, CH−C21, CH−C22), 2.01−1.93 (1H, m, CH−C22), 1.93−1.84 (1H, m, CH−C19), 1.87 (3H, br s, CH_3−C35), 1.83−1.74 (1H, m, CH−C19), 1.79 (3H, br s, CH_3−C29), 1.56−1.48 (1H, m, CH−C21), 1.18 (9H, s, CH_3−*t*-Bu Piv), 0.90 (9H, s, CH_3−*t*-Bu TBS), 0.12 (3H, s, CH_3−TBS), 0.11 (3H, s, CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6 (C−Piv), 148.7 (C−C28), 105.1 (CH−C27), 90.6 (C−C25), 83.3 (C−C26), 81.8 (CH−C23), 76.8 (CH−C20), 67.0 (CH−C24), 62.1 (CH_2−C18), 38.8 (C−*t*-Bu Piv), 34.8 (CH_2−C19), 32.3 (CH_2−C21), 28.0 (CH_2−C22), 27.3 (CH_3−*t*-Bu Piv), 26.0 (CH_3−*t*-Bu TBS), 24.9 (CH_3−C29), 21.1 (CH_3−C35), 18.5 (C−*t*-Bu TBS), −4.5 (CH_3−TBS), −4.8 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{24}H_{42}O_4SiNa$ 445.2745, found 445.2734, Δ 2.3 ppm.

2-((2*R*,5*R*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-methylhex-4-en-2-yn-1-yl)tetrahydrofuran-2-yl)ethanol 307

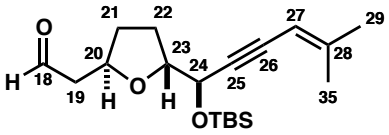


Chemical Formula: $C_{19}H_{34}O_3Si$
Molecular Weight: 338,56

To a solution of pivalate **306** (0.48 g, 1.1 mmol) in Et_2O (16 mL) at −20 °C, was added $LiAlH_4$ (0.11 g, 2.8 mmol, 2.5 equiv.) in one portion. The resulting solution was stirred at −20 °C for 20 min, before the dropwise addition of water (0.11 mL), a 15% NaOH aq. solution (0.11 mL) and water (0.33 mL). The mixture was stirred vigorously at RT for 20 min. The solids were filtered through a cotton plug and the filtrate was concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 80:20) to give alcohol **307** (0.37 g, 1.1 mmol, 96%) as a colourless oil. R_f = 0.30 (pet. ether/EtOAc, 80:20); $[\alpha]_D^{26}$ −17.5 (*c* = 2.00, $CHCl_3$); ν_{max} 3410, 2929, 2857, 1473, 1463, 1334, 1251, 1069 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.27−5.25 (1H, m, CH−C27), 4.48 (1H, dd, *J* = 6.1, 1.7 Hz, CH−C24), 4.23−4.16 (1H, m, CH−C20), 4.10 (1H, ddd, *J* = 7.6, 6.5, 6.1 Hz, CH−C23), 3.82−3.73 (2H, m, CH_2−C18), 2.90 (1H, dd, *J* = 7.0, 4.2 Hz, OH−C18), 2.11−2.03 (2H, m, CH−C21, CH−C22), 1.98−1.88 (1H, m, CH−C22), 1.87 (3H, br s,

CH_3−C35), 1.79 (3H, br s, CH_3−C29), 1.78−1.73 (2H, m, CH_2−C19), 1.62−1.54 (1H, m, CH−C21), 0.90 (9H, s, CH_3−*t*-Bu Piv), 0.13 (3H, s, CH_3−TBS), 0.11 (3H, s, CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9 (C−C28), 105.0 (CH−C27), 90.4 (C−C25), 83.4 (C−C26), 82.3 (CH−C23), 80.4 (CH−C20), 66.9 (CH−C24), 62.0 (CH_2−C18), 37.3 (CH_2−C19), 32.5 (CH_2−C21), 27.8 (CH_2−C22), 25.9 (CH_3−*t*-Bu TBS), 24.9 (CH_3−C29), 21.1 (CH_3−C35), 18.4 (C−*t*-Bu TBS), −4.5 (CH_3−TBS), −4.8 (CH_3−TBS); HRMS (CI+, isobutane) $[M+H]^+$ calcd for $C_{19}H_{35}O_3Si$ 339.2355, found 339.2351, Δ 1.2 ppm; LRMS (CI+, isobutane) *m/z* (intensity) 339.1 (19%), 263.1 (27%), 207.1 (100%), 135.0 (23%).

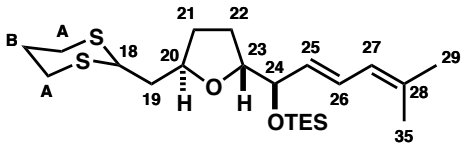
2-((2*R*,5*R*)-5-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-methylhex-4-en-2-yn-1-yl)tetrahydrofuran-2-yl)acetaldehyde 308



Chemical Formula: $C_{19}H_{32}O_3Si$
Molecular Weight: 336,54

To a solution of alcohol **307** (0.27 g, 0.79 mmol) in CH_2Cl_2 (11 mL) at RT, were added pyridine (0.39 mL, 4.8 mmol, 6.0 equiv.) and DMP (0.67 g, 1.6 mmol, 2.0 equiv.) sequentially. The resulting solution was stirred at RT for 1 h, before the addition of a sat. aq. $Na_2S_2O_3$ solution (10 mL). The layers were separated and the organic layer was washed with a sat aq. $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 90:10) to deliver aldehyde **308** (0.24 g, 0.71 mmol, 89%) as a colourless oil. R_f = 0.38 (pet. ether/EtOAc, 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (1H, dd, *J* = 2.5, 2.1 Hz, CH−C18), 5.28−5.25 (1H, m, CH−C27), 4.54 (1H, dd, *J* = 5.8, 1.5 Hz, CH−C24), 4.47 (1H, app ddt, *J* = 8.6, 7.2, 5.5 Hz, CH−C20), 4.10 (1H, app td, *J* = 7.1, 5.8 Hz, CH−C23), 2.68 (1H, ddd, *J* = 16.2, 7.2, 2.5 Hz, CH−C19), 2.56 (1H, ddd, *J* = 16.2, 5.5, 2.1 Hz, CH−C19), 2.24−2.16 (1H, m, CH−C21), 2.14−1.98 (2H, m, CH_2−C22), 1.88 (3H, br s, CH_3−C35), 1.80 (3H, br s, CH_3−C29), 1.56 (1H, app ddt, *J* = 12.1, 9.4, 8.6 Hz, CH−C21), 0.90 (9H, s, CH_3−*t*-Bu TBS), 0.12 (3H, s, CH_3−TBS), 0.11 (3H, s, CH_3−TBS).

(((*R*,*E*)-1-((2*R*,5*R*)-5-((1,3-Dithian-2-yl)methyl)tetrahydrofuran-2-yl)-5-methylhexa-2,4-dien-1-yl)oxy)triethylsilane 264



Chemical Formula: $C_{22}H_{40}O_2S_2Si$
Molecular Weight: 428,77

To a suspension of $MgBr_2 \bullet OEt_2$ (0.24 g, 0.92 mmol, 1.3 equiv.) in Et_2O (5 mL) at RT, was added 1,3-propanedithiol (86 µL, 0.85 mmol, 1.2 equiv.) followed by a solution of aldehyde **308** (0.24 g, 0.71 mmol) in Et_2O (2 mL). The resulting mixture was stirred at RT for 1.5 h and water (7 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 7 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was used directly in the next step without further purification.

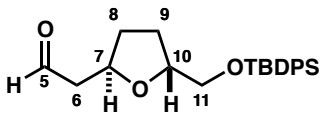
To a solution of the crude TBS ether in THF (7 mL) at 0 °C, was added TBAF (1.0 M in THF, 1.4 mL, 1.4 mmol, 2.0 equiv.) dropwise. The resulting solution was stirred at RT for 1 h, before the addition of water (7 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 7 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was used directly in the next step without further purification.

To a solution of the crude enyne in THF (10 mL) at 0 °C, was added sodium bis(2-methoxyethoxy)aluminium hydride (≥ 65 wt % in toluene, 0.67 mL, 2.2 mmol, 4.5 equiv.) dropwise. The resulting cloudy mixture was stirred at RT for 30 min and cooled to 0 °C, before the dropwise addition of a sat. aq. potassium sodium tartrate solution (20 mL). The layers were separated and the aqueous phase 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. Crude material was used directly in the next step without further purification.

To a solution of crude allylic alcohol **309** in CH_2Cl_2 (10 mL) at −78 °C, were added 2,6-lutidine (0.17 mL, 1.5 mmol, 3.0 equiv.) and TESOTf (0.17 mL, 0.74 mmol, 1.5 equiv.) sequentially. The resulting solution was stirred at −78 °C for 30 min, before the addition of water (8 mL) and the biphasic mixture allowed to warm to RT. The

layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were washed with brine (35 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 98:2) to deliver TES ether **264** (0.14 g, 0.33 mmol, 46% over 4 steps) as a colourless oil. R_f = 0.36 (pet. ether/EtOAc, 95:5); $[\alpha]_D^{29}$ +27.1 (*c* = 1.10, $CHCl_3$); ν_{max} 2930, 2874, 1458, 1377, 1242, 1117, 1069, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (1H, ddd, *J* = 15.1, 11.0, 1.1 Hz, CH−C26), 5.82 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.52 (1H, dd, *J* = 15.1, 5.8 Hz, CH−C25), 4.21 (1H, dd, *J* = 9.6, 4.9 Hz, CH−C18), 4.24−4.15 (2H, m, CH−C20, CH−C24), 3.93 (1H, ddd, *J* = 8.0, 7.1, 6.3 Hz, CH−C23), 2.94−2.77 (4H, m, 2 × CH_2−C_A), 2.16−2.06 (1H, m, CH−C_B), 2.03−1.78 (5H, m, CH−C_B, CH_2−C19, CH−C21, CH−C22), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.68 (1H, app ddt, *J* = 12.6, 9.0, 8.0 Hz, CH−C22), 1.45 (1H, app dtd, *J* = 11.8, 9.0, 8.1 Hz, CH−C21), 0.96 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.62 (6H, q, *J* = 7.9 Hz, CH_2−TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.2 (C−C28), 129.9 (CH−C25), 127.7 (CH−C26), 124.9 (CH−C27), 82.4 (CH−C23), 75.6 (CH−C24), 75.5 (CH−C20), 44.7 (CH−C18), 41.8 (CH_2−C19), 32.3 (CH_2−C21), 30.7 (CH_2−C_A), 30.2 (CH_2−C_A), 27.4 (CH_2−C22), 26.2 (CH_2−C_B), 26.1 (CH_3−C35), 18.4 (CH_3−C29), 7.1 (CH_3−TES), 5.1 (CH_2−TES); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{22}H_{40}O_2S_2SiNa$ 451.2131, found 451.2110, Δ 4.7 ppm.

2-((2*R*,5*R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)acetaldehyde 311

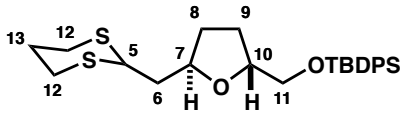


Chemical Formula: $C_{23}H_{30}O_3Si$
Molecular Weight: 382,57

To a solution of alcohol **310** (0.86 g, 2.2 mmol) in CH_2Cl_2 (25 mL) at RT, were added [bis(acetoxy)iodo]benzene (0.76 g, 2.4 mmol, 1.05 equiv.) and TEMPO (70 mg, 0.45 mmol, 20 mol %) sequentially. The resulting solution was stirred at RT for 6 h, before the addition of water (15 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (45 mL), dried over $MgSO_4$, filtered and

concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 80:20) to give aldehyde **311** (0.76 g, 2.0 mmol, 88%) as a yellow oil. R_f = 0.53 (pet. ether/EtOAc, 80:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (1H, dd, *J* = 2.6, 2.0 Hz, CH−C5), 7.71−7.64 (4H, m, CH−Ar TBDPS), 7.45−7.34 (6H, m, CH−Ar TBDPS), 4.41 (1H, dddd, *J* = 8.3, 7.4, 5.8, 5.3 Hz, CH−C7), 4.17 (1H, app tt, *J* = 7.0, 4.6 Hz, CH−C10), 3.67 (1H, dd, *J* = 10.7, 4.6 Hz, CH−C11), 3.64 (1H, dd, *J* = 10.7, 4.6 Hz, CH−C11), 2.66 (1H, ddd, *J* = 16.1, 7.4, 2.6 Hz, CH−C6), 2.56 (1H, ddd, *J* = 16.1, 5.3, 2.0 Hz, CH−C6), 2.17 (1H, dddd, *J* = 12.1, 8.1, 5.8, 3.8 Hz, CH−C8), 2.03 (1H, dddd, *J* = 12.4, 8.3, 7.0, 3.8 Hz, CH−C9), 1.90 (1H, dddd, *J* = 12.4, 9.0, 8.1, 7.0 Hz, CH−C9), 1.57 (1H, app ddt, *J* = 12.1, 9.0, 8.3 Hz, CH−C8), 1.05 (9H, s, CH_3−*t*-Bu TBDPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5 (CH−C5), 135.8 (CH−Ar TBDPS), 133.7 (C−Ar TBDPS), 129.8 (CH−Ar TBDPS), 127.8 (CH−Ar TBDPS), 79.6 (CH−C10), 74.4 (CH−C7), 66.5 (CH_2−C11), 49.7 (CH_2−C6), 32.3 (CH_2−C8), 27.9 (CH_2−C9), 27.0 (CH_3−*t*-Bu TBDPS), 19.4 (C−*t*-Bu TBDPS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{23}H_{30}O_3SiNa$ 405.1856, found 405.1839, Δ 4.4 ppm.

(2*R*,5*R*)-2-((2,2-Dimethyl-1,1-diphenylpropoxy)methyl)-5-(1,3-dithian-2-ylmethyl)oxolane 312

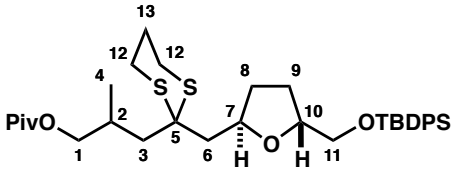


Chemical Formula: $C_{26}H_{36}O_2S_2Si$
Molecular Weight: 472,78

To a solution of aldehyde **311** (0.76 g, 2.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C, were added 1,3-propanedithiol (0.24 mL, 2.4 mmol, 1.2 equiv.) and $MgBr_2$•OEt_2 (0.51 g, 2.0 mmol, 1.0 equiv.) sequentially. The resulting solution was stirred at 0 °C for 5 min and at RT for 28 h. The reaction was quenched by the addition of a sat. aq. $NaHCO_3$ solution (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 90:10) to give dithiane **312** (0.87 g, 1.9 mmol, 93%) as a colourless solid. R_f = 0.48 (pet. ether/EtOAc, 90:10); $[\alpha]_D^{26}$ −11.5 (*c* = 1.01, $CHCl_3$); mp = 69.3−70.0 °C; ν_{max} 3071,

2931, 2857, 2362, 1473, 1427, 1265, 1112, 1078 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73−7.67 (4H, m, CH−Ar TBDPS), 7.45−7.36 (6H, m, CH−Ar TBDPS), 4.32−4.25 (1H, m, CH−C7), 4.21 (1H, dd, *J* = 9.4, 5.0 Hz, CH−C5), 4.18−4.11 (1H, m, CH−C10), 3.67 (1H, ddd, *J* = 10.5, 4.8, 0.4 Hz, CH−C11), 3.62 (1H, ddd, *J* = 10.5, 5.2, 0.6 Hz, CH−C11), 2.94−2.78 (4H, m, 2 × CH_2−C12), 2.14−1.99 (3H, m, CH−C8, CH−C9, CH−C13), 1.96 (1H, ddd, *J* = 13.7, 8.8, 5.0 Hz, CH−C6), 1.93−1.79 (3H, m, CH−C6, CH−C9, CH−C13), 1.52 (1H, app dq, *J* = 11.9, 8.2 Hz, CH−C8), 1.07 (9H, s, CH_3−*t*-Bu TBDPS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.8 (CH−Ar TBDPS), 135.8 (CH−Ar TBDPS), 133.9 (C−Ar TBDPS), 133.8 (C−Ar TBDPS), 129.7 (CH−Ar TBDPS), 127.7 (CH−Ar TBDPS), 79.1 (CH−C10), 75.7 (CH−C7), 66.6 (CH_2−C11), 44.6 (CH−C5), 41.9 (CH_2−C6), 32.0 (CH_2−C8), 30.6 (CH_2−C12), 30.2 (CH_2−C12), 28.2 (CH_2−C9), 27.0 (CH_3−*t*-Bu TBDPS), 26.1 (CH_2−C13), 19.4 (C−*t*-Bu TBDPS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{26}H_{36}O_2S_2SiNa$ 495.1818, found 495.1802, Δ 3.3 ppm.

3-(2-(((2*R*,5*R*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)methyl)-1,3-dithian-2-yl)-2-methylpropyl pivalate 317

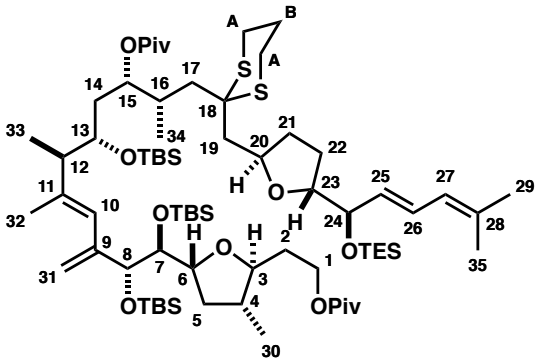


Chemical Formula: $C_{35}H_{52}O_4S_2Si$
Molecular Weight: 629,00

To a solution of dithiane **312** (dried by azeotropic distillation with benzene (4 ×), 0.12 g, 0.25 mmol, 1.8 equiv.) in a 9:1 mixture of THF and HMPA (0.80 mL) at −78 °C, was added *t*-BuLi (titrated at 1.4 M in pentane, 0.20 mL, 0.25 mmol, 1.8 equiv.) dropwise. The resulting red solution was stirred at −78 °C for 10 min, before the slow addition of a solution of iodide **314** (dried by azeotropic distillation with benzene (4 ×), 40 mg, 0.14 mmol) in THF (0.60 mL). The reaction mixture was stirred at −78 °C for 1 h, before the addition of aqueous pH 7 buffer (1 mL). The biphasic mixture was allowed to warm to RT and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 2 mL) and the combined organic extracts were washed with brine (6 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 90:10) to afford dithiane **317** (0.05 g, 0.07 mmol, 54%) as a 1:1

mixture of diastereomers, as a colourless oil. R_f = 0.33 (pet. ether/EtOAc, 90:10); v_{max} 3071, 2931, 2858, 1724, 1427, 1397, 1284, 1163, 1112, 1084 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71−7.66 (8H, m, CH−Ar TBDPS), 7.43−7.34 (12H, m, CH−Ar TBDPS), 4.33−4.25 (2H, m, CH−C7), 4.17−4.09 (2H, m, CH−C10), 4.05 (1H, dd, *J* = 10.6, 4.3 Hz, CH−C1), 4.04 (1H, dd, *J* = 10.6, 4.3 Hz, CH−C1), 3.93 (1H, dd, *J* = 10.6, 7.0 Hz, CH−C1), 3.88 (1H, dd, *J* = 10.6, 7.0 Hz, CH−C1), 3.67−3.58 (4H, m, CH_2−C11), 2.93−2.71 (8H, m, 2 × CH_2−C12), 2.28−1.75 (20H, m, CH−C2, CH_2−C3, CH_2−C6, CH−C8, CH_2−C9, CH_2−C13), 1.63−1.53 (2H, m, CH−C8), 1.20 (9H, s, CH_3−*t*-Bu Piv), 1.19 (9H, s, CH_3−*t*-Bu Piv), 1.07 (6H, d, *J* = 6.7 Hz, CH_3−C4), 1.05 (18H, s, CH_3−*t*-Bu TBDPS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7 (C−Piv), 178.6 (C−Piv), 135.8 (CH−Ar TBDPS), 135.8 (CH−Ar TBDPS), 135.8 (CH−Ar TBDPS), 133.9 (C−Ar TBDPS), 133.8 (C−Ar TBDPS), 129.7 (CH−Ar TBDPS), 127.8 (CH−Ar TBDPS), 127.8 (CH−Ar TBDPS), 79.1 (CH−C10), 79.1 (CH−C10), 76.6 (CH−C7), 76.3 (CH−C7), 69.8 (CH_2−C1), 69.8 (CH_2−C1), 66.8 (CH_2−C11), 66.7 (CH_2−C11), 53.0 (C−C5), 52.8 (C−C5), 45.4 (CH_2−C6), 45.4 (CH_2−C6), 42.9 (CH_2−C3), 42.3 (CH_2−C3), 39.0 (C−*t*-Bu Piv), 39.0 (C−*t*-Bu Piv), 34.0 (CH_2−C8), 34.0 (CH_2−C8), 29.8 (CH−C2), 29.7 (CH−C2), 28.4 (CH_2−C9), 28.2 (CH_2−C9), 27.4 (CH_3−*t*-Bu Piv), 27.0 (CH_3−*t*-Bu TBDPS), 26.6 (CH_2−C12), 26.5 (CH_2−C12), 26.5 (CH_2−C12), 26.4 (CH_2−C12), 25.2 (CH_2−C13), 25.1 (CH_2−C13), 19.9 (CH_3−C4), 19.7 (CH_3−C4), 19.4 (C−*t*-Bu TBDPS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{35}H_{52}O_4S_2SiNa$ 651.2968, found 651.2947, Δ 3.3 ppm.

(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 319



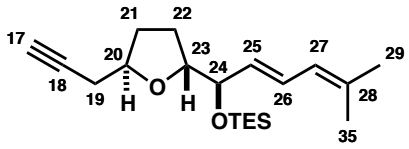
Chemical Formula: $C_{72}H_{136}O_{10}S_2Si_4$
Molecular Weight: 1338,32

Note: ^{1}H NMR and mass experiments were recorded by Dr Filippo Romiti.

To a solution of dithiane **264** (dried by azeotropic distillation with benzene (4 ×), 50 mg, 0.12 mmol, 1.5 equiv.) in a 4.5:1 mixture of THF and HMPA (0.43 mL) at −78 °C, was added *t*-BuLi (titrated at 2.5 M in hexanes, 47 µL, 0.12 mmol, 1.5 equiv.) dropwise. The resulting red solution was stirred at −78 °C for 10 min, followed by the slow addition of a solution of iodide **278**[73] (dried by azeotropic distillation with benzene (4 ×), 81 mg, 78 µmol) in THF (0.35 mL). The reaction mixture was stirred at −78 °C for 1 h, before the addition of aqueous pH 7 buffer (2 mL). The biphasic mixture was allowed to warm to RT and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 2 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 95:5) to afford recovered dithiane **264** (21 mg, 49 µmol, 42%), recovered iodide **278** (40 mg, 39 µmol, 50%) and desired dithiane **319** (14 mg, 10 µmol, 13% over 2 steps) as a colourless oil. R_f = 0.31 (pet. ether/EtOAc, 95:5); $[\alpha]_D^{28}$ +8.7 (*c* = 0.70, $CHCl_3$); ν_{max} 2956, 2930, 2878, 2857, 1728, 1462, 1283, 1252, 1160, 1079, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (1H, ddd, *J* = 15.3, 10.9, 0.9 Hz, CH−C26), 5.86−5.81 (1H, m, CH−C27), 5.72 (1H, br s, 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−C31), 5.06−5.01 (1H, m, CH−C15), 4.91−4.89 (1H, m, CH−C31), 4.23−4.16 (2H, m, CH−C1, CH−C24), 4.16−4.04 (4H, m, CH−C1,

CH−C6, CH−C8, CH−C20), 3.94 (1H, app dt, *J* = 7.3, 5.9 Hz, CH−C23), 3.86 (1H, app 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−C_A), 2.81−2.71 (3H, m, CH−C_A, CH_2−C_A), 2.40−2.33 (1H, m, CH−C12), 2.27 (1H, dd, *J* = 15.0, 4.5 Hz, CH−C19), 2.22−2.08 (3H, m, CH−C4, CH_2−C17), 2.06−1.45 (14H, m, CH_2−C2, CH_2−C5, CH_2−C14, CH−C16, CH−C19, CH_2−C21, CH_2−C22, CH_2−C_B), 1.77 (6H, br s, CH_3−C29, CH_3−C35), 1.75 (3H, d, *J* = 0.6 Hz, CH_3−C32), 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−C33), 1.03 (3H, d, *J* = 6.9 Hz, CH_3−C34), 0.95 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.91 (18H, s, 2 × CH_3−*t*-Bu TBS), 0.90 (3H, d, *J* = 6.2 Hz, CH_3−C30), 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, 2 × CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{72}H_{136}O_{10}S_2Si_4Na$ 1359.8544, found 1359.8398.

Triethyl(((*R*,*E*)-5-methyl-1-((2*R*,5*R*)-5-(prop-2-yn-1-yl)tetrahydrofuran-2-yl)hexa-2,4-dien-1-yl)oxy)silane 328

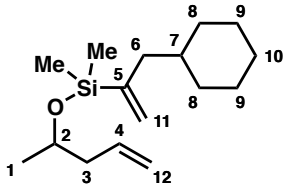


Chemical Formula: $C_{20}H_{34}O_2Si$
Molecular Weight: 334,57

To a solution of dimethyl-1-diazo-2-oxopropyl phosphonate (0.12 g, 0.64 mmol, 2.0 equiv.) in MeOH (2 mL) at 0 °C, was added K_2CO_3 (88 mg, 0.64 mmol, 2.0 equiv.). The mixture was stirred at 0 °C for 1 h, before the dropwise addition of aldehyde **302** (0.11 g, 0.32 mmol) in THF (1 mL). The resulting yellow suspension was stirred at 0 °C for 1 h and at RT for 45 min. The reaction was quenched by the addition of a sat. aq. NH_4Cl solution (3 mL) and Et_2O (3 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 3 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 99:1) to provide alkyne **328** (66 mg, 0.20 mmol, 61%) as a colourless oil. R_f = 0.32 (pet. ether/EtOAc, 98:2); $[\alpha]_D^{26}$ +31 (*c* = 0.33, $CHCl_3$); ν_{max} 3314, 2955, 2876, 1659, 1460, 1379, 1238, 1115, 1074, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (1H, ddd, *J* = 15.2, 11.0, 1.4 Hz,

CH−C26), 5.83 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.54 (1H, dd, *J* = 15.2, 5.8 Hz, CH−C25), 4.22 (1H, ddd, *J* = 5.8, 5.5, 1.4 Hz, CH−C24), 4.12−4.05 (1H, m, CH−C20), 4.04 (1H, app td, *J* = 7.1, 5.5 Hz, CH−C23), 2.46 (1H, ddd, *J* = 16.6, 5.1, 2.7 Hz, CH−C19), 2.33 (1H, ddd, *J* = 16.6, 7.2, 2.7 Hz, CH−C19), 2.04 (1H, dddd, *J* = 11.9, 8.1, 5.8, 3.9 Hz, CH−C21), 1.96 (1H, app t, *J* = 2.7 Hz, CH−C17), 1.95−1.88 (1H, m, CH−C22), 1.82−1.72 (1H, m, CH−C22), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.72−1.62 (1H, m, CH−C21), 0.95 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.60 (6H, q, *J* = 7.9 Hz, CH_2−TES); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2 (C−C28), 129.8 (CH−C25), 127.8 (CH−C26), 124.9 (CH−C27), 83.0 (CH−C23), 81.4 (C−C18), 77.7 (CH−C20), 75.1 (CH−C24), 69.6 (CH−C17), 31.4 (CH_2−C21), 27.0 (CH_2−C22), 26.1 (CH_3−C35), 25.5 (CH_2−C19), 18.4 (CH_3−C29), 7.0 (CH_3−TES), 5.1 (CH_2−TES); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{20}H_{34}O_2SiNa$ 357.2220, found 357.2225, Δ 1.3 ppm.

(3-Cyclohexylprop-1-en-2-yl)dimethyl(pent-4-en-2-yloxy)silane 335

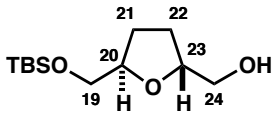


Chemical Formula: $C_{16}H_{30}OSi$
Molecular Weight: 266,49

To a solution of 3-cyclohexyl-1-propyne (0.12 mL, 0.80 mmol) in CH_2Cl_2 (1.6 mL) at 0 °C, was added chlorodimethylsilane (89 µL, 0.80 mmol, 1.0 equiv.) dropwise, followed by $[Cp^*Ru(MeCN)_3]PF_6$ (4 mg, 0.01 mmol, 1 mol %). The resulting yellow solution was stirred at RT for 1 h, before the addition of a solution of 4-penten-2-ol (82 µL, 0.80 mmol, 1.0 equiv.) and Et_3N (0.17 mL, 1.2 mmol, 1.5 equiv.) in CH_2Cl_2 (3.2 mL). The reaction mixture was stirred at RT for 17 h, diluted with toluene (6 mL), filtered through a pad of celite and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 99:1) to afford silyl ether **335** (0.16 g, 0.61 mmol, 76%) as a colourless oil. R_f = 0.32 (pet. ether/EtOAc, 99:1); ν_{max} 3078, 2922, 2853, 1641, 1449, 1375, 1250, 1128, 1088, 1044, 1001 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (1H, app ddt, *J* = 17.4, 10.3, 7.1 Hz, CH−C4), 5.57 (1H, dt, *J* = 3.1, 1.4 Hz, CH−C11), 5.47 (1H, dt, *J* = 3.1, 0.9 Hz, CH−C11), 5.07−5.03 (1H, m, CH−12), 5.05−4.98 (1H, m, CH−12), 3.84 (1H, app h, *J* = 6.1 Hz, CH−C2), 2.24 (1H, app dddt, *J* = 14.0, 7.1, 6.1, 1.3 Hz, CH−C3), 2.15 (1H, app

dddt, *J* = 14.0, 7.1, 6.1, 1.2 Hz, CH−C3), 2.04 (2H, ddd, *J* = 7.1, 1.4, 0.9 Hz, CH_2−C6), 1.77−1.60 (5H, m, 2 × CH−C8, 2 × CH−C9, CH−C10), 1.43 (1H, ttt, *J* = 10.8, 7.1, 3.4 Hz, CH−C7), 1.27−1.15 (3H, m, 2 × CH−C9, CH−C10), 1.13 (3H, d, *J* = 6.1 Hz, CH_3−C1), 0.92−0.75 (2H, m, 2 × CH−C8), 0.18 (3H, s, CH_3−Si), 0.18 (3H, s, CH_3−Si); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5 (C−C5), 135.6 (CH−C4), 127.0 (CH_2−C11), 116.8 (CH_2−C12), 68.6 (CH−C2), 44.6 (CH_2−C6), 44.3 (CH_2−C3), 36.6 (CH−C7), 33.6 (2 × CH_2−C8), 26.8 (CH_2−C10), 26.6 (2 × CH_2−C9), 23.4 (CH_3−C1), −0.9 (CH_3−Si), −1.0 (CH_3−Si); HRMS (CI+, isobutane) $[M+H]^+$ calcd for $C_{16}H_{31}OSi$ 267.2144, found 267.2139, Δ 2.1 ppm; LRMS (CI+, isobutane) *m/z* (intensity) 267.1 (86%), 225.1 (15%), 143.1 (23%), 73.1 (100%).

((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)methanol 347

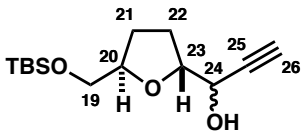


Chemical Formula: $C_{12}H_{26}O_3Si$
Molecular Weight: 246,42

To a solution of alcohol **346** (6.0 g, 26 mmol) in *i*-PrOH (220 mL) at RT, was added $Co(nmp)_2$ (1.5 g, 2.6 mmol, 10 mol %) and the mixture was purged with O_2 for 30 min. The flask headspace was evacuated and refilled with O_2 (3 ×), before the addition of *t*-BuOOH (5 M in decane, 0.52 mL, 2.6 mmol, 10 mol %). The resulting mixture was stirred at 55 °C under O_2 (1 atm) for 18 h and the solution was allowed to cool to RT, then purged with argon. The mixture was concentrated to a tenth of its volume by rotary evaporation (20 °C, 40 mbar) and partitioned between Et_2O (70 mL) and a 1 M HCl aq. solution (90 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 90 mL). The combined organic extracts were washed with water (3 × 120 mL), brine (250 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 80:20) to deliver 2,5-*trans* tetrahydrofyran **347** (3.7 g, 15 mmol, 58%) as a colourless oil. R_f = 0.34 (pet. ether/EtOAc, 80:20); $[\alpha]_D^{25}$ −4.10 (*c* = 1.44, $CHCl_3$) [lit for enantiomer[104] $[\alpha]_D^{25}$ +4.5 (*c* = 0.88, $CHCl_3$)]; ν_{max} 3443, 2955, 2928, 2859, 1472, 1464, 1362, 1254, 1086, 1007 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.12 (1H, app dtd, *J* = 7.4, 6.1, 3.3 Hz, CH−C23), 4.07 (1H,

app tt, *J* = 7.0, 4.8 Hz, CH−C20), 3.68−3.64 (1H, m, CH−C24), 3.63 (1H, dd, *J* = 10.7, 4.8 Hz, CH−C19), 3.60 (1H, dd, *J* = 10.7, 4.8 Hz, CH−C19), 3.48 (1H, dd, *J* = 11.5, 6.1 Hz, CH−C24), 2.03−1.89 (3H, m, CH−C21, CH−C22, OH−C24), 1.81−1.73 (1H, m, CH−C21), 1.73−1.65 (1H, m, CH−C22), 0.90 (9H, s, CH_3−*t*-Bu TBS), 0.06 (6H, s, 2 × CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 80.0 (CH−C20), 79.8 (CH−C23), 66.0 (CH_2−C19), 65.1 (CH_2−C24), 28.4 (CH_2−C21), 27.5 (CH_2−C22), 26.1 (CH_3−*t*-Bu TBS), 18.5 (C−*t*-Bu TBS), −5.1 (CH_3−TBS), −5.1 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{12}H_{26}O_3SiNa$ 269.1543, found 269.1535, Δ 3.1 ppm.

1-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)prop-2-yn-1-ol 349



Chemical Formula: $C_{14}H_{26}O_3Si$
Molecular Weight: 270,44

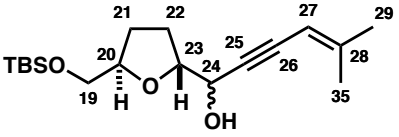
To a solution of alcohol **347** (3.2 g, 13 mmol) in CH_2Cl_2 (87 mL) at RT, was added pyridine (4.1 mL, 51 mmol, 3.9 equiv.), followed by a portionwise addition of DMP (7.2 g, 17 mmol, 1.3 equiv.). The resulting mixture was stirred at RT for 2.5 h, before the addition of a 1:1 mixture of a sat. aq. $Na_2S_2O_3$ solution and a sat. aq. $NaHCO_3$ solution (180 mL). The biphasic mixture was stirred vigorously for 10 min and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 150 mL) and the combined organic extracts were washed with brine (400 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was used directly in the next step without further purification.

To a solution of trimethylsilylacetylene (8.6 mL, 62 mmol, 4.8 equiv.) in Et_2O (62 mL) at 0 °C, was added *i*-PrMgCl (titrated at 1.6 M in THF, 33 mL, 52 mmol, 4.0 equiv.) dropwise *via* an addition funnel. The brown suspension was stirred at 0 °C for 1 h and transferred by cannula to a solution of aldehyde **348** in Et_2O (130 mL) at 0 °C. The resulting yellow suspension was stirred at RT for 2.5 h and cooled to 0 °C. The reaction was quenched by the slow addition of a 3:1 mixture of a sat. aq. NH_4Cl solution and water (400 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 250 mL). The combined organic extracts were

washed with brine (700 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was used directly in the next step without further purification.

To a solution of the crude alkyne in wet MeOH (87 mL) at RT, was added K_2CO_3 (3.6 g, 26 mmol, 2.0 equiv.) in one portion. The resulting suspension was stirred at RT for 2 h, after which volatiles were removed *in vacuo*, and the residue partitioned between CH_2Cl_2 (80 mL) and a sat. aq. NH_4Cl solution (80 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 80 mL). The combined organic extracts were washed with brine (240 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 85:15) to give propargylic alcohol **349** (2.6 g, 9.5 mmol, 73% over 3 steps) as a 1.3:1 mixture of diastereomers, as a yellow oil. R_f = 0.28 (pet. ether/EtOAc, 85:15); ν_{max} 3414, 3312, 2955, 2928, 2857, 1472, 1464, 1389, 1362, 1254, 1078, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.43 (1.0H, ddd, *J* = 5.9, 3.6, 2.3 Hz), 4.20 (1.3H, ddd, *J* = 6.8, 4.7, 2.2 Hz), 4.21−4.07 (4.6H, m), 3.66−3.59 (4.6H, m), 2.50 (1.3H, d, *J* = 4.7 Hz), 2.44 (1.3H, d, *J* = 2.2 Hz), 2.43 (1.0H, d, *J* = 2.3 Hz), 2.39 (1.0H, d, *J* = 5.9 Hz), 2.16−1.95 (5.9H, m), 1.88−1.75 (3.3H, m), 0.89 (9.0H, s), 0.89 (12H, s), 0.06 (14H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 82.4, 82.2, 82.0, 81.7, 81.3, 80.5, 74.1, 73.8, 65.9, 65.7, 65.3, 64.6, 28.1, 28.0, 28.0, 26.6, 26.1, 26.1, 18.5, 18.5, −5.1, −5.1, −5.2, −5.2; HRMS (ESI+) $[M+Na]^+$ calcd for $C_{14}H_{26}O_3SiNa$ 293.1543, found 293.1532, Δ 3.8 ppm.

1-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methylhex-4-en-2-yn-1-ol 350

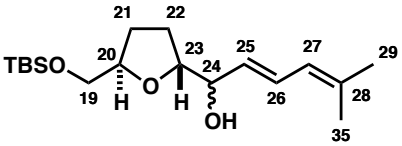


Chemical Formula: $C_{18}H_{32}O_3Si$
Molecular Weight: 324,53

To a suspension of $Pd(PPh_3)_4$ (0.22 g, 0.19 mmol, 5 mol %) in pyrrolidine (4.5 mL) at RT, was added 1-bromo-2-methyl-1-propene (1.2 mL, 11 mmol, 3.0 equiv.). The resulting suspension was stirred at RT for 5 min, before the addition of a solution of alkyne **349** (1.0 g, 3.8 mmol) in pyrrolidine (4.5 mL). The reaction mixture was stirred at 50 °C for 15 h and allowed to cool to RT. The solution was diluted with Et_2O (40 mL) and a sat. aq. NH_4Cl solution (50 mL) was slowly added. The layers

were separated and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with brine (120 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 90:10) to deliver enyne **350** (1.0 g, 3.2 mmol, 83%) as a 1.3:1 mixture of diastereomers, as a yellow oil. R_f = 0.26 (pet. ether/EtOAc, 90:10); ν_{max} 3418, 2953, 2928, 2857, 1462, 1381, 1254, 1086, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.29−5.25 (2.3H, m), 4.60 (1.0H, ddd, *J* = 5.6, 3.3, 1.9 Hz), 4.34 (1.3H, ddd, *J* = 7.0, 4.1, 1.7 Hz), 4.22−4.15 (2.0H, m), 4.13−4.06 (2.6H, m), 3.66−3.58 (4.6H, m), 2.48 (1.3H, d, *J* = 4.1 Hz), 2.33 (1.0H, d, *J* = 5.6 Hz), 2.16−1.96 (5.6H, m), 1.88 (6.9H, br s), 1.86−1.75 (3.6H, m), 1.80 (6.9H, br s), 0.89 (9.0H, s), 0.89 (12H, s), 0.06 (14H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 149.6, 104.8, 104.7, 89.1, 89.0, 84.0, 83.8, 82.8, 82.1, 81.2, 80.4, 66.2, 66.0, 65.8, 65.3, 28.3, 28.2, 28.1, 26.6, 26.1, 26.1, 24.9, 21.2, 21.2, 18.5, 18.5, −5.1, −5.1, −5.2, −5.2; HRMS (ESI+) $[M+Na]^+$ calcd for $C_{18}H_{32}O_3SiNa$ 347.2013, found 347.2005, Δ 2.2 ppm.

(*E*)-1-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methylhexa-2,4-dien-1-ol 351

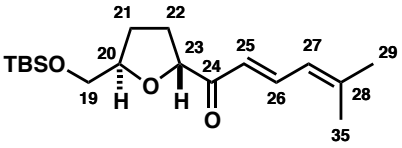


Chemical Formula: $C_{18}H_{34}O_3Si$
Molecular Weight: 326,55

To a solution of enyne **350** (2.2 g, 6.6 mmol) in THF (66 mL) at 0 °C, was added sodium bis(2-methoxyethoxy)aluminium hydride (≥ 60 wt % in toluene, 8.6 mL, 27 mmol, 4.0 equiv.) dropwise. The resulting cloudy mixture was stirred at RT for 2 h and cooled to 0 °C, before the dropwise addition of a sat. aq. potassium sodium tartrate solution (100 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 90 mL). The combined organic extracts were washed with brine (250 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 90:10) to deliver diene **351** (2.0 g, 6.3 mmol, 94%) as a 1.2:1 mixture of diastereomers, as a colourless oil. ν_{max} 3435, 2955, 2928, 2857, 1661, 1471, 1462, 1377, 1362, 1254, 1080, 1005 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.52 (1.2H, ddd, *J* = 15.2, 11.0, 1.1 Hz), 6.50

(1.0H, ddd, *J* = 15.3, 11.0, 1.1 Hz), 5.82 (2.2H, dm, *J* = 11.0 Hz), 5.48 (1.0H, dd, *J* = 15.3, 6.6 Hz), 5.47 (1.2H, dd, *J* = 15.2, 6.9 Hz), 4.34 (1.0H, dddd, *J* = 6.6, 3.5, 3.1, 1.1 Hz), 4.10 (1.0H, app tt, *J* = 6.8, 4.9 Hz), 4.07 (1.2H, app tdd, *J* = 6.9, 5.1, 4.7 Hz), 4.01 (1.0H, ddd, *J* = 7.8, 7.1, 3.5 Hz), 3.94 (1.2H, app tdd, *J* = 6.9, 2.9, 1.1 Hz), 3.87 (1.2H, app q, *J* = 6.9 Hz), 3.64 (1.2H, dd, *J* = 10.7, 4.7 Hz), 3.62 (1.0H, dd, *J* = 10.7, 4.9 Hz), 3.59 (1.2H, dd, *J* = 10.7, 5.1 Hz), 3.59 (1.0H, dd, *J* = 10.7, 4.9 Hz), 2.55 (1.2H, d, *J* = 2.9 Hz), 2.15 (1.0H, d, *J* = 3.1 Hz), 2.02−1.91 (3.4H, m), 1.88−1.82 (2.0H, m), 1.77 (6.6H, br s), 1.76 (6.6H, br s), 1.76−1.62 (3.4H, m), 0.89 (9.0H, s), 0.89 (11H, s), 0.06 (7.2H, s), 0.06 (6.0H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.5, 136.3, 129.3, 128.8, 128.6, 128.2, 124.6, 124.6, 82.9, 82.5, 80.7, 79.9, 75.6, 73.5, 66.1, 65.9, 28.4, 28.3, 28.0, 26.2, 26.1, 26.1, 25.6, 18.6, 18.5, 18.5, 18.5, −5.1, −5.1, −5.1; HRMS (ESI+) $[M+Na]^+$ calcd for $C_{18}H_{34}O_3SiNa$ 349.2169, found 349.2153, Δ 4.8 ppm.

(*E*)-1-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methylhexa-2,4-dien-1-one 352

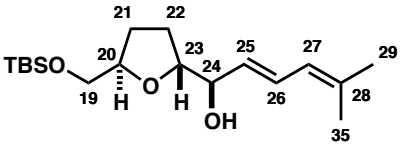


Chemical Formula: $C_{18}H_{32}O_3Si$
Molecular Weight: 324,53

To a solution of allylic alcohol **351** (494 mg, 1.51 mmol) in CH_2Cl_2 (10 mL) at RT, was added DMP (834 mg, 1.97 mmol, 1.3 equiv.) in one portion. The resulting mixture was stirred at RT for 1 h, followed by the addition of a 1:1 mixture of a sat. aq. $Na_2S_2O_3$ solution and a sat. aq. $NaHCO_3$ solution (20 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 95:5) to deliver enone **352** (333 mg, 1.03 mmol, 68%) as a colourless oil. R_f = 0.34 (pet. ether/EtOAc, 90:10); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (1H, dd, *J* = 15.2, 11.7 Hz, CH−C26), 6.42 (1H, d, *J* = 15.2 Hz, CH−C25), 6.03 (1H, dm, *J* = 11.7 Hz, CH−C27), 4.56 (1H, dd, *J* = 7.9, 6.2 Hz, CH−C23), 4.22 (1H, app tt, *J* = 6.7, 4.5 Hz, CH−C20), 3.67 (2H, d, *J* = 4.5 Hz, CH_2−C19), 2.29−2.22 (1H, m, CH−C22), 1.99−1.92 (2H, m, CH−C21, CH−C22),

1.92 (3H, br s, CH_3−C35), 1.89 (3H, br s, CH_3−C29), 1.86−1.79 (1H, m, CH−C21), 0.90 (9H, s, CH_3−*t*-Bu TBS), 0.07 (3H, s, CH_3−TBS), 0.07 (3H, s, CH_3−TBS).

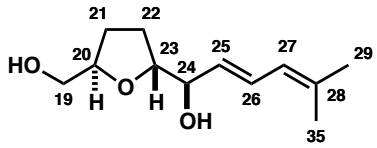
(*R*,*E*)-1-((2*R*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methylhexa-2,4-dien-1-ol 353



Chemical Formula: $C_{18}H_{34}O_3Si$
Molecular Weight: 326,55

To a solution of enone **352** (333 mg, 1.03 mmol) in MeOH (10 mL) at −78 °C, were added $CeCl_3$•$7H_2O$ (535 mg, 1.44 mmol, 1.4 equiv.) and $NaBH_4$ (54 mg, 1.4 mmol, 1.4 equiv.) sequentially. The resulting mixture was stirred at −78 °C for 45 min and concentrated. The residue was partitioned between Et_2O (30 mL) and a sat. aq. NH_4Cl solution (30 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 95:5) to deliver allylic alcohol **353** (0.20 g, 0.61 mmol, 60%) as a colourless oil. R_f = 0.33 (pet. ether/EtOAc, 90:10); $[\alpha]_D^{21}$ +13.6 (*c* = 1.29, $CHCl_3$); ν_{max} 3457, 2955, 2928, 2857, 1661, 1462, 1385, 1254, 1081, 1005 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.52 (1H, ddd, *J* = 15.1, 11.0, 1.1 Hz, CH−C26), 5.82 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.47 (1H, dd, *J* = 15.1, 6.9 Hz, CH−C25), 4.07 (1H, app tdd, *J* = 6.9, 5.0, 4.7 Hz, CH−C20), 3.94 (1H, app tdd, *J* = 6.9, 2.9, 1.1 Hz, CH−C24), 3.87 (1H, app q, *J* = 6.9 Hz, CH−C23), 3.64 (1H, dd, *J* = 10.6, 4.7 Hz, CH−C19), 3.59 (1H, dd, *J* = 10.6, 5.0 Hz, CH−C19), 2.54 (1H, d, *J* = 2.9 Hz, OH−C24), 2.02−1.91 (2H, m, CH−C21, CH−C22), 1.77 (3H, br s, CH_3−C35), 1.76 (3H, br s, CH_3−C29), 1.80−1.72 (1H, m, CH−C21), 1.70−1.62 (1H, m, CH−C22), 0.89 (9H, s, CH_3−*t*-Bu TBS), 0.06 (6H, s, 2 × CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.5 (C−C28), 129.3 (CH−C26), 128.6 (CH−C25), 124.6 (CH−C27), 82.9 (CH−C23), 79.9 (CH−C20), 75.6 (CH−C24), 65.9 (CH_2−C19), 28.4 (CH_2−C21), 28.0 (CH_2−C22), 26.2 (CH_3−C35), 26.1 (CH_3−*t*-Bu TBS), 18.5 (CH_3−C29), 18.5 (C−*t*-Bu TBS), −5.1 (CH_3−TBS), −5.1 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{18}H_{34}O_3SiNa$ 349.2169, found 349.2176, Δ 2.0 ppm.

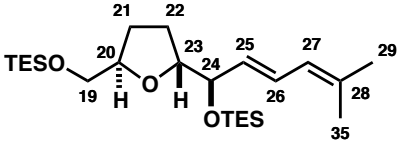
(*R*,*E*)-1-((2*R*,5*R*)-5-(Hydroxymethyl)tetrahydrofuran-2-yl)-5-methylhexa-2,4-dien-1-ol 354



Chemical Formula: $C_{12}H_{20}O_3$
Molecular Weight: 212,29

To a solution of TBS ether **353** (0.43 g, 1.3 mmol) in THF (13 mL) at 0 °C, was added TBAF (1.0 M in THF, 1.6 mL, 1.6 mmol, 1.2 equiv.) dropwise. The resulting solution was stirred at RT for 1 h. The reaction was quenched by the addition of a sat. aq. NH_4Cl solution (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (EtOAc) to give diol **354** (0.28 g, 1.3 mmol, quant.) as a colourless oil. R_f = 0.41 (EtOAc); $[\alpha]_D^{25}$ +9.13 (*c* = 2.24, $CHCl_3$); ν_{max} 3399, 2967, 2915, 2872, 1661, 1445, 1377, 1298, 1229, 1190, 1044 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.53 (1H, ddd, *J* = 15.2, 11.0, 1.1 Hz, CH−C26), 5.82 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.48 (1H, dd, *J* = 15.2, 6.9 Hz, CH−C25), 4.17−4.11 (1H, m, CH−C20), 3.99 (1H, app td, *J* = 6.9, 1.1 Hz, CH−C24), 3.94−3.88 (1H, m, CH−C23), 3.69 (1H, dd, *J* = 11.7, 3.2 Hz, CH−C19), 3.51 (1H, dd, *J* = 11.7, 5.9 Hz, CH−C19), 2.03−1.93 (2H, m, CH−C21, CH−C22), 1.78 (3H, br s, CH_3−C35), 1.77 (3H, br s, CH_3−C29), 1.76−1.67 (2H, m, CH−C21, CH−C22); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.8 (C−C28), 129.5 (CH−C26), 128.2 (CH−C25), 124.5 (CH−C27), 83.0 (CH−C23), 80.0 (CH−C20), 75.7 (CH−C24), 64.9 (CH_2−C19), 28.4 (CH_2−C22), 27.7 (CH_2−C21), 26.2 (CH_3−C35), 18.5 (CH_3−C29); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{12}H_{20}O_3Na$ 235.1305, found 235.1299, Δ 2.3 ppm.

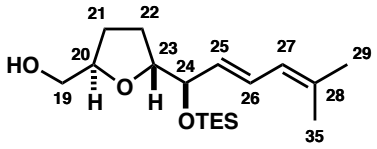
Triethyl(((*R*,*E*)-5-methyl-1-((2*R*,5*R*)-5-(((triethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)hexa-2,4-dien-1-yl)oxy)silane 355



Chemical Formula: $C_{24}H_{48}O_3Si_2$
Molecular Weight: 440,81

To a solution of diol **354** (261 mg, 1.23 mmol) in CH_2Cl_2 (12 mL) at −78 °C, were added 2,6-lutidine (0.85 mL, 7.4 mmol, 6.0 equiv.) and TESOTf (0.83 mL, 3.7 mmol, 3.0 equiv.) sequentially. The resulting solution was stirred at −78 °C for 1 h, before the addition of water (10 mL) and the biphasic mixture was allowed to warm to RT. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 98:2) to deliver *bis*-TES ether **355** (507 mg, 1.15 mmol, 94%) as a colourless oil. R_f = 0.26 (pet. ether/EtOAc, 98:2); $[\alpha]_D^{24}$ +26.2 (*c* = 2.43, $CHCl_3$); ν_{max} 2953, 2911, 2876, 1458, 1414, 1379, 1238, 1123, 1086, 1005 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (1H, ddd, *J* = 15.2, 11.0, 1.4 Hz, CH−C26), 5.82 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.56 (1H, dd, *J* = 15.2, 5.9 Hz, CH−C25), 4.22 (1H, app td, *J* = 5.9, 1.4 Hz, CH−C24), 4.04−3.94 (2H, m, CH−C20, CH−C23), 3.62 (1H, dd, *J* = 10.5, 4.9 Hz, CH−C19), 3.52 (1H, dd, *J* = 10.5, 5.6 Hz, CH−C19), 1.94−1.83 (2H, m, CH−C21, CH−C22), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.76−1.60 (2H, m, CH−C21, CH−C22), 0.95 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.95 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.60 (12H, q, *J* = 7.9 Hz, 2 × CH_2−TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.0 (C−C28), 130.1 (CH−C25), 127.5 (CH−C26), 124.9 (CH−C27), 82.9 (CH−C23), 80.1 (CH−C20), 75.1 (CH−C24), 65.8 (CH_2−C19), 28.6 (CH_2−C21), 26.8 (CH_2−C22), 26.2 (CH_3−C35), 18.4 (CH_3−C29), 7.0 (CH_3−TES), 6.9 (CH_3−TES), 5.1 (CH_2−TES), 4.6 (CH_2−TES); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{24}H_{48}O_3Si_2Na$ 463.3034, found 463.3018, Δ 3.4 ppm.

((2*R*,5*R*)-5-((*R*,*E*)-5-Methyl-1-((triethylsilyl)oxy)hexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)methanol 356

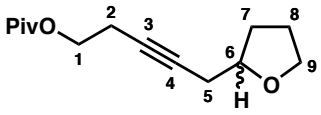


Chemical Formula: $C_{18}H_{34}O_3Si$
Molecular Weight: 326,55

Note: The HF•Pyr stock solution was prepared by mixing HF•Pyr (1.0 mL, 70% HF in pyridine), pyridine (2.0 mL) and THF (5.0 mL).

To a solution of *bis*-TES ether **355** (487 mg, 1.10 mmol) in THF (110 mL) at −20 °C, was added a stock solution of HF•Pyr (4.0 mL) and the resulting mixture was stirred for 20 h. The reaction was quenched by the slow addition of a sat. aq. Na_2CO_3 solution (50 mL) followed by the slow addition of a sat. aq. $NaHCO_3$ solution (250 mL) until gas evolution ceased. The biphasic mixture was allowed to warm to RT and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 300 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 85:15) to afford alcohol **356** (0.28 g, 0.85 mmol, 77%) as a colourless oil. R_f = 0.27 (pet. ether/EtOAc, 85:15); $[\alpha]_D^{24}$ +11.5 (*c* = 2.78, $CHCl_3$); ν_{max} 3424, 2953, 2876, 1659, 1458, 1379, 1238, 1119, 1067, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (1H, ddd, *J* = 15.2, 11.0, 1.4 Hz, CH−C26), 5.82 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.54 (1H, dd, *J* = 15.2, 6.1 Hz, CH−C25), 4.18 (1H, app td, *J* = 6.1, 1.4 Hz, CH−C24), 4.08 (1H, app dtd, *J* = 7.9, 6.0, 3.2 Hz, CH−C20), 3.99−3.92 (1H, m, CH−C23), 3.64 (1H, ddd, *J* = 11.6, 6.9, 3.2 Hz, CH−C19), 3.46 (1H, app dt, *J* = 11.6, 6.0 Hz, CH−C19), 1.91 (1H, dd, *J* = 6.9, 6.0 Hz, OH−C19), 1.95−1.85 (2H, m, CH−C21, CH−C22), 1.77 (3H, br s, CH_3−C35), 1.76 (3H, br s, CH_3−C29), 1.81−1.69 (1H, m, CH−C22), 1.69−1.59 (1H, m, CH−C21), 0.95 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.61 (6H, q, *J* = 7.9 Hz, CH_2−TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5 (C−C28), 129.8 (CH−C25), 127.8 (CH−C26), 124.7 (CH−C27), 83.0 (CH−C23), 79.8 (CH−C20), 75.6 (CH−C24), 65.1 (CH_2−C19), 27.7 (CH_2−C22), 27.6 (CH_2−C21), 26.2 (CH_3−C35), 18.4 (CH_3−C29), 7.0 (CH_3−TES), 5.1 (CH_2−TES); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{18}H_{34}O_3SiNa$ 349.2169, found 349.2173, Δ 1.1 ppm.

5-(Tetrahydrofuran-2-yl)pent-3-yn-1-yl pivalate 358



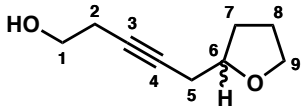
Chemical Formula: $C_{14}H_{22}O_3$
Molecular Weight: 238,32

To a solution of tetrahydrofurfuryl alcohol (0.24 mL, 2.5 mmol) in CH_2Cl_2 (25 mL) at −78 °C, was added 2,6-lutidine (0.85 mL, 7.3 mmol, 3.00 equiv.) and Tf_2O (0.43 mL, 2.6 mmol, 1.05 equiv.) sequentially. The resulting mixture was stirred at −78 °C for 30 min, diluted with pentane (25 mL) and a sat. aq. $NaHCO_3$ solution (25 mL) was added. The layers were separated and the aqueous phase was extracted with pentane (2 × 15 mL). The combined organic extracts were washed with a sat. aq. $CuSO_4$ solution (60 mL), brine (60 mL), dried over $MgSO_4$, filtered and concentrated. The residue was filtered rapidly through a short pad of silica gel (pentane/Et_2O, 50:50) to give the crude triflate which was used directly in the next step without further purification.

To a solution of *i*-Pr_2NH (0.34 mL, 2.5 mmol, 1.0 equiv.) in THF (12 mL) at 0 °C, was added *n*-BuLi (titrated at 2.28 M in hexanes, 1.1 mL, 2.5 mmol, 1.0 equiv.). The resulting mixture was stirred at 0 °C for 15 min, cooled to −78 °C, and known alkyne **357**[82] (0.34 g, 2.5 mmol, 1.0 equiv.) was added dropwise. The solution was stirred at −78 °C for 30 min, before adding the triflate as a solution in a 3:2 mixture of THF and HMPA (6 mL). The reaction mixture was stirred at −78 °C for 15 min, before the addition of a sat. aq. NH_4Cl solution (20 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/Et_2O, 90:10) to deliver alkyne **358** (0.39 g, 1.7 mmol, 68% over 2 steps) as a colourless oil. R_f = 0.35 (pet. ether/EtOAc, 90:10); ν_{max} 2970, 2872, 1730, 1481, 1283, 1152, 1069 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.12 (2H, t, *J* = 6.9 Hz, CH_2−C1), 3.98 (1H, app qd, *J* = 6.8, 5.4 Hz, CH−C6), 3.90 (1H, ddd, *J* = 8.3, 7.2, 6.2 Hz, CH−C9), 3.75 (1H, ddd, *J* = 8.3, 7.5, 6.4 Hz, CH−C9), 2.49 (2H, tt, *J* = 6.9, 2.4 Hz, CH_2−C2), 2.41 (1H, ddt, *J* = 16.5, 5.4, 2.4 Hz, CH−C5), 2.33 (1H, ddt, *J* = 16.5, 6.8, 2.4 Hz, CH−C5), 2.02 (1H, dddd, *J* = 12.1, 8.3, 6.8, 5.3 Hz, CH−C7), 1.97−1.82 (2H, m, CH_2−C8), 1.67 (1H, app ddt, *J* =

12.1, 8.5, 6.8 Hz, CH−C7), 1.20 (9H, s, CH_3−*t*-Bu Piv); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5 (C−Piv), 100.1 (C−C3), 78.5 (C−C4), 77.6 (CH−C6), 68.6 (CH_2−C9), 62.7 (CH_2−C1), 38.9 (C−*t*-Bu Piv), 30.8 (CH_2−C7), 27.3 (CH_3−*t*-Bu Piv), 25.9 (CH_2−C8), 25.7 (CH_2−C5), 19.4 (CH_2−C2); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{14}H_{22}O_3Na$ 261.1461, found 261.1462, Δ 0.4 ppm.

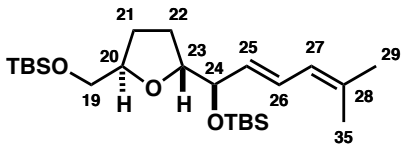
5-(Tetrahydrofuran-2-yl)pent-3-yn-1-ol 359



Chemical Formula: $C_9H_{14}O_2$
Molecular Weight: 154,21

To a solution of pivalate **358** (0.34 g, 1.4 mmol) in Et_2O (14 mL) at −78 °C, was added *i*-Bu_2AlH (1.0 M in CH_2Cl_2, 5.7 mL, 5.7 mmol, 4.0 equiv.) dropwise. The resulting solution was stirred at −78 °C for 30 min, before the dropwise addition of a sat. aq. potassium sodium tartrate solution (25 mL). The biphasic mixture was stirred vigorously at RT for 30 min. The layers were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 50:50) to afford alcohol **359** (0.17 g, 1.1 mmol, 78%) as a colourless oil. R_f = 0.27 (pet. ether/EtOAc, 50:50); ν_{max} 3389, 2932, 2874, 1422, 1182, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (1H, app p, *J* = 6.8 Hz, CH−C6), 3.90 (1H, ddd, *J* = 8.3, 7.1, 6.2 Hz, CH−C9), 3.76 (1H, ddd, *J* = 8.3, 7.4, 6.2 Hz, CH−C9), 3.68 (2H, t, *J* = 6.1 Hz, CH_2−C1), 2.46−2.37 (4H, m, CH_2−C2, CH_2−C5), 2.03 (1H, dddd, *J* = 11.8, 8.4, 6.8, 5.2 Hz, CH−C7), 2.00−1.84 (3H, m, OH−C1, CH_2−C8), 1.66 (1H, app ddt, *J* = 11.8, 8.3, 6.8 Hz, CH−C7); ^{13}C NMR (101 MHz, $CDCl_3$) δ 79.4 (C−C3), 78.0 (C−C4), 77.7 (CH−C6), 68.6 (CH_2−C9), 61.4 (CH_2−C1), 30.9 (CH_2−C7), 25.9 (CH_2−C8), 25.7 (CH_2−C5), 23.4 (CH_2−C2); HRMS (ESI+) $[M+Na]^+$ calcd for $C_9H_{14}O_2Na$ 177.0886, found 177.0883, Δ 1.4 ppm.

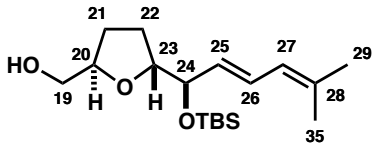
***tert*-Butyl(((2*R*,5*R*)-5-((*R*,*E*)-1-((*tert*-butyldimethylsilyl)oxy)-5-methylhexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)methoxy)dimethylsilane 364**



Chemical Formula: $C_{24}H_{48}O_3Si_2$
Molecular Weight: 440,81

To a solution of alcohol **353** (0.59 g, 1.8 mmol) in CH_2Cl_2 (18 mL) at −78 °C, were added 2,6-lutidine (0.54 mL, 4.7 mmol, 2.6 equiv.) and TBSOTf (0.54 mL, 2.3 mmol, 1.3 equiv.) sequentially. The resulting solution was stirred at −78 °C for 1 h, before the addition of water (18 mL) and the biphasic mixture was allowed to warm to RT. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 98:2) to deliver *bis*-TBS ether **364** (0.75 g, 1.7 mmol, 94%) as a colourless oil. R_f = 0.38 (pet. ether/EtOAc, 98:2); $[\alpha]_D^{25}$ +30.8 (*c* = 1.19, $CHCl_3$); ν_{max} 2955, 2928, 2857, 1472, 1462, 1387, 1362, 1254, 1125, 1088, 1005 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.46 (1H, ddd, *J* = 15.2, 11.0, 1.5 Hz, CH−C26), 5.83 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.56 (1H, dd, *J* = 15.2, 5.4 Hz, CH−C25), 4.23 (1H, app td, *J* = 5.4, 1.5 Hz, CH−C24), 4.02−3.95 (2H, m, CH−C20, CH−C23), 3.62 (1H, dd, *J* = 10.5, 4.7 Hz, CH−C19), 3.54 (1H, dd, *J* = 10.5, 5.4 Hz, CH−C19), 1.92−1.83 (2H, m, CH−C21, CH−C22), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.74−1.61 (2H, m, CH−C21, CH−C22), 0.90 (9H, s, CH_3−*t*-Bu TBS), 0.89 (9H, s, CH_3−*t*-Bu TBS), 0.06 (3H, s, CH_3−TBS), 0.05 (6H, s, 2 × CH_3−TBS), 0.04 (3H, s, CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.9 (C−C28), 130.0 (CH−C25), 127.4 (CH−C26), 124.9 (CH−C27), 82.9 (CH−C23), 80.1 (CH−C20), 75.1 (CH−C24), 66.1 (CH_2−C19), 28.5 (CH_2−C21), 26.8 (CH_2−C22), 26.1 (CH_3−C35), 26.1 (CH_3−*t*-Bu TBS), 26.0 (CH_3−*t*-Bu TBS), 18.5 (C−*t*-Bu TBS), 18.5 (C−*t*-Bu TBS), 18.4 (CH_3−C29), −4.5 (CH_3−TBS), −4.6 (CH_3−TBS), −5.1 (CH_3−TBS), −5.1 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{24}H_{48}O_3Si_2Na$ 463.3034, found 463.3019, Δ 3.2 ppm.

((2*R*,5*R*)-5-((*R*,*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-methylhexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)methanol 365



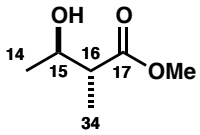
Chemical Formula: $C_{18}H_{34}O_3S_i$
Molecular Weight: 326,55

Note: The HF•Pyr stock solution was prepared by mixing HF•Pyr (1.0 mL, 70% HF in pyridine), pyridine (2.0 mL) and THF (5.0 mL).

To a solution of *bis*-TBS ether **364** (746 mg, 1.69 mmol) in THF (169 mL) at 0 °C, was added a stock solution of HF•Pyr (19 mL) and the resulting mixture was stirred for 24 h, after which more HF•Pyr (19 mL) was added. After another 36 h, the reaction was quenched by the slow addition of a sat. aq. Na_2CO_3 solution (60 mL) followed by the slow addition of a sat. aq. $NaHCO_3$ solution (540 mL) until gas evolution ceased. The biphasic mixture was allowed to warm to RT and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 400 mL) and the combined organic extracts were washed with brine (800 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 85:15) to afford alcohol **365** (474 mg, 1.45 mmol, 86%) as a colourless oil. R_f = 0.23 (pet. ether/EtOAc, 85:15); $[\alpha]_D^{26}$ +18.6 (*c* = 0.765, $CHCl_3$); ν_{max} 3449, 2955, 2928, 2857, 1659, 1472, 1379, 1362, 1254, 1119, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.47 (1H, ddd, *J* = 15.2, 11.0, 1.4 Hz, CH−C26), 5.83 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.55 (1H, dd, *J* = 15.2, 5.7 Hz, CH−C25), 4.20 (1H, app td, *J* = 5.7, 1.4 Hz, CH−C24), 4.07 (1H, app dtd, *J* = 8.0, 6.0, 3.3 Hz, CH−C20), 4.00−3.93 (1H, m, CH−C23), 3.64 (1H, ddd, *J* = 11.6, 6.9, 3.3 Hz, CH−C19), 3.46 (1H, app dt, *J* = 11.6, 6.0 Hz, CH−C19), 1.94−1.85 (2H, m, CH−C21, CH−C22), 1.89 (1H, dd, *J* = 6.9, 6.0 Hz, OH−C19), 1.77 (3H, br s, CH_3−C35), 1.81−1.71 (1H, m, CH−C22), 1.75 (3H, br s, CH_3−C29), 1.69−1.60 (1H, m, CH−C21), 0.91 (9H, s, CH_3−*t*-Bu TBS), 0.07 (3H, s, CH_3−TBS), 0.05 (3H, s, CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.4 (C−C28), 129.8 (CH−C25), 127.7 (CH−C26), 124.8 (CH−C27), 82.9 (CH−C23), 79.8 (CH−C20), 75.5 (CH−C24), 65.1 (CH_2−C19), 27.6 (CH_2−C21), 27.5 (CH_2−C22), 26.2 (CH_3−C35), 26.0 (CH_3−*t*-Bu TBS), 18.5 (C−*t*-Bu TBS), 18.4 (CH_3−C29), −4.4 (CH_3−TBS), −4.6

(CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{18}H_{34}O_3SiNa$ 349.2169, found 349.2161, Δ 2.5 ppm.

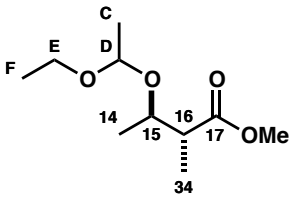
Methyl (2*R*,3*R*)-3-hydroxy-2-methylbutanoate 367[83]



Chemical Formula: $C_6H_{12}O_3$
Molecular Weight: 132,16

To a solution of *i*-Pr_2NH (16.8 mL, 120 mmol, 2.0 equiv.) in THF (120 mL) at 0 °C, was added *n*-BuLi (titrated at 2.32 M in hexanes, 51.7 mL, 120 mmol, 2.0 equiv.) dropwise over 10 min. The solution was stirred at 0 °C for 10 min before being cooled to −78 °C, and (*R*)-methyl-3-hydroxybutanoate (6.7 mL, 60 mmol) was slowly added over 5 min. The resulting mixture was stirred for 30 min and a solution of MeI (4.2 mL, 68 mmol, 1.1 equiv.) in HMPA (20 mL) was added dropwise over 15 min. The reaction mixture was stirred at −78 °C for 15 min, warmed to 0 °C and stirred for 30 min. The reaction was quenched by the addition of a cold sat. aq. NH_4Cl solution (100 mL). The layers were separated and the aqueous phase was extracted with Et_2O (4 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 75:25) to afford *β*-hydroxy ester **367** (5.1 g, 39 mmol, 65%) as a colourless oil. R_f = 0.37 (pet. ether/EtOAc, 60:40); $[\alpha]_D^{26}$ −27.0 (*c* = 2.29, $CHCl_3$) [lit[83] $[\alpha]_D^{26}$ −31.4 (*c* = 1.21, $CHCl_3$)]; ν_{max} 3435, 2976, 2953, 1717, 1437, 1379, 1261, 1198, 1173, 1111, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.88 (1H, dqd, *J* = 7.2, 6.4, 5.8 Hz, CH−C15), 3.72 (3H, s, CH_3−CO_2Me), 2.61 (1H, d, *J* = 5.8 Hz, OH−C15), 2.46 (1H, app p, *J* = 7.2 Hz, CH−C16), 1.22 (3H, d, *J* = 6.4 Hz, CH_3−C14), 1.19 (3H, d, *J* = 7.2 Hz, CH_3−C34); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5 (C−C17), 69.6 (CH−C15), 51.9 (CH_3−CO_2Me), 47.0 (CH−C16), 20.9 (CH_3−C14), 14.3 (CH_3−C34); HRMS (CI+) $[M+H]^+$ calcd for $C_6H_{13}O_3$ 133.0865, found 133.0867, Δ 1.7 ppm.

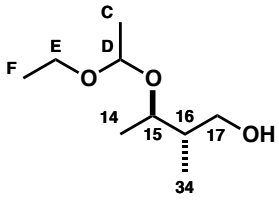
(2*R*,3*R*)-Methyl 3-((1*RS*-ethoxy)ethoxy)-2-methylbutanoate 368



Chemical Formula: $C_{10}H_{20}O_4$
Molecular Weight: 204,26

To a solution of *β*-hydroxy ester **367** (2.0 g, 15 mmol) in CH_2Cl_2 (150 mL) at 0 °C, were added ethyl vinyl ether (4.4 mL, 45 mmol, 3.0 equiv.) and PPTS (0.38 g, 1.5 mmol, 10 mol %) sequentially. The resulting mixture was stirred at 0 °C for 5 min and at RT for 1.5 h, then diluted with Et_2O (450 mL) and washed with brine (350 mL). The layers were separated and the organic phase was dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 95:5) to afford EE acetal **368** (2.9 g, 14 mmol, 94%) as a 1.1:1 mixture of diastereomers, as a colourless oil. R_f = 0.38 (pet. ether/EtOAc, 90:10); $[\alpha]_D^{26}$ −25.2 (*c* = 1.61, $CHCl_3$); ν_{max} 2978, 2938, 1738, 1435, 1379, 1335, 1260, 1200, 1126, 1076, 1055 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.75 (1.0H, q, *J* = 5.4 Hz, CH−C_D'), 4.69 (1.1H, q, *J* = 5.3 Hz, CH−C_D), 3.96 (1.0H, dq, *J* = 7.3, 6.3 Hz, CH−C15'), 3.87 (1.1H, dq, *J* = 7.3, 6.3 Hz, CH−C15), 3.67 (6.3H, s, CH_3−CO_2Me, CH_3−CO_2Me'), 3.61 (1.0H, dq, *J* = 9.2, 7.1 Hz, CH−C_E'), 3.61 (1.1H, dq, *J* = 9.2, 7.1 Hz, CH−C_E), 3.48 (1.1H, dq, *J* = 9.2, 7.1 Hz, CH−C_E), 3.41 (1.0H, dq, *J* = 9.2, 7.1 Hz, CH−C_E'), 2.64 (1.0H, app p, *J* = 7.3 Hz, CH−C16'), 2.60 (1.1H, app p, *J* = 7.3 Hz, CH−C16), 1.29 (3.0H, d, *J* = 5.4 Hz, CH_3−C_C'), 1.24 (3.3H, d, *J* = 5.3 Hz, CH_3−C_C), 1.21−1.16 (9.6H, m, CH_3−C14, CH_3−C_F, CH_3−C_F'), 1.13 (3.0H, d, *J* = 7.3 Hz, CH_3−C34'), 1.12 (3.0H, d, *J* = 6.3 Hz, CH_3−C14'), 1.10 (3.3H, d, *J* = 7.3 Hz, CH_3−C34); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6 (C−C17), 175.5 (C−C17'), 100.5 (CH−C_D), 98.3 (CH−C_D'), 75.2 (CH−C15), 72.5 (CH−C15'), 60.3 (CH_2−C_E'), 60.1 (CH_2−C_E), 51.7 (CH_3−CO_2Me, CH_3−CO_2Me'), 46.0 (CH−C16'), 46.0 (CH−C16), 20.8 (CH_3−C_C'), 20.6 (CH_3−C_C), 18.2 (CH_3−C14), 17.1 (CH_3−C14'), 15.5 (CH_3−C_F), 15.4 (CH_3−C_F'), 12.6 (CH_3−C34), 12.6 (CH_3−C34'); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{10}H_{20}O_4Na$ 227.1254, found 227.1245, Δ 3.9 ppm.

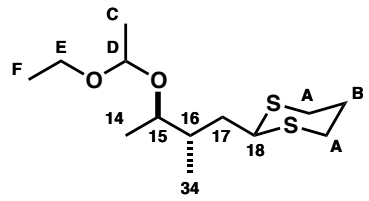
(2*S*,3*R*)-3-((1*RS*-Ethoxy)ethoxy)-2-methylbutan-1-ol 369



Chemical Formula: $C_9H_{20}O_3$
Molecular Weight: 176,25

To a suspension of $LiAlH_4$ (0.62 g, 16 mmol, 2.5 equiv.) in Et_2O (55 mL) at 0 °C, was slowly added a solution of methyl ester **368** (1.3 g, 6.6 mmol) in Et_2O (11 mL). The resulting mixture was stirred at 0 °C for 30 min. The reaction was quenched by the dropwise addition of water (0.62 mL), a 15% NaOH aq. solution (0.62 mL) and water (1.9 mL), sequentially, at 0 °C. The mixture was stirred vigorously at RT for 30 min and filtered through a cotton plug to remove the white solids. The filtrate was concentrated and the crude material was used directly in the next step without further purification. R_f = 0.46 (pet. ether/EtOAc, 60:40); ν_{max} 3437, 2976, 2880, 1449, 1377, 1337, 1126, 1078, 1051 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.71 (1.1H, q, *J* = 5.3 Hz, CH−C_D), 4.69 (1.0H, q, *J* = 5.2 Hz, CH−C_D'), 3.84 (1.0H, ddd, *J* = 11.2, 6.3, 3.3 Hz, CH−C17'), 3.70−3.61 (3.2H, m, CH−C15', CH−C17, CH−C_E), 3.61−3.44 (6.3H, m, CH−C15, CH−C17, CH−C17', CH−C_E, CH_2−C_E'), 3.15 (1.0H, app t, *J* = 6.3 Hz, OH−C17'), 2.57−2.54 (1.1H, m, OH−C17), 1.73 (1.1H, app hd, *J* = 6.9, 3.9 Hz, CH−C16), 1.69−1.59 (1.0H, m, CH−C16'), 1.33 (3.3H, d, *J* = 5.3 Hz, CH_3−C_C), 1.31 (3.0H, d, *J* = 5.2 Hz, CH_3−C_C'), 1.24 (3.3H, d, *J* = 6.2 Hz, CH_3−C14), 1.22 (3.0H, t, *J* = 7.0 Hz, CH_3−C_F'), 1.20 (3.3H, t, *J* = 7.1 Hz, CH_3−C_F), 1.17 (3.0H, d, *J* = 6.1 Hz, CH_3−C14'), 0.94 (3.0H, d, *J* = 7.0 Hz, CH_3−C34'), 0.93 (3.3H, d, *J* = 6.9 Hz, CH_3−C34); ^{13}C NMR (126 MHz, $CDCl_3$) δ 100.3 (CH−C_D), 98.4 (CH−C_D'), 78.1 (CH−C15), 75.8 (CH−C15'), 66.4 (CH_2−C17), 66.0 (CH_2−C17'), 61.3 (CH_2−C_E'), 60.6 (CH_2−C_E), 41.5 (CH−C16'), 41.2 (CH−C16), 20.8 (CH_3−C_C'), 20.6 (CH_3−C_C), 19.1 (CH_3−C14), 18.4 (CH_3−C14'), 15.4 (CH_3−C_F'), 15.4 (CH_3−C_F), 14.6 (CH_3−C34'), 14.0 (CH_3−C34); HRMS (ESI+) $[M+Na]^+$ calcd for $C_9H_{20}O_3Na$ 199.1305, found 199.1304, Δ 0.2 ppm.

2-((2*S*,3*R*)-3-((1*RS*-Ethoxy)ethoxy)-2-methylbutyl)-1,3-dithiane 362



Chemical Formula: $C_{13}H_{26}O_2S_2$
Molecular Weight: 278,47

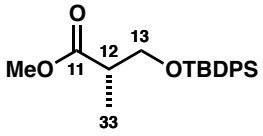
Note: The alkyl iodide intermediate is light-sensitive and all manipulations were performed in the dark.

To a solution of crude alcohol **369** in THF (42 mL) at 0 °C, were added PPh_3 (3.3 g, 13 mmol, 2.0 equiv.) and imidazole (1.7 g, 25 mmol, 4.0 equiv.) sequentially. The resulting mixture was stirred at 0 °C for 10 min, before the portionwise addition of iodine (3.2 g, 13 mmol, 2.0 equiv.). The brown solution was stirred at 0 °C for 10 min and at RT for 1 h. The reaction was quenched by the addition of a sat. aq. $Na_2S_2O_3$ solution (35 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 35 mL) and the combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The residue was filtered rapidly through a short pad of silica gel (pet. ether/EtOAc, 95:5) to give the crude alkyl iodide which was used directly in the next step without further purification.

To a solution of 1,3-dithiane (1.5 g, 12 mmol, 2.0 equiv.) in a 5:1 mixture of THF and HMPA (35 mL) at −20 °C, was added *n*-BuLi (titrated at 2.35 M in hexanes, 5.0 mL, 12 mmol, 1.9 equiv.) dropwise. The resulting dark yellow solution was stirred at −20 °C for 1 h, before the slow addition of a solution of the crude iodide (dried by azeotropic distillation with benzene (4 ×)) in THF (8 mL). The reaction mixture was stirred at −20 °C for 1.5 h, before the slow addition of a sat. aq. NH_4Cl solution (45 mL) and the biphasic mixture was allowed to warm to RT. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 45 mL). The combined organic extracts were washed with brine (120 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 90:10) to deliver dithiane **362** (1.3 g, 4.6 mmol, 71% over 3 steps) as a 1.1:1 mixture of diastereomers, as a colourless oil. R_f = 0.45 (pet. ether/EtOAc, 90:10); $[\alpha]_D^{24}$ −6.34 (*c* = 1.96, $CHCl_3$); ν_{max} 2975, 2933, 2898, 1424, 1377, 1276, 1127, 1079, 1056 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ

4.74 (1.0H, q, *J* = 5.3 Hz, CH−C_D'), 4.71 (1.1H, q, *J* = 5.3 Hz, CH−C_D), 4.08 (1.0H, dd, *J* = 9.4, 5.6 Hz, CH−C18'), 4.07 (1.1H, dd, *J* = 9.3, 5.6 Hz, CH−C18), 3.67−3.55 (4.2H, m, CH−C15, CH−C15', CH−C_E, CH−C_E'), 3.49 (1.1H, qd, *J* = 7.1, 4.0 Hz, CH−C_E), 3.47 (1.0H, qd, *J* = 7.1, 4.0 Hz, CH−C_E'), 2.94−2.78 (8.4H, m, 2 × CH_2−C_A, 2 × CH_2−C_A'), 2.16−2.09 (2.1H, m, CH−C_B, CH−C_B'), 2.05−1.96 (2.1H, m, CH−C16, CH−C16'), 1.92−1.82 (3.1H, m, CH−C17', CH−C_B, CH−C_B'), 1.79 (1.1H, ddd, *J* = 14.1, 9.3, 4.8 Hz, CH−C17), 1.53 (1.1H, ddd, *J* = 14.1, 9.2, 5.6 Hz, CH−C17), 1.52 (1.0H, ddd, *J* = 14.2, 9.2, 5.6 Hz, CH−C17'), 1.30 (3.3H, d, *J* = 5.3 Hz, CH_3−C_C), 1.29 (3.0H, d, *J* = 5.3 Hz, CH_3−C_C'), 1.20 (3.3H, t, *J* = 7.1 Hz, CH_3−C_F), 1.19 (3.0H, t, *J* = 7.1 Hz, CH_3−C_F'), 1.11 (3.3H, d, *J* = 6.4 Hz, CH_3−C14), 1.06 (3.0H, d, *J* = 6.3 Hz, CH_3−C14'), 0.95 (3.0H, d, *J* = 6.8 Hz, CH_3−C34'), 0.92 (3.3H, d, *J* = 6.8 Hz, CH_3−C34); ^{13}C NMR (126 MHz, $CDCl_3$) δ 99.6 (CH−C_D), 97.9 (CH−C_D'), 76.2 (CH−C15), 74.3 (CH−C15'), 60.1 (CH_2−C_E), 60.1 (CH_2−C_E'), 45.9 (CH−C18'), 45.8 (CH−C18), 38.6 (CH_2−C17), 38.5 (CH_2−C17'), 35.4 (CH−C16'), 34.6 (CH−C16), 30.7 (CH_2−C_A, CH_2−C_A'), 30.4 (CH_2−C_A), 30.4 (CH_2−C_A'), 26.3 (CH_2−C_B'), 26.2 (CH_2−C_B), 20.8 (CH_3−C_C'), 20.8 (CH_3−C_C), 16.8 (CH_3−C14), 16.1 (CH_3−C14'), 15.5 (CH_3−C_F, CH_3−C_F'), 15.0 (CH_3−C34'), 14.4 (CH_3−C34); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{13}H_{26}O_2S_2Na$ 301.1266, found 301.1258, Δ 2.7 ppm.

(*S*)-Methyl 3-((*tert*-butyldiphenylsilyl)oxy)-2-methylpropanoate 371[85]

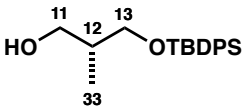


Chemical Formula: $C_{21}H_{28}O_3Si$
Molecular Weight: 356,53

To a solution of methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (1.0 g, 8.5 mmol) in CH_2Cl_2 (11 mL) at 0 °C, were added imidazole (0.75 g, 11 mmol, 1.3 equiv.) and TBDPSCl (2.2 mL, 8.5 mmol, 1.0 equiv.) sequentially. The resulting mixture was stirred at RT for 18 h, before the addition of water (20 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 98:2) to afford TBDPS ether **371** (2.9 g, 8.2 mmol, 97%) as a colourless oil. R_f = 0.23 (pet. ether/EtOAc, 98:2); $[\alpha]_D^{20}$ +16.9 (*c*

= 1.44, $CHCl_3$) [lit[85] $[\alpha]_D^{20}$ +16.9 (*c* = 1.11, $CHCl_3$)]; ν_{max} 2932, 2859, 1742, 1472, 1429, 1389, 1362, 1258, 1200, 1111, 1088, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70−7.62 (4H, m, CH−Ar TBDPS), 7.45−7.36 (6H, m, CH−Ar TBDPS), 3.82 (1H, dd, *J* = 9.8, 7.0 Hz, CH−C13), 3.72 (1H, dd, *J* = 9.8, 5.8 Hz, CH−C13), 3.69 (3H, s, CH_3−CO_2Me), 2.72 (1H, app pd, *J* = 7.0, 5.8 Hz, CH−C12), 1.16 (3H, d, *J* = 7.0 Hz, CH_3−C33), 1.03 (9H, s, CH_3−*t*-Bu TBDPS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5 (C−C11), 135.7 (CH−Ar TBDPS), 135.7 (CH−Ar TBDPS), 133.7 (C−Ar TBDPS), 133.6 (C−Ar TBDPS), 129.8 (CH−Ar TBDPS), 127.8 (CH−Ar TBDPS), 66.1 (CH_2−C13), 51.7 (CH_3−CO_2Me), 42.5 (CH−C12), 26.9 (CH_3−*t*-Bu TBDPS), 19.4 (C−*t*-Bu TBDPS), 13.6 (CH_3−C33); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{21}H_{28}O_3SiNa$ 379.1700, found 379.1687, Δ 3.3 ppm.

(*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropan-1-ol 372[105]

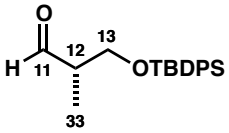


Chemical Formula: $C_{20}H_{28}O_2Si$
Molecular Weight: 328,52

To a solution of methyl ester **371** (2.9 g, 8.2 mmol) in CH_2Cl_2 (41 mL) at −78 °C, was added *i*-Bu_2AlH (1.0 M in hexane, 18 mL, 18 mmol, 2.2 equiv.) dropwise. The resulting solution was stirred at −78 °C for 5 min and at RT for 6 h. The reaction mixture was cooled to 0 °C and MeOH (5 mL) was added dropwise, followed by a sat. aq. potassium sodium tartrate solution (50 mL). The biphasic mixture was stirred vigorously at RT for 10 h and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 90:10) to afford alcohol **372** (2.3 g, 7.0 mmol, 86%) as a colourless oil. R_f = 0.28 (pet. ether/EtOAc, 90:10); $[\alpha]_D^{24}$ +4.75 (*c* = 1.26, $CHCl_3$) [lit[105] $[\alpha]_D^{22}$ +4.7 (*c* = 0.89, $CHCl_3$)]; ν_{max} 3379, 2931, 2858, 1473, 1428, 1391, 1112, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (4H, m, CH−Ar TBDPS), 7.48−7.36 (6H, m, CH−Ar TBDPS), 3.73 (1H, dd, *J* = 10.0, 4.5 Hz, CH−C13), 3.68 (2H, dd, *J* = 6.2, 5.3 Hz, CH_2−C11), 3.60 (1H, dd, *J* = 10.0, 7.7 Hz, CH−C13), 2.53−2.49 (1H, br s, OH−C11), 2.06−1.94 (1H, m, CH−C12), 1.06 (9H, s, CH_3−*t*-Bu TBDPS), 0.83 (3H,

d, *J* = 7.0 Hz, CH_3−C33); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.7 (CH−Ar TBDPS), 135.7 (CH−Ar TBDPS), 133.4 (C−Ar TBDPS), 133.3 (C−Ar TBDPS), 129.9 (CH−Ar TBDPS), 127.9 (CH−Ar TBDPS), 68.9 (CH_2−C11), 67.8 (CH_2−C13), 37.5 (CH−C12), 27.0 (CH_3−*t*-Bu TBDPS), 19.3 (C−*t*-Bu TBDPS), 13.3 (CH_3−C33); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{20}H_{28}O_2SiNa$ 351.1751, found 351.1734, Δ 4.9 ppm.

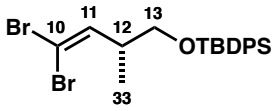
(*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpropanal 373[85]



Chemical Formula: $C_{20}H_{26}O_2Si$
Molecular Weight: 326,50

To a solution of alcohol **372** (1.8 g, 5.5 mmol) in CH_2Cl_2 (37 mL) at RT, was added DMP (2.7 g, 6.3 mmol, 1.15 equiv.) portionwise. The resulting mixture was stirred at RT for 1.5 h, before the addition of a sat. aq. $Na_2S_2O_3$ solution (50 mL). The layers were separated and the organic layer was washed with a sat. aq. $NaHCO_3$ solution (50 mL). The aqueous phase was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 95:5) to deliver aldehyde **373** (1.6 g, 4.9 mmol, 88%) as a colourless oil. R_f = 0.41 (pet. ether/EtOAc, 90:10); $[\alpha]_D^{27}$ +24.0 (*c* = 1.27, $CHCl_3$) [lit[85] $[\alpha]_D^{20}$ +20.0 (*c* = 2.42, $CHCl_3$)]; ν_{max} 2932, 2859, 1736, 1472, 1427, 1111, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (1H, d, *J* = 1.6 Hz, CH−C11), 7.67−7.62 (4H, m, CH−Ar TBDPS), 7.47−7.37 (6H, m, CH−Ar TBDPS), 3.90 (1H, dd, *J* = 10.4, 5.0 Hz, CH−C13), 3.84 (1H, dd, *J* = 10.4, 6.4 Hz, CH−C13), 2.57 (1H, qddd, *J* = 7.0, 6.4, 5.0, 1.6 Hz, CH−C12), 1.10 (3H, d, *J* = 7.0 Hz, CH_3−C33), 1.04 (9H, s, CH_3−*t*-Bu TBDPS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.6 (C−C11), 135.7 (CH−Ar TBDPS), 133.3 (C−Ar TBDPS), 130.0 (CH−Ar TBDPS), 130.0 (CH−Ar TBDPS), 127.9 (CH−Ar TBDPS), 64.3 (CH_2−C13), 49.0 (CH−C12), 26.9 (CH_3−*t*-Bu TBDPS), 19.4 (C−*t*-Bu TBDPS), 10.5 (CH_3−C33); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{20}H_{26}O_2SiNa$ 349.1594, found 349.1579, Δ 4.4 ppm.

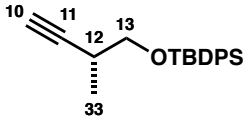
(*R*)-*tert*-Butyl((4,4-dibromo-2-methylbut-3-en-1-yl)oxy)diphenylsilane 374[106]



Chemical Formula: $C_{21}H_{26}Br_2OSi$
Molecular Weight: 482,32

To a solution of PPh_3 (5.1 g, 20 mmol, 4.0 equiv.) in CH_2Cl_2 (35 mL) at RT, was added CBr_4 (3.2 g, 9.7 mmol, 2.0 equiv.) portionwise. The resulting mixture was cooled to −78 °C, before the addition of a solution of aldehyde **373** (1.6 g, 4.9 mmol) and Et_3N (0.68 mL, 4.9 mmol, 1.0 equiv.) in CH_2Cl_2 (15 mL). The yellow suspension was stirred at −78 °C for 30 min and at RT for 1 h, and pet. ether (130 mL) was added. The suspension was stirred at RT for 10 min, filtered through a pad of celite and the filter cake was washed with pet. ether (3 × 45 mL). The filtrate was concentrated and the crude material was purified by silica gel chromatography (pet. ether/Et_2O, 100:1) to deliver dibromo olefin **374** (2.2 g, 4.5 mmol, 93%) as a colourless oil. R_f = 0.41 (pet. ether/EtOAc, 90:10); $[\alpha]_D^{25}$ −12.5 (*c* = 1.25, $CHCl_3$) [lit[106] $[\alpha]_D^{25}$ −14 (*c* = 0.58, $CHCl_3$)]; ν_{max} 3071, 2930, 2859, 1616, 1589, 1472, 1427, 1389, 1111, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70−7.62 (4H, m, CH−Ar TBDPS), 7.47−7.36 (6H, m, CH−Ar TBDPS), 6.27 (1H, d, *J* = 9.3 Hz, CH−C11), 3.57 (1H, dd, *J* = 9.9, 5.8 Hz, CH−C13), 3.53 (1H, dd, *J* = 9.9, 6.1 Hz, CH−C13), 2.75−2.65 (1H, m, CH−C12), 1.06 (9H, s, CH_3−*t*-Bu TBDPS), 1.04 (3H, d, *J* = 6.8 Hz, CH_3−C33); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.6 (CH−C11), 135.8 (CH−Ar TBDPS), 135.8 (CH−Ar TBDPS), 133.7 (C−Ar TBDPS), 133.6 (C−Ar TBDPS), 129.8 (CH−Ar TBDPS), 129.8 (CH−Ar TBDPS), 127.8 (CH−Ar TBDPS), 88.8 (C−C10), 66.9 (CH_2−C13), 41.2 (CH−C12), 27.0 (CH_3−*t*-Bu TBDPS), 19.4 (C−*t*-Bu TBDPS), 15.7 (CH_3−C33); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{21}H_{26}OSi^{79}Br^{81}BrNa$ 504.9991, found 504.9975, Δ 3.3 ppm.

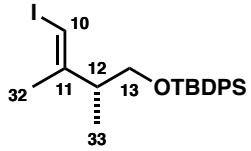
(*R*)-*tert*-Butyl((2-methylbut-3-yn-1-yl)oxy)diphenylsilane 375[86]



Chemical Formula: $C_{21}H_{26}OSi$
Molecular Weight: 322,52

To a solution of dibromo olefin **374** (1.7 g, 3.6 mmol) in THF (36 mL) at −78 °C, was added *n*-BuLi (titrated at 2.40 M in hexanes, 3.0 mL, 7.3 mmol, 2.05 equiv.) dropwise. The resulting mixture was stirred at −78 °C for 1.5 h, before the addition of a sat. aq. NH_4Cl solution (30 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (120 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/Et_2O, 100:1) to afford alkyne **375** (1.1 g, 3.5 mmol, 98%) as a colourless oil. R_f = 0.26 (pet. ether); $[\alpha]_D^{25}$ +5.55 (*c* = 1.21, $CHCl_3$) [lit[86] $[\alpha]_D^{25}$ +5.6 (*c* = 1.0, $CHCl_3$)]; ν_{max} 3308, 2932, 2859, 1589, 1472, 1427, 1389, 1113, 1018 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70−7.65 (4H, m, CH−Ar TBDPS), 7.45−7.35 (6H, m, CH−Ar TBDPS), 3.73 (1H, dd, *J* = 9.6, 5.7 Hz, CH−C13), 3.55 (1H, dd, *J* = 9.6, 7.6 Hz, CH−C13), 2.70−2.62 (1H, m, CH−C12), 2.03 (1H, d, *J* = 2.5 Hz, CH−C10), 1.23 (3H, d, *J* = 6.9 Hz, CH_3−C33), 1.06 (9H, s, CH_3−*t*-Bu TBDPS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.8 (CH−Ar TBDPS), 135.8 (CH−Ar TBDPS), 133.7 (C−Ar TBDPS), 133.7 (C−Ar TBDPS), 129.8 (CH−Ar TBDPS), 127.8 (CH−Ar TBDPS), 86.7 (C−C11), 69.2 (CH−C10), 67.6 (CH_2−C13), 29.0 (CH−C12), 27.0 (CH_3−*t*-Bu TBDPS), 19.5 (C−*t*-Bu TBDPS), 17.5 (CH_3−C33); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{21}H_{26}OSiNa$ 345.1645, found 345.1630, Δ 4.5 ppm.

(*R*,*E*)-*tert*-Butyl((4-iodo-2,3-dimethylbut-3-en-1-yl)oxy)diphenylsilane 376



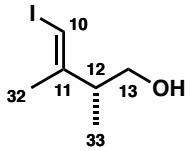
Chemical Formula: $C_{22}H_{29}IOSi$
Molecular Weight: 464,46

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

To a solution of Cp_2ZrCl_2 (1.0 g, 3.4 mmol, 1.5 equiv.) in 1,2-dichloroethane (13 mL) at RT, was added $AlMe_3$ (2.0 M in hexanes, 4.6 mL, 9.2 mmol, 4.0 equiv.) dropwise. The resulting yellow solution was stirred at RT for 30 min, before the dropwise addition of a solution of alkyne **375** (0.74 g, 2.3 mmol) in 1,2-dichloroethane (6 mL). The reaction mixture was stirred at RT for 24 h and cooled to −30 °C. A solution of iodine (1.2 g, 4.6 mmol, 2.0 equiv.) in THF (10 mL) was added dropwise, until the red-brown color remained. The solution was stirred at −30 °C for 30 min, before the dropwise addition of a sat. aq. potassium sodium tartrate solution (50 mL) and CH_2Cl_2 (25 mL). The biphasic mixture was stirred vigorously at RT for 1 h and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 75 mL) and the combined organic extracts were washed with brine (250 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/Et_2O, 100:1) to afford vinyl iodide **376** (1.0 g, 2.2 mmol, 96%) as a colourless oil. R_f = 0.32 (pet. ether); $[\alpha]_D^{25}$ +9.3 (*c* = 0.90, $CHCl_3$); ν_{max} 3071, 2961, 2930, 2859, 1472, 1427, 1389, 1271, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.61 (4H, m, CH−Ar TBDPS), 7.46−7.35 (6H, m, CH−Ar TBDPS), 5.96 (1H, app p, *J* = 1.1 Hz, CH−C10), 3.56 (1H, dd, *J* = 10.0, 7.0 Hz, CH−C13), 3.53 (1H, dd, *J* = 10.0, 6.2 Hz, CH−C13), 2.65−2.54 (1H, m, CH−C12), 1.70 (3H, d, *J* = 1.1 Hz, CH_3−C32), 1.04 (9H, s, CH_3−*t*-Bu TBDPS), 1.01 (3H, d, *J* = 6.9 Hz, CH_3−C33); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.7 (C−C11), 135.8 (CH−Ar TBDPS), 135.8 (CH−Ar TBDPS), 133.9 (C−Ar TBDPS), 133.8 (C−Ar TBDPS), 129.8 (CH−Ar TBDPS), 129.8 (CH−Ar TBDPS), 127.8 (CH−Ar TBDPS), 127.8 (CH−Ar TBDPS), 76.6 (CH−C10), 66.8 (CH_2−C13), 45.7 (CH−C12), 27.0 (CH_3−*t*-Bu TBDPS), 21.7 (CH_3−C32), 19.4 (C−*t*-Bu TBDPS), 15.7 (CH_3−C33); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{22}H_{29}IOSiNa$

487.0925, found 487.0911, Δ 2.8 ppm.

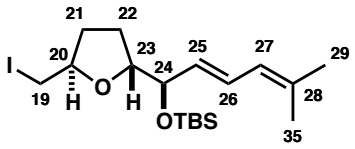
(*R*,*E*)-4-Iodo-2,3-dimethylbut-3-en-1-ol 377



Chemical Formula: $C_6H_{11}IO$
Molecular Weight: 226,06

To a solution of TBS ether **376** (1.0 g, 2.2 mmol) in THF (22 mL) at 0 °C, was added TBAF (1.0 M in THF, 3.3 mL, 3.3 mmol, 1.5 equiv.) dropwise. The resulting solution was stirred at RT for 1 h, before the addition of a 1:1 mixture of a sat. aq. NH_4Cl solution and water (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 80:20) to afford alcohol **377** (0.46 g, 2.0 mmol, 92%) as a colourless oil. R_f = 0.34 (pet. ether/EtOAc, 80:20); $[\alpha]_D^{24}$ +12.0 (*c* = 5.38, $CHCl_3$); ν_{max} 3329, 2963, 2930, 2874, 1613, 1452, 1377, 1267, 1157, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.08−6.05 (1H, m, CH−C10), 3.58−3.47 (2H, m, CH_2−C13), 2.66−2.58 (1H, m, CH−C12), 1.81 (3H, d, *J* = 1.1 Hz, CH_3−C32), 1.35−1.27 (1H, m, OH−C13), 1.04 (3H, d, *J* = 6.9 Hz, CH_3−C33); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1 (C−C11), 77.1 (CH−C10), 65.5 (CH_2−C13), 46.1 (CH−C12), 21.2 (CH_3−C32), 15.6 (CH_3−C33); HRMS (ESI+) $[M+Na]^+$ calcd for $C_6H_{11}IONa$ 248.9747, found 248.9755, Δ 3.4 ppm.

***tert*-Butyl(((*R*,*E*)-1-((2*R*,5*R*)-5-(iodomethyl)tetrahydrofuran-2-yl)-5-methylhexa-2,4-dien-1-yl)oxy)dimethylsilane 361**

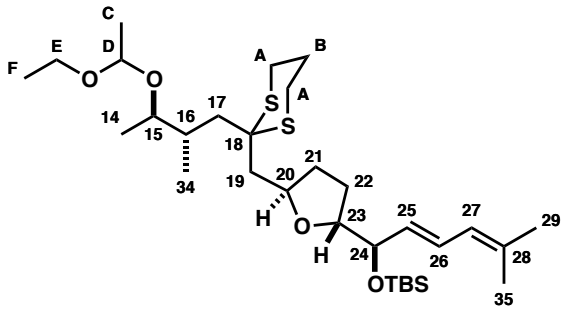


Chemical Formula: $C_{18}H_{33}IO_2Si$
Molecular Weight: 436,44

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

To a solution of alcohol **365** (0.25 g, 0.76 mmol) in THF (7.6 mL) at 0 °C, were added PPh_3 (337 mg, 1.29 mmol, 1.7 equiv.) and imidazole (154 mg, 2.27 mmol, 3.0 equiv.) sequentially. The resulting mixture was stirred at 0 °C for 10 min, before the portionwise addition of iodine (288 mg, 1.13 mmol, 1.5 equiv.). The brown solution was stirred at 0 °C for 10 min and at RT for 2 h. The reaction was quenched by the addition of a sat. aq. $Na_2S_2O_3$ solution (8 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 8 mL) and the combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue was filtered rapidly through a short pad of silica gel (pet. ether/EtOAc, 95:5) to give the crude alkyl iodide **361** which was used directly in the next step without further purification. R_f = 0.32 (pet. ether/EtOAc, 98:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (1H, ddd, *J* = 15.2, 11.1, 1.4 Hz, CH−C26), 5.83 (1H, dm, *J* = 11.1 Hz, CH−C27), 5.53 (1H, dd, *J* = 15.2, 5.6 Hz, CH−C25), 4.22 (1H, app td, *J* = 5.6, 1.4 Hz, CH−C24), 4.08 (1H, app td, *J* = 7.1, 5.6 Hz, CH−C23), 4.03 (1H, app tdd, *J* = 7.3, 6.2, 4.8 Hz, CH−C20), 3.25 (1H, dd, *J* = 9.8, 4.8 Hz, CH−C19), 3.16 (1H, dd, *J* = 9.8, 7.3 Hz, CH−C19), 2.11 (1H, dddd, *J* = 12.3, 8.5, 6.2, 4.1 Hz, CH−C21), 1.95 (1H, dddd, *J* = 12.6, 8.5, 7.1, 4.1 Hz, CH−C22), 1.80 (1H, app dtd, *J* = 12.6, 8.5, 7.1 Hz, CH−C22), 1.78 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.62 (1H, app dtd, *J* = 12.3, 8.5, 7.3 Hz, CH−C21), 0.90 (9H, s, CH_3−*t*-Bu TBS), 0.07 (3H, s, CH_3−TBS), 0.05 (3H, s, CH_3−TBS).

***tert*-Butyl(((1*R*,*E*)-1-((2*R*,5*R*)-5-((2-((2*S*,3*R*)-3-((1*RS*-ethoxy)ethoxy)-2-methylbutyl)-1,3-dithian-2-yl)methyl)tetrahydrofuran-2-yl)-5-methylhexa-2,4-dien-1-yl)oxy)dimethylsilane 380**

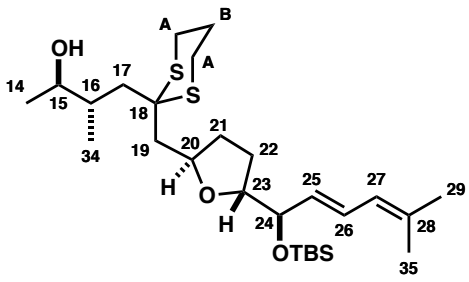


Chemical Formula: $C_{31}H_{58}O_4S_2Si$
Molecular Weight: 587,01

To a solution of dithiane **362** (dried by azeotropic distillation with benzene (4 ×), 421 mg, 1.51 mmol, 2.0 equiv.) in a 9:1 mixture of THF and HMPA (15 mL) at −78 °C, was added *t*-BuLi (titrated at 1.85 M in pentane, 820 µL, 1.51 mmol, 2.0 equiv.) dropwise. The resulting dark orange solution was stirred at −78 °C for 10 min, before the slow addition of a precooled solution of crude alkyl iodide **361** (dried by azeotropic distillation with benzene (4 ×)) in THF (2.5 mL). The dark green/black reaction mixture was stirred at −78 °C for 45 min, before the slow addition of a sat. aq. NH_4Cl solution (18 mL) and the biphasic mixture was allowed to warm to RT. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated. The residue was filtered through a short pad of silica gel (pet. ether/EtOAc, 90:10) to deliver the crude mixture (450 mg) consisting of a roughly 1:2 mixture of EE acetal **380** (*ca*. 0.39 mmol) and excess dithiane **362** (*ca*. 0.79 mmol) as a colourless oil. An analytical sample of the desired product could be obtained by treatment with TBAF in THF at RT and purification of the resulting alcohol by silica-gel chromatography to remove dithiane **362**, followed by a TBS reprotection using TBSOTf and 2,6-lutidine in CH_2Cl_2 at −78 °C. However, the crude mixture was generally used directly in the next step without further purification. R_f = 0.42 (pet. ether/EtOAc, 90:10); ν_{max} 2957, 2928, 2857, 1659, 1462, 1443, 1377, 1337, 1252, 1123, 1078, 1003 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (1H, ddd, *J* = 15.1, 11.0, 1.5 Hz), 6.44 (1H, ddd, *J* = 15.1, 11.1, 1.4 Hz), 5.83 (2H, dm, *J* = 11.0 Hz), 5.57 (2H, dd, *J* = 15.1, 5.7 Hz), 4.79 (1H, q, *J* = 5.3 Hz), 4.75 (1H, q, *J* = 5.3 Hz), 4.23−4.18 (2H, m), 4.17−4.10 (2H, m), 4.00−3.92 (2H, m), 3.75−3.62 (4H, m), 3.54−3.44 (2H, m), 2.94−2.69 (8H,

m), 2.29−2.25 (1H, m), 2.24 (1H, dd, *J* = 8.3, 5.5 Hz), 2.20−2.07 (6H, m), 2.02 (1H, dd, *J* = 15.1, 3.5 Hz), 2.02−1.91 (2H, m), 1.92−1.83 (5H, m), 1.77 (6H, br s), 1.75 (6H, br s), 1.76−1.70 (2H, m), 1.67 (2H, dd, *J* = 15.1, 5.8 Hz), 1.55−1.46 (2H, m), 1.31 (3H, d, *J* = 7.4 Hz), 1.30 (3H, d, *J* = 7.5 Hz), 1.20 (3H, t, *J* = 7.0 Hz), 1.20 (3H, t, *J* = 7.1 Hz), 1.11 (3H, d, *J* = 6.4 Hz), 1.06 (3H, d, *J* = 6.2 Hz), 1.05 (3H, d, *J* = 6.7 Hz), 1.02 (3H, d, *J* = 6.9 Hz), 0.90 (18H, s), 0.06 (6H, s), 0.04 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.9, 134.9, 130.2, 127.5, 127.5, 124.9, 124.9, 99.1, 98.3, 81.8, 81.8, 76.8, 76.8, 75.5, 75.5, 75.4, 60.7, 60.5, 53.5, 53.3, 45.0, 45.0, 42.8, 34.5, 34.2, 34.2, 33.4, 29.9, 27.3, 27.2, 26.5, 26.5, 26.5, 26.1, 26.1, 25.2, 25.2, 21.2, 21.0, 18.4, 16.9, 16.0, 15.8, 15.6, 15.5, 15.5, −4.3, −4.3, −4.6; HRMS (ESI+) $[M+Na]^+$ calcd for $C_{31}H_{58}O_4S_2SiNa$ 609.3438, found 609.3413, Δ 4.0 ppm.

(2*R*,3*S*)-4-(2-(((2*R*,5*R*)-5-((*R*,*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-methylhexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)methyl)-1,3-dithian-2-yl)-3-methylbutan-2-ol 381

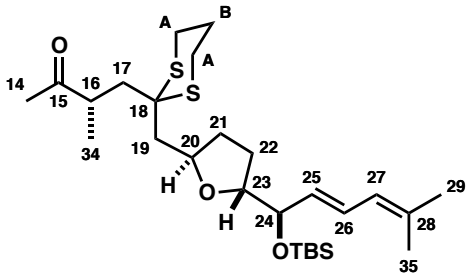


Chemical Formula: $C_{27}H_{50}O_3S_2Si$
Molecular Weight: 514,90

To a solution of crude **380** in a 3:1 mixture of EtOH and CH_2Cl_2 (59 mL) at RT, was added PPTS (45 mg, 0.18 mmol, 15 mol %). The resulting solution was stirred at RT for 9 h, before the addition of Et_3N (75 µL, 0.54 mmol) and the mixture was concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 85:15) to deliver alcohol **381** (0.17 g, 0.33 mmol, 44% over 3 steps) as a colourless oil. R_f = 0.20 (pet. ether/EtOAc, 85:15); $[\alpha]_D^{19}$ +16 (*c* = 0.49, $CHCl_3$); ν_{max} 3435, 2955, 2928, 2857, 1661, 1462, 1377, 1252, 1113, 1084, 1005 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (1H, ddd, *J* = 15.2, 11.0, 1.4 Hz, CH−C26), 5.83 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.56 (1H, dd, *J* = 15.2, 5.6 Hz, CH−C25), 4.20 (1H, app td, *J* = 5.6, 1.4 Hz, CH−C24), 4.16 (1H, app dq, *J* = 9.0, 5.3 Hz, CH−C20), 3.97 (1H, app td, *J* = 7.3, 5.6 Hz, CH−C23), 3.67 (1H, app pd, *J* = 6.1, 5.5 Hz, CH−C15), 2.91−2.71 (4H, m, 2 × CH_2−C_A), 2.24 (1H, dd, *J* = 15.0, 5.3 Hz, CH−C19), 2.18 (1H, dd, *J* = 15.0, 5.3 Hz, CH−C19), 2.17 (1H, dd, *J* = 15.0,

2.6 Hz, CH−C17), 2.10 (1H, dddd, *J* = 11.8, 7.9, 5.3, 2.6 Hz, CH−C21), 2.00−1.82 (4H, m, CH−C16, CH−C22, CH_2−C_B), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.76−1.69 (1H, m, CH−C22), 1.67 (1H, dd, *J* = 15.0, 6.2 Hz, CH−C17), 1.55 (1H, d, *J* = 5.5 Hz, OH−C15), 1.56−1.47 (1H, m, CH−C21), 1.15 (3H, d, *J* = 6.1 Hz, CH_3−C14), 1.05 (3H, d, *J* = 6.9 Hz, CH_3−C34), 0.90 (9H, s, CH_3−*t*-Bu TBS), 0.06 (3H, s, CH_3−TBS), 0.04 (3H, s, CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.9 (C−C28), 130.2 (CH−C25), 127.5 (CH−C26), 124.9 (CH−C27), 81.9 (CH−C23), 76.8 (CH−C20), 75.5 (CH−C24), 72.5 (CH−C15), 53.2 (C−C18), 45.3 (CH_2−C19), 43.0 (CH_2−C17), 37.0 (CH−C16), 34.3 (CH_2−C21), 27.3 (CH_2−C22), 26.5 (CH_2−C_A), 26.4 (CH_2−C_A), 26.1 (CH_3−C35), 26.1 (CH_3−*t*-Bu TBS), 25.1 (CH_2−C_B), 19.7 (CH_3−C14), 18.4 (CH_3−C29, C−*t*-Bu TBS), 17.9 (CH_3−C34), −4.3 (CH_3−TBS), −4.6 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{27}H_{50}O_3S_2SiNa$ 537.2863, found 537.2838, Δ 4.6 ppm.

(*S*)-4-(2-(((2*R*,5*R*)-5-((*R*,*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-methylhexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)methyl)-1,3-dithian-2-yl)-3-methylbutan-2-one 382

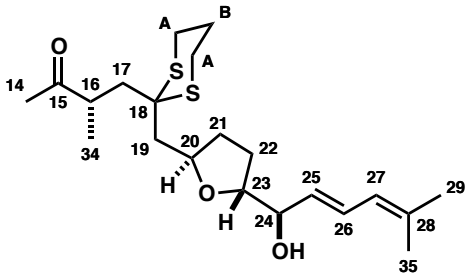


Chemical Formula: $C_{27}H_{48}O_3S_2Si$
Molecular Weight: 512,88

To a solution of alcohol **381** (0.17 g, 0.33 mmol) in CH_2Cl_2 (3.3 mL) at 0 °C, were added DMSO (0.33 mL, 4.7 mmol, 14.0 equiv.), Et_3N (0.32 mL, 2.3 mmol, 7.0 equiv.) and SO_3•Pyr (0.29 g, 1.8 mmol, 5.5 equiv.) sequentially. The resulting mixture was stirred at 0 °C for 24 h, after which more DMSO (0.17 mL, 2.3 mmol, 7.0 equiv.), Et_3N (0.16 mL, 1.2 mmol, 3.5 equiv.) and SO_3•Pyr (0.15 g, 0.93 mmol, 2.8 equiv.) were added. The reaction mixture was stirred at 0 °C for another 24 h, before the addition of a sat. aq. NH_4Cl solution (4 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 95:5) to deliver ketone **382** (0.13 g, 0.26 mmol,

78%) as a colourless oil. R_f = 0.23 (pet. ether/EtOAc, 95:5); $[\alpha]_D^{25}$ +26.1 (*c* = 1.52, $CHCl_3$); ν_{max} 2955, 2928, 2857, 1711, 1661, 1460, 1443, 1424, 1362, 1348, 1252, 1115, 1084, 1005 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.43 (1H, ddd, *J* = 15.2, 11.0, 1.4 Hz, CH−C26), 5.82 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.55 (1H, dd, *J* = 15.2, 5.7 Hz, CH−C25), 4.24−4.17 (2H, m, CH−C20, CH−C24), 3.99 (1H, app td, *J* = 7.3, 4.9 Hz, CH−C23), 3.03 (1H, ddd, *J* = 14.5, 9.1, 0.7 Hz, CH−C17), 3.00 (1H, ddd, *J* = 14.3, 11.2, 2.7 Hz, CH−C_A), 2.84 (1H, dqd, *J* = 9.1, 7.2, 1.4 Hz, CH−C16), 2.77 (1H, ddd, *J* = 14.3, 11.2, 2.7 Hz, CH−C_A), 2.66 (1H, dddd, *J* = 14.3, 5.8, 3.1, 1.0 Hz, CH−C_A), 2.48 (1H, dddd, *J* = 14.3, 5.8, 3.1, 1.0 Hz, CH−C_A), 2.25 (3H, s, CH_3−C14), 2.08 (1H, dd, *J* = 15.0, 7.4 Hz, CH−C19), 2.05−1.97 (2H, m, CH−C21, CH−C_B), 1.98 (1H, ddd, *J* = 15.0, 3.1, 0.7 Hz, CH−C19), 1.89 (1H, dd, *J* = 14.5, 1.4 Hz, CH−C17), 1.89−1.69 (3H, m, CH_2−C22, CH−C_B), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.48 (1H, app ddt, *J* = 12.0, 10.0, 8.5 Hz, CH−C21), 1.08 (3H, d, *J* = 7.2 Hz, CH_3−C34), 0.90 (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 212.6 (C−C15), 135.0 (C−C28), 130.1 (CH−C25), 127.6 (CH−C26), 124.8 (CH−C27), 82.2 (CH−C23), 75.3 (CH−C24), 75.1 (CH−C20), 51.9 (C−C18), 45.6 (CH_2−C19), 43.6 (CH−C16), 40.7 (CH_2−C17), 34.0 (CH_2−C21), 30.1 (CH_3−C14), 26.9 (CH_2−C_A), 26.7 (CH_2−C22), 26.1 (CH_3−C35), 26.1 (CH_2−C_A), 26.0 (CH_3−*t*-Bu TBS), 25.1 (CH_2−C_B), 18.9 (CH_3−C34), 18.4 (CH_3−C29), 18.4 (C−*t*-Bu TBS), −4.3 (CH_3−TBS), −4.6 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{27}H_{48}O_3S_2SiNa$ 535.2706, found 535.2680, Δ 4.8 ppm.

(*S*)-4-(2-(((2*R*,5*R*)-5-((*R*,*E*)-1-Hydroxy-5-methylhexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)methyl)-1,3-dithian-2-yl)-3-methylbutan-2-one 383

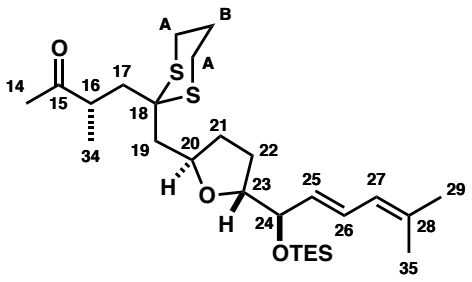


Chemical Formula: $C_{21}H_{34}O_3S_2$
Molecular Weight: 398,62

To a solution of TBS ether **382** (0.13 g, 0.26 mmol) in THF (6.5 mL) at 0 °C, was added TBAF (1.0 M in THF, 0.52 mL, 0.52 mmol, 2.0 equiv.) dropwise. The

resulting solution was stirred at RT for 5 h. The reaction was quenched by the addition of water (7 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 7 mL) and the combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 70:30) to give alcohol **383** (0.10 g, 0.26 mmol, quant.) as a colourless oil. R_f = 0.44 (pet. ether/EtOAc, 70:30); $[\alpha]_D^{26}$ +13.2 (*c* = 1.32, $CHCl_3$); ν_{max} 3451, 2963, 2924, 1709, 1661, 1443, 1422, 1375, 1350, 1261, 1169, 1080, 1044, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.52 (1H, ddd, *J* = 15.2, 11.0, 1.2 Hz, CH−C26), 5.81 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.45 (1H, dd, *J* = 15.2, 6.8 Hz, CH−C25), 4.29−4.22 (1H, m, CH−C20), 3.97 (1H, dddd, *J* = 7.1, 6.8, 2.9, 1.2 Hz, CH−C24), 3.89 (1H, app q, *J* = 7.1 Hz, CH−C23), 3.09 (1H, dd, *J* = 14.6, 9.4 Hz, CH−C17), 2.98 (1H, ddd, *J* = 14.4, 10.7, 2.8 Hz, CH−C_A), 2.88 (1H, dqd, *J* = 9.4, 7.2, 1.5 Hz, CH−C16), 2.77 (1H, ddd, *J* = 14.4, 10.7, 2.8 Hz, CH−C_A), 2.68 (1H, dddd, *J* = 14.4, 6.2, 3.1, 0.7 Hz, CH−C_A), 2.57 (1H, d, *J* = 2.9 Hz, OH−C24), 2.54 (1H, dddd, *J* = 14.4, 6.2, 3.1, 0.7 Hz, CH−C_A), 2.26 (3H, s, CH_3−C14), 2.14−2.07 (1H, m, CH−C21), 2.10 (1H, dd, *J* = 15.3, 7.7 Hz, CH−C19), 2.03 (1H, dd, *J* = 15.3, 3.0 Hz, CH−C19), 2.04−1.91 (2H, m, CH−C22, CH−C_B), 1.88−1.78 (1H, m, CH−C_B), 1.80 (1H, dd, *J* = 14.6, 1.5 Hz, CH−C17), 1.77 (3H, br s, CH_3−C35), 1.76 (3H, br s, CH_3−C29), 1.70−1.60 (1H, m, CH−C22), 1.61−1.52 (1H, m, CH−C21), 1.08 (3H, d, *J* = 7.2 Hz, CH_3−C34); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.2 (C−C15), 136.6 (C−C28), 129.4 (CH−C26), 128.2 (CH−C25), 124.5 (CH−C27), 82.5 (CH−C23), 75.5 (CH−C24), 74.9 (CH−C20), 52.0 (C−C18), 45.3 (CH_2−C19), 43.5 (CH−C16), 41.3 (CH_2−C17), 34.1 (CH_2−C21), 30.0 (CH_3−C14), 27.8 (CH_2−C22), 26.9 (CH_2−C_A), 26.2 (CH_3−C35), 26.1 (CH_2−C_A), 25.0 (CH_2−C_B), 19.1 (CH_3−C34), 18.5 (CH_3−C29); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{21}H_{34}O_3S_2Na$ 421.1842, found 421.1826, Δ 3.8 ppm.

(*S*)-3-Methyl-4-(2-(((2*R*,5*R*)-5-((*R*,*E*)-5-methyl-1-((triethylsilyl)oxy)hexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)methyl)-1,3-dithian-2-yl)butan-2-one 384

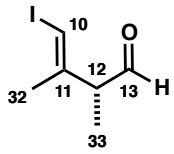


Chemical Formula: $C_{27}H_{48}O_3S_2Si$
Molecular Weight: 512,88

To a solution of alcohol **383** (0.10 g, 0.26 mmol) in CH_2Cl_2 (6.5 mL) at −78 °C, was added 2,6-lutidine (90 µL, 0.78 mmol, 3.0 equiv.) and, after 5 min, TESOTf (88 µL, 0.39 mmol, 1.5 equiv.). The resulting solution was stirred at −78 °C for 45 min, before the addition of water (7 mL) and the biphasic mixture was allowed to warm to RT. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 7 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated. Crude material was purified by silica gel chromatography (pet. ether/EtOAc, 95:5) to deliver TES ether **384** (0.12 g, 0.23 mmol, 89%) as a colourless oil. R_f = 0.28 (pet. ether/EtOAc, 95:5); $[\alpha]_D^{25}$ +26.8 (*c* = 1.00, $CHCl_3$); ν_{max} 2957, 2876, 1711, 1659, 1458, 1443, 1422, 1375, 1348, 1238, 1167, 1115, 1082, 1005 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.43 (1H, ddd, *J* = 15.2, 10.9, 1.3 Hz, CH−C26), 5.82 (1H, dm, *J* = 10.9 Hz, CH−C27), 5.53 (1H, dd, *J* = 15.2, 6.1 Hz, CH−C25), 4.24−4.15 (2H, m, CH−C20, CH−C24), 3.98 (1H, ddd, *J* = 7.6, 7.4, 5.3 Hz, CH−C23), 3.03 (1H, ddd, *J* = 14.5, 9.0, 1.0 Hz, CH−C17), 3.01 (1H, ddd, *J* = 14.2, 11.0, 2.7 Hz, CH−C_A), 2.84 (1H, dqd, *J* = 9.0, 7.1, 1.3 Hz, CH−C16), 2.77 (1H, ddd, *J* = 14.2, 11.3, 2.8 Hz, CH−C_A), 2.66 (1H, dddd, *J* = 14.2, 5.4, 3.1, 0.9 Hz, CH−C_A), 2.47 (1H, dddd, *J* = 14.2, 5.8, 3.1, 0.9 Hz, CH−C_A), 2.25 (3H, s, CH_3−C14), 2.09 (1H, dd, *J* = 15.0, 7.4 Hz, CH−C19), 2.06−1.98 (2H, m, CH−C21, CH−C_B), 1.97 (1H, ddd, *J* = 15.0, 3.3, 1.0 Hz, CH−C19), 1.90 (1H, dd, *J* = 14.5, 1.3 Hz, CH−C17), 1.88−1.78 (2H, m, CH−C22, CH−C_B), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.70 (1H, dddd, *J* = 12.6, 10.1, 7.9, 7.6 Hz, CH−C22), 1.48 (1H, app ddt, *J* = 12.0, 10.1, 8.4 Hz, CH−C21), 1.09 (3H, d, *J* = 7.1 Hz, CH_3−C34), 0.95 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.59 (6H, q, *J* = 7.9 Hz, CH_2−TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.6 (C−C15), 135.2 (C−C28), 130.1 (CH−C25), 127.8 (CH−C26), 124.8 (CH−C27), 82.4 (CH−C23), 75.6 (CH−C24),

75.0 (CH−C20), 51.9 (C−C18), 45.6 (CH_2−C19), 43.7 (CH−C16), 40.6 (CH_2−C17), 34.1 (CH_2−C21), 30.1 (CH_3−C14), 27.1 (CH_2−C22), 26.9 (CH_2−C_A), 26.1 (CH_3−C35), 26.1 (CH_2−C_A), 25.1 (CH_2−C_B), 18.9 (CH_3−C34), 18.4 (CH_3−C29), 7.1 (CH_3−TES), 5.2 (CH_2−TES); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{27}H_{48}O_3S_2SiNa$ 535.2706, found 535.2690, Δ 3.0 ppm.

(*R*,*E*)-4-Iodo-2,3-dimethylbut-3-enal 363



Chemical Formula: C_6H_9IO
Molecular Weight: 224,04

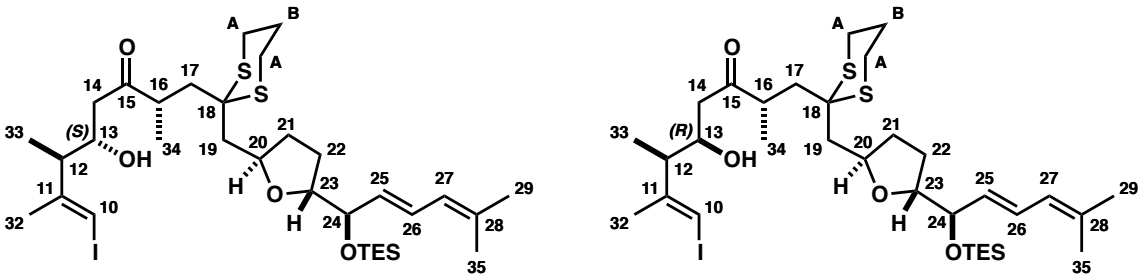
*Note: Aldehyde **363** was prone to decomposition and was therefore used in the next step as soon as possible.*

To a solution of alcohol **377** (70 mg, 0.31 mmol) in CH_2Cl_2 (3 mL) at RT, were added $NaHCO_3$ (0.16 g, 1.9 mmol, 6.0 equiv.) and DMP (0.20 g, 0.46 mmol, 1.5 equiv.) sequentially. The resulting mixture was stirred at RT for 1.5 h, before the addition of a 1:1 mixture of a sat. aq. $Na_2S_2O_3$ solution and a sat. aq. $NaHCO_3$ solution (6 mL). The biphasic mixture was stirred vigorously for 10 min and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 6 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Crude material was used directly in the next step without further purification.

(2*S*,5*S*,6*R*,*E*)-5-Hydroxy-8-iodo-2,6,7-trimethyl-1-(2-(((2*R*,5*R*)-5-((*R*,*E*)-5-methyl-1-((triethylsilyl)oxy)hexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)methyl)-1,3-dithian-2-yl)oct-7-en-3-one 385

and

(2*S*,5*R*,6*R*,*E*)-5-Hydroxy-8-iodo-2,6,7-trimethyl-1-(2-(((2*R*,5*R*)-5-((*R*,*E*)-5-methyl-1-((triethylsilyl)oxy)hexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)methyl)-1,3-dithian-2-yl)oct-7-en-3-one 386



Note: Starting materials were divided into three equal batches and the resulting crude mixtures were combined for purification.

To a solution of ketone **384** (dried by azeotropic distillation with benzene (4 ×), 46 mg, 90 μmol) in Et_2O (900 μL) at 0 °C, were added Et_3N (20 μL, 0.14 mmol, 1.6 equiv.) and Cy_2BCl (29 μL, 0.14 mmol, 1.5 equiv.) sequentially. The resulting mixture was stirred at 0 °C for 1 h (a white precipitate formed) and cooled to −78 °C. A solution of crude aldehyde **363** (dried by azeotropic distillation with benzene (4 ×)) in Et_2O (450 μL) was added and the mixture was stirred at −78 °C for 1.5 h, before the addition of aqueous pH 7 buffer (3 mL). The biphasic mixture was stirred at 0 °C for 30 min and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 4 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. A diastereomeric mixture of aldol products **386** and **385** (2.2:1 *dr*) was observed by ^1H NMR analysis of the crude mixture (integration of the signal corresponding to CH−C10). Crude material was purified by silica gel chromatography (pet. ether/CH_2Cl_2/Et_2O, 49:49:2) to afford in the order of elution, (*S*)-*β*-hydroxy ketone **385** (20 mg, 27 μmol, 10%) and (*R*)-*β*-hydroxy ketone **386** (0.11 g, 0.15 mmol, 55%) as colourless oils.

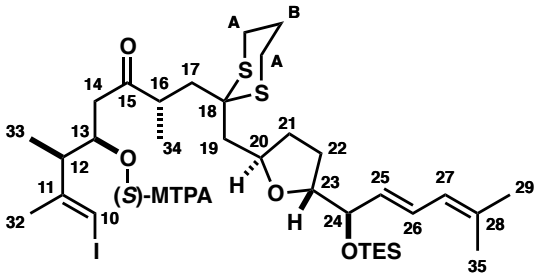
(*S*)-*β*-hydroxy ketone **385**: R_f = 0.29 (pet. ether/CH_2Cl_2/Et_2O, 49:49:2, eluted twice); ν_{max} 3501, 2930, 2874, 1697, 1659, 1456, 1375, 1263, 1080, 1017 cm^{-1}; ^1H

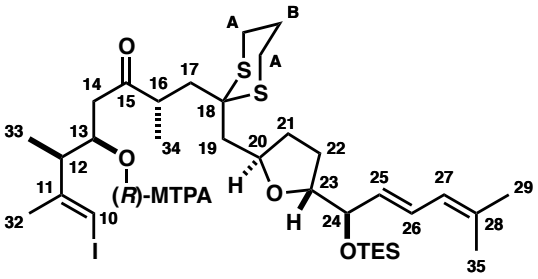
NMR (500 MHz, $CDCl_3$) δ 6.42 (1H, ddd, *J* = 15.3, 11.0, 1.4 Hz, CH−C26), 6.01 (1H, br s, CH−C10), 5.81 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.52 (1H, dd, *J* = 15.3, 6.2 Hz, CH−C25), 4.23−4.15 (2H, m, CH−C20, CH−C24), 4.02−3.93 (2H, m, CH−C13, CH−C23), 3.15 (1H, d, *J* = 3.1 Hz, OH−C13), 3.03 (1H, dd, *J* = 14.4, 8.9 Hz, CH−C17), 2.98 (1H, ddd, *J* = 14.0, 10.9, 2.7 Hz, $CH-C_A$), 2.85−2.79 (1H, m, CH−C16), 2.76−2.69 (3H, m, CH_2−C14, $CH-C_A$), 2.66 (1H, dddd, *J* = 14.0, 5.4, 2.7, 0.8 Hz, $CH-C_A$), 2.51 (1H, app p, *J* = 7.1 Hz, CH−C12), 2.50−2.44 (1H, m, $CH-C_A$), 2.06 (1H, dd, *J* = 15.0, 7.6 Hz, CH−C19), 2.03−1.96 (3H, m, CH−C19, CH−C21, $CH-C_B$), 1.94 (1H, dd, *J* = 14.4, 1.0 Hz, CH−C17), 1.90−1.78 (2H, m, CH−C22, $CH-C_B$), 1.84 (3H, d, *J* = 1.1 Hz, CH_3−C32), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.70 (1H, app ddt, *J* = 12.6, 10.1, 7.8 Hz, CH−C22), 1.47 (1H, app ddt, *J* = 12.0, 10.1, 8.4 Hz, CH−C21), 1.09 (3H, d, *J* = 7.2 Hz, CH_3−C34), 1.03 (3H, d, *J* = 7.1 Hz, CH_3−C33), 0.94 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.59 (6H, q, *J* = 7.9 Hz, CH_2−TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.5 (C−C15), 149.8 (C−C11), 135.3 (C−C28), 130.0 (CH−C25), 127.8 (CH−C26), 124.8 (CH−C27), 82.5 (CH−C23), 76.9 (CH−C10), 75.6 (CH−C24), 74.9 (CH−C20), 69.8 (CH−C13), 51.9 (C−C18), 48.4 (CH−C12), 46.0 (CH_2−C14), 45.5 (CH_2−C19), 44.0 (CH−C16), 40.4 (CH_2−C17), 34.0 (CH_2−C21), 27.0 (CH_2−C22), 26.8 (CH_2-C_A), 26.2 (CH_3−C35), 26.1 (CH_2-C_A), 25.0 (CH_2-C_B), 21.4 (CH_3−C32), 19.0 (CH_3−C34), 18.4 (CH_3−C29), 15.6 (CH_3−C33), 7.1 (CH_3−TES), 5.2 (CH_2−TES); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{33}H_{57}IO_4S_2SiNa$ 759.2404, found 759.2369, Δ 4.7 ppm.

(*R*)-*β*-hydroxy ketone **386**: R_f = 0.24 (pet. ether/CH_2Cl_2/Et_2O, 49:49:2, eluted twice); $[\alpha]_D^{30}$ +24.5 (*c* = 2.00, $CHCl_3$); ν_{max} 3499, 2928, 2874, 1703, 1659, 1454, 1377, 1261, 1080, 1017 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.42 (1H, ddd, *J* = 15.3, 11.0, 1.4 Hz, CH−C26), 6.03 (1H, br s, CH−C10), 5.81 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.52 (1H, dd, *J* = 15.3, 6.1 Hz, CH−C25), 4.22−4.16 (2H, m, CH−C20, CH−C24), 4.01−3.96 (1H, m, CH−C23), 3.90−3.83 (1H, m, CH−C13), 3.37 (1H, d, *J* = 3.4 Hz, OH−C13), 3.04−2.95 (2H, m, CH−C17, $CH-C_A$), 2.86 (1H, dd, *J* = 18.1, 2.2 Hz, CH−C14), 2.83−2.77 (1H, m, CH−C16), 2.75−2.63 (2H, m, 2 × $CH-C_A$), 2.49 (1H, dd, *J* = 18.1, 9.0 Hz, CH−C14), 2.49−2.42 (2H, m, CH−C12, $CH-C_A$), 2.05 (1H, dd, *J* = 15.1, 7.5 Hz, CH−C19), 2.05−1.97 (3H, m, CH−C19, CH−C21, $CH-C_B$), 1.95 (1H, dd, *J* = 14.6, 1.2 Hz, CH−C17), 1.90−1.78 (2H, m, CH−C22, $CH-C_B$), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.75 (3H, br s, CH_3−C32), 1.70 (1H, app ddt, *J* = 12.7, 10.2, 7.8 Hz, CH−C22), 1.48 (1H, app

ddt, *J* = 12.0, 10.2, 8.6 Hz, CH−C21), 1.13 (3H, d, *J* = 6.8 Hz, CH_3−C33), 1.06 (3H, d, *J* = 7.1 Hz, CH_3−C34), 0.95 (9H, t, *J* = 8.0 Hz, CH_3−TES), 0.59 (6H, q, *J* = 8.0 Hz, CH_2−TES); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.2 (C−C15), 149.9 (C−C11), 135.3 (C−C28), 130.0 (CH−C25), 127.8 (CH−C26), 124.8 (CH−C27), 82.5 (CH−C23), 76.9 (CH−C10), 75.6 (CH−C24), 74.9 (CH−C20), 70.1 (CH−C13), 51.8 (C−C18), 49.0 (CH−C12), 47.3 (CH_2−C14), 45.6 (CH_2−C19), 43.6 (CH−C16), 41.1 (CH_2−C17), 34.0 (CH_2−C21), 27.0 (CH_2−C22), 27.0 (CH_2−C_A), 26.2 (CH_3−C35), 26.1 (CH_2−C_A), 25.0 (CH_2−C_B), 21.5 (CH_3−C32), 18.9 (CH_3−C34), 18.4 (CH_3−C29), 15.5 (CH_3−C33), 7.1 (CH_3−TES), 5.2 (CH_2−TES); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{33}H_{57}IO_4S_2SiNa$ 759.2404, found 759.2383, Δ 2.8 ppm.

Mosher Ester Analysis of (2*S*,5*R*,6*R*,*E*)-5-Hydroxy-8-iodo-2,6,7-trimethyl-1-(2-(((2*R*,5*R*)-5-((*R*,*E*)-5-methyl-1-((triethylsilyl)oxy)hexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)methyl)-1,3-dithian-2-yl)oct-7-en-3-one 386





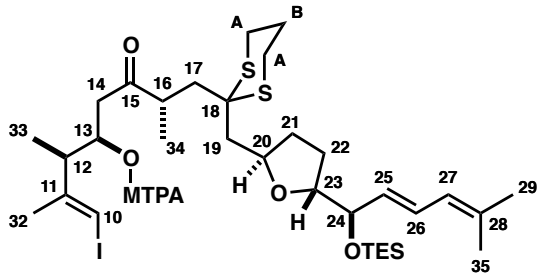
To a solution of (*R*)-*β*-hydroxy ketone **386** (7 mg, 9 µmol) in CH_2Cl_2 (0.5 mL) at RT, were added (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (7 mg, 0.03 mmol, 3.0 equiv.), DCC (6 mg, 0.03 mmol, 3.0 equiv.) and DMAP (4 mg, 0.03 mmol, 3.0 equiv.) sequentially. The resulting mixture was stirred at RT for 24 h, filtered through a cotton plug and concentrated. Crude material was purified by silica gel chromatography (hexane/EtOAc, 95:5) to afford (*S*)-Mosher ester **390** (5 mg, 5 µmol, 50%) as a colourless oil. R_f = 0.47 (hexane/EtOAc, 90:10); $[\alpha]_D^{21}$ −6.1 (*c* = 0.23, $CHCl_3$); ν_{max} 2959, 2926, 1749, 1711, 1661, 1452, 1260, 1169, 1080, 1017 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.45 (2H, m, CH−Ar MTPA), 7.45−7.38 (3H, m, CH−Ar MTPA), 6.42 (1H, ddd, *J* = 15.2, 11.0, 1.4 Hz, CH−C26), 5.94 (1H, br s, CH−C10), 5.81 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.64 (1H, ddd, *J* = 7.5, 5.9, 4.1 Hz, CH−C13), 5.51 (1H, dd, *J* = 15.2, 6.2 Hz, CH−C25), 4.21−4.14 (2H, m, CH−C20, CH−C24), 3.98 (1H, app td, *J* = 7.3, 5.0 Hz, CH−C23), 3.50 (3H,

s, CH_3−OMe MTPA), 3.08 (1H, dd, *J* = 18.7, 4.1 Hz, CH−C14), 3.06−2.93 (2H, m, CH−C17, CH−C_A), 2.84 (1H, dd, *J* = 18.7, 7.5 Hz, CH−C14), 2.77−2.63 (3H, m, CH−C16, 2 × CH−C_A), 2.63−2.57 (1H, m, CH−C12), 2.44−2.37 (1H, m, CH−C_A), 2.05 (1H, dd, *J* = 14.8, 7.4 Hz, CH−C19), 2.05−1.96 (3H, m, CH−C19, CH−C21, CH−C_B), 1.94 (1H, dd, *J* = 14.4, 0.9 Hz, CH−C17), 1.90−1.74 (2H, m, CH−C22, CH−C_B), 1.78 (3H, d, *J* = 0.7 Hz, CH_3−C32), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.73−1.65 (1H, m, CH−C22), 1.52−1.43 (1H, m, CH−C21), 1.00 (3H, d, *J* = 7.1 Hz, CH_3−C34), 0.99 (3H, d, *J* = 7.0 Hz, CH_3−C33), 0.94 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.59 (6H, q, *J* = 7.9 Hz, CH_2−TES); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{43}H_{64}F_3IO_6S_2SiNa$ 975.2803, found 975.2792, Δ 1.1 ppm.

The same procedure was followed for the preparation of (*R*)-Mosher ester **391**. R_f = 0.42 (hexane/EtOAc, 90:10); $[\alpha]_D^{17}$ +19 (*c* = 0.40, $CHCl_3$); ν_{max} 2953, 2930, 1751, 1715, 1663, 1452, 1377, 1260, 1169, 1082, 1017 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53−7.46 (2H, m, CH−Ar MTPA), 7.45−7.38 (3H, m, CH−Ar MTPA), 6.42 (1H, ddd, *J* = 15.3, 11.0, 1.4 Hz, CH−C26), 6.02 (1H, br s, CH−C10), 5.81 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.65 (1H, app dt, *J* = 6.7, 5.2 Hz, CH−C13), 5.51 (1H, dd, *J* = 15.3, 6.1 Hz, CH−C25), 4.21−4.14 (2H, m, CH−C20, CH−C24), 3.97 (1H, app td, *J* = 7.3, 5.3 Hz, CH−C23), 3.48 (3H, s, CH_3−OMe MTPA), 3.04 (1H, dd, *J* = 18.7, 5.2 Hz, CH−C14), 3.05−2.96 (2H, m, CH−C17, CH−C_A), 2.85 (1H, dd, *J* = 18.7, 6.7 Hz, CH−C14), 2.74−2.61 (4H, m, CH−C12, CH−C16, 2 × CH−C_A), 2.41−2.34 (1H, m, CH−C_A), 2.04 (1H, dd, *J* = 15.1, 7.6 Hz, CH−C19), 2.04−1.94 (3H, m, CH−C19, CH−C21, CH−C_B), 1.91 (1H, dd, *J* = 14.4, 0.6 Hz, CH−C17), 1.87 (3H, d, *J* = 1.0 Hz, CH_3−C32), 1.94−1.78 (2H, m, CH−C22, CH−C_B), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.74−1.67 (1H, m, CH−C22), 1.52−1.42 (1H, m, CH−C21), 1.05 (3H, d, *J* = 7.0 Hz, CH_3−C34), 0.96 (3H, d, *J* = 7.0 Hz, CH_3−C33), 0.95 (9H, t, *J* = 8.0 Hz, CH_3−TES), 0.59 (6H, q, *J* = 8.0 Hz, CH_2−TES); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{43}H_{64}F_3IO_6S_2SiNa$ 975.2803, found 975.2790, Δ 1.3 ppm.

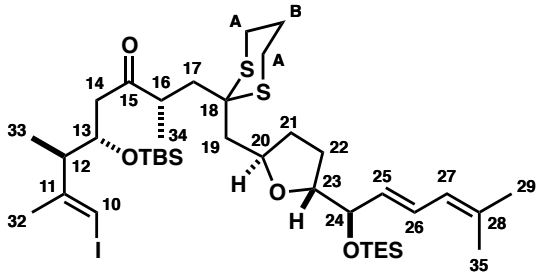
Both products were analysed according to Hoye and co-workers:[94]

Table S1. Mosher Ester Analysis for the Assignment of the C13 Stereocentre



Assignment	**386** (δ), ppm	δ (***S*-ester**), ppm	δ (***R*-ester**), ppm	Δ (δ-(***S*−*R***)), ppm
10	6.03	5.940	6.017	−0.077
14	2.86	3.083	3.036	+0.047
	2.49	2.844	2.854	−0.010
17	1.95	1.945	1.912	+0.033
19	2.05	2.047	2.038	+0.009
23	3.98	3.977	3.970	+0.007
32	1.75	1.778	1.873	−0.095
33	1.13	0.990	1.048	−0.058
34	1.06	0.998	0.956	+0.042

(2*S*,5*S*,6*R*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-8-iodo-2,6,7-trimethyl-1-(2-(((2*R*,5*R*)-5-((*R*,*E*)-5-methyl-1-((triethylsilyl)oxy)hexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)methyl)-1,3-dithian-2-yl)oct-7-en-3-one 360

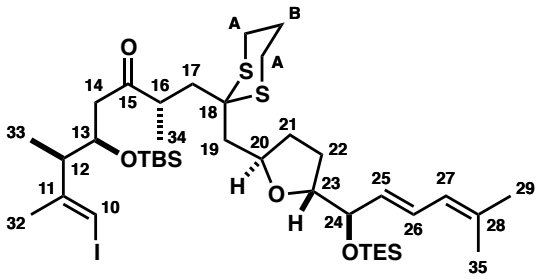


Chemical Formula: $C_{39}H_{71}IO_4S_2Si_2$
Molecular Weight: 851,18

To a solution of *β*-hydroxy ketone **385** (20 mg, 27 µmol) in CH_2Cl_2 (1.6 mL) at −78 °C, were added 2,6-lutidine (25 µL, 0.11 mmol, 8.0 equiv.) and TBSOTf (25 µL, 54 µmol, 4.0 equiv.) sequentially. The resulting solution was stirred at −78 °C for 5 h, before the addition of water (2 mL) and the biphasic mixture was allowed to warm to RT. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Crude material was purified by silica gel chromatography (hexane/EtOAc, 95:5) to deliver TBS ether **360** (22 mg, 26 µmol, 95%) as a colourless oil. R_f = 0.34 (pet. ether/EtOAc, 95:5); $[\alpha]_D^{28}$ +23.8 (*c* = 0.650, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (1H, ddd, *J* = 15.2, 11.0, 1.4 Hz, CH−C26), 5.83 (1H, br s, CH−C10), 5.82 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.52 (1H, dd, *J* = 15.2, 6.1 Hz, CH−C25), 4.22−4.15 (2H, m, CH−C20, CH−C24), 4.07 (1H, app dt, *J* = 9.1, 3.3 Hz, CH−C13), 3.98 (1H, app td, *J* = 7.6, 5.3 Hz, CH−C23), 3.04−2.93 (2H, m, CH−C17, CH−C_A), 2.86 (1H, dd, *J* = 18.9, 3.3 Hz, CH−C14), 2.78 (1H, dd, *J* = 18.9, 9.1 Hz, CH−C14), 2.76−2.69 (3H, m, CH−C12, CH−C16, CH−C_A), 2.66 (1H, dddd, *J* = 14.3, 5.7, 2.9, 0.9 Hz, CH−C_A), 2.49−2.41 (1H, m, CH−C_A), 2.06 (1H, dd, *J* = 15.0, 7.4 Hz, CH−C19), 2.07−1.95 (2H, m, CH−C21, CH−C_B), 1.97 (1H, dd, *J* = 15.0, 3.2 Hz, CH−C19), 1.88 (1H, dd, *J* = 14.6, 1.0 Hz, CH−C17), 1.90−1.78 (2H, m, CH−C22, CH−C_B), 1.82 (3H, d, *J* = 1.1 Hz, CH_3−C32), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.70 (1H, app ddt, *J* = 12.6, 10.1, 7.6 Hz, CH−C22), 1.47 (1H, app ddt, *J* = 11.8, 10.1, 8.4 Hz, CH−C21), 1.07 (3H, d, *J* = 7.1 Hz, CH_3−C33), 1.02 (3H, d, *J* = 7.1 Hz, CH_3−C34), 0.95 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.88 (9H, s, CH_3−*t*-Bu TBS), 0.59 (6H, q, *J* = 7.9 Hz, CH_2−TES), 0.03 (3H, s, CH_3−TBS), 0.01 (3H, s, CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.4

(C−C15), 150.1 (C−C11), 135.2 (C−C28), 130.0 (CH−C25), 127.8 (CH−C26), 124.8 (CH−C27), 82.4 (CH−C23), 77.6 (CH−C10), 75.5 (CH−C24), 75.0 (CH−C20), 70.2 (CH−C13), 51.9 (C−C18), 48.5 (CH_2−C14), 47.4 (CH−C12), 45.6 (CH_2−C19), 43.2 (CH−C16), 40.4 (CH_2−C17), 34.1 (CH_2−C21), 27.1 (CH_2−C22), 27.0 (CH_2−C_A), 26.2 (CH_3−C35), 26.1 (CH_2−C_A), 26.0 (CH_3−*t*-Bu TBS), 25.1 (CH_2−C_B), 22.4 (CH_3−C32), 19.2 (CH_3−C34), 18.5 (CH_3−C29), 18.1 (C−*t*-Bu TBS), 16.2 (CH_3−C33), 7.1 (CH_3−TES), 5.2 (CH_2−TES), −4.4 (CH_3−TBS), −4.8 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{39}H_{71}IO_4S_2Si_2Na$ 873.3269, found 873.3227, Δ 4.8 ppm.

(2*S*,5*R*,6*R*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-8-iodo-2,6,7-trimethyl-1-(2-(((2*R*,5*R*)-5-((*R*,*E*)-5-methyl-1-((triethylsilyl)oxy)hexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)methyl)-1,3-dithian-2-yl)oct-7-en-3-one 393

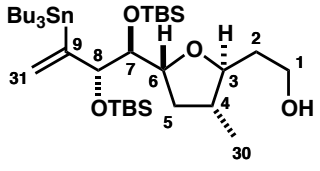


Chemical Formula: $C_{39}H_{71}IO_4S_2Si_2$
Molecular Weight: 851,18

To a solution of *β*-hydroxy ketone **386** (43 mg, 58 µmol) in CH_2Cl_2 (2.7 mL) at −78 °C, were added 2,6-lutidine (40 µL, 0.35 mmol, 6.0 equiv.) and TBSOTf (40 µL, 0.18 mmol, 3.0 equiv.) sequentially. The resulting solution was stirred at −78 °C for 5 h, before the addition of water (3 mL) and the biphasic mixture was allowed to warm to RT. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 3 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Crude material was purified by silica gel chromatography (hexane/EtOAc, 95:5) to deliver TBS ether **393** (46 mg, 54 µmol, 93%) as a colourless oil. R_f = 0.36 (hexane/EtOAc, 95:5); $[\alpha]_D^{23}$ +27.6 (*c* = 0.600, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.42 (1H, ddd, *J* = 15.3, 11.0, 1.4 Hz, CH−C26), 5.93−5.89 (1H, m, CH−C10), 5.81 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.52 (1H, dd, *J* = 15.3, 6.1 Hz, CH−C25), 4.22 (1H, app dt, *J* = 6.3, 4.8 Hz, CH−C13), 4.22−4.15 (2H, m, CH−C20, CH−C24), 3.98 (1H, app td, *J* = 7.6, 5.3 Hz, CH−C23), 3.08−2.98 (2H, m, CH−C17, CH−C_A), 2.97 (1H, dd, *J* = 18.8, 6.3 Hz,

CH−C14), 2.76−2.64 (3H, m, CH−C16, 2 × CH−C_A), 2.65 (1H, dd, *J* = 18.8, 4.8 Hz, CH−C14), 2.49−2.36 (2H, m, CH−C12, CH−C_A), 2.07 (1H, dd, *J* = 14.9, 7.3 Hz, CH−C19), 2.04−1.97 (2H, m, CH−C21, CH−C_B), 1.96 (1H, dd, *J* = 14.9, 3.2 Hz, CH−C19), 1.90 (1H, dd, *J* = 14.3, 1.0 Hz, CH−C17), 1.90−1.78 (2H, m, CH−C22, CH−C_B), 1.84 (3H, d, *J* = 1.1 Hz, CH_3−C32), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.70 (1H, app ddt, *J* = 12.8, 10.2, 7.6 Hz, CH−C22), 1.48 (1H, app ddt, *J* = 11.9, 10.2, 8.5 Hz, CH−C21), 1.06 (3H, d, *J* = 7.2 Hz, CH_3−C34), 1.00 (3H, d, *J* = 7.0 Hz, CH_3−C33), 0.95 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.85 (9H, s, CH_3−*t*-Bu TBS), 0.59 (6H, q, *J* = 7.9 Hz, CH_2−TES), 0.02 (3H, s, CH_3−TBS), −0.03 (3H, s, CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.1 (C−C15), 150.3 (C−C11), 135.2 (C−C28), 130.0 (CH−C25), 127.8 (CH−C26), 124.8 (CH−C27), 82.4 (CH−C23), 77.5 (CH−C10), 75.6 (CH−C24), 74.9 (CH−C20), 68.5 (CH−C13), 51.9 (C−C18), 48.7 (CH_2−C14), 47.6 (CH−C12), 45.6 (CH_2−C19), 43.3 (CH−C16), 40.4 (CH_2−C17), 34.0 (CH_2−C21), 27.0 (CH_2−C22), 27.0 (CH_2−C_A), 26.2 (CH_3−C35), 26.1 (CH_3−*t*-Bu TBS), 26.1 (CH_2−C_A), 25.1 (CH_2−C_B), 24.0 (CH_3−C32), 18.9 (CH_3−C34), 18.4 (CH_3−C29), 18.2 (C−*t*-Bu TBS), 13.3 (CH_3−C33), 7.1 (CH_3−TES), 5.2 (CH_2−TES), −4.3 (CH_3−TBS), −4.6 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{39}H_{71}IO_4S_2Si_2Na$ 873.3269, found 873.3230, Δ 4.5 ppm.

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)ethanol 394

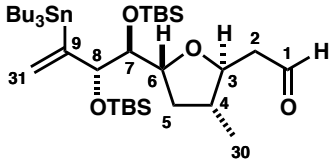


Chemical Formula: $C_{35}H_{74}O_4Si_2Sn$
Molecular Weight: 733,84

To a solution of pivalate **280**[73] (23 mg, 28 µmol) in Et_2O (2.3 mL) at −78 °C, was added *i*-Bu_2AlH (1.0 M in hexanes, 0.11 mL, 0.11 mmol, 4.0 equiv.) dropwise. The resulting solution was stirred at −78 °C for 30 min. The reaction was quenched by the dropwise addition of a sat. aq. potassium sodium tartrate solution (3 mL) and the biphasic mixture was stirred vigorously at RT for 30 min. The layers were

separated and the aqueous phase was extracted with Et_2O (3 × 3 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Crude material was purified by silica gel chromatography (CH_2Cl_2/EtOAc, 99:1) to give alcohol **394** (20 mg, 27 µmol, 97%) as a colourless oil. R_f = 0.36 (hexane/EtOAc, 90:10); $[\alpha]_D^{21}$ −16.4 (*c* = 0.950, $CHCl_3$); ν_{max} 3393, 2955, 2928, 2857, 1464, 1252, 1088, 1071, 1005 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.96 (1H, dd, *J* = 2.9, 1.9 Hz, $^3J_{SnH}$ = 132.3 Hz, CH−C31), 5.25 (1H, dd, *J* = 2.9, 1.9 Hz, $^3J_{SnH}$ = 64.0 Hz, CH−C31), 4.33 (1H, app q, *J* = 1.9 Hz, $^3J_{SnH}$ = 29.7 Hz, CH−C8), 4.16 (1H, app q, *J* = 7.3 Hz, CH−C6), 3.96 (1H, ddd, *J* = 10.5, 5.3, 3.0 Hz, CH−C3), 3.82−3.72 (2H, m, CH_2−C1), 3.54 (1H, dd, *J* = 7.3, 1.9 Hz, CH−C7), 2.65 (1H, dd, *J* = 7.8, 3.3 Hz, OH−C1), 2.21−2.11 (1H, m, CH−C4), 1.82 (1H, ddd, *J* = 12.7, 8.1, 7.3 Hz, CH−C5), 1.70 (1H, dddd, *J* = 13.7, 10.5, 8.3, 5.1 Hz, CH−C2), 1.58−1.40 (8H, m, CH−C2, CH−C5, 3 × CH_2−*n*-Bu_3Sn), 1.32 (6H, h, *J* = 7.2 Hz, 3 × CH_2−*n*-Bu_3Sn), 0.91 (9H, s, CH_3−*t*-Bu TBS), 0.90 (9H, s, CH_3−*t*-Bu TBS), 0.96−0.86 (18H, m, CH_3−C30, 3 × CH_2−*n*-Bu_3Sn, 3 × CH_3−*n*-Bu_3Sn), 0.11 (3H, s, CH_3−TBS), 0.09 (3H, s, CH_3−TBS), 0.08 (3H, s, CH_3−TBS), 0.00 (3H, s, CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9 (C−C9), 125.9 (CH_2−C31), 82.7 (CH−C8), 80.8 (CH−C3), 78.9 (CH−C6), 78.7 (CH−C7), 62.4 (CH_2−C1), 37.2 (CH_2−C5), 36.7 (CH−C4), 33.0 (CH_2−C2), 29.3 ($^1J_{119SnC}$ = 19 Hz, $^1J_{117SnC}$ = 19 Hz, CH_2−*n*-Bu_3Sn), 27.6 ($^1J_{119SnC}$ = 61 Hz, $^1J_{117SnC}$ = 59 Hz, CH_2−*n*-Bu_3Sn), 26.4 (CH_3−*t*-Bu TBS), 26.3 (CH_3−*t*-Bu TBS), 18.6 (C−*t*-Bu TBS), 18.6 (C−*t*-Bu TBS), 14.2 (CH_3−C30), 13.9 (CH_3−*n*-Bu_3Sn), 10.3 ($^1J_{119SnC}$ = 336 Hz, $^1J_{117SnC}$ = 321 Hz, CH_2−*n*-Bu_3Sn), −3.6 (CH_3−TBS), −3.9 (CH_3−TBS), −4.1 (CH_3−TBS), −4.3 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{35}H_{74}O_4Si_2SnNa$ 757.4040, found 757.4018, Δ 2.8 ppm.

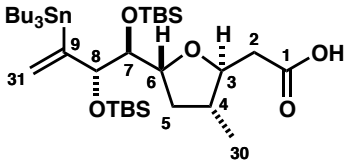
2-((2*S*,3*R*,5*R*)-3-Methyl-5-((5*S*,6*S*)-2,2,3,3,8,8,9,9-octamethyl-6-(1-(tributylstannyl)vinyl)-4,7-dioxa-3,8-disiladecan-5-yl)tetrahydrofuran-2-yl)acetaldehyde 395



Chemical Formula: $C_{35}H_{72}O_4Si_2Sn$
Molecular Weight: 731,82

To a solution of alcohol **394** (19 mg, 26 µmol) in CH_2Cl_2 (1.7 mL) at RT, was added DMP (22 mg, 52 µmol, 2.0 equiv.). The resulting solution was stirred at RT for 2 h. More DMP (22 mg, 52 µmol, 2.0 equiv.) was added and the reaction mixture was stirred for another 2 h. The reaction was quenched by the addition of a 1:1 mixture of a sat. aq. $Na_2S_2O_3$ solution and a sat. aq. $NaHCO_3$ solution (3 mL). The biphasic mixture was stirred vigorously until layers became clear (20 min). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Crude material was purified by silica gel chromatography (hexane/EtOAc, 95:5) to deliver aldehyde **395** (19 mg, 26 µmol, quant.) as a colourless oil. R_f = 0.45 (hexane/EtOAc, 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (1H, dd, *J* = 2.5, 2.0 Hz, CH−C1), 5.88 (1H, dd, *J* = 2.8, 2.0 Hz, $^3J_{SnH}$ = 131.7 Hz, CH−C31), 5.17 (1H, dd, *J* = 2.8, 2.0 Hz, $^3J_{SnH}$ = 63.7 Hz, CH−C31), 4.26 (1H, app q, *J* = 2.0 Hz, $^3J_{SnH}$ = 29.0 Hz, CH−C8), 4.18 (1H, app dt, *J* = 8.8, 4.9 Hz, CH−C3), 4.06 (1H, ddd, *J* = 9.1, 7.3, 6.6 Hz, CH−C6), 3.48 (1H, dd, *J* = 7.3, 2.0 Hz, CH−C7), 2.52 (1H, ddd, *J* = 16.1, 8.8, 2.5 Hz, CH−C2), 2.34 (1H, ddd, *J* = 16.1, 4.9, 2.0 Hz, CH−C2), 2.24−2.16 (1H, m, CH−C4), 1.72 (1H, ddd, *J* = 12.9, 9.1, 6.9 Hz, CH−C5), 1.50 (1H, ddd, *J* = 12.9, 6.6, 2.4 Hz, CH−C5), 1.46−1.35 (6H, m, 3 × CH_2−*n*-Bu_3Sn), 1.25 (6H, h, *J* = 7.3 Hz, 3 × CH_2−*n*-Bu_3Sn), 0.89−0.77 (36H, m, CH_3−C30, 2 × CH_3−*t*-Bu TBS, 3 × CH_2−*n*-Bu_3Sn, 3 × CH_3−*n*-Bu_3Sn), 0.01 (3H, s, CH_3−TBS), 0.00 (3H, s, CH_3−TBS), −0.01 (3H, s, CH_3−TBS), −0.07 (3H, s, CH_3−TBS).

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)acetic acid 396

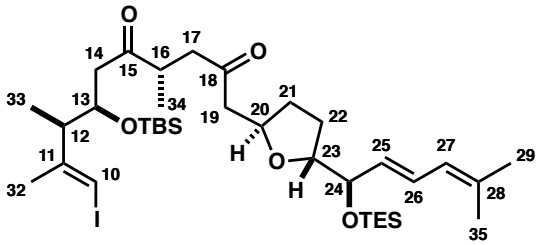


Chemical Formula: $C_{35}H_{72}O_5Si_2Sn$
Molecular Weight: 747,82

To a vigorously stirred solution of aldehyde **395** (19 mg, 26 µmol) in a 2:1 mixture of *t*-BuOH and water (3.7 mL) at 0 °C, were added 2-methyl-2-butene (0.14 mL, 1.3 mmol, 50 equiv.), $NaH_2PO_4 \bullet 2H_2O$ (40 mg, 0.26 mmol, 10 equiv.) and $NaClO_2$ (12 mg, 0.13 mmol, 5.0 equiv.) sequentially. The resulting mixture was stirred at 0 °C for 15 min and at RT for 1 h. The reaction mixture was diluted with CH_2Cl_2 (4 mL) and water (4 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Crude material was purified by silica gel chromatography (hexane/EtOAc, 90:10) to give acid **396** (17 mg, 23 µmol, 88%) as a colourless oil. R_f = 0.21 (hexane/EtOAc, 90:10); $[\alpha]_D^{19}$ −18.4 (*c* = 0.800, $CHCl_3$); ν_{max} 2957, 2926, 2855, 1713, 1464, 1256, 1084, 1022 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.62 (1H, br s, OH−C1), 5.96 (1H, dd, *J* = 2.5, 1.5 Hz, $^3J_{SnH}$ = 131.6 Hz, CH−C31), 5.26 (1H, dd, *J* = 2.5, 1.5 Hz, $^3J_{SnH}$ = 63.7 Hz, CH−C31), 4.35−4.33 (1H, m, $^3J_{SnH}$ = 28.6 Hz, CH−C8), 4.24−4.14 (2H, m, CH−C3, CH−C6), 3.55 (1H, dd, *J* = 7.1, 2.2 Hz, CH−C7), 2.52 (1H, dd, *J* = 15.9, 8.1 Hz, CH−C2), 2.45 (1H, dd, *J* = 15.9, 5.4 Hz, CH−C2), 2.34−2.25 (1H, m, CH−C4), 1.87−1.80 (1H, m, CH−C5), 1.57 (1H, ddd, *J* = 13.0, 6.8, 3.2 Hz, CH−C5), 1.53−1.42 (6H, m, 3 × CH_2−*n*-Bu_3Sn), 1.32 (6H, h, *J* = 7.2 Hz, 3 × CH_2−*n*-Bu_3Sn), 0.96−0.87 (36H, m, 2 × CH_3−*t*-Bu TBS, CH_3−C30, 3 × CH_2−*n*-Bu_3Sn, 3 × CH_3−*n*-Bu_3Sn), 0.08 (3H, s, CH_3−TBS), 0.08 (3H, s, CH_3−TBS), 0.07 (3H, s, CH_3−TBS), 0.00 (3H, s, CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7 (C−C1), 153.9 (C−C9), 126.0 (CH_2−C31), 82.6 ($^1J_{119SnC}$ = 57 Hz, $^1J_{117SnC}$ = 56 Hz, CH−C8), 79.1 (CH−C6), 78.5 (CH−C7), 76.6 (CH−C3), 37.3 (CH_2−C5), 36.2 (CH−C4, CH_2−C2), 29.3 ($^1J_{119SnC}$ = 19 Hz, $^1J_{117SnC}$ = 19 Hz, CH_2−*n*-Bu_3Sn), 27.6 ($^1J_{119SnC}$ = 61 Hz, $^1J_{117SnC}$ = 59 Hz, CH_2−*n*-Bu_3Sn), 26.5 (CH_3−*t*-Bu TBS), 26.3 (CH_3−*t*-Bu TBS), 18.7 (C−*t*-Bu TBS),

18.6 (C−*t*-Bu TBS), 14.0 (CH_3−C30), 13.8 (CH_3−*n*-Bu_3Sn), 10.3 ($^1J_{119SnC}$ = 336 Hz, $^1J_{117SnC}$ = 321 Hz, CH_2−*n*-Bu_3Sn), −3.7 (CH_3−TBS), −3.9 (CH_3−TBS), −4.2 (CH_3−TBS), −4.3 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{35}H_{72}O_5Si_2SnNa$ 771.3832, found 771.3808, Δ 3.1 ppm.

(4*S*,7*R*,8*R*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-10-iodo-4,8,9-trimethyl-1-((2*R*,5*R*)-5-((*R*,*E*)-5-methyl-1-((triethylsilyl)oxy)hexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)dec-9-ene-2,5-dione 399

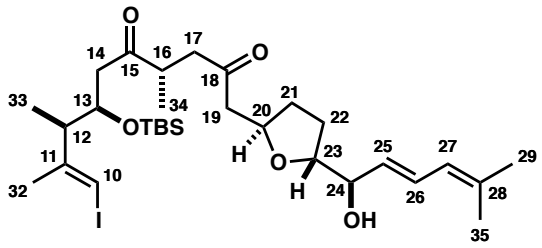


Chemical Formula: $C_{36}H_{65}IO_5Si_2$
Molecular Weight: 760,97

To a solution of dithiane **393** (6 mg, 7 µmol) in a 10:4:1 mixture of MeCN, THF and water (400 µL) at 0 °C, were added 2,6-di-*tert*-butyl-4-methylpyridine (8 mg, 0.04 mmol, 6.0 equiv.) and $PhI(OCOCF_3)_2$ (8 mg, 0.02 mmol, 3.0 equiv.) sequentially. The resulting solution was stirred at 0 °C for 45 min, before the addition of a sat. aq. $NaHCO_3$ solution (600 µL) and Et_2O (600 µL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 1 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. A 1:1.5 ratio of 1,4-diketones **400** and **399** was observed by ^1H NMR analysis of the crude mixture (integration of the signals corresponding to CH−C25 and CH−C26). Crude material was purified by silica gel chromatography (hexane/EtOAc, 90:10) to afford 1,4-diketone **399** (2 mg, 3 µmol, 41%) as a colourless oil. R_f = 0.38 (hexane/EtOAc, 90:10); $[\alpha]_D^{24}$ +24 (*c* = 0.29, $CHCl_3$); ν_{max} 2959, 2926, 1713, 1661, 1460, 1377, 1260, 1084, 1017 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.44 (1H, ddd, *J* = 15.2, 11.0, 1.1 Hz, CH−C26), 5.97−5.92 (1H, m, CH−C10), 5.82 (1H, dm, *J* = 11.0 Hz, CH−C27), 5.52 (1H, dd, *J* = 15.2, 5.9 Hz, CH−C25), 4.28 (1H, app dq, *J* = 8.3, 6.4 Hz, CH−C20), 4.22 (1H, ddd, *J* = 5.9, 5.5, 4.5 Hz, CH−C13), 4.16 (1H, app td, *J* = 5.9, 1.1 Hz, CH−C24), 3.93 (1H, app td, *J* = 7.2, 5.9 Hz, CH−C23), 2.99−2.89 (2H, m, CH−C16, CH−C17), 2.74 (1H, dd, *J* = 17.9, 5.9 Hz, CH−C14), 2.68 (1H, dd, *J* = 15.5, 6.4 Hz, CH−C19), 2.62 (1H, dd, *J* = 17.9, 5.5 Hz, CH−C14), 2.50 (1H, dd, *J* =

15.5, 6.4 Hz, CH−C19), 2.50−2.41 (2H, m, CH−C12, CH−C17), 2.09−1.98 (1H, m, CH−C21), 1.91−1.82 (1H, m, CH−C22), 1.83 (3H, d, *J* = 1.1 Hz, CH_3−C32), 1.77 (3H, br s, CH_3−C35), 1.75 (3H, br s, CH_3−C29), 1.79−1.68 (1H, m, CH−C22), 1.43 (1H, app ddt, *J* = 12.2, 9.7, 8.3 Hz, CH−C21), 1.06 (3H, d, *J* = 6.9 Hz, CH_3−C34), 1.06 (3H, d, *J* = 7.1 Hz, CH_3−C33), 0.94 (9H, t, *J* = 7.9 Hz, CH_3−TES), 0.85 (9H, s, CH_3−*t*-Bu TBS), 0.59 (6H, q, *J* = 7.9 Hz, CH_2−TES), 0.02 (3H, s, CH_3−TBS), −0.04 (3H, s, CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.2 (C−C15), 207.7 (C−C18), 150.0 (C−C11), 135.4 (C−C28), 129.8 (CH−C25), 127.8 (CH−C26), 124.8 (CH−C27), 82.4 (CH−C23), 77.8 (CH−C10), 75.5 (CH−C20 or CH−C24), 75.4 (CH−C20 or CH−C24), 69.2 (CH−C13), 49.1 (CH_2−C19), 48.4 (CH−C12), 47.5 (CH_2−C14), 46.0 (CH_2−C17), 41.6 (CH−C16), 32.3 (CH_2−C21), 27.3 (CH_2−C22), 26.2 (CH_3−C35), 26.1 (CH_3−*t*-Bu TBS), 23.9 (CH_3−C32), 18.4 (CH_3−C29), 18.2 (C−*t*-Bu TBS), 16.4 (CH_3−C34), 13.9 (CH_3−C33), 7.0 (CH_3−TES), 5.1 (CH_2−TES), −4.3 (CH_3−TBS), −4.5 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{36}H_{65}IO_5Si_2Na$ 783.3307, found 783.3277, Δ 3.9 ppm.

(4*S*,7*R*,8*R*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-1-((2*R*,5*R*)-5-((*R*,*E*)-1-hydroxy-5-methylhexa-2,4-dien-1-yl)tetrahydrofuran-2-yl)-10-iodo-4,8,9-trimethyldec-9-ene-2,5-dione 400

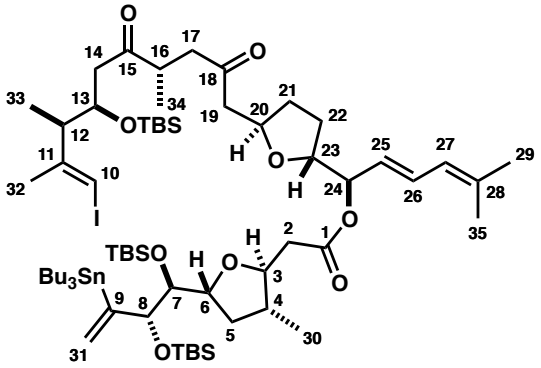


Chemical Formula: $C_{30}H_{51}IO_5Si$
Molecular Weight: 646,71

To a solution of dithiane **393** (6 mg, 7 µmol) in a 10:4:1 mixture of MeCN, THF and water (400 µL) at 0 °C, were added $CaCO_3$ (7 mg, 0.07 mmol, 10 equiv.) and $Hg(ClO_4)•4H_2O$ (6 mg, 0.01 mmol, 2.0 equiv.) sequentially. The resulting mixture was stirred at 0 °C for 15 min (a white precipitate formed), before the addition of a sat. aq. $NaHCO_3$ solution (600 µL) and Et_2O (600 µL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 1 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. A 9:1 ratio of 1,4-diketones **400** and **399** was observed by ^{1}H NMR analysis of the crude mixture

(integration of the signals corresponding to CH−C25 and CH−C26). Crude material was purified by silica gel chromatography (hexane/EtOAc, 70:30) to afford 1,4-diketone **400** (3 mg, 5 μmol, 77%) as a colourless oil. R_f = 0.36 (hexane/EtOAc, 70:30); $[\alpha]_D^{24}$ +15 (*c* = 0.38, $CHCl_3$); ν_{max} 3426, 2926, 2855, 1709, 1663, 1460, 1377, 1258, 1082, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.53 (1H, ddd, *J* = 15.2, 10.9, 1.0 Hz, CH−C26), 5.95 (1H, m, CH−C10), 5.82 (1H, dm, *J* = 10.9 Hz, CH−C27), 5.45 (1H, dd, *J* = 15.2, 6.9 Hz, CH−C25), 4.28 (1H, app ddt, *J* = 8.5, 7.1, 5.8 Hz, CH−C20), 4.21 (1H, ddd, *J* = 5.9, 5.4, 4.9 Hz, CH−C13), 3.95 (1H, ddd, *J* = 7.2, 6.9, 1.0 Hz, CH−C24), 3.87 (1H, app q, *J* = 7.2 Hz, CH−C23), 3.04 (1H, dd, *J* = 17.8, 9.0 Hz, CH−C17), 3.00−2.92 (1H, m, CH−C16), 2.75 (1H, dd, *J* = 17.9, 5.9 Hz, CH−C14), 2.74 (1H, dd, *J* = 15.1, 7.1 Hz, CH−C19), 2.72−2.69 (1H, m, OH−C24), 2.63 (1H, dd, *J* = 17.9, 5.4 Hz, CH−C14), 2.50 (1H, dd, *J* = 15.1, 5.8 Hz, CH−C19), 2.46 (1H, qd, *J* = 7.1, 4.9 Hz, CH−C12), 2.39 (1H, dd, *J* = 17.8, 4.2 Hz, CH−C17), 2.13 (1H, dddd, *J* = 12.0, 8.3, 5.8, 3.2 Hz, CH−C21), 1.95 (1H, dddd, *J* = 12.5, 8.5, 7.2, 3.2 Hz, CH−C22), 1.83 (3H, d, *J* = 0.9 Hz, CH_3−C32), 1.78 (3H, br s, CH_3−C35), 1.76 (3H, br s, CH_3−C29), 1.66 (1H, dddd, *J* = 12.5, 9.8, 8.3, 7.2 Hz, CH−C22), 1.53 (1H, app ddt, *J* = 12.0, 9.8, 8.5 Hz, CH−C21), 1.07 (3H, d, *J* = 7.0 Hz, CH_3−C34), 1.06 (3H, d, *J* = 7.1 Hz, CH_3−C33), 0.85 (9H, s, CH_3−*t*-Bu TBS), 0.03 (3H, s, CH_3−TBS), −0.04 (3H, s, CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.1 (C−C15), 207.7 (C−C18), 150.0 (C−C11), 136.7 (C−C28), 129.5 (CH−C26), 128.1 (CH−C25), 124.6 (CH−C27), 82.4 (CH−C23), 77.8 (CH−C10), 75.7 (CH−C24), 75.4 (CH−C20), 69.3 (CH−C13), 48.6 (CH_2−C19), 48.4 (CH−C12), 47.6 (CH_2−C14), 46.5 (CH_2−C17), 41.6 (CH−C16), 32.5 (CH_2−C21), 28.1 (CH_2−C22), 26.2 (CH_3−C35), 26.1 (CH_3−*t*-Bu TBS), 23.8 (CH_3−C32), 18.5 (CH_3−C29), 18.2 (C−*t*-Bu TBS), 16.4 (CH_3−C34), 14.0 (CH_3−C33), −4.3 (CH_3−TBS), −4.5 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{30}H_{51}IO_5SiNa$ 669.2443, found 669.2412, Δ 4.5 ppm.

(*R*,*E*)-1-((2*R*,5*R*)-5-((4*S*,7*R*,8*R*,*E*)-7-((*tert*-Butyldimethylsilyl)oxy)-10-iodo-4,8,9-trimethyl-2,5-dioxodec-9-en-1-yl)tetrahydrofuran-2-yl)-5-methylhexa-2,4-dien-1-yl 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)acetate 402



Chemical Formula: $C_{65}H_{121}IO_9Si_3Sn$
Molecular Weight: 1376,52

To a solution of acid **396** (dried by azeotropic distillation with benzene (2 ×), 9.4 mg, 13 µmol, 1.1 equiv.) in toluene (220 µL) at RT, were added Et_3N (15 µL, 0.11 mmol, 9.6 equiv.) in toluene (100 µL) and 2,4,6-trichlorobenzoyl chloride (4 µL, 0.03 mmol, 2.3 equiv.) in toluene (100 µL) sequentially. The resulting mixture was stirred at RT for 1 h. To a separate vial containing alcohol **400** (dried by azeotropic distillation with benzene (2 ×), 7.5 mg, 12 µmol) was added DMAP (5 mg, 0.04 mmol, 3.7 equiv.) in toluene (100 µL). The resulting solution was added to the vial containing the Yamaguchi anhydride and the vial was rinsed with toluene (3 ×100 µL). The cloudy mixture was stirred at RT for 3 h and diluted with toluene (1.6 mL). The reaction was quenched by the addition of a sat. aq. $NaHCO_3$ solution (1 mL) and the layers were separated. The aqueous phase was diluted with water (3 mL) and extracted with toluene (3 × 3 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. Crude material was purified by silica gel chromatography (hexane/EtOAc, 90:10) to afford ester **402** (11 mg, 8.0 µmol, 69%) as a colourless oil. R_f = 0.33 (hexane/EtOAc, 90:10); $[\alpha]_D^{22}$ −2.9 (*c* = 0.55, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.49 (1H, ddd, *J* = 15.1, 10.9, 1.0 Hz, CH−C26), 5.95−5.94 (1H, m, CH−C10), 5.93 (1H, dd, *J* = 2.7, 1.9 Hz, $^3J_{SnH}$ = 132.0 Hz, CH−C31), 5.78 (1H, dm, *J* = 10.9 Hz, CH−C27), 5.42 (1H, dd, *J* = 15.1, 7.8 Hz, CH−C25), 5.28 (1H, ddd, *J* = 7.8, 6.2, 1.0 Hz, CH−C24), 5.23 (1H, dd, *J* = 2.7, 1.8 Hz, $^3J_{SnH}$ = 63.7 Hz, CH−C31), 4.35−4.27 (2H, m,

CH−C8, CH−C20), 4.24−4.16 (2H, m, CH−C3, CH−C13), 4.10−4.03 (2H, m, CH−C6, CH−C23), 3.51 (1H, dd, *J* = 7.4, 2.5 Hz, CH−C7), 2.97−2.89 (2H, m, CH−C16, CH−C17), 2.74 (1H, dd, *J* = 17.8, 6.0 Hz, CH−C14), 2.70 (1H, dd, *J* = 15.5, 6.2 Hz, CH−C19), 2.62 (1H, dd, *J* = 17.8, 5.4 Hz, CH−C14), 2.59 (1H, dd, *J* = 15.8, 6.6 Hz, CH−C2), 2.51 (1H, dd, *J* = 15.5, 6.8 Hz, CH−C19), 2.48−2.39 (3H, m, CH−C2, CH−C12, CH−C17), 2.30−2.22 (1H, m, CH−C4), 2.12 (1H, dddd, *J* = 12.0, 8.0, 5.7, 3.6 Hz, CH−C21), 1.94 (1H, dddd, *J* = 12.4, 8.3, 7.0, 3.6 Hz, CH−C22), 1.83 (3H, d, *J* = 1.1 Hz, CH_3−C32), 1.77 (3H, br s, CH_3−C35), 1.74 (3H, br s, CH_3−C29), 1.78−1.65 (2H, m, CH−C5, CH−C22), 1.54−1.41 (8H, m, CH−C5, CH−C21, 3 × CH_2−*n*-Bu_3Sn), 1.32 (6H, h, *J* = 7.3 Hz, 3 × CH_2−*n*-Bu_3Sn), 1.06 (3H, d, *J* = 6.7 Hz, CH_3−C34), 1.06 (3H, d, *J* = 7.0 Hz, CH_3−C33), 0.91 (9H, s, CH_3−*t*-Bu TBS), 0.88 (9H, s, CH_3−*t*-Bu TBS), 0.85 (9H, s, CH_3−*t*-Bu TBS), 0.96−0.83 (18H, m, CH_3−C30, 3 × CH_2−*n*-Bu_3Sn, 3 × CH_3−*n*-Bu_3Sn), 0.08 (3H, s, CH_3−TBS), 0.07 (3H, s, CH_3−TBS), 0.06 (3H, s, CH_3−TBS), 0.03 (3H, s, CH_3−TBS), −0.01 (3H, s, CH_3−TBS), −0.04 (3H, s, CH_3−TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.1 (C−C15), 207.4 (C−C18), 170.7 (C−C1), 154.2 (C−C9), 150.0 (C−C11), 137.6 (C−C28), 131.4 (CH−C26), 125.8 (CH_2−C31), 124.5 (CH−C25), 124.4 (CH−C27), 82.7 (CH−C8), 79.7 (CH−C23), 79.3 (CH−C7), 78.8 (CH−C6), 77.7 (CH−C10), 76.5 (CH−C3), 76.5 (CH−C24), 75.4 (CH−C20), 69.3 (CH−C13), 48.9 (CH_2−C19), 48.4 (CH−C12), 47.5 (CH_2−C14), 45.8 (CH_2−C17), 41.6 (CH−C16), 37.6 (CH_2−C5), 36.7 (CH_2−C2), 36.0 (CH−C4), 32.1 (CH_2−C21), 29.3 (CH_2−*n*-Bu_3Sn), 28.0 (CH_2−C22), 27.6 (CH_2−*n*-Bu_3Sn), 26.6 (CH_3−*t*-Bu TBS), 26.3 (CH_3−*t*-Bu TBS), 26.2 (CH_3−C35), 26.1 (CH_3−*t*-Bu TBS), 23.9 (CH_3−C32), 18.8 (C−*t*-Bu TBS), 18.7 (C−*t*-Bu TBS), 18.6 (CH_3−C29), 18.2 (C−*t*-Bu TBS), 16.4 (CH_3−C34), 14.2 (CH_3−C30), 13.9 (CH_3−C33), 13.9 (CH_3−*n*-Bu_3Sn), 10.3 (CH_2−*n*-Bu_3Sn), −3.6 (CH_3−TBS), −3.9 (CH_3−TBS), −4.2 (CH_3−TBS), −4.3 (CH_3−TBS), −4.3 (CH_3−TBS), −4.5 (CH_3−TBS); HRMS (ESI+) $[M+Na]^+$ calcd for $C_{65}H_{121}IO_9Si_3SnNa$ 1399.6277, found 1399.6253, Δ 1.7 ppm.

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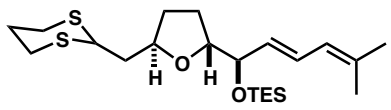
Appendices

^{1}H and ^{13}C NMR Spectra of Selected Compounds



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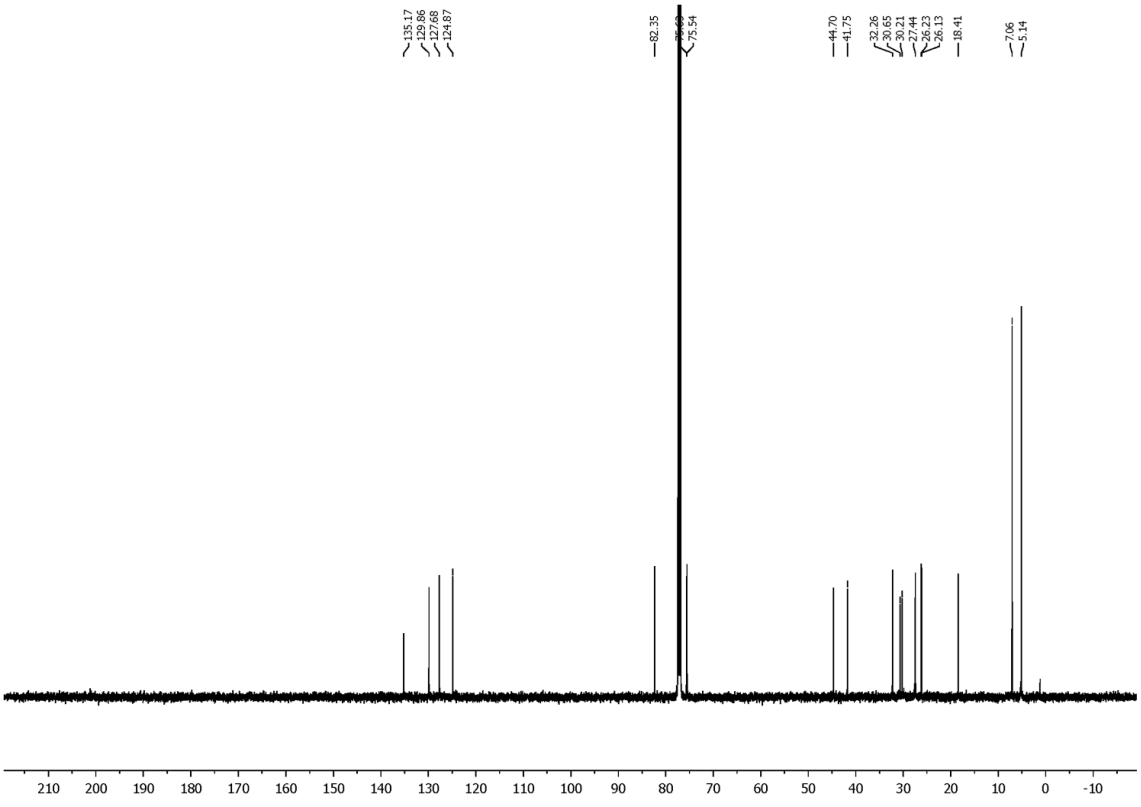

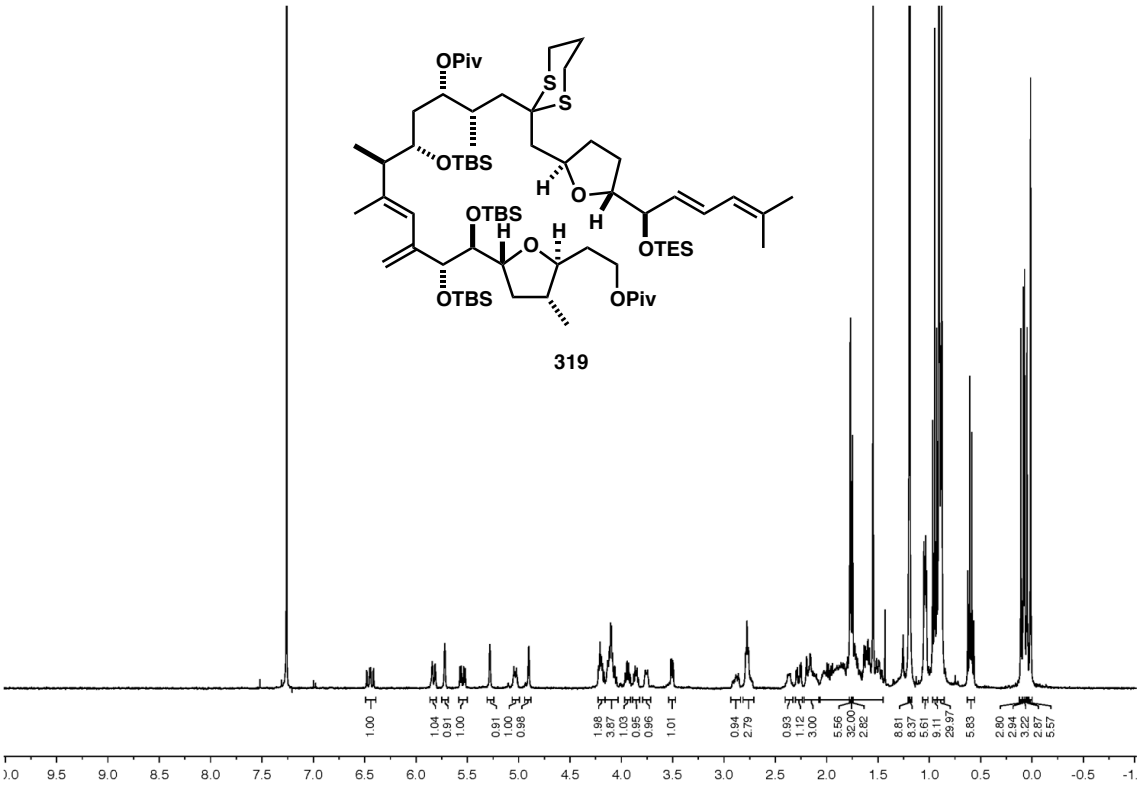
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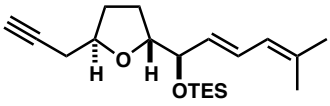
OPiv
319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O
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328

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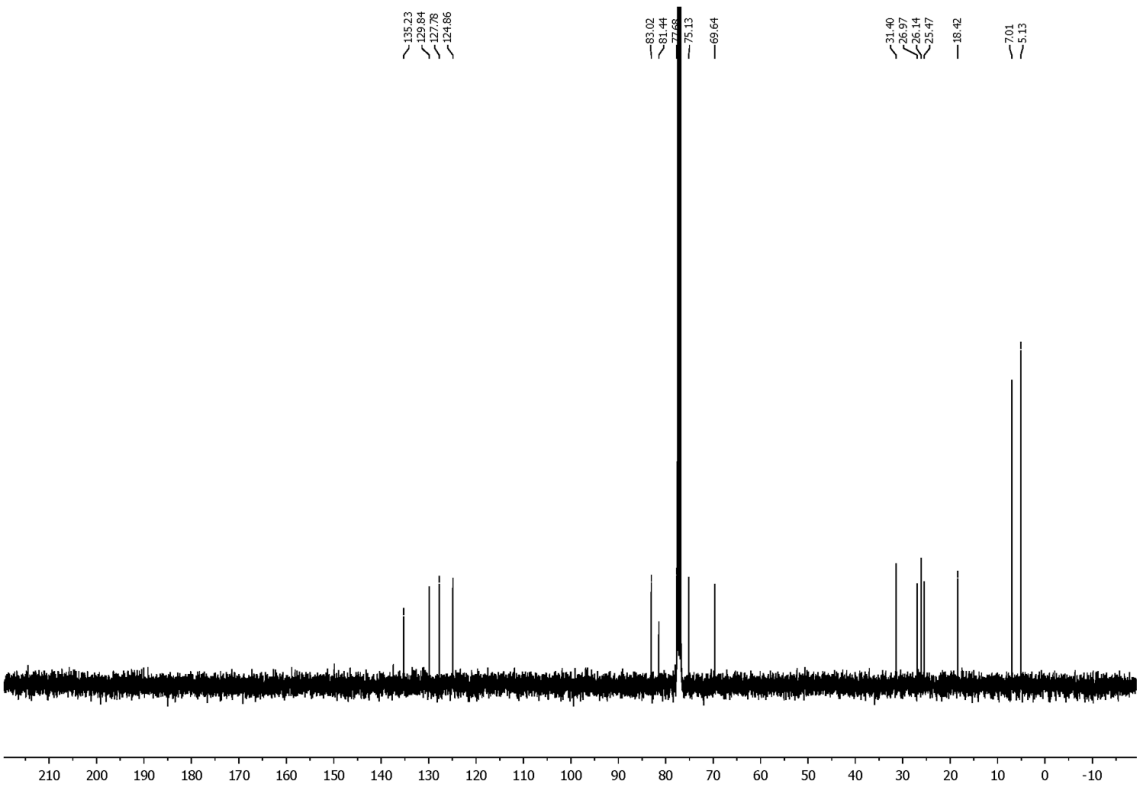
1.00
0.99
1.11
1.09
0.97
0.99
1.03
0.91
1.01
3.46
7.10
3.14
1.11
8.95
6.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5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7.01
5.13
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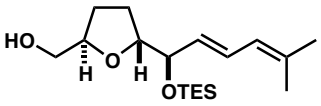
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O
H
H
OTES

356

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3.01
7.13
1.14
8.91
5.97
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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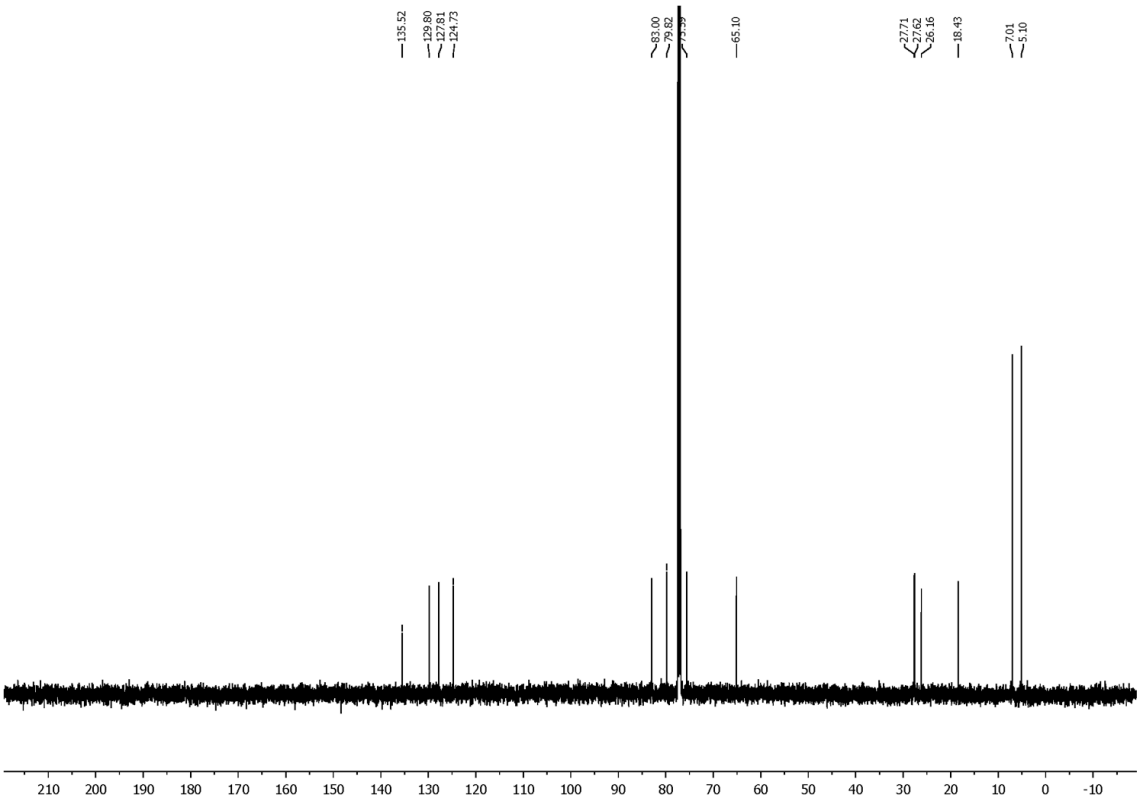
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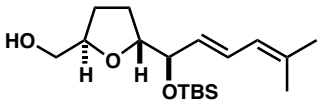
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H
OTBS

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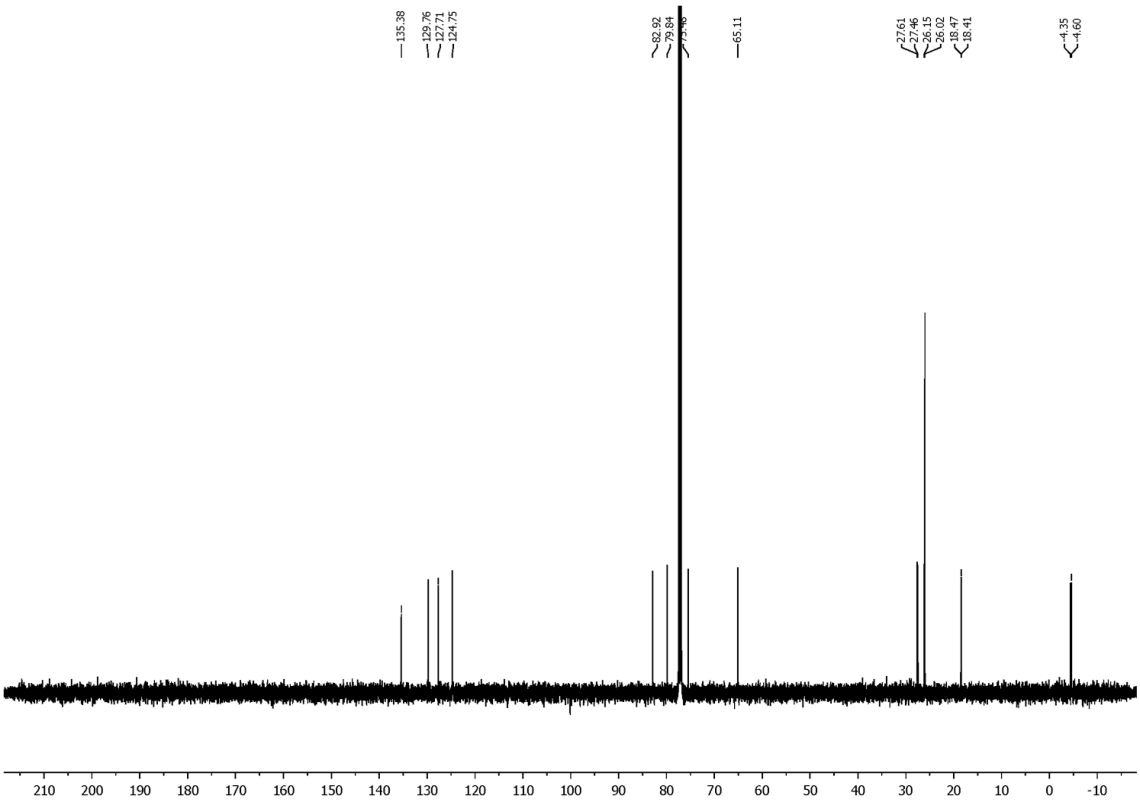
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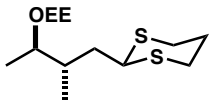
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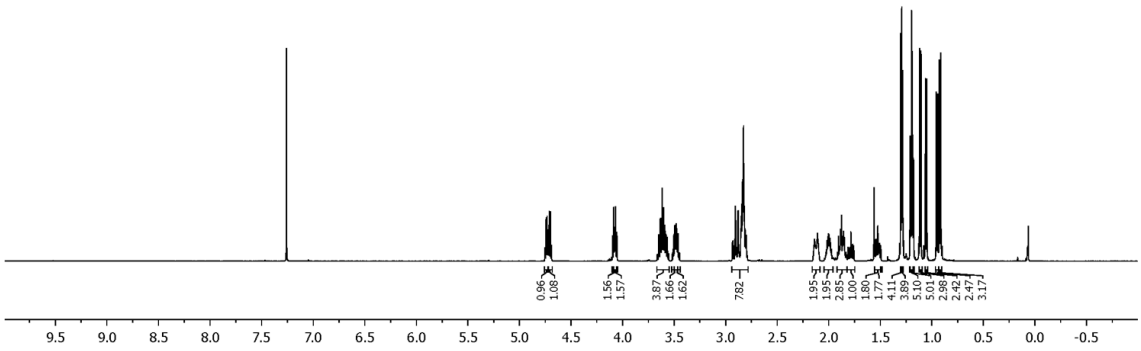
362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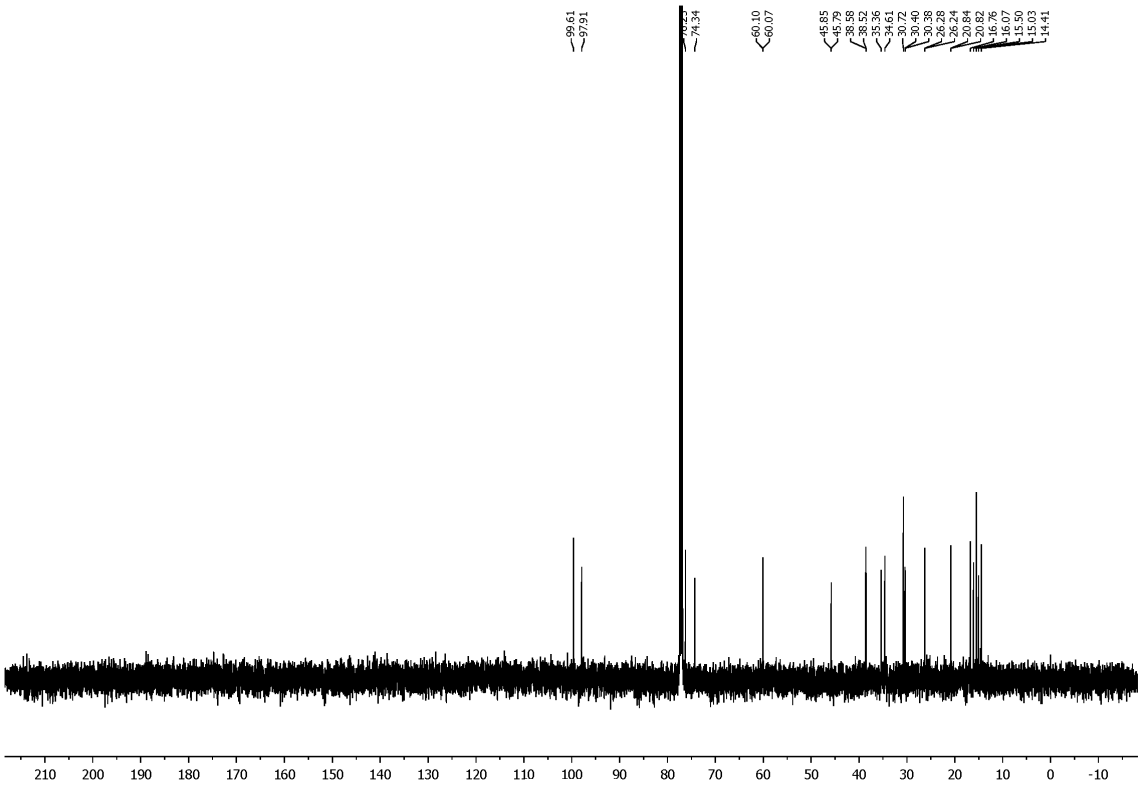
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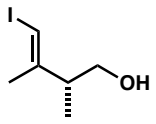
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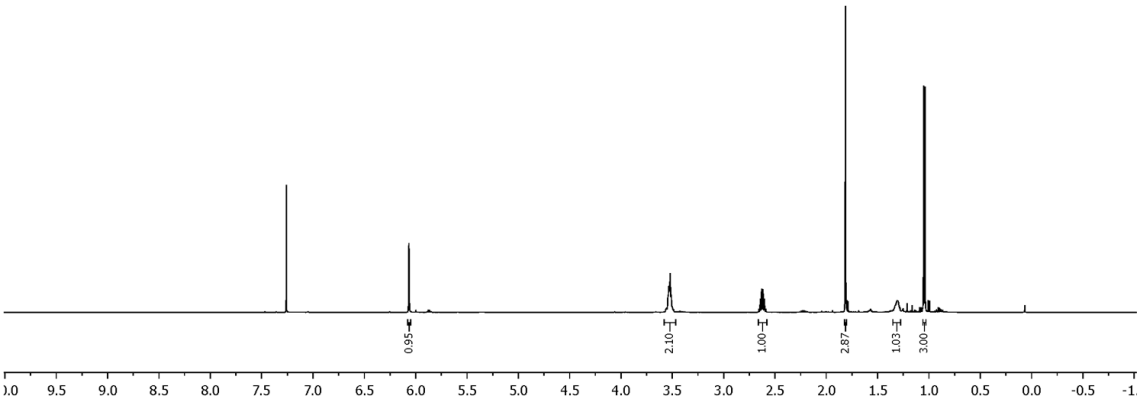
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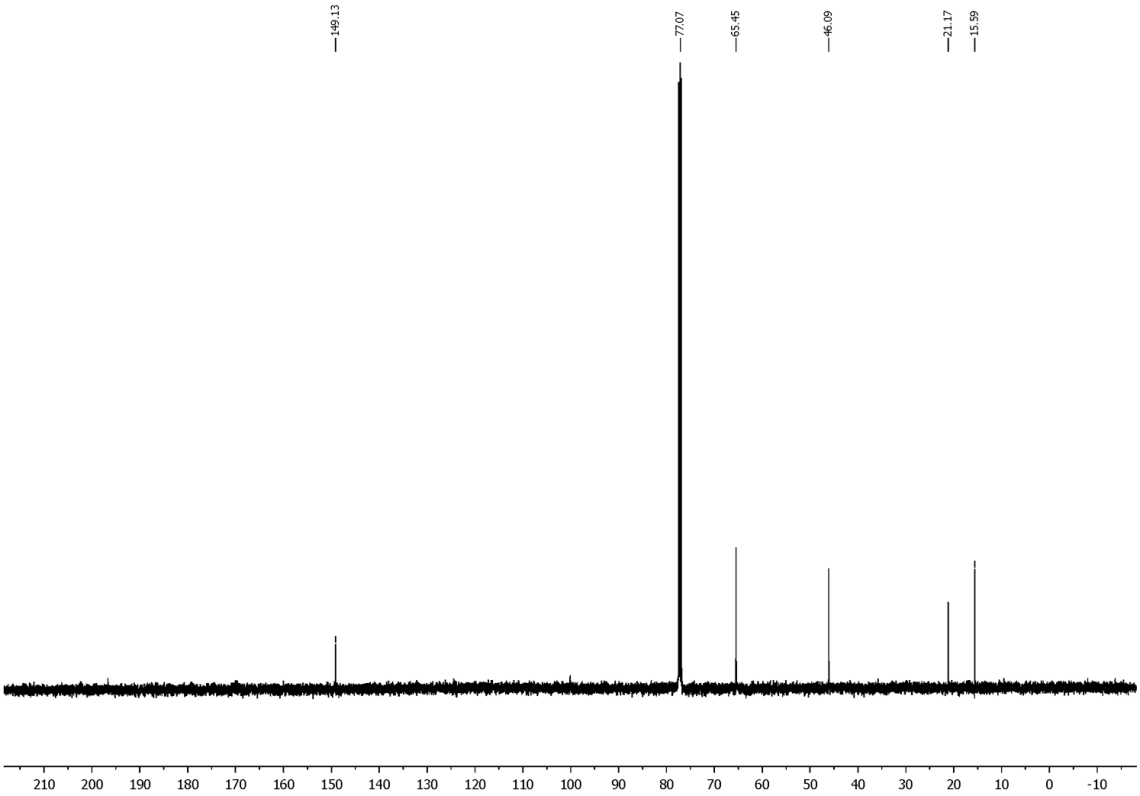
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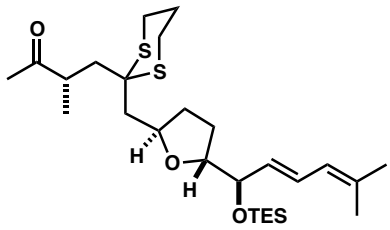
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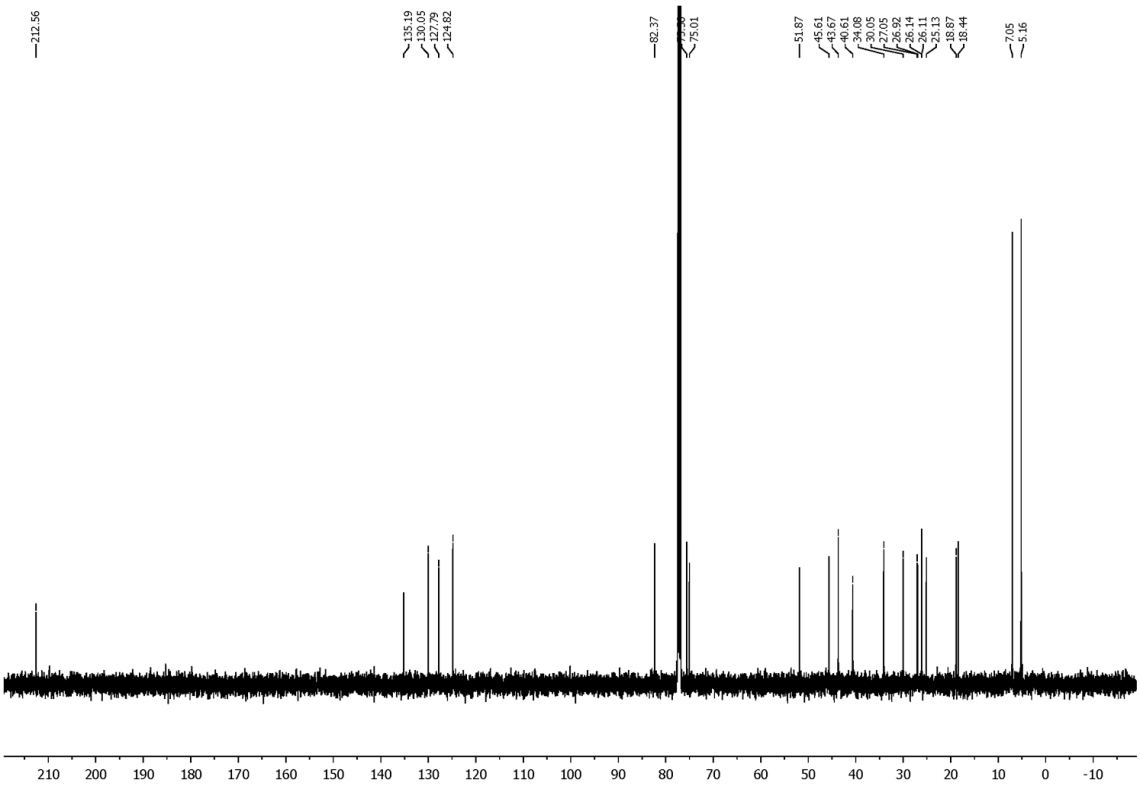
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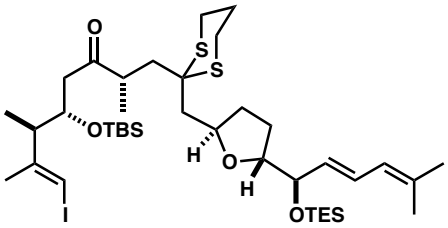
O
S
S
OTBS
H
O
H
I
OTES

360

1.00
1.34
1.93
1.01
2.02
0.94
1.01
2.14
0.98
1.21
3.09
1.18
1.04
1.03
3.57
1.70
1.37
6.10
2.83
3.05
2.94
4.42
1.42
2.80
2.78
8.55
8.06
5.75
2.79
2.76
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
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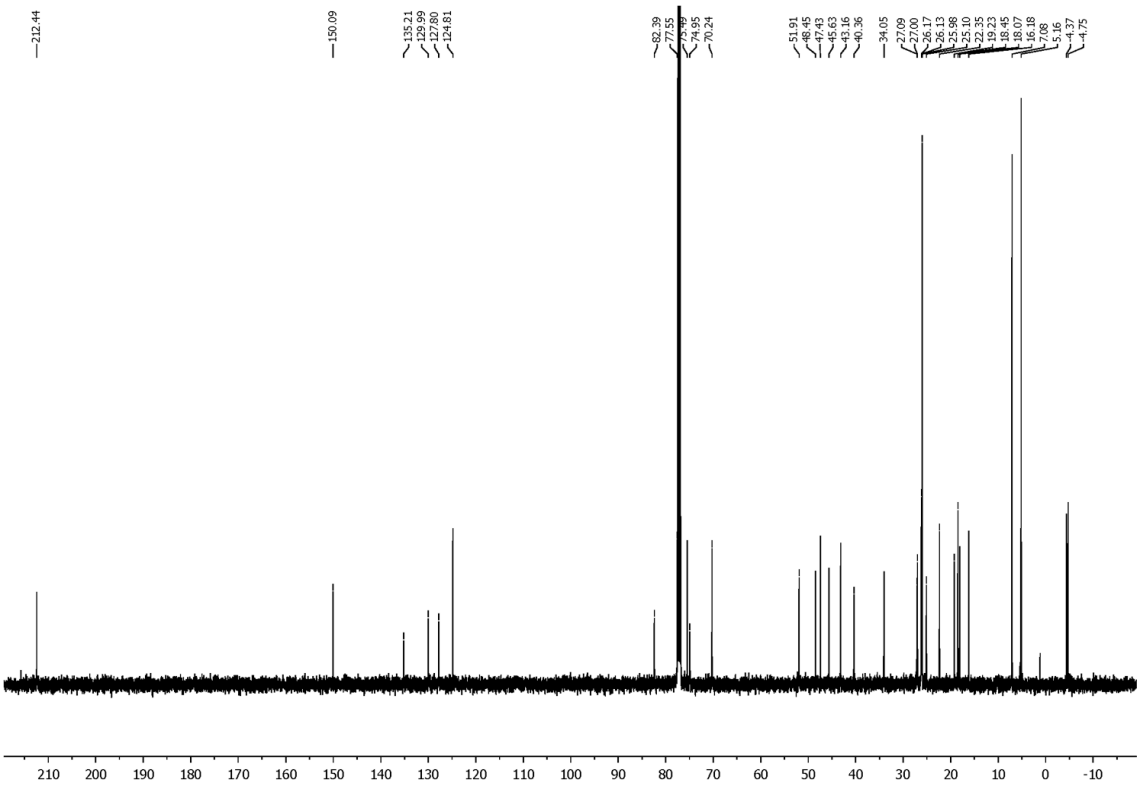
0.0
-0.5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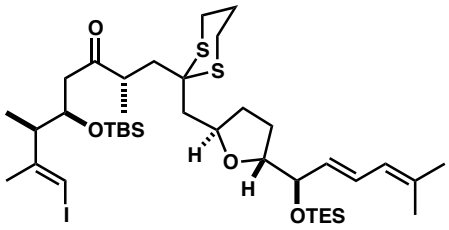
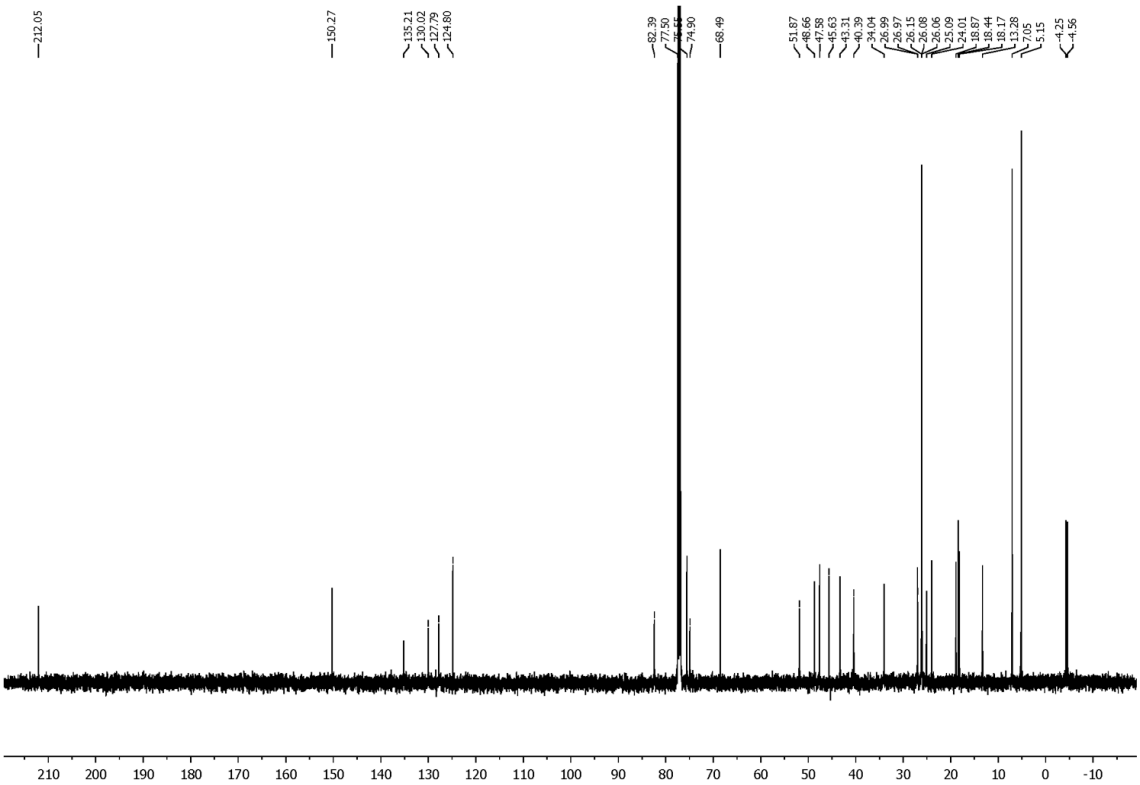
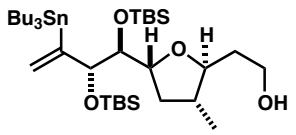
135.21
129.99
127.80
124.81
82.39
77.55
75.49
74.95
70.24
51.91
48.45
47.43
45.63
43.16
40.36
34.05
27.09
27.00
26.17
26.13
25.98
25.10
22.35
19.23
18.45
18.07
16.18
7.08
5.16
-4.37
-4.75
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10



393




Bu3Sn
OTBS
H
O
H
OTBS
OH

394

1.06
1.05
1.03
1.00
1.01
2.14
0.98
0.94
0.99
1.03
1.10
9.03
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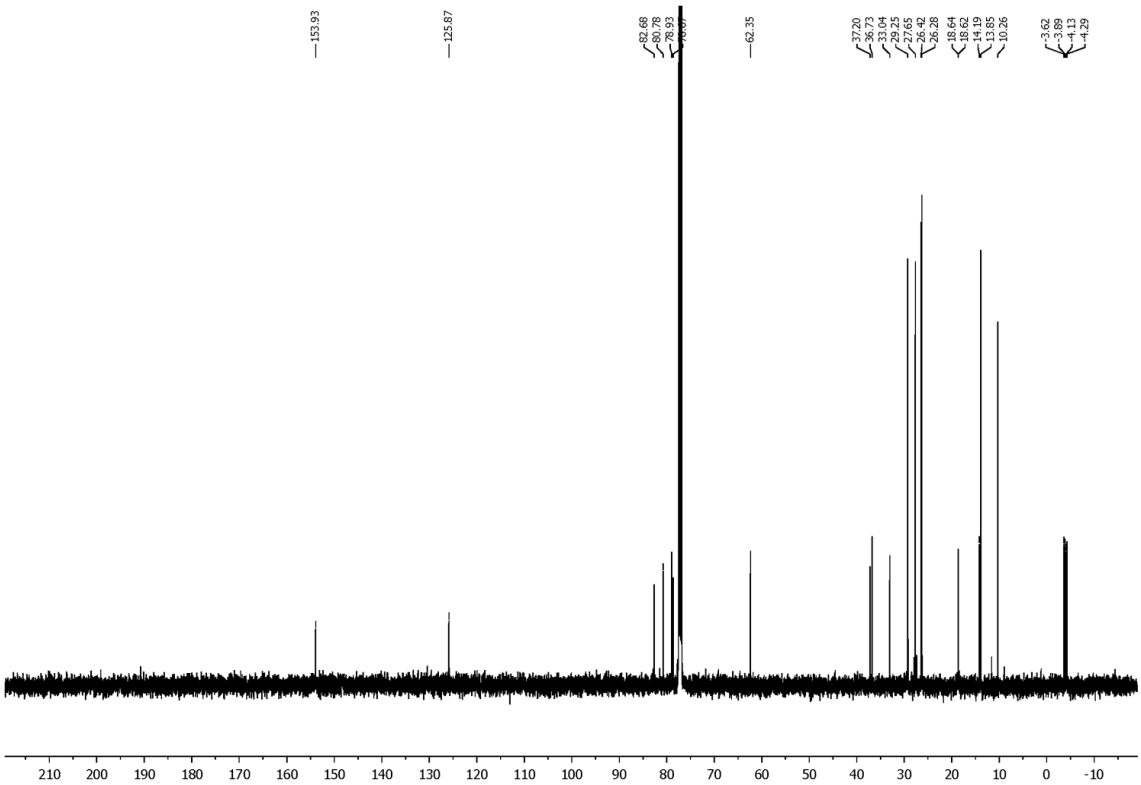
37.77
8.26
3.10
3.03
2.98
2.99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82.68
80.78
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36.73
33.04
29.25
27.65
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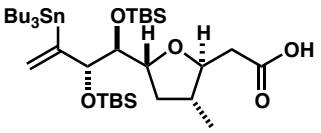
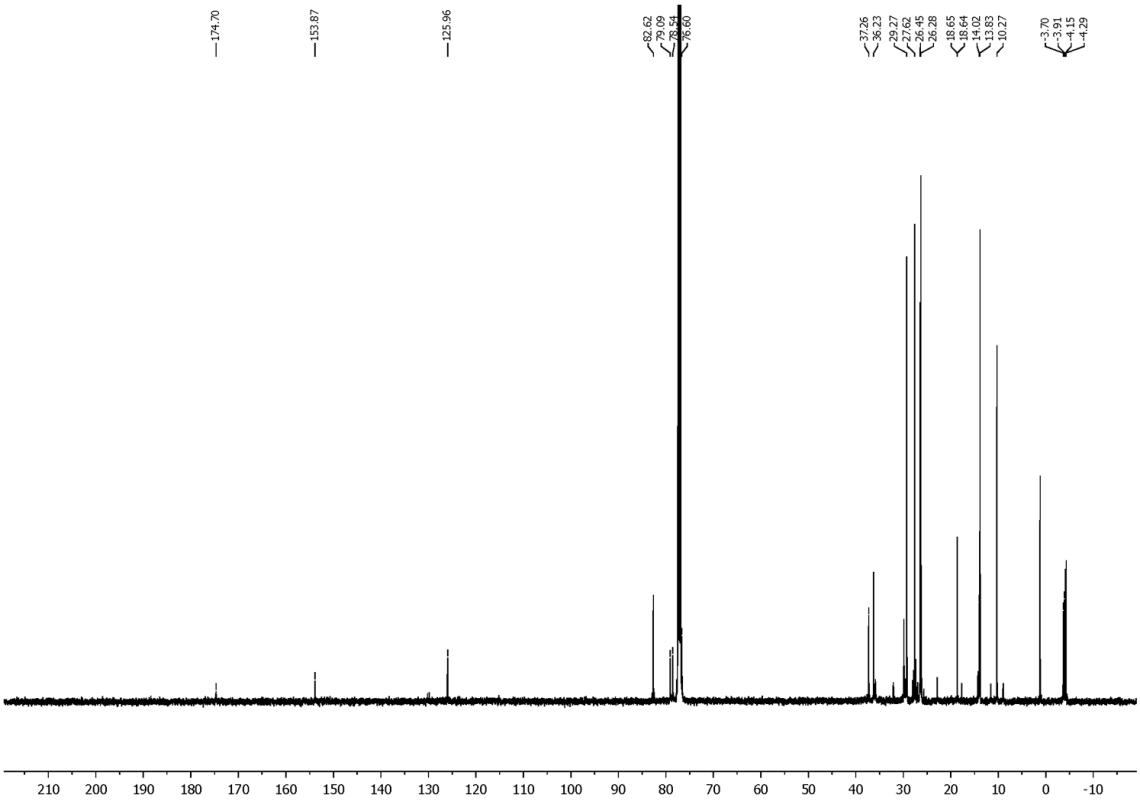
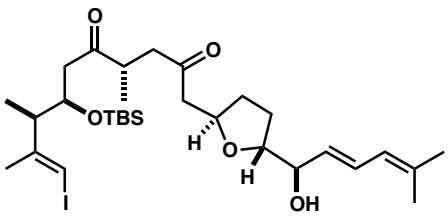
18.64
18.62
14.19
13.85
10.26
-3.62
-3.89
-4.13
-4.29


Bu3Sn
OTBS
H
O
H
OH
OTBS
O

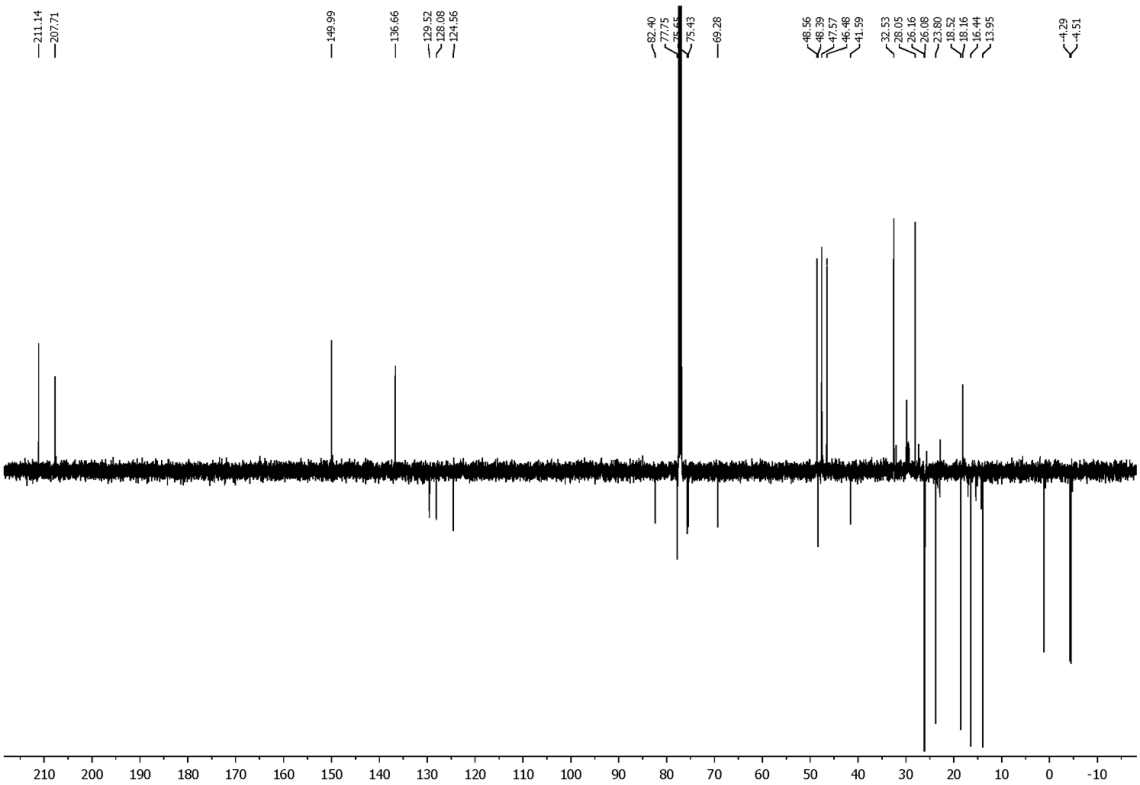
396

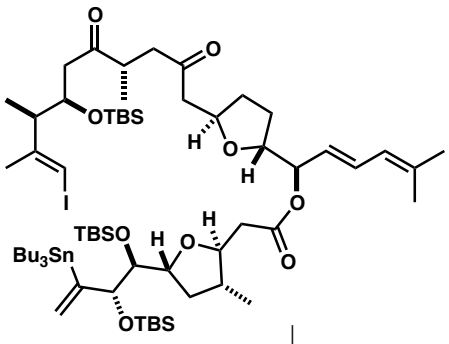
0.79
1.05
1.03
1.00
1.96
0.92
0.99
1.05
1.10
1.00
1.11
6.43
7.39
36.16
2.80
2.85
2.52
2.69
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1


174.70
153.87
125.96
82.62
79.09
78.54
76.60
37.26
36.23
29.27
27.62
26.45
26.28
18.65
18.64
14.02
13.83
10.27
-3.70
-3.91
-4.15
-4.29
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10



400





402