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An Iterative Approach to the Stereocontrolled Total Synthesis of Bahamaolide A and Mycapolyol E

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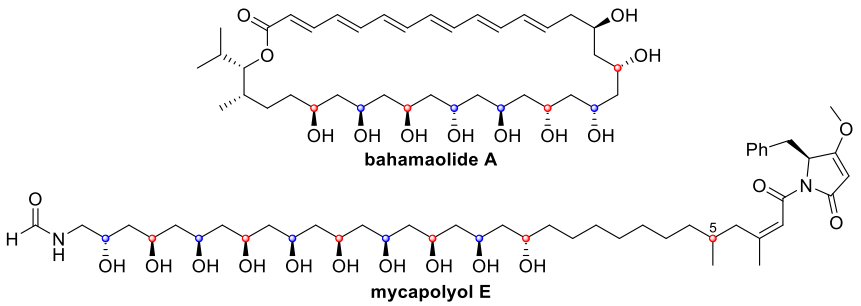
Abstract

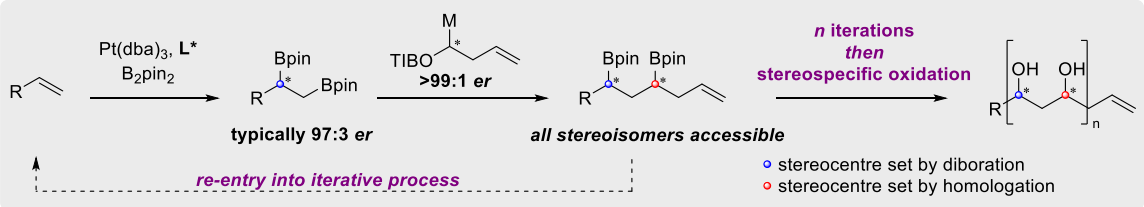
Polyketide natural products are of particular interest due to their highly specific and potent biological activity and structural diversity. The recurring motifs, such as (deoxy)propionate or acetate, often present in this class of molecules can be synthesised through iterative processes.

Bahamaolide A and mycapolyol E contain an extended 1,3-polyol, comprising nine or ten stereodefined 1,3-related hydroxyl groups, respectively; to date, the total synthesis of these compounds has not been reported. Herein the application of an iterative protocol to construct the 1,3-polyol is described; specifically, asymmetric diboration of a terminal alkene followed by primary-selective homologation of the resulting 1,2-bis(boronic ester) with an enantiopure carbenoid bearing a pendent alkene primed to undergo subsequent diboration. When performed iteratively this enabled the synthesis of a 1,3-poly(boronic ester) with exquisite levels of stereocontrol. Functional group interconversions were not necessary between iterations, since the boronic esters themselves masked the hydroxyl functionality, which was revealed in a later stereospecific oxidation.

This was employed in a bidirectional manner to prepare the 1,3-polyol in bahamaolide A. Diboration–homologation–diboration proved a step-efficient approach to rapidly access a C_2-symmetric octa(boronic ester) from 1,4-pentadiene. The octa(boronic ester) was desymmetrised through sequential homologation at the terminal primary boronic esters before poly(oxidation) where eight boronic esters were converted to the corresponding polyol in one operation. Cross-metathesis then a Horner-Wadsworth-Emmons reaction proceeded with high selectivity for six *E*-alkenes. The first total synthesis of bahamaolide A was completed in fourteen steps (LLS).

The 1,3-polyol in mycapolyol E is not C_2-symmetric and so the iterative protocol was applied unidirectionally. The C5 stereocentre in mycapolyol E was assigned through synthesis of both diastereomers of the eastern fragment and comparison of NMR data with the isolated natural product. This work discusses the optimised synthesis of the three fragments, their combination through lithiation–borylation reactions and endgame model studies.





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Charlotte and I started our PhDs on the same day and I'm so glad to have had her as an ally for the PhD journey; her positive attitude and sense of perspective was always helpful. Thank you to Joe for a practical induction to organoboron chemistry when I started in the group, and for being such a great fumehood neighbour during my first two years. Joe and the rest of the original N209 core—Alex, Rory, Steve—taught me what it meant to be a PhD student in the Aggarwal group and never let me doubt I'd make it in the end. N209 is the best lab to work in, despite our widely differing tastes in music... The Aggarwal Group Climbing Club (AGCC) provided friendship and bouldering analogies (formal synthesis anyone?) especially appreciated during a period when I was rather busy with people to supervise in the lab. Thank you to Jack for his patience in spending a lot of time working in the dark, and to Molly for all the chats at the microwave and coffee machine as well as her support as a fellow lab manager this year.

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Many thanks to the rest of the polyboron subgroup, to all of my proof-readers for their feedback and encouragement, and to Paul Lawrence and Chris Williams for their assistance in running NMRs on the 700Cryo.

I acknowledge the European Research Council for funding, and the University of Bristol for a COVID-19 related funded extension.

My family asked me once after my undergraduate degree if I wanted to stay in chemistry, and have never questioned that since. This thesis would not have been possible without your continuous love, understanding, tolerance and support.

Certum pete finem.

Author’s Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: DATE:

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List of Abbreviations

Ac	acetyl
acac	acetylacetone
ACP	acyl carrier protein
APCI	Atmospheric Pressure Chemical Ionisation
app.	apparent
aq.	aqueous
Ar	general aromatic group
AT	acyl transferase
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
biPh	biphenyl
BIPHEP	2,2'-bis(diphenylphosphino)biphenyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bpin	boronic acid pinacol ester
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
ca.	circa
calc.	calculated
cat.	catalytic
cod	1,5-cyclooctadiene
conc.	concentration
conv.	conversion
COSY	correlation spectroscopy
CPME	cyclopentyl methyl ether
CSA	camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
de	diastereomeric excess
DFT	density functional theory
DG	directing group
DHP	3,4-dihydropyran
DIBAL-H	diisobutylaluminium hydride
DICHED	1,2-dicyclohexylethane-1,2-diol
DIPEA	*N*,*N*-diisopropylethylamine
DIPED	diisopropylethanediol
DMAP	4-dimethylaminopyridine

DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
2,2-DMP	2,2-dimethoxypropane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppm	bis(diphenylphosphino)methane
dr	diastereomeric ratio
E^+	general electrophile
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
ent	enantiomer
equiv	equivalent(s)
er	enantiomeric ratio
ESI	electrospray ionisation
FT	Fourier transform
GC-MS	Gas Chromatography Mass Spectrometry
h	hour(s)
H-G II	Hoveyda-Grubbs second generation catalyst
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	hexamethylphosphoramide
HOAt	1-hydroxy-7-azabenzotriazole
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
HWE	Horner-Wadsworth-Emmons
I.D.	internal diameter
IC_{50}	half maximal inhibitory concentration
IPA	isopropanol
Ipc	isopinocampheyl
i-Pr	*iso*-propyl
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide
KR	keto reductase
KS	keto synthase
L	ligand
(*R*,*R*)- or (*S*,*S*)-**L***	3,5-diisopropylphenyltaddol-PPh
LA	general Lewis acid
LC-MS	Liquid Chromatography Mass Spectrometry
LDA	lithium diisopropylamide
LG	leaving group
LiDBB	lithium 4,4'-di-*tert*-butylbiphenylide
LiHMDS	Lithium bis(trimethylsilyl)amide

LLS	longest linear sequence
MALDI	Matrix assisted Laser Desorption/Ionisation
m-CPBA	*meta*-chloroperoxybenzoic acid
Mes	mesityl
MOM	methoxymethyl
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
n.r.	not recorded
NADPH	nicotinamide adenine dinucleotide phosphate
NBO	natural bond order
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
nd	not determined
NIS	N-iodosuccinimide
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
Nu	general nucleophile
OCb	*N*,*N*-diisopropylcarbamoyl
OTf	trifluoromethanesulfonate
OTIB	2,4,6-triisopropylbenzoyl
P:SM	product:starting material
PG	protecting group
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
PMDTA	*N*,*N*,*N′*,*N″*,*N″*-pentamethyldiethylenetriamine
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
PTFE	Polytetrafluoroethylene
p-Tol	*para*-tolyl
PTSA	*para*-toluenesulfonic acid
pybox	bis(oxazolinyl)pyridyl
pyr	pyridine
quant.	quantitative
R	general carbon-based organic group
ref	reference
R_f	retention factor
Red-Al	Sodium bis(2-methoxyethoxy)aluminum dihydride
ROESY	rotating-frame nuclear Overhauser effect correlation spectroscopy
rt	room temperature
sat.	saturated
S_N2	bimolecular nucleophilic substitution
sp	sparteine
sps	sparteine surrogate
$t_{1/2}$	half-life

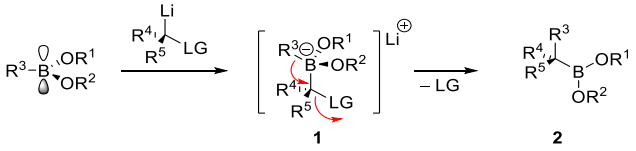
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
TCBC	2,4,6-trichlorobenzoyl chloride
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TIDA	tetramethyl *N*-methyliminodiacetic acid
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
t_R	retention time
Ts	toluenesulfonyl
TTMSS	$(Me_3Si)_3Si$
UV	ultraviolet
wrt	with respect to

1 Boron-mediated Asymmetric Synthesis

This section was adapted from a book chapter written by the author, which has been published in Science of Synthesis: Advances in Organoboron Chemistry towards Organic Synthesis.[1]

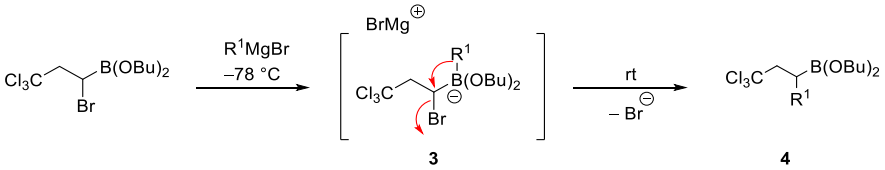
1.1 The 1,2-Metalate Rearrangement

In a borane or boronic ester, the vacant *p* orbital on the boron atom is sufficiently electrophilic to accept a lone pair of electrons from an incoming nucleophile generating a tetravalent boronate complex (**1**). If there is a leaving group stationed on the carbon atom *alpha* to the boron atom, boronate complex **1** can undergo stereospecific 1,2-migration with concomitant expulsion of the leaving group to form homologated boronic ester **2** (**Scheme 1**). The 1,2-metalate rearrangement requires the migrating- and leaving groups to be *anti*-periplanar, which renders the operation stereospecific, occurring with inversion of configuration at the α-carbon centre. As the 1,2-metalate rearrangement is stereospecific, this migration represents a powerful method for the formation of stereodefined boronic esters.



Scheme 1 Boronate complex formation and subsequent 1,2-migration. LG: leaving group.

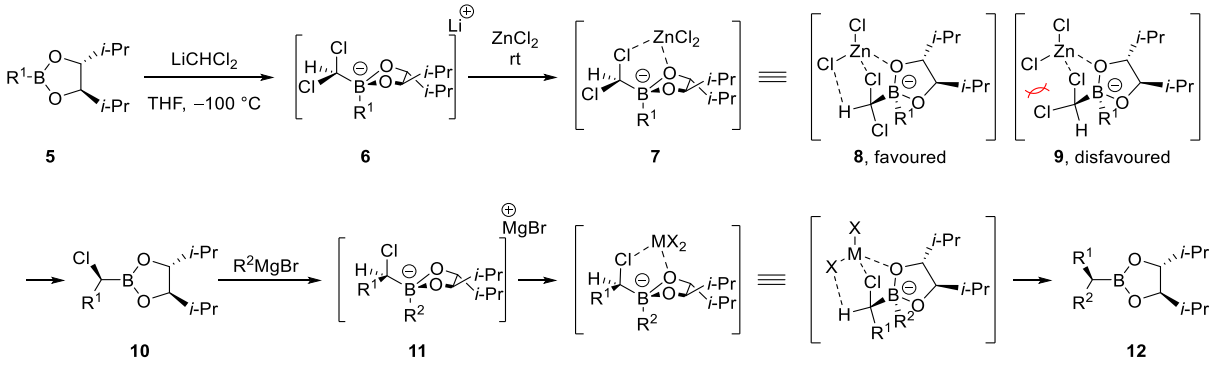
1,2-Migration is a phenomenon first reported by Matteson.[2] It was observed that several nucleophiles could displace the halide ion of α-haloalkyl boronic esters much faster than in a traditional S_N2 process with activated electrophiles such as allyl bromides, which led them to propose that an alternative mechanism was in action (**Scheme 2**). Initial nucleophilic addition to boron resulted in the formation of boronate complex **3**. Chemoselective 1,2-migration of a carbon ligand on boron to the electrophilic α-carbon atom with expulsion of the halide gave rearranged substitution product **4**. This nucleophilic attack followed by 1,2-rearrangement represents a homologation of the original boronic ester.



Scheme 2 Boron-assisted nucleophilic substitution. rt: room temperature.

1.2 Substrate-controlled Homologation of Boronic Esters

The Matteson reaction is the displacement of a leaving group from the α-carbon atom of an alkylboronic ester through addition of a nucleophile.[3] Typically, this reaction is performed in an iterative two-step sequence: 1) initial formation of an α-halo boronic ester through homologation of an alkylboronic ester with (dihalomethyl)lithium, followed by 2) displacement of the α-halide upon addition of a nucleophile to afford a homologated boronic ester, which can itself be re-subjected to the same two-step sequence, thus enabling the construction of contiguous stereocentres. The product can be obtained with exquisite levels of diastereoselectivity (>99:1 diastereomeric ratio, *dr*) through the use of chiral diol ligands on boron and the addition of zinc chloride, where the diastereoselectivity is controlled by the stereochemical environment imparted by the chiral ligand (**Scheme 3**).[4]



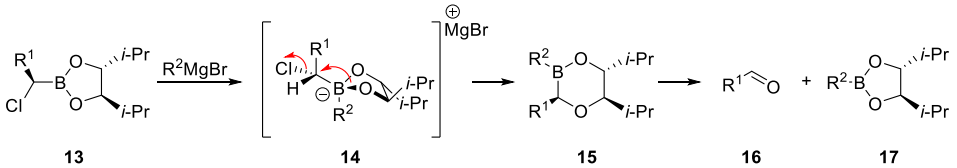
Scheme 3 Diastereoselective Matteson homologation in the presence of $ZnCl_2$.

Addition of (dichloromethyl)lithium—preformed from butyllithium (BuLi) and dichloromethane at −100 °C—to alkylboronic ester **5** affords boronate complex **6** (**Scheme 3**). Zinc chloride then coordinates to both the less sterically hindered oxygen atom of the boronic ester moiety and to the *pro-R* chloride, placing it *anti*-periplanar to the migrating R^2 group and so facilitating migration of complex **7** upon warming to ambient temperature. In the favoured transition state (**8**) there is also a further stabilising interaction between a chloride of zinc chloride and the proton at the α-boryl carbon centre.[5] In the disfavoured case (**9**), zinc chloride coordinates the less hindered oxygen atom of the boronic ester and the *pro-S* chloride; however, there is now an unfavourable steric interaction between two chloride ions instead of the favourable chloride-proton interaction. Midland has shown through calculation that the difference in energy between transition states **8** and **9** is 12.6 kcal mol^{-1}.[6] Subsequent treatment of α-chloro boronic ester **10** with a Grignard reagent gives boronate complex **11**, which undergoes stereospecific 1,2-metalate rearrangement to afford secondary boronic ester **12** essentially as a single diastereomer with inversion of stereochemistry at the α-carbon atom.

In the presence of lithium chloride, epimerisation of α-chloro boronic ester **10** can occur through halide ion exchange, resulting in an erosion in diastereoselectivity.[7] The epimerisation is accelerated by dimethyl sulfoxide and water, since these can promote ionisation of lithium chloride, so it is important that any zinc chloride added is rigorously dried prior to use. In addition, quenching the reaction with a small amount of water prior to extraction can lead to a reduction in diastereoselectivity to ~90:10 *dr*. Despite this, epimerisation can be avoided by quenching with a saturated solution of ammonium chloride, which was postulated to keep the boronic ester and zinc chloride in separate phases and so affords the homologated product in 99:1 *dr*.[8]

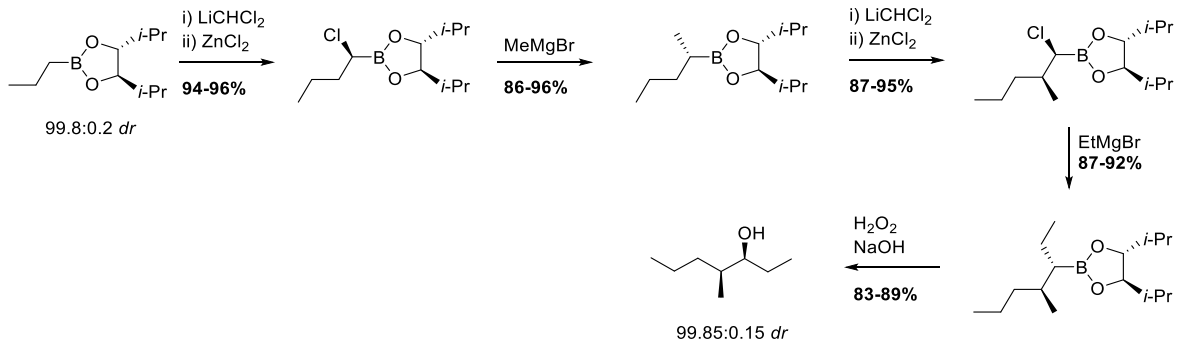
Matteson showed that the C_2-symmetric diols diisopropylethanediol (DIPED)[9] and 1,2-dicyclohexylethane-1,2-diol (DICHED)[10] performed superbly as chiral ligands in the asymmetric homologation of boronic esters. The reason for this is that in certain cases C_2-symmetric boronic esters undergo sequential double stereodifferentiation, where the contra kinetic minor diastereomer is discriminated against twice within the reaction sequence.[11] In the first step, the favoured transition state **8** migrates smoothly to give the major diastereomer **10**, which, following addition of a Grignard reagent, undergoes clean 1,2-migration to desired product **12** (**Scheme 3**). In contrast, when the minor diastereomer **13** (arising from disfavoured transition state **9**) is treated with a Grignard reagent, the resulting boronate complex **14** undergoes contra thermodynamic *O*-migration to afford borinic ester **15**, which decomposes upon isolation to aldehyde **16** and boronic ester **17** (**Scheme 4**).

The observed *O*-migration can be understood by examining the favoured conformations of the intermediate boronate complexes.[11] In the case of diastereomer **11**, the favoured conformation places the departing chloride ion *anti*-periplanar to the migrating R^2 group, resulting in smooth rearrangement to the desired product **12** (**Scheme 3**). However, boronate complex **14** adopts a conformation where the R^1 group is *anti* to the migrating R^2 group to avoid a disfavourable steric interaction between R^1 and the chiral ligand, which results in a DIPED oxygen atom positioned *anti* to the departing chloride ion leading to *O*-migration (**Scheme 4**).



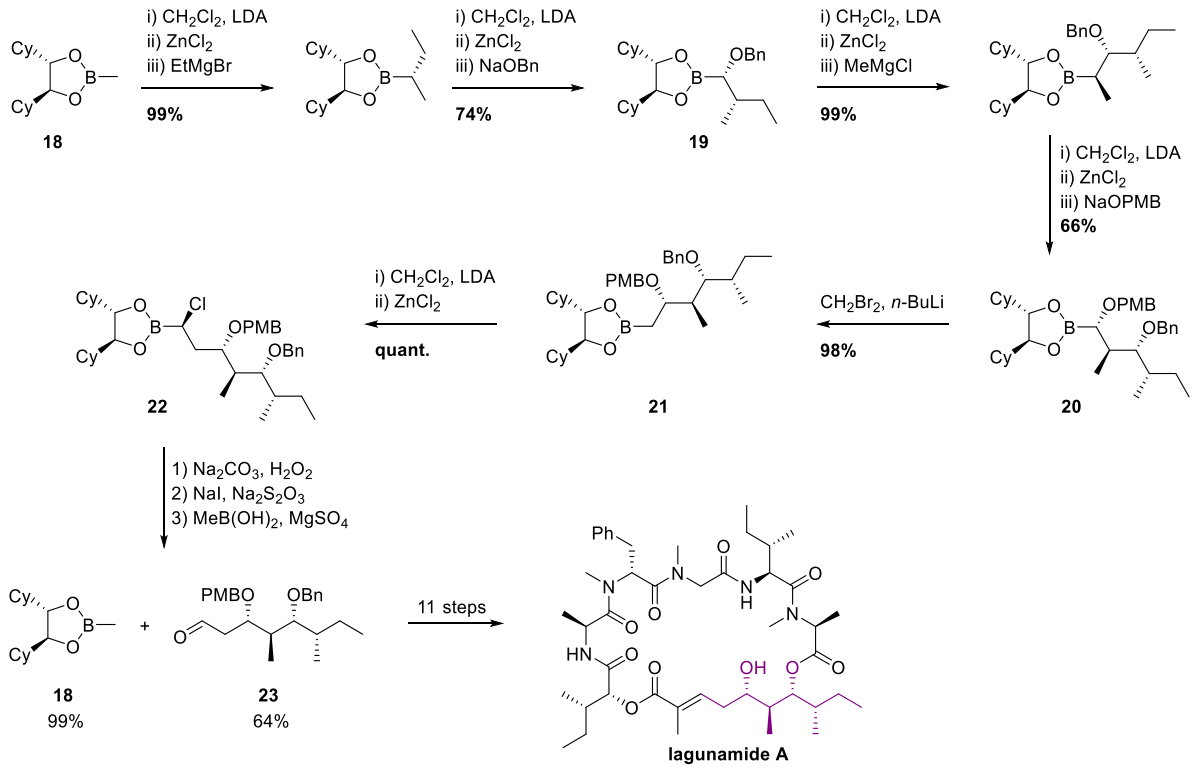
Scheme 4 *O*-Migration upon treatment of minor isomer **13** with a Grignard reagent.

Practically this phenomenon results in matched case homologations, where the substrate and reagent stereocontrol work together to yield products with very high *dr* values, as demonstrated in the synthesis of all four stereoisomers of the insect pheromone 4-methyl-3-heptanol in almost perfect diastereoselectivity (**Scheme 5**).[11]



Scheme 5 Synthesis of (3*S*,4*S*)-4-methyl-3-heptanol.

Kazmaier reported the synthesis of polyketide fragment **23** as an intermediate in the synthesis of lagunamide A using six sequential Matteson homologation reactions starting from methyl boronic ester **18** (**Scheme 6**).[12] (Dichloromethyl)lithium was generated *in situ* through the addition of lithium diisopropylamide (LDA) to a mixture of the boronic ester substrate and dichloromethane.[13] The first four homologations to obtain **20** proceeded smoothly in high yield to afford essentially a single diastereomer; the lower isolated yields for homologated products **19** and **20** were due to partial decomposition on silica gel. However, introduction of a methylene group to **20** was more challenging and required (bromomethyl)lithium as the homologating agent with the reaction temperature being strictly maintained at –60 °C, which permitted the formation of **21** in 98% yield. Following the final Matteson homologation, oxidation of **22** gave terminal aldehyde **23**, which was transformed to lagunamide A in a further eleven steps. Recovery of the chiral ligand 1,2-dicyclohexylethane-1,2-diol was achieved in quantitative yield through the addition of methylboronic acid, thus regenerating methyl boronic ester **18**.



Scheme 6 Six consecutive Matteson reactions in the synthesis of lagunamide A. PMB: *para*-methoxybenzyl. quant.: quantitative.

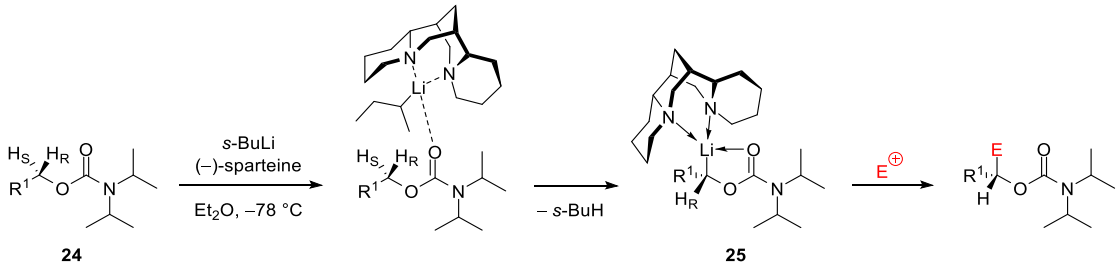
1.3 Reagent-controlled Homologation of Boronic Esters

Matteson's approach to the substrate-controlled homologation of boronic esters enables the synthesis of complex motifs with excellent control over stereoselectivity. However, a superior process would operate under reagent control, where the stereochemical information is imparted through a chiral reagent and not through a chiral auxiliary appended to the substrate. Reagent-controlled homologation has the advantage over substrate-controlled homologation in that either enantiomer/diastereoisomer of the product can be obtained by selecting the appropriate enantiomorph of the chiral reagent, whereas in a substrate-controlled process a two-step sequence to exchange the enantiomer of chiral ligand must be performed prior to homologation. In addition, since the stereoselectivity is now set by the reagent and not the substrate, the desired configuration at a particular stereocentre can be generated independently of any existing stereocentres.

For a reagent-controlled homologation of boronic esters to be successful a number of criteria must be fulfilled: (i) the chiral reagent must be chemically and configurationally stable under the reaction conditions; (ii) the formation of the boronate complex and the subsequent 1,2-metalate rearrangement must be stereospecific; (iii) any excess carbenoid must decompose prior to 1,2-metalate rearrangement to prevent over-homologation; (iv) the

stereoselectivity of the reaction should not be influenced by stereogenic centres already present in either the carbenoid or the boronic ester.

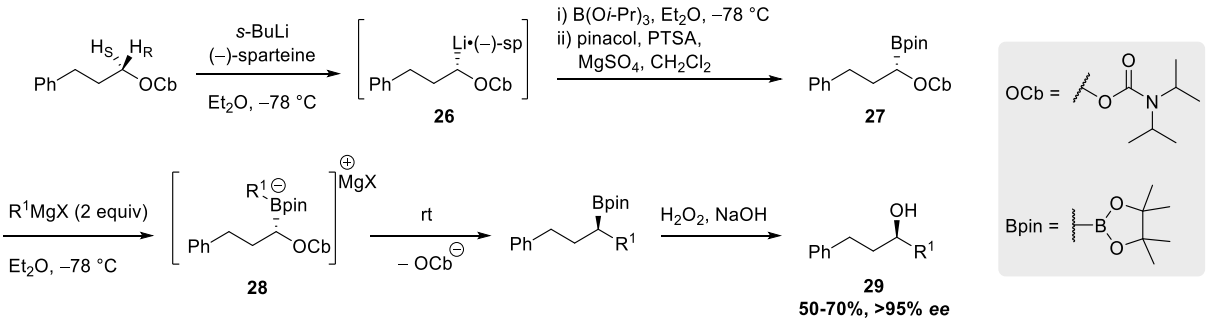
Enantioselective deprotonation of Hoppe-type carbamates[14] or Beak-type triisopropylbenzoates[15] gives dipole stabilised carbanions, which fulfil the criteria for reagent-controlled homologation of boronic esters. Hoppe reported the preparation of enantioenriched lithiated carbenoids, which were chemically and configurationally stable at −78 °C, through the reagent-controlled deprotonation of *O*-alkyl carbamate **24** using (−)-sparteine ligated *s*-BuLi (**Scheme 7**).[16,17] No deprotonation was observed in the absence of diamine and the *iso*-propyl substituents on the nitrogen atom were necessary in order to prevent *s*-BuLi attack at the carbonyl carbon atom. Following deprotonation, stereoretentive trapping of lithiated carbamate **25** with a range of electrophiles was demonstrated.



Scheme 7 Generation of chiral lithiated carbenoids through (–)-sparteine mediated asymmetric deprotonation. E^+: general electrophile.

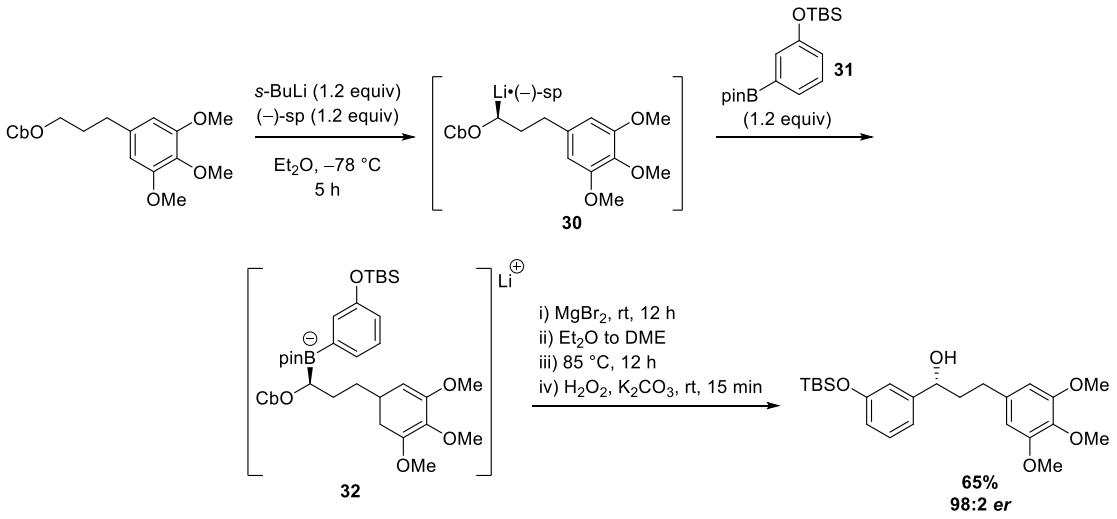
Hoppe demonstrated the first example of a reagent-controlled homologation of boronic esters with the conversion of primary alcohols to enantioenriched secondary alcohols in a two-step process: 1) electrophilic trapping of lithiated carbamate **26** with triisopropyl borate with retention of configuration to generate α-carbamoyloxy-alkyl boronic ester **27** (analogous to Matteson's α-haloalkyl boronic esters) in 95% enantiomeric excess (*ee*) after transesterification with pinacol, followed by 2) nucleophilic attack by a Grignard reagent at −78 °C generating boronate complex **28**, which undergoes stereospecific 1,2-metalate rearrangement with inversion of configuration upon warming to ambient temperature, with concomitant expulsion of the carbamate (**Scheme 8**).[16] Oxidation using basic hydrogen peroxide revealed the secondary alcohols (**29**) in good yield and high enantiomeric excess. The electron-withdrawing carbamate is not only necessary as a leaving group for the rearrangement step, but is involved in promoting lithiation, both by increasing the acidity of the α-proton and as a directing group, by coordinating to the lithium ion (**Scheme 7**). The use of two equivalents of Grignard reagent was crucial to obtain high yields, presumably due to

one equivalent acting as a Lewis acid and aiding in the expulsion of the carbamate. Use of the corresponding organolithium reagent led to depleted yields.



Scheme 8 Hoppe's two-step boronic ester homologation. PTSA: *para*-toluenesulfonic acid.

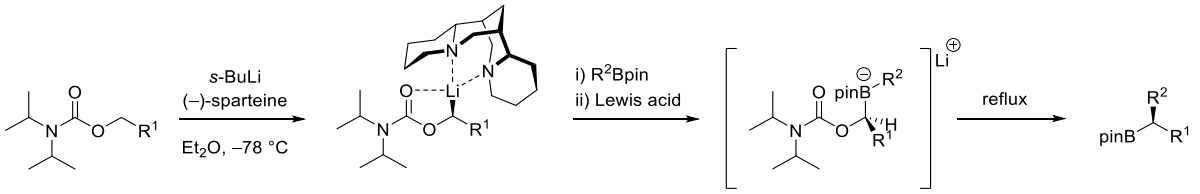
The requirement to isolate intermediate boronic ester **27** in Hoppe's reagent-controlled process left clear room for improvement. Kocienski showed a one-step variant of Hoppe's homologation in his synthesis of (*S*)-(–)-*N*-acetylcolchinol by trapping lithiated carbamate **30** directly with a boronic ester (**Scheme 9**).[18]



Scheme 9 Kocienski's one-pot homologation in the synthesis of (S)-(–)-*N*-acetylcolchinol. sp: sparteine; TBS: *tert*-butyldimethylsilyl; *er*: enantiomeric ratio.

The direct trapping of lithiated carbamate **30** with boronic ester **31** proceeded smoothly to provide boronate complex **32**. The migration step proved more challenging and required the addition of magnesium bromide (a weak Lewis acid which increases the leaving group ability of the carbamate by binding to the carbonyl oxygen), a solvent change to dimethoxyethane (DME) and elevated temperatures to facilitate 1,2-rearrangement. This highlighted that there is an order of migratory aptitude and that aryl groups are clearly more challenging migrating groups than alkyl substituents (*vide infra*).

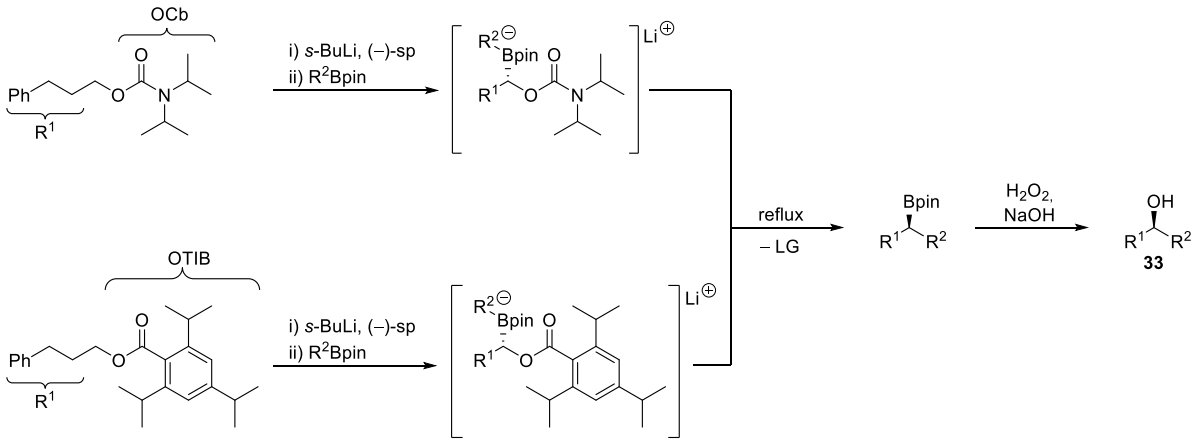
Aggarwal reported an analogous 'one-pot' homologation of boronic esters through the direct trapping of a lithiated carbamate with a boronic ester (**Scheme 10**), a process now colloquially referred to as lithiation–borylation. This process was shown to be a powerful method to prepare a wide range of chiral secondary alcohols in good yield and high enantioselectivity.[19] This approach showed a considerable substrate scope, including methyl carbamates and those with primary or branched secondary alkyl chains, together with aryl and alkyl boranes and boronic esters. In general, 1,2-migration of boronate complexes derived from boronic esters was slower and required the addition of the Lewis acid magnesium bromide and heating at reflux, compared to boranes where 1,2-metalate rearrangement commenced at −40 °C.



Scheme 10 Aggarwal's lithiation–borylation of Hoppe-type carbamates.

The necessity for forcing conditions for migration was proved to be general while exploring the scope of the homologation of boronic esters with lithiated carbamates. As a result, even though a boronate complex could be efficiently formed, this slow migration and tendency for the reaction not to go to completion led to a low yield of product. In order to increase the rate of 1,2-metalate rearrangement, efforts were made to find an alternative leaving group. Beak reported that 2,4,6-triisopropylbenzoates can be deprotonated with *s*-BuLi/*N,N,N',N'*-tetramethylethylenediamine (TMEDA) to generate a racemic carbenoid which was quenched with electrophiles.[20] Hammerschmidt subsequently showed that lithiated triisopropylbenzoates, generated by the tin-lithium exchange of the corresponding enantioenriched α-stannyl benzoate, are configurationally stable at –78 ºC.[21] After showing that the deprotonation of triisopropylbenzoates could be rendered asymmetric through the use of a chiral diamine such as (–)-sparteine and the resulting enantioenriched carbenoid subsequently trapped with boronic esters to yield boronate complexes,[22] Aggarwal demonstrated that these hindered benzoates were comparable to their carbamate analogues when employing fragments known to be efficient migrating groups (**Table 1**, entries 1-4). However, the benzoate leaving group proved far superior in the cases of poor migrating groups. A combination of (i) steric, (ii) conformational and (iii) electronic effects can hinder the rate of 1,2-migration.[23] (i) The C–B bond with a methyl migrating group will be shorter, and therefore stronger, due to the small size of the methyl substituent. (ii) Conformational

effects may interfere with the migration of phenyl groups when the leaving group is a sulfonium ion.[24] (iii) 1,2-Migration will be slower for groups bearing a β-electron withdrawing group due to their decreased nucleophilicity.[25] By using triisopropylbenzoates instead of carbamates, the scope of homologation using lithiation–borylation reactions was dramatically expanded to include synthetically important methyl (**Table 1**, entry 6), aryl (**Table 1**, entry 8) and β-electron withdrawing groups (**Table 1**, entries 10 and 12) which all underwent clean migration after two hours at reflux to yield the corresponding products.



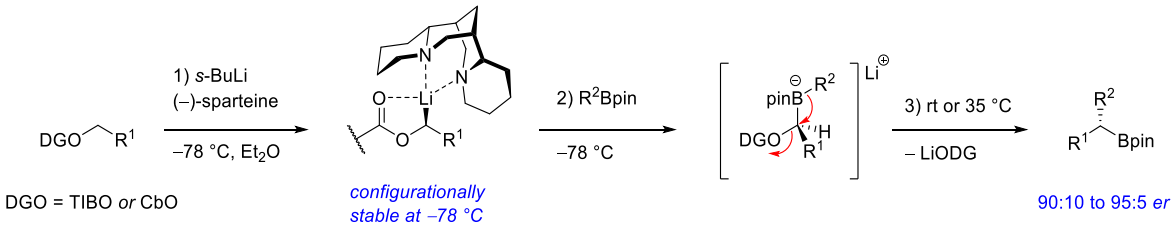
Entry	Migrating group, R^2	Leaving group	Migration time /h	Yield 33 /%	*er*
1	Et	OCb	16	73	99:1
2	Et	OTIB	2	84	96:4
3	Cyclopropyl	OCb	16	71	98:2
4	Cyclopropyl	OTIB	2	86	96:4
5	Me	OCb	16	<10	nd
6	Me	OTIB	2	76	96:4
7	Ph	OCb	16	<10	nd
8	Ph	OTIB	2	79	96:4
9	$(CH_2)_2COO$*t*-Bu	OCb	16	0	nd
10	$(CH_2)_2COO$*t*-Bu	OTIB	2	63	96:4
11	$(OCH_2)_2CN$	OCb	16	0	nd
12	$(OCH_2)_2CN$	OTIB	16	46	97:3

Table 1 Comparison of carbamates and benzoates as leaving groups for lithiation–borylation. nd: not determined.

1.3.1 The Lithiation–borylation reaction

The lithiation–borylation reaction consists of three phases (**Scheme 11**): 1) the generation of a chiral lithiated carbenoid through the enantioselective or enantiospecific deprotonation of a suitable carbamate or benzoate, or through the stereospecific tin-lithium exchange of an

enantioenriched α-stannyl benzoate; 2) the stereoretentive formation of a boronate complex; 3) the stereoinvertive 1,2-metalate rearrangement of the boronate complex to yield a homologated boronic ester with concomitant expulsion of the carbamate or benzoate leaving group. The rates of lithiation, borylation and 1,2-migration are impacted by the identity of the directing group, the solvent, the diamine and steric hinderance at the β-position of the carbamate/benzoate.[26]



Scheme 11 The lithiation–borylation reaction: 1) asymmetric lithiation; 2) stereoretentive borylation; 3) stereospecific 1,2-metalate rearrangement with inversion. DG: directing group.

Lithiation of 2,4,6-triisopropylbenzoates with *s*-BuLi and (+)-sparteine occurs two to three times faster than the corresponding diisopropyl carbamates due to a parasitic interaction between the carbamate, *s*-BuLi and (+)-sparteine, which is observable by *in situ* IR spectroscopy.[26] No such interaction was detected upon lithiation of a benzoate; however, borylation of a lithiated carbamate occurs more rapidly than with the corresponding lithiated benzoate, which has been attributed to a steric effect.[26] The rate of 1,2-migration is faster for benzoates than carbamates, which permits challenging migrating groups, including synthetically important methyl, aryl and β-electron withdrawing groups such as esters, to be tolerated in lithiation–borylation reactions (*vide supra*, **Table 1**).[22] However, solvent exchange to chloroform and heating to reflux can enable a more facile 1,2-migration with carbamates.[27]

Diamine-mediated lithiation of carbamates and benzoates is typically conducted in diethyl ether;[28] however, higher yields are achieved when using cyclopentyl methyl ether (CPME) as the lithiation solvent for secondary dialkyl benzoates[29] and for an advanced tertiary amine-containing primary alkyl benzoate,[30] whilst *tert*-butyl methyl ether (TBME) is superior for the lithiation of highly lipophilic substrates, which are insoluble in diethyl ether at –78 °C.[31] Interestingly, performing the lithiation in tetrahydrofuran (THF) affords products with diminished enantiomeric excess values, since THF competes with sparteine as the ligand on lithium.[30,31] Using the non-coordinating solvent toluene enhances the rate of lithiation for benzoates, potentially due to a higher concentration of the active monomeric diamine-ligated

lithiated species, but reduces the rate of lithiation for carbamates, which has been attributed to an increase in the concentration of parasitic pre-lithiation complexes.[26] The rate of borylation in toluene is much slower for both lithiated carbamates and benzoates; however, carbamates are still borylated faster than benzoates.[26] The rate of borylation can be dramatically increased through addition of the boronic ester as a solution in THF, without erosion of enantioenrichment. THF efficiently displaces sparteine from the lithium ion of the lithiated species, engendering a less hindered carbenoid that can more readily undergo borylation.[26]

The identity of the diamine in the *s*-BuLi/diamine complex also impacts the rate of lithiation of benzoates and carbamates, where the rate increases across the series: sparteine < TMEDA < sparteine surrogate < *N*,*N*'-dimethylbispidine (**Figure 1**).[26] The rate of borylation increases across the series: sparteine surrogate < sparteine < *N*,*N*'-dimethylbispidine < TMEDA.[26] It was suggested that prior to borylation either the diamine or the carbonyl of the leaving group must dissociate from the lithium ion of the lithiated species. The rate of borylation is likely to be impacted by the strength of coordination of the diamine to the lithium ion, which is in turn determined by the same features of the diamine which influence the rate at which they facilitate deprotonation, namely steric hindrance, basicity and flexibility.

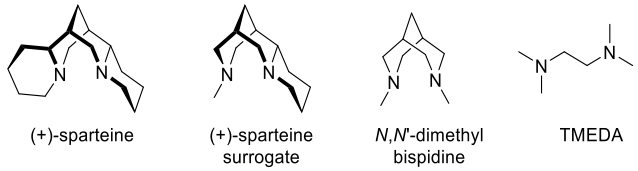
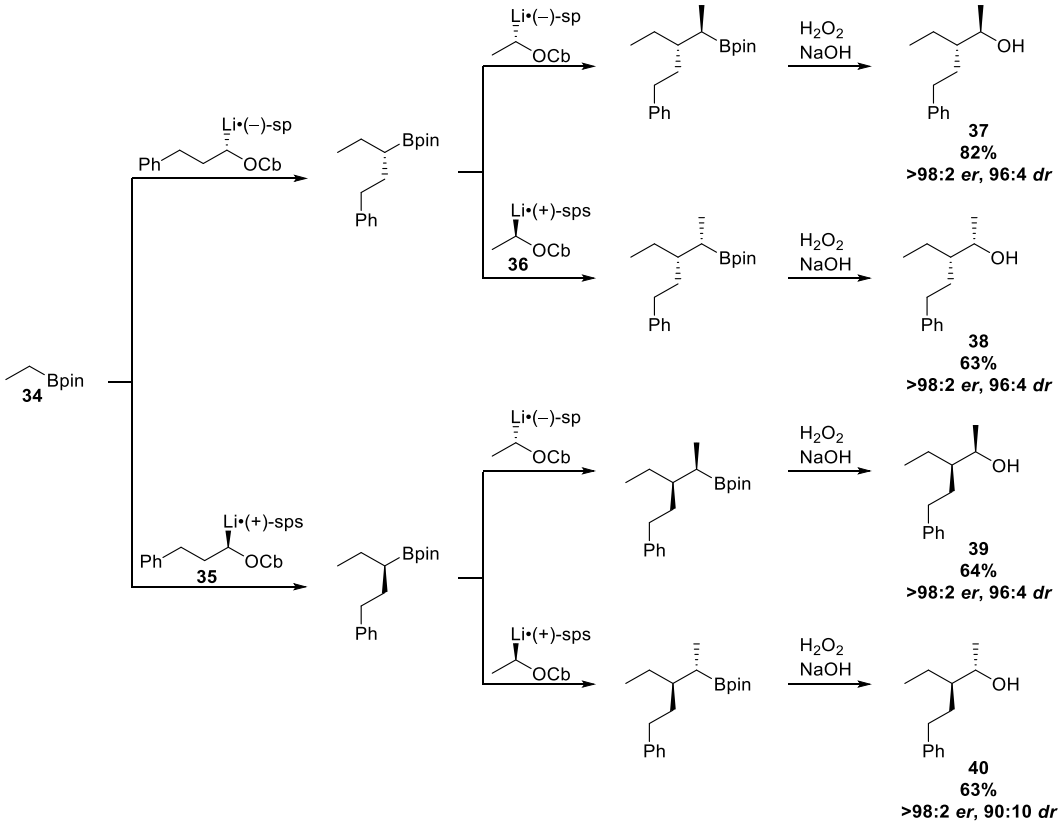


Figure 1 Diamines commonly used as ligands for lithiation.

1.4 Iterative Asymmetric Homologation of Boronic Esters

The iterative application of a reagent-controlled process can result in a product with poor diastereomeric purity for two reasons. Firstly, reagents must be available with perfect *er* values since any minor enantiomers formed in each reagent-controlled step will be delivered into a separate diastereomeric series to that of the desired product, as explained by Horeau's principle,[32] which will result in many diastereomers after a sequence of operations that may be difficult to separate. Secondly, the substrate may influence the enantio-determining step. If the substrate and chiral reagent reinforce one another then a product of very high *dr* will be obtained (matched case); however, if the directing effects of the substrate and chiral reagent oppose one another then poor *dr* will be observed in the product (mis-matched case). A superior process is one which operates entirely under reagent control, where the substrate has no influence over the diastereomeric ratio of the products.

As the homologation of boronic esters with lithiated carbamates proceeds under reagent control, and since the product of such a homologation is itself a boronic ester (**Scheme 10**), Aggarwal has shown that it can be performed iteratively to generate molecules containing contiguous stereocentres with complete control of the relative and absolute configuration.[19] In this vein, all four stereoisomers of 3-ethyl-5-phenylpentan-2-ol were prepared through two sequential homologations of ethyl boronic ester **34** by varying the enantiomer of chiral reagent used in each step (**Scheme 12**). No matched or mis-matched effects were observed in the synthesis of **37**, **38**, **39** and **40**, showing that the process operates under complete reagent control.[19] Given the limited availability of (+)-sparteine at the time, the required enantiomeric diamine for asymmetric lithiation, O'Brien's sparteine surrogate, (+)-sps (**Figure 1**), derived from (–)-cytisine, was used to prepare the opposite carbenoid enantiomer (**35** and **36**).[33]



Scheme 12 Two successful iterations of the lithiation–borylation process.

1.4.1 Assembly–line synthesis

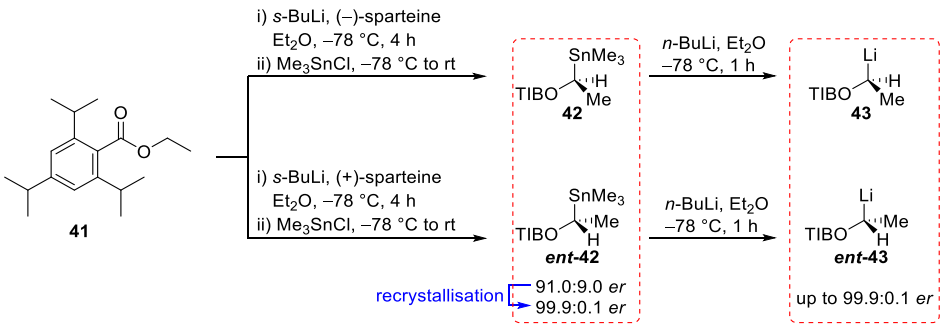
Aggarwal sought to extend this iterative process by developing a method for multiple homologations, resembling a molecular 'assembly line' where simple units are added successively to a growing chain. Assembly–line synthesis involves using lithiation–borylation chemistry in an iterative manner to form multiple contiguous defined stereocentres with high

stereocontrol and without functional group interconversion or intermediate purification between chain extension steps.[34] Using the assembly–line synthesis complex molecules can be prepared with exquisite levels of stereocontrol from a simple boronic ester that is subjected to multiple homologations. Assembly–line synthesis is therefore a way to homologate molecules in a similar fashion to polyketide biosynthesis in nature, where small building blocks are added to 'grow' the molecule through a sequence of chain extension steps.

In addition to the general requirements for an iterative process, namely the availability of chiral reagents with very high enantiomeric excess and that the process is operating exclusively under reagent control, for the iterative homologation of boronic esters there must be complete boronate complex formation in order to prevent under-homologation. Moreover, in order to prevent over-homologation, any excess carbenoid must decompose before migration.

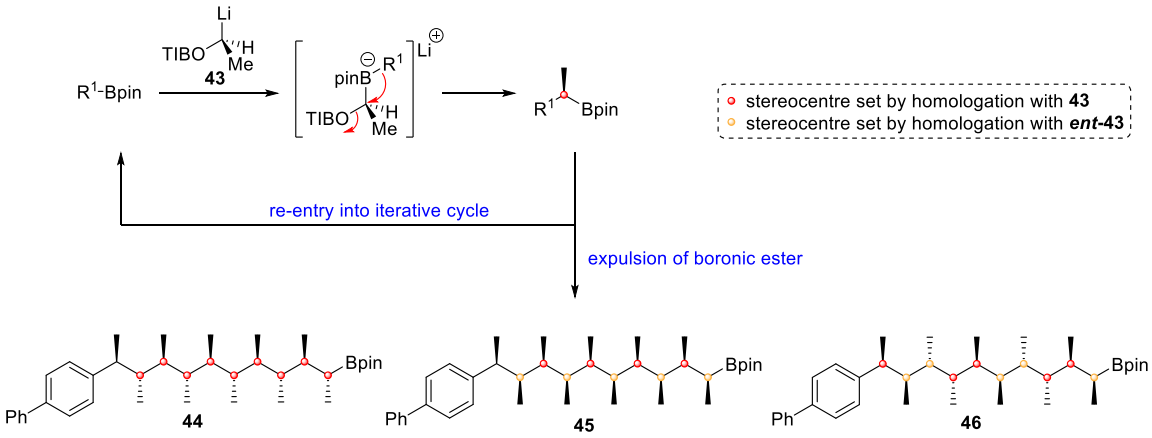
Since the stereocontrol in reagent controlled asymmetric homologation of boronic esters is set by the metalated carbenoid, access to bench stable carbenoid precursors that can be prepared in high enantiopurity is crucial. The carbenoid precursor must possess both a suitable leaving group for the 1,2-migration and principally a substituent that can rapidly undergo stereospecific transmetalation to furnish the lithiated species.

Aggarwal reported the development of α-stannyl ethyl benzoate (**42**) as a carbenoid precursor for the assembly–line synthesis of contiguous methylated hydrocarbons.[34] These carbenoid precursors can be prepared on a multi-gram scale through sparteine-mediated asymmetric deprotonation of *O*-ethyl triisopropylbenzoate **41** followed by electrophilic trapping with trimethyltin chloride, and then recrystallised from methanol to achieve perfect levels of enantiopurity (**Scheme 13**). Stereospecific tin-lithium exchange regenerates the required enantioenriched lithiated benzoate **43** with retention of configuration.



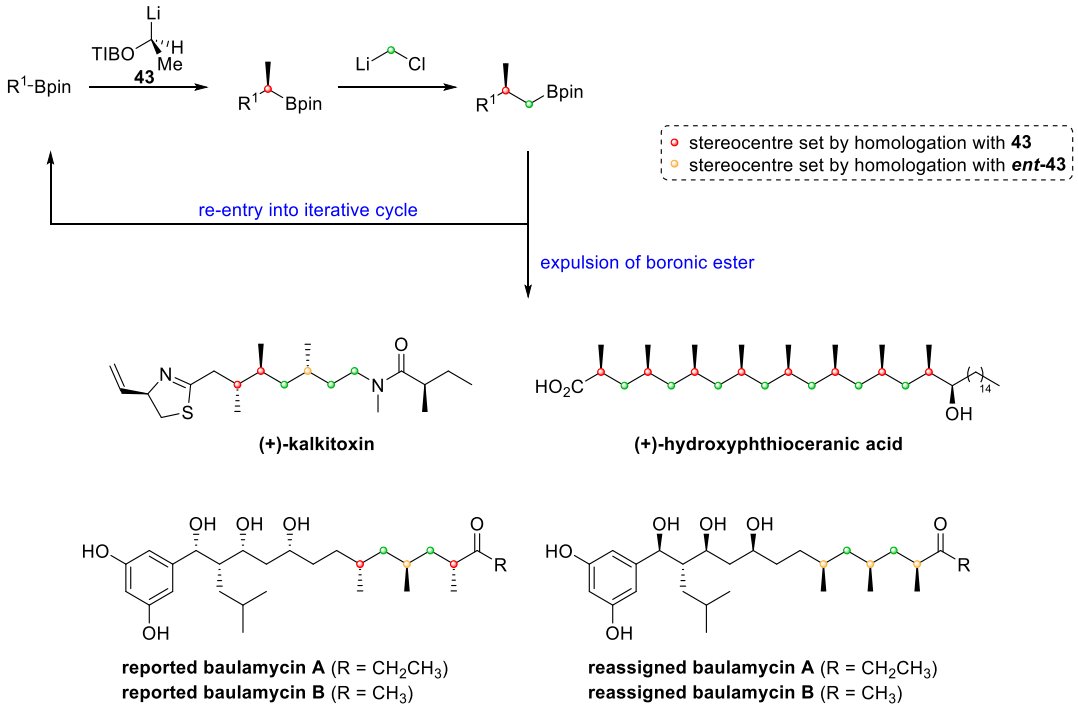
Scheme 13 Preparation of α-stannyl ethyl benzoate carbenoid precursor; typically 55% isolated yield of **42** after two recrystallisations.

This enabled the construction of the all-*anti* (**44**), all-*syn* (**45**) and alternating *anti*-*syn* (**46**) isomers of a homologated boronic ester in good yield (44–58% over nine steps) and essentially as single diastereoisomers, following nine iterative homologations using the (*S*)- or (*R*)-carbenoid as appropriate with an aqueous work-up every three homologations and no intervening column chromatography (**Scheme 14**). No matched or mis-matched effects were observed, confirming that the homologation process was operating exclusively under reagent control. In order to prevent under-homologation, an excess of stannane was used to ensure full boronate complex formation and to prevent over-homologation, following borylation the temperature was raised from −78 °C to −42 °C for one hour (at which temperature the boronate complex is still chemically stable) to allow any excess carbenoid to decompose, before warming to ambient temperature to enable 1,2-migration.



Scheme 14 Assembly–line synthesis using carbenoid **43**.

In addition to installing methyl groups, methylene units can be installed using the Matteson carbenoid, (chloromethyl)lithium, which can be generated through halogen-lithium exchange of bromochloromethane. Alternating between homologation with the (*S*)- or (*R*)-methyl stannane and (chloromethyl)lithium allows the construction of a 1,3-methyl substituted hydrocarbon backbone, *i.e.* the 1,3-polydeoxypropionate structural motif common in natural products.[35] Aggarwal reported the total synthesis of (+)-kalkitoxin and (+)-hydroxyphthioceranic acid using six and sixteen consecutive homologations, respectively, with no intermediate work up or purification during the assembly–line sequence for (+)-kalkitoxin, and column chromatography only after every fourth homologation for (+)-hydroxyphthioceranic acid (**Scheme 15**). The limit of assembly–line homologations was not discovered with these targets as there was no decrease in the efficiency of the homologations of the growing carbon chain towards the end of the sequence compared to those at the start, demonstrating these reagents' reliability.



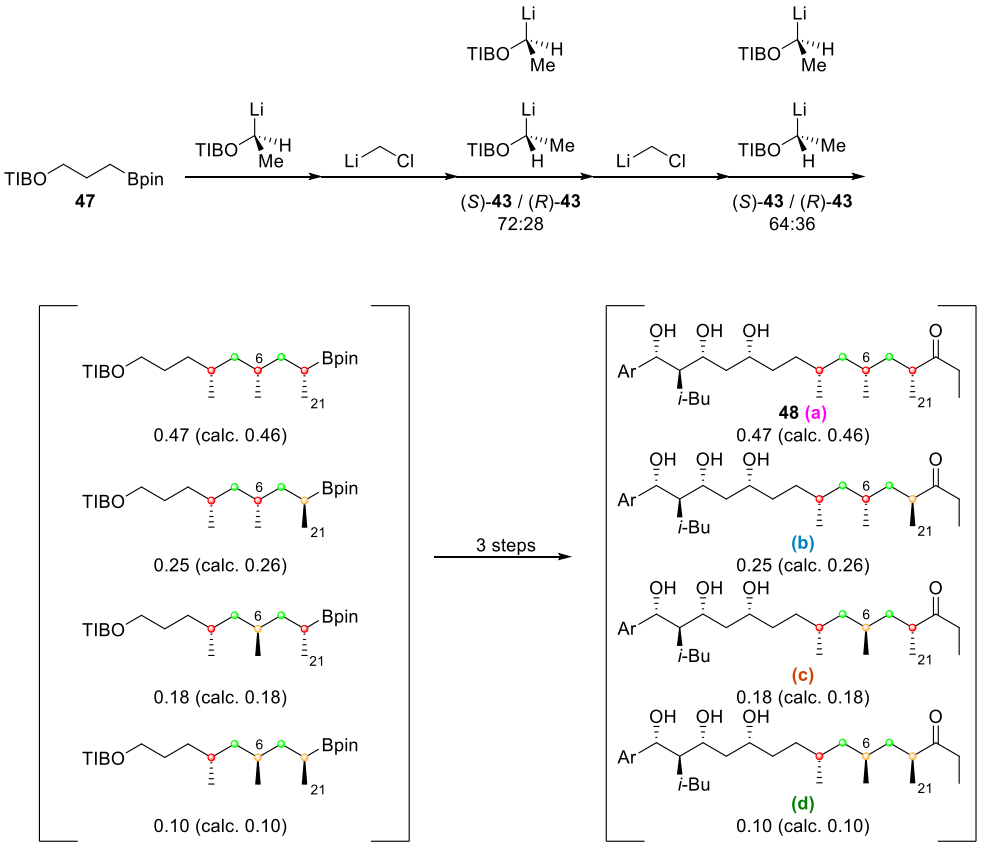
Scheme 15 Assembly–line synthesis of 1,3-polydeoxypropionates.

The power of assembly–line synthesis methodology was further exploited by Aggarwal and co-workers in the recent structural revision of baulamycins A and B.[36] The reported structures were first prepared in 10 steps (longest linear sequence), including a 5-step assembly–line sequence and a late stage lithiation–borylation/oxidation. However, NMR analysis of synthetic baulamycin A and B revealed significant discrepancies with the reported ^{1}H and ^{13}C NMR data for the natural product, suggesting that one or more stereocentres had been misassigned.

The relative configuration of the four stereocentres in the western fragment of baulamycin was determined through analysis of the experimental NMR data for the isolated natural product and comparison with computed parameters, generated after conformational analysis, submitting the returned low-energy conformers to density functional theory (DFT) geometry optimisation and free-energy calculations, and then calculating the ^{1}H–^{1}H coupling constants and NOE-derived interproton distances. For the three stereocentres in the eastern fragment, a mixture study was conducted, which was made possible through the high conversion and exquisite levels of stereocontrol exhibited in assembly–line synthesis.

Boronic ester **47** was subjected to the 5-step assembly–line sequence. Importantly, for the third and fifth homologations a mixture of the (*S*)- and (*R*)- α-stannyl ethyl benzoates was used with the ratio chosen carefully to maximise the differing peak intensities for the four

diastereomers in the ^{13}C NMR spectrum of the encoded mixture. The observed ratio of diastereomers matched the expected ratio almost perfectly, since the homologations operated exclusively under reagent control (**Scheme 16**, **Figure 2**). The chemical shifts for the major diastereomer in this mixture (**48**) closely matched the natural product ^{13}C NMR spectrum, giving the correct relative configuration of the western fragment (**Figure 2**). Diastereomer **48** was finally identified to be the enantiomer of the natural product, given its optical rotation was positive, rather than the reported negative value for isolated baulamycin A.



Scheme 16 Synthesis of an encoded mixture of baulamycin A diastereomers. calc.: calculated.

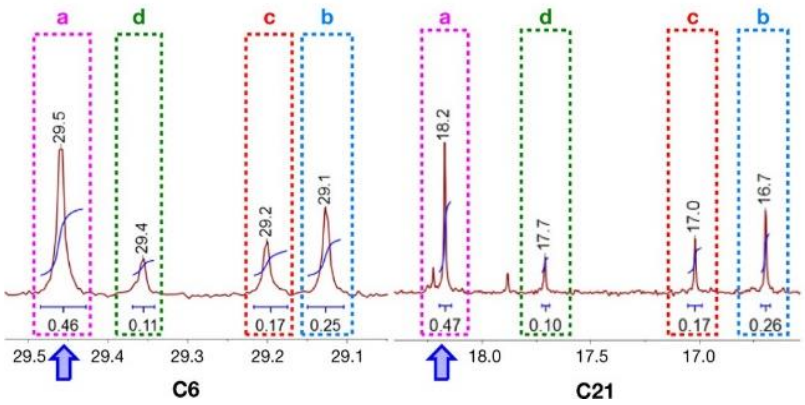
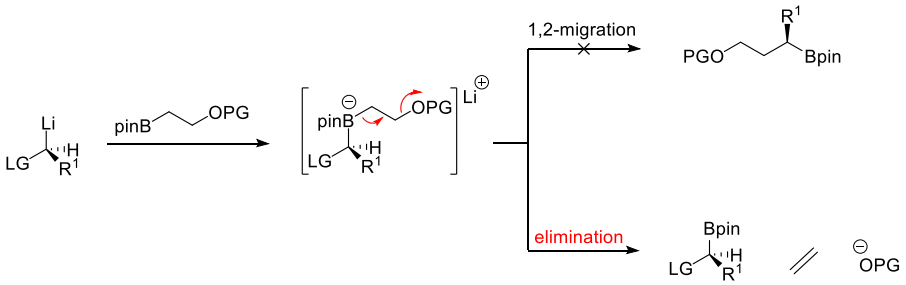


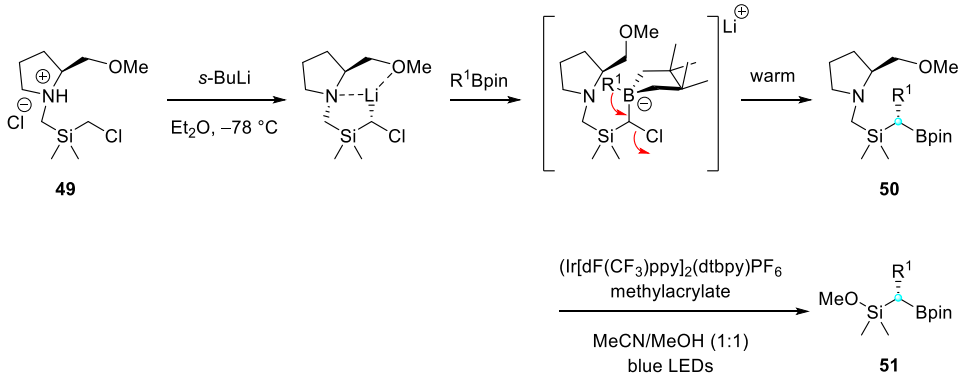
Figure 2 Comparison of the ^{13}C NMR spectrum for the mixture generated as shown in **Scheme 16**, figure reproduced from ref. 36.

Further efforts sought to enable the introduction of oxygen functionality in assembly–line synthesis. To this end, Aggarwal reported silyl-based building blocks and described the stereocontrolled synthesis of polypropionate fragments such as **53** (**Scheme 18**, **Scheme 19**).[37] Since the oxygen functionality is masked as a silyl group, this approach avoids the problem of β-elimination competing with 1,2-migration of boronate complexes which contain an electronegative group *beta* to the boronic ester (**Scheme 17**).



Scheme 17 Competing elimination of electronegative groups β to boron. PG: protecting group.

The enantioenriched lithiated α-chlorosilane **49** has a tethered chiral side arm which can direct lithiation and thus promote homologations with very high stereocontrol[38] (**Scheme 18**). However, the nitrogen atom can coordinate to the boron atom in the boronic ester product **50** preventing boronate complex formation during subsequent homologations. Light-mediated oxidative cleavage of the aminosilane **50** using an iridium photocatalyst gives the corresponding methoxysilane **51** which can be subjected to further homologations. Final stereoretentive oxidative cleavage of the carbon–silicon bond after the last iteration reveals the hydroxyl groups.[39] The optimised conditions tolerated substrates containing terminal alkenes, protected alcohols, *tert*-butyl esters, azides and heterocycles, and reagent control was shown to dominate over substrate control when three enantioenriched boronic esters were homologated with both enantiomers of the α-chlorosilane with only a small mis-matched effect in one case.[37]



Scheme 18 Lithiation–borylation using α-chloromethyl silane **49**.

The development of lithiated α-chlorosilanes to incorporate oxygen functionality provided an arsenal of chiral building blocks available in enantiopure form for the programmed synthesis of polydeoxypropionate, polypropionate and polyacetate natural products and related chemical motifs (**Table 2**). Any prescribed diastereomer of a carbon chain bearing methyl and hydroxyl groups can be constructed with complete stereocontrol through iterative homologations of a simple boronic ester simply by varying the sequence of addition and, where necessary, the configuration of the appropriate lithiated α-chloromethyl silane, ethyl benzoate or (chloromethyl)lithium.

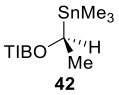
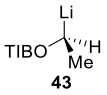
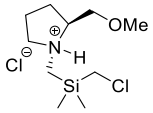
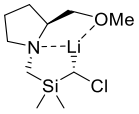
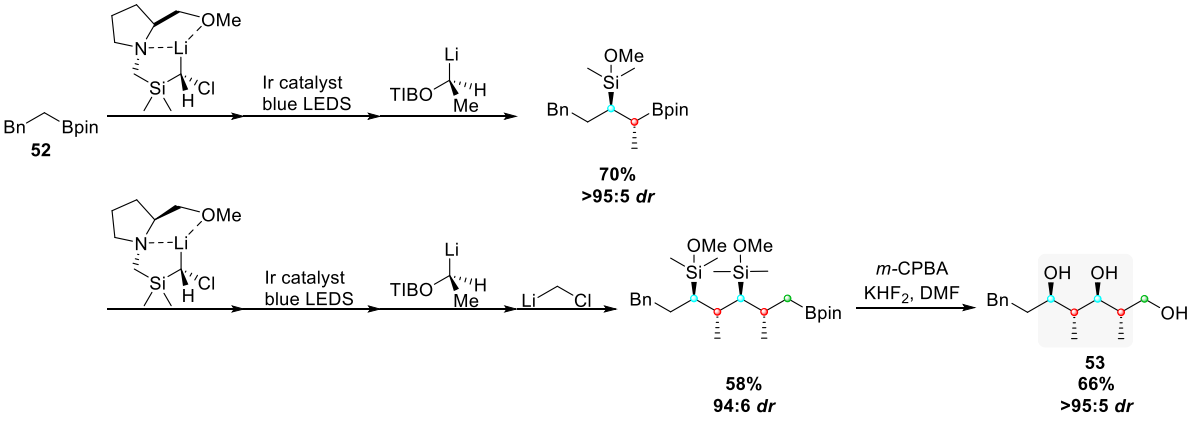
Functional group to be introduced	Building block	Carbenoid
	 **42**	 **43**
		
	 **49**	

Table 2 Aggarwal's building blocks for assembly–line synthesis.

Alternating the addition of lithiated α-chlorosilanes and lithiated ethyl benzoates to boronic ester **52** followed by homologation with (chloromethyl)lithium and oxidation represented a veritable 'assembly–line' and was used to construct several diastereomers of a polypropionate stereotetrad in good yields and exquisite levels of stereocontrol, including the all-*anti* isomer **53** (**Scheme 19**), which is challenging to synthesise with high diastereoselectivity using iterative aldol or crotylation reactions.[40]



52

70%
>95:5 *dr*

58%
94:6 *dr*

53
66%
>95:5 *dr*

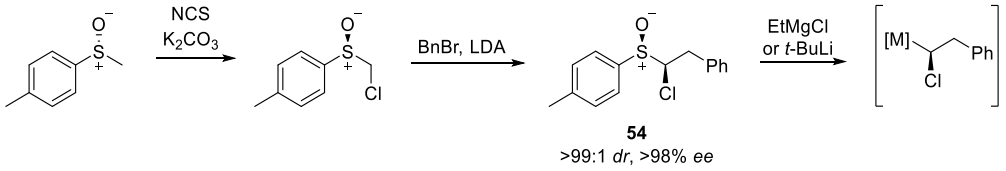
Scheme 19 Assembly–line synthesis of polypropionate fragment **53**. *m*-CPBA: *meta*-chloroperoxybenzoic acid.

1.5 α-Sulfinyl Benzoates as Carbenoid Precursors

The drawbacks associated with α-stannyl benzoates have prevented their wider application as carbenoid precursors, namely their inherent toxicity and difficulty in preparation in high levels of enantiopurity since only the methyl substituted precursor is crystalline.

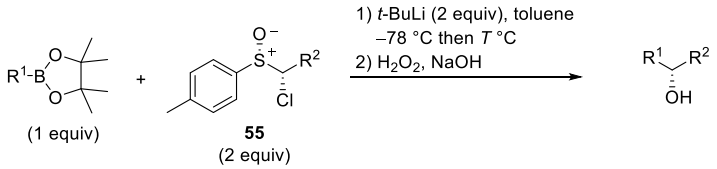
Hoffman first prepared α-chloro and α-bromoalkyl Grignard reagents in >97% enantiomeric excess which were configurationally stable below –60 °C, through stereospecific sulfoxide-magnesium exchange from the enantiopure corresponding sulfoxide.[41,42]

Blakemore subsequently utilised enantioenriched α-chloroalkyl metal carbenoids (**Scheme 20**)—generated *in situ* from the corresponding enantiopure Hoffmann α-chloroalkyl sulfoxides—such as **54** which could be isolated as a single diastereoisomer (>99:1 *dr*, >98% *ee*) following three cycles of fractional recrystallisation from diethyl ether.



Scheme 20 α-Chlorosulfoxide carbenoid precursors. M: MgCl or Li. NCS: *N*-chlorosuccinimide.

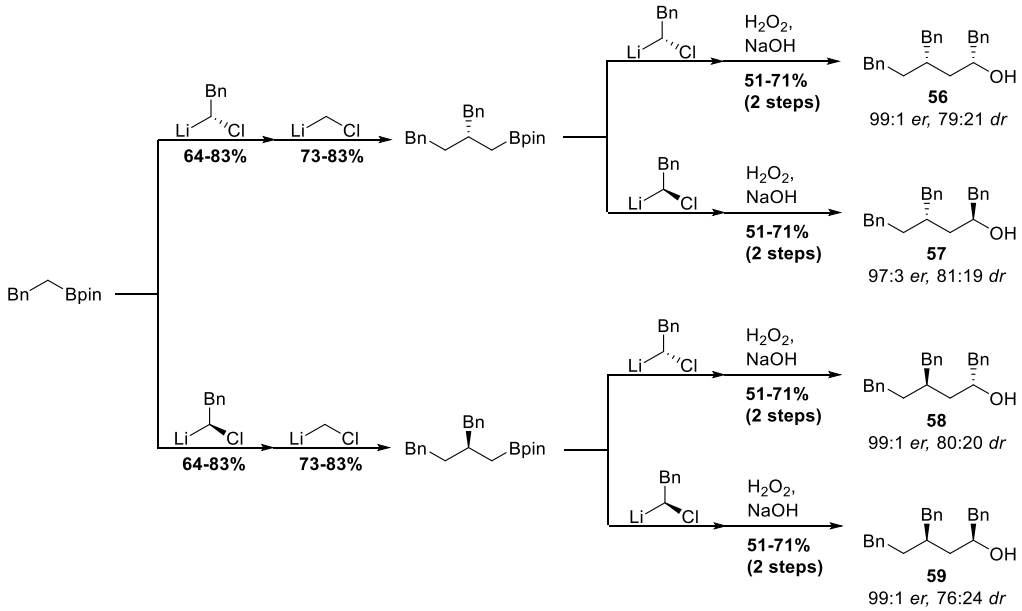
Blakemore demonstrated reagent-controlled asymmetric homologation of boronic esters using enantioenriched α-halo sulfoxide **55**,[43,44] where the lithiated carbenoid was generated *in situ* and upon treatment with a boronic ester formed a boronate complex. 1,2-Metalate rearrangement with expulsion of the chloride yielded the homologated boronic ester which, following oxidation, was isolated as the enantioenriched secondary alcohol (**Table 3**). The carbenoid was liberated through addition of *t*-BuLi to a mixture of α-chloro sulfoxide and boronic ester (Barbier conditions), to avoid decomposition of the carbenoid before addition of the boronic ester, enabling the preparation of a range of secondary alcohols after oxidation in moderate to excellent yield. Disappointingly, the observed stereospecificities decreased drastically with increasing steric hinderance. No product was formed when engaging *i*-Pr substituted α-chloro sulfoxide (entry 5).



Entry	R^1	R^2	Sulfoxide *ee* /%	*T* /°C	Yield /%	Product *ee* /%
1	$BnCH_2$	Bn	99	rt	76	92
2	Cy	Bn	99	rt	67	82
3	$BnCH_2$	Me	66	rt	23	60
4	$BnCH_2$	Et	nd	rt	29	98
5	$BnCH_2$	*i*-Pr	40	reflux	0	-
6	$BnCH_2$	*i*-Bu	99	rt	64	92
7	$BnCH_2$	$BnCH_2$	99	reflux	26	86
8	Cy	$BnCH_2$	99	rt	71	44

Table 3 Homologation of boronic esters with α-chloroalkyllithiums. nd: not determined.

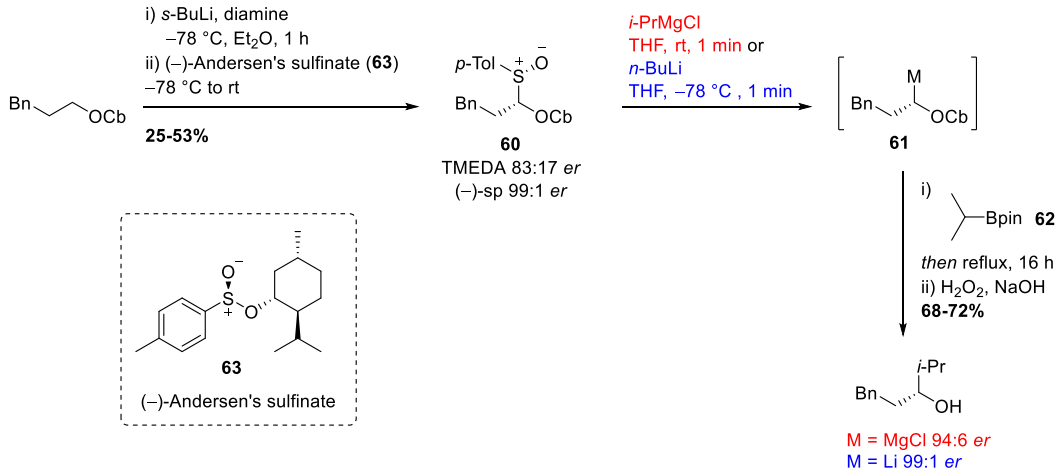
Blakemore sought to demonstrate the power of this methodology through the synthesis of all four stereoisomers of alcohol **56–59** by three consecutive boronic ester homologations—two steps using α-chloro sulfoxides and one Matteson homologation—followed by oxidation (**Scheme 21**). As expected in a reagent-controlled process, all four stereoisomers were obtained with excellent *er* values but only moderate *dr* values, as a consequence of Horeau's principle (*vide supra*).



Scheme 21 Iterative boronic ester homologation using α-chloroalkyllithiums derived from α-chloro sulfoxides.

In order to avoid the side-reactions possible with α-haloalkyllithiums—such as elimination, nucleophilic substitution or intramolecular hydride/alkyl shifts[45]—ensuing protocols sought to employ an alternative leaving group to the chloride utilised by Blakemore.

O'Brien described the preparation of α-sulfinyl carbamate **60** in >99:1 *dr* and >99:1 *er*, which readily underwent sulfoxide-magnesium exchange to generate enantiomerically pure α-functionalised Grignard reagent **61** which could be trapped with a range of electrophiles, including boronic ester **62** (**Scheme 22**).[46]



Scheme 22 Preparation and electrophilic trapping of α-functionalised Grignard reagent **60** with a boronic ester.

The α-sulfinyl benzoate carbenoid precursors developed by Aggarwal and co-workers can be prepared from the corresponding alkyl triisopropylbenzoate through deprotonation with diamine-ligated *s*-BuLi, transmetalation with magnesium bromide etherate and then trapping with Andersen's sulfinate (**63**) (**Scheme 23**).[47] Conversion to the less nucleophilic α-magnesiated benzoate is necessary to avoid erosion of enantiopurity through degenerate sulfinyl transfer with the product instead of exclusively the sulfinate reagent. The sulfoxide stereochemistry is set by the choice of either (+)- or (−)-Andersen's sulfinate. The achiral diamine TMEDA can be used for the deprotonation to prepare α-sulfinyl benzoates in high *dr* values since the product diastereomers, following trapping with Andersen's sulfinate, can be separated by column chromatography. If only one diastereomer is required, the stereochemistry of the carbenoid carbon is set by using either (+)- or (−)-sparteine for an asymmetric deprotonation. In this way, all four possible isomers can be prepared selectively. The minor diastereoisomer from the asymmetric deprotonation with either (+)- or (−)-sparteine can be separated by column chromatography, and so the desired carbenoid precursor can be isolated in high *er* values (typically >99:1), regardless of whether it is an oil or a solid, compared to 95:5 or 96:4 *er* for α-stannyl

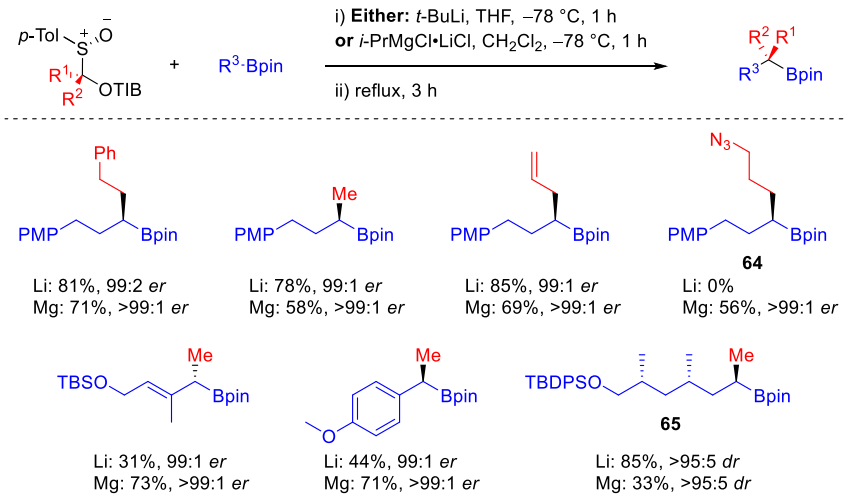
benzoates where the enantiomeric ratio for asymmetric deprotonation varies depending on the substrate and the enantiopurity can only be improved by recrystallisation.

Scheme 23 Preparation of α-sulfinyl triisopropylbenzoates.

α-Sulfinyl benzoates readily undergo stereospecific sulfoxide-metal exchange upon treatment with *t*-BuLi or *i*-PrMgCl·LiCl, revealing the lithiated or magnesiated carbenoid nucleophile, respectively, which will undergo stereoretentive borylation upon addition of a boronic ester at –78 °C. Stereoinvertive 1,2-metalate rearrangement of the resulting boronate complex yields the homologated product.

Homologations using both lithiated and magnesiated carbenoids generated from α-sulfinyl benzoates through retentive sulfoxide-metal exchange typically proceed with high yields and perfect enantiospecificity when performed *in situ* (**Scheme 24**).[47] Magnesiated carbenoids enable homologations of carbon chains containing electrophilic functional groups such as alkyl halides, azides and esters, *e.g.* product **64**. Lithiated carbenoids allow the construction of sterically hindered carbon–carbon bonds, *e.g.* product **65**.

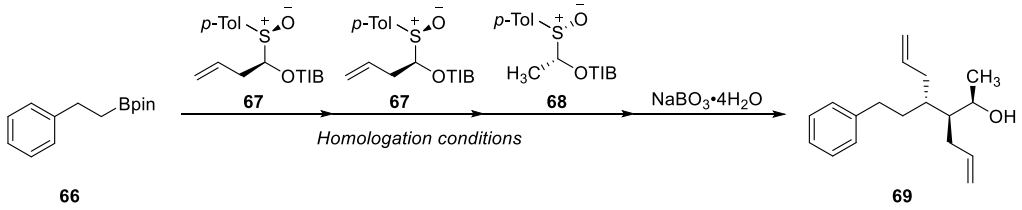
Non-diamine ligated lithiated carbenoids indiscriminately attack primary and secondary boronic esters[48] whereas magnesiated carbenoids are less reactive and, even when used in excess, will selectively attack primary boronic esters. However, for the homologation of sterically hindered boronic esters where a lithiated carbenoid was reported to be necessary, conditions have been developed to improve the primary selectivity by adding the sterically bulky tridentate ligand *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA).[47]



Scheme 24 Selected homologations of boronic esters with carbenoids derived from α-sulfinyl benzoates. TBDPS: *tert*-butyldiphenylsilyl.

Having demonstrated the efficient and highly stereospecific homologation of boronic esters with a range of α-sulfinyl benzoate derivatives, Aggarwal sought to extend the application of these chiral carbenoid precursors to an iterative process in order to construct contiguously substituted carbon chains with exquisite levels of stereocontrol.

Phenethyl boronic ester **66** was subjected to three consecutive homologations, with a simple filtration through silica between each iterative homologation, and a final oxidation step (**Table 4**). While the first homologation proceeded smoothly with both lithium and magnesiated carbenoids (entries 1 and 2), the efficiency and stereoselectivity of the second iteration with a magnesiated carbenoid decreased markedly, due to their increased sensitivity to steric hindrance. The third iterative homologation was therefore attempted using only the lithiated carbenoid and following oxidation the homologated product **69** was isolated in 29% overall yield (entry 1); this could be improved to 41% by increasing the equivalents of α-sulfinyl benzoate in order to push the third homologation closer to completion (entry 3), owing to the substantial steric hindrance now impacting even homologation with lithiated carbenoids.



Entry	Homologation conditions	1st P:SM	2nd P:SM	3rd P:SM	Yield 69 /%	*dr*
1	**67** (1.05 equiv), *t*-BuLi (2.00 equiv), THF	98:2	96:4	60:40	29	>95:5
2	**67** (1.3 equiv), *i*-PrMgCl·LiCl (1.2 equiv), CH_2Cl_2	99:1	26:74	-	-	-
3	**68** (1.5 equiv), *t*-BuLi (3.0 equiv), THF	98:2	96:4	85:15	41	>95:5

Table 4 Iterative homologation of boronic ester **66** using α-sulfinyl benzoates. P:SM (product:starting material) ratios measured by GC-MS analysis of the crude mixtures.

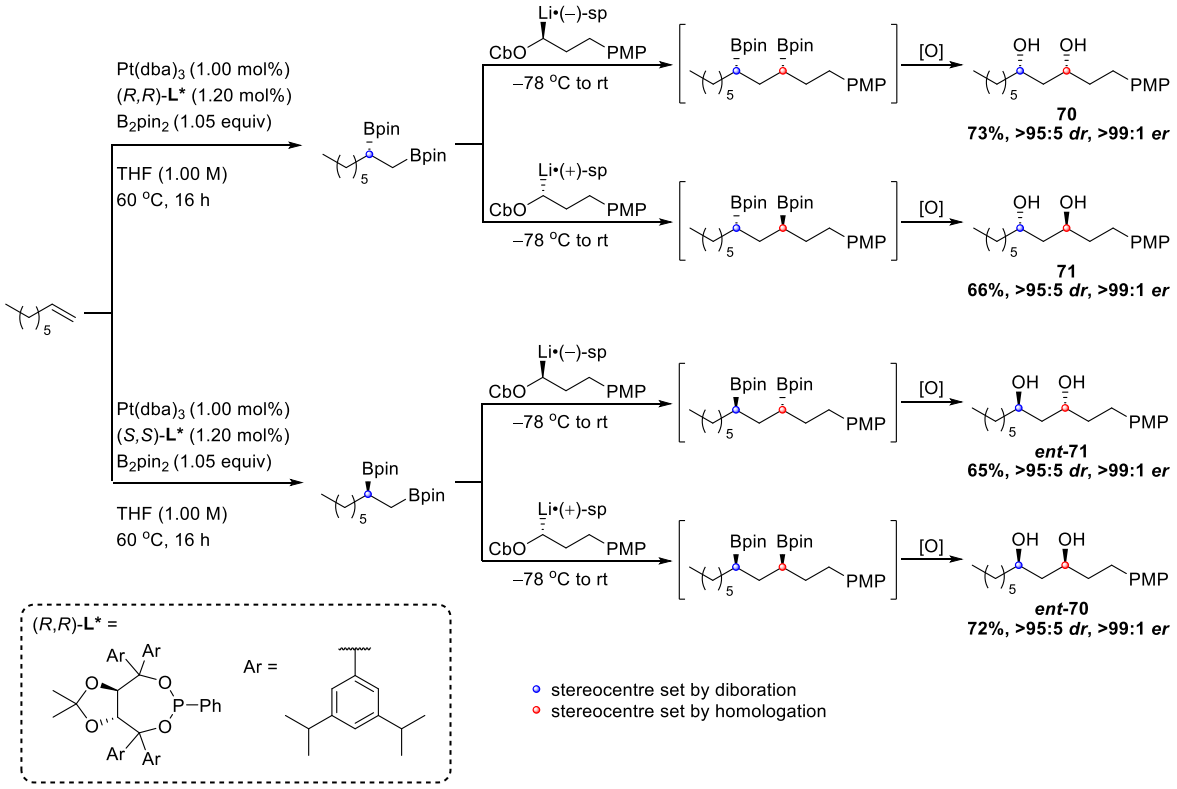
1.6 Stereocontrolled Synthesis of 1,3-Diols

The key challenge in preparing 1,3-diols using lithiation–borylation reactions is that boronate complexes which contain an electronegative group *beta* to the boronic ester are known to decompose through β-elimination (*vide supra*, **Scheme 17**). Aggarwal has shown that boronate complexes containing β-boronic esters do not decompose through β-elimination but undergo 1,2-migration to yield 1,3-bis(boronic esters) which can be stereospecifically oxidised to the corresponding 1,3-diols.[48] In order to extend the application of assembly–line synthesis to targets containing polar residues, Aggarwal demonstrated two methods to access 1,3-diols using this strategy, the first by performing lithiation–borylation reactions with 1,2-bis(boronic esters),[48] which can be obtained through Morken[49,50] (platinum catalysed) or Nishiyama[51] (rhodium catalysed) asymmetric diboration of terminal alkenes, and the second by using diborylmethane (**73**) as a linchpin reagent.[52]

The reaction of a 1,2-bis(boronic ester) with a (+)- or (−)-sparteine-ligated lithiated benzoate or carbamate at –78 ºC results in a regioselective reaction at the less hindered terminal boronic ester to give a single boronate complex.[48] To prevent the formation of a second boronate complex upon warming the reaction mixture to ambient temperature, methanol is added at –78 ºC to quench the small excess of lithiated species remaining. The internal boronic ester does not undergo β-elimination, and oxidation of the 1,3-bis(boronic ester) product reveals the target 1,3-diol (**Scheme 25**). The choice of a suitably hindered carbenoid is crucial for the success of this reaction; employing a less hindered TMEDA-ligated or diamine free carbenoid yields a mixture of single homologation, double homologation—

which arises from reaction of the carbenoid at both the terminal and internal boronic esters—and unreacted starting material.

No matched or mismatched effects were observed when all four stereoisomers **70**, **71**, ***ent*-71** and ***ent*-70** of a 1,3-diol were prepared. This was achieved by switching the enantiomer of chiral ligand for the Morken asymmetric diboration, which sets the first stereocentre, and by changing from (+)- to (−)-sparteine for the asymmetric lithiation, which sets the second, allowing all four isomers to be generated in good yield and with perfect *dr* and *er* values, thus showing that the process is operating exclusively under reagent control (**Scheme 25**).



Scheme 25 Stereocontrolled synthesis of 1,3-diols. Oxidation conditions: 3 M aq. NaOH/30% aq. H_2O_2 (2:1 v/v), THF, 0 °C to rt. PMP: *para*-methoxyphenyl.

Treatment of 1,2-bis(boronic esters) with a range of lithiated primary benzoates and carbamates afforded the corresponding 1,3-diols in moderate to good yields and high levels of stereocontrol; selected examples are shown in **Figure 3**. More significantly, employing a secondary benzylic or allylic carbamate permitted the formation of any stereochemical permutation of a secondary-tertiary 1,3-diol in high selectivity, which was not possible using previously available methods.[53,54] Finally, a derivative of the blockbuster statin atorvastatin was synthesised in high yield and excellent *dr* (**72**).

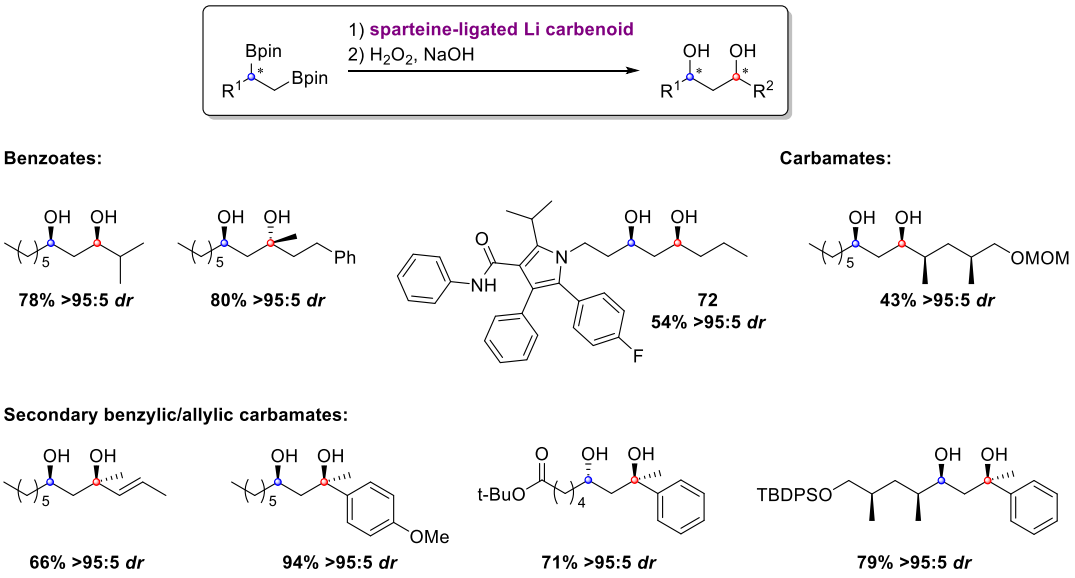
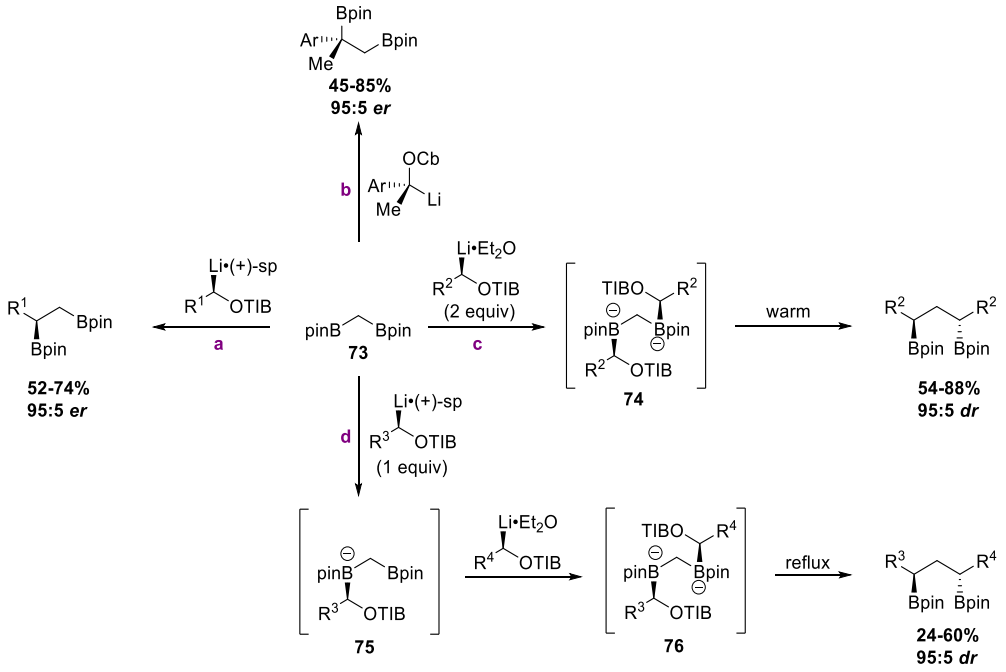


Figure 3 Selected examples of 1,3-diols prepared through homologation of 1,2-bis(boronic esters). MOM: methoxymethyl.

The synthesis of 1,2- or 1,3-bis(boronic esters), and therefore the corresponding 1,2- and 1,3-diols, can also be achieved through the stereospecific homologation of diborylmethane (**73**) with an enantioenriched lithiated carbamate or benzoate (**Scheme 26**).[52] Critically, it was observed that the outcome of the reaction is determined by the carbenoid used, with hindered carbenoids reacting at one boronic ester to generate 1,2-bis(boronic esters), while unhindered (diamine-free) carbenoids react with both boronic esters to generate symmetrical 1,3-bis(boronic esters).

The regioselective single homologation of diborylmethane (**73**) with sparteine-ligated carbenoids enabled the preparation of primary-secondary and primary-tertiary 1,2-bis(boronic esters) in high yield and enantiopurity (**Scheme 26** a). This methodology is especially useful for preparing 1,2-bis(boronic esters) which bear terminal alkynes, alkenes and proximal stereocentres, as these substrates cannot be accessed with high selectivity using current metal catalysed diboration reactions. Secondary benzylic carbenoids could also be used to homologate diborylmethane (**73**) at one boronic ester to generate primary-tertiary 1,2-bis(boronic esters) in moderate to good yields and excellent levels of enantioselectivity with electron-rich, electron-deficient and *ortho*-substituted benzylic carbamates (**Scheme 26** b).



Scheme 26 Synthesis of 1,2- and 1,3-bis(boronic esters) through homologation of diborylmethane (**73**).

The boronate complex formed upon treatment of diborylmethane (**73**) with a sparteine-ligated carbenoid is too sterically hindered to form a double boronate complex. However, less hindered diamine-free carbenoids—generated through tin-lithium exchange of the corresponding α-stannyl benzoate—can form boronate complexes at both boronic esters in the same operation (**75**), which was used for the preparation of C_2-symmetric 1,3-diols (**Scheme 26** c) in generally high yield and diastereomeric excess following 1,2-metalate rearrangement at both centres in a one-pot process and stereospecific oxidation. Interestingly, direct deprotonation of the acidic methylene group of diborylmethane (**73**) by the carbenoid was not observed. Fragmentation of boronate complex **74** to yield a stabilised α-boryl anion was only observed once in a very hindered substrate where 1,2-metalate rearrangement was impeded.[55]

Non-symmetrical 1,3-bis(boronic esters) can be prepared through a one-pot carbenoid–carbenoid coupling using diborylmethane (**73**) as a linchpin reagent, exploiting the selective single boronate complex formation with a sparteine-ligated carbenoid to generate mixed-valent diboryl species **75** (**Scheme 26** d). Addition of α-stannyl benzoate **42** followed by *n*-BuLi liberates diamine-free carbenoid **43**, which reacts with **75** to form double boronate complex **76.** Warming to reflux effects 1,2-migration at both centres to afford non-symmetrical enantioenriched 1,3-bis(boronic esters), with complete control over both the absolute and relative stereochemistry.

2 The Stereocontrolled Synthesis of 1,3-Polyols

Polyketide-derived natural products are of particular interest due to their highly specific and potent biological activity and structural diversity. A common structural motif among polyketide synthase (PKS) metabolites is the (*syn*- or *anti*-) 1,3-diol unit, or higher order 1,3-polyol arrays (**Figure 4**). The principal source of bioactive PKS metabolites is soil bacteria, yet the majority of soil bacteria are not amenable to culture and so the development of methodology to prepare these structures in the synthetic chemistry laboratory is of continuing importance.

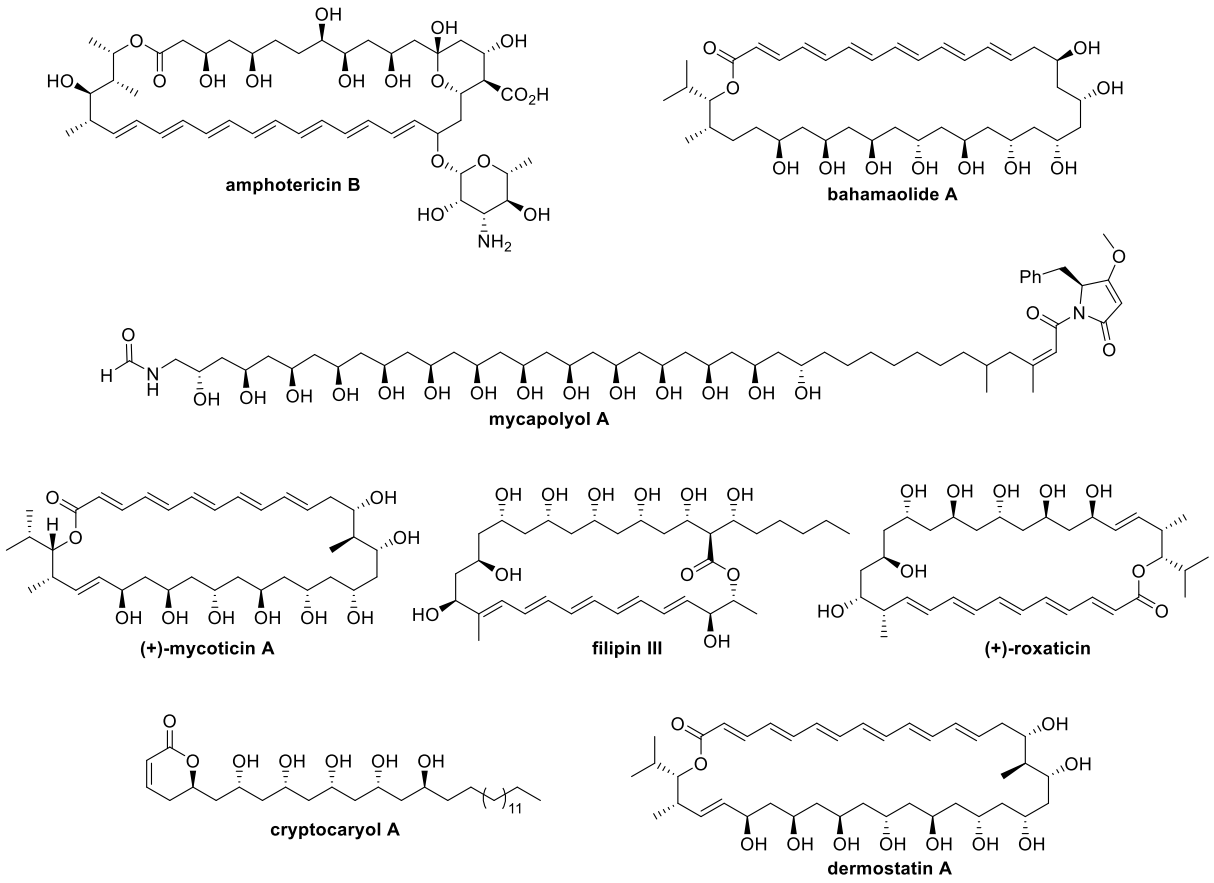


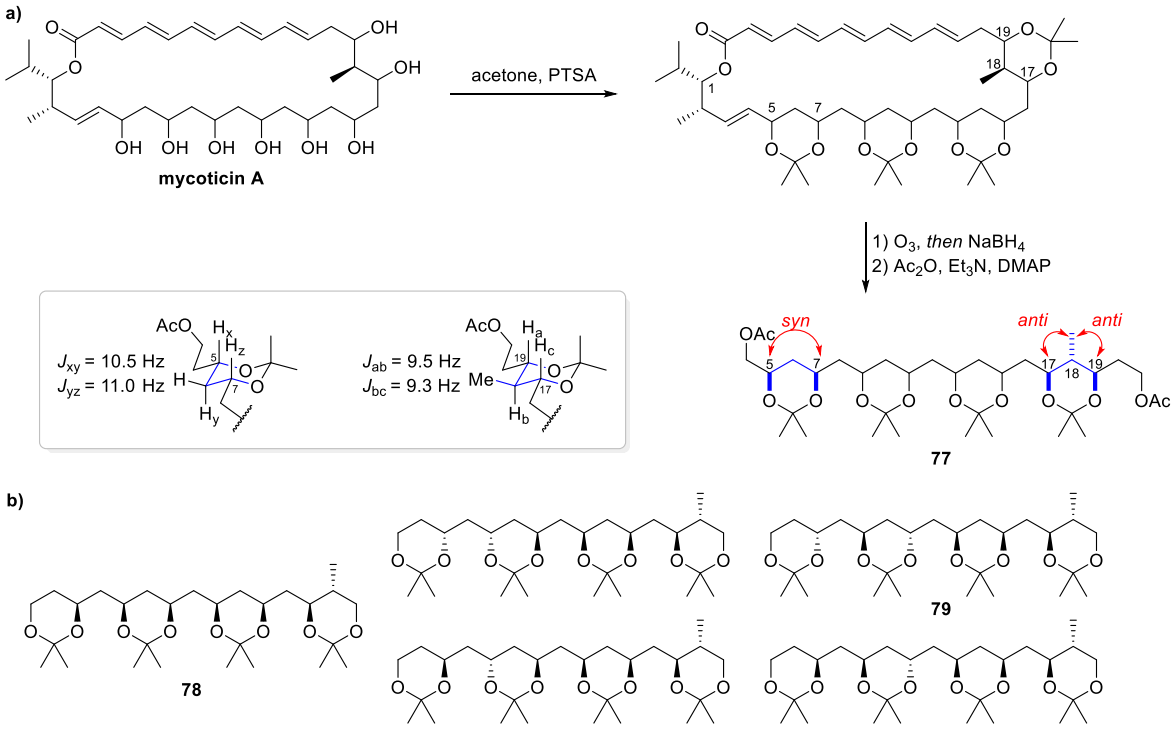
Figure 4 Selected 1,3-polyol containing natural products.

2.1 Stereochemical Assignment of 1,3-Polyols

Mycoticin, the first of the oxopolyene macrolides to be isolated, was discovered by Burke during work to identify novel antifungal agents[56] and its structure was later determined by Wasserman.[57] Amphotericin B was the first oxopolyene macrolide whose absolute stereostructure was known; a single crystal of *N*-iodoacetylamphotericin B confirmed the absolute configuration[58] and by analogy it was generally assumed that other related natural

products, such as mycoticin, also contained an all-*syn* polyol which led to the development of several methods to construct *syn* 1,3-polyols (*vide infra*).

The structure of roxaticin was also determined by crystallography,[59] but attempts to crystallise mycoticin A failed, and so Schreiber and co-workers moved to using degradation studies (**Scheme 27** a).[60] Acetonide protection of the natural product, followed by ozonolytic destruction of the polyene moiety and acetylation afforded degradation product **77**. *J* coupling analysis showed that the protected 1,3-diol at C5 and C7 was *syn*, and that the hydroxyl groups at C17 and C19 were both *anti* to the methyl group at C18.[60,61] This information in conjunction with the known all-*syn* polyol in amphotericin B led Schreiber to synthesise the all-*syn* polyol fragment **78** (**Scheme 27** b); however, this was shown to be an isomer of the analogous degradation product (**77**), which led to the conclusion that mycoticin did not contain an all-*syn* 1,3-polyol.[62] Schreiber and co-workers later synthesised four other diastereomers of the 1,3-polyol portion of mycoticin A and identified **79** as matching the stereochemistry in the natural product,[63] allowing the full stereostructure of mycoticin A to be elucidated through chemical degradation studies combined with partial synthesis.



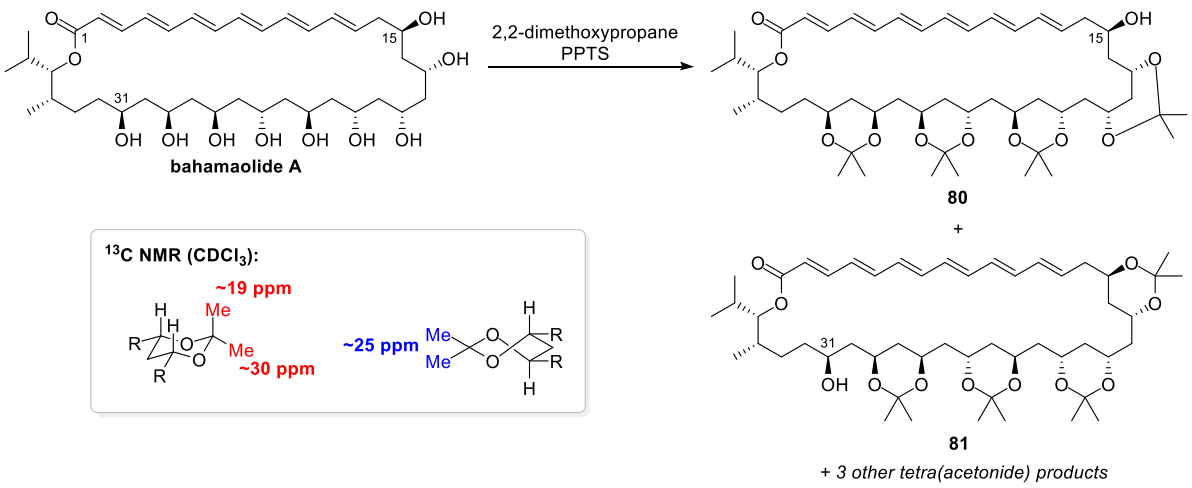
Scheme 27 Structural determination of mycoticin A through a) chemical degradation and b) partial synthesis. DMAP: 4-dimethylaminopyridine.

Clearly there was a need for simple spectroscopic methods to determine the stereochemistry of 1,3-polyol chains. Rychnovsky and co-workers reported a system to assign the relative stereochemistry of a 1,3-diol by analysis of the corresponding 1,3-diol acetonide

(2,2-dimethyl-1,3-dioxane, **Scheme 28**).[64] *syn*-1,3-Diol acetonides exist in a well-defined chair conformation, with the two alkyl substituents equatorial. Acetonides derived from *anti*-1,3-diols adopt a twist boat conformation, in order to avoid the disfavourable 1,3-diaxial interaction present in the corresponding chair conformation. These conformational differences between *syn* and *anti* acetonides result in significantly different ^{13}C NMR spectra; the chemical shift of both acetonide methyl groups in an *anti*-1,3-diol acetonide is around 25 ppm, whereas for a *syn*-1,3-diol acetonide, the axial methyl group will appear at around 19 ppm and the equatorial methyl group around 30 ppm.

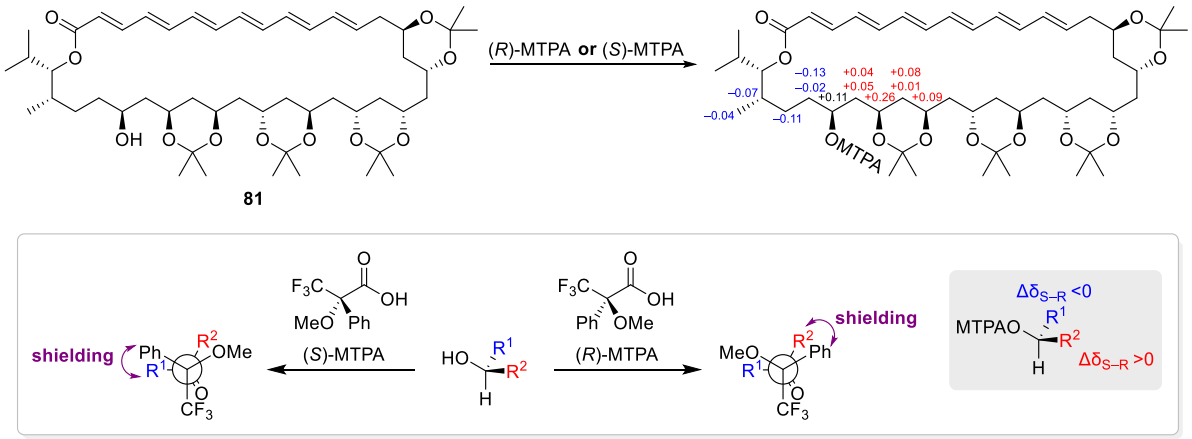
In order to extend Rychnovsky's method to a 1,3-polyol, it is necessary to prepare at least two poly(acetonides) which are frame shifted with respect to one another, to determine the position of each *syn* and *anti* 1,3-diol pair, and not merely the number present; the first poly(acetonide) will give the relative stereochemistry of each pair of 1,3-diols, and the second poly(acetonide) will give the relative stereochemistry of every other pair of 1,3-diols and so together this should reveal the stereochemical assignment of the full 1,3-polyol.

This approach was key to the deduction of the relative configuration of the polyol portion of bahamaolide A.[65] A sample of the natural product, cultured from a sediment sample collected in North Cat Cay in the Bahamas, was treated with excess 2,2-dimethyoxypropane and pyridinium *p*-toluenesulfonate (PPTS) to afford five acetonide protected compounds. ^{13}C NMR analysis of **80** indicated the presence of two *syn* and two *anti* acetonides. The ^{13}C NMR chemical shifts of the acetonide methyl groups for **80** and **81**, in combination with ROESY correlations revealed the relative configuration of the polyol. Interestingly this also showed that the hydroxyl group at C15 had the opposite stereochemistry to the corresponding hydroxyl group in similar oxopolyene macrolides such as roxaticin, mycoticin and dermostatin A.



Scheme 28 Rychnovsky's ^{13}C NMR analysis and its application to the stereochemical assignment of bahamaolide A.

The absolute configuration of the 1,3-polyol moiety in bahamaolide A was determined through Mosher ester analysis of **81** (**Scheme 29**). Mosher's reagent, α-methoxy-α-trifluoromethylphenylacetic acid (MTPA), is a chiral derivatising agent which allows discrimination by ^1H NMR analysis of the two diastereomeric derivatised alcohols.[66] A lower chemical shift will be observed for substituents in the *syn* position to the aromatic ring due to the shielding effect of the ring current, and the electron withdrawing trifluoromethyl group of MTPA means that one conformer dominates, where the trifluoromethyl group is eclipsed by the carbonyl. The difference in chemical shift between the esters prepared using (*S*)-MTPA and (*R*)-MTPA is used to assign groups R^1 and R^2, and therefore the stereochemistry at the unknown centre. Since $\Delta\delta_{S-R}$ for the protons to the left of the derivatised alcohol as drawn was negative (in blue, R^1) and $\Delta\delta_{S-R}$ for the protons to the right of the derivatised alcohol was positive (in red, R^2), the absolute stereochemistry at C31, and therefore bahamaolide A, was assigned as shown (**Scheme 29**).



Scheme 29 Mosher ester analysis; $\Delta\delta_{S-R}$ in toluene-d_8 for Mosher ester derivative of **81**.

A complementary approach to Rychnovsky's acetonides, still using ^{13}C NMR analysis, was developed by Kishi and co-workers which allows stereochemical assignment of 1,3-polyols without derivatisation.[67] Kishi showed that the central carbon atom of the four diastereomeric triols shown in **Figure 6** has a diagnostic chemical shift that depends on the relative configuration of the 1,3- and 3,5-diols but is not affected by functionality beyond the triol motif.

The reported structure of mycapolyol B was deduced by NMR analysis.[68] A sequence of non-equivalent methylene units coupled to hydroxylated methines revealed the extended 1,3-polyol system. Since these signals were highly homogeneous, this was expected to be either an isotactic or syndiotactic polyol, similar to isotactic polymethoxy-1-alkenes (**Figure 5**).[69]

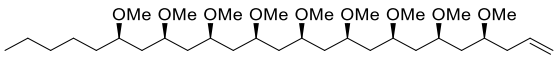


Figure 5 An isotactic polymethoxy-1-alkene, a cyanobaterium metabolite.

Kishi's ^{13}C NMR database for the 1,3,5-polyol system was used to assign the relative stereochemistry of the 1,3-polyol domain (**Figure 6**).[67] In DMSO-d_6, a chemical shift of 68 ppm implies a *syn/syn* relationship, 66 ppm *anti/syn* and 64 ppm *anti/anti*. Since C17, C19, C21, C23, C25, C27, C29, C31 and C33 had chemical shifts of 67.5 ppm (suggesting a *syn/syn* relationship), and C15 and C35 had chemical shifts of 66 ppm (suggesting an *anti/syn* relationship) the relative stereochemistry of the 1,3-polyol was inferred as shown. This proposed isotactic polyol structure was supported by the observation that all the methylene protons between C13 and C37 were non-equivalent.

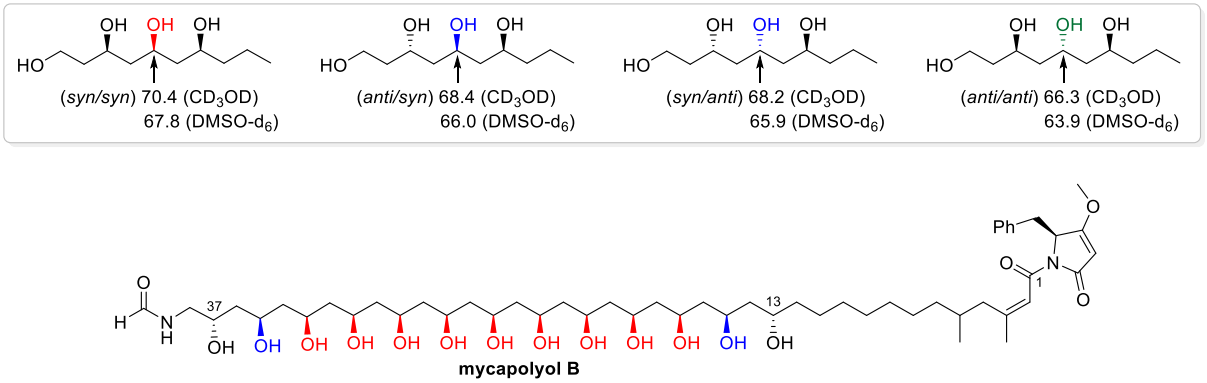


Figure 6 Kishi's ^{13}C NMR database and its application to the stereochemical assignment of mycapolyol B.

2.2 Nature's Approach: Biosynthesis of Polyacetates

Polyketide natural products are biosynthesised through the stepwise condensation of acetate units to form chains which in turn may cyclise; the key step is carbon–carbon bond formation through a decarboxylative Claisen condensation.[70]

This is usually visualised as a sequence of functional units or modules (**Figure 7**), with several domains executing different functions. One iterative cycle of the chain extension generally requires at least three domains: a keto synthase (KS), acyl transferase (AT) and acyl carrier protein (ACP).

At the start of the module, the growing polyketide chain is transferred to the KS domain from the ACP domain of the preceding module, catalysed by the KS domain. The AT domain then catalyses the addition of the elongation group, generally malonyl-CoA for polyacetates, onto the ACP domain of the current module. The enolate of the ACP-bound elongation group is generated *in situ* and reacts with the thioester of the KS-bound polyketide chain in a Claisen condensation with the evolution of CO_2, leaving the homologated polyketide chain now attached to the ACP domain. Prior to the next Claisen condensation, the extended polyketide chain can undergo modification by additional domains; in the case of polyacetates, the β-keto group is reduced to a β-hydroxy group by the keto-reductase (KR) domain.

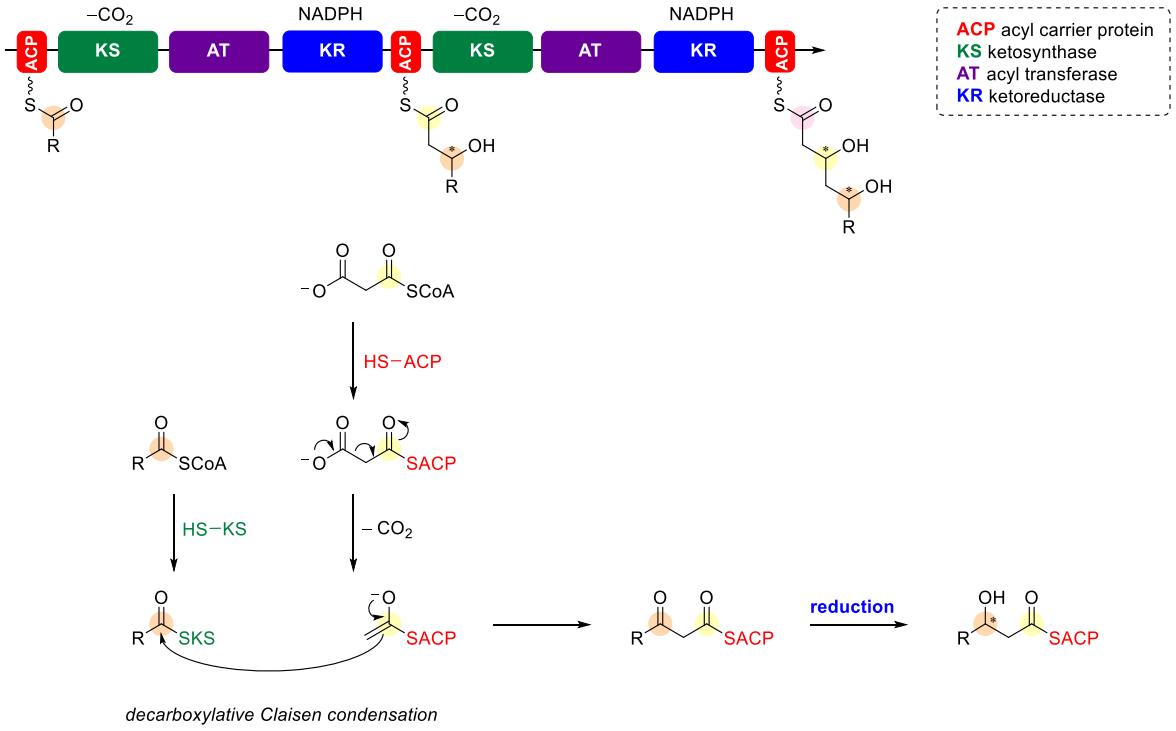


Figure 7 The iterative modular biosynthesis of polyacetates. NADPH: nicotinamide adenine dinucleotide phosphate.

2.3 Asymmetric Allylation–Oxidation Approach

A common approach to synthesise stereodefined secondary alcohols, and by extension, 1,3-diols and 1,3-polyols, is through an asymmetric allylation. This can be achieved by reacting an aldehyde with either a chiral and enantioenriched allylating agent, or an achiral allylating agent and a chiral catalyst, as depicted in **Figure 8**. This could be extended to allow an iterative process: protection of the homoallylic alcohol product and ozonolysis of the terminal alkene would give a β-alkoxyaldehyde, which could undergo another asymmetric allylation and so enable the construction of a 1,3-polyol.

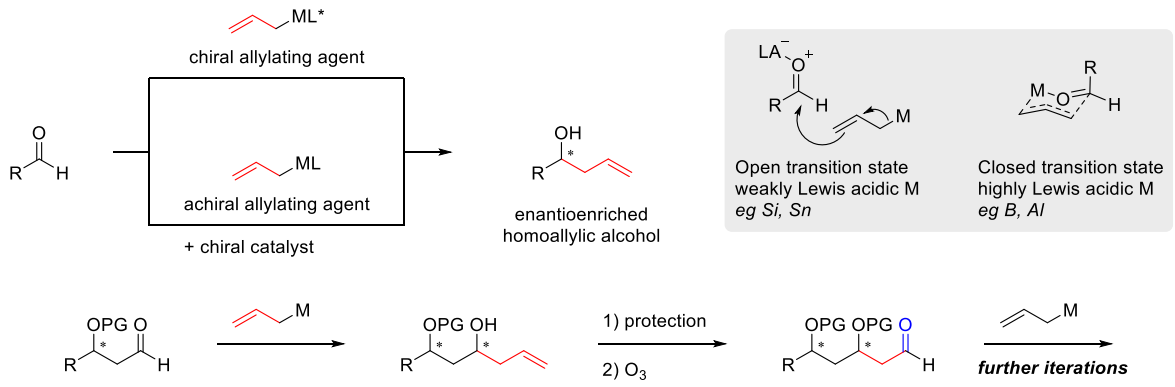
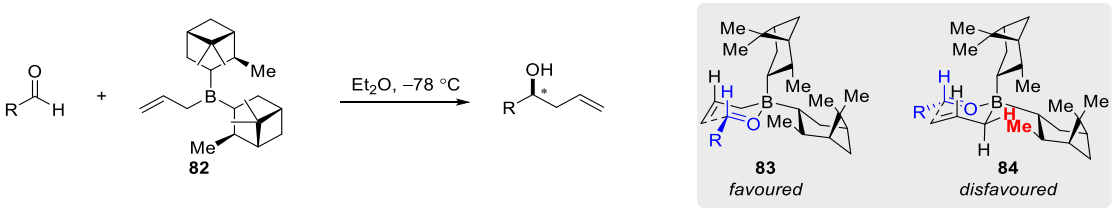


Figure 8 Asymmetric allylation followed by oxidation to construct 1,3-polyols.

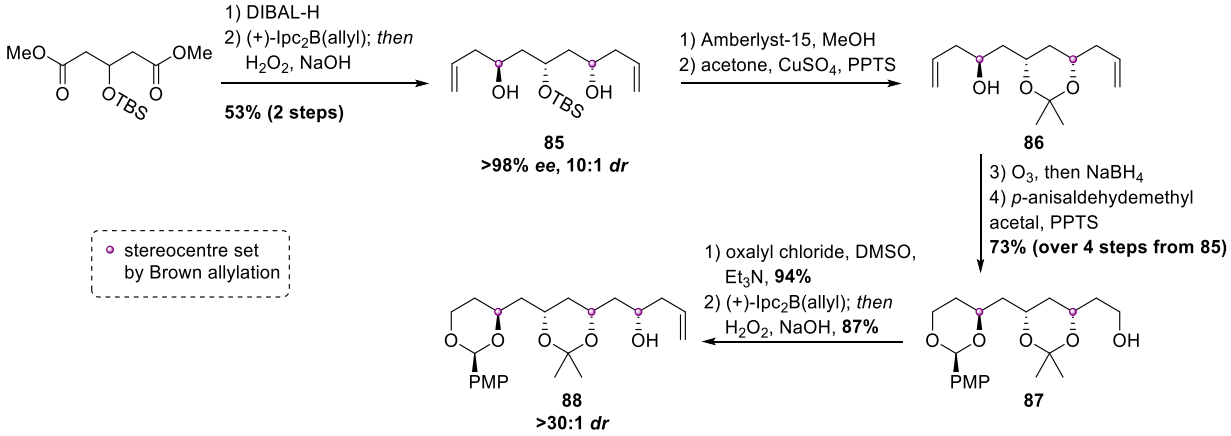
2.3.1 Brown allylation

Brown's allylation conditions, using allyl diisopinocampheylborane ($Ipc_2B(allyl)$, **82**) (**Scheme 30**), are well known and widely used since the reaction is quite general, proceeding to give the expected product under reagent control since the selectivity of these reagents typically overrides any aldehyde facial preference.[71–73] The allylation occurs *via* a chair-like or Zimmerman-Traxler like transition state (**83**), where the aldehyde R group occupies an equatorial position and the aldehyde facial approach is governed by minimising steric clash between the Ipc ligand and the allyl group (compare **83** and **84**, where there is now an unfavourable interaction with the highlighted methyl group). In general, lower reaction temperatures lead to increased enantioselectivity and Brown allylboration of aldehydes is essentially instantaneous at –78 °C, or –100 °C in the absence of magnesium salts, to give products with >99% *ee*. At –100 °C it is necessary to remove the magnesium salts generated through forming the Brown allylation reagent from $(Ipc)_2BOMe$ and allylMgBr since at this temperature boronate complex formation with MeOMgBr sequesters the reactive borane.[73]



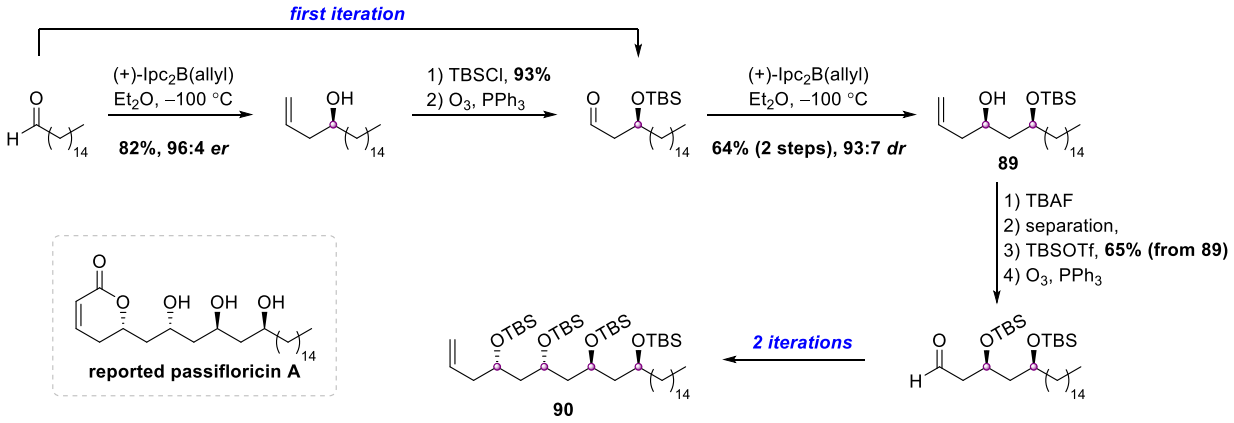
Scheme 30 Brown allylation of a simple aldehyde.

Brown allylation has been applied in several total syntheses of 1,3-polyol natural products, notably in Sammakia's synthesis of RK-397[74] (**Scheme 31**) and García-Fortanet's synthesis of reported passifloricin A[75] (**Scheme 32**) where it was employed as part of an iterative sequence, with hydroxyl protection and ozonolysis. Sammakia first used a bidirectional Brown allylation to prepare triol **85** which was transformed to the acetonide derivative **86**. Ozonolysis of both terminal alkenes followed by reduction of the resulting aldehydes gave two primary alcohol groups, one of which could be engaged as part of the acetal with the adjacent free hydroxyl group. Swern oxidation of the free alcohol in **87** yielded the required terminal aldehyde, which was subjected to a second Brown allylation to give **88** essentially as a single diastereomer.



Scheme 31 Brown allylation in Sammakia's synthesis of RK-397.

The iterative combination of Brown allylation, protection and oxidation for the synthesis of 1,3-polyols is perhaps more clearly demonstrated in García-Fortanet's synthesis of reported passifloricin A[75] (**Scheme 32**), where four iterations of this cycle were used to prepare protected tetraol **90**; however, one drawback is the additional deprotection/reprotection steps required to obtain the product with high *dr* since the undesired diastereomer of homoallylic alcohol **89** could only be removed by column chromatography as the corresponding diol.

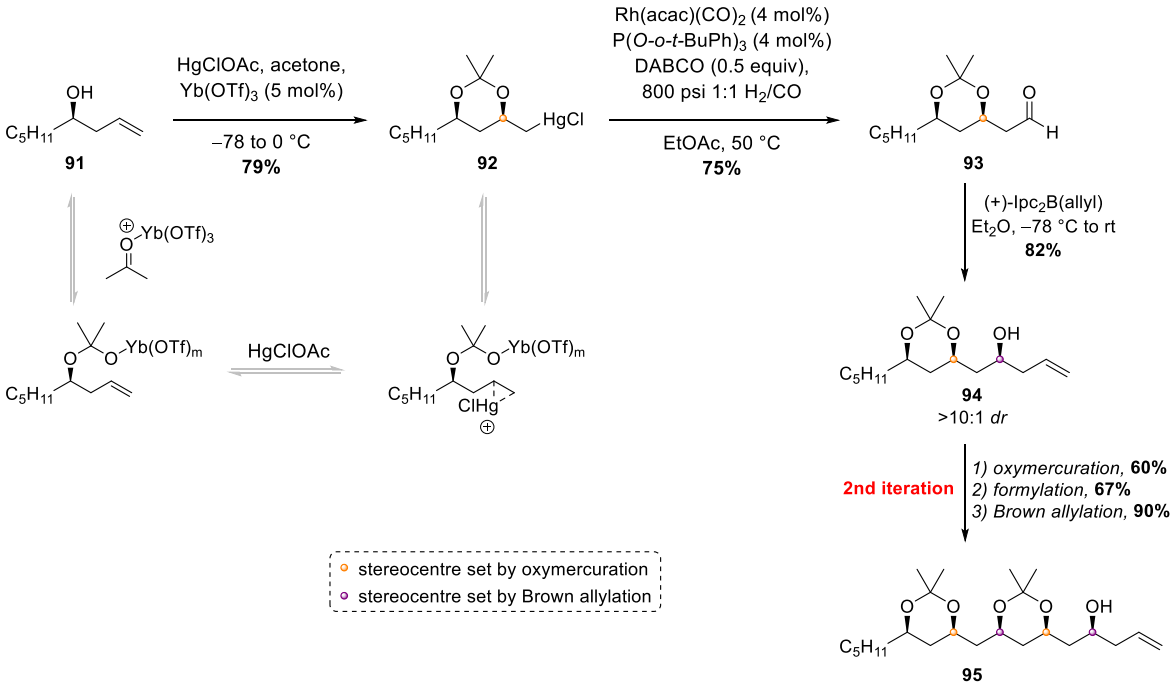


Scheme 32 Brown allylation in García-Fortanet's synthesis of reported passifloricin A. (−)-Ipc$_2$B(allyl) was used for the third and fourth Brown allylations.

2.3.2 Oxymercuration–hydroformylation

Leighton developed a variation of the allylation–oxidation approach, namely oxymercuration of a terminal alkene followed by rhodium-catalysed formylation to generate the next aldehyde for subsequent allylation. This protocol was applied in an iterative fashion in a formal synthesis of the *Tolypothrix* pentaether (**Scheme 33**),[76] and this 3-step sequence (Brown allylation–oxymercuration–formylation) was also employed in Leighton's synthetic route to mycoticin A.[77]

Homoallylic alcohol **91** underwent substrate-directed Leighton oxymercuration to give *syn*-acetonide **92**; the stereochemistry of the secondary alcohol already present in **91** directed the acetone oxygen to the same face of the alkyl chain. Rhodium-catalysed formylation of **92** proceeded through oxidative addition of Rh(I) into the carbon–mercury bond, insertion of carbon monoxide and reductive elimination to generate aldehyde **93**. Inclusion of the additive 1,4-diazabicyclo[2.2.2]octane (DABCO), which was postulated to act as a ligand for mercury, proved beneficial in promoting the desired formylation reaction and minimising undesired acetate transfer, which results in the carboxylic acid by-product. A diastereoselective Brown allylation of aldehyde **93** completed the first iteration and homoallylic alcohol **94** was then subjected to a second iteration to afford the Brückner intermediate **95,** which can be converted to the *Tolypothrix* pentaether in a further 2 steps.[78]

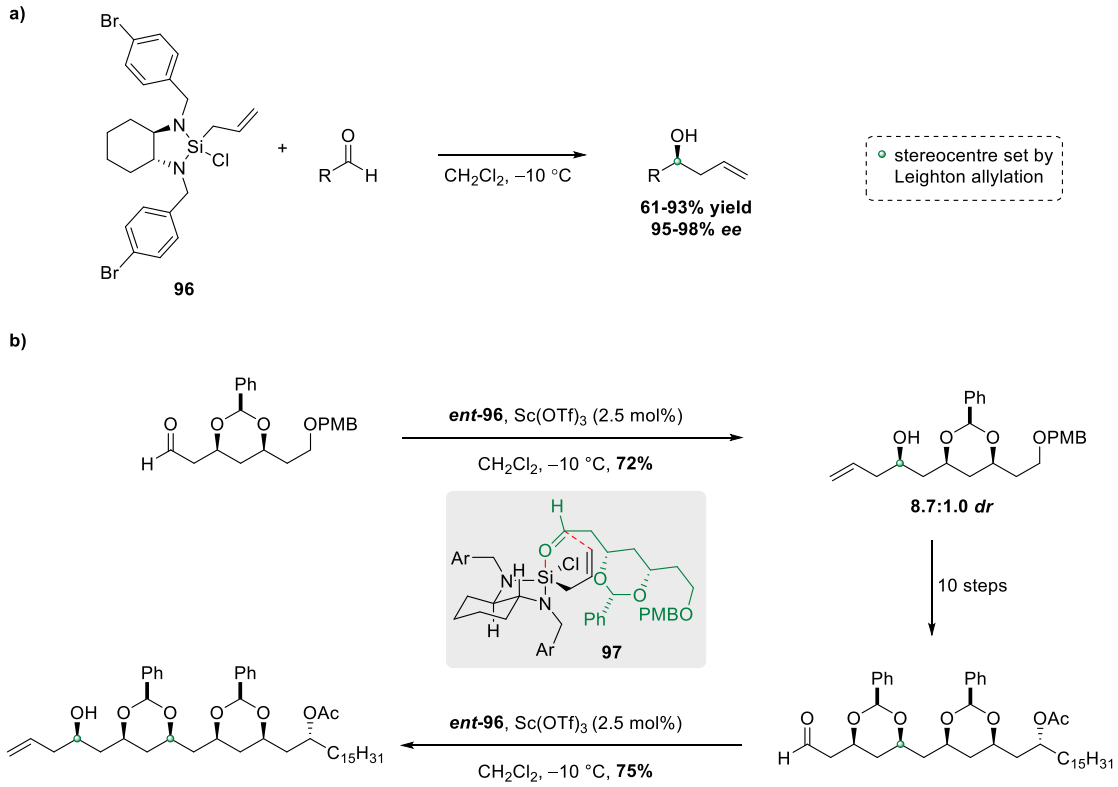


Scheme 33 Iterative Leighton oxymercuration–formylation–Brown allylation to construct a *syn* 1,3-polyol.

2.3.3 Leighton allylation

When constrained in a four- or five-membered ring, silicon exhibits substantial ring-strain-release Lewis acidity that Leighton and co-workers have exploited for allylation reactions.[79] Nucleophilic attack on the strained silane in Leighton's allylation reagent (**96**, **Scheme 34**), with its long Si–N bonds and short C–N bonds, gives a trigonal bipyramidal intermediate **97**, which then undergoes allyl transfer to give the homoallylic alcohol product in good yield and *dr*,[80] as shown in O'Doherty's synthesis of purported cryptocaryol B.[81]

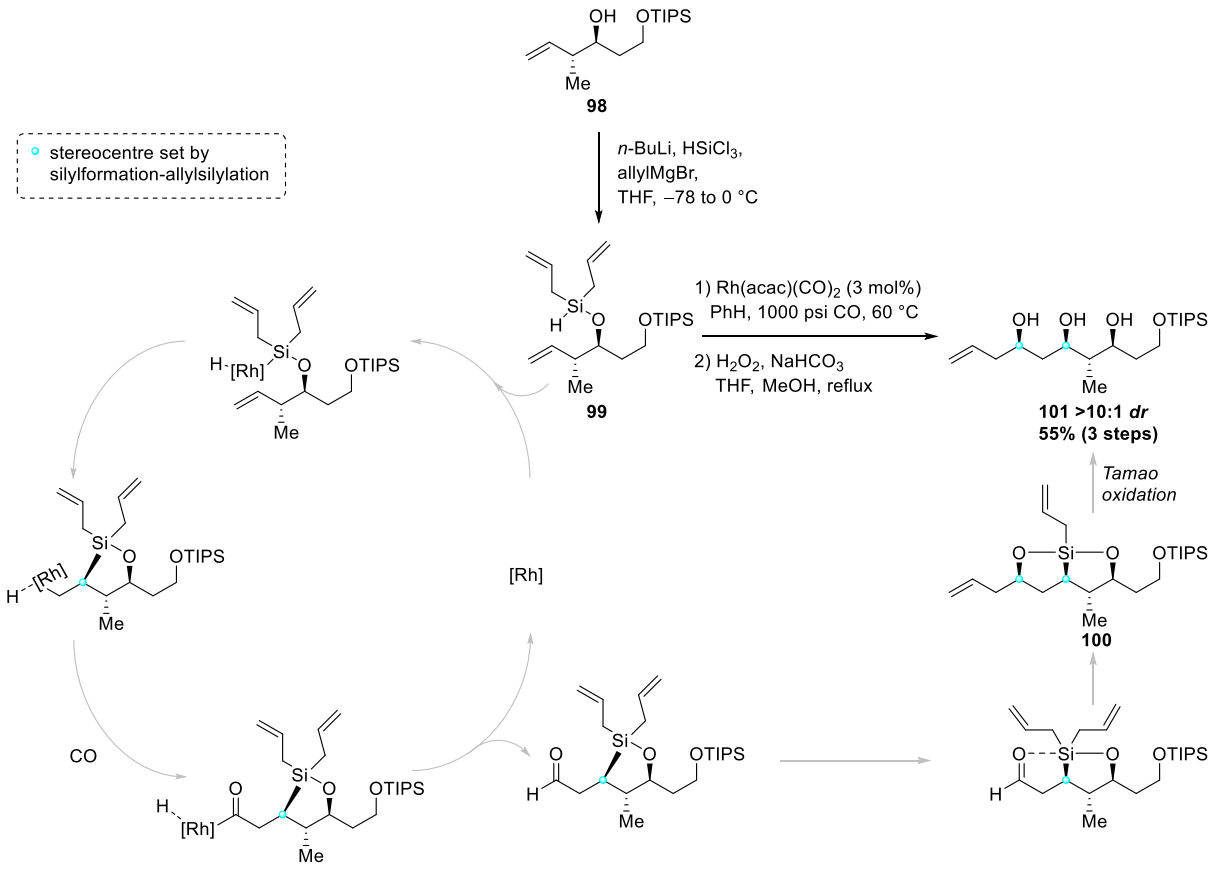
As an alternative to Brown's allylation conditions, Leighton's allylation reagent has the advantage of being readily prepared in bulk quantities from commercially available starting materials in a single step and it is stable enough to be stored for several weeks, or even longer in a freezer under inert atmosphere.[79]



Scheme 34 a) Leighton allylation using strained silacycle **96**, and b) its application by O'Doherty and co-workers in the synthesis of purported cryptocaryol B.

2.3.4 Tandem intramolecular silylformylation–allylsilylation

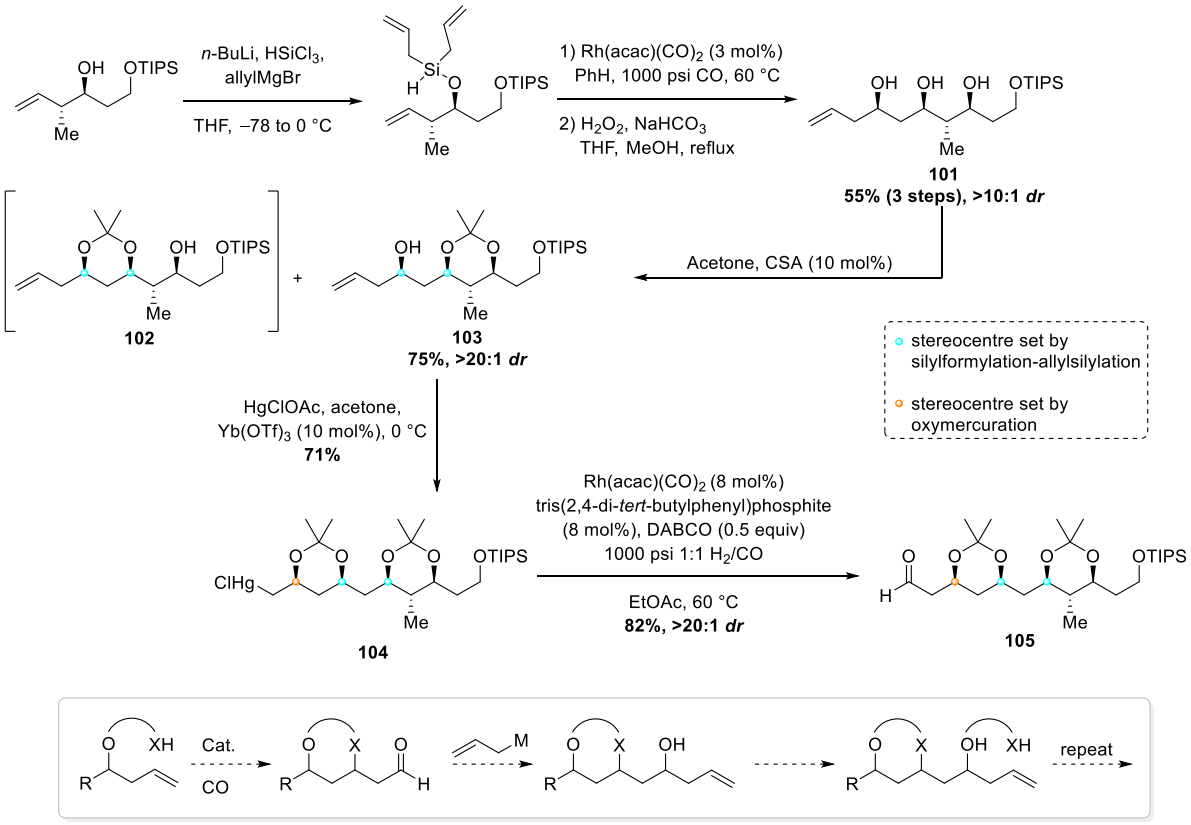
In addition to the Brown allylation–oxymercuration–formylation sequence discussed above, Leighton and co-workers used their formal synthesis of mycoticin A to demonstrate another approach to construct *syn* 1,3-polyols, tandem intramolecular silylformylation–allylsilylation (**Scheme 35**).[77,82] Sequential treatment of alcohol **98** with *n*-BuLi, $HSiCl_3$ and then allylmagnesium bromide afforded diallylsilane **99**. Rhodium-catalysed silylformylation followed by a spontaneous *syn*-allylsilylation reaction afforded homoallylic alcohol **100**, which was subjected to a stereospecific Tamao oxidation to generate the stereodefined triol **101**.



Scheme 35 Leighton's tandem intramolecular silylformylation–allylsilylation. TIPS: triisopropylsilyl.

Acetonide protection of triol **101** yielded a 7:1 mixture of regioisomers **102** and **103** (**Scheme 36**), however these could be separated by column chromatography. Isolated **103** underwent *syn*-hemiketal oxymercuration to afford **104** and following formylation**,** aldehyde **105** was obtained in high yield and >20:1 *dr*.

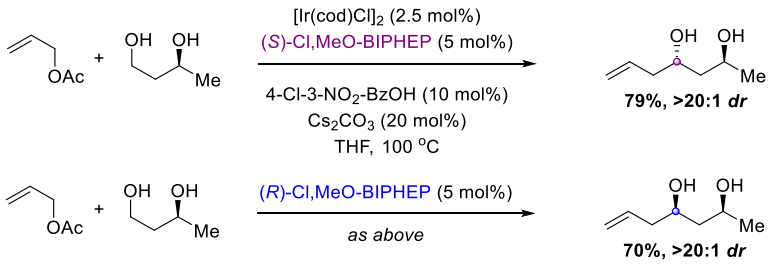
Although Leighton's oxymercuration–formylation and silylformylation–allylsilylation reactions are substrate directed, giving accessing to *syn* 1,3-poylols, this approach closely resembles the desired three-step iterative sequence, with no protection steps or oxidation level adjustments, as depicted in **Scheme 36**.



Scheme 36 Combining tandem intramolecular silylformylation–allylsilylation and oxymercuration–formylation in the formal synthesis of mycoticin A. CSA: camphorsulfonic acid.

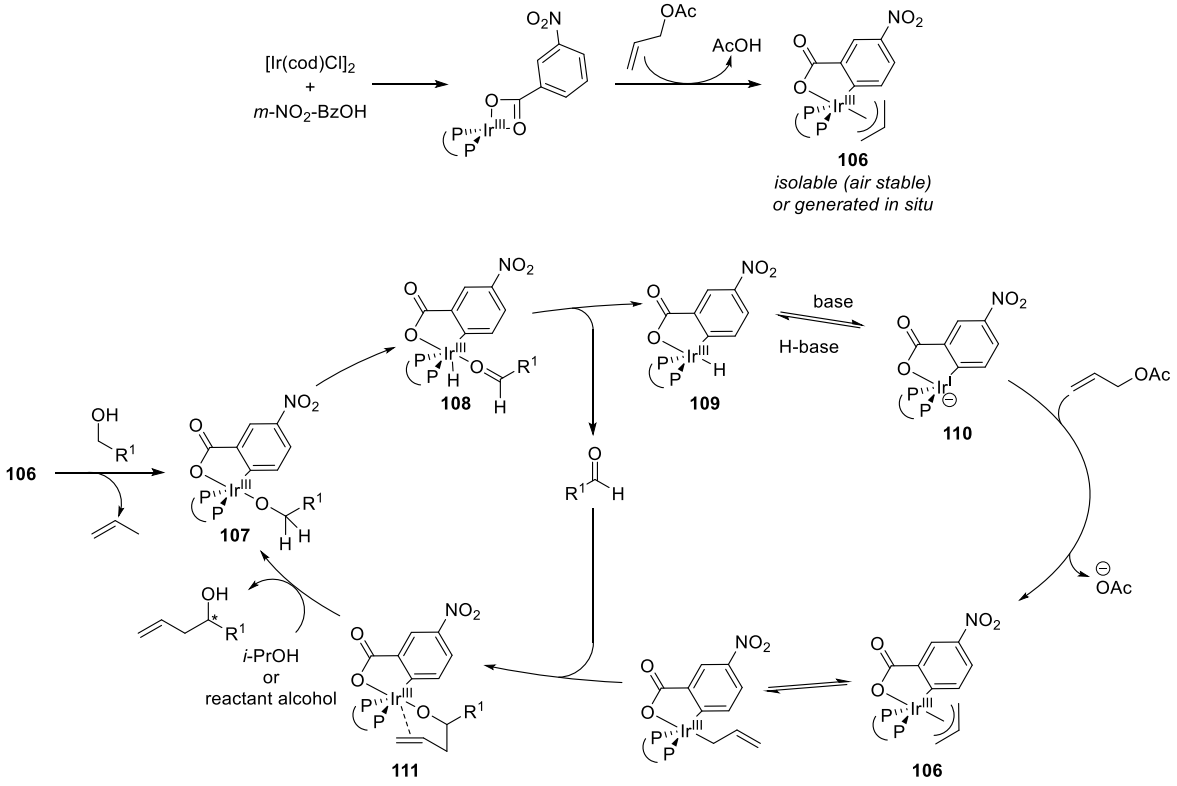
2.3.5 Krische allylation: Ir(III)-catalysed C–C coupling of primary alcohols

Given the role of substrate control and the stoichiometric chiral reagents in the reactions discussed so far, clearly a catalytic asymmetric allylation reaction would be highly attractive. Krische and co-workers reported an Ir-catalysed transfer hydrogenation reaction to give homoallylic alcohols in high *er*, directly from the alcohol oxidation level (**Scheme 37**).[83–85] Krische's chiral iridium *C,O*-benzoate catalyst both oxidises the reactant alcohol to the required aldehyde, and then facilitates the allylation step.



Scheme 37 Catalyst-controlled allylation from the alcohol oxidation level. cod: 1,5-cyclooctadiene. BIPHEP: 2,2'-Bis(diphenylphosphino)biphenyl.

The catalytic cycle starts with aldehyde addition to afford Ir(III) alkoxide **111**, where the alkene is postulated to occupy a coordination site preventing further dehydrogenation through β-hydride elimination (**Scheme 38**).[83] The homoallylic product is generated upon ligand exchange with the reactant alcohol (isopropanol serves as the terminal reductant for aldehyde substrates), leading to a free coordination site and subsequent β-hydride elimination of iridium alkoxide **107** to give Ir(III) hydride **108**. Dissociation of the aldehyde leads to Ir(III) hydride **109** which undergoes deprotonation affording the Ir(I) anion **110**. π-Allyl Ir(III) catalyst **106** is regenerated upon oxidative addition of allyl acetate to complete the catalytic cycle.

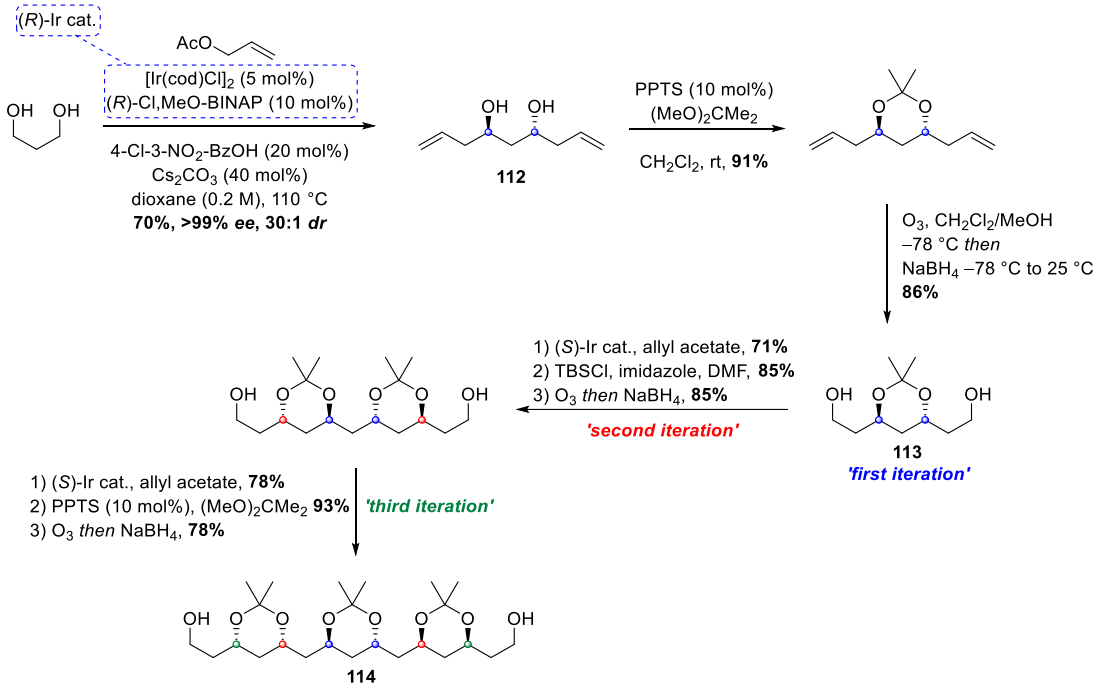


Scheme 38 Ir(III)-catalysed C–C coupling of primary alcohols.

This allylation methodology enabled Krische's synthesis of (+)-roxaticin in just 20 steps (longest linear sequence, LLS) using an iterative and bidirectional synthetic strategy from 1,3-propane diol.[86] The key iridium catalysed alcohol C–C coupling meant chiral reagents and chiral auxiliaries were not necessary in order to construct the acetonide-protected 1,3-polyol **114** in a stereocontrolled and atom efficient manner, setting 6 stereocentres in 9 steps.

Bidirectional iridium-catalysed allylation of 1,3-propanediol directly from the alcohol oxidation level, (>99% *ee*, 30:1 *dr*), followed by diol protection and ozonolysis with a reductive work up yielded the C_2-symmetric tetraol **113** which could be subjected to further

iterations of this three-step process (**Scheme 39**). Three iterations of this sequence enabled the preparation of 1,3-polyol intermediate **114** as a single diastereoisomer and enantiomer, since the allylation proceeded under complete catalyst control with no interference from the intermediate chiral β-branched aldehydes.



Scheme 39 Krische's synthesis of the 1,3-polyol in (+)-roxaticin.

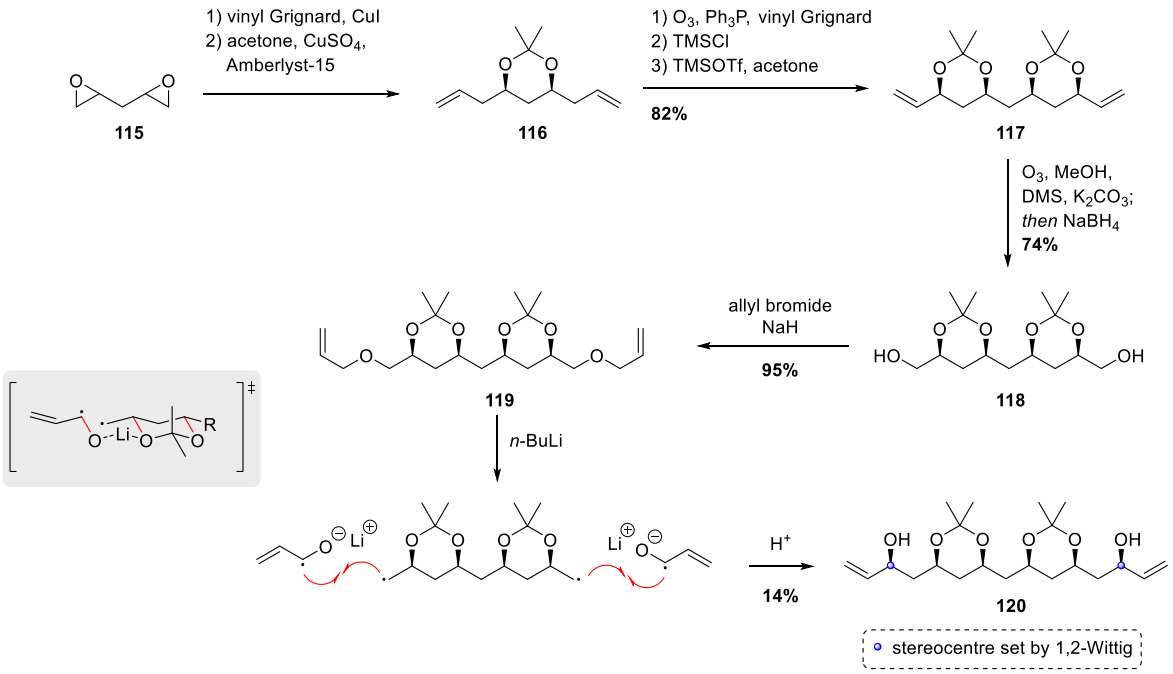
Bidirectional Krische allylation of 1,3-propane diol was also employed by She and co-workers, who used homoallylic diol **112** in the formal synthesis of (+)-neopeltolide,[87] and by Fürstner and Willwacher as an early step in the synthesis of reported mandelalide A, giving multigram quantities of the C_2-symmetric diol ***ent*-112** in high *dr* and *er*.[88]

2.3.6 1,2-Wittig rearrangement

Schreiber described the enantioselective preparation of *syn* 1,3-polyols from a *meso* precursor using bidirectional chain elongation (**Scheme 40**).[62] Simultaneous homologation of the chain from both termini, as also demonstrated by Krische and co-workers (*vide supra*),[86] represents a highly step-efficient process.

Copper-catalysed Grignard ring opening of **115** followed by protection yielded acetonide **116**.[62] Simultaneous ozonolysis of both terminal alkenes, vinyl Grignard addition and protection afforded tetraol derivative **117**. Ozonolytic cleavage of the terminal alkenes followed by a reductive work-up afforded polyol derivative **118**. Alkylation with allyl

bromide and subsequent bidirectional 1,2-Wittig rearrangement of **119** yielded all-*syn* hexaol **120**, although in low yield.



Scheme 40 Schreiber's synthesis of the all-*syn* mycoticin polyol. DMS: dimethyl sulfide.

The 1,2-Wittig rearrangement is the base-promoted carbanion rearrangement of an ether to give the corresponding secondary (or tertiary) alcohol. Carbon–carbon bond formation between the incoming allyl reagent and the substrate occurs concomitantly with formation of the *syn* 1,3-diol preferentially.[89]

A radical pair cleavage–recombination mechanism has been proposed to account for the *syn* selectivity. Following lithiation, a ketyl radical and a carbon radical are formed which undergo fast recombination within the solvent cage, so preventing stereochemical scrambling. However, the 1,2-rearrangement competes with ß-elimination and pericyclic reactions, resulting in only poor to modest yields of products.

2.4 Ring Opening of Chiral Epoxides

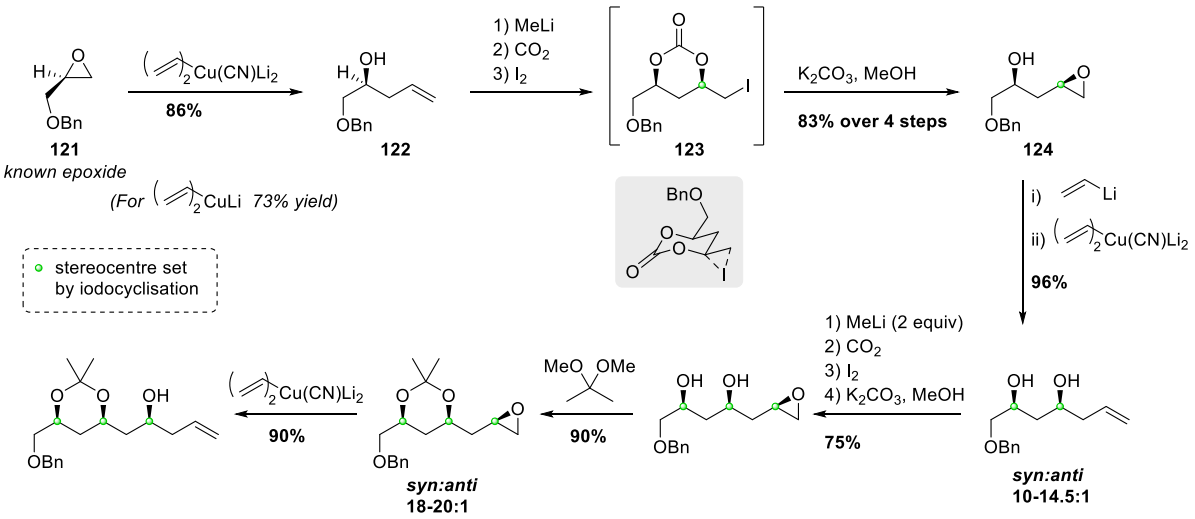
Nucleophilic opening of an epoxide is a logical approach to consider upon retrosynthetic analysis of a target molecule containing a hydroxyl group and a nucleophile in the 2-position.

2.4.1 Iodocyclisation

While still working under the assumption that all natural 1,3-polyols were *syn* (*vide supra*), Lipshutz developed an iterative 2-step protocol to access all-*syn* 1,3-polyols by opening a

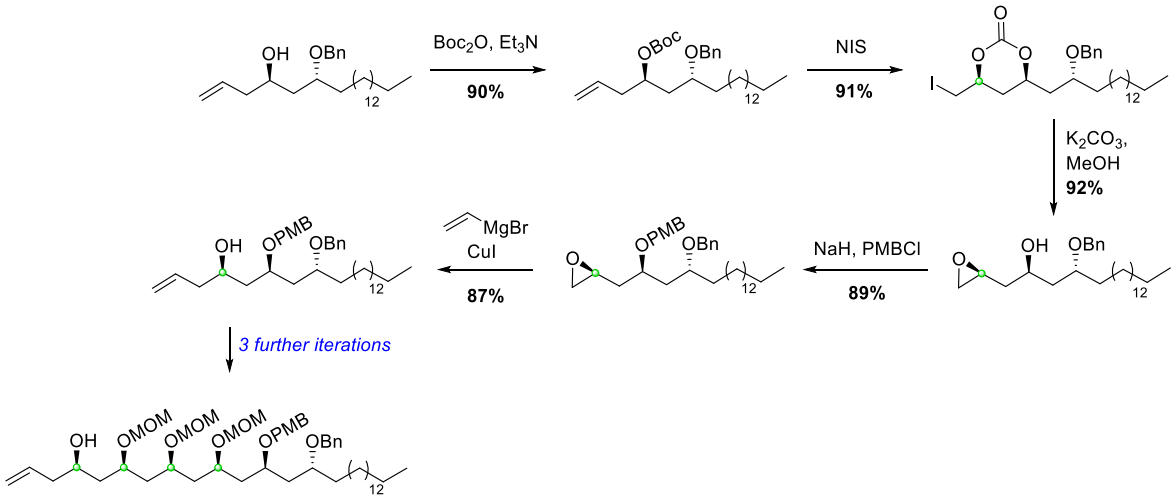
chiral epoxide with a higher order vinyl cuprate to form a homoallylic alcohol, which was subsequently epoxidised.[90] This strategy was applied iteratively in the partial synthesis of all-*syn* roflamycoin by Lipshutz and co-workers (**Scheme 41**).[91]

The cuprate addition to enantioenriched epoxide **121** proceeded in high yield when using a higher order vinyl cuprate. Homoallylic alcohol **122** was subjected to Cardillo epoxidation[92] to access the next chiral enantioenriched epoxide (**124**). Specifically, carbonate formation and alkene activation with iodine, leading to substrate directed attack giving *syn* intermediate **123**. The carbonate was cleaved upon addition of base, and ring closing with loss of the iodide ion revealed epoxide **124**, which could undergo further iterations (**Scheme 41**). It was suggested that more sterically demanding substrates would lead to higher levels of selectivity by further disfavouring formation of the iodonium on the same face as the alkyl substituent.



Scheme 41 Lipshutz' iterative diastereoselective iodocyclisation in the synthesis of all-*syn* roflamycoin.

This strategy of opening chiral epoxides with vinyl cuprates to prepare stereodefined 1,3-polyols has also been applied recently by Mohapatra and co-workers: four iterations of epoxide opening, Cardillo epoxidation and hydroxyl protection were used to set four stereocentres in the 1,3-polyol of cryptocaryol A (**Scheme 42**).[93]

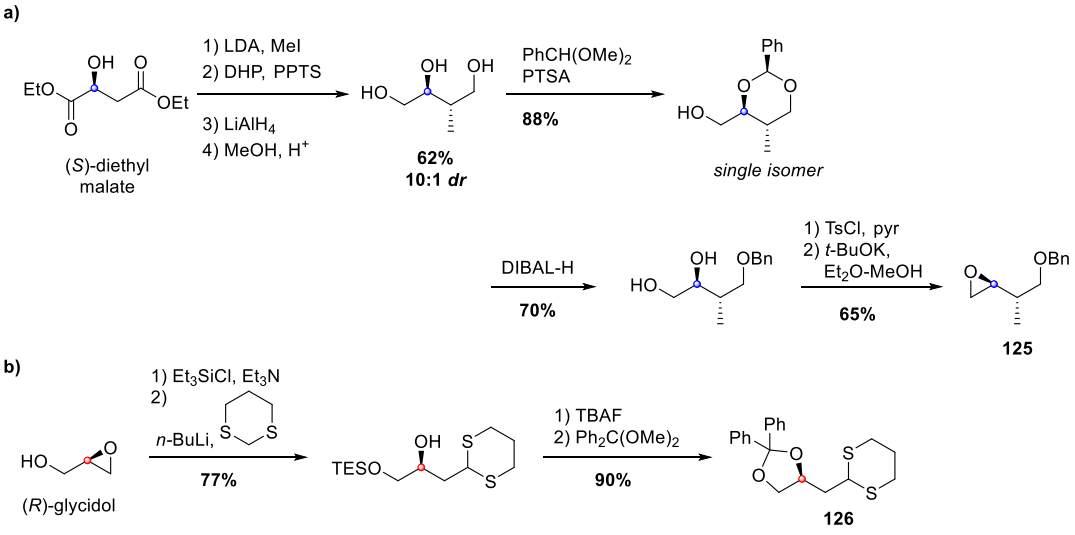


Scheme 42 Mohapatra's iterative synthesis of the 1,3-polyol domain in cryptocaryol A. Boc: *tert*-butoxycarbonyl; NIS: *N*-iodosuccinimide.

2.4.2 Epoxide opening followed by β-hydroxy ketone reduction

Nucleophilic opening of a chiral epoxide was also used in Mori's synthesis of (+)-roxaticin;[94–96] specifically this was an umpolung approach employing lithiated dithianes as nucleophilic acylating agents.

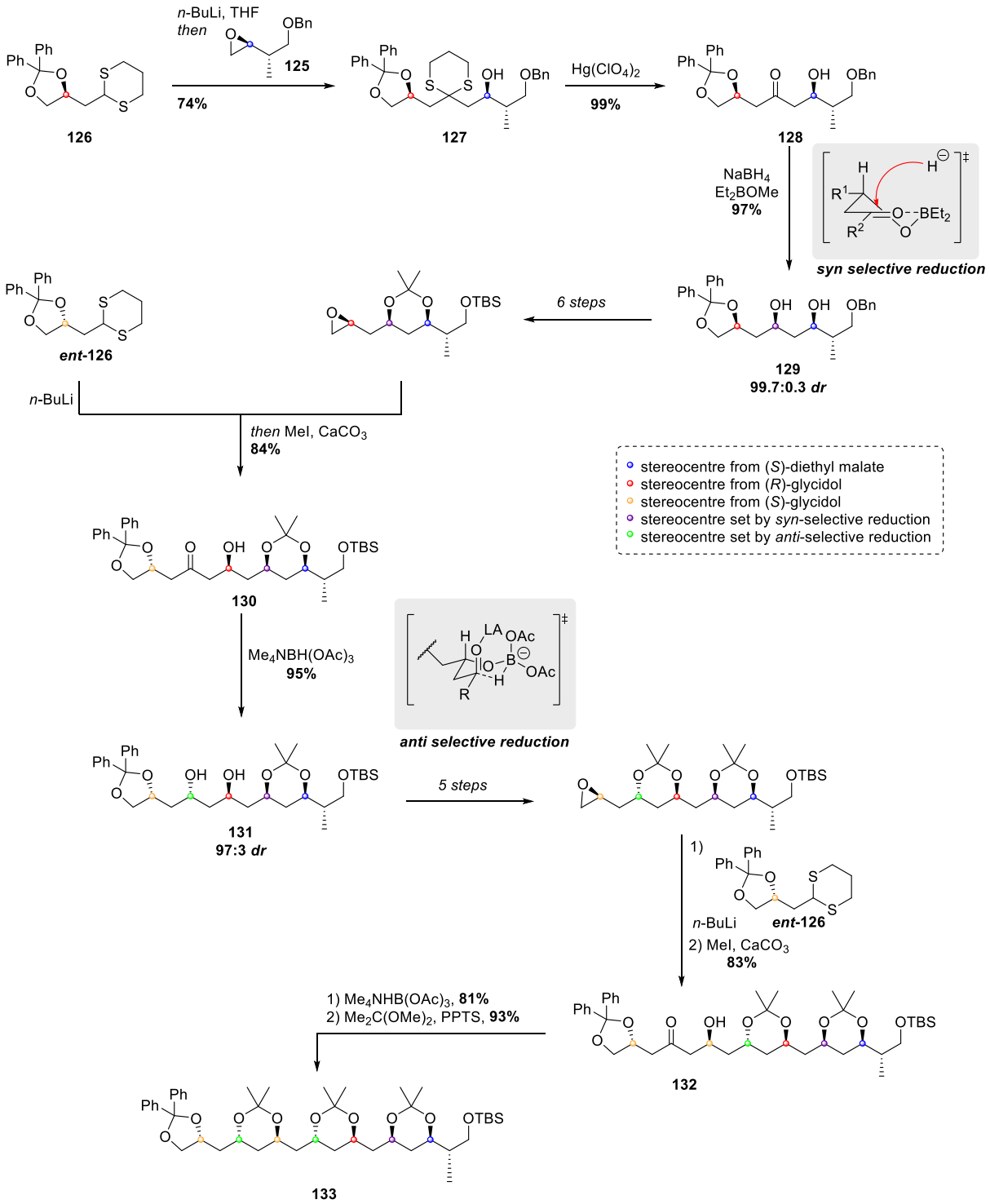
Mori's strategy involved the use of 4-carbon chiral building blocks **125**, **126** and ***ent*-126**, where the stereochemical information was installed through the choice of the appropriate chiral starting material, (*S*)-diethyl malate, (*R*)-glycidol or (*S*)-glycidol (**Scheme 43**).[94]



Scheme 43 Synthesis of Mori's building blocks. DHP: 3,4-dihydropyran; DIBAL-H: Diisobutylaluminium hydride; Ts: toluenesulfonyl; pyr: pyridine; TBAF: tetrabutylammonium fluoride.

The synthesis of the required building blocks was rather lengthy (8 and 4 steps, **Scheme 43**), with several protection group manipulations and only 2 steps adding to the carbon skeleton,

but **125**, **126** and ***ent*-126** could be isolated in high enantiopurity allowing the unambiguous installation of that hydroxylated stereocentre in each homologation reaction of a chiral epoxide with a lithiated dithiane shown in **Scheme 44.**[94,95]



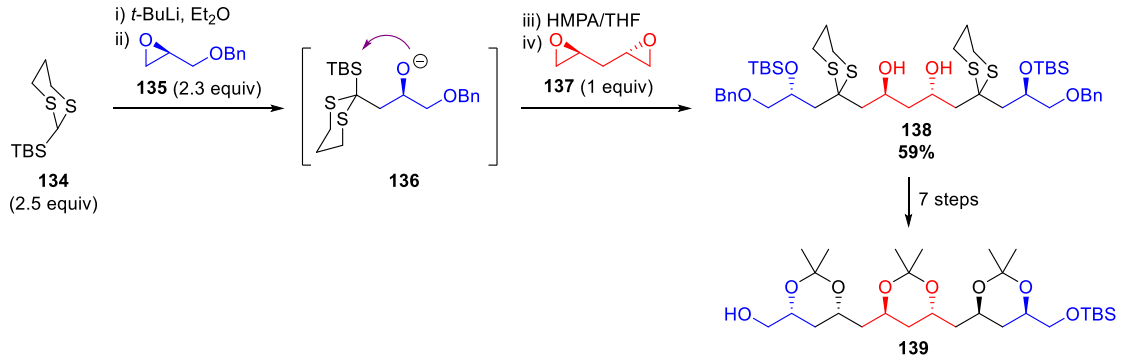
Scheme 44 Epoxide opening with dithiane anions and substrate-selected reduction of β-hydroxy ketones in Mori's synthesis of (+)-roxaticin.

First, treatment of dithiane **126** with *n*-BuLi gave the corresponding anion which regioselectively opened chiral epoxide **125** to give **127**, which upon treatment with $Hg(ClO_4)_2$ revealed the β-hydroxy ketone **128**. A *syn* selective substrate-directed reduction of **128** was required to obtain triol **129**, which took place upon addition of a Lewis acid (Et_2BOMe) and the reducing agent sodium borohydride; axial attack of the hydride through the Narasaka-Prasad transition state, where the Lewis acid is chelated to the β-hydroxy ketone substrate, provides the *syn* 1,3-diol.

In contrast, *anti* selective reduction occurs when using a bulky coordinating hydride source such as tetramethylammonium triacetoxyborohydride; this was required after two further homologation reactions, to transform epoxide opening products **130** and **132** to polyols **131** and **133**, respectively.

2.4.3 Anion relay chemistry

The opening of chiral epoxides using dithiane anions has been further developed by Amos B. Smith, III and co-workers in their anion relay chemistry and applied to the synthesis of 1,3-diol and 1,3-polyol motifs in diverse natural products.[97] A five-component type 1 anion relay chemistry coupling reaction was used to construct in one-pot the polyol backbone of the Schreiber intermediate **139** in the total synthesis of mycoticin (**Scheme 45**).[98] Lithiated dithiane **134** was used as the linchpin reagent for nucleophilic ring opening of epoxide **135**. [1,4]-Brook rearrangment of oxyanion **136** upon addition of hexamethylphosphoramide (HMPA) regenerated the dithiane anion for alkylation of bis(epoxide) **137** in a bidirectional manner to yield the desired adduct **138** in 59% yield, having forged four new carbon–carbon bonds. This strategy proved to be highly efficient, and allowed the synthesis of intermediate **139** in 8 steps instead of the 13 steps required by Schreiber and co-workers.[99]



Scheme 45 Five-component anion relay chemistry in the synthesis of the mycoticin polyol domain.

2.5 Acetate Aldol Addition Followed by Diastereoselective Reduction

Another general approach to the stereocontrolled synthesis of 1,3-polyols is an acetate aldol addition, followed by diastereoselective reduction of the aldol adduct, a β-hydroxy ketone (**Figure 9**). In the general scheme shown below, the boron enolate is generated upon treatment of the methyl ketone to be homologated with the appropriate dialkylborane and a tertiary amine, usually triethylamine or *N*,*N*-diisopropylethylamine (DIPEA). Stereoselective reduction of a chiral β-hydroxy ketone can provide access to *syn* 1,3-diols *via* the Narasaka-Prasad transition state; a bulky and coordinating hydride source such as $Me_4NBH(OAc)_3$ results in *anti* reduction (*vide supra*, **Scheme 44**). This combination of a diastereoselective aldol reaction followed by substrate-directed reduction can be applied to the synthesis of any stereodefined 1,3-diol subunit simply through the appropriate choice of aldol conditions and reducing agent. This strategy of aldol addition could be considered the closest mimic to the biosynthesis of polyacetates (*vide supra*, section **2.2**), namely homologation followed by ketone reduction.

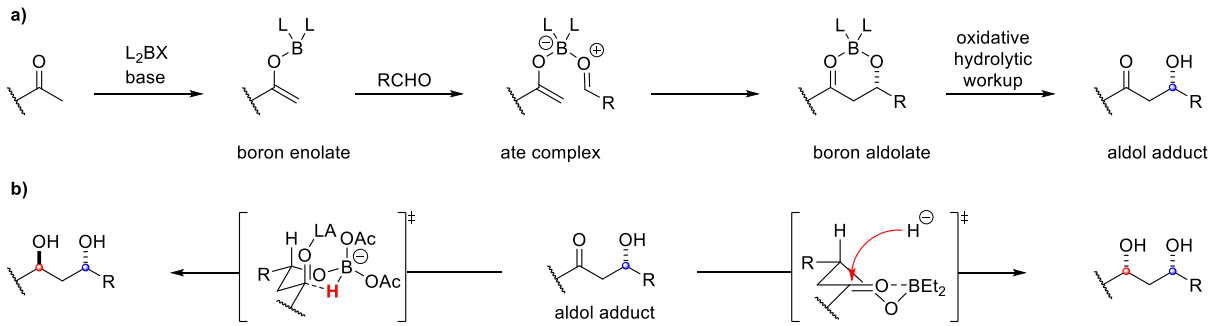
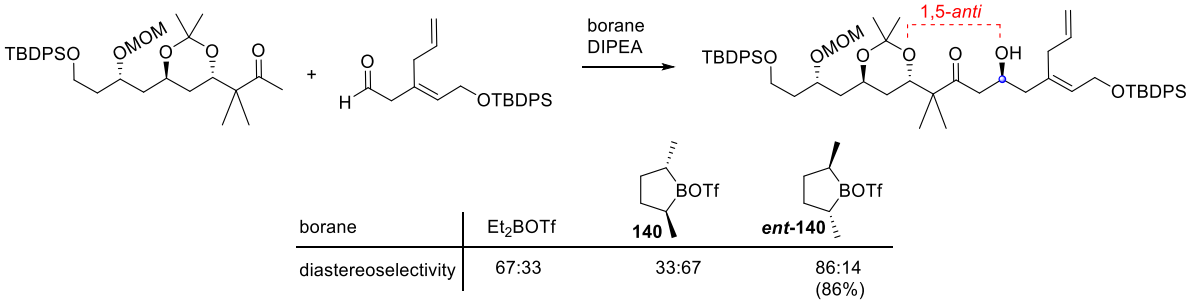


Figure 9 a) Aldol addition followed by b) diastereoselective reduction.

2.5.1 Boron-mediated aldol addition with 1,5-*anti* stereoinduction

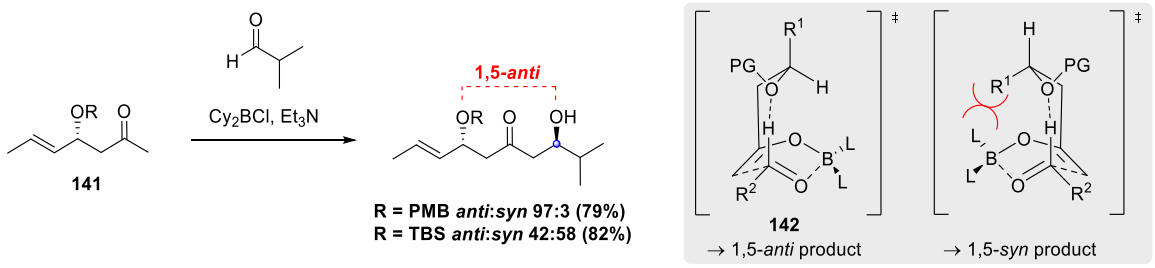
The boron-mediated aldol addition of chiral ketones is commonly employed in the synthesis of polyketides and in the case of ethyl ketones—for the synthesis of polypropionates—it frequently proceeds with high stereocontrol without the need for chiral reagents. As for the preparation of polyacetates, the corresponding aldol reaction with a methyl ketone tends to show lower stereoselectivity (although this can be addressed to some degree through the use of chiral ligands on boron).[100] However, the aldol addition of β-hydroxy methyl ketones with aldehydes has been observed to occur with high levels of 1,5-*anti* stereoinduction under substrate control. Reduction of the β-hydroxy ketone addition product affords a stereodefined 1,3,5-triol.

Masamune and co-workers first reported this 1,5-*anti* asymmetric induction in the aldol addition in their synthesis of the AB fragment of bryostatin 1 (**Scheme 46**).[101] Furthermore, they demonstrated that the levels of diastereoselectivity obtained depended on the boron reagent: achiral diethyl boron triflate gave a 67:33 mixture favouring the 1,5-*anti* adduct, showing clear substrate control; chiral boron reagent **140** showed a mis-matching effect, as the product was obtained as a 33:66 mixture of 1,5-*anti*:1,5-*syn* aldol adducts; finally, the enantiomer ***ent*-140** afforded the product with 86:14 *dr*, where clearly the reagent control was reinforced by the substrate facial preference leading to a matched case.



Scheme 46 1,5-anti stereoinduction in a boron aldol reaction in Masamune's synthesis of bryostatin 1.

This preferential formation of the 1,5-*anti* product is dominated by the strong internal stereoinduction from the β-alkoxy stereocentre but the β-alkoxy protecting group itself influences the degree of diastereocontrol;[100] high 1,5-*anti* selectivity is observed with benzylic protecting groups yet the use of silyl protecting groups results in little or no selectivity. Paterson and co-workers demonstrated this systematically through the boron-mediated aldol reaction of **141** with isobutyraldehyde;[102] when the protecting group was *para*-methoxybenzyl (PMB), the 1,5-*anti* product was obtained with 97:3 *dr* but when the protecting group was *tert*-butyldimethylsilyl (TBS) this stereochemical preference was lost resulting in 42:58 *dr* (**Scheme 47**).

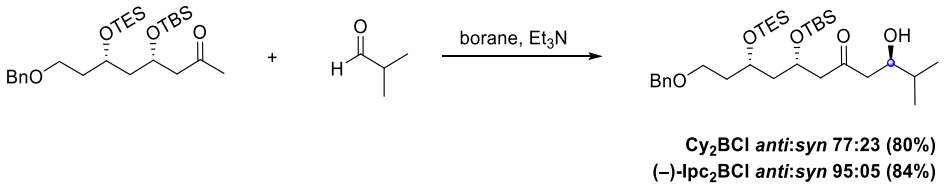


Scheme 47 Stereochemical model for 1,5-*anti* selectivity with different protecting groups.

In order to explain this enhanced 1,5-*anti* selectivity with benzylic protecting groups, it was first suggested by Hoberg and co-workers that a π-stacking interaction between the benzylic

protecting group and the boron enolate could be important in a cyclic transition state.[103] However, high levels of 1,5-*anti* stereoinduction may be obtained with β-alkoxy substituents including methoxy and cyclic ethers such as THF.[100] Paton and Goodman later performed theoretical studies and concluded that these boron-mediated aldol reactions of methyl ketones with a β-alkoxy substituent proceed instead through a boat-like transition state (**142**), which avoids an unfavourable 1,3-diaxial interaction between the ligands on boron and the β-alkyl group in a chair-like transition state (**Scheme 47**).[104,105] The most stable calculated conformation for a boron enolate of a β-alkoxy methyl ketone had the alkoxy side chain bent towards the incoming aldehyde, which did not seem favourable considering sterics alone, yet the methoxy-oxygen and formyl-proton were observed to be just 2.355 Å apart and so they postulated that the transition state leading to the 1,5-*anti* aldol adduct has a stabilising formyl hydrogen bond between the aldehyde proton and the alkoxy oxygen. The 1,5-*anti* selectivity was lower in dichloromethane than in diethyl ether which is as expected if formyl hydrogen bonding is present, since this electrostatic interaction would be diminished in a more polar solvent.[106]

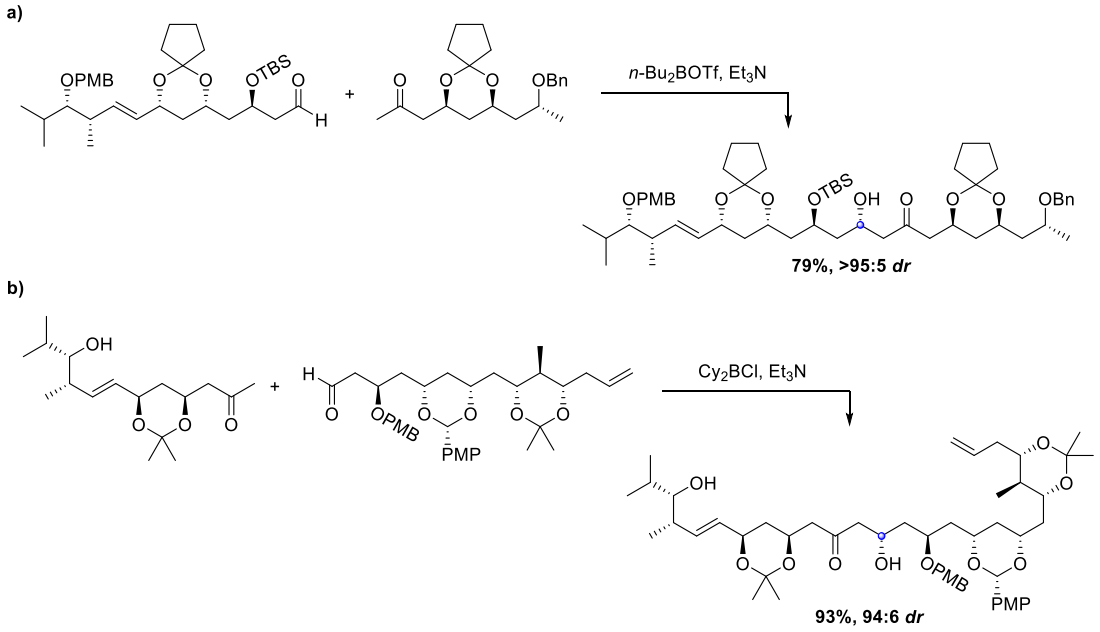
Compared to benzyl ether protecting groups, silyl ether protecting groups are more sterically demanding and natural bond order (NBO) analysis showed that the oxygen was more electron deficient. Therefore substrates with a silyl group protecting the β-oxygen are assumed not to exhibit this formyl hydrogen bonding since there is not enough electronic stabilisation to make up for the large steric penalty when adopting this transition structure with the enolate pointing inwards, and so this may explain the low selectivity observed with OTBS (**Scheme 47**). Nevertheless, when a silyl ether protecting group is required, a chiral boron reagent such as (–)-Ipc_2BCl can be used to combat the expected low selectivity in this case, improving the diastereoselectivity from 77:23 to 95:5 *dr* through asymmetric induction from the chiral ligands on boron (**Scheme 48**).[107]



Scheme 48 Paterson's synthetic studies towards spongistatin 1. TES: triethylsilyl.

This 1,5-*anti* stereoinduction has been applied at a crucial step in several total syntheses of 1,3-polyol natural products (**Scheme 49**), including roxaticin (Paterson,[108] Evans[109]), mycoticin A (Leighton[77]), RK-397 (Denmark[110]) and dermostatin A (Sammakia[111]); in each

case the 1,5-*anti* boron aldol adduct was obtained in excellent yield and diastereoselectivity and was then subjected to substrate directed reduction and acetonide protection. The 1,5-*anti* boron aldol addition was used three times in Dias and co-workers' synthesis of (−)-cryptocaryol.[112]



Scheme 49 1,5-*anti* boron aldol addition applied in a) Evans' total synthesis of (+)-roxaticin and b) Sammakia's total synthesis of dermostatin A.

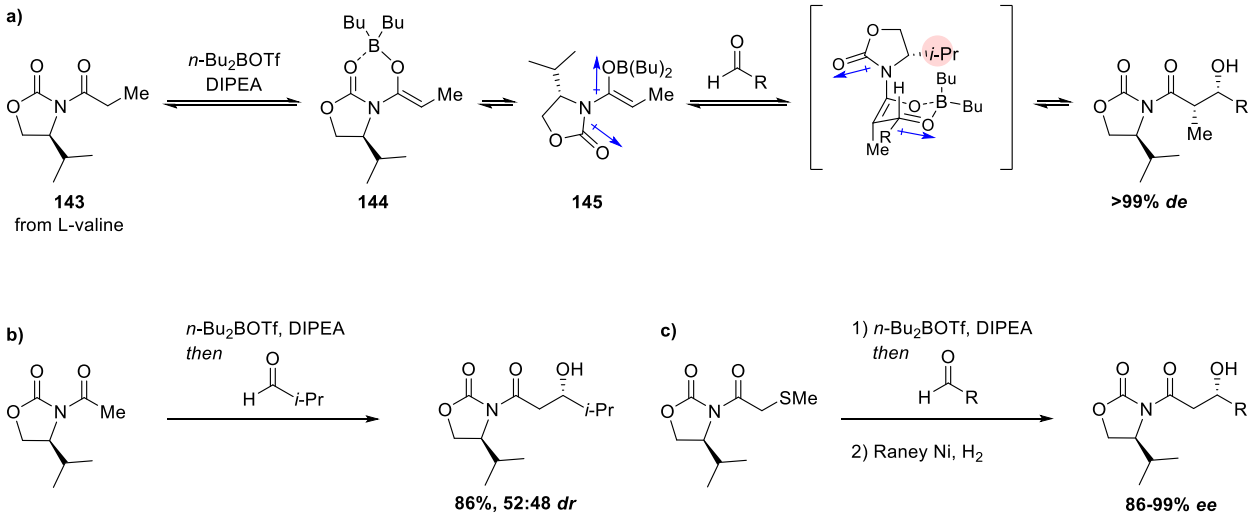
2.5.2 Chiral auxiliaries for the acetate aldol addition

The classic approach to induce and control enantioselectivity in an aldol addition reaction between two prochiral reagents is to use a chiral auxiliary, such as Evans' oxazolidinones (**Scheme 50** a).[113] Evans' auxiliary **143** is easily prepared from L-valine and mediates highly diastereoselective aldol reactions. This high diastereoselectivity results from: (i) exclusive formation of the *cis*-enolate (**144**), which sets the Me stereocentre, as chelation leads to a single rigid conformation; this then rotates to the reactive conformer **145**, where dipolar repulsion through the imide is minimised; (ii) π-facial selectivity, which sets the OH stereocentre, means the aldehyde does not approach from the back face, due to steric hindrance with the *i*-Pr group; in addition, the R group on the aldehyde always prefers to be equatorial to minimise 1,3-diaxial interactions in the chair transition state. In this way, excellent levels of diastereoselectivity are obtained by disfavouring one transition state (avoiding steric clash) and favouring another (opposing dipoles).

If the methyl group was replaced by hydrogen, one might expect the same transition state, *i.e.* no attack from behind due to steric clash with *i*-Pr, and the R group on aldehyde equatorial,

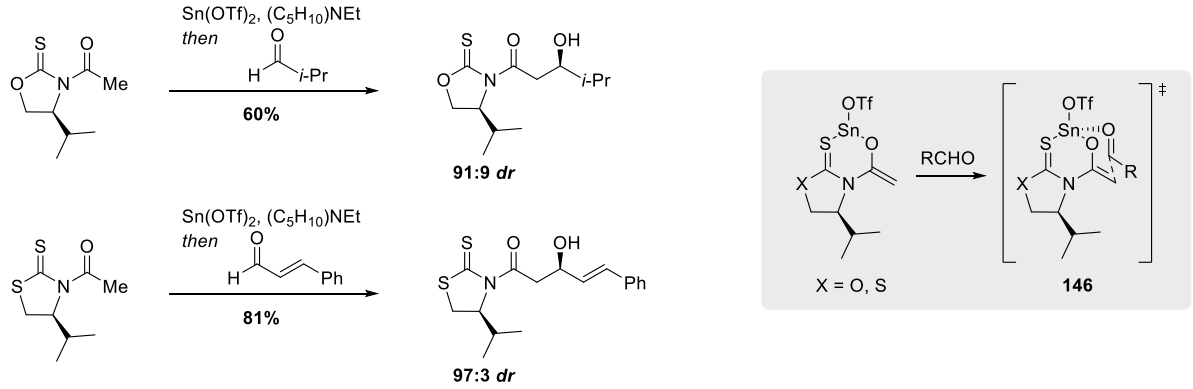
but diastereofacial selectivity is greatly diminished (**Scheme 50** b).[114] When the α-methyl group is not present (as it is in the acetate aldol), the unfavourable interaction is lost (no more steric clash between the enolate and the auxiliary), leaving only the favourable dipole-dipole minimisation. In an acetate aldol addition, the corresponding enolate without the α-methyl group is considerably smaller, so the reaction can proceed with a less highly organised transition state, which may also contribute to the loss of diastereoselectivity.

An early attempt to address this issue was to use a temporary thioether group (**Scheme 50** c), which could be removed after the aldol addition by reduction over Raney nickel.[114]



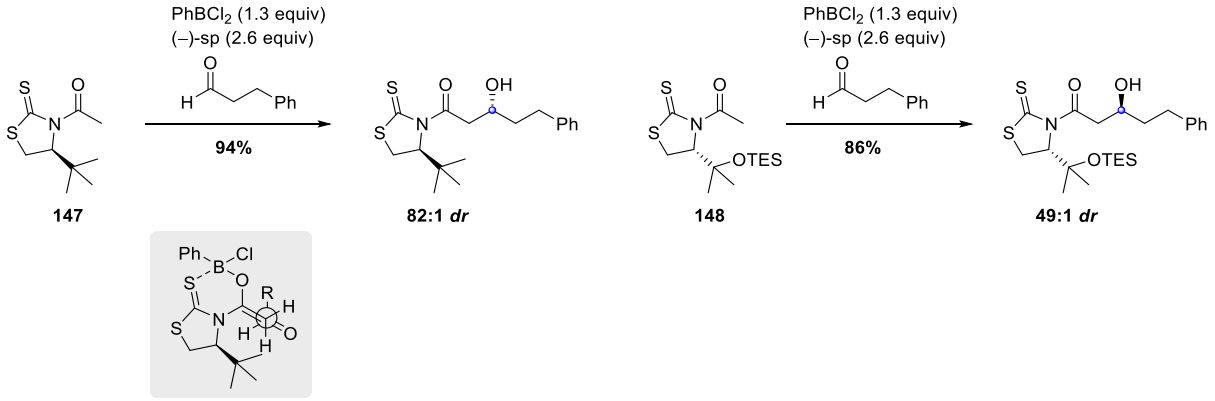
Scheme 50 Evans' oxazolidine auxiliary. *de*: diastereomeric excess.

Switching from boron to tin and using a slightly modified auxiliary does allow for selectivity to be achieved (**Scheme 51**).[115,116] Since sulfur is more Lewis basic than oxygen, it remains coordinated to the tin throughout the reaction, locking the enolate configuration, as opposed to Evans' aldol reaction (*vide supra*) where the oxygen points into space to allow the dipoles to oppose. The incoming aldehyde then coordinates to the opposite face of the *i*-Pr group of the chiral auxiliary, transition state **146** accounts for the observed major diastereomer.



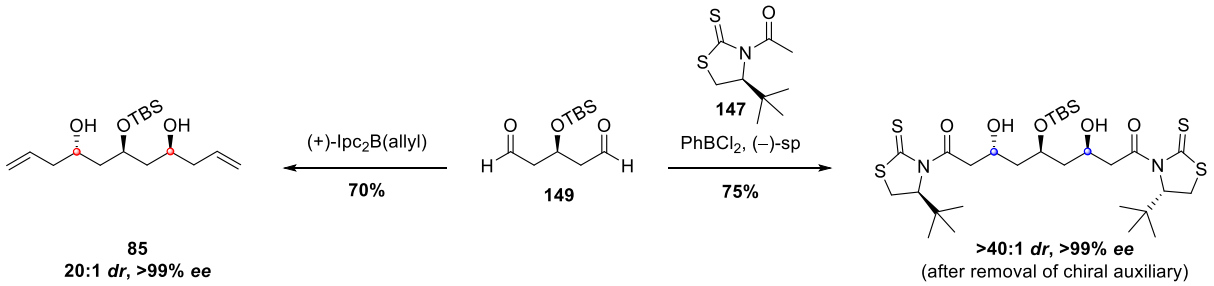
Scheme 51 Alternative chiral auxiliaries for acetate aldol. OTf: trifluoromethanesulfonate.

The closed transition state with Evans' auxiliary does not include the exocylic oxygen, since it is not so Lewis basic that it cannot dissociate from the Lewis acidic boron. As with the auxiliaries in **Scheme 51**, Sammakia developed an auxiliary also exploiting the increased Lewis basicity of sulfur (**Scheme 52**).[117–119] Sammakia's conditions involve enolisation with the hindered base sparteine and $PhBCl_2$, resulting in high yields and diastereoselectivity, however some matching/mis-matching effects are observed with chiral aldehydes. Sammakia's auxiliary (**147**) for acetate aldol additions is derived from *tert*-leucine; the pseudo-enantiomeric reagent **148** is derived from the inexpensive L-cysteine but shows remarkably similar behaviour; clearly substitution of a methyl group with OTES has little effect on reactivity.



Scheme 52 Sammakia's auxiliary for acetate aldol.

In order to showcase the application of the new auxiliary, Sammakia and co-workers compared it to the Brown allylation of **149**, an intermediate in their total synthesis of dermostatin A; an acetate aldol addition mediated by auxiliary **147** proceeded in comparably good yield and excellent selectivity (**Scheme 53**).

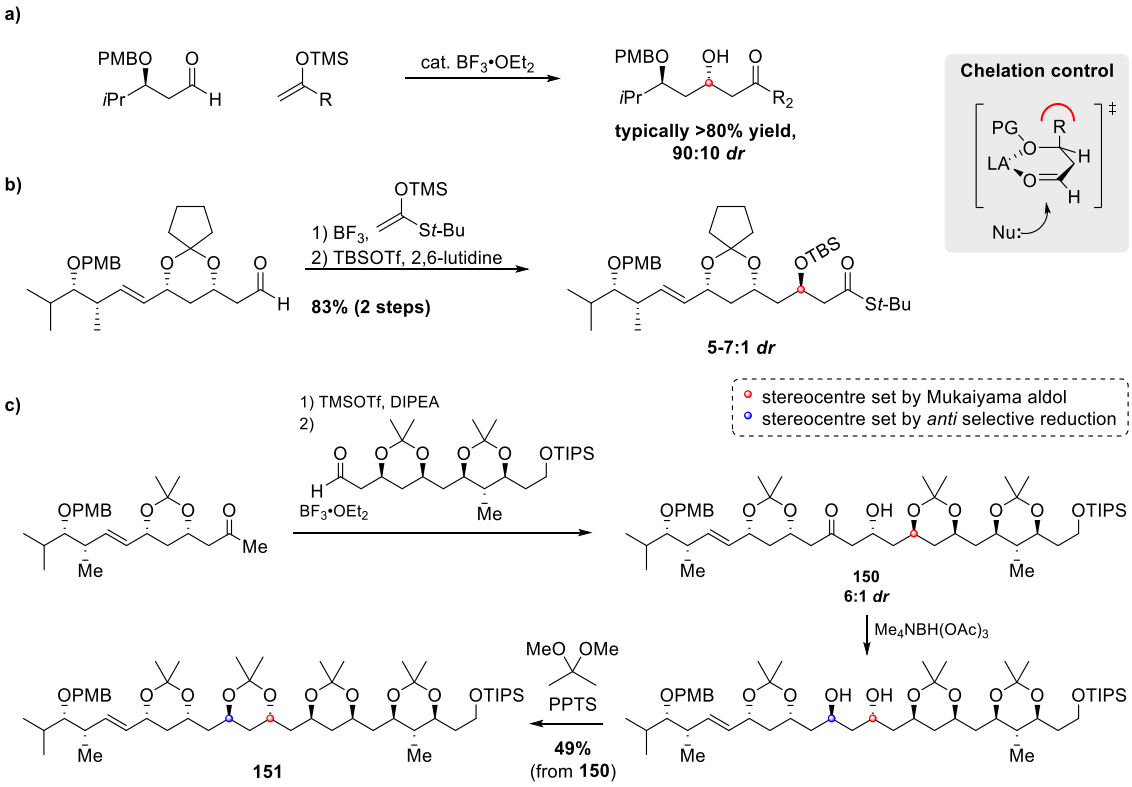


Scheme 53 Sammakia's auxiliary acetate aldol reaction compared to Brown allylation.

2.5.3 Mukaiyama aldol addition

The Mukaiyama aldol addition is the reaction of an aldehyde and a silyl enol ether to give a β-hydroxy ketone using a Lewis acid catalyst (such as $TiCl_4$), followed by aqueous work-up (**Scheme 54**). The trimethylsilyl (TMS) enol ether is a sterically demanding enolate equivalent and the reaction prefers an open transition state, where both the Lewis acid employed and the size of the substituents contribute to the observed stereochemistry (*syn* or *anti*) in the product.[120–122]

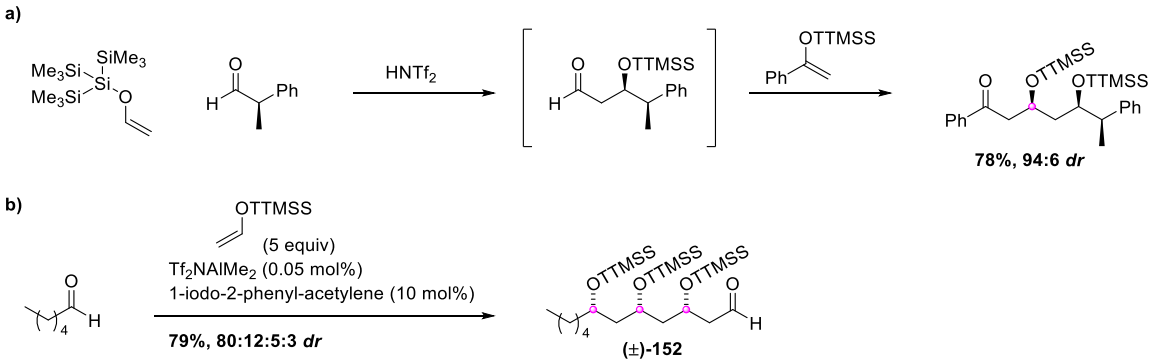
Mukaiyama aldol additions to chiral β-alkoxy aldehydes usually proceed with high levels of 1,3-*anti* stereoinduction under chelation control[121,122] and have been used in several total syntheses of 1,3-polyol natural products, including Evans' synthesis of (+)-roxaticin[109] and Leighton's formal synthesis of mycoticin;[77] the drop in diastereoselectivity is attributed to the steric bulk of these advanced intermediates (**Scheme 54**). However, the minor diastereomer can sometimes be removed at a later step; Leighton's β-hydroxy ketone product **150**, generated as an inseparable 6:1 mixture of diastereoisomers, was subjected to substrate directed *anti*-diastereoselective reduction using tetramethylammonium triacetoxyborohydride and then acetonide protection, at which point **151** could be separated from the minor diastereoisomer.[77]



Scheme 54 Mukaiyama aldol reaction a) 1,3-*anti* asymmetric induction with β-hydroxy aldehydes, applied in b) Evans' synthesis of (+)-roxaticin, and c) Leighton's formal synthesis of mycoticin.

The predictable and high levels of 1,3-*anti* asymmetric induction are not universal; not only can matching/mismatching effects be observed with certain substrates,[123] but the diastereoselectivity is reduced with increasing steric demand of the β-hydroxy protecting group. In fact Yamamoto reported that the hypersilyl protecting group ($(Me_3Si)_3Si$, TTMSS) leads to remarkable 1,3-*syn* stereoinduction (**Scheme 55**);[124,125] the carbonyl group must now be *anti*-periplanar to this extremely bulky protecting group, on the opposite face to the alkyl substituent.

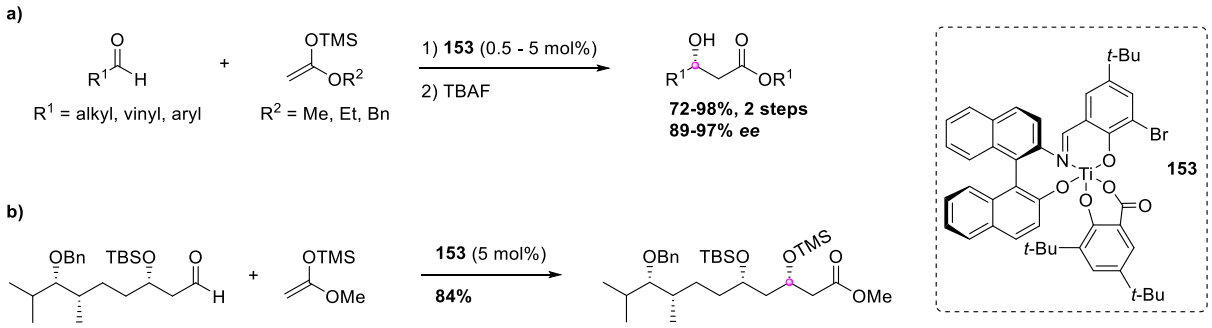
Although perhaps the closest biomimetic approach, there are very few reported examples of iterative acetate aldol reactions being using for the synthesis of 1,3-polyol fragments, presumably due mainly to challenges related to stereocontrol. However, Yamamoto and co-workers extended their work on 1,3-*syn* selective aldol reactions with TTMSS protecting groups to a one-pot polyaldol cascade to give the stereodefined triol **152** with high 1,3-*syn* stereoinduction (**Scheme 55**).[126]



Scheme 55 a) 1,3-*syn* stereoinduction with β-OTTMSS, b) Yamamoto's triple aldol cascade.

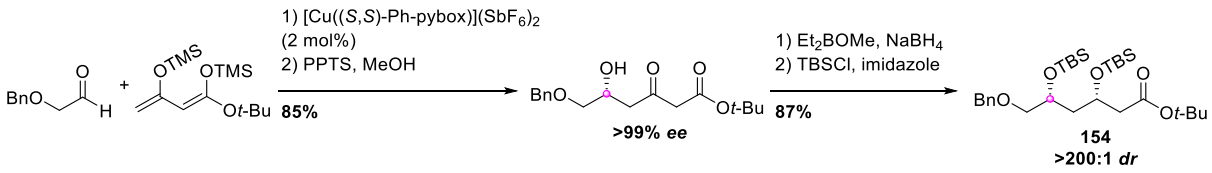
Chiral Lewis acids have been developed for Mukaiyama aldol additions in order to both increase and dictate the exhibited stereocontrol, along with enhancing the electrophilicity of the aldehyde.[120]

Carreira and co-workers reported high levels of enantioselectivity and a wide substrate scope with a chiral binol-derived titanium catalyst (**153**) (**Scheme 56** a).[127] This catalyst-controlled aldol addition has been applied in the synthesis of 1,3-polyols, such as in Rychnovsky's total synthesis of roflamycoin (**Scheme 56** b).[128]



Scheme 56 Mukaiyama aldol reactions with chiral Lewis acids. a) Carreira's chiral binol-derived titanium catalyst and b) its application by Rychnovsky in the total synthesis of roflamycoin.

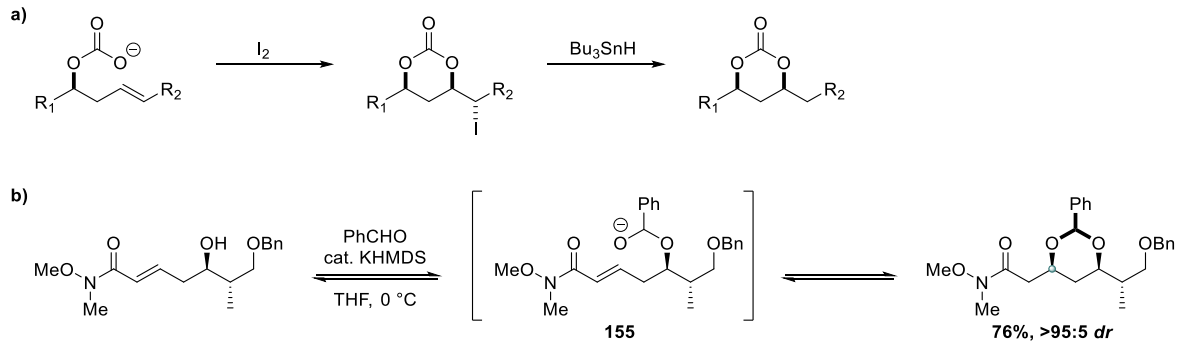
In the total synthesis of (+)-roxaticin,[109] Evans' used an enantioselective Mukaiyama aldol reaction employing a C_2-symmetric Cu(II) complex as a Lewis acid catalyst (**Scheme 57**). With one stereocentre set, substrate directed *syn* reduction followed by protection of the resulting *syn* 1,3-diol yielded **154** essentially as a single diastereomer.



Scheme 57 Enantioselective Mukaiyama aldol using a chiral Cu(II) complex in Evans' total synthesis of (+)-roxaticin.

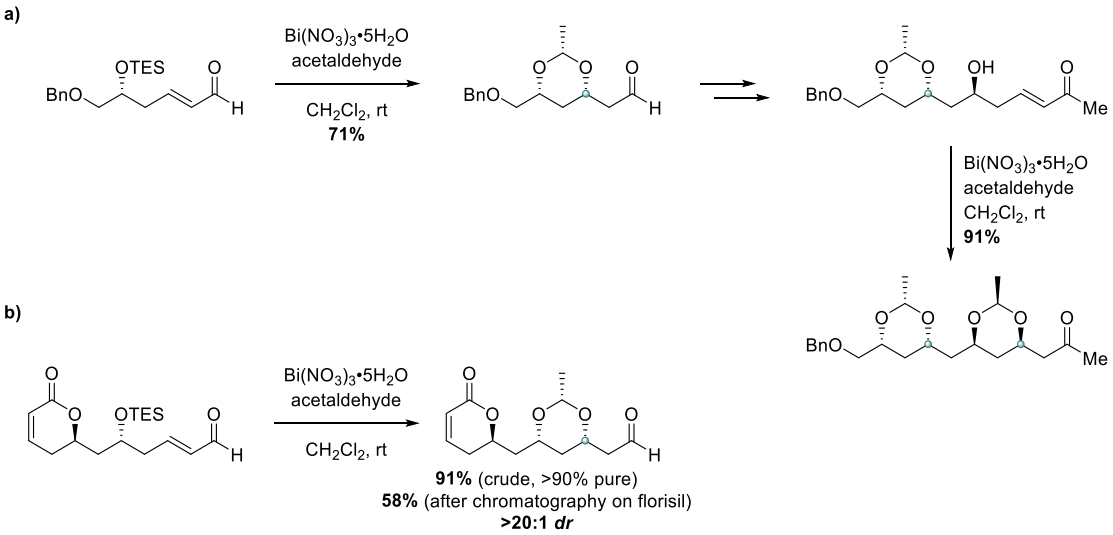
2.6 Oxa-Conjugate Addition: Protected *syn* 1,3-Diols

The iodocyclisation/Cardillo epoxidation strategy for the preparation of *syn* 1,3-diols[90] (*vide supra*, section **2.4.1**) inspired the development of oxa-conjugate addition methodology for the preparation of protected *syn* 1,3-diols (**Scheme 58** a).[129] Treatment of a homoallylic alcohol with excess benzaldehyde in the presence of catalytic base results in the formation of an alkoxy intermediate (**155**), which can then undergo substrate-directed intramolecular hemiacetal conjugate addition to afford the thermodynamically favoured *syn*-protected 1,3-diol in good yields and high *dr* (>95:5); these conditions were used in Evans' total synthesis of (+)-roxaticin (**Scheme 58** b).[109] However there are some limitations, namely the loss of *syn* selectivity with aliphatic aldehydes such as acetaldehyde; this could be due to the corresponding alkoxide intermediate being less stabilised, interfering with equilibration to the thermodynamic *syn* configuration.



Scheme 58 Oxa-conjugate addition. a) iodocyclisation, which inspired methodology applied in b) Evans' total synthesis of (+)-roxaticin. cat.: catalytic. KHMDS: potassium bis(trimethylsilyl)amide.

However, P. Andrew Evans and co-workers were able to perform oxa-conjugate additions with acetaldehyde when using bismuth(III) nitrate as a substoichiometric mediator,[130] affording the required protected *syn* 1,3-diols in good yield; this reaction was used twice in their synthesis of the C19–C28 polyacetate unit of macrolide RK-397 (**Scheme 59** a)[130] and has also been applied by Krische and co-workers in their synthesis of cryptocaryol A (**Scheme 59** b).[131]

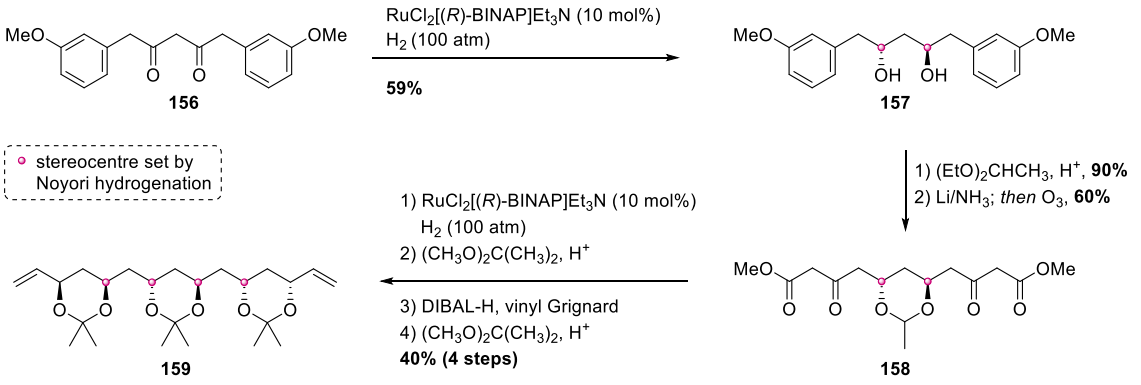


Scheme 59 Oxa-conjugate addition: a) P. Andrew Evans' synthesis of the RK-397 polyol and b) Krische's synthesis of cryptocaryol A.

2.7 Noyori Asymmetric Transfer Hydrogenation

Schreiber and co-workers reported the total synthesis of (+)-mycoticin A through bidirectional growth of a C_2-symmetric skipped polyol using Noyori transfer hydrogenation[132,133] as the stereodefining step (**Scheme 60**).[134] This iterative and highly step-efficient approach involved asymmetric ketone reduction, followed by unmasking of the terminal phenyl groups to ketones ready for another asymmetric ketone reduction.

Bidirectional asymmetric reduction of C_2-symmetric diketone **156** using the Noyori-Akutagawa catalyst system afforded *anti* 1,3-diol **157** which was protected before dissolving metal reduction and ozonolysis to furnish keto ester **158**. Another double asymmetric reduction and acetonide protection afforded a tetraol derivative. Subsequent DIBAL-H reduction of both terminal esters, bidirectional Grignard addition and protection in a 'one-pot sequence' generated hexaol derivative **159**.

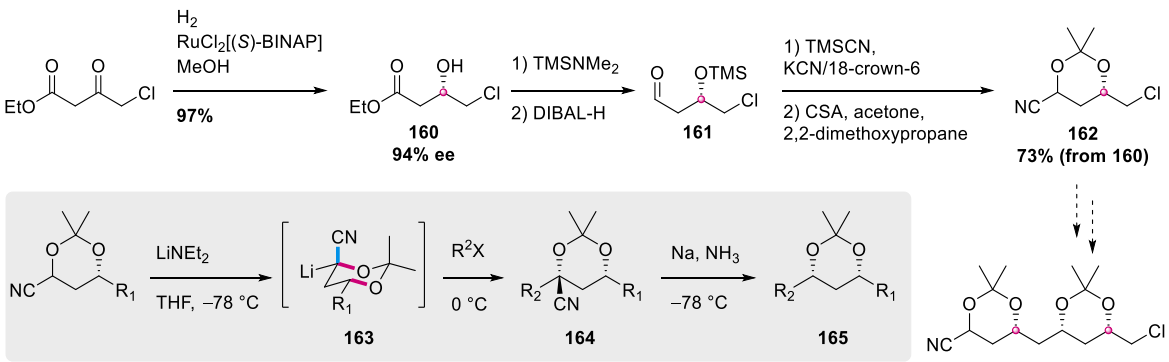


Scheme 60 Noyori transfer hydrogenation as the stereodefining step in Schreiber's synthesis of (+)-mycoticin A. BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

Rychnovsky and co-workers also used Noyori hydrogenation as the stereodefining step in the preparation of cyanohydrin acetonides as 1,3-diol synthons, such as **162**, which could be prepared in enantiomerically enriched form (94% *ee*) in 5 steps from ethyl 4-chloroacetate (**Scheme 61**).[135] Noyori enantioselective reduction of ethyl 4-chloroacetoacetate afforded **160** in high yield and enantiomeric excess. Silylation of the hydroxy ester followed by reduction with DIBAL-H yielded the terminal aldehyde **161**. The terminal nitrile was installed using trimethylsilyl cyanide and potassium cyanide/18-crown-6 and acetonide protection yielded cyanohydrin acetonide **162** as a 1.7:1 mixture of *syn*- and *anti*-isomers. Synthon **162** can be subjected to orthogonal nucleophilic or electrophilic activation, at the terminal nitrile (*e.g.* using $LiNEt_2$) or chloride (*e.g.* using KI), respectively, to enable the synthesis of 1,3-polyol chains in an efficient and convergent manner through an iterative strategy.[135]

The exquisite *syn* selectivity observed in the alkylation of these cyanohydrin acetonides is attributed to a kinetic anomeric effect, where the kinetically preferred axial isomer equilibrates to the equatorial (*syn*) isomer by instead putting the nitrile into the axial position following deprotonation (**163**). *syn*-1,3-Diol acetonides (**165**) are produced with >99:1 selectivity by reductive decyanation of the corresponding cyanohydrin acetonides (**164**).[135,136]

The very high levels of stereoselectivity observed with these cyanohydrin acetonides make them attractive 1,3-diol synthons by minimising the need for tedious separation of diastereomers. In addition, the coupling products are themselves already protected by the acetonide which can often be taken through the synthesis, also removing the need for reprotection steps.

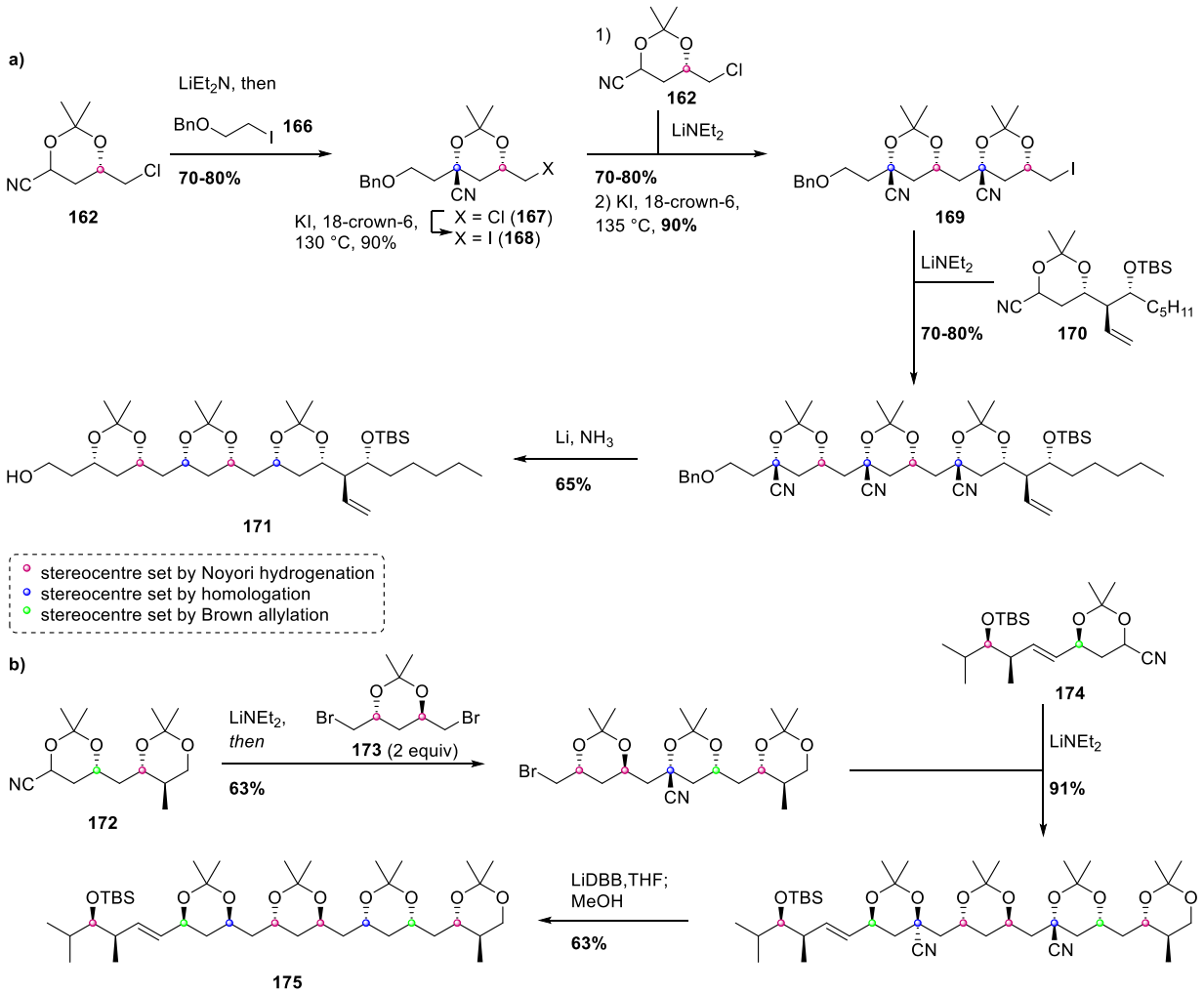


Scheme 61 Rychnovsky's cyanohydrin acetonide building blocks.

The polyol fragment **171** of filipin III was prepared from protected 1,3-diol **162** using an iterative strategy of alkylation followed by chloride to iodide exchange under Finkelstein's conditions (**Scheme 62** a).[137] Nucleophilic activation of **162** with lithium diethylamide followed by alkylation with **166** afforded the homologated product **167** as a single isomer,

which was smoothly converted to the corresponding iodide **168** through electrophilic activation of the alkyl chloride. Alkylation with another equivalent of **162** followed by Finkelstein's iodination yielded protected tetraol **169**. The eastern portion of the polyol fragment was then installed by alkylation of **169** with cyanohydrin acetonide **170** which also contained the pentane side chain and a pendent alkene. Reductive removal of the cyanide groups and the benzyl protecting group yielded intermediate **171**, with the polyol fragment in filipin III constructed in a stereocontrolled manner.

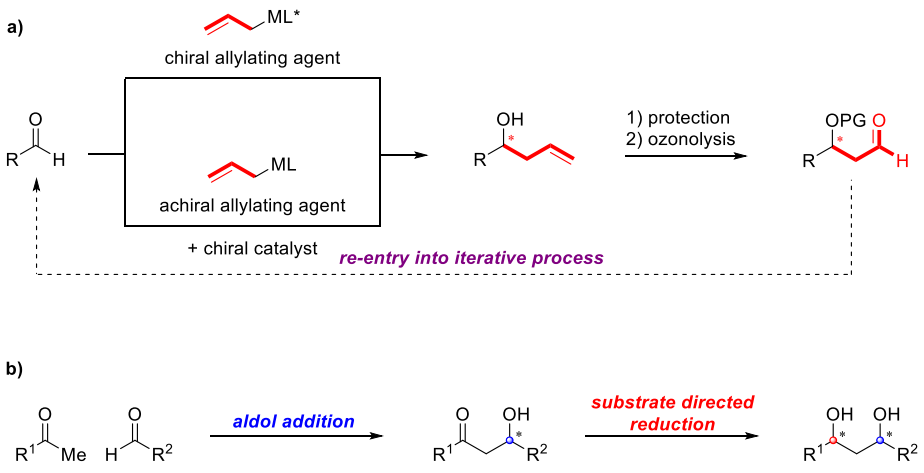
Rychnovsky employed a bidirectional modular strategy to construct the polyol segment of (−)-roxaticin (**Scheme 62** b).[138] C_2-symmetric dibromoacetonide **173** was subjected to iterative alkylation, first with cyanohydrin acetonide **172** then **174**. Reductive decyanation with the single electron reductant lithium 4,4'-di-*tert*-butylbiphenylide (LiDBB) revealed protected 1,3-polyol **175**. Rychnovsky exploited similar ambiphilic 1,3-diol building blocks in the total synthesis of dermostatin,[139] roflamycoin[128] and 17-deoxyroflamycoin.[140]



Scheme 62 Rychnovsky's chiral building blocks approach in the total synthesis of a) filipin III and b) (−)-roxaticin.

2.8 Proposed Polyboron Approach

The synthetic approaches to prepare stereodefined 1,3-polyols described so far in this chapter fall broadly into three categories: (i) asymmetric allylation of an aldehyde followed by oxidation of the terminal alkene and potential iteration (**Scheme 63** a); (ii) an acetate aldol reaction followed by substrate-directed reduction of the resulting β-hydroxy ketone to give a 1,3-diol (**Scheme 63** b); and (iii) the modular combination of chiral building blocks, such as Rychnovsky's cyanohydrin acetonides or the ring opening of chiral epoxides.

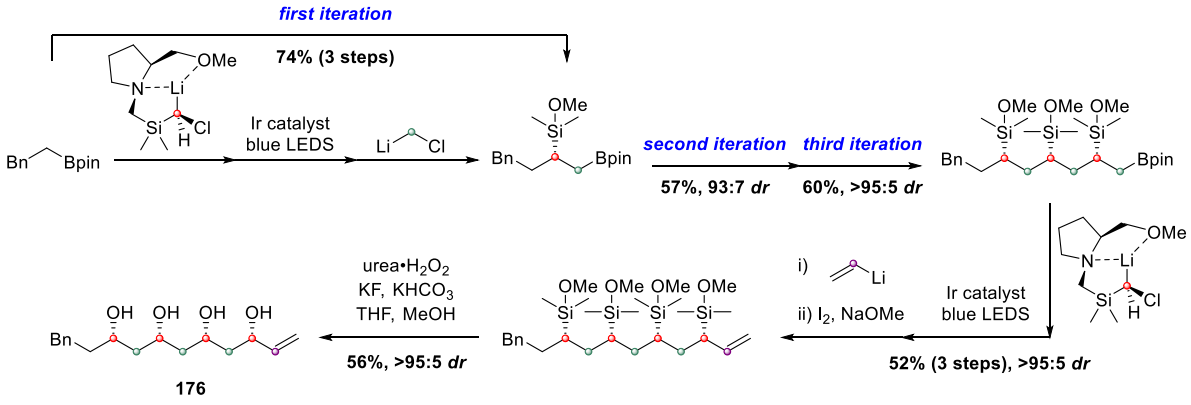


Scheme 63 Conventional literature methods for the stereocontrolled synthesis of 1,3-polyols.

While aldol methodology has been widely applied to the synthesis of polypropionates, and indeed represents the strategic approach closest to the biosynthesis, this fails when applied to the synthesis of polyacetates. However, several substrate-controlled acetate aldol reactions such as the Mukaiyama (1,3-*anti*) aldol and 1,5-*anti* boron aldol have been developed and utilised in the synthesis of 1,3-polyols, although rarely in a true iterative fashion.

The most efficient modern method to date for the synthesis of 1,3-polyols is Krische's Ir-catalysed allylation, which has been extended to an iterative bidirectional strategy (*vide supra*, section **2.3.5**). Each iteration involves 3 steps: 1) iridium-catalysed stereoselective allylation of two primary alcohols, 2) acetal protection of the secondary alcohols, and 3) oxidative cleavage of the terminal olefins to the corresponding primary alcohols. Krische's method enabled a rapid construction of **114** (only 9 steps), which after a further 11 steps completed the total synthesis of (+)-roxaticin, in almost half the number of steps of the previous shortest synthesis. However, adapting this methodology unidirectionally to a non-C_2-symmetric polyol, such as that of RK-397, would require considerably more steps. It was therefore clear that new strategies need to be developed that not only allow the rapid assembly of C_2-symmetric polyols but also non-C_2-symmetric polyols.

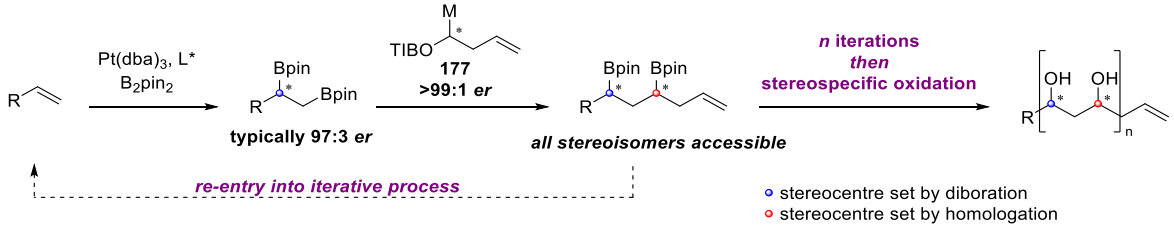
An iterative synthetic strategy would be a highly attractive approach to construct polyketide natural products bearing repeated motifs, such as these 1,3-diols and 1,3-polyols, as also stated by Mlynarski, Grzybowski and co-workers in their recent report describing a computer algorithm to discover plausible iterative sequences, which included a computer-generated synthetic route to dermostatin A and cryptocaryol A involving iterative allylation, protection and ozonolysis.[141] Aggarwal's assembly–line synthesis involves using lithiation–borylation chemistry in an iterative manner to install multiple contiguous defined stereocentres with high stereocontrol and without intermediate purifications (*vide supra*, section **1.4.1**). Assembly–line synthesis is therefore a way to homologate molecules in a similar fashion to polyketide biosynthesis in nature, where small building blocks are added to 'grow' the molecule through a sequence of chain extension steps. This iterative process has been applied to the synthesis of a 1,3-tetraol fragment, **176**,[37] (**Scheme 64**) yet each homologation step only extended the growing chain by one carbon and so efforts progressed to developing a more efficient approach.



Scheme 64 Assembly–line synthesis of polyacetate fragment **189** using chiral lithiated α-chloromethyl silane ***ent*-49** and (chloromethyl)lithium as the key building blocks.

Aggarwal and co-workers demonstrated the stereocontrolled synthesis of secondary-secondary and secondary-tertiary 1,3-diols (*vide supra*, section **1.6**).[48] Asymmetric diboration of terminal alkenes afforded vicinal bis(boronic esters)[50] which were homologated selectively at the less hindered primary boronic ester with a sparteine-ligated lithiated carbamate or benzoate to give 1,3-bis(boronic esters). Oxidation using basic hydrogen peroxide revealed the target 1,3-diols. Crucially, this process operated exclusively under reagent control and provided access to every stereoisomeric form of the 1,3-diol products, simply by switching enantiomer of chiral ligand for the Morken asymmetric diboration, which sets the first stereocentre, and by changing from (+)- to (−)-sparteine for the asymmetric lithiation (**Scheme 25**).

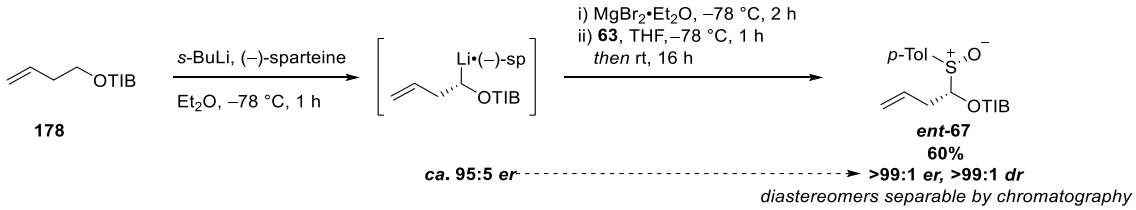
It was reasoned that iterative enantioselective alkene diboration and reagent-controlled homologation with an enantiopure carbenoid bearing a butenyl unit would enable the construction of a stereodefined 1,3-polyol (**Scheme 65**).[142] Each stereocentre is unambiguously and independently set by the choice of (*R*,*R*)- or (*S*,*S*)-ligand for the diboration, or (+)- or (−)-sparteine for the asymmetric lithiation. Since Morken's diboration protocol[50] allows the preparation of 1,2-bis(boronic esters) in typically 97:3 *er* and butenyl carbenoid **177** can be prepared in >99:1 *er*,[47] this strategy enables the synthesis of any desired 1,3-polyol diastereoisomer with exquisite levels of stereocontrol. This approach also avoids repetitive oxidation level changes or functional group interconversions between iterations, as the boronic esters both enable the homologation and mask the hydroxyl functionality.



Scheme 65 Proposed iterative synthesis of 1,3-poly(boronic esters) as masked 1,3-polyols. L*: 3,5-diisopropylphenyltaddol-PPh.

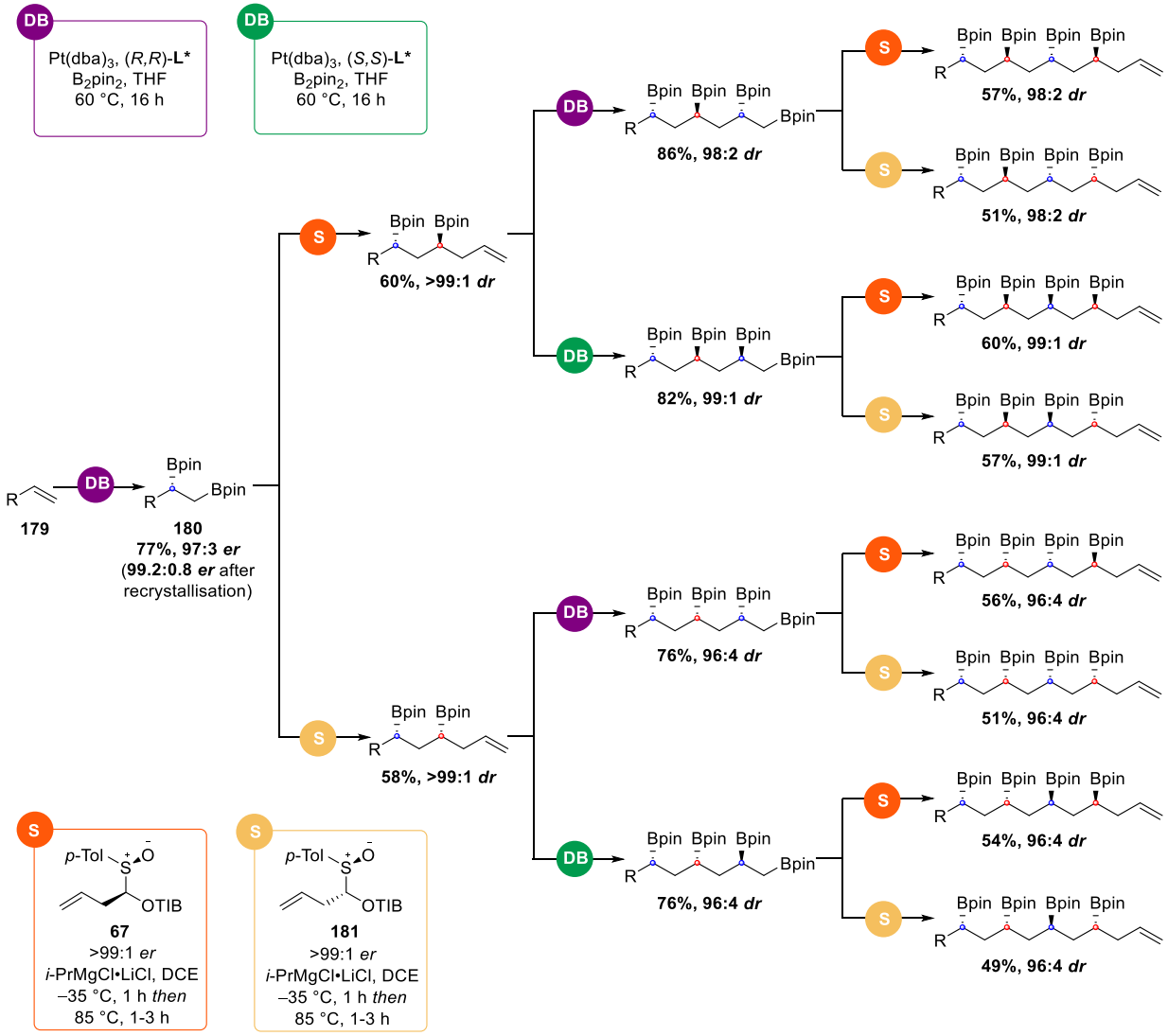
The butenyl carbenoid employed needed to adhere to several criteria: (i) the precursor would need to be accessible in high enantiopurity (>99:1 *er*) since any minor enantiomers formed in each homologation step will be moved to a different diastereomeric series in later homologations that may prove difficult to separate; (ii) the precursor would need to be converted cleanly and stereospecifically into the corresponding α-metalated species with no erosion of *ee*; (iii) which would undergo highly selective lithiation–borylation reactions with primary boronic esters in the presence of secondary boronic esters. Aggarwal recently reported on the synthesis and use of α-sulfinyl benzoates as precursors of α-metalated benzoates including α-sulfinyl butenyl benzoate **67**, which fulfils the above criteria (*vide supra*, section **1.5**).[47] These substrates are generated by the asymmetric deprotonation and subsequent trapping of *O*-alkylbenzoates with Andersen's sulfinate esters (**Scheme 66**). The stereochemistry at the metalation centre is set by the choice of either (+)- or (−)-sparteine during the lithiation of benzoate **178**. Transmetalation to the Mg carbenoid and subsequent sulfinylation of this α-magnesiated species with Andersen's menthol-derived sulfinate yields the required α-sulfinyl benzoate, with the sulfoxide stereochemistry set by the choice of either (+)- or (−)-Andersen's sulfinate (***ent*-63** or **63**). Treatment of the isolated α-sulfinyl benzoate with *t*-BuLi or *i*-PrMgCl·LiCl generates the lithiated or magnesiated carbenoid, respectively,

with complete enantiospecificity. In the case of the magnesiated carbenoid no further additive was required; however, the increased reactivity of the lithiated carbenoid necessitated the addition of a bulky di- or triamine, for example PMDTA, to obtain high selectivity for reaction at the primary over the secondary boronic ester.



Scheme 66 Preparation of homoallylic α-sulfinyl benzoate **67** from benzoate **178**. Isolated yield by the author for desired diastereomer, *dr* as determined by NMR analysis and *er* for **67** measured by chiral HPLC analysis.

Having identified the two stereocontrolling components of the proposed iterative process, namely catalyst-controlled diboration using Morken's conditions and primary-selective homologation of the resulting 1,2-bis(boronic ester) using an enantiopure carbenoid derived from an α-sulfinyl benzoate, Aggarwal and co-workers first sought to generate all diastereoisomers of a 1,3-poly(boronic ester) at will (**Scheme 67**).[142] Alkene **179** was subjected to 2 full iterations, *i.e.* 4 steps in total, to give 8 diastereoisomers of a 1,3-tetra(boronic ester) (**Scheme 67**). The comparable yields and high *dr* observed in all cases indicated the complete lack of matching/mis-matching effects in operation for either the diboration or homologation steps, highlighting the reliability and flexibility of this reagent-controlled approach which can enable the preparation of any desired diastereomer at will.



Scheme 67 Iterative diboration and homologation to prepare all diastereomers of a 1,3-tetra(boronic ester). R: CH_2CH_2-1,1'-biphenyl; L*: 3,5-diisopropylphenyltaddol-PPh. DCE: dichloroethane.

3 The Total Synthesis of Bahamaolide A

The work described in this chapter contributed to the following manuscript currently under consideration (preprint available)[142]:

Iterative Synthesis of 1,3-Polyboronic Esters with High Stereocontrol: Applications to Bahamaolide A and Polyfunctionalised Hydrocarbons

Sheenagh G. Aiken†, Joseph M. Bateman†, Hsuan-Hung Liao†, Alexander Fawcett, Teerawut Bootwicha, Paolo Vincetti, Eddie L. Myers, Adam Noble, Varinder K. Aggarwal*

†*These authors contributed equally to this work.*

3.1 Introduction to Bahamaolide A and Retrosynthetic Analysis

Bahamaolide A was isolated along with bahamaolide B from a *Streptomyces* species, cultured from a sediment sample collected in North Cat Cay, Bahamas.[65] It is an oxopolyene macrolide which displays significant inhibitory potential against *Candida albicans* isocitrate lyase and antifungal activity against various pathogenic fungi.[65,143] This challenging molecule bears a hexaenoate component (C1–C13) together with nine stereodefined, contiguous but skipped, hydroxyl groups from C15 to C31 (**Figure 10**). Bahamaolides A and B differ only in the geometry of the C13 double bond, yet interestingly bahamaolide B was completely inactive in the tested biological assays. There is no reported synthesis of either bahamaolide A or B to date.

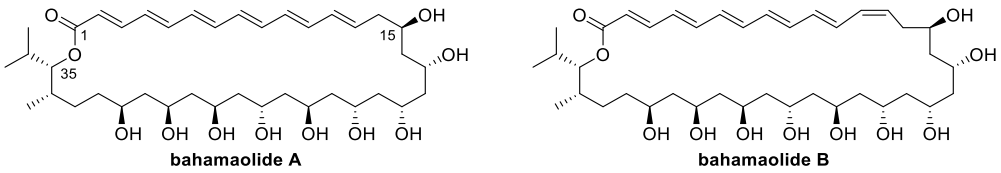
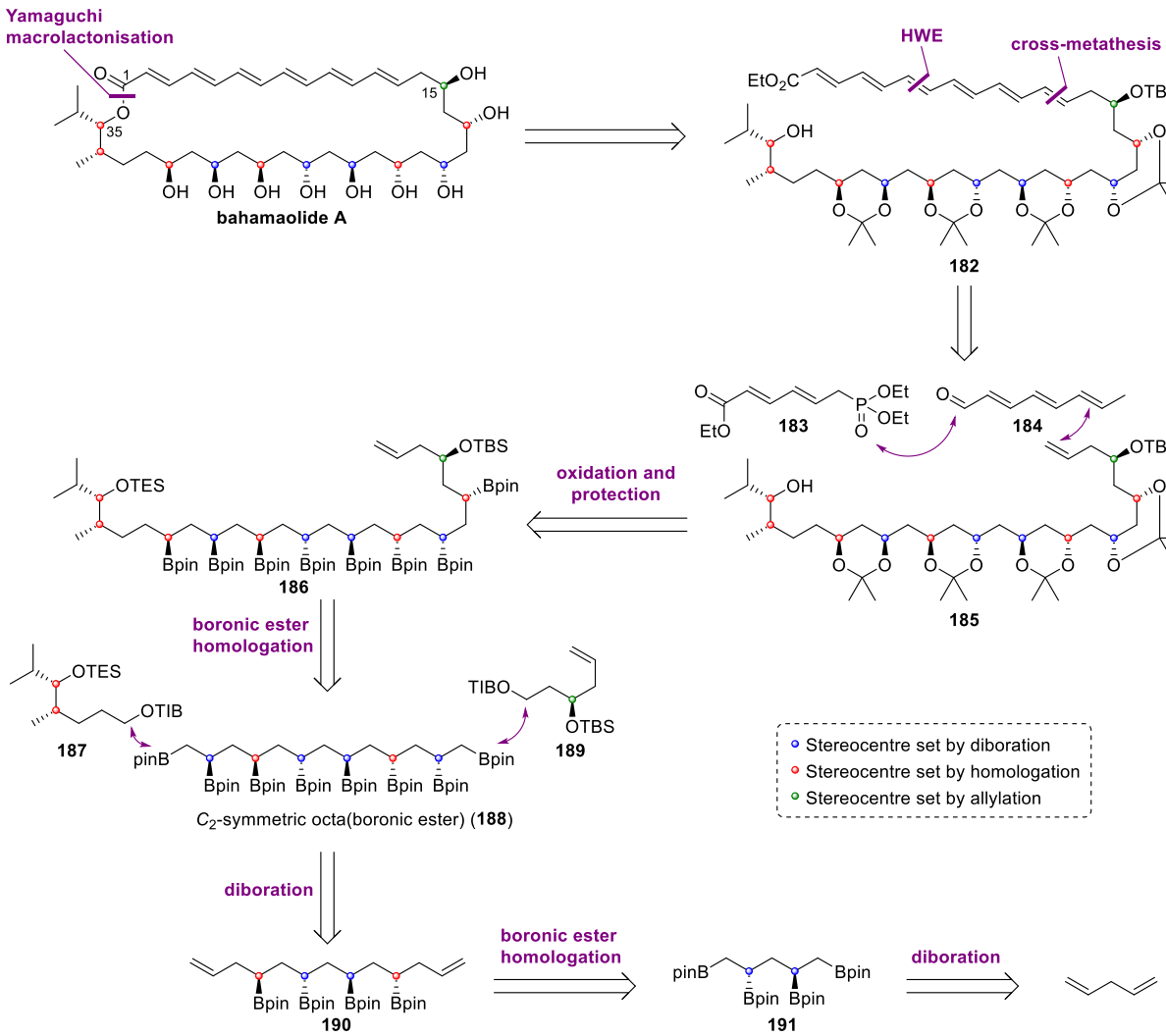


Figure 10 Bahamaolides A and B, reported in 2012 by Oh and co-workers.

The C_2-symmetric nature of the polyol portion of bahamaolide A prompted consideration of an iterative bidirectional strategy, as shown in the retrosynthetic analysis (**Scheme 68**). Recognition of symmetry in total synthesis targets, either bilateral symmetry or from a biosynthetic dimerisation, can be a powerful approach to dramatically streamline the synthetic route[144,145] and symmetric strategies have been applied to the concise synthesis of oxopolyene macrolides with great effect, notably by Krische and co-workers to prepare roxaticin as discussed above (**Scheme 39**).[86]

The retrosynthetic analysis commenced with opening the 36-membered macrocycle and disconnecting the polyene to reveal advanced intermediate **185** (**Scheme 68**). In a forward sense, the hexaene fragment would be installed through cross-metathesis followed by a Horner-Wadsworth-Emmons (HWE) reaction, inspired by Sammakia's approach to dermostatin A (*vide infra*, **Scheme 80**).[111] **185** would be prepared from poly(boronic ester) **186**, which would be accessed from octa(boronic ester) **188** through sequential homologations with benzoates **187** and **189**. Different silyl protecting groups at C15 and C35 are necessary since Krische has shown en route to roxaticin that the hydroxyl group at C15 must be protected during macrolactonisation (*vide infra*, **Scheme 85**),[86] whereas the hydroxyl group at C35 was unprotected in Sammakia's reported metathesis–HWE–macrolactonisation endgame in the total synthesis of dermostatin A.[111] The key C_2-symmetric octa(boronic ester) **188** would be rapidly assembled from 1,4-pentadiene through iterative diboration and lithiation–borylation reactions.



Scheme 68 Retrosynthetic analysis of bahamaolide A.

3.2 Previous Work and Project Aims

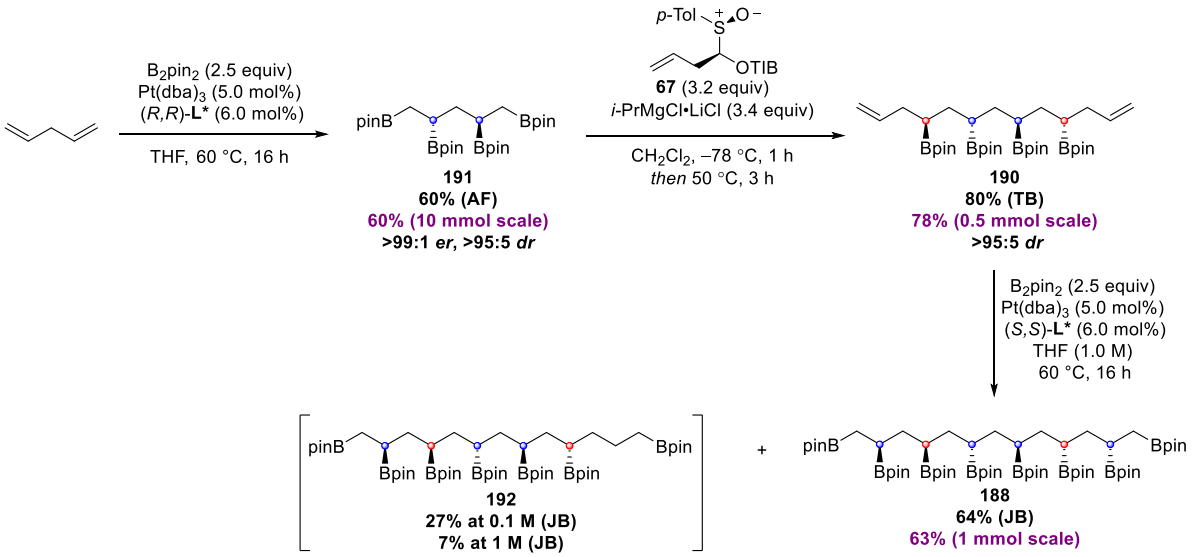
Dr Alex Fawcett and Dr Teerawut Bootwicha initiated synthetic work towards bahamaolide A (2014–2017, **Scheme 69**). Dr Fawcett optimised the synthesis of tetra(boronic ester) **191** and its recrystallisation; he was also the first person to synthesise octa(boronic ester) **188**, described in June 2015.[146] Dr Bootwicha later optimised the double homologation of tetra(boronic ester) **191** and the purification of **190**, and the double diboration to achieve octa(boronic ester) **188**. Then from summer 2017, Dr Joe Bateman optimised purification of octa(boronic ester) **188**, developed the synthesis of the side chains (**196** and **200**, **Scheme 70**), investigated the homologation of octa(boronic ester) **188** (**Scheme 71**) and performed model studies for construction of the polyene moiety.[147] For 6 weeks in summer 2019 I worked alongside Dr Bateman, during which time he attempted the endgame steps and I was assisting in bringing material through; when he finished his PhD studies in the Aggarwal group in July 2019, he had subjected one batch of trienal **221** to the final 4 steps (HWE–saponification–macrolactonisation–deprotection) to afford our first sample of crude synthetic bahamaolide. Where indicated (initials), these results were obtained by one of my previous co-workers and are included here to provide a complete picture of the work.

My initial tasks were to scale-up synthesis of the two side chains (**196** and **200**) in order to bring more material through the complete synthetic route for full characterisation, along with the purification of synthetic bahamaolide A by reverse phase preparative high performance liquid chromatography (HPLC). In the course of my synthetic studies, I further optimised the homologation of octa(boronic ester) **188** (section **3.4**) and revised the synthetic strategy to construct the hexaene moiety in high isomeric purity (section **3.6**) and so was able to complete the first total synthesis of bahamaolide A ready for publication.

3.3 Synthesis of Key Building Blocks

Octa(boronic ester) **188** was prepared using the proposed iterative diboration–homologation approach in a bidirectional manner, setting 6 stereocentres in just 3 operations (**Scheme 69**). Double diboration of 1,4-pentadiene afforded tetra(boronic ester) **191** which could be isolated as a single diastereomer in 60% yield upon recrystallisation from pentane. The double diboration reaction benefits from an enhancement of enantioselectivity (>99:1 *er* for **191** before recrystallisation, *vs*. 97:3 *er* for **180, Scheme 67**) based on Horeau's principle,[32] but at the expense of diastereoselectivity, which in this case was still very high (95:5 *dr*, improved to >95:5 *dr* through recrystallisation). Although the reaction conditions for the double

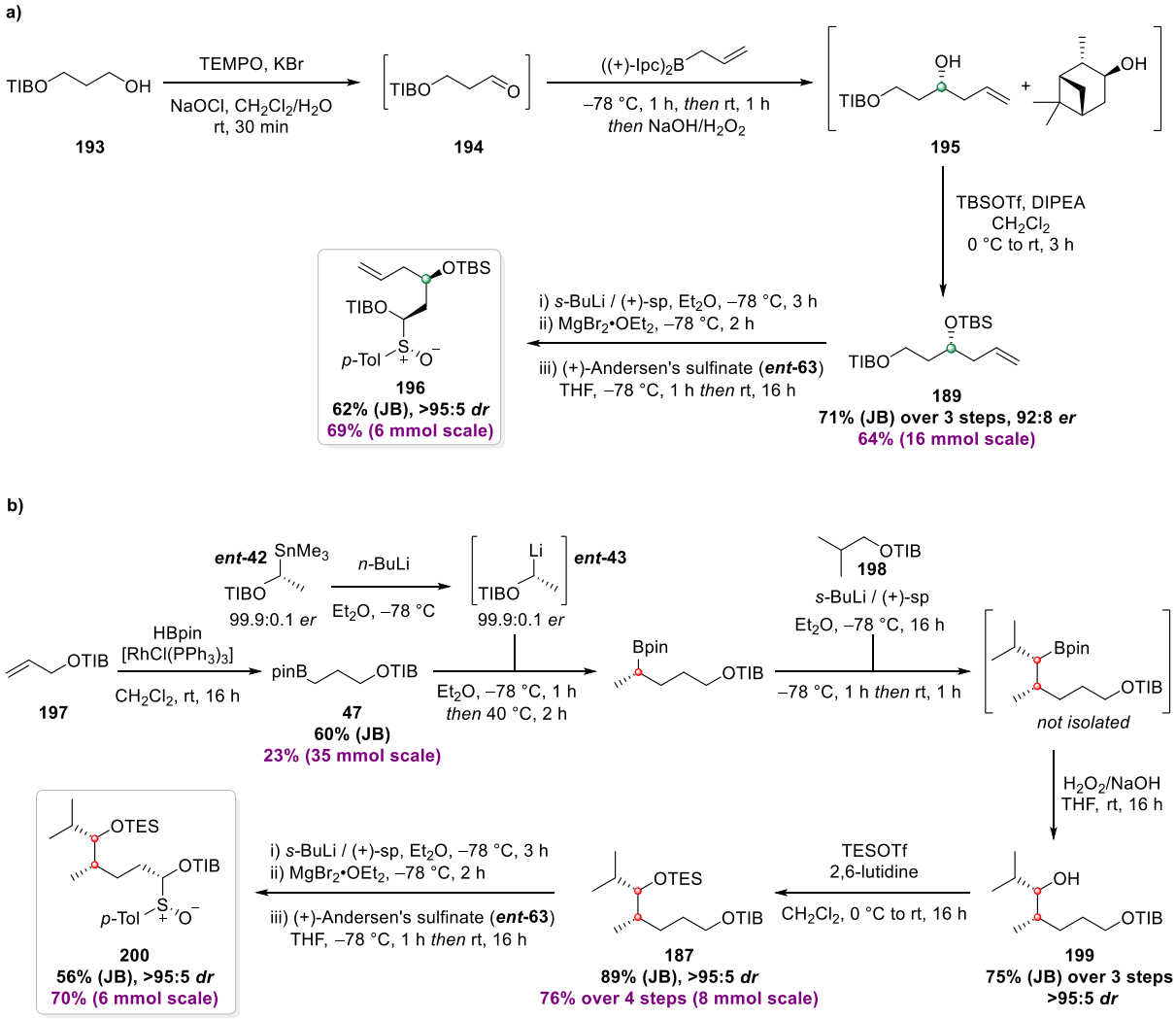
homologation of **191** and the second double diboration reaction had been optimised to give acceptable yields, the purification remained a challenge. A slight excess of *i*-PrMgCl·LiCl relative to α-sulfinyl benzoate **67** was used in the homologation step since **67** was found to co-elute with the desired product **190**. Bis homoallylic tetra(boronic ester) **190** showed some instability on silica and so its purification was limited by scale (see experimental section for details). 1 g crude octa(boronic ester) **188** could be purified in a single pass with high silica loading and 4% acetone in hexane as eluent; this took around 7-8 hours, and any deviation from these conditions resulted in mixed fractions with the hydroboration side-product **192**. Unfortunately, the *dr* could not be determined at this point due to the many overlapping resonances in the ^{1}H and ^{13}C NMR spectra, but it was expected to be high.



Scheme 69 Synthesis of octa(boronic ester) **188**, optimised by AF, TB and JB and all steps reproducible by the author (yields in purple). **L***: 3,5-diisopropylphenyltaddol-PPh, structure shown in **Scheme 25**.

With the key C_2-symmetric octa(boronic ester) **188** in hand, the required α-sulfinyl benzoates **196** and **200** bearing the east and west side chains were prepared on multi-gram scale and isolated as essentially a single enantiomer and diastereomer (**Scheme 70**). 1,3-Propanediol was desymmetrised by conversion to benzoate ester **193**. Anelli oxidation of the free alcohol gave aldehyde **194** which was directly subjected to Brown asymmetric allylation. Homoallylic alcohol **195** co-eluted with the isopinocampheol by-product and so the mixture was taken through the TBS protection step, at which point **189** could be isolated in 71% yield over 3 steps from **193**. Benzoate **189** was transformed to α-sulfinyl benzoate **196** using (+)-sparteine for the asymmetric lithiation and trapping with enantiopure (+)-Andersen's sulfinate, allowing separation of the minor diastereomer by column chromatography.

Allyl triisopropylbenzoate (**197**), prepared in one step from allyl bromide, was subjected to hydroboration using Wilkinson's catalyst. The resulting primary boronic ester **47** was homologated using assembly–line synthesis methodology; specifically, homologation with enantioenriched carbenoids derived from α-stannyl ethyl benzoate ***ent*-42**, then isopropyl benzoate **198**, followed by oxidation to achieve the stereodefined alcohol **199** as a single diastereomer by NMR analysis and isolated in high yield over 3 steps. TES protection of **199** afforded benzoate **187** which was smoothly converted to the corresponding α-sulfinyl benzoate **200**.

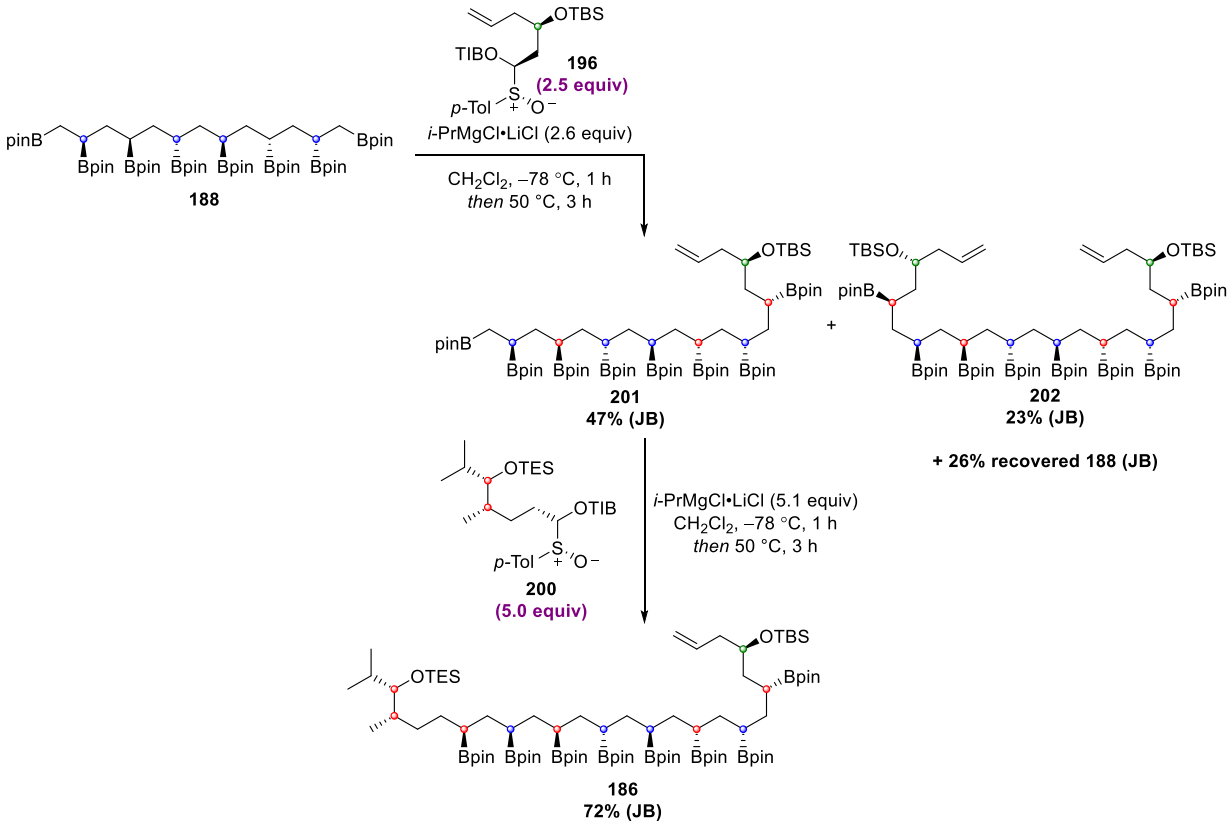


Scheme 70 Synthesis of α-sulfinyl benzoates bearing the a) east and b) west side chains in 5 and 9 total steps, respectively, optimised by JB and largely reproducible by the author (yields in purple). Isopropyl benzoate **198** prepared in one step from isopropyl bromide. α-Stannyl ethyl benzoate ***ent*-42** prepared as shown in **Scheme 13**.

3.4 Desymmetrisation and Homologation of Octa(boronic ester) 188: Investigations into the Reactivity of Magnesiated Carbenoids

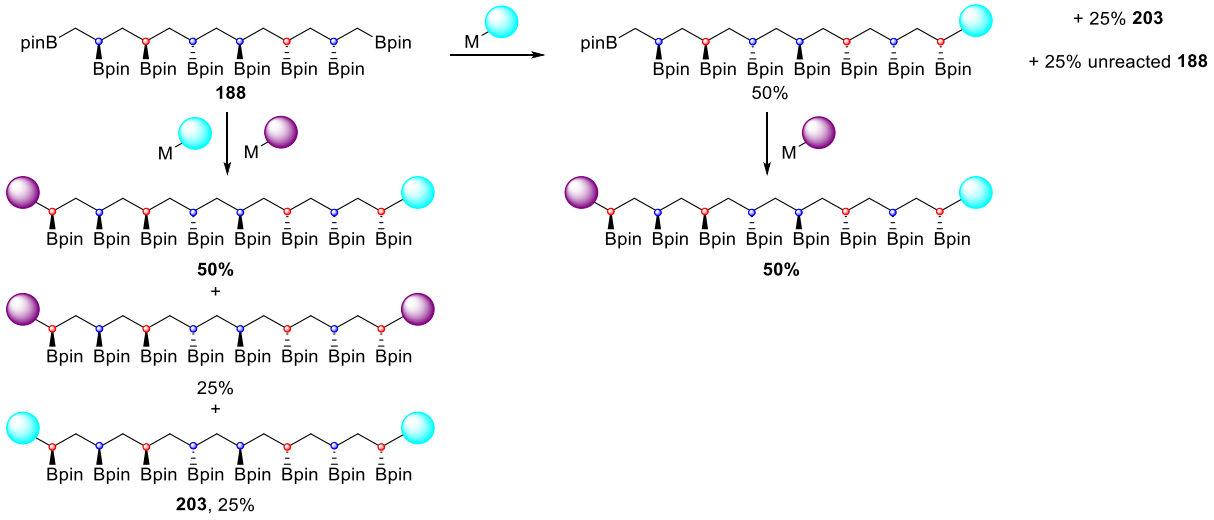
The standard reaction set-up for the homologation of a boronic ester with a magnesiated carbenoid derived from an α-sulfinyl benzoate is as follows: dropwise addition of *i*-PrMgCl·LiCl to a mixture of boronic ester and α-sulfinyl benzoate in dichloromethane at −78 °C, the reaction temperature is maintained at −78 °C for 1 hour, during which sulfoxide-magnesium exchange and borylation is expected to occur, then the reaction mixture is heated at reflux for 3 hours, or overnight, to promote 1,2-migration of the boronate complex to the desired product.[47]

Dr Bateman's optimised conditions for the homologation of octa(boronic ester) **188** with the two side chains are shown in **Scheme 71**; the use of 2.5 equivalents of α-sulfinyl benzoate **196** was required to obtain a statistical product distribution for the desymmetrisation step, and 5 equivalents of α-sulfinyl benzoate **200** for full consumption of starting material **201**.[147] Since both α-sulfinyl benzoates **196** and **200** require several steps to prepare, clearly using such a great excess is not ideal and so it would be preferable to identify more optimal reaction conditions.



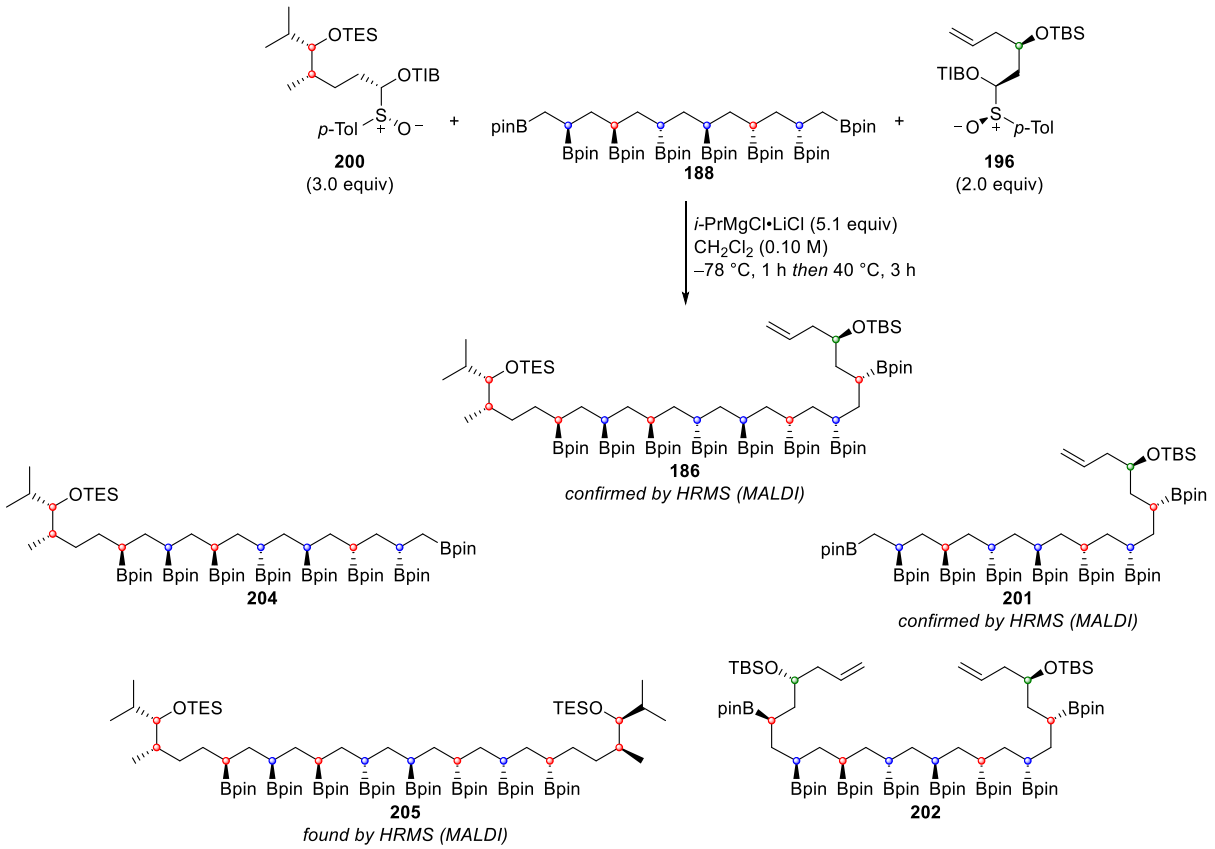
Scheme 71 Dr Bateman's optimised homologation conditions.

Given that the first homologation is a desymmetrisation, the maximum theoretical yield of the desired product (**201**) is 50%, along with 25% 'double', **202**, where both primary boronic esters have been homologated, and 25% unreacted octa(boronic ester) **188** (**Scheme 71**, **Scheme 72**). Therefore, taking the desymmetrised product (**201**) through to the second homologation gives a maximum theoretical yield of 50% for **186** over 2 steps. Treatment of octa(boronic ester) **188** with both side chain α-sulfinyl benzoates **196** and **200** in a 'one-pot' double homologation process was proposed; in this case the theoretical product distribution would be 50% yield of **186**, 25% double addition of the east side chain and 25% double addition of the west side chain (**Scheme 72**).



Scheme 72 Graphical representation of one or two-step desymmetrisation product distribution.

This 'one-pot' desymmetrising double homologation reaction was attempted as shown in **Scheme 73** and **Table 5**; 3 equivalents of α-sulfinyl benzoate **200** and 2 equivalents of α-sulfinyl benzoate **196** were used due to perceived differences in their reactivity from Dr Bateman's early desymmetrisation results.[147]



Scheme 73 'One-pot' desymmetrising double homologation of octa(boronic ester) **188**.

Entry	Scale /mmol 188	Yield 186 + 202 + 205 /%	Yield 201 + 204 /%	Recovered 188 /%
1	0.05	70	8	5
2	0.1	69	-[a]	-[a]
3	0.2	71	9	8
4[b]	0.2	62	21	2

Table 5 Attempted 'one-pot' desymmetrising double homologation of octa(boronic ester) **188**.
[a] Overlapping fractions of **201** + **204** and **188** – further purification not pursued so these yields are not reported.
[b] α-sulfinyl benzoate **200** had started to solidify – this may be associated with some decomposition.

The resulting reaction mixture appeared to contain 3 main poly(boronic ester) components, which could be separated by column chromatography: a trace of unreacted octa(boronic ester) **188**, a single homologation product and a double homologation product. The single and double homologation products were shown to be in fact mixtures of **201** and **204**, and **186**, **202** and **205**, respectively, which were inseparable by column chromatography (see experimental section for details).

Analysis of the reaction/product mixture was challenging since signals in the ^{1}H and ^{13}C NMR spectra for desired desymmetrisation product **186**, 'double west' (**205**) and 'double east' (**202**) homologation products all overlapped (demonstrated using pure samples from

earlier desymmetrisation reactions in several different deuterated solvents). Silver nitrate TLC analysis was able to show that the product isolated from the reaction shown in **Scheme 73** contained all 3 double homologation products (**186**, **205** and **202**) and that both single homologation products (**201** and **204**) were also present (**Figure 11**), however chromatographic purification was not successful.

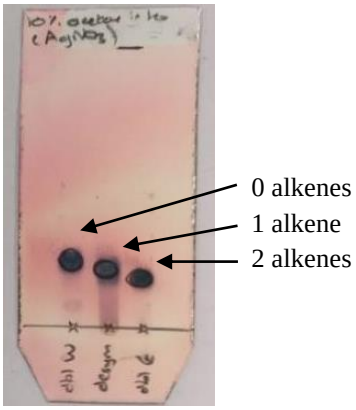
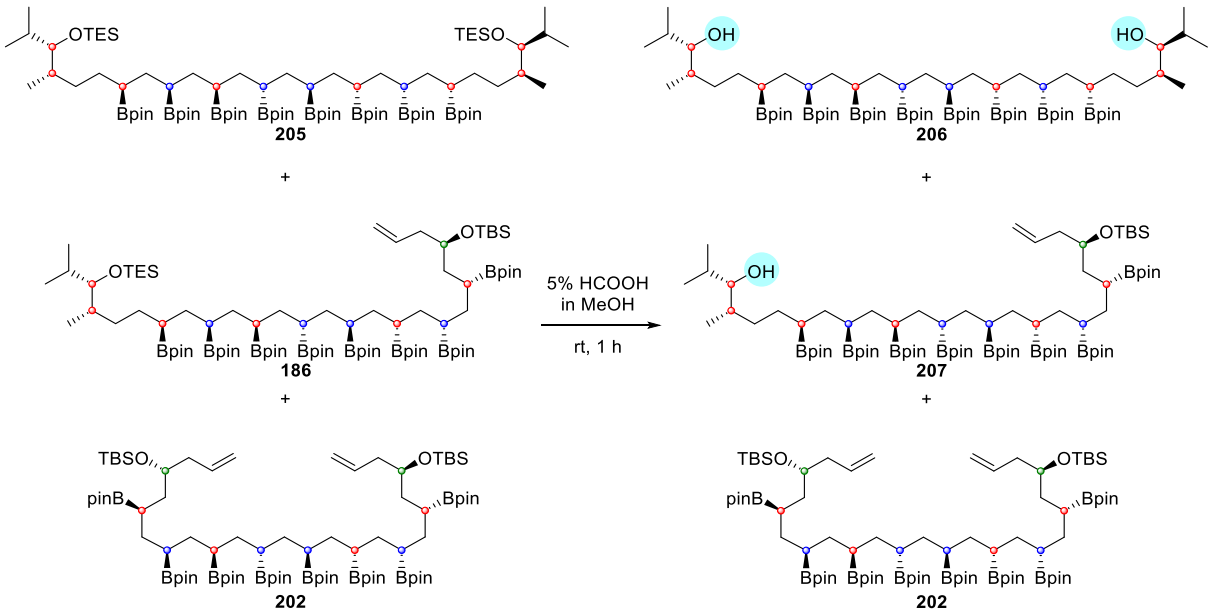


Figure 11 TLC separation of **205** (left hand lane), **186** (middle lane) and **202** (right hand lane) on a silver nitrate impregnated TLC plate, solvent system 10% acetone in hexane. Visualised using *p*-anisaldehyde stain.

Nevertheless it was possible to separate the different poly(boronic ester) homologation products by first performing a selective TES deprotection in the presence of a TBS group using the conditions reported by Broderick and co-workers[148] (**Scheme 74**). The three resultant products **206**, **207** and **202** (with two, one or no hydroxyl groups, respectively) then differed sufficiently in polarity to be separated by careful column chromatography. This approach could also be used to separate the single homologation products **201** and **204**.



Scheme 74 TES deprotection of homologation product mixture.

Although the relative amounts of the three poly(boronic esters) separated after the TES deprotection could give some indication of their yield in the 'one-pot' homologation reaction, a method to directly analyse the product mixture from the homologation was sought. While there were no peaks in the ^{1}H or ^{13}C NMR spectra that corresponded to just one product due to the overlap between these highly similar aliphatic molecules, the ratio of the three double homologation products (**186**, **205** and **202**) could potentially be inferred by comparing the ratios of the integration of certain signals in the ^{1}H NMR spectrum. A multiplet at 3.66 ppm, a triplet at 3.19 ppm, a quartet at 0.60 ppm and two singlets at 0.06 ppm and 0.03 ppm were identified (**Figure 12**). If it was a statistical product distribution (*vide supra*, **Scheme 72**), the integration for the TES methylene protons and the TBS methyl groups should be the same—24 protons each—and the integral for CHOTBS and CHOTES should also be the same—4 protons each (ratio 6:1). As shown in **Figure 12**, this was not the case and so three simultaneous equations were constructed to determine the ratio of the 3 products **186**, **205** and **202**. Where $\boldsymbol{x}$ corresponds to the amount of **186**, $\boldsymbol{y}$ will give the amount of **205** and $\boldsymbol{z}$ **202**, respectively, when $\boldsymbol{x + y + z = 1}$ (1). As it is the ratio of the products to each other being considered, a ratio of integrals from the ^{1}H NMR spectrum was required. The second equation was derived from the quartet at 0.60 ppm ($\boldsymbol{6x + 12y}$ = total number of TES CH_2 protons) and the multiplet at 3.66 ppm ($\boldsymbol{x + 2z}$ = total number of CHOTBS protons): $\frac{(6x+12y)}{x+2z} = \mathbf{12.61}$ (2). The TBS singlets ($\boldsymbol{6x + 12z}$ = total number of TBS CH_3 protons) and the triplet at 3.19 ppm ($\boldsymbol{x + 2y}$ = total number of CHOTES protons) provide the third equation: $\frac{(6x+12z)}{x+2y} = \mathbf{2.88}$ (3).

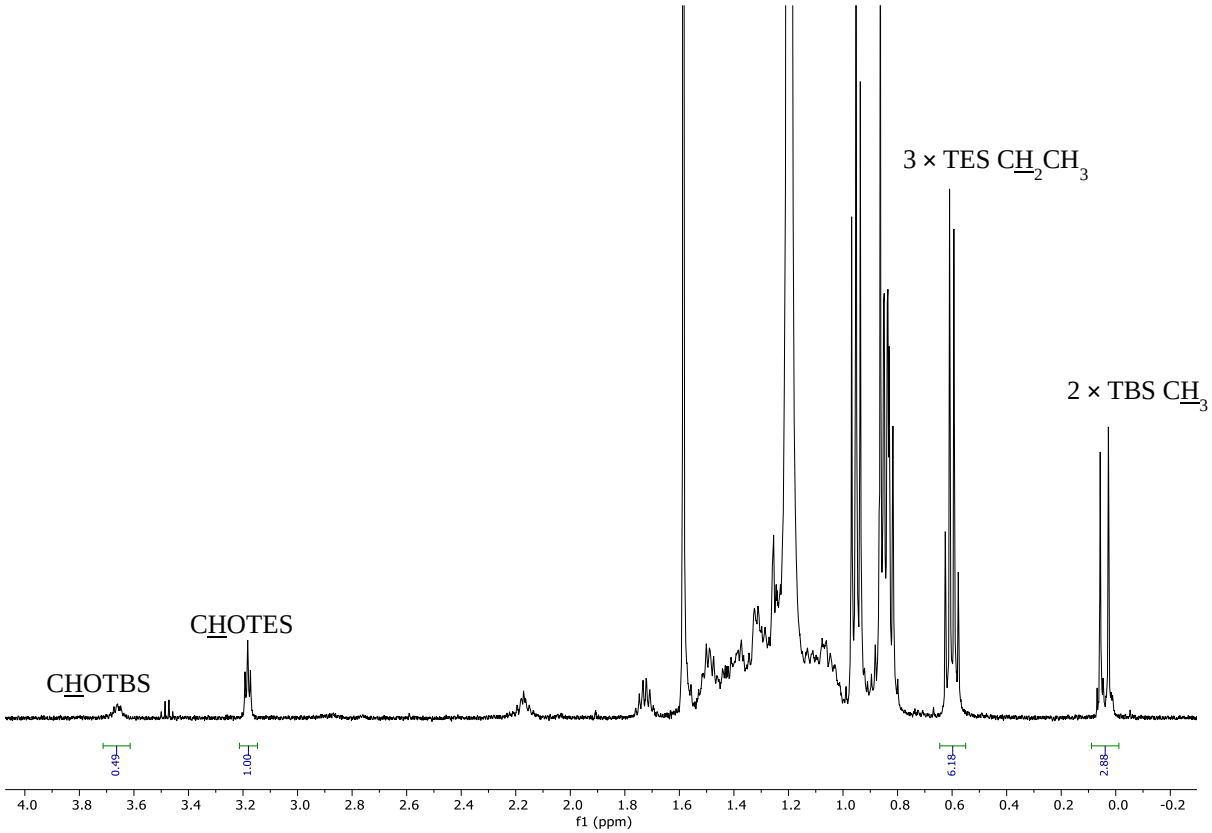


Figure 12 ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of the double homologation product mixture.

Considering equations (1), (2) and (3) together gave the tentative approximate values of $\boldsymbol{x}$ = 0.45, $\boldsymbol{y}$ = 0.45 and $\boldsymbol{z}$ = 0.1, which could imply that the west side chain carbenoid is more reactive than the east side chain carbenoid, in agreement with Dr Bateman's experimental observations,[142,147] since more of the 'double west' (**205**) than 'double east' (**202**) homologation product was observed. However, this result should be taken with some caution since equimolar amounts of the two α-sulfinyl benzoates were not used in this reaction (**Scheme 73**).

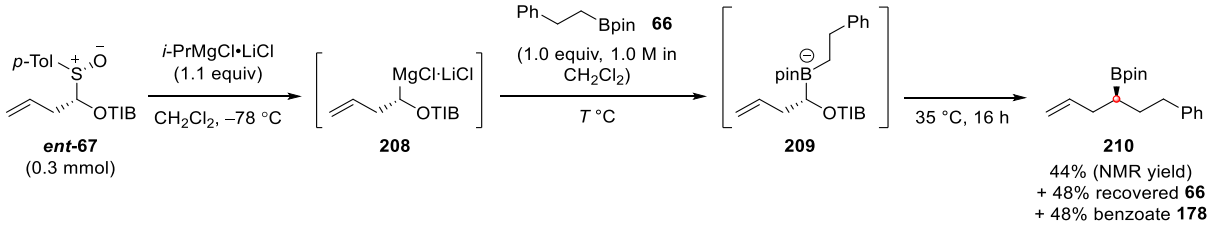
The same sample was then subjected to the TES deprotection shown in **Scheme 74**; following column chromatography, the molar ratio of the three isolated products appeared to largely agree with the ratio from the ^{1}H NMR analysis (**Table 6**).

Entry	Amount starting material (186 + 205 + 202)	'Double west' (205) $\boldsymbol{y}$	Desired product (186) $\boldsymbol{x}$	'Double east' (202) $\boldsymbol{z}$
1	50 mg	0.41	0.44	0.15
2	128 mg	0.39	0.44	0.17

Table 6 Molar ratios of isolated products.

This uneven product distribution appeared to suggest a difference in reactivity of the west and east side chain carbenoids for the homologation of octa(boronic ester) **188**, in line with Dr Bateman's earlier observations which led to the decision to use the east side chain for the desymmetrisation followed by the second homologation with the west side chain, instead of the other way around (**Scheme 71**).[147] This prompted investigation into the reactivity of these carbenoids through the use of *in situ* IR monitoring to study the rate of sulfoxide-magnesium exchange and the rate of borylation. This may provide evidence to support hypothesis 1, where the rate of reaction with the 'east' carbenoid is faster, then the 'west' carbenoid participates in the 'more challenging' second homologation, or hypothesis 2, where the 'east' carbenoid may coordinate to both the carbonyl of the benzoate and the OTBS group resulting in a sterically hindered carbenoid and thus slow rate of borylation.

In situ IR monitoring is a powerful analytical technique for lithiation–borylation reactions as it is possible to follow the carbonyl peak of the benzoate throughout the reaction; due to its proximity to the lithiation centre, the C–O bond strength and therefore IR absorbance is altered distinctly as the reaction progresses, allowing insight into the rate of the reaction.[26] As magnesiated carbenoids had not previously been studied by *in situ* IR, for the first experiment, a more simple homoallylic α-sulfinyl benzoate (***ent*-67**) was used as a model (**Scheme 75**). In the general procedure developed by Casoni *et al.*, a mixture of the α-sulfinyl benzoate and boronic ester is treated with *i*-PrMgCl·LiCl solution at −78 °C; the reaction mixture is kept at −78 °C for 1 hour for sulfoxide-magnesium exchange and borylation, and then heated at reflux for 3 hours for 1,2-metalate rearrangement.[47] (In this case, *in situ* conditions were not used so the rate of sulfoxide-magnesium exchange could be studied.)



Scheme 75 Homologation of primary boronic ester **66** using α-sulfinyl benzoate ***ent*-67**, monitored by *in situ* IR. 1,4-dinitrobenzene was used as an internal standard to report NMR yields; see **Figure 13** for indicative durations.

i-PrMgCl·LiCl was added dropwise to a solution of α-sulfinyl benzoate ***ent*-67** in dichloromethane at −78 °C. Sulfoxide-magnesium exchange could be followed by *in situ* IR (**Figure 13**) and it was found to be fast but not instantaneous and so could potentially be compared for different α-sulfinyl benzoates. After sulfoxide-magnesium exchange was

complete, monitored by disappearance of the α-sulfinyl benzoate carbonyl peak at 1735 cm^{-1} and appearance of the magnesiated species carbonyl peak at 1635 cm^{-1}, boronic ester **66** was added and the temperature maintained at −78 °C. Surprisingly no borylation was observed at −78 °C in this case, whereas it is known that borylation of the corresponding lithiated benzoate occurs at −78 °C and this has been monitored previously by *in situ* IR.[26] The reaction temperature was raised to −60 °C then −40 °C by moving to appropriate cooling baths, but still no borylation was observed. It could be concluded that in contrast to lithiated carbenoids, borylation of the less reactive magnesiated carbenoids must only occur as the reaction mixture is warmed to ambient temperature, and so the *effective borylation time* is perhaps only a few minutes; perhaps this could explain why a large excess of α-sulfinyl benzoate has been necessary for challenging homologations (**Scheme 71**),[147] and better results were obtained with *t*-BuLi for more hindered carbenoids (**Scheme 24**).[47]

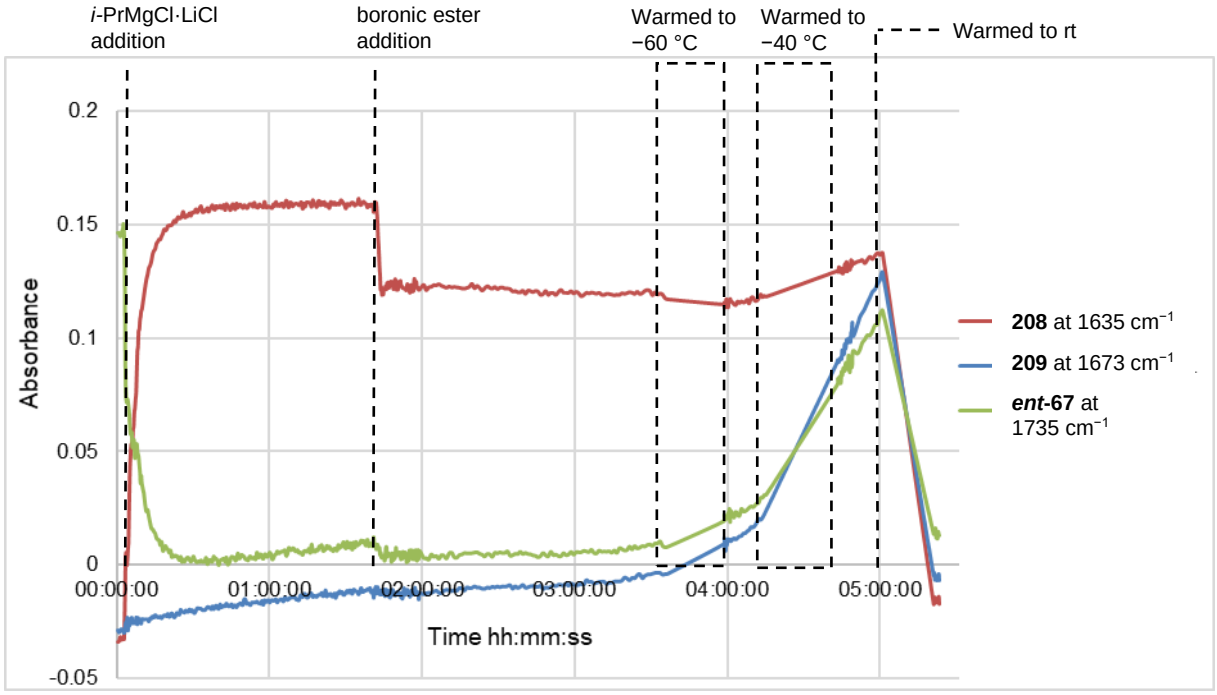
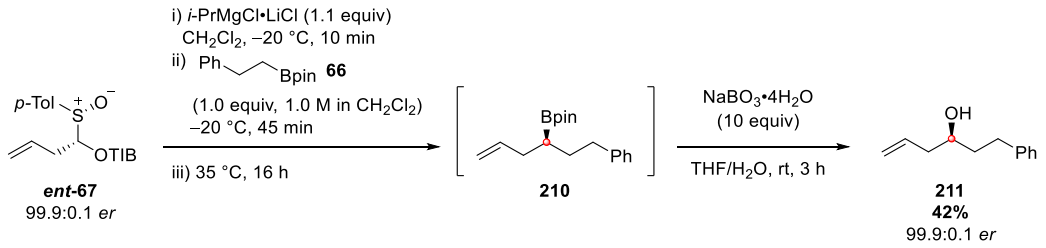


Figure 13 *In situ* IR trace for the reaction shown in **Scheme 75**. This graph shows the IR absorbance at 3 different wavelengths, which are distinctive of the 3 species in the reaction (α-sulfinyl benzoate ***ent*-67**, magnesiated species **208** and boronate complex **209**). The change in IR absorbance shows the relative concentration of the species in the reaction. The IR probe was removed after 5 hours monitoring and the reaction mixture heated overnight at 35 °C.

The next reaction followed by *in situ* IR is shown in **Scheme 76**; *i*-PrMgCl·LiCl was added to ***ent*-67** in dichloromethane at −20 °C, followed by boronic ester **66**. At this temperature, sulfoxide-magnesium exchange was fast ($t_{1/2}$ Mg < 15 s) and borylation could be observed ($t_{1/2}$ B = 2 min 15 s), as shown by disappearance of the magnesiated species at 1636 cm^{-1} and

appearance of a new peak at 1673 cm^{-1} (**Figure 14**). After heating at 35 °C overnight for 1,2-migration, the crude boronic ester **210** was oxidised to aid separation from the by-product homallylic benzoate **178**. Chiral HPLC analysis of the alcohol product **211** showed that there had been no erosion in enantiopurity from α-sulfinyl benzoate ***ent*-67**, leading to the conclusion than magnesiated carbenoids are configurationally stable at −20 °C.



Scheme 76 Second homologation experiment monitored by *in situ* IR. Reported *er* values as measured by chiral HPLC analysis.

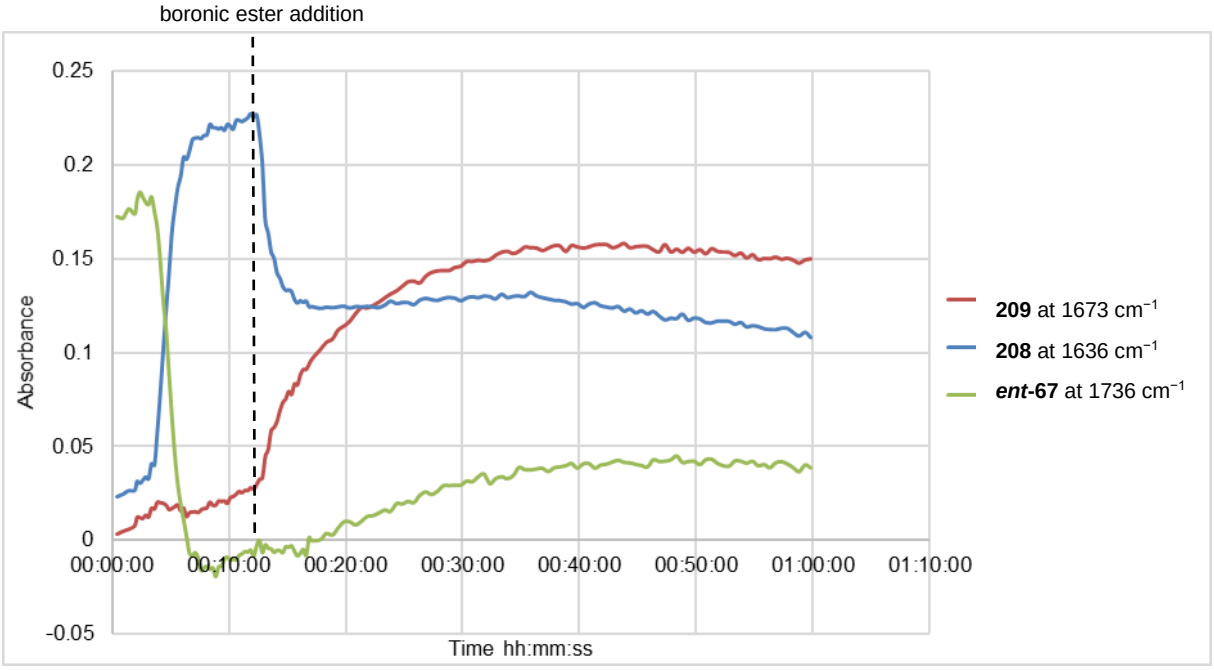
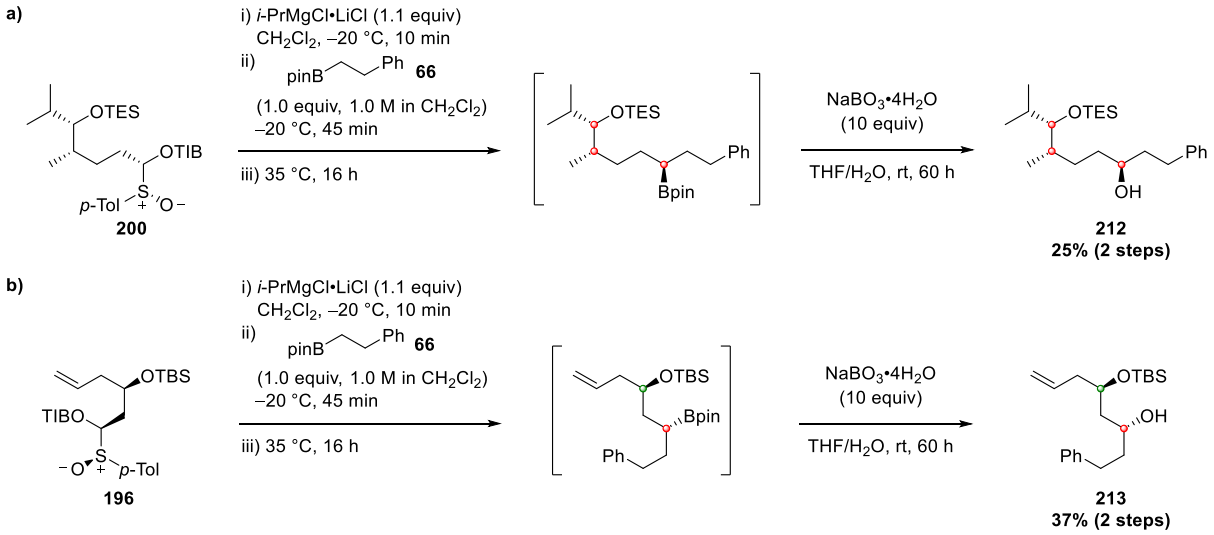


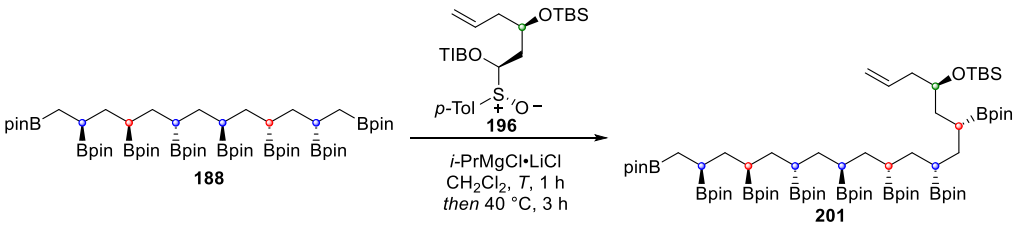
Figure 14 *In situ* IR trace for the reaction shown in **Scheme 76**. The IR probe was removed after 1 hour monitoring and the reaction mixture heated overnight at 35 °C.

These conditions (−20 °C for sulfoxide-magnesium exchange and borylation, then heating overnight for 1,2-migration) were then used to investigate the homologation of boronic ester **66** with α-sulfinyl benzoates of interest **196** and **200** (**Scheme 77**). Borylation of both the west and east side chain carbenoids could be observed at −20 °C, with half lives of 2 min and 3 min, respectively, which may suggest a small difference in reactivity.



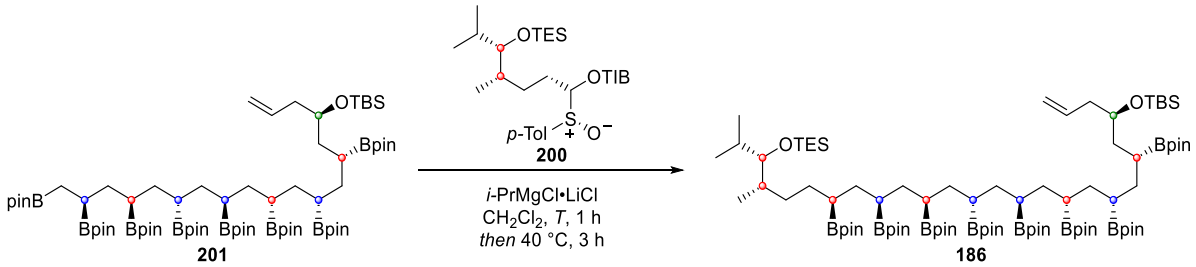
Scheme 77 Homologation of boronic ester **66** with α-sulfinyl benzoates **200** or **196**, monitored by *in situ* IR. a) boronate at 1668 cm^{-1}, $t_{1/2}$ Mg < 15 s, $t_{1/2}$ B = 2 min; b) boronate at 1670 cm^{-1}, $t_{1/2}$ Mg < 15 s, $t_{1/2}$ B = 3 min. See experimental section for further details.

Although it was not possible to definitively conclude a difference in reactivity of the east and west side chain carbenoids, the observation that magnesiated carbenoids do not undergo borylation at −78 °C merited further attention. Previously, by analogy with lithiated carbenoids, it had been assumed that sulfoxide-metal exchange and borylation all occurred during the time the reaction mixture was at −78 °C and so the procedure generally involved one hour at −78 °C then heating for 3 hours for 1,2-migration (*vide supra*).[47] Raising the temperature for the sulfoxide-magnesium exchange and borylation phases of the reaction to −20 °C was investigated with the aim to reduce the equivalents of α-sulfinyl benzoate necessary for the homologation of octa(boronic ester) **188**. When the reaction was performed at −20 °C, only 1.3 equivalents of α-sulfinyl benzoate **196** were required to achieve an almost statistical product distribution for the desymmetrisation (**Table 3**, entry 3) and the equivalents of α-sulfinyl benzoate **200** for the second homologation could be more than halved with no detriment to product yield (**Table 4**, entry 2).



Entry	196 /equiv	*i*-PrMgCl·LiCl /equiv	*T* /°C	Recovered 188 /%	Product 201 /%	Double 202 /%
1 (JB)	2.5	2.6	−78	26	47	23
2	1.0	2	−20	35	31	13
3	1.3	1.4	−20	20	45	21

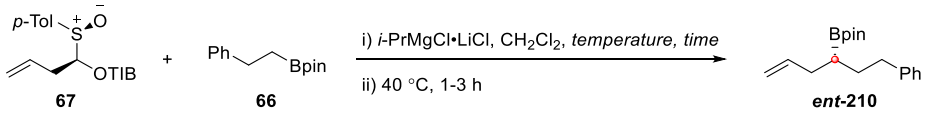
Table 7 Effect of changing borylation temperature on equivalents of α-sulfinyl benzoate necessary for desymmetrisation of octa(boronic ester) **188**. Isolated yields reported.



Entry	200 /equiv	*i*-PrMgCl·LiCl /equiv	*T* /°C	Yield 186 /%
1 (JB)	5.0	5.1	−78	72
2	2.0	2.1	−20	79 (90 brsm)

Table 8 Effect of changing borylation temperature on equivalents of α-sulfinyl benzoate necessary for homologation of octa(boronic ester) **201**. Isolated yields reported. brsm: based on recovered starting material.

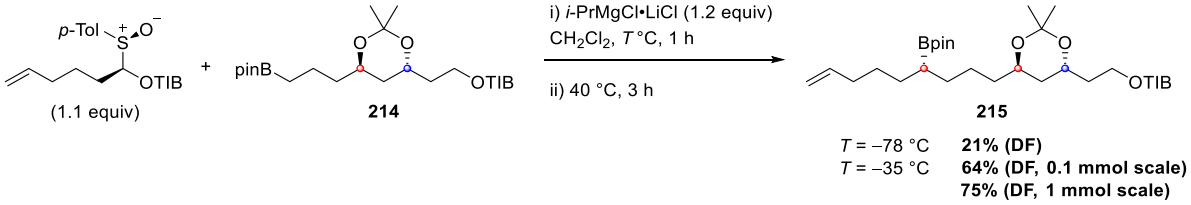
Further investigations into the reactivity of magnesiated carbenoids were conducted by a BSc project student, Michaelina Poyiatji, working under the supervision of the author (**Table 9**). A systematic screen of conditions for the homologation of a simple boronic ester (**66**) with α-sulfinyl benzoate **67** was conducted, focusing on the temperature for sulfoxide-metal exchange and borylation, which showed that in fact −35 °C was the optimal temperature for this reaction (entries 9 and 10).



Entry	67 /equiv	*i*-PrMgCl·LiCl /equiv	Temperature /°C	NMR yield *ent*-210 /%
1	1.3	1.4	–78	78 (47)
2	1.0	1.1	–78	56
3	1.0	1.1	–60	56
4	1.0	1.1	–40	51
5	1.0	1.1	–18	69
6	1.0	1.1	3	72
7	1.0	1.1	–30	78
8	1.0	1.1	–20	65
9	1.0	1.1	–35	81
10	1.1	1.2	–35	96 (69)

Table 9 Homologation reaction optimisation; the reactions reported in this table were carried out by MP working under the supervision of the author. All reactions on 0.5 mmol scale. 1,4-dinitrobenzene was used as an internal standard for ^{1}H NMR yields. Isolated yields in parentheses.

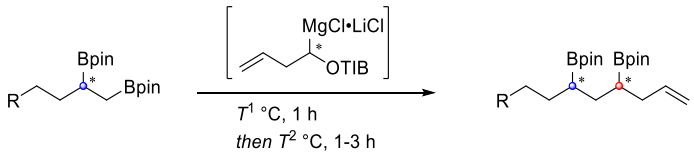
Dr Daniele Fiorito then applied these conditions, that is carrying out the sulfoxide-magnesium exchange and borylation at −35 °C, to the homologation of unhindered primary boronic ester **214** in the total synthesis of bastimolide B,[149] which greatly improved the yield of the homologated product **215** and scaled well (**Scheme 78**).



Scheme 78 Homologation of **214** with a magnesiated carbenoid by Dr Daniele Fiorito.

Furthermore, Michaelina attempted the primary-selective homologation of an enantioenriched 1,2-bis(boronic ester), which resulted in an acceptable yield of the homologated product using only a slight excess of α-sulfinyl benzoate **67** (**Table 10**, entry 1). Previously when optimising the one-directional iterative process,[142] Dr Hsuan-Hung Liao concluded that changing the reaction solvent from dichloromethane to 1,2-dichloroethane (DCE) was beneficial since its higher boiling point meant that the 1,2-migration could be carried out at 85 °C instead of 40 °C (**Table 10**, entry 2). However, 1,2-DCE freezes at −35 °C and so this necessitated conducting the sulfoxide-magnesium exchange and borylation at a higher temperature than the usual −78 °C. As there is now evidence to support that borylation of magnesiated

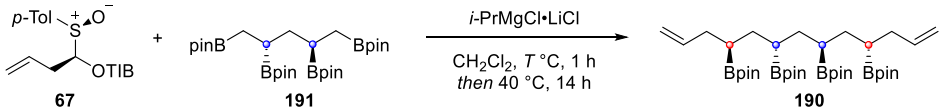
carbenoids does not occur at temperatures below −40 °C, this is probably what led to the optimised yield of 60%. Indeed, Dr Fiorito showed that the temperature for borylation was the key variable and not 1,2-migration, or the solvent itself, in another homologation step from the total synthesis of bastimolide B (**Table 10**, entries 3 and 4).[149]



Entry	R	α-sulfinyl benzoate /equiv	*i*-PrMgCl·LiCl /equiv	Solvent	T^1 /°C	T^2 /°C	Yield /%
1 (MP)	Ph	1.1[a]	1.2	CH_2Cl_2	–35	40	47
2 (HL)	biPh	1.3[a]	1.4	1,2-DCE	–35	85	60
3 (DF)	OTIB	1.2[b]	1.3	1,2-DCE	–35	85	48
4 (DF)	OTIB	1.2[b]	1.3	CH_2Cl_2	–35	40	54

Table 10 Primary-selective homologation of enantioenriched 1,2-bis(boronic esters) using magnesiated carbenoids. [a] α-sulfinyl benzoate **67**. [b] α-sulfinyl benzoate ***ent*-67.** Isolated yields reported, these reactions were conducted by the author's co-workers as indicated by their initials.

Bringing through material to investigate the later steps in the total synthesis of bahamaolide A provided the opportunity to test these optimised conditions for magnesiated carbenoids on the bidirectional homologation of tetra(boronic ester) **191** to afford doubly homoallylic tetra(boronic ester) **190** (**Table 11**). Pleasingly raising the temperature for sulfoxide-magnesium exchange and borylation from −78 °C to −35 °C resulted in a comparable yield with a smaller excess of α-sulfinyl benzoate **67** (1.3 equivalents per primary boronic ester instead of 1.6, compare entries 1 and 3, **Table 11**).



Entry	Scale /mmol 191	67 /equiv	*i*-PrMgCl·LiCl /equiv	T^1 /°C	Yield /%
1	0.2	3.2	3.4	–78	72[a]
2	0.2	2.4	2.6	–35	69
3	0.2	2.6	2.8	–35	72
4	0.4	2.6	2.8	–35	67[a]

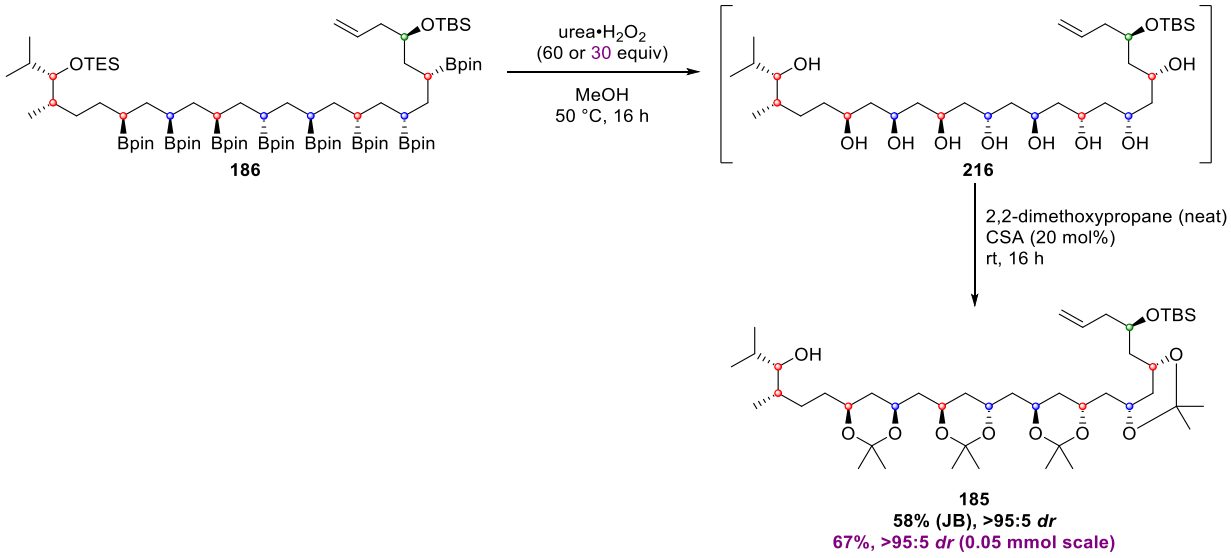
Table 11 Double homologation of tetra(boronic ester) **191** using a magnesiated carbenoid. Crude reaction mixture filtered through Et_3N-deactivated silica, then purified by flash column chromatography on a Biotage Isolera One system (4:96 acetone:hexane). [a] average of 2 runs.

3.5 Poly(oxidation) of Octa(boronic ester) 186 to Reveal the Stereodefined 1,3-Polyol

Stereospecific oxidation of the C–B bonds and acetonide protection was performed prior to installing the hexaene fragment, as Cossy has shown the polyene fragment in filipin III was not stable to oxidising conditions.[150] Thus, treatment of octa(boronic ester) **186** with urea·hydrogen peroxide complex afforded smooth conversion to the 'nonol' **216**, where the triethylsilyl protecting group had also been cleaved under the reaction conditions (**Scheme 79**). The crude polyol was directly protected, affording tetra(acetonide) **185** in an acceptable yield of 58% over 2 steps and >95:5 *dr* by ^{13}C NMR analysis, as first reported by Dr Bateman. The *dr* of the octa(boronic ester) must have been high since the steps to convert octa(boronic ester) **188** to **185** are known to be stereospecific, *i.e.* homologation with enantiopure chiral carbenoids, oxidation and protection. This transformation was operationally challenging due to the polar nature of the nonol intermediate **216**. Aqueous work-up and chromatographic purification of nonol **216** was initially avoided, but it appeared that removal of the urea was necessary for the subsequent acetonide protection to go to completion. Following complete conversion to nonol **216** by LC-MS analysis, the reaction mixture was instead filtered through a short plug of sand, washing with cold ethyl acetate, then concentrated under reduced pressure. 2,2-Dimethoxypropane and catalytic camphorsulfonic acid were added to crude nonol **216** and the protection was monitored by TLC analysis.

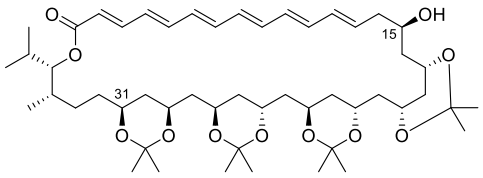
It was found that the equivalents of urea·hydrogen peroxide complex could be reduced from 60 to 30, however an alternative purification method would be preferred since the sand filtration process to remove urea was challenging to reproduce. Purification of nonol **216** was therefore performed by silica column chromatography on a Biotage Isolera One system using methanol in dichloromethane as the eluent. Although urea was removed using this method, the column fractions containing nonol **216** were typically mixed with pinacol but, unlike urea, pinacol did not affect the next reaction so the mixed fractions were concentrated and subjected to the acetonide protection conditions. After stirring at ambient temperature overnight, the majority of nonol **216** converted to tetra(acetonide) **185** and any spots isolated through column chromatography that corresponded to differing levels of protection were resubmitted to the reaction conditions and pushed through to the product. However, this 2-step sequence proved to be one of the bottleneck steps in bringing through sufficient material to complete the synthesis. While this revised procedure was reasonably reproducible,

since the molecular weight of **185** is essentially half that of the starting poly(boronic ester) **186** (827 compared to 1661), even a yield of 50-60% means 'losing' three quarters of the mass submitted to the oxidation and acetonide protection. Going back a couple of steps to further illustrate this, 179 mg (0.15 mmol) octa(boronic ester) **188** is transformed to just 25 mg (0.03 mmol) tetra(acetonide) **185** after 4 steps in a single pass.

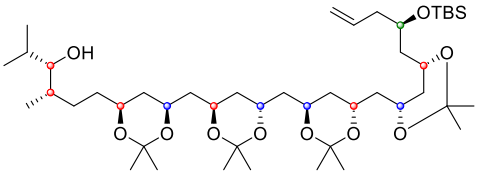


Scheme 79 Poly(oxidation) of octa(boronic ester) **186** and acetonide protection using Dr Bateman's conditions; yield in purple by the author. Reported *dr* values determined by ^{13}C NMR analysis. CSA: camphorsulfonic acid.

Protected polyol **185** represented the first synthetic compound which could be compared with data for bahamaolide A derivatives reported in the isolation paper, which was an attractive possibility both to validate the synthetic approach and since the stereochemistry at C15 in bahamaolide is reported to be opposite to that for the corresponding stereocentre in related oxopolyene macrolides including dermostatin A. In order to assign the stereochemistry of the 1,3-polyol domain, natural bahamaolide A was subjected to acetonide protection by the isolation team to give several tetra(acetonide) compounds, including **80** (*vide supra*, section **2.1** and **Scheme 28**).[65] The ^{1}H and ^{13}C NMR chemical shifts for all the hydroxylated stereocentres in **80** and **185** were compared (**Table 12**). Pleasingly the NMR data appeared to match reasonably well, and it was assumed that these differences (≤1.1 ppm for δ_C, ≤0.33 ppm for δ_H) could possibly be attributed to the different environments experienced in the open chain (**185**) as opposed to the closed macrocycle (**80**) with a more restricted conformation.



80



185

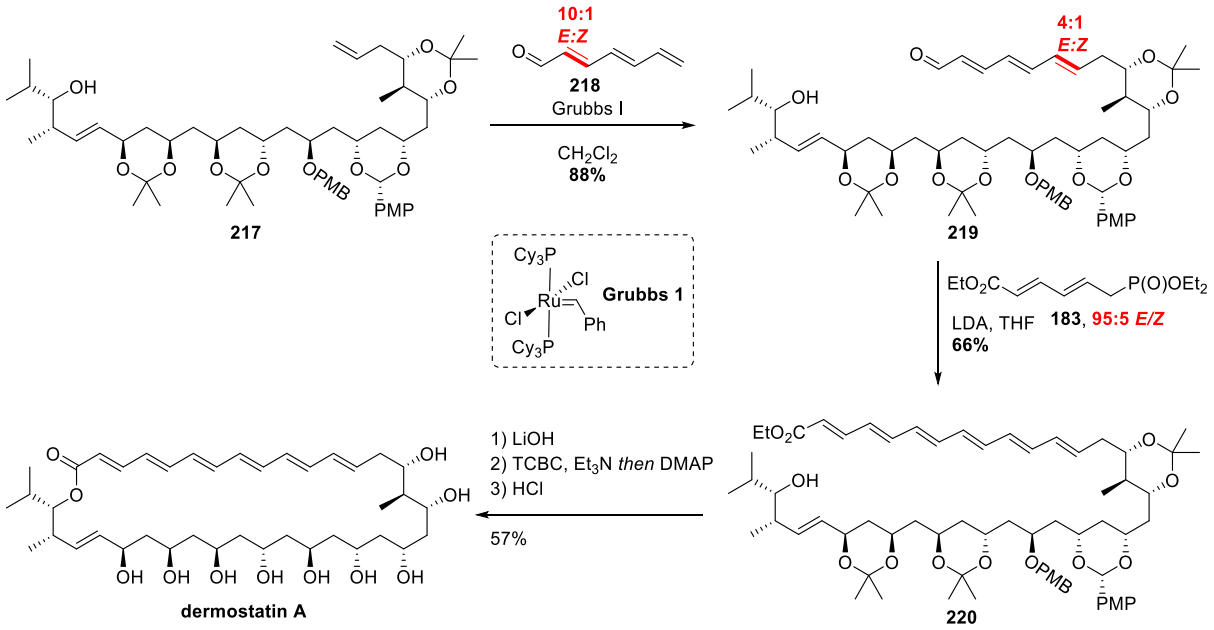
position	80 (800 MHz)[65]		185 (500 MHz)			
	δ_C	δ_H	δ_C	Δ	δ_H	Δ
15	68.5	4.04	68.5	**0.0**	4.14	**+0.10**
17	67.2	4.15	66.3	**−0.9**	4.10	**−0.05**
19	62.9	4/00	63.7	**+0.8**	4.14	**+0.14**
21	62.5	3.84	63.6	**+1.1**	4.17	**+0.33**
23	62.4	4.02	63.4	**+1.0**	4.21	**+0.19**
25	62.3	4.07	63.4	**+1.1**	4.22	**+0.15**
27	65.8	3.99	66.2	**+0.4**	4.08	**+0.09**
29	65.7	3.93	66.2	**+0.5**	4.03	**+0.10**
31	70.0	3.70	69.7	**−0.3**	3.70	**0.00**

Table 12 ^{13}C and ^{1}H NMR data for **185** in toluene-d_8 compared with tetra(acetonide) **80** from the isolation paper.

3.6 Synthetic Endgame: Installation of the Polyene and Macrocyclisation

3.6.1 First generation synthesis of hexaenoate 182

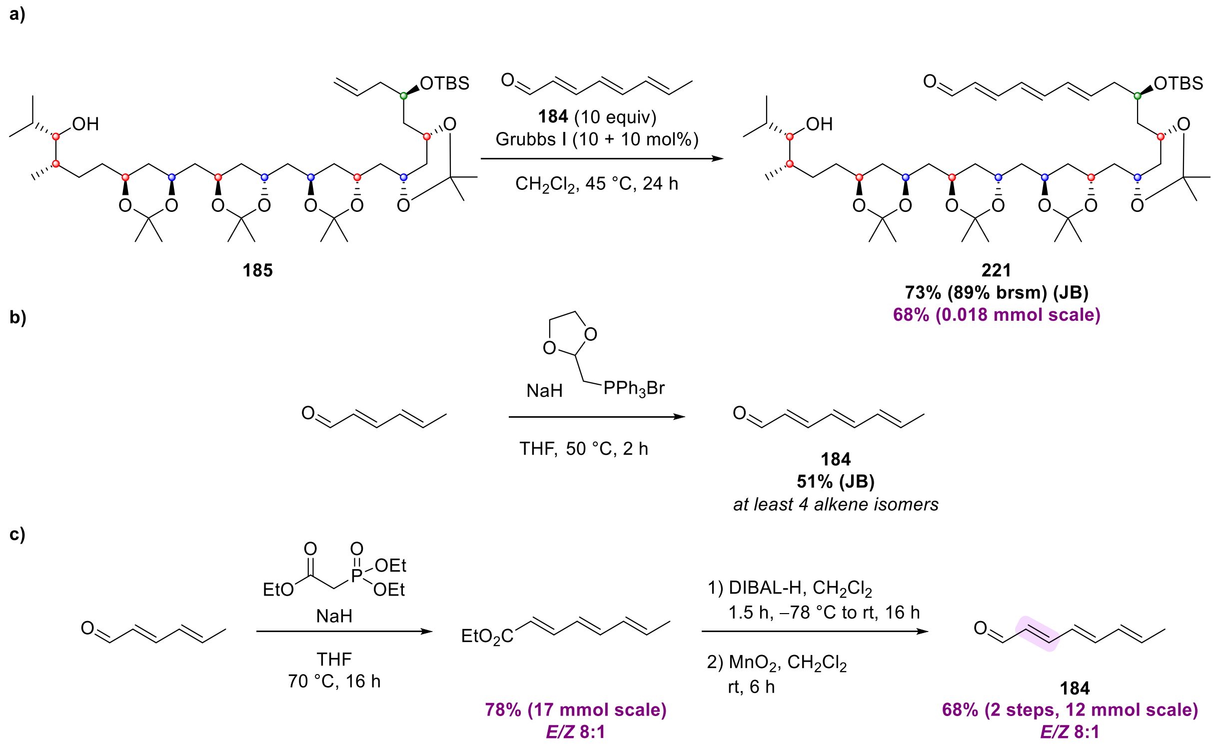
With the key 1,3-polyol fragment constructed, the remaining steps concerned installation of the hexaene and macrocyclisation. When Dr Bateman left the project, the planned route was largely inspired by Sammakia's total synthesis of dermostatin A (**Scheme 80**), the only oxopolyene macrolide containing a hexaenoate to have succumbed to total synthesis to date (also reported by Rychnovsky).[111,139,151] Sammakia and co-workers employed an analogous approach to that exemplified in their total synthesis of pentaene-containing RK-397,[74] specifically cross-metathesis between **217** and trienal **218** to generate **219** as a 4:1 mixture of alkene isomers, followed by a HWE reaction with phosphonate **183**. It was reported that **220** could be isolated in isomerically pure form. Hydrolysis of **220** to the seco-acid, Yamaguchi macrolactonisation and global deprotection under acidic conditions completed the total synthesis.



Scheme 80 Sammakia's endgame steps in the total synthesis of dermostatin A. TCBC: 2,4,6-trichlorobenzoyl chloride.

3.6.1.1 Cross-metathesis with trienal 184

As for the corresponding intermediate towards bahamaolide A, the terminal alkene of **5** engaged in selective cross-metathesis with trienal **184** (**Scheme 81** a); the absence of homodimers confirmed their classification as type 2 and type 3 olefins, respectively.[152] While this reaction was remarkably clean, it was necessary to add a further portion of Grubbs catalyst after 6 hours to increase consumption of starting material. Dr Bateman performed this cross-metathesis with trienal **184** prepared through a Wittig reaction[111] (**Scheme 81** b). It has now been shown that trienal **184** can be accessed with improved *Z:E* selectivity when a Horner-Wadsworth-Emmons reaction is used to forge the alkene, and additionally using MnO_2 instead of Dess-Martin periodinane (DMP) for the oxidation step[153] resulted in a much cleaner reaction by ^{1}H NMR analysis of the product (**Scheme 81** c). However, **221** prepared using this batch of trienal **184** was still a considerable mixture of alkene isomers (**Figure 15**) which could not be separated by column chromatography (appeared as a single spot by TLC analysis).



Scheme 81 a) Cross-metathesis of **185.** b) Synthesis of trienal **184** by JB. c) Optimised synthesis of trienal **184**. Yields in purple by the author.

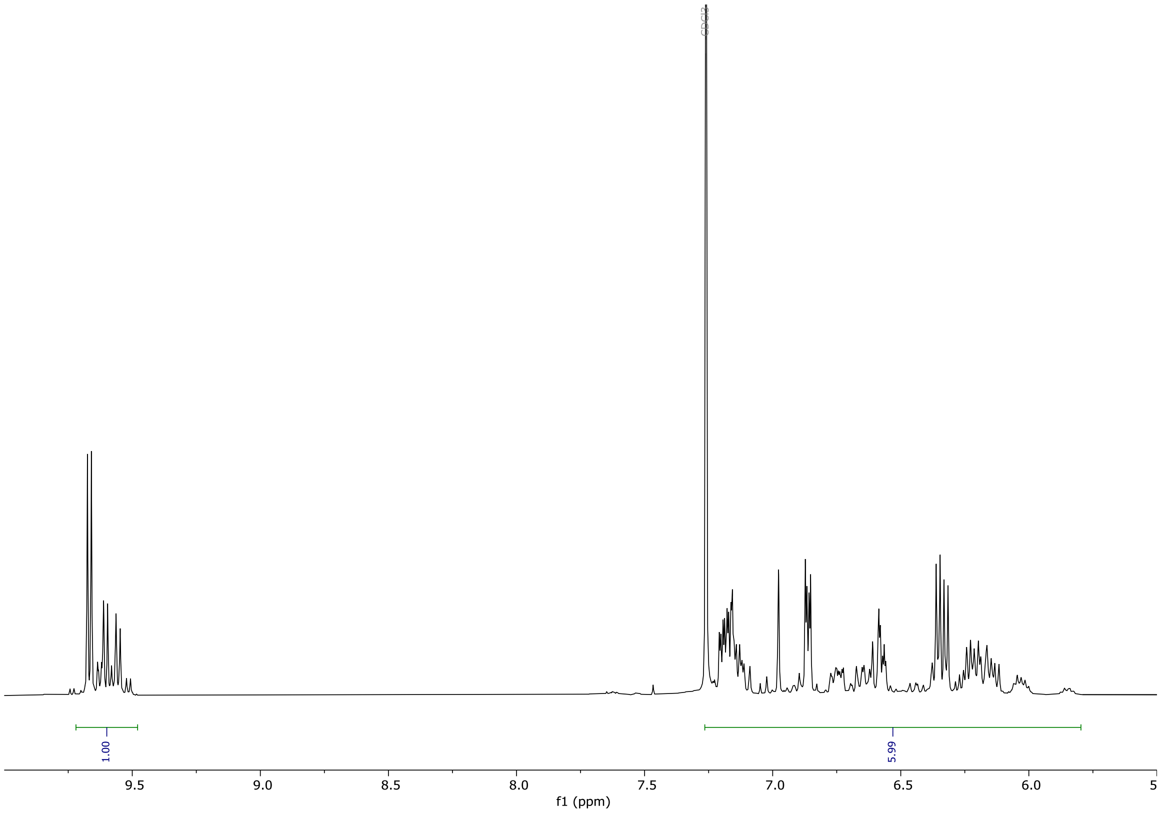
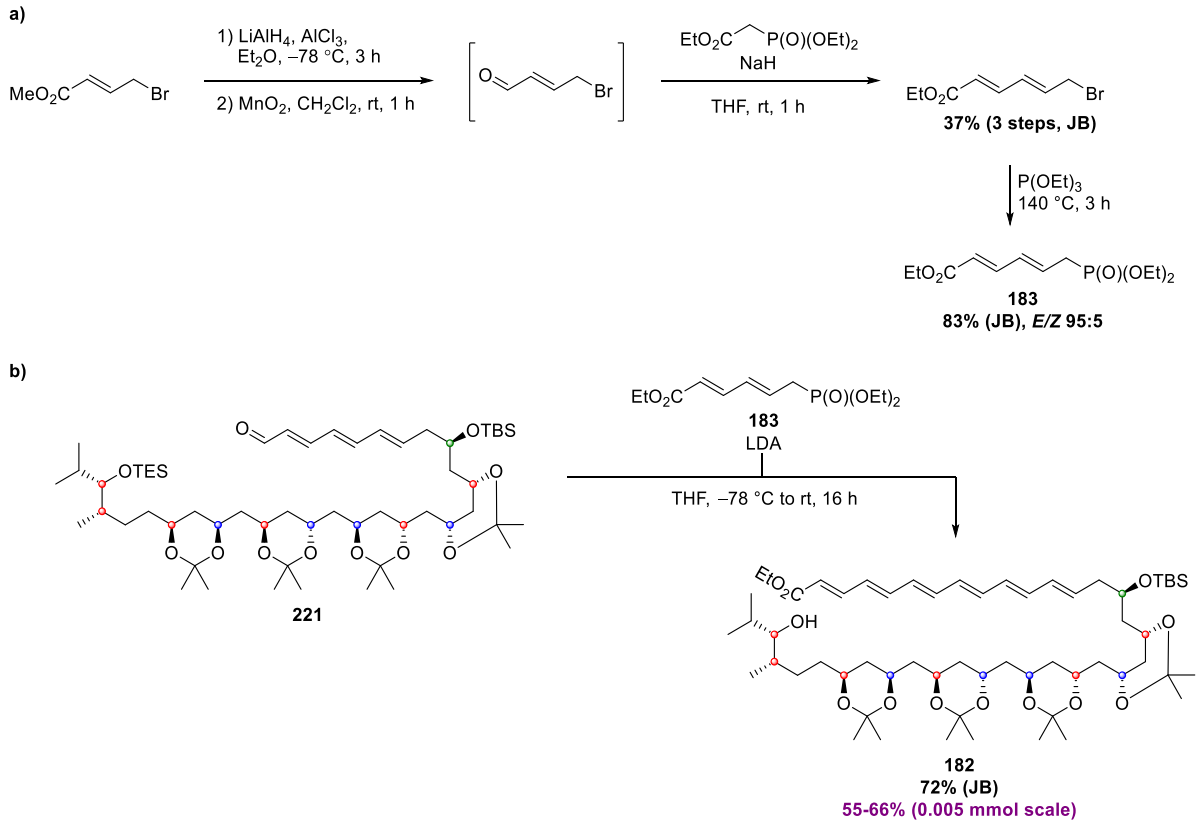


Figure 15 Alkene region of ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **221** prepared as shown in **Scheme 81** a.

3.6.1.2 Horner-Wadsworth-Emmons reaction using phosphonate 183

The Horner-Wadsworth-Emmons reaction between **221** and literature known phosphonate[154] **183** was performed once by Dr Bateman to afford **182** in 72% yield, containing both the full 1,3-polyol and the hexaene moiety (**Scheme 82**), yet again as a mixture of alkene isomers which was difficult to analyse due to many overlapping multiplets in the ^{1}H NMR spectrum.

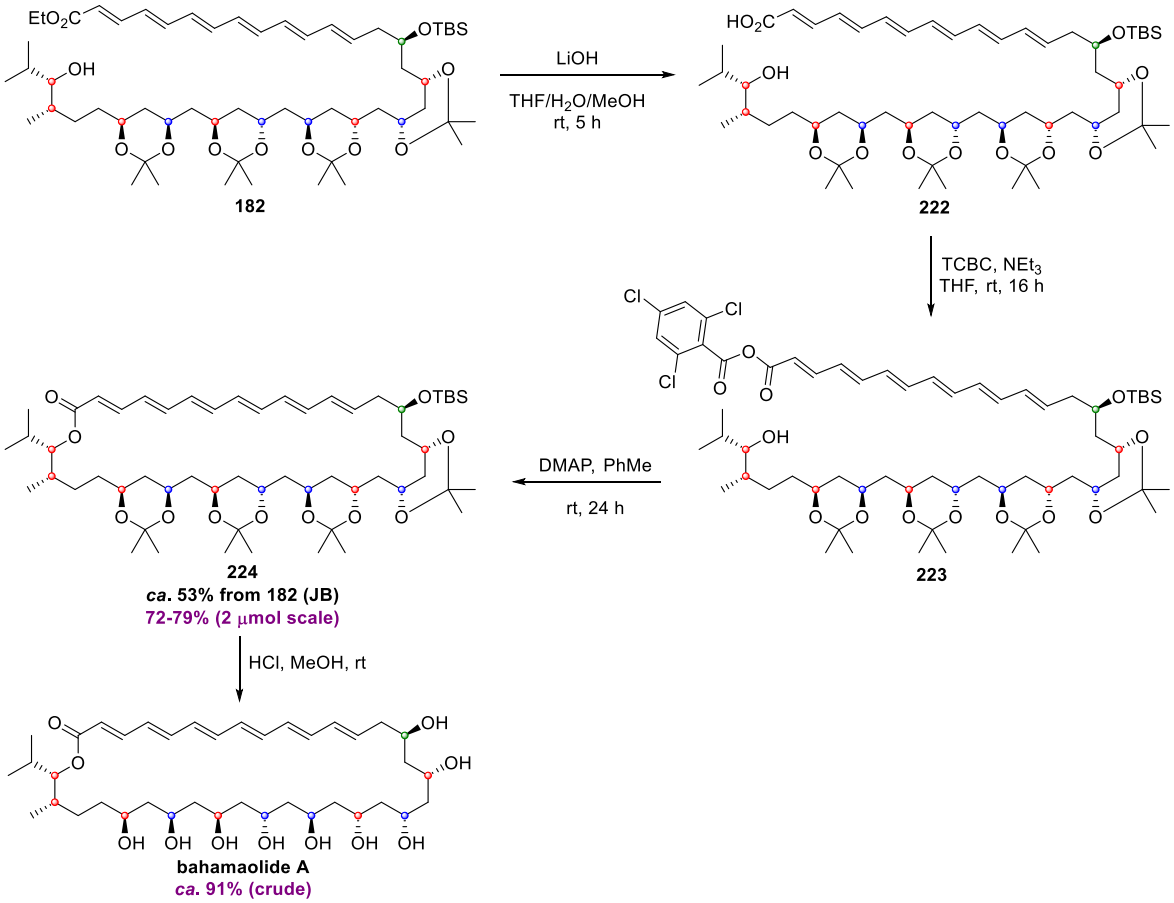


Scheme 82 a) Synthesis of phosphonate **183** (JB). b) HWE reaction with **221**. Yield in purple by the author.

3.6.1.3 Saponification, Yamaguchi macrolactonisation and global deprotection

Dr Bateman first showed that **182** could successfully be transformed to the natural product in a further 3 steps (**Scheme 83**), following the procedure reported by Sammakia for dermostatin A.[111] Saponification of **182** with lithium hydroxide gave the free terminal carboxylic acid **222**, which was activated as the Yamaguchi mixed anhydride and isolated by filtration through Celite®. Evans reported this was necessary to avoid decomposition of the corresponding intermediate in (+)-roxaticin, presumably initiated through Et_3NHCl-mediated destruction of the polyene.[109] Slow addition of **223** to DMAP facilitated macrolactonisation to yield protected bahamaolide A (**224**). Sammakia and Evans stated that the corresponding intermediates in the synthesis of dermostatin A and roxaticin, respectively, were not stable to chromatographic purification,[109,111] and so, following filtration of **224** through a short pad of

silica gel to remove DMAP, global deprotection was effected using concentrated HCl in methanol at ambient temperature over 24 hours for complete conversion to crude bahamaolide A, as monitored by LC-MS analysis.



Scheme 83 Saponification–macrolactonisation–deprotection to complete the synthesis of bahamaolide A, starting from **182** prepared as shown in **Scheme 81** and **Scheme 82**. Yields in purple by the author.

While this route enabled a small batch of material to be taken through to yield the first crude sample of synthetic bahamaolide, attempts to separate the alkene isomers (mainly generated in the cross-metathesis step) by reverse phase preparative HPLC were not successful.

The LC-MS UV trace showed several peaks with the molecular weight of bahamaolide A, which were presumed to be the natural product and its alkene isomers (**Figure 16**). After lengthy optimisation on an analytical LC-MS system—changing detection wavelength, eluent composition, gradient or isocratic runs, flow rate and column length—it was determined that isocratic 38% acetonitrile in water gave the best separation of these bahamaolide peaks.

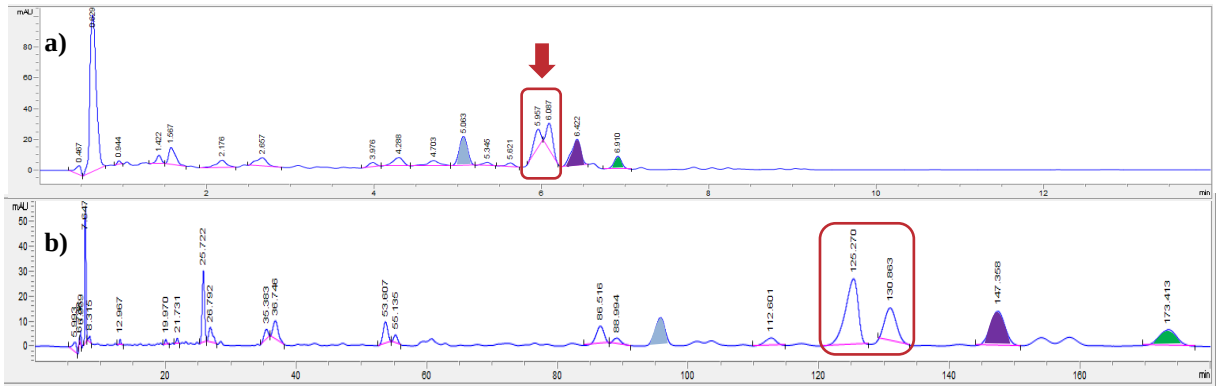


Figure 16 Analytical LC-MS UV traces for crude bahamaolide; coloured/circled peaks contain bahamaolide's mass and are presumed to be alkene isomers. a) 10-90% MeCN in H_2O over 8 min, 0.5 ml/min, 50 mm C18 column, 3 mm I.D., detecting at 360 nm. b) isocratic 38% MeCN in H_2O, 0.1 ml/min, 150 mm C18 column, 3 mm I.D., detecting at 360 nm.

These analytical conditions were then transferred to a semi-preparative system with a fraction collector. Initial runs were discouraging due to problems with overloading the reverse phase columns available. A larger 25 cm C18 column was later found which was comparable to that used by Sammakia to purify synthetic dermostatin A. Using this column, the UV trace on the preparative HPLC looked better with either the 38% acetonitrile in water conditions (**Figure 17** b) or using 5:1 methanol:water as eluent (Sammakia's conditions for dermostatin A). However in both cases when the fractions corresponding to the presumed major peak for bahamaolide were checked by LC-MS analysis, disappointingly several peaks were still present (**Figure 18**). ^{1}H NMR analysis confirmed that this was still a mixture of at least 3 alkene isomers.

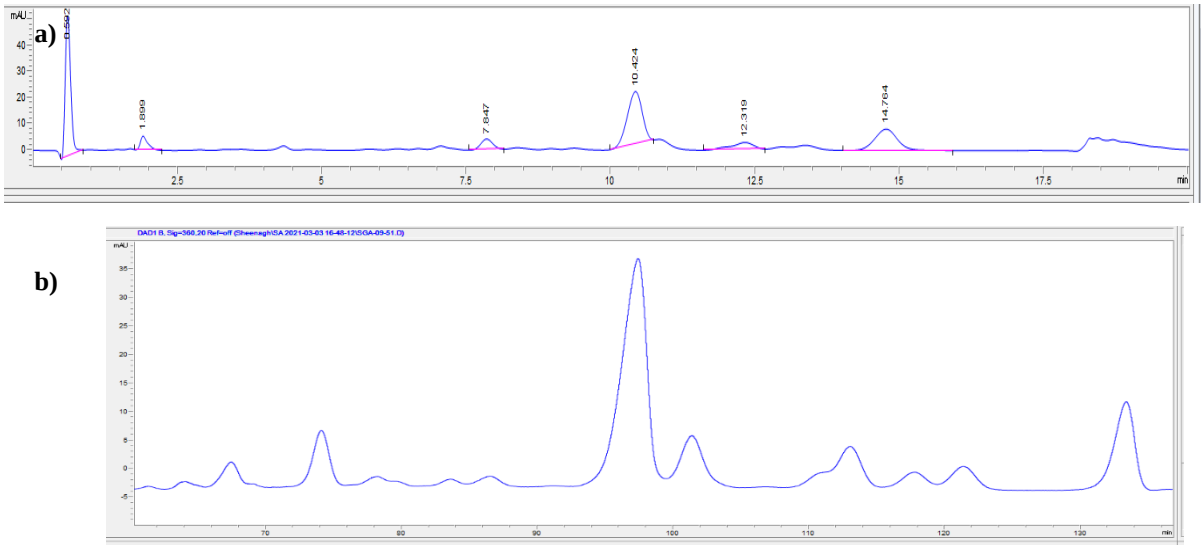


Figure 17 a) Crude LC-MS; isocratic 38% MeCN in H_2O, 0.5 ml/min, 50 mm C18 column, 3 mm I.D. b) UV trace on reverse phase preparative HPLC; isocratic 38% MeCN in H_2O, 2 ml/min, 250 mm C18 column, 10 mm I.D.

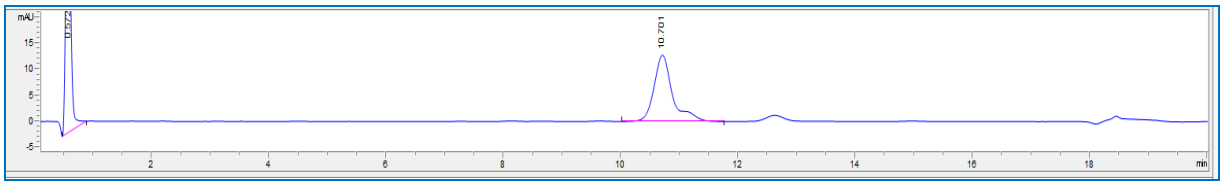


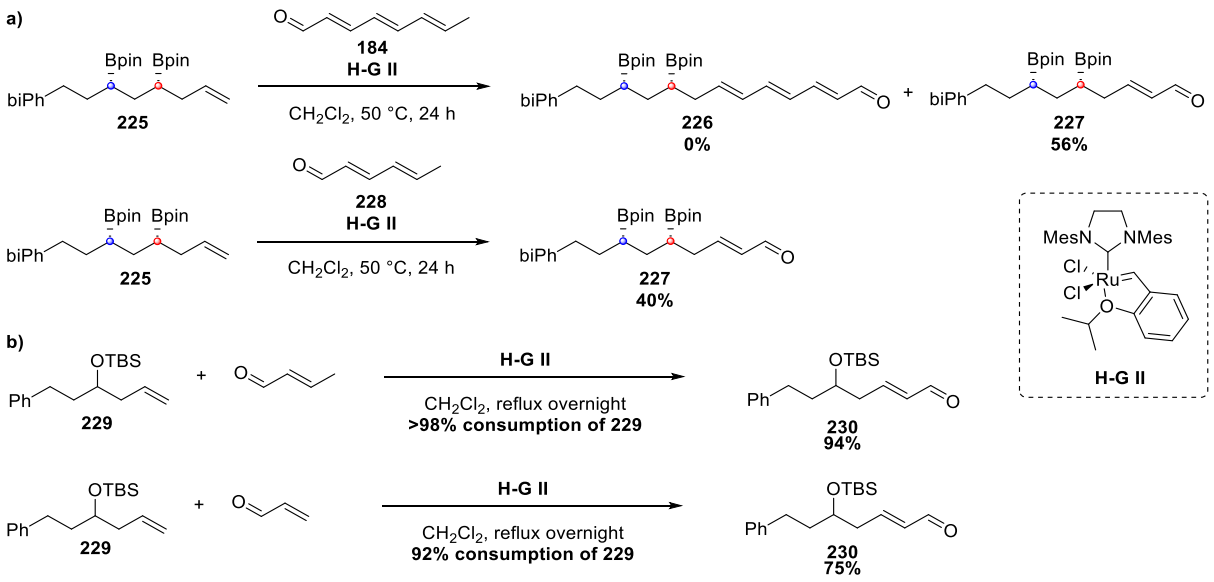
Figure 18 LC-MS for major peak in **Figure 17** trace b; isocratic 38% MeCN in H_2O, 0.5 ml/min, 50 mm C18 column, 3 mm I.D.

There have been a number of reported stability issues encountered with the polyene moiety in the total synthesis of related natural products.[151] Schreiber stated that both natural and synthetic (+)-mycoticin A convert to a mixture of five alkene isomers under exposure to light.[134] Mori reported that the seco-ester for roxaticin isomerised under exposure to light to give a mixture of alkene isomers and was also observed to decompose in chloroform.[95] These initial observations indicating potential photoreactivity of the conjugated polyene prompted other groups targeting oxopolyene macrolides to conduct these later steps in the synthesis in the dark as strictly as possible. Evans reported that the seco-ester for roxaticin "was very sensitive to air and light" and the seco-acid was also unstable.[109] Efforts to purify protected roxaticin by normal phase chromatography by Evans and co-workers were abandoned due to rapid olefin isomerisation. Sammakia also observed rapid olefin isomerisation after attempted HPLC isolation of protected dermostatin A.[111]

Cognizant of these reports, great care was taken to minimise exposure of the polyene to light by performing all reactions in the dark and all manipulations in low/red lighting. In addition, samples of synthetic bahamaolide were left out in the light and there was no change in the ratio of the peaks observable by LC-MS analysis, and so rather than the main problem being light-mediated isomerisation or decomposition of the deprotected macrocycle, it was suggested that instead hexaenoate **182** needed to be of much higher isomeric purity prior to the final saponification–macrolactonisation–deprotection sequence.

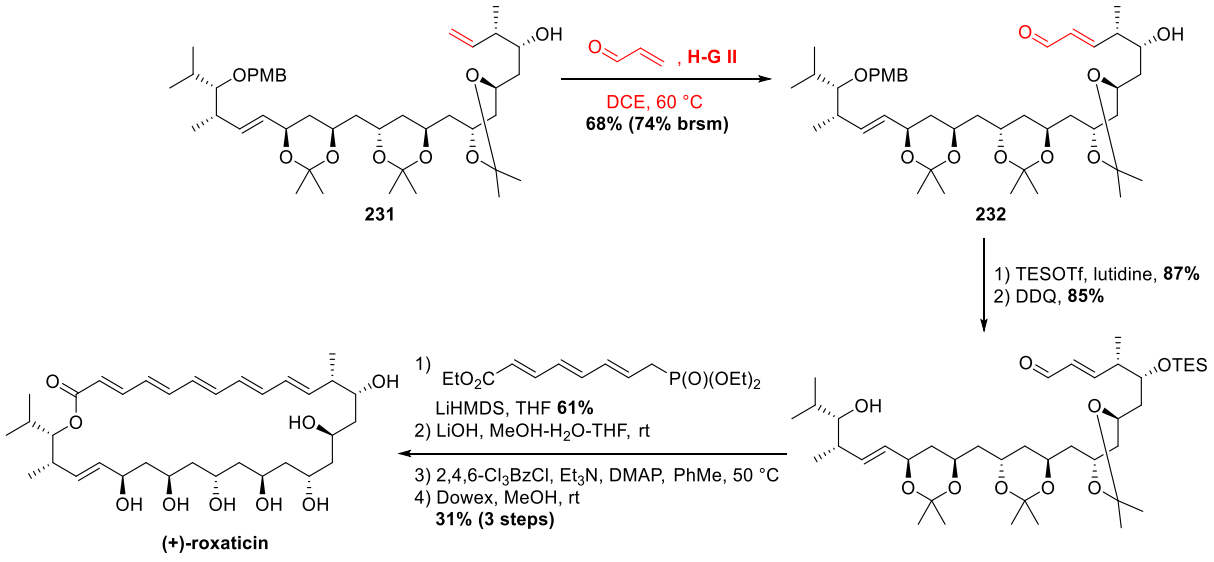
3.6.2 Second generation synthesis of hexaenoate 182

When choosing the catalyst for the cross-metathesis, Dr Bateman first used the model compound **225** (**Scheme 84** a). With Hoveyda-Grubbs second generation metathesis catalyst (**H-G II**), the desired trienal **226** was not observed and instead there was exclusive formation of α,β-unsaturated aldehyde **227** with high *E*-selectivity, when using either trienal **185** or dienal **228**. In addition, as part of Sammakia's cross-metathesis studies, alkene **229** was smoothly converted to α,β-unsaturated aldehyde **230** with either acrolein or crotonaldehyde, using **H-G II** (**Scheme 84** b).[111]



Scheme 84 Cross-metathesis using Hoveyda-Grubbs second generation catalyst (H-G II). a) Dr Bateman's model studies on the cross-metathesis step. b) Sammakia's cross metathesis studies for the total synthesis of dermostatin A. biPh: biphenyl.

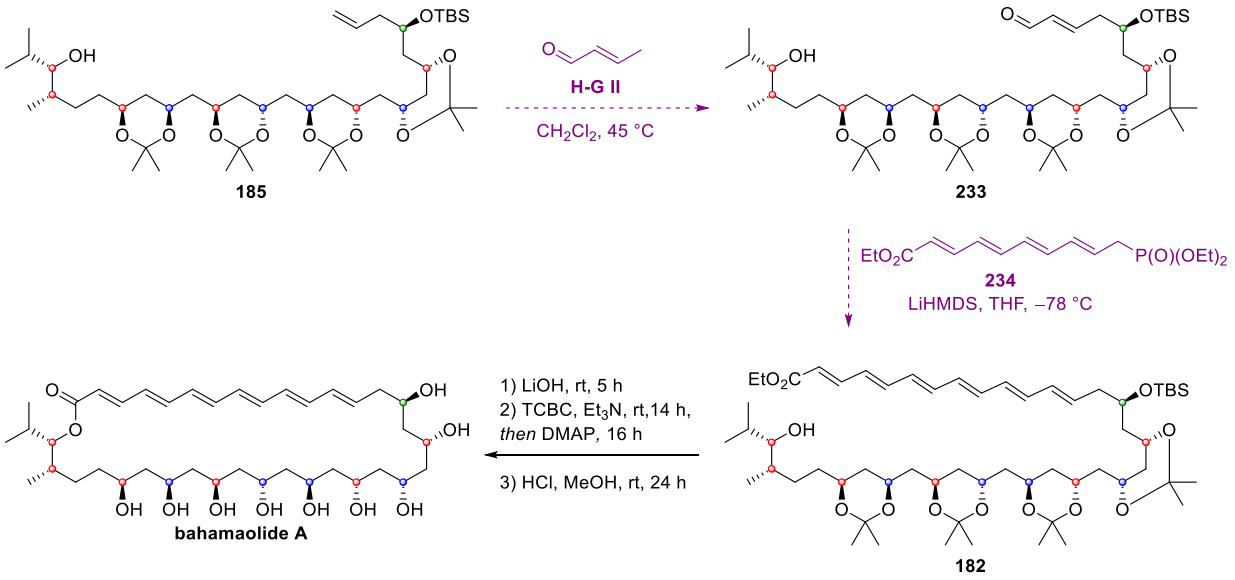
Similar conditions were employed by Krische to commence the construction of the pentaene moiety in (+)-roxaticin (**Scheme 85**), namely cross-metathesis of **231** and acrolein, using catalyst **H-G II** which gave **232** with complete *E*-selectivity.[86]



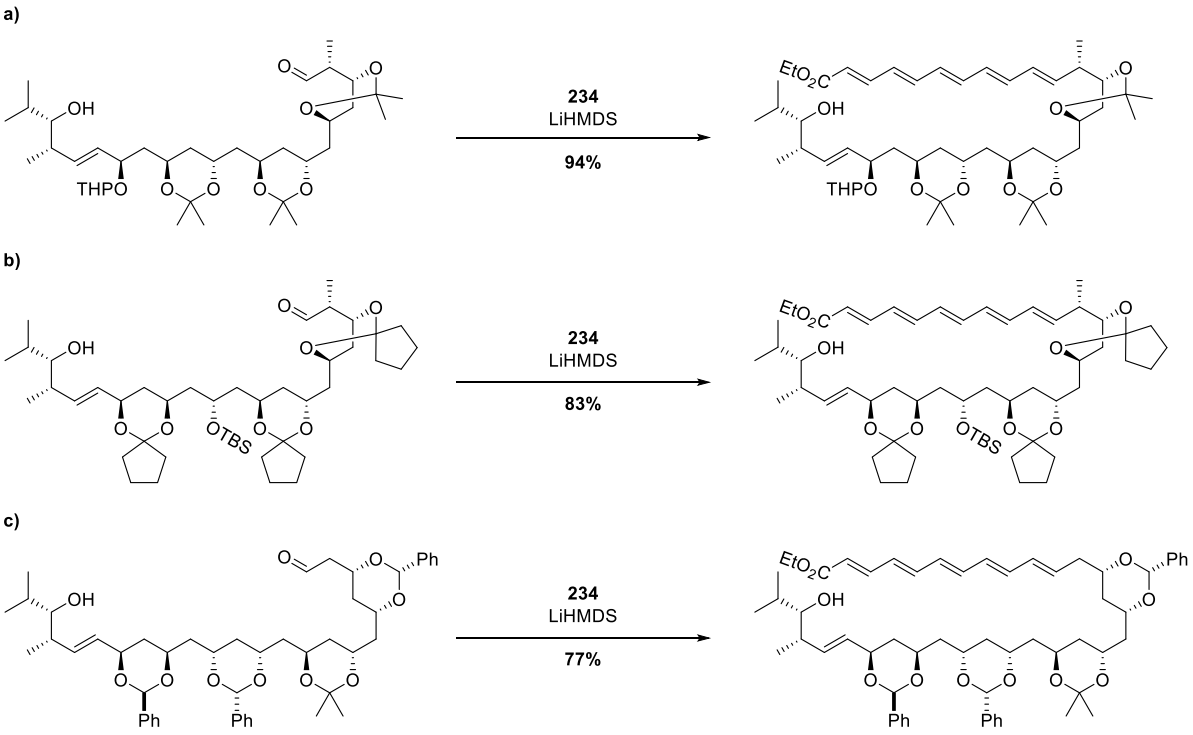
Scheme 85 Cross-metathesis with acrolein in Krische's total synthesis of roxaticin. DDQ: 2,3-dichloro-5,6-dicyanobenzoquinone. LiHMDS: Lithium bis(trimethylsilyl)amide.

Based on this precedent, conducting a simple cross-metathesis of **185** with crotonaldehyde was proposed, which should proceed in high *E*-selectivity to afford **233** (**Scheme 86**). The majority of the polyene domain would then be introduced through a HWE reaction with known phosphonate[95,109] **234**, which can itself be prepared as essentially a single alkene isomer (7 steps from cyclooctatetraene, *vide infra*). High selectivity for 5 *E*-alkenes was

reported for this HWE reaction when employed in the total synthesis of the pentaene moiety in roxaticin by Mori and Evans,[95,109] and in RK-397 by Denmark[110] (**Scheme 87**). **182** would then be transformed to bahamaolide A in a further 3 steps as before.



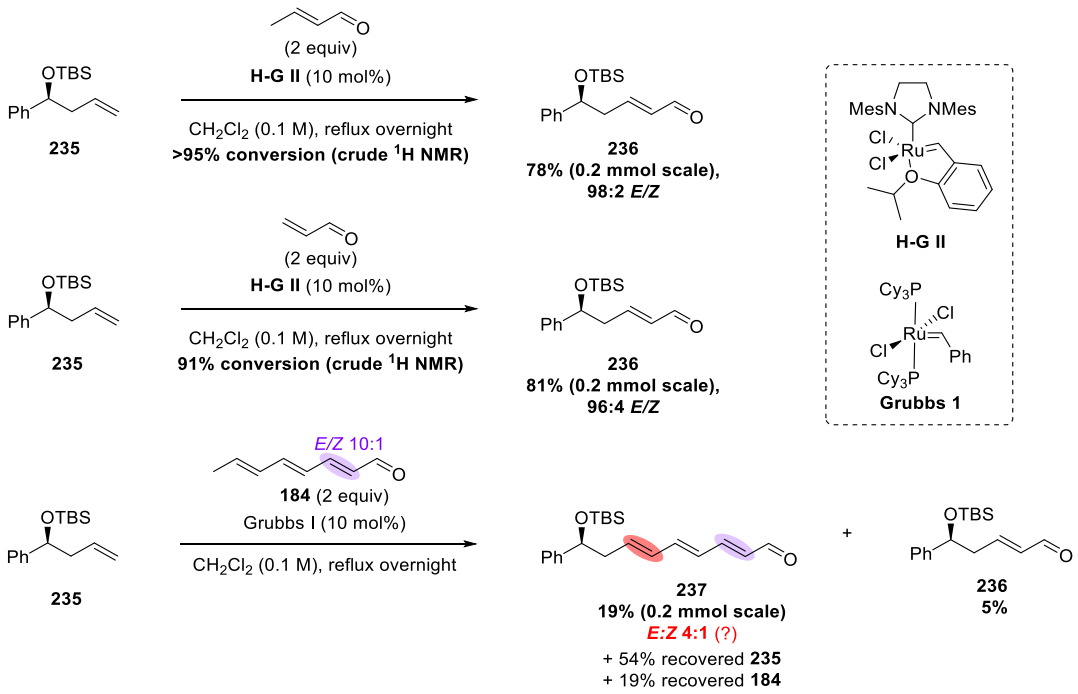
Scheme 86 Revised strategy to construct the hexaenoate moiety in bahamaolide A.



Scheme 87 HWE with phosphonate **234** employed by a) Mori in the total synthesis of roxaticin, b) Evans in the total synthesis of roxaticin, and c) Denmark in the total synthesis of RK-397.

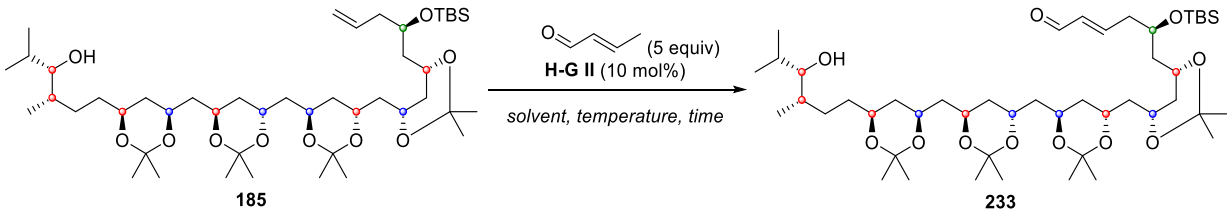
3.6.2.1 Cross-metathesis with crotonaldehyde

(*S*)-1-Phenylbut-3-en-1-ol was available in-house, and following silyl protection, homoallylic alcohol **235** was used as a model compound to investigate the cross-metathesis with either acrolein or crotonaldehyde using catalyst **H-G II** (**Scheme 88**). Pleasingly both reactions worked well to yield α,β-unsaturated aldehyde **236** in high yield and *E*-selectivity. Model substrate **235** was also subjected to a cross-metathesis reaction under the conditions originally employed, namely trienal **184** and Grubbs 1st generation metathesis catalyst. A poor yield of the desired product **237** was obtained, with worse *E*:*Z* selectivity and more worryingly, product **236** was also isolated from this reaction which suggests that perhaps other cross-metathesis products were also being generated in the reaction shown in **Scheme 81** (note the higher catalyst loading and greater excess of **184** used in this case above). Further analysis/optimisation of the reaction with trienal **184** was not pursued.



Scheme 88 Cross-metathesis model studies. Reported *E*/*Z* ratios by ^{1}H NMR analysis.

The slightly better *E*:*Z* ratio for the reaction of **235** with crotonaldehyde led to these conditions being applied to the substrate of interest, protected homoallylic alcohol **185**, which worked well (**Table 13**). Simply changing the solvent from dichloromethane to 1,2-DCE and so allowing the reaction to be conducted at a higher temperature led to full consumption of starting material **185** and α,β-unsaturated aldehyde **233** was isolated in excellent yield and *E*-selectivity (>95:5 *E*:*Z*).

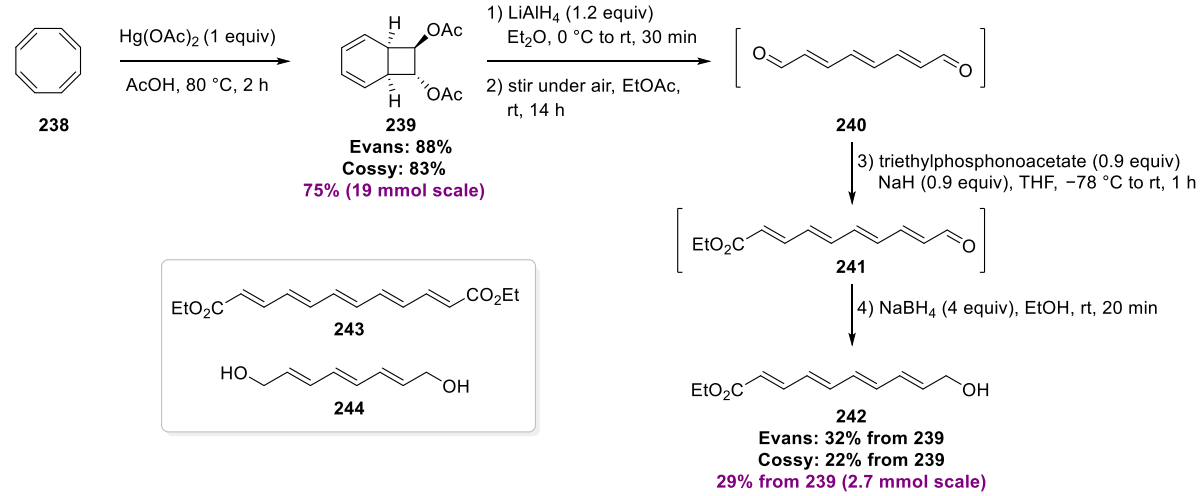


Entry	Scale /mmol 185	Solvent (0.05 M)	Temperature /°C	Time /h	Yield 233 /%
1	0.010	CH_2Cl_2	40	20	64[a]
2	0.008	1,2-DCE	70	14	87
3	0.014	1,2-DCE	70	14	86

Table 13 Cross-metathesis of **185** with crotonaldehyde. [a] plus 15% recovered **185**.

3.6.2.2 Horner-Wadsworth-Emmons reaction using phosphonate 234

Attention then turned to the preparation of the required tetraene-bearing phosphonate **234** for the HWE reaction to access the full hexaene domain. The synthesis of alcohol **242** has also been reported by Mori and Denmark,[95,110] who both crucially used photochemical isomerisation with iodine to access the all *E*-tetraenoate, but Evans' approach was selected to be followed for this work (**Scheme 89**),[109] which had also been reproduced by Cossy and co-workers.[155]

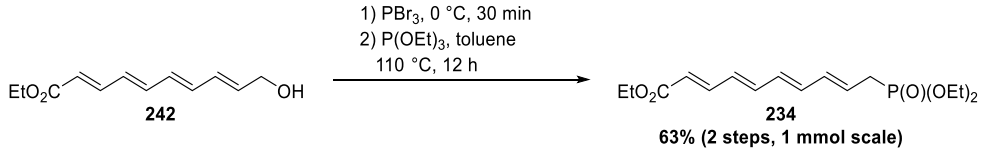


Scheme 89 Synthesis of alcohol **242**; yields in purple by the author.

Cyclooctatetraene (**238**) was subjected to a one-pot electrocyclic ring closure and mercury-catalysed *trans*-acetoxyation procedure[156] to give diacetate **239** as an orange crystalline solid, which was stable when stored at −20 °C for at least 4 months. Reductive cleavage of the acetate groups revealed the transient diol which was stirred in ethyl acetate under air overnight leading to dialdehyde **240** through a 2-electron oxidative ring fragmentation and

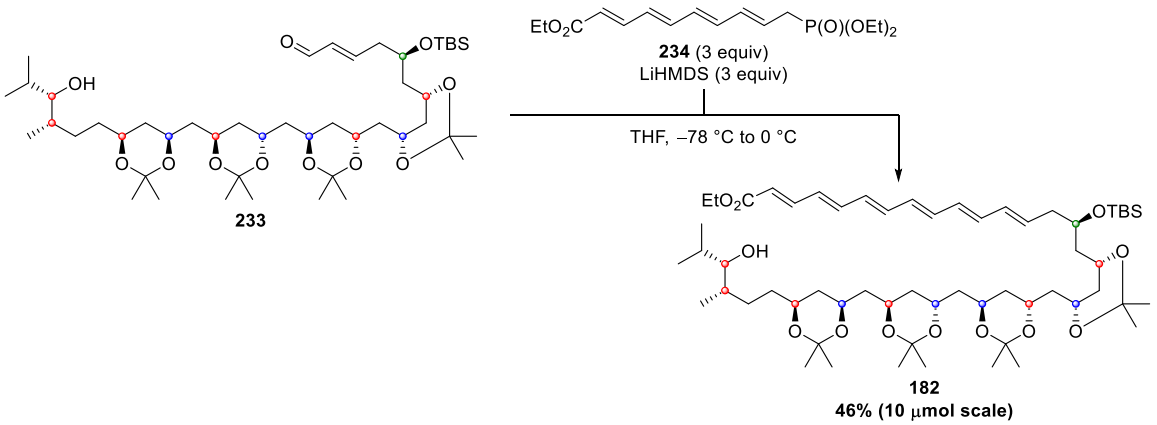
alkene isomerisation process.[157] These two steps from **239** appeared to proceed with full consumption of starting material by TLC analysis. Dialdehyde **240** was highly light- and air-sensitive and on initial attempts, significant levels of polymerisation occurred (observed as a brown gummy residue). Eventually it was found to be beneficial to perform a Fieser work-up on the $LiAlH_4$ reaction mixture, which resulted in far less decomposition. Furthermore, it was important to quantify the dialdehyde to avoid losing too much material as the undesired 'double' product (**243**) in the next step, a mono-HWE reaction, and this was more difficult with higher levels of polymerisation/decomposition. This was typically achieved through a crude mass, and ^1H NMR analysis. With a reasonable handle on the amount of dialdehyde **240**, this yellow-orange solid was treated with 0.9 equivalents of the sodium salt of triethylphosphonoacetate. TLC and NMR analysis showed this led to a mixture of the desired monoester-monoaldehyde **241**, pentaene **243**, where a HWE reaction had occurred at both terminal aldehydes, and unreacted dialdehyde **240**. Treatment of this crude mixture with excess sodium borohydride ensured that any unreacted dialdehyde was converted to the diol **244**, since dialdehyde **240** co-eluted with alcohol **242**. This reaction sequence was conducted in dimmed/red lighting since dialdehyde **240** was particularly unstable to light (see experimental section for details).

With alcohol **242** in hand, a final 2 steps were required to convert it to phosphonate **234** (**Scheme 90**), using conditions reported by Mori and Denmark.[95,110] Both alcohol **242** and phosphonate **234** were isolated as essentially a single alkene isomer by NMR analysis. Phosphonate **234** could be stored under argon at −20 °C for up to 3 months, consistent with Evans' statement that "this polyene was the most stable of any intermediate in this sequence".[109]



Scheme 90 Conversion of alcohol **242** to phosphonate **234**.

The key HWE reaction was then attempted (**Scheme 91**). Phosphonate **234** was deprotonated with LiHMDS at −78 °C then α,β-unsaturated aldehyde **233** was added as a solution in THF. The reaction mixture was stirred at −78 °C for a further 30 min, then warmed slowly to 0 °C and quenched with a saturated aqueous solution of sodium bicarbonate. Hexaenoate **182** was isolated in 46% yield with a clear major alkene isomer (**Figure 19**).



Scheme 91 HWE reaction of **233** and **234**.

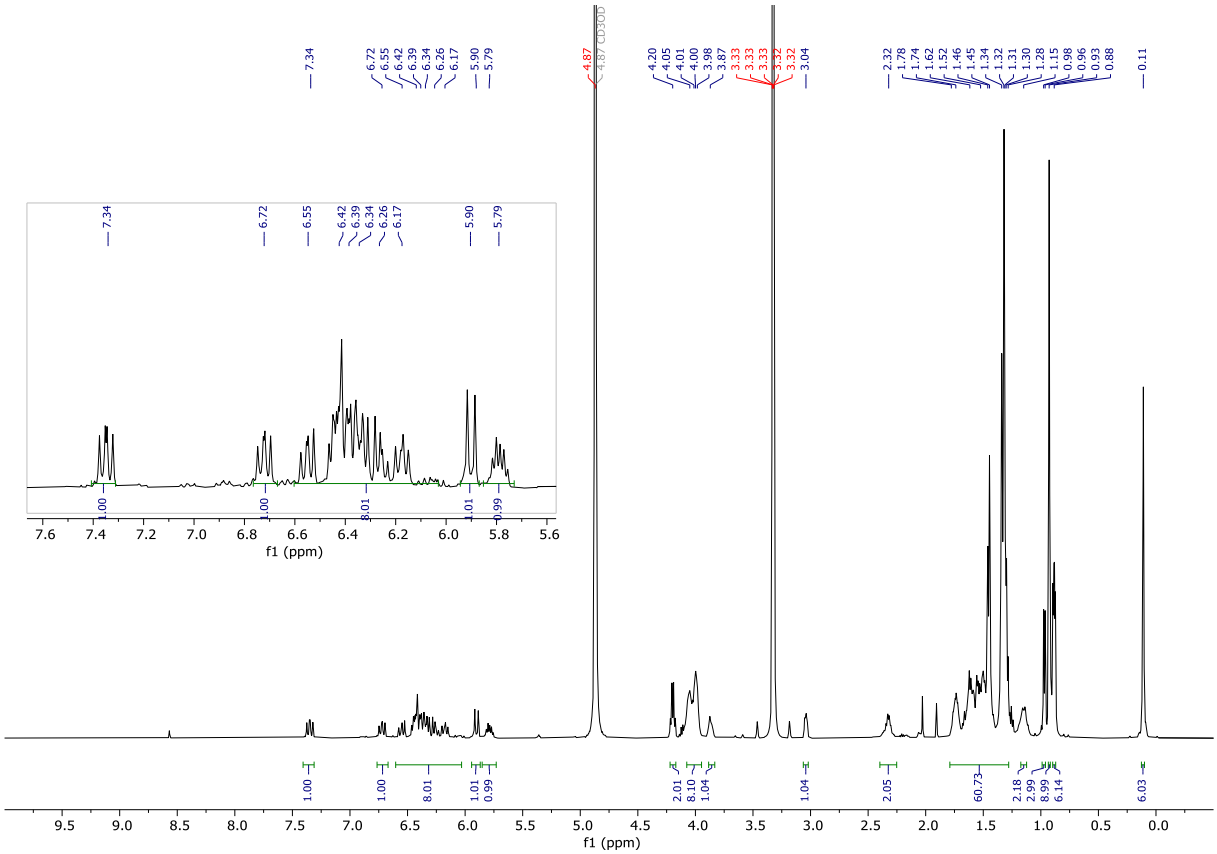


Figure 19 ^{1}H NMR (500 MHz, CD_3OD) spectrum for **182** prepared as shown in Scheme 91.

3.6.2.3 Saponification, Yamaguchi macrolactonisation and global deprotection

The first batch of hexaenoate **182** prepared in this way was then taken through the final saponification–macrolactonisation–deprotection sequence (**Scheme 83**). However, significant decomposition of the seco-acid **222** was observed by TLC analysis, and LC-MS analysis of the crude material showed some bahamaolide along with several presumed decomposition/side products and so the reaction was abandoned.

Reported issues with the polyene moiety have already been discussed (*vide supra*), in particular, both Mori and Evans stated that the roxaticin seco-ester/seco-acid was unstable and light-sensitive, leading to both isomerisation and decomposition.[95,109] These concerns prompted an in-depth review of all the literature syntheses that employ this 3-step sequence as the endgame steps to an oxopolyene macrolide (**Table 14**).

Following Sammakia's experimental procedure—which had been successful in affording the macrocyclic hexaenoate dermostatin A[111]—involved carrying out the saponification of **182** and work-up on day 1; the mixed anhydride reaction mixture was left stirring overnight, then filtered on day 2 and added slowly to DMAP (over 6 hours in Sammakia's procedure, which translated to an addition rate of 0.16 ml/h for this reaction on 3 µmol scale) then the macrolactonisation reaction mixture was stirred overnight at ambient temperature. On day 3 the reaction mixture was concentrated under reduced pressure and rapidly purified by column chromatography using 25% ethyl acetate in hexane as eluent. Protected bahamaolide **(224**) was then treated with HCl in methanol; the deprotection was monitored by LC-MS and usually neutralised with polymer-bound piperidine and filtered on day 4.

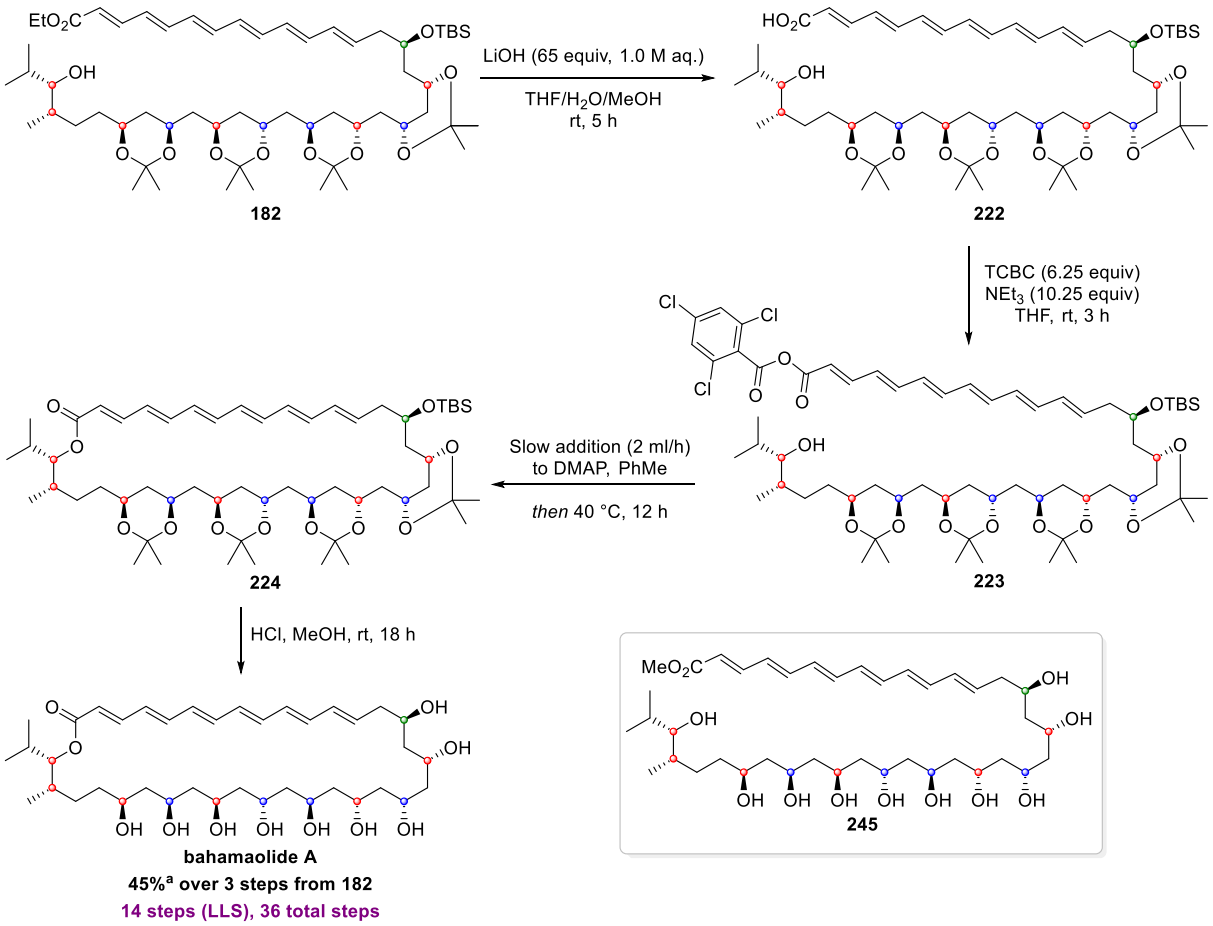
	Dermostatin A[111] Sammakia, 2011	**RK-397**[74] Sammakia, 2006	**Roxaticin**[86] Krische, 2010	**Roxaticin**[109] Evans, 2003	**Roxaticin**[95] Mori, 1995	**RK-397**[110] Denmark, 2005
Saponification 4:1:1 THF/H_2O/MeOH rt	LiOH (65 equiv) 5 h Aq. work-up, filter through Celite®	LiOH (50 equiv) 22 h Aq. work-up, filter through Celite®	LiOH (5.0 equiv) 6 h Aq. work-up	LiOH (50 equiv) 24 h Aq. work-up	LiOH (5.0 equiv) 8 h Aq. work-up	LiOH (70 equiv) 16 h Aq. work-up
Mixed anhydride All in THF, rt	Et_3N (10 equiv) TCBC (7.0 equiv) 15 h Filter through Celite®	Et_3N (10 equiv) TCBC (5.0 equiv) 3 h Filter through Celite®	Et_3N (2.0 equiv) TCBC (1.5 equiv) 3 h Filter through Celite®	Et_3N (10.25 equiv) TCBC (6.25 equiv) 45 min Filter through Celite®	Et_3N (2.0 equiv) TCBC (1.5 equiv) 2 h (not isolated – dilute with PhMe)	Et_3N (10 equiv) TCBC (7 equiv) 1 h Filter through Celite®
Macrolactonisation Add mixed anhydride in toluene (0.001-0.002 M) to DMAP in toluene	Addition 2 ml/h DMAP (20 equiv) rt, 12 h Rapid flash chromatography on silica gel (3:1 hexanes/EtOAc)	Addition 2 ml/h DMAP (20 equiv) rt, 5 h Dilute with 1:1 hexane:EtOAc, filter through silica plug over a pad of Celite®, wash with 1:1 hexane:EtOAc	Addition 1.25 ml/h DMAP (4 equiv) 50 °C, 4 h Dilute with 1:1 hexane:EtOAc, filter through silica plug over a pad of Celite®, wash with 1:1 hexane:EtOAc	Addition 2.8 ml/h DMAP (0.5 equiv) rt, 30 min Aq. work-up then "rapid chromatography (10% EtOAc in hexanes) to remove the DMAP and using the combined eluent"	Addition 2 ml/h DMAP (40 equiv) reflux, 1 h Directly column toluene solution, eluting with 1:1 hexane:EtOAc, then preparative TLC	Addition 6.25 ml/h DMAP (17.5 equiv) rt, 12 h Aq. work-up Column 20% EtOAc in hexane
Global deprotection All in MeOH, rt	HCl (60 equiv) 12 h, then neutralise with polymer-bound piperidine *(No TBS but PMB)*	HCl (100 equiv) 24 h, then neutralise with polymer-bound piperidine *(TBS and PMB)*	Dowex 50Wx8 *(no TBS, only TES)*	1 crystal PPTS 1.5 h, aq. work-up *(one TBS, cyclopentylidene ketals)*	Dowex 50Wx8 *(no TBS)*	HCl (60 equiv) 5 h, then neutralise with polymer-bound piperidine *(No TBS)*

Table 14 Comparison of literature conditions for saponification, Yamaguchi macrolactonisation and deprotection to afford a synthetic oxopolyene macrolide.

After careful consideration of the literature procedures summarised in **Table 14**, a few points were identified which could be expedited and so hopefully minimise any opportunity for decomposition or isomerisation, in particular of the unstable seco-acid; specifically, making the mixed anhydride, which in Evans' case only needed 45 minutes, and the addition rate to DMAP, where 2 ml/h appeared to be most common. It was envisaged that with a few modifications, the 3-step sequence could instead take only 48 hours. In addition to changing the timing, it was decided to follow Evans' procedure more closely (4 mg, 4 μmol scale) instead of Sammakia's, *i.e.* the addition of lithium hydroxide as an aqueous solution, and triethylamine and 2,4,6-trichlorobenzoyl chloride (TCBC) as stock solutions in THF.[109]

Saponification was monitored by TLC analysis and appeared complete after 2 hours at ambient temperature. Following the usual work-up, the crude seco-acid was treated with stock solutions of triethylamine and then 2,4,6-trichlorobenzoyl chloride in THF and stirred at ambient temperature for 1 hour before filtering through Celite®, pre-washed with anhydrous THF. Mixed anhydride **223** was concentrated under reduced pressure and re-dissolved in anhydrous toluene for subsequent addition at 2 ml/h to DMAP in toluene, then the reaction mixture stirred overnight at ambient temperature (end of day 1). On day 2, the macrolactonisation reaction mixture was concentrated followed by rapid column chromatography and the protected macrocycle **224** was treated with HCl in methanol, stirring at ambient temperature for a further 24 hours. TLC analysis suggested the macrocyclisation had not gone to completion and this was confirmed by the presence of another peak by LC-MS analysis after the deprotection step with a mass corresponding to the open chain methyl ester **245** (further corroborated by ^{1}H NMR analysis following isolation by reverse phase preparative HPLC).

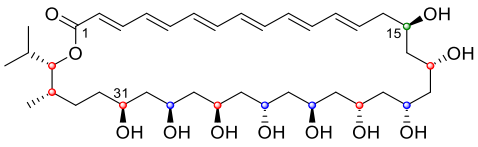
The final optimised conditions for the saponification–Yamaguchi macrolactonisation–deprotection steps are as shown in **Scheme 92**. The time for saponification and formation of the Yamaguchi mixed anhydride was extended slightly to ensure full conversion of starting material and once the addition to DMAP was complete, the reaction mixture was heated at 40 °C overnight. On day 2, the crude material from the macrolactonisation was filtered through a plug of silica on top of a pad of Celite®, washing with 1:1 hexane:ethyl acetate and the combined effluent was concentrated and then treated with HCl in methanol. LC-MS analysis of the reaction mixture on day 3 showed a clear major peak for bahamaolide, now with no peak for the undesired product **245**.



Scheme 92 Optimised saponification–Yamaguchi macrolactonisation–global deprotection reaction sequence. [a] NMR yield using dimethoxymethane as internal standard.

The last challenge remaining to complete the project was to isolate an analytically pure sample of bahamaolide A by reverse phase preparative HPLC. Progress was significantly hindered by ongoing problems with the reverse phase preparative HPLC instrument available at the time, but ultimately it was found that an analytically pure sample of synthetic bahamaolide A could be obtained using the previously optimised conditions (38% MeCN in H_2O, 2 ml/min, 50 × 10.0 mm C18 column, see experimental section for details). It was important to exclude any acid additives as when the solvent system contained 0.05% formic acid, considerable isomerisation of the polyene was observed by ^{1}H NMR analysis.

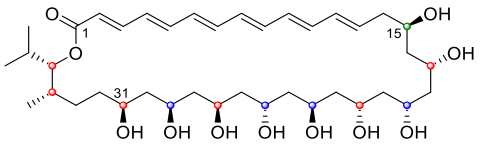
Analytical data for synthetic bahamaolide A was shown to match that reported for the isolated natural product[65]: HRMS (APCI), ^{1}H and ^{13}C chemical shifts in CD_3OD (**Table 15**) and pyridine-d_5 (**Table 16**), and optical rotation.



bahamaolide A

	Isolated[65] (900 MHz)			**Synthetic** (700 MHz)				
	δ_C, type	δ_H	Multiplet (*J* in Hz)	δ_C	Δ	δ_H	Δ	Multiplet (*J* in Hz)
1	169.9, C							
2	121.8, CH	5.95	d (15.0)	121.5	**−0.3**	5.97	**−0.02**	d (15.1)
3	147.7, CH	7.39	dd (15.0, 11.5)	147.7	**0.0**	7.39	**0.00**	dd (15.1, 11.4)
4	131.5, CH	6.47	dd (14.5, 11.5)	131.4	**−0.1**	6.47	**0.00**	*overlapping m*
5	143.9, CH	6.77	dd (14.5, 11.5)	143.8	**−0.1**	6.76	**−0.01**	dd (14.7, 11.1)
6	134.3, CH	6.42	dd (14.5, 11.5)	134.2	**−0.1**	6.38	**−0.04**	*overlapping m*
7	140.2, CH	6.59	dd (14.5, 10.5)	140.1	**−0.1**	6.58	**−0.01**	dd (14.8, 11.0)
8	138.2, CH	6.47	dd (14.5, 10.5)	138.0	**−0.2**	6.46	**−0.01**	*overlapping m*
9	133.5, CH	6.37	dd (15.0, 11.0)	133.5	**0.0**	6.42	**−0.05**	*overlapping m*
10	133.5, CH	6.31	dd (15.0, 11.0)	133.3	**−0.2**	6.30	**−0.01**	dd (15.0, 10.6)
11	136.7, CH	6.38	dd (15.0, 10.5)	136.6	**−0.1**	6.37	**−0.01**	*overlapping m*
12	135.4, CH	6.24	dd (15.0, 10.5)	135.4	**0.0**	6.24	**0.00**	dd (15.3, 10.4)
13	133.5, CH	5.92	m	133.3	**−0.2**	5.91	**−0.01**	m

Table 15 Partial ^{1}H and ^{13}C NMR data for the polyene region of bahamaolide A in CD_3OD. δ for isolated bahamaolide A taken from Table S1 in ref. 65, δ for synthetic bahamaolide A extracted from HSQC (included in section **6.5**).



bahamaolide A

	Isolated[65] (800 MHz)			**Synthetic** (700 MHz)				
	δ_C, type	δ_H	Multiplet (*J* in Hz)	δ_C	Δ	δ_H	Δ	Multiplet (*J* in Hz)
1	168.0, C			167.8	**−0.2**			
2	121.2, CH	6.12	d (15.0)	120.9	**−0.3**	6.14	**+0.02**	d (15.1)
3	146.0, CH	7.63	dd (15.0, 11.5)	145.7	**−0.3**	7.63	**0.00**	dd (15.1, 11.5)
4	130.3, CH	6.46	m	130.0	**−0.3**	6.47	**+0.01**	m
5	142.2, CH	6.68	dd (14.5, 11.5)	142.0	**−0.2**	6.69	**+0.01**	dd (14.8, 11.3)
6	132.3, CH	6.38	m	132.1	**−0.2**	6.40	**+0.02**	m
7	138.8, CH	6.54	dd (14.5, 11.5)	138.6	**−0.2**	6.55	**+0.01**	dd (14.7, 11.1)
8	132.9, CH	6.37	m	132.6	**−0.3**	6.38	**+0.01**	m
9	137.1, CH	6.47	m	136.8	**−0.3**	6.48	**+0.01**	m
10	131.9, CH	6.31	m	131.6	**−0.3**	6.34	**+0.03**	m
11	135.8, CH	6.32	m	135.5	**−0.3**	6.34	**+0.02**	m
12	133.6, CH	6.32	m	133.3	**−0.3**	6.33	**+0.01**	m
13	133.9, CH	6.18	m	133.6	**−0.3**	6.18	**0.00**	m
14	42.4, CH_2	2.75	m	42.1	**−0.3**	2.75	**0.00**	m
		2.60	m			2.60	**0.00**	m
15	69.1, CH	4.52	m	68.8	**−0.3**	4.52	**0.00**	m
16	44.4, CH_2	2.13	m	43.9	**−0.5**	2.13	**0.00**	m
		2.10	m			2.10	**0.00**	m
17	67.2, CH	4.70	m	66.9	**−0.3**	4.72	**+0.02**	m
18	47.6, CH_2	2.25	m	47.3	**−0.3**	2.26	**+0.01**	m
		2.01	m			2.04	**+0.03**	m
19	70.7, CH	4.52	m	70.4	**−0.3**	4.52	**0.00**	m
20	45.8, CH_2	1.93	m	45.5	**−0.3**	1.94	**+0.01**	m
21	69.5, CH	4.79	m	69.1	**−0.4**	4.80	**+0.01**	m
22	47.7, CH_2	1.88	m	47.4	**−0.3**	1.88	**0.00**	m

		1.82	m			1.83	**+0.01**	m
23	65.0, CH	5.07	m	64.7	**−0.3**	5.08	**+0.01**	m
24	48.3, CH_2	1.84	m	48.0	**−0.3**	1.89	**+0.05**	m
		1.76	m			1.80	**+0.04**	m
25	65.0, CH	5.04	m	64.7	**−0.3**	5.05	**+0.01**	m
26	48.0, CH_2	1.80	m	47.6	**−0.4**	1.82	**+0.02**	m
27	69.7, CH	4.74	m	69.4	**−0.3**	4.75	**+0.01**	m
28	46.1, CH_2	1.94	br d (14.0)	45.8	**−0.3**	1.96	**+0.02**	m
		1.59	m			1.61	**+0.02**	m
29	74.3, CH	4.41	m	74.0	**−0.3**	4.42	**+0.01**	m
30	44.2, CH_2	1.86	m	43.9	**−0.3**	1.84	**−0.02**	m
		1.83	m			1.77	**−0.06**	m
31	73.3, CH	4.03	m	73.0	**−0.3**	4.05	**+0.02**	m
32	36.4, CH_2	1.97	m	36.2	**−0.2**	2.00	**+0.03**	m
		1.76	m			1.78	**+0.02**	m
33	30.9, CH_2	1.31	m	30.7	**−0.2**	1.33	**+0.02**	m
		1.26	m			-	**-**	m
34	34.9, CH	1.75	m	34.6	**−0.3**	1.76	**+0.01**	m
35	79.3, CH	5.08	br d (9.5)	79.1	**−0.2**	5.08	**0.00**	d (10.0)
36	30.2, CH	1.88	m	29.9	**−0.3**	1.91	**+0.03**	m
37	20.6, CH_3	0.96	d (6.5)	20.3	**−0.3**	0.96	**0.00**	d (6.7)
38	19.0, CH_3	0.78	d (6.5)	18.8	**−0.2**	0.80	**+0.02**	d (6.8)
39	14.9, CH_3	0.96	d (6.5)	14.6	**−0.3**	0.96	**0.00**	d (6.7)

Table 16 ^{1}H and ^{13}C NMR data for bahamaolide A in pyridine-d_5. δ for isolated bahamaolide A taken from table 1 in ref. 65, δ for synthetic bahamaolide A extracted from HSQC, or HMBC (C1), referenced to pyridine-d_5, (included in section **6.5**).

4 Towards the Total Synthesis of Mycapolyol E

Where indicated (DF), these results were obtained by Dr Daniele Fiorito who joined the project part-time in August 2021 with the aim of further optimising the synthesis of fragment 1 (**274**, section **4.2.2.2**) and the lithiation–borylation of **303** (section **4.5.3.5**) while I finished synthetic work on bahamaolide A (chapter **3**).

4.1 Introduction to Mycapolyol E: Structural Determination and Retrosynthetic Analysis

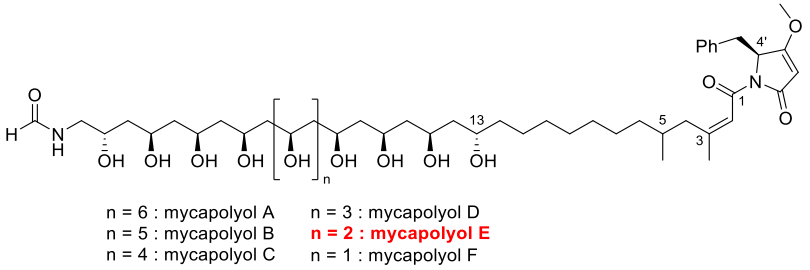


Figure 20 Mycapolyols A-F, reported in 2005 by Fusetani and co-workers.

Mycapolyol E (**Figure 20**) is one of a family of six unusual polyketide synthase metabolites isolated from the marine sponge *Mycale izuensis*, collected in the Amakusa Islands 1700 km southwest of Tokyo.[68] After a lipophilic extract of this sponge showed cytotoxicity, bio-assay directed fractionation was used to identify the mycapolyols which exhibit cytotoxicity against HeLa cells (mycapolyol E IC_{50} 0.425 μM). Although mycapolyols A-F were isolated and reported in 2005, there are no reported syntheses of any mycapolyols in the literature to date.

The mycapolyols have an extended 1,3-polyol unit, comprising 9-14 stereodefined contiguous but skipped hydroxyl groups, a terminal formamide at the western end and a 4-methoxypyrrolidone unit at the eastern end. The molecular formula was elucidated using HRMS and a UV absorption at 250 nm was attributed to an α,β-unsaturated amide. 2D NMR experiments were used to assign the rest of the reported structure. In addition to HMBC correlations, the tetramic acid (2,4-pyrrolidinedione) derived headgroup was identified by comparison of NMR data with the dolapyrrolidinone unit in dolastatin 15 (**Figure 21**).

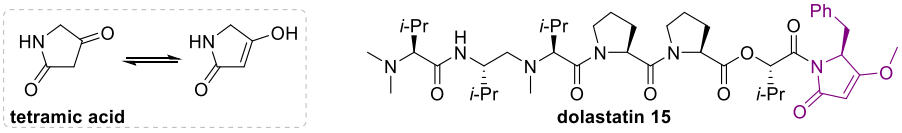
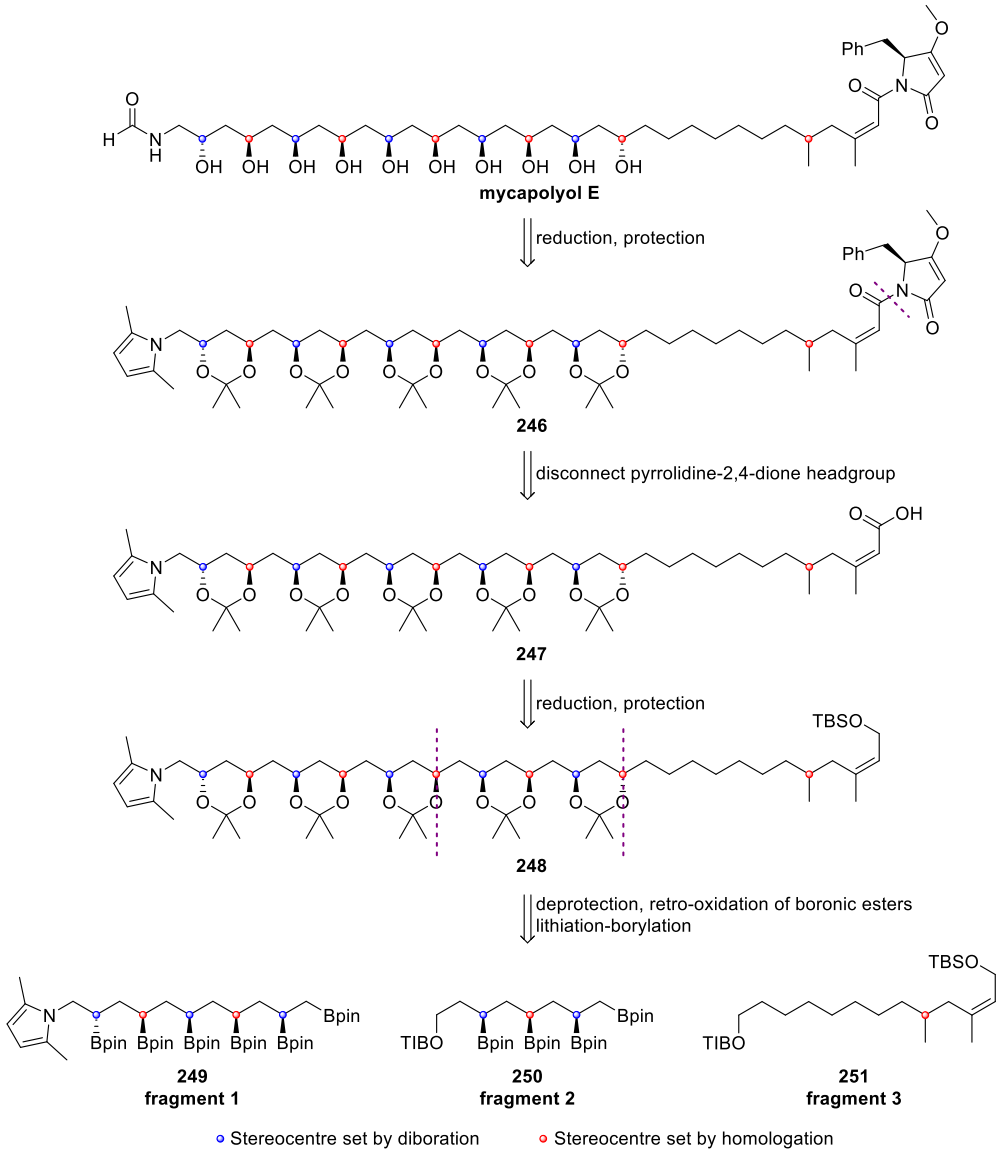


Figure 21 General tetramic acid structure and highlighted in dolastatin 15.

L-Phenylalanine was detected during degradation studies of mycapolyol B,[158] which implied the 4' *S* configuration. The *Z* alkene geometry was assigned based on the chemical shift of the methyl substituent at C3 (δ_C 25.3 ppm). The relative stereochemistry of the 1,3-polyol domain was assigned using Kishi's ^{13}C NMR database for the 1,3,5-polyol system[67] (*vide supra*, section **2.1**) but its absolute configuration is unknown. It should also be noted that there is one unassigned stereocentre in the mycapolyols' structure, at C5, presumably since this is remote from the other stereocentres, although the isolation team did not comment on this. Having determined the structure of mycapolyol B in this way, Fusetani and co-workers assigned the structures of the rest of the mycapolyols by analogy with mycapolyol B, owing to their very similar ^{1}H and ^{13}C NMR spectra.

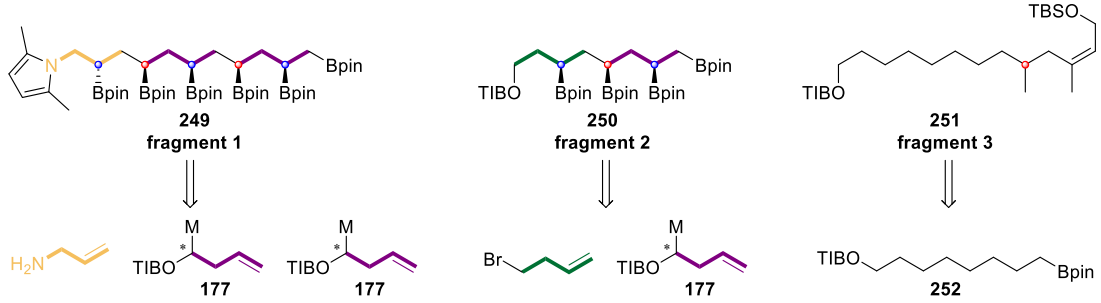
The key synthetic challenge in mycapolyol E is the extended 1,3-polyol unit, comprising 10 hydroxylated stereocentres. Since the 1,3-polyol is not C_2-symmetric (unlike in bahamaolide A), the synthetic approach using iterative diboration and homologation with a butenyl carbenoid would need to be applied in a unidirectional manner. The stereochemistry at each hydroxylated centre is essentially 'dialled in' through the choice of chiral ligand for the diboration, and by selecting the correct optical isomer of enantiopure α-sulfinyl benzoate for the homologation. Therefore, if the current synthesis revealed that the absolute configuration of mycapolyol E was not that proposed by Fusetani and co-workers,[68] the synthetic sequence could be tuned to access other diastereoisomers.

The first step of the retrosynthetic analysis involved protection of the 1,3-polyol and retro(reduction) of the terminal formamide to a primary amine which would be protected as a pyrrole moiety (**246**, **Scheme 93**). The pyrrole moiety can be installed through a Paal-Knorr reaction between a primary amine and acetonyl acetone, and deprotected using mild aqueous acid. A pyrrole moiety has previously been used as a protecting group for a primary amine undergoing lithiation–borylation reactions.[48] Disconnecting the dolapyrrolidinone headgroup exposed α,β-unsaturated carboxylic acid **247**. Retro(reduction) of carboxylic acid **247** and silyl protection of the primary alcohol revealed advanced intermediate **248** which was further disconnected using retro(lithiation–borylation) reactions into fragments 1, 2 and 3 (**249**, **250**, **251**, **Scheme 93**).



Scheme 93 Retrosynthetic analysis of mycapolyol E.

Fragments 1 and 2, which contain the entire 1,3-polyol domain, will be prepared from simple terminal alkenes, allylamine and 4-bromobut-2-ene, respectively, using the iterative diboration–homologation protocol (**Scheme 94**). Stereospecific boronic ester homologation and transformation will also be used to synthesise fragment 3 from a simple primary boronic ester.



Scheme 94 Building blocks approach to fragments 1, 2 and 3.

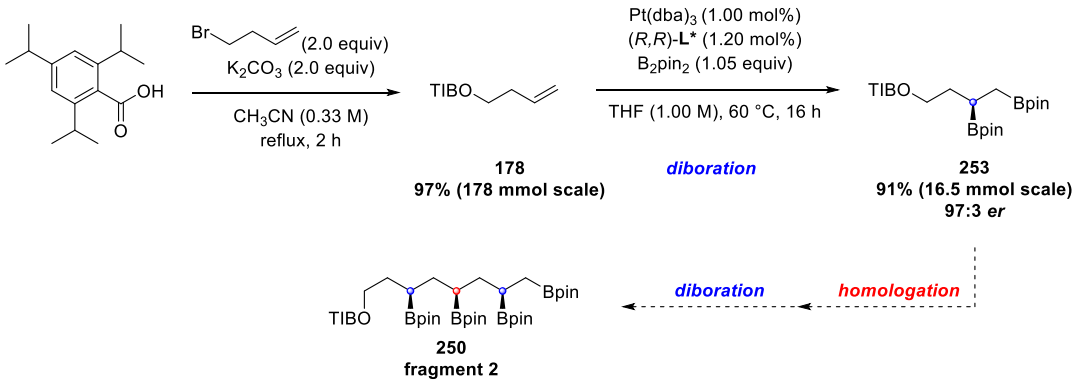
4.2 Synthesis of Fragments 1 and 2 by Iterative Diboration and Homologation Reactions

The proposed synthesis of mycapolyol E employed a modular approach; fragments 1, 2 and 3 were prepared separately then coupled together using lithiation–borylation reactions. The merging of catalyst-controlled diboration of a terminal alkene using Morken's conditions[50] and reagent-controlled primary-selective homologation of the resulting enantioenriched 1,2-bis(boronic ester) was applied iteratively using homoallylic α-sulfinyl benzoate ***ent*-67** to extend the carbon chain of fragments 1 and 2 (see **Scheme 66** for its synthesis).

4.2.1 Synthesis of fragment 2 (250)

The central fragment **250** can be considered as a bifunctional, linchpin reagent since it contains both a triisopropylbenzoate leaving group and a primary boronic ester for orthogonal homologation at both termini through lithiation–borylation reactions.

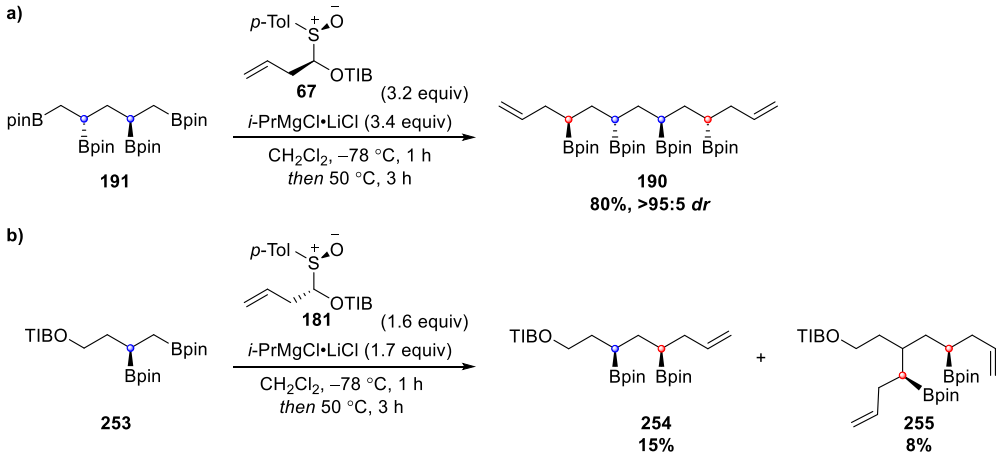
4-Bromobut-1-ene was converted in almost quantitative yield to benzoate **178** which was then subjected to a three-step iterative diboration–homologation–diboration sequence (**Scheme 95**). This commenced with Morken enantioselective diboration of alkene **178** using (*R*,*R*)-**L*** which yielded 1,2-bis(boronic ester) **253** as a viscous yellow oil in 91% yield and 97:3 *er* (*er* determined by chiral HPLC analysis of the corresponding diol).



Scheme 95 Esterification and diboration to access 1,2-bis(boronic ester) **253**. A portion of **253** was oxidised to the corresponding diol to determine the *er* by chiral HPLC analysis.
L*: 3,5-diisopropylphenyltaddol-PPh, structure shown in **Scheme 25**.

The conditions for the first homologation reaction of **253** were adapted from those used for the double homologation of tetra(boronic ester) **191** in the synthesis of bahamaolide A (**Scheme 96**).[142] Desired product **254** was isolated in 15% yield, along with double homologation product **255** in 8% yield and recovered boronic ester starting material **253** in 77% yield. ^{11}B NMR analysis showed very little boronate formation (7 ppm) after 1 hour at

−78 °C (**Figure 22**). Poor conversion and difficult separation of 1,2-bis(boronic ester) **253** and homologated product **254** prompted an optimisation campaign with the aim of improving conversion of 1,2-bis(boronic ester) **253** to ease purification.



Scheme 96 a) Double homologation of tetra(boronic ester) **191**; b) Initial conditions trialled for homologation of **253.**

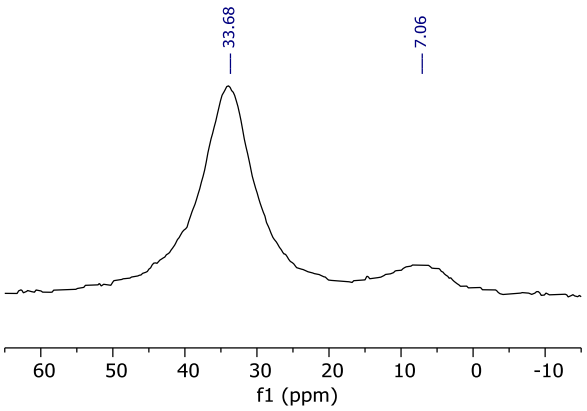


Figure 22 ^{11}B NMR (96 MHz) spectrum for the reaction shown in **Scheme 96** b after 1 h at −78 °C. Boronic ester(s) typically ~30-35 ppm, boronate complex ~5-8 ppm.

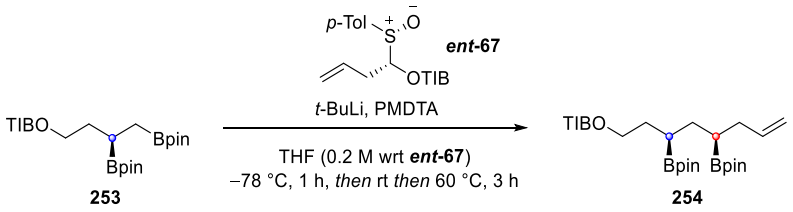
Since both starting materials, 1,2-bis(boronic ester) **253** and α-sulfinyl benzoate **181**, were viscous oils, the reaction was repeated using stock solutions in dichloromethane with similar results. NMR analysis showed that the starting materials had not degraded. It was decided at this point to switch to the *syn* diastereomer of the α-sulfinyl benzoate, ***ent*-67**, prepared using (−)-sparteine and (−)-Andersen's sulfinate, which is a solid, and therefore easier to dry and handle.

TLC analysis determined that a considerable amount of α-sulfinyl benzoate ***ent*-67** was present in the crude reaction mixture. This was surprising as the sulfoxide-metal exchange was expected to be rapid, and therefore there should be complete magnesiation. ^{11}B NMR

analysis (**Figure 22**) showed only a small amount of boronate formation which suggested that the problem was either metalation of the α-sulfinyl benzoate or borylation. The synthesis of fragment 2 (**250**) described in the rest of this section was carried out prior to the discovery on the bahamaolide project that magnesiated carbenoids do not react with boronic esters at temperatures below −40 °C (section **3.4**).

To check the metalation of α-sulfinyl benzoate ***ent*-67**, a magnesiation–protonation experiment was conducted. TLC analysis showed remaining ***ent*-67** when quenched with methanol after 30 min or 1 hour at −78 °C, indicative of incomplete metalation with *i*-PrMgCl·LiCl, and so it was decided to move to homologation conditions using *t*-BuLi to generate the more reactive lithiated carbenoid; the homologation of 1,2-bis(boronic esters) with lithiated carbenoids had been previously reported (*vide supra*, section **1.6**).[48,52] PMDTA, a sterically bulky tridentate ligand, was also included in order to promote selectivity for the primary boronic ester, given that diamine-free lithiated carbenoids can also undergo borylation with secondary boronic esters (*vide supra*, **Scheme 26**).[52]

The conditions for the first homologation reaction with a lithiated carbenoid (**Table 17**, entry 1) were adapted from the double homologation of tetra(boronic ester) **191** for polyfunctionalisation studies.[142] Gratifyingly, the desired homologated product was the major spot by TLC analysis, with very little over-homologation, showing the PMDTA-ligated lithiated carbenoid was sufficiently hindered to give good selectivity for the primary boronic ester under the described reaction conditions. In addition the ^{11}B NMR spectrum looked more promising using these conditions (**Figure 23** a shows much more boronate complex than in **Figure 22**) and so it was decided to continue the optimisation by simply increasing equivalents of *t*-BuLi and α-sulfinyl benzoate ***ent*-67** (**Table 17**, entries 2-5).



Entry	*ent*-67 /equiv	*t*-BuLi /equiv	PMDTA /equiv	NMR yield 254 /%	Remaining boronic ester 253 by TLC analysis of crude mixture?
1	1.2	1.56	1.56	54	Yes
2	1.25	1.63	1.63	50	Yes
3	1.3	1.69	1.69	62	Yes
4	1.4	1.82	1.82	72	Yes (fainter spot)
5	1.5	1.95	1.95	75	trace
6	1.5	1.95	1.95	38[a]	No
7	1.5	1.95	1.95	63[b]	No

Table 17 Homologation optimisation (fragment 2). Entries 1-5 on 0.05 mmol scale, NMR yields were determined using 1,3,5-trimethoxybenzene as an internal standard. [a] Isolated yield following manual column chromatographic purification, reaction on 1.4 mmol scale. [b] Isolated yield following chromatographic purification on a Biotage Isolera One system, reaction on 1.8 mmol scale. wrt: with respect to.

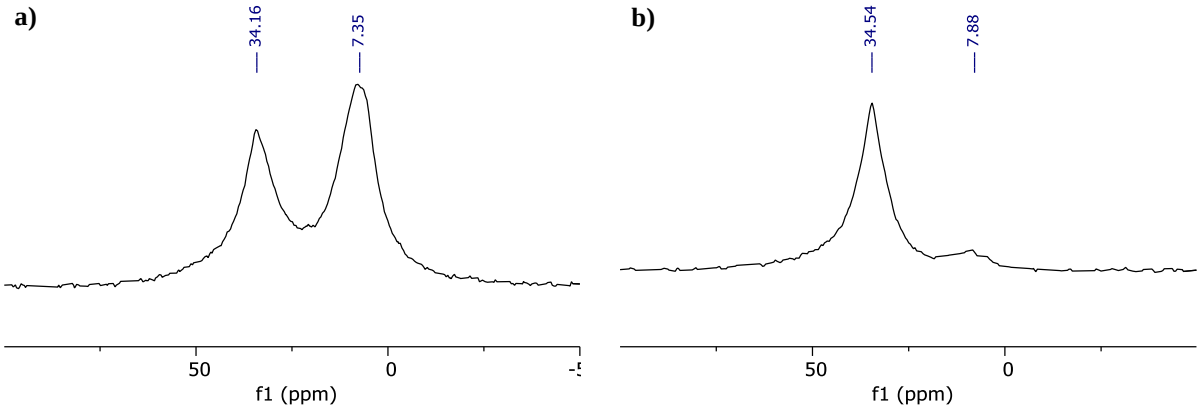
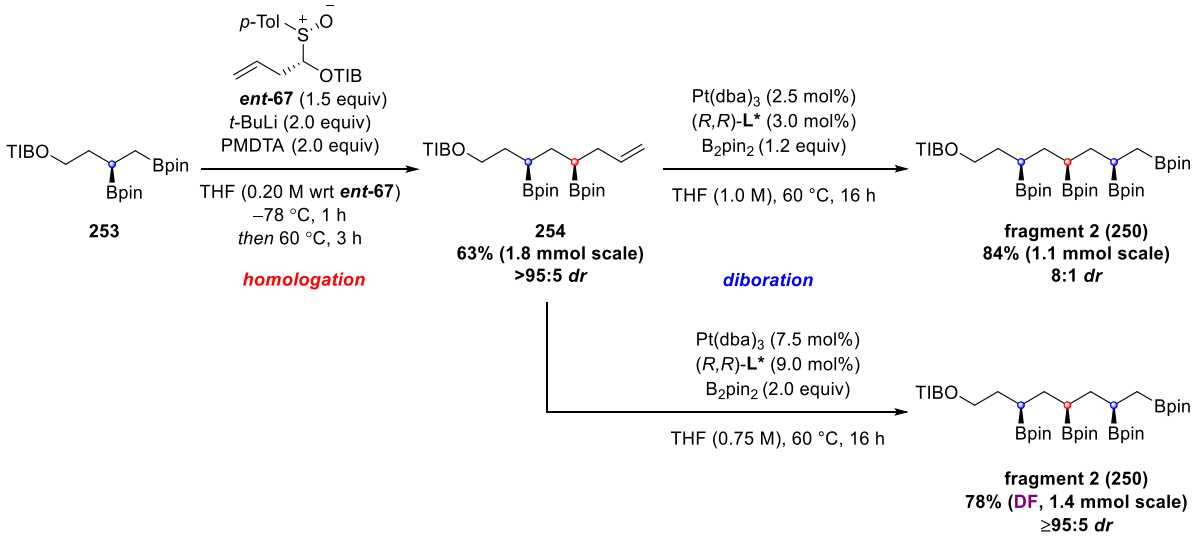


Figure 23 ^{11}B NMR (96 MHz) spectra of entry 1, **Table 17** a) after 1 h at −78 °C, b) after 3 h migration at 60 °C.

When the reaction was scaled-up using the optimised homologation conditions (entry 6, **Table 17**), the homologated product **254** could be isolated in 38% yield, yet the NMR yield with these conditions was 75%. This discrepancy was clarified by 2D TLC analysis which showed that **254** is unstable on silica gel, as has been the case with other homoallylic boronic esters (see product **190** in section **3.3**). Previously, the product had been purified using by manual column chromatography with high silica loading (100:1) and an isocratic eluent system (93:7 pentane:diethyl ether), which allowed homoallylic benzoate by-product **178**, then over-homologation product **255**, then desired product **254** and finally unreacted

1,2-bis(boronic ester) **253** to be isolated. Instead, now with little remaining boronic ester starting material, the crude mixture was separated on a Biotage Isolera One system which enabled purification with a higher flow rate and lower silica loading to afford product **254** in 63% isolated yield (entry 7, **Table 17**).

The final step in the synthesis of fragment 2 (**250**) was a catalyst-controlled diboration, using (*R*,*R*)-**L***, which proceeded to give tetra(boronic ester) **250** in high yield (**Scheme 97**).



Scheme 97 1,2-bis(boronic ester) **253** was transformed to fragment 2 (**250**) in 2 steps. The *dr* of fragment 2 (**250**) was determined by NMR analysis, see **Figure 24**.

The initial conditions afforded fragment 2 (**250**) in approximately 8:1 *dr* by NMR analysis (**Figure 24**). However, when bringing more material through for fragment couplings, Dr Fiorito proposed that increasing the pre-catalyst loading (from 2.5 to 7.5 mol%) for the diboration of **254** could be beneficial, and fragment 2 (**250**) was isolated in excellent *dr* by NMR analysis after chromatographic purification on a Biotage Isolera One system, which allowed separation of a more non-polar minor diastereomer. In this way, fragment 2 (**250**) has been prepared in 4 steps from 2,4,6-triisopropylbenzoic acid, in high *dr* (≥95:5) and 43% overall yield.

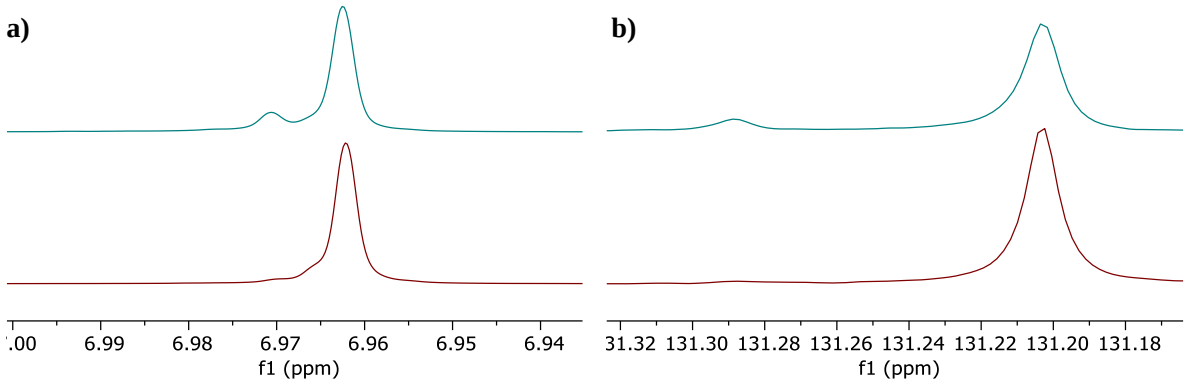
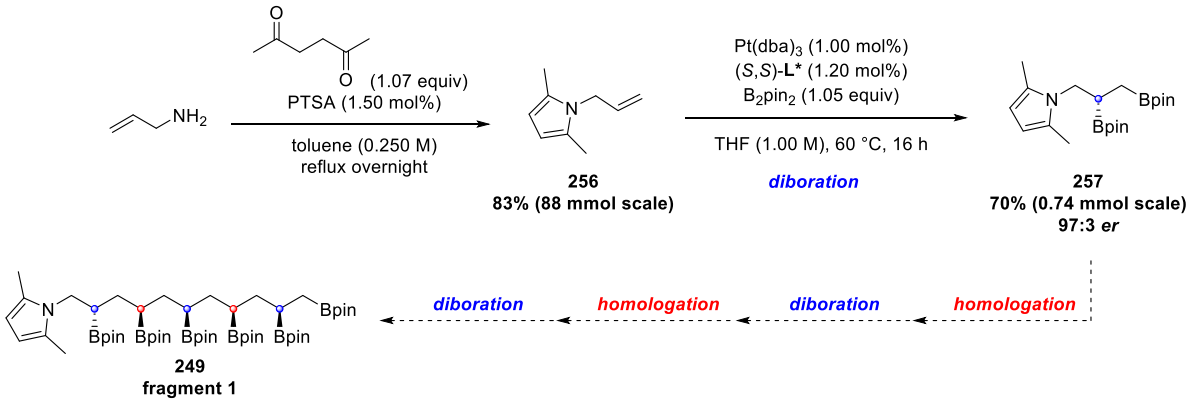


Figure 24 a) ^{1}H NMR (500 MHz, $CDCl_3$) CH_2OTIB and b) ^{13}C NMR (126 MHz, $CDCl_3$) CO *ipso* OTIB. Trace in teal for fragment 2 (**250**) with 8:1 *dr* prepared using original conditions; trace in red for fragment 2 with ≥95:5 *dr* prepared with increased pre-catalyst loading and after Biotage purification (DF).

4.2.2 Synthesis of fragment 1 (249)

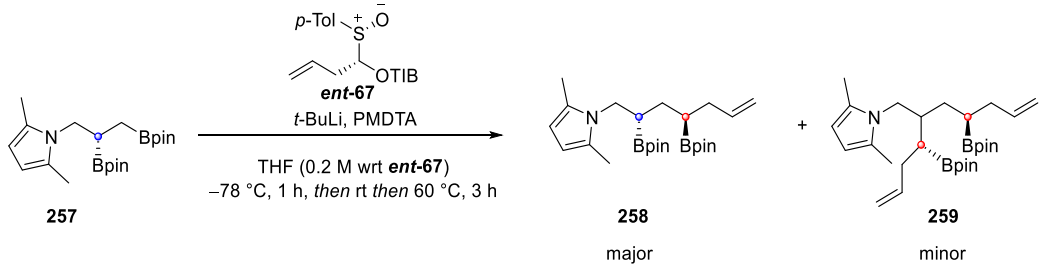
A similar strategy of iterative catalyst-controlled diboration and reagent-controlled homologation of each resulting primary boronic ester was employed to extend the carbon chain in fragment 1 (**249**). It was originally envisaged to use a pyrrole moiety as a protecting group for the primary amine in fragment 1 (**249**), which was constructed through a Paal-Knorr reaction between allylamine and acetonyl acetone, to give pyrrole **256** as a pale yellow liquid in 83% yield (**Scheme 98**).[159] This liquid turned dark red/brown when exposed to light and some decomposition could be seen by both TLC and NMR analysis. As a precaution all pyrrole-containing fragments were stored at −20 °C and exposure to light kept to a minimum.

With pyrrole **256** in hand, the terminal alkene was subjected to asymmetric diboration using (*S*,*S*)-**L*** to afford 1,2-bis(boronic ester) **257** in 70% yield and 97:3 *er* (determined by chiral HPLC analysis of the corresponding diol, **Scheme 98**).



Scheme 98 Synthesis of 1,2-bis(boronic ester) **257.** An aliquot of **257** was oxidised to the corresponding diol in order to determine the enantiomeric ratio by chiral HPLC analysis.

The next step in the synthesis of fragment 1 was a homologation reaction using homoallylic α-sulfinyl benzoate ***ent*-67**, which required a simple optimisation campaign to maximise consumption of starting material **257** and formation of product **258** (**Table 18**), performed concurrently with that for the corresponding reaction for fragment 2 (**Table 17**).



Entry	*ent*-67 /equiv	*t*-BuLi /equiv	PMDTA /equiv	NMR yield 258 /%	NMR yield 259 /%	Remaining 257 by TLC analysis of crude mixture?
1	1.20	1.56	1.56	62	13	Yes
2	1.25	1.63	1.63	59	13	Yes
3	1.30	1.69	1.69	74	22	Yes
4	1.40	1.82	1.82	73	10	Yes (fainter spot)
5	1.50	1.95	1.95	60	11	Yes (even fainter)
6	1.50	1.95	1.95	48[a]	n.r.	No

Table 18 Homologation optimisation (fragment 1). Entries 1-5 on 0.05 mmol scale, NMR yields were determined using 1,3,5-trimethoxybenzene as an internal standard. [a] Isolated yield, on 0.25 mmol scale. n.r. not recorded.

Again, the reaction was also monitored by ^{11}B NMR analysis (**Figure 25**). As starting material **257** is a 1,2-bis(boronic ester), it would be expected that the ^{11}B NMR spectrum after full boronate formation of the primary boronic ester should have 2 peaks of roughly equal intensity at around 34 ppm (the secondary boronic ester) and 7 ppm (the boronate complex). There appeared to be more boronate complex than boronic ester under these optimised conditions (**Figure 25** a), so this could perhaps be rectified by reducing the equivalents of *t*-BuLi slightly, since the extra ate complex presumably resulted from direct attack of the *t*-BuLi and so was non-productive. The expected ^{11}B NMR spectrum after 1,2-migration would be one peak for both boronic esters around 34 ppm, but there is some persistent boronate complex under these conditions (**Figure 25** b).

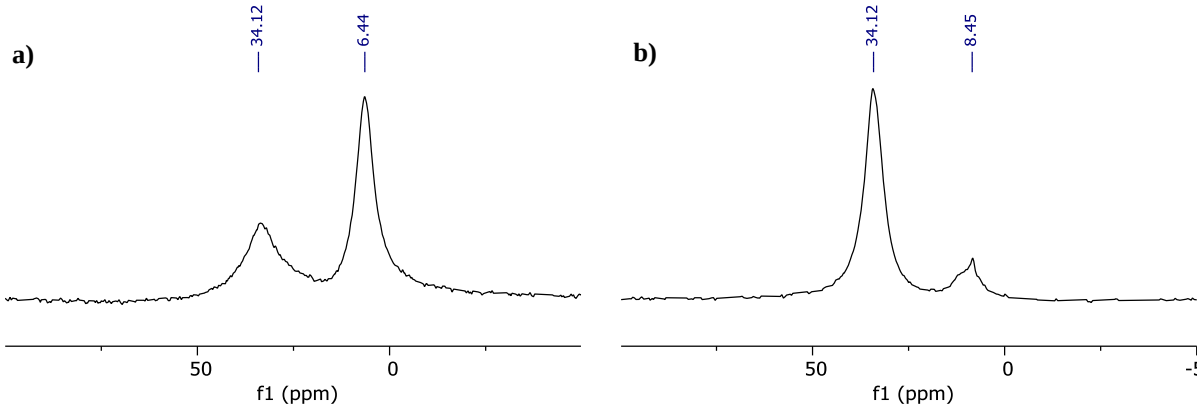
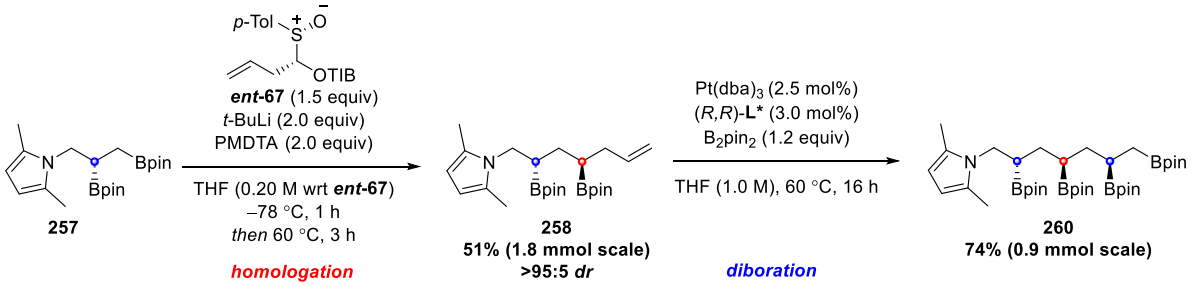


Figure 25 ^{11}B NMR (96 MHz) spectra for **Table 18**, entry 5, a) after 1 h at −78 °C, b) after 3 h migration at 60 °C.

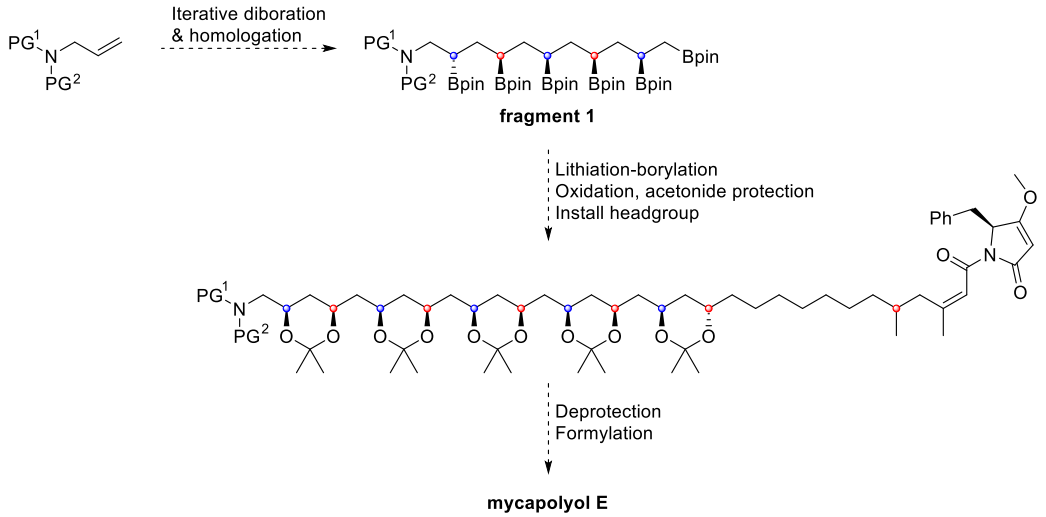
With 1,3-bis(boronic ester) **258** in hand, the terminal alkene was subjected to enantioselective diboration using (*R*,*R*)-**L*** to afford tetra(boronic ester) **260** in 74% yield and high *dr* by ^{13}C NMR analysis (**Scheme 99**). Another iteration of the homologation and diboration sequence would give the full fragment 1 (**249**), which was to be executed following successful investigations into the key fragment coupling step.



Scheme 99 Synthesis of tetra(boronic ester) **260** by homologation–diboration of 1,2-bis(boronic ester) **257**.

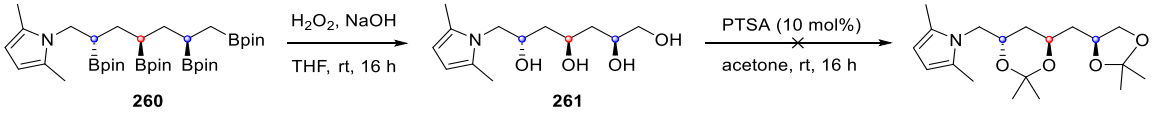
4.2.2.1 Protection/deprotection model studies

The retrosynthetic analysis of mycapolyol E shown in **Scheme 93** proposed retro(reduction) of the terminal formamide to a primary amine which would then need a suitable protecting group. 2,4-Dimethylpyrrole was originally proposed as the protecting group for the primary nitrogen in fragment 1 (**249**); this could be easily installed through a Paal Knorr reaction and it was stable to the homologation conditions (**Scheme 98**, **Table 18**). However it would also need to be stable to the acidic conditions for acetonide protection, as well as undergoing deprotection and formylation of the resulting terminal amine at a late stage (**Scheme 100**).



Scheme 100 Requirements for the nitrogen protecting group in the synthesis of mycapolyol E.

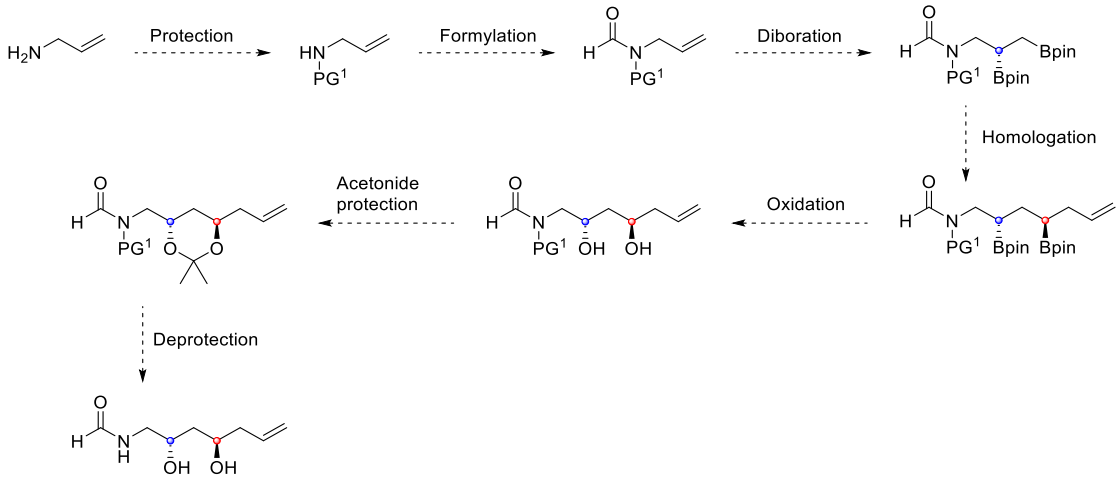
A portion of tetra(boronic ester) **260**—an intermediate in the synthesis of fragment 1 (**249**)—was oxidised to the corresponding tetraol **261** using basic hydrogen peroxide; full conversion was observed by TLC analysis (**Scheme 101**). Crude tetraol **261** was then subjected to the acetonide protection conditions used to successfully prepare bis(acetonide) **311** (*vide infra*, **Scheme 135**), however this resulted in non-specific decomposition by TLC and ^{1}H NMR analysis. Other catalytic acids and Lewis acids used in the literature for acetonide protections were screened, resulting in either decomposition (camphorsulfonic acid, pyridinium *p*-toluenesulfonate) or no reaction (Dowex 50 resin, iron trichloride). It was concerning that substrate decomposition occurred rather than simply acidic hydrolysis of the pyrrole group to give the deprotected amine and so it was necessary to re-evaluate the protection strategy.



Scheme 101 Oxidation and attempted acetonide protection of pyrrole-containing substrate **260**.

It was suggested that instead of using a protected amine which would need to be deprotected and formylated at the end of the synthesis, the formamide group could instead be carried through the synthesis, since it should be stable to strong base (*i.e.* BuLi) and mild acidic conditions (pyridinium *p*-toluenesulfonate or *p*-toluenesulfonic acid). Indeed, formylation has been used as a protection strategy for amino groups,[160] but no conversion to product was observed when direct diboration of *N*-allylformamide was attempted, indicating that a protecting group for the formamide group itself was required.

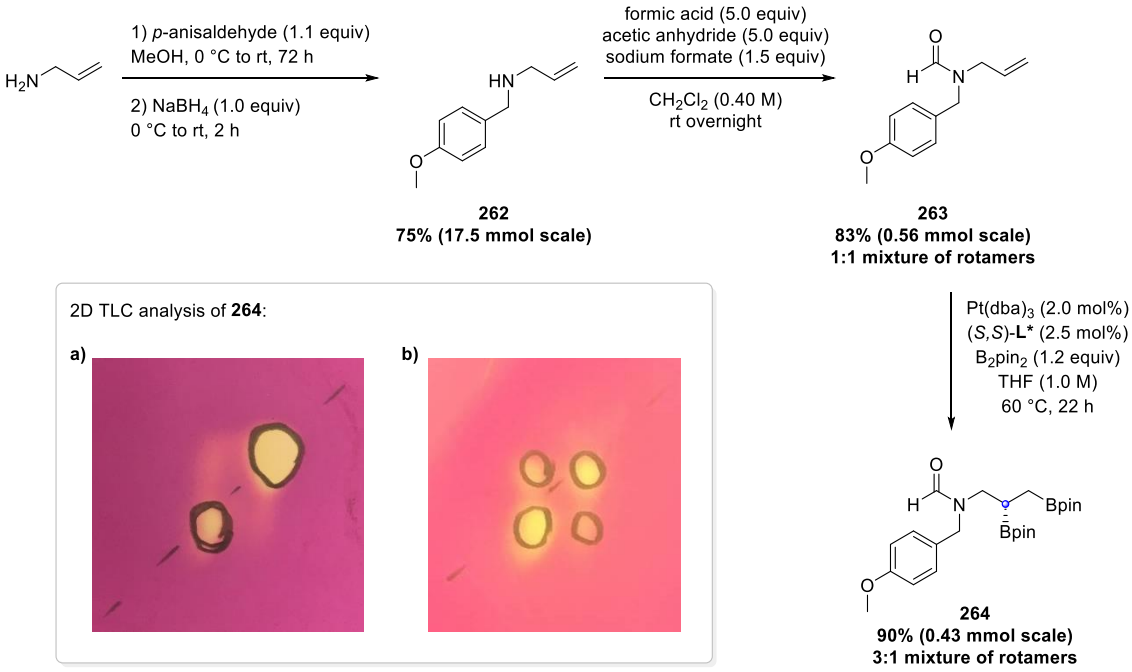
A model study was devised in order to test the key steps for a protected formamide strategy (**Scheme 102**). This approach would also reduce the number of late stage manipulations of an increasingly polar compound in the total synthesis and instead the endgame would conclude with global deprotection of the formamide and the 1,3-polyol to reveal the target mycapolyol E.



Scheme 102 Formamide protection/deprotection model study.

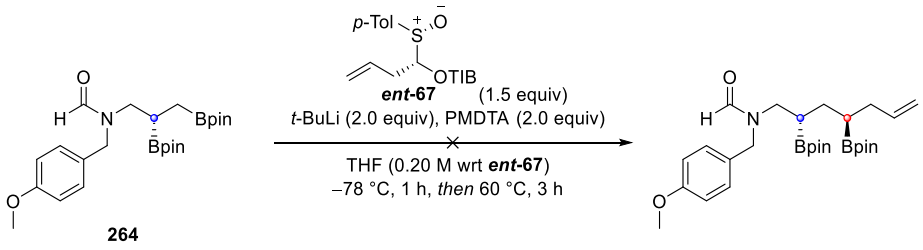
The first protecting group investigated was *para*-methoxybenzyl (PMB). Reductive amination of *p*-anisaldehyde with allylamine[161] gave PMB-protected amine **262** which was then formylated[162] to yield PMB-protected formamide **263** as a 1:1 mixture of rotamers by ^{1}H NMR analysis at ambient temperature (**Scheme 103**). Asymmetric diboration using Morken's conditions proceeded smoothly to give 1,2-bis(boronic ester) **264** in high yield and as a 3:1 mixture of rotamers by ^{1}H NMR analysis.

Interestingly, although the rotamers could not be separated by column chromatography, two discrete spots were visible by TLC analysis. Double bands in TLC corresponding to stable formamide rotamers were observed and reported by Opatz and co-workers, who also described a simple 2D TLC experiment to show these two spots were indeed rotamers.[163] When a 2D TLC was run as usual—where it was developed in the second direction immediately following air drying—two spots on the diagonal were observed. The next 2D TLC plate was left for one hour at ambient temperature between development in the first and second directions; in addition to the two spots on the diagonal, there were also two weak off-diagonal spots indicating slow interconversion of the two species at ambient temperature and identifying them to be rotamers (**Scheme 103** inset figures).



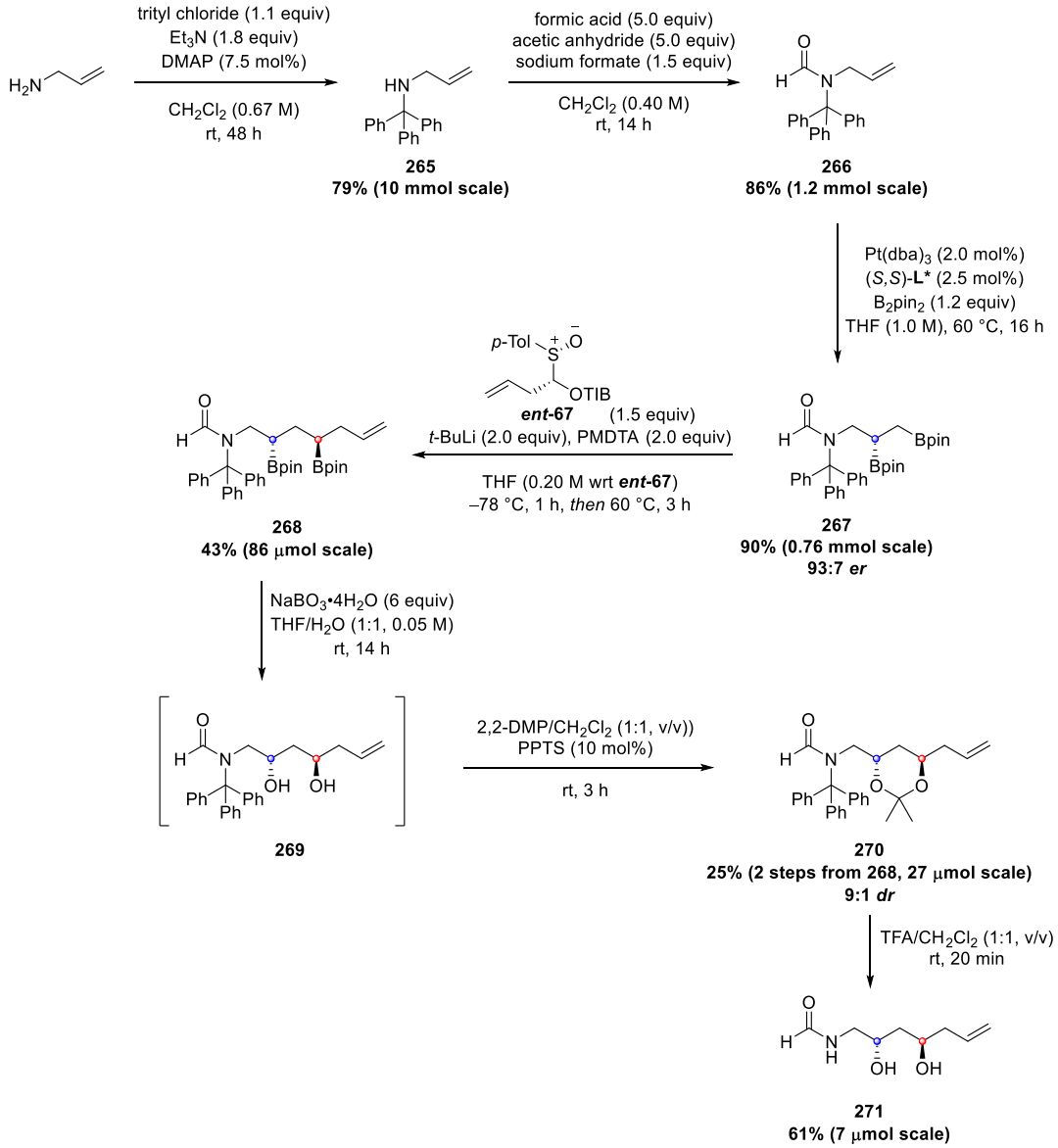
Scheme 103 PMB protected formamide model study. Ratio of rotamers as observed by NMR analysis, *er* of **264** not determined. Inset figures show 2D TLC analysis of **264**: a) second development immediately after air-drying; b) TLC place left at rt for 1 hour in between development in first and second directions. Circled spots visualised under UV irradiation then by $KMnO_4$ stain.

1,2-Bis(boronic ester) **264** was carried forward as a mixture of rotamers and subjected to the standard homologation conditions (**Scheme 104**), however, only the α-sulfinyl benzoate by-products (homoallylic benzoate **178** and *t*-butyl sulfoxide) were isolated from the reaction mixture. It was believed the benzylic protons of the PMB protecting group could be attacked by *t*-BuLi, leading to decomposition.



Scheme 104 The homologation of **264** with a lithiated carbenoid derived from α-sulfinyl benzoate ***ent*-67** was not successful.

A trityl (triphenylmethyl) group was trialled as replacement for a PMB group, as a formamide protecting group without benzylic protons (**Scheme 105**). Tritylamine **265** was prepared according to the literature procedure[164] and formylation proceeded under the same conditions as for the PMB protected amine (**Scheme 103**). ^{1}H NMR analysis of trityl protected formamide **266** showed no rotamers, presumably due to the steric bulk of the trityl group forcing the formamide into one preferred conformation.



Scheme 105 Trityl protected formamide model study. A portion of **267** was oxidised to the corresponding diol **273** to determine the *er* by chiral HPLC analysis. Reported *dr* for **270** determined by ^{13}C NMR analysis. 2,2-DMP: 2,2-dimethoxypropane. TFA: trifluoroacetic acid.

Terminal alkene **266** was subjected to Morken diboration and the resulting 1,2-bis(boronic ester) **267** was homologated with homoallylic α-sulfinyl benzoate ***ent*-67** to give the desired product **268** in 43% isolated yield and 9:1 *dr* (**Scheme 105**). Oxidation of 1,3-bis(boronic ester) **268** using basic hydrogen peroxide resulted in isolation following column chromatography of both the desired diol **269** and the over-oxidation product, where both the boronic esters and the formamide had been oxidised. However, full conversion to diol **269** could be achieved using the milder oxidising agent sodium perborate. In the interest of quickly establishing whether the formamide could be deprotected under the same conditions as the poly(acetonide), formation of **269** was confirmed by TLC-MS analysis and the crude

diol was carried forward to the acetonide protection, resulting in clean conversion to acetonide **270**. Treatment of **270** with TFA/CH_2Cl_2 resulted in clean removal of both the trityl protecting group and the acetonide to reveal the formamide and diol in the model target **271**, characterised by NMR analysis and confirmed by HRMS (ESI) analysis.

4.2.2.2 Synthesis of revised fragment 1 (274)

Following these successful model studies, fragment 1 was revised to include a trityl protected formamide instead of 2,5-dimethylpyrrole (**Scheme 106**). The first two steps—trityl protection and formylation—already worked well using the conditions described in the previous section (**Scheme 105**). However, although the first diboration reaction to afford 1,2-bis(boronic ester) **267** was high yielding, the *er* value of 93:7 was unacceptably low for the first step in an iterative sequence.

Morken's diboration typically proceeds in >95:5 *er*, although higher catalyst loadings were required and lower enantioselectivity was reported for substrates bearing sterically bulky substituents close to the metalation centre such as **272**, which may explain the lower than expected enantiomeric ratio for 1,2-bis(boronic ester) **267** (93:7, determined by chiral HPLC analysis of the corresponding diol **273**) (**Figure 26**).

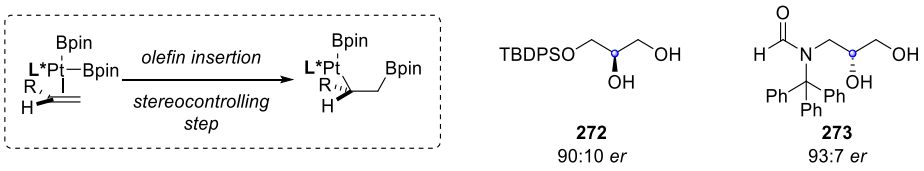
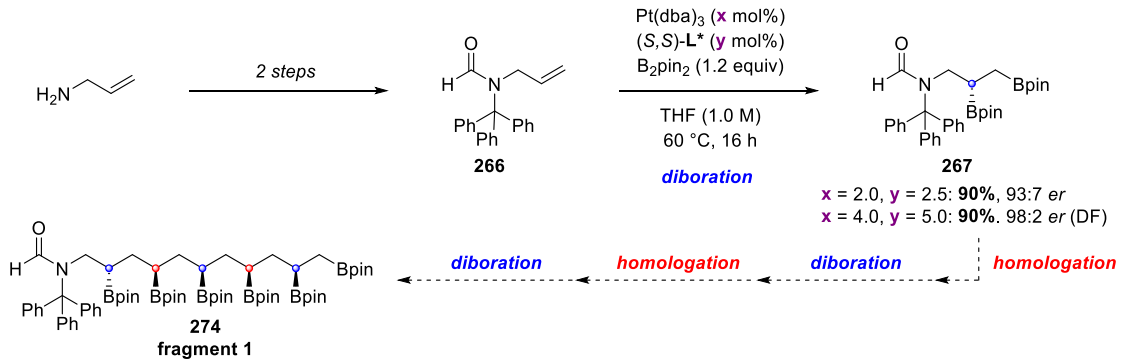


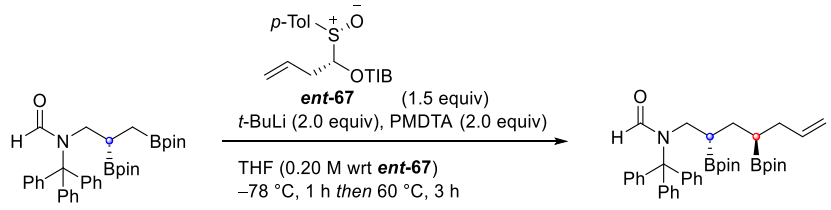
Figure 26 Lower diboration enantioselectivity for sterically bulky substrates.

Pleasingly, Dr Fiorito showed that simply increasing the pre-catalyst loading from 2 to 4 mol% improved the *er* to 98:2, with the same yield on gram-scale (**Scheme 106**).



Scheme 106 Optimised first diboration in the synthesis of new fragment 1 (**274**). A portion of **267** was oxidised to the corresponding diol to determine the *er* by chiral HPLC analysis.

The first homologation of 1,2-bis(boronic ester) **267** using the standard conditions with *t*-BuLi was quite low yielding (**Scheme 105**) and therefore merited optimisation (**Table 19**). TLC analysis of the crude mixture showed 3 major spots corresponding to the expected α-sulfinyl benzoate by-products (homoallylic benzoate **178** and *t*-butyl sulfoxide) and the desired product **268**, with no detectable over-homologation and only a trace of 1,2-bis(boronic ester) starting material **267**.



267
50 mg, 0.086 mmol

268

Entry	Deviation from conditions above	Isolated yield 268 /%
1	None	43
2	$MgBr_2$ in MeOH (1.0 M, 1.5 equiv) for migration	49
3	Solvent swap to $CHCl_3$ for migration	52
4	2-methyl THF instead of THF	31 (46 brsm)
5	***ent*-67** (2.0 equiv), *i*-PrMgCl·LiCl (2.1 equiv) CH_2Cl_2 (0.10 M)	No product formation, **267** recovered
6	***ent*-67** (2.0 equiv), *t*-BuLi (2.7 equiv), PMDTA (2.7 equiv)	40
7	***ent*-67** (2.0 equiv), *t*-BuLi (2.0 equiv), PMDTA (2.0 equiv)	43

Table 19 Optimisation of homologation of 1,2-bis(boronic ester) **267**.

^{11}B NMR analysis revealed a persistent boronate complex, even after heating at 60 °C for 20 hours. Addition of the Lewis acid magnesium bromide in methanol or a solvent swap to chloroform prior to migration were both effective in promoting full 1,2-migration (entries 1–3 **Table 19**, **Figure 27**).

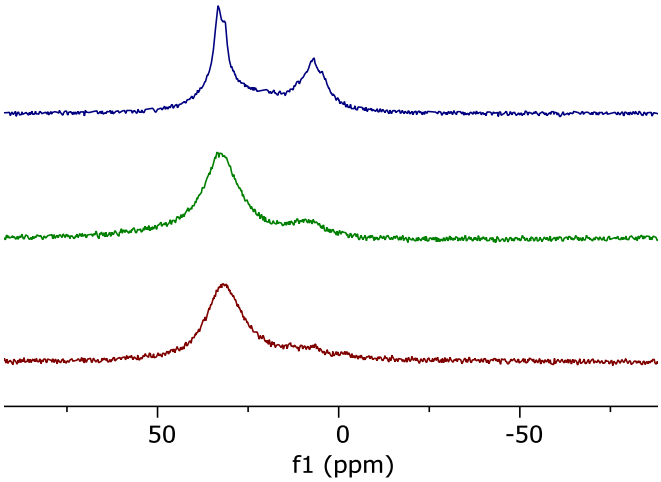
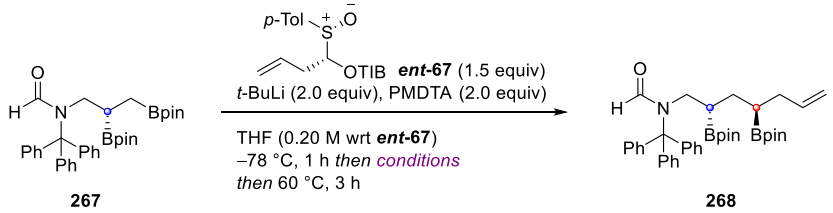


Figure 27 ^{11}B NMR (96 MHz) after 3 h at 60 °C (blue), solvent swap to $CHCl_3$ then 3 h at 60 °C (green), addition of $MgBr_2$ in MeOH then 3 h at 60 °C (red).

1,2-Bis(boronic ester) **267** showed poor solubility in THF so the reaction was repeated in 2-methyl THF with no improvement and in fact poorer conversion (entry 4, **Table 19**). 1,2-Bis(boronic ester) **267** was readily soluble in dichloromethane so the reaction was attempted using the magnesiated carbenoid (entry 5, **Table 19**) generated using *i*-PrMgCl·LiCl. Unfortunately, this substrate must be too sterically hindered for the less reactive magnesiated carbenoid (*vs.* the lithiated carbenoid) at −78 °C. Increasing the equivalents of α-sulfinyl benzoate ***ent*-67** (entries 6 and 7, **Table 19**) did not improve isolated product yield, which could be expected given that no considerable 1,2-bis(boronic ester) starting material **267** was recovered (entry 1).

The only modification in **Table 19** that improved the initial isolated yield of 43% of **268** concerned ensuring full 1,2-migration of this sterically hindered migrating group. The migrating group also contains a formamide, which could also render it electron deficient (entries 1-3 **Table 19** repeated in **Table 20** for comparison). Magnesium bromide etherate was also competent at promoting 1,2-migration (entry 4, **Table 20**). The reaction could be scaled-up to 0.2 mmol (entries 5 and 6, **Table 20**) to give the product in similar yields, however the isolated yield did drop when the reaction was attempted using 1 mmol of the 1,2-bis(boronic ester) (entry 7, **Table 20**). On 1 mmol scale splitting the crude material into 5 batches for chromatographic purification did improve the overall yield slightly (entry 8, **Table 20**), consistent with the observation that such homoallylic boronic esters show some instability on silica gel (see products **190** and **254** in sections **3.3** and **4.2.1**, respectively).

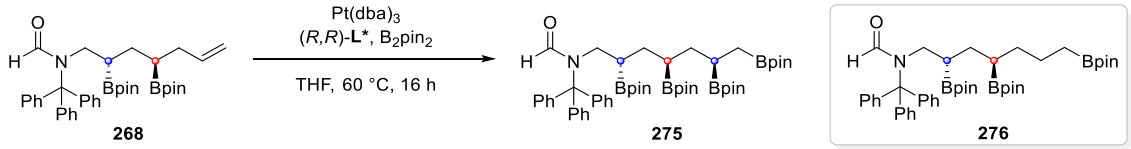


Entry	Scale /mmol	Migration conditions	Isolated yield 268 /%
1	0.1	None	43
2	0.1	$MgBr_2$ in MeOH (1.0 M, 1.5 equiv)	49
3	0.1	Solvent swap to $CHCl_3$	52
4	0.1	$MgBr_2 \cdot Et_2O$	50
5	0.2	$MgBr_2$ in MeOH (1.0 M, 1.5 equiv)	52
6	0.2	Solvent swap to $CHCl_3$	42, 45
7	1	$MgBr_2$ in MeOH (1.0 M, 1.5 equiv)	36
9	1	$MgBr_2$ in MeOH (1.0 M, 1.5 equiv)	44[a]

Table 20 Scaling-up homologation of 1,2-bis(boronic ester) **267**. [a] Crude split into 5 batches for purification by flash column chromatography on silica gel.

The next step in the synthesis of fragment 1 (**274**) was another enantioselective diboration reaction, which required relatively high pre-catalyst loading (7.5 mol% *vs*. 2.5 mol%) to ensure full conversion of alkene **268** to tetra(boronic ester) **275** (**Table 21**). The first diboration reaction was performed on a small scale so was more dilute than usual, which resulted in formation of the hydroboration side-product **276** being observed (entry 1, **Table 21**). This has been previously reported when the diboration is carried out at a low concentration (**Scheme 69**) and **276** was difficult to separate from the diboration product **275** by column chromatography, so all further diboration reactions were only attempted at 1 M concentration. Pleasingly, this modification led to clean conversion of starting material **268** to desired tetra(boronic ester) **275** in 59% isolated yield, or 89% based on recovered starting material (entry 2, **Table 21**). On a larger scale, the pre-catalyst and ligand loading was decreased (entry 3), but no product was formed and in fact starting material **268** was recovered almost quantitatively. This requirement for higher catalyst loadings was also observed for the first diboration reaction, of alkene **266** to generate 1,2-bis(boronic ester) **267**; for a 5 mmol scale reaction, decreasing the catalyst loading to 1.0 mol% $Pt(dba)_3$ and 1.2 mol% (*S*,*S*)-**L***—Morken's standard catalyst loading[50]— led to a decreased isolated yield of 70%, or 86% based on recovered starting material (cf. **Scheme 106**). Morken did report that higher catalyst loadings were required for electron deficient alkenes;[50] increasing the pre-catalyst loading from 2.5 mol% to 7.5 mol% (and maintaining the ratio of ligand to pre-catalyst) allowed complete consumption of starting material **268** and product **275** was

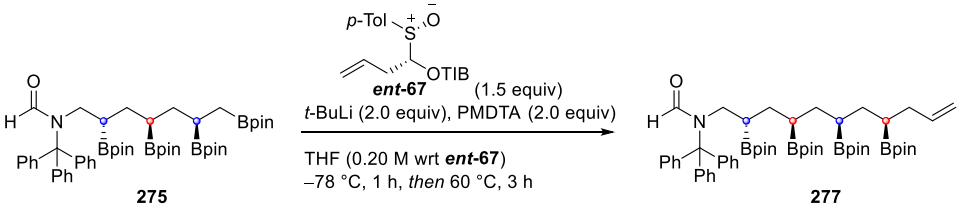
isolated in 89% yield (entry 4, **Table 21**). Importantly, these conditions were reproducible in Dr Fiorito's hands (entry 5). The pre-catalyst loading could be decreased slightly to 6 mol% and still afford the tetra(boronic ester) product in good yield (entry 6).



Entry	Scale /mmol	$Pt(dba)_3$ /equiv	(*R,R*)-L* /equiv	B_2pin_2 /equiv	Conc. /M	Isolated yield 275 /%
1	0.16	0.050	0.060	1.2	0.3	40[a]
2	0.20	0.050	0.060	1.2	1	59 (89 brsm)
3	1.8	0.025	0.030	1.2	1	0 (**268** recovered)
4	0.36	0.075	0.090	2.0	1	89
5 (DF)	1.5	0.075	0.090	2.0	1	91
6	0.23	0.060	0.075	2.0	1	83 (85 brsm)

Table 21 Optimisation of diboration of **268**. Conc.: concentration. [a] plus mixed fractions with **276**.

Tetra(boronic ester) **275** was then subjected to the standard homologation conditions (**Table 22**). ^{11}B NMR analysis again showed it was necessary to add a Lewis acid or change to a non-coordinating solvent to promote 1,2-migration. More equivalents of α-sulfinyl benzoate ***ent*-67** did not improve the isolated yield of 39% of homologated product **277** (entry 3, **Table 22**), and both the aqueous work up and column chromatography conditions were carefully scrutinised to ensure material was not being lost during isolation and purification.

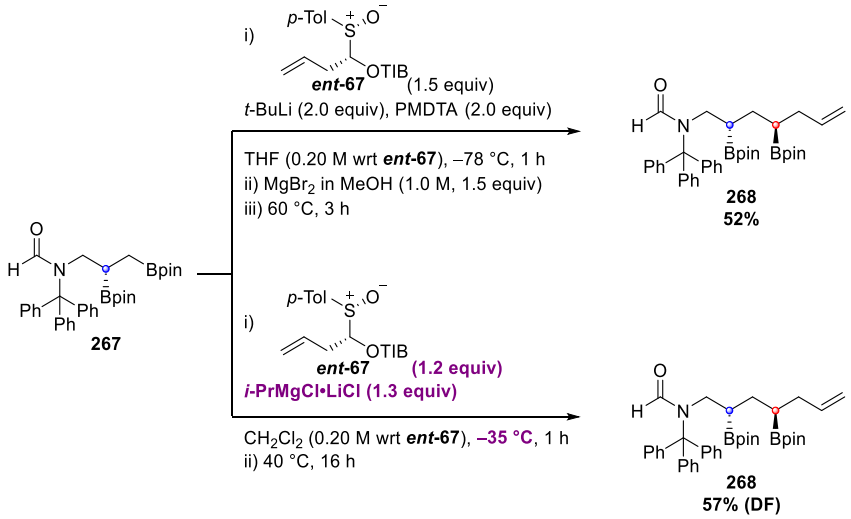


Entry	Deviation from conditions above	Isolated yield 277 /%
1	None	33
2	$MgBr_2$ in MeOH (1.0 M, 1.5 equiv) for migration	38
3	Solvent swap to $CHCl_3$ for migration	39

Table 22 Second homologation in synthesis of fragment 1 (**274**). All reactions on 0.1 mmol scale.

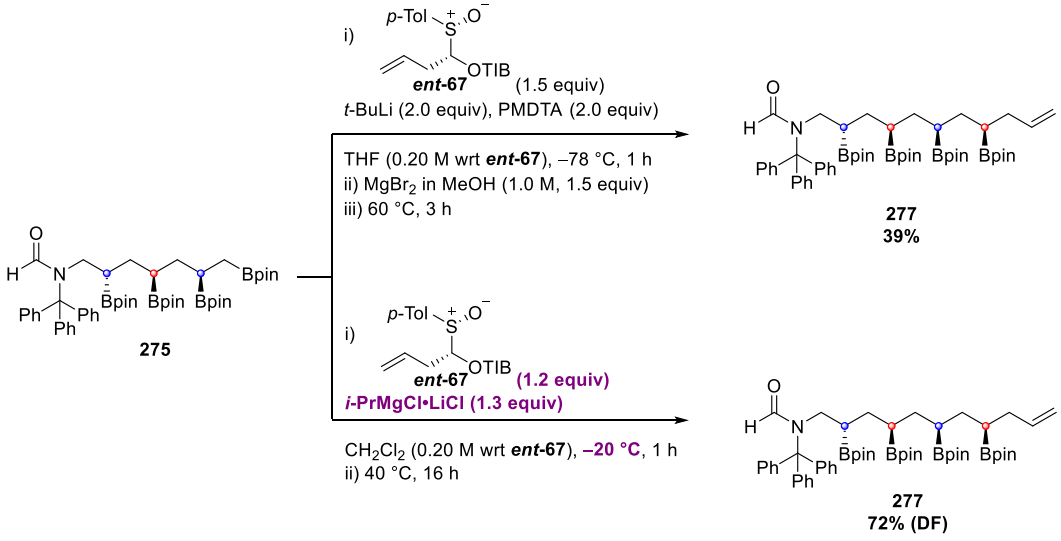
In light of the improved results for challenging homologations using magnesiated carbenoids derived from α-sulfinyl benzoates when the borylation temperature was raised above −40 °C (*vide supra*, section **3.4**), Dr Fiorito applied these conditions to both homologation steps in the synthesis of fragment 1 (**Scheme 107**, **Scheme 108**). When the metalation and borylation

phases were carried out at −35 °C using the optimised conditions from **Table 10**, the magnesiated carbenoid offered milder (*vs.* the lithiated carbenoid) and equally efficient conditions to access homologated product **268** (**Scheme 107**).



Scheme 107 Optimised homologations conditions for 1,2-bis(boronic ester) **267** using a magnesiated carbenoid.

For the second homologation step, a more efficient homologation was realised using the magnesiated carbenoid at −35 °C, affording homologated product **277** in 51% yield (75% brsm), compared to at best 39% yield with the lithiated carbenoid (**Table 22**). Given that this magnesiated carbenoid had been shown to be configurationally and chemically stable at −20 °C (*vide supra*, **Scheme 76**), the temperature for borylation was raised further resulting in the optimal yield of 72% tetra(boronic ester) **277** (**Scheme 108**).



Scheme 108 Optimised homologations conditions for tetra(boronic ester) **277** using a magnesiated carbenoid.

The late alkene-bearing intermediate **277** presented a clear handle for detailed NMR analysis to investigate the diastereopurity at this point, and to illustrate the importance of starting with 1,2-bis(boronic ester) **267** in as high enantiopurity as possible. Minor diastereomers are clearly visible in both the ^{1}H and ^{13}C NMR spectra of **277** prepared from **267** with 93:7 *er* (**Figure 28**, upper traces in green). However, the ^{1}H and ^{13}C NMR spectra for **277** prepared from **267** with 98:2 *er* indicate there is one major diastereomer at this point, with ≥95:5 *dr* (**Figure 28**, lower traces in red, this material prepared by DF).

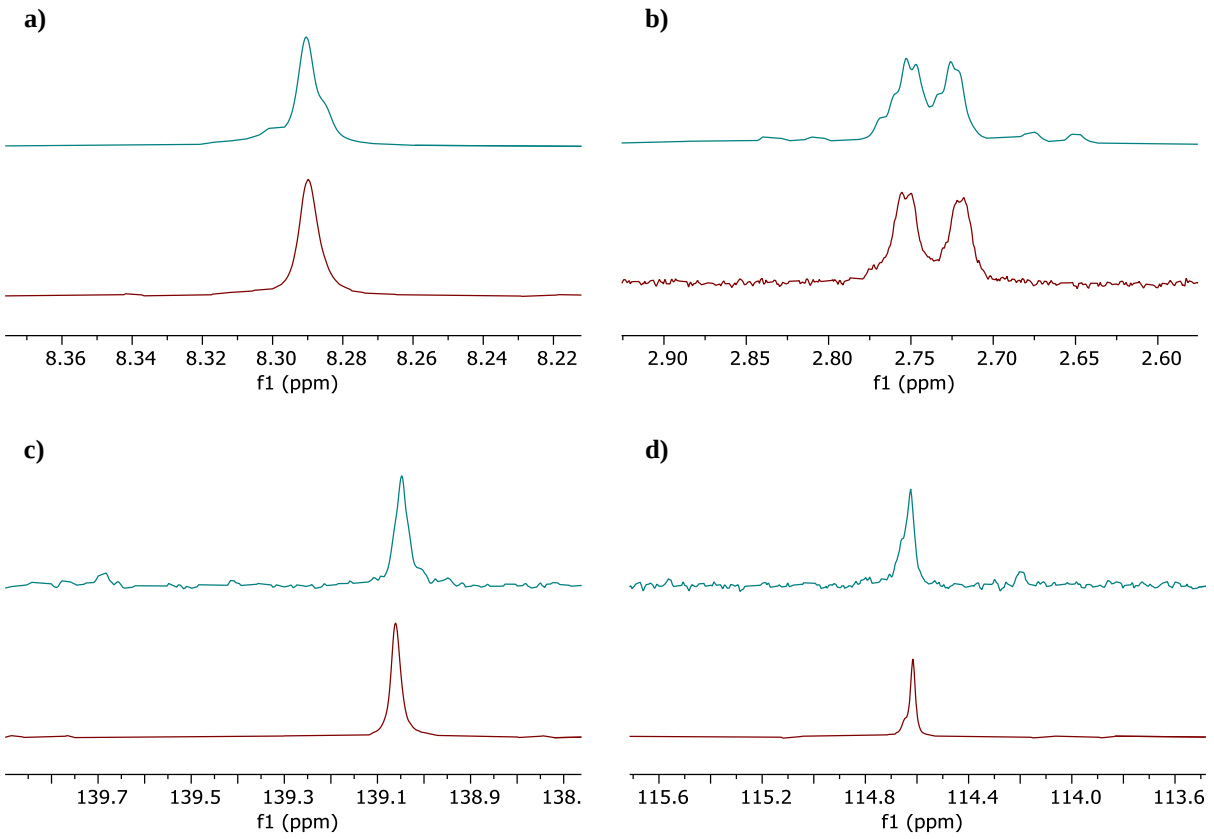
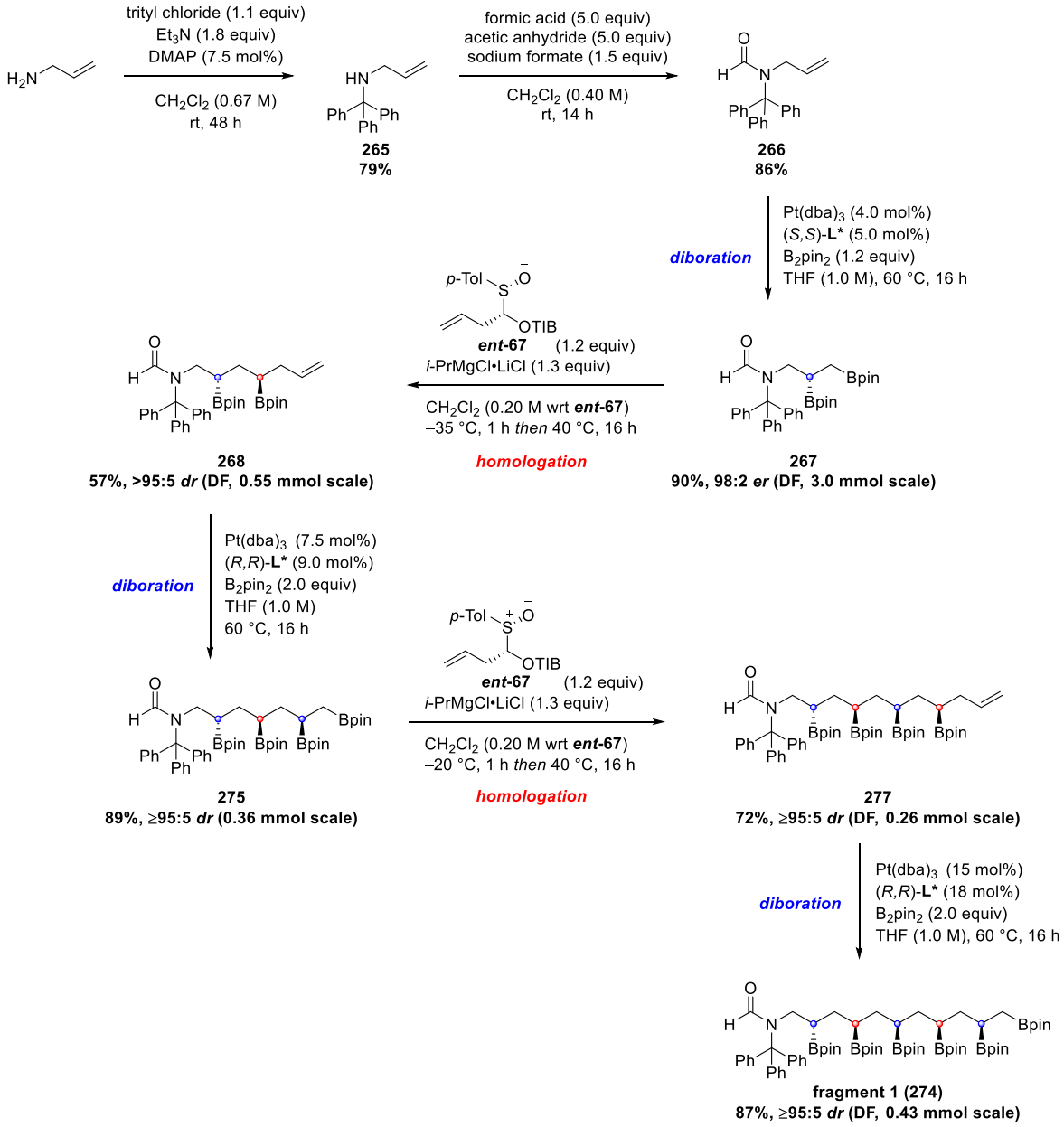


Figure 28 NMR analysis of **277** to determine *dr* (DF). a) ^{1}H NMR (500 MHz, $CDCl_3$) C(O)H; b) ^{1}H NMR (500 MHz, $CDCl_3$) NCH_2; c) ^{13}C NMR (126 MHz, $CDCl_3$) alkene CH; d) ^{13}C NMR (126 MHz, $CDCl_3$) alkene CH_2.

The final step to afford full fragment 1 (**274**) was a third asymmetric diboration reaction (**Scheme 109**). With relatively high catalyst loading (15 mol% $Pt(dba)_3$ and 18 mol% (*R*,*R*)-**L***), to ensure consumption of **277** and high diastereoselectivity, and at Morken's concentration of 1 M, to minimise formation of the hydroboration side-product, fragment 1 (**274**) was first prepared in 71% isolated yield on 0.09 mmol scale. When this was repeated on a larger scale (0.43 mmol), Dr Fiorito obtained an isolated yield of 87%. Thus, fragment 1 (**274**) has been prepared in 7 steps from allylamine in ≥95:5 *dr* and 19% overall yield.

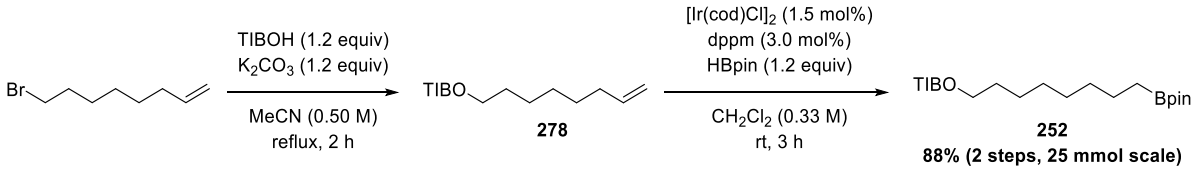


Scheme 109 Summary of optimised iterative synthesis of new fragment 1 (**274**).

4.3 Synthesis of Fragment 3 (251): Optimisation of the Zweifel-type Olefination

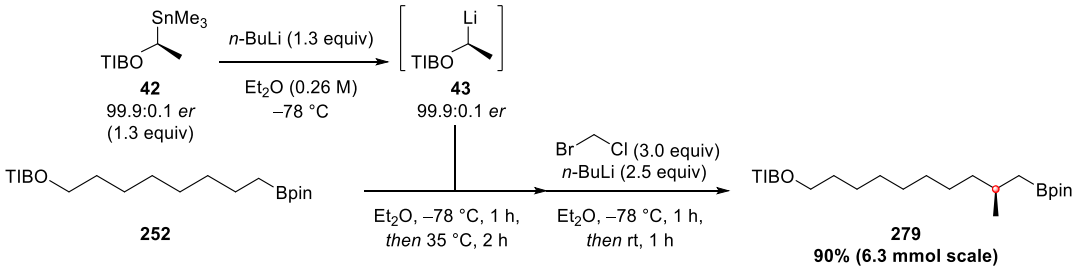
Fragment 3 (**251**) was prepared in 5 linear steps (10 total steps) from 8-bromo-oct-1-ene.

8-Bromo-oct-1-ene was smoothly converted to triisopropylbenzoate **278** which was then subjected to iridium-catalysed hydroboration of the terminal alkene[165] to give primary boronic ester **252** in 88% isolated yield over 2 steps (**Scheme 110**).



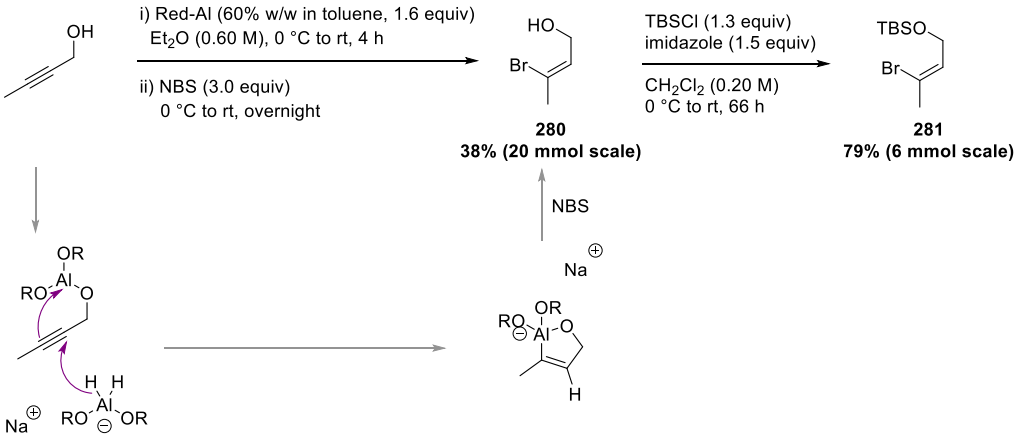
Scheme 110 Synthesis of primary boronic ester **252**.

Primary boronic ester **252** was then subjected to a short assembly–line sequence[34,35] affording boronic ester **279** in 90% yield over 2 steps (**Scheme 111**). First carbenoid precursor **42** was used to stereospecifically install the methyl group, followed by homologation with the Matteson carbenoid, (chloromethyl)lithium, to give homologated product **279**.



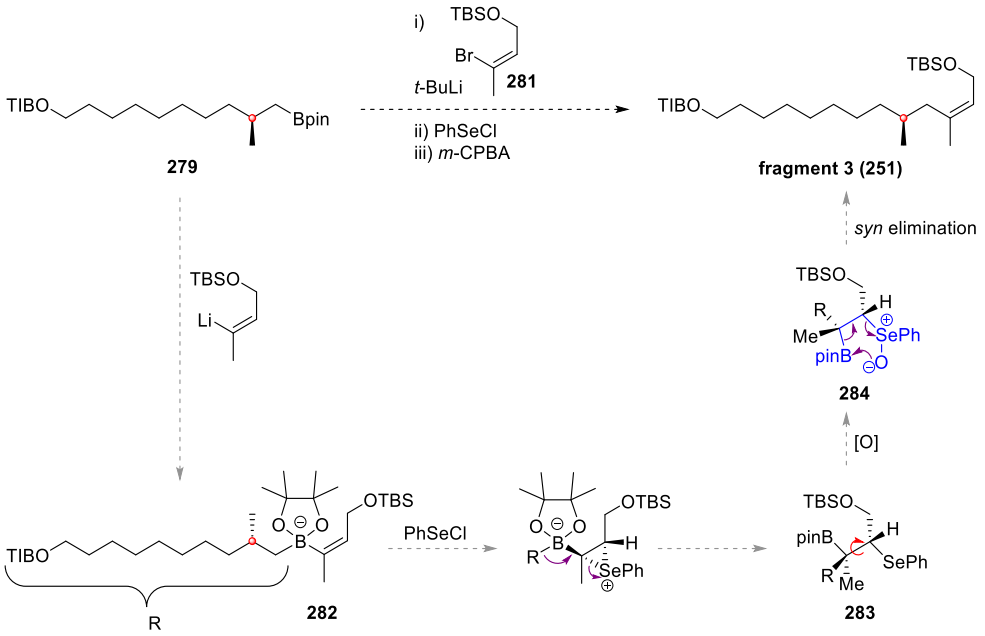
Scheme 111 Assembly–line synthesis of boronic ester **279**.

Trisubstituted olefin **280** was synthesised in 38% yield through hydroxyl-directed hydroalumination of 2-butyn-1-ol followed by stereospecific bromination of the vinylaluminium intermediate (**Scheme 112**).[166] This low isolated yield (literature 55% yield[166]) may be due to its volatility or material being lost during work-up; formation of a gummy brown residue, presumably from the excess Red-Al, was observed. Silyl protection of **280** proceeded to afford protected vinyl bromide coupling partner **281** in 79% yield.



Scheme 112 Synthesis of vinyl bromide coupling partner **281**.

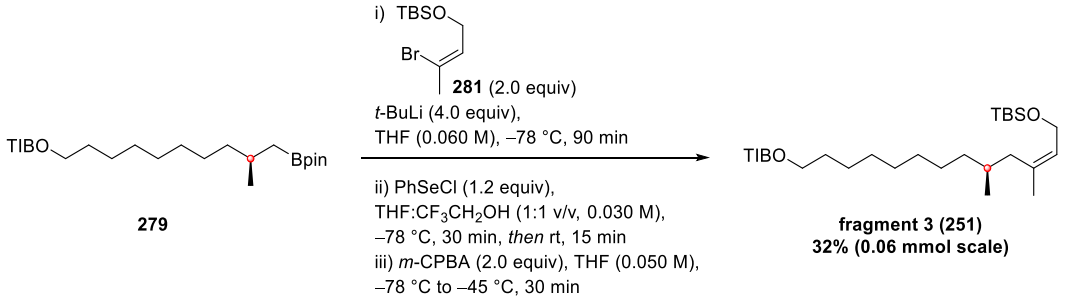
The final step to prepare fragment 3 (**251**) was a Zweifel-type olefination[166] where the required *Z* selectivity is achieved through (i) electrophilic selenation of the vinyl boronate complex **282**, triggering a 1,2-metalate rearrangement, (ii) chemoselective oxidation of the resulting selenide **283** and (iii) stereospecific *syn*-elimination of β-selenoxyboronic ester **284** (**Scheme 113**).



Scheme 113 Proposed *Z*-selective coupling of boronic ester **279** and vinyl bromide **281**.

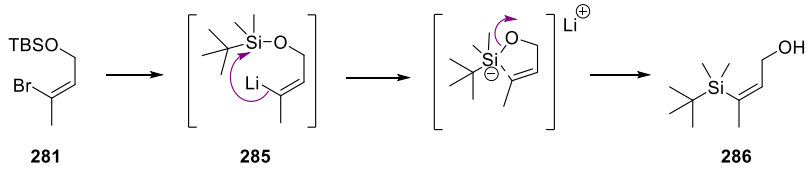
This was first attempted using the conditions reported for a similar vinyl bromide and a secondary alkyl boronic ester[166] (**Scheme 114**). Halogen-lithium exchange was carried out *in situ* using 2 equivalents of *t*-BuLi, since after Br-Li exchange the second equivalent reacts with the resultant *tert*-butyl bromide. The H-bond donor solvent 2,2,2-trifluoroethanol (TFE) was added before phenylselenyl chloride to ensure high levels of diastereoselectivity, through

reducing the nucleophilicity of the pinacol oxygen lone pairs.[167,168] The crude mixture was filtered through silica gel prior to the addition of *m*-CPBA in order to remove the precipitated lithium bromide, which has been shown to potentially trigger *anti*-elimination of the β-selenoxyboronic ester intermediate resulting in formation of a mixture of the *Z* and *E* alkenes.[166]



Scheme 114 Initial conditions for *Z*-selective olefination; also entry 1, **Table 23**.

Under these conditions, desired product **251** was isolated in 32% yield, as an inseparable 6:1 mixture of *Z*:*E* alkene isomers, contaminated with minor impurities, along with 18% recovered boronic ester **279** and 56% yield of the retro-Brook rearrangement side product **286** (see **Scheme 115** for its formation). These conditions already aimed to minimise any retro-Brook rearrangement by performing the halogen-lithium exchange *in situ* so that as soon as vinyllithium **285** formed, it would be trapped with boronic ester **279** instead.

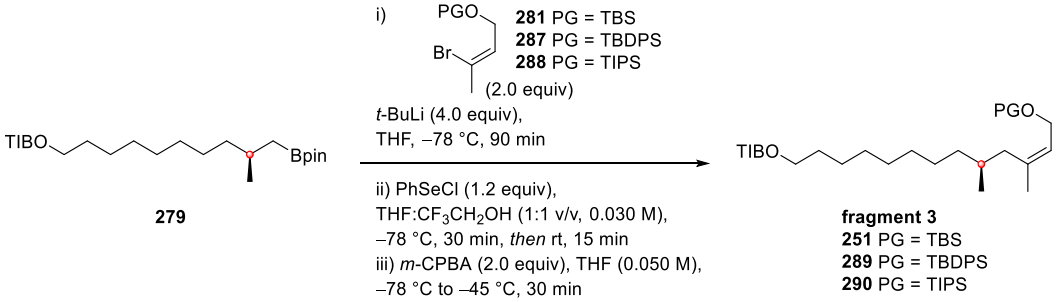


Scheme 115 Retro-Brook rearrangement of **285** under reaction conditions shown in **Scheme 114**.

Dieter reported when working with similar vinyl iodides that "This retro-Brook rearrangement could be prevented by carrying out the halogen-metal exchange reaction in Et_2O."[169] The reaction shown in **Scheme 114** was repeated in diethyl ether on the same scale, with formation of **286** observed by TLC analysis, and a low yield of desired product **251** in 6:1 *Z*:*E* ratio, and so further investigations in diethyl ether were not pursued.

Table 23 summarises the conditions screened for the *Z*-selective olefination of boronic ester **279**; entry 1 corresponds to the reaction shown in **Scheme 114**. After considering the mechanism for the retro-Brook rearrangement, it was reasoned that using a silyl protecting group with increased steric bulk such as TBDPS (entry 2) may improve formation of the desired product. It was hoped that a bulkier silyl group would lead to increased steric

hindrance in the transition state for the retro-Brook pathway, thereby disfavouring it. Gratifyingly, the corresponding alkene product was isolated in 51% yield; much closer to the literature yield of 55% with the same vinyl bromide **287** and a simple enantioenriched boronic ester.[166] However repeating these conditions on a slightly larger scale (entry 3) resulted in a decrease in the isolated yield and so the next change was to increase the concentration for the *in situ* halogen-lithium exchange and borylation, with the aim of favouring the intermolecular reaction of **285** with boronic ester **279** over the intramolecular retro-Brook rearrangement (entry 4). This did not greatly improve the isolated yield of product, and in fact Šebesta and co-workers reported that "The concentration of the reactants affects the rate of the bimolecular lithiation more significantly than the rate of the intramolecular rearrangement".[170] Šebesta also showed a clear trend for decreasing yields, and therefore less favourable retro-Brook rearrangement, with increasing bulk of the silyl substituents. This prompted a test reaction with TIPS (entry 5) which did result in a significant improvement in isolated yield but poorer *Z/E* selectivity by ^{1}H NMR analysis; repeating this on a larger scale (entry 6) afforded only 35% isolated yield of the product with no preference for the desired *Z*-alkene, which was inseparable from the *E* isomer by silica column chromatography.

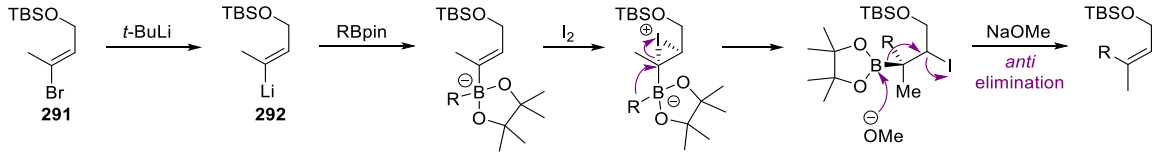


Entry	Protecting group	Scale /mmol 279	Initial conc. /M	Yield /% (product)	Recovered 279 /%	Product *Z*:*E* [a]
1	TBS	0.06	0.06	32 (**251**)	18	6:1
2	TBDPS	0.06	0.06	51 (**289**)	15	15:1
3	TBDPS	0.10	0.06	36 (**289**)	n.r.	
4	TBDPS	0.19	0.20	43 (**289**)	n.r.	
5	TIPS	0.19	0.20	68[b] (**290**)	37	6:1
6	TIPS	0.47	0.20	35[b] (**290**)	64	2:3

Table 23 Conditions screened for the *Z*-selective olefination of boronic ester **279**. [a] Determined by ^{1}H NMR analysis of the isolated product. [b] Contaminated with diphenyldiselenide. n.r. not recorded, but present by TLC analysis of crude.

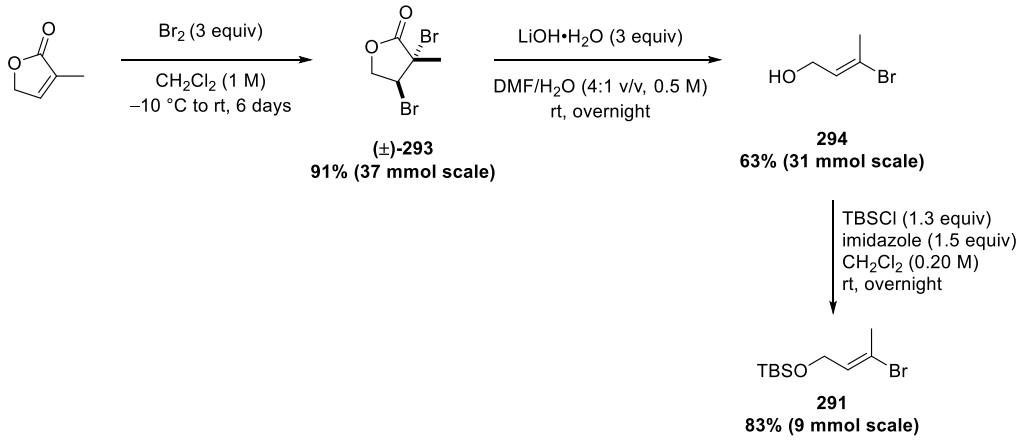
With no clear optimal conditions for the olefination of **279** with (*Z*)-vinyl bromide **281**, an alternative route to fragment 3 was sought. If the alternative geometric isomer of the vinyl

bromide was accessible (**291**), it was reasoned that it would be possible to proceed instead with a more classical Zweifel olefination (**Scheme 116**). This is where the vinyl boronate complex is treated with iodine and the resulting β-iodoboronic ester undergoes *anti*-elimination upon treatment with sodium methoxide to give the desired *Z* alkene. In addition, intramolecular retro-Brook rearrangement of the corresponding (*E*)-vinyllithium **292** would be much less likely due to the silyl protecting group now being situated on the opposite side of the alkene.



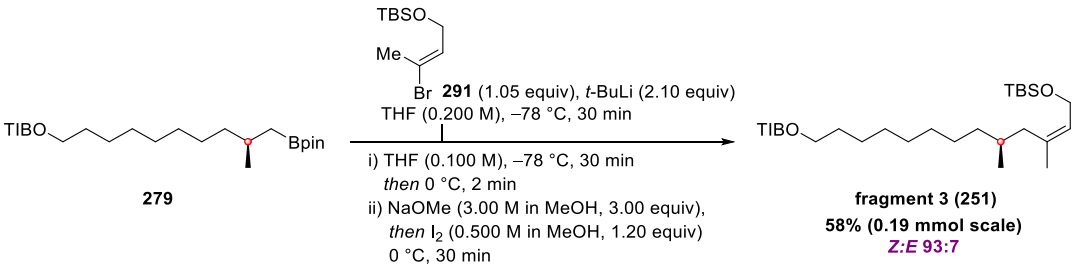
Scheme 116 Zweifel olefination, where the *Z*-alkene is accessed through *anti*-elimination of the β-iodoboronic ester intermediate.

Allylic alcohol **294** was prepared according to the literature procedure: bromination of commercially available 3-methyl butanolide followed by decarboxylative debromination.[171] Subsequent silyl protection afforded the required (*E*)-vinyl bromide **291,** with no detectable formation of the *Z* isomer by ^{1}H NMR analysis (**Scheme 117**).



Scheme 117 Preparation of (*E*)-vinyl bromide **291**.

With (*E*)-vinyl bromide **291** in hand, a Zweifel olefination was attempted. Boronic ester **279** was added as a solution in THF to the preformed vinyllithium (generated with 2 equivalents *t*-BuLi at −78 °C). Following addition of sodium methoxide and iodine, fragment 3 (**251**) was obtained in 58% isolated yield (**Scheme 118**).



Scheme 118 Zweifel olefination of boronic ester **279**.

^{1}H NMR analysis of the isolated fragment 3 (**251**) showed it was a 93:7 mixture of the *Z* and *E* alkene isomers (**Figure 29**). *Anti*-elimination brings the substituents into close proximity and so this lower than ideal *Z/E* selectivity can be attributed to the steric bulk of boronic ester **279** resulting in a small amount of *syn*-elimination, which avoids steric clash between the alkyl chain and the silyl ether (**Scheme 119**).

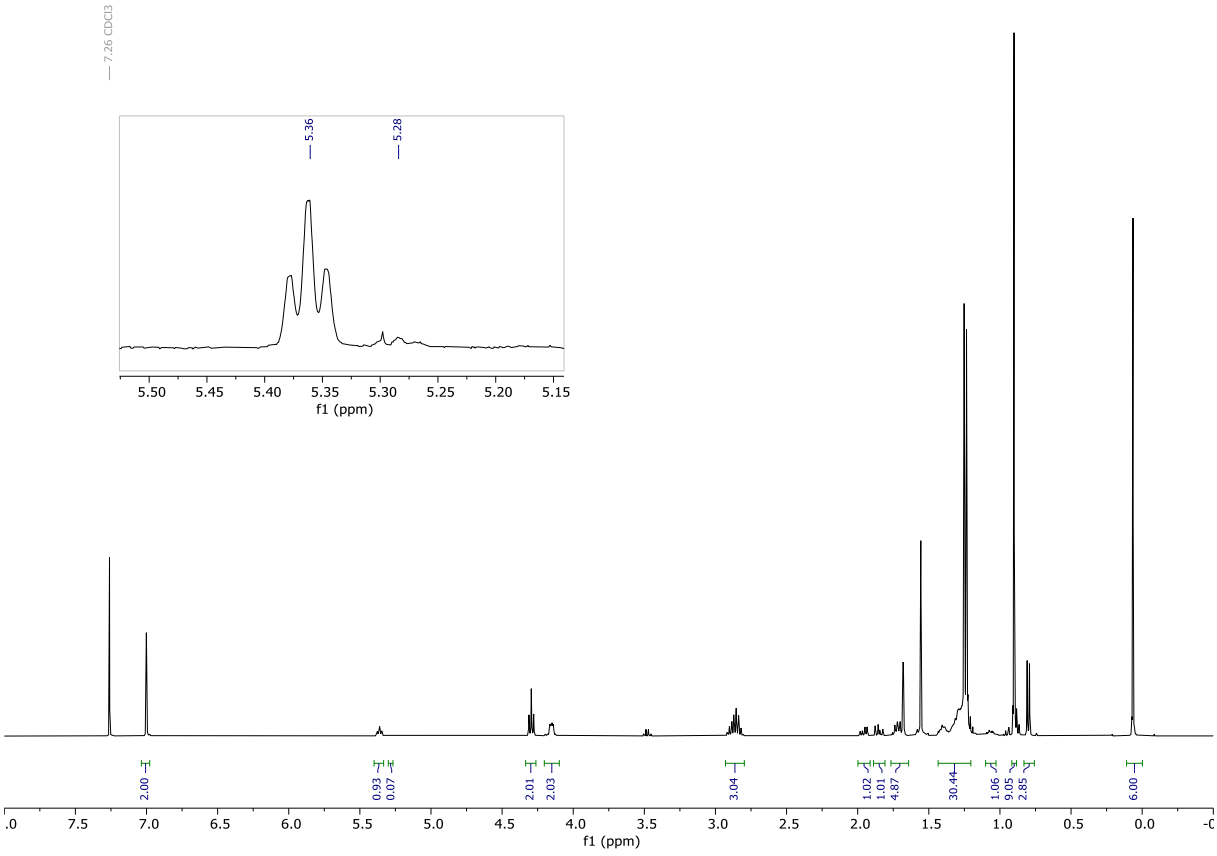
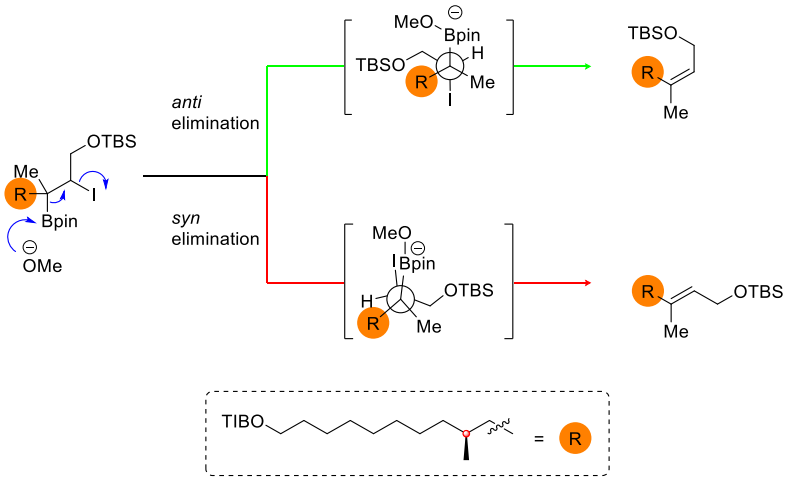
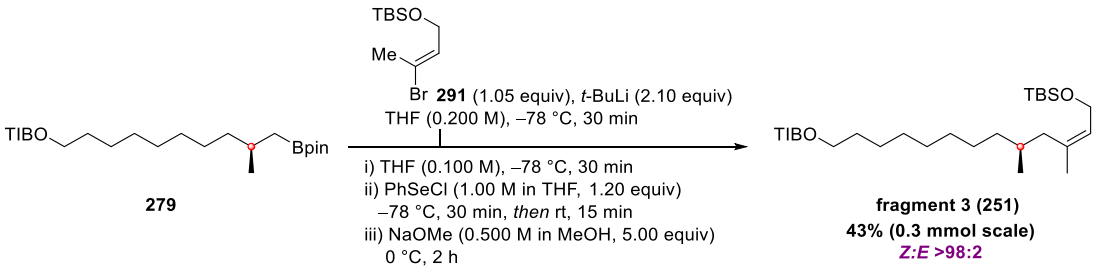


Figure 29 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of fragment 3 (**251**) prepared as shown in **Scheme 118**; expansion shows triplet for the alkene proton.



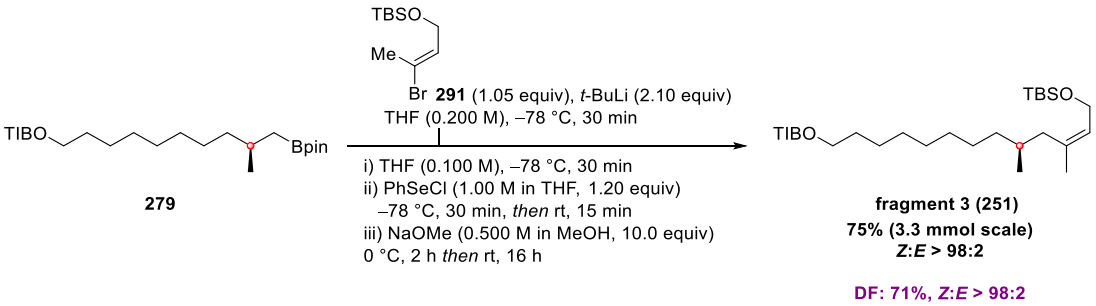
Scheme 119 Transition state explanation for lower *Z*/*E* selectivity in Zweifel with bulkier coupling partners.

Aggarwal and co-workers also developed conditions to enable a highly *Z*-selective coupling with sterically bulky substrates.[166] The *syn*-elimination pathway can be further disfavoured by using a poorer leaving group, such as a selenide instead of iodide. With this modification, fragment 3 (**251**) could be prepared with essentially perfect *Z*/*E* selectivity by ^{1}H NMR analysis, albeit with a decrease in isolated yield (**Scheme 120**).



Scheme 120 Highly *Z*-selective selenium-mediated coupling.

Aggarwal and co-workers reported that more forcing conditions for the methoxide-promoted *anti*-elimination of β-selenylboronic esters were required for the most sterically demanding substrates such as cyclic secondary boronic esters with proximal stereocentres.[166] Doubling the equivalents of sodium methoxide and leaving the reaction stirring overnight at ambient temperature for the elimination resulted in the formation of fragment 3 (**251**) in 72% isolated yield, with the same excellent levels of *Z*/*E* selectivity. These conditions were reproducible and scaled well, allowing the preparation of fragment 3 (**251**) on gram scale with no decrease in yield (**Scheme 121**).



Scheme 121 Optimised Zweifel-type olefination of boronic ester **279**.

4.4 Assignment of the Undefined Stereocentre at C5

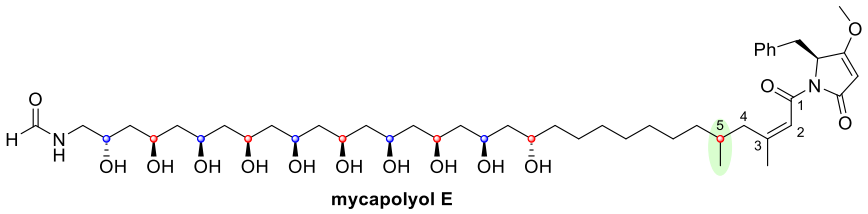
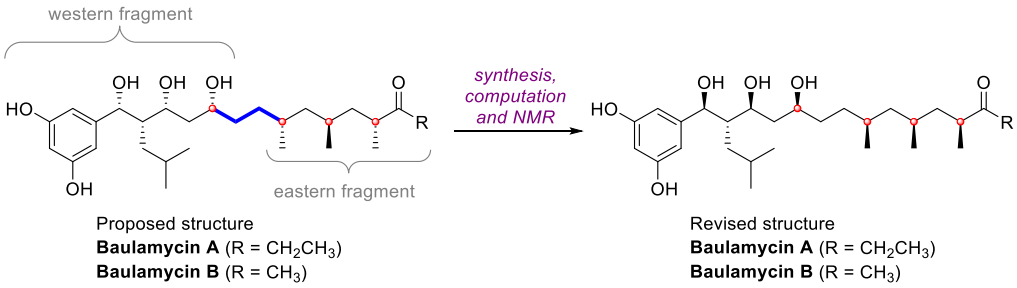


Figure 30 The undefined stereocentre in mycapolyol E.

There is one undefined stereocentre in all 6 mycapolyols, a methyl group at C5 in the eastern fragment (highlighted in **Figure 30**). Presumably since this centre is remote from the stereodefined polyol chain, the relative, and absolute, stereochemistry has not been discerned.

In the context of remote stereocentre assignment, Aggarwal and co-workers revised the relative and absolute configuration of baulamycins A and B using a combination of DFT calculations, NMR spectroscopy and synthesis (*vide supra*, **Scheme 16**, **Figure 2**).[36] Due to the flexible hydrocarbon linker in the middle of the molecule (in blue), the eastern and western fragments could be considered independently in order to discern the correct stereochemical assignment (**Scheme 122**).

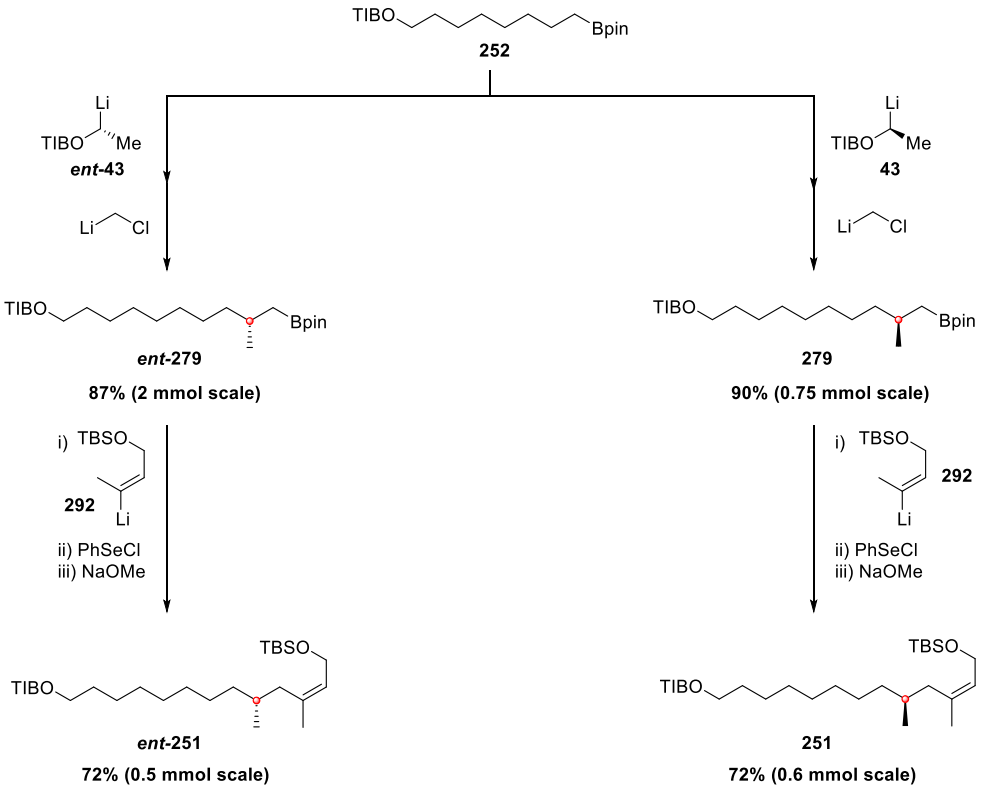


Scheme 122 Structural revision of baulamycins A and B through synthesis, computation and NMR.

The mycapolyols have an 8-carbon linker between the 1,3-polyol and the undefined stereocentre so it was proposed to make both diastereoisomers of the eastern fragment and then compare NMR data with the natural product.

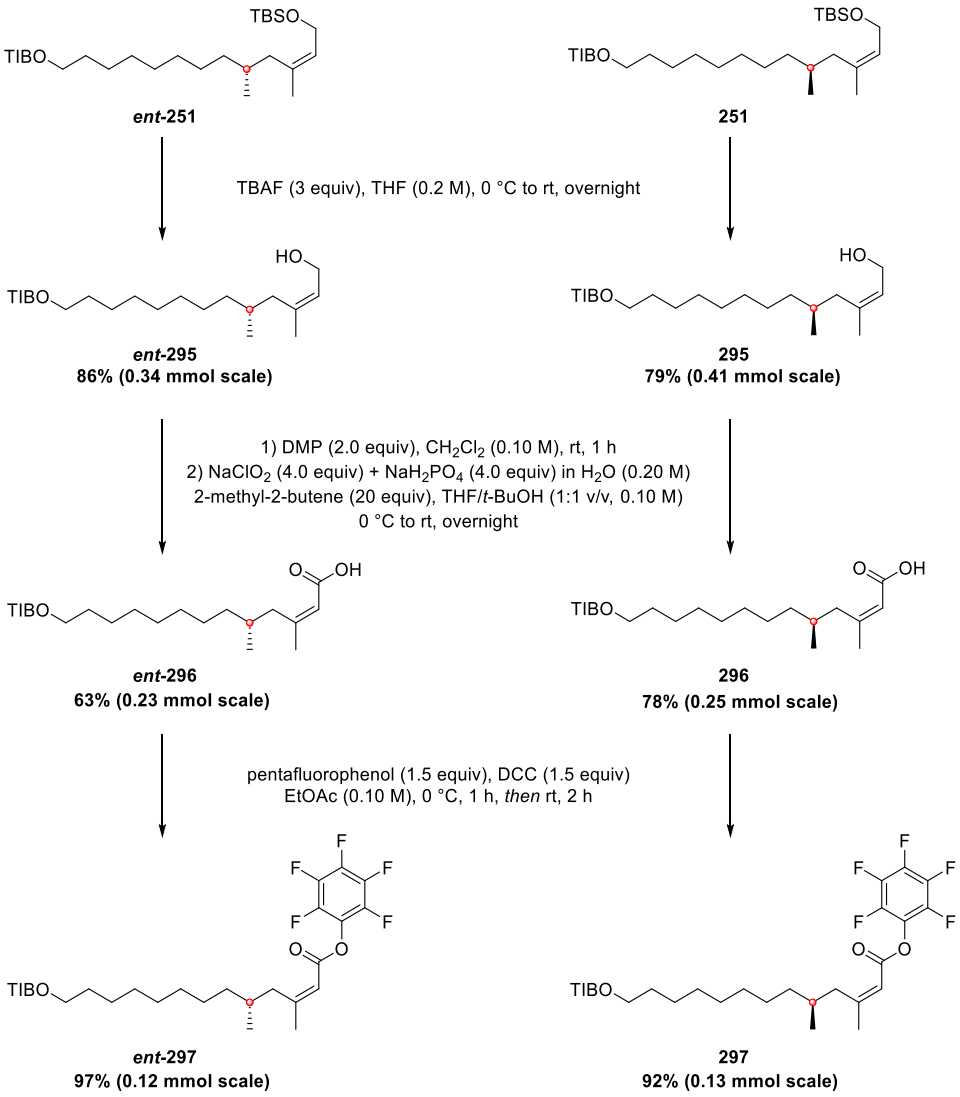
The stereocentre in question can be unambiguously set through the choice of either enantiomer of α-stannyl ethyl benzoate **42** for the homologation of boronic ester **252**. Once both enantiomers of fragment 3 have been prepared, the *O*-methoxy pyrrolin-2-one unit will be installed. This deprotection, oxidation and coupling strategy also provided the opportunity to optimise conditions for these steps in the endgame for the full mycapolyol E synthesis.

Starting from primary boronic ester **252**, one batch was homologated with (*S*)-stannane **42** and a second batch was homologated with (*R*)-stannane ***ent*-42**; the two enantiomeric products were both subjected to a Matteson homologation and Zweifel-type olefination, using the previously optimised conditions (**Scheme 111**, **Scheme 121**), to give fragment 3 **251** and ***ent*-251** (**Scheme 123**).



Scheme 123 Synthesis of both enantiomers of fragment 3 (**251** and ***ent*-251**). See **Scheme 111** and **Scheme 121** for detailed conditions.

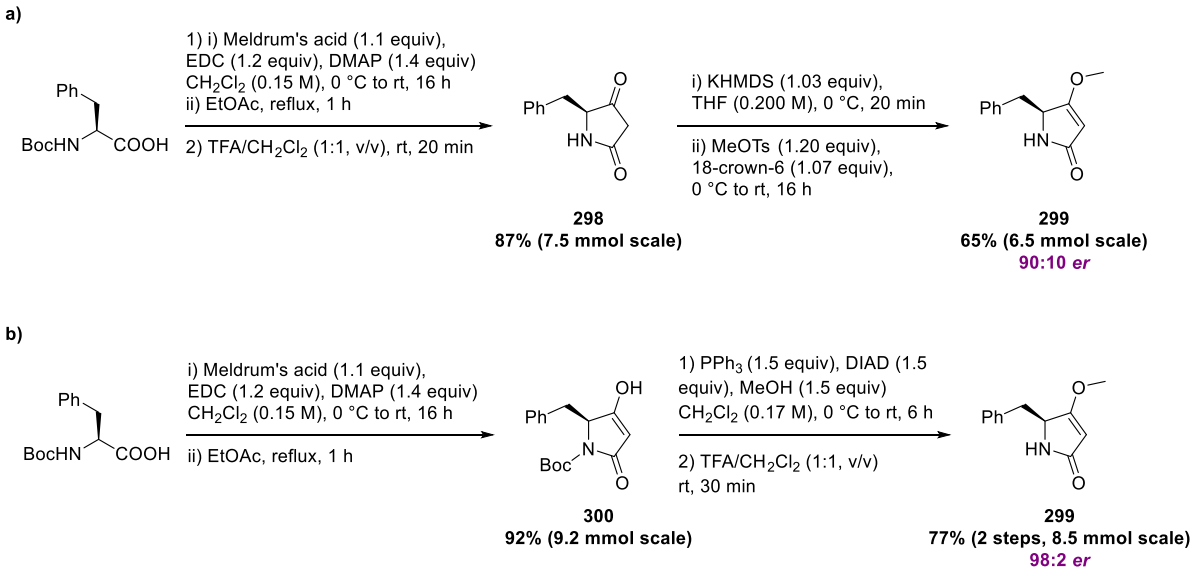
Silyl deprotection of both enantiomers of fragment 3 proceeded smoothly to give the corresponding allylic alcohols **295** and ***ent*-295** (**Scheme 124**). Oxidation using Dess-Martin periodinane afforded the terminal aldehyde which was then subjected to a Pinnick oxidation without intermediate purification affording the required carboxylic acids **296** and ***ent*-296** in good yield. Carboxylic acids **296** and ***ent*-296** were activated as the pentafluorophenyl esters **297** and ***ent*-297** for the key coupling with *O*-methoxy pyrrolin-2-one **299** using Andrus' protocol.[172]



Scheme 124 Synthesis of pentafluorophenyl esters **297** and ***ent*-297**. DCC: N,N'-Dicyclohexylcarbodiimide.

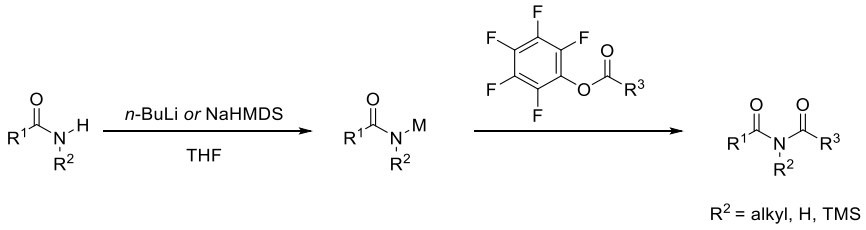
The required *O*-methoxy pyrrolin-2-one (**299**) was originally prepared following the literature procedure described by Tønder and co-workers (**Scheme 125** a).[173] Boc-protected L-phenylalanine was activated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), condensed with Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione), and finally cyclised to give the Boc-protected pyrrolidine-2,4-dione; treatment with trifluoroacetic acid revealed **298**. Deprotonation by KHMDS followed by alkylation with methyl tosylate afforded *O*-methoxy pyrrolin-2-one **299**. However, chiral HPLC analysis of **299** indicated some erosion in enantiopurity from the chiral pool starting material to 90:10 *er*, presumably through KHMDS-mediated epimerisation of intermediate **298**. This was supported by the improvement in *er* value to 98:2 when **299** was prepared following Piccialli and co-workers' strategy *via* **300**, where the *O*-methylation occurs through a Mitsunobu reaction instead (**Scheme 125** b).[174] It is possible that excess DMAP could also epimerise this stereocentre and so the synthesis was

repeated using 1-hydroxy-7-azabenzotriazole (HOAt) for the first step in an attempt to preserve the enantiopurity from the starting material L-phenylalanine, however no formation of the Meldrum's acid adduct was observed. Akaji *et al*. also reported better results with DMAP than HOAt in the analogous condensation step in their preparation of dolastatin 15, and they postulated that this was due to its higher basicity.[175]



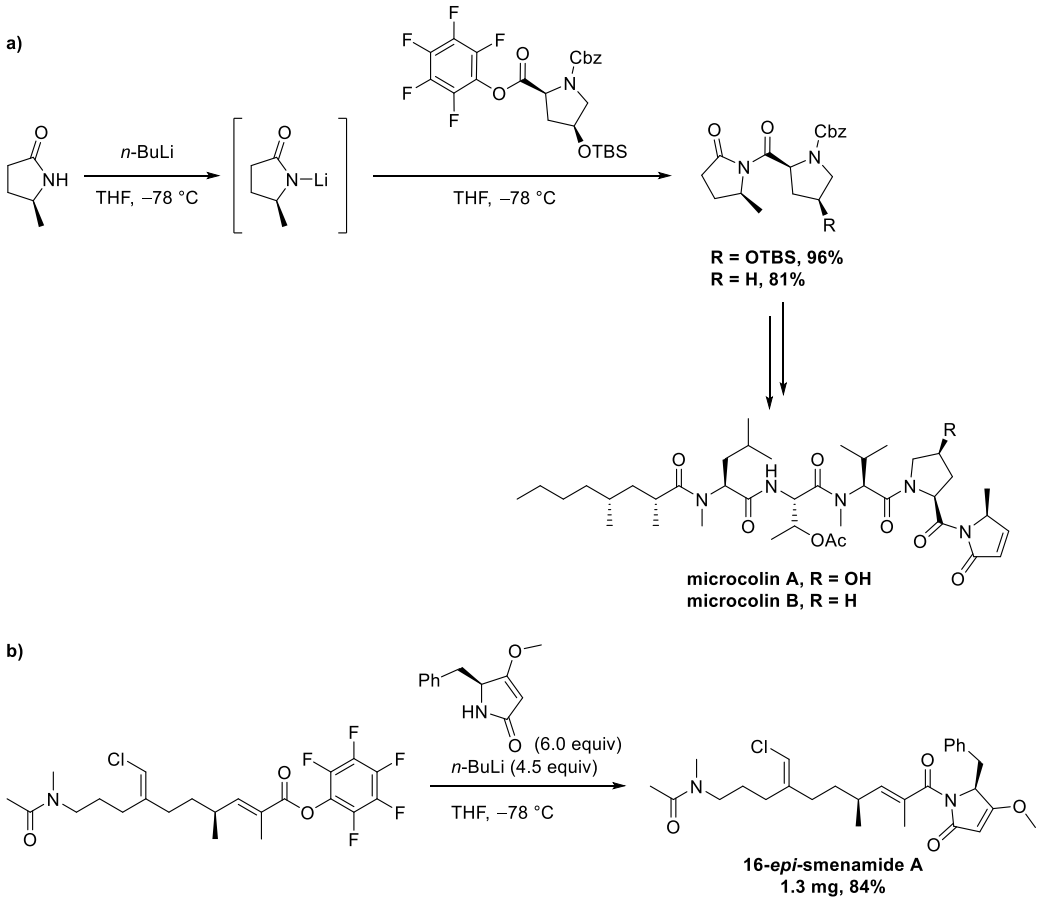
Scheme 125 Synthesis of *O*-methoxy pyrrolin-2-one **299**.

The synthesis of the mixed acyclic imide was performed following a protocol developed by Andrus using pentafluorophenyl esters (**Scheme 126**, **Scheme 127**).[172,176] This mild and general approach tolerates a range of protecting groups and functionality including acid and base sensitive substrates. Moreover it does not require a labile acid chloride and instead uses stable pentafluorophenyl esters which are readily available or easily prepared in one high yielding step from the corresponding carboxylic acid and pentafluorophenol (**Scheme 124**).



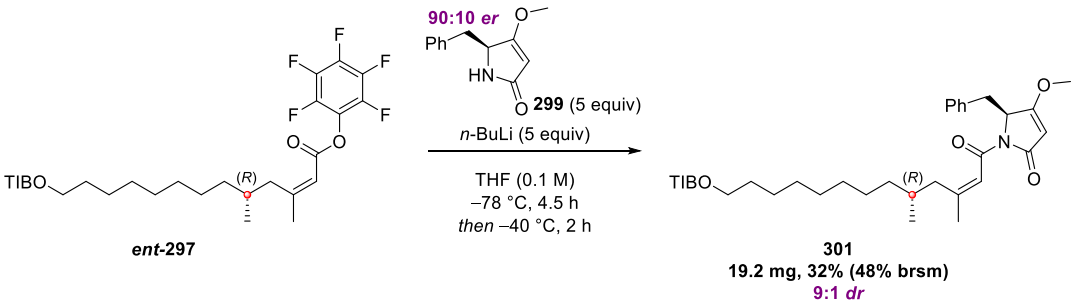
Scheme 126 Synthesis of mixed acyclic imides using pentafluorophenyl esters.

This pentafluorophenyl-based imide formation was applied to the synthesis of microcolin B by Andrus and co-workers (**Scheme 127** a),[172] and as the final step in the recent total synthesis of 16-*epi*-smenamide A by Piccialli and co-workers (**Scheme 127** b).[174]



Scheme 127 Andrus' protocol in total synthesis.

Inspired by these conditions, the synthesis of the first diastereomer of the eastern portion of mycapolyol E was executed as shown in **Scheme 128**. *n*-BuLi was added to *O*-methoxy pyrrolin-2-one **299** in THF at −78 °C. After 15 min lithiation time, pentafluorophenyl ester ***ent*-297** was added as a solution in THF. The reaction was monitored by TLC analysis which showed clean conversion of starting material to product but after 4.5 hours there was still considerable starting material ***ent*-297** remaining. Tønder reported when optimising the *N*-acylation of *O*-ethoxy pyrrolin-2-ones using *n*-BuLi that "raising the temperature from −78 °C to −50 °C led to the increase in nucleophilic reactivity which was necessary for obtaining a synthetically useful reaction"[173] and so the temperature was raised to −40 °C for a further two hours before the reaction was quenched and product **301** was isolated by column chromatography in 32% yield.



Scheme 128 Synthesis of **301** through Andrus' protocol.

Despite this low yield, enough material was obtained to allow ^{1}H and ^{13}C NMR analysis, which confirmed the desired product had been formed as a 9:1 mixture of diastereomers, as expected when using the first batch of **299** with 90:10 *er* (*vide supra*, **Scheme 125** a). The presence of this minor diastereomer was encouraging when the chemical shift of the methyl protons at the stereocentre of interest was compared with the reported data for mycapolyols A-F (**Figure 31**, **Table 26**).[68] The major diastereomer **301** had a doublet at 0.87 ppm but there was another small doublet at 0.83 ppm which was attributed to the minor diastereomer ***ent*-302** (corresponding to epimerisation of the pyrrolinone), which would in fact be an enantiomer of diastereomer **302** (**Scheme 129**), suggesting that the undefined stereocentre at C5 in the natural product has the *S* configuration.

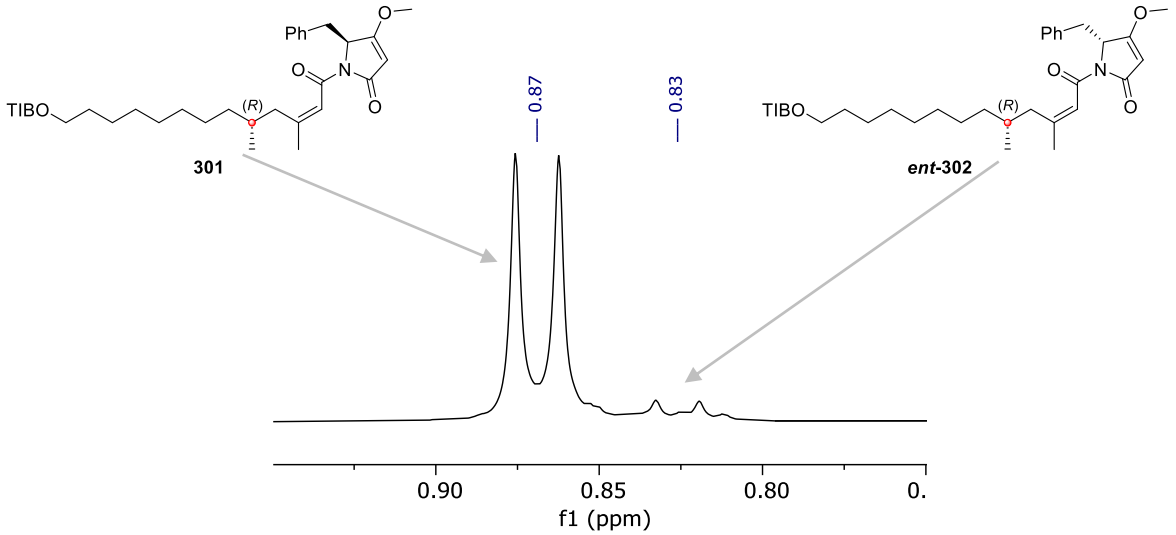
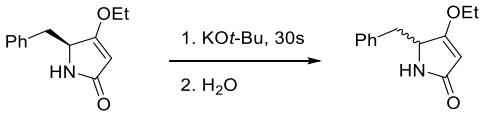


Figure 31 Expansion of ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of **301** (9:1 *dr*) showing doublet for methyl group at C5.

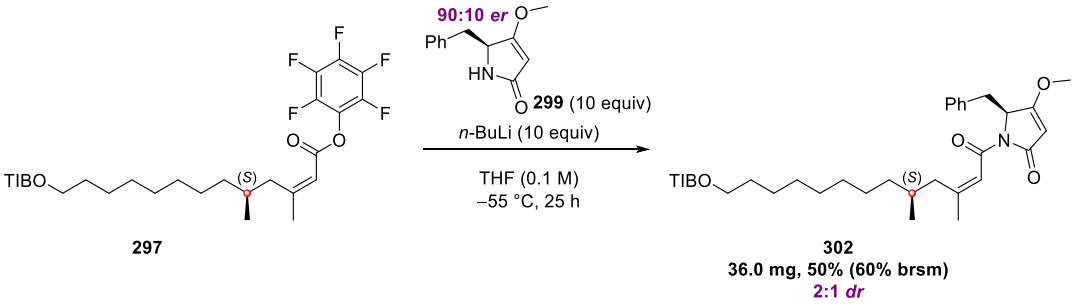
Closer inspection of Tønder's results suggested that the pyrrolinones start to epimerise between −45 and −30 °C (**Table 24**) and indeed it was noted that balancing the poor nucleophilicity and the retention of enantiopurity was an important consideration for *N*-acylation of these substrates.[173]



entry	Temperature /°C	*ee* /%
1	20	0
2	0	79
3	−30	91
4	−45	>99

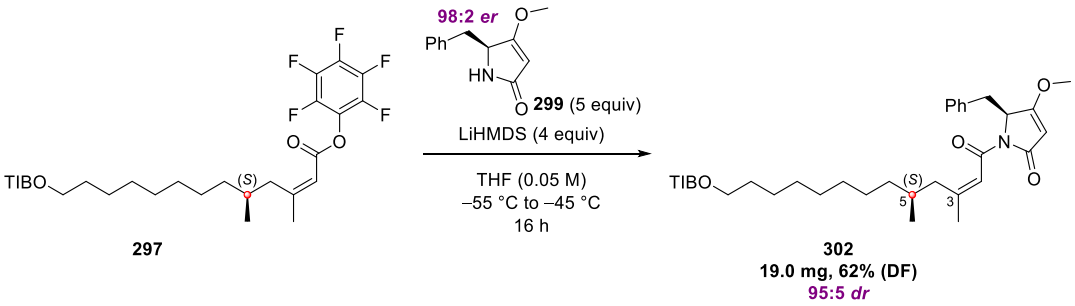
Table 24 Tønder's epimerisation study, reproduced from ref. 173. KO*t*-Bu was used for these experiments which were conducted during investigations into *O*-alkylation prior to optimising *N*-acylation, at which point lithium bases were shown to be superior to potassium bases.

After considering **Table 24**, when preparing diastereomer **302** from pentafluorophenyl ester **297** the temperature was maintained at −55 °C and the reaction again monitored by TLC analysis (**Scheme 129**). After 25 hours there was still some unreacted starting material remaining, a further indication of the poor nucleophilicity of pyrrolinone **299**. This did result in an increased isolated yield of 50% but disappointingly with a lower diastereomeric ratio.



Scheme 129 Synthesis of **302** through Andrus' protocol.

Further work from Tønder and co-workers presented a range of conditions for the optimised *N*-acylation of 4-alkylated pyrroline-2-ones, including the option of using LiHMDS instead of *n*-BuLi, and a yield enhancement upon raising the temperature to −45 °C.[177] These conditions were applied by Ye and co-workers in the total synthesis of sintokamide C where the yield of the desired coupled product was more than doubled (30% to 71%) when the lithium amide was generated at −55 °C using LiHMDS instead of *n*-BuLi, and then reacted with the required pentafluorophenyl ester at −45 °C.[178] Pleasingly these conditions also proved superior for the *N*-acylation of **299** with **297** when attempted by Dr Fiorito (**Scheme 130**, also using **299** with higher *er* prepared as shown in **Scheme 125** b), affording **302** in an improved 62% isolated yield and high *dr* by NMR analysis (**Figure 32**).



Scheme 130 Synthesis of **302** in high *dr* using Ye and co-workers' conditions (DF).

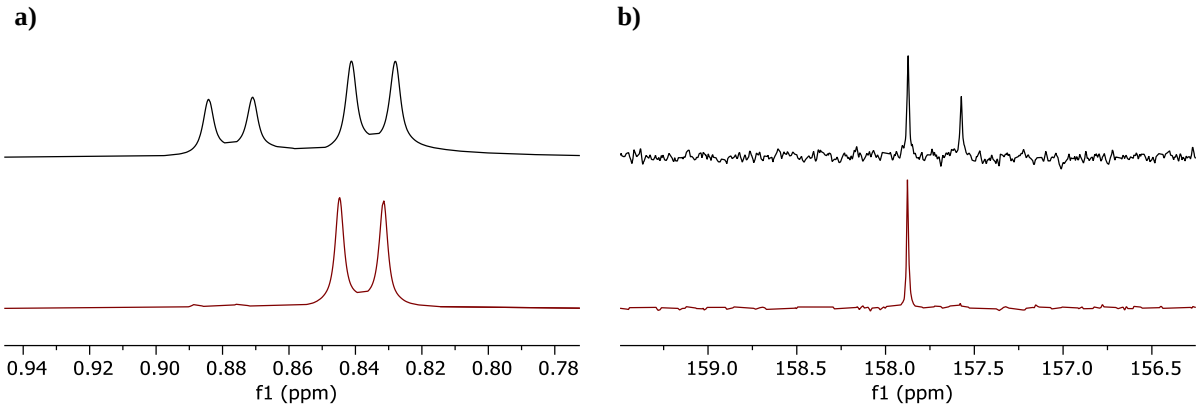


Figure 32 a) ^{1}H NMR (500 MHz, DMSO-d_6) C5-CH_3; b) ^{13}C NMR (126 MHz, DMSO-d_6) C3. Upper trace in black for **302** with 2:1 *dr*; lower trace in red for **302** with 95:5 *dr* (DF).

With both diastereomers of the eastern portion of mycapolyol E prepared, detailed analysis of their ^{13}C and ^{1}H NMR spectra was carried out and compared with the reported data for the natural product from the isolation paper.[1] As shown in **Table 25** and **Table 26**, most of the chemical shifts matched well, validating this approach of considering the eastern fragment independently from the 1,3-polyol. However, while the ^{13}C NMR data for diastereomer **302** matched the natural product perfectly, there were noticeable differences for diastereomer **301** at positions C2, C3, C4, C5 and C5-Me; the alkene carbons and the stereocentre in question, leading to the conclusion that diastereomer **302** has the correct configuration (**Table 25**). This was corroborated by ^{1}H NMR analysis, where the chemical shift of the methyl group at C5 in diastereomer **302** matched that of the natural product (0.82 ppm) but there was a marked shift in the wrong diastereomer **301** (0.87 ppm) (**Table 26**).

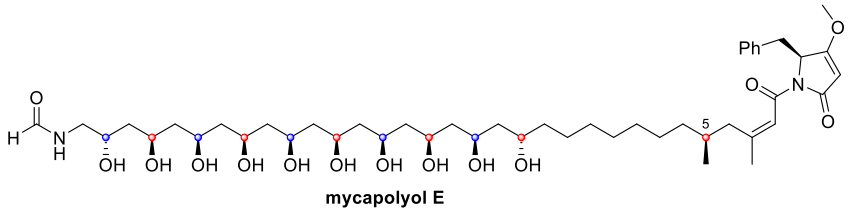
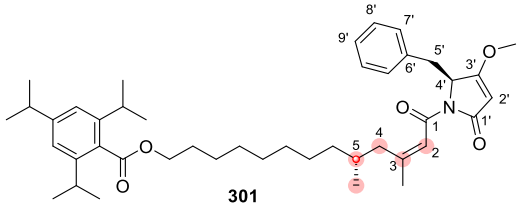
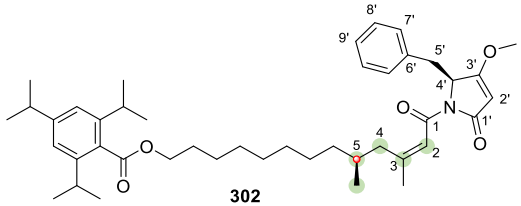


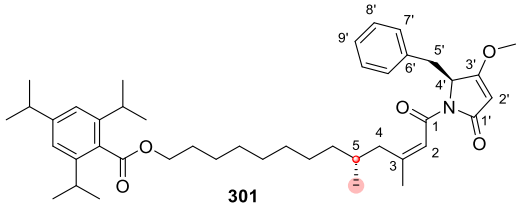
Figure 33 Assignment of stereochemistry at C5 in mycapolyol E.



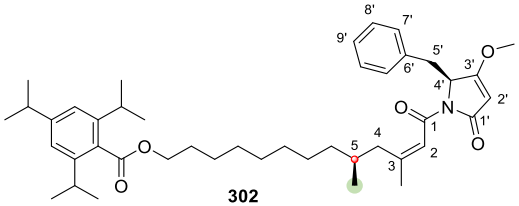


Position	δC mycapolyols							δC 301	Δ	δC 302	Δ
	A	B	C	D	E	F	average				
1	164.0	163.9	164.0	164.0	164.0	164.0	164.0	164.0	0.0	164.0	0.0
2	119.5	119.5	119.5	119.5	119.5	119.5	119.5	119.7	**0.2**	119.5	**0.0**
3	157.9	157.8	157.9	157.8	157.9	157.9	157.9	157.6	**−0.3**	157.9	**0.0**
Me-3	25.3	25.3	25.3	25.3	25.4	25.4	25.3	25.4	0.0	25.5	0.1
4	40.4	40.4	40.4	40.4	40.4	40.4	40.4	40.2	**−0.2**	40.4	**0.0**
5	31.3	31.3	31.3	31.3	31.4	31.3	31.3	31.2	**−0.1**	31.3	**0.0**
Me-5	19.4	19.4	19.4	19.4	19.4	19.4	19.4	19.3	**−0.1**	19.4	**0.0**
1'	169.2	169.2	169.2	169.2	169.3	169.2	169.2	169.2	0.0	169.2	0.0
2'	95.0	95.0	95.0	95.0	95.0	95.0	95.0	95.0	0.0	95.0	0.0
3'	177.5	177.5	177.5	177.5	177.6	177.1	177.5	177.5	0.0	177.5	0.1
OMe-3'	58.7	58.7	58.7	58.7	58.8	58.7	58.7	58.8	0.0	58.7	0.0
4'	58.8	58.8	58.8	58.8	58.9	58.8	58.8	58.8	0.0	58.8	0.0
5'	33.8	33.9	33.8	33.9	33.9	33.8	33.9	33.9	0.0	33.9	0.0
6'	134.3	134.3	134.3	134.3	134.3	134.3	134.3	134.3	0.0	134.3	0.0
7'	129.3	129.3	129.3	129.3	129.4	129.4	129.3	129.3	0.0	129.3	0.0
8'	128.0	128.0	128.0	128.0	128.0	127.9	128.0	128.0	0.0	128.0	0.0
9'	126.8	126.8	126.8	126.8	126.8	126.8	126.8	126.8	0.0	126.8	0.0

Table 25 Comparison of ^{13}C NMR chemical shifts between mycapolyols A-F,[68] **301** and **302**.
All spectra recorded in DMSO-d_6; isolated mycapolyols 151 MHz, **301** and **302** 126 MHz.



301



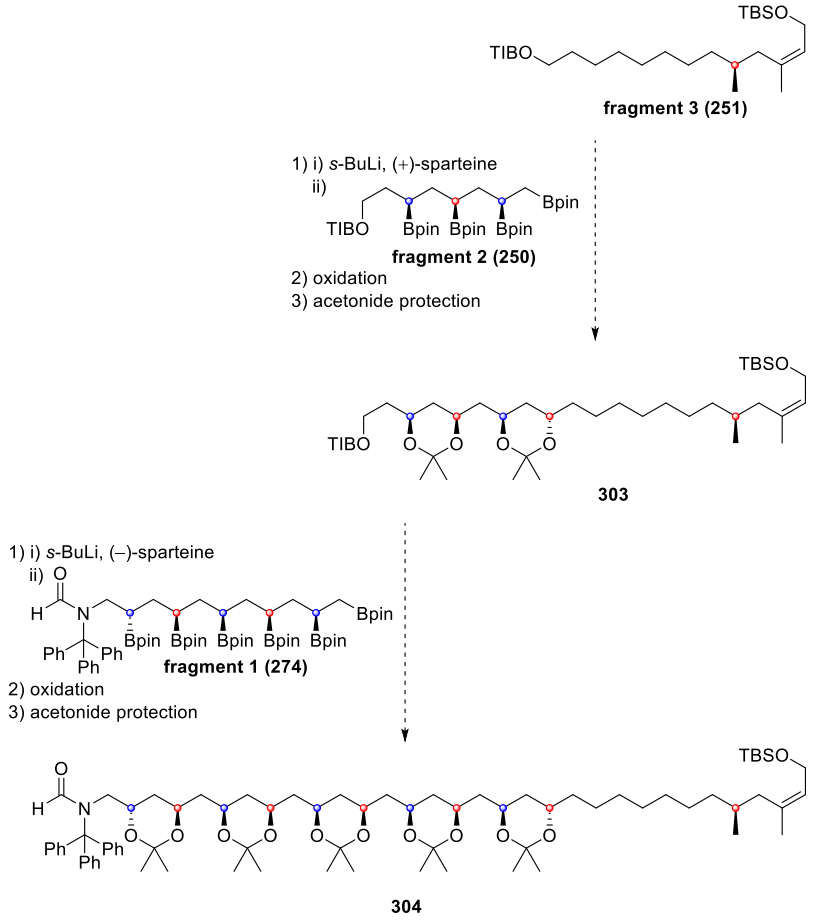
302

position	δH mycapolyols							δH 301	Δ	δH 302	Δ
	A	B	C	D	E	F	average				
2	6.82	6.82	6.78	6.82	6.82	6.82	6.81	6.80	−0.01	6.83	0.02
Me-3	1.87	1.87	1.83	1.87	1.86	1.87	1.86	1.86	0.00	1.87	0.01
4	2.61	2.62	2.58	2.62	2.62	2.62	2.61	2.63	0.02	2.64	0.03
	2.55	2.55	2.51	2.55	2.55	2.55	2.54	2.52	−0.02	2.53	−0.01
5	1.75	1.75	1.70	1.74	1.75	1.74	1.74	1.76	0.02	1.75	0.01
Me-5	0.82	0.82	0.78	0.82	0.82	0.82	0.81	0.87	**0.06**	0.82	**0.01**
2'	5.08	5.08	5.05	5.08	5.08	5.09	5.08	5.09	0.01	5.09	0.01
OMe-3'	3.81	3.81	3.78	3.82	3.81	3.82	3.81	3.82	0.01	3.82	0.01
4'	4.91	4.91	4.87	4.91	4.91	4.91	4.90	4.90	0.00	4.91	0.01
5'	3.40	3.40	3.36	3.40	3.40	3.40	3.39	3.41	0.02	3.40	0.01
	2.99	3.00	2.95	3.00	3.00	2.99	2.99	3.00	0.01	3.00	0.01
7'	6.86	6.87	6.82	6.87	6.86	6.86	6.86	6.87	0.01	6.87	0.01

Table 26 Comparison of ^{1}H NMR chemical shifts between mycapolyols A-F,[68] **301** and **302**.
All spectra recorded in DMSO-d_6; isolated mycapolyols 600 MHz, **301** and **302** 500 MHz.

4.5 Fragment Unification through Lithiation–Borylation Reactions

With a reasonable amount of fragments 1, 2 and 3 in hand, the next step was to couple the fragments together through lithiation–borylation reactions (**Scheme 131**).



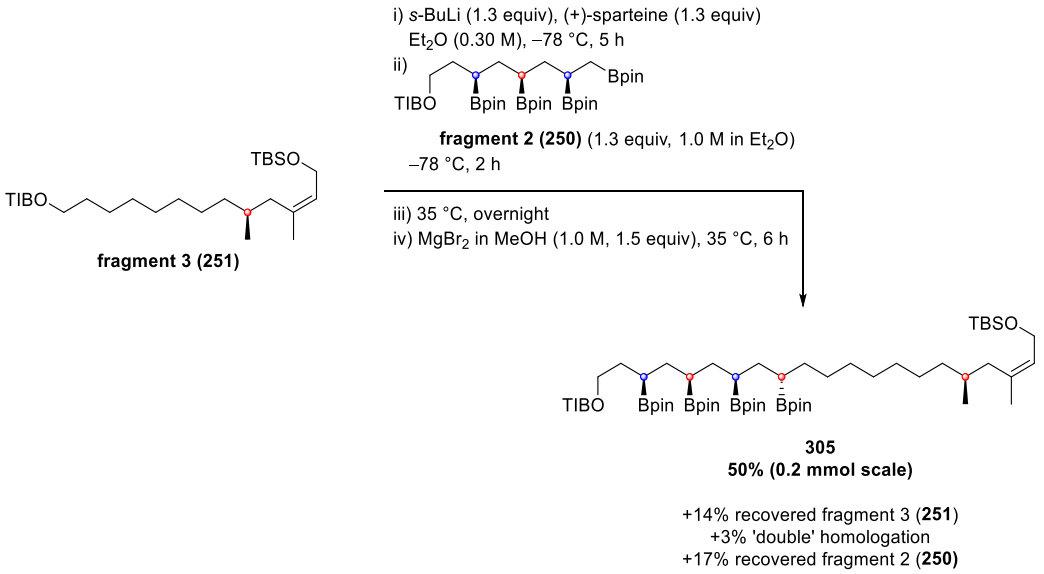
Scheme 131 Proposed coupling of fragments 1, 2 and 3 in the synthesis of mycapolyol E.

Fragment 3 (**251**) will be subjected to lithiation–borylation reactions with first fragment 2 (**250**) and then fragment 1 (**274**) to construct advanced intermediate **304** containing the full stereodefined 1,3-polyol domain of mycapolyol E (**Scheme 131**). After each homologation, the boronic esters will be oxidised and protected as 1,3-diol acetonides to avoid nucleophilic attack by *s*-BuLi during subsequent lithiation.

4.5.1 Lithiation–borylation of fragment 3 (251) with fragment 2 (250)

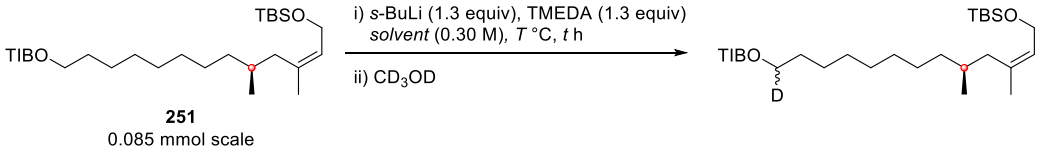
The first homologation reaction was attempted as shown in **Scheme 132**. Fragment 3 (**251**) was treated with 1.3 equivalents of (+)-sparteine ligated *s*-BuLi and the temperature maintained at −78 °C for 5 hours lithiation time. Fragment 2 (**250**) was added as a solution in diethyl ether and the reaction mixture kept at −78 °C for 2 hours borylation time. The reaction mixture was then heated overnight at 35 °C for 1,2-migration. After this time ^{11}B NMR

analysis showed some remaining boronate complex so magnesium bromide in methanol was added and heating continued until no further change was observed by ^{11}B NMR analysis. Following an aqueous work-up and column chromatography, the desired homologated product **305** was obtained in 50% isolated yield.



Scheme 132 Initial conditions for lithiation–borylation of fragment 3 (**251**) with fragment 2 (**250**).

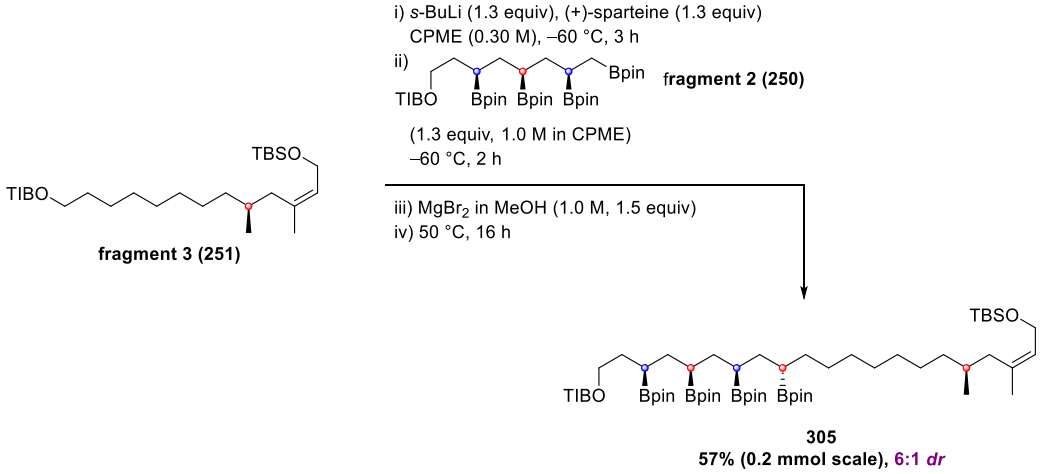
As some unreacted fragment 3 (**251**) was recovered, this suggested that it had not been fully lithiated under these conditions (**Scheme 132**) which prompted a lithiation–deuteration study (**Table 27**). Similar levels of deuterium incorporation—and therefore lithiation—were observed when quenching with deuterated methanol after 5 hours at −78 °C in either diethyl ether or CPME (entries 1 and 2, **Table 27**). Raising the lithiation temperature to −60 °C resulted in a small improvement in diethyl ether (entry 3) but complete lithiation in CPME (entry 4). The lithiation time at −60 °C in CPME could be reduced to 3 hours (entry 5).



Entry	Solvent	Temperature /°C	Time /h	D incorporation
1	Et_2O	−78	5	86%
2	CPME	−78	5	87%
3	Et_2O	−60	5	92%
4	CPME	−60	5	100%
5	CPME	−60	3	100%

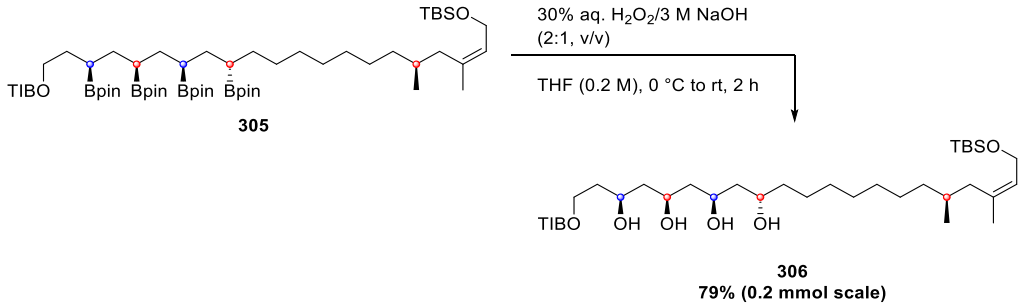
Table 27 Optimisation of lithiation conditions for fragment 3 (**251**).

These optimised lithiation conditions (entry 5, **Table 27**) were then applied to the lithiation–borylation of fragment 3 (**251**) with fragment 2 (**250**) and afforded homologation product **305** in 57% isolated yield (**Scheme 133**), also in Dr Fiorito's hands.



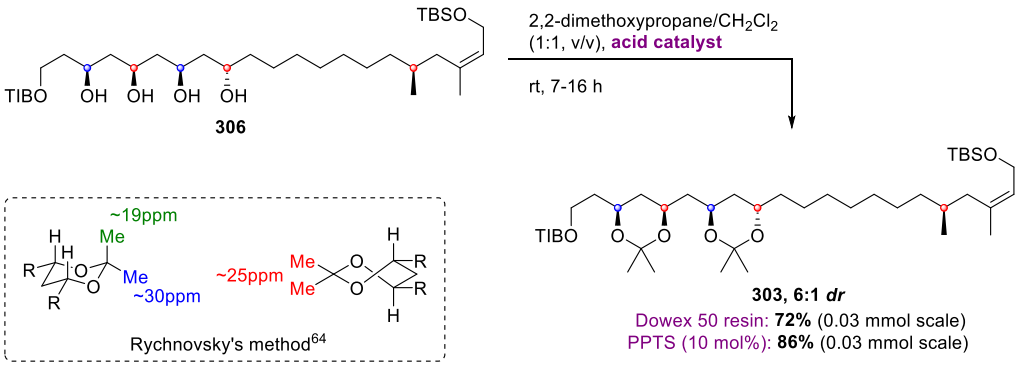
Scheme 133 Optimised lithiation–borylation of fragment 3 (**251**) with fragment 2 (**250**); *dr* determined by ^{13}C NMR analysis.

Poly(oxidation) of tetra(boronic ester) **305** using basic hydrogen peroxide proceeded smoothly to give tetraol **306** in 79% isolated yield (**Scheme 134**).



Scheme 134 Oxidation of tetra(boronic ester) **305**.

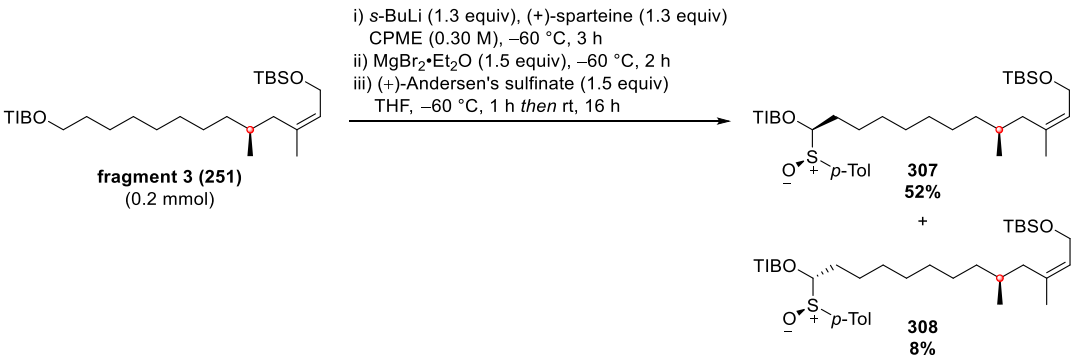
Acetonide protection of tetraol **306** was first attempted in neat 2,2-dimethoxypropane with catalytic PTSA; while the acetonide groups were installed and ^{13}C NMR analysis confirmed the expected stereochemistry of the major diastereomer (Rychnovsky's method),[64] the TBS protecting group was not stable to these acidic conditions. Using Dowex 50[179]—a cation exchange resin—effected acetonide protection without cleaving the silyl group and afforded bis(acetonide) **303** in 72% isolated yield (**Scheme 135**), and this yield could be improved to 86% with pyridinium *p*-toluenesulfonate (PPTS), with the TBS-protected alcohol intact.



Scheme 135 Acetonide protection of tetraol **306**. Reported *dr* determined by ^{13}C NMR analysis.

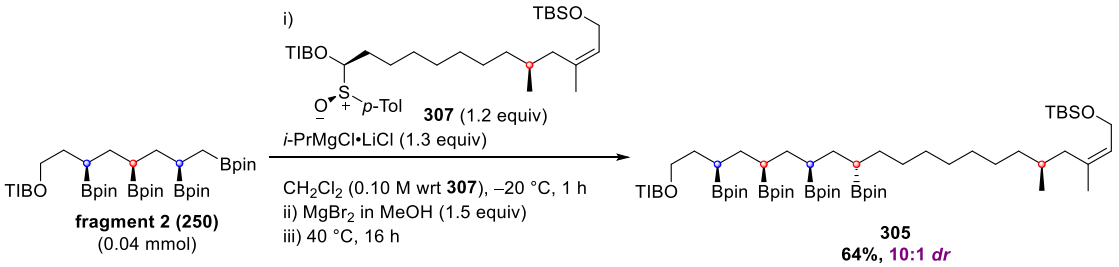
At this point, minor diastereomers—presumably mainly generated in the diboration steps—were observable by TLC analysis, as well as NMR analysis (**Figure 35** a), but unfortunately conditions were not identified to fully separate these by column chromatography. Purification on a normal phase preparative HPLC system (hexane:ethyl acetate, Kromasil 60-5SIL 250 mm × 21.2 mm column) did result in separation of a minor diastereomer containing 2 *anti* 1,3-diol acetonides by ^{13}C NMR analysis from the desired (major) diastereomer **303**, which was isolated with a slightly improved diastereomeric ratio of 7:1 (**Figure 35** b). It was speculated that starting with fragment 2 (**250**) with a higher *dr* value (*vide supra*, **Scheme 97**) would be more likely to enable access to **303** in higher *dr* than pursuing further optimisation of the chromatographic separation of diastereomers. However, the lithiation–borylation of fragment 3 (**251**) with ≥95:5 *dr* fragment 2 (**250**) did not significantly improve the *dr* of the homologated product **305** (**Figure 34** b) and so it was concluded that the stereoselectivity of the (+)-sparteine mediated asymmetric lithiation was not as high as hoped; perhaps fragment 3 (**251**) falls into a mis-matched case with (+)-sparteine, repeating the homologation reaction with (−)-sparteine for comparison could verify this.

Instead it was decided to explore the homologation of fragment 2 (**250**) using α-sulfinyl benzoate **307**, prepared from fragment 3 (**251**) (**Scheme 136**). As previously discussed, trapping with enantiopure (+)-Andersen's sulfinate allowed separation of the minor diastereomer **308**, generated in the asymmetric deprotonation step. The ratio of isolated **307** to **308** (6.5:1) did indicate that the lithiation step was contributing to the diastereomeric mixture observed before (**Scheme 133**). This ratio, and therefore the level of stereocontrol exerted by (+)-sparteine in the lithiation of **251**, was confirmed by ^{1}H NMR analysis of the crude mixture before chromatographic purification when the synthesis of α-sulfinyl benzoate **307** was repeated.



Scheme 136 Preparation of α-sulfinyl benzoate **307** from fragment 3 **(251)**.

α-Sulfinyl benzoate **307** was then employed in a homologation reaction with fragment 2 (**250**) (**Scheme 137**), using the previously optimised conditions for homologation of a tetra(boronic ester) using a magnesiated carbenoid (*vide supra*, **Scheme 108**), with the inclusion of magnesium bromide in methanol to aid 1,2-migration. This proceeded in acceptable yield, with no detectable formation of the over-homologation product, and importantly allowed isolation of **305** in high *dr* (**Figure 34** c).



Scheme 137 Homologation of fragment 2 (**250**) with α-sulfinyl benzoate **307**.

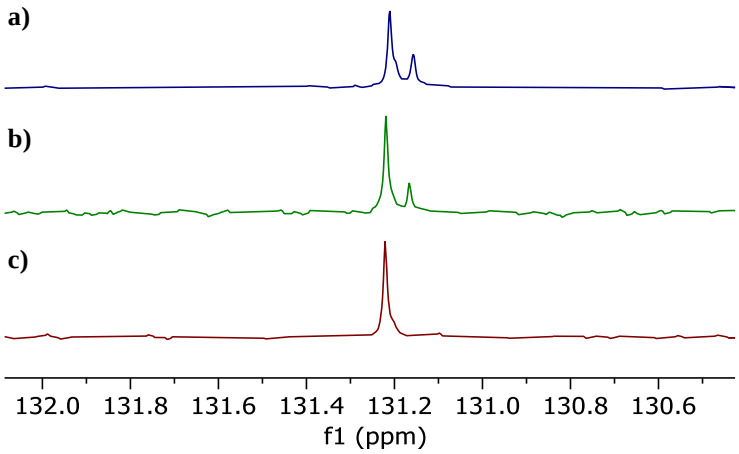


Figure 34 ^{13}C NMR (126 MHz, $CDCl_3$) CO *ipso* OTIB for **305**: a) prepared as shown in **Scheme 133** with 8:1 *dr* fragment 2 (**250**); b) prepared as shown in **Scheme 133** with ≥95:5 *dr* fragment 2 (**250**); c) prepared as shown in **Scheme 137** with ≥95:5 *dr* fragment 2 (**250**).

Poly(oxidation) of **305** (prepared as shown in **Scheme 137**) using basic hydrogen peroxide and protection of the resultant tetraol **306** as before yielded bis(acetonide) **303** which was isolated with an improved *dr* value of 95:5 (**Figure 35** c).

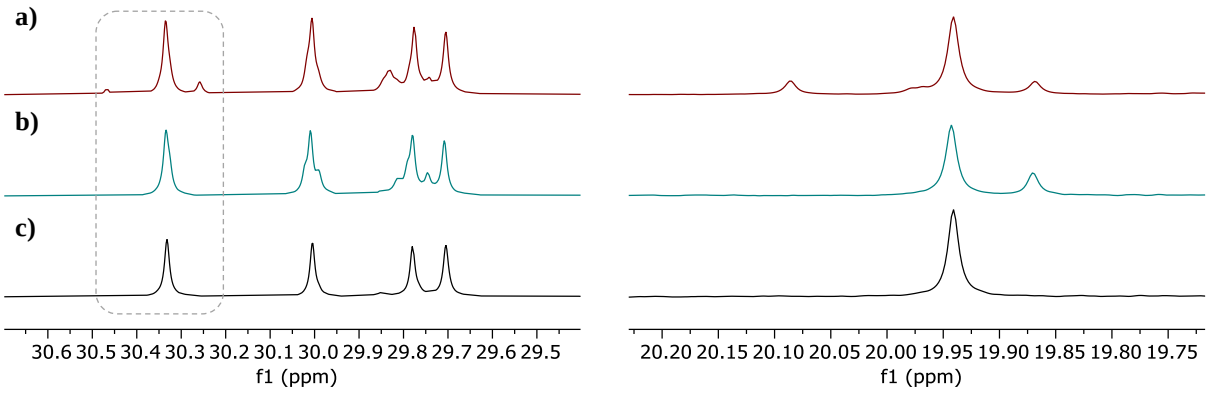


Figure 35 ^{13}C NMR (126 MHz, $CDCl_3$) *syn*-acetonide CH_3 in **303**: a) prepared from 6:1 *dr* **305**, lithiation–borylation product (**Scheme 133**); b) after normal phase preparative HPLC; c) prepared from 10:1 *dr* **305**, product from α-sulfinyl benzoate homologation (**Scheme 137**).

The presence of some minor diastereomers was not altogether surprising, and was taken to represent a limitation of the iterative diboration–homologation protocol for the preparation of stereodefined 1,3-polyols pioneered in this work, namely the accumulation of minor diastereomers from the diboration steps which are expected to proceed in typically 97:3 *er*. ^{13}C NMR analysis of **305** did suggest the presence of some minor diastereomers even after switching to the use of α-sulfinyl benzoate **307** for the homologation of fragment 2 (**251**) (**Figure 36** c, suspected minor peaks slightly downfield). This was corroborated by analytical work performed by collaborators at Merck Research Laboratories (Merck and Co., Inc, USA) using tetraol **309**, prepared through oxidation of fragment 2 (**250**) (**Figure 37**).[180] Regalado and co-workers developed a trapping-enrichment multi-dimensional liquid chromatography platform which is capable of separating closely related components such as diastereomers for rapid structure elucidation and characterisation, on 100 µg material in this case. Separation on a chiral stationary phase using an acidic mobile phase revealed that even when fragment 2 (**250**) appeared to have been isolated in >95:5 *dr* by ^{13}C NMR analysis (**Scheme 97**) it still contained at least 2 minor diastereomers identified by MS detection in a ratio 95:2.4:2.6 (UV data).

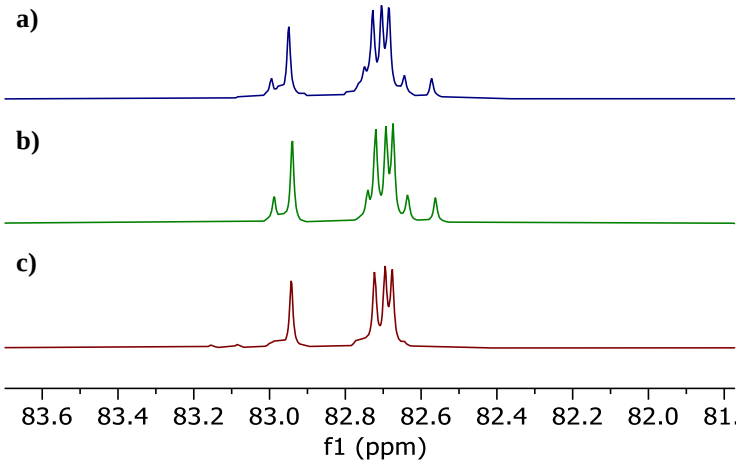


Figure 36 ^{13}C NMR (126 MHz, $CDCl_3$) 8 × pinacol C-O for **305**: a) prepared as shown in **Scheme 133** with 8:1 *dr* fragment 2 (**250**); b) prepared as shown in **Scheme 133** with ≥95:5 *dr* fragment 2 (**250**); c) prepared as shown in **Scheme 137** with ≥95:5 *dr* fragment 2 (**250**).

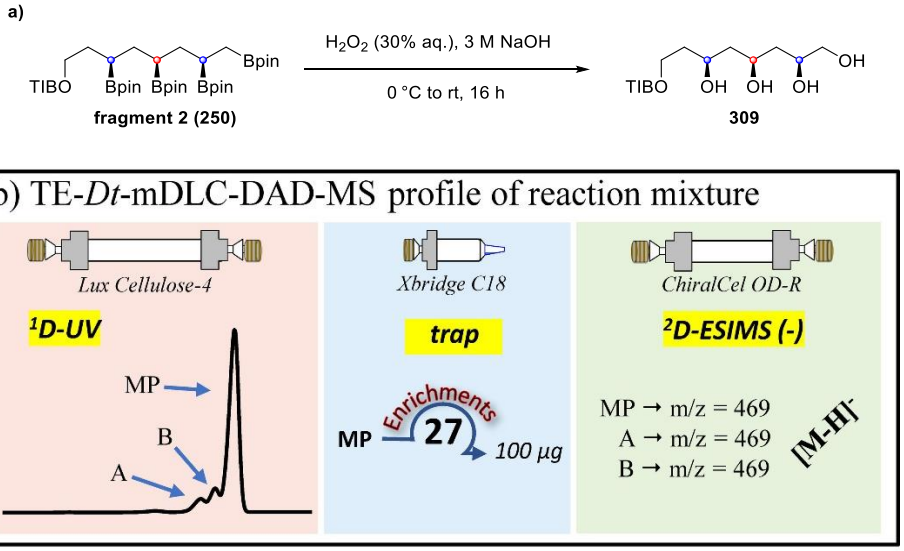
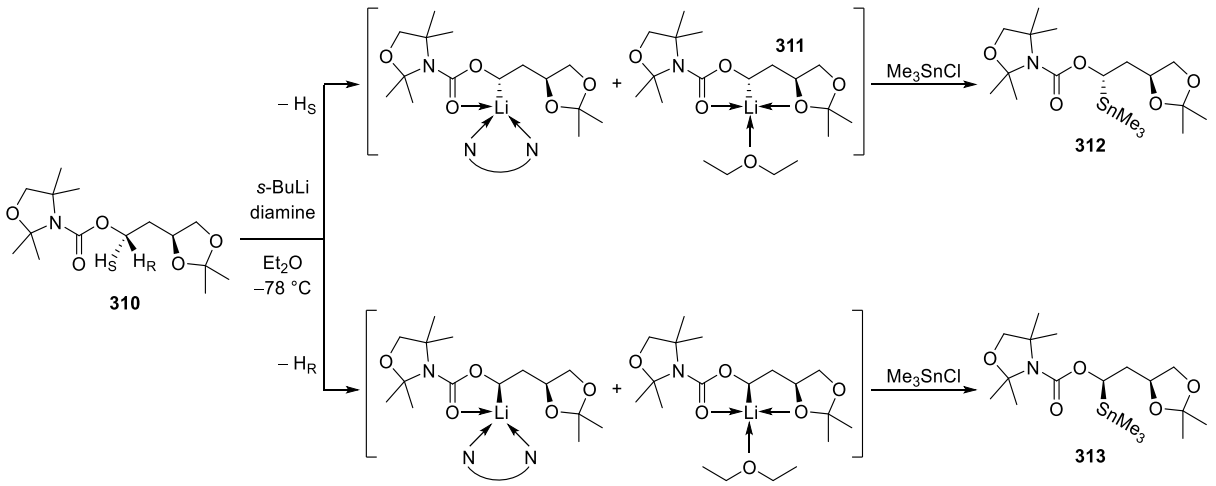


Figure 37 a) Oxidation of tetra(boronic ester) **250**. b) purification and identification of reaction components by trapping enrichment multi-dimensional liquid chromatography, reproduced from ref. 180.

4.5.2 Acetonide-directed lithiation

The lithiation–borylation of bis(acetonide) **303** (**Scheme 138** a) required some investigation; it was speculated that the presence of a 6-membered acetonide in the β-position with respect to the metalation centre could exert some control both on the selectivity of the deprotonation step and on the stability of the lithiated species. Acetonide-directed lithiation has been described by Hoppe who showed that a 5-membered acetonide could direct lithiation *anti* to the acetonide, through coordination of the acetonide oxygens to the lithium ion (**Table 28**).[181]



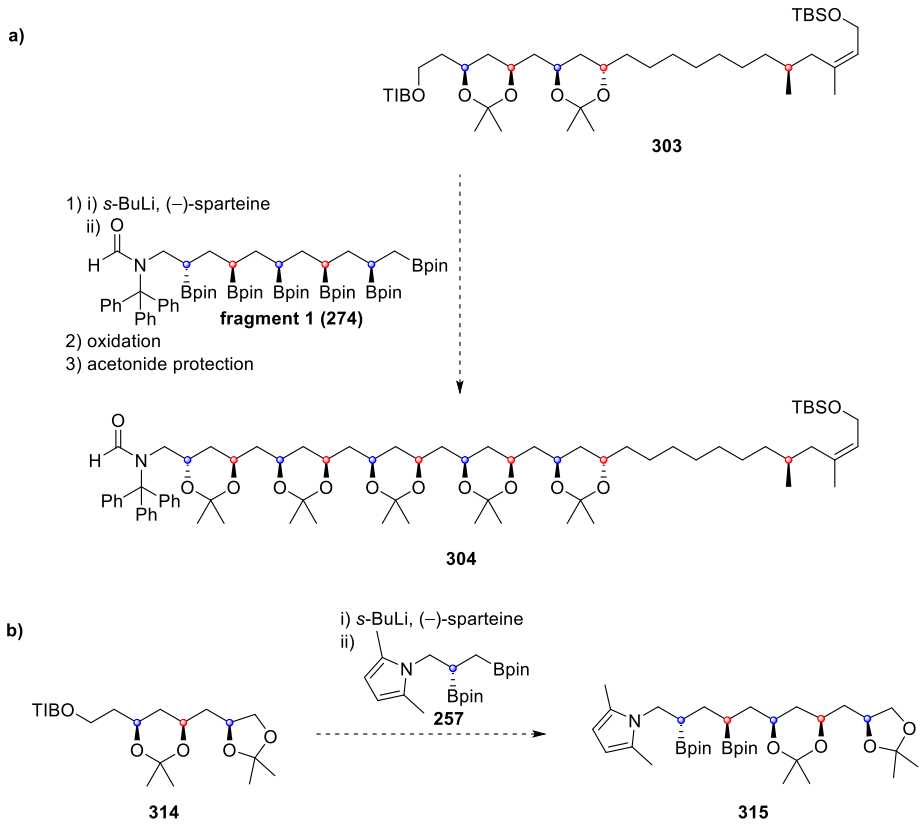
Entry	diamine	Yield /%	*dr* (ratio 312:313)
1	TMEDA	71	65:35
2	none	63	98:2
3	(−)-sparteine	61	>99:1
4	(+)-sparteine	75	28:72

Table 28 Hoppe's matched/mis-matched lithiation of 5-membered acetonides.

Carbamate **310** could be deprotonated with *s*-BuLi/TMEDA; electrophilic trapping with trimethyltin chloride yielded a 65:35 mixture of stannane **312** (corresponding to removal of the pro-*S* proton) and stannane **313** (corresponding to removal of the pro-*R* proton) (entry 1, **Table 28**). In the absence of a chelating diamine ligand, the ratio increased to 98:2, showing clear substrate control (entry 2). This was attributed to the β-oxygen atom of the acetonide coordinating to the lithium ion to give bicyclic chelate complex **311** preferentially. This induction in the deprotonation step caused by the chiral acetonide was decreased in the presence of the achiral bidentate ligand TMEDA (entry 1). With the chiral diamine (−)-sparteine, the combined directing effects of both the acetonide oxygen and (−)-sparteine resulted in no detectable formation of the minor isomer **313** (entry 3). Deprotonation with the enantiomer (+)-sparteine ligated *s*-BuLi yielded **313** as the major product, but in a poorer enantiomeric ratio due to this being the mis-matched case (entry 4).

By analogy with Hoppe's observations, it was postulated that substrate **303**, with its 6-membered acetonide, should also fall into the matched case with (−)-sparteine and so any substrate control affecting lithiation should work with the reagent to maximise the stereoselectivity, if 6-membered acetonides direct in the same way as 5-membered acetonides. In order to probe this key homologation, a test coupling between model substrate **314** (derived

from fragment 2) and pyrrole 1,2-bis(boronic ester) **257**—a truncated version of the original fragment 1 (**249**)—was investigated first (**Scheme 138** b).

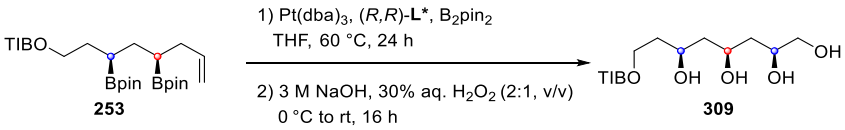


Scheme 138 a) Lithiation–borylation of a 6-membered acetonide containing triisopropylbenzoate ester in the proposed synthesis of mycapolyol E. b) Planned model test coupling.

4.5.3 Model studies for lithiation–borylation of a 6-membered acetonide-containing benzoate

4.5.3.1 Synthesis of model substrate 314

Model substrate **314** was initially prepared from homologated intermediate **253** (see **Scheme 97** for its preparation). Enantioselective diboration can be followed directly by oxidation using basic hydrogen peroxide, as reported by Morken,[50] which afforded tetraol **309**, without isolation of the intermediate tetra(boronic ester) **250** (**Table 29**).

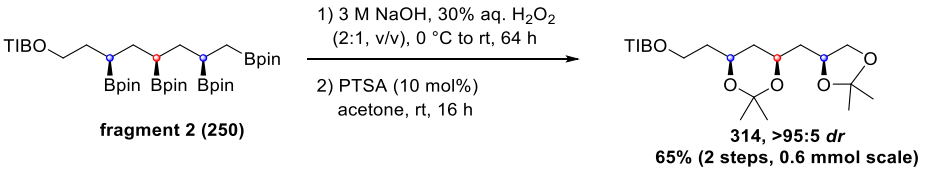


Entry	Scale /mmol 253	Pt(dba)$_3$ /equiv	(*R*,*R*)-L* /equiv	B_2pin_2 /equiv	Concentration /M	Yield 309 /%
1	0.1	0.03	0.06	1.20	0.1	32
2	0.4	0.05	0.06	1.05	1	23
3	0.5	0.05	0.06	1.05	1	27

Table 29 Varying diboration–oxidation conditions.

Initial difficulties with accessing tetraol **309** could be attributed to the challenge of isolating this relatively polar molecule. ^{1}H NMR analysis of the crude material showed no alkenes remaining, indicating the diboration reaction had worked well. New work-up conditions using 17% aqueous sodium sulfate and ethyl acetate, developed by Merck to isolate polar molecules,[182] were successful in ensuring no product was lost in the aqueous layer. The crude material could then be purified by flash column chromatography on silica gel using 5% methanol in dichloromethane as eluent, but this purification was time consuming and the isolated yields were still disappointing (**Table 29**).

In view of this, it was decided to instead isolate and purify the tetra(boronic ester), *i.e.* fragment 2 (**250**). Crude tetraol **309** was directly subjected to the acetonide protection conditions; the reaction proceeded cleanly to the bis(acetonide) product with no intermediates isolated or apparent during TLC monitoring. Chromatographic purification after 2 steps afforded model substrate **314** in good yield and high *dr* (**Scheme 139**).



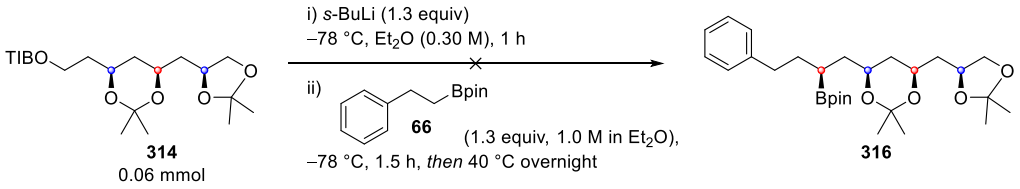
Scheme 139 Optimised synthesis of model substrate **314** from fragment 2 (**250**). Reported *dr* value determined by NMR analysis after purification.

With sufficient quantities of the model substrate in hand, attention then turned to investigating and optimising each of the 3 phases of the lithiation–borylation reaction.

4.5.3.2 Lithiation of bis(acetonide) benzoate ester 314

In view of the acetonide-directed lithiation reported by Hoppe (*vide supra*), it was decided to first examine whether lithiation of model substrate **314** without diamine was feasible, and if so, to obtain an indication of any operative substrate control.

First, a lithiation–borylation reaction of the model substrate **314** using boronic ester **66** (**Scheme 140**), in order to avoid any potential issues with selectivity for the primary or secondary boronic ester when using a less hindered carbenoid; diamine-free lithiated carbenoids have been shown to undergo borylation with secondary boronic esters (*vide supra*, **Scheme 26**). After 1 hour lithiation time at −78 °C and 1.5 hours borylation time at −78 °C, the reaction was checked by ^{11}B NMR analysis (**Figure 38**) which showed very little boronate formation (6.1 ppm).



Scheme 140 Lithiation–borylation without diamine.

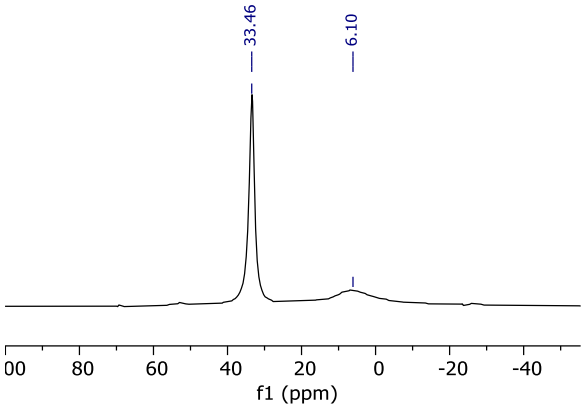
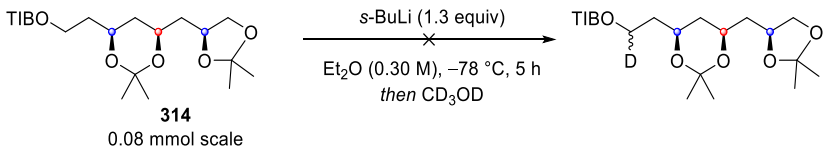


Figure 38 ^{11}B NMR (96 MHz) spectrum after 1 h lithiation time at −78 °C and 1.5 h borylation time at −78 °C.

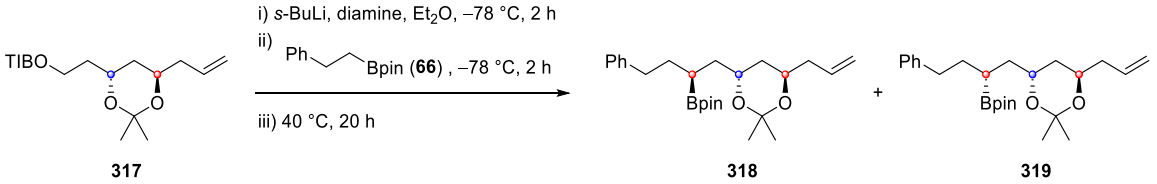
Consequently, a lithiation–trapping experiment was conducted (**Scheme 141**) which revealed that lithiation of **314** does not occur in the absence of a diamine ligand, in contrast to Hoppe's results (**Table 28**). After 5 hours lithiation time, the reaction was quenched with deuterated methanol. Crude ^{1}H NMR analysis showed no deuterium incorporation.



Scheme 141 Lithiation–deuteration of **314**.

It should be noted that Hoppe's substrate **310**, which did undergo lithiation without diamine, bears a carbamate directing group in contrast to the triisopropylbenzoate ester in model substrate **314** in this work. During comparison of diisopropyl carbamates and triisopropylbenzoates using *in situ* IR monitoring, an additional transient signal was observed for carbamates upon the addition of *s*-BuLi which was tentatively attributed to a prelithiation complex,[26] where the carbamate carbonyl oxygen binds a lithium ion.[183] This potential difference in the intermediates on the pathway to the lithiated species from a carbamate or benzoate could mean that the carbamate in **310** contributes to it being susceptible to lithiation in the absence of a diamine ligand, in contrast to the triisopropylbenzoate of interest in this work.

Model studies with a similar fragment (**317**) were later performed by Dr Fiorito when probing a key lithiation–borylation reaction in the total synthesis of bastimolide B (**Table 30**).[149] In this case there was also no lithiation of 6-membered acetonide-containing **317** without diamine (entry 1), and so it was concluded that these 6-membered acetonide benzoates behave differently to Hoppe's 5-membered acetonide carbamates. In the presence of TMEDA, deprotonation of **317** occurred to give a 1.3:1 diastereomeric mixture (entry 2). Reagent control was shown to dominate over this small level of substrate control in the selective preparation of **318** or **319** through the choice of either (−)- or (+)-sparteine, respectively (entries 3 and 4).



317 **318** **319**

Entry	diamine	Yield /%	*dr* (ratio 318:319)
1	none	0	-
2	TMEDA	89	1.3:1
3	(−)-sparteine	64	20:1
4	(+)-sparteine	69	1:12

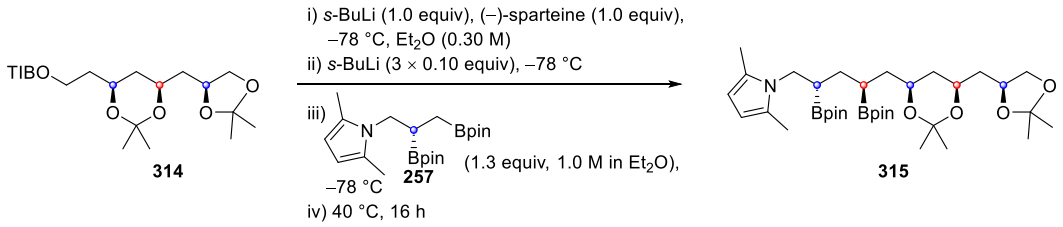
Table 30 Lithiation study of **317** (DF).

4.5.3.3 Lithiation–borylation with *in situ* IR monitoring

Having tested the lithiation qualitatively and established that there is no lithiation of model substrate **314** in the absence of a diamine ligand, efforts moved to collecting quantitative data regarding lithiation time and stoichiometry.

^{11}B NMR analysis is a useful technique to monitor the latter stages of the lithiation–borylation reaction (*i.e.* checking full boronate complex formation and monitoring the 1,2-migration) as demonstrated in the homologation optimisation for the synthesis of fragments 1 and 2 (see section **4.2**), but it is more difficult to probe the lithiation and borylation processes since these are carried out at cryogenic temperatures. *In situ* IR monitoring can be used to follow the benzoate carbonyl peak; its proximity to the lithiation centre means the C–O bond strength and therefore IR absorbance is altered distinctly as the reaction progresses.[26] The carbonyl peak in benzoate ester starting material **314** was observed at 1729 cm^{-1}. Once *s*-BuLi and (−)-sparteine are added, this peak would be expected to decay as a new peak for the carbonyl in the lithiated species at 1636 cm^{-1} appears. Upon addition of the boronic ester, the peak for the carbonyl bond in the lithiated species should decay as a new peak for the carbonyl in the boronate complex appears.

A lithiation–borylation reaction between bis(acetonide) **314** and 1,2-bis(boronic ester) **257** was conducted with *in situ* IR monitoring (**Scheme 142**, **Figure 39**), using (−)-sparteine. A TMEDA-assisted lithiation–borylation reaction between **314** and **257** was not attempted since it had been previously shown that a TMEDA-ligated lithiated carbenoid is not sufficiently hindered to ensure good selectivity for the primary boronic ester[48] and so the reaction mixture would be expected to contain significant amounts of the undesired over-homologation product.



Scheme 142 Test couping between model substrate **314** and pyrrole 1,2-bis(boronic ester) **257** monitored using *in situ* IR.

Upon addition of 1 equivalent of *s*-BuLi and (−)-sparteine (**Figure 39** (i)), the benzoate peak decayed and the lithiated species appeared rapidly and then plateaued. A further 0.1 equivalents of *s*-BuLi was added 3 times (**Figure 39** (ii), (iii), (iv)), until the benzoate had

been consumed and all the material was present as the lithiated species. This shift in the carbonyl peak (benzoate to lithiated species) confirmed that lithiation with (−)-sparteine does occur at the expected position, *alpha* to the triisopropylbenzoate ester, given that the previous experiments showed no lithiation of **314** in the absence of diamine.

Boronic ester **257** was added in diethyl ether (**Figure 39** (v)) and subsequent borylation, monitored by disappearance of the lithiated species and appearance of the boronate, was slow. Diethyl ether had been chosen as the solvent for borylation instead of THF to avoid displacing (−)-sparteine from the lithiated complex so that selectivity for the primary boronic ester was as high as possible. After 2.5 hours borylation time, the reaction was quenched with methanol (**Figure 39** (vi)), to protonate any excess lithiated carbenoid and so prevent over-homologation, then the IR probe was removed and the reaction mixture was heated at 40 °C for 1,2-migration, which was complete after 16 hours at which point ^{11}B NMR analysis showed mainly boronic ester.

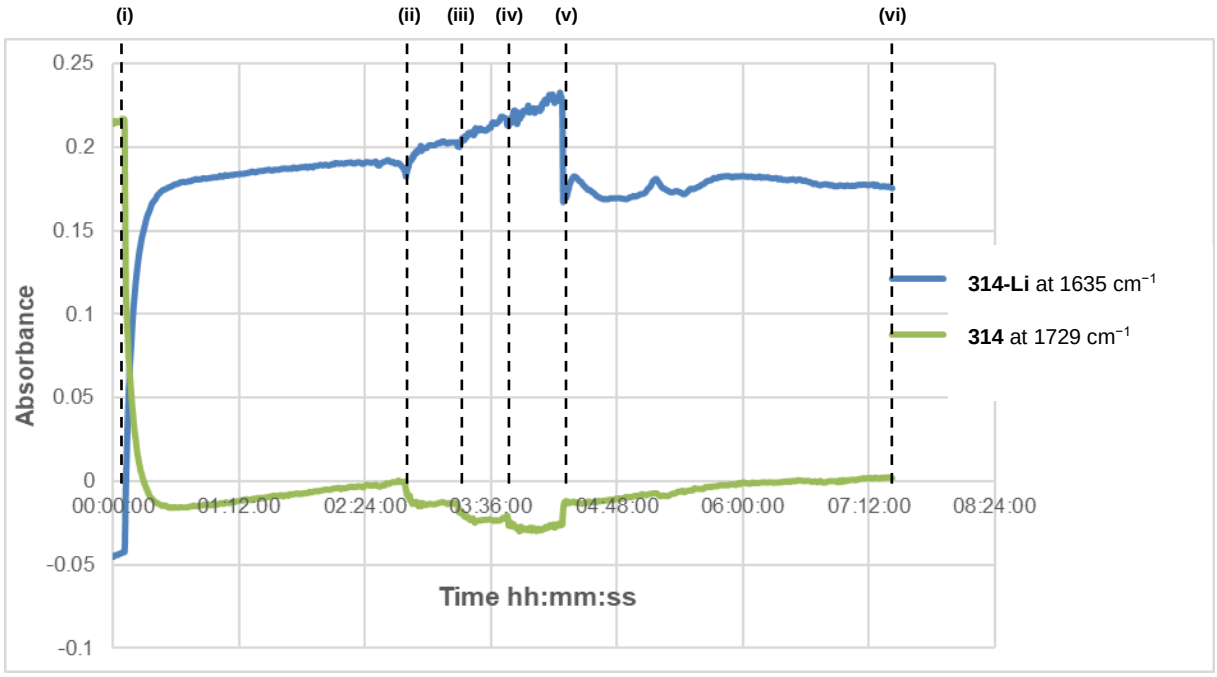
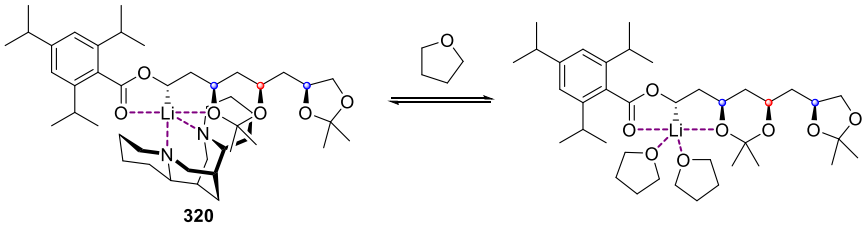


Figure 39 *In situ* IR trace for the reaction shown in **Scheme 142**. (i) *s*-BuLi (1 equiv) and (−)-sparteine (1 equiv) added; (ii) *s*-BuLi (0.1 equiv) added; (iii) *s*-BuLi (0.1 equiv) added; (iv) *s*-BuLi (0.1 equiv) added; (v) boronic ester **257** (1.3 equiv, 1 M in Et_2O) added; (vi) quenched with MeOH.

4.5.3.4 Borylation of lithiated bis(acetonide) benzoate ester 314 and subsequent 1,2-migration

In situ IR monitoring suggested a fast lithiation but a slow borylation, presumably due to the difficulty of adding the boronic ester to such a sterically congested lithiated species. Coordination of the acetonide oxygen to the lithium ion would stabilise the lithiated species and also hinder borylation.[181]

To counter this, the boronic ester would be added in THF going forward. THF is able to displace (−)-sparteine from the lithiated complex (**Scheme 143**) making it easier for the boronic ester to access the sterically congested carbenoid and so expediting borylation.[26]



Scheme 143 Displacement of (−)-sparteine from the lithiated complex by THF resulting in a less sterically hindered carbenoid.

Full borylation of lithiated species **320**—generated using 1.3 equivalents of (−)-sparteine ligated *s*-BuLi in diethyl ether at −78 °C—was observed by ^{11}B NMR analysis (**Figure 40**) after 2 hours at −78 °C, when boronic ester **66** was added as a 1 M solution in THF.

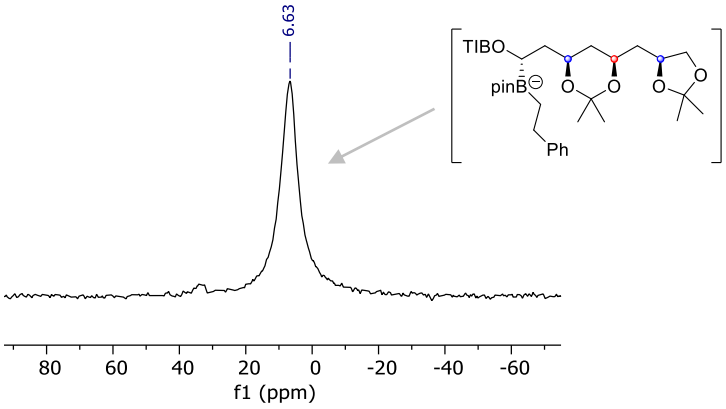
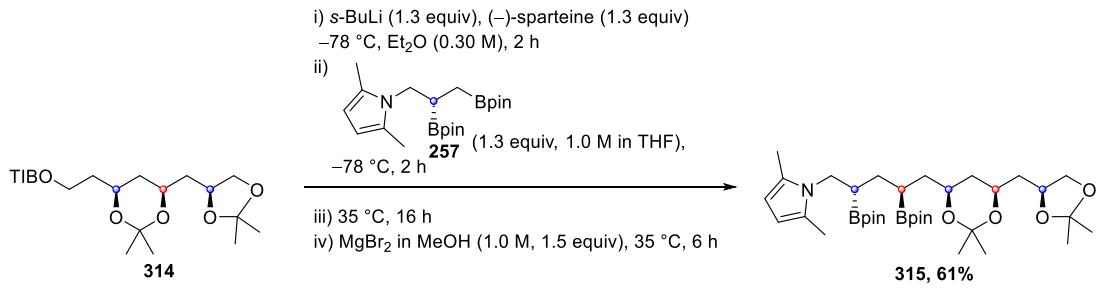


Figure 40 ^{11}B NMR (96 MHz) spectrum after 2 h borylation time at −78 °C.

These conditions were then used for another lithiation–borylation reaction between model substrate **314** and 1,2-bis(boronic ester) **257** (**Scheme 144**). The reaction was monitored by ^{11}B NMR analysis (**Figure 41** a) which showed full boronate formation after 2 hours of borylation at −78 °C. ^{11}B NMR analysis after heating overnight showed some persistent boronate complex (**Figure 41** b) so magnesium bromide in methanol was added. The reaction

was stopped when there was no further change in the ^{11}B NMR spectrum (**Figure 41** c). After heating overnight for 1,2-migration, saturated aqueous ammonium chloride was used for the aqueous work-up instead of 2 M HCl to recover (−)-sparteine, since it had been reported that 1,3-diol acetonides do not survive work up with HCl,[184] which was also observed in the course of this project. Following chromatographic purification, the desired 1,3-bis(boronic ester) **315** was isolated in 61% yield, along with 3% yield of recovered 1,2-bis(boronic ester) **257** and 32% yield of triisopropylbenzoate ester **314**.



Scheme 144 Test coupling with diamine-mediated lithiation and addition of boronic ester **257** in THF. Reaction performed on 0.1 mmol scale.

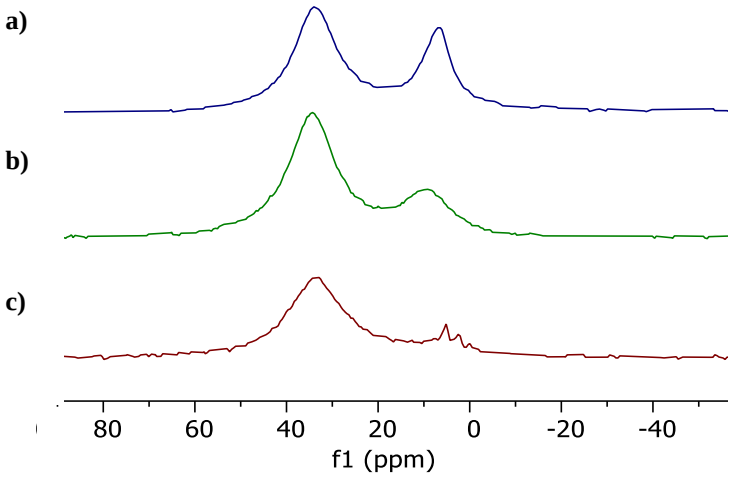
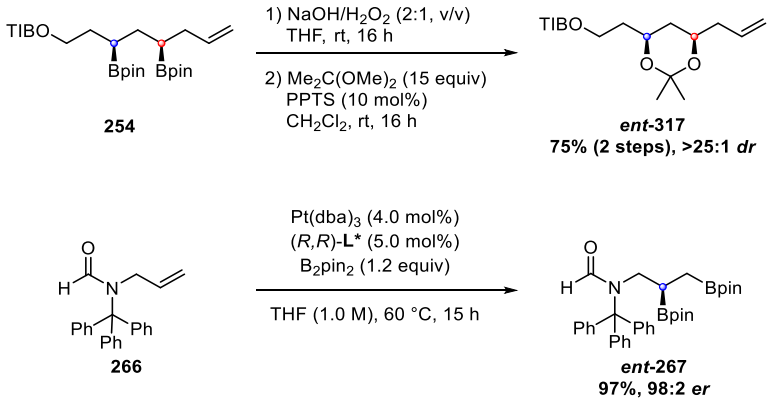


Figure 41 ^{11}B NMR spectra a) after 2 h of borylation at −78 °C; b) after heating overnight at 35 °C; c) after adding $MgBr_2$ in MeOH (1.0 M, 1.5 equiv) and heating for a further 6 h at 35 °C. Boronic ester(s) at 34.1 ppm, boronate complex at 6.6 ppm.

Thus, it was concluded that: (i) a diamine ligand is necessary for the deprotonation of bis(acetonide) **314** with *s*-BuLi; (ii) the boronic ester must be added in THF to achieve borylation of the resulting hindered carbenoid; (iii) subsequent 1,2-migration requires prolonged heating and/or addition of the weak Lewis acid magnesium bromide in methanol.

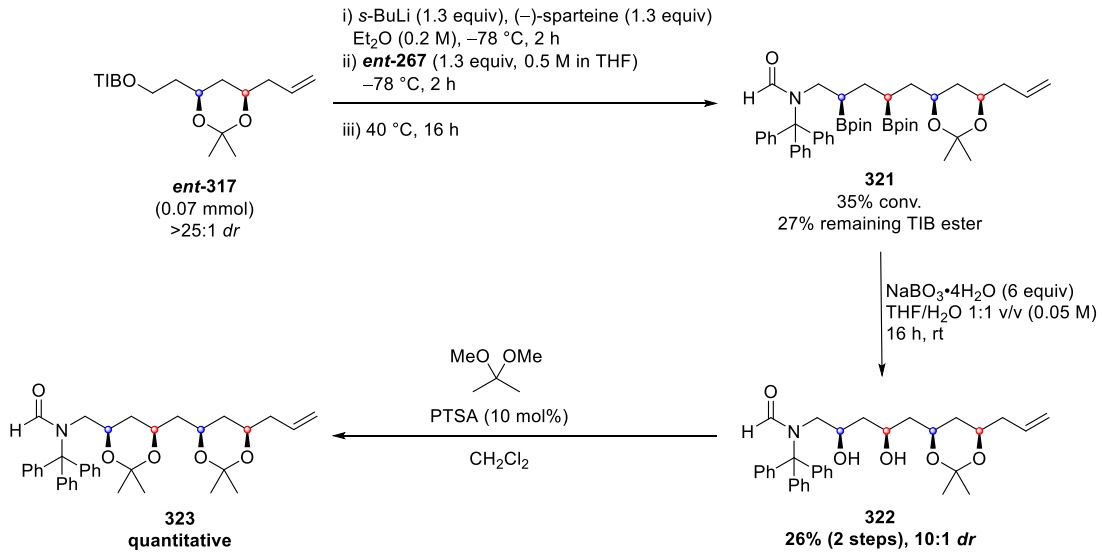
4.5.3.5 Lithiation–borylation of triisopropylbenzoate ester *ent*-317 with 1,2-bis(boronic ester) *ent*-267

To further understand the most promising conditions for lithiation–borylation of 6-membered acetonide-bearing triisopropylbenzoate esters, Dr Fiorito later investigated the homologation of 1,2-bis(boronic ester) ***ent*-267** with ***ent*-317**. These model compounds were synthesised as shown in **Scheme 145**; ***ent*-317** is derived from **254**, an intermediate in fragment 2, and ***ent*-267** contains a terminal trityl-protected formamide instead of a pyrrole moiety, in light of the results discussed in section **4.2.2.1**. It was also decided to use the opposite stereochemistry at the secondary boronic ester next to the homologation centre compared to pyrrole **257**. This was prompted by developing ideas around the effect of the relative stereochemistry on the ease of borylation and/or 1,2-migration and so a closer model to the desired coupling (**Scheme 138** a), where a *syn* 1,3-bis(boronic ester) is the desired product, was sought.



Scheme 145 Synthesis of model compounds ***ent*-317** and ***ent*-267** (DF). Reported *dr* values determined by ^{13}C NMR analysis; *er* of ***ent*-267** determined by chiral HPLC analysis of the corresponding diol.

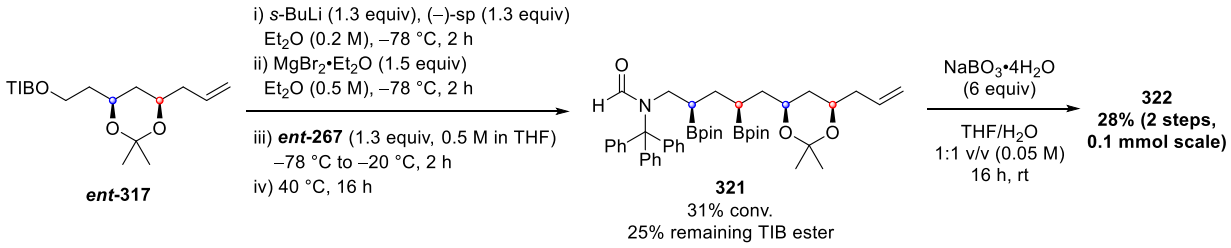
The results from the previous section were used to select the initial conditions for the lithiation–borylation of triisopropylbenzoate ester ***ent*-317** with 1,2-bis(boronic ester) ***ent*-267** conducted by Dr Fiorito (**Scheme 146**): 1.3 equivalents of (−)-sparteine ligated *s*-BuLi for the lithiation and addition of the boronic ester in THF to aid borylation of this sterically congested carbenoid. This resulted in 35% conversion by NMR analysis to the desired product **321**, which could not be separated from the unreacted boronic ester ***ent*-267** by chromatography until after oxidation, at which point partially protected tetraol **322** was isolated in 26% yield over 2 steps from triisopropylbenzoate ester ***ent*-317**. Acetonide protection afforded **323**, at which point the *syn* relative stereochemistry was confirmed by ^{13}C NMR analysis (Rychnovsky's method,[64] δ_C acetonide-CO *syn* 98.89, 98.84; acetonide-CH_3 *syn* 20.03, 20.15, 30.36, 30.51 ppm).



Scheme 146 Lithiation–borylation of ***ent*-317** with ***ent*-267** (DF). Reported *dr* values determined by ^{13}C NMR analysis. conv.: conversion.

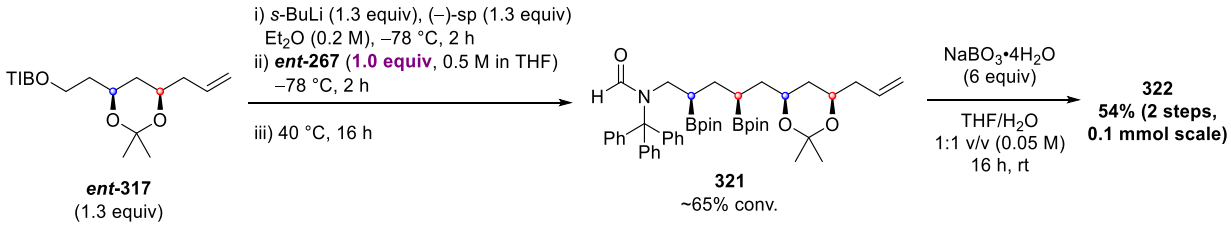
Although the yield in this first attempt was relatively low, it was encouraging to note that: (i) the formamide moiety appeared to be compatible with the lithiation conditions; (ii) the product was obtained in an acceptable 10:1 *dr*; (iii) there was no observed formation of the over-homologation product, resulting from reaction at the secondary boronic ester as well, indicating good selectivity for the primary boronic ester under these conditions. However the use of TMEDA instead of sparteine did result in over-homologation, with only traces of the desired product **321**, confirming that a diamine-free lithiated carbenoid is not an option for this homologation step. With the previous model substrate (**Scheme 139**), addition of magnesium bromide in methanol appeared beneficial for ensuring complete 1,2-migration but in this case, its inclusion did not improve conversion to **321** (only 29%, with 45% remaining triisopropylbenzoate ester ***ent*-317**). For the homologation of 1,2-bis(boronic ester) **267** in the synthesis of fragment 1 (**274**), the optimised results giving high yield and excellent primary selectivity use the magnesiated carbenoid generated from α-sulfinyl benzoate ***ent*-67** (**Scheme 107**). Transforming benzoate ***ent*-317** to the corresponding α-sulfinyl benzoate was discounted as an option since this synthesis and purification typically affords the α-sulfinyl benzoate in 50-60% yield (and is a rather lengthy procedure in operational terms), for a subsequent homologation in at best 60-70% yield, so this was not deemed appropriate for such an advanced substrate in the synthesis (**303**). Instead triisopropylbenzoate ***ent*-317** was subjected to sparteine-mediated lithiation as before, then transmetalated to the magnesiated carbenoid through the addition of freshly prepared magnesium bromide etherate, and the reaction temperature was raised to −20 °C for borylation (**Scheme 147**). However these

modifications did not greatly improve the conversion to homologated boronic ester **321**, or the yield of **322** over 2 steps.



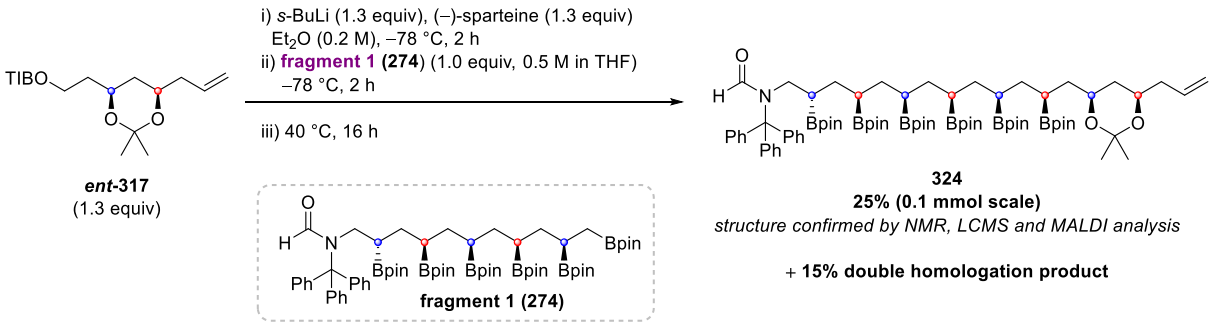
Scheme 147 Lithiation–transmetalation–borylation of ***ent*-317** with ***ent*-267** (DF).

An excess of benzoate ester ***ent*-317** with respect to the boronic ester (***ent*-267**) proved beneficial for the homologation and the lithiation–borylation–oxidation product **322** could be isolated in 54% yield over 2 steps (**Scheme 148**). The excess of benzoate ***ent*-317** could be easily recovered by column chromatography, whereas in the previous reactions (**Scheme 146**, **Scheme 147**) the homologation product **321** was not separable from 1,2-bis(boronic ester) ***ent*-267** and so the excess of boronic ester was lost as diol ***ent*-273** following oxidation of the homologation mixture.



Scheme 148 Lithiation–borylation of ***ent*-317** with ***ent*-267**, when the boronic ester is the limiting reagent (DF).

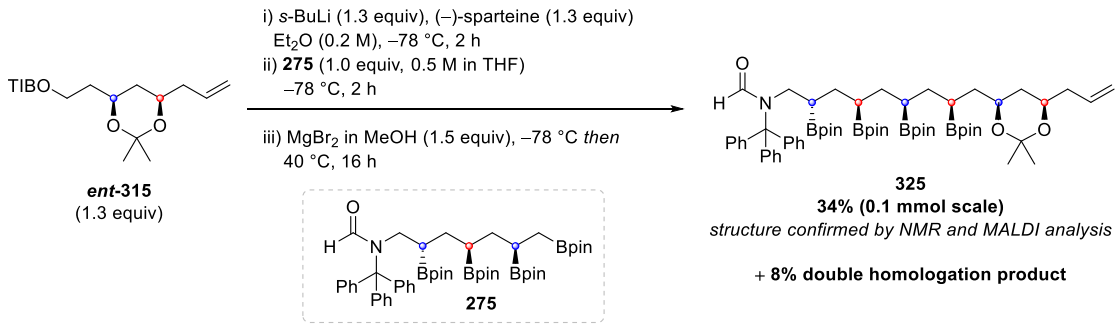
These conditions were then applied to the homologation of model substrate ***ent*-317** with fragment 1, **274** (**Scheme 149**). While the desired homologated product **324** was isolated in 25% yield, disappointingly 15% yield of an over-homologation product was also isolated, where one of the secondary boronic esters has also reacted with the lithiated carbenoid. This was surprising given that high selectivity for the primary boronic ester is generally observed with sparteine-ligated lithiated carbenoids (*vide supra*, section **1.6**) and no over-homologation was observed with 1,2-bis(boronic ester) ***ent*-267** (**Scheme 148**), however it could be that the trityl protecting group sufficiently shielded the secondary boronic ester in this case.



Scheme 149 Lithiation–borylation of ***ent*-317** with fragment 1 (**274**) (DF).

Fawcett *et al*. described a methanol-quench protocol for homologations of 1,2-bis(boronic esters) when the carbenoid is used in excess;[48] they speculated that the bis(boronate complex) leading to the double-addition product was generated at temperatures above −78 °C, during warming of the reaction mixture to ambient temperature. The addition of methanol at −78 °C after borylation protonates the excess carbenoid and was successful in suppressing over-homologation.

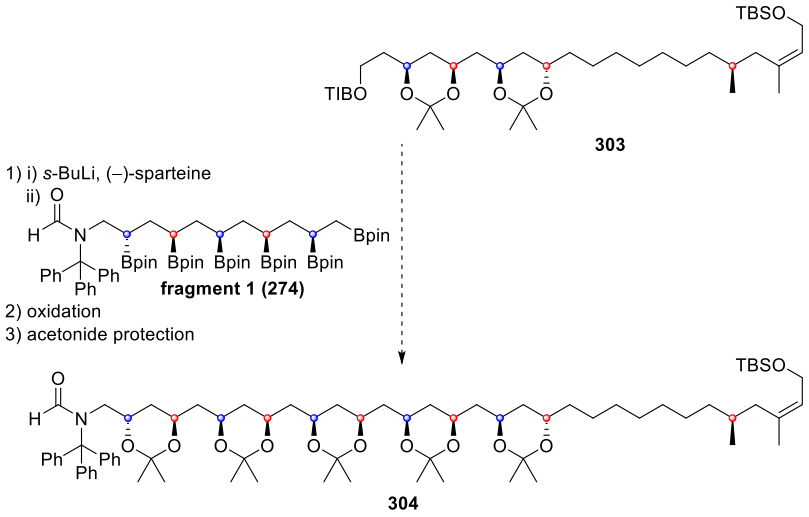
The final lithiation–borylation reaction of model substrate ***ent*-317** included the addition of magnesium bromide in methanol at −78 °C; the methanol was expected to quench the excess carbenoid and magnesium bromide could aid 1,2-migration (**Scheme 150**). This resulted in an improved isolated yield of 34% of the corresponding homologation product **325**, although still with 8% yield of a double homologation product, however these were separable by column chromatography.



Scheme 150 Lithiation–borylation of ***ent*-315** with tetra(boronic ester) **275**; methanol quench before warming (DF).

Further work is anticipated to trial the transformation of model substrate ***ent*-315** to the corresponding α-sulfinyl benzoate to allow homologation of **275** or **274** using an enantiopure carbenoid generated through sulfoxide-magnesium exchange with *i*-PrMgCl·LiCl, which may after all be necessary here to avoid homologation at a secondary boronic ester in addition to the desired coupling. This will help determine the best conditions for the required lithiation–

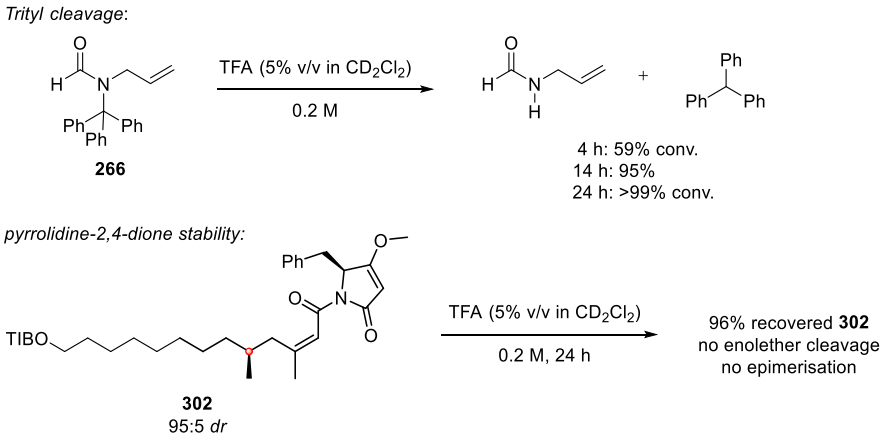
borylation of bis(acetonide) boronic ester **303** with fragment 1 (**274**) (**Scheme 151**) which will be attempted soon, now that **303** has been isolated in high *dr* (*vide supra*, **Figure 35** c).



Scheme 151 Hexa(boronic ester) **274** will be homologated with bis(acetonide) **303** to afford the full 1,3-polyol.

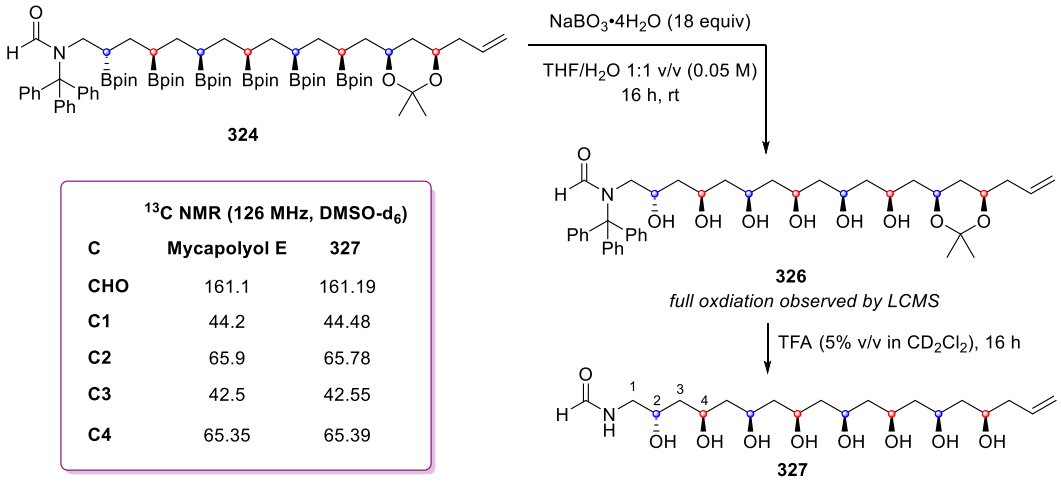
4.6 Proposed Endgame

Advanced intermediate **304** contains the entire stereodefined 1,3-polyol system of mycapolyol E, protected as 1,3-diol acetonides. The next 5 steps have been performed starting with fragment 3 (**251**), when preparing the eastern portion of mycapolyol E for NMR studies to determine the stereochemistry at C5 (*vide supra*, section **4.4**). Initial silyl deprotection using TBAF followed by Dess-Martin oxidation and Pinnick oxidation of the resultant aldehyde is proposed to give terminal carboxylic acid **326** (**Scheme 154**), using the conditions from **Scheme 124**. **326** will be activated as the pentafluorophenyl ester **327** for installation of the pyrrolidine-2,4-dione head group through a modified Andrus' coupling, as successfully applied to model substrate **297** in **Scheme 130**. The final step to reveal synthetic mycapolyol E is global deprotection; model studies showed that the trityl group and acetonides can be cleaved using TFA/CH_2Cl_2 (*vide supra*, **Scheme 105**) and Dr Fiorito showed that 5% TFA/CH_2Cl_2 v/v is sufficient to effect this deprotection. In addition, the tetramic-acid derived headgroup has been shown to be stable to these conditions (DF, **Scheme 152**).



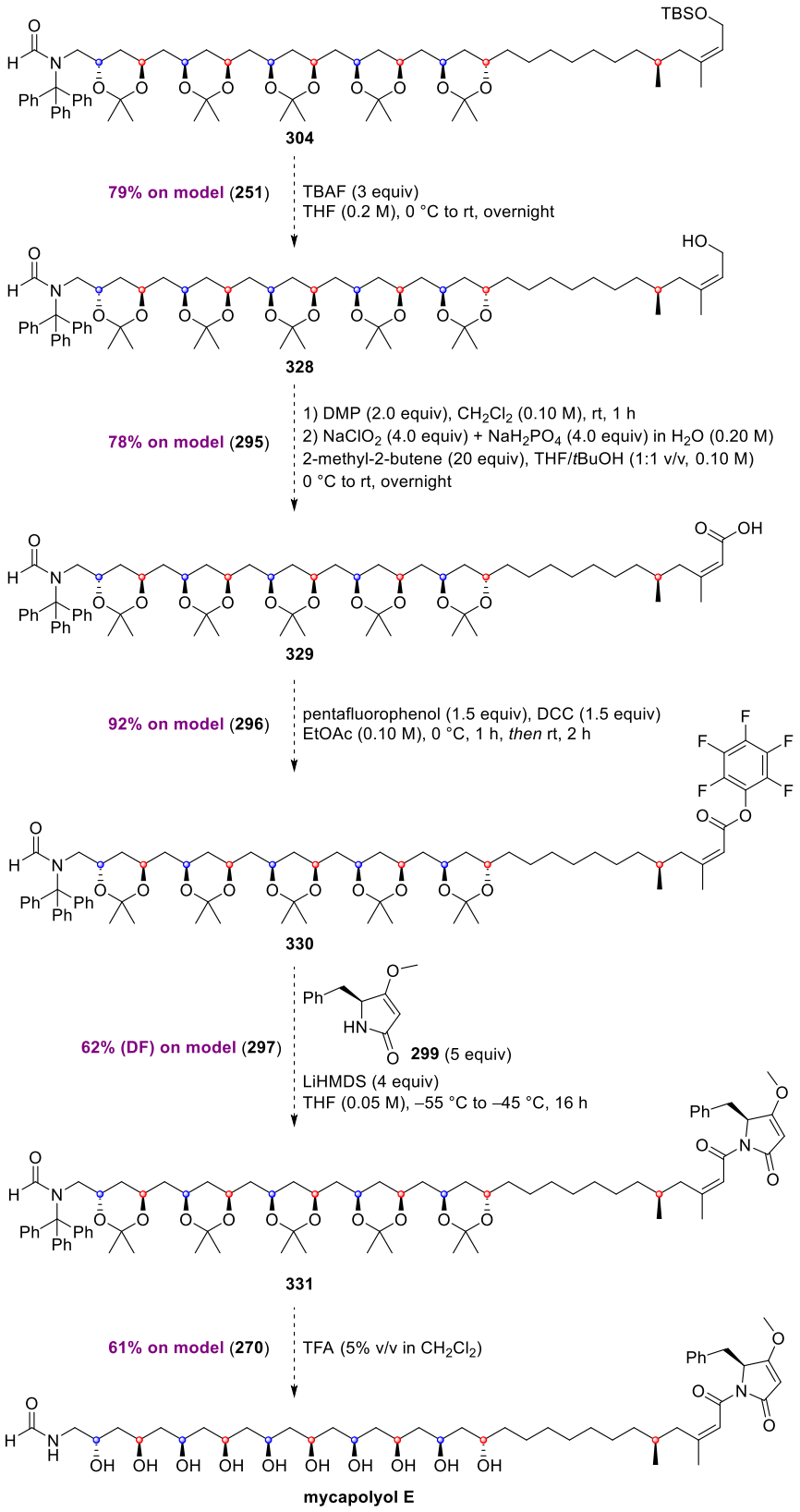
Scheme 152 Global deprotection model studies (DF). Yields reported are as determined by NMR analysis, with 1,3,5-trimethoxybenzene as an internal standard.

Successful execution of this endgame strategy (**Scheme 154**) will thus conclude the first total synthesis of mycapolyol E in 36 total steps, with 18 steps in the longest linear sequence. Furthermore, oxidation and deprotection of the homologation product **324** afforded a model compound for the western terminus of mycapolyol E (**Scheme 153**); comparison of NMR data with that reported for the isolated natural product provided confidence regarding the relative stereochemistry at this end of the 1,3-polyol domain (*vide supra*, section **4.1**).



^{13}C NMR (126 MHz, DMSO-d_6)		
C	**Mycapolyol E**	**327**
CHO	161.1	161.19
C1	44.2	44.48
C2	65.9	65.78
C3	42.5	42.55
C4	65.35	65.39

Scheme 153 Oxidation and deprotection of **324** to afford polyol model **327** (DF).



Scheme 154 Proposed endgame synthesis of mycapolyol E.

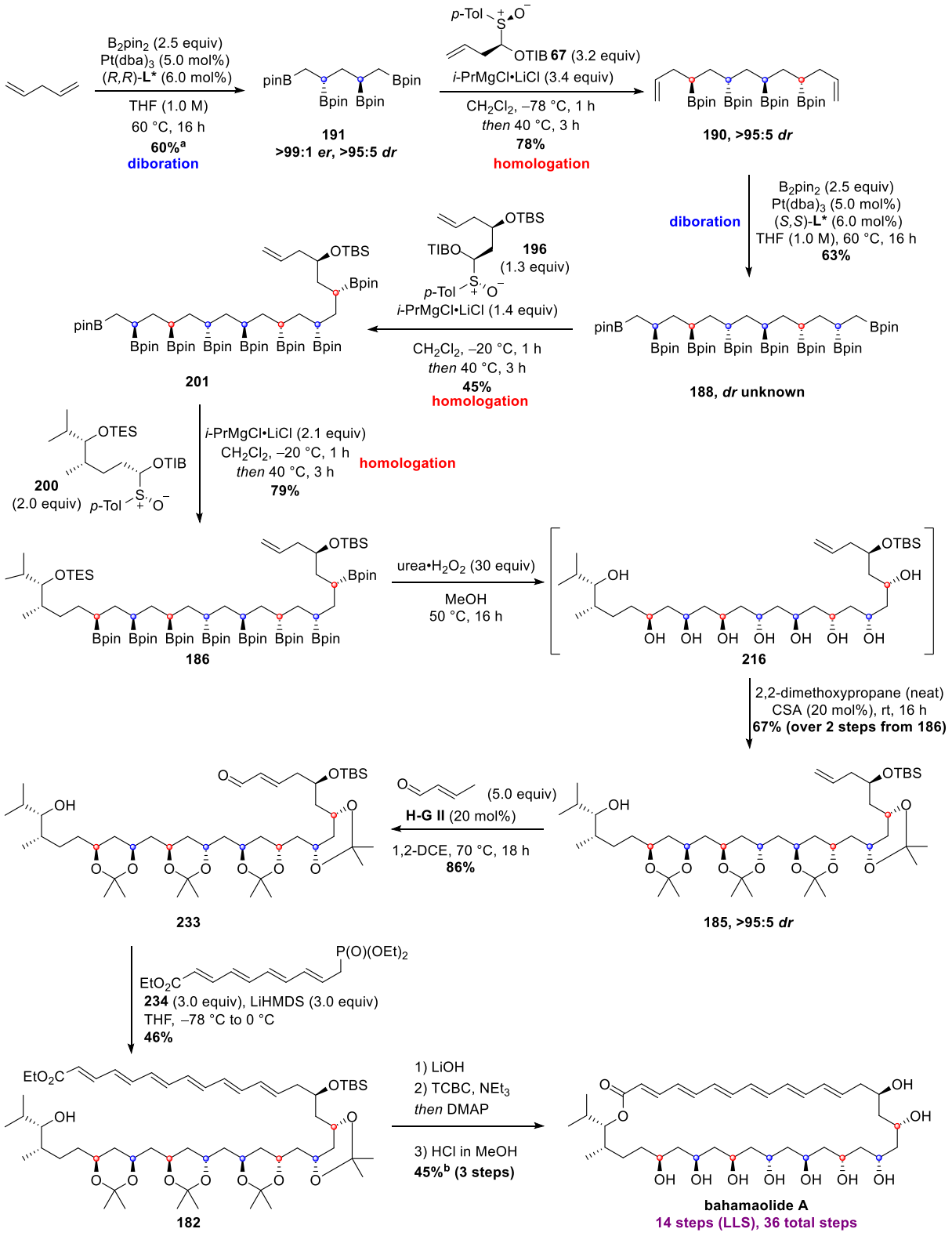
5 Summary and Outlook

Iterative Morken diboration of a terminal alkene and primary-selective homologation of the resulting 1,2-bis(boronic ester) with an enantiopure butenyl carbenoid has been applied successfully to construct the stereodefined 1,3-polyol motif in two polyketide natural products, bahamaolide A and mycapolyol E.

5.1 Bahamaolide A

The first total synthesis of bahamaolide A has been completed in 36 total steps (**Scheme 155**), with 14 steps in the longest linear sequence.

The synthetic approach to bahamaolide A focused on the rapid construction of the key C_2-symmetric octa(boronic ester) building block **188**. The merging of catalyst-controlled diboration and reagent-controlled homologation reactions in a bidirectional manner enabled its preparation in just 3 steps from 1,4-pentadiene, setting 6 stereocentres. Homologation of **188** with α-sulfinyl benzoate **196** to install the east side chain represented a desymmetrisation and a statistical product distribution could be achieved following an optimisation campaign, where the key improvement came upon observation by *in situ* IR monitoring. The temperature at which magnesiated carbenoids generated from α-sulfinyl benzoates undergo borylation had not been investigated until this study. Unlike lithiated carbenoids that undergo borylation at −78 °C, it was a critical finding that borylation of magnesiated carbenoids generated from α-sulfinyl benzoates using *i*-PrMgCl·LiCl does not occur at temperatures below −40 °C. Performing borylation at a higher temperature permitted the use of fewer equivalents of reagents **196** and **200**, representing a more efficient homologation process. Following the second homologation reaction of the primary boronic ester in **201** with the west side chain, global oxidation of all eight boronic esters and acetonide protection of the resulting alcohols afforded advanced intermediate **185** which contained the entire stereodefined 1,3-polyol motif of bahamaolide A. **185** was then transformed to the natural product in a further 5 steps to afford synthetic bahamaolide A. Attempts to isolate an isomerically pure sample of bahamaolide A where the endgame had been inspired by Sammakia's approach to dermostatin A were unsuccessful and so the synthetic route was revised in order to prepare the polyene domain in much higher isomeric ratio.



Scheme 155 Linear route to bahamaolide A from 1,4-pentadiene. [a] yield of desired diastereomer after recrystallisation from pentane. [b] NMR yield using dimethoxymethane as internal standard.

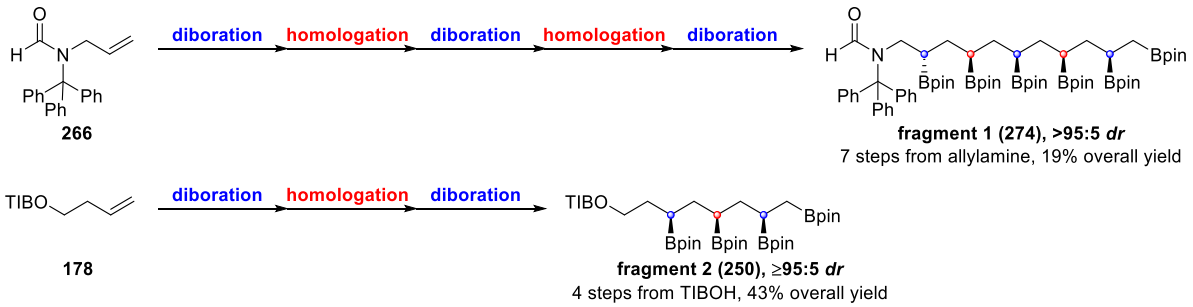
The instability of the polyene moiety, to both (presumably mainly light-mediated) decomposition and isomerisation, proved challenging, both in its construction and the isolation of an isomerically pure sample of synthetic bahamaolide A. Several earlier steps in

the sequence also greatly hindered bringing sufficient material through to the final purification: (i) the chromatographic purification of **190** was limited by scale, since these homoallylic boronic esters show some instability to silica gel; (ii) the desymmetrisation of octa(boronic ester) **188** has a maximum theoretical yield of 50%; (iii) it was difficult (but possible) to separate **201** from unreacted octa(boronic ester) **188** and over-homologated product **202**, and this chromatographic purification was also limited by scale; (iv) oxidising eight boronic esters in one step halves molecular weight; (v) the HWE reaction only proceeded in 45-50% yield, albeit with high selectivity for 6 *E* alkenes.

5.2 Mycapolyol E

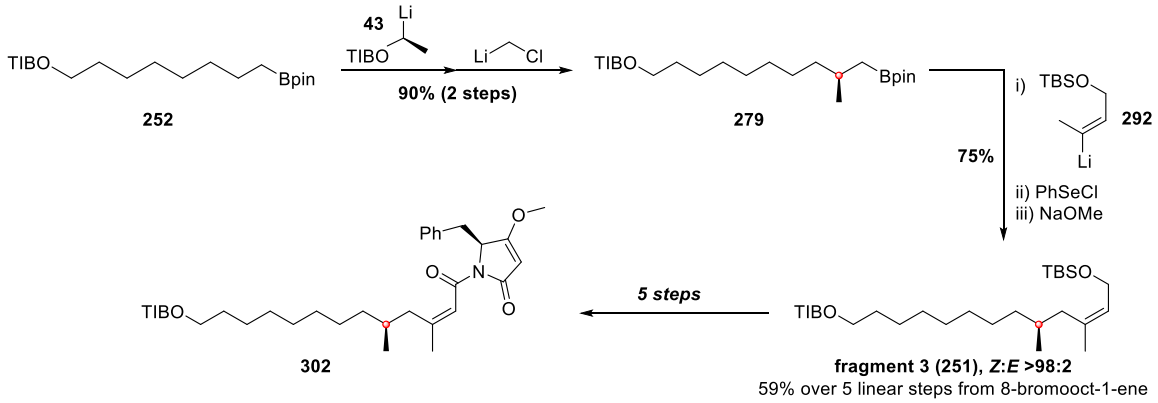
Retrosynthetic analysis of mycapolyol E suggested a modular approach; the target structure was divided into three fragments of similar complexity which would be joined through lithiation–borylation reactions.

Iterative Morken diboration and homologation reactions were performed to extend the carbon chain of the western (**274**) and middle fragments (**250**), which contain all the polyol stereocentres (**Scheme 156**). The diboration steps typically proceeded in high yield but it was beneficial to increase the catalyst loading to improve the *dr* of poly(boronic ester) intermediates. The homologation steps proceeded with high selectivity for the primary boronic ester under the optimised conditions. Raising the temperature for borylation of magnesiated carbenoids also proved advantageous in this project. The pinacol boronic esters were retained in fragments 1 and 2 masking the hydroxyl functionality, and only oxidised and protected as acetonides upon fragment unification. Model studies have shown that the terminal formamide can be carried through the whole synthesis when protected with a trityl group.



Scheme 156 Iterative synthesis of fragments 1 and 2. See sections **4.2.2.2** and **4.2.1** for detailed conditions.

The eastern fragment (**251**) was prepared efficiently using Aggarwal's assembly–line synthesis to install the stereogenic methyl group, and an optimised Zweifel-type olefination to construct the alkene with essentially perfect Z/*E* selectivity (**Scheme 157**).



Scheme 157 Fragment 3 (**251**) was prepared in 10 total steps, see section **4.3** for detailed conditions.

Fragment 3 (**251**) contains the one undefined stereocentre at C5 in mycapolyol E; its configuration was set unambiguously through the choice of enantiomer of α-stannyl ethyl benzoate **42** for the homologation of **252**. Both diastereomers of the eastern fragment of mycapolyol E were synthesised (**Figure 42**) and the (*S*)-configuration was assigned following comparison of measured ^{1}H and ^{13}C NMR chemical shifts for **301** and **302** with that reported for the natural product in the isolation paper.

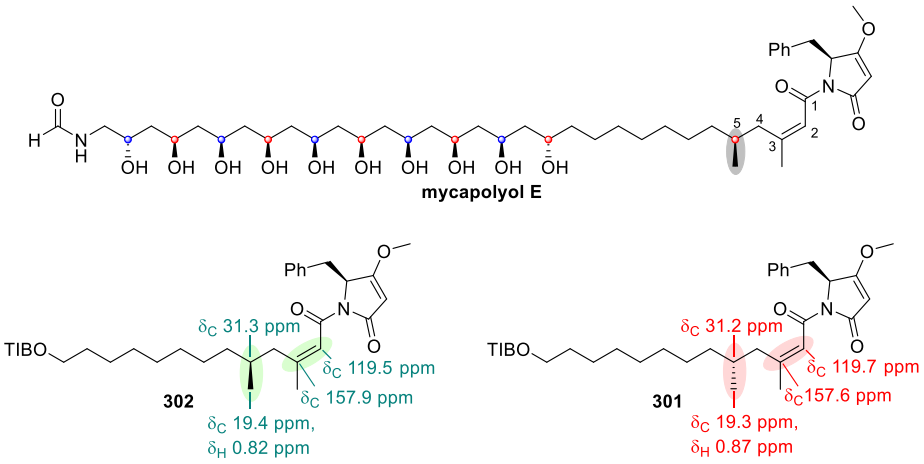
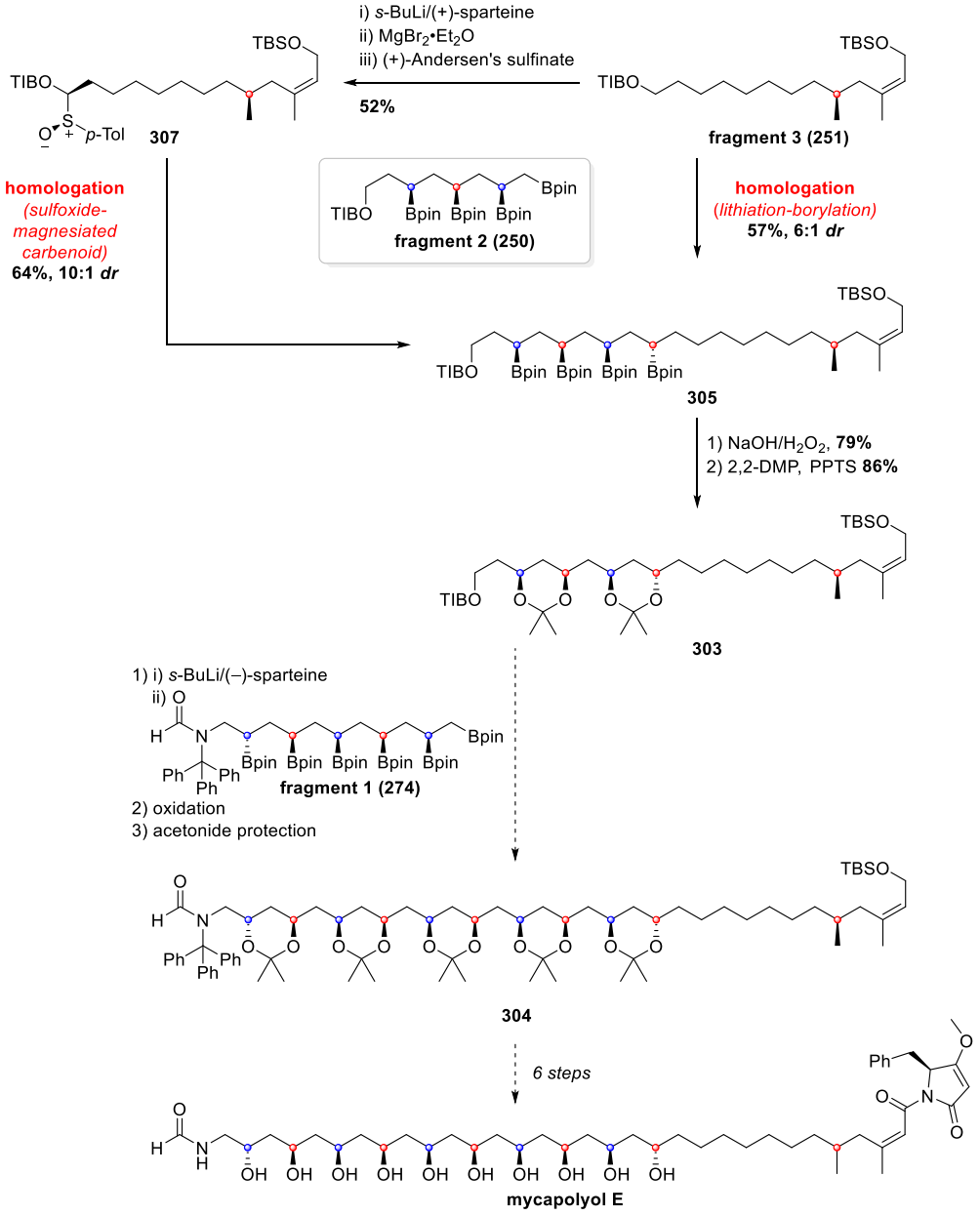


Figure 42 Assignment of the undefined stereocentre in mycapolyol E, with key chemical shifts highlighted: green = matched natural product (diastereomer **302**), red = different to natural product (diastereomer **301**).

The synthesis of the 3 key fragments has been optimised on gram-scale and the lithiation–borylation of fragment 3 (**251**) with fragment 2 (**250**) was next investigated (**Scheme 158**). Under the optimised conditions, the homologation of fragment 2 proceeds with good yield and excellent stereospecificity under reagent control when using an enantiopure magnesiated carbenoid derived from fragment 3, and following oxidation and acetonide protection, bis(acetonide) **303** was isolated in 95:5 *dr*.

Extensive model studies were conducted to explore the required lithiation–borylation of bis(acetonide) **303** with fragment 1 (**274**) which showed that: (i) the lithiation of such

benzoate esters with *s*-BuLi requires a diamine ligand; (ii) the presence of a β-oxygen moiety accelerates lithiation, as observed through *in situ* IR monitoring, but exerts only minimal substrate control; (iii) subsequent borylation is fast when the boronic ester is added in THF; (iv) it was surprising that over-homologation occurred in the reaction of a tetra- or hexa(boronic ester) with a sparteine-ligated lithiated carbenoid, suggesting that 1,3-poly(boronic esters) are not as sterically hindered as expected.



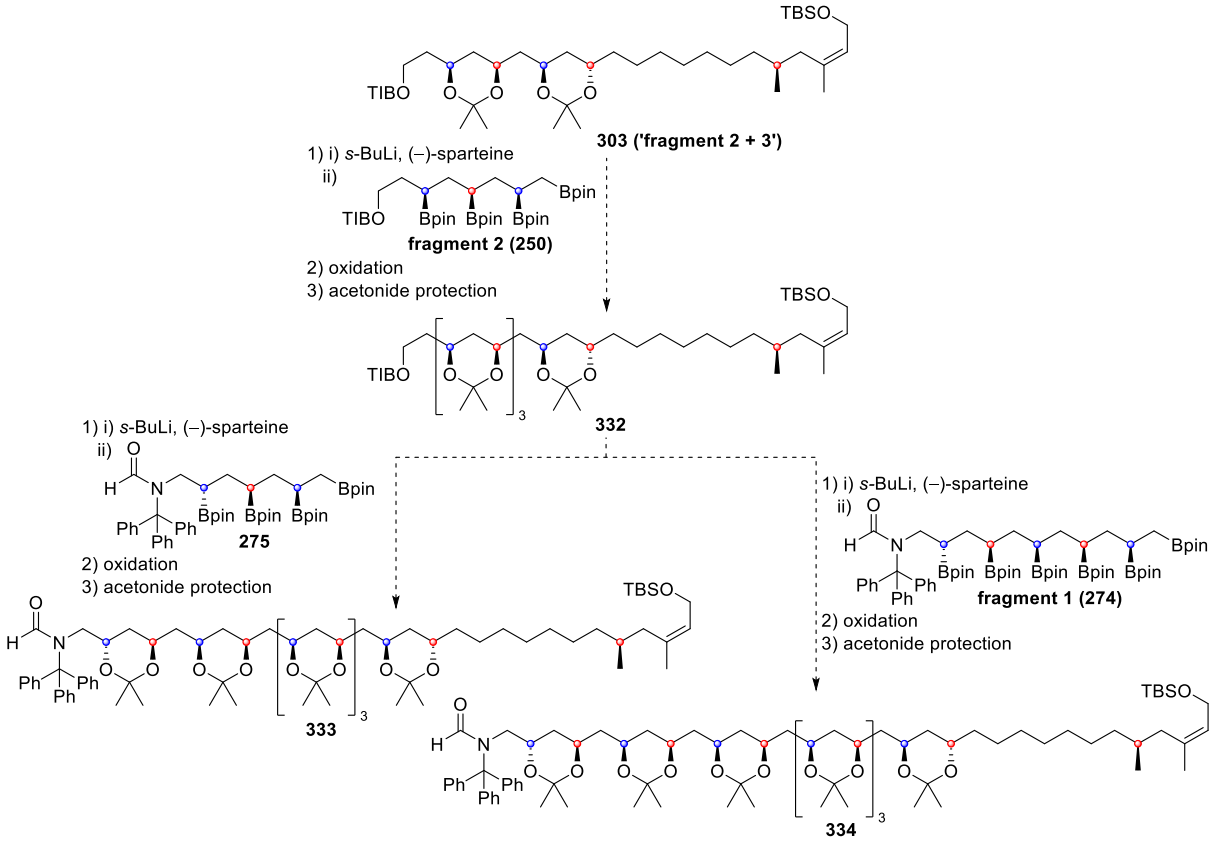
Scheme 158 Fragment couplings towards mycapolyol E. See **Scheme 133** and **Scheme 137** for detailed homologation conditions. See **Scheme 154** for proposed endgame steps.

With successful model studies now in hand for the remaining steps, current efforts are focused on fragment unification and then the synthetic endgame to transform **304** to mycapolyol E, and thus realise the first total synthesis (18 steps LLS, 36 total steps).

5.3 Application to Other Polyols

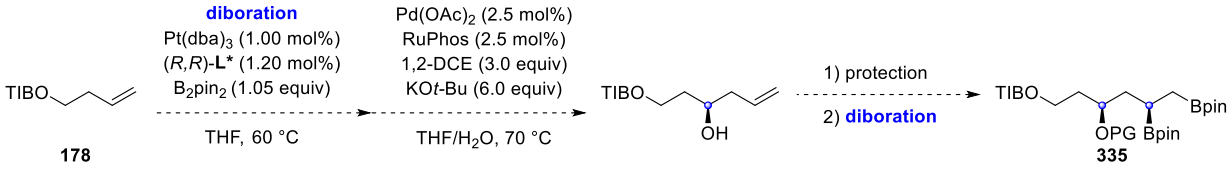
The iterative diboration–homologation protocol is highly flexible, allowing the synthesis of any desired 1,3-polyol diastereomer with exquisite levels of stereocontrol since each stereocentre is independently set by the choice of (*R*,*R*)- or (*S*,*S*)-ligand for the diboration, and by selecting the correct optical isomer of enantiopure α-sulfinyl benzoate **67** or ***ent*-67** for the homologation. This strategy could therefore be easily extended to the synthesis of analogues with different stereochemistry and with different numbers of hydroxyl groups.

Moreover, the building blocks already in hand would permit fairly straightforward access to mycapolyol C (12 hydroxyl groups) and mycapolyol A (14 hydroxyl groups). Lithiation–borylation of bis(acetonide) benzoate ester **303** with another equivalent of fragment 2 (**250**), then oxidation and protection would give tetra(acetonide) **332**. Lithiation–borylation of **332** with fragment 1 (**274**) followed by oxidation and protection would afford **334**, which contains the entire stereodefined 1,3-polyol of mycapolyol A. Alternatively, lithiation–borylation of **332** with tetra(boronic ester) **275**—an intermediate in the synthesis of fragment 1—would result in **333**, which could be transformed to mycapolyol C following the same proposed endgame as for mycapolyol E (*vide supra*, **Scheme 154**).



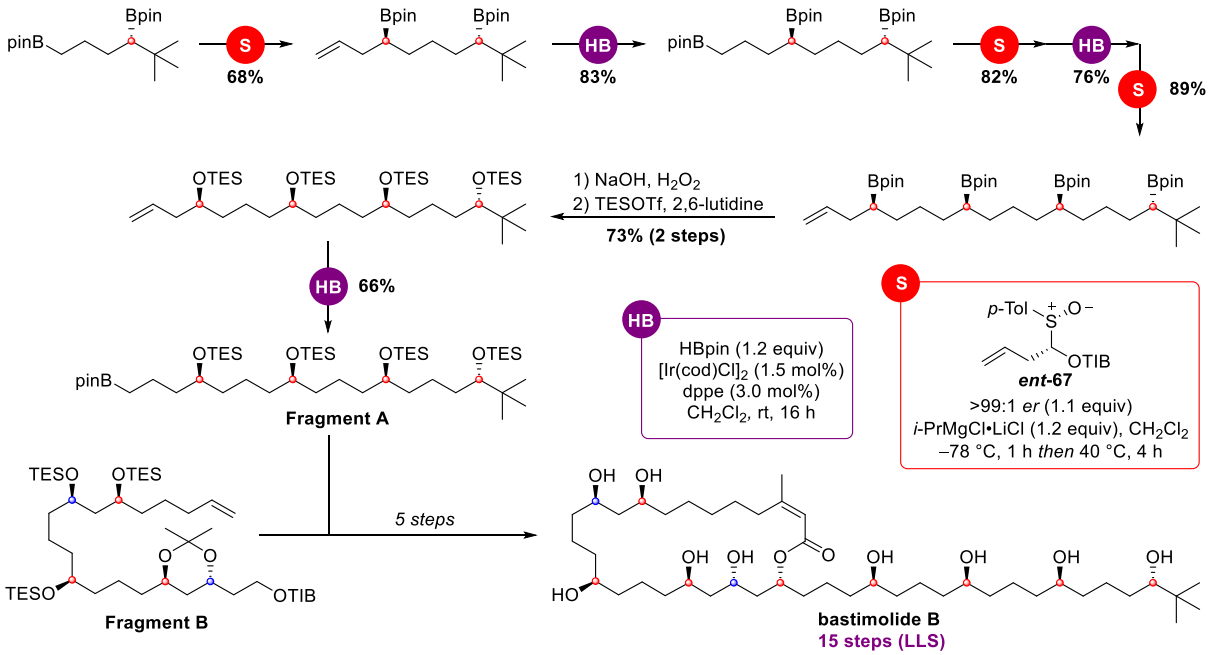
Scheme 159 Proposed synthesis of the protected 1,3-polyol in mycapolyols C and A.

The mycapolyols with an odd number of hydroxyl groups in the 1,3-polyol would require an additional building block. This could perhaps be addressed using Morken's tandem diboration–cross-coupling protocol.[185] Indeed, Morken and co-workers reported the synthesis of (*S*)-dec-1-en-4-ol in 90% yield and 96:4 *er* in one-pot from 1-octene, using dichloroethane to presumably generate vinyl chloride *in situ*. These conditions could potentially be applied to homoallylic benzoate **178**, and then followed by diboration to give a new masked triol building block **335** (**Scheme 160),** which could be substituted for fragment 2 (**250**) in the lithiation–borylation of fragment 3 (**251)** and carried forward to mycapolyols B, D and F (with 13, 11 and 9 hydroxyl groups, respectively) in an analogous way to mycapolyols A, C and E. The choice of protecting group is likely to be rather important, given its proximity to the lithiation centre, however OTBS in this position was tolerated in the homologation of octa(boronic ester) **188** with α-sulfinyl benzoate **196** bearing the east side chain (*vide supra*).



Scheme 160 Proposed synthesis of a masked triol building block to access odd numbered 1,3-polyol chains.

Replacing diboration with *anti*-Markovnikov hydroboration enables stereodefined 1,5-polyols to be created instead of 1,3-polyols, which has been recently demonstrated by Dr Fiorito and Dr Selbi Keskin in the total synthesis of bastimolide B (**Scheme 161**).[149]

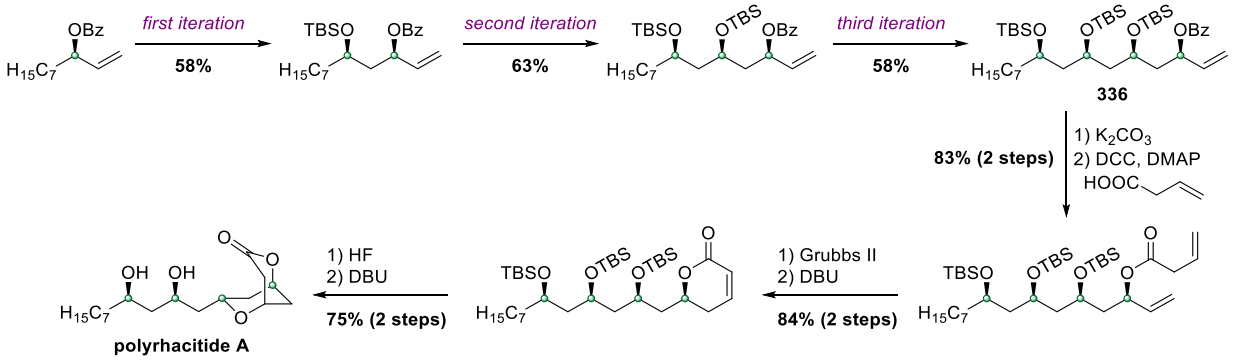


Scheme 161 Iterative synthesis of a 1,5-polyol in bastimolide B.

In the projects presented in this work, the boronic esters were oxidised and protected as 1,3-diol acetonides; in the case of bahamaolide A, this was since the polyene moiety was not expected to be stable to oxidising conditions, and for mycapolyol E, this was necessary to avoid nucleophilic attack by *s*-BuLi during the planned fragment unification through lithiation–borylation reactions. The total synthesis of another 1,3-poyol natural product where oxidation of the 1,3-poly(boronic ester) is performed at the most expedient point at a late stage in the synthesis—when subsequent protection of the polyol would not be required—would be an attractive opportunity to demonstrate the tactical advantages of this synthetic strategy based on boronic ester homologations.

(+)-Polyrhacitide A is a bicyclic polyketide lactone isolated from the Chinese medicinal ant *Polyrhacis lamellidens* which is used in traditional remedies to treat rheumatoid arthritis and hepatitis.[186]

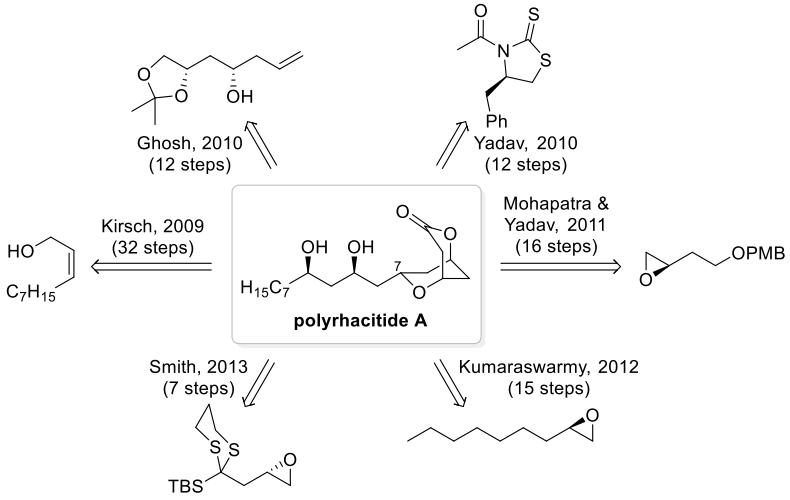
The first total synthesis of polyrhacitide A was reported by Kirsch and Menz,[187] where the stereodefining step was an asymmetric Overman esterification[188] which formed part of an eight-step sequence that could be performed iteratively; although each iteration required a relatively large number of manipulations, these reactions were all well established and operationally simple, and the full homologation cycle proceeded in high overall yields. 3 iterations of this sequence afforded **336** containing all the 1,3-polyol stereocentres (**Scheme 162**).



Scheme 162 Iterative Overman esterification in Kirsch's total synthesis of (+)-polyrhacitide A. DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene.

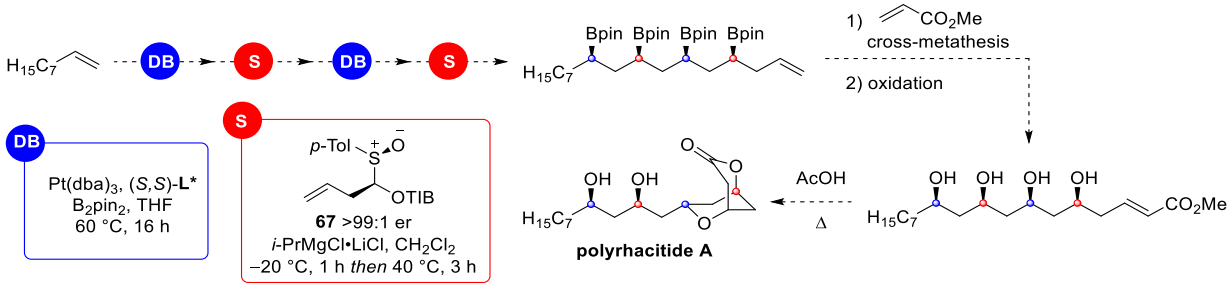
To date, approaches to construct the stereodefined 1,3-tetraol in polyrhacitide A (**Scheme 163**) invariably involve numerous oxidation level changes and generally substrate directed ketone reductions. A common strategy was the opening of chiral epoxides, with lithiated dithianes[189,190] or Grignard reagents as part of an iterative iodocyclisation strategy.[191] Yadhav

commenced with a modified Evans aldol reaction of *n*-octanal and the remaining stereocentres were set by oxa-conjugate addition and chelation-controlled *syn* reduction.[192]



Scheme 163 Summary of previous syntheses of polyrhacitide A.

All bar one of the literature total syntheses rely on the use of orthogonal protecting groups on the 1,3-tetraol to selectively acylate the C7 hydroxyl group followed by ring closing metathesis to construct a dihydropyrone ring (**Scheme 162** for example). The iterative diboration–homologation protocol instead utilises boronic esters as masked hydroxyl groups which would only be revealed in the penultimate step, prior to acid-mediated lactonisation and oxa-Michael reaction[192] to afford polyrhacitide A in 7 steps with an expected *dr* value of ≥95:5, by analogy with **Scheme 67** (**Scheme 164**).



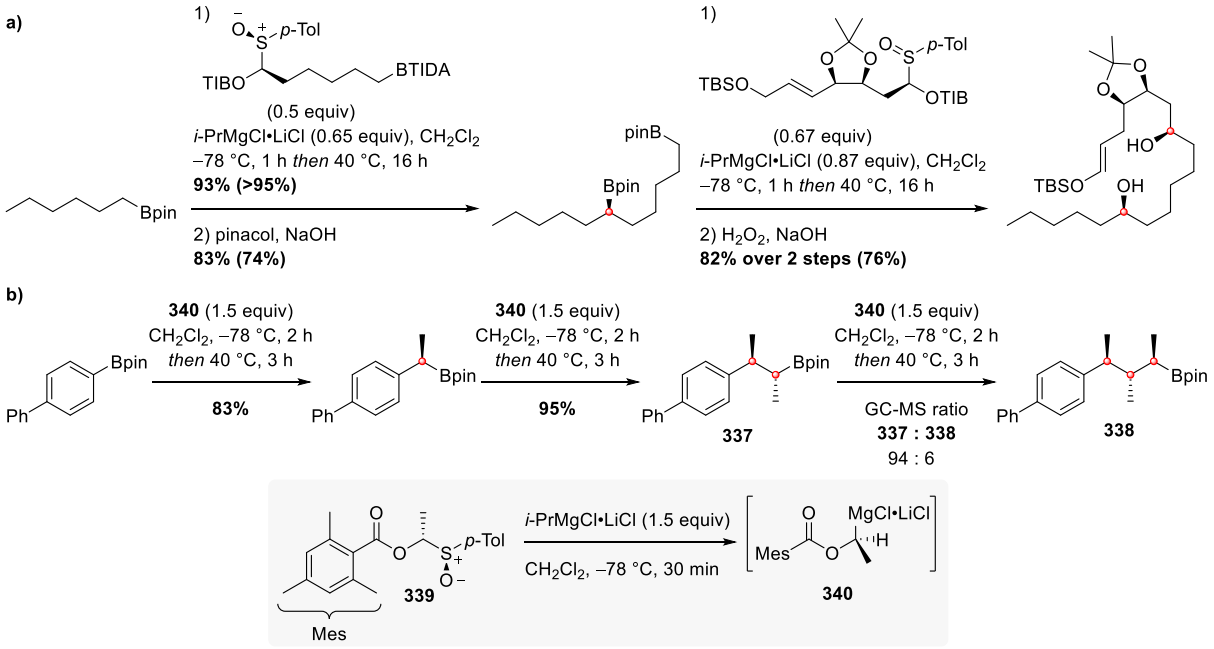
Scheme 164 Proposed concise iterative synthesis of polyrhacitide A.

5.4 Homologation of Boronic Esters with Magnesiated Carbenoids

During synthetic work towards bahamaolide A, initial investigations were conducted into the reactivity of magnesiated carbenoids for the homologation of boronic esters upon observing no borylation at −78 °C, in contrast to lithiated carbenoids. Magnesiated carbenoids were shown to be configurationally stable at −20 °C, again in contrast to lithiated carbenoids (*vide supra*, section **3.4**). Prior to these findings, previous attempts in the Aggarwal group to

perform lithiation–borylation reactions using magnesiated carbenoids were conducted at low temperatures (typically −78 °C).

The homologation of boronic esters bearing electrophilic functionality with magnesiated carbenoids derived from α-sulfinyl benzoates has been reported (*vide supra*, **Scheme 24**),[47] and such reagents have recently enabled iterative automated homologation of a primary boronic ester (**Scheme 165** a).[193] However, magnesiated carbenoids have not yet been widely applied since they were deemed not suitably reactive for the homologation of sterically hindered substrates, including their employment for the installation of multiple contiguous stereocentres, which was attempted by Dr Matthew Burns during postgraduate studies in the Aggarwal group (**Scheme 165** b).[194] Indeed, in the total synthesis of bahamaolide A and mycapolyol E, the high selectivity for reaction at the primary boronic ester over the (many) secondary boronic esters was advantageous.



Scheme 165 a) 2 iterative homologations of a primary boronic ester with a magnesiated carbenoid by Burke and co-workers. Yields for automated synthesis shown in parentheses. TIDA = tetramethyl *N*-methyliminodiacetic acid. b) 3 iterative homologations attempted by Dr Burns.

Taking the successful results from section **3.4** into consideration with raised temperatures for the borylation phase above −40 °C, it may be worth revisiting previous work in the group to probe whether the scope of boronic esters for homologation with magnesiated carbenoids can be expanded beyond primary boronic esters with even higher temperatures for borylation.

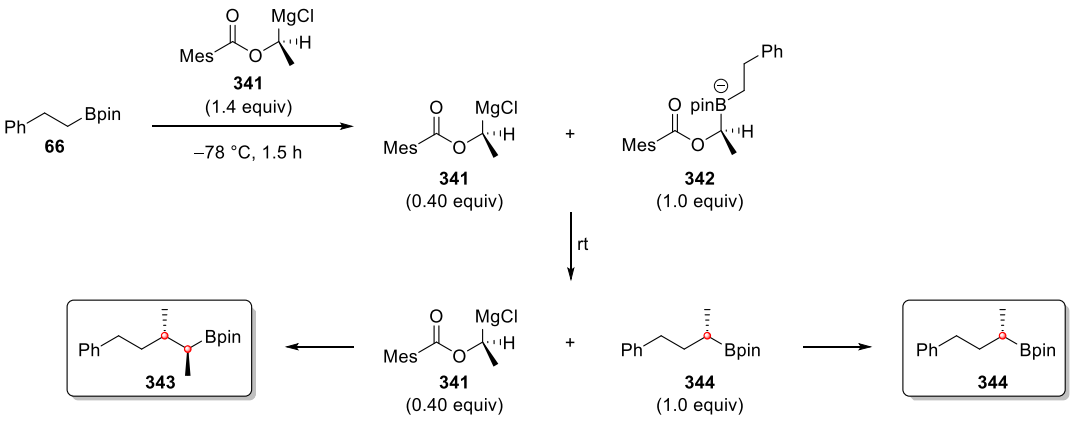
Furthermore, it would be beneficial to conduct a systematic study into the reactivity of magnesiated carbenoids and explore the limits of their chemical and configurational stability.

The magnesiated carbenoid generated using *i*-PrMgCl·LiCl appears to occupy a sweet spot in between organolithiums and Grignard reagents in terms of balancing reactivity and chemical stability when applied to the homologation of boronic esters.

When the boronic ester is the limiting reagent, the excess metalated carbenoid must decompose at a lower temperature than that at which 1,2-migration can take place, in order to prevent over-homologation, which is particularly important when contemplating iterative homologations (*vide supra*, section **1.4**).

O'Brien showed that α-carbamoyl Grignard reagent **61** (**Scheme 22**) is configurationally stable at ambient temperature for 30 minutes.[46]

Such α-alkoxy Grignard reagents are also presumably chemically stable at ambient temperature given that Dr Burns observed 20% over-homologation (**343**) by GC-MS analysis when treating boronic ester **66** with the Grignard reagent generated from **339** and *i*-PrMgCl.[194] The level of over-homologation was independent of the rate at which the reaction mixture was warmed to ambient temperature suggesting that this magnesiated carbenoid is chemically stable at ambient temperature, when 1,2-migration occurs and so when used in excess carbenoid **341** can subsequently react with the product boronic ester **344** to give the undesired over-homologated product **343** (**Scheme 166**).



Scheme 166 Over-homologation of boronic ester **66** upon treatment with excess carbenoid **341**.

Dr Burns performed a series of metalation–deuteration experiments with carbenoid precursor **339** to investigate the chemical stability and showed that even after 1-3 hours at ambient temperature carbenoid **341** had not fully decomposed.[194]

This prompted a switch to *i*-PrMgCl·LiCl for sulfoxide-metal exchange of carbenoid precursor **339**; the lithium chloride complex of Grignard reagents has been shown to exhibit increased reactivity and so was postulated to be less chemically stable at temperatures high

enough for 1,2-migration to occur. Therefore, over-homologation would be prevented if the magnesiated carbenoid generated using *i*-PrMgCl·LiCl decomposed at a temperature below ambient temperature.

Dr Burns subjected **339** to sulfoxide-metal exchange using *i*-PrMgCl·LiCl at −78 °C, followed by 1 hour at ambient temperature before quenching with deuterated methanol; in this case, the carbenoid was shown to have completely decomposed.[194] Michaelina reported an NMR yield of 72% (entry 6, **Table 9**) for the homologation of **66** with the magnesiated carbenoid derived from homoallylic α-sulfinyl benzoate **67** and *i*-PrMgCl·LiCl, when the temperature for the sulfoxide-metal exchange and borylation phases of the reaction was 3 °C, indicating either that this 'MgCl·LiCl' carbenoid is reasonably chemically stable at 3 °C, or that it is sufficiently reactive at this temperature to undergo borylation before significant chemical decomposition.

It was demonstrated that magnesiated carbenoids generated using *i*-PrMgCl·LiCl are configurationally stable at −20 °C for at least 1 hour (*vide supra*, **Scheme 76**). Once the limit of chemical stability has been established, verifying the maximum temperature at which this carbenoid is configurationally stable would be requisite.

Magnesiated carbenoids can also be generated through transmetalation of the corresponding lithiated species, generated through *s*-BuLi/sparteine mediated asymmetric deprotonation. However given the notable differences in reactivity and stability already observed between 'MgCl' and 'MgCl·LiCl' carbenoids, predicting the reactivity of such carbenoids by analogy necessitates caution. Hoffman and co-workers reported that the extent of racemisation with increasing temperature for α-chloroalkyl Grignard reagents such as **54** (*vide supra*, **Scheme 20**) varied depending on the Grignard reagent used for sulfoxide-metal exchange,[41] and so the configurational stability of α-benzoyl Grignard reagents might also be expected to vary similarly.

Following investigations into the chemical and configurational stability of magnesiated carbenoids generated using *i*-PrMgCl·LiCl for the homologation of boronic esters, further work could use *in situ* IR monitoring to explore reaction times, given this technique has been shown to be successful in recording the rate of sulfoxide-metal exchange and borylation at appropriate temperatures (*vide supra*, **Figure 13**, **Figure 14**).

6 Experimental

6.1 General Information

Reaction mixtures were stirred magnetically. Air- and moisture-sensitive reactions were carried out in flame-dried glassware under a nitrogen atmosphere using standard Schlenk manifold technique.

^{1}H Nuclear magnetic resonance (NMR) spectra were recorded at ambient temperature in $CDCl_3$, CD_3OD, toluene-d_8, pyridine-d_5 or DMSO-d_6 at 400, 500 or 700 MHz on a Bruker Nano 400, Jeol ECZ 400, Varian 400-MR or a Bruker Avance III HD 500 Cryo or Bruker Avance III HD Cryo-700 Fourier transform spectrometer. Chemical shifts (δ_H) are quoted in parts per million (ppm) and referred to the residual proton solvent signals of $CDCl_3$ (7.26 ppm), CD_3OD (3.31 ppm), toluene-d_8 (7.09, 7.00, 6.98, 2.09 ppm), pyridine-d_5 (8.74, 7.58, 7.22 ppm) or DMSO-d_6 (2.50 ppm). ^{1}H NMR coupling constants are reported in Hertz and refer to apparent multiplicities. Data are reported as follows: chemical shift, multiplicity (s = singlet, br. s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sext = sextet, sept = septet, m = multiplet, dd = doublet of doublets, etc.), coupling constant, integration, and assignment. Assignment of signals in ^{1}H spectra was performed using ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC experiments where appropriate. ^{13}C NMR spectra were recorded at 101 or 126 MHz. Chemical shifts (δ_C) are quoted in ppm referenced to $CDCl_3$ (77.16 ppm), CD_3OD (49.00 ppm), toluene-d_8 (137.86, 129.24, 128.33, 125.49, 20.4 ppm), pyridine-d_5 (150.35, 135.91, 123.87 ppm) or DMSO-d_6 (39.52 ppm). ^{13}C signals adjacent to boron are generally not observed due to quadrupolar relaxation.

Mass spectra were recorded by the University of Bristol, School of Chemistry departmental mass spectrometry service using electron ionisation (EI), electrospray ionisation (ESI), Matrix-assisted Laser Desorption/Ionisation (MALDI), Atmospheric Pressure Chemical Ionisation (APCI) or Nanospray Ionisation techniques for low- and high-resolution mass spectra. HRMS EI was performed on a QExactive. HRMS ESI was performed on either an Esquire 6000, Orbitrap Elite or micrOTOF II. HRMS MALDI was performed on an UltrafleXtreme. HRMS APCI was performed on an Orbitrap Elite. HRMS Nanospray was performed on a Synapt G2S or Orbitrap Elite.

All **infrared spectra** were recorded on a PerkinElmer Spectrum One FT-IR spectrometer as a thin film, irradiating between 4000 cm^{-1} and 600 cm^{-1}. Only strong and selected absorbance values (ν_{max}) are reported in wavenumbers (cm^{-1}).

Optical rotations were obtained using a Bellingham + Stanley Ltd. ADP220 polarimeter at 589 nm (Na D-line) in a cell with a path length of 1 dm. Specific rotation values are given in (deg mL)/(g dm).

Analytical thin layer chromatography (TLC) was performed on aluminium-backed silica plates (Merck, Silica Gel 60 F254, 0.25 mm). Compounds were visualised by UV irradiation or by staining the plates with an ethanolic solution of phosphomolybdic acid (PMA), ethanolic acidic *p*-anisaldehyde or aqueous basic $KMnO_4$ followed by heating.

Flash column chromatography was performed on silica gel (Aldrich, Silica Gel 60, 40–63 μm) or on a Biotage Isolera One flash purification system as stated. All mixed solvent eluents are reported as v/v solutions.

Reverse-phase **Liquid Chromatography-Mass Spectrometry (LC-MS)** analysis was performed on an Agilent 1260 Infinity II system with an Agilent PoroShell 120 EC-C18 column (50 × 3.0 mm, 2.7 μm) and acetonitrile/water mobile phase with 0.1% formic acid, observing at 254 or 360 nm.

Reverse-phase **preparative high performance liquid chromatography (HPLC)** was performed on an Agilent 1260 Infinity II system with an Agilent Zorbax Prep-C18 column (50×10.0 mm, 5 μm) and acetonitrile/water mobile phase, observing at 360 nm.

Chiral HPLC separations were performed on an Agilent 1100 Series HPLC unit equipped with UV-Vis diode-array detector.

***In Situ* IR spectroscopy** (React-IR): The reactions were monitored using Mettler Toledo React-IR 15 mid-infrared spectrometer equipped with a Silver Halide (AgX) FiberConduit with integrated DiComp probe, using the iC IR Reaction Analysis software (version 4.3).

Compound names are those generated by ChemDraw 20.0 software (PerkinElmer), following the IUPAC nomenclature.

6.2 Materials and Reagents

Anhydrous THF, CH_2Cl_2, toluene, hexane, acetonitrile and Et_2O were obtained from a modified Grubbs system of alumina columns,[195] manufactured by Anhydrous Engineering, and stored over thoroughly dried 3 Å mol sieves. Anhydrous methanol, 1,2-dichloroethane (DCE) and pyridine were commercially supplied.

$Pt(dba)_3$ [CAS 11072-92-7] was purchased from Strem Chemicals, Inc. and used as received. Morken's diboration ligands, (*R*,*R*)-3,5-di-*iso*-propylphenylTADDOLPPh [(*R*,*R*)-**L***] and (*S*,*S*)-3,5-di-*iso*-propylphenylTADDOLPPh [(*S*,*S*)-**L***], were prepared in-house according to the published procedure.[50] (+)-Andersen's sulfinate [CAS 91796-57-5] was purchased from Sigma Aldrich and used as received. (−)-Andersen's sulfinate [CAS 1517-82-4] was purchased from Henan Tianfu Chemical Co., Ltd and used as received. Hoveyda Grubbs catalyst, 2nd generation [CAS 301224-40-8] was purchased from Sigma Aldrich and used as received.

n-Butyllithium [CAS 109-72-8] was purchased from Acros as a 1.6 M solution in *n*-hexane. *s*-Butyllithium [CAS 598-30-1] was purchased from Acros Organics as a 1.3 M solution in cyclohexane:*n*-hexane 98:2. *t*-Butyllithium [CAS 594-19-4] was purchased from Sigma Aldrich as a 1.7 M solution in *n*-pentane, or a 1.6 – 3.2 M solution in heptane. The molarity of organolithium solutions was regularly determined by titration with *N*-benzylbenzamide.[196] *i*-PrMgCl·LiCl was purchased from Sigma Aldrich as a 1.2 M solution in THF and the molarity was verified by titration with iodine.[197] LiHMDS [CAS 4039-32-1] was purchased from Sigma Aldrich as a 1 M solution in THF.

$MgBr_2$ in MeOH (1.0 M) was prepared from commercially available $MgBr_2$ which was dried for 2 h (150 °C/0.1 mbar) and then dissolved in anhydrous MeOH under inert atmosphere.[198] TMEDA, Et_3N, PMDTA, TESOTf and TMSCl were distilled over CaH_2 before use. Pinacolborane and 2,4,6-trichlorobenzoyl chloride were distilled before use. (–)-Sparteine was isolated from the commercially available sulfate pentahydrate salt following a procedure by Beak.[199] (+)-Sparteine was purchased as the free base and distilled over CaH_2. The sparteine free base readily absorbs atmospheric carbon dioxide (CO_2) and so should be stored under argon/nitrogen at −20 °C in a sealed Schlenk tube. Sparteine can be recovered reliably during work-up with aqueous HCl as reported in the literature.[22,34]

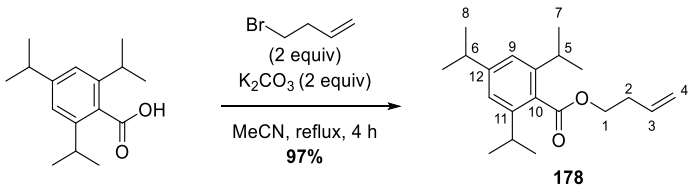
All other reagents were purchased from various commercial sources and used as received.

6.3 The Total Synthesis of Bahamaolide A

Two previous PhD students, Dr Alex Fawcett and Dr Joe Bateman, worked on the total synthesis of bahamaolide A prior to the work detailed in this thesis.[142]

All procedures described below are those carried out by the author.

But-3-en-1-yl 2,4,6-triisopropylbenzoate (178)



178

According to the literature procedure,[36] potassium carbonate (49.1 g, 356 mmol, 2.00 equiv) was added to a stirred solution of 2,4,6-triisopropylbenzoic acid (44.2 g, 178 mmol, 1.00 equiv) in acetonitrile (540 mL, 0.330 M). The mixture was stirred vigorously for 10 min then 4-bromo-1-butene (48.0 g, 356 mmol, 2.00 equiv) was added and the resulting mixture was refluxed (oil bath at 95 °C) for 4 h. The reaction mixture was cooled to ambient temperature. The K_2CO_3 was removed by filtration through Celite®, washing with EtOAc (2 × 150 mL), and the filtrate was concentrated under reduced pressure. The crude yellow liquid was purified by flash column chromatography on a Biotage Isolera One system (680 g SiO_2, 100:0 to 80:20 pentane:Et_2O) to afford benzoate **178** (52.2 g, 173 mmol, 97%) as a pale yellow oil.

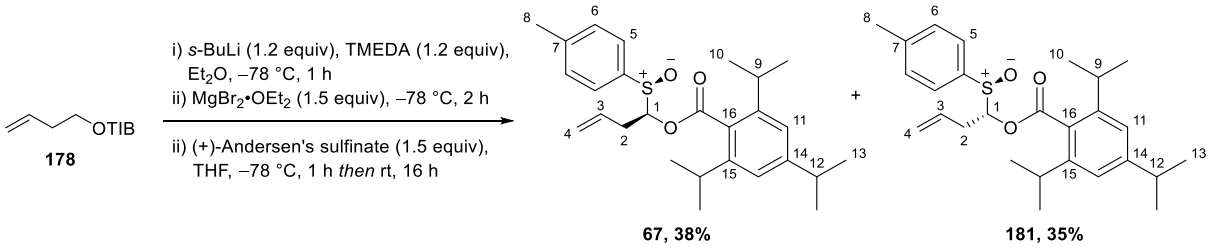
All recorded spectroscopic data matched that previously reported.[47]

TLC: R_f = 0.72 (80:20 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.00 (s, 2H, 2 × C9H), 5.84 (ddt, $^3J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 6.7 Hz, 1H, C3H), 5.15 (dq, $^3J_{HH}$ = 17.2 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, C4H^aH^b), 5.09 (dq, $^3J_{HH}$ = 10.2 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, C4H^aH^b), 4.37 (t, $^3J_{HH}$ = 6.7 Hz, 2H, C1H_2), 2.88 (sept, $^3J_{HH}$ = 7.0 Hz, 1H, C6H) 2.86 (sept, $^3J_{HH}$ = 6.7 Hz, 2H, 2 × C5H), 2.50 (qt, $^3J_{HH}$ = 6.7 Hz, $^4J_{HH}$ = 1.4 Hz, 2H, C2H_2), 1.24 (d, $^3J_{HH}$ = 7.0 Hz, 6H, 2 × C8H_3), 1.24 (d, $^3J_{HH}$ = 6.7 Hz, 12 H, 4 × C7H_3) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.0 (C=O), 150.3 (C12), 144.9 (2C, 2 × C11), 134.2 (C3), 130.7 (C10), 121.0 (2C, 2 × C9), 117.5 (C4), 64.2 (C1), 34.6 (C6), 33.2 (C2), 31.6 (2C, 2 × C5), 24.3 (2C, 2 × C8), 24.1 (4C, 4 × C7) ppm.

(*R*)-1-((*R*)-*p*-tolylsulfinyl)but-3-en-1-yl 2,4,6-triisopropylbenzoate (67) and (*S*)-1-((*R*)-*p*-tolylsulfinyl)but-3-en-1-yl 2,4,6-triisopropylbenzoate (181)



According to a literature procedure,[47] *s*-BuLi (1.30 M in hexanes, 30.5 mL, 39.7 mmol, 1.20 equiv) was added dropwise (syringe pump, 0.3 mL/min) to a stirred solution of benzoate **178** (10.0 g, 33.1 mmol, 1.00 equiv) and freshly distilled TMEDA (5.95 mL, 39.7 mmol, 1.20 equiv) in anhydrous Et_2O (110 mL, 0.300 M) under N_2 at −78 °C (acetone/dry ice) and stirred at −78 °C for 1 h. Freshly prepared* $MgBr_2{\cdot}OEt_2$ (49.6 mmol, 1.50 equiv) was added *via* cannula and the resulting reaction mixture was stirred for 2 h at −78 °C. A solution of (+)-Andersen's sulfinate (14.6 g, 49.6 mmol, 1.50 equiv) in anhydrous THF (50.0 mL, 1.00 M) was added and the reaction mixture was stirred for a further 1 h at −78 °C, then warmed to ambient temperature and stirred for 16 h. The reaction was quenched with 2 M aq. HCl (120 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (4 × 100 mL) and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

Purification was aided by silylation of the menthol by-product: The crude mixture was stirred under vacuum for 2 h then dissolved in anhydrous CH_2Cl_2 (66.0 mL, 0.500 M). Triethylamine (6.91 mL, 49.6 mmol, 1.50 equiv) was added followed by dropwise addition of TMSCl (5.45 mL, 43.0 mmol, 1.30 equiv). The resulting mixture was stirred at ambient temperature under N_2 overnight. The reaction mixture was diluted with Et_2O (80 mL), washed with water (80 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 90:10 to 0:100 pentane:Et_2O, to remove TMS-menthol and most of excess Andersen's sulfinate) then on a Biotage Isolera One system (dry loaded, 2 × 100 g Sfär column, 7:93 EtOAc:hexane) to afford *syn* α-sulfinyl benzoate **67** (5.54 g, 12.6 mmol, 38%, >99:1 *er*, >95:5 *dr*) as a white solid and *anti* α-sulfinyl benzoate **181** (5.10 g, 11.6 mmol, 35%, >99:1 *er*, >95:5 *dr*) as a viscous yellow oil.

*Preparation of $MgBr_2{\cdot}OEt_2$: To a flame dried 3 neck flask fitted with a reflux condenser under N_2 was charged oven dried magnesium turnings (3.22 g, 132 mmol, 4.00 equiv) and anhydrous Et_2O (62.0 mL, 0.800 M wrt 1,2-dibromoethane). To this stirred suspension was

added 1,2-dibromoethane (0.10 mL) and the resulting suspension was gently heated until the reaction initiated. Following initiation, 1,2-dibromoethane (4.17 mL, 49.6 mmol (total volume 4.27 mL)) was added dropwise at a rate determined by the vigorousness of the reaction. Upon completion of the addition of 1,2-dibromoethane, the reaction was biphasic with a colourless upper layer and a grey bottom layer. After gas evolution had stopped, the mixture was stirred for 30 min at ambient temperature. Both layers were transferred to the main reaction vessel by cannula. The unreacted Mg was cooled to 0 °C (water/ice) and quenched through the slow addition of an appropriate amount of 2 M aq. HCl.

All recorded spectroscopic data matched that previously reported.[47]

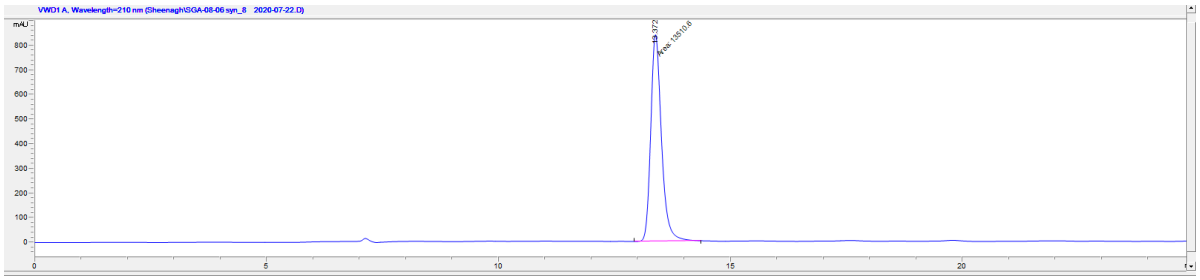
67

TLC: R_f = 0.33 (80:20 hexane:EtOAc, PMA).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.65 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2 × C5H), 7.39 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2 × C6H), 7.03 (s, 2H, 2 × C11H), 5.75 (dd, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 3.1 Hz, 1H, C1H), 5.65 (m, 1H, C3H), 5.12 – 5.05 (m, 2H, $C4H_2$), 2.91 (sept, $^3J_{HH}$ = 6.8 Hz, 2H, 2 × C9H), 2.91 (sept, $^3J_{HH}$ = 6.8 Hz, C12H), 2.72 (m, 1H, C2H^aH^b), 2.44 (s, 3H, $C8H_3$), 2.40 (m, 1H, C2H^aH^b), 1.31 – 1.17 (m, 18H, 4 × $C10H_3$, 2 × $C13H_3$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 170.5 (C=O), 151.0 (C14), 145.4 (2 × C15), 141.9 (Tol CS), 137.5 (C7), 131.6 (C3), 130.2 (2C, 2 × C6), 128.9 (C16), 124.6 (2C, 2 × C5), 121.1 (2C, 2 × C11), 119.4 (C4), 91.6 (C1), 34.6 (C12), 31.7 (C2), 28.0 (2C, 2 × C9), 24.6 (2C, 2 × CH_3), 24.3 (2C, 2 × CH_3), 24.1 (2C, 2 × CH_3), 21.6 (C8) ppm.

Chiral HPLC: (Daicel Chiralcel-IA column (25 cm) with guard, hexane:isopropanol 95:5, 0.5 mL/min, ambient temperature, 210.8 nm) t_R = 12.8 min (minor), 13.4 min (major), *er* >99:1. *Chiral HPLC conditions previously reported and used in-house,*[47] ***ent*-67** *also synthesised by the author and was available for comparison.*



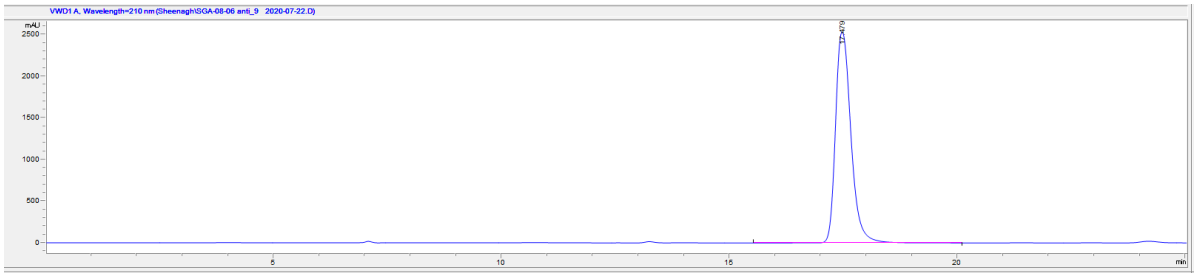
181

TLC: R_f = 0.29 (80:20 hexane:EtOAc, PMA).

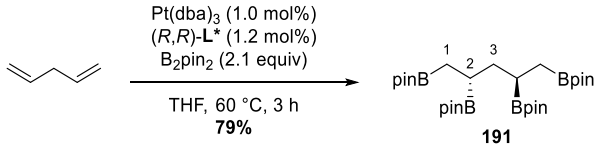
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.55 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2 × C5H), 7.32 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2 × C6H), 7.02 (s, 2H, 2 × C11H), 6.07 (dd, $^3J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 3.7 Hz, 1H, C1H), 5.77 (m, 1H, C3H), 5.18 – 5.11 (m, 2H, $C4H_2$), 2.90 (sept, $^3J_{HH}$ = 6.8 Hz, 1H, C12H), 2.83 (sept, $^3J_{HH}$ = 6.8 Hz, 2H, 2 × C9H), 2.70 (m, 1H, C2$H^a$$H^b$), 2.42 (s, 3H, $C8H_3$), 2.10 (m, 1H, C2$H^a$$H^b$), 1.26 (d, $^3J_{HH}$ = 6.8 Hz, 6H, 2 × $C10H_3$), 1.23 (d, $^3J_{HH}$ = 6.8 Hz, 6H, 2 × $C10H_3$), 1.19 (d, $^3J_{HH}$ = 6.8 Hz, 6H, 2 × $C13H_3$) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 169.3 (C=O), 150.9 (C14), 145.4 (2 × C15), 142.3 (Tol CS), 136.2 (C7), 131.6 (C3), 130.1 (2C, 2 × C6), 129.0 (C16), 125.7 (2C, 2 × C5), 121.2 (2C, 2 × C11), 119.7 (C4), 87.4 (C1), 34.6 (C12), 32.1 (C2), 31.6 (2C, 2 × C9), 24.7 (2C, 2 × CH_3), 24.3 (2C, 2 × CH_3), 24.1 (2C, 2 × CH_3), 21.6 (C8) ppm.

Chiral HPLC: (Daicel Chiralcel-IA column (25 cm) with guard, hexane:isopropanol 95:5, 0.5 mL/min, ambient temperature, 210.8 nm) t_R = 12.7 min (minor), 17.5 min (major), *er* >99:1. *Chiral HPLC conditions previously reported and used in-house*.[47]



2,2',2'',2'''-((2*R*,4*R*)-Pentane-1,2,4,5-tetrayl)tetrakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (191)



$Pt(dba)_3$ (89.8 mg, 0.100 mmol, 1.00 mol%), (*R*,*R*)-**L*** (109 mg, 0.120 mmol, 1.20 mol%) and B_2pin_2 (5.33 g, 21.0 mmol, 2.10 equiv) were dissolved in THF (10.0 mL, 1.00 M) before sealing the Schlenk tube (closing the tap) and heating to 80 °C (oil bath) for 60 min. After cooling to ambient temperature 1,4-pentadiene (1.03 mL, 10.0 mmol, 1.00 equiv) was quickly added before resealing and heating for 16 h at 60 °C (oil bath). The solution was then cooled to ambient temperature and concentrated under reduced pressure. The crude residue was directly purified by flash column chromatography (SiO_2; 80:20 pentane:Et_2O) to yield the tetra(boronic ester) **191** (4.56 g, 7.92 mmol, 79%, >99:1 *er*, 95:5 *dr*) as a white solid. The solid was recrystallised (pentane; 0.80 mL/g; freezer overnight) to yield tetra(boronic ester) **191** (3.44 g, 5.97 mmol, 60%, >95:5 *dr*) as a white crystalline solid.

All recorded spectroscopic data matched that previously reported.[142]

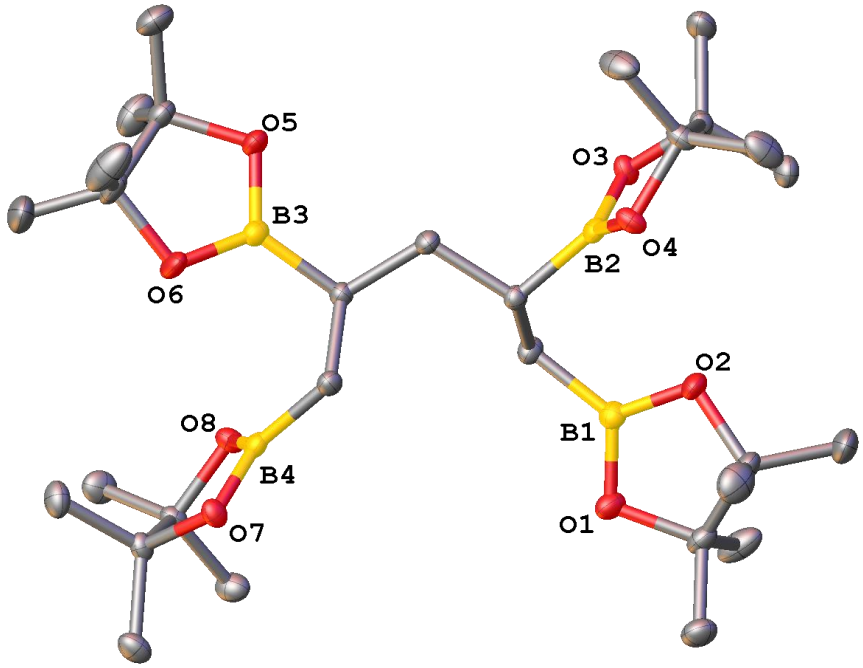
TLC: R_f = 0.19 (85:15 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 1.43 (t, $^3J_{HH}$ = 7.7 Hz, 2H, C3H_2), 1.20 (s, 48H, 16 × pinacol-CH_3), 1.31 – 1.03 (m, 2H, 2 × C2H), 0.82 (dd, $^2J_{HH}$ = 15.8 Hz, $^3J_{HH}$ = 5.4 Hz, 2H, 2 × C1$H^a$$H^b$), 0.73 (dd, $^2J_{HH}$ = 15.8 Hz, $^3J_{HH}$ = 9.8 Hz, 2H, 2 × C1H^aH^b) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 82.8 (pinacol-C), 82.7 (pinacol-C), 36.8 (C3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.9 (pinacol-CH_3), 17.5 (C2), 12.3 (C1) ppm.

Crystal Structure (obtained by Dr Fawcett):

X-ray diffraction experiments on **191** were carried out at 100(2) K on a Bruker APEX II diffractometer using Mo-K$_\alpha$ radiation (λ = 0.71073 Å). Intensities were integrated in SAINT[200] and absorption corrections based on equivalent reflections were applied using SADABS.[201] The structure of **191** was solved using Superflip[202,203] and refined by full matrix least squares against F^2 in ShelXL[204,205] using Olex2.[206] All of the non-hydrogen atoms were refined anisotropically. While all of the hydrogen atoms were located geometrically and refined using a riding model. The absolute structure was not determined. Crystal structure and refinement data are given in Supplementary Table 1. Crystallographic data for **191** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 2150709.

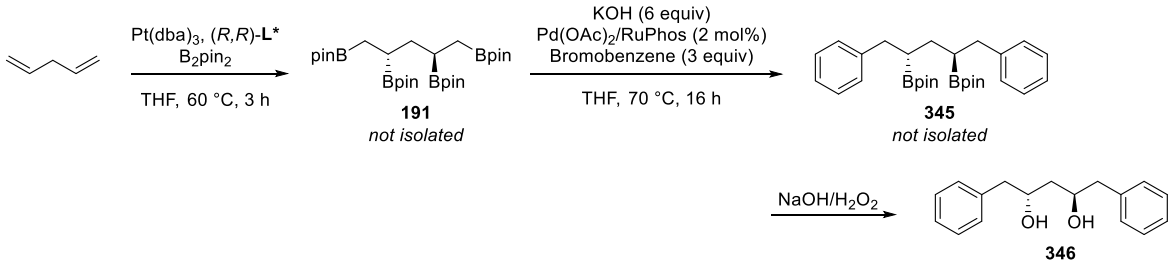


Supplementary figure 1 Illustration of the atom connectivity for **191**. Anisotropic displacement parameters depicted at the 50% probability level. Hydrogen atoms omitted for clarity.

Supplementary table 1 Crystal data and structure refinement for **191**.

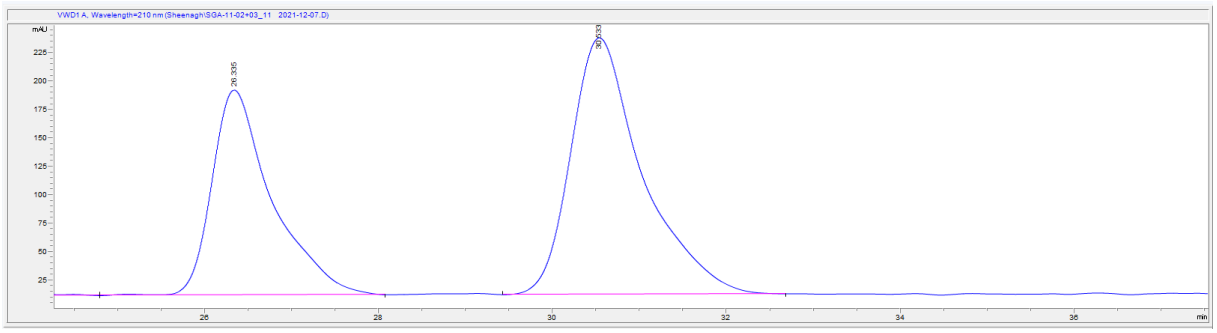
Identification code	**191**
Empirical formula	$C_{29}H_{56}B_4O_8$
Formula weight	575.97
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	9.2971(2)
b/Å	15.6157(4)
c/Å	12.1000(3)
α/°	90
β/°	95.4976(13)
γ/°	90
Volume/Å^3	1748.61(7)
Z	2
ρ_{calc}g/cm^3	1.094
μ/mm^{-1}	0.075
F(000)	628.0
Crystal size/mm^3	0.61 × 0.47 × 0.47
Radiation	MoKα (λ = 0.71073)
2θ range for data collection/°	3.382 to 55.834
Index ranges	$-12 \leq h \leq 12$, $-20 \leq k \leq 18$, $-15 \leq l \leq 15$
Reflections collected	15873
Independent reflections	8051 [R_{int} = 0.0200, R_{sigma} = 0.0317]
Data/restraints/parameters	8051/1/386
Goodness-of-fit on F^2	1.021
Final R indexes [I>=2σ (I)]	R_1 = 0.0369, wR_2 = 0.0898
Final R indexes [all data]	R_1 = 0.0418, wR_2 = 0.0925
Largest diff. peak/hole / e Å^{-3}	0.32/-0.16

Chiral separation was achieved by preparing a small sample of **191** (not recrystallised) and derivatising as follows: selective coupling of the 2 primary boronic esters with bromobenzene, as described by Morken,[185] followed by oxidation of **345** to known diol[207] **346**.

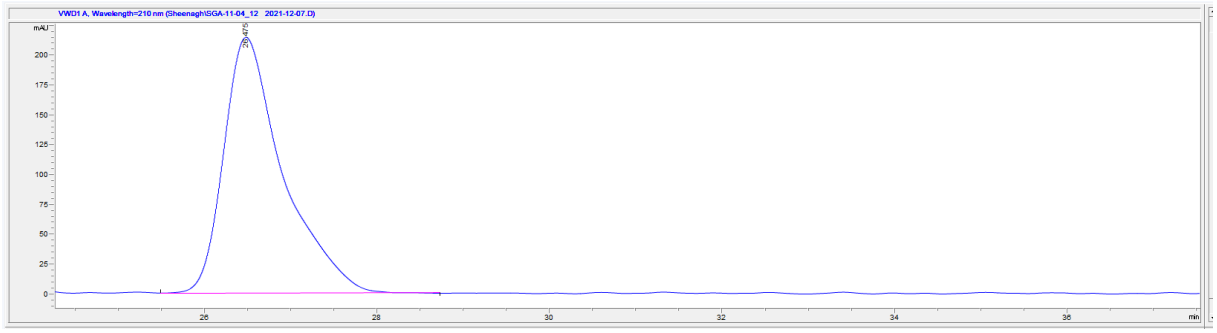


Chiral HPLC: (Daicel Chiralpak AD-H (25 cm), hexane:isopropanol 95:5, 1.0 mL/min, ambient temperature, 210 nm) t_R = 26.4 min (major), 30.5 min (minor).

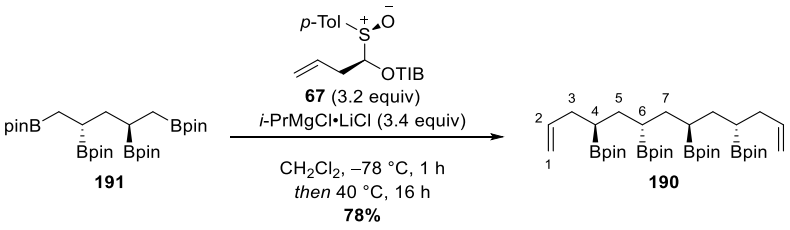
Mixture of diols from (*S*,*S*)-**L*** and (*R*,*R*)-**L***:



346 after column, >99:1 *er*



2,2',2'',2'''-((4*R*,6*S*,8*S*,10*R*)-Trideca-1,12-diene-4,6,8,10-tetrayl)tetrakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (190)



i-PrMgCl·LiCl (1.12 M in THF, 1.52 mL, 1.70 mmol, 3.40 equiv) was added to a solution of tetra(boronic ester) **191** (288 mg, 0.500 mmol, 1.00 equiv) and α-sulfinyl benzoate **67** (705 mg, 1.60 mmol, 3.20 equiv) in anhydrous CH_2Cl_2 (2.50 mL, 0.200 M) at −78 °C (acetone/dry ice) under N_2. The resulting mixture was stirred at −78 °C for 1 h. The reaction was warmed to ambient temperature, then heated to 40 °C (oil bath) for 16 h. The reaction was cooled to ambient temperature, filtered through Et_3N-deactivated silica, washing with Et_2O, and concentrated under reduced pressure. The crude residue was purified on a Biotage Isolera One system (loaded in hexane, 25 g Sfär HC column, 96:4 hexane:acetone) to yield tetra(boronic ester) **190** (267 mg, 0.390 mmol, 78%, >95:5 *dr*) as a colourless oil.

All recorded spectroscopic data matched that previously reported.[142]

TLC: R_f = 0.23 (94:6 hexane:acetone, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.79 (ddt, $^3J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 10.1, Hz, $^3J_{HH}$ = 6.9 Hz, 2H, 2 × C2*H*), 4.98 (dd, $^3J_{HH}$ = 17.1 Hz, $^4J_{HH}$ = 2.2 Hz, 2H, 2 × C1*H*^{a}H^b), 4.88 (app. d, $^3J_{HH}$ = 10.1 Hz, 2H, 2 × C1H^a*H*^{b}), 2.18 – 2.02 (m, 4H, C3H$_2$), 1.48 – 1.40 (m, 2H, CH$_2$), 1.39 – 1.30 (m, 4H, CH$_2$), 1.20 (s, 48H, 4 × pinacol-C*H*$_3$), 1.15 – 1.05 (m, 4H, 2 × C4H, 2 × C6H) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 139.0 (2 × C2), 114.7 (2 × C1) 82.9 (pinacol-C), 82.7 (pinacol-C), 36.0 (2 × C3), 33.7 (CH$_2$), 33.1 (2 × CH$_2$), 25.1 (pinacol-CH$_3$), 25.1 (pinacol-CH$_3$), 25.0 (pinacol-CH$_3$), 24.9 (pinacol-CH$_3$) ppm.

Carbon next to boron not observed due to quadrupolar relaxation.

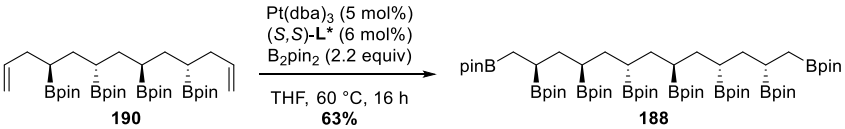
N.B. Dr Bateman's procedure involved filtering the crude reaction mixture through Celite®. However, significant quantities of triisopropylbenzoic acid (TIBOH) were still present as a sticky white solid which meant excess TELOS (diatomaceous earth) was required for dry loading and the TIBOH often still co-eluted with **190**, requiring further separation after column chromatography. While bringing more material through, the work-up and isolation protocol were varied as shown in **Supplementary table 2**. Filtering through Et_3N-deactivated

silica was the best method to remove the TIBOH before rapid chromatographic purification on the Biotage Isolera One system, which was beneficial since these homoallylic boronic esters show some instability on silica gel.

Entry	Scale /mmol 191	Yield /%	Comments on work-up and isolation
1	0.1	51	Filter through Celite® then column on Biotage Isolera One system, 5 g Sfär HC, 4:96 acetone:hexane.
2	0.1	37	Filter through Celite® then manual column, 5 g SiO_2, 4:96 acetone:hexane.
3	0.1	73	Dry load on Celite®, no filtration. Biotage column.
4	0.1	57	Work up with sat. aq. NH_4Cl and Et_2O. Biotage column.
5	0.2	61	Dry load on Celite®. Biotage column.
6	0.2	73	Dry load on Et_3N-deactivated silica. Biotage column.
7	0.2	72	Filter through Et_3N-deactivated silica, Biotage column, load in hexane; no mixed fractions.
8	0.2	67	Filter through Celite®, Biotage column, load in hexane. (mixed fractions)
9	0.5	76,78,78	Filter through Et_3N-deactivated silica, Biotage column, load in hexane.

Supplementary table 2 Investigations into the isolation of **190** by the author.

2,2',2'',2''',2'''',2''''',2'''''',2''''''-((2*S*,4*S*,6*R*,10*S*,12*S*)-Tridecan-1,2,4,6,8,10,12,13-octayl)octakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (188)



$Pt(dba)_3$ (43.6 mg, 48.6 µmol, 5.00 mol%), (*S*,*S*)-**L*** (53.0 mg, 58.3 µmol, 6.00 mol%) and B_2pin_2 (543 mg, 2.14 mmol, 2.20 equiv) were dissolved in anhydrous THF (0.970 mL, 1.00 M) before sealing the flask and heating to 80 °C (oil bath) for 30 min. After cooling to ambient temperature, the pre-complexed mixture was transferred to a vial containing tetra(boronic ester) **190** (665 mg, 0.972 mmol, 1.00 equiv). The vial was sealed and heated for 16 h at 60 °C (oil bath). The solution was then cooled to ambient temperature and

concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 96:4 hexane:acetone) to yield octa(boronic ester) **188** (730 mg, 0.612 mmol, 63%) as a white voluminous foam.

All recorded spectroscopic data matched that previously reported.[142]

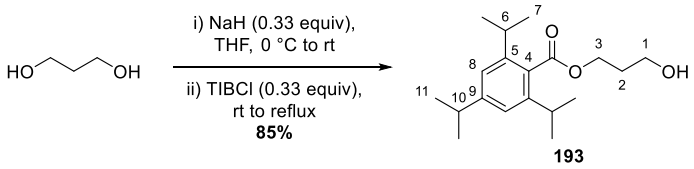
TLC: R_f = 0.17 (92:8 hexane:acetone, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 1.60 – 0.98 (m, 112H), 0.91 (dd, $^2J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 4.2 Hz, 2H, 2 × BC*H*^{a}H^b), 0.72 (dd, $^2J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 11.1 Hz, 2H, 2 × BCH^a*H*^{b}) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 82.7 (pinacol-C), 82.7 (pinacol-C), 82.6 (pinacol-C), 82.6 (pinacol-C), 82.6 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 35.3 (CH_2), 35.2 (CH_2), 35.1 (CH_2), 25.2 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.9 (pinacol-CH_3), 24.9 (pinacol-CH_3) ppm.

Carbon attached to boron not observed due to quadrupolar relaxation.

3-Hydroxypropyl 2,4,6-triisopropylbenzoate (193)



193

According to a literature procedure,[208] 1,3-propanediol (2.28 g, 30.0 mmol, 3.00 equiv) was added dropwise to sodium hydride (400 mg, 60 wt% in mineral oil, 10.0 mmol, 1.00 equiv) in anhyd. THF (30.0 mL, 0.330 M) at 0 °C under inert atmosphere. The mixture was stirred at 0 °C for 1 h then at ambient temperature for 1 h. Triisopropylbenzoyl chloride (2.67 g, 10.0 mmol, 1.00 equiv) was added portionwise and the reaction mixture was stirred at ambient temperature for 30 min then reflux (oil bath, 70 °C) overnight.

The reaction mixture was cooled to ambient temperature, quenched with H_2O (30 mL) and diluted with EtOAc (30 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organics were washed with 1 M aq. HCl (2 × 30 mL), 1 M aq. NaOH (2 × 30 mL), H_2O (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude oil was purified by flash column chromatography using a Biotage Isolera One system (50 g Sfär column, Et_2O:pentane 1:4 to 4:1) to give benzoate **193** (2.62 g, 8.55 mmol, 85%) as a pale yellow oil.

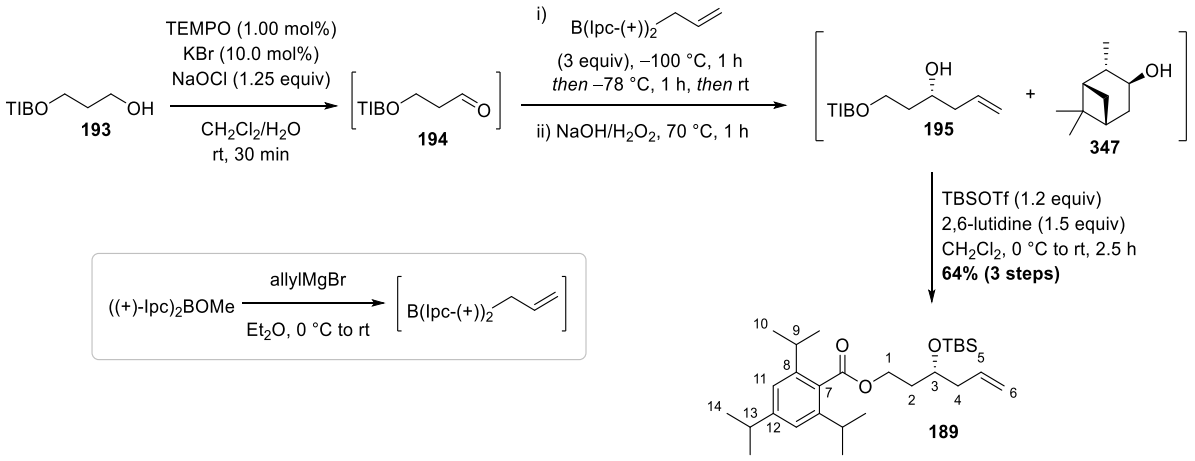
All recorded spectroscopic data matched that previously reported.[208]

TLC: $\mathbf{R_f}$ = 0.15 (70:30 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.01 (s, 2H, 2 × C8H), 4.46 (t, $^3J_{HH}$ = 6.3 Hz, 2H, $C3H_2$), 3.78 (t, $^3J_{HH}$ = 6.1 Hz, 2H, $C1H_2$), 2.94 – 2.78 (m, 3H, 2 × C6H, C10H), 2.03 – 1.95 (m, 2H, $C2H_2$), 1.24 (d, $^3J_{HH}$ = 6.9 Hz, 18H, 4 × $C7H_3$, 2 × $C11H_3$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 171.3 (C=O), 150.4 (C9), 144.9 (2C, 2 × C5), 130.5 (C4), 121.0 (2C, 2 × C8), 62.1, (C3) 59.5 (C1), 34.6 (C10), 31.8 (C2), 31.7 (2C, 2 × C6), 24.3 (2C, 2 × C11), 24.1 (4C, 4 × C7) ppm.

(*R*)-3-((*tert*-butyldimethylsilyl)oxy)hex-5-en-1-yl 2,4,6-triisopropylbenzoate (189)



Oxidation of alcohol **193**

To a stirred solution of alcohol **193** (5.00 g, 16.3 mmol, 1.00 equiv) in CH_2Cl_2 (20.4 mL, 0.800 M) at 0 °C was added sequentially TEMPO (25.5 mg, 0.163 mmol, 1.00 mol%) in CH_2Cl_2 (20.4 mL, 8.00 mM), KBr (194 mg, 1.63 mmol, 10.0 mol%) in H_2O (3.26 mL, 0.500 M) and $NaOCl{\cdot}5H_2O$ (3.36 g, 20.4 mmol, 1.25 equiv) as a solution in H_2O (58.3 mL, 0.350 M). The resulting biphasic mixture was stirred vigorously at ambient temperature for 1 h. After this time the phases were separated and the organics were dried over anhydrous $MgSO_4$ and filtered through a small silica plug washing with Et_2O. The filtrate was diluted with anhydrous THF (33.0 mL, 0.500 M) and Et_2O and CH_2Cl_2 removed under reduced pressure to yield aldehyde **194** as a *ca*. 0.5 M solution in THF.

TLC: R_f = 0.27 (70:30 pentane:Et_2O, $KMnO_4$).

Allylboration

According to a modified literature procedure,[73] allylMgBr (1.00 M in Et_2O, 78.0 mL, 49.0 mmol, 3.00 equiv) was added to a stirred solution of (+)-Ipc_2BOMe (15.5 g, 49.0 mmol, 3.00 equiv) in anhydrous Et_2O (49.0 mL, 1.00 M) under N_2 at 0 °C (water/ice). The resulting mixture was warmed to ambient temperature and stirred for 1 h before the solvent was removed under high vacuum. Pentane (50 mL) was added and the mixture was stirred vigorously for 2 min before the stirring was stopped and the solids were allowed to settle. The pentane was transferred to a separate flask through a sintered PTFE cannula and the extraction process was repeated a further two times. The pentane was removed under high vacuum to give the crude allylboron reagent. The resulting residue was diluted with anhydrous Et_2O (49.0 mL, 0.330 M) and cooled to −100 °C (cryostat) at which point aldehyde **194** was added dropwise (syringe pump, 0.5 mL/min) as a *ca*. 0.5 M solution in THF. The reaction was stirred at −100 °C for 1 h, warmed to −78 °C (acetone/dry ice) and stirred for a further 1 h at −78 °C. MeOH (HPLC grade, 35 mL) was added and the reaction was allowed to warm to ambient temperature overnight. The flask was fitted with a reflux condenser before the addition of NaOH (3.00 M aq., 40.0 mL) and 30% aq. H_2O_2 (20.0 mL) (caution: autoreflux) and the mixture was heated at 70 °C (oil bath) for 1 h. The reaction mixture was cooled to ambient temperature and sat. aq. $Na_2S_2O_3$ (50 mL) and Et_2O (100 mL) were added. The phases were separated, and the aqueous phase was extracted with Et_2O (3 × 80 mL). The combined organics were washed with sat. aq. $Na_2S_2O_3$ (150 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified on a Biotage Isolera One system (loaded in pentane, 200 g Sfär column, 80:20 pentane:Et_2O) to give secondary alcohol **195** as an inseparable mixture with (+)-isopinocampheol (**347**). ^{1}H NMR analysis showed this was a ~1:3 mixture of **195**:**347**.

TLC: R_f = 0.19 (80:20 pentane:Et_2O, anisaldehyde).

Silyl protection

To a stirred solution of secondary alcohol **195** and (+)-isopinocampheol (**347**) ((estimate 3.40 g, 9.81 mmol **195** + 4.70 g, 30.5 mmol **347**) total 40.3 mmol, 1.00 equiv) in anhydrous CH_2Cl_2 (98.0 mL, 0.100 M wrt **195**) under N_2 at 0 °C was added dropwise 2,6-lutidine (7.04 mL, 60.4 mmol, 1.50 equiv) followed by TBSOTf (11.1 mL, 48.3 mmol, 1.20 equiv). The resulting mixture was warmed to ambient temperature and stirred for 2.5 h. The reaction was diluted with H_2O (70 mL) and the phases were separated. The aqueous phase was

extracted with CH_2Cl_2 (2 × 50 mL) and the combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO_2, 100% pentane for removal of TBS-protected isopinocampheol, then 98:2 pentane:Et_2O) to yield benzoate **189** (4.51 g, 10.5 mmol, 64%, 92:8 *er*) as a colourless oil.

All recorded spectroscopic data matched that previously reported.[142]

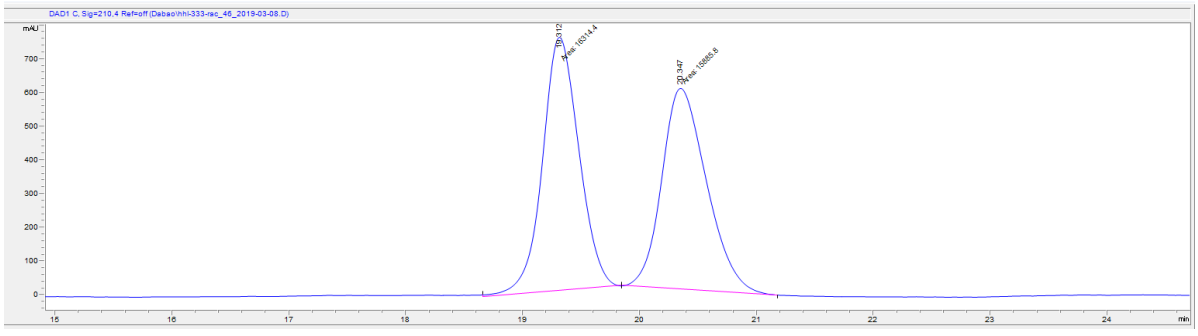
TLC: R_f = 0.55 (95:5 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.02 (s, 2H, 2 × C11H), 5.81 (m, 1H, C5H), 5.09 – 5.03 (m, 2H, $C6H_2$), 4.47 (ddd, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = 5.5 Hz, 1H, C1H^aH^b), 4.35 (ddd, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 6.5 Hz, 1H, C1H^aH^b), 3.90 (m, 1H, C3*H*), 2.93 – 2.79 (m, 3H, 2 × C9H, C13H), 2.28 (ddt, $^3J_{HH}$ = 7.1 Hz, $^3J_{HH}$ = 5.8 Hz, $^4J_{HH}$ = 1.3 Hz, 2H, $C4H_2$), 1.93 (dddd, $^2J_{HH}$ = 14.4 Hz, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = 4.1 Hz, 1H, C2H^aH^b), 1.84 (dddd, $^2J_{HH}$ = 14.4 Hz, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 6.5 Hz, $^3J_{HH}$ = 5.6 Hz, 1H, C2H^aH^b), 1.29 – 1.23 (m, 18H, 4 × $C10H_3$, 2 × $C14H_3$), 0.92 (s, 9H, $SiC(CH_3)_3$), 0.09 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$) ppm.

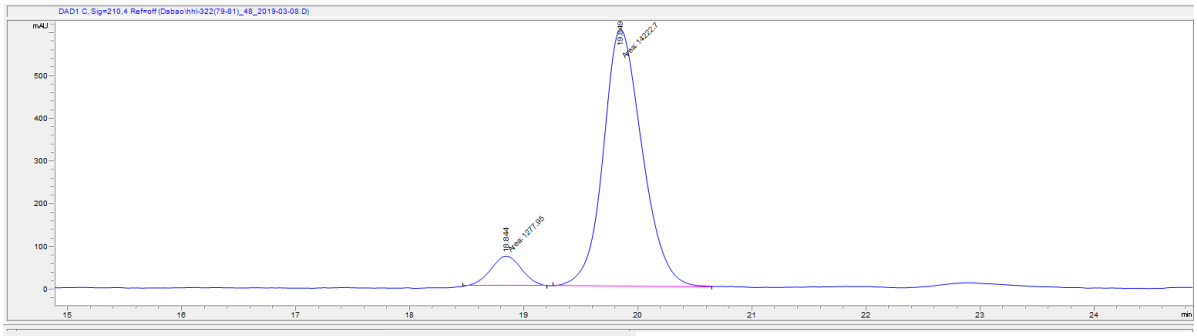
^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.1 (C=O), 150.2 (C13), 144.9 (2C, 2 × C8), 134.6 (C5), 130.7 (C7), 121.0 (2C, 2 × C11), 117.5 (C6), 69.0 (C3), 62.1 (C1), 42.4 (C4), 35.8 (C2), 34.6 (C13), 31.6 (2C, 2 × C9), 26.0 ($SiC(\underline{C}H_3)_3$), 24.4 (2C, 2 × CH_3), 24.3 (2C, 2 × CH_3), 24.1 (2C, 2 × CH_3), 18.2 ($Si\underline{C}(CH_3)_3$), –4.2 ($SiCH_3$), –4.6 ($SiCH_3$) ppm.

Chiral HPLC: Chiral separation was achieved by deprotecting a small aliquot of **189** to give secondary alcohol **195** (Daicel Chiralpak-IA (25 cm) with guard, hexane:isopropanol 99:1, 1.0 mL/min, ambient temperature, 210 nm) t_R = 18.8 min (minor), 19.8 min (major), *er* = 92:8. Performed by Dr Hsuan-Hung Liao.

Racemic sample:

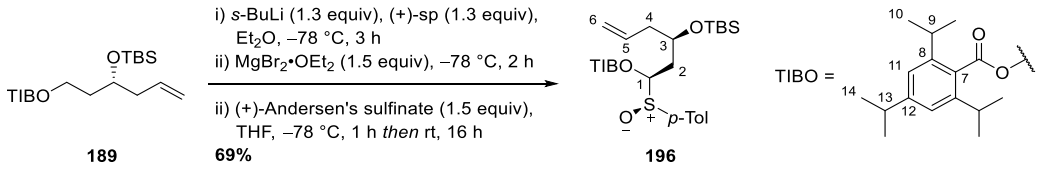


195:



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	18.844	MM	1278	68.4	0.3114	8.245	0.957
2	19.849	MM	14222.7	600	0.395	91.755	0.778

(1*R*,3*R*)-1-((l1-Oxidaneyl)(*p*-tolyl)-l3-sulfaneyl)-3-((*tert*-butyldimethylsilyl)oxy)hex-5-en-1-yl 2,4,6-triisopropylbenzoate (196)



According to a modified literature procedure,[47] *s*-BuLi (1.30 M in hexanes, 6.29 mL, 8.18 mmol, 1.30 equiv) was added dropwise (syringe pump, 0.3 mL/min) to a stirred solution of benzoate **189** (2.90 g, 6.29 mmol, 1.00 equiv) and (+)-sparteine (1.88 mL, 8.18 mmol, 1.30 equiv) in anhydrous Et_2O (21.0 mL, 0.300 M) under N_2 at −78 °C (acetone/dry ice). The resulting reaction mixture was stirred at −78 °C for 3 h. Freshly prepared* $MgBr_2{\cdot}OEt_2$ (9.44 mmol, 1.50 equiv) was added to the reaction *via* cannula and the resulting reaction mixture was stirred for 2 h at −78 °C. A solution of (+)-Andersen's sulfinate (2.78 g, 9.44 mmol, 1.50 equiv) in anhydrous THF (9.40 mL, 1.00 M) was added (syringe pump, 0.5 mL/min) and the resulting reaction mixture was stirred for a further 1 h at −78 °C. The reaction mixture was then warmed to ambient temperature and stirred for 16 h. The reaction was quenched with 2 M aq. HCl (30 mL) and the phases were separated. The organics were washed with 2 M aq. HCl (2 × 20 mL). The combined aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure and the aqueous phase was retained for (+)-sparteine recovery.

Purification was aided by silylation of the menthol by-product: The crude residue was stirred under high vacuum until it became a paste then re-dissolved in anhydrous CH_2Cl_2 (12.6 mL,

0.500 M) and cooled to 0 °C (water/ice). NEt_3 (1.32 mL, 9.44 mmol, 1.50 equiv) and TMSCl (1.04 mL, 8.18 mmol, 1.30 equiv) were added dropwise at 0 °C then the reaction mixture was stirred at ambient temperature for 4 h before being diluted with water (15 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified using a Biotage Isolera One system (split into 2 batches, dry loaded, 100 g Sfär HC column, 95:5 to 90:10 pentane:Et_2O) to give α-sulfinyl benzoate **196** (2.60 g, 4.35 mmol, 69%, >95:5 *dr*) as a white solid.

*Preparation of $MgBr_2 \cdot OEt_2$: To a flame dried 3 neck flask fitted with a reflux condenser under N_2 was charged oven dried magnesium turnings (612 mg, 25.2 mmol, 4.00 equiv) and anhydrous Et_2O (11.8 mL, 0.800 M wrt 1,2-dibromoethane). To this stirred suspension was added 1,2-dibromoethane (0.10 mL) and the resulting suspension was gently heated until the reaction initiated. Following initiation, 1,2-dibromoethane (0.710 mL, 9.44 mmol (total volume 0.810 mL)) was added dropwise at a rate determined by the vigorousness of the reaction. Upon completion of the addition of 1,2-dibromoethane, the reaction was biphasic with a colourless upper layer and a grey bottom layer. After gas evolution had stopped, the mixture was stirred for 30 min at ambient temperature. Both layers were transferred to the main reaction vessel by cannula. The unreacted Mg was cooled to 0 °C (water/ice) and quenched through the slow addition of an appropriate amount of 2 M aq. HCl.

All recorded spectroscopic data matched that previously reported.[142]

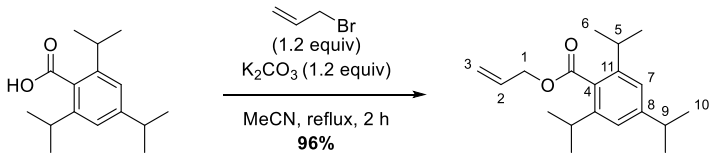
TLC: R_f = 0.29 (90:10 pentane:Et_2O, PMA).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.64 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2 × Tol-*o*CH), 7.35 (d, $^3J_{HH}$ = 7.8 Hz, 2H, 2 × Tol-*m*CH), 7.06 (s, 2H, 2 × ArCH), 5.79 (dd, $^3J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 1.4 Hz, 1H, C1H), 5.63 (ddt, $^3J_{HH}$ = 16.6 Hz, $^3J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 7.1 Hz, 1H, C5H), 5.04 – 4.99 (m, 2H, $C6H_2$), 3.71 (tdd, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 4.3 Hz, $^3J_{HH}$ = 2.6 Hz, 1H, C3H), 3.00 (sept, $^3J_{HH}$ = 6.9 Hz, 2H, 2 × *o*ArCH), 2.91 (sept, $^3J_{HH}$ = 6.9 Hz, 1H, *p*ArCH), 2.41 (s, 3H, Tol-*p*CH_3), 2.22 (m, 1H, C4H^aH^b), 2.15 (m, 1H, C4H^aH^b), 2.00 (ddd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 1.8 Hz, 1H, C2H^aH^b), 1.69 (ddd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 1.4 Hz, 1H, C2H^aH^b), 1.32 – 1.25 (m, 18H, 3 × ArCH(CH_3)$_2$), 0.67 (s, 9H, SiC(CH_3)$_3$), −0.05 (s, 6H, Si(CH_3)$_2$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 170.6 (C=O), 151.0 (C13), 145.5 (2C, 2 × C8), 141.5 (Tol CS), 137.6 (Tol *p*C), 133.5 (C5), 130.1 (2C, 2 × Tol *m*CH), 129.0 (C7), 124.3 (2C, 2 × Tol

*o*CH), 121.2 (2C, 2 × C11), 118.3 (C6), 91.9 (C1), 68.0 (C3), 42.9 (C4), 34.6 (C13), 31.8 (2C, 2 × C9), 30.9 (C2), 25.7 (SiC($\underline{C}H_3)_3$), 24.6 (2C, 2 × CH_3), 24.4 (2C, 2 × CH_3), 24.1 (CH_3), 24.1 (CH_3), 21.5 (Tol-*p*CH_3), 17.8 (Si$\underline{C}(CH_3)_3$), −3.9 ($SiCH_3$), −4.7 ($SiCH_3$) ppm.

Allyl 2,4,6-triisopropylbenzoate (197)



197

According to a literature procedure,[36] K_2CO_3 (19.2 g, 139 mmol, 1.20 equiv) was added to a stirred solution of 2,4,6-triisopropylbenzoic acid (34.5 g, 139 mmol, 1.20 equiv) in acetonitrile (231 mL, 0.500 M). The resulting suspension was stirred vigorously for 10 min before allyl bromide (10.0 mL, 116 mmol, 1.00 equiv) was added. The resulting reaction mixture was heated at 95 ºC (oil bath) for 2 h. The reaction mixture was cooled to ambient temperature and filtered, washing with EtOAc, and the filtrate concentrated under reduced pressure. The residue was redissolved in EtOAc (200 mL) and was successively washed with water (3 × 80 mL), brine (80 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to afford benzoate **197** (31.9 g, 111 mmol, 96%) as a colourless oil.

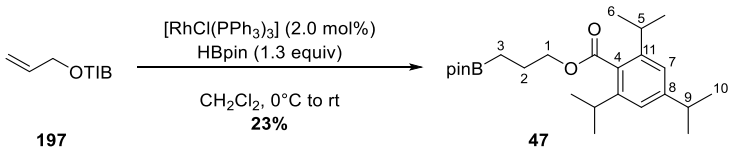
All recorded spectroscopic data matched that previously reported.[36]

TLC: R_f = 0.36 (98:2 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.01 (s, 2H, 2 × C7H), 6.02 (ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 6.0 Hz, 1H, C2H), 5.41 (dq, $^3J_{HH}$ = 17.2, $^4J_{HH}$ = 1.3 Hz, 1H, C3H^aH^b), 5.28 (dq, $^3J_{HH}$ = 10.4 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, C3H^aH^b), 4.81 (dt, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, $C1H_2$), 2.89 (sept, $^3J_{HH}$ = 6.9 Hz, 1H, C9H) 2.86 (sept, $^3J_{HH}$ = 6.9 Hz, 2H, 2 × C5H), 1.24 (d, $^3J_{HH}$ = 6.9 Hz, 18H, 4 × $C6H_3$, 2 × $C10H_3$) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 170.7 (C=O), 150.3 (C8), 145.0 (2C, 2 × C11), 132.1 (C2), 130.4 (C4), 121.0 (2C, 2 × C7), 119.1 (C3), 65.7 (C1), 34.6 (C9), 31.6 (2C, 2 × C5), 24.3 (2C, 2 × C10), 24.1 (4C, 4 × C6) ppm.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)propyl 2,4,6-triisopropylbenzoate (47)



According to a modified literature procedure,[36] allyl 2,4,6-triisopropylbenzoate (**197**) (10.0 g, 34.7 mmol, 1.00 equiv) and Wilkinson's catalyst (642 mg, 0.693 mmol, 2.00 mol%) were added to a flame dried Schlenk tube. The flask was evacuated and backfilled with N_2 three times. Anhydrous CH_2Cl_2 (34.7 mL, 1.00 M) was added and the resulting solution cooled to 0 ºC (water/ice). Pinacol borane (6.54 mL, 45.1 mmol, 1.30 equiv) was added dropwise over 5 min and the resulting solution was stirred at 0 ºC for 15 min before being warmed to ambient temperature and stirred for 2 days. The reaction mixture was then diluted with water (50 mL) and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 95:5 pentane:Et_2O) to yield boronic ester **47** (3.37 g, 8.09 mmol, 23%) as a white amorphous solid.

All recorded spectroscopic data matched that previously reported.[36]

N.B. An old batch of Wilkinson's catalyst was used (given the amount required for this relatively large scale reaction), which was presumed to lead to this lower yield compared to that reported by Dr Bateman (**Scheme 70**).

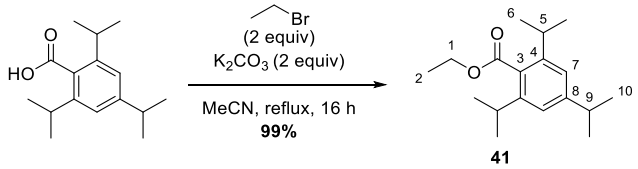
TLC: R_f = 0.22 (90:10 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.99 (s, 2H, 2 × C7H), 4.27 (t, $^3J_{HH}$ = 6.7 Hz, 2H, C1H_2), 2.92 – 2.81 (m, 3H, 2 × C5H, C9H), 1.84 (tt, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 6.7 Hz, 2H, C2H_2), 1.24 (d, $^3J_{HH}$ = 7.0 Hz, 18H, 4 × C6H_3, 2 × C10H_3), 1.23 (s, 12H, 4 × pinacol-CH_3), 0.87 (t, $^3J_{HH}$ = 7.9 Hz, 2H, C3H_2) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 171.2 (C=O), 150.1 (C8), 144.9 (2C, 2 × C11), 130.9 (C4), 120.9 ((2C, 2 × C7), 83.3 (pinacol-C), 66.9 (C1), 34.6 (C9), 31.6 (2C, 2 × C5), 24.9 (2 × pinacol-CH_3), 24.3 (2C, 2 × C10), 24.1 (4C, 4 × C6), 23.3 (C2) ppm.

Carbon next to boron not observed due to quadrupolar relaxation.

Ethyl 2,4,6-triisopropylbenzoate (41)



According to a literature procedure,[36] K_2CO_3 (11.1 g, 80.5 mmol, 2.00 equiv) was added to a stirred solution of 2,4,6-triisopropylbenzoic acid (10.0 g, 40.3 mmol, 1.00 equiv) in acetonitrile (122 mL, 0.333 M). The resulting suspension was stirred vigorously for 10 min before ethyl bromide (6.01 mL, 80.5 mmol, 2.00 equiv) was added. The resulting reaction mixture was heated at 95 ºC (oil bath) overnight. The reaction mixture was cooled to ambient temperature, filtered through a pad of Celite® (EtOAc) and concentrated under reduced pressure to afford benzoate **41** (11.0 g, 39.8 mmol, 99%) as a colourless oil, judged as sufficiently pure by NMR analysis to carry forward.

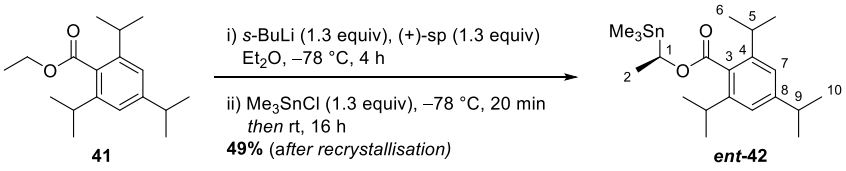
All recorded spectroscopic data matched that previously reported.[209]

TLC: $\mathbf{R}_f$ = 0.53 (95:5 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.00 (s, 2H, 2 × C7H), 4.37 (q, $^3J_{HH}$ = 7.2 Hz, 2H, $C1_2$), 2.88 (m, 3H, 2 × C5H, C9H), 1.37 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $C2H_3$), 1.26 (d, $^3J_{HH}$ = 6.9 Hz, 12H, 4 × $C6H_3$), 1.25 (d, $^3J_{HH}$ = 6.9 Hz, 6H, 2 × $C10H_3$) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.0 (C=O), 150.2 (C8), 144.9 (2C, 2 × C4), 130.8 (C3), 121.0 (2C, 2 × C7), 60.9 (C1), 34.6 (C9), 31.6 (2C, 2 × C5), 24.3 (2C, 2 × C10), 24.1 (4C, 4 × C6), 14.4 (C2) ppm.

(*R*)-1-(Trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (*ent*-42)



According to a literature procedure,[34] *s*-BuLi (1.30 M in hexanes, 20.1 mL, 26.2 mmol, 1.30 equiv) was added dropwise (syringe pump, 0.3 mL/min) to ethyl 2,4,6-triisopropylbenzoate (**41**) (5.56 g, 20.1 mmol, 1.00 equiv) and (+)-sparteine (6.00 mL, 26.0 mmol, 1.30 equiv) in anhydrous Et_2O (100 mL, 0.200 M) at −78 ºC (acetone/dry ice). The resulting mixture was stirred at −78 ºC for 4 h. Me_3SnCl (1.00 M in hexanes, 26.2 mL,

26.1 mmol, 1.30 equiv) was added dropwise and the resulting solution was stirred at −78 ºC for 20 min, and then at ambient temperature for 16 h. The reaction mixture was quenched with 2 M aq. HCl (70 mL) and the phases were separated. The organic phase was washed with 2 M aq. HCl (3 × 60 mL) and the combined aqueous phases were extracted with Et_2O (3 × 70 mL). The aqueous phase was retained for (+)-sparteine recovery. The combined organics were washed with sat. aq. $NaHCO_3$ (40 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to an off-white solid (9.6 g). The crude material was purified by recrystallisation from hot MeOH (3 mL/g) to afford α-stannyl benzoate ***ent*-42** (4.34 g, 9.88 mmol, 49%, 99.9:0.1 *er*) as white needles (2 crops).

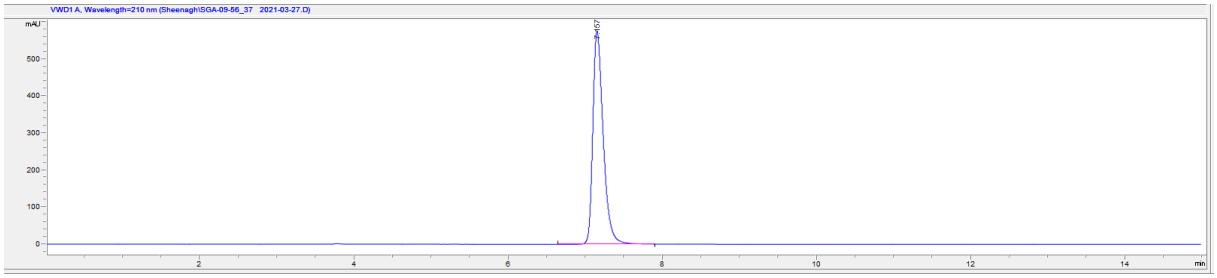
All recorded spectroscopic data matched that previously reported.[34]

^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.99 (s, 2H, 2 × C7H), 5.04 (q, $^3J_{HH}$ = 7.7 Hz, 1H, C1H), 2.80 – 2.95 (m, 3H, 2 × C5H, C9H), 1.68 – 1.50 (m, 3H, $C2H_3$), 1.24 (d, $^3J_{HH}$ = 6.9 Hz, 18H, 4 × $C6H_3$, 2 × $C10H_3$), 0.18 (s and d, $^2J_{SnH}$ = 54.2 Hz and d, $^2J_{SnH}$ = 53.0 Hz, 9H, $Sn(Me)_3$) ppm.

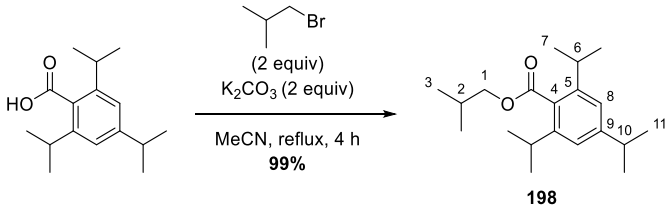
^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.4 (C=O), 150.1 (C8), 145.0 (2C, 2 × C4), 130.9 (C3), 120.9 (2C, 2 × C7), 67.2 (C1), 34.6 (C9), 31.5 (2C, 2 × C5), 24.5 (2C, 2 × C10), 24.2 (2C, 2 × C6), 24.1 (2C, 2 × C6), 19.4 (C2), −9.8 ($Sn(CH_3)_3$) ppm.

Chiral HPLC: (Daicel Chiralpak-IB column (25 cm) with guard, 100% hexane, 0.9 mL/min, ambient temperature, 210 nm) t_R = 5.3 min (minor), 7.1 min (major), *er* >99.9:0.1.

Chiral HPLC conditions previously reported and used in-house,[34] the enantiomer was also synthesised by the author and was available for comparison.



Isobutyl 2,4,6-triisopropylbenzoate (198)



198

According to a modified literature procedure,[36] K_2CO_3 (11.2 g, 80.0 mmol, 2.00 equiv) was added to a stirred solution of 2,4,6-triisopropylbenzoic acid (10.2 g, 40.0 mmol, 1.00 equiv) in acetonitrile (120 mL, 0.333 M). The resulting suspension was stirred vigorously for 10 min before isobutyl bromide (8.80 mL, 80.0 mmol, 2.00 equiv) was added. The resulting reaction mixture was heated at 95 ºC (oil bath) for 4 h. The reaction mixture was cooled to ambient temperature, filtered through a pad of Celite® (EtOAc) and the filtrate concentrated under reduced pressure. The crude residue was purified on a Biotage Isolera One system (100 g Sfär column, 95:5 pentane:Et_2O) to afford benzoate **198** (12.0 g, 39.4 mmol, 99%) as a colourless oil.

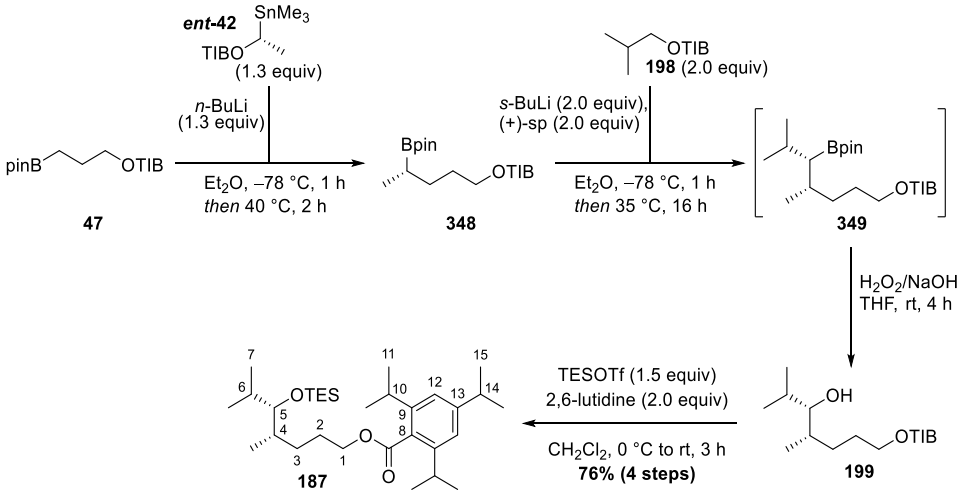
All recorded spectroscopic data matched that previously reported.[22]

TLC: R_f = 0.65 (90:10 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.01 (s, 2H, 2 × C8H), 4.09 (d, $^3J_{HH}$ = 6.5 Hz, 2H, C1H_2), 2.95 – 2.80 (m, 3H, 2 × C6H, C10H), 2.03 (app. non, $^3J_{HH}$ = 6.6 Hz, 1H, C2H), 1.25 (d, $^3J_{HH}$ = 6.9 Hz, 18H, 4 × C7H_3, 2 × C11H_3), 0.99 (d, $^3J_{HH}$ = 6.6 Hz, 6H, 2 × C3H_3) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.3 (C=O), 150.1 (C9), 144.9 (2C, 2 × C5), 130.9 (C4), 121.0 (2C, 2 × C8), 71.5 (C1), 34.6 (C10), 31.7 (2C, 2 × C6), 27.8 (C2), 24.3 (2C, 2 × C11), 24.1 (4C, 4 × C7), 19.4 (2C, 2 × C3) ppm.

(4*S*,5*S*)-4,6-Dimethyl-5-((triethylsilyl)oxy)heptyl-2,4,6-triisopropylbenzoate (187)



s-BuLi (1.30 M in hexanes, 12.7 mL, 16.5 mmol, 2.00 equiv) was added dropwise (syringe pump, 0.3 mL/min) to isobutyl 2,4,6-triisopropylbenzoate (**198**) (5.01 g, 16.5 mmol, 2.00 equiv) and (+)-sparteine (3.78 mL, 16.5 mmol, 2.00 equiv) in anhydrous Et_2O (55.0 mL, 0.300 M) at −78 °C (acetone/dry ice). The resulting mixture was stirred at −78 °C for 18 h.

Meanwhile, *n*-BuLi (1.60 M in hexane, 4.28 mL, 10.7 mmol, 1.30 equiv) was added dropwise (syringe pump, 0.3 mL/min) to (*R*)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (***ent*-42**) (4.70 g, 10.7 mmol, 1.30 equiv) in anhydrous Et_2O (41.0 mL, 0.260 M) at −78 °C (acetone/dry ice). The reaction mixture was stirred at −78 °C for 1 h. A solution of boronic ester **47** (3.43 g, 8.23 mmol, 1.00 equiv) in anhydrous Et_2O (16.5 mL, 0.500 M) was added dropwise (syringe pump, 0.3 mL/min) and the reaction mixture stirred at −78 °C for 1 h. The reaction mixture was warmed to ambient temperature and then heated at 40 °C (oil bath) for 2 h. The reaction mixture was cooled to ambient temperature, filtered through a small pad of SiO_2 (Et_2O) and concentrated under reduced pressure. The crude homologated boronic eater was purified on a Biotage Isolera One system (loaded in pentane, 100 g Sfär column, 95:5 to 90:10 pentane:Et_2O) to give boronic ester **348** (3.63 g) as a colourless oil.

TLC: R_f = 0.28 (90:10 pentane:Et_2O, anisaldehyde).

Secondary boronic ester **348** (8.23 mmol, 1.00 equiv) was dissolved in anhydrous Et_2O (8.20 mL, 1.00 M) and added dropwise (syringe pump, 0.3 mL/min) to the solution of lithiated isobutyl benzoate at −78 °C and the resulting solution was stirred at −78 °C for 1 h. The reaction mixture was warmed to ambient temperature and then heated at 35 °C (oil bath) for 16 h. The reaction mixture was cooled to ambient temperature, quenched with a 2 M aq. HCl (70 mL) and the phases separated. The organic phase was washed with 2 M HCl (2 × 30 mL)

and the combined aqueous phases were extracted with Et_2O (3 × 60 mL) and then retained for (+)-sparteine recovery. The combined organics were washed with sat. aq. $NaHCO_3$ (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield boronic ester **349** (8.50 g) as a viscous yellow cloudy oil, which was used immediately with no further purification.

TLC: R_f = 0.34 (90:10 pentane:Et_2O, anisaldehyde).

Oxidation

To a stirred solution of boronic ester **349** (8.23 mmol, 1.00 equiv) in THF (41.0 mL, 0.200 M) at 0 °C (water/ice) was added a degassed ice cold mixture of 3 M aq. NaOH and 30% aq. H_2O_2 (2:1 v/v, 5.00 mL per mmol boronic ester, 41.0 mL) *via* cannula. The reaction mixture was warmed to ambient temperature and stirred vigorously (biphasic) for 4 h. The reaction mixture was then diluted with water (20 mL) and Et_2O (20 mL) and the phases separated. The aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic phases were washed with sat. aq. $Na_2S_2O_3$ (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified on a Biotage Isolera One system (100 g Sfär column, loaded in minimal pentane/toluene, 80:20 pentane:Et_2O) to yield alcohol **199** (3.51 g) as a colourless oil.

TLC: R_f = 0.14 (80:20 pentane:Et_2O, anisaldehyde).

Silyl protection

Triethylsilyltrifluoromethanesulfonate (2.80 mL, 12.4 mmol, 1.50 equiv) and 2,6-lutidine (1.92 mL, 16.5 mmol, 2.00 equiv) were added to a stirred solution of alcohol **199** (8.23 mmol, 1.00 equiv) in anhydrous CH_2Cl_2 (27.0 mL, 0.300 M) at 0 °C (water/ice). The resulting solution was stirred at ambient temperature for 3 h, at which point TLC analysis suggested full consumption of the starting material. The reaction was diluted with water (30 mL) and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified on a Biotage Isolera One system (100 g Sfär column, loaded in pentane, 100:0 to 90:10 pentane:Et_2O) to yield benzoate **187** (3.16 g, 6.26 mmol, 76% over 4 steps, >95:5 *dr*) as a colourless oil.

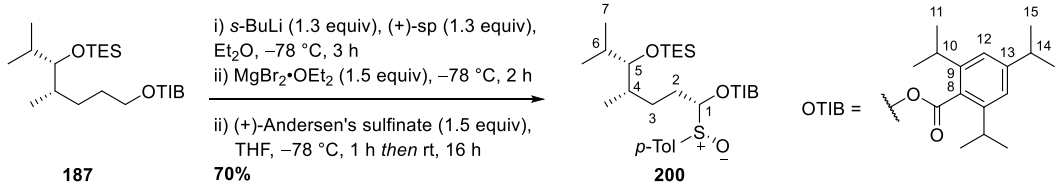
All recorded spectroscopic data matched that previously reported.[142]

TLC: R_f = 0.53 (95:5 pentane:Et_2O, PMA).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.00 (s, 2H, 2 × C12H), 4.34 – 4.24 (m, 2H, $C1H_2$), 3.24 (dd, $^{3}J_{HH}$ = 6.1 Hz, $^{3}J_{HH}$ = 3.6 Hz, 1H, C5H), 2.93 – 2.81 (m, 3H, 2 × C10H, C14H), 1.86 – 1.65 (m, 3H, $C2H_2$ and C4H), 1.59 (m, 1H, C6H), 1.46 (m, 1H, C3H^{a}H^{b}), 1.32 – 1.24 (m, 19H, 4 × $C11H_3$, 2 × $C15H_3$, C3H^{a}H^{b}), 0.95 (t, $^{3}J_{HH}$ = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.91 – 0.86 (m, 9H, $C7H_3$, C7'H_3, C4Me), 0.60 (q, $^{3}J_{HH}$ = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 171.2 (C=O), 150.2 (C13), 144.8 (2C, 2 × C9), 130.8 (C8), 121.0 (2C, 2 × C12), 81.6 (C5), 65.5 (C1), 36.2 (C4), 34.6 (C14), 31.8 (2C, 2 × C10), 31.6 (C6), 31.1 (C3), 27.0 (C2), 24.3 (2C, 2 × C15), 24.1 (4C, 4 × C11), 20.2 (C7), 19.0 (C7'), 14.3 (C4Me), 7.3 ($Si(CH_2CH_3)_3$), 5.8 ($Si(CH_2CH_3)_3$) ppm.

(1*R*,4*S*,5*S*)-1-((λ^{1}-Oxidaneyl)(*p*-tolyl)-l3-sulfaneyl)-4,6-dimethyl-5-((triethylsilyl)oxy)heptyl 2,4,6-triisopropylbenzoate (200)



According to a modified literature procedure,[47] *s*-BuLi (1.30 M in hexanes, 6.14 mL, 7.98 mmol, 1.30 equiv) was added dropwise to a stirred solution of benzoate **187** (3.10 g, 6.14 mmol, 1.00 equiv) and (+)-sparteine (1.83 mL, 7.98 mmol, 1.30 equiv) in anhydrous Et_2O (20.5 mL, 0.300 M) under N_2 at −78 °C (acetone/dry ice) and the reaction mixture was stirred at −78 °C for 3 h. Freshly prepared* $MgBr_2{\cdot}OEt_2$ (9.21 mmol, 1.50 equiv) was added to the reaction dropwise *via* cannula and the resulting reaction mixture was stirred for 2 h at −78 °C. A solution of (+)Andersen's sulfinate (2.71 g, 9.21 mmol, 1.50 equiv) in anhydrous THF (9.20 mL, 1.00 M) was added and the resulting reaction mixture was stirred for a further 1 h at −78 °C. The reaction mixture was then warmed to ambient temperature and stirred for 16 h. The reaction was diluted with 2 M aq. HCl (25 mL) and Et_2O (25 mL) and the phases separated. The organic phase was washed with 2 M aq. HCl (2 × 25 mL). The combined aqueous phase was extracted with Et_2O (3 × 50 mL), the aqueous phase was retained for (+)-sparteine recovery. The combined organic phases were washed with sat. aq. $NaHCO_3$ (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

Purification was aided by silylation of the menthol by-product: The crude residue was stirred under high vacuum until it became a paste then re-dissolved in anhydrous CH_2Cl_2 (12.3 mL,

0.500 M) and cooled to 0 °C (water/ice). NEt_3 (1.28 mL, 9.21 mmol, 1.50 equiv) and TMSCl (1.01 mL, 7.98 mmol, 1.30 equiv) were added dropwise at 0 °C then the reaction mixture was stirred at ambient temperature for 16 h before being diluted with water (10 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

The crude residue was purified using a Biotage Isolera One system (dry loaded, 100 g Sfär HC column, 95:5 to 90:10 pentane:Et_2O) to give α-sulfinyl benzoate **200** (2.76 g, 4.29 mmol, 70%, >95:5 *dr*) as a colourless oil.

*Preparation of $MgBr_2 \cdot OEt_2$: To a flame dried 3 neck flask fitted with a reflux condenser under N_2 was charged oven dried Magnesium turnings (597 mg, 24.6 mmol, 4.00 equiv) and anhydrous Et_2O (11.5 mL, 0.800 M wrt 1,2-dibromoethane). To this stirred suspension was added 1,2-dibromoethane (0.10 mL) and the resulting suspension was gently heated until the reaction initiated. Following initiation, 1,2-dibromoethane (0.690 mL (total volume 0.790 mL, 9.21 mmol)) was added dropwise at a rate determined by the vigorousness of the reaction. Upon completion of the addition of 1,2-dibromoethane, the reaction was biphasic with a colourless upper layer and a grey bottom layer. Both layers were transferred by cannula. The unreacted Magnesium turnings were cooled to 0 °C (water/ice) and quenched through the slow addition of 2 M $HCl_{(aq)}$.

All recorded spectroscopic data matched that previously reported.[142]

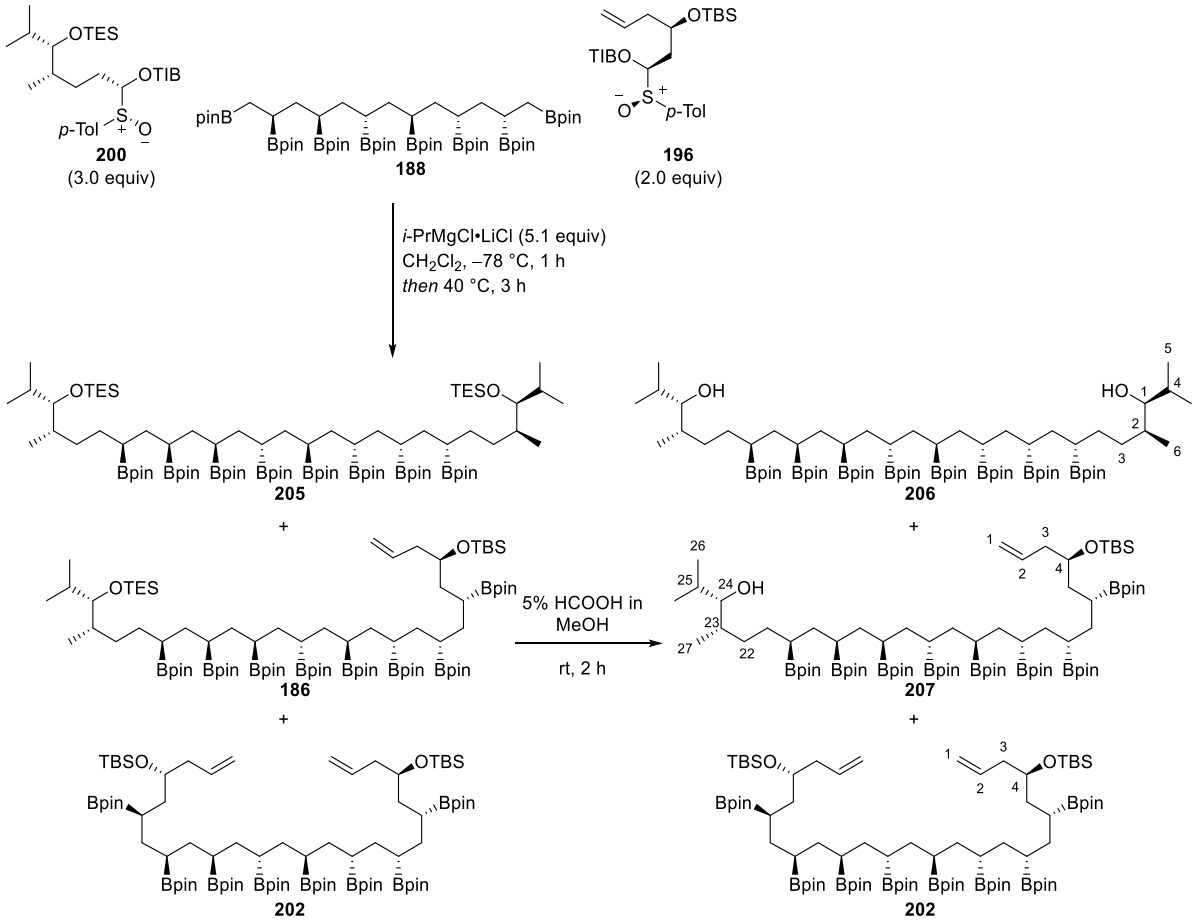
TLC: R_f = 0.40 (80:20 pentane:Et_2O, PMA).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.65 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2 × Tol-*o*CH), 7.37 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2 × Tol-*m*CH), 7.05 (s, 2H, 2 × C12H), 5.63 (dd, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 2.6 Hz, 1H, C1H), 3.11 (dd, $^3J_{HH}$ = 5.9, 3.5 Hz, 1H, C5H), 2.99 – 2.88 (m, 3H, 2 × C10H, C14H), 2.43 (s, 3H, Tol-CH_3), 1.95 (dtd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 4.9 Hz, 1H, C2H^aH^b), 1.66 – 1.57 (m, 2H, C6H and C2H^aH^b), 1.44 (m, 1H, C4H), 1.31 – 1.24 (m, 8H, 2 × C15H_3, C3H_2), 1.27 (d, $^3J_{HH}$ = 6.9 Hz, 12H, 4 × C11H_3), 0.86 (t, $^3J_{HH}$ = 7.9 Hz, 9H, Si(CH_2CH_3)$_3$), 0.80 (dd, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 4.3 Hz, 6H, C7H_3, C7'H_3), 0.68 (d, $^3J_{HH}$ = 6.8 Hz, 3H, C4CH_3), 0.49 (q, $^3J_{HH}$ = 7.9 Hz, 6H, Si(CH_2CH_3)$_3$) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 170.7 (C=O), 151.0 (C13), 145.3 (2C, 2 × C10), 141.6 (Tol CS), 137.6 (Tol *p*C), 130.2 (2C, 2 × Tol *m*CH), 129.0 (C8), 124.4 (2C, 2 × Tol *o*CH), 121.2 (2C, 2 × C12), 93.3 (C1), 80.6 (C5), 36.5 (C4), 34.6 (C14), 31.8 (2C, 2 × C10), 31.5 (C6),

29.1 (C3), 24.6 (2C, 2 × CH_3), 24.3 (2C, 2 × CH_3), 24.1 (2C, 2 × CH_3), 21.6 (Tol-*p*CH_3), 21.2 (C2), 20.3 (C7), 19.0 (C7'), 14.4 (C4Me), 7.2 ($Si(CH_2\underline{C}H_3)_3$), 5.6 ($Si(\underline{C}H_2CH_3)_3$) ppm.

(3*S*,4*S*,7*S*,9*S*,11*S*,13*R*,15*S*,17*R*,19*R*,21*R*,23*S*)-23-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethyl-7,9,11,13,15,17,19,21-octakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexacos-25-en-3-ol (207)



Homologation

Octa(boronic ester) **188** (238 mg, 0.200 mmol, 1.00 equiv), α-sulfinyl benzoate **196** (240 mg, 0.400 mmol, 2.00 equiv) and α-sulfinyl benzoate **200** (386 mg, 0.600 mmol, 3.00 equiv) were charged to a flame dried Schlenk tube under N_2, which was put under high vacuum and stirred for 15 min. The Schlenk tube was backfilled with N_2 and anhydrous CH_2Cl_2 (2.00 mL, 0.100 M) was added. The resulting mixture was cooled to −78 °C (acetone/dry ice) and *i*-PrMgCl·LiCl (1.13 M in THF, 0.900 mL, 1.02 mmol, 5.10 equiv) was added dropwise. The resulting reaction mixture was stirred at −78 °C for 1 h, removed from the cooling bath and allowed to warm to ambient temperature, and then was stirred at 40 °C (oil bath) for 3 h. The

reaction was cooled to ambient temperature and concentrated under reduced pressure. The crude residue was dissolved in a small amount of Et_2O, filtered through a plug of Et_3N-deactivated silica and concentrated under reduced pressure. The crude residue was purified using a Biotage Isolera One system (loaded in hexane, 100 g Sfär HC column, 97:3 hexane:acetone) to give an inseparable mixture of the three double homologation products **205**, **186** and **202** (206 mg) as a colourless oil (white foam under high vacuum), along with an inseparable mixture of the mono homologation products **201** and **204** (59 mg) and recovered octa(boronic ester) **188** (5 mg).

N.B. The mixture of **205**, **186** and **202** could not be separated by manual column chromatography or on a Biotage Isolera One system; there was also no separation on neutral alumina or reverse phase TLC plates. Screening >20 solvent systems for TLC analysis showed no difference in R_f for pure samples of **186**, **205** and **202**. However, when using silver nitrate impregnated silica[210–213] these spots could be separated for TLC analysis (**Figure 11**). These conditions could not be translated to chromatographic purification of the product mixture despite several attempts varying silica loading, solvent gradients and the method of impregnating the silica with silver nitrate. Direct oxidation of the mixture of **186**, **205** and **202** was attempted; although LC-MS analysis confirmed the presence of the 3 corresponding polyols, these could not be separated either.

Selective TES deprotection

A portion of the mixture of double homologation products (128 mg) was dissolved in anhydrous MeOH (1.00 mL) and cooled to 4 °C (water/ice). 10% formic acid in MeOH (1.00 mL) was added dropwise, the cooling bath was removed and the reaction mixture stirred at ambient temperature for 2 h. The reaction was neutralised with Et_3N and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (loaded and packed in hexane, SiO_2, 95:5 to 80:20 hexane:acetone) to give doubly protected **202** (20.4 mg), mono protected **207** (52.8 mg) and diol **206** (46.8 mg).

(5*S*,7*R*,9*R*,11*R*,13*S*,15*S*,17*R*,19*R*,21*R*,23*S*)-5,23-diallyl-2,2,3,3,25,25,26,26-octamethyl-7,9,11,13,15,17,19,21-octakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4,24-dioxa-3,25-disilaheptacosane (202)

All recorded spectroscopic data matched that previously reported.[142]

TLC: R_f = 0.48 (80:20 hexane:acetone, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.86 – 5.76 (m, 2H, 2 × C2H), 5.03 – 4.95 (m, 4H, 2 × C1H_2), 3.75 – 3.63 (m, 2H, 2 × C4H), 2.30 – 2.12 (m, 4H, 2 × C3H_2), 1.56 – 0.95 (m, 122H), 0.86 (s, 18H, 2 × SiC(CH_3)$_2$), 0.06 (s, 6H, 2 × SiCH_3), 0.03 (s, 6H, 2 × SiCH_3) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 136.1 (C2), 116.2 (C1), 82.6 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 82.4 (pinacol-C), 72.6 (C4), 42.9 (CH_2), 38.5 (CH_2), 35.0 (CH_2), 33.8 (CH_2), 32.5 (CH_2), 26.2 (pinacol-CH_3), 26.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 18.3 (C), −4.0 (SiCH_3), −4.3 (SiCH_3) ppm.

Carbon next to boron not observed due to quadrupolar relaxation.

(3*S*,4*S*,7*S*,9*S*,11*S*,13*R*,15*S*,17*R*,19*R*,21*R*,23*S*)-23-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethyl-7,9,11,13,15,17,19,21-octakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexacos-25-en-3-ol (207)

TLC: R_f = 0.28 (80:20 hexane:acetone, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.81 (ddt, $^{3}J_{HH}$ = 17.2 Hz, $^{3}J_{HH}$ = 10.2 Hz, $^{3}J_{HH}$ = 7.0 Hz, 1H, C2H), 5.02 – 4.92 (m, 2H, C1H_2), 3.68 (m, 1H, C4H), 3.14 (m, 1H, C24H), 2.23 – 2.10 (m, 2H, C3H_2), 1.79 – 1.67 (m, 2H), 1.54 – 0.99 (m, 124H), 0.91 – 0.80 (m, 18H, C26H_3, C26'H_3, C27H_3, SiC(CH_3)$_3$), 0.06 (s, 3H, SiCH_3), 0.03 (s, 3H, SiCH_3) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 136.1 (C2), 116.3 (C1), 82.8 (pinacol-C), 82.6 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 79.4 (C24), 72.6 (C4), 42.9 (CH_2), 41.5 (CH_2), 38.5 (CH_2), 36.2 (CH), 33.9 (CH_2), 33.4 (CH_2), 30.6 (C23), 29.9 (CH_2), 29.2 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 26.2 (TBS C($\underline{C}H_3$)$_3$), 25.3 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.8 (pinacol-CH_3), 24.7 (pinacol-CH_3), 20.6 (C26), 19.6 (CH_2), 18.9 (C26'), 18.3 (TBS $\underline{C}$(CH_3)$_3$), 14.5 (C27), 7.4 (Si($CH_2\underline{C}H_3$)$_3$), 5.8 (Si($\underline{C}H_2CH_3$)$_3$), −4.0 (SiCH_3), −4.3 (SiCH_3) ppm.

HRMS (*m/z*): (MALDI) calculated for $C_{82}H_{158}O_{18}{}^{11}B_8Si$ $[M+Na]^+$ 1569.1935, found 1569.1927.

IR (ν_{max}/cm^{-1}, neat): 2923, 2853, 1459, 1379, 1309 and 1144.

$[\alpha]_D^{24}$: +20 (*c* = 0.1, $CHCl_3$).

(3*S*,4*S*,7*S*,9*S*,11*S*,13*R*,15*R*,17*S*,19*S*,21*S*,24*S*,25*S*)-2,4,24,26-tetramethyl-7,9,11,13,15,17,19,21-octakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptacosane-3,25-diol (206)

TLC: R_f = 0.15 (80:20 hexane:acetone, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 3.13 (dd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 3.9 Hz, 2H, 2 × C1H), 1.80 – 1.64 (m, 2H, 2 × C4H), 1.58 – 1.01 (m, 128H), 0.96 (d, 6H, 2 × C4Me), 0.83 (d, $^3J_{HH}$ = 6.8 Hz, 6H, 2 × C3H_3), 0.83 (d, $^3J_{HH}$ = 6.8 Hz, 6H, 2 × C3'H_3) ppm.

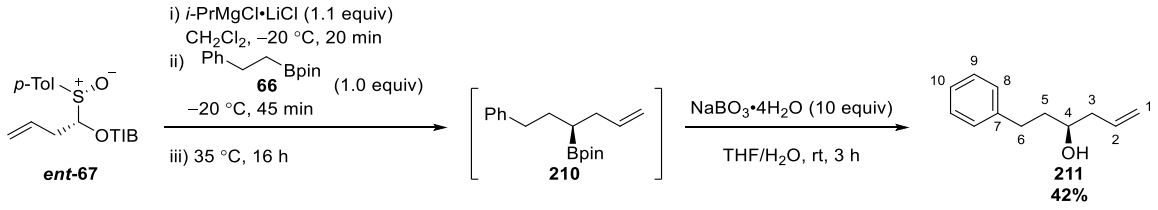
^{13}C NMR: (126 MHz, $CDCl_3$) δ 82.8 (pinacol-C), 82.6 (pinacol-C), 82.6 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 79.4 (C1), 35.3 (CH_2), 35.0 (C2), 34.2 (CH_2), 33.4 (CH_2), 31.1 (CH_2), 30.6 (C4), 26.6 (CH_2), 25.2 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.9 (pinacol-CH_3), 24.8 (pinacol-CH_3), 19.5 (C5), 19.1 (C6), 13.4 (C5') ppm.

HRMS (*m/z*): (MALDI) calculated for $C_{79}H_{152}O_{18}{}^{11}B_8$ $[M+Na]^+$ 1499.1694, found 1499.1688.

IR (ν_{max}/cm^{-1}, neat): 3499, 2977, 2924, 1460, 1378, 1371, 1307 and 1141.

$[\alpha]_D^{23}$: −8, (*c* = 1, $CHCl_3$).

(*S*)-1-phenylhex-5-en-3-ol (211)



Homologation

A three-necked round-bottomed flask equipped with a stirring bar was connected to the React-IR probe and flushed with N_2. A solution of α-sulfinyl benzoate ***ent*-67** (220 mg, 0.500 mmol, 1.00 equiv) in anhydrous CH_2Cl_2 (1.00 mL, 0.500 M) was added and the React-IR acquisition was started. The peak at 1736 cm^{-1} was selected to follow α-sulfinyl benzoate ***ent*-67**. The solution was cooled to −20 °C (tetrachloroethylene/dry ice) and *i*-PrMgCl·LiCl (1.14 M in THF, 0.480 mL, 0.550 mmol, 1.10 equiv) was added dropwise. The peak at 1736 cm^{-1} decreased as a new peak at 1636 cm^{-1} appeared, which was selected to

follow the magnesiated intermediate. After 10 min at −20 °C (when sulfoxide-metal exchange was complete by *in situ* IR monitoring), boronic ester **66** (116 mg, 0.500 mmol, 1.00 equiv, available in-house[26]) in CH_2Cl_2 (0.500 mL, 1.00 M) was added and the temperature maintained at −20 °C. The peak at 1673 cm^{-1} was selected to follow the boronate complex. After 45 min at −20 °C, when the boronate peak had appeared to plateau, the React-IR probe was removed and the reaction mixture was heated at 35 °C overnight.

The reaction mixture was cooled to ambient temperature. Sat. aq. NH_4Cl (2 mL) and CH_2Cl_2 (2 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organics were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

Oxidation

$NaBO_3{\cdot}4H_2O$ (769 mg, 5.00 mmol, 10.0 equiv) was added to crude boronic ester **210** in THF/H_2O (3:2 v/v, 5.00 mL, 0.100 M) and the reaction mixture was stirred for 3 h at ambient temperature, at which point TLC analysis showed consumption of starting material **210**. The reaction mixture was diluted with Et_2O (5 mL) and H_2O (5 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organics were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography using a Biotage Isolera One system (loaded in minimal pentane/toluene, 5 g Sfär column, Et_2O:pentane 10:90 to 40:60) to give alcohol **211** (37 mg, 0.210 mmol, 42%, 99.9:0.1 *er*) as a colourless oil.

All recorded spectroscopic data matched that previously reported.[26]

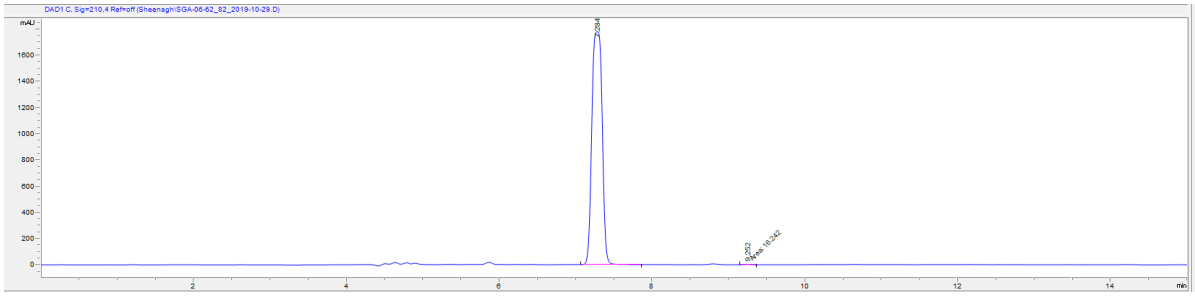
TLC: R_f = 0.21 (80:20 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H, 2 × C9H), 7.24 – 7.15 (m, 3H, 2 × C8H, C10H), 5.82 (m, 1H, C2H), 5.19 – 5.11 (m, 2H, $C1H_2$), 3.69 (ddd, $^3J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 7.7, Hz, $^3J_{HH}$ = 4.6 Hz, 1H, C4H), 2.82 (ddd, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 8.8 Hz, $^3J_{HH}$ = 6.7 Hz, 1H, C6H^aH^b), 2.69 (m, 1H, C6H^aH^b), 2.33 (m, 1H, C3H^aH^b), 2.19 (dt, $^2J_{HH}$ = 14.6 Hz, $^3J_{HH}$ = 7.9 Hz, 1H, C3H^aH^b), 1.86 – 1.75 (m, 2H, $C5H_2$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 142.2 (C7), 134.7 (C2), 128.6 (2C, 2 × C9), 128.5 (2C, 2 × C8), 126.0 (C10), 118.5 (C1), 70.1 (C4), 42.2 (C3), 38.6 (C5), 32.2 (C6) ppm.

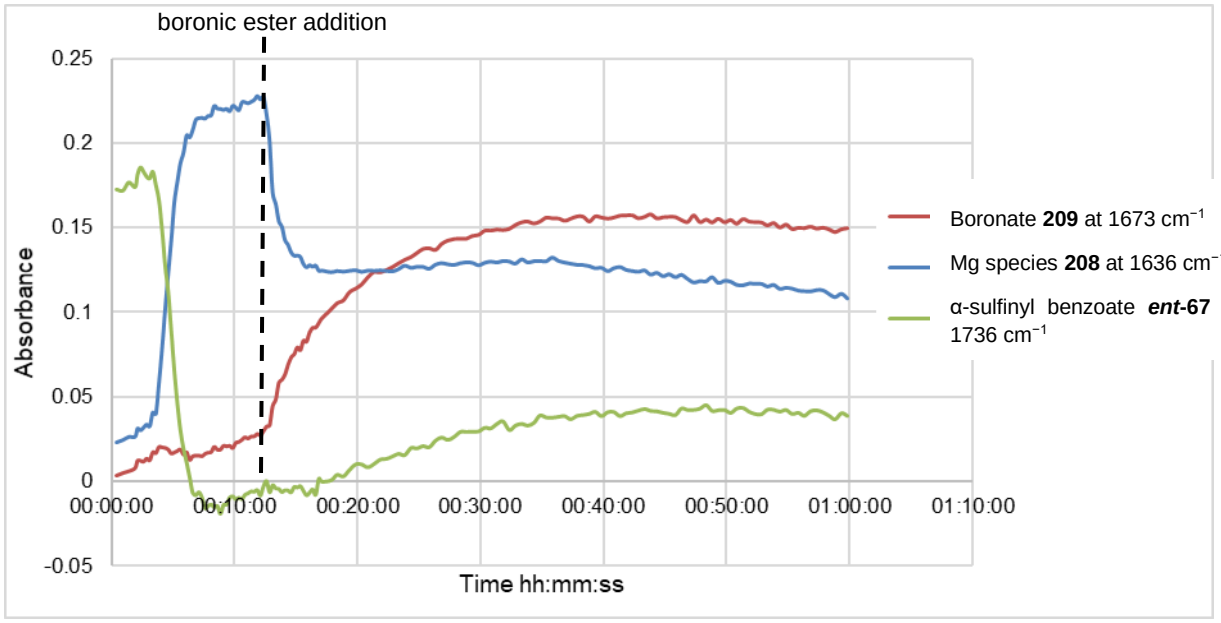
Chiral HPLC: (Daicel Chiralpak-IB column (25 cm) with guard, hexane:isopropanol 90:10, 0.7 mL/min, ambient temperature, 210 nm) t_R = 7.28 min (major), 9.25 min (minor), *er*

99.9:0.1. *Chiral HPLC conditions previously reported and used in-house.*[26] *A sample of the enantiomer was also available from Michaelina Poyiatji for comparison.*

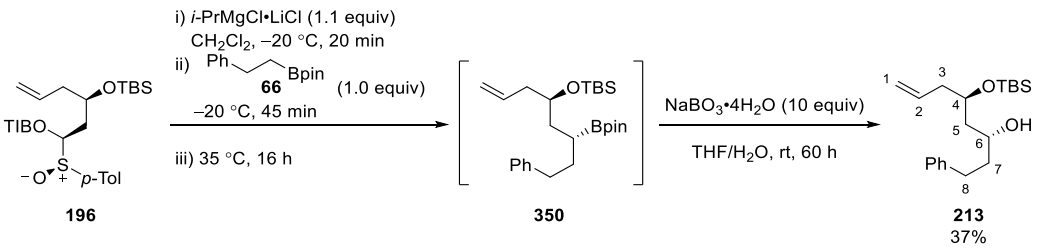


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.284	BV R	16659.4	1784.7	0.1528	99.903	1.035
2	9.252	MM	16.2	2.3	0.1159	0.097	1.057

React-IR trace:



(3*R*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)-1-phenyloct-7-en-3-ol (213)



Homologation

A three-necked round-bottomed flask equipped with a stirring bar was connected to the React-IR probe and flushed with N_2. A solution of α-sulfinyl benzoate **196** (150 mg, 0.250 mmol, 1.00 equiv) in anhydrous CH_2Cl_2 (0.500 mL, 0.500 M) was added and the React-IR acquisition was started. The peak at 1734 cm^{-1} was selected to follow α-sulfinyl benzoate **196**. The solution was cooled to −20 °C (tetrachloroethylene/dry ice) and *i*-PrMgCl·LiCl (1.14 M in THF, 0.240 mL, 0.275 mmol, 1.10 equiv) was added dropwise. The peak at 1734 cm^{-1} decreased as a new peak at 1630 cm^{-1} appeared, which was selected to follow the magnesiated intermediate. After 10 min at −20 °C (when sulfoxide-metal exchange was complete by *in situ* IR monitoring), boronic ester **66** (58.0 mg, 0.250 mmol, 1.00 equiv, available in-house[26]) in CH_2Cl_2 (0.500 mL, 1.00 M) was added and the temperature maintained at −20 °C. The peak at 1670 cm^{-1} was selected to follow the boronate complex. After 45 min at −20 °C, when the boronate peak had appeared to plateau, the reaction mixture was heated at 35 °C overnight and the React-IR probe removed.

The reaction mixture was cooled to ambient temperature. Sat. aq. NH_4Cl (2 mL) and CH_2Cl_2 (2 mL) were added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organics were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

Oxidation

$NaBO_3·4H_2O$ (115 mg, 0.750 mmol, 10.0 equiv) was added to crude boronic ester **350** in THF/H_2O (3:2 v/v, 2.50 mL, 0.100 M) and the reaction mixture was stirred at ambient temperature over the weekend (60 h). The reaction mixture was diluted with Et_2O (5 mL) and H_2O (5 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organics were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was filtered through Et_3N-deactivated silica and

purified by flash column chromatography (SiO_2, loaded in minimal pentane/toluene, 90:10 pentane:Et_2O) to give alcohol **213** (31 mg, 92.7 µmol, 37%) as a colourless oil.

TLC: R_f = 0.25 (80:20 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.29 – 7.14 (m, 5H, 5 × PhH), 5.73 (m, 1H, C2H), 5.09 – 5.00 (m, 2H, C1H_2), 4.05 (m, 1H, C4H), 3.98 (m, 1H, C6H), 2.79 (ddd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 5.5 Hz, 1H, C8H^aH^b), 2.66 (ddd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 6.4 Hz, 1H, C8H^aH^b), 2.39 – 2.25 (m, 2H, C3H_2), 1.80 (dddd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ 10.0 Hz, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 5.5 Hz, 1H, C7H^aH^b), 1.71 – 1.58 (m, 3H, C5H_2, C7H^aH^b), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.09 (s, 6H, 2 × SiCH_3) ppm.

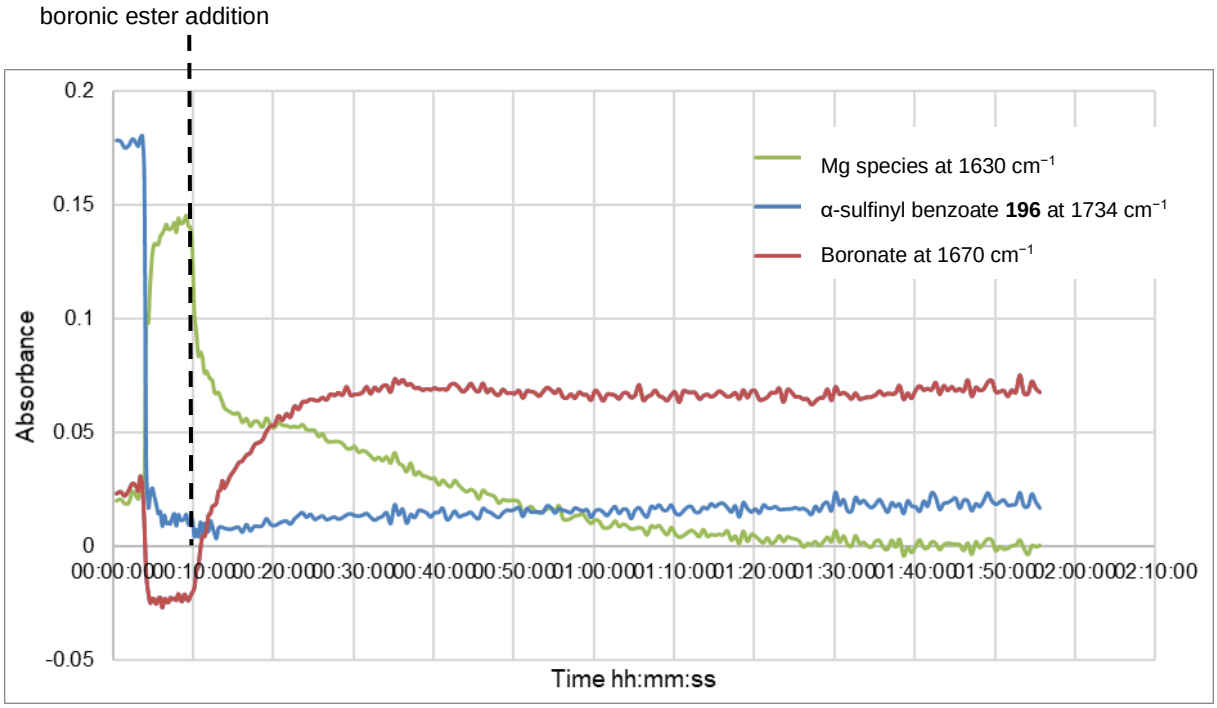
^{13}C NMR: (126 MHz, $CDCl_3$) δ 142.4 (Ph quat C), 134.8 (C2), 128.6 (2C, 2 × *m*Ph C), 128.5 (2C, 2 × *o*Ph C), 125.9 (*p*Ph C), 117.6 (C1), 71.4 (C4), 67.8 (C6), 41.5 (C5), 41.2 (C3), 39.8 (C7), 32.1 (C8), 26.0 (TBS C($\underline{C}H_3$)$_3$), 18.1 (TBS $\underline{C}$(CH_3)$_3$), −4.4 (TBS Me), −4.7 (TBS Me) ppm.

HRMS (*m/z*): (ESI) calculated for $C_{20}H_{34}O_2Si$ $[M+H]^+$ 335.2401, found 335.2397.

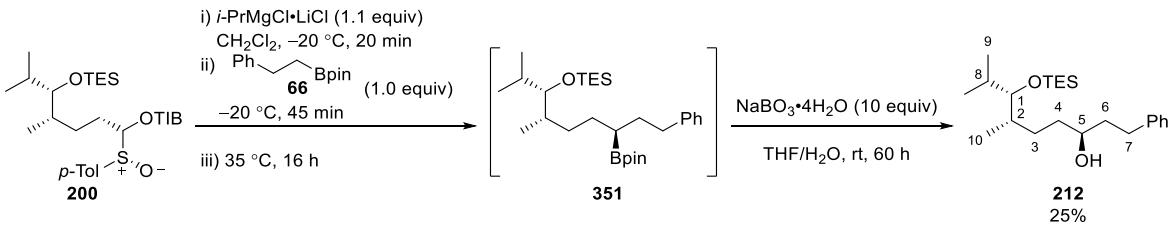
IR (ν_{max}/cm^{-1}, neat): 3450, 2928, 2856, 1472, 1254 and 1067.

$[\alpha]_D^{23}$: −6.7 (*c* = 0.6, $CHCl_3$).

React-IR trace:



(3*S*,6*S*,7*S*)-6,8-dimethyl-1-phenyl-7-((triethylsilyl)oxy)nonan-3-ol (212)



Homologation

A three-necked round-bottomed flask equipped with a stirring bar was connected to the React-IR probe and flushed with N_2. A solution of α-sulfinyl benzoate **200** (161 mg, 0.250 mmol, 1.00 equiv) in anhydrous CH_2Cl_2 (0.500 mL, 0.500 M) was added and the React-IR acquisition was started. The peak at 1734 cm^{-1} was selected to follow α-sulfinyl benzoate **200**. The solution was cooled to −20 °C (tetrachloroethylene/dry ice) and *i*-PrMgCl·LiCl (1.14 M in THF, 0.240 mL, 0.275 mmol, 1.10 equiv) was added dropwise. The peak at 1734 cm^{-1} decreased as a new peak at 1634 cm^{-1} appeared, which was selected to follow the magnesiated intermediate. After 10 min at −20 °C (when sulfoxide-metal exchange was complete by *in situ* IR monitoring), boronic ester **66** (58.0 mg, 0.250 mmol, 1.00 equiv, available in-house[26]) in CH_2Cl_2 (0.500 mL, 1.00 M) was added and the temperature maintained at −20 °C. The peak at 1668 cm^{-1} was selected to follow the boronate complex. After 45 min at −20 °C, when the boronate peak had appeared to plateau, the reaction mixture was heated at 35 °C overnight and the React-IR probe removed.

The reaction mixture was cooled to ambient temperature. Sat. aq. NH_4Cl (2 mL) and CH_2Cl_2 (2 mL) were added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organics were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

Oxidation

$NaBO_3·4H_2O$ (115 mg, 0.750 mmol, 10.0 equiv) was added to crude boronic ester **351** in THF/H_2O (3:2 v/v, 2.50 mL, 0.100 M) and the reaction mixture was stirred at ambient temperature over the weekend (60 h). The reaction mixture was diluted with Et_2O (5 mL) and H_2O (5 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organics were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography

using a Biotage Isolera One system (5 g Sfär column, loaded in pentane/toluene, Et_2O:pentane 10:90 to 30:70) to give alcohol **212** (24 mg, 63.4 µmol, 25%) as a colourless oil.

TLC: R_f = 0.19 (80:20 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.32 – 7.16 (m, 5H, Ph-H), 3.63 (m, 1H, C5H), 3.24 (dd, $^3J_{HH}$ = 6.0 Hz, $^3J_{HH}$ = 3.8 Hz, 1H, C1H), 2.80 (ddd, $^2J_{HH}$ = 14.6 Hz, $^3J_{HH}$ = 9.5 Hz, $^3J_{HH}$ = 5.9 Hz, 1H, C3H^aH^b), 2.68 (ddd, $^2J_{HH}$ = 14.6 Hz, $^3J_{HH}$ = 9.5 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, C3H^aH^b), 1.86 – 1.68 (m, 3H, C2H, $C4H_2$), 1.60 – 1.34 (m, 5H, C8H, $C6H_2$, $C7H_2$), 0.96 (t, $^3J_{HH}$ = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.90 – 0.83 (m, 9H, 2 × $C9H_3$ and $C10H_3$), 0.61 (q, $^3J_{HH}$ = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$) ppm.

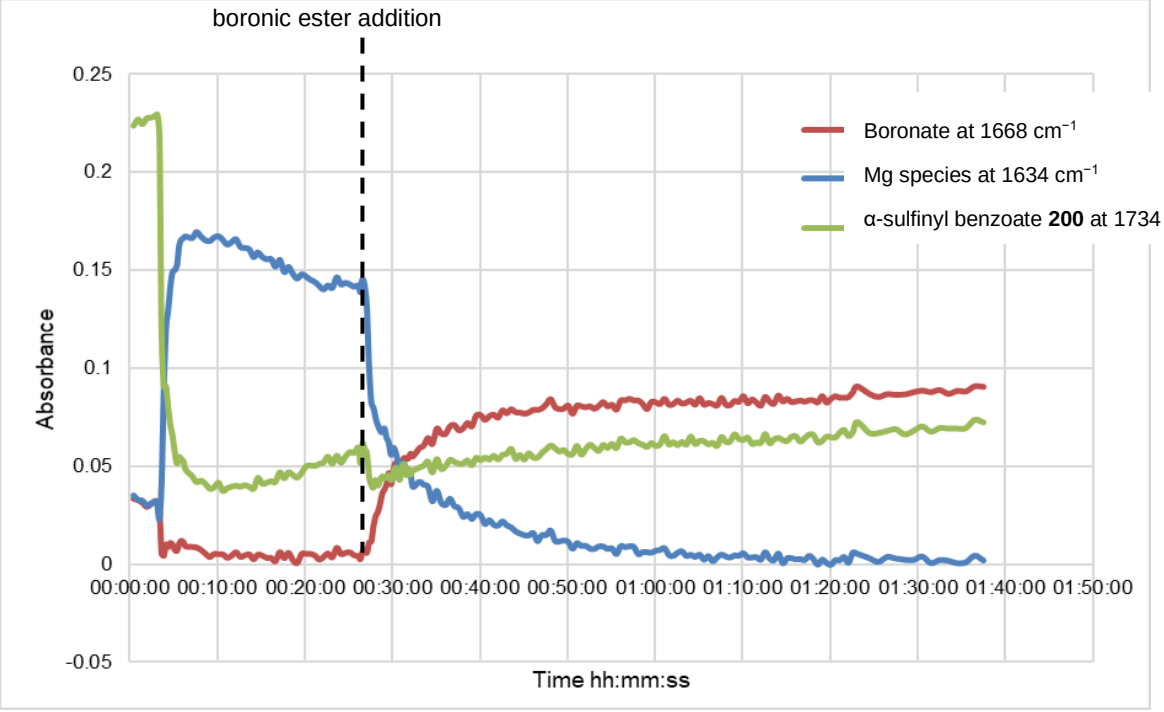
^{13}C NMR: (101 MHz, $CDCl_3$) δ 142.3 (Ph quat C), 128.6 (2C, 2 × *m*Ph C), 128.5 (2C, 2 × *o*Ph C), 126.0 (*p*Ph C), 81.7 (C1), 71.8 (C5), 39.2 (C4), 36.6 (C8), 35.8 (C7), 32.2 (C3), 31.7 (C2), 30.4 (C6), 20.3 (C9), 19.0 (C9'), 14.5 (C10), 7.3 ($Si(CH_2\underline{C}H_3)_3$), 5.8 ($Si(\underline{C}H_2CH_3)_3$) ppm.

HRMS (*m/z*): (ESI) calculated for $C_{23}H_{42}O_2Si$ $[M+H]^+$ 379.3027, found 379.3018.

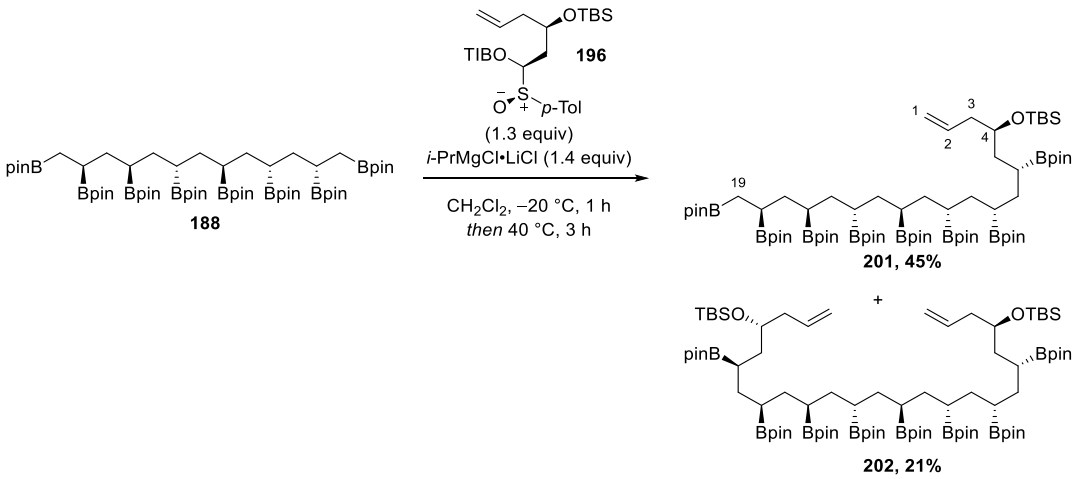
IR (ν_{max}/cm^{-1}, neat): 3356, 2955, 2875, 1640, 1455, 1104 and 1053.

$[\alpha]_D^{23}$: +7.5 (*c* = 0.3, $CHCl_3$).

React-IR trace:

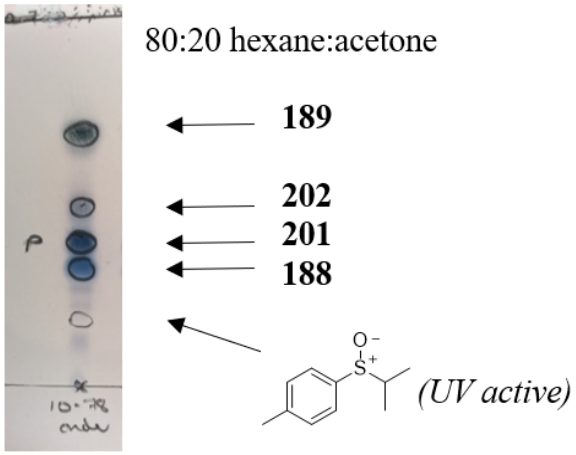


tert-Butyldimethyl(((4*S*,6*R*,8*R*,10*R*,12*S*,14*R*,16*S*,18*S*)-6,8,10,12,14,16,18,19-octakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonadec-1-en-4-yl)oxy)silane (201)



Octa(boronic ester) **188** (59.6 mg, 50.0 μmol, 1.00 equiv) and α-sulfinyl benzoate **196** (38.9 mg, 65.0 μmol, 1.30 equiv) were charged to a flame dried Schlenk tube under N_2, which was put under high vacuum and stirred for 15 min. The Schlenk tube was backfilled with N_2 and anhydrous CH_2Cl_2 (0.25 mL, 0.20 M) was added. The resulting mixture was cooled to −20 °C (acetonitrile/dry ice) and *i*-PrMgCl·LiCl (1.2 M in THF, 60 μL, 70 μmol, 1.4 equiv) was added dropwise. The resulting reaction mixture was stirred at −20 °C for 1 h, removed from the cooling bath and allowed to warm to ambient temperature, and then was stirred at 40 °C (oil bath) for 3 h. The reaction was cooled to ambient temperature and diluted with Et_2O (1 mL) and sat. aq. NH_4Cl (1 mL). The phases were separated and the aqueous phase was extracted with Et_2O (4 × 1 mL). The combined organics were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified using a Biotage Isolera One system (loaded in hexane, Sfär Silica HC 10 g, 97:3 to 90:10 hexane:acetone, 15 column volumes) to give octa(boronic ester) **201** (31.6 mg, 22.5 μmol, 45%) as a colourless oil (white foam under high vacuum) and over-homologated octa(boronic ester) **202** (17.0 mg, 10.5 μmol, 21%) as a colourless oil (white foam under high vacuum).

All recorded spectroscopic data matched that previously reported.[142]



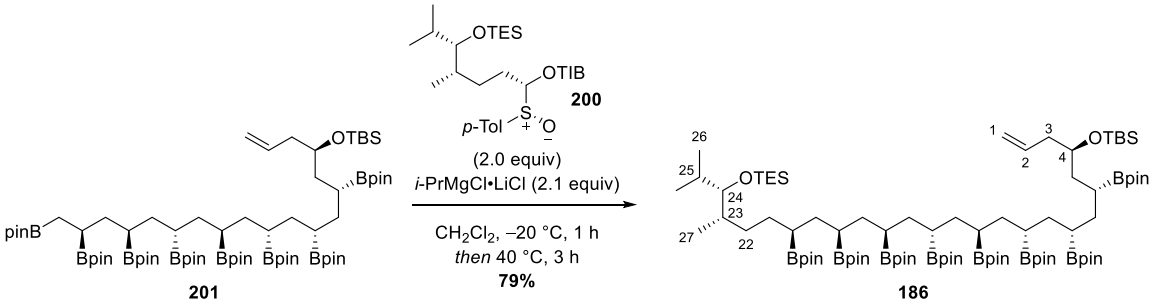
TLC: R_f = 0.31 (90:10 hexane:acetone, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.81 (ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 7.0 Hz, 1H, C2H), 5.03 – 4.95 (m, 2H, $C1H_2$), 3.66 (m, 1H, C4H), 2.23 – 2.11 (m, 2H, $C3H_2$), 1.58 – 0.98 (m, 117H), 0.90 (dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 4.3 Hz, 1H, C19H^aH^b) 0.86 (s, 9H, $SiC(CH_3)_3$), 0.71 (dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 11.1 Hz, 1H, C19H^aH^b), 0.06 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 136.1 (C2), 116.2 (C1), 82.7 (pinacol-C), 82.6 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 72.6 (C4), 42.9 (CH_2), 38.5 (CH_2), 35.6 (CH_2), 35.3 (CH_2), 35.2 (CH_2), 34.9 (CH_2), 33.8 (CH_2), 32.6 (CH_2), 31.7 (CH_2), 26.2 (TBS $C(\underline{C}H_3)_3$), 25.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.9 (pinacol-CH_3), 24.9 (pinacol-CH_3), 18.3 (TBS $\underline{C}(CH_3)_3$), −4.0 ($SiCH_3$), −4.3 ($SiCH_3$) ppm.

Carbon next to boron not observed due to quadrupolar relaxation.

(5*S*,7*R*,9*R*,11*R*,13*S*,15*R*,17*S*,19*S*,21*S*,24*S*,25*S*)-5-Allyl-27,27-diethyl-25-isopropyl-2,2,3,3,24-pentamethyl-7,9,11,13,15,17,19,21-octakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4,26-dioxa-3,27-disilanonacosane (186)



Octa(boronic ester) **201** (20.0 mg, 14.2 µmol, 1.00 equiv) and α-sulfinyl benzoate **200** (18.3 mg, 285 µmol, 2.00 equiv) were charged to a flame dried Schlenk tube under N_2 and stirred for 15 min under high vacuum. The Schlenk tube was backfilled with N_2 and anhydrous CH_2Cl_2 (0.140 mL, 0.100 M) was added. The resulting mixture was cooled to −20 °C (acetonitrile/dry ice) and *i*-PrMgCl·LiCl (1.2 M in THF, 25 µL, 30 µmol, 2.1 equiv) was added dropwise. The resulting reaction mixture was stirred at −20 °C for 1 h, removed from the cooling bath and allowed to warm to ambient temperature, and then was stirred at 40 °C (oil bath) for 3 h. The reaction was cooled to ambient temperature and diluted with Et_2O (1 mL) and sat. aq. NH_4Cl (1 mL). The phases were separated and the aqueous phase was extracted with Et_2O (4 × 1 mL). The combined organics were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified using a Biotage Isolera One system (loaded in minimal toluene/hexane, Sfär Silica HC 5 g, 97:3 to 88:12 hexane:acetone, 20 column volumes) to give octa(boronic ester) **186** (18.6 mg, 11.2 µmol, 79%) as a colourless oil (white foam under high vacuum).

All recorded spectroscopic data matched that previously reported.[142]

TLC: R_f = 0.34 (92:8 hexane:acetone, anisaldehyde).

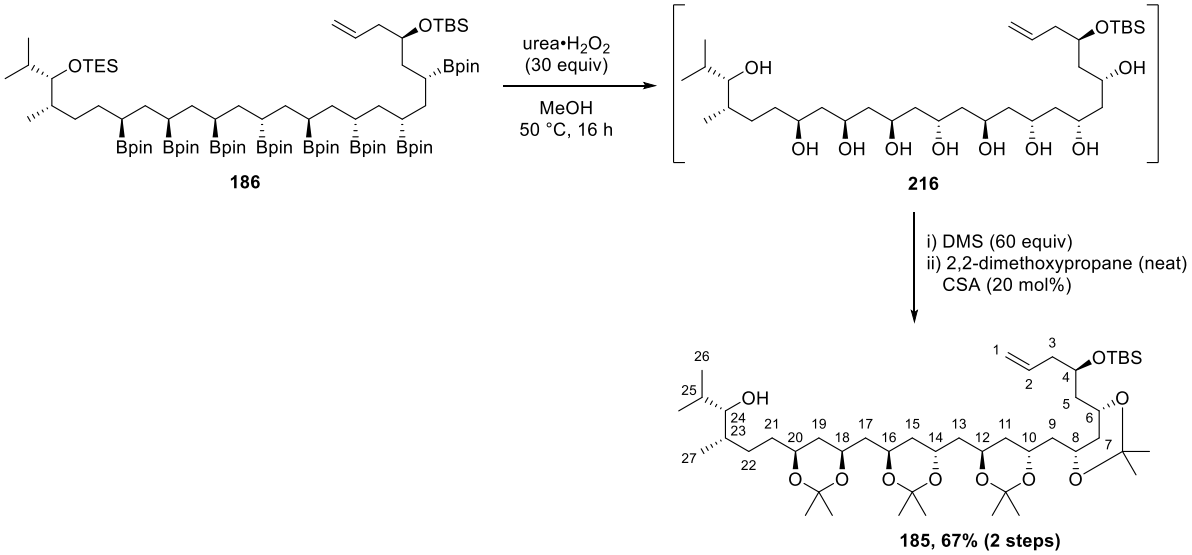
^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.81 (ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 7.0 Hz, 1H, C2H), 5.03 – 4.95 (m, 2H, $C1H_2$), 3.66 (m, 1H, C4H), 3.18 (app. t, $^3J_{HH}$ = 5.0 Hz, 1H, C24H), 2.23 – 2.13 (m, 2H, $C3H_2$), 1.77 – 1.67 (m, 2H), 1.54 – 1.00 (m, 124H), 0.95 (t, $^3J_{HH}$ = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 0.88 – 0.81 (m, 18H, $C26H_3$, C26'H_3, $C27H_3$ and $SiC(CH_3)_3$), 0.60 (q, $^3J_{HH}$ = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$), 0.06 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 136.0 (C2), 116.3 (C1), 82.7 (pinacol-C), 82.6 (pinacol-C), 82.6 (pinacol-C), 82.6 (pinacol-C), 82.4 (C24), 72.6 (C4), 42.9 (CH_2), 38.5 (CH_2), 36.9 (CH),

35.7 (CH_2), 35.0 (CH_2), 34.9 (CH_2), 34.7 (CH_2), 34.1 (CH_2), 33.8 (CH_2), 32.5 (CH_2), 32.1 (CH_2), 31.6 (CH), 28.4 (CH_2), 26.2 (TBS C($\underline{C}H_3)_3$), 25.2 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.7 (pinacol-CH_3), 24.9 (pinacol-CH_3), 24.9 (pinacol-CH_3), 24.9 (pinacol-CH_3), 20.5 (C26), 18.34 (C26'), 18.27 (TBS $\underline{C}(CH_3)_3$), 14.6 (C27), 7.4 (Si($CH_2\underline{C}H_3)_3$), 5.8 (Si($\underline{C}H_2CH_3)_3$), −4.0 ($SiCH_3$), −4.3 ($SiCH_3$) ppm.

NMR spectra included in section **6.5**

(3*S*,4*S*)-6-((4*S*,6*S*)-6-(((4*R*,6*R*)-6-(((4*R*,6*R*)-6-(((6*S*)-6-((*R*)-2-((*tert*-Butyldimethylsilyl)oxy)pent-4-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2,4-dimethylhexan-3-ol (185)



Poly(oxidation)

Urea·H_2O_2 complex (130 mg, 1.38 mmol, 30.0 equiv) was added to a stirred solution of **186** (76.6 mg, 46.1 µmol, 1.00 equiv) in anhydrous MeOH (0.920 mL, 0.0500 M) and the reaction mixture was stirred at 50 °C (oil bath) for 16 h. The reaction mixture was then cooled to ambient temperature and DMS (0.200 mL, 2.72 mmol, 60.0 equiv) was added (to quench excess peroxide). The reaction mixture was stirred at ambient temperature for 5 min, concentrated under reduced pressure and then purified using a Biotage Isolera One system (dry loaded, Sfär Silica HC 5 g, 95:5 to 85:15 CH_2Cl_2:MeOH). Fractions containing nonol **216** (mixed with pinacol) were combined and concentrated under reduced pressure.

TLC: R_f = 0.16 (90:10 CH_2Cl_2:MeOH, anisaldehyde).

Acetonide protection

Dimethoxypropane (0.960 mL, 9.22 mmol, 200 equiv) and CSA (2.1 mg, 9.2 µmol, 20 mol%) were added. The resulting reaction mixture was stirred at ambient temperature for 16 h. TLC analysis showed one main product spot in addition to several more polar spots, which were presumably differing levels of acetonide protection. The reaction mixture was basified with Et_3N and purified by flash column chromatography (SiO_2, 75:25 to 0:100 pentane:Et_2O). Mixed fractions were resubmitted to the acetonide protection conditions. Product fractions from both columns were combined to give tetra(acetonide) **185** (25.7 mg, 31.1 µmol, 67%, >95:5 *dr*) as a colourless oil.

All recorded spectroscopic data matched that previously reported.[142]

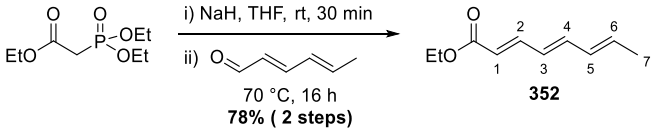
TLC: R_f = 0.38 (50:50 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, toluene-d_8) δ 5.90 (m, 1H, C2H), 5.12 – 5.05 (m, 2H, C1H_2), 4.28 – 3.99 (m, 8H, 7 × acetonide OCH, C4H), 3.70 (m, 1H, C24H), 2.98 (m, 1H, CH), 2.34 – 2.23 (m, 2H, C3H_2), 2.06 – 1.97 (m, 2H, CH_2), 1.73 – 1.55 (m, 10H, 5 × CH_2), 1.53 (s, 6H, 2 × *syn*-acetonide CH_3), 1.49 (s, 3H, *syn*-acetonide CH_3), 1.46 (s, 3H, *anti*-acetonide CH_3), 1.45 (s, 6H, 2 × *anti*-acetonide CH_3), 1.42 (s, 3H, *anti*-acetonide CH_3), 1.39 (s, 3H, *syn*-acetonide CH_3), 1.36 – 1.21 (m, 8H, 4 × CH_2), 1.03 (s, 9H, Si(CH_3)$_3$), 0.96 (d, $^3J_{HH}$ = 6.6 Hz, 3H, C26H_3), 0.89 (d, $^3J_{HH}$ = 6.6 Hz, 3H, C27H_3), 0.81 (d, $^3J_{HH}$ = 6.9 Hz, 3H, C26'H_3), 0.16 (s, 3H, SiCH_3), 0.14 (s, 3H, SiCH_3) ppm.

^{13}C NMR: (126 MHz, toluene-d_8) δ 135.4 (C2), 117.6 (C1), 100.7 (2 × *anti*-acetonide C), 98.9 (*syn*-acetonide C), 98.9 (*syn*-acetonide C), 80.0 (C24), 69.7 (C20), 68.5 (C4), 66.3 (C6), 66.2 (C16), 66.2 (C18), 63.7 (C8), 63.6 (C10), 63.4 (C12), 63.4 (C14), 45.4 (C9), 43.7 (C17), 43.5 (C13), 43.5 (C5), 43.3 (C3), 39.6 (C11), 38.5 (C19), 37.9 (C7), 35.8 (C21), 34.9 (C23), 31.7 (C22), 31.1 (*syn*-acetonide CH_3), 31.0 (*syn*-acetonide CH_3), 30.1 (C25), 26.6 (SiC($\underline{C}H_3$)$_3$), 25.7 (*anti*-acetonide CH_3), 25.6 (*anti*-acetonide CH_3), 25.4 (*anti*-acetonide CH_3), 25.4 (*anti*-acetonide CH_3), 21.9 (Si$\underline{C}$(CH_3)$_3$), 20.2 (*syn*-acetonide CH_3), 19.9 (*syn*-acetonide CH_3), 19.0 (C26), 18.7 (C26'), 13.8 (C27), −3.4 (SiCH_3), −4.0 (SiCH_3) ppm.

NMR spectra included in section **6.5**

Ethyl (2*E*,4*E*,6*E*)-octa-2,4,6-trienoate (352)



According to a modified literature procedure,[74] triethylphosphonoacetate (5.95 mL, 30.0 mmol, 1.74 equiv) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil, 1.12 g, 28.0 mmol, 1.63 equiv) in anhydrous THF (100 mL, 0.280 M) at 0 °C. The resulting mixture was warmed to ambient temperature and stirred for 30 min. Freshly distilled sorbaldehyde (1.85 mL, 17.2 mmol, 1.00 equiv) was then added in anhydrous THF (3.90 mL, 2.68 M) and the resulting mixture heated at 70 °C for 16 h. The reaction mixture was diluted with water (100 mL) and Et_2O (100 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 100 mL) and the combined organics were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 95:5 to 85:15 pentane:Et_2O) to yield trienoate **352** (2.23 g, 13.4 mmol, 78%, *E/Z* 8:1) as a white solid.

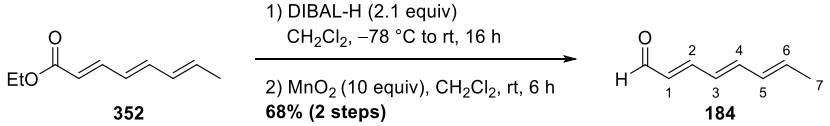
All recorded spectroscopic data matched that previously reported.[153]

TLC: R_f = 0.38 (90:10 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.29 (dd, $^3J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 11.1 Hz, 1H, C2H), 6.51 (dd, $^3J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 10.8 Hz, 1H, C4H), 6.24 – 6.10 (m, 2H, C3H and C5H), 5.93 (m, 1H, C6H), 5.83 (d, $^3J_{HH}$ = 15.2 Hz, 1H, C1H), 4.20 (q, $^3J_{HH}$ = 7.1 Hz, 2H, OC*H*$_2$), 1.83 (d, $^3J_{HH}$ = 6.9 Hz, 3H, C7H_3) 1.29 (t, $^3J_{HH}$ = 7.1 Hz, 3H, OCH$_2$C*H*$_3$) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 167.5 (C=O), 145.0 (C2), 141.2 (C4), 135.2 (C6), 131.4 (C5H), 127.7 (C3H), 120.2 (C1), 60.4 (OCH_2), 18.7 (C7), 14.5 (OCH$_2$CH_3) ppm.

(2*E*,4*E*,6*E*)-Octa-2,4,6-trienal (184)



According to a modified literature procedure,[153] DIBAL-H (1.00 M in hexanes, 5.82 mL, 5.82 mmol, 2.10 equiv) was added dropwise to a stirred solution of polyene **352** (460 mg,

2.77 mmol, 1.00 equiv) in anhydrous CH_2Cl_2 (6.92 mL, 0.400 M) at −78 °C. The resulting mixture was warmed to ambient temperature and stirred for 16 h. The reaction was then diluted with Et_2O (10 mL) and quenched through the slow addition of sat. aq. Rochelle's salt solution (20 mL). The reaction was stirred at ambient temperature for 1 h, after which two phases were visible. The phases were separated, and the organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was dissolved in anhydrous CH_2Cl_2 (27.7 mL, 0.100 M). MnO_2 (2.41 g, 27.7 mmol, 10.0 equiv) was added in one portion and the reaction was stirred at ambient temperature for 6 h. The reaction was filtered through a pad of Celite® (CH_2Cl_2) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 90:10 pentane:Et_2O) to afford trienal **184** (230 mg, 1.88 mmol, 68%, *E/Z* 8:1) as a yellow amorphous solid.

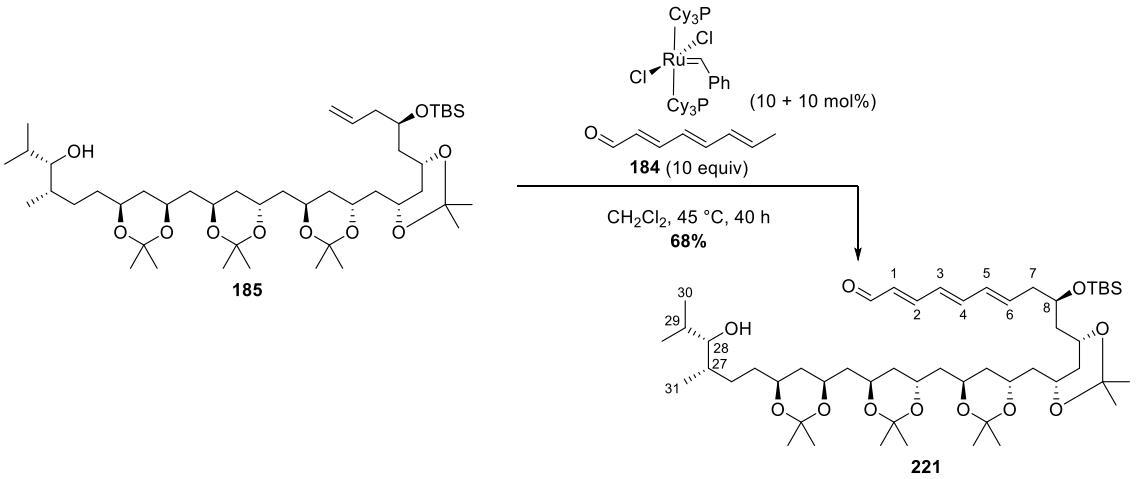
All recorded spectroscopic data matched that previously reported.[153]

TLC: R_f = 0.49 (70:30 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.55 (d, $^3J_{HH}$ = 8.0 Hz, 1H, C*H*O), 7.11 (dd, $^3J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 11.2 Hz, 1H, C2H), 6.64 (dd, $^3J_{HH}$ = 14.9 Hz, $^3J_{HH}$ = 10.6 Hz, 1H, C4H), 6.33 (dd, $^3J_{HH}$ = 14.9 Hz, $^3J_{HH}$ = 11.2 Hz, C3H), 6.10 (m, 1H, C5H), 6.03 (m, 1H, C1H), 5.96 (m, 1H, C6H), 1.86 (d, $^3J_{HH}$ = 6.9 Hz, 3H, C7H_3) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 193.8 (CHO), 152.6 (C2), 143.3 (C4), 137.3 (C6), 131.3 (C5), 130.9 (C1), 127.8 (C3), 18.9 (C7) ppm.

(2*E*,4*E*,6*E*,9*R*)-9-((*tert*-Butyldimethylsilyl)oxy)-10-((4*S*)-6-(((4*R*,6*R*)-6-(((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((3*S*,4*S*)-4-hydroxy-3,5-dimethylhexyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)deca-2,4,6-trienal (221)



Grubbs first generation metathesis catalyst [CAS 172222-30-9] (1.5 mg, 1.8 µmol, 10 mol%) was added to a stirred solution of tetra(acetonide) **185** (15.0 mg, 18.0 µmol, 1.00 equiv) and trienal **184** (22.2 mg, 0.181 mmol, 10.0 equiv) in anhydrous CH_2Cl_2 (0.910 mL, 0.0200 M) under an atmosphere of N_2. The resulting mixture was stirred at 45 °C (sand bath) for 16 h, at which point TLC analysis showed incomplete consumption of **185**. A further portion of Grubbs first generation catalyst (1.5 mg, 1.8 µmol, 10 mol%) was added and the reaction was stirred for a further 24 h at 45 °C. The reaction was cooled to ambient temperature and the volatile components were removed under reduced pressure. The crude residue was purified by column chromatography (SiO_2, loaded in toluene, 75:25 to 60:40 pentane:Et_2O) to yield trienal **221** (11.2 mg, 12.3 µmol, 68%, 90% brsm) as a yellow oil.

All recorded spectroscopic data matched that previously reported.[142]

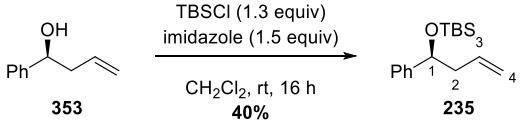
TLC: R_f = 0.15 (50:50 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.76 (d, $^3J_{HH}$ = 7.8 Hz, 1H, C*H*O), 7.11 (m, 1H, C2H), 6.65 (dd, $^3J_{HH}$ = 14.9 Hz, $^3J_{HH}$ = 10.8 Hz, 1H, C4H), 6.31 (m, 1H, C3H), 6.21 (m, 1H, C5H), 6.18 – 6.11 (m, 2H, C1H, C6H), 4.02 – 3.92 (m, 8H, 8 × acetonide OCH), 3.79 (m, 1H, C8H), 3.11 (m, 1H, C28H), 2.34 – 2.28 (m, 2H, $C7H_2$), 1.86 – 1.77 (m, 2H, CH_2), 1.75 – 1.66 (m, 2H, CH_2), 1.65 – 1.39 (m, 16H), 1.36 (s, 3H, *syn*-acetonide CH_3), 1.34 (s, 3H, *syn*-acetonide CH_3), 1.32 (s, 12H, 4 × *anti*-acetonide CH_3), 1.25 (s, 3H, *syn*-acetonide CH_3), 1.23 (s, 3H, *syn*-

acetonide CH_3), 1.16 (m, 2H, CH_2), 0.96 (d, $^3J_{HH}$ = 6.6 Hz, 3H, C31H_3), 0.90 – 0.84 (m, 15H, C30H_3, C30'H_3, SiC(CH_3)$_3$), 0.07 (s, 6H, Si(CH_3)$_2$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 193.2 (CHO), 148.8 (C2), 143.0 (C4), 135.1 (C6), 132.2 (C5), 131.1 (C1), 130.5 (C3), 100.5 (2 × *anti*-acetonide C), 98.5 (2 × *syn*-acetonide C), 80.0 (C28), 69.2 (CH), 66.1 (CH), 65.8 (CH), 65.6 (CH), 63.1 (CH), 62.8 (CH), 44.8 (CH_2), 42.5 (CH_2), 42.2 (CH_2), 38.9 (CH_2), 36.8 (CH_2), 35.0 (CH), 34.2 (CH_2), 31.7 (CH_2), 31.1 (CH), 30.5 (*syn*-acetonide CH_3), 30.4 (*syn*-acetonide CH_3), 29.9 (CH_2), 26.0 (SiC(CH_3) $_3$), 25.0 (*anti*-acetonide CH_3), 25.0 (*anti*-acetonide CH_3), 20.3 (*syn*-acetonide CH_3), 20.0 (*syn*-acetonide CH_3), 19.5 (C30), 18.8 (C31), 18.3 (SiC(CH_3)$_3$), 13.2 (C30'), −3.8 ($SiCH_3$), −4.3 ($SiCH_3$) ppm.

(*S*)-*tert*-butyldimethyl((1-phenylbut-3-en-1-yl)oxy)silane (235)



Imidazole (0.689 g, 10.1 mmol, 1.50 equiv) then TBSCl (1.32 g, 8.77 mol, 1.30 equiv) were added to homoallylic alcohol **353** (1.00 g, 6.75 mmol, 1.00 equiv, available in-house) in CH_2Cl_2 (34.0 mL, 0.200 M) and the resulting reaction mixture stirred at ambient temperature overnight. Water (20 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 0:100 to 10:90 Et_2O:pentane) to give protected alcohol **235** as a colourless oil (0.710 g, 2.71 mmol, 40%).

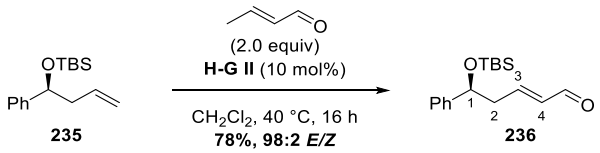
All recorded spectroscopic data matched that previously reported.[214]

TLC: R_f = 0.30 (100% pentane, PMA).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 4H, Ph-H), 8.19 (m, 1H, Ph-H), 5.75 (m, 1H, C3H), 5.01 – 4.94 (m, 2H, C4H_2), 4.64 (dd, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 5.2 Hz, 1H, C1H), 2.48 – 2.28 (m, 2H, C2H_2), 0.84 (s, 9H, SiC(CH_3)$_3$), −0.01 (s, 3H, $SiCH_3$), −0.16 (s, 3H, $SiCH_3$) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 145.3 (Ph quat C), 135.4 (C3), 128.2 (2 × *m*Ph C), 127.1 (*p*Ph C), 126.1 (2 × *o*Ph C), 117.0 (C4), 75.2 (C1), 45.7 (C2), 26.0 ($SiC(\underline{C}H_3)_3$), 18.4 ($Si\underline{C}(CH_3)_3$), −4.5 ($SiCH_3$), −4.7 ($SiCH_3$) ppm.

(*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-5-phenylpent-2-enal (236)



Hoveyda-Grubbs second generation metathesis catalyst (12.5 mg, 20.0 μmol, 10.0 mol%) was added in one portion to alkene **235** (52.0 mg, 0.200 mmol, 1.00 equiv) and freshly distilled crotonaldehyde (33 μL, 0.40 mmol, 2.0 equiv) in anhydrous CH_2Cl_2 (2.00 mL, 0.100 M) under inert atmosphere and the reaction mixture was heated at 40 °C overnight.

The reaction mixture was cooled to ambient temperature and filtered through a silica plug on top of a Celite® pad, washing with CH_2Cl_2 (~20 mL). The filtrate was concentrated under reduced pressure and the crude residue was purified by flash column chromatography on a Biotage Isolera One system (5 g Sfär column, loaded in pentane, Et_2O:pentane 8:92) to give aldehyde **236** (45.4 mg, 0.156 mmol, 78%, 98:2 *E*:*Z*) as a colourless oil.

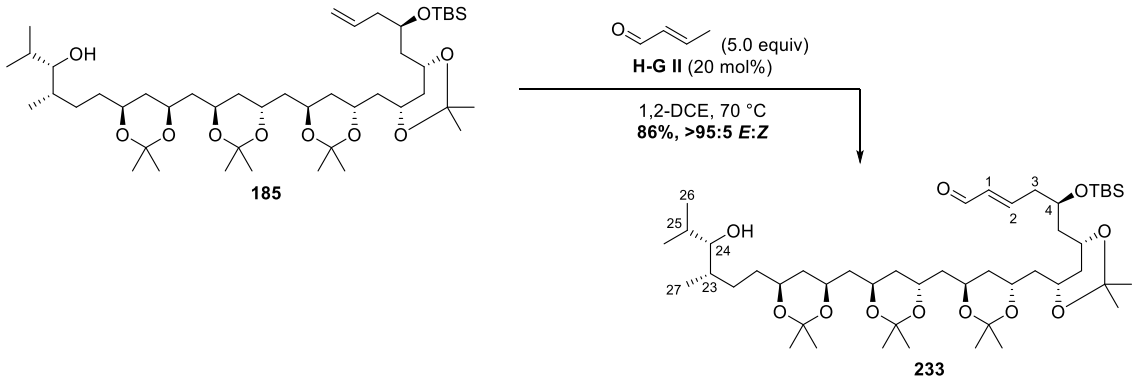
All recorded spectroscopic data matched that previously reported.[215]

TLC: R_f = 0.41 (80:20 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 9.47 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H, CHO), 7.37 – 7.22 (m, 5H, 5 × Ph-H), 6.81 (dt, $^{3}J_{HH}$ = 15.7 Hz, $^{3}J_{HH}$ = 7.3 Hz, 1H, C3H), 6.10 (ddt, $^{3}J_{HH}$ = 15.7 Hz, $^{3}J_{HH}$ = 7.9 Hz, $^{4}J_{HH}$ = 1.4 Hz, 1H, C4H), 4.84 (dd, $^{3}J_{HH}$ = 7.0 Hz, $^{3}J_{HH}$ = 4.8 Hz, 1H, C1H), 2.78 – 2.63 (m, 2H, $C2H_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.03 (s, 3H, $SiCH_3$), −0.13 (s, 3H, $SiCH_3$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 194.0 (CHO), 154.9 (C3), 144.0 (Ph quat C), 135.1 (C4), 128.5 (2 × *m*Ph C), 127.7 (*p*Ph C), 125.8 (2 × *o*Ph C), 73.9 (C1), 44.2 (C2), 25.9 ($Si\underline{C}(CH_3)_3$), 18.3 ($SiC(\underline{C}H_3)_3$), −4.5 ($SiCH_3$), −4.9 ($SiCH_3$) ppm.

(5*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-6-((4*S*)-6-(((4*R*,6*R*)-6-(((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((3*S*,4*S*)-4-hydroxy-3,5-dimethylhexyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)hex-2-enal (233)



A degassed solution of Hoveyda-Grubbs second generation metathesis catalyst (1.7 mg, 2.7 µmol, 20 mol%) in anhydrous 1,2-DCE (0.200 mL) was added to a stirred solution of tetra(acetonide) **185** (11.2 mg, 13.5 µmol, 1.00 equiv) and crotonaldehyde (6.0 µL, 70 µmol, 5.0 equiv) in anhydrous 1,2-DCE (0.380 mL [0.680 mL overall, 0.0200 M wrt **185**]) under an atmosphere of N_2. The resulting mixture was stirred at 70 °C (oil bath) for 14 h. The reaction was cooled to ambient temperature and the volatile components were removed under reduced pressure. The crude residue was purified by column chromatography (dry loaded, Et_3N-deactivated SiO_2, 3:1 hexane:EtOAc) to yield aldehyde **233** (10.0 mg, 11.7 µmol, 86%, >95:5 *dr*) as a pale yellow oil.

TLC: R_f = 0.13 (50:50 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, CD_3OD) δ 9.49 (d, $^3J_{HH}$ = 7.9 Hz, 1H, CHO), 7.03 (dt, $^3J_{HH}$ = 15.7 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, C2H), 6.17 (dd, $^3J_{HH}$ = 15.7 Hz, $^3J_{HH}$ = 7.9 Hz, 1H, C1H), 4.17 (quint, $^3J_{HH}$ = 5.8 Hz, 1H, C4H), 4.10 – 3.74 (m, 8H, 8 × acetonide OC*H*), 3.04 (dd, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 4.2 Hz, 1H, C24H), 2.67 – 2.50 (m, 2H, $C3H_2$), 1.80 – 1.68 (m, 3H, C23H, CH_2), 1.67 – 1.48 (m, 17H, C6H, 8 × CH_2), 1.47 (s, 3H, *syn*-acetonide CH_3), 1.45 (s, 3H, *syn*-acetonide CH_3), 1.34 (s, 6H, 2 × *syn*-acetonide CH_3), 1.32 (s, 9H, 3 × *anti*-acetonide CH_3), 1.31 (s, 3H, *anti*-acetonide CH_3), 1.16 (m, 2H, CH_2), 0.97 (d, $^3J_{HH}$ = 6.6 Hz, 3H, $C27H_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.89 (dd, $^3J_{HH}$ = 6.7 Hz, $^3J_{HH}$ = 3.8 Hz, 6H, $C26H_3$, C26'H_3), 0.13 (d, $^3J_{HH}$ = 1.8 Hz, 6H, $Si(CH_3)_2$) ppm.

^{13}C NMR: (126 MHz, CD_3OD) δ 195.9 (CHO), 157.0 (C2), 136.2 (C1), 101.5 (*anti*-acetonide C), 99.8 (*syn*-acetonide C), 99.8 (*syn*-acetonide C), 80.7 (C5), 70.5 (acetonide OCH), 68.8

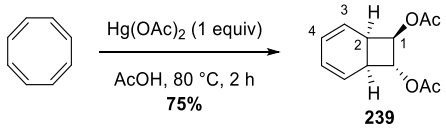
(C4), 67.1 (acetonide OCH), 67.0 (acetonide OCH), 67.0 (acetonide OCH), 64.4 (acetonide OCH), 64.4 (CH acetonide OCH), 64.1 (acetonide OCH), 45.8 (CH_2), 43.4 (CH_2), 43.3 (CH_2), 43.1 (CH_2), 42.4 (C3), 39.8 (CH_2), 39.7 (CH_2), 38.6 (CH_2), 38.2 (CH_2), 36.1 (CH_2), 35.0 (CH_2), 32.0 (OCH<u>C</u>H(CH_3)$_2$), 30.6 (HOCH<u>C</u>HCH$_3$), 30.6 (*syn*-acetonide CH_3), 30.5 (*syn*-acetonide CH_3), 26.4 (SiC(<u>C</u>H$_3$)$_3$), 25.3 (2 × *anti*-acetonide CH_3), 25.1 (2 × *anti*-acetonide CH_3), 20.6 (*syn*-acetonide CH_3), 20.1 (*syn*-acetonide CH_3), 20.0 (C26H$_3$), 19.1 (C27), 18.9 (Si<u>C</u>(CH$_3$)$_3$), 13.7 (C26'H$_3$), −3.8 (SiCH$_3$), −4.3 (SiCH$_3$) ppm.

HRMS (*m/z*): (nanospray) calculated for $C_{47}H_{87}O_{11}Si$ $[M+H]^+$ 855.6018, found 855.6028.

IR (ν_{max}/cm^{-1}, neat): 3609, 2997, 2939, 2855, 1694, 1472 and 1379.

$[\alpha]_D^{24}$: +12.9 (*c* = 0.2, $CHCl_3$).

(1*R*,6*S*,7*R*,8*R*)-bicyclo[4.2.0]octa-2,4-diene-7,8-diyl diacetate (239)



239

According to the literature procedure,[155] cyclooctatetraene (2.16 mL, 19.2 mmol, 1.00 equiv) was added to a stirred suspension of $Hg(OAc)_2$ (6.12 g, 19.2 mmol, 1.00 equiv) in acetic acid (16.0 mL, 2.40 M). The reaction mixture was heated at 80 °C (oil bath) for 2 h. The reaction mixture was cooled to ambient temperature and filtered through a plug of cotton wool to remove mercury, washing with water (160 mL). The filtrate was stirred at 0 °C (water/ice) for 20 min then filtered through a Büchner funnel. The residue was dried over anhydrous silica gel under vacuum overnight to give diacetate **239** (3.22 g, 14.5 mmol, 75%) as an orange solid.

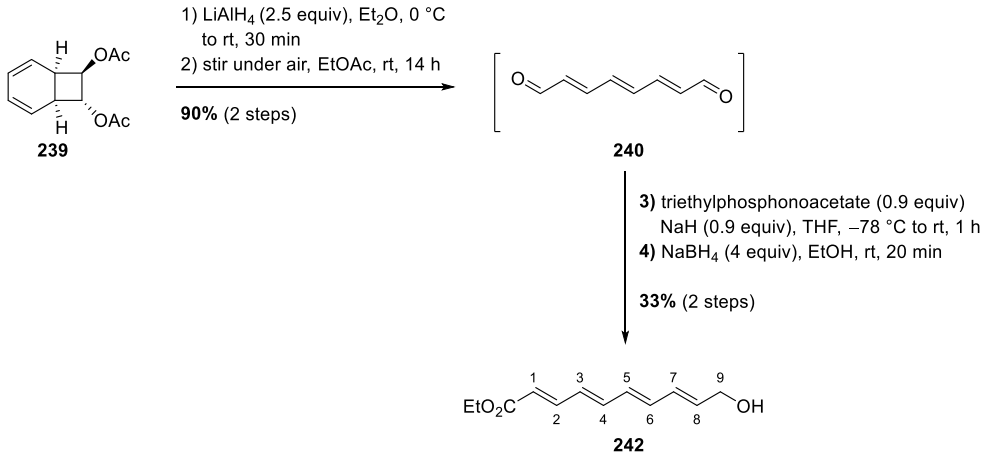
All recorded spectroscopic data matched that previously reported.[155]

TLC: R$_f$ = 0.52 (50:50 EtOAc:hexane, anisaldehyde).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.94 (dddd, $^3J_{HH}$ = 9.9 Hz, $^3J_{HH}$ = 5.5 Hz, $^4J_{HH}$ = 2.4 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, C4H), 5.85 (ddt, $^3J_{HH}$ = 9.5 Hz, $^3J_{HH}$ = 5.5 Hz, $^4J_{HH}$ = 0.7 Hz, 1H, C4'H), 5.75 (m, 1H, C3H), 5.46 (m, 1H, C3'H), 5.36 – 5.23 (m, 2H, C1H, C1'H), 3.52 (m, 1H, C2H), 2.66 (m, 1H, C2'H), 2.10 (s, 3H, Me), 2.06 (s, 3H, Me') ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 170.6 (C=O), 170.0 (C=O'), 125.1 (C4H), 124.2 (C3H), 123.1 (C4'H), 122.6 (C3'H), 78.7 (C1), 78.6 (C1'), 34.3 (C2'H), 33.9 (C3 or C4, C2H), 21.0 (Me'), 20.8 (Me) ppm.

Ethyl (2*E*,4*E*,6*E*,8*E*)-10-hydroxydeca-2,4,6,8-tetraenoate (242)



Reductive cleavage of diacetates

According to a modified literature procedure,[109] $LiAlH_4$ (256 mg, 6.75 mmol, 2.50 equiv) was added to diacetate **239** (600 mg, 2.70 mmol, 1.00 equiv) in Et_2O (13.5 mL, 0.200 M) at 0 °C (water/ice). The reaction mixture was stirred at ambient temperature for 30 min, at which point TLC analysis indicated consumption of **239** and full conversion.

TLC: R_f = 0.14 (40:60 hexane:EtOAc, PMA).

Oxidative ring fragmentation

The reaction mixture was diluted with EtOAc (50 mL) and cooled to 0 °C. Water (0.3 mL) then 3 M aq. NaOH (1 mL), then water (0.5 mL) was added. The mixture was warmed to ambient temperature and stirred for 15 min. Anhydrous $MgSO_4$ was added and stirring continued for 15 min. The mixture was filtered through a sinter funnel and the filtrate stirred at ambient temperature under air in the dark overnight. The solvent was removed under reduced pressure to give the crude dialdehyde **240** (330 mg, 2.42 mmol) as an orange-yellow solid.

TLC: R_f = 0.48 (40:60 hexane:EtOAc, anisaldehyde).

Mono HWE

Triethylphosphonoacetate (0.430 mL, 2.18 mmol, 0.900 equiv) was added dropwise to NaH (60 wt% in mineral oil, 87.0 mg, 2.18 mmol, 0.900 equiv, washed with hexane, 2 × 0.500 mL) in anhyd. THF (14.5 mL, 0.150 M) at 0 °C. The mixture was stirred at ambient temperature for 20 min then added dropwise to crude dialdehyde **240** in THF (11 mL) at −78 °C. The reaction mixture was stirred at ambient temperature for 1 h. Sat. aq. $NaHCO_3$ (30 mL) and EtOAc (30 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined organics were washed with brine (30 mL), dried over anhyd. $MgSO_4$ and concentrated under reduced pressure.

TLC: R_f = 0.61 (40:60 hexane:EtOAc, anisaldehyde).

Aldehyde reduction

$NaBH_4$ (367 mg, 9.70 mmol, 4.00 equiv) was added to the crude tetraenal **241** in EtOH (24.0 mL) and stirred at ambient temperature for 20 min. Water (20 mL) was added and most of the EtOH removed under reduced pressure. The solution was diluted with EtOAc (30 mL) and the phases separated. The aqueous was extracted with EtOAc (2 × 30 mL). The combined organics were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure.

The crude residue was purified by flash column chromatography (SiO_2, 20:80 to 50:50 EtOAc:hexane) to give tetraenoate **242** (164 mg, 0.787 mmol, 29% over 4 steps, >98:2 *E*:*Z*) as a pale yellow solid.

N.B. This procedure was conducted in the dark and all manipulations were performed in low/red lighting. It was important to isolate alcohol **242** as soon as possible, as considerable decomposition was observed when the crude material was stored at −20 °C overnight, which made the chromatographic purification more challenging.

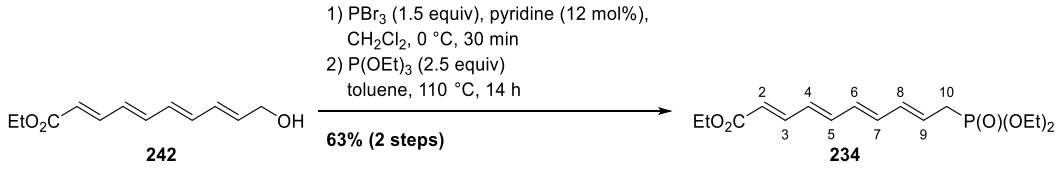
All recorded spectroscopic data matched that previously reported.[109]

TLC: R_f = 0.42 (40:60 hexane:EtOAc, anisaldehyde).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.31 (dd, $^3J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 11.3 Hz, 1H, C2H), 6.58 (dd, $^3J_{HH}$ = 14.8 Hz, $^3J_{HH}$ = 10.7 Hz, 1H, C4H), 6.47 – 6.22 (m, 4H, 4 × CH), 5.97 (dt, $^3J_{HH}$ = 14.5 Hz, $^3J_{HH}$ = 5.7 Hz, 1H, C8H), 5.87 (d, $^3J_{HH}$ = 15.3 Hz, 1H, C1H), 4.25 (d, $^3J_{HH}$ = 5.8 Hz, 3H, C9H_3), 4.20 (q, $^3J_{HH}$ = 7.1 Hz, 2H, OCH_2), 1.57 (s, 1H, OH), 1.30 (t, $^3J_{HH}$ = 7.1 Hz, 3H, OCH_2CH_3) ppm.

^{13}C NMR 101 MHz, $CDCl_3$) δ 144.3 (C2), 140.4 (C4), 136.1 (CH), 134.9 (C8), 132.1 (CH), 130.8 (CH), 130.4 (CH), 121.0 (C1), 63.3 (C9), 60.3 (OCH_2), 14.4 ($OCH_2\underline{C}H_3$) ppm.

Ethyl (2*E*,4*E*,6*E*,8*E*)-10-(diethoxyphosphoryl)deca-2,4,6,8-tetraenoate (234)



According to a modified literature procedure,[95,110] pyridine (4.0 µL, 46 µmol, 12 mol%) then PBr_3 (50.0 µL, 0.576 mmol, 1.50 equiv) was added to alcohol **242** (80.0 mg, 0.384 mmol, 1.00 equiv) in anhyd. CH_2Cl_2 (1.30 mL, 0.300 M) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 30 min then water (3 mL) was added followed by Et_2O (3 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 3 mL). The combined organics were washed with sat. aq. $NaHCO_3$ (5 mL), brine (5 mL), passed through Sartorius™ Grade 480 silicon-impregnated phase separator paper and concentrated under reduced pressure to give a yellow solid.

$P(OEt)_3$ (0.16 mL, 0.96 mmol, 2.5 equiv) was added to the crude bromide in toluene (2.60 mL, 0.150 M) and the reaction mixture was heated at 110 °C for 14 h. The reaction mixture was cooled to ambient temperature and diluted with EtOAc (5 mL). The organics were washed with water (3 × 5 mL), brine (5 mL), passed through through Sartorius™ Grade 480 silicon-impregnated phase separator paper and most of the solvent was removed under reduced pressure. The crude material in residual toluene (~0.5 mL) was purified by flash column chromatography (SiO_2, 5:1 EtOAc:hexane) to give phosphonate **234** (80 mg, 0.244 mmol, 63%, >98:2 *E*:*Z*) as a yellow solid.

N.B. This procedure was conducted in the dark and all manipulations in low/red lighting.

All recorded spectroscopic data matched that previously reported.[109]

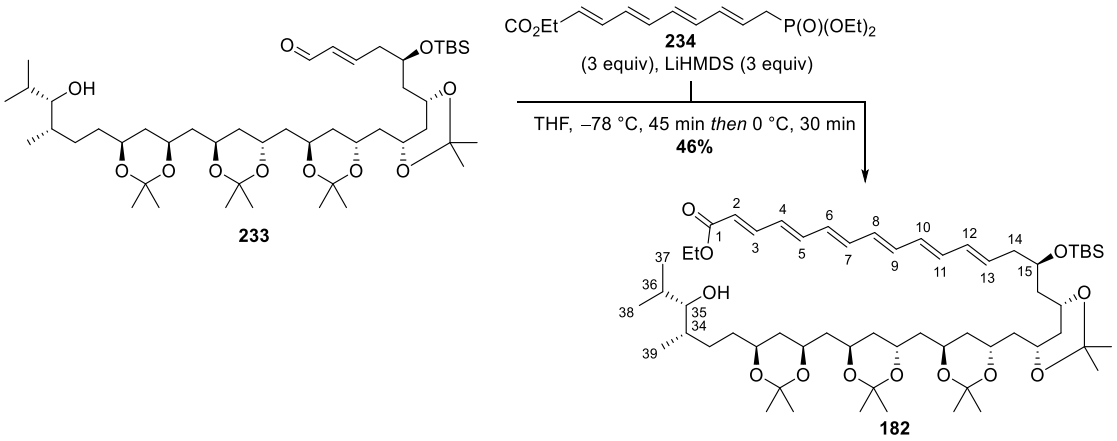
TLC: R_f = 0.12 (1:5 hexane:EtOAc, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.31 (dd, $^{3}J_{HH}$ = 15.3 Hz, $^{3}J_{HH}$ = 11.4 Hz, 1H, C3H), 6.56 (dd, $^{3}J_{HH}$ = 14.8 Hz, $^{3}J_{HH}$ = 11.0 Hz, 1H, C5H), 6.41 – 6.21 (m, 4H, C4H, C6H, C7H, C8H), 5.87 (d, $^{3}J_{HH}$ = 15.2 Hz, 1H, C2H), 5.77 (dq, $^{3}J_{HH}$ = 15.4 Hz, $^{3}J_{HH}$ = 7.8 Hz, 1H, C9H), 4.20 (q,

$^{3}J_{HH}$ = 7.1 Hz, 2H, C(O)OCH$_2$), 4.17 – 4.03 (m, 4H, 2 × P(O)OCH$_2$), 2.68 (dd, $^{2}J_{PH}$ = 23.0 Hz, $^{3}J_{HH}$ = 7.7 Hz, 2H, C10H$_2$), 1.30 (m, 9H, 3 × CH$_3$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 167.2 (C=O), 144.4 (C3), 140.5 (C5), 136.2 (CH), 134.9 (CH), 131.6 (CH), 130.4 (CH), 125.4 (C9), 121.0 (C2), 62.2 ($CO_2\underline{C}H_2$), 60.4 (2 × P(O)OCH$_2$), 31.3 (d, $^{1}J_{CP}$ = 140 Hz, C10), 16.6 (P(O)OCH$_2\underline{C}H_3$), 14.5 ($CO_2CH_2\underline{C}H_3$) ppm.

Ethyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,15*R*)-15-((*tert*-butyldimethylsilyl)oxy)-16-((4*S*)-6-(((4*R*,6*R*)-6-(((4*R*,6*R*)-6-(((4*S*,6*S*)-6-((3*S*,4*S*)-4-hydroxy-3,5-dimethylhexyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)hexadeca-2,4,6,8,10,12-hexaenoate (182)



According to a modified literature procedure,[95,109] phosphonate **234** (10.4 mg, 31.6 μmol, 3.00 equiv) in anhydrous THF (0.320 mL, 0.100 M) was added to LiHMDS (0.20 M in THF, 0.16 mL, 32 μmol, 3.0 equiv) at −78 °C (acetone/dry ice). The reaction mixture was stirred at −78 °C for 30 min then aldehyde **233** (9.0 mg, 11 μmol, 1.0 equiv) in anhydrous THF (0.530 mL, 0.0200 M) was added. The syringe was washed with THF (2 × 0.20 mL). The reaction mixture was stirred at −78 °C for 45 min then warmed slowly to 0 °C over 15 min and stirred at 0 °C for 30 min. The reaction was quenched at 0 °C with sat. aq. NH_4Cl (1 mL), warmed to ambient temperature and diluted with Et_2O (1 mL). The phases were separated and the aqueous phase was extracted with Et_2O (5 × 1 mL). The combined organics were washed with brine (2 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (dry loaded, SiO_2; 1:3 EtOAc:hexane) to yield hexaenoate **182** (5.0 mg, 4.9 μmol, 46%) as a yellow oil.

N.B. This procedure was conducted in the dark and all manipulations in low/red lighting. When phosphonate **234** was added directly to the Schlenk tube where the LiHMDS had been freshly prepared, the product of *n*-BuLi addition to aldehyde **233** was also isolated following column chromatography, presumably due to excess *n*-BuLi being present given the volumes involved on such a small scale. This issue could be avoided by making LiHMDS in a separate vessel on a larger scale and then transferring the amount required by syringe, or by simply using the commercially supplied 1 M solution in THF.

All recorded spectroscopic data matched that previously reported.[142]

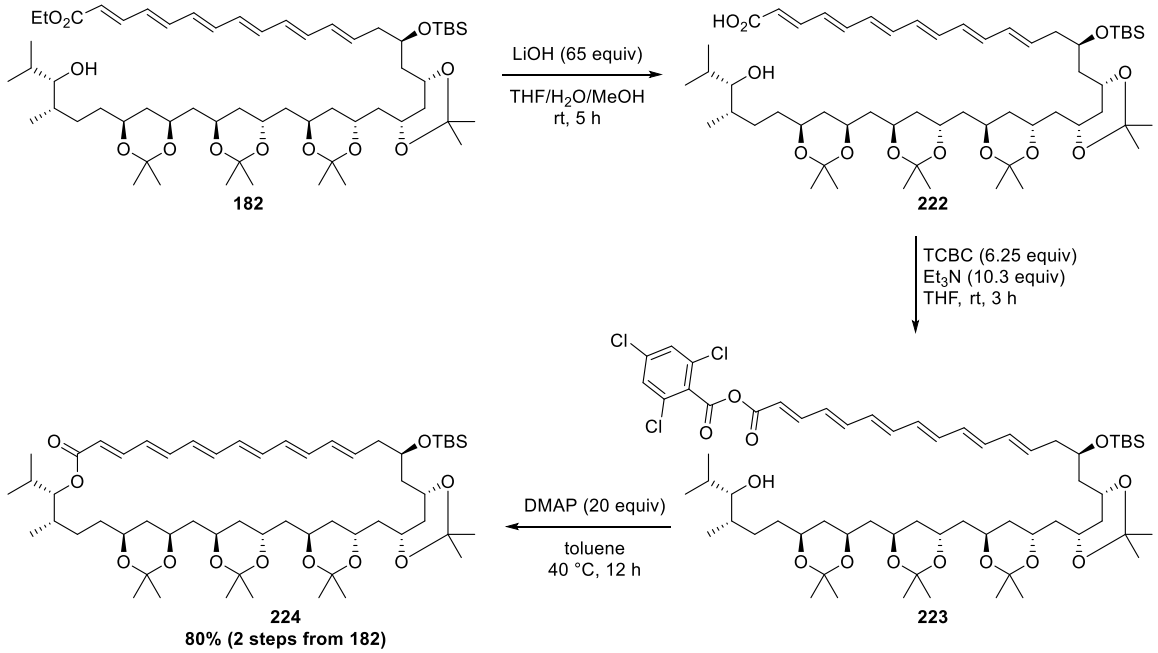
TLC: R_f = 0.33 (2:1 hexane:EtOAc, anisaldehyde).

^{1}H NMR: (500 MHz, CD_3OD) δ 7.34 (dd, $^3J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 11.3 Hz, 1H, C3H), 6.72 (dd, $^3J_{HH}$ = 14.7 Hz, $^3J_{HH}$ = 11.1 Hz, 1H), 6.55 (dd, $^3J_{HH}$ = 14.7 Hz, $^3J_{HH}$ = 10.9 Hz, 1H), 6.49 – 6.22 (m, 6H), 6.17 (dd, $^3J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 10.4 Hz, 1H), 5.90 (d, $^3J_{HH}$ = 15.2 Hz, 1H, C2H), 5.79 (dt, $^3J_{HH}$ = 15.1 Hz, $^3J_{HH}$ = 7.6 Hz, 1H, C13H), 4.20 (q, $^3J_{HH}$ = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.10 – 3.84 (m, 9H, 8 × acetonide OCH, C15H), 3.04 (dd, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 4.2 Hz, 1H, C35H), 2.38 – 2.29 (m, 2H, $C14H_2$), 1.78 – 1.40 (m, 21H), 1.45 (s, 3H, *syn*-acetonide CH_3), 1.46 (s, 3H, *syn*-acetonide CH_3), 1.34 (s, 6H, 2 × *syn*-acetonide CH_3), 1.32 (s, 12 H, 4 × *anti*-acetonide CH_3), 1.30 (m, 3H, $CO_2CH_2CH_3$) 1.20 – 1.09 (m, 2H, CH_2), 0.97 (d, $^3J_{HH}$ = 6.5 Hz, 3H, C39), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.88 (dd, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 3.8 Hz, 6H, $C37H_3$, $C38H_3$), 0.11 (s, 6H, $Si(CH_3)_2$) ppm.

^{13}C NMR: (126 MHz, CD_3OD) δ 167.0 (C=O), 146.2 (C3), 142.7 (CH), 139.1 (CH), 137.2 (CH), 136.0 (CH), 134.5 (CH), 133.4 (CH), 133.0 (C13), 132.9 (CH), 132.5 (CH), 130.8 (CH), 120.9 (C1), 101.5 (*anti*-acetonide C), 99.8 (*syn*-acetonide C), 80.7 (C16), 70.5 (acetonide OCH), 69.6 (acetonide OCH), 67.1 (acetonide OCH), 64.4 (acetonide OCH), 64.1 (acetonide OCH), 61.4 ($CO_2\underline{C}H_2CH_3$), 43.4 (CH_2), 43.1 (C14), 39.8 (CH_2), 38.2 (diastereotopic CH_2), 36.1 (CH), 35.0 (CH_2), 32.0 ($OCH\underline{C}H(CH_3)_2$), 30.6 ($HOCH\underline{C}HCH_3$), 30.6 (*syn*-acetonide CH_3), 30.5 (*syn*-acetonide CH_3), 26.5 ($SiC(\underline{C}H_3)_3$), 25.3 (2 × *anti*-acetonide CH_3, 25.1 (2 × *anti*-acetonide CH_3), 20.7 (*syn*-acetonide CH_3), 20.1 (*syn*-acetonide CH_3), 20.0 (C37 or C38), 19.1 (C39), 19.0 ($Si\underline{C}(CH_3)_3$), 14.6 ($CO_2CH_2\underline{C}H_3$), 13.7 (C37 or C38), −3.7 ($SiCH_3$), −4.2 ($SiCH_3$) ppm.

NMR spectra included in section **6.5**

Protected bahamaolide A (224)



Ester saponification

According to a modified literature procedure,[109] aq. LiOH (1.0 M, 0.19 mL, 0.19 mmol, 65 equiv) was added to a stirred solution of hexaenoate **182** (3.0 mg, 2.9 µmol, 1.0 equiv) in a mixture of THF:H_2O:MeOH (0.80 mL:0.20 mL). The resulting mixture was stirred at ambient temperature for 5 h. The reaction was diluted with H_2O (1.5 mL) and EtOAc (1.5 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (5 × 1.5 mL) and the combined organics were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was taken forward to the next step with no additional purification.

TLC: R_f = 0.06 (2:1 hexane:EtOAc, anisaldehyde).

Formation of mixed anhydride

NEt_3 (0.0400 M in THF, 0.750 mL, 29.9 µmol, 10.3 equiv) then 2,4,6-trichlorobenzoyl chloride (0.0400 M in THF, 0.460 mL, 18.2 µmol, 6.25 equiv) were added to the crude seco-acid **222** under an atmosphere of N_2. The resulting mixture was stirred at ambient temperature for 3 h before being filtered through a Celite® pad, which had been pre-washed with 5.0 mL of anhydrous THF and then rinsed with excess anhydrous THF (10 mL). The filtrate was concentrated and used directly in the next step with no additional purification.

Macrolactonisation

A solution of the mixed anhydride **223** in anhydrous toluene (1.50 mL, 2.00 mM) was added slowly (syringe pump, 2 mL/h) to a stirred solution of DMAP (7.1 mg, 58 µmol, 20 equiv) in anhydrous toluene (5.80 mL, 0.500 mM) at ambient temperature under an atmosphere of N_2. After the addition was complete, the syringe was washed with anhydrous toluene (0.50 mL + 0.30 mL), which was also added to the reaction. The resulting mixture was stirred at 40 °C for 12 h, after which the solvent was removed under reduced pressure. The cloudy oil was diluted with hexane:EtOAc (1:1) and filtered through a plug of silica gel on top of a pad of Celite® (washing with hexane:EtOAc 1:1) and the filtrate concentrated to afford protected bahamaolide A (**224**) (2.3 mg, 2.3 µmol, 80%) as a yellow film.

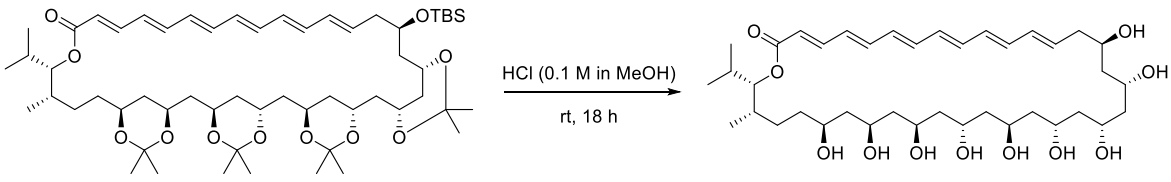
TLC: R_f = 0.43 (2:1 hexane:EtOAc, anisaldehyde).

N.B. This procedure was conducted in the dark and all manipulations in low/red lighting.

Sammakia has shown that the corresponding intermediate in the synthesis of dermostatin A is not stable to HPLC purification[111] *and so* **224** *was characterised by HRMS only and then carried forward to the deprotection step.*

HRMS (*m/z*): (MALDI) calculated for $C_{57}H_{94}NaO_{11}Si$ $[M+Na]^+$ 1005.6458 found 1005.6468.

Bahamaolide A



224

Protected bahamaolide A (**224**) (2.3 mg, 2.3 µmol, 1.0 equiv) was treated with HCl (0.10 M in MeOH, 2.0 mL). The reaction was stirred at ambient temperature for 18 h and checked by TLC and LC-MS analysis, which indicated consumption of **224** and product formation, respectively. The reaction mixture was neutralised by the dropwise addition of Et_3N and concentrated under reduced pressure to afford crude bahamaolide as a yellow powder (1.4 mg crude, *ca*. 45% NMR yield over 3 steps from **182** using dimethoxymethane as an internal standard). LC-MS analysis suggested the presence of other minor alkene isomers (additional small peaks in UV trace with $[M+H]^+$ and $[M+Na]^+$ matching bahamaolide A). This isomeric mixture was separated by reverse phase preparative HPLC (Agilent Zorbax C18, 50 × 10 mm,

5 µm, isocratic MeCN:H_2O 38:62, flow rate 2 mL/min, UV detector at 360 nm, retention time 23.5 min) to obtain an analytical sample of synthetic bahamaolide A.

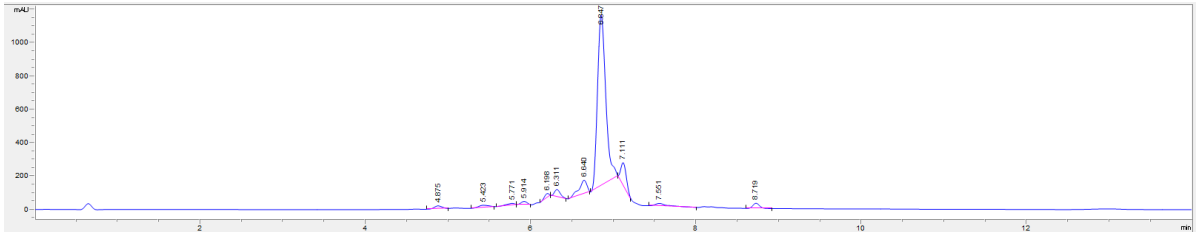
N.B. This procedure was conducted in the dark and all manipulations in low/red lighting. There have been a number of reported stability issues encountered with the polyene moiety in the total synthesis of related natural products.[63,94,95,109,111] Varying levels of decomposition were observed after hydrolysis of **182** and during macrolactonisation, in addition to the isomerisation evident in the LC-MS UV trace for crude bahamaolide. Considerable isomerisation and degradation was also observed when the HPLC solvent system contained 0.05% formic acid additive. This along with ongoing problems with the reverse phase preparative HPLC instrument available greatly limited the amount of pure bahamaolide A that could be isolated for NMR analysis.

Analytical LC conditions:

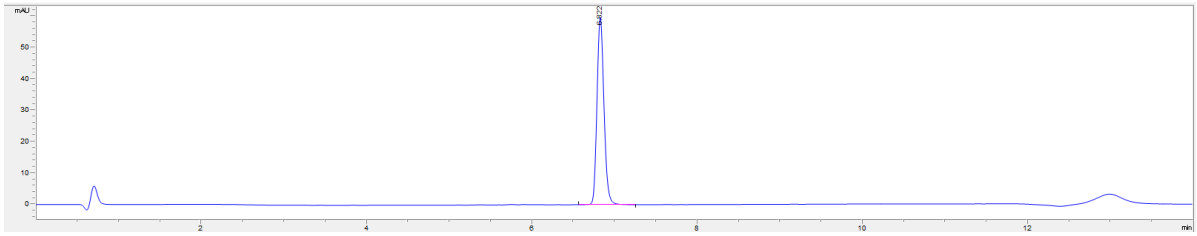
Agilent InfinityLab Poroshell 120 EC-C18, 50 × 3.0 mm, 2.7 µm

10–90% MeCN in H_2O over 8 min, flow rate 0.5 mL/min, UV detector at 360 nm, t_R 6.8 min.

Before reverse phase preparative HPLC purification:



After reverse phase preparative HPLC purification:



All recorded spectroscopic data matched that reported for natural bahamaolide A.[65]

^{1}H NMR: (500 MHz, CD_3OD) δ 7.37 (dd, $^3J_{HH}$ = 15.1 Hz, $^3J_{HH}$ = 11.5 Hz, 1H, C3H), 6.75 (dd, $^3J_{HH}$ = 14.7 Hz, $^3J_{HH}$ = 11.1 Hz, 1H, C5H), 6.57 (dd, $^3J_{HH}$ = 14.6 Hz, $^3J_{HH}$ = 10.9 Hz, 1H, C7H), 6.50 – 6.31 (m, 5H), 6.28 (dd, $^3J_{HH}$ = 14.6 Hz, $^3J_{HH}$ = 10.2 Hz, 1H, C10H), 6.22 (dd, $^3J_{HH}$ =15.2 Hz, $^3J_{HH}$ = 10.2 Hz, 1H, C12H), 5.96 (d, $^3J_{HH}$ = 15.2 Hz, 1H, C2H), 5.90 (dt, $^3J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 7.6 Hz, 1H, C13H), 4.19 – 3.87 (m, 8H, C35H, 7 × C<u>H</u>(OH)), 3.80 (m, 1H,

C<u>H</u>(OH)), 3.60 (m, 1H, C<u>H</u>(OH)), 2.66 (m, 1H, C34H), 2.44 (m, 1H, C14*H*^{a}H^{b}), 2.35 (m, 1H, C14H^{a}*H*^{b}), 2.21 – 1.00 (m, 21H), 0.95 (d, $^{3}J_{HH}$ =7.1 Hz, 3H, C39H$_3$), 0.93 (d, $^{3}J_{HH}$ = 6.9 Hz, 3H, C37H$_3$), 0.89 (d, $^{3}J_{HH}$ = 6.8 Hz, 3H, C38H$_3$) ppm.

^{1}H NMR: (700 MHz, pyridine-d$_5$) **see ***Table 16***

^{13}C NMR: (176 MHz, pyridine-d$_5$) **see ***Table 16***

Due to sample quantity limitation, δ^{13}C were extracted from HSQC and HMBC.

NMR spectra included in section ***6.5*

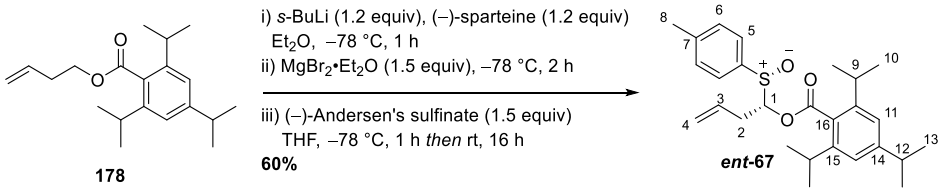
HRMS (*m/z*): (APCI) calculated for $C_{39}H_{64}O_{11}$ $[M+H]^+$ 709.4521, found 709.4515.

IR (ν_{max}/cm^{-1}, neat): 3358 (br), 2919, 2850, 1632 and 1541.

$[\alpha]_D^{22}$**:** −200 (*c* = 0.01, MeOH). Isolated[65] $[\alpha]_D^{25}$**:** −190 (*c* = 0.01, MeOH).

6.4 Towards the Total Synthesis of Mycapolyol E

(*R*)-1-((*R*)-*p*-tolylsulfinyl)but-3-en-1-yl 2,4,6-triisopropylbenzoate (*ent*-67)



According to the literature procedure,[47] *s*-BuLi (1.30 M in hexanes, 30.5 mL, 39.7 mmol, 1.20 equiv) was added slowly (syringe pump, 0.3 mL/min) to a stirred solution of (−)-sparteine (9.12 mL, 39.7 mmol, 1.20 equiv) and benzoate **178** (10.0 g, 33.1 mmol, 1.00 equiv) in anhydrous Et_2O (110 mL, 0.300 M) at −78 °C (acetone/dry ice) under N_2. The reaction mixture was stirred at −78 °C for 1 h before the addition of freshly prepared* $MgBr_2 \cdot Et_2O$ (1.50 equiv) *via* cannula. After a further 2 h at −78 °C, (−)-Andersen's sulfinate (14.6 g, 49.6 mmol, 1.50 equiv) in THF (50.0 mL, 1.00 M) was added slowly (syringe pump, 0.5 mL/min). The reaction mixture was stirred at −78 °C for 1 h then the cooling bath was removed and the mixture allowed to warm to ambient temperature overnight. The reaction was quenched with 2 M aq. HCl (120 mL), the phases were separated and the organics washed with 2 M aq. HCl (4 × 50 mL). The combined aqueous phase were extracted with Et_2O (3 × 120 mL). The combined organics were washed with sat. aq. $NaHCO_3$ (120 mL) and brine (120 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

Purification was aided by silylation of the menthol by-product: The crude mixture was stirred under vacuum for 1 h then dissolved in anhydrous CH_2Cl_2 (66.0 mL, 0.500 M). Triethylamine (6.91 mL, 49.6 mmol, 1.50 equiv) was added followed by the dropwise addition of TMSCl (5.45 mL, 43.0 mmol, 1.30 equiv). The resulting mixture was stirred at ambient temperature under N_2 for 2 h. The reaction mixture was diluted with Et_2O (70 mL), washed with water (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 90:10 to 0:100 pentane:Et_2O) to remove TMS-menthol and most of the excess Anderse

n's sulfinate, then on a Biotage Isolera One system (dry loaded, split into 2 batches, 2 × 100 g Ultra column, 93:7 hexane:EtOAc) to afford α-sulfinyl benzoate ***ent*-67** (8.73 g, 19.8 mmol, 60%, >99:1 *er*, >95:5 *dr*) as a white solid.

*Preparation of $MgBr_2 \cdot OEt_2$: To a flame dried 2 necked flask fitted with a reflux condenser under N_2 was charged oven dried magnesium turnings (3.22 g, 132 mmol, 4.00 equiv) and anhydrous Et_2O (62.0 mL, 0.800 M wrt 1,2-dibromoethane). To this stirred suspension was added 1,2-dibromoethane (0.10 mL) and the resulting suspension was gently heated until the reaction initiated. Following initiation, 1,2-dibromoethane (4.17 mL, 49.6 mmol (total volume 4.27 mL)) was added dropwise at a rate determined by the vigorousness of the reaction. Upon completion of the addition of 1,2-dibromoethane, the reaction was biphasic with a colourless upper layer and a grey bottom layer. After gas evolution had stopped, the mixture was stirred for 30 min at ambient temperature. Both layers were transferred to the main reaction vessel by cannula. The unreacted Mg was cooled to 0 °C (water/ice) and quenched through the slow addition of an appropriate amount of 2 M aq. HCl.

All recorded spectroscopic data matched that previously reported.[47]

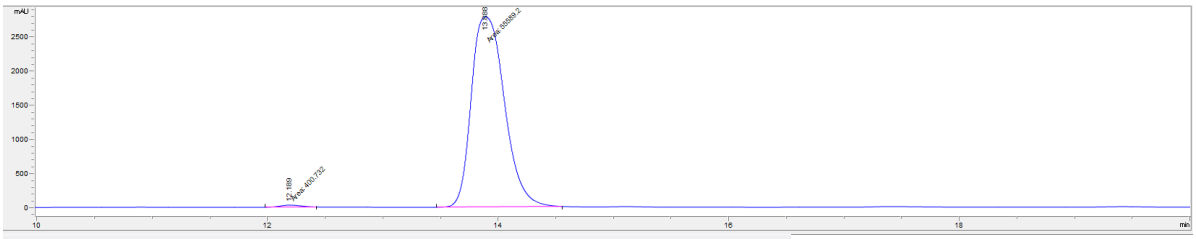
TLC: R_f = 0.30 (80:20 hexane:EtOAc, PMA).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.66 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2 × C5H), 7.37 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2 × C6H), 7.04 (s, 2H, 2 × C11H), 5.75 (dd, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 3.1 Hz, 1H, C1H), 5.66 (m, 1H, C3H), 5.12 – 5.05 (m, 2H, $C4H_2$), 2.92 (sept, $^3J_{HH}$ = 6.8 Hz, 2H, 2 × C9), 2.91 (sept, $^3J_{HH}$ = 6.9 Hz, 1H, C12H), 2.72 (m, 1H, $C2H^aH^b$), 2.44 (s, 3H, $C8H_3$), 2.41 (m, 1H, $C2H^aH^b$), 1.29 – 1.22 (m, 18H, 4 × $C10H_3$, 2 × $C13H_3$) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 170.5 (C=O), 151.0 (C14), 145.4 (2 × C15), 141.9 (Tol CS), 137.5 (C7), 131.6 (C3), 130.2 (2C, 2 × C6), 128.9 (C16), 124.6 (2C, 2 × C5), 121.1 (2C, 2 × C11), 119.4 (C4), 91.6 (C1), 34.6 (C12), 31.7 (C2), 28.0 (2C, 2 × C9), 24.6 (2C, 2 × CH_3), 24.3 (2C, 2 × CH_3), 24.1 (2C, 2 × CH_3), 21.6 (C8) ppm.

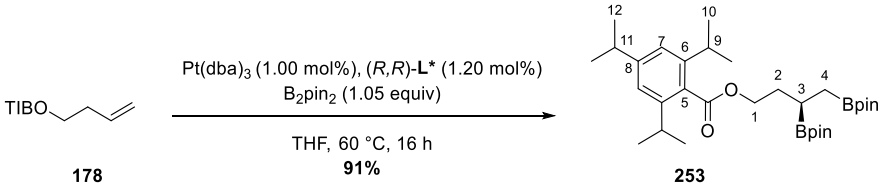
Chiral HPLC: (Daicel Chiralcel-IA column (25 cm) with guard, hexane:isopropanol 95:5, 0.5 mL/min, ambient temperature, 210.8 nm): t_R = 12.2 minutes (minor), 13.9 minutes (major), *er* >99:1.

Chiral HPLC conditions previously reported and used in-house,[47] the enantiomer was also synthesised by the author and was available for comparison.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.189	MM	400.7	30.9	0.2164	0.716	0.872
2	13.888	MM	55589.2	2779.3	0.3334	99.284	0.751

(*R*)-3,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl 2,4,6-triisopropylbenzoate (253)



178 **253**

According to a literature procedure,[50] anhydrous THF (16.5 mL, 1.00 M) was added to a mixture of $Pt(dba)_3$ (148 mg, 0.165 mmol, 1.00 mol%), (*R*,*R*)-**L*** (180 mg, 0.198 mol, 1.20 mol%) and B_2pin_2 (4.41 g, 17.4 mmol, 1.05 equiv) under N_2 and the mixture was stirred at 80 °C (oil bath) for 30 min. The reaction mixture was cooled to ambient temperature, alkene **178** (5.00 g, 16.5 mmol, 1.00 equiv) was added and the reaction mixture was stirred at 60 °C (oil bath) for 16 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude brown oil was purified by flash column chromatography (SiO_2, 85:15 pentane:Et_2O) to afford 1,2-bis(boronic ester) **253** (8.35 g, 15.0 mmol, 91%, 98:2 *er*) as a viscous yellow oil.

TLC: R_f = 0.40 (80:20 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.98 (s, 2H, 2 × C7H), 4.36 – 4.30 (m, 2H, C1H_2), 2.87 (sept, $^3J_{HH}$ = 6.9 Hz, 1H, C11H), 2.87 (sept, $^3J_{HH}$ = 6.8 Hz, 2H, 2 × C9H), 1.91 (m, 1H, C2H^aH^b), 1.74 (m, 1H, C2H^aH^b), 1.33 – 1.13 (m, 43H, 4 × C10H_3, 2 × C12H_3, 8 × pinacol-CH_3, C3H), 0.95 – 0.83 (m, 2H, C4H_2) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.1 (C=O), 150.0 (C8), 144.9 (2C, 2 × C6), 131.1 (C5), 120.9 (2C, 2 × C7), 83.1 (2C, 2 × pinacol-C), 83.1 (2C, 2 × pinacol-C), 64.7 (C1), 34.6 (C11), 32.2 (C2), 31.6 (2C, 2 × C9), 25.0 (2C, 2 × CH_3), 25.0 (4C, 4 × CH_3), 24.9 (2C, 2 × CH_3), 24.3 (2C, 2 × CH_3), 24.3 (2C, 2 × CH_3), 24.1 (2C, 2 × CH_3) ppm.

carbon next to boron not observed due to quadrupolar relaxation

HRMS (*m/z*): (ESI) calculated for $C_{32}H_{54}{}^{11}B_2O_6$ [*M*+Na]$^+$ 579.4010, found 579.4005.

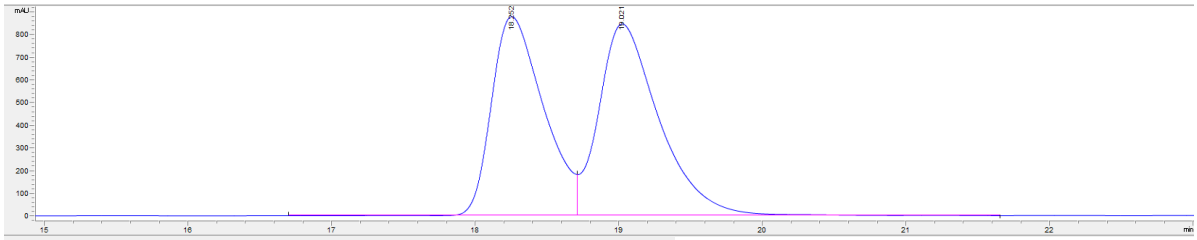
IR (ν_{max}/cm^{-1}, neat): 2962, 1723, 1370, 1315, 1250, 1138, 1105 and 1076.

$[\alpha]_D^{23}$: −75.1 (*c* = 0.9, $CHCl_3$).

An aliquot of *bis*(boronic ester) **253** was oxidised to the corresponding diol using basic H_2O_2 in order to determine the enantiomeric ratio by chiral HPLC.

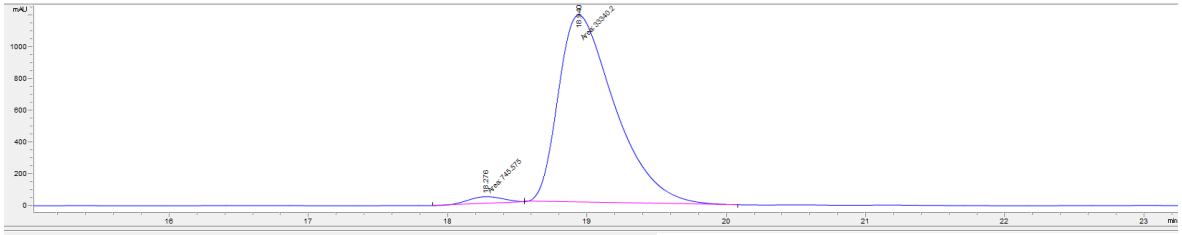
Chiral HPLC: (Daicel Chiralcel-IB column (25 cm) with guard, hexane:isopropanol 95:5, 0.5 mL/min, ambient temperature, 210.8 nm): t_R = 18.3 minutes (minor), 18.9 minutes (major), *er* = 98:2.

Racemic sample:



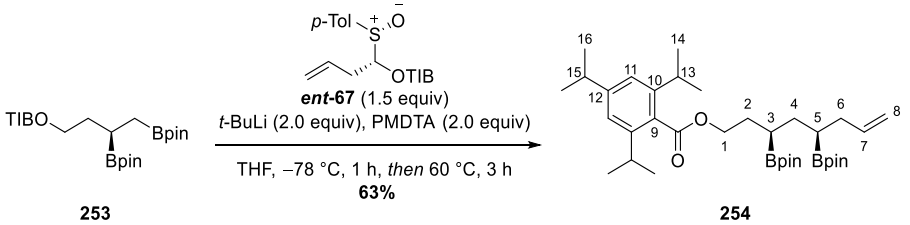
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	18.252	VV R	22066.5	877.4	0.3717	47.046	0.607
2	19.021	VV R	24837.2	844.8	0.4351	52.954	0.587

Diol from **253**:



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	18.276	MM	745.6	42.5	0.2927	2.187	1.14
2	18.94	MM	33340.2	1181.2	0.4704	97.813	0.547

(3*R*,5*S*)-3,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-7-en-1-yl 2,4,6-triisopropylbenzoate (254)



PMDTA (0.730 mL, 3.50 mmol, 1.95 equiv) and anhydrous THF (13.5 mL, 0.200 M wrt ***ent*-67**) were added to 1,2-bis(boronic ester) **253** (1.00 g, 1.80 mmol, 1.00 equiv) and α-sulfinyl benzoate ***ent*-67** (1.19 g, 2.70 mmol, 1.50 equiv) under N_2. The mixture was cooled to −78 °C (acetone/dry ice) before the dropwise addition of *t*-BuLi (2.80 M in heptane, 1.25 mL, 3.50 mmol, 1.95 equiv). The reaction mixture was stirred at −78 °C for 1 h then 60 °C (oil bath) for 3 h. The reaction mixture was then cooled to ambient temperature and diluted with sat. aq. NH_4Cl (20 mL) and Et_2O (20 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on a Biotage Isolera One system (50 g Ultra column, EtOAc:hexane 2:98 to 20:80) to afford 1,3-bis(boronic ester) **254** (695 mg, 1.14 mmol, 63%, >95:5 *dr*) as a viscous yellow oil.

TLC: R_f = 0.32 (85:15 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.98 (s, 2 × C11H), 5.78 (ddt, $^3J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, C7H), 5.00 (ddt, $^3J_{HH}$ = 17.1 Hz, $^2J_{HH}$ = 2.2 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, C8H^aH^b), 4.93 – 4.89 (ddt, $^3J_{HH}$ = 10.1 Hz, $^2J_{HH}$ = 2.2 Hz, $^4J_{HH}$ = 1.1 Hz, 1H, C8H^aH^b), 4.37 – 4.23 (m, 2H, C1H_2), 2.86 (sept, $^3J_{HH}$ = 6.8 Hz, 3H, 2 × C13H, C15H), 2.22 – 2.06 (m, 2H, C6H_2), 1.86 – 1.73 (m, 2H, C2H_2), 1.64 (m, 1H, C3H), 1.32 – 1.11 (m, 45H, 4 × C14H_3, 2 × C16H_3, 8 × pinacol-CH_3, C4H_2, C5H) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.0 (C=O), 150.0 (C12), 144.9 (2C, 2 × C10), 138.6 (C7), 131.1 (C9), 120.9 (2C, 2 × C11), 115.0 (C8), 83.2 (2C, 2 × pinacol-C), 83.1 (2C, 2 × pinacol-C), 64.9 (C1), 35.2 (C6), 34.6 (C15), 31.6 (2C, 2 × C13), 31.3 (C4), 29.8 (C2), 25.0 (2C, 2 × CH_3), 25.0 (2C, 2 × CH_3), 24.9 (2C, 2 × CH_3), 24.9 (2C, 2 × CH_3), 24.3 (4C, 4 × CH_3), 24.1 (2C, 2 × CH_3) ppm.

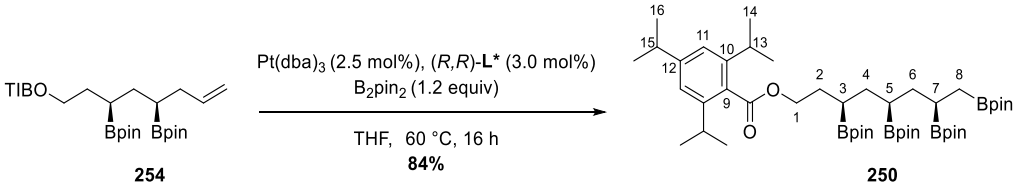
carbon next to boron not observed due to quadrupolar relaxation

HRMS (*m/z*): (ESI) calculated for $C_{36}H_{60}{}^{11}B_2O_6$ $[M+Na]^+$ 633.4480, found 633.4498.

IR (ν_{max}/cm^{-1}, neat): 2962, 2928, 1724, 1462, 1379, 1371, 1316, 1250, 1140 and 1076.

$[\alpha]_D^{24}$: −71.0 (*c* = 1, $CHCl_3$).

(3*R*,5*R*,7*R*)-3,5,7,8-tetrakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octyl 2,4,6-triisopropylbenzoate (250)



According to a modified literature procedure,[50] anhydrous THF (1.10 mL, 1.00 M) was added to a mixture of $Pt(dba)_3$ (25.5 mg, 28.4 µmol, 2.50 mol%), (*R*,*R*)-**L*** (31.0 mg, 34.1 µmol, 3.00 mol%) and B_2pin_2 (0.346 g, 1.36 mmol, 1.20 equiv) under N_2 and the mixture was stirred at 80 °C (oil bath) for 30 min. The reaction mixture was cooled to ambient temperature, alkene **254** (0.694 g, 1.14 mmol, 1.00 equiv) was added and the reaction mixture was stirred at 60 °C (oil bath) for 16 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude brown oil was purified by flash column chromatography (SiO_2, 80:20 pentane:Et_2O) to afford tetra(boronic ester) **250** (0.827 g, 0.957 mmol, 84%, 8:1 *dr*) as a viscous oil which solidified under high vacuum to an amorphous white solid.

TLC: R_f = 0.26 (75:25 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.96 (s, 2H, 2 × C11H), 4.31 – 4.23 (m, 2H, C1H_2), 2.85 (app. sept, $^3J_{HH}$ = 6.7 Hz, 3H, C15H, 2 × C13H), 1.86 (m, 1H, C2*H*^{a}H^b), 1.75 (m, 1H, C2H^a*H*^{b}), 1.62 – 1.54 (m, 2H, C2*H*^{a}H^b, C4*H*^{a}H^b), 1.40 (m, 1H, C4H^a*H*^{b}), 1.33 (m, 1H, C2H^a*H*^{b}), 1.27 – 1.06 (m, 69H, 4 × C14H_3, 2 × C16H_3, 16 × pinacol-CH_3, C3H, C5H, C7H), 0.87 (dd, $^2J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 4.3 Hz, 1H, C8*H*^{a}H^b), 0.76 (dd, $^2J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 10.7 Hz, 1H, C8H^a*H*^{b}) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 171.1 (C=O), 149.9 (C12), 144.9 (2C, 2 × C10), 131.2 (C9), 120.8 (2C, 2 × C11), 83.0 (2C, 2 × pinacol-C), 82.8 (2C, 2 × pinacol-C), 82.7 (2C, 2 × pinacol-C), 82.7 (2C, 2 × pinacol-C), 65.2 (C1), 34.6 (C16), 34.5 (C4), 32.2 (C2), 31.5 (2C, 2

× C13), 29.3 (C6), 25.2 (2C, 2 × CH_3), 25.0 (2C, 2 × CH_3), 25.0 (2C, 2 × CH_3), 25.0 (2C, 2 × CH_3), 25.00 (2C, 2 × CH_3), 24.9 (6C, 6 × CH_3), 24.4 (4C, 4 × CH_3), 24.1 (2C, 2 × CH_3), 21.3 (CHB), 19.7 (CHB), 17.7 (CHB), 12.0 (C8) ppm.

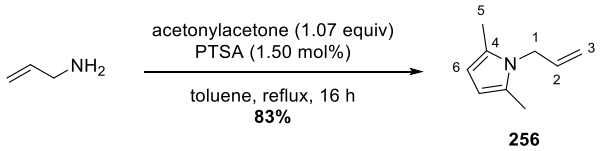
NMR spectra included in section **6.5**

HRMS (*m/z*): (MALDI) calculated for $C_{48}H_{84}{}^{11}B_4O_{10}$ [*M*+Na]$^+$ 887.6358, found 887.6366.

IR (ν_{max}/cm^{-1}, neat): 2975, 2929, 1724, 1377, 1370, 1310, 1251, 1214, 1141, 1106 and 1076.

$[\alpha]_D^{24}$: −99.0 (*c* = 0.8, $CHCl_3$).

1-Allyl-2,5-dimethyl-1*H*-pyrrole (256)



256

Acetonyl acetone (11.0 mL, 93.7 mmol, 1.07 equiv) was added to a stirred solution of allylamine (6.60 mL, 87.6 mmol, 1.00 equiv) and PTSA (0.250 g, 1.31 mmol, 1.50 mol%) in toluene (350 mL, 0.250 M) and the resulting reaction mixture was refluxed (oil bath at 115 °C, using Dean Stark apparatus) for 16 h. The reaction mixture was then cooled to ambient temperature and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 90:10 pentane:Et_2O) to afford pyrrole **256** (9.87 g, 73.0 mmol, 83% yield) as a yellow oil.

All recorded spectroscopic data matched that previously reported.[216]

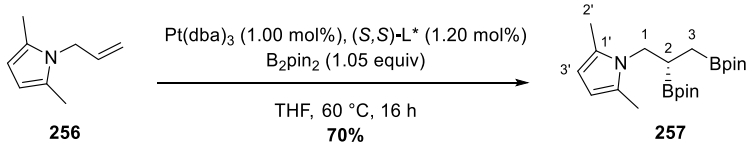
TLC: R_f = 0.61 (80:20 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.34 (m, 1H, C2H), 5.80 (s, 2H, 2 × C6H), 5.10 (dd, $^3J_{HH}$ = 10.3 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, C3H^aH^b), 4.73 (dq, $^3J_{HH}$ = 17.0 Hz, $^4J_{HH}$ = 1.3 Hz, 1H, C3H^aH^b), 4.38 – 4.35 (dt, $^3J_{HH}$ = 4.2 Hz, $^4J_{HH}$ = 1.3 Hz, 2H, C1H_2), 2.18 (s, 6H, 2 × C5H_3) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 134.2 (2C, 2 × C4), 127.8 (C2), 115.7 (C3), 105.2 (2C, 2 × C6), 45.7 (C1), 12.4 (2C, 2 × C5) ppm.

HRMS (*m/z*): (ESI) calculated for $C_9H_{12}N$ [*M*+H]$^+$ 136.1121, found 136.1123.

(*S*)-1-(2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)-2,5-dimethyl-1*H*-pyrrole (257)



According to a literature procedure,[50] anhydrous THF (0.740 mL, 1.00 M) was added to a mixture of $Pt(dba)_3$ (6.6 mg, 7.4 µmol, 1.0 mol%), (*S*,*S*)-**L*** (8.1 mg, 8.9 µmol, 1.2 mol%) and B_2pin_2 (0.197 g, 0.777 mmol, 1.05 equiv) under N_2 and the mixture was stirred at 80 °C (oil bath) for 30 min. The reaction mixture was cooled to ambient temperature, alkene **256** (0.100 g, 0.740 mmol, 1.00 equiv) was added and the reaction mixture was stirred at 60 °C (oil bath) for 16 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude brown oil was purified by flash column chromatography (SiO_2, 80:20 pentane:Et_2O) to afford 1,2-bis(boronic ester) **257** (202 mg, 0.519 mmol, 70%, 97:3 *er*) as a viscous yellow oil.

TLC: R_f = 0.28 (80:20 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.72 (s, 2H, 2 × C3'H), 3.91 (dd, $^2J_{HH}$ = 14.5 Hz, $^3J_{HH}$ = 6.0 Hz, 1H, C1*H*^{a}H^b), 3.64 (dd, $^2J_{HH}$ = 14.5 Hz, $^3J_{HH}$ = 10.6 Hz, 1H, C1H^a*H*^{b}), 2.22 (s, 6H, 2 × C2'H_3), 1.64 (m, 1H, C2H), 1.24 – 1.20 (m, 24H, 8 × pinacol-CH_3), 0.82 – 0.71 (m, 2H, C3H_2) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 128.2 (2C, 2 × C1'), 104.9 (2C, 2 × C3'), 83.4 (2C, 2 × pinacol-C), 83.2 (2C, 2 × pinacol-C), 46.4 (C1), 25.0 (4C, 4 × pinacol-CH_3), 24.8 (4C, 4 × pinacol-CH_3), 13.1 (2C, 2 × C2') ppm.

carbon next to boron not observed due to quadrupolar relaxation

HRMS (*m/z*): (ESI) calculated for $C_{21}H_{37}{}^{11}B_2NO_4$ [*M*+Na]$^+$ 412.2808, found 412.2804.

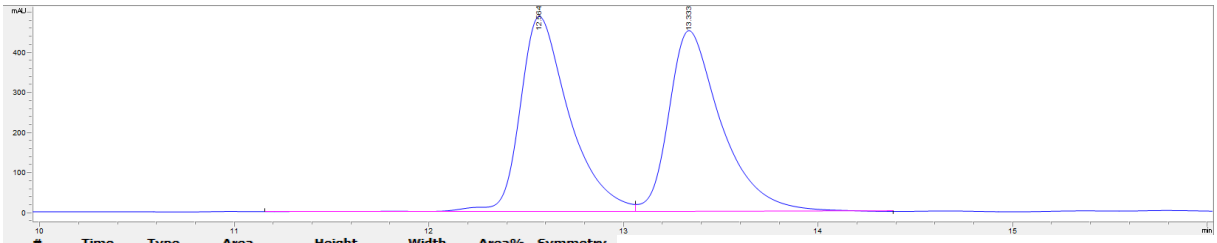
IR (ν_{max}/cm^{-1}, neat): 2977, 2931, 1369, 1316, 1251, 1214 and 1141.

$[\alpha]_D^{24}$: −106.7 (*c* = 0.9, $CHCl_3$).

An aliquot of 1,2-bis(boronic ester) **257** was oxidised to the corresponding diol using basic H_2O_2 in order to determine the enantiomeric ratio by chiral HPLC.

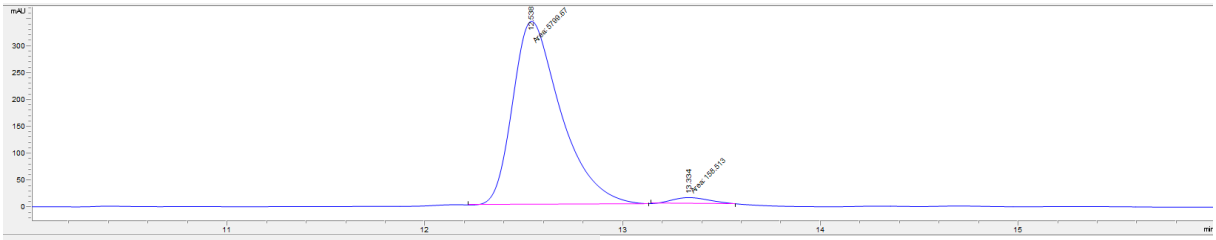
Chiral HPLC: (Daicel Chiralcel-IB column (25 cm) with guard, hexane:isopropanol 85:15, 0.5 mL/min, ambient temperature, 210.8 nm): t_R = 12.5 minutes (major), 13.3 minutes (minor), *er* = 97:3.

Racemic sample:



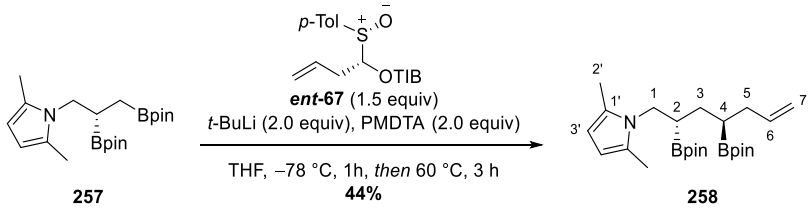
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.564	VV R	8541.4	485.6	0.258	50.239	0.619
2	13.333	VB	8460.2	450.3	0.2781	49.761	0.578

Diol from **257**:



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.538	MM	5799.7	342.2	0.2825	97.340	0.626
2	13.334	MM	158.5	11.7	0.2257	2.660	0.797

1-((2*S*,4*S*)-2,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-1-yl)-2,5-dimethyl-1*H*-pyrrole (258)



PMDTA (0.730 mL, 3.51 mmol, 1.95 equiv) and anhydrous THF (13.5 mL, 0.200 M wrt ***ent*-67**) were added to a mixture of bis(boronic ester) **257** (0.700 g, 1.80 mmol, 1.00 equiv) and α-sulfinyl benzoate ***ent*-67** (1.19 g, 2.70 mmol, 1.50 equiv) under N_2. The mixture was cooled to −78 °C (acetone/dry ice) before the dropwise addition of *t*-BuLi (2.80 M in heptane, 1.25 mL, 3.51 mmol, 1.95 equiv). The reaction mixture was stirred at −78 °C for 1 h then 60 °C (oil bath) for 3 h. The reaction mixture was then cooled to ambient temperature and diluted with sat. aq. NH_4Cl (20 mL) and Et_2O (20 mL). The phases were separated and the

aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on a Biotage Isolera One system (100 g Ultra column, 98:2 to 80:20 hexane:EtOAc) to afford 1,3-bis(boronic ester) **258** (0.354 g, 0.799 mmol, 44%, >95:5 *dr*) as a viscous yellow oil.

TLC: R_f = 0.52 (80:20 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.78 (ddt, $^3J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 6.9 Hz, 1H, C6H), 5.68 (s, 2H, 2 × C3'H), 4.99 (dq, $^3J_{HH}$ = 17.1 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, C7H^aH^b), 4.93 (dq, $^3J_{HH}$ = 10.0 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, C7H^aH^b), 3.77 (dd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 9.0 Hz, 1H, C1H^aH^b), 3.68 (dd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 9.0 Hz, 1H, C1H^aH^b), 2.23 (s, 6H, 2 × C2'H_3), 2.21 – 2.04 (m, 2H, C5H_2), 1.71 (m, 1H, C2H), 1.50 – 1.39 (m, 2H, C3H_2), 1.20 (s, 12H, 4 × pinacol H_3), 1.18 (s, 6H, 2 × pinacol H_3), 1.12 (s, 6H, 2 × pinacol H_3), 1.06 (m, 1H, C4H) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 138.5 (C6), 127.9 (2C, 2 × C1'), 115.1 (C7), 105.1 (2C, 2 × C3'), 83.3 (2C, 2 × pinacol-C), 83.1 (2C, 2 × pinacol-C), 45.7 (C1), 36.6 (C5), 30.7 (C3), 25.3 (2C, 2 × pinacol-CH_3), 25.0 (2C, 2 × pinacol-CH_3), 25.0 (2C, 2 × pinacol-CH_3), 24.6 (2C, 2 × pinacol-CH_3), 13.1 (2C, 2 × C2') ppm.

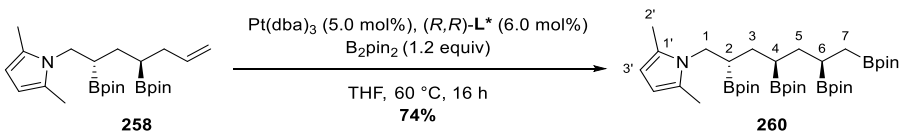
carbon next to boron not observed due to quadrupolar relaxation

HRMS (*m/z*): (ESI) calculated for $C_{25}H_{43}{}^{11}B_2NO_4$ $[M+Na]^+$ 466.3279, found 466.3225.

IR (ν_{max}/cm^{-1}, neat): 2976, 2927, 1406, 1379, 1371, 1317, 1299, 1213 and 1141.

$[\alpha]_D^{24}$: −43.5 (*c* = 1, $CHCl_3$).

2,5-dimethyl-1-((2*S*,4*R*,6*R*)-2,4,6,7-tetrakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptyl)-1*H*-pyrrole (260)



According to a modified literature procedure,[50] anhydrous THF (0.900 mL, 1.00 M) was added to a mixture of $Pt(dba)_3$ (40.5 mg, 45.1 µmol, 5.00 mol%), (*R*,*R*)-**L*** (49.2 mg, 54.1 µmol, 6.00 mol%) and B_2pin_2 (0.275 g, 1.08 mmol, 1.20 equiv) under N_2 and the mixture

was stirred at 80 °C (oil bath) for 30 min. The reaction mixture was cooled to ambient temperature, alkene **258** (0.400 g, 0.902 mmol, 1.00 equiv) was added and the reaction mixture was stirred at 60 °C (oil bath) for 16 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude brown oil was purified by flash column chromatography (SiO_2, 85:15 pentane:Et_2O) to afford tetra(boronic ester) **260** (465 mg, 0.667 mmol, 74%) as a viscous yellow oil which solidified under high vacuum to an amorphous light brown solid.

TLC: R_f = 0.23 (75:25 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.65 (s, 2H, 2 × C3'H), 3.73 (dd, $^2J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 9.0 Hz, 1H, C1H^aH^b), 3.67 (dd, $^2J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 9.0 Hz, 1H, C1H$^a H^b$), 2.22 (s, 6H, 2 × C2'H_3), 1.73 – 1.57 (m, 2H, C3H_2), 1.45 – 1.26 (m, 5H, C2H, C5H_2, C7H_2), 1.22 – 1.09 (m, 48H, 12 × pinacol-CH_3), 0.90 (m, 1H, C4H or C6H), 0.76 (dd, $^3J_{HH}$ = 15.8 Hz, $^3J_{HH}$ = 10.6 Hz, 1H, C4H or C6H) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 127.9 (2C, 2 × C1'), 105.0 (2C, 2 × C3'), 83.2 (2C, 2 × pinacol-C), 82.8 (4C, 4 × pinacol-C), 82.8 (2C, 2 × pinacol-C), 45.9 (C1), 35.2 (C3), 31.9 (C5), 25.3 (2C, 2 × pinacol-CH_3), 25.1 (2C, 2 × pinacol-CH_3), 25.1 (2C, 2 × pinacol-CH_3), 25.0 (2C, 2 × pinacol-CH_3), 25.0 (2C, 2 × pinacol-CH_3), 24.9 (2C, 2 × pinacol-CH_3), 24.9 (2C, 2 × pinacol-CH_3), 24.6 (2C, 2 × pinacol-CH_3), 13.1 (2C, 2 × C2') ppm.

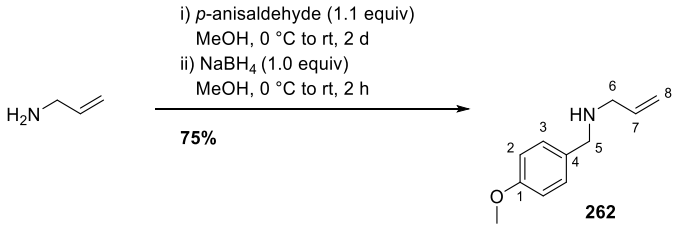
carbon next to boron not observed due to quadrupolar relaxation

IR (ν_{max}/cm^{-1}, neat): 2976, 2929, 1370, 1310, 1214, 1165, 1140 and 1108.

HRMS (*m/z*): (MALDI) calculated for $C_{37}H_{67}{}^{11}B_4NO_8$ [*M*+Na]$^+$ 720.5155, found 720.5166.

$[\alpha]_D^{24}$: −72.8 (*c* = 1.2, $CHCl_3$)

_N_-(4-methoxybenzyl)prop-2-en-1-amine (262)



According to the literature procedure, [161] *p*-anisaldehyde (2.34 mL, 19.3 mmol, 1.10 equiv) was added to allylamine (1.30 mL, 17.5 mmol, 1.00 equiv) in MeOH (20.0 mL, 0.875 M) at 0 °C. The reaction mixture was stirred at 0 °C (water/ice) for 2 h then ambient temperature for 2 days. The reaction mixture was cooled to 0 °C (water/ice) and sodium borohydride (0.660 g, 17.5 mmol, 1.00 equiv) was added portionwise. The reaction mixture was stirred for 2 h, warming slowly to ambient temperature, then concentrated under reduced pressure. The residue was redissolved in water (20 mL) and extracted with Et_2O (3 × 15 mL). The combined organics were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 100% Et_2O) to afford secondary amine **262** (2.32 g, 13.1 mmol, 75%) as a yellow liquid.

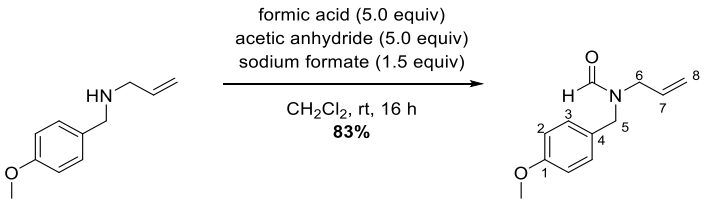
All recorded spectroscopic data matched that previously reported.[161]

TLC: R_f = 0.10 (100% Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.25 (d, $^3J_{HH}$ = 8.7 Hz, 2H, 2 × C2H), 6.87 (d, $^3J_{HH}$ = 8.7 Hz, 2H, 2 × C3H), 5.94 (ddt, $^3J_{HH}$ = 16.7 Hz, $^3J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 6.0 Hz, 1H, C7H), 5.20 (ddt, $^3J_{HH}$ = 16.7 Hz, $^4J_{HH}$ = 1.5 Hz, $^2J_{HH}$ = 1.4 Hz, 1H, C8H^aH^b), 5.12 (dd, $^3J_{HH}$ = 10.3 Hz, $^2J_{HH}$ = 1.4 Hz, C8H^aH^b), 3.81 (s, 3H, OMe), 3.74 (s, 2H, $C5H_2$), 3.27 (dt, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 1.5 Hz, 2H, $C6H_2$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 158.8 (C1), 137.0 (C7), 132.6 (2 × C3), 129.5 (C4), 116.1 (C8), 113.9 (2 × C2), 55.4 (OMe), 52.8 (C5), 51.8 (C6) ppm.

***N*-allyl-*N*-(4-methoxybenzyl)formamide (263)**



A mixture of formic acid (0.110 mL, 2.80 mmol, 5.00 equiv) and acetic anhydride (0.270 mL, 2.80 mmol, 5.00 equiv) was stirred at 50 °C (oil bath) for 20 min. The mixture was cooled to ambient temperature then sodium formate (58.0 mg, 0.846 mmol, 1.50 equiv) was added in one portion followed by secondary amine **262** (100 mg, 0.564 mmol, 1.00 equiv) in CH_2Cl_2 (1.40 mL, 0.400 M). The resulting mixture was stirred at ambient temperature overnight and then basified with 2 M aq. NaOH. The phases were separated and the organic phase was washed with water (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford formamide **263** (96.0 mg, 0.468 mmol, 83%) as a yellow oil, judged as sufficiently pure to be carried forward to the next step without purification.

TLC: R_f = 0.29 (100% Et_2O, $KMnO_4$).

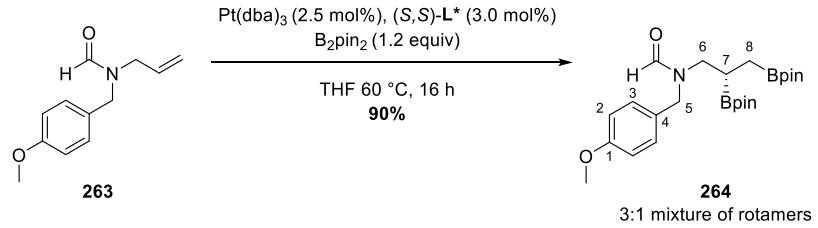
^{1}H NMR: (400 MHz, $CDCl_3$) [Note: **263** appears as a 1:1 mixture of two rotamers observable by ^{1}H NMR] δ [rotamer 1] 8.29 (s, 1H, NC(O)H), 7.10 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 2 × C3H), 6.87 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 2 × C2H), 5.68 (m, 1H, C7H), 5.18 – 5.07 (m, 2H, $C8H_2$), 4.29 (s, 2H, $C5H_2$), 3.82 (d, $^3J_{HH}$ = 6.2 Hz, 2H, $C6H_2$), 3.79 (d, $^5J_{HH}$ = 1.0 Hz, 3H, OMe) ppm. δ [rotamer 2] 8.17 (s, 1H, NC(O)H), 7.16 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 2 × C3H), 6.83 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 2 × C2H), 5.72 (m, 1H, C7H), 5.26 – 5.16 (m, 2H, $C8H_2$), 4.44 (s, 2H, $C5H_2$), 3.78 (d, $^5J_{HH}$ = 1.0 Hz, 3H, OMe), 3.69 (d, $^3J_{HH}$ = 5.8 Hz, 2H, $C6H_2$) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ [rotamer 1] 162.4 (NCO), 159.5 (C1), 132.1 (C7), 129.1 (2 × C3), 127.8 (C4), 118.3 (C8), 114.3 (2 × C2), 55.3 (OMe), 50.0 (C5), 43.9 (C6) ppm. δ [rotamer 2] 162.8 (NCO), 159.2 (C1), 133.1 (C7), 129.9 (2 × C3), 128.5 (C4), 118.8 (C8), 114.1 (2 × C2), 55.4 (OMe), 49.0 (C6), 44.4 (C5) ppm.

HRMS (*m/z*): (ESI) calculated for $C_{12}H_{16}NO_2$ $[M+H]^+$ 206.1176, found 206.1180.

IR (ν_{max}/cm^{-1}, neat): 2836, 1667, 1611, 1512, 1246, 1175.

(*S*)-*N*-(2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)-*N*-(4-methoxybenzyl)formamide (264)



According to a modified literature procedure,[50] anhydrous THF (0.430 mL, 1.00 M) was added to a mixture of $Pt(dba)_3$ (9.7 mg, 11 µmol, 2.5 mol%), (*S*,*S*)-**L*** (11.8 mg, 13.0 µmol, 3.00 mol%) and B_2pin_2 (132 mg, 0.520 mmol, 1.20 equiv) under N_2 and the mixture was stirred at 80 °C (oil bath) for 30 min. The reaction mixture was cooled to ambient temperature, alkene **263** (89.0 mg, 0.434 mmol, 1.00 equiv) was added and the reaction mixture was stirred at 60 °C (oil bath) for 16 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude brown oil was purified by flash column chromatography (SiO_2, 100% Et_2O) to afford 1,2-bis(boronic ester) **264** (180 mg, 0.392 mmol, 90%) as a yellow oil.

TLC: R_f = 0.21 (rotamer 1), 0.29 (rotamer 2) (100% Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) [Note: **264** appears as a 76:24 mixture of two rotamers observable by ^{1}H NMR] δ [major rotamer] 8.15 (s, 1H, NC(O)H), 7.19 (d, $^3J_{HH}$ = 8.7 Hz, 2H, 2 × C3H), 6.82 (d, $^3J_{HH}$ = 8.7 Hz, 2H, 2 × C2H), 4.45 (s, 2H, C5H_2), 3.78 (s, 3H, OMe), 3.24 (dd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, C6H^aH^b), 3.10 (dd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 8.6 Hz, 1H, C6H^aH^b), 1.53 (m, 1H, C7H), 1.24 – 1.18 (m, 24H, 8 × pinacol-CH_3), 0.75 (d, $^3J_{HH}$ = 7.3 Hz, 2H, C8H_2) ppm. δ [minor rotamer] 8.25 (s, 1H, NC(O)H), 7.12 (d, $^3J_{HH}$ = 8.6 Hz, 2H, 2 × C3H), 6.85 (d, $^3J_{HH}$ = 8.8 Hz, 2H, 2 × C2H), 4.33 (s, 2H, C5H_2), 3.79 (s, 3H, OMe), 3.32 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 9.1 Hz, 1H, C6H^aH^b), 3.25 (dd, $^3J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 7.4 Hz, 1H, C6H^aH^b), 1.53 (m, 1H, C7H), 1.24 – 1.18 (m, 24H, 8 × pinacol-CH_3), 0.83 (d, $^3J_{HH}$ = 9.4 Hz, 2H, C8H_2) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ [major rotamer] 163.5 (NCO), 159.0 (C1), 129.7 (2 × C3), 128.9 (C4), 114.0 (2 × C2), 83.6 (pinacol-C), 83.3 (pinacol-C), 55.4 (OMe), 49.5 (C6), 44.1 (C5), 25.0 (8 × pinacol-CH_3) ppm. δ [minor rotamer] 163.2 (NCO), 159.4 (C1), 129.1 (2 × C3), 128.6 (C4), 114.2 (2 × C2), 83.3 (pinacol-C), 83.1 (pinacol-C), 55.4 (OMe), 50.4 (C5), 44.3 (C6), 25.0 (8 × pinacol-CH_3) ppm.

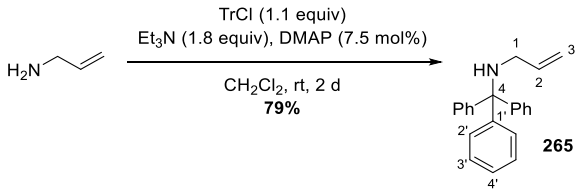
carbon next to boron not observed due to quadrupolar relaxation

HRMS (*m/z*): (ESI) calculated for $C_{24}H_{39}{}^{11}B_2NO_6$ $[M+H]^+$ 460.3045, found 460.3058.

IR (ν_{max}/cm^{-1}, neat): 2977, 2931, 1669, 1513, 1371, 1318, 1247, 1142.

$[\alpha]_D^{26}$: −20 (*c* = 1, $CHCl_3$).

N-tritylprop-2-en-1-amine (265)



According to the literature procedure[164], allylamine (0.750 mL, 10.0 mmol, 1.00 equiv) in CH_2Cl_2 (5.00 mL, 2.00 M) was added to a solution of trityl chloride (3.10 g, 11.0 mmol, 1.10 equiv), triethylamine (2.50 mL, 17.6 mmol, 1.76 equiv) and 4-(dimethylamino)pyridine (92.0 mg, 0.753 mmol, 7.50 mol%) in CH_2Cl_2 (10.0 mL [15.0 mL, 0.667 M overall wrt allylamine]) and the resulting mixture was stirred at ambient temperature for 2 days. The reaction mixture was diluted with water (20 mL) and EtOAc (15 mL) and the phases separated. The aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organics were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Et_3N-deactivated SiO_2, 90:10 hexane:EtOAc) to afford secondary amine **265** (2.37 g, 7.92 mmol, 79%) as a white solid.

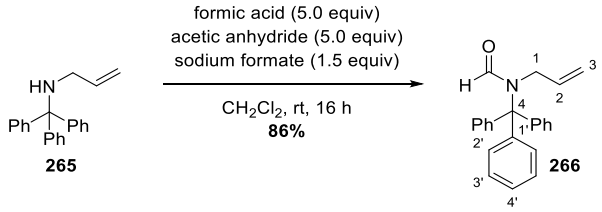
All recorded spectroscopic data matched that previously reported.[217]

TLC: R_f = 0.46 (90:10 hexane:EtOAc, PMA).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.54 – 7.46 (m, 6H, 6 × Ph C-H), 7.31 – 7.26 (m, 6H, 6 × Ph C-H), 7.22 – 7.17 (m, 3H, 3 × Ph C4H), 5.96 (ddt, $^3J_{HH}$ = 17.3, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 5.4 Hz, 1H, C2H), 5.28 (dq, $^3J_{HH}$ = 17.3 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, C3H^aH^b), 5.07 (dq, $^3J_{HH}$ = 10.5 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, C3H^aH^b), 2.76 (dt, $^3J_{HH}$ = 5.5 Hz, $^4J_{HH}$ = 1.7 Hz, 2H, C1H_2), 1.65 (br. s, 1H, NH) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 146.1 (3 × Ph C1'), 137.3 (C2), 128.6 (6 × Ph C3'), 127.8 (6 × Ph C2'), 126.3 (3 × Ph C4'), 114.8 (C3), 70.8 (CPh_3), 46.5 (C1) ppm.

_N_-allyl-_N_-tritylformamide (266)



A mixture of formic acid (0.220 mL, 5.90 mmol, 5.00 equiv) and acetic anhydride (0.550 mL, 5.90 mmol, 5.00 equiv) was stirred at 50 °C (oil bath) for 20 min. The mixture was cooled to ambient temperature then sodium formate (119 mg, 1.75 mmol, 1.50 equiv) was added in one portion followed by secondary amine **265** (350 mg, 1.17 mmol, 1.00 equiv) in CH_2Cl_2 (2.90 mL, 0.40 M). The resulting mixture was stirred at ambient temperature overnight and then basified with 2 M aq. NaOH. The phases were separated and the organic phase was washed with water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford formamide **266** (329 mg, 1.00 mmol, 86%) as a white solid, judged as sufficiently pure to be carried forward to the next step without purification.

TLC: R_f = 0.31 (50:50 pentane:Et_2O, $KMnO_4$).

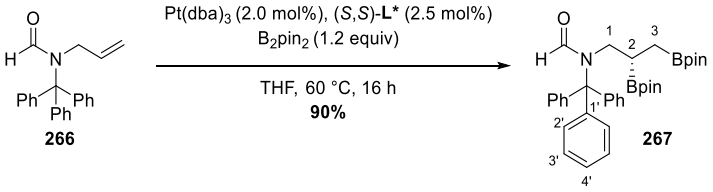
^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.56 (s, 1H, NC(H)O), 7.35 – 7.26 (m, 15H, 15 × Ph C-H), 5.61 (ddt, $^3J_{HH}$ = 16.8 Hz, $^3J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 5.9 Hz, 1H, C2H), 4.92 (d, $^3J_{HH}$ = 10.7 Hz, 1H, C3H^aH^b), 4.85 (dd, $^3J_{HH}$ = 16.8 Hz, $^2J_{HH}$ = 1.7 Hz, 1H, C3H^aH^b), 3.87 (d, $^3J_{HH}$ = 5.9 Hz, 2H, $C1H_2$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 166.7 (NCO), 142.5 (3 × Ph C1'), 133.6 (C2), 130.1 (6 × Ph C3'), 128.2 (6 × Ph C2'), 127.6 (3 × Ph C4'), 116.9 (C3), 63.7 (CPh_3), 53.2 ($\underline{C}1NCOH^+$), 48.3 (C1), 8.4 ($N\underline{C}OH^+$) ppm.

HRMS (*m/z*): (MALDI) calculated for $C_{23}H_{21}NO$ $[M+Na]^+$ 350.1515, found 350.1522.

IR (ν_{max}/cm^{-1}, neat): 1652, 1447, 1360, 1331, 1265, 1068.

(*S*)-*N*-(2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)-*N*-tritylformamide (267)



According to a literature procedure,[50] anhydrous THF (0.760 mL, 1.00 M) was added to a mixture of $Pt(dba)_3$ (13.7 mg, 15.3 µmol, 2.00 mol%), (*S*,*S*)-**L*** (17.4 mg, 19.1 µmol, 2.50 mol%) and B_2pin_2 (233 mg, 0.916 mmol, 1.20 equiv) under N_2 and the mixture was stirred at 80 °C (oil bath) for 30 min. The reaction mixture was cooled to ambient temperature, alkene **266** (250 mg, 0.764 mmol, 1.00 equiv) was added and the reaction mixture was stirred at 60 °C (oil bath) for 16 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude brown oil was purified by flash column chromatography (SiO_2, 70:30 pentane:Et_2O) to afford 1,2-bis(boronic ester) **267** (398 mg, 0.685 mmol, 90%, 93:7 *er*) as a white amorphous solid.

TLC: R_f = 0.33 (50:50 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.29 (s, 1H, NC(H)O), 7.36 – 7.27 (m, 15H, 15 × Ph C-H), 3.51 (d, $^3J_{HH}$ = 7.2 Hz, 2H, C1H_2), 1.22 – 1.16 (m, 24H, 8 × pinacol-CH_3), 0.83 (dd, $^2J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 8.6 Hz, 1H, C3H^aH^b), 0.68 (m, 1H, C2H), 0.50 (dd, $^2J_{HH}$ = 15.9 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, C3H^aH^b) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 167.5 (NCO), 142.9 (3 × Ph C1'), 130.6 (6 × Ph C3'), 128.0 (6 × Ph C2'), 127.6 (3 × Ph C4'), 82.9 (2 × pinacol-C), 82.7 (2 × pinacol-C), 63.6 (CPh_3), 53.2 ($\underline{C}$1NCOH$^+$), 47.4 (C1), 25.2 (2 × pinacol-CH_3), 25.1 (2 × pinacol-CH_3), 25.0 (2 × pinacol-CH_3), 25.0 (2 × pinacol-CH_3), 8.3 (N$\underline{C}$OH$^+$) ppm.

carbon next to boron not observed due to quadrupolar relaxation

HRMS (*m/z*): (MALDI) calculated for $C_{35}H_{45}{}^{11}B_2NO_5$ [*M*+K]$^+$ 620.3127, found 620.3135.

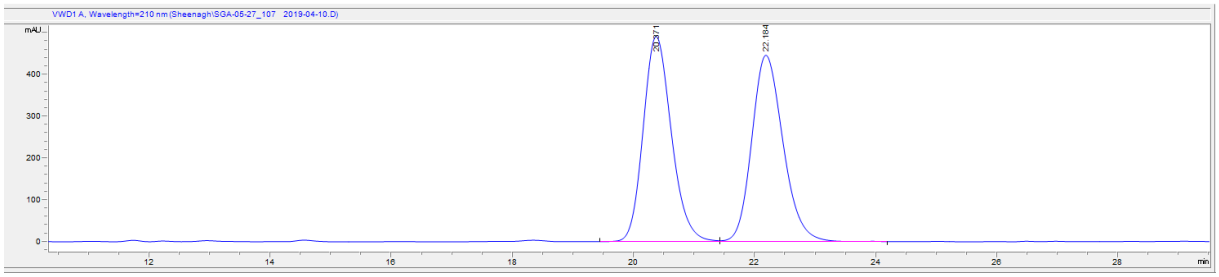
IR (ν_{max}/cm^{-1}, neat): 1664, 1360, 1312, 1141.

$[\alpha]_D^{26}$: +11 (*c* = 0.6, $CHCl_3$).

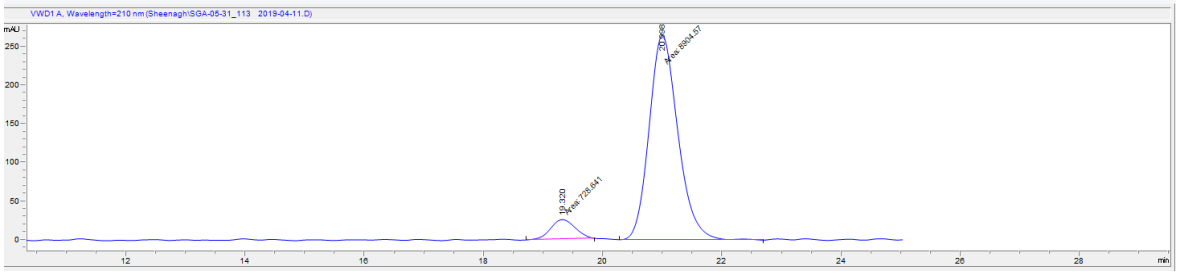
An aliquot of 1,2-bis(boronic ester) **267** was oxidised to the corresponding diol using sodium perborate in order to determine the enantiomeric ratio by chiral HPLC.

Chiral HPLC: (Chiralpak AD-H column, hexane:isopropanol 90:10, 1.0 mL/min, ambient temperature, 210.8 nm): t_R = 19.3 minutes (minor), 21.0 minutes (major), *er* 93:7.

Racemic sample:

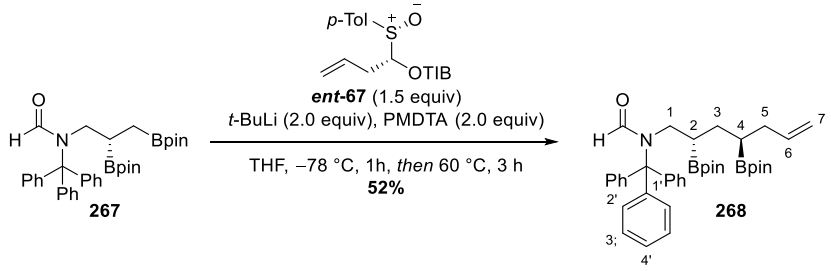


Diol from **267**:



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	19.32	MM	728.6	25.3	0.4805	7.564	0.907
2	20.998	MM	8904.6	264.8	0.5606	92.436	0.812

***N*-((2*S*,4*S*)-2,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-1-yl)-*N*-tritylformamide (268)**



PMDTA (40 µL, 0.20 mmol, 2.0 equiv) and anhydrous THF (0.650 mL, 0.200 M wrt ***ent*-67**) were added to a mixture of bis(boronic ester) **267** (50.0 mg, 86.0 µmol, 1.00 equiv) and α-sulfinyl benzoate ***ent*-67** (56.8 mg, 0.129 mmol, 1.50 equiv) under N_2. The mixture was cooled to −78 °C (acetone/dry ice) before the dropwise addition of *t*-BuLi (2.8 M in heptane, 60 µL, 0.20 mmol, 2.0 equiv). The reaction mixture was stirred at −78 °C for 1 h then warmed to ambient temperature. THF was removed under reduced pressure and the mixture was

redissolved in $CHCl_3$ (0.65 mL) and heated at 60 °C (oil bath) for 3 h. The reaction mixture was then cooled to ambient temperature and diluted with sat. aq. NH_4Cl (2 mL) and Et_2O (2 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 3 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 80:20 to 50:50 pentane:Et_2O) to afford 1,3-bis(boronic ester) **268** (28.4 mg, 44.7 µmol, 52%) as a colourless oil (white foam under high vacuum).

TLC: R_f = 0.28 (60:40 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.32 (s, 1H, NC(H)O), 7.36 – 7.27 (m, 15H, Ph C-H), 5.70 (ddt, $^3J_{HH}$ = 17.0 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 6.9 Hz, 1H, C6H), 4.92 (dd, $^3J_{HH}$ = 17.1 Hz, $^2J_{HH}$ = 2.0 Hz, 1H, C7H^aH^b), 4.87 (dd, $^3J_{HH}$ = 10.3 Hz, $^2J_{HH}$ = 2.0 Hz, 1H, C7H^aH^b), 3.48 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 8.4 Hz, 1H, C1H^aH^b), 2.87 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 3.9 Hz, 1H, C1H^aH^b), 1.97 (t, $^3J_{HH}$ = 7.3 Hz, 2H, C5H_2), 1.30 – 1.13 (m, 26H, C2H, C4H, 8 × pinacol-CH_3, 4), 0.95 – 0.80 (m, 2H, C3H_2) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 167.3 (NCO), 143.0 (3 × Ph C1'), 138.6 (C6), 130.3 (6 × Ph C3'), 128.1 (6 × Ph C2'), 127.5 (3 × Ph C4'), 114.9 (C7), 83.0 (pinacol-C), 82.8 (pinacol-C), 63.2 (CPh_3), 47.8 (C1), 36.3 (C5), 31.8 (C3), 25.7 (2 × pinacol-CH_3), 25.6 (2 × pinacol-CH_3), 25.2 (2 × pinacol-CH_3), 24.8 (2 × pinacol-CH_3) ppm.

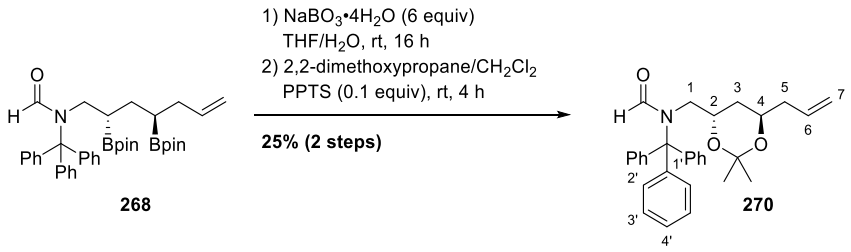
carbon next to boron not observed due to quadrupolar relaxation

HRMS (*m/z*): (MALDI) calculated for $C_{39}H_{51}{}^{11}B_2NO_5$ [*M*+K]$^+$ 674.3598, found 674.3591.

IR (ν_{max}/cm^{-1}, neat): 2976, 1662, 1444, 1371, 1354, 1321, 1142.

$[\alpha]_D^{26}$: +14 (*c* = 1, $CHCl_3$).

***N*-(((4*S*,6*R*)-6-allyl-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-*N*-tritylformamide (270)**



Oxidation

Sodium perborate·tetrahydrate (25.0 mg, 0.161 mmol, 6.00 equiv) was added to a solution of bis(boronic ester) **268** (17.0 mg, 26.8 µmol, 1.00 equiv) in THF/H_2O (1:1 v/v, 0.540 mL, 0.0500 M) at ambient temperature. The reaction mixture was stirred at ambient temperature overnight then diluted with water (2 mL) and Et_2O (2 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 3 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

TLC: R_f = 0.28 (100% Et_2O, anisaldehyde).

Acetonide protection

2,2-dimethoxypropane (0.13 mL) followed by pyridinium *p*-toluenesulfonate (0.7 mg, 3 µmol, 0.1 equiv) was added to the crude diol **269** in CH_2Cl_2 (0.13 mL). The reaction mixture was stirred at ambient temperature for 4 h. Sat. aq. $NaHCO_3$ (2 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 50:50 pentane:Et_2O) to afford acetonide **270** (3.0 mg, 6.6 µmol, 25%, 90:10 *dr*) as a colourless oil.

TLC: R_f = 0.26 (2:1 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.34 (s, 1H, NC(H)O), 7.35 – 7.27 (m, 15H, 15 × Ph C-H), 5.73 (ddt, $^3J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 6.8 Hz, 1H, C6H), 5.08 – 5.00 (m, 2H, C7H^{a}H^b), 3.74 (m, 1H, C4H), 3.65 (m, 1H, C2H), 3.49 (dd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 4.7 Hz, 1H, C1*H*^{a}H^b), 3.42 (dd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 7.5 Hz, 1H, C1H^a*H*^{b}), 2.22 (m, 1H, C5*H*^{a}H^b), 2.11 (m, 1H, C5H^a*H*^{b}), 1.50 – 1.46 (m, 2H, $C3H_2$), 1.25 (s, 3H, CH_3), 1.23 (s, 3H, CH_3) ppm.

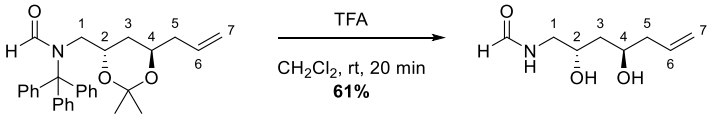
^{13}C NMR: (126 MHz, $CDCl_3$) δ 168.4 (NCO), 143.1 (3 × Ph C1'), 134.6 (C6), 130.6 (6 × Ph C3'), 128.1 (6 × Ph C2'), 127.8 (3 × Ph C4'), 116.9 (C7), 100.3 (OCO), 76.5 (CPh_3), 66.3 (C4), 65.1 (C2), 48.3 (C1), 40.1 (C5), 35.8 (C3), 25.1 (CH_3), 25.0 (CH_3) ppm.

HRMS (*m/z*): (MALDI) calculated for $C_{30}H_{33}NO_3$ [*M*+Na]$^+$ 478.2353, found 478.2365.

IR (ν_{max}/cm^{-1}, neat): 1667, 1491, 1443,1278, 1222, 1172.

$[\alpha]_D^{24}$: −18 (*c* = 0.16, $CHCl_3$).

N-((2*S*,4*R*)-2,4-dihydroxyhept-6-en-1-yl)formamide (271)



270 **271**

Trifluoroacetic acid (0.33 mL) was added to acetonide **270** (3.0 mg, 6.6 µmol, 1.0 equiv) in CH_2Cl_2 (0.33 mL). The mixture was stirred at ambient temperature for 20 min then concentrated under reduced pressure. Residual trifluoroacetic acid was removed by co-evaporation with toluene (3 × 3 mL). The crude product was purified by flash column chromatography (SiO_2, 95:5 to 60:40 Et_2O:MeOH) to afford 1,3-diol **271** (0.7 mg, 4 µmol, 61%) as a colourless oil.

TLC: R_f = 0.41 (25:75 MeOH:Et_2O, anisaldehyde).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.23 (s, 1H, NC(H)O), 6.03 (br. s, 1H, NH), 5.80 (td, $^3J_{HH}$ = 16.7 Hz, $^3J_{HH}$ = 7.3 Hz, 1H, C6H), 5.22 – 5.13 (m, 2H, $C7H_2$), 4.06 (m, 1H, C2H), 3.99 (m, 1H, C4H), 3.57 (ddd, $^2J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 3.2 Hz, 1H, C1*H*^{a}H^b), 3.39 (br. s, 1H, O*H*), 3.27 (m, 1H, C1H^a*H*^{b}), 2.37 – 2.16 (m, 3H, $C5H_2$, OH), 1.74 (ddd, $^3J_{HH}$ = 14.5 Hz, $^2J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 3.1 Hz, 1H, C3*H*^{a}H^b), 1.63 (ddd, $^3J_{HH}$ = 11.0 Hz, $^2J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 3.9 Hz, 1H, C3H^a*H*^{b}) ppm.

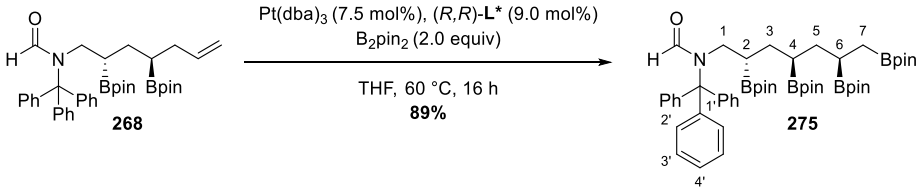
^{13}C NMR: (126 MHz, $CDCl_3$) δ 162.0 (NCO), 134.2 (C6), 119.2 (C7), 68.7 (C2), 68.3 (C4), 44.4 (C1), 42.1 (C5), 39.5 (C3) ppm.

HRMS (*m/z*): (ESI) calculated for $C_8H_{15}NO_3$ [*M*+H]$^+$ 174.1125, found 174.1120.

IR (ν_{max}/cm^{-1}, neat): 3301, 2922, 1661, 1538, 1385, 1203, 1088.

$[\alpha]_D^{24}$**:** −10 (*c* = 0.1, $CHCl_3$).

_N_-((2_S_,4_R_,6_R_)-2,4,6,7-tetrakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptyl)-_N_-tritylformamide (275)



According to a modified literature procedure,[50] anhydrous THF (0.360 mL, 1.00 M) was added to a mixture of $Pt(dba)_3$ (24.4 mg, 27.1 µmol, 7.50 mol%), (*R*,*R*)-**L*** (29.6 mg, 32.6 µmol, 9.00 mol%) and B_2pin_2 (184 mg, 0.724 mmol, 2.00 equiv) under N_2 and the mixture was stirred at 80 °C (oil bath) for 30 min. The reaction mixture was cooled to ambient temperature, alkene **268** (230 mg, 0.362 mmol, 1.00 equiv) was added and the reaction mixture was stirred at 60 °C (oil bath) for 16 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude brown oil was purified by flash column chromatography (SiO_2, 70:30 to 30:70 pentane:Et_2O) to afford tetra(boronic ester) **275** (286 mg, 0.322 mmol, 89%) as a colourless oil (white foam under high vacuum).

TLC: R_f = 0.22 (50:50 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.29 (s, 1H, NC(H)O), 7.34 – 7.23 (m, 15H, 15 × Ph C-H), 3.48 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 8.1 Hz, 1H, C1*H*^{a}H^b), 2.74 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 2.9 Hz, 1H, C1H^a*H*^{b}), 1.52 (ddd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 5.5 Hz, 1H, C5*H*^{a}H^b), 1.34 – 1.02 (m, 53H, C2H, C3H$_2$, C4H, C5H^a*H*^{b}, 16 × pinacol-CH$_3$), 0.86 (dd, $^2J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 4.5 Hz, C7*H*^{a}H^b), 0.85 (m, 1H, C6H), 0.71 (dd, $^2J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 10.3 Hz, 1H, C7H^a*H*^{b}) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 167.1 (NCO), 143.1 (3 × Ph C1'), 130.1 (6 × Ph C3'), 128.0 (6 × Ph C2'), 127.3 (3 × Ph C4'), 82.7 (pincaol-C), 82.6 (pinacol-C), 82.5 (pinacol-C), 47.8 (C1), 35.1 (C5), 33.3 (C3), 25.6 (pinacol-CH$_3$), 25.5 (pinacol-CH$_3$), 25.1 (pinacol-CH$_3$), 24.8 (pinacol-CH$_3$), 24.7 (pinacol-CH$_3$) ppm.

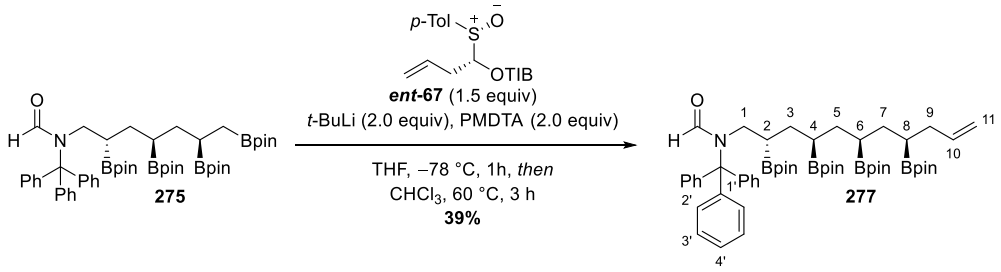
carbon next to boron not observed due to quadrupolar relaxation

HRMS (*m/z*): (MALDI) calculated for $C_{51}H_{75}{}^{11}B_4NO_9$ [*M*+Na]$^+$ 912.5736, found 912.5749.

IR (ν_{max}/cm^{-1}, neat): 2975, 1668, 1378, 1370, 1309, 1141.

$[\alpha]_D^{26}$**:** +7 (*c* = 1, $CHCl_3$).

***N*-((2*S*,4*R*,6*S*,8*S*)-2,4,6,8-tetrakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undec-10-en-1-yl)-*N*-tritylformamide (277)**



PMDTA (40 µL, 0.20 mmol, 2.0 equiv) and anhydrous THF (0.750 mL, 0.200 M wrt ***ent*-67**) were added to a mixture of tetra(boronic ester) **275** (88.9 mg, 0.100 mmol, 1.00 equiv) and α-sulfinyl benzoate ***ent*-67** (66.1 mg, 0.150 mmol, 1.50 equiv) under N_2. The mixture was cooled to −78 °C (acetone/dry ice) before the dropwise addition of *t*-BuLi (2.8 M in heptane, 70 µL, 0.20 mmol, 2.0 equiv). The reaction mixture was stirred at −78 °C for 1 h then warmed to ambient temperature. THF was removed under reduced pressure and the mixture was redissolved in $CHCl_3$ (0.75 mL) and heated at 60 °C (oil bath) for 3 h. The reaction mixture was then cooled to ambient temperature and diluted with sat. aq. NH_4Cl (2 mL) and Et_2O (2 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 3 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 70:30 to 40:60 pentane:Et_2O) to afford homologated tetra(boronic ester) **277** (36.8 mg, 39.0 µmol, 39%) as a colourless oil (white foam under high vacuum).

TLC: R_f = 0.36 (50:50 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.31 (s, 1H, NC(H)O), 7.37 – 7.25 (m, 15H, 15 × Ph C-H), 5.83 (ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 6.9 Hz, 1H, C10H), 5.01 (dd, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = 2.3 Hz, 1H, C11H^aH^b), 4.88 (dd, $^3J_{HH}$ = 10.2 Hz, $^2J_{HH}$ = 2.3 Hz, 1H, C11H^aH^b), 3.52 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 8.7 Hz, 1H, C1H^aH^b), 2.76 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 3.2 Hz, 1H, C1H^aH^b), 2.26 – 2.03 (m, 2H, C9H_2), 1.52 – 0.76 (m, 58H, 4 × CH, 3 × CH_2, 16 × pinacol-CH_3) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 167.3 (NCO), 143.2 (3 × Ph C1'), 139.0 (C10), 130.3 (6 × Ph C3'), 128.1 (6 × Ph C2'), 127.4 (3 × Ph C4'), 114.6 (C11), 82.9 (pinacol-C), 82.9 (pinacol-C), 82.8 (pinacol-C), 82.7 (pinacol-C), 82.7 (pinacol-C), 82.7 (pinacol-C), 82.7 (pinacol-C), 82.5 (pinacol-C), 48.0 (C1), 34.4 (CH_2), 33.9 (CH_2), 33.2 (CH_2), 30.5 (CH_2), 25.8 (pinacol-CH_3), 25.6 (pinacol-CH_3), 25.4 (pinacol-CH_3), 25.3 (pinacol-CH_3), 25.2 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.9 (pinacol-CH_3), 24.8 (pinacol-CH_3) ppm.

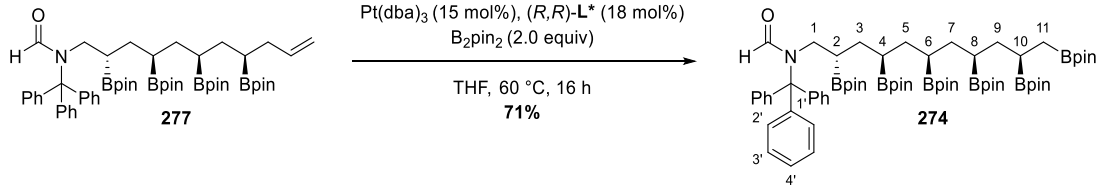
carbon next to boron not observed due to quadrupolar relaxation

HRMS (*m/z*): (MALDI) calculated for $C_{55}H_{81}{}^{11}B_4NO_9$ $[M+K]^+$ 982.5947, found 982.5939.

IR (ν_{max}/cm^{-1}, neat): 2975, 2926, 1668, 1378, 1371, 1310, 1141.

$[\alpha]_D^{25}$: +14 (*c* = 1, $CHCl_3$).

N-((2*S*,4*R*,6*R*,8*R*,10*R*)-2,4,6,8,10,11-hexakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undecyl)-*N*-tritylformamide (274)



According to a modified literature procedure,[50] anhydrous THF (90 µL, 1.0 M) was added to a mixture of $Pt(dba)_3$ (12.7 mg, 14.2 µmol, 15.0 mol%), (*R*,*R*)-**L*** (15.4 mg, 17.0 µmol, 18.0 mol%) and B_2pin_2 (47.9 mg, 0.189 mmol, 2.00 equiv) under N_2 and the mixture was stirred at 80 °C (oil bath) for 30 min. The reaction mixture was cooled to ambient temperature, alkene **277** (89.0 mg, 94.3 µmol, 1.00 equiv) was added and the reaction mixture was stirred at 60 °C (oil bath) for 16 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude brown oil was purified by flash column chromatography (SiO_2, 50:50 pentane:Et_2O) to afford hexa(boronic ester) **274** (80.5 mg, 67.2 µmol, 71%) as a colourless oil (white foam under high vacuum).

TLC: R_f = 0.23 (40:60 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.29 (s, 1H, NC(H)O), 7.35 – 7.22 (m, 15H, 15 × Ph C-H), 3.49 (dd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 8.8 Hz, 1H, C1H^aH^b), 2.71 (dd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 2.5 Hz, 1H, C1H^aH^b), 1.32 – 0.86 (m, 86H, C2H, $C3H_2$, C4H, $C5H_2$, C6H, $C7H_2$, C8H, $C9H_2$,

C10H, C11*H*^{a}H^{b}, 24 × pinacol-CH_3), 0.66 (dd, $^{2}J_{HH}$ = 16.0 Hz, $^{3}J_{HH}$ = 11.6 Hz, 1H, C11H^{a}*H*^{b}) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 167.2 (NCO), 143.2 (3 × Ph C1'), 130.3 (6 × Ph C3'), 128.2 (6 × Ph C2'), 127.5 (3 × Ph C4'), 82.8 (pinacol-C), 82.7 (pinacol-C), 82.6 (pinacol-C), 82.6 (pinacol-C), 82.6 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 82.5 (pinacol-C), 82.4 (pinacol-C), 48.2 (C1), 33.7 (CH_2), 33.6 (CH_2), 33.2 (CH_2), 32.6 (CH_2), 25.8 (pinacol-CH_3), 25.6 (pinacol-CH_3), 25.3 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.1 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 25.0 (pinacol-CH_3), 24.9 (pinacol-CH_3) ppm.

carbon next to boron not observed due to quadrupolar relaxation

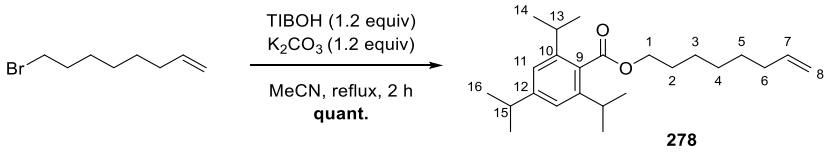
NMR spectra included in section **6.5**

HRMS (*m/z*): (MALDI) calculated for $C_{67}H_{105}{}^{11}B_6NO_{13}$ [*M*+Na]$^{+}$ 1220.8087, found 1220.8069.

IR (ν_{max}/cm^{-1}, neat): 2976, 2928, 1669, 1378, 1371, 1309, 1142.

$[\alpha]_D^{27}$: +6 (*c* = 0.7, $CHCl_3$).

oct-7-en-1-yl 2,4,6-triisopropylbenzoate (278)



278

According to a modified literature procedure,[36] potassium carbonate (4.17 g, 30.1 mmol, 1.20 equiv) was added to a stirred solution of 2,4,6-triisopropylbenzoic acid (7.49 g, 30.1 mmol, 1.20 equiv) in acetonitrile (50.0 mL, 0.500 M). The mixture was stirred vigorously for 10 min then 8-bromo-1-octene (4.73 g, 25.1 mmol, 1.00 equiv) was added and the resulting mixture was refluxed (oil bath at 85 °C) for 2 h. The reaction mixture was cooled to ambient temperature. The precipitate was filtered off and washed with EtOAc (2 × 50 mL). The combined organics were concentrated under reduced pressure and the resulting yellow residue was dissolved in EtOAc (100 mL), washed with water (2 × 50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford

benzoate **278** (9.33 g, quantitative) as a yellow oil which was carried forward without further purification.

TLC: R_f = 0.52 (95:5 pentane:Et_2O, $KMnO_4$).

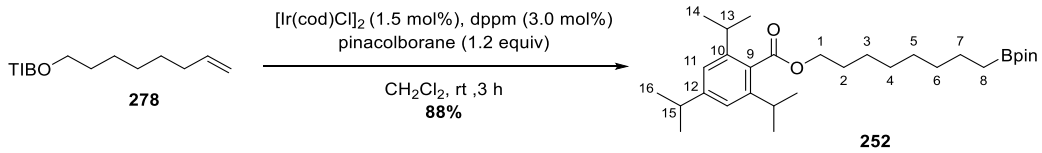
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.01 (s, 2H, 2 × C11H), 5.80 (ddt, $^3J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 6.7 Hz, 1H, C7H), 5.00 (app. dq, $^3J_{HH}$ = 17.1 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, C8H^aH^b), 4.94 (m, 1H, C8H^aH^b), 4.30 (t, $^3J_{HH}$ = 6.7 Hz, 2H, $C1H_2$), 2.86 (sept, $^3J_{HH}$ = 6.7 Hz, 3H, 2 × C13H, C15H), 2.05 (app. q, $^3J_{HH}$ = 6.6 Hz, 2H, $C6H_2$), 1.77 – 1.69 (m, 2H, $C2H_2$), 1.47 – 1.31 (m, 6H, $C3H_2$, $C4H_2$, $C5H_2$), 1.26 – 1.23 (m 18H, 4 × $C14H_3$, 2 × $C16H_3$) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.2 (C=O), 150.2 (C12), 144.9 (2C, 2 × C10), 139.1 (C7), 130.9 (C12), 121.0 (2C, 2 × C11), 114.5 (C8), 65.1 (C1), 34.6 (C15), 33.8 (C6), 31.6 (2C, 2 × C13), 29.0 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 26.1 (CH_2), 24.3 (4C, 4 × CH_3), 24.1 (2C, 2 × CH_3) ppm.

HRMS (*m/z*): (ESI) calculated for $C_{24}H_{38}O_2$ [*M*+Na]$^+$ 381.2764, found 381.2758.

IR (ν_{max}/cm^{-1}, neat): 2960, 2929, 2868, 1725, 1606, 1461, 1283, 1250, 1137, 1104, 1075.

8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octyl 2,4,6-triisopropylbenzoate (252)



According to a modified literature procedure,[165] a flask was charged with $[Ir(cod)Cl]_2$ (0.251 g, 0.374 mmol, 1.50 mol%) and bis(diphenylphosphino)methane (0.288 g, 0.749 mmol, 3.00 mol%) and flushed with N_2. CH_2Cl_2 (76.0 mL, 0.330 M), pinacolborane (4.35 mL, 30.0 mmol, 1.20 equiv) and alkene **278** (8.95 g, 25.0 mmol, 1.00 equiv) were added sequentially and the reaction stirred at ambient temperature for 3 h. The reaction was quenched with MeOH (30 mL) and water (100 mL), the phases separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were passed through through Sartorius™ Grade 480 silicon-impregnated phase separator paper and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on a Biotage Isolera One system (split into 2 batches, dry loaded, 100 g Ultra column,

hexane:EtOAc 99:1 to 95:5) to afford primary boronic ester **252** (10.7 g, 22.0 mmol, 88%) as a colourless oil.

TLC: R_f = 0.14 (95:5 hexane:EtOAc, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.01 (s, 2H, 2 × C11H), 4.30 (t, $^3J_{HH}$ = 6.7 Hz, 2H, C1H_2), 2.87 (sept, $^3J_{HH}$ = 6.9 Hz, 1H, C15H), 2.86 (sept, $^3J_{HH}$ = 6.8 Hz, 2H, 2 × C13H), 1.76 – 1.68 (m, 2H, C2H_2), 1.45 – 1.18 (m, 40H, 4 × pinacol-CH_3, 2 × C16H_3, 4 × C14H_3, C3H_2, C4H_2, C5H_2, C6H_2, C7H_2), 0.77 (t, $^3J_{HH}$ = 7.6 Hz, C8H_2) ppm.

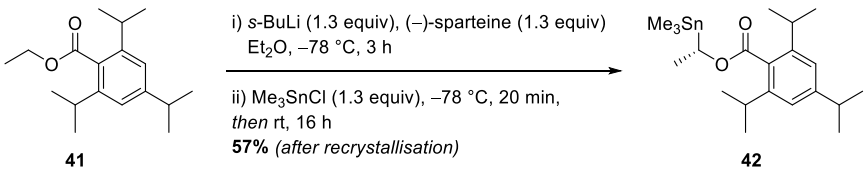
^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.1 (C=O), 150.1 (C12), 144.8 (2C, 2 × C10), 130.9 (C9), 120.9 (2C, 2 × C11), 82.9 (2C, 2 × pinacol-C), 65.1 (C1), 34.5 (C15), 32.4 (CH_2), 31.6 (2C, 2 × C13), 29.4 (CH_2), 29.3 (CH_2), 28.8 (C2), 26.2 (CH_2), 24.9 (4C, 4 × CH_3), 24.3 (4C, 4 × CH_3), 24.1 (3C, CH_2, 2 × CH_3) ppm.

carbon next to boron not observed due to quadrupolar relaxation

HRMS (*m/z*): (ESI) calculated for $C_{30}H_{51}{}^{11}BO_4$ $[M+Na]^+$ 509.3778, found 509.3786.

IR (ν_{max}/cm^{-1}, neat): 2960, 2927, 2868, 1725, 1606, 1462, 1378, 1318, 1250, 1144, 1104, 1075.

(*S*)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (42)



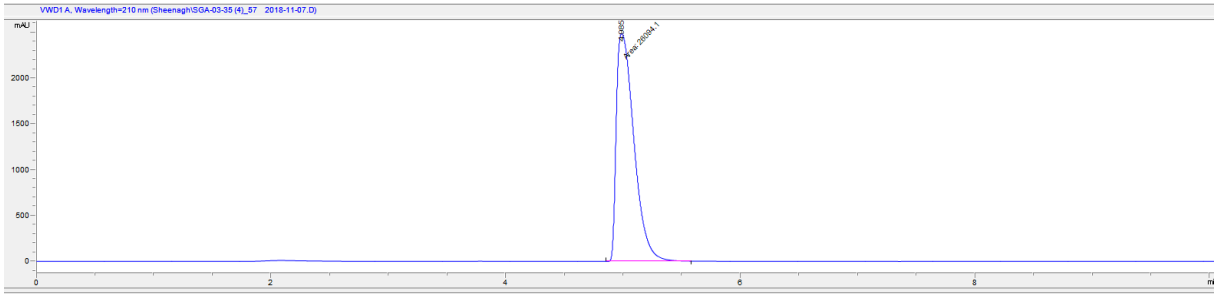
According to the literature procedure,[34] *s*-BuLi (1.30 M in hexanes, 33.5 mL, 43.5 mmol, 1.30 equiv) was added dropwise (syringe pump, 0.3 mL/min) to ethyl 2,4,6-triisopropylbenzoate (**41**) (9.26 g, 33.5 mmol, 1.00 equiv) and (−)-sparteine (10.0 mL, 43.5 mmol, 1.30 equiv) in anhydrous Et_2O (167 mL, 0.200 M) at −78 ºC (acetone/dry ice) under N_2. The resulting mixture was stirred at −78 ºC for 3 h. Me_3SnCl (1.00 M in hexanes, 43.5 mL, 43.5 mmol, 1.30 equiv) was added dropwise and the resulting solution was stirred at −78 ºC for 20 min, and then at ambient temperature for 16 h. The reaction mixture was quenched with 2 M aq. HCl (100 mL) and the phases were separated. The organic phase was washed with 2 M aq. HCl (3 × 60 mL) and the combined aqueous phases were extracted with Et_2O (3 × 100 mL). The aqueous phase was retained for (−)-sparteine recovery. The combined

organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to a yellow solid (15.8 g). The crude product was purified by recrystallisation from hot MeOH (3 mL/g) to afford α-stannyl benzoate **42** (8.36 g, 19.0 mmol, 57%, >99.9:0.1 *er*) as white needles (2 crops).

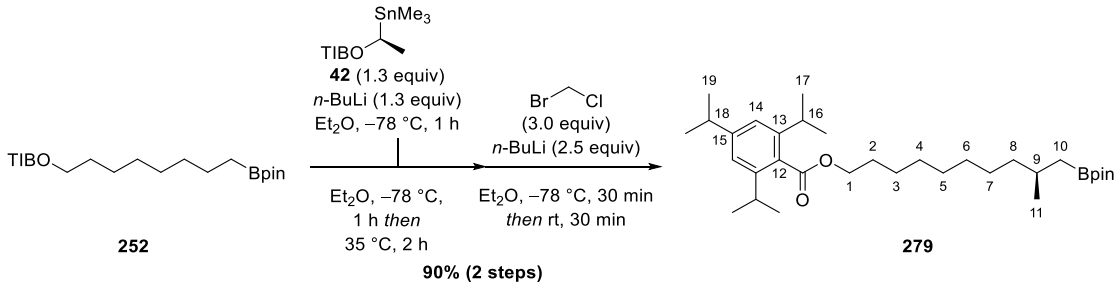
All recorded spectroscopic data matched the enantiomer ***ent*-42** (see bahamaolide SI), and that previously reported.[34]

Chiral HPLC: (Daicel Chiralpak-IB column (25 cm) with guard, 100% hexane, 0.9 mL/min, ambient temperature, 210 nm) t_R = 5.0 min (major), 8.3 min (minor), *er* >99.9:0.1.

Chiral HPLC conditions previously reported and used in-house,[34] the enantiomer was also synthesised by the author and was available for comparison.



(*R*)-9-methyl-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)decyl 2,4,6-triisopropylbenzoate (279)



According to the literature procedure,[34,35] *n*-BuLi (1.60 M in hexanes, 0.610 mL, 0.980 mmol, 1.30 equiv) was added dropwise to a stirred solution of (*S*)-stannane **42** (0.430 g, 0.979 mmol, 1.30 equiv) in anhydrous Et_2O (3.80 mL, 0.260 M) at −78 °C (acetone/dry ice) under N_2. The reaction mixture was stirred at −78 °C for 1 h then boronic ester **252** (0.366 g, 0.753 mmol, 1.00 equiv) in Et_2O (0.750 mL, 1.00 M) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h then at 35 °C (oil bath) for 2 h. The reaction mixture was cooled to ambient

temperature and filtered through a plug of Et_2O-wetted silica into a flame dried flask. The filtrate was concentrated under reduced pressure and the crude boronic ester used directly for the next homologation.

Bromochloromethane (0.150 mL, 2.30 mmol, 3.00 equiv) was added to the crude boronic ester in anhydrous Et_2O (3.80 mL, 0.200 M) and the mixture cooled to −78 °C (acetone/dry ice) under N_2 before the slow addition (syringe pump, 0.05 mL/min) of *n*-BuLi (1.60 M in hexanes, 1.18 mL, 1.88 mmol, 2.50 equiv). When the addition was complete the reaction mixture was stirred at −78 °C for 30 min then at ambient temperature for 30 min. The reaction mixture was filtered through a plug of Et_2O-wetted silica and the filtrate concentrated under reduced pressure. The crude residue was purified by flash column chromatography on a Biotage Isolera One system (30 g ZIP Sphere column, pentane:Et_2O 98:2 to 93:7) to afford boronic ester **279** (359 mg, 0.679 mmol, 90%) as a colourless oil.

TLC: R_f = 0.19 (94:6 pentane:Et_2O, PMA).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.00 (s, 2H, 2 × C14H), 4.29 (t, $^3J_{HH}$ = 6.7 Hz, C1H_2), 2.87 (sept, $^3J_{HH}$ = 6.9 Hz, 1H, C16H), 2.86 (sept, $^3J_{HH}$ = 6.8 Hz, 2H, 2 × C18H), 1.76 – 1.61 (m, 3H, C9H, C2H_2), 1.44 – 1.08 (m, 42H, 4 × C17H_3, 2 × C19H_3, 4 × pinacol-CH_3, C3H_2, C4H_2, C5H_2, C6H_2, C7H_2, C8H_2), 0.90 (d, $^3J_{HH}$ = 6.9 Hz, 3H, C11H_3), 0.82 (dd, $^2J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 5.8 Hz, C10*H*^{a}H^b), 0.64 (dd, $^2J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 8.3 Hz, C10H^a*H*^{b}) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.2 (C=O), 150.1 (C15), 144.9 (2C, 2 × C13), 130.9 (C12), 121.0 (2C, 2 × C14), 83.0 (2C, 2 × pinacol-C), 65.2 (C1), 39.8 (CH_2), 34.6 (C16), 31.6 (2C, 2 × C13), 30.0 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 28.8 (C2), 27.4 (CH_2), 26.3 (CH_2), 25.0 (2C, 2 × CH_3), 25.0 (2C, 2 × CH_3), 24.3 (4C, 4 × CH_3), 24.1 (2C, 2 × CH_3), 22.6 (C11) ppm.

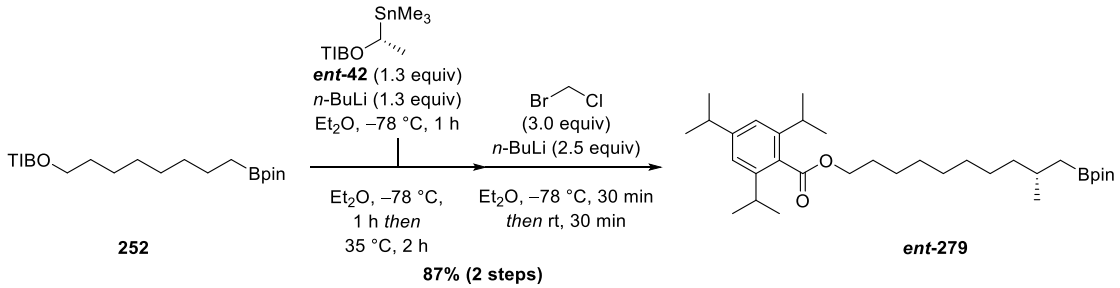
carbon next to boron not observed due to quadrupolar relaxation

HRMS (*m/z*): (ESI) calculated for $C_{33}H_{57}{}^{11}BO_4$ [*M*+Na]$^+$ 551.4248, found 551.4244.

IR (ν_{max}/cm^{-1}, neat): 2960, 2926, 2868, 1725, 1606, 1461, 1369, 1315, 1250, 1140, 1076.

$[\alpha]_D^{25}$: −70.7 (*c* = 0.9, $CHCl_3$).

(*S*)-9-methyl-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)decyl 2,4,6-triisopropylbenzoate (*ent*-279)



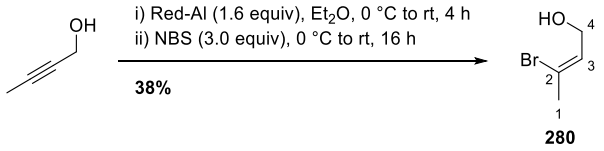
According to the literature procedure,[34,35] *n*-BuLi (1.60 M in hexanes, 1.67 mL, 2.67 mmol, 1.30 equiv) was added dropwise to a stirred solution of (*R*)-stannane ***ent*-42** (1.17 g, 2.67 mmol, 1.30 equiv) in anhydrous Et_2O (10.3 mL, 0.260 M) at −78 °C (acetone/dry ice) under N_2. The reaction mixture was stirred at −78 °C for 1 h then boronic ester **252** (1.00 g, 2.06 mmol, 1.00 equiv) in Et_2O (2.06 mL, 1.00 M) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h then at 35 °C (oil bath) for 2 h. The reaction mixture was cooled to ambient temperature and filtered through a plug of Et_2O-wetted silica into a flame dried flask. The filtrate was concentrated under reduced pressure and the crude boronic ester used directly for the next homologation.

Bromochloromethane (0.400 mL, 6.20 mmol, 3.00 equiv) was added to the crude boronic ester in anhydrous Et_2O (10.3 mL, 0.200 M) and the mixture cooled to −78 °C (acetone/dry ice) under N_2 before the slow addition (syringe pump, 0.05 mL/min) of *n*-BuLi (1.60 M in hexanes, 3.21 mL, 5.14 mmol, 2.50 equiv). When the addition was complete the reaction mixture was stirred at −78 °C for 30 min then at ambient temperature for 30 min. The reaction mixture was filtered through a plug of Et_2O-wetted silica and the filtrate concentrated under reduced pressure. The crude residue was purified by flash column chromatography on a Biotage Isolera One system (80 g ZIP Sphere column, pentane:Et_2O 99:1 to 92:8) to afford boronic ester ***ent*-279** (948 mg, 1.79 mmol, 87%) as a colourless oil.

All recorded spectroscopic data matched the enantiomer **279**.

$[\alpha]_D^{25}$: +3.9 (*c* = 1, $CHCl_3$).

(*Z*)-3-bromobut-2-en-1-ol (280)



According to the literature procedure,[166] a solution of Red-Al (60% w/w in toluene, 10.4 mL, 32.0 mmol, 1.60 equiv) was added dropwise to a stirred solution of 2-butyn-1-ol (1.50 mL, 20.0 mmol, 1.00 equiv) in anhydrous Et_2O (33.0 mL, 0.600 M) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 4 h. The reaction was then cooled to 0 °C again and *N*-bromosuccinimide (10.7 g, 60.0 mmol, 3.00 equiv) was added in one portion. The resulting mixture was allowed to warm to ambient temperature with stirring overnight. The reaction was cooled to 0 °C and quenched with sat. aq. $Na_2S_2O_3$ (30 mL) and 2 M aq. HCl (6 mL, added dropwise). 50% sat aq. Rochelle's salt was added then the mixture was warmed to ambient temperature and stirred for 20 min. The mixture was diluted with ethyl acetate (50 mL) and water (50 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 80 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 70:30 pentane:Et_2O) to afford alcohol **280** (1.16 g, 7.68 mmol, 38%) as a colourless oil. Isolated with 2.5% Et_2O by weight due to concerns about the compound's volatility under high vacuum.

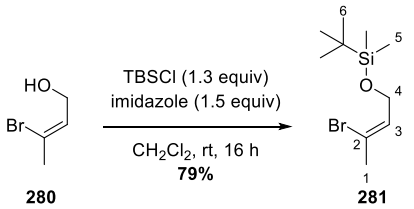
All recorded spectroscopic data matched that previously reported.[166]

TLC: R_f = 0.21 (60:40 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.91 (tq, $^3J_{HH}$ = 6.1 Hz,4 = 1.3 Hz, 1H, C3H), 4.26 – 4.21 (m, 2H, C4H_2), 2.32 (q, $^4J_{HH}$ = 1.3 Hz, 3H, C1H_3), 1.61 (t, $^3J_{HH}$ = 5.7 Hz, 1H, OH) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 128.2 (C3), 124.7 (C2), 62.6 (C4), 29.0 (C1) ppm.

(*Z*)-((3-bromobut-2-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (281)



Imidazole (0.622 g, 9.14 mmol, 1.50 equiv) was added to a solution of **280** (0.920 g, 6.09 mmol, 1.00 equiv) in CH_2Cl_2 (30.0 mL, 0.200 M). The resulting mixture was cooled to 0 °C and *tert*-butyldimethylsilyl chloride (1.19 g, 7.92 mmol, 1.30 equiv) was added in one portion. The reaction mixture was warmed to ambient temperature and left to stir overnight. The reaction was quenched with water (30 mL), the phases separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 100% pentane) to afford protected alcohol **281** (1.28 g, 4.83 mmol, 79%) as a colourless oil.

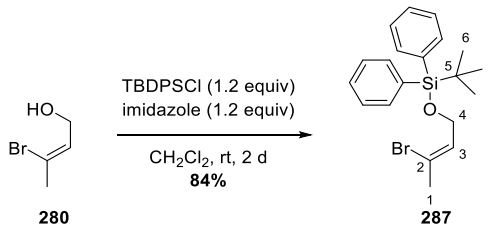
All recorded spectroscopic data matched that previously reported.[218]

TLC: R_f = 0.67 (96:4 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.80 (tq, $^3J_{HH}$ = 5.5 Hz, $^4J_{HH}$ = 1.4 Hz, 1H, C3H), 4.26 (dq, $^3J_{HH}$ = 5.5 Hz, $^5J_{HH}$ = 1.4 Hz, 2H, C4H_2), 2.29 (q, $^4J_{HH}$ = 1.4 Hz, 3H, C1H_3), 0.91 (s, 9H, 3 × C6H_3), 0.08 (s, 6H, 2 × C5H_3) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 129.5 (C3), 121.8 (C2), 63.7 (C4), 28.9 (C1), 26.1 (3C, 3 × C6), −5.0 (2C, 2 × C5) ppm.

(*Z*)-((3-bromobut-2-en-1-yl)oxy)(*tert*-butyl)diphenylsilane (287)



Allylic alcohol **280** (2.08 g, 13.7 mmol, 1.00 equiv) in CH_2Cl_2 (13.7 mL, 1.00 M), was added to imidazole (1.01 g, 16.5 mmol, 1.20 equiv) and *tert*-butyldiphenylsilyl chloride (4.30 mL, 16.5 mmol, 1.20 equiv) in CH_2Cl_2 (33.0 mL, 0.300 M overall wrt **280**) at ambient temperature.

The reaction mixture was left stirring at ambient temperature for 2 days then diluted with water (40 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organics were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 97.5:2.5 to 95:5 pentane:Et_2O) to afford protected alcohol **287** (4.48 g, 11.5 mmol, 84%) as a colourless oil.

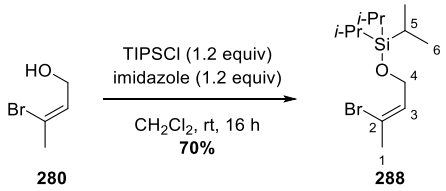
All recorded spectroscopic data matched that previously reported.[166]

TLC: R_f = 0.47 (98:2 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 4H, 4 × Ph-H), 7.46 – 7.37 (m, 6H, 6 × Ph-H), 5.89 (m, 1H, C3H), 4.34 – 4.30 (m, 2H, C4H_2), 2.28 – 2.26 (m, 3H, C1H_3), 1.07 (s, 9H, 3 × C6H_3) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 135.7 (4 × *m*Ph C), 133.7 (2 × Ph-CSi), 129.8 (2 × *p*Ph C), 129.2 (C3), 127.8 (4 × *o*Ph C), 121.9 (C2), 64.4 (C4), 28.8 (C1), 27.0 (C6), 19.3 (C5) ppm.

(*Z*)-((3-bromobut-2-en-1-yl)oxy)triisopropylsilane (288)



280 **288**

Allylic alcohol **280** (0.100 g, 0.662 mmol, 1.00 equiv) in CH_2Cl_2 (0.660 mL, 1.00 M), was added to imidazole (54.1 mg, 0.795 mmol, 1.20 equiv) and triisopropylsilyl chloride (0.17 mL, 0.80 mmol, 1.2 equiv) in CH_2Cl_2 (1.60 mL, 0.300 M overall wrt **280**) at ambient temperature. The reaction mixture was left stirring at ambient temperature overnight then diluted with water (3 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organics were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 97.5:2.5 pentane:Et_2O) to afford protected alcohol **288** (142 mg, 0.464 mmol, 70%) as a colourless oil.

TLC: R_f = 0.70 (96:4 pentane:Et_2O, $KMnO_4$).

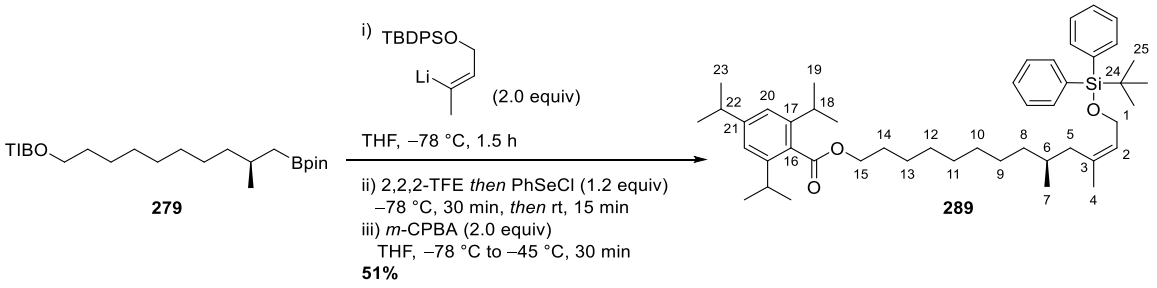
^{1}H NMR: (500 MHz, $CDCl_3$) δ 5.84 (tq, $^{3}J_{HH}$ = 5.1 Hz, $^{4}J_{HH}$ = 1.4 Hz, 1H, C3H), 4.33 (dq, $^{3}J_{HH}$ = 5.1 Hz, $^{5}J_{HH}$ = 1.5 Hz, 2H, C4H_2), 2.29 (dt, $^{4}J_{HH}$ = 1.4 Hz, $^{5}J_{HH}$ = 1.5 Hz, 3H, C1H_3), 1.14 – 1.04 (m, 21H, 3 × C5H, 6 × C6H_3) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 129.9 (C3), 121.2 (C2), 63.9 (C4), 28.8 (C1), 18.1 (C6), 12.1 (C5) ppm.

HRMS (*m/z*): (APCI) calculated for $C_{13}H_{27}{}^{79}BrOSi$ $[M+H]^+$ 307.1093, found 307.0901.

IR (ν_{max}/cm^{-1}, neat) 2942, 2865, 1664, 1462, 1104, 1058, 882.

(*S*,*Z*)-13-((*tert*-butyldiphenylsilyl)oxy)-9,11-dimethyltridec-11-en-1-yl 2,4,6-triisopropylbenzoate (289)



According to the literature procedure,[166] *t*-BuLi (1.60 M in pentane, 0.160 mL, 0.260 mmol, 4.00 equiv) was added dropwise over 5 min to a mixture of vinyl bromide **287** (49.7 mg, 0.128 mmol, 2.00 equiv) and boronic ester **279** (33.9 mg, 64.2 µmol, 1.00 equiv) in anhydrous THF (1.00 mL) at −78 °C (acetone/dry ice) under N_2. The resulting solution was stirred at −78 °C for 90 min and then 2,2,2-trifluoroethanol (1.00 mL) was added dropwise. Freshly ground phenylselenyl chloride (14.7 mg, 77.0 µmol, 1.20 equiv) was added in a single portion and the resulting mixture was stirred vigorously at −78 °C for 30 min then ambient temperature for 15 min. The mixture was concentrated under reduced pressure and filtered through Et_2O-wetted silica, washing with Et_2O. The filtrate was concentrated under reduced pressure and redissolved in THF (0.60 mL). The solution was cooled to −78 °C (acetone/dry ice) and 3-chloroperoxybenzoic acid (22.1 mg, 0.128 mmol, 2.00 equiv) in THF (0.60 mL) was added dropwise. The reaction mixture was warmed to −45 °C (acetonitrile/dry ice) and stirred for 30 min. Dimethyl sulfide (0.10 mL, 1.3 mmol) was added and the mixture warmed to ambient temperature, filtered through Et_2O-wetted silica (washing with Et_2O) and concentrated under reduced pressure. The crude residue was purified by flash column

chromatography (SiO_2, 97.5:2.5 to 50:50 pentane:Et_2O) to afford alkene **289** (23.1 mg, 32.5 µmol, 51%) as a colourless oil.

TLC: R_f = 0.37 (96:4 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 4H, 4 × Ph-H), 7.45 – 7.33 (m, 6H, 6 × Ph-H), 7.01 (s, 2H, 2 × C20H), 5.45 (t, $^3J_{HH}$ = 6.5 Hz 1H, C2H), 4.30 (t, $^3J_{HH}$ = 6.7 Hz, 2H, $C15H_2$), 4.19 (d, $^3J_{HH}$ = 6.5 Hz, 2H, $C1H_2$), 2.88 (sept, $^3J_{HH}$ = 6.8 Hz, 1H, C22H), 2.86 (sept, $^3J_{HH}$ = 6.8 Hz, 2H, 2 × C18H), 1.81 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 6.1 Hz, 1H, C5H^aH^b), 1.76 – 1.66 (m, 3H, C5H^aH^b, $C14H_2$), 1.67 (d, $^4J_{HH}$ = 1.3 Hz, 3H, $C4H_3$), 1.53 – 1.12 (m, 13H, C6H, $C8H_2$, $C9H_2$, $C10H_2$, $C11H_2$, $C12H_2$, $C13H_2$), 1.25 (d, $^3J_{HH}$ = 6.8 Hz, 18H, 4 × $C19H_3$, 2 × $C23H_3$), 1.05 (s, 9H, 3 × $C25H_3$), 0.71 (d, $^3J_{HH}$ = 6.6 Hz, 3H, $C7H_3$) ppm.

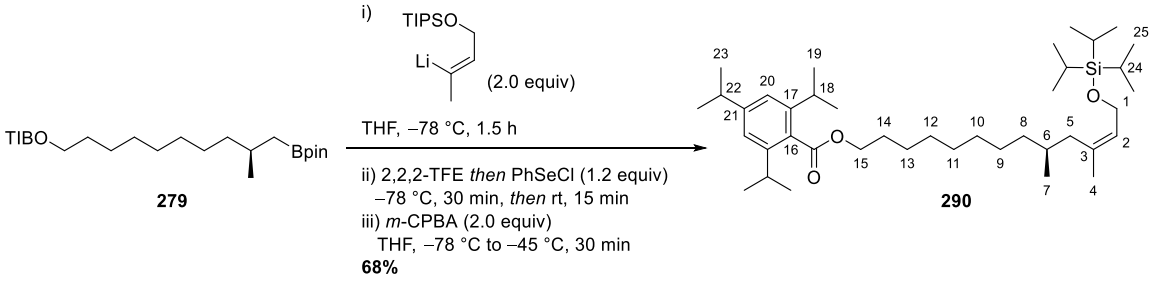
^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.2 (C=O), 150.2 (C16), 144.9 (C17), 136.9 (C3), 135.8 (4 × Ph-C3), 134.2 (2 × Ph-CSi), 130.9 (C21), 129.6 (2 × Ph-C4), 127.7 (4 × Ph-C2), 126.0 (C2), 121.0 (C20), 65.2 (C15), 61.0 (C1), 39.9 (C5), 37.1 (CH_2), 34.6 (C22), 31.6 (2 × C18), 31.4 (C6), 30.0 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 28.8 (C14), 27.3 (C24), 27.0 (3 × C25), 26.2 (C13), 24.3 (4 × C19), 24.1 (2 × C23), 23.9 (C4), 19.5 (C7) ppm.

HRMS (*m/z*): (ESI) calculated for $C_{47}H_{70}O_3Si$ [*M*+NH_3]$^+$ 728.5432, found 728.6435.

IR (ν_{max}/cm^{-1}, neat): 2958, 2026, 2855, 1725, 1462, 1251, 1106, 1076.

$[\alpha]_D^{25}$: −5 (*c* = 0.2, $CHCl_3$).

(*S*,*Z*)-9,11-dimethyl-13-((triisopropylsilyl)oxy)tridec-11-en-1-yl 2,4,6-triisopropylbenzoate (290)



According to the literature procedure,[166] *t*-BuLi (1.50 M in pentane, 0.510 mL, 0.760 mmol, 4.00 equiv) was added dropwise over 15 min to a mixture of vinyl bromide **288** (116 mg, 0.378 mmol, 2.00 equiv) and boronic ester **279** (100 mg, 0.189 mmol, 1.00 equiv) in

anhydrous THF (0.950 mL, 0.200 M) at −78 °C (acetone/dry ice) under N_2. The resulting solution was stirred at −78 °C for 90 min and then 2,2,2-trifluoroethanol (0.950 mL) was added dropwise. Freshly ground phenylselenyl chloride (43.5 mg, 0.227 mmol, 1.20 equiv) was added in a single portion and the resulting mixture was stirred vigorously at −78 °C for 30 min then ambient temperature for 15 min. The mixture was concentrated under reduced pressure and filtered through Et_2O-wetted silica, washing with Et_2O. The filtrate was concentrated under reduced pressure and redissolved in THF (1.50 mL). The solution was cooled to −78 °C (acetone/dry ice) and 3-chloroperoxybenzoic acid (65.3 mg, 0.378 mmol, 2.00 equiv) in THF (0.380 mL) was added dropwise. The reaction mixture was warmed to −45 °C (acetonitrile/dry ice) and stirred for 30 min. Dimethyl sulfide (0.15 mL, 3.80 mmol) was added and the mixture warmed to ambient temperature, filtered through Et_2O-wetted silica (washing with Et_2O) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 97.5:2.5 to 50:50 pentane:Et_2O) to afford alkene **290** (81.0 mg, 0.129 mmol, 68%) as a colourless oil, contaminated with a small amount of diphenyldiselenide.

TLC: R_f = 0.60 (96:4 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.00 (s, 2H, 2 × C20H), 5.39 (t, $^3J_{HH}$ = 6.4 Hz, 1H, C2H), 4.30 (t, $^3J_{HH}$ = 6.7 Hz, 2H, C15H_2), 4.26 – 4.17 (m, 2H, C1H_2), 2.87 (sept, $^3J_{HH}$ = 6.8 Hz, 1H, C22H), 2.86 (sept, $^3J_{HH}$ = 6.8 Hz, 2H, 2 × C18H), 1.96 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 6.3 Hz, 1H, C5H^aH^b), 1.83 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 8.5 Hz, 1H, C5H^aH^b), 1.76 – 1.66 (m, 2H, C14H_2), 1.68 (d, $^4J_{HH}$ = 1.2 Hz, 3H, C4H_3), 1.37 – 0.99 (m, 52H, 6 × C25H_3, 3 × C24H, 2 × C23H_3, 4 × C19H_3, C13H_2, C12H_2, C11H_2, C10H_2, C9H_2, C8H_2, C6H), 0.80 (d, $^3J_{HH}$ = 6.6 Hz, 3H, C7H_3) ppm.

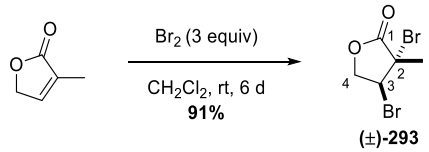
^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.2 (C=O), 150.2 (C21), 144.9 (C17), 136.2 (C3), 131.7 (C16), 126.8 (C2), 121.0 (C20), 65.2 (C15), 60.4 (C1), 40.1 (C5), 37.2 (CH_2), 34.6 (C22), 31.6 (2 × C18), 31.6 (C6), 30.0 (CH_2), 29.8 (CH_2), 29.4 (CH_2), 28.8 (C14), 27.4 (CH_2), 26.3 (C13), 24.3 (4 × C19), 24.1 (2 × C23), 23.9 (C4), 19.7 (C7), 18.2 (6 × C25), 12.2 (3 × C24) ppm.

HRMS (*m/z*): (ESI) calculated for $C_{40}H_{72}O_3Si$ [*M*+NH_3]$^+$ 646.5589, found 646.5580.

IR (ν_{max}/cm^{-1}, neat): 2959, 2953, 2865, 1726, 1461, 1250, 1075, 881.

$[\alpha]_D^{26}$: +1 (*c* = 1, $CHCl_3$).

3,4-dibromo-3-methyldihydrofuran-2(3*H*)-one (293)



According to the literature procedure,[171] bromine (5.64 mL, 110 mmol, 3.00 equiv) was added slowly to 3-methyl-2-(5*H*)-furanone (3.60 g, 36.7 mmol, 1.00 equiv) in CH_2Cl_2 (37.0 mL, 1.00 M) at −10 °C (acetone/wet ice) and the reaction mixture was stirred at ambient temperature for 6 days (until full consumption of starting material by TLC analysis). The reaction mixture was poured into ice/sat. aq. $Na_2S_2O_3$ (100 g/100 mL), stirring vigorously. CH_2Cl_2 (100 mL) was added and the phases separated. The organic phase was washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 80:20 pentane:Et_2O) to afford dibromide **293** (8.58 g, 33.3 mmol, 91%) as a pale yellow solid.

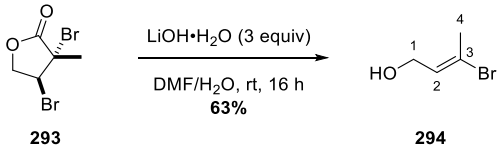
All recorded spectroscopic data matched that previously reported.[171]

TLC: R_f = 0.51 (50:50 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.00 (dd, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 3.7 Hz, 1H, C4*H*^{a}H^b), 4.84 (d, $^3J_{HH}$ = 3.7 Hz, 1H, C3H), 4.55 (d, $^2J_{HH}$ = 11.1 Hz, 1H, C4H^a*H*^{b}), 2.10 (s, 3H, C2-Me) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.9 (C1), 73.9 (C4), 54.4 (C2), 52.9 (C3), 25.4 (Me) ppm.

(*E*)-3-bromobut-2-en-1-ol (294)



According to the literature procedure,[171] lithium hydroxide·monohydrate (3.85 g, 91.7 mmol, 3.00 equiv) was added to dibromide **293** (7.88 g, 30.6 mmol, 1.00 equiv) in DMF/H_2O (4:1, 60.0 mL, 0.510 M) at ambient temperature. After stirring at ambient temperature overnight, the reaction mixture was directly purified by flash column chromatography (SiO_2, 2:1 pentane:Et_2O) to afford alcohol **294** (2.91 g, 19.3 mmol, 63%) as a pale yellow oil.

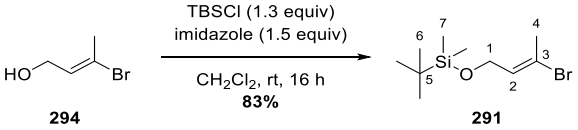
All recorded spectroscopic data matched that previously reported.[219]

TLC: R_f = 0.29 (50:50 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.10 (tq, $^{3}J_{HH}$ = 7.2 Hz, $^{4}J_{HH}$ = 1.3 Hz, 1H, C2H), 4.12 (d, $^{3}J_{HH}$ = 7.2 Hz, 2H, C1H_2), 2.30 (d, $^{4}J_{HH}$ = 1.3 Hz, 3H, C4H_3) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 131.0 (C2), 124.4 (C3), 59.8 (C1), 23.8 (C4) ppm.

(*E*)-((3-bromobut-2-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (291)



tert-Butyldimethylsilyl chloride (0.428 g, 2.84 mmol, 1.30 equiv) was added to a mixture of allylic alcohol **294** (0.330 g, 2.19 mmol, 1.00 equiv) and imidazole (0.223 g, 68.1 mmol, 1.50 equiv) in CH_2Cl_2 (11.0 mL, 0.200 M) at 0 °C and the reaction mixture was stirred at ambient temperature overnight. Water (10 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 100% pentane) to afford protected alcohol **291** (0.483 g, 1.82 mmol, 83%) as a colourless oil.

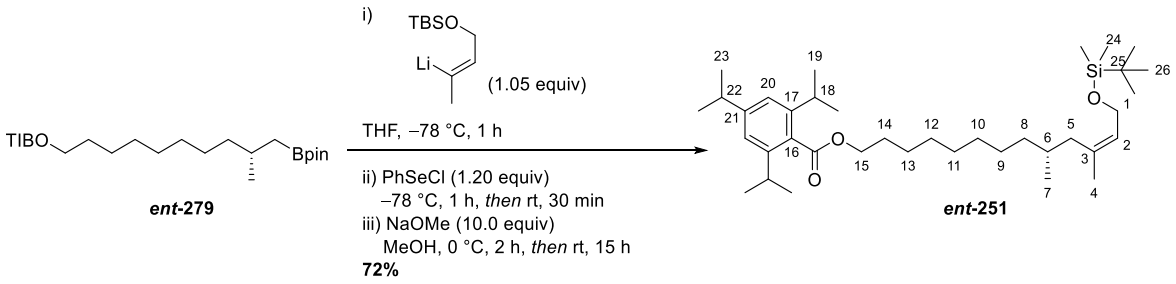
All recorded spectroscopic data matched that previously reported.[220]

TLC: R_f = 0.78 (96:4 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.00 (tq, $^{3}J_{HH}$ = 6.7 Hz, $^{4}J_{HH}$ = 1.3 Hz, 1H, C2H), 4.13 (dq, $^{3}J_{HH}$ = 6.7, $^{5}J_{HH}$ 0.9 Hz, 2H, C1H_2), 2.26 (dt, $^{4}J_{HH}$ = 1.3 Hz, $^{5}J_{HH}$ = 0.9 Hz, 3H, C4H_3), 0.90 (s, 9H, 3 × C6H_3), 0.07 (s, 6H, 2 × C7H_3) ppm.

^{13}C NMR: (101 MHz, $CDCl_3$) δ 131.9 (C2), 122.0 (C3), 60.5 (C1), 26.0 (3 × C6), 23.9 (C4), 18.5 (C5), −5.0 (2 × C7) ppm.

(*R*,*Z*)-13-((*tert*-butyldimethylsilyl)oxy)-9,11-dimethyltridec-11-en-1-yl 2,4,6-triisopropylbenzoate (*ent*-251)



According to the modified literature procedure,[166] *t*-BuLi (2.80 M in heptane, 0.380 mL, 1.05 mmol, 2.10 equiv) was added dropwise to a solution of vinyl bromide **291** (0.139 g, 0.525 mmol, 1.05 equiv) in anhydrous THF (2.63 mL, 0.200 M) at −78 °C (acetone/dry ice) under N_2. The resulting mixture was stirred at −78 °C for 30 min before the dropwise addition of boronic ester ***ent*-279** (0.264 g, 0.500 mmol, 1.00 equiv) in THF (2.50 mL, 0.200 M). The reaction mixture was stirred at −78 °C for 1 h then phenylselenyl chloride (0.115 g, 0.600 mmol, 1.20 equiv) in THF (0.60 mL, 1.00 M) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h then ambient temperature for 30 min. The reaction mixture was cooled to 0 °C (water/ice); sodium methoxide (0.270 g, 5.00 mmol, 10.0 equiv) in MeOH (10.0 mL, 0.500 M) was added and stirring continued at 0 °C for 2 h, then ambient temperature overnight. Sat. aq. $Na_2S_2O_3$ (10 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2, 100% pentane to elute yellow diphenyldiselenide, then 99:1 to 97.5:2.5 pentane:Et_2O) to afford alkene ***ent*-251** (0.212 g, 0.361 mmol, 72%) as a colourless oil.

TLC: R_f = 0.35 (96:4 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.00 (s, 2H, 2 × C20H), 5.36 (t, $^3J_{HH}$ = 6.4 Hz, 1H, C2H), 4.30 (t, $^3J_{HH}$ = 6.6 Hz, 2H, $C15H_2$), 4.20 – 4.11 (m, 2H, $C1H_2$), 2.87 (sept, $^3J_{HH}$ = 7.0 Hz, 3H, 2 × C18H), 2.84 (sept, $^3J_{HH}$ = 6.9 Hz, 3H, C22H), 1.96 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 6.2 Hz, 1H, C5H^aH^b), 1.86 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 8.5 Hz, 1H, C5H^aH^b), 1.76 – 1.69 (m, 2H, $C14H_2$), 1.68 (s, 3H, $C4H_3$), 1.48 – 0.98 (m, 31H, C6H, $C8H_2$, $C9H_2$, $C10H_2$, $C11H_2$, $C12H_2$, $C13H_2$, 4 × $C19H_3$, 2 × $C23H_3$), 0.90 (s, 9H, 3 × $C26H_3$), 0.80 (d, $^3J_{HH}$ = 6.6 Hz, 3H, $C7H_3$), 0.07 (s, 6H, 2 × $C24H_3$) ppm.

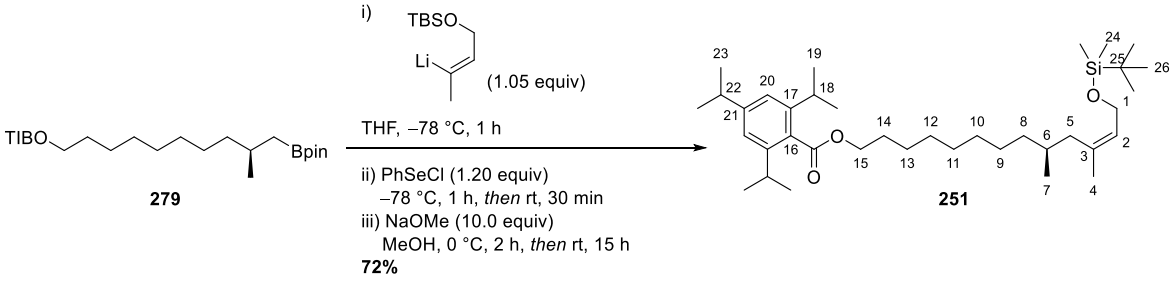
^{13}C NMR: (126 MHz, $CDCl_3$) δ 171.2 (C=O), 150.2 (C21), 144.8 (C17), 136.7 (C3), 130.9 (C16), 126.3 (C2), 121.0 (C20), 65.2 (C15), 60.2 (C1), 40.0 (C5), 37.2 (CH_2), 34.6 (C22), 31.6 (2 × C18), 31.5 (C6), 30.0 (CH_2), 29.8 (CH_2), 29.4 (CH_2), 28.8 (C14), 27.4 (CH_2), 26.2 (C26), 26.2 (C13), 24.3 (4 × C19), 24.1 (2 × C23), 23.9 (C4), 19.6 (C7), 18.6 (C25), −4.9 (C24) ppm.

HRMS (*m/z*): (ESI) calculated for $C_{37}H_{66}O_3Si$ $[M+Na]^+$ 609.4673, found 609.4673.

IR (ν_{max}/cm^{-1}, neat): 2960, 2928, 2856, 1722, 1462, 1251, 1076, 908, 835.

$[\alpha]_D^{26}$: −2 (*c* = 1, $CHCl_3$).

(*S*,*Z*)-13-((*tert*-butyldimethylsilyl)oxy)-9,11-dimethyltridec-11-en-1-yl 2,4,6-triisopropylbenzoate (251)



According to the modified literature procedure,[166] *t*-BuLi (2.80 M in heptane, 0.450 mL, 1.30 mmol, 2.10 equiv) was added dropwise to a solution of vinyl bromide **291** (0.167 g, 0.630 mmol, 1.05 equiv) in anhydrous THF (3.15 mL, 0.200 M) at −78 °C (acetone/dry ice) under N_2. The resulting mixture was stirred at −78 °C for 30 min before the dropwise addition of boronic ester **279** (0.317 g, 0.600 mmol, 1.00 equiv) in THF (3.00 mL, 0.200 M). The reaction mixture was stirred at −78 °C for 1 h then phenylselenyl chloride (0.138 g, 0.720 mmol, 1.20 equiv) in THF (0.720 mL, 1.00 M) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h then ambient temperature for 30 min. The reaction mixture was cooled to 0 °C (water/ice); sodium methoxide (0.324 g, 6.00 mmol, 10.0 equiv) in MeOH (12.0 mL, 0.500 M) was added and stirring continued at 0 °C for 2 h, then ambient temperature overnight. Sat. aq. $Na_2S_2O_3$ (10 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2, 100% pentane to elute yellow

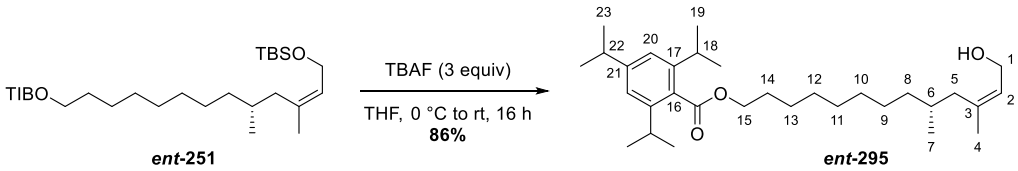
diphenyldiselenide, then 99:1 to 97.5:2.5 pentane:Et_2O) to afford alkene **251** (0.254 g, 0.433 mmol, 72%) as a colourless oil.

All recorded spectroscopic data matched the enantiomer ***ent*-251**.

$[\alpha]_D^{26}$**:** +5 (*c* = 1, $CHCl_3$).

NMR spectra included in section **6.5**

(*R*,*Z*)-13-hydroxy-9,11-dimethyltridec-11-en-1-yl 2,4,6-triisopropylbenzoate (*ent*-295)



Tetrabutylammonium fluoride (1.00 M in THF, 1.02 mL, 3.00 equiv) was added dropwise to silyl ether ***ent*-251** (0.200 g, 0.341 mmol, 1.00 equiv) in THF (1.70 mL, 0.200 M) at 0 °C (water/ice) and the reaction mixture was stirred at ambient temperature overnight. Sat. aq. NH_4Cl (2 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (5 × 3 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 95:5 to 60:40 pentane:Et_2O) to afford alcohol ***ent*-295** (139 mg, 0.294 mmol, 86%) as a colourless oil.

TLC: R_f = 0.25 (70:30 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.00 (s, 2H, 2 × C20H), 5.48 (t, $^3J_{HH}$ = 7.0 Hz, 1H, C2H), 4.30 (t, $^3J_{HH}$ = 6.7 Hz, 2H, $C15H_2$), 4.17 – 4.07 (m, 2H, $C1H_2$), 2.87 (sept, $^3J_{HH}$ = 7.0 Hz, 3H, 2 × C18H), 2.85 (sept, $^3J_{HH}$ = 6.9 Hz, 3H, C22H), 2.01 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 6.2 Hz, 1H, C5H^aH^b), 1.92 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 8.5 Hz, 1H, C5H^aH^b), 1.76 – 1.69 (m, 2H, $C14H_2$), 1.68 (d, $^4J_{HH}$ = 1.3 Hz, 3H, $C4H_3$), 1.45 – 1.04 (m, 31H, C6H, $C8H_2$, $C9H_2$, $C10H_2$, $C11H_2$, $C12H_2$, $C13H_2$, 4 × $C19H_3$, 2 × $C23H_3$), 0.81 (d, $^3J_{HH}$ = 6.6 Hz, 3H, $C7H_3$) ppm.

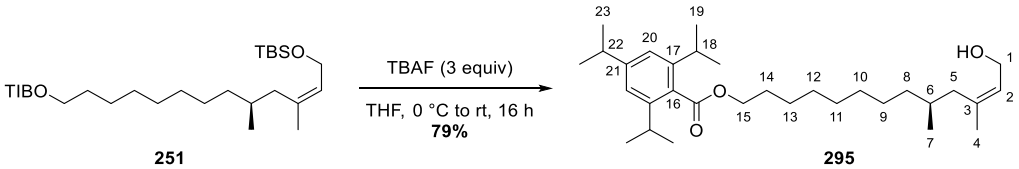
^{13}C NMR: (126 MHz, $CDCl_3$) δ 171.2 (C=O), 150.2 (C21), 144.8 (C17), 139.4 (C3), 130.9 (C16), 125.3 (C2), 121.0 (C20), 65.2 (C15), 59.4 (C1), 39.7 (C5), 37.2 (CH_2), 34.6 (C22), 31.6 (2 × C18), 31.4 (C6), 29.9 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 28.8 (C14), 27.3 (CH_2), 26.2 (C13), 24.3 (4 × C19), 24.10 (2 × C23), 23.9 (C4), 19.6 (C7) ppm.

HRMS (*m/z*): (ESI) calculated for $C_{31}H_{52}O_3$ [*M*+Na]$^+$ 495.3809, found 495.3831.

IR (ν_{max}/cm^{-1}, neat): 2960, 2926, 2855, 1721, 1606, 1481, 1252, 1076, 909.

$[\alpha]_D^{26}$**:** −7 (*c* = 1, $CHCl_3$).

(*S*,*Z*)-13-hydroxy-9,11-dimethyltridec-11-en-1-yl 2,4,6-triisopropylbenzoate (295)

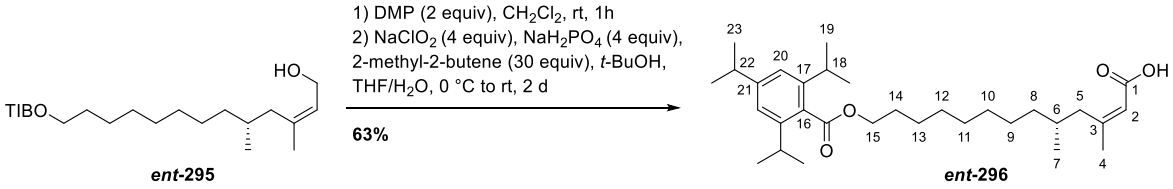


Tetrabutylammonium fluoride (1.00 M in THF, 1.23 mL, 3.00 equiv) was added dropwise to silyl ether **251** (0.240 g, 0.409 mmol, 1.00 equiv) in THF (2.00 mL, 0.200 M) at 0 °C (water/ice) and the reaction mixture was stirred at ambient temperature overnight. Sat. aq. NH_4Cl (2 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (5 × 3 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 95:5 to 60:40 pentane:Et_2O) to afford alcohol **295** (153 mg, 0.323 mmol, 79%) as a colourless oil.

All recorded spectroscopic data matched the enantiomer ***ent*-295**.

$[\alpha]_D^{26}$**:** +8 (*c* = 1, $CHCl_3$).

(*R*,*Z*)-3,5-dimethyl-13-((2,4,6-triisopropylbenzoyl)oxy)tridec-2-enoic acid (*ent*-296)



<u>Dess-Martin oxidation</u>

Dess-Martin periodinane (197 mg, 0.465 mmol, 2.00 equiv) was added to a solution of allylic alcohol ***ent*-295** (110 mg, 0.233 mmol, 1.00 equiv) in CH_2Cl_2 (2.30 mL, 0.100 M) at ambient temperature. The reaction mixture was stirred at ambient temperature for 1 h then sat. aq.

$NaHCO_3$ (2 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

Pinnick oxidation

tert-Butanol (2.30 mL) and 2-methyl-2-butene (0.520 mL, 7.00 mmol, 30.0 equiv) were added to the crude aldehyde in THF (2.30 mL, 0.100 M) and the mixture cooled to 0 °C (water/ice). A mixture of sodium chlorite (84.2 mg, 0.931 mmol, 4.00 equiv) and sodium phosphate monobasic (112 mg, 0.931 mmol, 4.00 equiv) in H_2O (1.10 mL) was added dropwise and the resulting mixture was stirred at ambient temperature for 2 days. The reaction mixture was diluted with 2 M aq. HCl (5 mL) and Et_2O (5 mL); the phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure and purified by flash column chromatography (SiO_2, 90:10 to 50:50 pentane:Et_2O) to afford carboxylic acid ***ent*-296** (71.4 mg, 0.147 mmol, 63%) as a colourless oil.

TLC: R_f = 0.56 (50:50 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.00 (s, 2H, 2 × C20H), 5.74 (s, 1H, C2H), 4.30 (t, $^3J_{HH}$ = 6.7 Hz, 2H, $C15H_2$),), 2.87 (sept, $^3J_{HH}$ = 6.9 Hz, 3H, 2 × C18H), 2.85 (sept, $^3J_{HH}$ = 6.8 Hz, 3H, C22H), 2.58 (dd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 8.8 Hz, 1H, C5H^aH^b), 2.52 (dd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 6.1 Hz, 1H, C5H^aH^b), 1.89 (d, $^4J_{HH}$ = 1.3 Hz, 3H, $C4H_3$), 1.76 – 1.69 (m, 3H, $C14H_2$, C6H), 1.44 – 1.10 (m, 30H, $C8H_2$, $C9H_2$, $C10H_2$, $C11H_2$, $C12H_2$, $C13H_2$, 4 × $C19H_3$, 2 × $C23H_3$), 0.86 (d, $^3J_{HH}$ = 6.6 Hz, 3H, $C7H_3$) ppm.

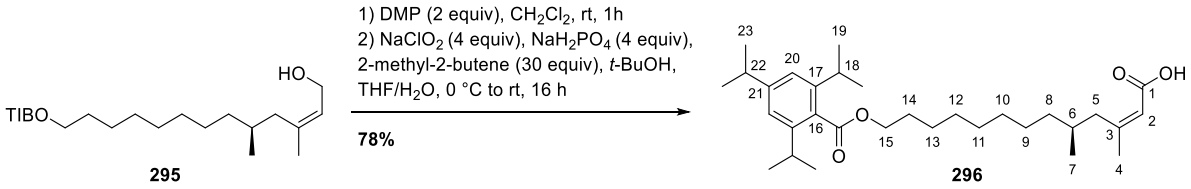
^{13}C NMR: (126 MHz, $CDCl_3$) δ 171.2 (C=O), 171.0 (C1), 163.1 (C2), 150.2 (C21), 144.8 (C17), 130.9 (C16), 121.0 (C20), 116.7 (C2), 65.2 (C15), 40.4 (C5), 37.2 (CH_2), 34.6 (C22), 32.2 (C6), 31.6 (2 × C18), 29.9 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 28.8 (C14), 27.2 (CH_2), 26.2 (C13), 25.8 (C4), 24.3 (4 × C19), 24.1 (2 × C23), 19.4 (C7) ppm.

HRMS (*m/z*): (ESI) calculated for $C_{37}H_{50}O_4$ [*M*+Na]$^+$ 509.3601, found 509.3598.

IR (ν_{max}/cm^{-1}, neat): 2960, 2927, 2856, 1723, 1690, 1653, 1460, 1252, 909.

$[\alpha]_D^{26}$: −37 (*c* = 0.5, $CHCl_3$).

(*S*,*Z*)-3,5-dimethyl-13-((2,4,6-triisopropylbenzoyl)oxy)tridec-2-enoic acid (296)



Dess-Martin oxidation

Dess-Martin periodinane (215 mg, 0.254 mmol, 2.00 equiv) was added to a solution of allylic alcohol **295** (125 mg, 0.254 mmol, 1.00 equiv) in CH_2Cl_2 (2.50 mL, 0.100 M) at ambient temperature. The reaction mixture was stirred at ambient temperature for 1 h then sat. aq. $NaHCO_3$ (2 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

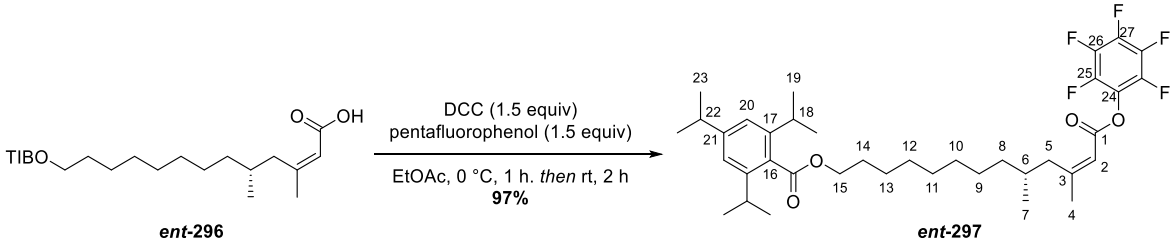
Pinnick oxidation

tert-Butanol (2.50 mL) and 2-methyl-2-butene (0.810 mL, 7.61 mmol, 30.0 equiv) were added to the crude aldehyde in THF (2.50 mL, 0.100 M) and the mixture was cooled to 0 °C (water/ice). A mixture of sodium chlorite (115 mg, 1.27 mmol, 5.00 equiv) and sodium phosphate monobasic (152 mg, 1.27 mmol, 5.00 equiv) in H_2O (1.25 mL) was added dropwise and the resulting mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with 2 M aq. HCl (5 mL) and Et_2O (5 mL); the phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure and purified by flash column chromatography (SiO_2, 90:10 to 50:50 pentane:Et_2O) to afford carboxylic acid **296** (96.0 mg, 0.197 mmol, 78%) as a colourless oil.

All recorded spectroscopic data matched the enantiomer ***ent*-296**.

$[\alpha]_D^{26}$**:** +13 (*c* = 1, $CHCl_3$).

(*R*,*Z*)-9,11-dimethyl-13-oxo-13-(perfluorophenoxy)tridec-11-en-1-yl 2,4,6-triisopropylbenzoate (*ent*-297)



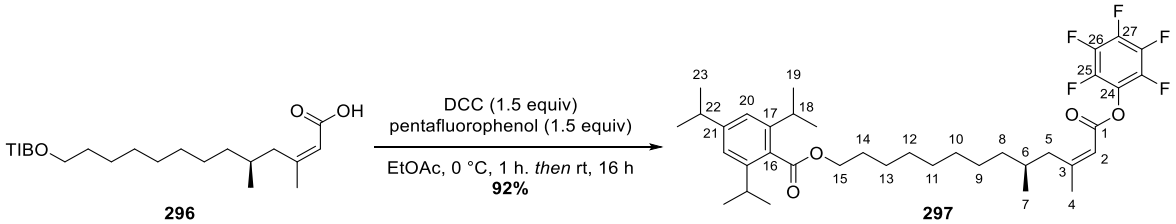
ent-296 *ent*-297

N,*N*′-Dicyclohexylcarbodiimide (38.2 mg, 0.185 mmol, 1.50 equiv) and pentafluorophenol (34.0 mg, 0.185 mmol, 1.50 equiv) were added to carboxylic acid ***ent*-296** (60.0 mg, 0.123 mmol, 1.00 equiv) in EtOAc (1.20 mL, 0.100 M) at 0 °C (water/ice). The reaction mixture was stirred at 0 °C for 1 h then ambient temperature for 2 h and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 95:5 to 50:50 pentane:Et_2O) to afford pentafluorophenyl ester ***ent*-297 (**77.9 mg, 0.119 mmol, 97%) as a pale yellow oil.

All recorded spectroscopic data matched the enantiomer **297**.

$[\alpha]_D^{26}$**:** −65 (*c* = 0.15, $CHCl_3$).

(*S*,*Z*)-9,11-dimethyl-13-oxo-13-(perfluorophenoxy)tridec-11-en-1-yl 2,4,6-triisopropylbenzoate (297)



296 297

N,*N*′-Dicyclohexylcarbodiimide (41.3 mg, 0.200 mmol, 1.50 equiv) and pentafluorophenol (36.9 mg, 0.200 mmol, 1.50 equiv) were added to carboxylic acid **296** (65.0 mg, 0.134 mmol, 1.00 equiv) in EtOAc (1.34 mL, 0.100 M) at 0 °C (water/ice). The reaction mixture was stirred at 0 °C for 1 h then at ambient temperature overnight and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 97:3 pentane:Et_2O) to afford pentafluorophenyl ester **297** (80.2 mg, 0.123 mmol, 92%) as a pale yellow oil.

TLC: R_f = 0.81 (50:50 pentane:Et_2O, $KMnO_4$).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.00 (s, 2H, 2 × C20H), 6.01 (s, 1H, C2H), 4.29 (t, $^3J_{HH}$ = 6.7 Hz, 2H, C15H_2), 2.87 (sept, $^3J_{HH}$ = 6.9 Hz, 3H, 2 × C18H), 2.85 (sept, $^3J_{HH}$ = 6.8 Hz, 3H, C22H), 2.70 (dd, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 8.7 Hz, 1H, C5H^aH^b), 2.56 (dd, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 6.2 Hz, 1H, C5H^aH^b), 2.01 (d, $^4J_{HH}$ = 1.3 Hz, 3H, C4H_3), 1.77 – 1.68 (m, 3H, C6H, C14H_2), 1.37 – 1.17 (m, 30H, C8H_2, C9H_2, C10H_2, C11H_2, C12H_2, C13H_2, 4 × C19H_3, 2 × C23H_3), 0.87 (d, $^3J_{HH}$ = 6.6 Hz, 3H, C7H_3) ppm.

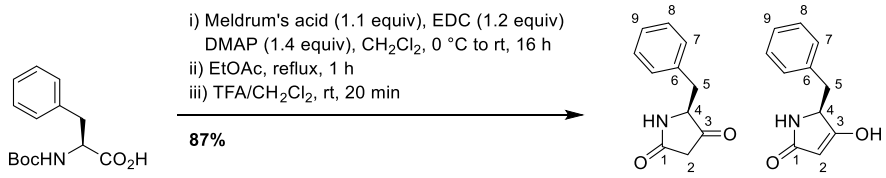
^{13}C NMR: (126 MHz, $CDCl_3$) δ 171.2 (C=O), 167.8 (C1), 161.6 (C3), 150.2 (C21), 144.8 (C17), 141.5 (2 × C25F), 139.3 (C27F), 138.0 (2 × C26F), 130.9 (C16), 125.4 (C24), 121.0 (C20), 113.8 (C2), 65.2 (C15), 41.0 (C5), 37.2 (CH_2), 34.6 (C22), 32.4 (C6), 31.6 (2 × C18), 29.9 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 28.8 (C14), 27.1 (CH_2), 26.2 (C4), 26.2 (C13), 24.3 (4 × C19), 24.1 (2 × C23), 19.3 (C7) ppm.

HRMS (*m/z*): (ESI) calculated for $C_{37}H_{49}F_5O_4$ [*M*+Na]$^+$ 675.3443, found 675.3452.

IR (ν_{max}/cm^{-1}, neat): 2927, 2850, 2119, 1725, 1626, 1571, 1519, 1243, 1086, 1004.

$[\alpha]_D^{26}$: +8 (*c* = 0.7, $CHCl_3$).

(*S*)-5-benzylpyrrolidine-2,4-dione (298)



298

According to the literature procedure,[173] boc-L-phenylalanine (2.00 g, 7.54 mmol, 1.00 equiv) and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.73 g, 9.05 mmol, 1.20 equiv) were added sequentially to a solution of Meldrum's acid [2,2-dimethyl-1,3-dioxane-4,6-dione] (1.20 g, 8.29 mmol, 1.10 equiv) and 4-(dimethylamino)pyridine (1.29 g, 10.6 mmol, 1.40 equiv) in CH_2Cl_2 (50.0 mL, 0.150 M) at 0 °C (water/ice). The resulting reaction mixture was stirred at ambient temperature overnight.

TLC: R_f = 0.57 (25:75 MeOH:EtOAc, anisaldehyde).

The reaction mixture was poured into EtOAc (200 mL) and washed with brine (2 × 100 mL), 5% aq. citric acid (3 × 300 mL) and brine (300 mL). The organic phase was refluxed (oil bath at 85 °C) for 1 h then concentrated under reduced pressure.

TLC: R_f = 0.38 (25:75 MeOH:EtOAc, anisaldehyde).

The residue was redissolved in CH_2Cl_2 (10.0 mL) then treated with trifluoroacetic acid/CH_2Cl_2 (1:1, 10.0 mL). The resulting mixture was stirred at ambient temperature for 20 min then concentrated under reduced pressure. Residual trifluoroacetic acid was co-evaporated with toluene (3 × 50 mL) to afford **298** (1.24 g, 6.55 mmol, 87%) as an off-white solid.

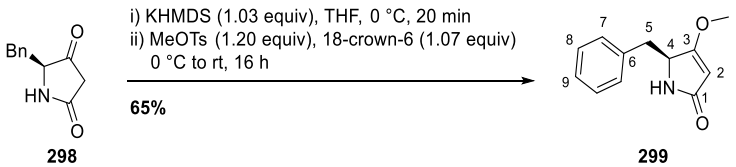
All recorded spectroscopic data matched that previously reported.[173]

TLC: R_f = 0.42 (25:75 MeOH:EtOAc, anisaldehyde).

^{1}H NMR: (400 MHz, DMSO-d_6) δ [keto form] 8.42 (s, 1H, NH), 7.11 – 7.30 (m, 5H, 5 × Ph-H), 4.25 (tt, $^4J_{HH}$ = 5.3 Hz, $^3J_{HH}$ = 1.0 Hz, 1H, C4H), 2.91 (d, $^4J_{HH}$ = 5.3 Hz, 2H, C2H$_2$), 2.90 (dd, $^2J_{HH}$ = 21.8 Hz, $^3J_{HH}$ = 1.0 Hz, 1H, C5*H*^{a}H^b), 2.44 (dd, $^2J_{HH}$ = 21.8 Hz, $^3J_{HH}$ = 1.0 Hz, 1H, C5H^a*H*^{b}) ppm. δ [enol form] 11.36 (s, 1H, OH), 7.11 – 7.30 (m, 6H, 5 × Ph-H, C2H), 4.58 (s, 1H, NH), 4.17 (t, $^3J_{HH}$ = 5.0 Hz, 1H, C4H), 2.98 (dd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 5.0 Hz, 1H, C5*H*^{a}H^b), 2.79 (dd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 5.0 Hz, 1H, C5H^a*H*^{b}) ppm.

^{13}C NMR: (101 MHz, DMSO-d_6) δ [keto form] 209.3 (C1), 170.2 (C3), 136.0 (C6), 129.7 (2 × C8), 128.2 (2 × C7), 126.5 (C9), 64.1 (C4), 40.9 (C5), 37.2 (C2) ppm. δ [enol form] 175.0 (C1), 173.8 (C3), (C2), 136.3 (C6), 129.6 (2 × C8), 127.7 (2 × C7), 126.2 (C9), 94.6 (C2), 57.4 (C4), 36.8 (C5) ppm.

(*S*)-5-benzyl-4-methoxy-1,5-dihydro-2*H*-pyrrol-2-one (299)



298 **299**

According to the literature procedure,[173] potassium bis(trimethylsilyl)amide (1.00 M in THF, 6.70 mL, 6.70 mmol, 1.03 equiv) was added dropwise over 15 min to a stirred solution of (*S*)-5-benzylpyrrolidine-2,4-dione (**298**) (1.23 g, 6.50 mmol, 1.00 equiv) in anhydrous THF (33.0 mL, 0.200 M) at 0 °C (water/ice). The resulting suspension was stirred at 0 °C for

20 min before the addition of methyl *p*-toluenesulfonate (1.18 mL, 7.80 mmol, 1.20 equiv) and 18-crown-6 (1.84 g, 6.96 mmol, 1.07 equiv) and the reaction mixture was warmed slowly to ambient temperature stirring overnight. The reaction mixture was concentrated under reduced pressure and the crude residue purified by flash column chromatography (dry loaded, SiO_2, 100% EtOAc) to afford **299** (0.860 g, 4.23 mmol, 65%) as a white powder.

All recorded spectroscopic data matched that previously reported.[174]

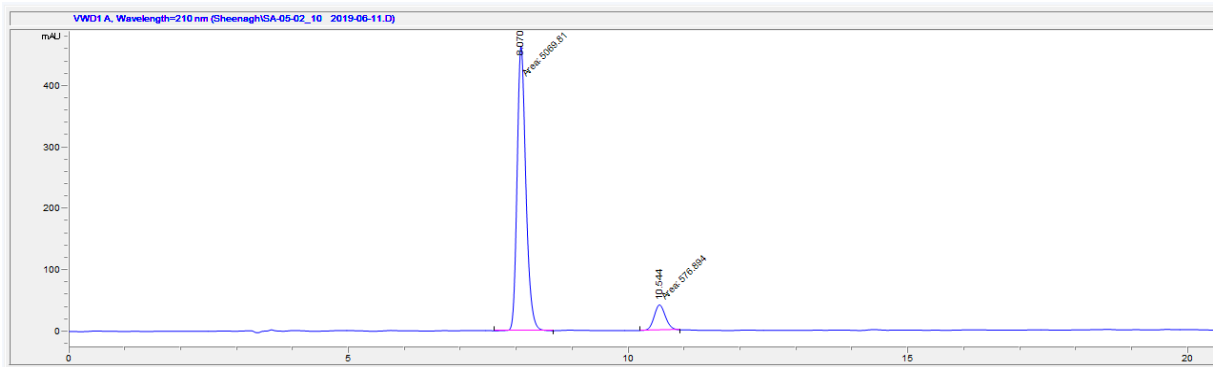
TLC: R_f = 0.46 (10:90 MeOH:EtOAc, anisaldehyde).

^{1}H NMR: (500 MHz, DMSO-d_6) δ 7.50 (br. s, 1H, NH), 7.26 – 7.11 (m, 5H, 5 × Ph-H), 4.85 (s, 1H, C2H), 4.29 (app. t, $^3J_{HH}$ = 4.7 Hz, 1H, C4H), 3.72 (s, 3H, OMe), 2.94 (dd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 4.4 Hz, 1H, C5H^aH^b), 2.80 (dd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 5.3 Hz, 1H, C5H^aH^b) ppm.

^{13}C NMR: (126 MHz, DMSO-d_6) δ 176.4 (C3), 172.5 (C1), 135.8 (C6), 129.6 (2 × C8), 127.8 (2 × C7), 126.3 (C9), 94.8 (C2), 58.1 (C4), 56.8 (OMe), 36.8 (C5) ppm.

Chiral HPLC: (Chiralpak AD-H column, hexane:isopropanol 80:20, 1.0 mL/min, ambient temperature, 210.8 nm): t_R = 8.07 minutes (major), 10.54 minutes (minor), *er* 90:10.

Chiral HPLC conditions from ref. 221.



#	Time	Type	Area	Height	Width	Area%	Symmetry
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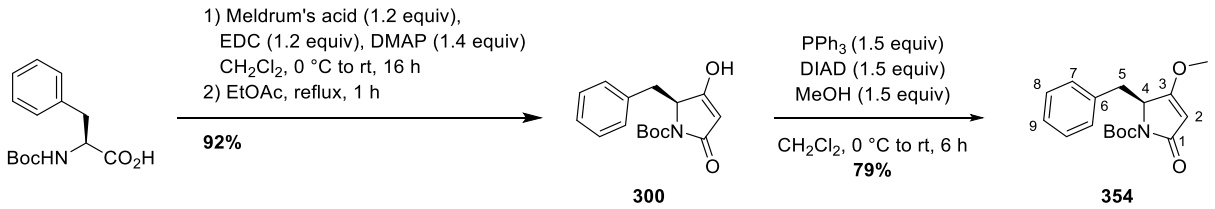
2	10.544	MM	576.9	41.1	0.2337	10.216	0.879

tert-butyl (_S_)-2-benzyl-3-methoxy-5-oxo-2,5-dihydro-1_H_-pyrrole-1-carboxylate (354)



According to the literature procedure,[174] Boc-L-phenylalanine (2.44 g, 9.21 mmol, 1.00 equiv) and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.76 g, 11.1 mmol, 1.20 equiv) were added sequentially to a solution of Meldrum's acid [2,2-dimethyl-1,3-dioxane-4,6-dione] (1.60 g, 11.1 mmol, 1.20 equiv) and 4-(dimethylamino)pyridine (1.57 g, 12.9 mmol, 1.40 equiv) in CH_2Cl_2 (60.0 mL, 0.150 M) at 0 °C (water/ice). The resulting reaction mixture was stirred at ambient temperature overnight. The reaction mixture was poured into EtOAc (200 mL) and washed with brine (2 × 100 mL), 5% aq. citric acid (3 × 300 mL) and brine (300 mL). The organic phase was refluxed (oil bath at 85 °C) for 1 h then cooled to ambient temperature, passed through through Sartorius™ Grade 480 silicon-impregnated phase separator paper and concentrated under reduced pressure to afford **300** (2.454 g, 92%) as an off-white solid that was carried forward to the next step without further purification.

According to the literature procedure,[174] MeOH (0.510 mL, 13.0 mmol, 1.50 equiv) then DIAD (2.50 mL, 12.7 mmol, 1.50 equiv) were added dropwise to **300** (2.45 g, 8,47 mmol, 1.00 equiv) and PPh_3 (3.33 g, 12.7 mmol, 1.50 equiv) in anhydrous CH_2Cl_2 (49.0 mL, 0.170 M) at 0 °C (water/ice). The reaction mixture was stirred at 0 °C for 20 min then at ambient temperature for 6 h and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on a Biotage Isolera One system (dry loaded, 120 g ZIP Sphere column, EtOAc:hexane 40:60) to afford **354** (2.21 g, 7.28 mmol, 79%) as a colourless oil.

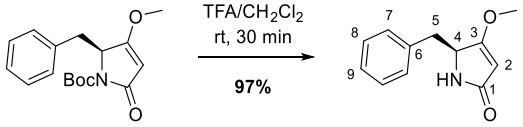
All recorded spectroscopic data matched that previously reported.[174]

TLC: R_f = 0.14 (60:40 hexane:EtOAc, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.26 – 7.15 (m, 3H, 3 × PhH), 7.06 – 6.94 (m, 2H, 2 × PhH), 4.82 (s, 1H, C2H), 4.67 (dd, $^3J_{HH}$ = 5.3 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, C4H), 3.78 (s, 3H, OMe), 3.45 (dd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 5.3 Hz, 1H, C5H^aH^b), 3.12 (dd, $^2J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, C5H^aH^b), 1.60 (s, 9H, $C(CH_3)_3$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 176.3 (C=O), 168.8 (C=O), 149.7 (C3), 134.3 (C6), 129.7 (2 × C7 or C8), 128.4 (2 × C7 or C8), 127.2 (C9), 95.4, 82.8 ($\underline{C}(CH_3)_3$), 60.3 (C4), 58.3 (OMe), 35.5 (C5), 28.4 ($C(\underline{C}H_3)_3$) ppm.

(*S*)-5-benzyl-4-methoxy-1,5-dihydro-2*H*-pyrrol-2-one (299)



According to the literature procedure,[174] **354** (2.03 g, 6.69 mmol, 1.00 equiv) was treated with TFA/CH_2Cl_2 (1:1 v/v, 10.0 mL) and the reaction mixture stirred at ambient temperature for 30 min, at which point TLC analysis showed full conversion to product. The reaction mixture was concentrated under reduced pressure and residual TFA removed by co-evaporation with toluene (3 × 10 mL) to give **299** (1.32 g, 6.49 mmol, 97%) as a white waxy solid.

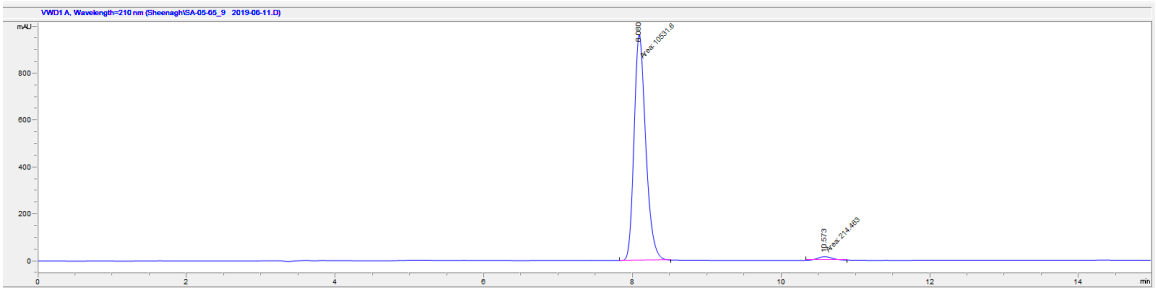
All recorded spectroscopic data matched that previously reported.[174]

TLC: R_f = 0.39 (10:90 MeOH:EtOAc, anisaldehyde).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 3H, 3 × PhH), 7.22 – 7.11 (m, 2H, 2 × PhH), 5.06 (s, 1H, C2H), 4.33 (dd, $^{3}J_{HH}$ = 8.3 Hz, $^{3}J_{HH}$ = 3.8 Hz, 1H, C4H), 3.87 (s, 3H, OMe), 3.20 (dd, $^{2}J_{HH}$ = 13.9 Hz, $^{3}J_{HH}$ = 3.8 Hz, 1H, C5$H^a$$H^b$), 2.76 (dd, $^{2}J_{HH}$ = 13.8 Hz, $^{3}J_{HH}$ = 8.3 Hz, 1H, C5$H^a$$H^b$) ppm.

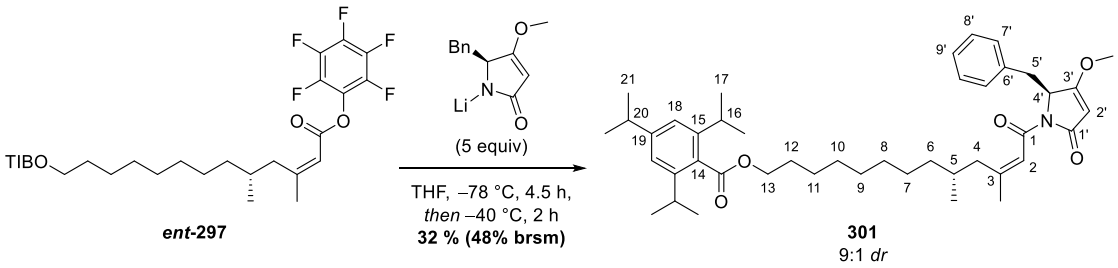
^{13}C NMR: (126 MHz, $CDCl_3$) δ 179.1 (C3), 176.3 (C1), 135.4 (C6), 129.3 (2 × C8), 128.9 (2 × C7), 127.5 (C9), 93.2 (C2), 60.0 (C4), 59.0 (OMe), 37.9 (C5) ppm.

Chiral HPLC: (Chiralpak AD-H column, hexane:isopropanol 80:20, 1.0 mL/min, ambient temperature, 210.8 nm): t_R = 8.08 minutes (major), 10.57 minutes (minor), *er* 98:2.
Chiral HPLC conditions from ref. 221.



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.08	MM	10531.6	964.5	0.182	98.004	0.765
2	10.573	MM	214.5	15.4	0.2316	1.996	0.874

(*R*,*Z*)-13-((*S*)-2-benzyl-3-methoxy-5-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)-9,11-dimethyl-13-oxotridec-11-en-1-yl 2,4,6-triisopropylbenzoate (301)



n-BuLi (1.60 M in hexanes, 0.280 mL, 0.450 mmol, 5.00 equiv) was added dropwise to a vigorously stirred solution of (*S*)-5-benzyl-4-methoxy-1,5-dihydro-2*H*-pyrrol-2-one (**299**) (*er* 90:10, 91.8 mg, 0.452 mmol, 5.00 equiv) in anhydrous THF (0.300 mL) at −78 °C (acetone/dry ice) and stirred at −78 °C for 15 min. Pentafluorophenyl ester ***ent*-297** (59.0 mg, 90.4 µmol, 1.00 equiv) in THF (0.300 mL) was added dropwise (washing with 2 × 0.150 mL THF). The reaction was monitored by TLC analysis. After 4.5 h at −78 °C, the reaction mixture was warmed to −40 °C (acetonitrile/dry ice) for 2 h. The reaction was quenched with sat. aq. NH_4Cl (2 mL) and the phases separated. The aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organics were washed with water (5 mL), brine (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 80:20 to 50:50 pentane:Et_2O) to afford **301** (19.2 mg, 28.6 µmol, 32%, 9:1 *dr*) as a pale pink oil.

TLC: R_f = 0.22 (60:40 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, DMSO-d_6) δ 7.24 – 7.16 (m, 3H, 2 × C8'H, C9'H), 7.05 (s, 2H, 2 × C18H), 6.87 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.8 Hz, 2H, 2 × C7'H), 6.80 (m, 1H, C2H), 5.09 (s,

1H, C2'H), 4.90 (dd, $^3J_{HH}$ = 5.3 Hz, $^3J_{HH}$ = 2.8 Hz, 1H, C4'H), 4.23 (t, $^3J_{HH}$ = 6.3 Hz, 2H, C13H_2), 3.82 (s, 3H, C3'OMe), 3.41 (dd, $^2J_{HH}$ = 13.8, $^3J_{HH}$ = 5.3 Hz, 1H, C5'H^aH^b), 3.00 (dd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 2.8 Hz, 1H, C5'H$^aH^b$), 2.88 (sept, $^3J_{HH}$ = 6.9 Hz, 1H, C20H), 2.73 (sept, $^3J_{HH}$ = 6.9 Hz, 2H, 2 × C16H), 2.63 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 8.4 Hz, 1H, C4H^aH^b), 2.52 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 6.7 Hz, 1H, C4H$^aH^b$), 1.86 (d, $^4J_{HH}$ = 1.3 Hz, 3H, C3-Me), 1.76 (m, 1H, C5H), 1.67 – 1.60 (m, 2H, C6H_2), 1.36 – 1.21 (m, 12H, C7H_2, C8H_2, C9H_2, C10H_2, C11H_2, C12H_2,), 1.19 (d, $^3J_{HH}$ = 6.9 Hz, 6H, 2 × C21H_3), 1.17 (d, $^3J_{HH}$ = 6.9 Hz, 12H, 4 × C17H_3), 0.87 (d, $^3J_{HH}$ = 6.6 Hz, 3H, C5-Me) ppm.

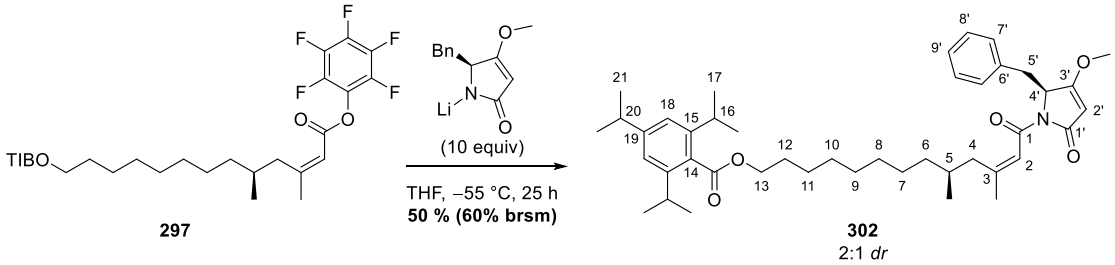
^{13}C NMR: (126 MHz, DMSO-d$_6$) δ 177.5 (C3'), 170.0 (TIB CO), 169.2 (C1'), 164.0 (C1), 157.6 (C3), 149.8 (C19), 144.0 (C15), 134.3 (C6'), 130.5 (C14), 129.3 (2 × C7'), 128.0 (2 × C8'), 126.8 (C9'), 120.6 (2 × C18), 119.7 (C2), 95.00 (C2'), 64.6 (C13), 58.8 (C4'), 58.8 (C3'OMe), 40.4 (C4), 36.4 (CH_2), 33.9 (C20), 33.7 (C5'), 31.2 (C5), 31.0 (2 × C16), 30.4 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.5 (C12), 28.1 (CH_2), 26.3 (C4), 25.5 (C12), 25.4 (C3-Me), 23.9 (4 × C17), 23.8 (2 × C21), 19.3 (C5-Me) ppm.

HRMS (*m/z*): (ESI) calculated for $C_{43}H_{61}NO_5$ [*M*+Na]$^+$ 694.4442, found 694.4453.

IR (ν_{max}/cm^{-1}, neat): 2960, 2927, 1721, 1665, 1629, 1380, 1304, 1242, 1075, 970.

$[\alpha]_D^{27}$: +146 (*c* = 0.6, $CHCl_3$).

(*S*,*Z*)-13-((*S*)-2-benzyl-3-methoxy-5-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)-9,11-dimethyl-13-oxotridec-11-en-1-yl 2,4,6-triisopropylbenzoate (302)



n-BuLi (1.60 M in hexanes, 0.660 mL, 1.10 mmol, 10.0 equiv) was added dropwise to a vigorously stirred solution of (*S*)-5-benzyl-4-methoxy-1,5-dihydro-2*H*-pyrrol-2-one (**299**) (*er* 90:10, 215 mg, 1.06 mmol, 10.0 equiv) in anhydrous THF (0.460 mL) at −55 °C (cryostat) and stirred at −55 °C for 15 min. Pentafluorophenyl **297** (69.0 mg, 0.106 mmol, 1.00 equiv) in THF (0.400 mL) was added dropwise (washing with 2 × 0.200 mL THF). The reaction was

monitored by TLC analysis. After 25 h at −55 °C, the reaction was quenched with sat. aq. NH_4Cl (2 mL) and the phases separated. The aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organics were washed with water (5 mL), brine (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 80:20 to 50:50 pentane:Et_2O) to afford **302** (36.0 mg, 53.6 µmol, 50%, 2:1 *dr*) as a pale pink oil.

TLC: R_f = 0.22 (60:40 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, DMSO-d_6) δ 7.23 – 7.14 (3H, m, 2 × C8'H, C9'H), 7.05 (s, 2H, 2 × C18H), 6.87 (dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.8 Hz, 2H, 2 × C7'H), 6.83 (s, 1H, C2H), 5.09 (s, 1H, C2'H), 4.91 (dd, $^3J_{HH}$ = 5.2 Hz, $^3J_{HH}$ = 2.8 Hz, 1H, C4'H), 4.21 (t, $^3J_{HH}$ = 6.3 Hz, 2H, $C13H_2$), 3.82 (s, 3H, C3'OMe), 3.40 (dd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 5.2 Hz, 1H, C5'H^aH^b), 3.00 (dd, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 2.8 Hz, 1H, C5'H^aH^b), 2.87 (sept, $^3J_{HH}$ = 7.0 Hz, 1H, C20H), 2.73 (sept, $^3J_{HH}$ = 7.0 Hz, 2H, 2 × C16H), 2.64 (dd, $^2J_{HH}$ = 12.7 Hz, $^3J_{HH}$ = 6.9 Hz, 1H, C4H^aH^b), 2.53 (dd, $^2J_{HH}$ = 12.7 Hz, $^3J_{HH}$ = 8.0 Hz, 1H, C4H^aH^b), 1.87 (d, $^4J_{HH}$ = 1.2 Hz, 3H, C3-Me), 1.75 (m, 1H, C5H), 1.67 – 1.58 (m, 2H, $C6H_2$), 1.38 – 1.21 (m, 12H, $C7H_2$, $C8H_2$, $C9H_2$, $C10H_2$, $C11H_2$, $C12H_2$,), 1.19 (d, $^3J_{HH}$ = 7.0 Hz, 6H, 2 × $C21H_3$), 1.16 (d, $^3J_{HH}$ = 7.0 Hz, 12H, 4 × $C17H_3$), 0.82 (d, $^3J_{HH}$ = 6.6 Hz, 3H, C5-Me) ppm.

^{13}C NMR: (126 MHz, DMSO-d_6) δ 177.5 (C3'), 170.0 (TIB CO), 169.2 (C1'), 164.0 (C1), 157.9 (C3), 149.8 (C19), 144.0 (C15), 134.3 (C6'), 130.5 (C14), 129.3 (2 × C7'), 128.0 (2 × C8'), 126.8 (C9'), 120.6 (2 × C18), 119.5 (C2), 95.0 (C2'), 64.5 (C13), 58.8 (C4'), 58.7 (C3'OMe), 40.4 (C4), 36.4 (CH_2), 33.9 (C20), 33.7 (C5'), 31.3 (C5), 31.0 (2 × C16), 29.2 (CH_2), 29.0 (CH_2), 28.5 (C12), 28.0 (CH_2), 26.5 (C4), 25.5 (C12, C3-Me), 23.8 (4 × C17), 23.8 (2 × C21), 19.4 (C5-Me) ppm.

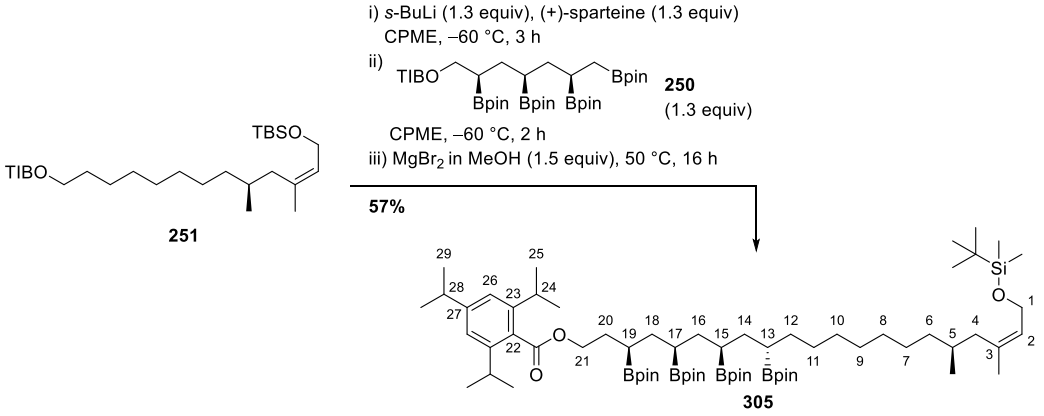
HRMS (*m/z*): (ESI) calculated for $C_{43}H_{61}NO_5$ $[M+H]^+$ 672.4623, found 672.4615.

IR (ν_{max}/cm^{-1}, neat): 2960, 2927, 1721, 1665, 1629, 1380, 1304, 1242, 1075, 970.

$[\alpha]_D^{27}$: +48 (*c* = 1, $CHCl_3$).

NMR spectra included in section **6.5**

(2*R*,4*R*,6*R*,8*S*,16*S*,*Z*)-20-((*tert*-butyldimethylsilyl)oxy)-16,18-dimethyl-2,4,6,8-tetrakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)icos-18-en-1-yl 2,4,6-triisopropylbenzoate (305)



s-BuLi (1.30 M in hexanes, 0.200 mL, 0.270 mmol, 1.30 equiv) was added dropwise to a mixture of fragment 3 (**251**) (120 mg, 0.204 mmol, 1.00 equiv) and (+)-sparteine (60.0 µL, 0.300 mmol, 1.30 equiv) in anhydrous CPME (0.680 mL, 0.300 M) at −60 °C (chloroform/dry ice). The resulting mixture was stirred at −60 °C for 3 h. Fragment 2 (**250**) (230 mg, 0.266 mmol, 1.30 equiv) in CPME (0.270 mL, 1.00 M wrt boronic ester) was added dropwise and stirring continued at −60 °C for 2 h. $MgBr_2$ in MeOH (1.00 M, 0.310 mL, 0.310 mmol, 1.50 equiv) was added at −60 °C and the reaction mixture was heated at 50 °C (oil bath) overnight. The reaction mixture was cooled to ambient temperature and diluted with 2 M aq. HCl (3 mL) and Et_2O (3 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 95:5 to 60:40 pentane:Et_2O) to afford 1,3-tetra(boronic ester) **305** (140 mg, 0.116 mmol, 57%) as a colourless oil.

TLC: R_f = 0.38 (75:25 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 6.96 (s, 2H, 2 × C26H), 5.36 (t, $^3J_{HH}$ = 6.4 Hz, 1H, C2H), 4.31 – 4.21 (m, 2H, C21H_2), 4.19 – 4.11 (m, 2H, C1H_2), 2.85 (app. sept, $^3J_{HH}$ = 6.8 Hz, 3H, C24H, 2 × C24H), 1.95 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 6.2 Hz, 1H, C4H^aH^b), 1.86 (m, 1H, C20H^aH^b), 1.84 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 8.6 Hz, 1H, C4H^aH^b), 1.80 – 1.50 (m, 6H, C20H^aH^b, C5H, C6H_2, CH_2), 1.68 (s, 3H, C3-Me), 1.49 – 0.91 (m, 86H, 4 × CH, 8 × CH_2, 2 × C29H_3, 4 × C25H_3, 16 × pinacol-CH_3), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.79 (d, $^3J_{HH}$ = 6.6 Hz, 3H, C5-Me), 0.06 (s, 6H, Si(CH_3)$_2$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 171.1 (C=O), 149.9 (C27), 144.9 (2 × C23), 136.8 (C3), 131.2 (C22), 126.3 (C2), 120.8 (2 × C26), 83.0 (pinacol-C), 82.7 (pinacol-C), 82.7 (pinacol-C), 82.7 (pinacol-C), 65.3 (C21), 60.2 (C1), 40.0 (C4), 37.3 (CH_2), 37.3 (CH_2), 34.6 (C28), 33.8 (CH_2), 33.7 (CH_2), 32.5 (CH_2), 31.6 (C5), 31.5 (2 × C24), 30.2 (CH_2), 30.1 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 27.4 (CH_2), 26.2 (SiC($\underline{C}H_3$)$_3$), 25.1 (CH_3), 25.0 (CH_3), 25.0 (CH_3), 24.9 (CH_3), 24.8 (CH_3), 24.4 (CH_3), 24.3 (CH_3), 24.2 (CH_3), 23.9 (C3-Me), 19.6 (C5-Me), 18.6 (Si$\underline{C}$(CH$_3$)$_3$), −4.9 (Si($\underline{C}H_3$)$_2$) ppm.

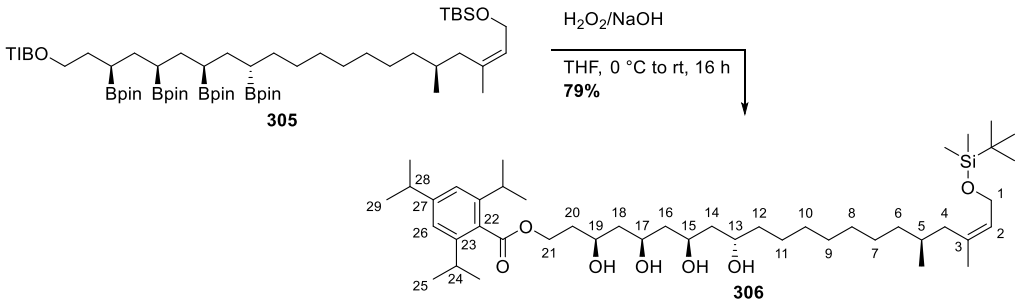
carbon next to boron not observed due to quadrupolar relaxation

HRMS (*m/z*): (MALDI) calculated for $C_{69}H_{126}{}^{11}B_4O_{11}Si$ [*M*+Na]$^+$ 1225.9372, found 1225.9386.

IR (ν_{max}/cm^{-1}, neat): 2961, 2926, 2854, 1724, 1371, 1378, 1311, 1252, 1142.

$[\alpha]_D^{25}$: −3 (*c* = 0.6, $CHCl_3$).

(2*R*,4*R*,6*R*,8*S*,16*S*,*Z*)-20-((*tert*-butyldimethylsilyl)oxy)-2,4,6,8-tetrahydroxy-16,18-dimethylicos-18-en-1-yl 2,4,6-triisopropylbenzoate (306)



A solution of tetra(boronic ester) **305** (0.265 g, 0.220 mmol, 1.00 equiv) in THF (1.10 mL, 0.200 M) at 0 °C (water/ice) was treated with pre-mixed and degassed ice-cold 30% aq. H_2O_2/3 M NaOH (1:2 v/v, 1.10 mL). The reaction mixture was stirred at ambient temperature overnight then diluted with 17% aq. Na_2SO_4 (5 mL) and EtOAc (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (5 × 5 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 100% Et_2O) to afford 1,3-tetraol **306** (133 mg, 0.174 mmol, 79%) as a colourless oil.

TLC: R_f = 0.17 (100% Et_2O, anisaldehyde).

^{1}H NMR: (500MHz, $CDCl_3$) δ 7.00 (s, 2H, 2 × C26H), 5.36 (t, $^{3}J_{HH}$ = 6.5 Hz, 1H, C2H), 4.55 (ddd, $^{2}J_{HH}$ = 11.2 Hz, $^{3}J_{HH}$ = 7.5 Hz, $^{3}J_{HH}$ = 6.1 Hz, 1H, C21H^{a}H^{b}), 4.37 (dt, $^{2}J_{HH}$ = 11.2 Hz, $^{3}J_{HH}$ = 5.9 Hz, 1H, C21H$^{a}H^{b}$), 4.23 (m, 1H, C13H), 4.15 (m, 2H, $C1H_2$), 4.13 (m, 1H, C15H), 4.05 (m, 1H, C19H), 3.95 (m, 1H, C17H), 2.88 (sept, $^{3}J_{HH}$ = 6.9 Hz, 1H, C28H), 2.83 (sept, $^{3}J_{HH}$ = 6.8 Hz, 2H, 2 × C24H), 1.95 (dd, $^{2}J_{HH}$ = 13.2 Hz, $^{3}J_{HH}$ = 6.2 Hz, 1H, C4H^{a}H^{b}), 1.91 – 1.81 (m, 3H, $C20H_2$, C4H$^{a}H^{b}$), 1.76 – 1.50 (m, 8H, $C12H_2$, $C14H_2$, $C16H_2$, $C18H_2$), 1.68 (s, 3H, C3-Me), 1.45 (m, 1H, C5H), 1.35 – 1.26 (m, 12H, $C11H_2$, $C10H_2$, $C9H_2$, $C8H_2$, $C7H_2$, $C6H_2$), 1.24 (d, $^{3}J_{HH}$ = 6.9 Hz, 18H, 4 × $C25H_3$, 2 × $C29H_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.80 (d, $^{3}J_{HH}$ = 6.6 Hz, 3H, C5-Me), 0.06 (s, 6H, $Si(CH_3)_2$) ppm.

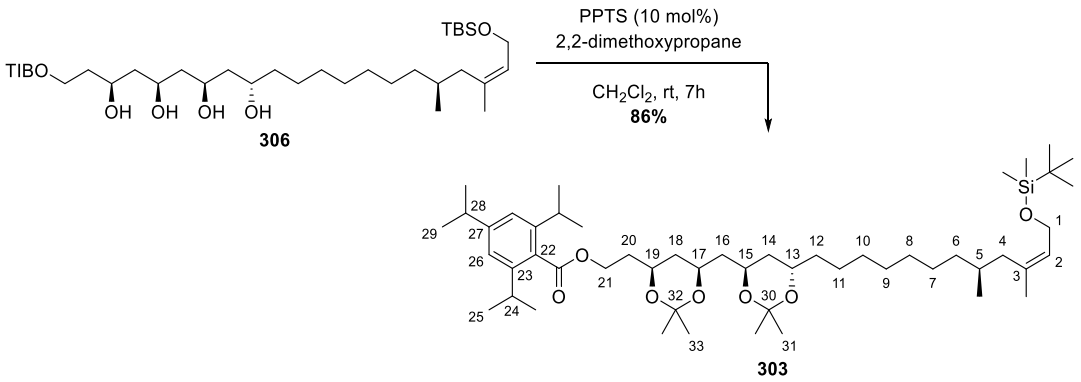
^{13}C NMR: (126 MHz, $CDCl_3$) δ 171.4 (C=O), 150.4 (C27), 144.9 (2 × C23), 136.7 (C3), 130.4 (C22), 126.3 (C2), 121.0 (2 × C26), 73.9 (C15), 70.8 (C13), 69.7 (C19), 69.6 (C17), 62.0 (C21), 60.2 (C1), 43.7 (C18), 43.3 (C16), 42.6 (C14), 40.0 (C4), 37.7 (CH_2), 37.2 (CH_2), 37.1 (C20), 34.6 (C28), 31.7 (2 × C24), 31.5 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 27.4 (CH_2), 26.2 ($SiC(\underline{C}H_3)_3$), 25.9 (CH_2), 24.3 (C25), 24.3 (C25), 24.1 (C29), 23.9 (C3-Me), 19.7 (C5-Me), 18.6 ($Si\underline{C}(CH_3)_3$), −4.9 ($Si(CH_3)_2$) ppm.

HRMS (*m/z*): (MALDI) calculated for $C_{45}H_{82}NO_7Si$ [*M*+Na]$^{+}$ 785.5722, found 785.5732.

IR (ν_{max}/cm^{-1}, neat): 3350, 2927, 2855, 1725, 1462, 1251, 1076, 835.

$[\alpha]_D^{25}$: −8 (*c* = 1, $CHCl_3$).

((4*R*,6*R*)-6-(((4*R*,6*S*)-6-((*S*,*Z*)-12-((*tert*-butyldimethylsilyl)oxy)-8,10-dimethyldodec-10-en-1-yl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl 2,4,6-triisopropylbenzoate (303)



Pyridinium *p*-toluenesulfonate (0.7 mg, 3 µmol, 10 mol%) was added to tetraol **306** (21.0 mg, 27.5 µmol, 1.00 equiv) in 2,2-dimethoxypropane/CH_2Cl_2 (1:1, 1.00 mL, 0.0275 M) at ambient temperature. The reaction mixture was stirred at ambient temperature for 7 h. Sat. aq. $NaHCO_3$ (3 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 100:0 to 80:20 hexane:EtOAc) to afford bis(acetonide) **303** (20.0 mg, 23.7 µmol, 86%) as a colourless oil.

TLC: R_f = 0.40 (80:20 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.01 (s, 2H, 2 × C26H), 5.36 (t, $^3J_{HH}$ = 6.4 Hz, 1H, C2H), 4.46 – 4.35 (m, 2H, $C21H_2$), 4.20 – 4.11 (m, 2H, $C1H_2$), 4.03 – 3.90 (m, 3H, C19H, C17H, C15H), 3.75 (m, 1H, C13H), 2.89 (sept, $^3J_{HH}$ = 6.9 Hz, 1H, C28H), 2.84 (sept, $^3J_{HH}$ = 6.9 Hz, 2H, 2 × C24H), 1.95 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 6.2 Hz, 1H, C4H^aH^b), 1.92 – 1.79 (m, 4H, C4H^aH^b, $C20H_2$, C18H^aH^b), 1.68 (s, 3H, C3-Me), 1.63 – 1.20 (m, 20H, C18H^aH^b, $C16H_2$, $C14H_2$, $C12H_2$, $C11H_2$, $C10H_2$, $C9H_2$, $C8H_2$, $C7H_2$, $C6H_2$, C5H), 1.40 (s, 3H, $C33H_3$), 1.38 (s, 3H, $C33H_3$), 1.33 (s, 3H, $C31H_3$), 1.32 (s, 3H, $C31H_3$), 1.24 (d, $^3J_{HH}$ 6.9 = Hz, 18H, 2 × $C25H_3$, 4 × $C29H_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.80 (d, $^3J_{HH}$ = 6.6 Hz, 3H, C5-Me), 0.07 (s, 6H, $Si(CH_3)_2$) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 171.1 (C=O), 150.3 (C27), 144.8 (2 × C23), 136.8 (C3), 130.7 (C22), 126.3 (C2), 121.0 (2 × C26), 100.3 (C30), 98.7 (C32), 66.8 (C15), 65.9 (C13), 65.8 (C19), 62.9 (C17), 61.5 (C21), 60.2 (C1), 42.4 (C18), 40.0 (C4), 38.8 (C14), 37.2 (CH_2), 36.8 (CH_2), 36.1 (C16), 35.7 (C20), 34.6 (C28), 31.5 (2 × C24), 30.3 (C5), 30.0 ($C33H_3$), 29.8

(CH_2), 29.7 (CH_2), 27.4 (CH_2), 26.2 (SiC($\underline{C}H_3$)$_3$), 25.6 (CH_2), 25.1 (C31H_3), 24.9 (C31H_3), 24.3 (2 × C29H_3), 24.3 (2 × C25H_3), 24.1 (2 × C25H_3), 23.9 (C3-Me), 20.0 (C33H_3), 19.7 (C5-Me), 18.6 (Si$\underline{C}$(CH$_3$)$_3$), −4.9 (Si(CH$_3$)$_2$) ppm.

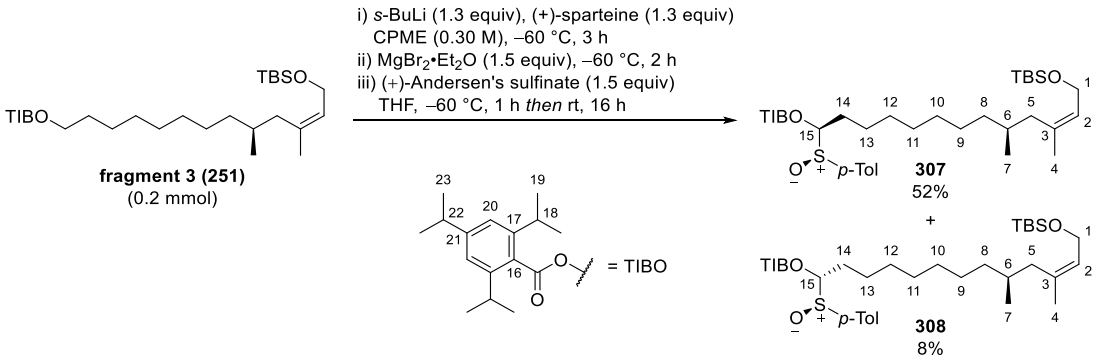
NMR spectra included in section **6.5**

HRMS (*m/z*): (MALDI) calculated for $C_{51}H_{90}O_7Si$ [*M*+Na]$^+$ 865.6348, found 865.6357.

IR (ν_{max}/cm^{-1}, neat): 2958, 2927, 2855, 1727, 1462, 1378, 1250, 1075.

$[\alpha]_D^{24}$: +6.0 (*c* = 0.4, $CHCl_3$).

(1*R*,9*S*,*Z*)-13-((*tert*-butyldimethylsilyl)oxy)-9,11-dimethyl-1-(*p*-tolylsulfinyl)tridec-11-en-1-yl 2,4,6-triisopropylbenzoate (307)



s-BuLi (1.3 M in hexanes, 0.20 mL, 0.26 mmol, 1.2 equiv) was added dropwise to a stirred solution of (+)-sparteine (60 µL, 0.26 mmol, 1.2 equiv) and benzoate **251** (117 mg, 0.200 mmol, 1.00 equiv) in anhydrous CPME (0.67 mL, 0.30 M) at −60 °C (cryostat) under N_2. The reaction mixture was stirred at −60 °C for 3 h before the addition of freshly prepared* $MgBr_2 \cdot Et_2O$ (1.5 equiv) *via* cannula. After a further 2 h at −60 °C, (+)-Andersen's sulfinate (88 mg, 0.30 mmol, 1.5 equiv) in THF (0.30 mL, 1.0 M) was added dropwise. The reaction mixture was stirred at −60 °C for 1 h then the cooling bath was removed and the mixture allowed to warm to ambient temperature overnight. The reaction was quenched with sat. aq. NH_4Cl (5 mL), the phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

Purification was aided by silylation of the menthol by-product: The crude mixture was stirred under vacuum for 1 h then dissolved in anhydrous CH_2Cl_2 (0.40 mL, 0.50 M). Triethylamine

(40 µL, 0.30 mmol, 1.5 equiv) was added followed by the dropwise addition of TMSCl (30 µL, 0.26 mmol, 1.3 equiv). The resulting mixture was stirred at ambient temperature under N_2 for 24 h. The reaction mixture was diluted with Et_2O (5 mL), washed with water (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on a Biotage Isolera One system (25 g Sfär HC, 95:5 to 85:15 pentane:Et_2O) to afford α-sulfinyl benzoate **307** (75 mg, 0.13 mmol, 52%, >99:1 *dr*) as a colourless oil and α-sulfinyl benzoate **307** (11 mg, 55 µmol, 8%, >99:1 *dr*).

*Preparation of $MgBr_2{\cdot}OEt_2$: To a flame dried 2 necked flask fitted with a reflux condenser under N_2 was charged oven dried magnesium turnings (19.4 g, 24.3 mmol, 4.00 equiv) and anhydrous Et_2O (0.38 mL, 0.80 M wrt 1,2-dibromoethane). To this stirred suspension was added 1,2-dibromoethane (30 µL, 0.30 mmol, 1.5 equiv) and the resulting suspension was gently heated until the reaction initiated. Upon completion of the addition of 1,2-dibromoethane, the reaction was biphasic with a colourless upper layer and a grey bottom layer. After gas evolution had stopped, the mixture was stirred for 30 min at ambient temperature. Both layers were transferred to the main reaction vessel by syringe. The unreacted Mg was cooled to 0 °C (water/ice) and quenched through the slow addition of an appropriate amount of 2 M aq. HCl.

307

TLC: R_f = 0.27 (80:20 pentane:Et_2O, PMA).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.65 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2 × Tol *o*CH), 7.37 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2 × Tol *m*CH), 7.04 (s, 2H, 2 × C20H), 5.67 (dd, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 2.9 Hz, 1H, C15H), 5.36 (t, $^3J_{HH}$ = 6.5 Hz, 1H, C2H), 4.19 – 4.11 (m, 2H, C1H_2), 2.99 – 2.87 (app. sept, $^3J_{HH}$ = 7.0 Hz, 3H, C22H, 2 × C18H), 2.44 (s, 3H, Tol CH_3), 1.99 (m, 1H, C14*H*^{a}H^b), 1.93 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 6.2 Hz, 1H, C5*H*^{a}H^b) 1.84 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 8.5 Hz, 1H, C5*H*^{a}H^b), 1.67 (d, $^4J_{HH}$ = 1.5 Hz, 3H, C4H_3), 1.72 – 1.07 (m, 32H), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.78 (d, $^3J_{HH}$ = 6.6 Hz, 3H, C7H_3), 0.06 (s, 6H, 2 × SiCH_3) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ 170.7 (C=O), 151.0 (C21), 145.3 (2 × C17), 141.7 (Tol CS), 137.8 (Tol *p*C), 136.7 (C3), 130.1 (2 × Tol *m*CH), 129.1 (C16), 126.4 (C2), 124.5 (2 × Tol *o*CH), 121.2 (2 × C20), 92.7 (C15), 60.2 (C1), 40.0 (C5), 37.2 (CH_2), 34.6 (C22), 31.8 (2 × C18), 31.5 (C6), 29.9 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 27.3 (CH_2), 26.2 (SiC(CH_3)$_3$), 24.9

(CH_2), 24.6 (2 × CH_3), 24.4 (2 × CH_3), 24.1 (CH_3), 24.1 (CH_3), 23.9 (C4), 23.0 (C14), 21.6 (Tol CH_3), 19.6 (C7), 18.6 ($SiC(CH_3)_3$), −4.9 (2 × $SiCH_3$) ppm.

HRMS (*m/z*): (ESI) calculated for $C_{44}H_{72}O_4SSi$ [*M*+Na]$^+$ 747.4813, found 747.4820.

IR (ν_{max}/cm^{-1}, neat): 2958, 2926, 2855, 1732, 1461, 1247, 1057, 1047.

$[\alpha]_D^{21}$: −50 (*c* = 0.2, $CHCl_3$).

308

TLC: R_f = 0.20 (80:20 pentane:Et_2O, PMA).

^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.55 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2 × Tol *o*CH), 7.31 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2 × Tol *m*CH), 7.02 (s, 2H, 2 × C20H), 6.00 (dd, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 3.9 Hz, 1H, C15H), 5.36 (t, $^3J_{HH}$ = 6.2 Hz, 1H, C2H), 4.28 – 4.08 (m, 2H, $C1H_2$), 2.90 (sept, $^3J_{HH}$ = 6.9 Hz, 1H, C22H), 2.85 (sept, $^3J_{HH}$ = 7.0 Hz, 2H, 2 × C18H), 2.42 (s, 3H, Tol CH_3), 1.94 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 6.2 Hz, 1H, C5H^aH^b) 1.85 (dd, $^2J_{HH}$ = 13.2 Hz, $^3J_{HH}$ = 8.5 Hz, 1H, C5H^aH^b), 1.83 (m, 1H, C14H^aH^b), 1.67 (d, $^4J_{HH}$ = 1.2 Hz, 3H, $C4H_3$), 1.62 – 0.98 (m, 32H), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.79 (d, $^3J_{HH}$ = 6.6 Hz, 3H, $C7H_3$), 0.06 (s, 6H, 2 × $SiCH_3$) ppm.

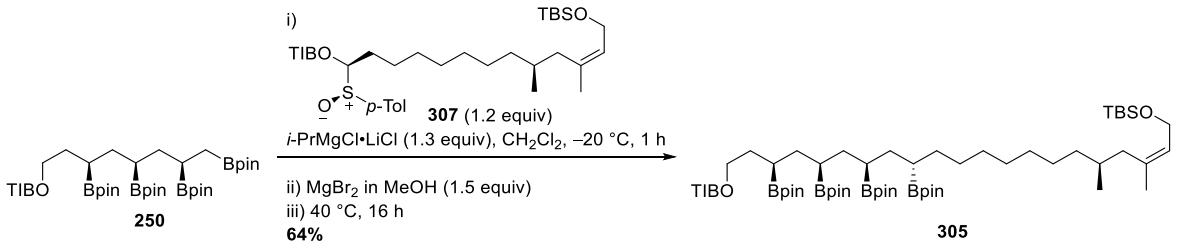
^{13}C NMR: (126 MHz, $CDCl_3$) δ 169.5 (C=O), 150.8 (C21), 145.3 (2 × C17), 142.2 (Tol CS), 136.7 (Tol *p*C), 136.6 (C3), 130.0 (2 × Tol *m*CH), 129.2 (C16), 126.4 (C2), 125.7 (2 × Tol *o*CH), 121.2 (2 × C20), 88.6 (C15), 60.2 (C1), 40.0 (C5), 37.2 (CH_2), 34.6 (C22), 31.7 (2 × C18), 31.5 (C6), 29.9 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 27.6 (CH_2), 27.3 (C14), 26.2 ($SiC(CH_3)_3$), 25.5 (CH_2), 24.7 (2 × CH_3), 24.3 (2 × CH_3), 24.1 (CH_3), 24.1 (CH_3), 23.9 (C4), 21.6 (Tol CH_3), 19.6 (C7), 18.6 ($SiC(CH_3)_3$), −4.9 (2 × $SiCH_3$) ppm.

HRMS (*m/z*): (ESI) calculated for $C_{44}H_{72}O_4SSi$ [*M*+Na]$^+$ 747.4813, found 747.4819.

IR (ν_{max}/cm^{-1}, neat): 2958, 2926, 2855, 1740, 1461, 1231, 1056, 1041.

$[\alpha]_D^{21}$: −6 (*c* = 0.7, $CHCl_3$).

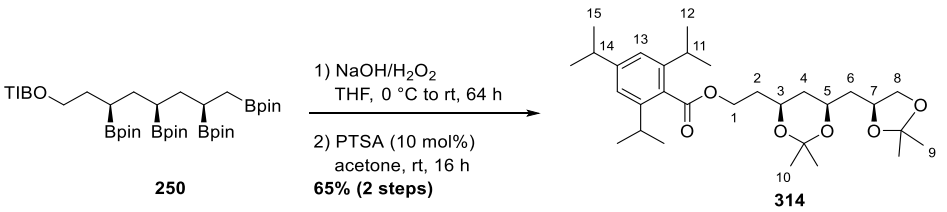
(2*R*,4*R*,6*R*,8*S*,16*S*,*Z*)-20-((*tert*-butyldimethylsilyl)oxy)-16,18-dimethyl-2,4,6,8-tetrakis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)icos-18-en-1-yl 2,4,6-triisopropylbenzoate (305)



i-PrMgCl·LiCl (1.2 M in THF, 40 µL, 52 µmol, 1.3 equiv) was added dropwise to a mixture of tetra(boronic ester) **250** (35 mg, 40 µmol, 1.0 equiv) and α-sulfinyl benzoate **307** (35 mg, 48 µmol, 1.2 equiv) in anhydrous CH_2Cl_2 (0.48 mL, 0.10 M) −20 °C (acetonitrile/dry ice). The resulting reaction mixture was stirred at −20 °C for 1 h, $MgBr_2$ (1 M in MeOH, 0.06 mL, 60 µmol, 1.5 equiv) was added at −20 °C before the reaction mixture was removed from the cooling bath and allowed to warm to ambient temperature, and then stirred at 40 °C (oil bath) for 16 h. The reaction mixture was cooled to ambient temperature, filtered through a plug of Et_3N-deactivated silica (washing with Et_2O) and concentrated under reduced pressure. The crude residue was purified using a Biotage Isolera One system (Sfär Silica 5 g, 95:5 to 80:20 pentane:Et_2O) to give tetra(boronic ester) **305** (31 mg, 26 µmol, 64%) as a colourless oil.

All recorded spectroscopic data matched that previously reported for the major diastereomer (*vide supra*).

2-((4*S*,6*S*)-6-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl 2,4,6-triisopropylbenzoate (314)



<u>Oxidation</u>

A solution of fragment 2 (**250**) (531 mg, 0.614 mmol, 1.00 equiv) in THF (3.00 mL, 0.200 M) at 0 °C (water/ice) was treated with pre-mixed and degassed ice-cold 30% aq. H_2O_2/3 M NaOH (1:2 v/v, 3 mL). The reaction mixture stirred vigorously, warming slowly to ambient

temperature over the weekend. The reaction mixture was cooled to 0 °C and quenched with aqueous $Na_2S_2O_3$, then diluted with ethyl acetate (20 mL) and 17% w/w aq. Na_2SO_4 (20 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3× 25 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure.

TLC: R_f = 0.10 (95:5 Et_2O:MeOH, anisaldehyde).

Acetonide protection

Anhydrous $MgSO_4$ (148 mg, 1.23 mmol, 2.00 equiv) followed by *p*-toluenesulfonic acid (11.7 mg, 61.3 µmol, 10.0 mol%) was added to the crude tetraol **309** in acetone (6.00 mL, 0.100 M) and the reaction mixture was stirred at ambient temperature overnight. $NaHCO_3$ (26.0 mg, 0.309 mmol, 0.500 equiv) was added to the reaction mixture which was then filtered through a plug of Celite® and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 80:20 pentane:Et_2O) to afford bis(acetonide) **314** (0.201 g, 0.399 mmol, 65%) as a pale yellow oil which formed a white amorphous solid under high vacuum.

TLC: R_f = 0.30 (70:30 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.01 (s, 2H, 2 × C13H), 4.45 – 4.34 (m, 2H, C1H_2), 4.25 – 4.18 (m, 1H, C5H), 4.03 (dd, $^2J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 5.8 Hz, 1H, C8*H*^{a}H^b), 4.05 – 3.95 (m, 2H, C3H, C7H), 3.58 (dd, $^2J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 8.0 Hz, 1H, C8H^a*H*^{b}), 2.85 (sept, $^3J_{HH}$ = 6.8 Hz, 3H, 2 × C11H, C14H), 1.95 – 1.79 (m, 2H, C2H_2), 1.63 (ddd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 6.0 Hz, $^3J_{HH}$ = 6.0 Hz, 1H, C4*H*^{a}H^b), 1.54 (ddd, $^3J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 2.4 Hz, $^3J_{HH}$ = 2.4 Hz, 1H, C4H^a*H*^{b}), 1.42 – 1.23 (m, 32H, 4 × C12H_3, 2 × C15H_3, 2 × C9H_3, 2 × C10H_3, C6H_2) ppm.

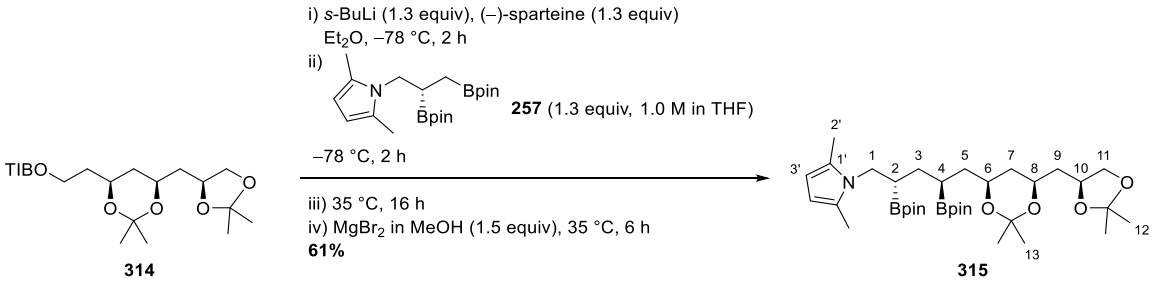
^{13}C NMR: (101 MHz, $CDCl_3$) δ 171.0 (C=O), 150.3 (Ar *p*C), 144.8 (2C, 2 × Ar *o*C), 130.7 (Ar *ipso* C), 121.0 (2C, 2 × C13), 108.7 (OCO), 98.8 (*syn*-acetonide C), 72.4 (C5), 69.5 (C8), 66.1 (C3 or C7), 66.0 (C3 or C7), 61.5 (C1), 39.6 (C4), 36.7 (C6), 35.6 (C2), 34.6 (C14), 31.7 (2C, 2 × C11), 30.3 (C10H_3), 27.0 (C9H_3), 26.0 (C9H_3), 24.3 (2C, 2 × CH_3), 24.3 (2C, 2 × CH_3), 24.1 (2C, 2 × CH_3), 19.9 (C10H_3) ppm.

HRMS (*m/z*): (ESI) calculated for $C_{30}H_{48}O_6$ $[M+H]^+$ 505.3524, found 505.3515.

IR (ν_{max}/cm^{-1}, neat): 2960, 2870, 1724, 1606, 1462, 1379, 1368, 1250, 1200, 1169, 1137, 1101, 1075 and 1068.

$[\alpha]_D^{24}$: −52.1 (*c* = 0.9, $CHCl_3$).

1-((2*S*,4*S*)-5-((4*S*,6*S*)-6-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-2,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)-2,5-dimethyl-1*H*-pyrrole (315)



s-BuLi (1.30 M in hexanes, 0.100 mL, 0.130 mmol, 1.30 equiv) was added dropwise to a mixture of bis(acetonide) **314** (50.0 mg, 99.0 µmol, 1.00 equiv) and (−)-sparteine (30.0 µL, 0.100 mmol, 1.30 equiv) in anhydrous Et_2O (0.330 mL, 0.300 M) at −78 °C (acetone/dry ice) under N_2. After 2 h lithiation time, bis(boronic ester) **257** (50.1 mg, 0.130 mmol, 1.30 equiv) in anhydrous THF (0.130 mL, 1.00 M) was added dropwise. After 2 h borylation time at −78 °C, the reaction mixture was heated at 35 °C (oil bath) overnight. ^{11}B NMR analysis suggested some persistent boronate complex; $MgBr_2$ in MeOH (1.00 M, 0.150 mL, 0.150 mmol, 1.50 equiv) was added and the mixture heated at 35 °C for a further 6 h. The reaction was cooled to ambient temperature and diluted with 50% sat. aq. NH_4Cl (5 mL) and Et_2O (5 mL). The phases were separated and the organic washed with sat. aq. NH_4Cl (6 × 5mL). The combined aqueous phases were extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 75:25 pentane:Et_2O) to afford the homologated product **315** (39.0 mg, 60.4 µmol, 61%) as a white amorphous solid.

TLC: R_f = 0.32 (60:40 pentane:Et_2O, anisaldehyde).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 5.68 (s, 2H, 2 × C3'H), 4.21 (m, 1H, C10H), 4.03 (dd, $^2J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 5.7 Hz, 1H, C11H^aH^b), 3.94 (m, 1H, C8H), 3.83 (m, 1H, C6H), 3.76 (dd, $^2J_{HH}$ = 14.3 Hz, $^3J_{HH}$ = 8.5 Hz, 1H, C1H^aH^b), 3.67 (dd, $^2J_{HH}$ = 14.3 Hz, $^3J_{HH}$ = 9.0 Hz, 1H, C1H^aH^b), 3.58 (dd, $^2J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, C11H^aH^b), 2.23 (s, 6H, 2 × C2'H_3), 1.89

(m, 1H, C9*H*^{a}H^{b}), 1.76 – 1.57 (m, 3H, C7H$_2$, C9H^{a}*H*^{b}), 1.45 – 1.02 (m, 42H, 8 × pinacol-CH$_3$, 2 × C13H$_3$, 2 × C12H$_3$, C5H$_2$, C4H, C3H$_2$, C2H) ppm.

^{13}C NMR: (126 MHz, CDCl$_3$) δ 127.8 (2C, 2 × C1'), 108.6 (OCO), 105.1 (2C, 2 × C3'), 98.5 (*syn* acetonide C), 83.3 (2C, 2 × pinacol-C), 83.0 (2C, 2 × pinacol-C), 72.6 (C10), 69.5 (C11), 68.1 (C6), 66.3 (C8), 45.7, (C1) 39.7 (C9), 39.0 (CH$_2$), 36.9 (C7), 31.3 (CH$_2$), 30.4 (C13), 27.1 (C12), 26.0 (C12), 25.2 (2C, 2 × CH$_3$), 25.0 (4C, 4 × CH$_3$), 24.7 (2C, 2 × CH$_3$), 19.9 (C13), 13.1 (2C, 2 × C2') ppm.

carbon next to boron not observed due to quadrupolar relaxation

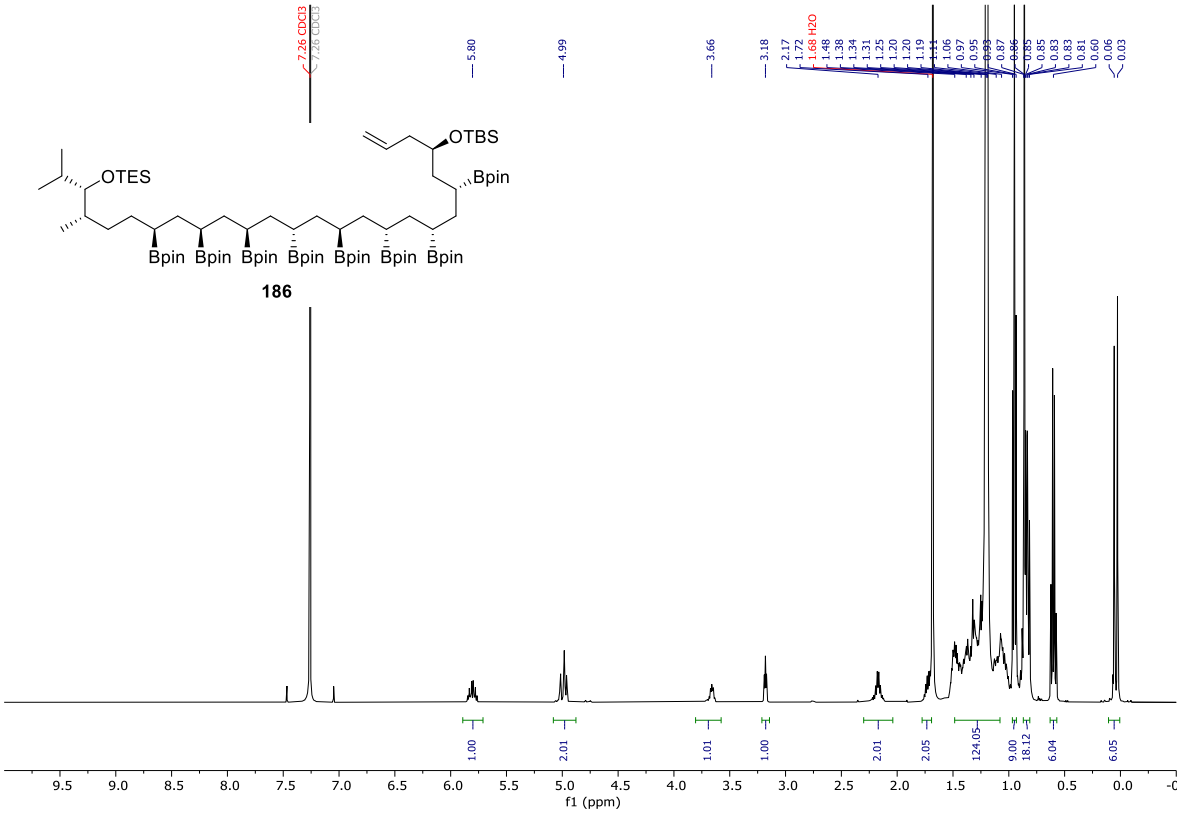
HRMS (*m/z*): (MALDI) calculated for C$_{35}$H$_{61}$^{11}B$_2$NO$_8$ [*M*+Na]$^+$ 668.4487, found 668.4495.

IR (ν_{max}/cm^{-1}, neat): 2977, 2942, 1406, 1374, 1319, 1234, 1208, 1139 and 1096.

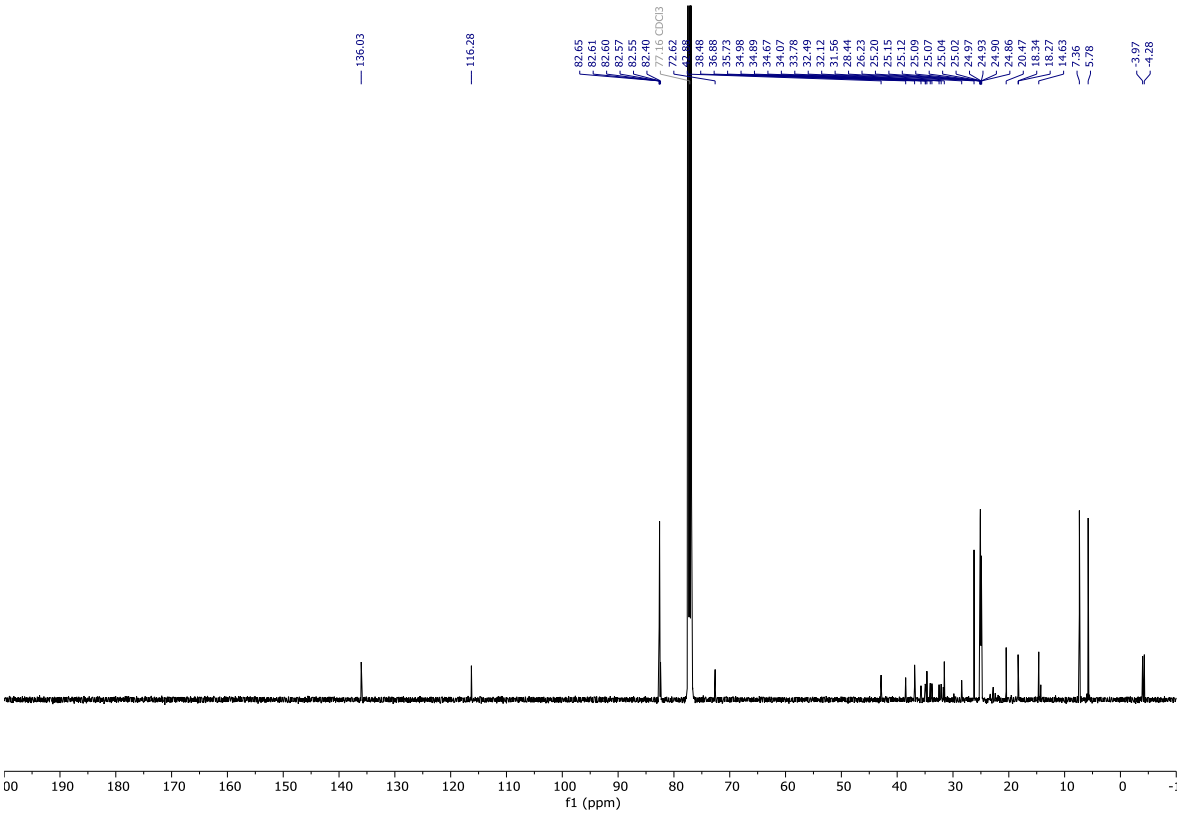
$[\alpha]_D^{25}$: −74.9 (*c* = 0.9, CHCl$_3$).

6.5 Selected NMR Spectra for Key Compounds

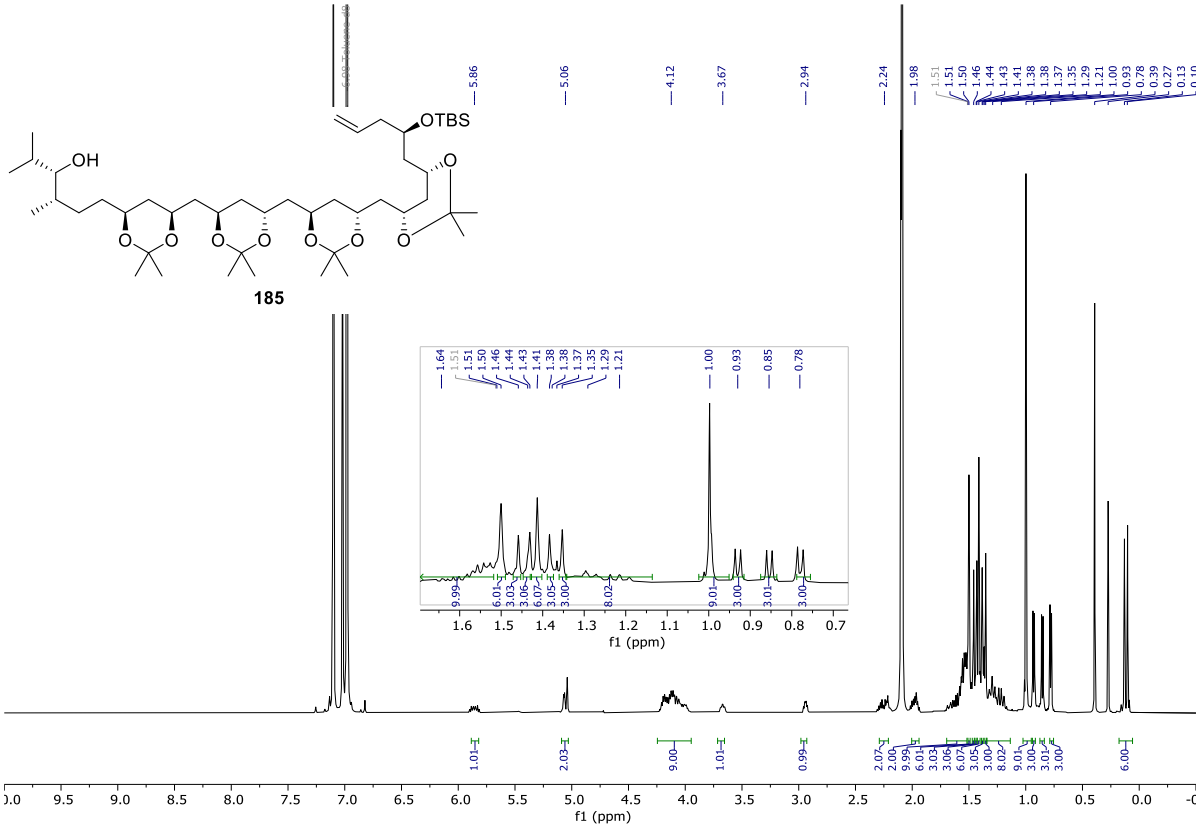
^{1}H NMR (500 MHz, $CDCl_3$) of **186**



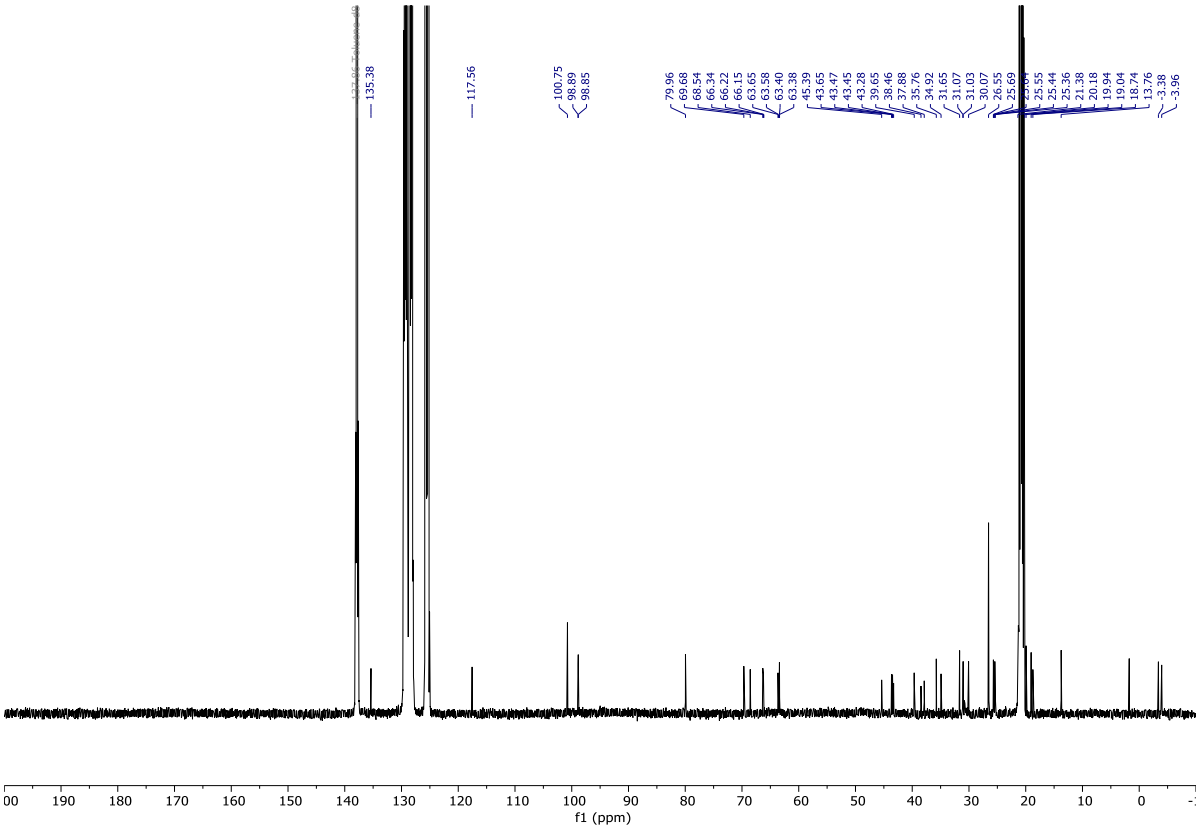
^{13}C NMR (126 MHz, $CDCl_3$) of **186**



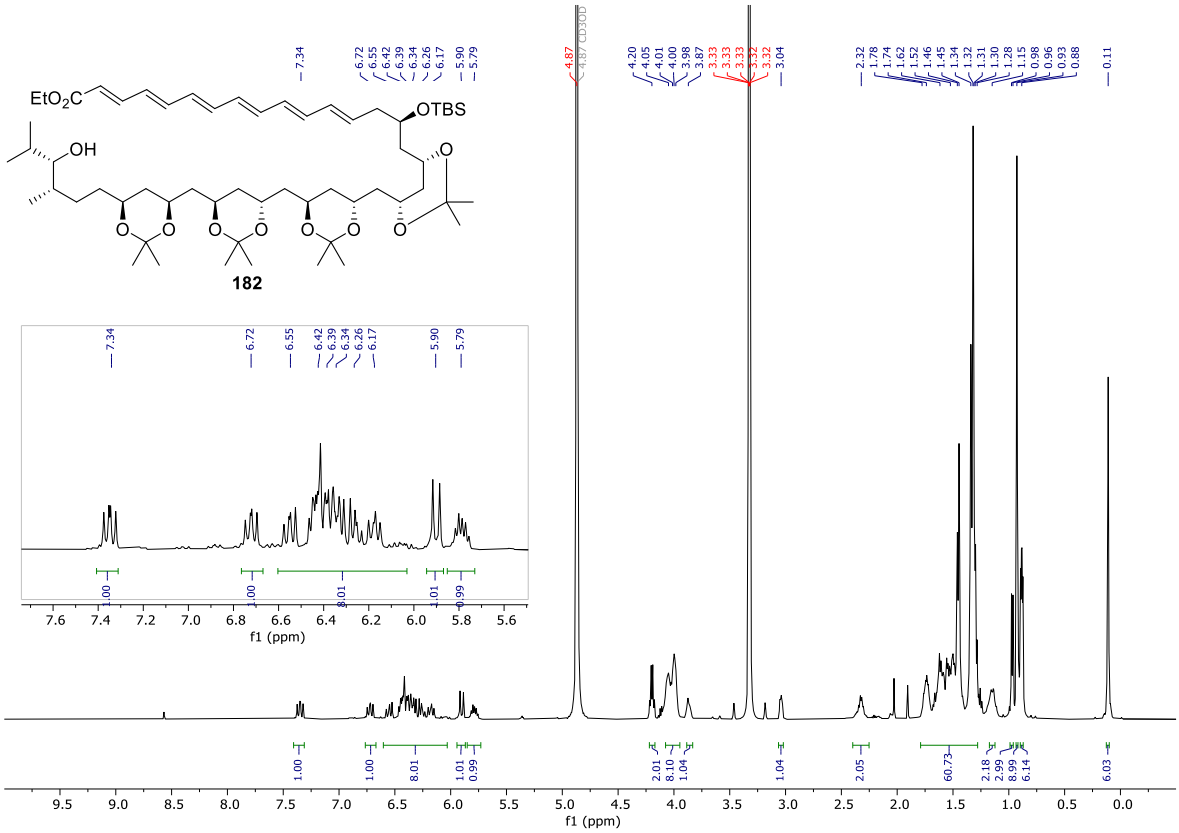
^{1}H NMR (500 MHz, toluene-d_8) of **185**



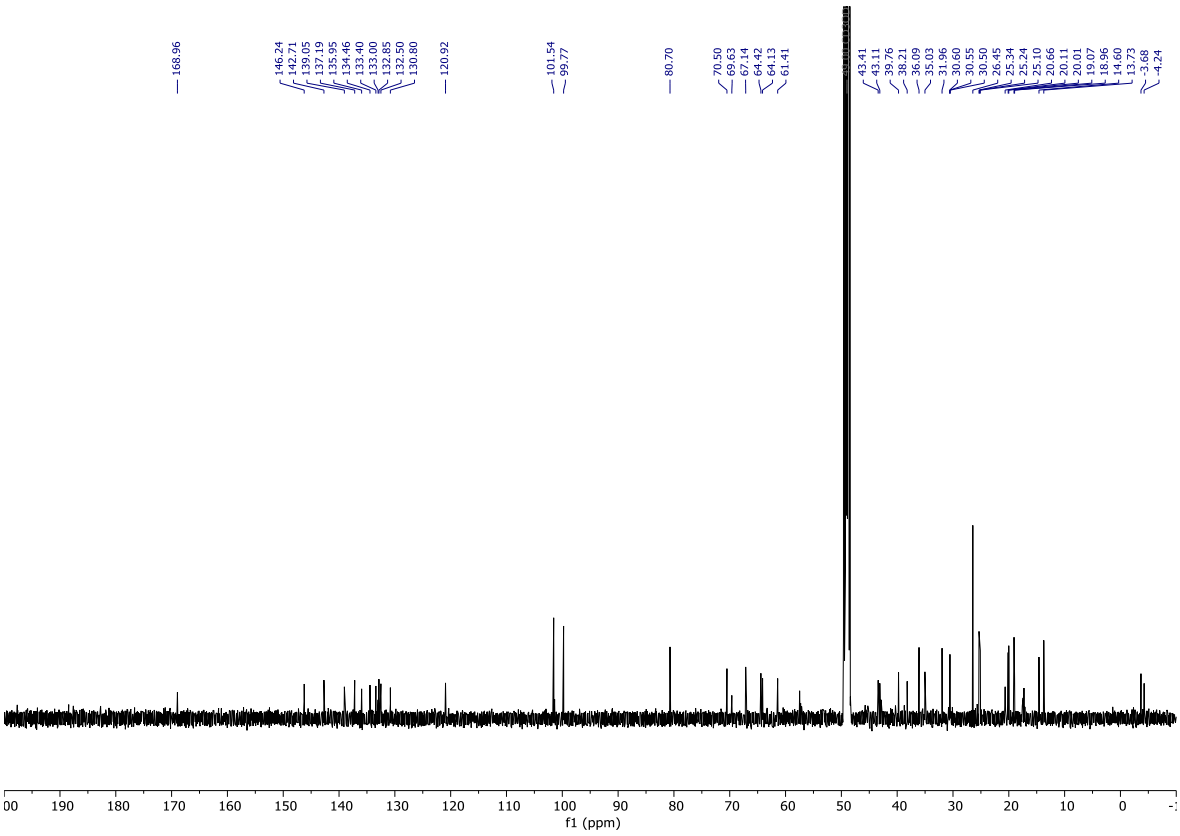
^{13}C NMR (126 MHz, toluene-d_8) of **185**



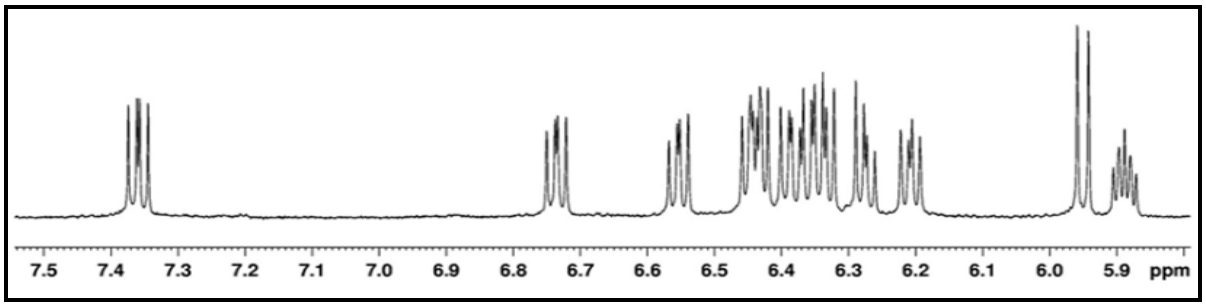
^{1}H NMR (500 MHz, CD_3OD) of **182**



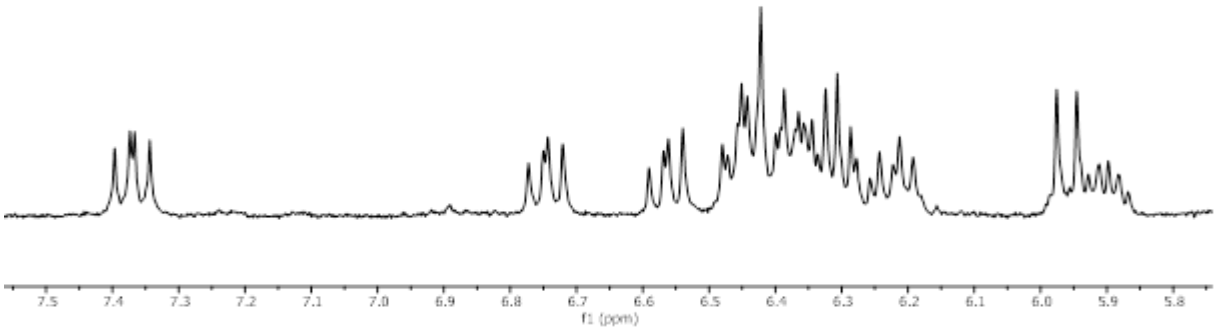
^{13}C NMR (126 MHz, CD_3OD) of **182**



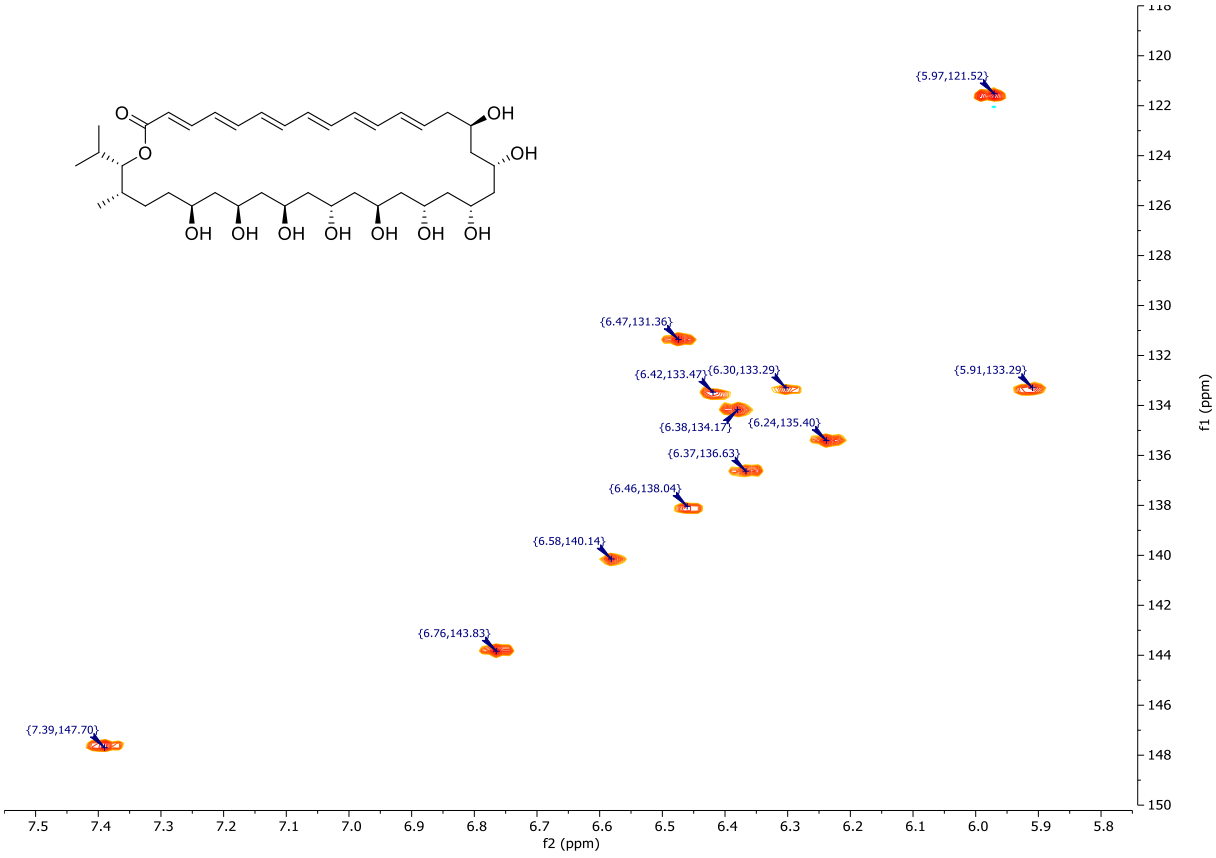
Isolated bahamaolide A ^{1}H NMR (900 MHz, CD_3OD)[65]:



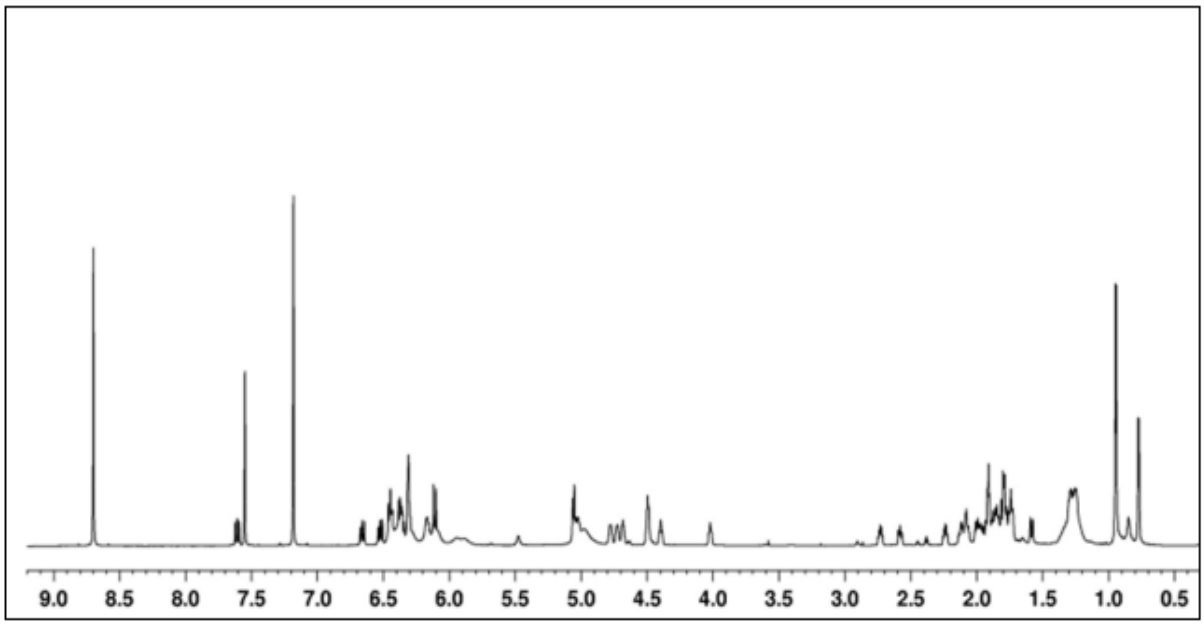
Synthetic bahamaolide A ^{1}H NMR (500 MHz, CD_3OD):



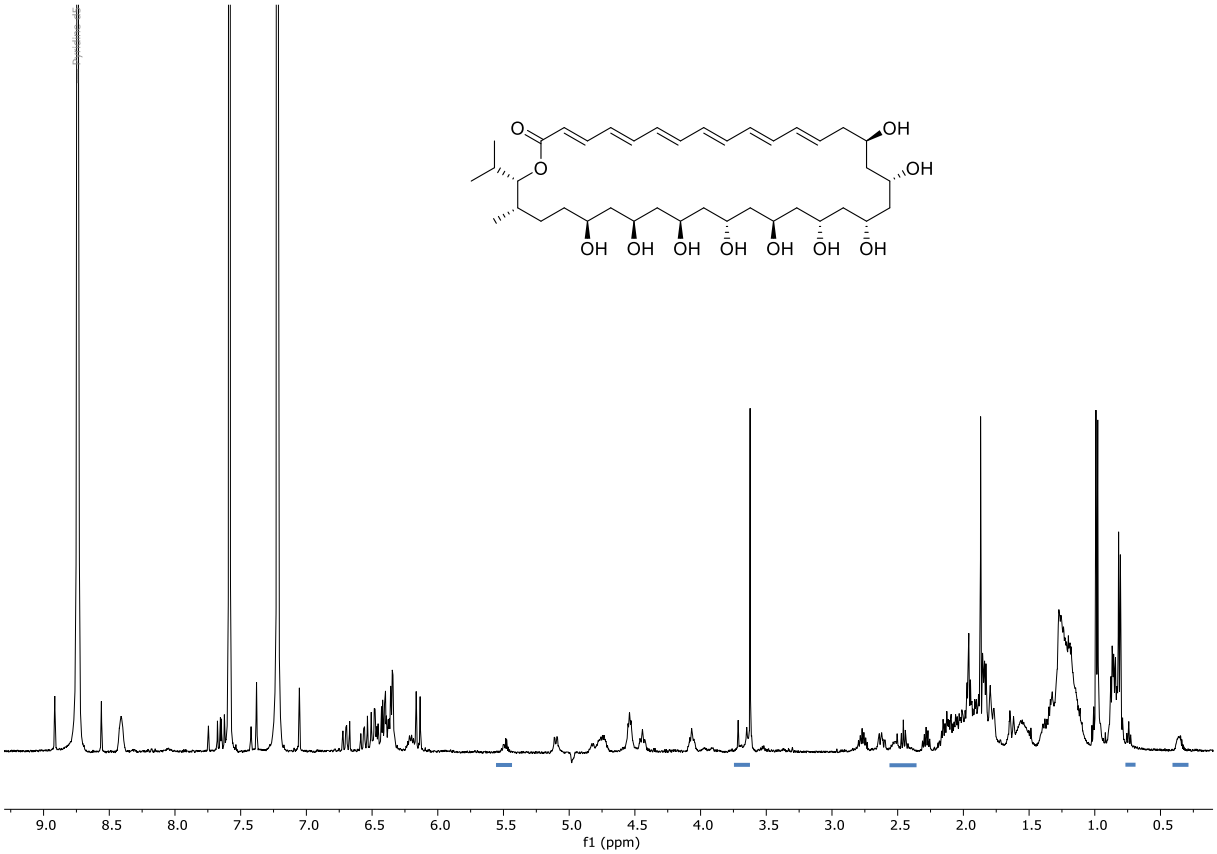
Synthetic bahamaolide A HSQC (700 MHz, CD_3OD):



Isolated bahamaolide A ^{1}H NMR (800 MHz, pyridine-d_5)[65]:

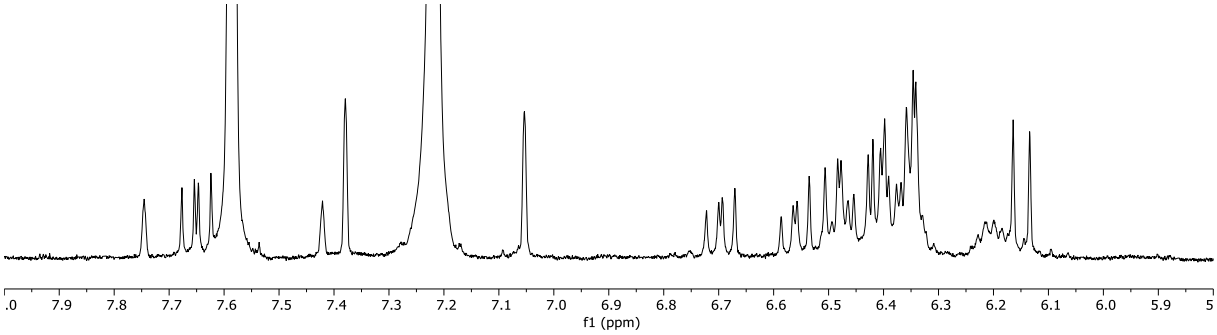


Synthetic bahamaolide A ^{1}H NMR (500 MHz, pyridine-d_5):

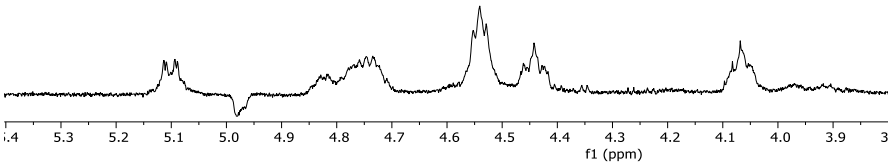


** Methanol contamination, singlet at 3.62 ppm. Contaminants associated with pyridine-d_5 indicated in blue. Experiment ran with water suppression (4.98 ppm).*

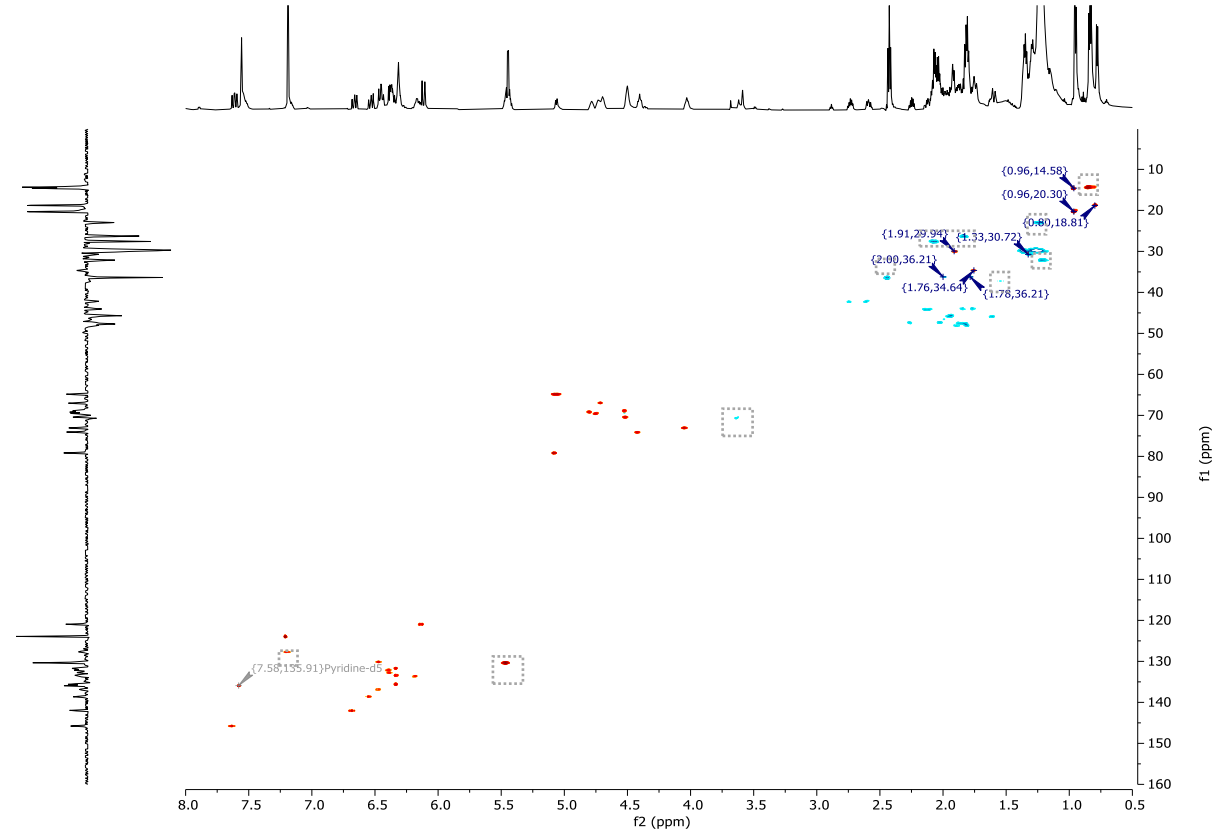
Polyene region ^{1}H NMR (500 MHz, pyridine-d_5):



Polyol CH region ^{1}H NMR (500 MHz, pyridine-d_5):

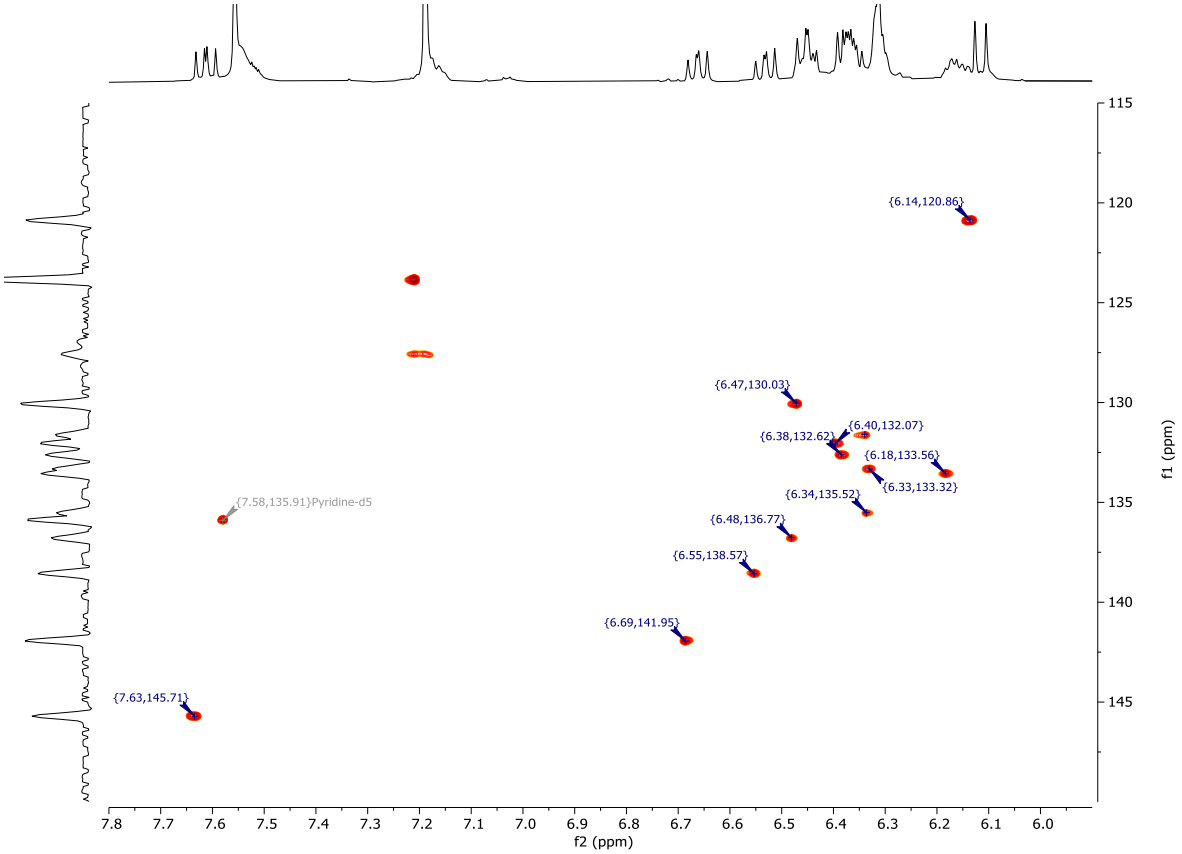


Synthetic bahamaolide A HSQC (700 MHz, pyridine-d_5):

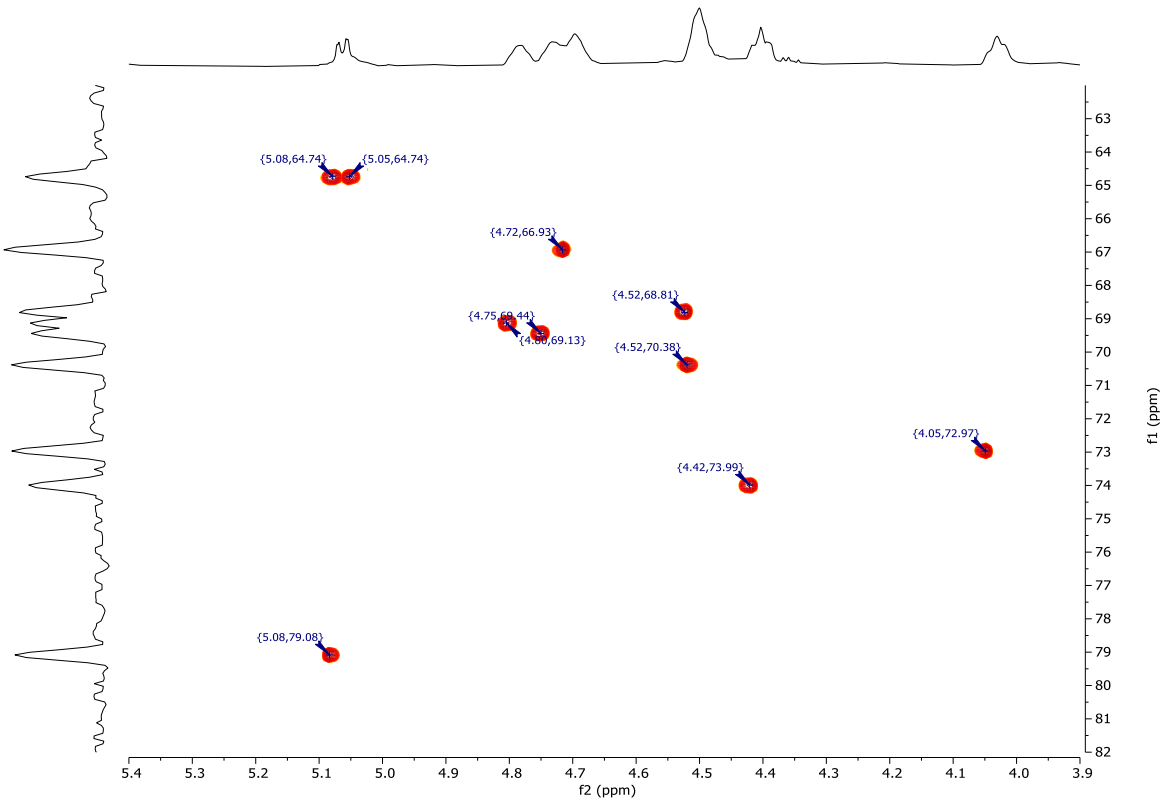


Grey dashed boxes indicate contaminants coming from pyridine-d_5.

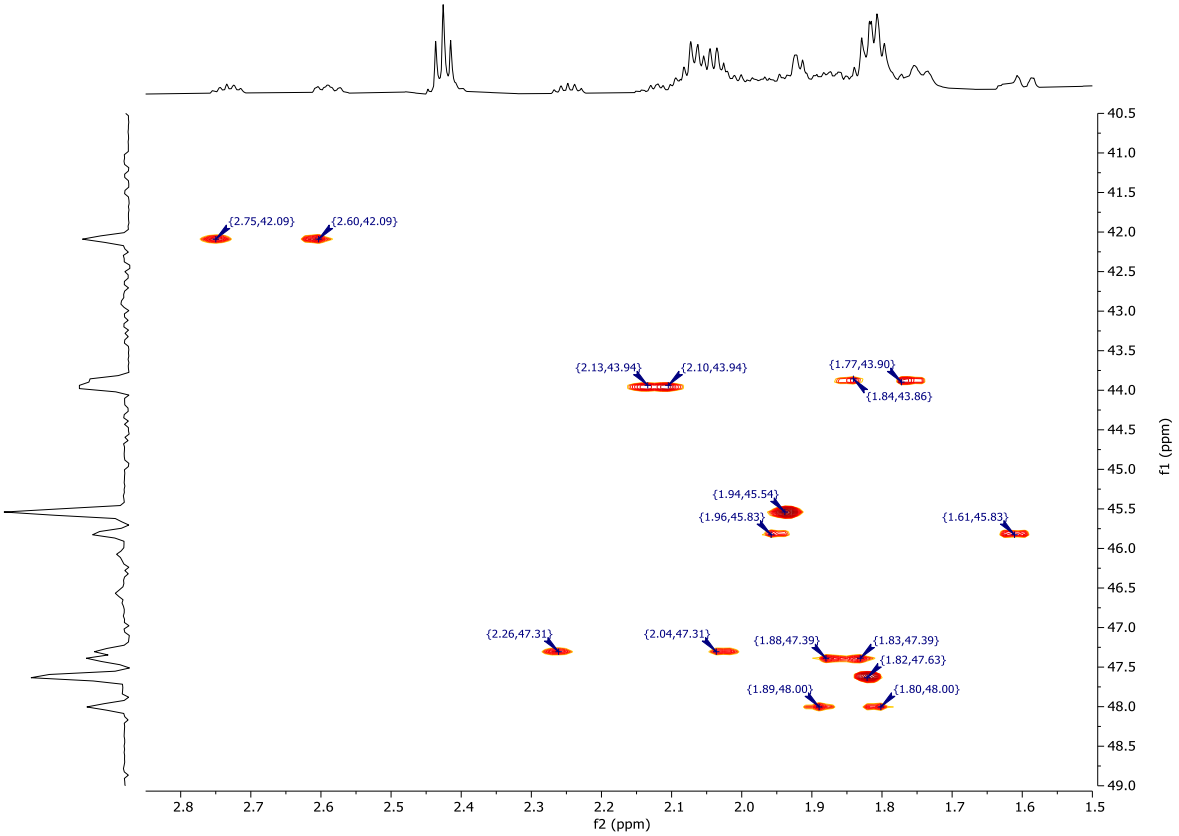
HSQC (700 MHz, pyridine-d_5) of synthetic bahamaolide A, polyene region:



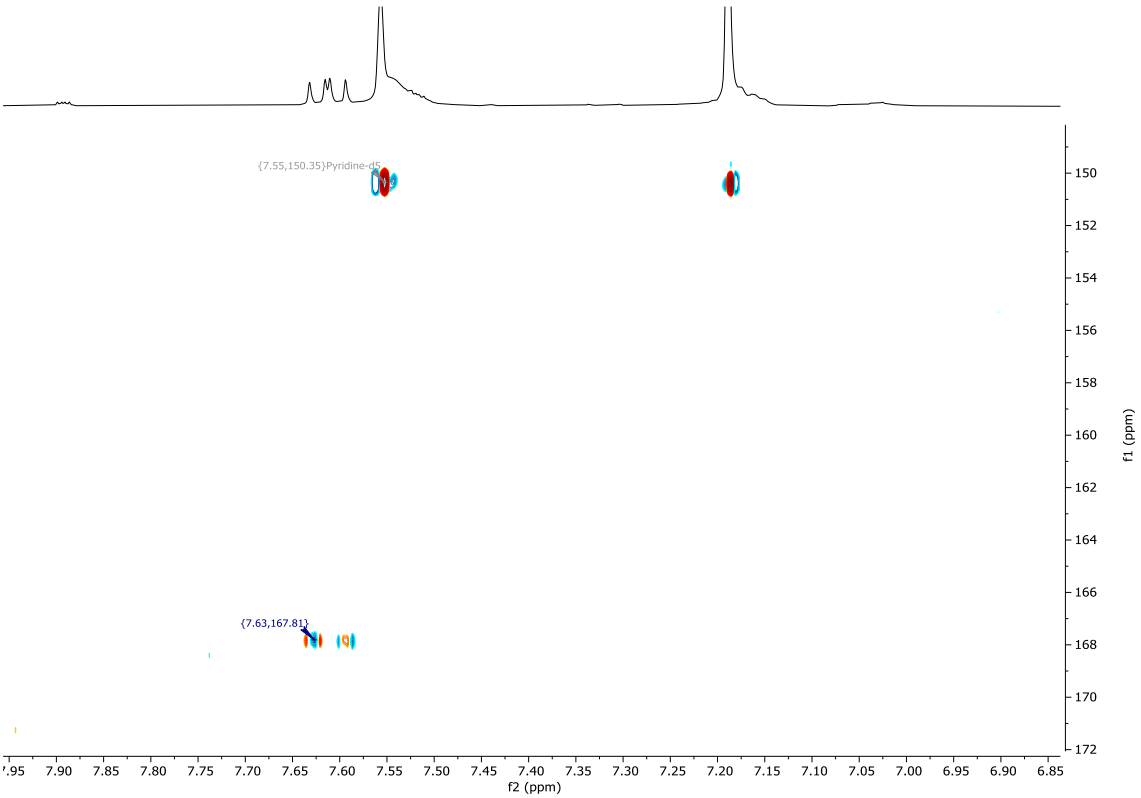
HSQC (700 MHz, pyridine-d_5) of synthetic bahamaolide A, polyol region:



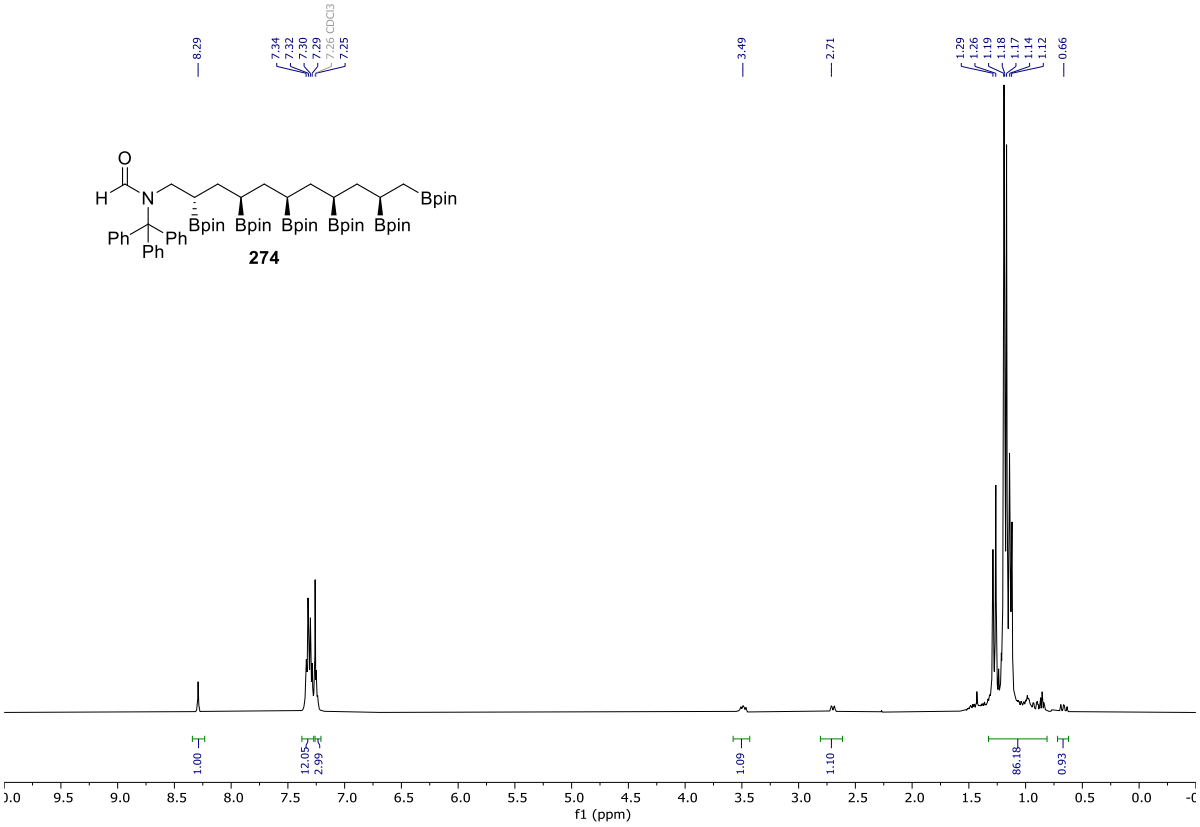
HSQC (700 MHz, pyridine-d_5) of synthetic bahamaolide A, polyol CH_2 region:



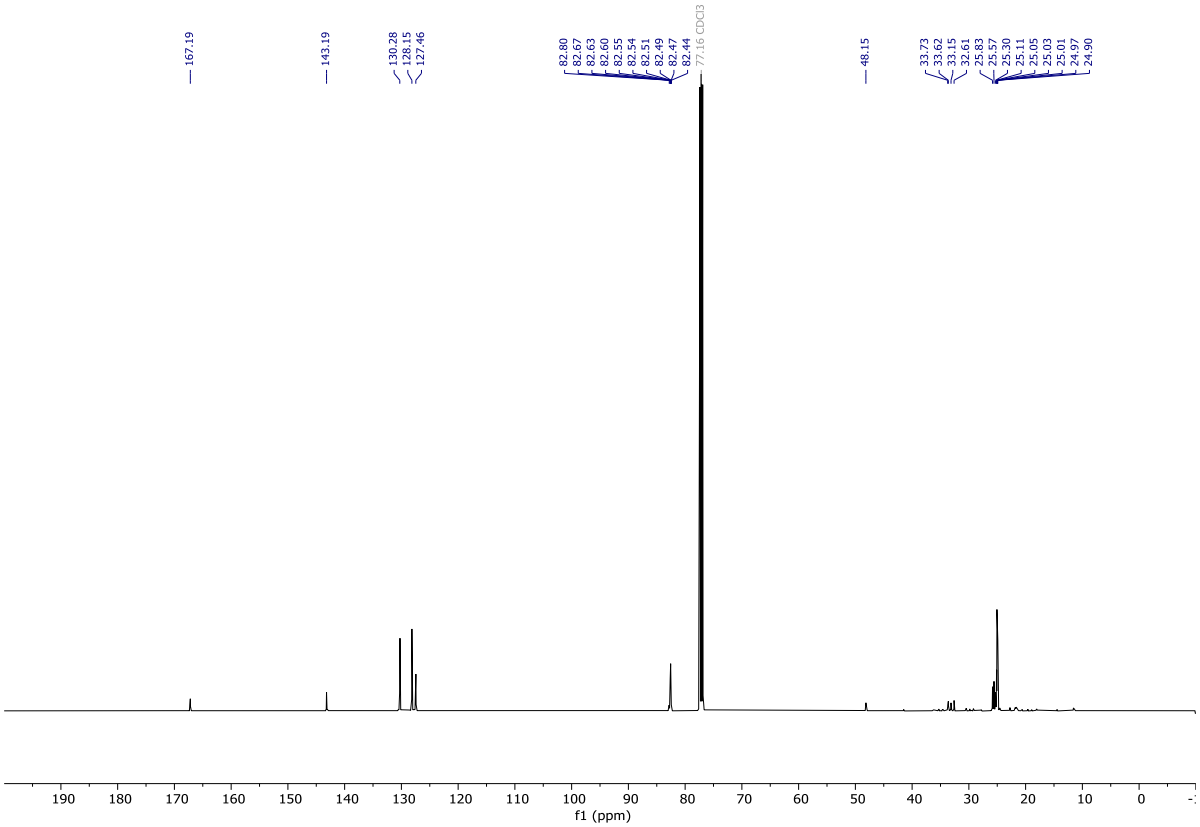
HMBC correlation C3H to C1 (700 MHz, pyridine-d_5) for synthetic bahamaolide A:



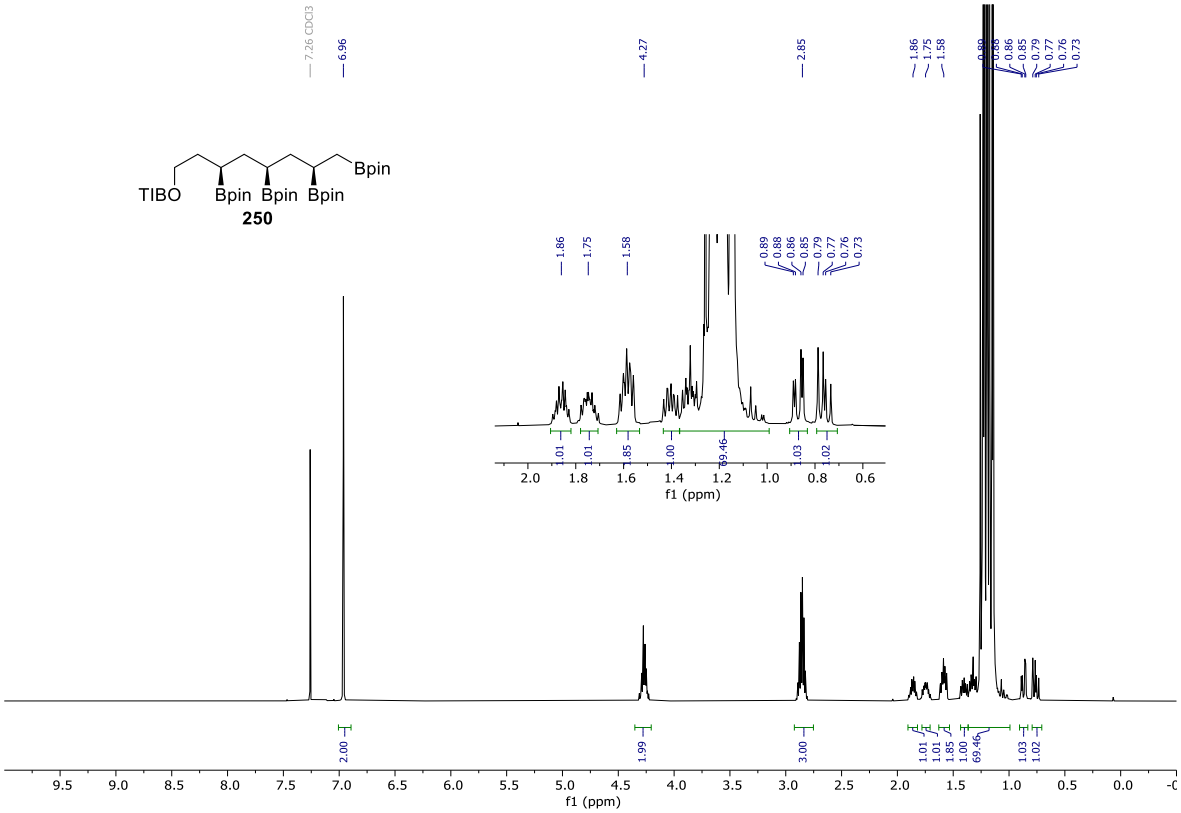
^{1}H NMR (500 MHz, $CDCl_3$) of fragment 1 (**274**)



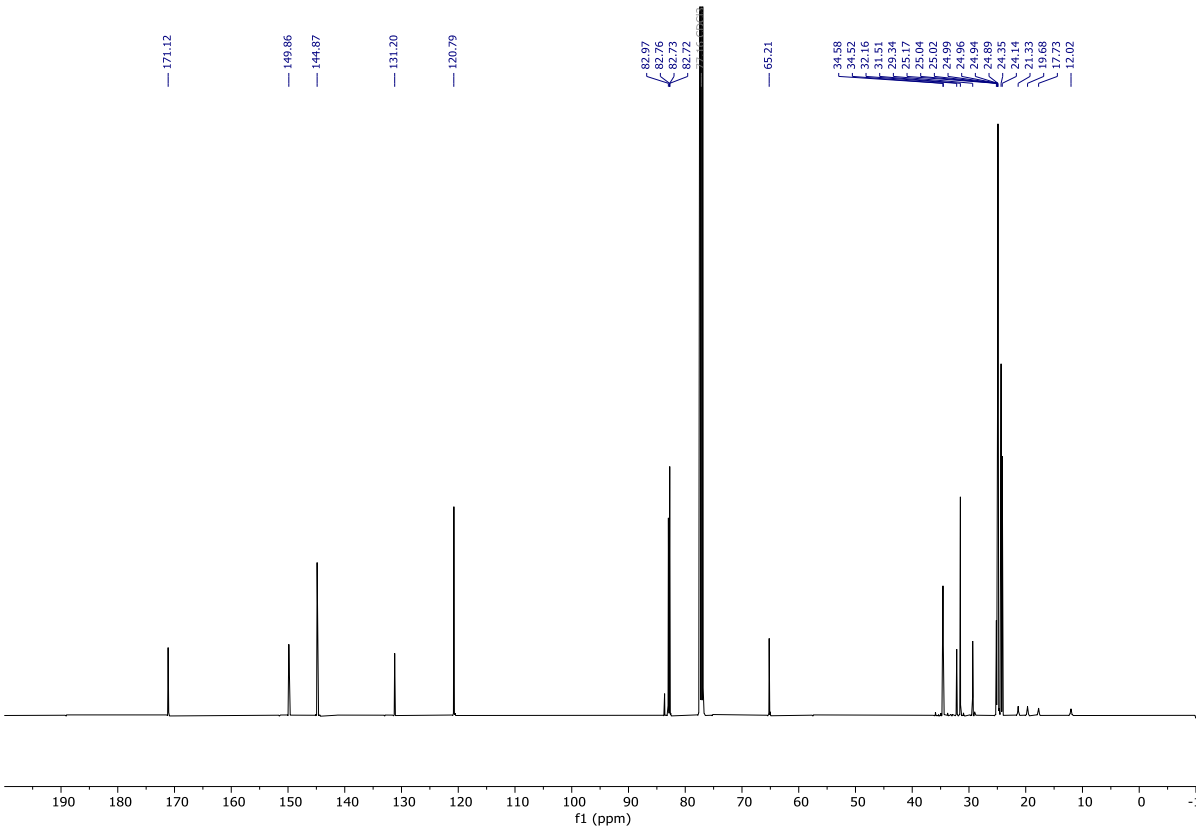
^{13}C NMR (126 MHz, $CDCl_3$) of fragment 1 (**274**)



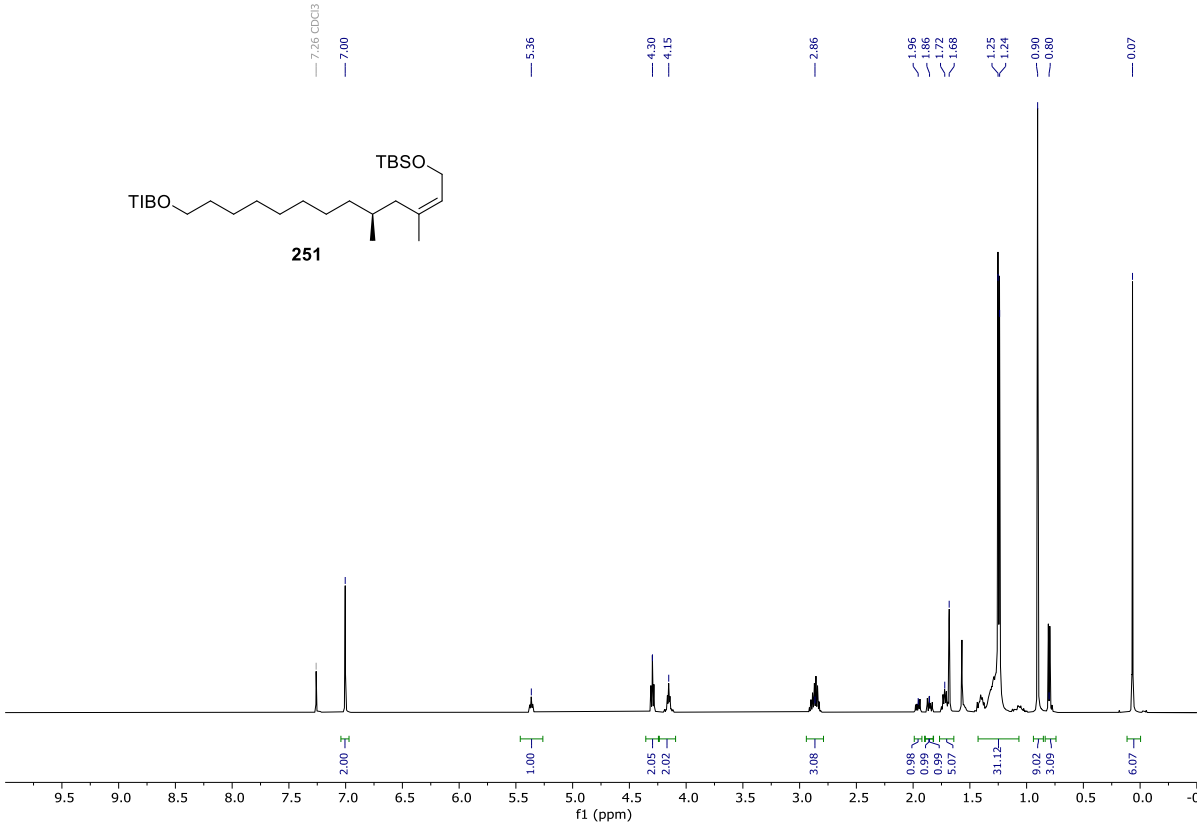
^{1}H NMR (500 MHz, $CDCl_3$) of fragment 2 (**250**)



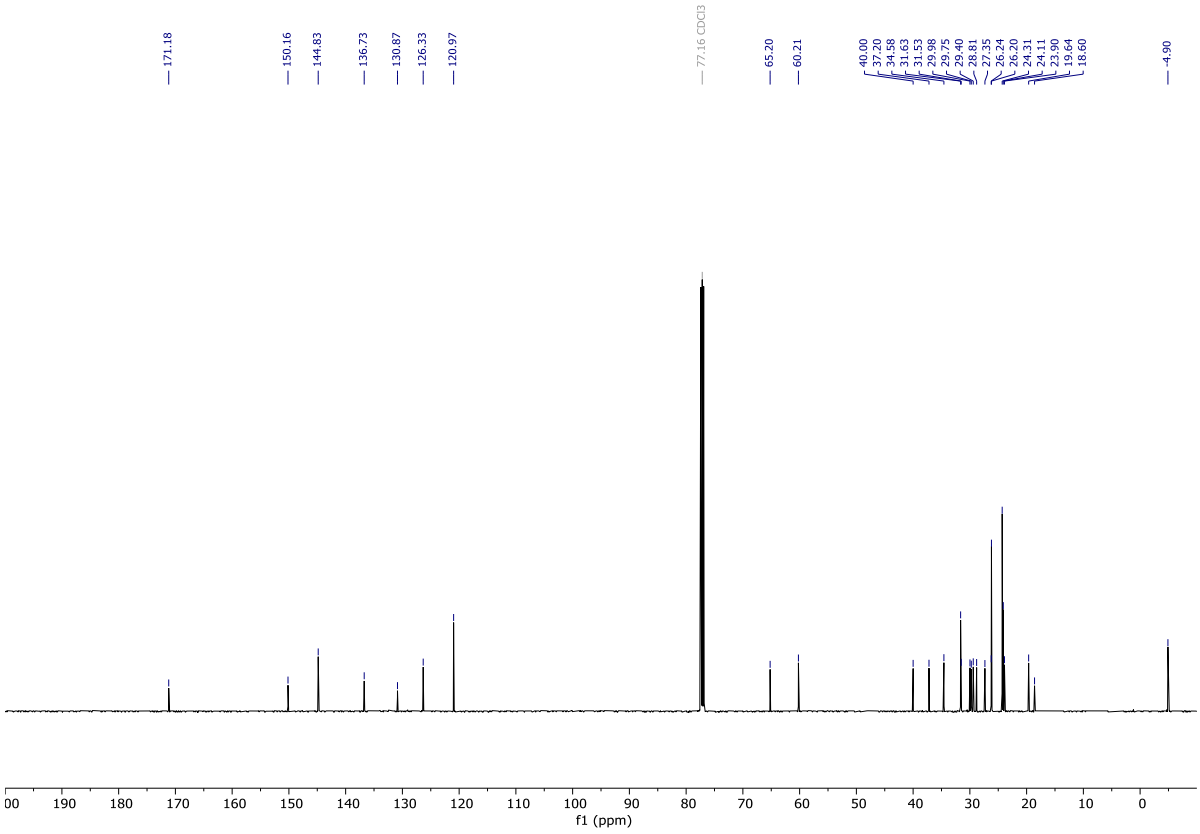
^{13}C NMR (126 MHz, $CDCl_3$) of fragment 2 (**250**)



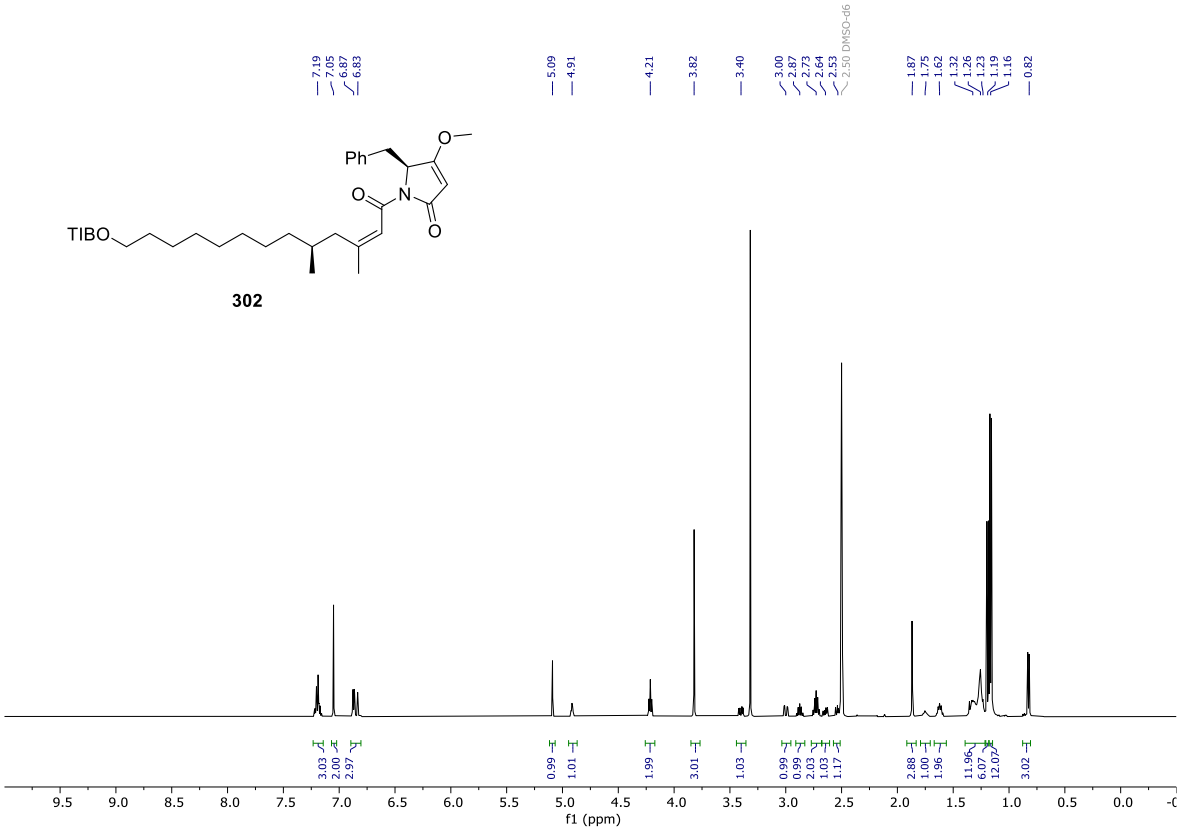
^{1}H NMR (500 MHz, $CDCl_3$) of fragment 3 (**251**)



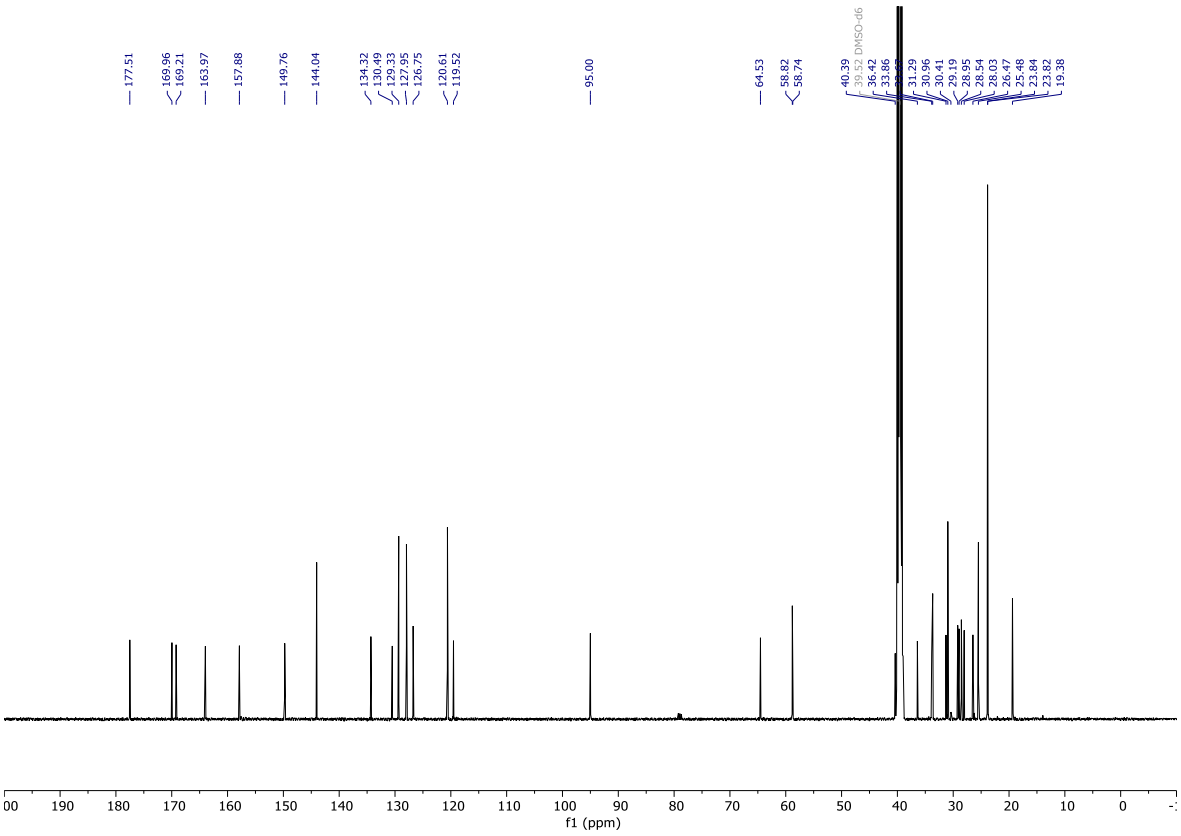
^{13}C NMR (126 MHz, $CDCl_3$) of fragment 3 (**251**)



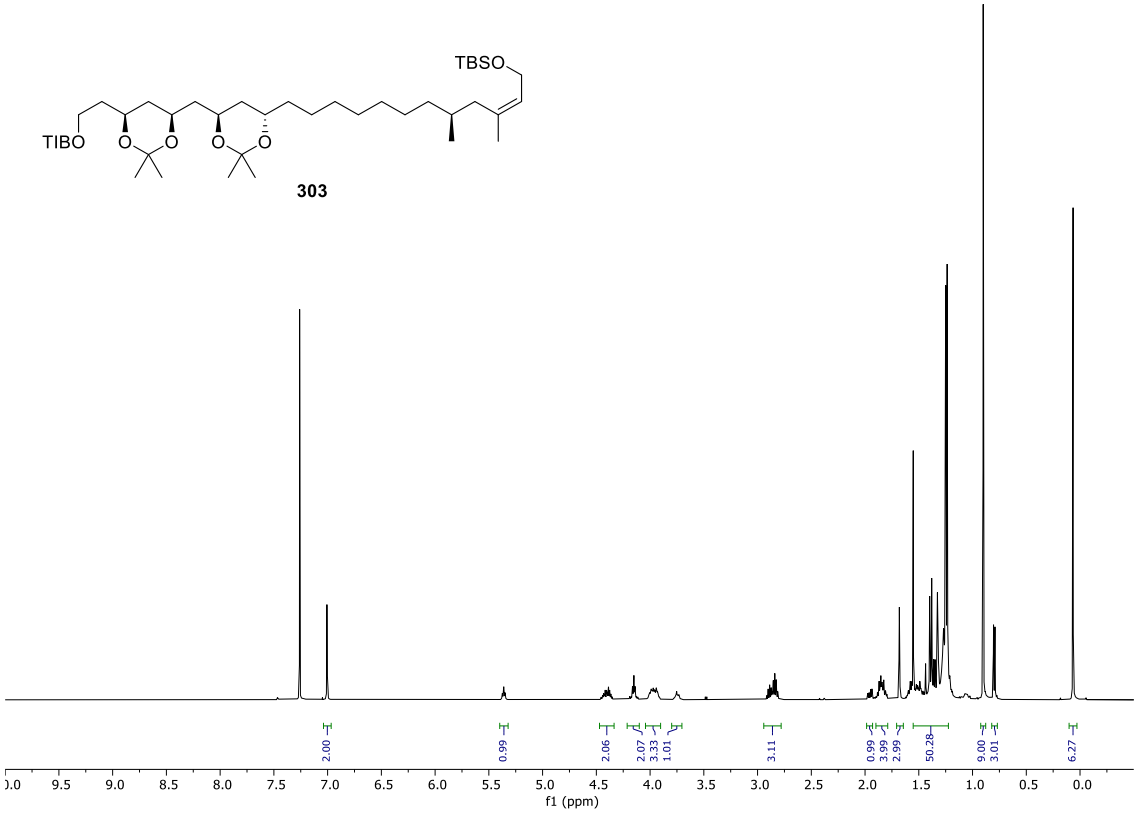
^{1}H NMR (500 MHz, DMSO-d_6) of eastern fragment, correct diastereomer (**302**)



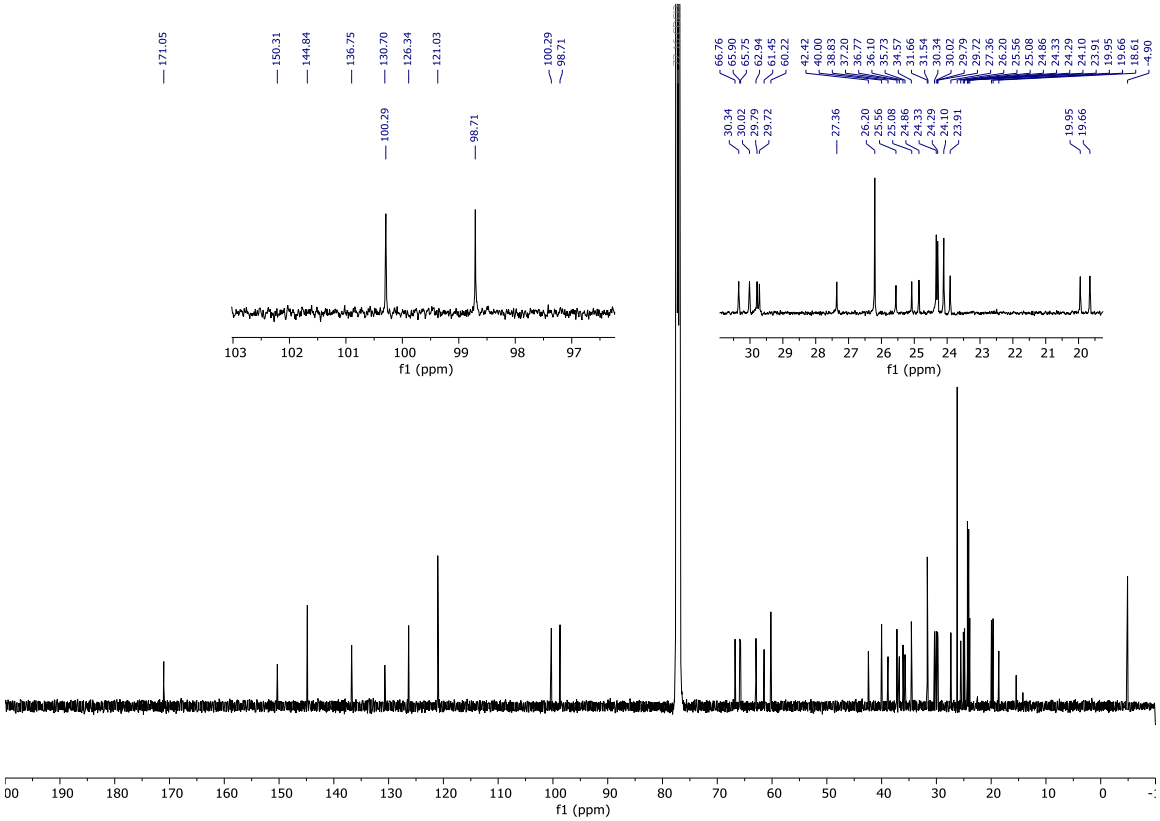
^{13}C NMR (126 MHz, DMSO-d_6) of eastern fragment, correct diastereomer (**302**)



^{1}H NMR (500 MHz, $CDCl_3$) of **303**



^{13}C NMR (126 MHz, $CDCl_3$) of **303**



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