Studies Towards the Total Synthesis of the Heronamide Family of Natural Products

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Edmond C. Toma

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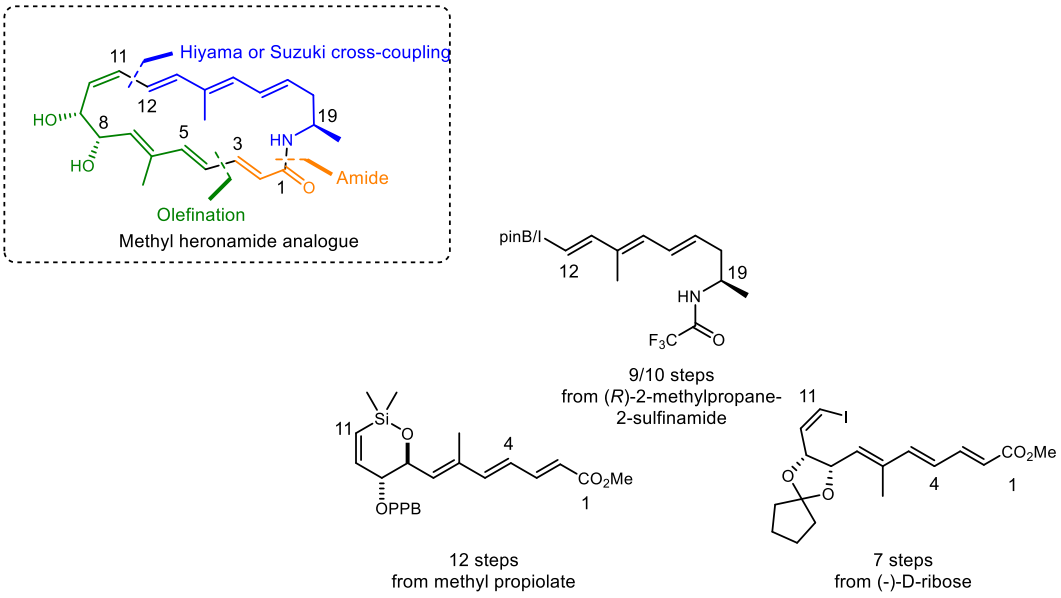


Studies Towards the Total Synthesis of the Heronamide Family of Natural Products

Doctor of Philosophy **Edmond Toma**

Michaelmas, 2021 **Brasenose College**

This thesis explores the use of Hiyama cross-couplings and Suzuki cross-couplings towards the synthesis of the heronamide family of natural products which consist of a 20 membered macrolactam core. The early chapters will discuss the development of cyclic dimethyl alkenylsiloxanes to construct the acyclic methyl heronamide analogue (Scheme 1). Later chapters will discuss the implementation of Suzuki cross-couplings to construct the acyclic heronamide analogue and cyclise *via* a macrolactamisation or Horner-Wadsworth-Emmons reaction.



Scheme 1. Methyl heronamide analogue fragments.

In dedication to my father, for his unwavering support in all things great and small.

Widad Jean Toma

Acknowledgements

First and foremost, I would like to thank Prof Ed Anderson for his supervision and mentorship. Ed has gone far and beyond what most supervisors would do to help me master organic chemistry. His enthusiasm and dedication to chemistry has inspired me greatly. I am forever grateful.

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Most importantly I want to thank my family, the group of people who have had the most impact on my life. I was very fortunate to not grow up with one family, but two, the

Kazangy and Toma family. My cousins and I were raised as one, and the greatest hardship in my life was the loss of my uncle, Dr Falih Kazangy. He always pushed me to do better and was there for me through every injury, sickness, and hospital visit. His love for me was masked, but on few occasions the mask would drop and those moments I'll never forget and like to remember him by. His support for my family was always without question, and the hole from his loss is felt to this day. My aunt, Dr Zeena Kazangy, is less like an aunt, but more of a second mother. Her love for her kids is strong and deep. I thank my mother, Fatin, for her strong, no nonsense attitude; my sister for her courage to continuously change her career path and resisting the pressure to maintain status quo; my brother for supporting our family while I have been away; and most importantly my father. The importance of education was high in our family, which I am extremely fortunate to be born into. My dad and mom worked 7 days a week, never went on holidays, and sacrificed so much more to make sure all their kids received the best education possible. The bar was always set high, and I just hope that with the completion of this degree, I have finally achieved what my parents dreamed for their children when immigrating from Iraq.

In particular, I want to thank my dad for his unending support and love. I don't know where in life I would be without his influence. I learned a lot from him, but the most important thing I learned from my father is nothing in life is given, all things are earned. This was the mentality he instilled in me from a young age which has given me the work ethic to never stop trying and gave me the emotional durability for total synthesis. His hands off attitude of allowing me to make my own mistakes (which were abundant) and never chastising me for them let me develop and take chances. Lastly, I want to thank my father in Heaven and end with one of his teachings. 'All things are possible to him who believes' – Mark 9:23

Ac	Acetyl
ACP	Acyl carrier protein
APC	Allylpalladium(II) chloride dimer
AT	Acyltransferase
BAIB	(Diacetoxyiodo)benzene
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
brsm	based on recovered starting material
Bz	Benzoyl
CAN	Cerium Ammonium Nitrate
COSY	Correlation Spectroscopy
CSA	Camphorsulfonic acid
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7- ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPC	Diethyl cyanophosphonate
DIBALH	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DMTMM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
dppf	Bis(diphenylphosphino)ferrocene

dr	Diastereomeric ratio
DTBMP	2,6-Di-*tert*-butyl-4-methylpyridine
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	Ethylenediaminetetraacetic acid
equiv.	Equivalents
ESI	Electrospray ionisation
Fmoc	Fluorenylmethyloxycarbonyl
gly	glycol
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HOBt	1-Hydroxybenzotriazole
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
IBX	2-Iodoxybenzoic acid
IC_{50}	Half-maximal inhibitory concentration
IPA	Isopropyl alcohol
IR	Infrared
KR	Ketoreductase
KS	Ketosynthase
LDA	Lithium diisopropylamine
LN_2	Liquid nitrogen
m-CPBA	*m*-Chloroperoxybenzoic acid

MIC	Minimum inhibitory concentration
MS	Molecular sieves
NBS	*N*-bromosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
PAB	*p*-Acetoxybenzyl
PCP	Peptidyl carrier protein
PG	Protecting group
Ph	Phenyl
pin	Pinacol
piv	Pivaloyl
PKS	Polyketide synthase
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
PPB	*p*-Pivaloxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate
py	Pyridine
PyBOP	Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
RCM	Ring-closing metathesis
Red-Al®	Sodium bis(2-methoxyethoxy)aluminum dihydride
R*f*	Retention factor
ROESY	Rotating frame Overhauser effect correlation spectroscopy

RT	Room temperature
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TE	Thiolesterase
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TES	Triethylsilyl
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TFP	Tri-2-furanylphosphine
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TLC	Thin layer chromatography
TPAP	Tetrapropylammonium perruthenate
w/v	Weight/volue

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1. Introduction

Polyketide natural products have led to significant breakthroughs in the pharmaceutical industry as antimicrobial or immunosuppressive therapies. Among the polyketide family, a sub-genre of polyene natural products exist and have found their way to the drug market, showing high anticancer and antifungal activity.[1] Due to toxic side effects, over 90% of new antifungal agents fail in drug development.[2] Amphotericin B − despite its nephrotoxicity − continues to be the most common treatment for systemic fungal infections.[3]

A new generation of antifungal medications are needed not only for the adverse side effects of current medications, but also to tackle an emerging class of antifungal resistant strains, such as *Candida albicans* and *Candida krusei*.[4-5] While fluconazole, an antifungal azole, has become increasingly ineffective, polyenes are showing promise in combating these antifungal resistant strains.[6] These polyenes tend to bind to the cell membrane, forming ionophores which enable potassium efflux and ultimately lead to fungal death.[7] This work will examine the total synthesis of the heronamide carbon skeleton with the ability to enable diversification in order to study its structure-activity relationship in more detail.

1.1 Isolation and elucidation of the heronamide family

The first member of the heronamide family, BE-14106, was isolated in 1992 by Kojiri *et al.* from *Streptomyces spheroids* (A14106).[8] This novel 20-membered macrolactam ring (Figure 1.1) was found in the course of screening new antibiotic compounds from soil collected in Shiroyama-cho, Mie Prefecture, Japan. Displaying interesting biological properties, the structure was elucidated to enable further study.

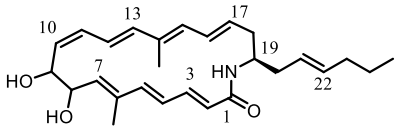
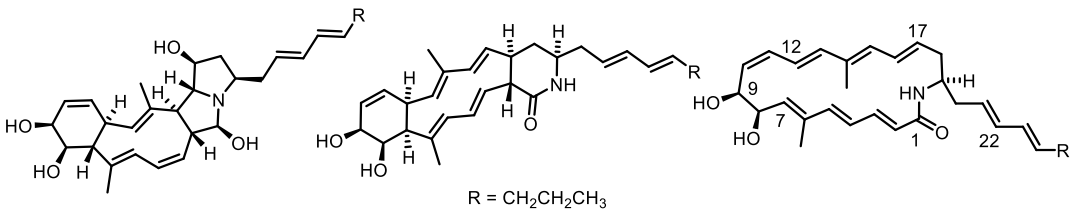


Figure 1.1. The proposed structure of BE-14106.

The molecular formula of BE-14106, obtained from high resolution fast atom bombardment mass spectrometry (HRFAB-MS) and NMR experiments, was identified to be $C_{27}H_{37}NO_3$. While the stereochemistry of the diol remained elusive, acetylation of the two alcohols improved solubility in $CDCl_3$ and CD_3OD to analyse overlapping peaks. Fourteen olefinic protons were seen in the ^{1}H NMR spectrum and a stereochemical analysis using 1D and 2D NMRs in DMSO-d_6 established: *E* $\Delta^{2,3}$ ($J_{2,3}$ 15.0 Hz), *E* $\Delta^{4,5}$ ($J_{4,5}$ 15.3 Hz), *Z* $\Delta^{10,11}$ ($J_{10,11}$ 10.4 Hz), *E* $\Delta^{12,13}$ ($J_{12,13}$ 15.0 Hz), *E* $\Delta^{16,17}$ ($J_{16,17}$ 15.0 Hz), *E* $\Delta^{21,22}$ ($J_{21,22}$ 15.4 Hz). Using ^{1}H-^{1}H COSY spectra, the *n*-propyl and diol moiety were deduced and the carbonyl identified with ^{13}C NMR data. The *trans*-configuration at C6-C7 and C14-C15 was confirmed using NOE experiments.

Off the coast of Heron Island, Australia, Capon *et al.* isolated and proposed the structures of three polyketide natural products, heronamides A-C (Figure 1.2), from *Streptomyces sp.* CMB-M04006 in <1 m shallow-water sediment.[9] The heavily conjugated system of heronamide C provides an interesting insight into the biosynthetic pathway towards heronamides A and B, which contain similar skeletons. Due to this similarity, these 20-membered macrolactam rings, isolated between 2-5 mg/L, were proposed to engage in oxidations and electrocyclisations to produce heronamides A and B from heronamide C.[8] As BE-14106 and heronamide C are nearly identical and heronamide A and B are thought to derive from heronamide C, heronamide C will be the focus of the discussion.



Heronamide A Heronamide B Heronamide C

Figure 1.2. Proposed structures of Heronamide A-C.

The structural elucidation of heronamide C began with an analysis of the HRMS $(M+Na)^+$ ion, which indicated a molecular formula of $C_{29}H_{39}NO_3$. Showing poor solubility in common NMR solvents ($CDCl_3$, acetone-d_6, DMSO-d_6, and methanol-d_4), use of pyridine-d_5 was required in which the ^{13}C NMR displayed a peak at δ_C 168.3, which signified a single amide/ester carbonyl.[9] Eighteen sp^2 carbons were observed from δ_C 124.4 to 143.9 which correlates with nine double bonds.

Heronamide C was found to contain eight (*E*)-double bonds and one (*Z*)-double bond, as deduced from ^1H NMR, ^1H-^1H COSY and ROESY experiments: *E* $\Delta^{2,3}$ ($J_{2,3}$ 14.9 Hz), *E* $\Delta^{6,7}$ (C-28, δ_C 12.7), *E* $\Delta^{14,15}$ (C-29, δ_C 12.5), *E* $\Delta^{16,17}$ ($J_{16,17}$ 14.9 Hz), *E* $\Delta^{21,22}$ ($J_{21,22}$ 15.1 Hz), and *E* $\Delta^{23,24}$ ($J_{23,24}$ 14.8 Hz); however, the elucidation of the stereochemistry of C4-C5, C10-C11, and C12-C13 remained difficult due to overlapping and broad peaks.[9] A diacetate derivative of heronamide C was synthesised to better solubilise the compound in methanol-d_4 and help assign the remaining stereochemistry due to improved dispersion (Figure 1.3): *E* $\Delta^{4,5}$ ($J_{4,5}$ 15.1 Hz), *Z* $\Delta^{10,11}$ ($J_{10,11}$ 10.8 Hz), and *E* $\Delta^{12,13}$ ($J_{12,13}$ 15.1 Hz). The C8 and C9 configuration could not be assigned absolutely, but instead hypothesised from the biosynthesis.

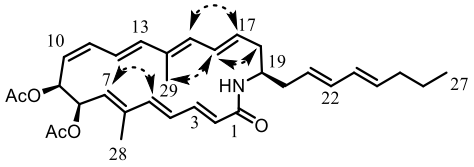


Figure 1.3. A diacetate derivative of the proposed structure of heronamide C with ROESY correlations.[9]

Later, heronamides D-F were isolated from sediment off the coast of the Bay of Bengal at a depth of 3412 m from *Streptomyces sp.* SCSIO 03032, and were found to contain a similar structural motif as heronamides A-C.[10] Heronamide D, E and F (Figure 1.4) are thought to have inverted stereocenters at the secondary alcohols, and a methyl instead of the *n*-propyl group. Heronamide D and E are thought to originate from the same oxidation and cycloaddition process from heronamide F as heronamide A and B; thus, heronamide F will be the focus of the structural elucidation for the carbon skeleton.

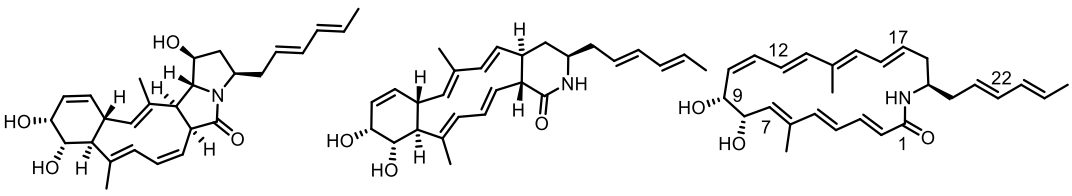


Figure 1.4. Proposed structures of Heronamide D-F.

The structure of heronamide F has an ESI HRMS indicating a molecular formula of $C_{27}H_{35}NO_3$, showing eleven degrees of saturation.[10] Observing the same issues with solubility in common NMR solvents as BE-14106 and heronamide C, pyridine-d_5 was used to obtain ^{1}H NMR, ^{1}H-^{1}H COSY and NOESY spectra to provide data for the initial stereochemical assignment of the (*E*)-double bonds: *E* $\Delta^{2,3}$ ($J_{2,3}$ 14.5 Hz), *E* $\Delta^{16,17}$ ($J_{16,17}$ 15.0 Hz), *E* $\Delta^{21,22}$ ($J_{21,22}$ 15.0 Hz), and *E* $\Delta^{23,24}$ ($J_{23,24}$ 15.0 Hz); however, the clarification of the

stereochemistry of C4-C5, C10-C11, and C12-C13 remained difficult. *E* $\Delta^{6,7}$ and *E* $\Delta^{14,15}$ was determined by NOESY correlation from H8 to H26 and H16 to H27. Similar to heronamide C, a diacetate derivative of heronamide F was synthesised to better solubilise the compound in methanol-d_4 and help assign the remaining stereochemistry with improved dispersion (Figure 1.5): *E* $\Delta^{4,5}$ ($J_{4,5}$ 15.5 Hz), *Z* $\Delta^{10,11}$ ($J_{10,11}$ 10.0 Hz), and *E* $\Delta^{12,13}$ ($J_{12,13}$ 16.5 Hz).

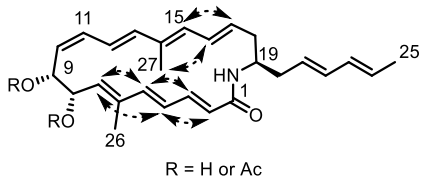


Figure 1.5. Heronamide F NOESY correlations.[10]

A double Mosher ester analysis of heronamide D and E confirms the suggested diol (as drawn), and with the proposed biosynthetic pathway of an cycloaddition of heronamide F to make heronamide D and E, heronamide F was tentatively assigned to have a 8*S*,9*R*-diol.[9-10]

Recently, heronamides G-L (Figure 1.6) have been discovered as metabolites of *Streptomyces niveus* (YIM 32862).[11] These were isolated from the Great Khingan Mountains in Northeast China. Once again, ESI HRMS and NMR experiments were used to propose the structures of heronamide G-L; where assignments could not be secured, the stereochemistry was predicted according to the biosynthetic pathway.

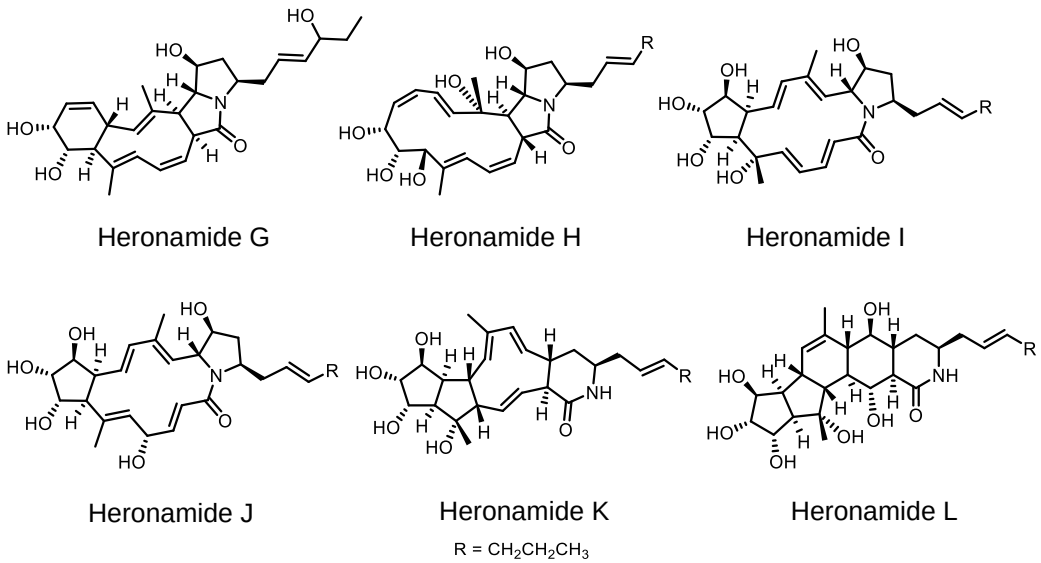


Figure 1.6. Proposed structures of Heronamide G-L.

As the heronamide family grew, the core 20-membered macrolactam remained the same. The structure elucidation has shown that heronamide C, F and BE-14106 are the core structures, while the other members are derived from various oxidations and electrocyclisations. This thesis will focus on developing methods for building the heronamide core skeleton to enable a robust, facile synthesis towards the heronamide family of natural products.

1.2 Biological activity of heronamides and other polyene natural products

Apoptosis, programmed cell death; autophagy, self-degradation of cellular contents; or necrosis, traumatic cell death, are the main classifications of cell death with each having their own benefits and drawbacks. The main advantage of apoptosis is not inducing an inflammation response upon demise; this is desirable because if the response does not maintain its delicate balance, damage to the heart, brain or other vital organs can ensue.[12] Therefore, causing apoptosis in either cancer cell lines or fungal infections remains a highly advantageous process and target for new therapies.[13]

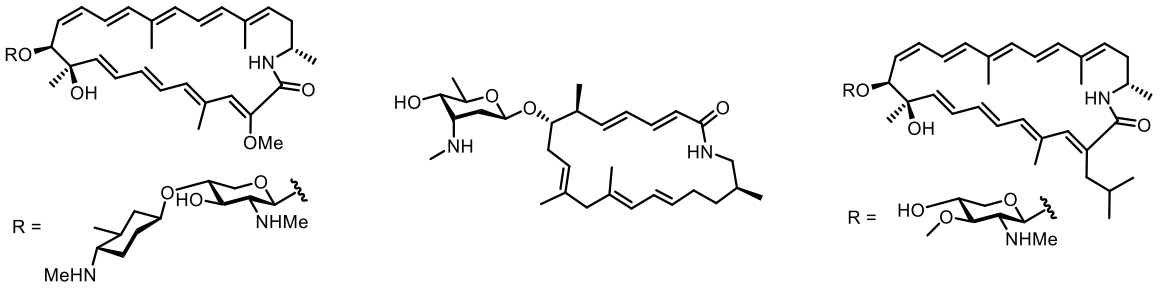
While BE-14106 and heronamide C show modest antimicrobial activity, their antifungal activity has shown to be quite interesting with MIC values of 0.50 µM and 0.13–0.28 µM, respectively, against fission yeast cells.[11, 14-15] When compared to amphotericin B, which displays an MIC value of 0.27 µM, it is less effective; however, new drugs are needed to combat fungi, as the side effects of amphotericin B are well known to be severe and potentially lethal.[16] The BE-14106 IC_{50} of *C. albicans* (CCUG3943) and *C. glabrata* (CCUG3942), antifungal resistant strains, was found to be 7.1 and 3.5 µM respectively, showing promise towards these dangerous strains.[17]

Not all pancreatic cancer cell lines have been shown to have strong inhibition by BE-14106; however, the IC_{50} of cancer cell lines P388/S and P388/VCR remains promising.[18] These P388 murine leukaemia cell lines are resistant to vincristine, and testing with BE-14106 led to IC_{50} values of 1.65 µm for P388/S and 1.89 µm for P388/VCR. More importantly, after five days of mice administration at 100 mg/kg, no deaths were observed.[8]

The difference in structures among these natural products resides in the C19 side chain. BE-14106 has the same carbon skeleton as heronamide F and C, but a more saturated side chain; the level of saturation at the side chain is seen to have an effect towards inhibition, which requires further study to determine the optimal structure.

The diols at C8–C9 seem to be necessary to exert strong biological effects and − as seen in incednine, silvalactam, and vicenistatin (Figure 1.7) − potential glycosylation of these alcohols might lead to even higher potency. Incednine, which possesses a 24 membered macrolactam core, has been shown to sensitise anti-tumour agent resistant Bcl-2/Bcl-xL-overexpressing cells and induce apoptosis when used in combination with adriamycin, an anti-tumour agent.[19] A similar structed core in silvalactam shows strong biological activity against pancreatic cancer cells lines Panc-1, PancTu-1, Panc-89 with EC_{50}

values 0.6, 0.38, and 0.31 μM, respectively.[20] Vicenistatin shows cytotoxicity towards human leukaemia HL-60 cells and human colon carcinoma Co-3 cells with IC_{50} values of 0.12 and 0.19 μg/ml, respectively.[21] The consistent methyl side chain on all these natural products provides interesting insight into the strong effects the sugars have on biological activity when compared with the heronamides.



Incednine Vincenistatin Silvalactam

Figure 1.7. Different glycosylated polyene macrolactams.

1.3 Biosynthesis of the heronamides

The biosynthesis of the heronamide family begins with the core structures of heronamide C and F, which are structurally similar to BE-14106. Although BE-14106 was first isolated from *Streptomyces spheroids*, *Streptomyces* sp. DSM 21069 was chosen for the study of its biosynthesis since it is able to produce ~1 g/L of BE-14106.[17]

The roles of the polyketide synthase (PKS) genes needed to be established and their translation products analysed for domain organisation, as shown in Figure 1.8. BecA was found to be the loading module for the sidechain of C20-C25. The ketoacyl synthase (KS) domain of the loading module contains a glutamine residue instead of the typical cysteine in the active site. The starting unit that the acetyltransferase (AT) domain selects is theorised to proceed *via* decarboxylation by the KS domains for the chain initialisation. The AT domain in the BecA loading module is specific for methylmalonyl-CoA, and as the KS

domain decarboxylates methylmalonyl-CoA, it leaves propionate to be installed as the first unit in the side chain.

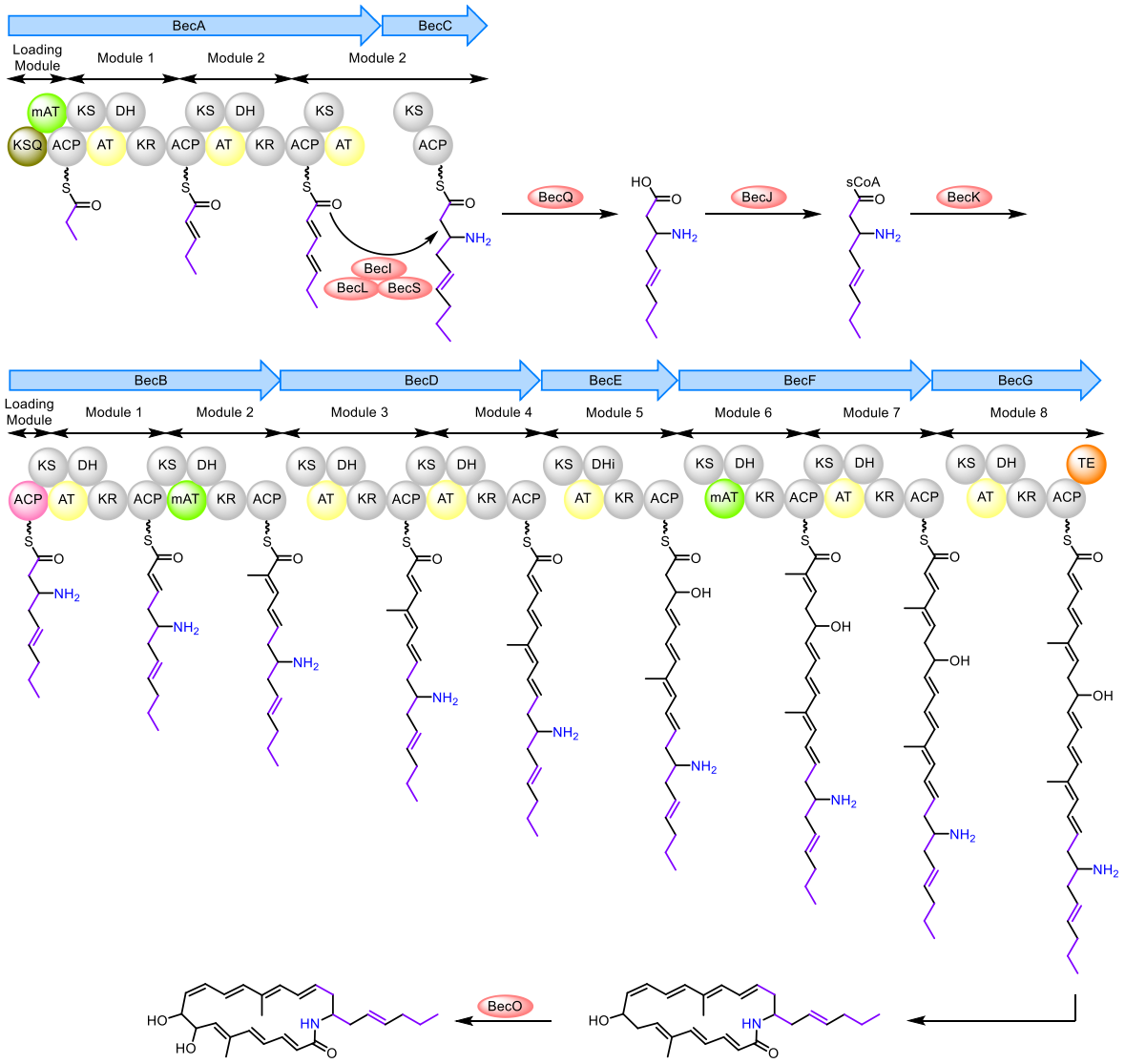


Figure 1.8. Biosynthesis of BE-14106.[17]

For the extender modules 1, 2 and 3, the AT domains are specific for malonyl-CoA.[17] Module 3 lacks reductive ACP domains, and thus truncates after the AT domain. BecL, BecI and BecS proteins are theorised to be involved in the modification of the aminoacyl starter unit. The BecL protein is thought to be used for the activation of a glycine substrate in order for BecI protein, which is tethered to peptidyl carrier protein (PCP) BecS, to aminate the

side chain. The KR domain of BecC is possibly involved in the reduction, which leads to the C21-22 sp^2 bond.

The thioesterase BecQ protein likely releases the aminoacyl molecule as a carboxylic acid, which is activated by the acyl-CoA ligase protein, BecJ, to produce the CoA thioester. This results in the acyltransferase BecK protein to select the aminoacyl-CoA substrate and transfer it to the ACP domain of the loading module of the BecB PKS.[17]

The polyketide chain extends by the condensation of six malonyl-CoA and two methylmalonyl-CoA units by BecB, BecD, BecE, BecF, and BecG PKS. The thioesterase (TE) domain hydrolyses the thioester bond, catalyses the macrolactamisation, and releases the polyene from the PKS complex. Finally, C8 is hydroxylated by BecO, a P450 monooxygenase.[17]

Heronamide C and F were found to be biosynthetically similar, as shown in Figure 1.9; however, cremimycin biosynthesis studies helped illuminate some of the questions surrounding other proteins made, but not defined in the BE-14106 study.[22] The gene cluster similarities of *her* and *bec* indicates that the biosynthetic pathways should be similar, differentiating only in their side chains.[23] The clarification of HerU, HerI, and HerJ show a different pathway than originally thought for BE-14106. HerU (BecU) is proposed to assist in the Michael addition by glycine, in which HerI (BecI) removes the glyoxylate unit by an oxidative hydrolysis.[23] HerJ (BecJ) is used as an acyl-CoA synthase.

In order to better characterise the P450 monooxygenase (HerO, BecO), Zhu *et al.* engineered a reductase domain to the *herO* gene in order to generate a self-sufficient recombinant cytochrome P450. This mutant enzyme was able to convert the monohydroxylated product to heronamide F in the presence of NADPH, and control

experiments lacking the HerO or NADPH cofactor failed to convert the starting material which confirms that HerO hydroxylates at the C8 position.[23]

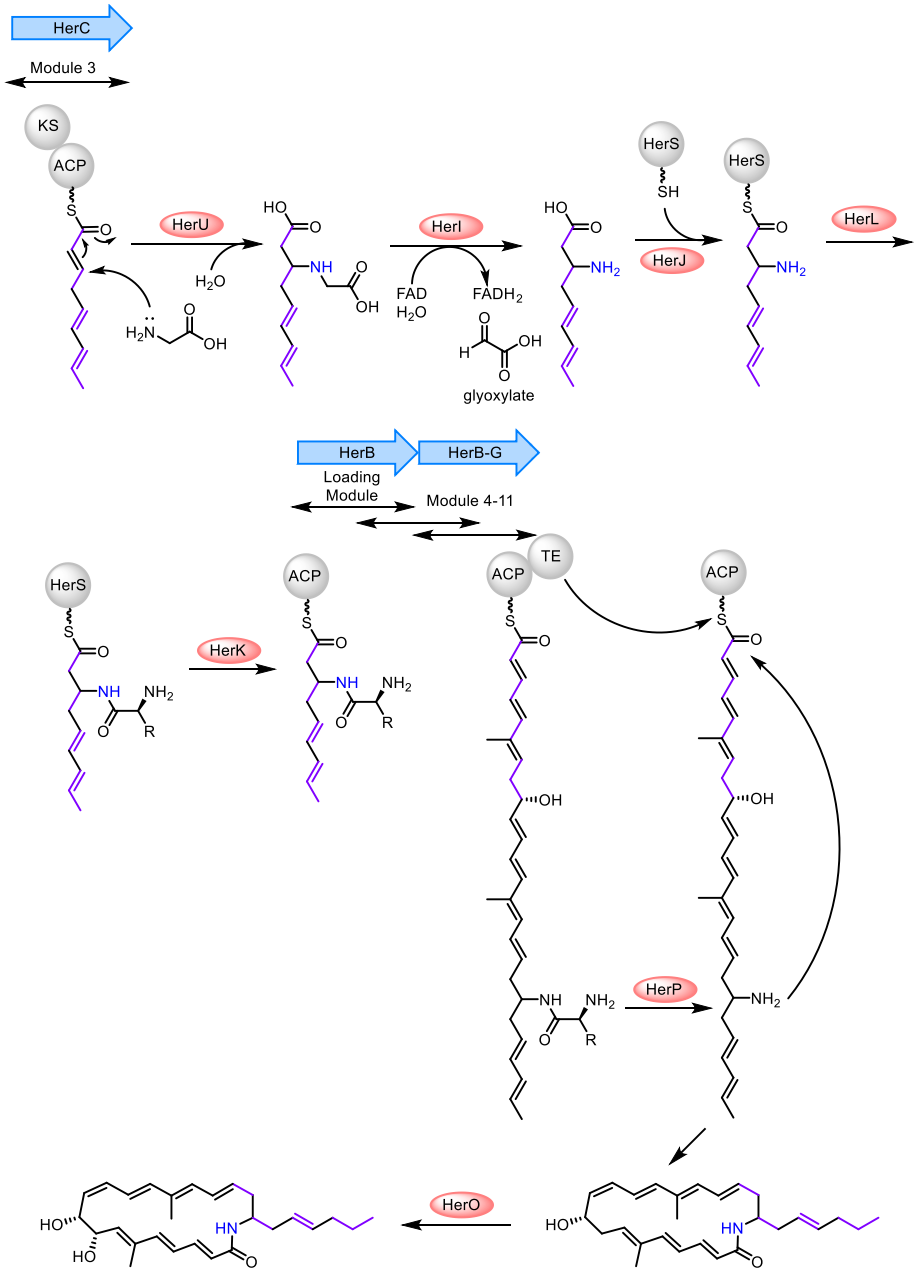
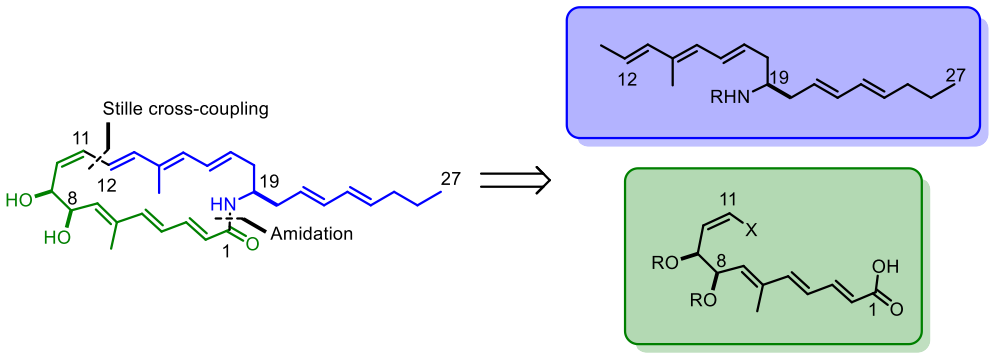


Figure 1.9. The biosynthesis of heronamide F.[23]

1.4 Previous synthesis of heronamide C

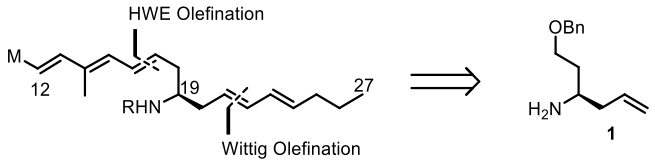
In 2014, Sugiyama *et al.* reassigned the stereocenters of heronamide A and theorised that other members of the heronamide family will also need to be reassigned.[24] To confirm the structure, Sakanishi *et al.* set out to synthesise the proposed structure of heronamide C to unambiguously define these key stereocenters.[25] Scheme 1.1 shows the key disconnections Sakanishi made at C11 with C12, and the amide connection between C1 and C19.



Scheme 1.1. Retrosynthesis of the proposed structure of heronamide C.

Amide bond formation is a very well-studied reaction, and a plethora of conditions are able to obtain high yields in this connection.[26] Notably, the Stille cross-coupling remains one of the premier methods for Pd-catalysed cross-coupling of sensitive molecules, tolerating a large variety of functional groups with its mild conditions for forming *C-C* bonds.[27,28] This organotin cross-coupling virtually guarantees the (*Z*)-alkene at C11-C12, and was planned to be used for the intramolecular connection to form the macrocycle.

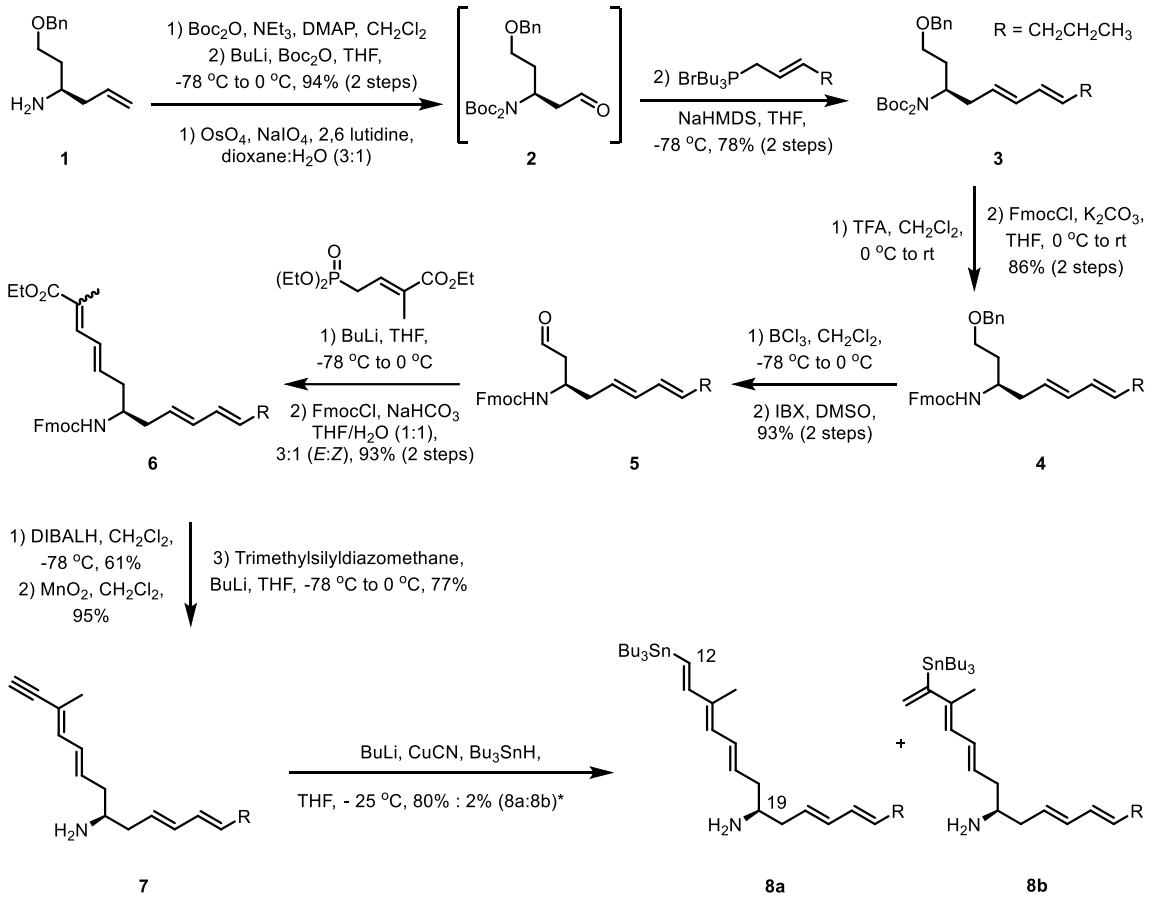
The C12-C27 fragment can be further broken down to the basic building block of the enantioenriched homoallylamine **1** as shown in Scheme 1.2, where (*E*)-selective Wittig or Horner-Wadsworth-Emmons (HWE) olefinations could be used to install the C21-C27 sidechain, and chain extend from C18.[25]



Scheme 1.2. Retrosynthesis C12-C27.

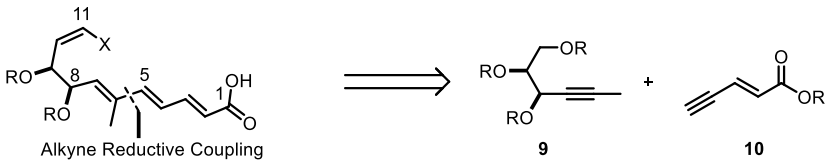
The synthesis of the C12-C27 fragment is summarised in Scheme 1.3. This commenced with a di-Boc protection of known amine **1** which proceeded in two steps in 94% yield, and an oxidative cleavage of the terminal alkene forming the corresponding aldehyde **2.**[29-30] This was carried without purification into an (*E*)-selective Wittig olefination (78% over two steps) to install the side chain with moderate selectivity (10:1 *E*:*Z* ratio, **3**). A series of deprotections, reprotections (**4**), and an oxidation afforded aldehyde **5** in 80% yield over four steps. This set up an HWE olefination to form dienoate **6**, which proved only mildly (*E*)-selective (3:1 (*E*:*Z*) ratio); however, an Fmoc reprotection was also required (93% over two steps). The reduction of the ester to an alcohol (61%) was followed by an oxidation to afford the aldehyde in 95% yield with minimal purification. This underwent a Colvin rearrangement to afford the tetraenyne **7** in 77% yield, but another Fmoc protection was unfortunately required, which set up the tetraenyne **7** for hydrostannylation.

In the investigation of the hydrostannylation, it was found that there was an (inseparable) regioselectivity issue, forming stannanes **8a** and **8b**; luckily, when the amine was not Fmoc protected, the regioselectivity improved to form stannanes **8a** and **8b** in 80% and 2% respectively. The reasons for this are not clear; the necessity of the free amine could implicate a copper amine complex, but this was not further studied. Since the free amine was desired for the amide bond formation and offered higher regioselectivity in the hydrostannylation, the last Fmoc reprotection was deemed unnecessary. In total, **8a** was prepared in 17 steps with a 14% overall yield.



Scheme 1.3. The synthesis of C12—C27.

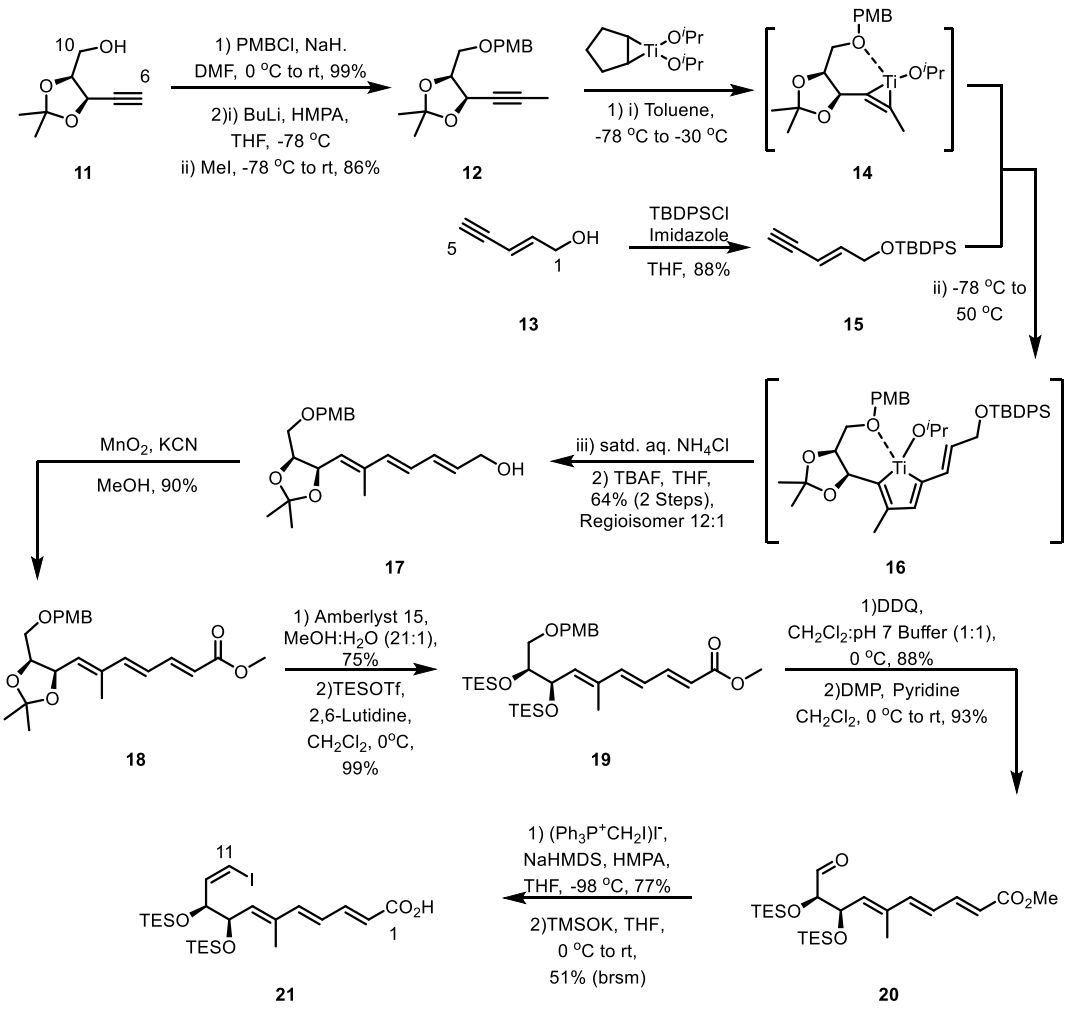
The C1-C11 carboxylic acid can be further broken down to **9** and **10**, as shown in Scheme 1.4.[25, 31] Alkyne **9** ultimately comes from the naturally occurring sugar (−)-D-ribose.[32-33]



Scheme 1.4. Retrosynthesis of C1-C11.

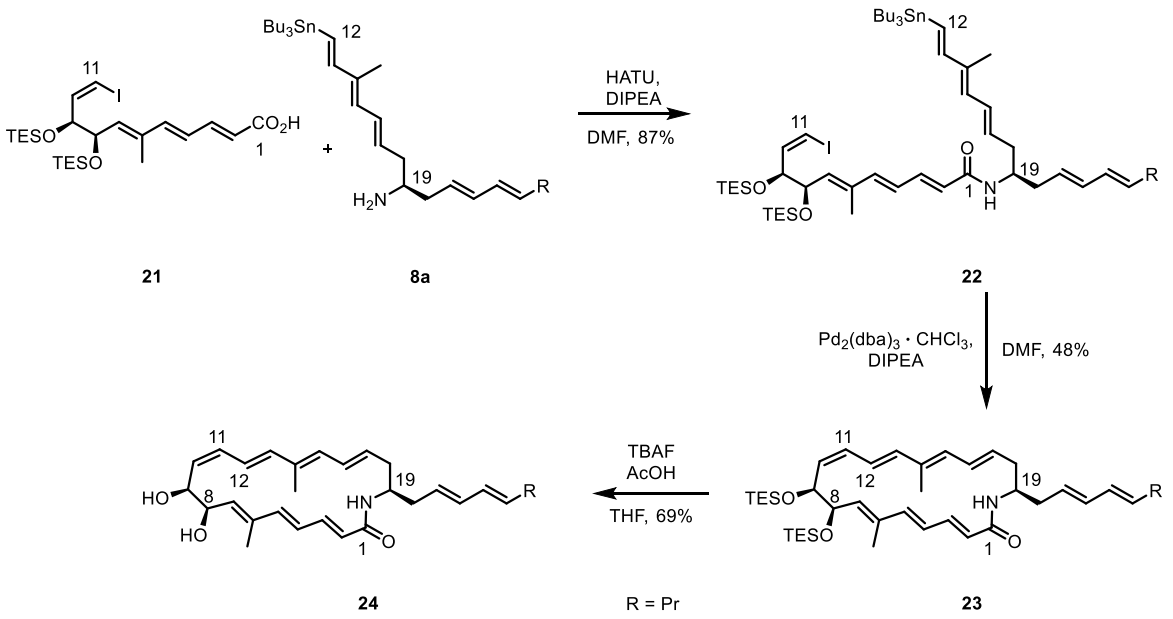
The synthesis commenced with literature-known acetylene **11**, which first required alkyne methylation (Scheme 1.5). A PMB protection of the C10 alcohol was carried out in

99% yield, and deprotonation of the alkyne for electrophilic methylation afforded the PMB ether **12** in 86% yield.[25, 32-33] The coupling partner enyne **13** was protected with as a silyl ether in (88%) before the reductive coupling.[31] In this key process, chlorotriisopropoxytitanium was first treated with *c*-C_5H_9MgCl under Micalizo's conditions to form an *in situ* low-valent titanium species, and PMB ether **12** was then added to form complex **14**.[34] Addition of TBDPS-protected enyne **15** leads to titanocyclopentadiene **16** *via* migratory insertion. Addition of saturated ammonium chloride effects protodemetallation to form the triene product, which was carried directly into deprotection of the silyl ether to afford triene **17** in 64% yield over the two steps, as an inseparable mixture of regioisomers (12:1) from the alkyne reductive coupling. A series of deprotections, reprotections and oxidations (**18**, **19)** led to aldehyde **20** in 55% yield over five steps, which was subjected to a Stork-Zhao olefination to install the (*Z*)-vinyl iodide in 77% yield. Cleavage of the methyl ester provided the C1-C11 carboxylic acid fragment **21** in 51% yield based on recovered starting material (brsm). The synthesis of **21** was achieved in 15 steps with an overall yield of 7%.



Scheme 1.5. Synthesis of C1-C11.

The union of fragments **21** and **8a** requires Stille cross-coupling and amide bond formation, with the order of events being important for the macrocyclisation step. As shown in Scheme 1.6, the amide bond was initially formed using HATU as the activating agent, (**22**, 87%); this was followed by the intramolecular Stille cross-coupling which proceeded in a respectable 48% yield. An intramolecular Heck reaction with the halide at C11 and the double bond of C6 and C7 was of potential concern, but this was not observed. A final deprotection of the silyl ethers was conducting using TBAF and acetic acid in 69% yield, to form the proposed structure of heronamide C **24**.



Scheme 1.6. Union of fragments **21** and **8a** and macrocyclisation.

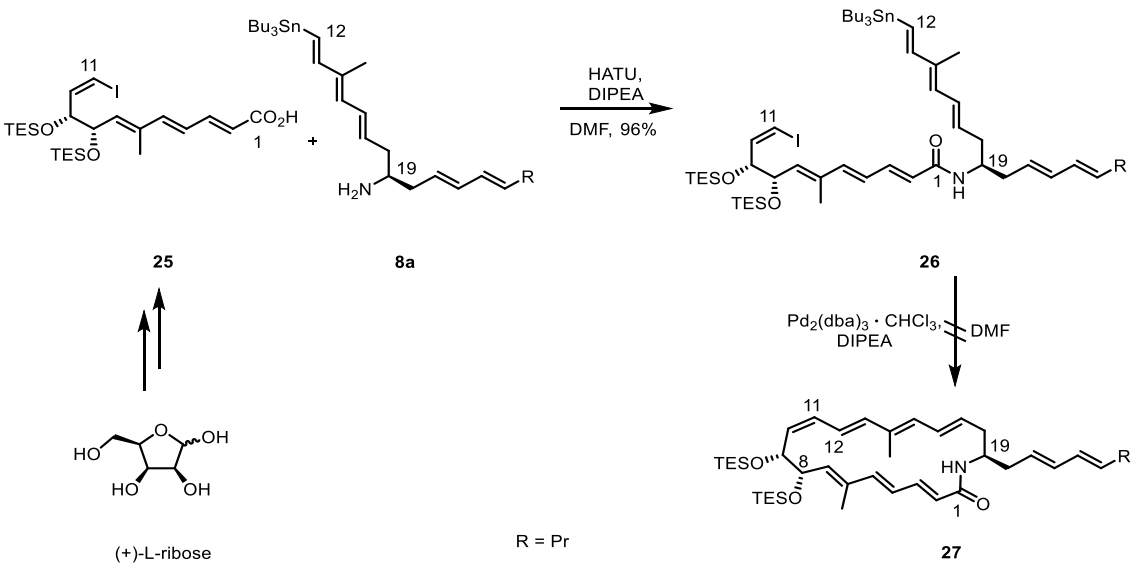
The authors also attempted to first combine the fragments with a Stille cross-coupling, followed by macrolactamisation, but this coupling proceeded in low yield. The macrolactamisation was then found to be even lower yielding (~8%), which forced the authors to abandon this approach.

Upon completion of the total synthesis of the proposed structure of heronamide C **24**, it was observed that the spectroscopic data of **24** did not match that of the natural product.[25] Furthermore, the optical rotation of synthetic compound **24** and heronamide C obtained in DMSO were different. Extensive NMR experiments were conducted to elucidate overlapping and broad peaks, and NMR experiments confirmed the geometry assignment of all the double bonds of the synthetic sample, which indicated the proposed structure of heronamide C needed to be revised.

1.5 Structure correction and synthesis of reassigned heronamide C

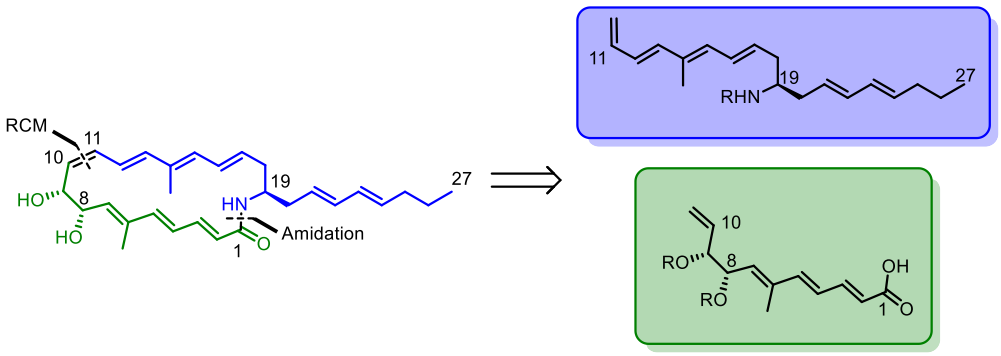
Kanoh *et al.* set out to correct the proposed structure of heronamide C by synthesising a version of the natural product with the opposite stereochemistry at C8 and

C9.[35] They theorised that the chemical assignment was not 8*R*, 9*S*, and 19*R* but 8*S*, 9*R* and 19*R*. As shown in Scheme 1.7, carboxylic acid **25** was synthesised through an equivalent sequence using the expensive, unnatural sugar (+)-L-ribose as the starting material**.** The amide coupling to make **26** proceeded in excellent yield (96%); disappointingly, the Stille cross-coupling to form macrocycle **27** did not work. A variety of substrates with different protecting groups on the diol or with the free alcohols did not help, only showing decomposition of the starting material. The dialdehyde at C10 and C11 was constructed for an attempted pinacol coupling to form the macrocycle, but the only observable product had the C10 aldehyde still intact, which indicates C10 was inactive under pinacol conditions.[35]



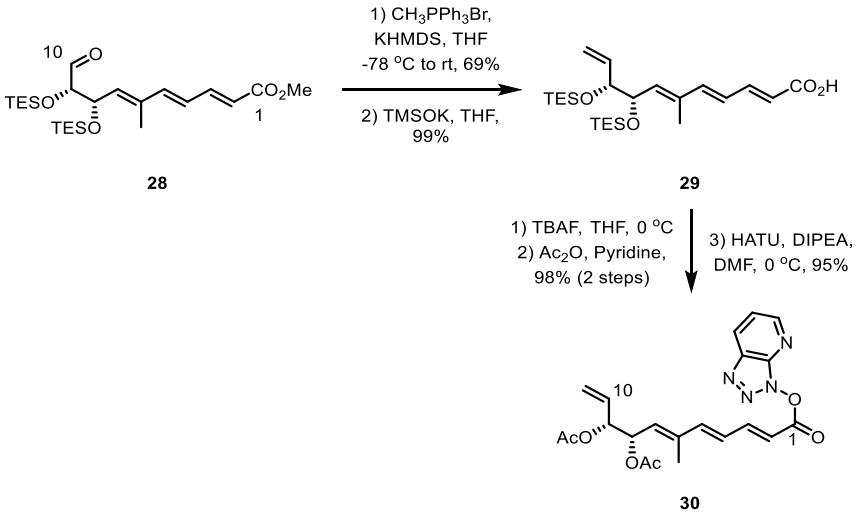
Scheme 1.7. Union of fragments **25** and **8a** and macrocyclisation.

The group had previously encountered success with ring closing metathesis (RCM) in a total synthesis of another heavily conjugated macrocyclic lactam, vicenistatin, and decided to try to close the heronamide ring with RCM as shown in Scheme 1.8.[36] The appeal of this strategy is that intermediates from the previous routes can be employed.



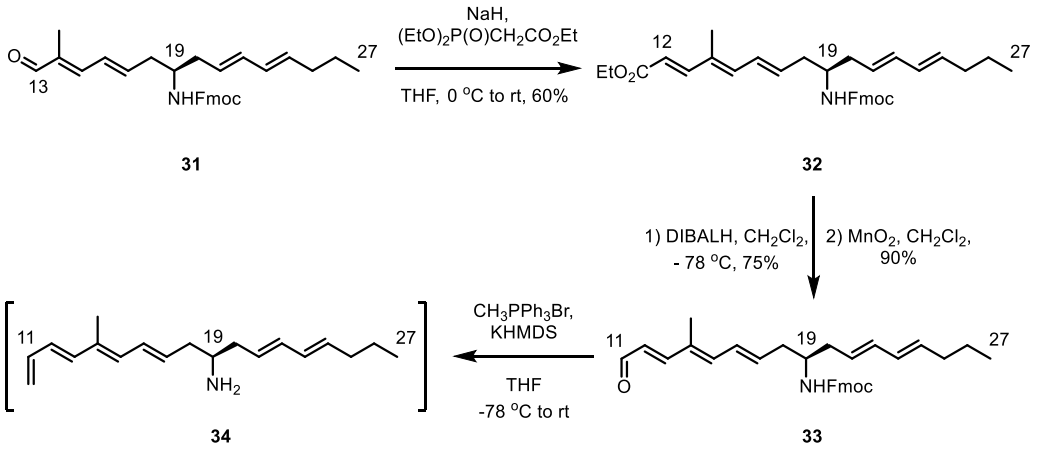
Scheme 1.8. Retrosynthesis of heronamide corrected structure.

The synthesis of the C1-C10 RCM precursor **28** proceeds *via* the enantiomeric synthesis of **20**, using (+)-L-ribose again as the starting material (Scheme 1.9). Aldehyde **28** was converted to the terminal alkene by generating methylene triphenylphosphine *in situ* (69%), and treated with TMSOK to produce the carboxylic acid **29** in 99% yield. Deprotection of the silyl ethers using TBAF revealed the diol, which was carried forward directly into a double acetylation (98% yield over the two steps). The carboxylic acid was then activated using HATU in 95% yield to form triene **30**.



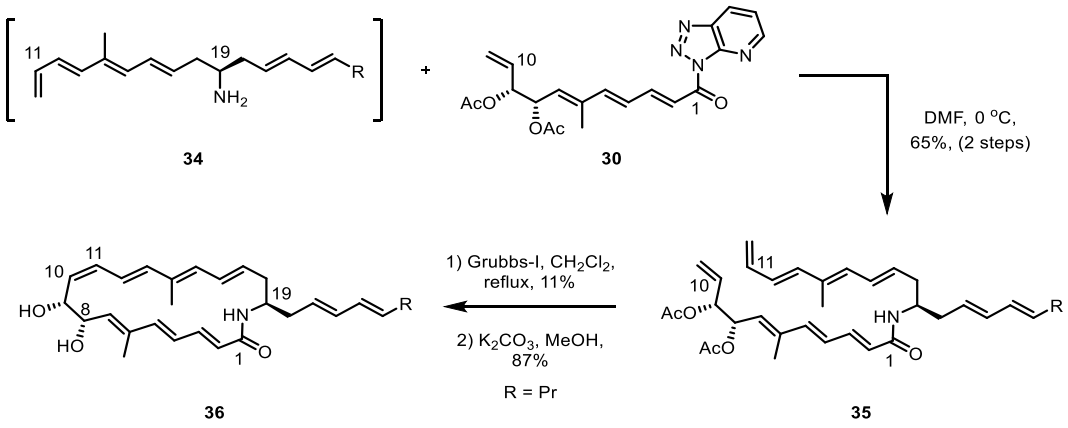
Scheme 1.9. Synthesis of C1- C10.

The synthesis of the C11-C27 fragment intercepted with previous work at **31**; the chain was extended with an HWE olefination in 60% yield (Scheme 1.10). Trienoate **32** was reduced with DIBALH in 75% yield and oxidised with manganese dioxide to afford aldehyde **33** in 90% yield. Methylene triphenylphosphine was generated *in situ* to afford the tetraene **34**, but was found to be an unstable intermediate and was therefore carried directly into the next reaction.



Scheme 1.10. Synthesis of C11- C27.

The union of the unstable tetraene **34** and the activated carboxylic acid **30** proceeded by simple mixing of the two substrates in DMF (Scheme 1.11) which gave amide **35** in 65% over the Wittig and amide bond-forming steps. Amide **35** was heated to reflux in the presence of the Grubbs I catalyst, which achieved RCM in a rather low 11% yield. Deprotection of the acetate groups with methanolic potassium carbonate gave diol **36** in 87% yield. Unsuccessful attempts to close the macrocycle in the presence of the free alcohols showed that some form of protecting group was necessary.



Scheme 1.11. Union of fragments **34** and **30** and macrocyclisation.

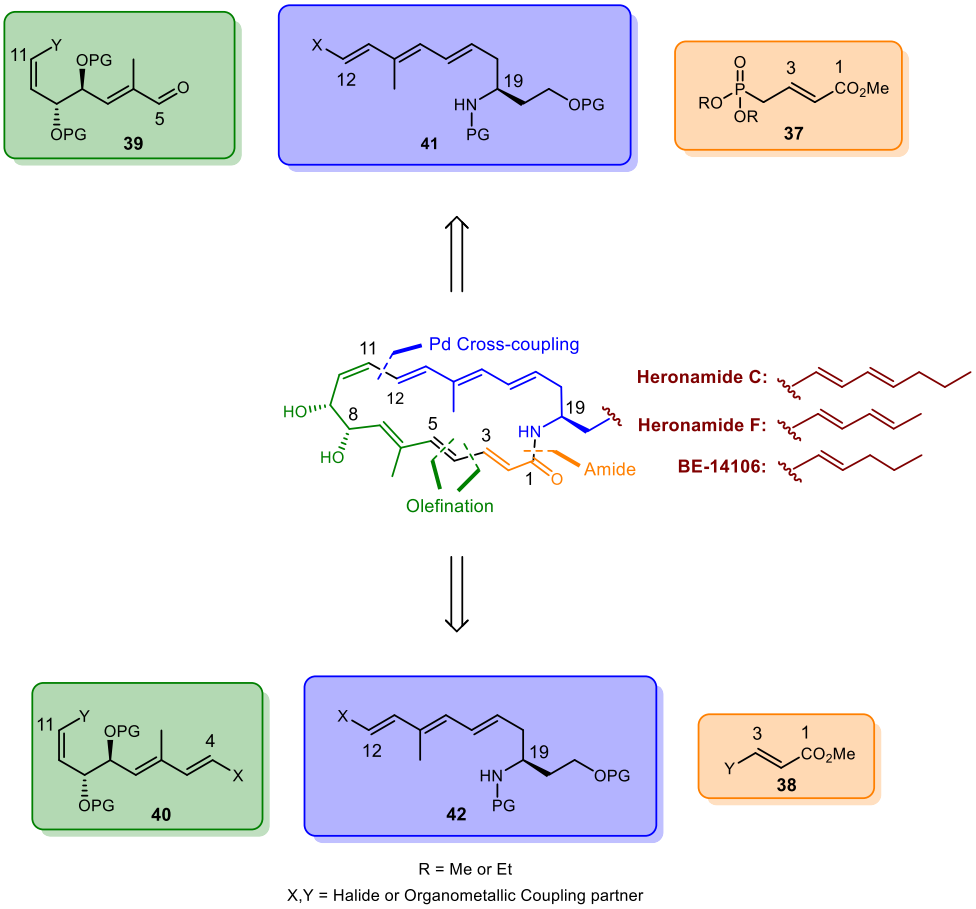
With the newly proposed structure **36** of heronamide C in hand, its spectroscopic data were compared with that of the natural product. Pleasingly, all data matched and the structure of heronamide C was therefore corrected. Since heronamide A and B are thought to derive from heronamide C, their structures were also adjusted to have the diols 8*S* and 9*R*. To confirm, Kanoh *et al.* synthesised heronamide A and B from heronamide C in 45% (brsm) and 27% yield respectively.

1.6 Proposed retrosynthesis of the heronamide core

With the correct structure identified, our group set on identifying a concise route to synthesise the core heronamide skeleton, with the possibility of late-stage installation of various side chains. This would allow a study of the effects of degree of side chain saturation on biological properties, which would potentially identify a better candidate for inhibition of fungal, parasitic or cancer targets.

The C1-C19 skeleton is similar across the heronamide family, such that the stereochemistry is maintained for the different family members. As shown in Scheme 1.12, the amide bond at C1 appeared the most logical disconnection due to the vast precedent for forming amide bonds.[26] Olefination at C3 or C4 allows the use of either cross-coupling or

an HWE reaction. We planned to use the known α,β-unsaturated esters **37** and **38** in these disconnections.



Scheme 1.12. Retrosynthesis of the heronamide core structure.

The synthesis of enantiopure diols in **39** and **40**, and the preparation of the (*Z*)-vinyl halide or organometallic coupling partner were identified as key challenges in our proposed synthesis. The former was planned to be resolved using a Sharpless asymmetric epoxidation reaction, whereas the challenge was envisaged to be overcome by employing cyclic siloxanes with a (*Z*)-double bond inscribed, or a Stork-Zhao iodoolefination.

The trienes **41** and **42** would feature either a halide or organometallic handle to couple with **39** or **40**, thus ensuring the *Z*,*E*-stereochemistry at C11 and C12. The side chain

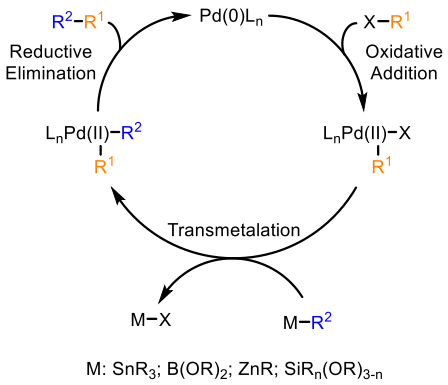
at C19 can be extended as desired by including a protected alcohol at C21 which can be functionalized at a late stage either *via* cross-coupling or Wittig olefination strategies.

2. Hiyama Cross-coupling and macrolactamisation strategy

Sustainable chemistry is an ever growing field with international adoption, but still needs transformative innovations to have a wider impact.[37-38] In the context of cross-coupling reactions, although Stille couplings offer powerful advantages for coupling complex fragments due to the low nucleophilicity of organotin reagents and high stereo and regioselectivity, the toxicity of organotin is seen as its downfall. Organotin exposure can lead to cerebral edema, encephalopathy, dermatitis, damaged mitochondria, and reproductive failure.[39] Alternative methods have therefore been developed, such as the use of organosilanes for cross-coupling, as pioneered by Tamejiro Hiyama in 1988 and later expanded upon by Scott Denmark, which are similarly regio- and chemoselective.[40] Organosilanes have many other advantages: silicon is abundant and of low toxicity, and is therefore environmentally friendly.[41] This has led to an increase in the use of Hiyama cross-coupling in total synthesis over the last two decades.[42]

2.1 Palladium cross-coupling mechanism

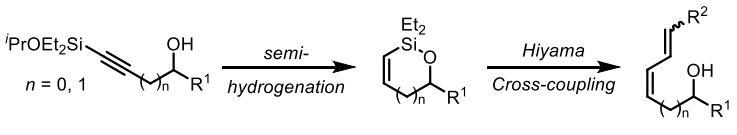
The generally accepted mechanism of palladium cross-coupling reactions begins with oxidative addition of the palladium(0) into a carbon-halide or -pseudohalide bond to form an organopalladium(II) species (Scheme 2.0). This undergoes transmetalation with R^2–organometallic to form a *cis*-diorganopalladium(II) species which reductively eliminates. This completes the catalytic cycle by re-forming the palladium(0) species and the new C–C bond.



Scheme 2.0. General catalytic cycle of palladium catalysed cross-couplings.

2.2 Previous work within the group

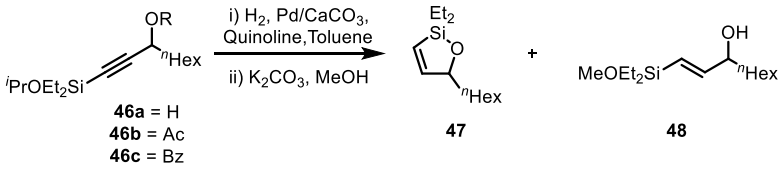
Our group has been working on methodology to improve the use of Hiyama cross-couplings in total synthesis, specifically forming (*Z*)-alkene containing polyene motifs (**43**) as are found in many bioactive compounds. This methodology centres on a new approach to synthesise cyclic siloxanes by using a Lindlar *semi*-hydrogenation of an alkynylsiloxane **44** to form a cyclic (*Z*)-alkenylsiloxane **45**, which simultaneously ensures the desired alkene geometry, and also acts as an internal alcohol protecting group.[43] Scheme 2.1 shows this generalised approach; in terms of cyclic alkenylsiloxane synthesis, this method improves on previous methodologies such as RCM (which requires the use of the air- and moisture-sensitive Schrock catalyst), intramolecular hydrosilylation (which is limited to internal alkynes), and alkynylsilane enyne metathesis.[44-46]



44 **45** **43**

Scheme 2.1. Group methodology for the formation and use of cyclic alkenylsiloxanes.

When initially screening conditions for the Lindlar reduction, it was found that an unprotected allylic alcohol **46a** proceeded with poor diasteroselectivity, giving cyclic siloxane **47** and the (*E*)-alkene **48** (52:48) (Scheme 2.2). A footnote in a 1992 paper from Panek and Clark revealed a similar issue when working with a phenyldimethylsilylalkynyl propargylic alcohol, which also resulted in poor selectivity of *Z*:*E* (5-7:1); however, when the alcohol was protected as an acetate selectivity increased to *Z*:*E* (14:1).[47] Anderson and co-workers have shown that when acetate **46b** or benzoyl ester **46c** were subjected to the Lindlar reduction, and subsequent hydrolytic cyclisation conditions, the stereoselectivity increased to 96:4 (**47**:**48**). An assortment of five and six membered rings was made with variations on the side chain, which were then successfully cross-coupled.

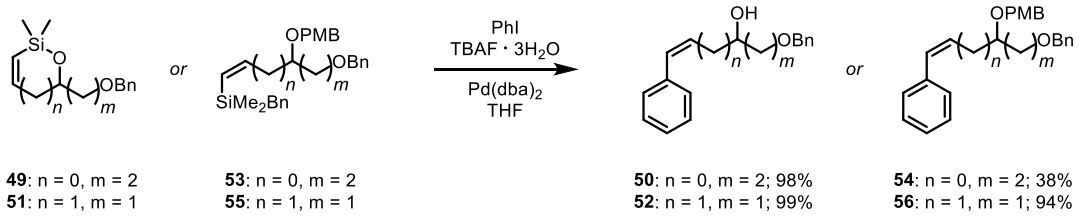


Scheme 2.2. Screening for Lindlar hydrogenation conditions.

The Anderson group has elegantly expand upon this methodology to form five and six membered rings and further manipulate these structures for the synthesis of natural products.[48] The initial work by Anderson co-workers did not explore the application of cyclic siloxanes in complex natural product synthesis, raising questions on the importance of the substituents on the silane and proximal alcohol (i.e., diethyl vs dimethyl silanes, cyclic vs acyclic, and five vs six membered rings). Anderson and co-workers set out to determine the answers to these key questions.

To explore the advantage of a cyclic dimethylsiloxane over the acyclic form, Anderson and co-workers compared their Hiyama cross-couplings with iodobenzene as the coupling partner (Scheme 2.4). The five membered ring **49** coupled rapidly within five minutes in

98% yield (**50**), while the six membered **51** proceeded in 15 min in 99% yield (**52**).[48] However, [43] The acyclic benzyldimethyl silane **53** was only able to couple in 38% yield (**54**) after 30 min, with 48% desilylation and a mix of stereoisomers observed (*Z*:*E* = 3:1); this revealed the advantage of the cyclic form. Remarkably, the acyclic benzyldimethyl silane **55** was able to couple in 94% yield (**56**).



49: n = 0, m = 2
51: n = 1, m = 1

53: n = 0, m = 2
55: n = 1, m = 1

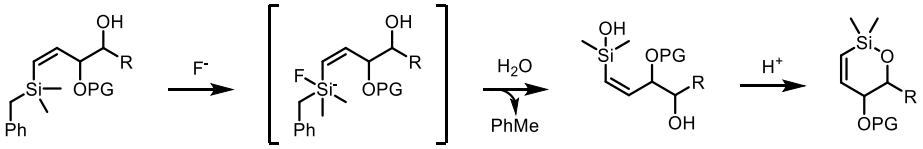
50: n = 0, m = 2; 98%
52: n = 1, m = 1; 99%

54: n = 0, m = 2; 38%
56: n = 1, m = 1; 94%

Scheme 2.4. Cyclic vs Acyclic Hiyama Cross-coupling.[48]

The benefits of reactivity of five vs six membered rings for the Hiyama cross-coupling remain to have a convincing answer. Denmark has proposed that cyclic siloxanes do not themselves transmetalate, but must first form a disiloxane ate species which undergoes the transmetalation.[49] The Anderson group conducted NMR experiments in THF-d_8 to probe the equilibrium between the cyclic form and the disiloxane or acyclic silanol.[48] They observed that the equilibrium ($K_{6\text{-mem}}$ = 1.3) remained at a constant ratio in favour of the acyclic disiloxane for the six membered ring, while the five membered ring's equilibrium ($K_{5\text{-mem}}$ = 0.59) rapidly established in favour of the five membered ring to the disiloxane species. Interestingly, the disiloxane of the five membered ring slowly decomposed after 8 hours to the de-silylated product. Even though the equilibrium is marginally in favour of the cyclic compound for the five membered ring, the couplings that Anderson and co-workers performed consistently show that the five membered siloxane couples more rapidly and in higher yields. This shows that the position of equilibrium itself is not important for reactivity (a Curtin-Hammett scenario).

The requirement for a protecting group to further functionalise alkoxysilanes has been explored by the Anderson group. The need to intercept the cyclised siloxane at the appropriate time, to counter the ease with which (*Z*)-alkenylsilanes form (hydrolytically unstable) 5 membered rings when a neighbouring alcohol is present, means a protecting group is required on both the proximal alcohol and silane that is stable to acid, hydrogenation, and base conditions. Trost *et al.* had demonstrated that a benzyl group on a dimethylsilane can be selectively removed using TBAF in THF.[50] The benzyldimethyl silane group itself is stable towards acid, strong base and buffered fluoride conditions (TBAF / AcOH), and our group has found that it is stable towards the Lindlar hydrogenation conditions. Debenzylation is near instantaneous on introduction of TBAF, and is thought to proceed *via* a silicon ate complex which readily loses toluene (Scheme 2.3).[51-53] With this precedent in mind, Anderson and co-workers explored the possibility of using a benzyl group on the silane instead of the previous acid or base labile isopropxy group, making the use of the benzyl group even more attractive.[48, 54-55]



Scheme 2.3. Debenzylation and acid promoted cyclisation hypothesis

Anderson and co-workers wanted to keep the reactivity of the cyclised dimethyl silane but needed greater stability. The dimethylalkoxyalkynylsilane was shown to be sensitive towards hydrolysis and possessed lower overall stability than its diethylsilane counterpart; however, in relation towards the Hiyama cross-coupling, the dimethylsilane has much greater reactivity.[48] Anderson and co-workers have shown that while the diethylsiloxane coupled with iodobenzene in similar yields, it required a prolonged 24 hour reaction time.[43]

This indicated the importance of sterics on the siloxane. An ideal solution would be to unmask the cyclised dimethylsilane only after the alkyne semi-hydrogenation.

2.3 Natural products made in our group

This methodology has enabled the group to make several natural products or natural product fragments as shown in Figure 2.0. Leukotriene B_3 was prepared in high yield by Gudmundsson and Kuper *et al*,[48] while the fragments of larger natural products were synthesised by Elbert *et al*.[43] The most complex natural products achieved in the group to date are resolvin D3 (RvD3) and resolvin E1 (RvE1), synthesised by Urbitsch *et al*.[56]

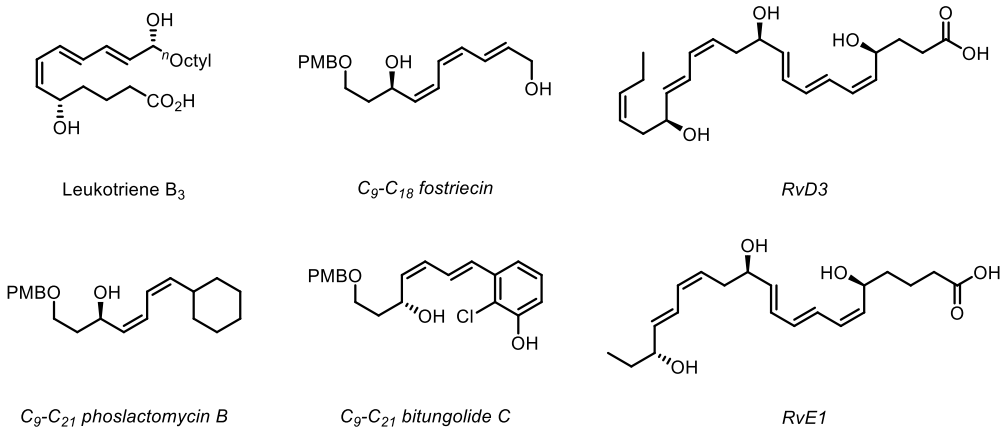
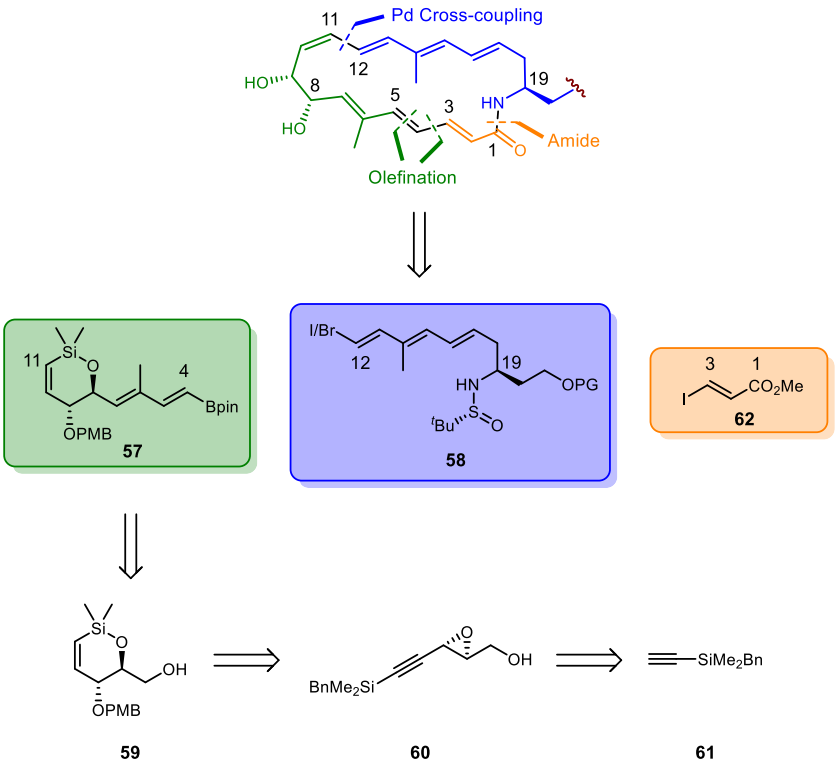


Figure 2.0. Total syntheses achieved using cyclic siloxanes

With this methodology in hand, we set out to apply it to larger polyene-containing natural products, including functionalisations of the cyclic siloxane side chains which had not been extensively explored in prior work. In this context, the cyclic siloxane would indeed not only preserve alkene stereochemistry, but would also be used use as an *in situ* protecting group. The heronamide family of natural products contain a (*Z*)-alkene that we envisage can be installed by using the Hiyama cross-coupling of cyclic dimethyl alkenylsiloxanes.

Having this in mind, a retrosynthetic scheme was designed where cyclic siloxane **57** would be coupled with sulfinamide-containing fragment **58**, as shown in Scheme 2.5. The pinacol boronic ester / cyclic siloxane **57** can arise from chain extension of cyclic siloxane **59**. The stereocenters of the diol (heronamide depiction) would be set by Sharpless asymmetric epoxidation / ring opening (**60**), with this epoxide in turn deriving from a benzyldimethylsilyl alkyne **61** *via* Sonogashira cross-coupling with vinyl iodide **62**.

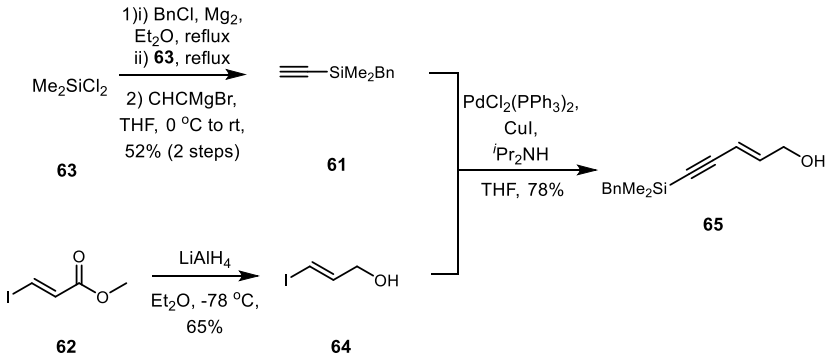


Scheme 2.5. Retrosynthesis of the heronamide core.

2.4 Synthesis of cyclic dimethyl alkenylsiloxanes

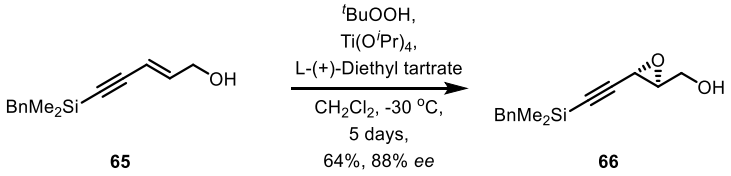
The synthesis commenced with formation of alkyne **61** by sequential Grignard additions to dichlorodimethylsilane **63** (52% over two steps), according to literature procedures (Scheme 2.6).[57-58] Vinyl iodide **62** was also prepared according to a literature procedure, and reduced to allylic alcohol **64** in 65% yield using lithium aluminium hydride (purified by

distillation).[31, 59] This set up a Sonogashira cross-coupling between alkyne **61** and vinyl iodide **64**, which initially gave moderate to low yields. This reaction remains one of the most widely used couplings for sp-sp^2 carbon formation, and typically proceeds in high yields.[60] Mindful of the potential degradation of the Pd(0) resting state by oxidation by molecular oxygen, simple degassing of the solvent for fifteen minutes, followed by an overnight reaction time increased the yield to 78% for enyne **65** on multi-gram scales with consistency.



Scheme 26. Synthesis of enyne **65**.

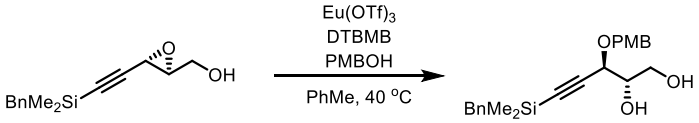
With enyne **65** in hand, the Sharpless asymmetric epoxidation was addressed (Scheme 2.7). This robust, cost effective and often used technique was first described by Katsuki and Sharpless in 1980, who found a selective asymmetric epoxidation (with *t*-butyl hydroperoxide as stoichiometric oxidant) can occur from the *Si* or *Re* face of an allylic alcohol depending on which enantiomer of tartrate ligand is used for the titanium catalyst.[61] In this work, the epoxidation at first was troubling due to low conversion; however with an extra loading of peroxide (3.7 equiv.) and patience, the alkene was fully converted after five days producing epoxide **66** in 64% yield and 88% *ee*. The racemic substrate was prepared using *m*-CPBA (71%). Attempts using diisopropyl tartrate led to lower enantioselectivity (52% *ee*) which suggested dimethyl tartrate might perform better. Unfortunately, no reaction was observed using this tartrate ester.



Scheme 2.7. Sharpless asymmetric epoxidation.

A regioselective epoxide opening was sought to install the 1,2-oxygenation. Based on work by Uesugi *et al.*,[62] who explored epoxide openings with methanol and other nucleophiles, europium(III) triflate (with 2,6-di-*tert*-butyl-4-methylpyridine) was tested as a Lewis acid to chelate the epoxide and the primary alcohol, leading to a regioselective nucleophilic attack β to the alcohol. PMB alcohol was identified as a potential nucleophile, as Uesugi *et al.* had achieved ring opening using benzyl alcohol. However, initial attempts using PMB alcohol showed a slow reaction and low yields for diol **67** (Table 2.0, entry 1), with much starting material remaining after stirring at 40 °C for 16 hrs. Increasing the amount of PMB alcohol resulted in higher yield, but caused a troublesome purification due to the excess PMB alcohol which tended to co-elute with the product (entry 2). Pleasingly, a slight reduction in the amount of nucleophile (to 2.7 equiv.) but with increased time gave the highest yield obtained (89%, entry 3). Other conditions were tested but no further improvement was observed.

Table 2.0. Opening of epoxide **66**.

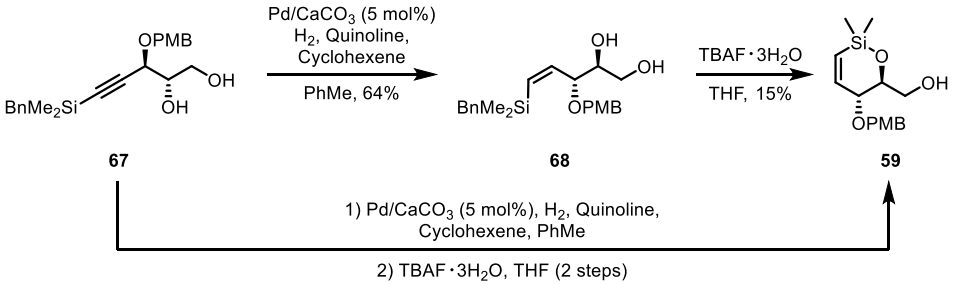


66 **67**

Entry	Eu(OTf)$_3$ (Equiv.)	DTBMB (Equiv.)	PMBOH (Equiv.)	Time (hrs)	Yield (%)
1	0.2	0.2	2	16	44
2	0.2	0.2	3	16	68
3	0.18	0.18	2.7	96	89

The key Lindlar reduction of homopropargylic alcohol **67** was next tested. Unlike previous systems examined in the development of this methodology, this reaction proved to be quite challenging, and often suffered from competing over-reduction of the alkene or the formation of small amounts of (*E*)-isomer depending on the batch of palladium catalyst used (Scheme 2.8). The benefit of this approach though is that only (*Z*)-isomer **68** will cyclise at the debenzylation stage, such that non-cyclised side-products could be separated quite easily by column chromatography. In the event, isolation of the pure (*Z*)-isomer proved difficult as the alkyne starting material, and (*E*)- and (*Z*)-isomers of product would co-elute on silica gel column chromatography, providing up to a 64% yield of the desired product after extensive purification. Debenzylation and an attempt at cyclisation led to a low 15% yield for cyclic siloxane **59**, which was quite surprising. The thought of instability on silica gel led to a telescoped process. Following the Lindlar hydrogenation, the palladium was filtered over Celite® and subsequent concentration *in vacuo* between the two steps was utilised instead of purification by column chromatography. This led to using an aqueous work-up after the debenzylation to remove the quinoline before column chromatography to ease purification, as established by others in the group. This observation of instability towards silica gel column chromatography remained an issue through-out the use of cyclic siloxanes

but quick purifications helped overcome this problem. A yield of 66% over two steps was the best achieved, provided a rapid purification was employed, which then enabled manipulation of the primary alcohol.

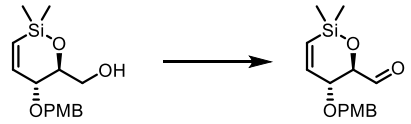


Scheme 2.8. Lindlar hydrogenation and cyclisation.

2.5 Synthesis of cyclic dimethyl siloxane substrates for Hiyama cross-coupling studies

Several conditions were attempted to oxidise the primary alcohol to aldehyde **69** (Table 2.1). An oxidation using the Dess-Martin periodinane was tested, but the crude ^{1}H NMR spectrum showed no aldehyde proton, although the starting material had been consumed (entry 1).[63] A Swern oxidation (entry 2) showed the desired product in the crude ^{1}H NMR spectrum; however, column chromatography on silica gel gave a complex mixture.[64] The Parikh-Doering oxidation was tried next, and again while the crude ^{1}H NMR spectrum looked pure, chromatography led to partial degradation.[65] This led us to question whether the aldehyde was unstable to silica gel, indeed a simple aqueous acidic and two brine washes were sufficient to remove amine base and DMSO; **69** was therefore carried without further purification to the next reaction.

Table 2.1. Oxidation of alcohol **59** to form aldehyde **69**.



59 **69**

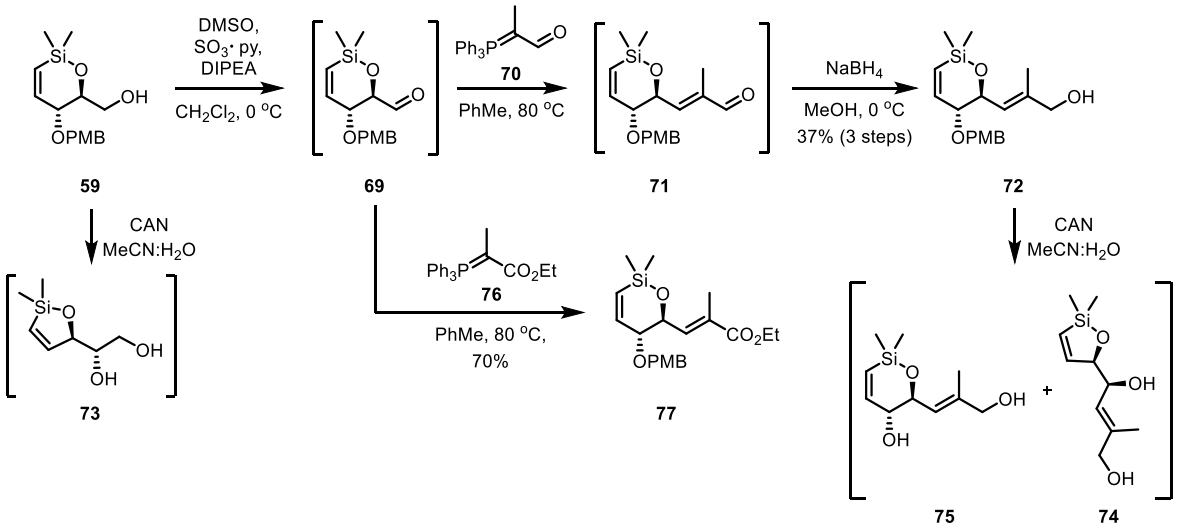
Entry	Conditions	Purification	Result
1	DMP, CH_2Cl_2	Sat. $NaHCO_3$	No Product
2	DMSO, Oxalyl chloride, NEt_3, CH_2Cl_2, −78 °C	Silica Column Chromatography	Degradation
3	DMSO, SO_3·py. DIPEA, CH_2Cl_2, 0 °C	Silica Column Chromatography	Degradation
4	DMSO, SO_3·py. DIPEA, CH_2Cl_2, 0 °C	1N HCl Work-up	Product

Aldehyde **69** provided us with the opportunity to extend the lower polyene chain, and thereby test which derivatives were best suited to Hiyama coupling. **69** was therefore subjected to a Wittig reaction with the ylide **70** in toluene to obtain enal **71**, which proved unstable to silica gel column chromatography. However, precipitation of triphenylphosphine oxide (pentane) provided material of sufficient purity to carry out sodium borohydride reduction to allylic alcohol **72**. This reaction was carried out cold, and afforded the desired product in 37% yield over the three steps.

To test efficiency of five-membered cyclic siloxane coupling, DDQ was first attempted to deprotect the PMB ether, but the observed product, although not purified, was a six membered PMP acetal formed with the primary alcohol. Ceric ammonium nitrate (CAN) was tested instead, and while this successfully removed the PMB ether, the five membered cyclic siloxane product was rather unstable to silica gel column chromatography.[66] Interestingly, alcohol **59** was observed to only form five membered ring **73** upon treatment

with CAN, while allylic alcohol **72** formed a 1:1 ratio of the five (**74**) and six (**75**) membered rings. The reasons for this are unknown.

With the 'full length' trienoate of heronamide in mind, we were keen to test how an α,β-unsaturated ester would perform in the Hiyama cross-coupling. Attempts at HWE olefination revealed instability of aldehyde **69** towards the reaction conditions and no product could be isolated. However, a Wittig olefination using ylide **76** successfully produced the α,β-unsaturated ester **77** in 70% yield.



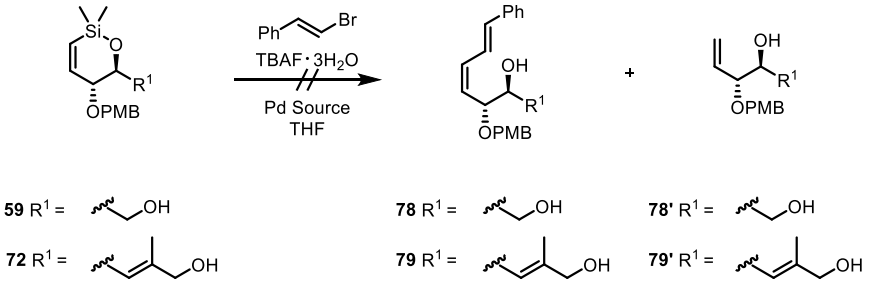
Scheme 2.9. Formation of various cyclic siloxanes for model Hiyama cross-couplings.

2.6 Palladium catalyst comparison

Model substrates **59** and **72** were used to compare the efficiency of allylpalladium chloride dimer (APC) and $Pd(dba)_2$ with TBAF as the fluoride source. When cross-coupling **59** and β-bromostyrene with APC and $Pd(dba)_2$, in the presence of 3.0 equiv. of TBAF, the yields were 63 and 55% respectively (**78**). Interestingly, desilylated product **78'** that was inseparable from the desired product was also observed (up to 9%).

Allylic alcohol **72** was also subjected to these cross-coupling conditions, and this more elaborate substrate gave a similar desilylated product **79'** that was inseparable as well. Cross-coupling allylic alcohol **72** with β-bromostyrene using APC or $Pd(dba)_2$ led to 42% and 24% yield (**79**) respectively, showing again that APC was the superior palladium source for the cross-coupling. Moving forward, APC would therefore be used as the palladium source.

Table 2.2. Model Hiyama cross-couplings with $[PdCl(C_3H_5)]_2$ or $Pd(dba)_2$.



R^1	Catalyst	Yield (Product)[a]	Yield (Product)[a]
59	**$[PdCl(C_3H_5)]_2$**	63% (**78**)	9% (**78'**)
59	**$Pd(dba)_2$**	55% (**78**)	7% (**78'**)
72	**$[PdCl(C_3H_5)]_2$**	42% (**79**)	11% (**79'**)
72	**$Pd(dba)_2$**	24% (**79**)	4% (**79'**)

[a]Inseparable mixture of products

2.7 Study of the Hiyama cross-coupling mechanism

One question the group set out to study is whether an open-chain disiloxane is formed before transmetalation, or whether transmetalation could proceed *via* the six membered ring. A ^1H NMR experiment was conducted by treating cyclic siloxane **59** with TBAF in THF-d_8 to examine the equilibrium between the cyclic siloxane **59** and open chain diol **80**. It appears

that the cyclic siloxane exclusively (and rapidly, < 5min) favours the open form. Dr Haraldur Gudmundsson studied this equilibrium as well for other cyclic siloxanes and showed that depending on the ring size and substituents on the ring, an equilibrium establishes between the open form and closed form; however, some siloxanes, for example diol **80**, do favour the open form.[54]

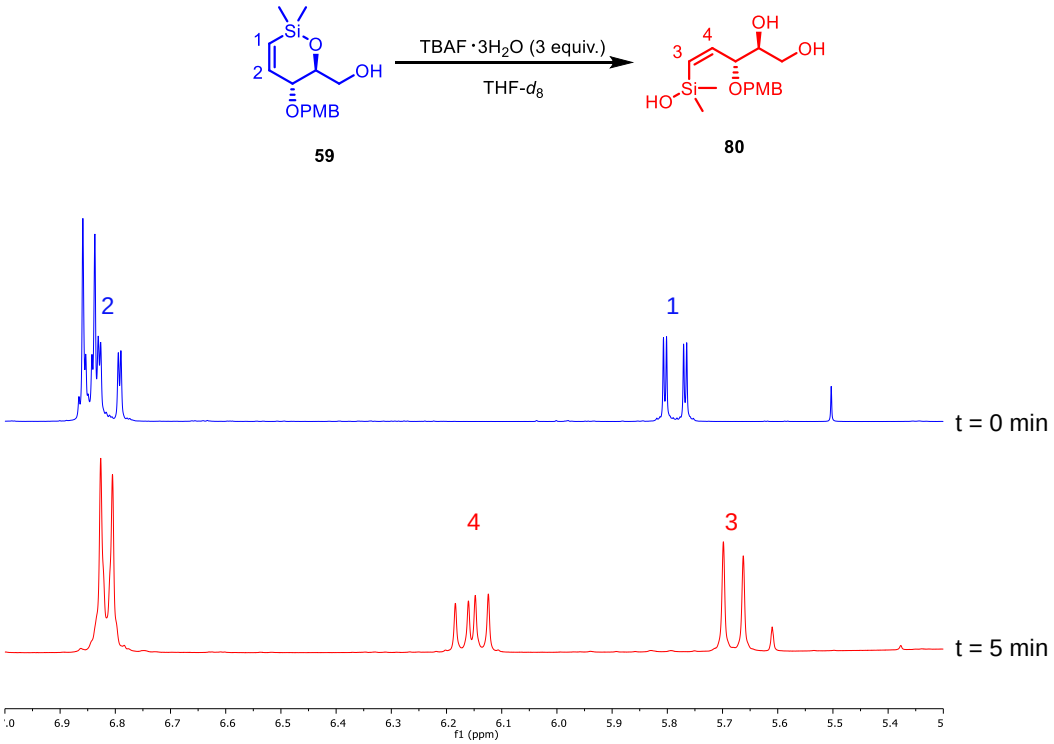


Figure 2.1. ^{1}H NMR of cyclic siloxane **59** when treated with TBAF.

The exclusive formation of the acyclic silanol **80** on treatment with a fluoride source suggests the mechanistic pathway proposed in Figure 2.2 to be the most plausible. It is worth noting that the role of fluoride during cross-coupling reactions, ring size, bulk of the silane and concentration of fluoride play the most important roles in the reaction; as shown by Denmark *et al.*, the groups on the silicon atom determine the position of the open–closed equilibrium, and Gudmundsson found that ring size also determines the equilibrium.[54] As the steric bulk increased on the silane (from Me_2 to Pr_2), Denmark *et al.* showed an increase

in the propensity of the dimethyl group to form the disiloxane which Hiyama and Denmark both proposed is necessary for the transmetalation.

When cyclic dimethylalkenylsiloxane **81** is treated with fluoride and water, acyclic silanol **82** forms an equilibrium with inactive tetracoordinate silane **83**. Importantly, the concentration of fluoride is a factor in whether the inactive tetracoordinate disiloxane **83** forms, or favours silane salt **84**. Fluoride activates the inactive tetracoordinate silane **83** to achieve pentacoordinate 'ate' complex **85** which is primed for transmetalation.

The palladium(0) complex oxidatively inserts into the carbon halogen bond to form the palladium(II) complex, and then undergoes a fluoride attack to displace the halogen in bromine/iodine. This square planar complex will then transmetalate due to the fluorophilicity of the silicon atom as shown by Amatore *et al.*[67] In their study of the kinetics of the Hiyama cross-coupling, they found that the active transmetalating species was a tetracoordinate silane which directly contradicts the results from the Denmark group. This can ultimately be due to the variation of the silane as Amatore *et al*. used a trimethoxy silane, instead of the di-methyl, ethyl, isopropyl silane that Denmark *et al*. used. Experimentally we have found that much is dependent on the entire molecule that the silane is attached to, and it is hard to make generalities in the mechanism. After transmetalation, a fluoride attack promotes reductive elimination which regenerates the metal catalyst and forms the *C*-*C* bonded product **86**.

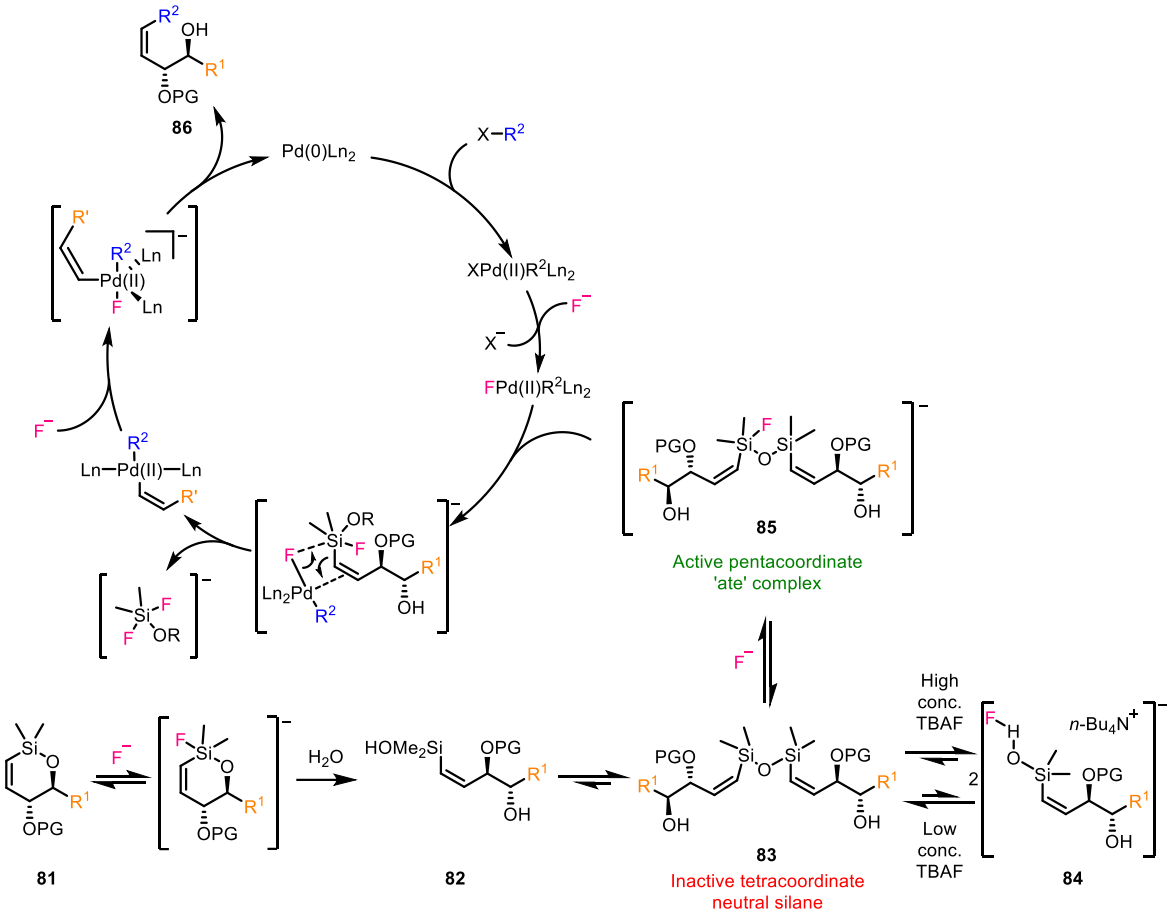


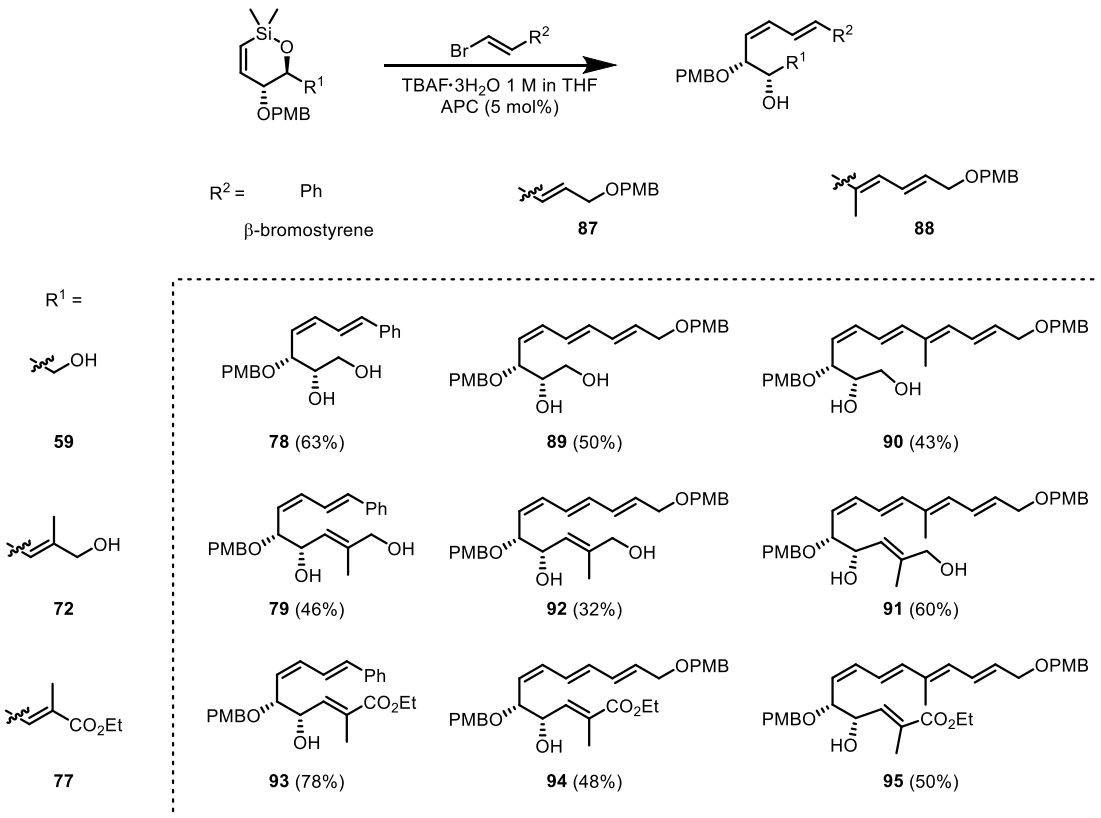
Figure 2.2. Proposed Hiyama cross-coupling mechanism.

2.8 Model Hiyama cross-couplings with six membered cyclic dimethyl alkenylsiloxanes

The dependence of the cross-coupling on catalyst and silane had been revealed in the above studies. It was decided to expand the scope of these model cross-couplings (Scheme 2.10) to vary not only the siloxane, but also the halide coupling partner. As previously discussed in Section 2.6, the 6-membered cyclic siloxane alcohol **59** was coupled with β-bromostyrene to afford diene **78** in 63% yield. As the degree of unsaturation in the halide coupling partner increased, the yield dropped slightly – **59** coupled with dienyl bromide **87** and trienyl bromide **88** to produce triene **89** and tetraene **90** in 50% and 43% yield, respectively.

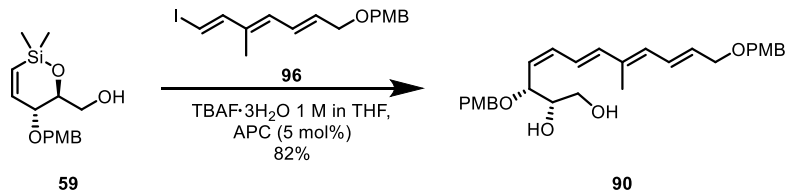
Interestingly, cyclic siloxane allylic alcohol **72** showed a different trend. When **72** was coupled with trienyl bromide **87**, this resulted in the highest yield of the allylic alcohol tetraene **91** (60%), as opposed to 32% (**92**) with the dienyl bromide and 46% (**79**) for β-bromostyrene (previously discussed in Section 2.6).

Considering that in our planned strategy, the cyclic siloxane might be equipped with the 'full length' trienoate chain, we also examined couplings of the α,β-unsaturated ester cyclic siloxane **77**. Pleasingly, this behaved similarly to the two alcohols, giving diene **93** in 78% yield on reaction with β-bromostyrene. The assembly of triene **94** and tetraene **95** was similarly efficient (48% and 50% yield, respectively). The yield of these Hiyama cross-couplings varies due to: sensitivity of the substrate to purification using silica gel column chromatography, high temperatures when removing solvent (above 25 °C), and exposure to light.



Scheme 2.10. Model Hiyama cross-coupling reactions.

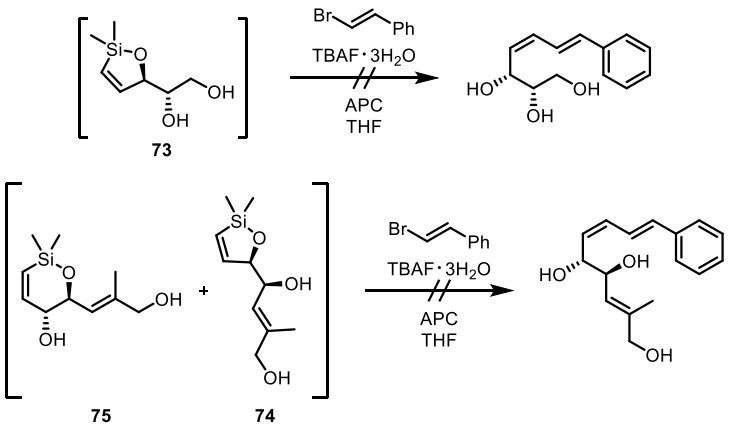
A comparison of bromine vs iodine as the halide coupling partner was undertaken to see if the yields could be further increased. Scheme 2.11 shows the coupling of cyclic siloxane alcohol **59** with trienyl iodide **96**, which gave tetraene **90** in 82% yield. This represents an almost two-fold increase in yield compared to the bromide, and confirmed the ideal requirement to make a trienyl iodide coupling partner.



Scheme 2.11. Model Hiyama cross-coupling with trienyl iodide **90**.

2.9 Attempted model Hiyama cross-couplings with five-membered cyclic dimethyl alkenylsiloxanes

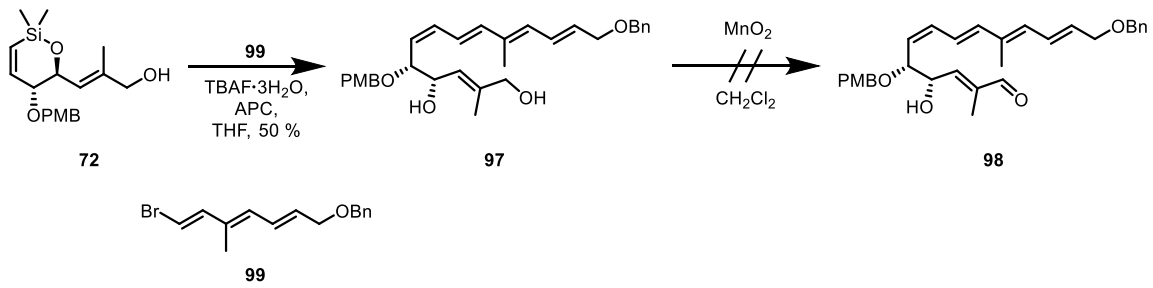
Upon treatment with CAN of cyclic siloxane **59** and **72** (as shown in Scheme 2.9), the solutions were briefly purified by an aqueous work-up, and not subjected to column chromatography due to instability to silica. Using TBAF and APC, β-bromostyrene was attempted to Hiyama cross-couple with crude diol **73** and five- and six-membered allylic alcohol **74** and **75** (Scheme 2.12). Neither of these cross-couplings managed to proceed with an observable product by TLC or crude NMR, which ultimately deems them not useful for the coupling strategy.



Scheme 2.12. Failed five membered cyclic siloxane Hiyama cross-couplings.

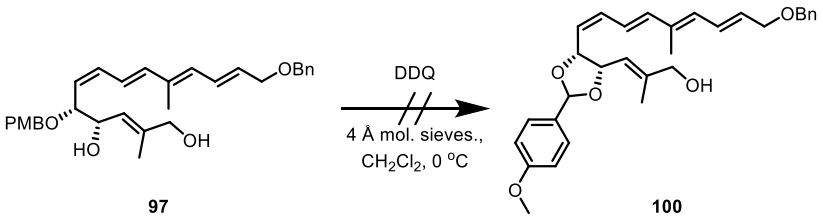
2.10 Oxidation attempts

Although the cross-coupling yields in Section 2.8 are promising, an oxidation of the primary alcohol in products such as **97** to extend the trienoate chain would prove to be difficult. An attempt at oxidising allylic alcohol **97** to synthesise enal **98** was unfruitful (Scheme 2.13); benzyl ether tetraene **97** was prepared in 50% yield using trienyl bromine **99**, but the attempted oxidation using manganese(IV) oxide (known to be selective for allylic alcohol oxidations) was not successful and decomposition was observed.[68] One problem is that **97** has two allylic alcohols, but it was hoped that the less hindered primary alcohol would react first.



Scheme 2.13. Hiyama cross-coupling and an allylic oxidation attempt.

To overcome this issue, we explored oxidation of the PMB ether in **97** to a PMP acetal in Scheme 2.14. Oikawa *et al*. developed an elegant method using DDQ under dry conditions to protect an α or β hydroxyl group instead of removing a PMB ether, and showed that it would only require mild acidic conditions to remove the PMP acetal, instead of strong acidic conditions that is normally required when removing acetals.[69] Unfortunately, attempts using DDQ showed no peaks where the acetal hydrogen should appear in the crude ^{1}H NMR spectrum, and the alkene hydrogens were also not visible.

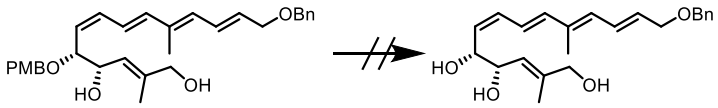


Scheme 2.14. An attempt to make PMP acetal **100**.

2.11 Late-stage deprotection study

This brief study suggested that it would be beneficial to remove the PMB ether in allylic alcohol **97** before homologation of the chain, and a screen of conditions was performed as shown in Table 2.3. The PMB ether protecting group proved surprisingly difficult to remove: DDQ was attempted, but this time with the inclusion of water to deprotect fully, but this again led to degradation.[70] CAN was tried under the same conditions as for the cyclic siloxane **72** (see Scheme 2.9). Unfortunately, this gave the same result as DDQ with the disappearance of the alkene hydrogen peaks in the crude ^{1}H NMR spectrum. Another common condition for PMB cleavage is TFA; however this did not show a desired product either.[71] A range of other conditions were tested, but did not give a productive result.[72]

Table 2.3. Attempts at deprotecting the PMB ether.



97

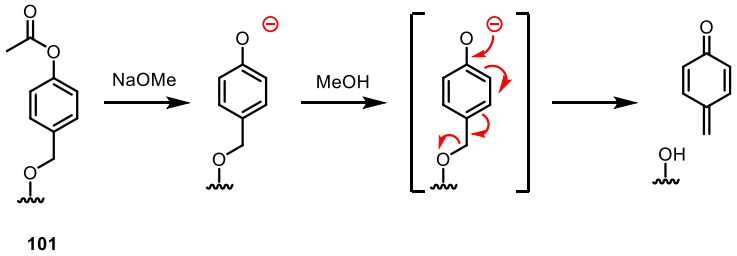
Entry	Conditions	Result
1	DDQ, CH_2Cl_2:H_2O (10:1), 0 °C	No product
2	CAN, MeCN:H_2O (10:1), 0 °C	No product
3	10 % TFA, CH_2Cl_2, 0 °C to rt	No product

2.12 *p*-Acetoxybenzyl protecting group strategy

The failure to remove the PMB ether or cross-couple the deprotected siloxane was quite a dilemma and a change in protecting group was deemed necessary. The new protecting group would need to be base labile, but would need to survive conditions such as the Hiyama cross-coupling; acidic deprotection conditions were undesirable, as acids could isomerise the conjugated polyene systems or promote an unsought cyclisation, as has been used to form different heronamides.[35] Clearly, silyl ethers or groups revealed by hydrogenolysis would need to be avoided.

Having similar issues for late stage deprotection, previous group member Dr Christian Kuper has theorised that *p*-acetoxybenzyl (PAB) ether **101** might serve a similar role in work towards a related unsaturated carbon skeleton in the polyketide incednine, but he did not have the time to explore its use.[55] This seemed an attractive solution for the heronamide core as the optimised route towards the cyclic siloxane already utilised a benzyl ether, and the installation of the PAB group could presumably follow similar conditions for epoxide

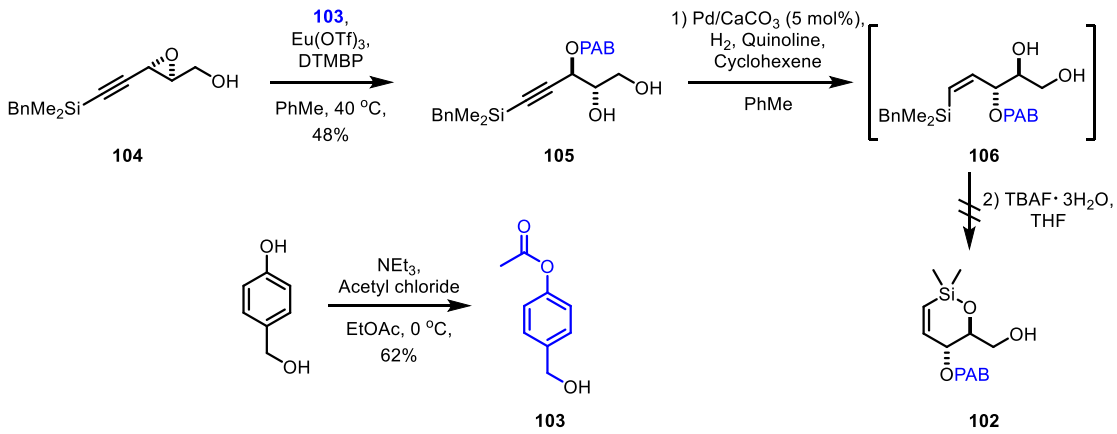
opening as used with PMB alcohol. The deprotection of the PAB group was explored by Jobron and Hindsgaul, who showed that mild solvolysis conditions could be used to remove this group, including the use of sodium methoxide to solvolyse the acetal group.[73] The deprotection mechanism is theorised to proceed *via* the formation of the methylene quinone as shown in Scheme 2.15.



101

Scheme 2.15. Deprotection mechanism of the PAB ether.

Using an equivalent synthetic route as for the PMB ether synthesis, Scheme 2.16 shows the process of attempting to form cyclic siloxane PAB ether **102**. PAB alcohol **103** successfully opened epoxide (±)-**104** to form alkynyl diol (±)-**105** in 48% yield in three days. This diol was carried forward to the semi-hydrogenation Lindlar conditions, with just a filtration through Celite® as work up, to form intermediate ene diol (±)-**106**. Unfortunately, the PAB ether did not survive the benzyl deprotection with TBAF, likely due to the enhanced electrophilicity and therefore hydrolytic susceptibility of the phenolic acetate. This led us to consider that a modification of the PAB group was needed to make it less labile.



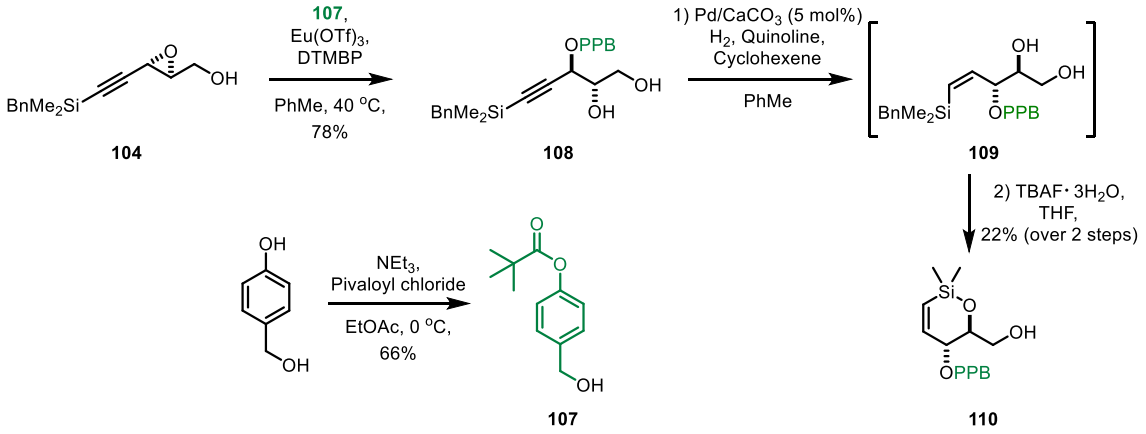
Scheme 2.16. Attempt at the construction of the cyclic siloxane PAB ether.

2.13 *p*-Pivaloxybenzyl protecting group strategy

It was hoped that changing the acetate ester to a pivalate ester would lead to an increase in stability; however, to our knowledge the use of the *p*-pivaloxybenzyl (PPB) ether as an alcohol protecting group has not been explored. A literature search revealed a specific use of the PPB ether as a protecting group was to mask different phosphate prodrugs, as the benzyl phosphate ester can survive hydrolysis under physiological conditions until it crosses cell membranes.[74-77] After crossing the membrane, enzymatic cleavage would ensue and liberate the phosphate.

Epoxide (±)-**104** was submitted to the ring-opening conditions as previously used but with PPB alcohol **107**, and after six days alkynyl (±)-diol **108** was obtained in 78% yield. The Lindlar semi-hydrogenation conditions were applied to alkynyl diol (±)-**108** to provide alkenyl diol intermediate (±)-**109**, and pleasingly the PPB ether remained in place upon debenzylation of the silane to promote cyclisation, giving cyclic siloxane PPB ether (±)-**110** in a modest 22% yield over the two steps. At the time, this was a great result as it suggested that the PPB group could also survive the Hiyama cross-coupling conditions; the low yield

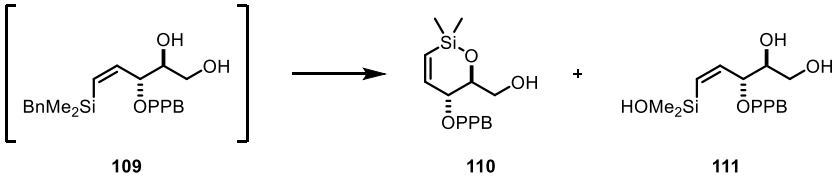
was explained in that much of the product remained uncyclised (3:1 ratio favouring the uncyclised product).



Scheme 2.17. Synthesis of cyclic siloxane PPB ether (±)-**110**.

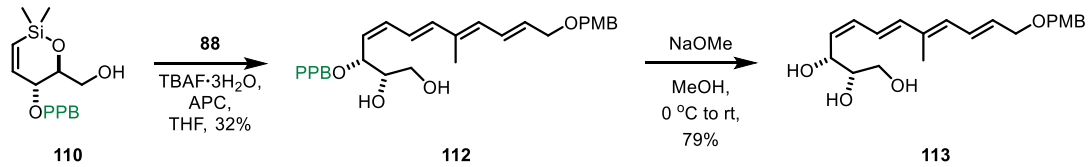
Due to the cyclisation not going to completion, a screen of conditions previously used in the group to promote silanol cyclisation for 6-membered cyclic siloxanes (Table 2.4) was tried. Potassium carbonate was first attempted with hopes that the increased stability in the pivalate would prevent solvolysis (entry 1); however excess aromatic peaks appeared in the ^{1}H NMR, indicating deprotection. KOTMS was tested, but despite an increase in the ratio of (±)-**110**: (±)-**111**, this still favoured the acyclic form (1:1.2). PPTS (Entry 3) was found to be optimal, giving a 5:1 ratio in favour of the cyclic form. Using this acid, with stirring overnight, the three-step reaction from diol (±)-**108** to cyclic siloxane (±)-**110** proceeded in 79% overall yield.

Table 2.4. Cyclisation conditions.



Entry	Conditions	Result (110:111)
1	K_2CO_3, MeOH	Apparent deprotection of PPB ether
2	KOTMS, THF	1:1.2
3	PPTS, CH_2Cl_2	5:1

A Hiyama cross-coupling was planned to see if the PPB ether would survive, and could be easily deprotected (Scheme 2.18). (±)-**110** was coupled with trienyl bromide **88** using APC as catalyst to form tetraene (±)-**112** (32% yield). To attempt deprotection, this was initially stirred with 1.0 equiv. of freshly prepared sodium methoxide at 0 °C, but after bringing the reaction mixture to room temperature the reaction was incomplete. An additional 3.0 equiv. was added at 0 °C, which was then left to stir in the dark overnight. Pleasingly, the PPB ether was deprotected in 79% yield to form triol (±)-**113**.

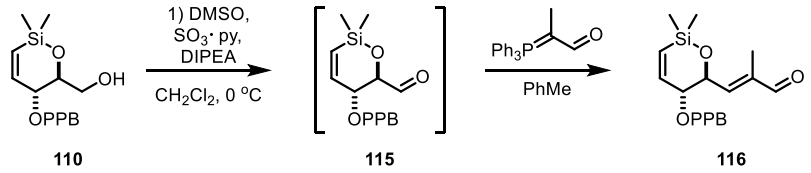


Scheme 2.18. Hiyama cross-coupling with the PPB ether and deprotection of the PPB ether.

2.14 C1-C11 Cyclic dimethyl alkenylsiloxane synthesis

With the knowledge that the primary alcohol of the cyclic siloxane would not be easily manipulated post coupling in the presence of the released secondary allylic alcohol, we started work on building the full length C1-C11 trienoate (±)-**114**. Intermediate cyclic siloxane aldehyde (±)-**115** was first formed from cyclic siloxanol (±)-**110** using Parikh-Doering conditions with an aqueous work-up. This was taken without purification into a Wittig olefination which showed low to moderate yields. Table 2.5 shows a screen of reaction temperatures which revealed that higher yields were obtained at lower reaction temperatures, with minimised exposure time to silica gel column chromatography. At 30 °C (entry 2), this gave (±)-**116** in an impressive 82% yield over two steps.

Table 2.5. Temperature screen for the Wittig olefination.



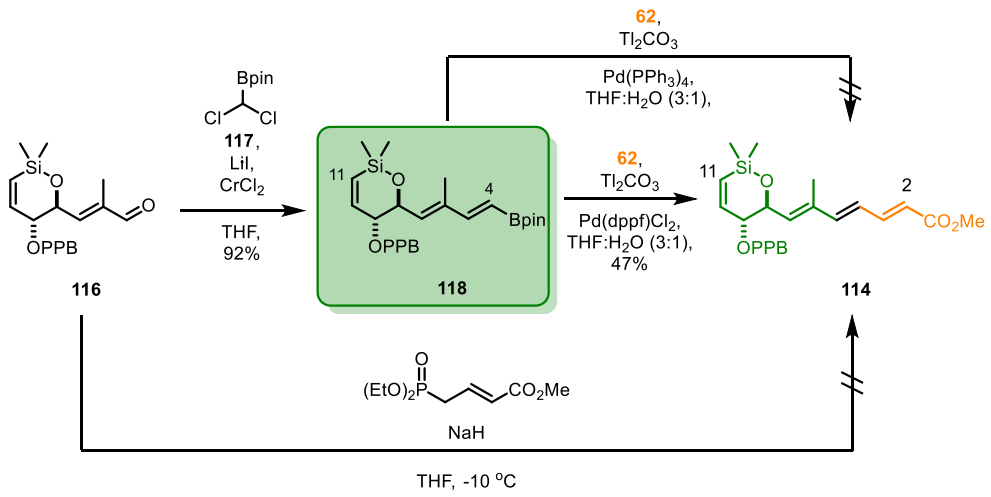
110 **115** **116**

Entry	Temp (°C)	Yield (%)
1	rt	76
2	30	82
3	40	70
4	50	34
5	80	15

This sensitivity to silica gel chromatography was a consideration for future reactions. For each reaction, a screen of isocratic eluent conditions was carried out such that the

product was on the column for less than 10 mins, which generally boosted yields dramatically.

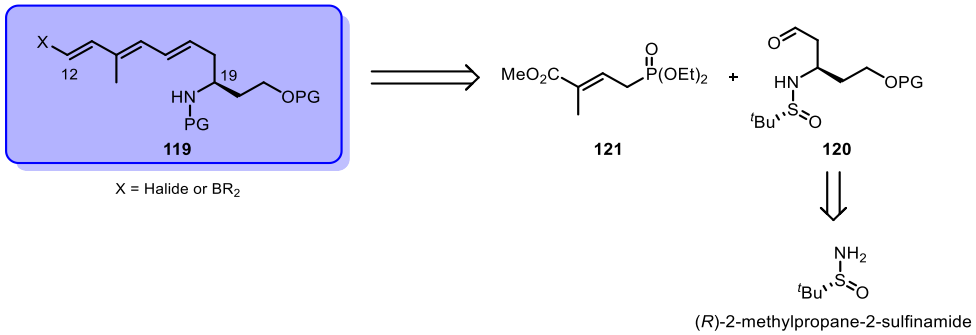
With aldehyde (±)-**116** in hand, an HWE olefination was attempted to form the full trienoate framework (Scheme 2.19); regrettably, no product was observed and degradation of the starting material was seen in the crude ^{1}H NMR spectrum. A two-step route was then implemented, based on a chromium-mediated Takai borono-olefination.[78] In these conditions, a vinyl boronic ester is installed using $Cl_2CHBpin$ **117** to form a geminal dichromium reagent, which adds to the carbonyl carbon. The elimination of the metal and oxymetal substituent forms the vinyl boronic ester in a highly selective (*E*)-fashion. Applied to our system, pinacol boronic ester **117** was installed to make cyclic siloxane boronic ester (±)-**118** in a high yield (92%). Now primed for Suzuki cross-coupling with iodide **62**, cyclic siloxane trienoate (±)-**114** was formed in 47% yield when using $Pd(dppf)Cl_2$. Surprisingly, no product was observed when using $Pd(PPh_3)_4$. The orthogonality of this step is notable, as the cyclic siloxane remained intact, with the moderate yield most likely due to base sensitivity rather than Hiyama coupling. With the synthesis of the C1-C11 fragment optimised, the focus turned to the northern C12-C19 amine containing segment.



Scheme 2.19. Construction of the C1-C11 cyclic siloxane.

2.15 Retrosynthesis of C12-C19

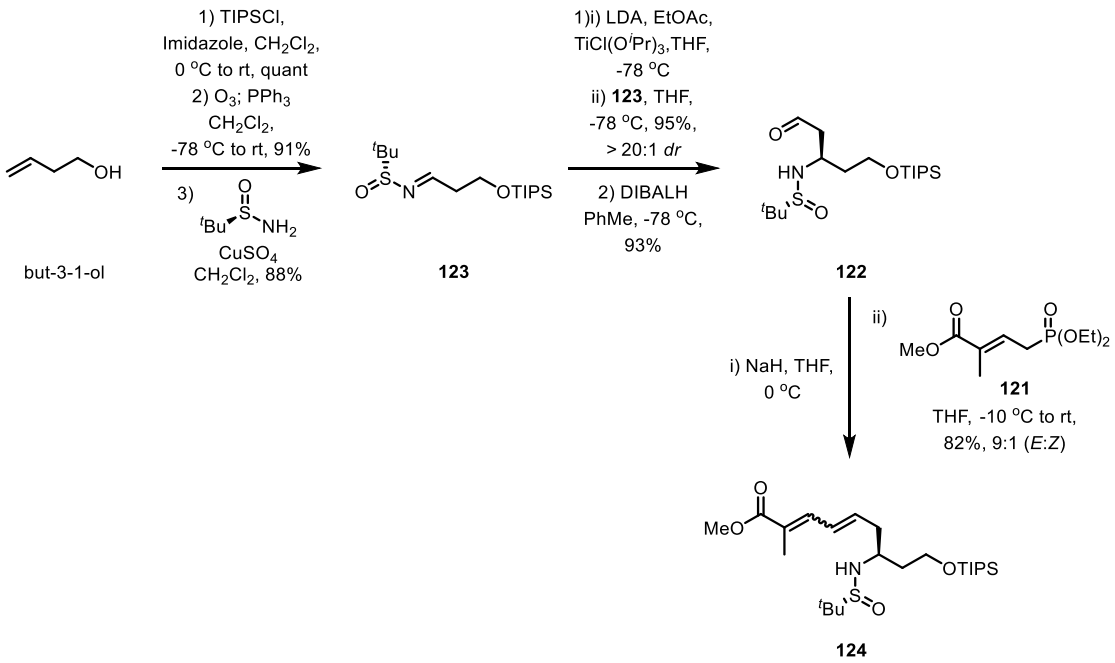
It was felt that the synthesis of the northern C12-C19 fragment could be shortened compared to previous heronamide C synthetic work. The trienyl coupling partner **119** can be broken down to aldehyde **120** and phosphonate **121** as shown in Scheme 2.2. Aldehyde **120** comes from the (*R*)-2-methylpropane-2-sulfinamide, which allows the stereocenter at C19 to be set in a highly stereoselective fashion using an Ellman auxiliary approach.[79]



Scheme 2.20. Retrosynthesis of C12-C19.

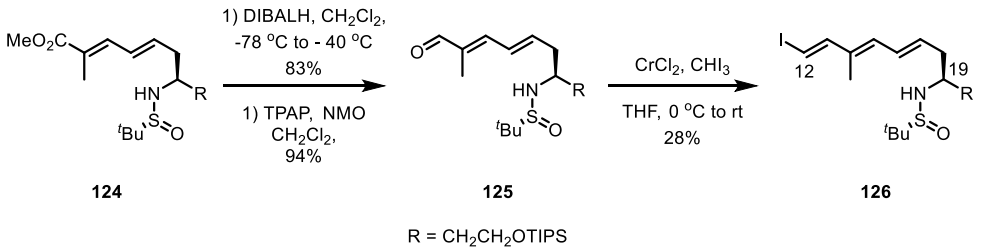
2.16 Previous synthesis of C12-C19 from our group

An investigation in the synthesis of the northern C12-C19 fragment was previously conducted by Masters student Alistair Sterling, who examined different protecting group strategies and nucleophilic additions into the sulfinyl imine.[80] The TIPS group was chosen for the synthesis, as it provided the highest *dr* and a strategy was implemented starting from but-3-en-1-ol, which was carried through to the corresponding aldehyde **122** (from **123**) in order to study the HWE reaction (Scheme 2.21). ^{n}BuLi was first tested, but with no success in favouring one geometric isomer over another in the study of the 'extended' HWE reaction. Lithium tetramethylpiperidide (LiTMP) only afforded a small increase in selectivity. Pleasingly, the use of sodium hydride at –10 °C increased the selectivity to 9:1 ((*E*)-**124**:(*Z*)-**124**). A work-up procedure involving quenching excess phosphonate **121** with benzaldehyde facilitated purification *via* silica gel column chromatography. Pre-drying phosphonate **121** (toluene azeotrope) drastically improved the yield.



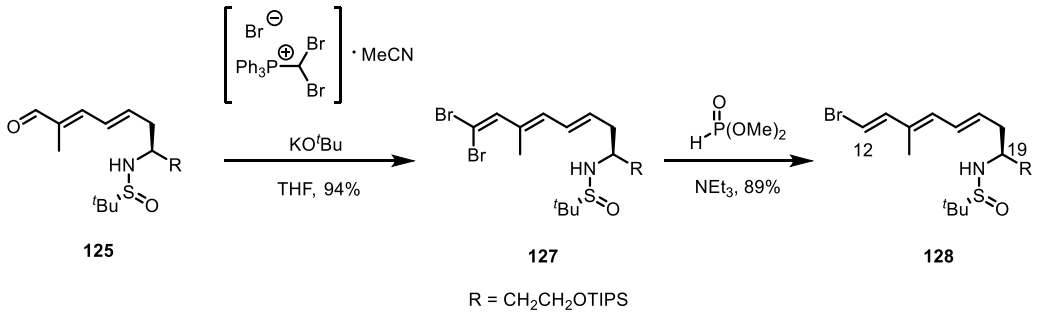
Scheme 2.21. Synthesis of dienoate **124** (Sterling).

With the dienoate in hand, conversion of the ester to a vinylic halide was explored by Alistair Sterling (Scheme 2.22). The reduction of the ester proved not to be straightforward, but was best achieved by initiating at −78 °C and then warming the to −40 °C, providing an 83% yield. Ley–Griffith oxidation gave the best yield of aldehyde **125**, with only a separation from residual NMO required through rapid column chromatography.[81] The Takai olefination was then attempted to install the vinyl iodide (**126**); however, this proved incompatible with the Ellman auxiliary (28% yield). A different strategy was therefore planned using a Ramirez olefination and a Hirao reduction.[82-83]



Scheme 2.22. Synthesis of trienyl iodide **122** (Sterling).

The standard Ramirez reaction conditions were tried by Alistair Sterling on **125** (Scheme 2.23), but gave limited success in forming the *gem*-dibromide in the presence of the Ellman auxiliary, again presumably due to the susceptibility of the Ellman auxiliary to cleave under electrophilic conditions.[83] This issue was solved by deprotonating the ylide first with potassium ^{t}butoxide, then stirring it overnight with the aldehyde, forming *gem*-dibromide **127** in 94% yield. Reduction to the (*E)*-vinyl bromide **128** was achieved in 89% yield using Hirao's conditions.



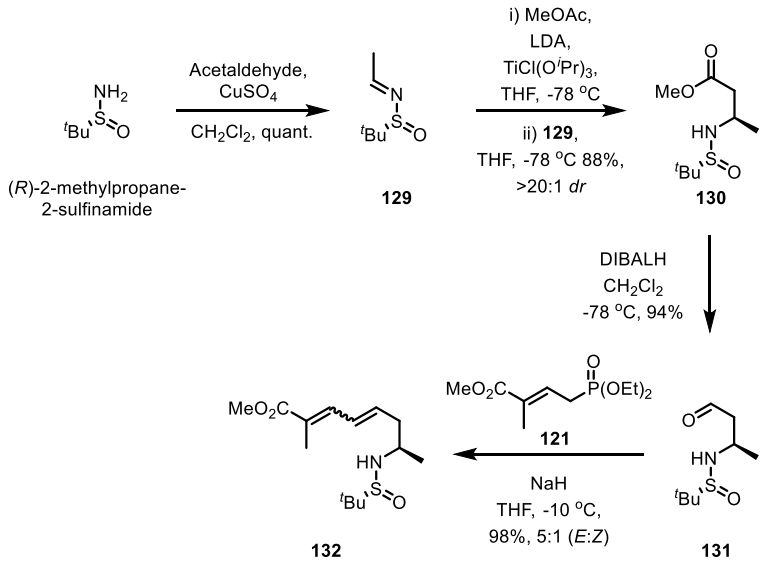
Scheme 2.23. Synthesis of trienyl bromide **128** (Sterling).

2.17 Synthesis of C12-C19

With a route to the C12-C19 fragment established, we nonetheless thought to simplify the system in order to study cross-coupling strategies and macrocyclisation, to avoid possible problems with the silyl ether. As such, the C20 position was adjusted to be a simple methyl group, which would be a representative model for any heronamide sidechain.

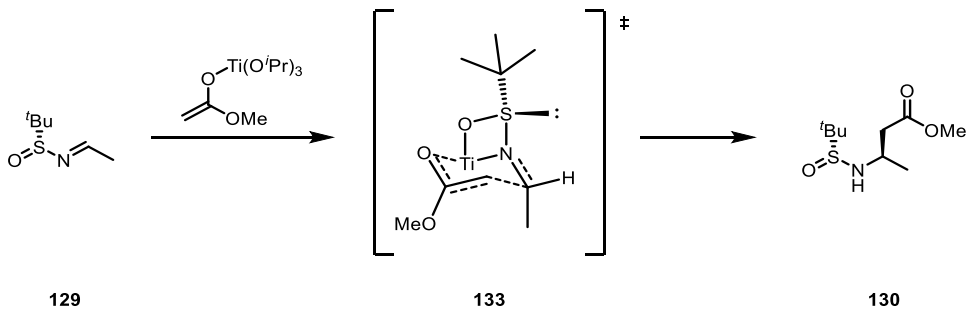
Sulfinylimine **129** was first formed from acetaldehyde in quantitative yield, as shown in Scheme 2.24. Due to the low boiling point of acetaldehyde, an extra portion was needed to achieve complete conversion. The titanium-mediated addition of the enolate of methyl acetate was used to provide ester **130**, the *dr* for which is reported to be greater than 99:1, and, in our hands, no other diastereomer was observed in the ^{1}H NMR spectrum (>20:1 *dr*).[84] The DIBALH reduction of ester **130** to the corresponding aldehyde proved tricky at first, with overreduction to the alcohol being readily observed. With experience and on multigram scale, successful reduction was achieved using a large round-bottom flask, cooling both the DIBALH and ester **130** solution to −78 °C before addition, transferring the DIBALH solution dropwise using a cannula against the wall of the fully submerged receiving flask. This highly reproducible procedure gave yields of aldehyde **131** in excess of 90% yield. Even though the substrates **124** and **132** are structurally very similar, the HWE reaction of aldehyde **131** proceeded with only moderate selectivity (5:1, *E*:*Z*) but in a high yield of 98%.

The reaction was attempted at cooler temperatures using LDA and LHMDS as the base, but it appeared that the lithium enolate would not add into the aldehyde at lower temperatures and no reaction was observed. The inseparable mixture was therefore carried forward in hopes to be able to separate it upon reduction of ester **132** to the alcohol.



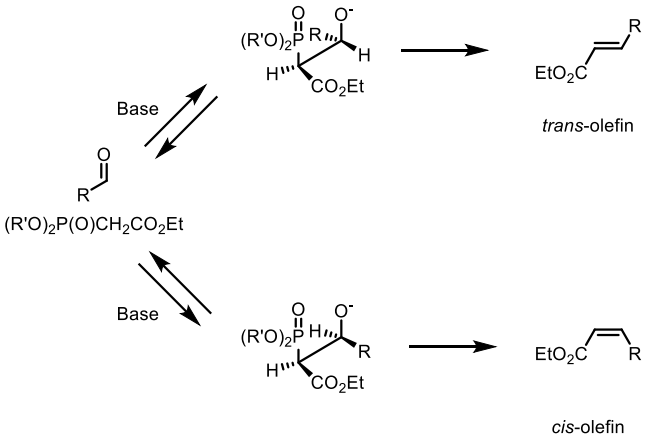
Scheme 2.24. Synthesis of C13-C19.

The diastereoselectivity of the nucleophilic addition into the imine is thought to arise from a Lewis-acid-coordinated [6,4]-bicyclic transition state (**133**), as shown in Scheme 2.25.[84] This chelation is only stable at low temperatures, and explains the necessity of careful and slow additions to maintain –78 °C to achieve an excellent *dr*.



Scheme 2.25. Nucleophilic addition into imine **125**.

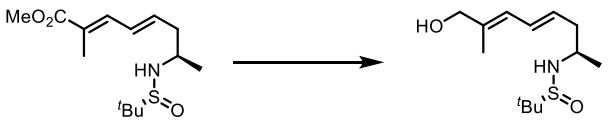
The Horner-Wadsworth-Emmons reaction operates under both kinetic and thermodynamic control in terms of the reversibility (or otherwise) in the first step of the reaction, in determining the stereoselectivity.[85-88] The *cis*-olefin intermediate leads to the *cis*-olefin, and is favoured due to rapid cyclisation of this kinetically-favoured diastereomer, while the thermodynamically controlled *trans*-olefin intermediate, which is more stable and eliminates *via* a lower energy transition state, leads to the *trans*-olefin as shown in Scheme 2.26.[89]



Scheme 2.26. *Trans-olefins vs cis-olefins.*[87]

For the ensuing ester reduction to alcohol **130**, various conditions were attempted to see if an alternative procedure could be identified instead of the −78 °C to −40 °C DIBALH protocol previously used, which now gave inconsistent yields (Table 2.6). When DIBALH was used at −78 °C and quenched at the same temperature, a 40% yield was obtained. Running the reaction at −100 °C gave a slightly higher yield of 62%. Other reductants led to no improvement (Red-Al®, 38%; lithium borohydride, 58%). In the end, the use of lithium aluminium hydride proved the highest yielding (67%), and upon scale up to a multigram scale, this improved to 83%. Pleasingly, careful silica gel column purification allowed the separation of the (*E*) and (*Z*) isomers to provide the pure (*E*) isomer.

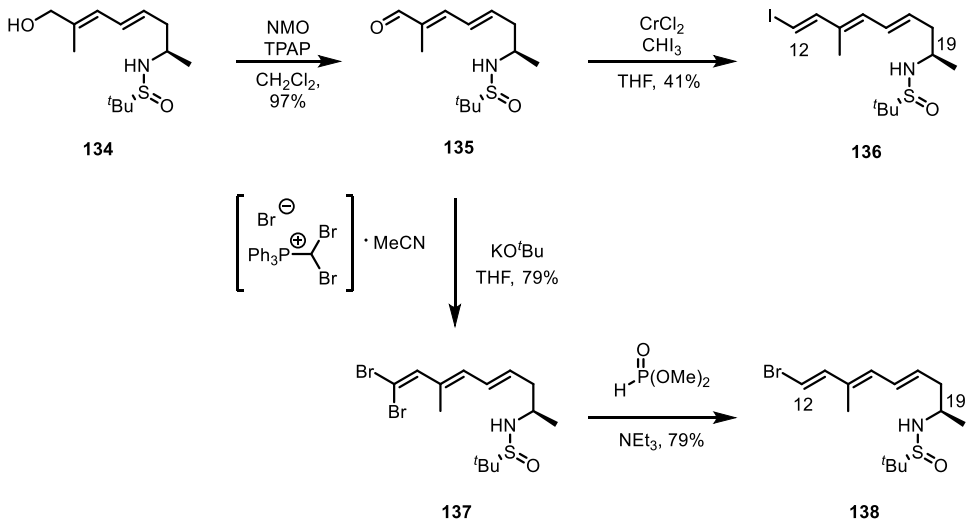
Table 2.6. Reduction of dienoate **132**.



132 **134**

Entry	Reductant	T (°C)	Yield (%)
1	DIBALH	−78	40
2	DIBALH	−100	62
3	Red-Al®	−78	38
4	$LiBH_4$	0 to rt	58
5	$LiAlH_4$	−78 to 0	67

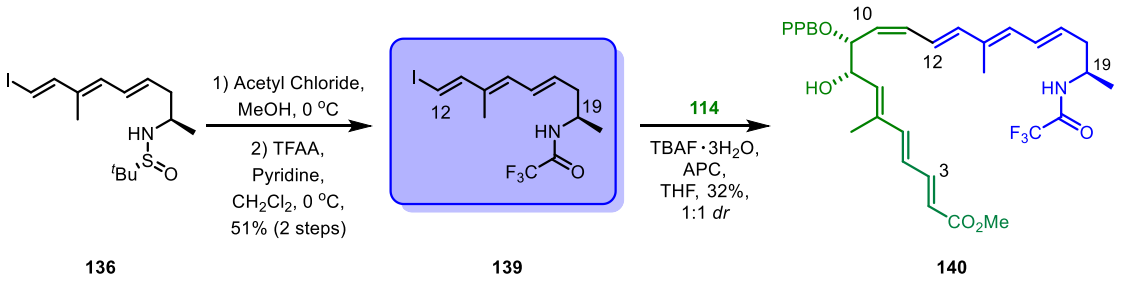
With allylic alcohol **134** in hand, the Ley-Griffith oxidation was used to generate aldehyde **135** in high yield (Scheme 2.27).[81] Takai iodoolefination proceeded in only 41% yield, but did deliver desired iodoalkene **136**.[90] As an alternative coupling partner, Ramirez olefination was used to yield the *gem*-dibromide **137** in 79% yield, reduction of which to (*E*)-vinyl bromide **138** using triethyl phosphite and triethylamine proceeded in another 79% yield.[82, 91]



Scheme 2.27. Synthesis of trienyl halides **136** and **138**.

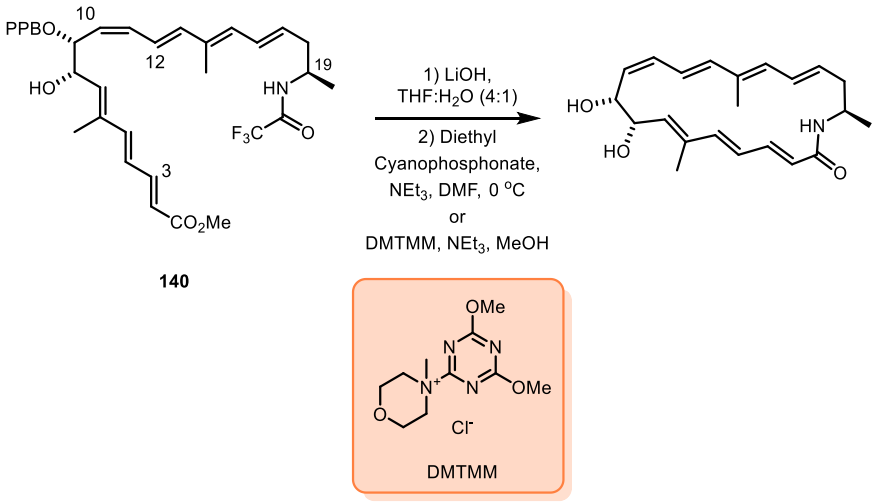
2.18 Coupling with trienyl iodide 139

With both key fragments in hand, their union was now addressed. Previous DPhil student Christian Kuper had faced numerous problems when trying to carry out Hiyama cross-couplings in the presence of an Ellman auxiliary, due to potential coordination of the lone pairs of either the sulfur or nitrogen to the Pd catalyst.[55] With this in mind, the auxiliary was cleaved under acidic conditions using dry HCl conditions (acetyl chloride / methanol), then the amine was protected as its trifluoroacetamide **139** in 51% yield over the two steps. It was expected that the electron withdrawing nature of the trifluoroacetamide would prevent coordination to the palladium catalyst. In the event this indeed turned out to be the case, and to our delight trifluoroacetamide **139** was coupled with trienoate (±)-**114** to make full C1-C20 skeleton **140** in 32% yield in a 1:1 *dr*.



Scheme 2.28. Union of C1-C11 and C12-C20.

The hydrolysis of the ester on C1-C20 **140** used the common conditions of lithium hydroxide in THF:H_2O as shown in Scheme 2.29. Kakinuma and co-workers embarked on the total synthesis of vicenistatin, a 20-membered macrolactam, and used Shioiri's conditions for peptide synthesis of diethyl cyanophosphonate and triethyl amine in DMF at 0 °C to successfully form the macrocycle.[92-93] Macrolactamisation of the crude amino acid on a 4 µM scale was attempted using the diethyl cyanophosphonate conditions, but only unreacted starting material was observed in the crude ^{1}H NMR. An alternative strategy using conditions developed by Toshima and co-workers who employed the use of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) as their coupling agent for the final macrolactamisation when completing the synthesis of incednine, a 24 membered polyene macrolactam, was tried on a 11 µM scale.[94] Unfortunately, no cyclised product was able to be observed by ^{1}H NMR.



Scheme 2.29. Hydrolysis and macrolactamisation attempts.

After attempting the macrocyclisations on a 4 and 11 μM scale, a study of the macrolactamisation on a larger scale was deemed necessary. As material was carried through the synthesis, problems with reaction times and yields occurred. The Sharpless asymmetric epoxidation time increased by one day (from 4 days to 5 days) as the scale was increased from 20 mmol to 57.7 mmol. The yield decreased as well from 65% to 54%, and the *ee*'s reduced to 75% from 88%. The problems continued with the epoxide opening reaction using PPBOH to form diol (±)-**108** in 61% yield, compared to 78%. The modified Takai olefination on cyclic siloxane (±)-**118** to form boronic ester (±)-**118** yield decreased from 92% on a 0.38 mmol scale to 23% when conducting the reaction on a 0.65 mmol scale. It was proposed that the biggest issue was the suitability of the cyclic siloxane towards large scale purifications; while rapid chromatography is possible on smaller scales, contact time with silica gel inevitably increases on scale up, at a cost to yield and processability. This led to the thinking that while cyclic siloxanes do provide the benefit of the guarantee of the (*Z*)-stereocenter and the internal protection of the secondary alcohol, it was not possible to bring through sufficient material to complete the synthesis.

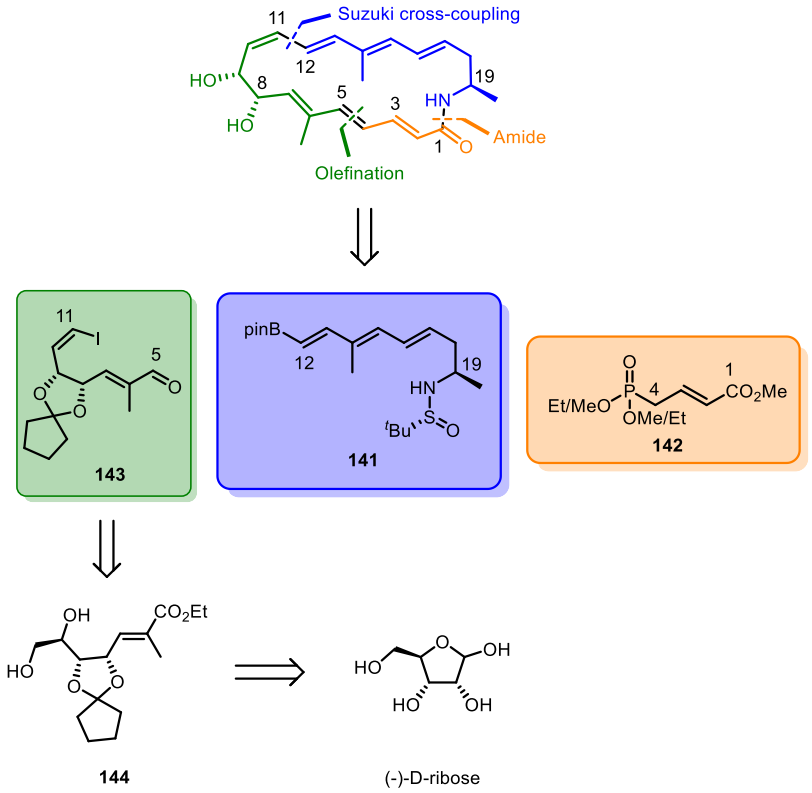
2.19 Summary

Various cyclic dimethylalkenylsiloxanes were synthesised for studying the Hiyama cross-couplings in a polyene system. This led to preparing the C1-C11 (±)-cyclic siloxane fragment in 12 steps with a 4% overall yield from methyl propiolate. This was successfully Hiyama cross-coupled to the C12-C20 fragment, which was prepared in 10 steps with a 14% overall yield using the Ellman auxiliary to set the C19 stereocenter. The acyclic heronamide analogue was not able to be cyclised, and, upon scale up of the route, many issues occurred with reaction times, yields and isolation of pure compounds. A change in strategy was deemed necessary, and use of a Suzuki cross-coupling was viewed as an attractive alternative. These results will be discussed in the next chapter.

3. Suzuki Cross-coupling Strategy

3.1 Revised synthesis of the heronamide core

In the previous chapter, the C1-C20 core had been prepared in its acyclic form, but failed to cyclise. When scaling up the cyclic siloxane methodology, numerous issues with lower yields and longer reaction times were encountered which ultimately led to the abandonment of the synthetic route. A revised strategy was conceived of a more robust route, which fortunately could take advantage of the same C12-C20 northern fragment **141** and either the literature methyl or ethyl phosphonate **142**. (*Z*)-vinyl iodide **143** can be made from diol **144** which derives from (–)-D-ribose.



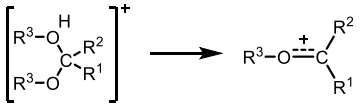
Scheme 3.0. Revised retrosynthesis of heronamide core structure.

3.2 Choice of protecting group for the diol

Contrary to using the unnatural (+)-L-ribose as previously used for total synthesis of heronamide C, we aimed instead to employ natural (cheaper) (–)-D-ribose.[35] This would require a protecting group for the diol to be selectively added to the 2,3-positions by use of an acetal. A literature investigation was conducted to decide which acetal can be removed under mild acidic conditions, which revealed that Hampton *et al*. had explored the rate of hydrolysis of different acetal protecting groups on uridine at the 2,3-diol position.[95]

The rate of acetal hydrolysis depends on the formation of the characteristic carbonium ion intermediate (Table 3.0).[96] The rate of hydrolysis of different acetals can be related to strain energy changes in this step. For the isopropylidene acetal (entry 7), the rate of release can be attributed to relief of steric repulsion on R^1–C–R^2 angle enlargement; however, this acetal has a long 'half-life' that likely reflects steric hindrance towards protonation and hence requires strong acidic conditions to be removed. The cyclopentylidene acetal, entry 5, is an interesting choice, as the acetal derives from inexpensive cyclopentanone and shows a fivefold smaller half-life than the isopropylidene acetal. The cyclopentane ring locks the R^1CR^2 position, which indicates that steric repulsion does not play a role in removing the cyclopentylidene acetal. The decrease in ring torsional strain from the cyclopentylidene to cyclopentanone ketal in the transition state, instead of steric repulsion, can instead explain the significant decrease in half-life from isopropylidene. This is seen for the other cyclo ketal groups − cycloheptylidene and cyclooctylidene − as they have similar hydrolysis rates. The cyclopentylidene acetal was therefore selected, as it was hoped it would not only hydrolyse rapidly, but also under 'softer' hydrolysis conditions.

Table 3.0. Rate of hydrolysis of uridine 2',3'-ketals at pH 2, 26 °C.[95]

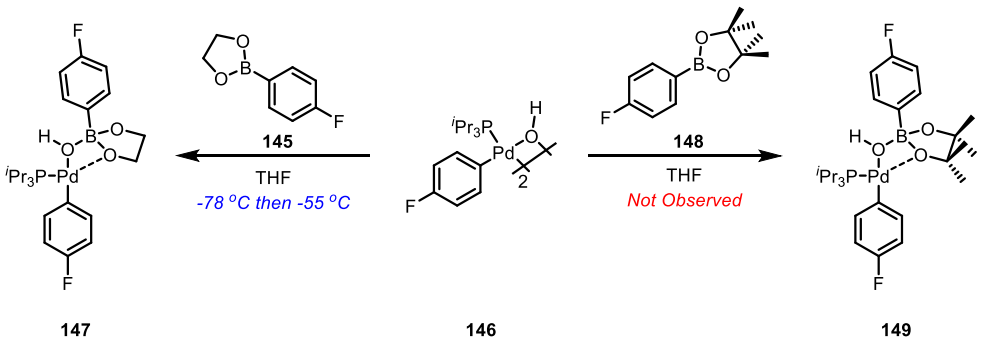


Entry	2',3' Substituent	Half-life of ketal (hr)
1	Methoxymethylidene	0.08
2	Crotonylidene	0.5
3	Cyclooctylidene	2.5
4	Cycloheptylidene	3
5	Cyclopentylidene	4
6	Methyl-*t*-butylmethylidene	20
7	Isopropylidene	20
8	Diethylmethylidene	40
9	Diphenylmethylidene	>40

3.3 Mechanism of Suzuki cross-couplings

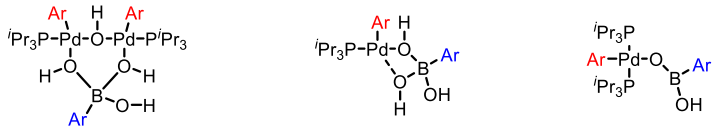
The palladium cross-coupling of an organic halide with a boronic acid is thought to go *via* the same general palladium cross-coupling mechanism as shown in Scheme 2.0. The role of boronic esters and acids in the Suzuki cross-coupling was investigated by Denmark and co-workers, who examined whether arylboronic esters can complex with palladium prior to transmetalation instead of requiring hydrolysis to the boronic acid in order to achieve this complex.[97] Scheme 3.1 shows the possibility of this coordination, however it heavily depends on steric bulk. For example, glycol boronic ester **145** was added to a solution of palladium dimer **146** at −78 °C and warmed to −55 °C. The major product observed was the palladium-glycol boronic ester complex **147** which showed that complexation is possible. On the contrary, when pinacol boronic ester **148** was added into a cooled solution of the

palladium dimer **146**, no complexation was observed. Denmark and co-workers attributed the inability to form palladium-pinacol boronic ester complex **149** to steric bulk; these results indicate that a hydrolysis step prior to transmetalation is not required when using sterically less-hindered boronic esters.[97]



Scheme 3.1. Boronic ester complexes with palladium.[96]

Denmark and co-workers studied the transmetalation event using low-temperature NMR spectroscopy, which showed evidence of two tetracoordinate (**150** and **151**) and one tricoordinate palladium species (**152**), as shown in Figure 3.0.[98] All three complexes are able to transfer their boron-aryl group to palladium, showing the importance of all three species in the transmetalation. The dimer tetracoordinate species **150** was thermally stable at −78 °C but decomposed at −30 °C into the monomer tetracoordinate specie **152** and the cross-coupled product. This indicates that the dimer **150** converts to the monomer **152** prior to transmetalation. The −30 °C thermally stable tricoordinate species **152** was warmed at 10 °C intervals, and a considerable amount of the cross-coupled product was observed at 20 °C from 3 to 12 hrs by ^{19}F NMR spectroscopy.



150 151 152

Figure 3.0. Different boronic acid-palladium species.

The role of hydroxide in the Suzuki cross-coupling of an aromatic halide with phenylboronic acid was studied by Amatore *et al.*[99] Figure 3.1 shows four plausible pathways of the transmetalation transition state, where pathways A and B have a halide-palladium complex while pathways C and D have a hydroxide-palladium complex. The authors first tried to react [ArPd(Br)(PPh_3)$_2$] with phenylboronic acid, and, in the absence of OH^-, no reaction took place. They then generated Ar'$B(OH)_3^-$ and attempted to react it with [ArPd(Br)(PPh_3)$_2$], but no reaction was observed. This indicates that pathway A and B are unfavoured, and the formation of the reactive palladium species, [ArPd(OH)(PPh_3)$_2$], is involved in the transmetalation event. Ar'$B(OH)_3^-$ did not react with [ArPd(OH)(PPh_3)$_2$] as well (pathway D), which can be due to the slow and difficult transfer of an OH group to a negatively charged species.[100] Route C is the favoured pathway and was supported with DFT calculations and experimentally by reacting [ArPd(OH)(PPh_3)$_2$] with phenylboronic acid.

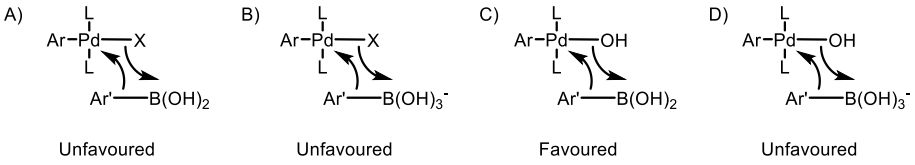
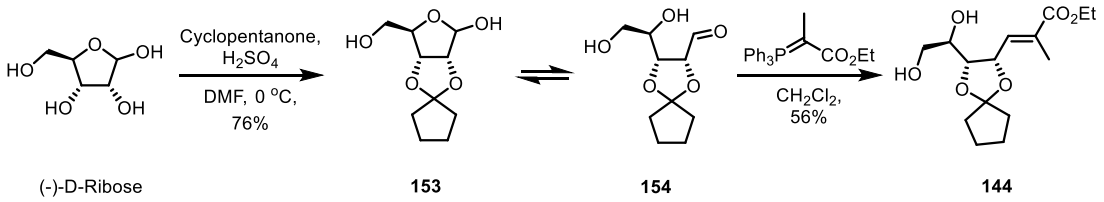


Figure 3.1. Suzuki cross-coupling transmetalation pathways.

3.4 Synthesis of the revised southern C1-C11 fragment

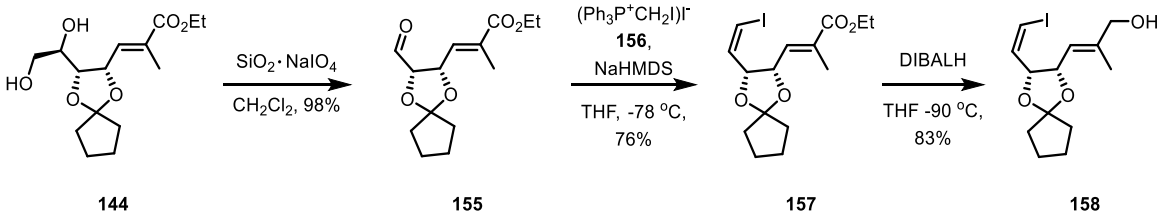
The protection of (–)-D-ribose proceeded under conditions developed by Hirano *et al.*, with a modified reaction work-up procedure which avoided bubbling ammonia gas to quench residual sulfuric acid.[101] Solid sodium bicarbonate was instead added until neutral pH was reached, and the residue filtered off. The yields obtained were comparable to the literature with a slight decrease to 76% for protected ribose **153** compared to the literature value of 83% (Scheme 3.2). Taking advantage of the equilibrium sugars possess with their open chain aldehyde form (**154**), a Wittig reaction was envisioned to extend the carbon chain.[102] Kane and Mann found that use of CH_2Cl_2 as solvent, at room temperature, supresses formation of the oxacyclic side-product.[103] Purifying diol **144** proved to be tricky, as the excess equivalents of ylide would co-elute with our desired product. This led to reacting excess ylide with benzaldehyde and the excess triphenylphosphine oxide that is generated was triturated. Following a filtration and flash silica gel column chromatography, diol **144** was purified in 56% yield.



Scheme 3.2. Forming Diol **144**.

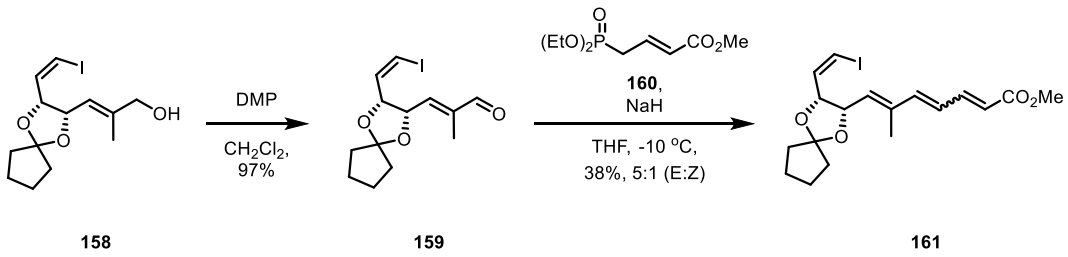
With diol **144** in hand, an oxidative cleavage was attempted using sodium periodate (Scheme 3.3). This led to a low yield of 50% due to degradation in the reaction. Pleasingly, employing Shing and co-workers' modification of silica-supported sodium periodate led to a dramatic increase in yield to 98% for aldehyde **155**.[104] Stork-Zhao conditions (iodophosphorane **156** and sodium hexamethyldisilazide) were then used to convert

aldehyde **155** into (*Z*)-iodo alkene **157** in 76% yield (15:1, *E*:*Z*).[105] Subsequent ester reduction using DIBALH led to (*Z*)-vinyl iodoalcohol **158** in 83% yield.



Scheme 3.3. (*Z*)-Vinyl iodoalcohol **158**.

The facile oxidation of the primary alcohol in **158** was conducted using DMP, which afforded (*Z*)-vinyl iodoaldehyde **159** in 97% yield (Scheme 3.4). An HWE olefination with (*Z*)-vinyl iodoaldehyde **159** and phosphonate **160** was used to fashion the (*Z*)-vinyl iodotrienoate **161** in 38% yield. Different conditions (addition of **161** over a longer duration and colder temperatures) were attempted to increase this yield, but none were successful.

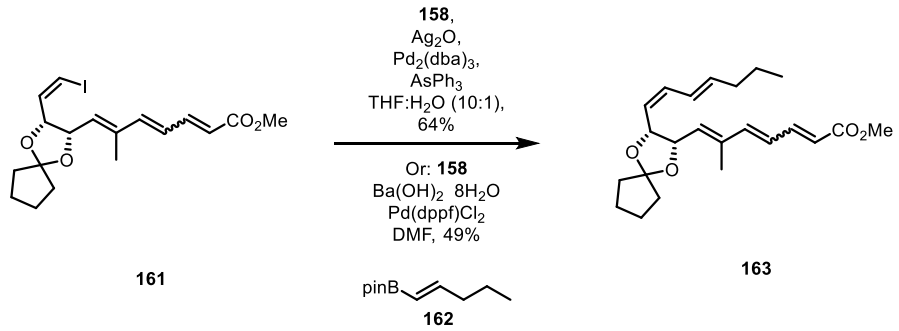


Scheme 3.4. Synthesis of (*Z*)-Vinyl iodotrienoate **161**.

3.5 Model Suzuki cross-coupling

With the full-length protected C1-C11 fragment in hand, the next challenge was to identify optimal Suzuki cross-coupling conditions. Model boronic ester **162** was used as the coupling partner and two different conditions were tried (Scheme 3.5). The first involved the relatively unusual triphenylarsine ligand, which is quite rare in Suzuki cross-couplings,

but can be found for attempting Stille cross-couplings when having a conjugated system.[106] In 1991, Farina and Krishnan studied the effects of different ligands in palladium cross-couplings involving olefinic stannanes and electrophiles.[107] They observed that triphenylarsine was among the highest yielding of all the ligands and, surprisingly, a relative rate of 1100 for triphenylarsine was observed compared to 1.0 for triphenylphosphine.[107] The conditions Fuwa *et al.* involving silver oxide as base were attempted, and a satisfactory 64% yield (**163**) was obtained. In comparison, the barium hydroxide octahydrate conditions used by Menche and co-workers when coupling conjugated systems provided a 49% yield.[108] Despite its toxicity, the triphenylarsine conditions were selected as these afforded the higher yielding result.

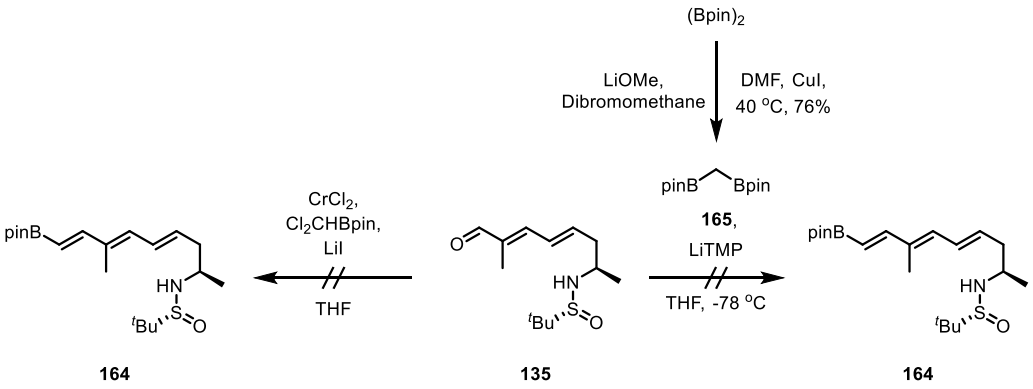


Scheme 3.5. Model Suzuki cross-coupling

3.6 Union of northern and southern fragments

In this revised strategy in which the halide is now installed on the C1-C11 fragment, the C12-C20 fragment required a slight revision of strategy in order to feature the transmetalating organometallic species. Two different methods were explored, as shown in Scheme 3.6, using aldehyde **135**. The modified Takai borylolefination conditions (which had previously been explored with the cyclic siloxane system) were attempted, and all starting material was consumed; however, no observable boronic ester **164** was seen by

crude NMR spectroscopic analysis. Morken and co-workers developed a transition metal free method to construct *trans*-vinyl boronate esters with bis(pinacolato)boryl methane **165**.[109] Bis(pinacolato)boryl methane **165** is deprotonated using lithium tetramethylpiperidide as the base, and then added into an aldehyde with high stereoselectivity in the ensuing elimination; this reaction is able to form challenging conjugated boronic esters in high yields. Using conditions developed from Fu and co-workers, bis(pinacolato)boryl methane **165** was synthesised from dibromomethane in 76% yield.[110] With **165** in hand, the conditions developed by Morken and co-workers were attempted; unfortunately, only starting material was recovered from the reaction mixture.

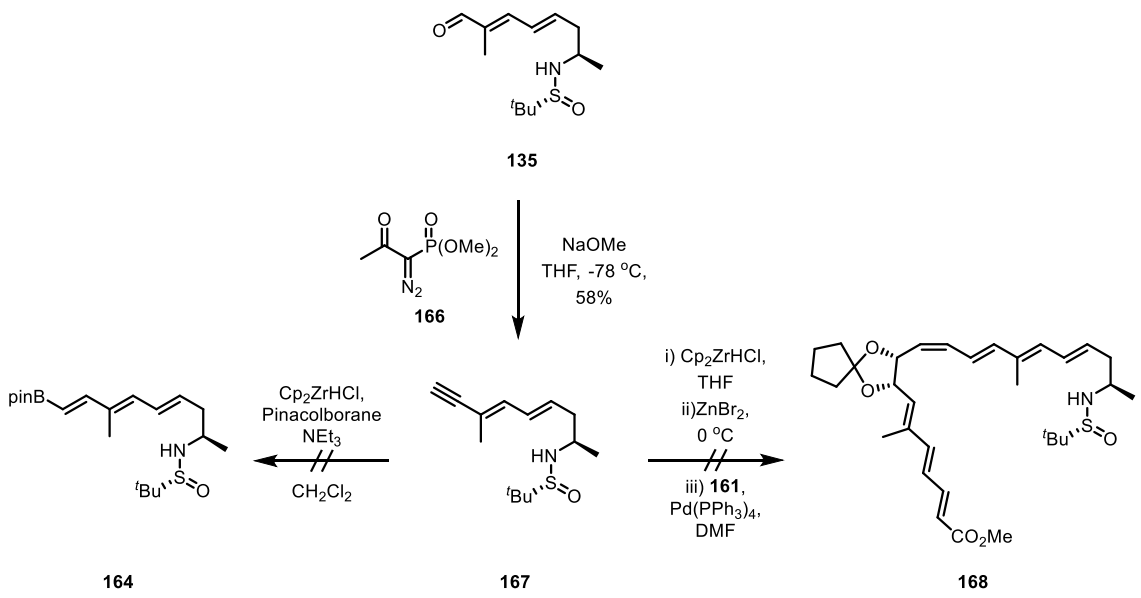


Scheme 3.6. Attempted synthesis of boronic ester **164**.

With one-step procedures to install the vinyl boronic ester proving ineffective, a two-step method was conceived. Alkyne hydroboration was envisioned to be a facile way to install the boronic ester. Using the Ohira-Bestmann modification of the Gilbert-Seyferth procedure, **166** and sodium methoxide were reacted with aldehyde **135** to give enyne **167** in 58% yield (Scheme 3.7).[111-114]

Schwartz and co-workers established the wide applicability of organozirconium chemistry, and the use of the Cp_2ZrHCl reagent − known as the Schwartz reagent − has been

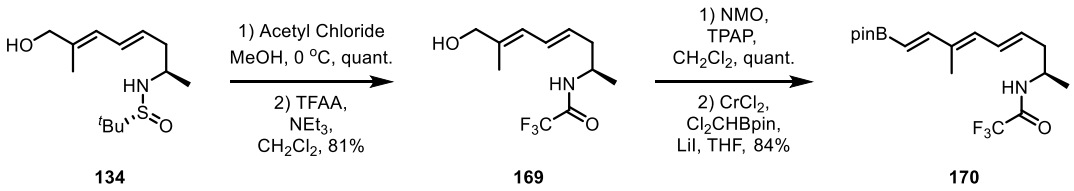
expanded on over the years.[115-118] Hu and Panek reported a one-pot procedure hydrozirconation / Negishi cross-coupling using this reagent, where the hydrozirconation would occur first, followed by transmetalation with zinc dichloride, and then finally a Negishi cross-coupling with tetrakis(triphenylphosphine)palladium and a vinyl halide.[119] These conditions were tried, but with zinc dibromide instead of the zinc dichloride, and using full-length trienoate **161** to hopefully achieve the full-length acyclic product **168**. Unfortunately, no discernible product was obtained and mainly decomposition was observed in the crude ^{1}H NMR spectrum. The Schwartz reagent was then used in an attempted Zr-catalysed hydroboration with pinacolborane, as reported by Pereira and Srebnik.[120] Triethylamine was added to neutralise any acid that may form, but when enyne **167** was subjected to the conditions, mainly starting material was observed.



Scheme 3.7. Synthesis of alkyne **167** and attempted hydrozirconation.

We considered that the failure of these reactions might derive from the nature of the nitrogen atom with its Ellman auxiliary, and a protecting groups switch was considered. Dienol **134** was used as the point to remove the Ellman auxiliary, even though there could

be a potential chemoselectivity issue for the subsequent trifluoroacetylation. Initial attempts of using CH_2Cl_2 to azeotrope the dry HCl generated − after removing the Ellman auxiliary − and then directly submitting the crude amine to a slow addition of TFAA to make trifluoroacetamide dienol **169** provided low yielding results (12-34% over two steps), as shown in Scheme 3.8. A stepwise approach was instead adopted in which the crude free amine was subjected to a simple acid-base extraction to purify the compound − negating the need of silica-gel column chromatography − in quantitative yield. Having purified the amine *via* this method, dropwise addition of TFAA to the amino alcohol over 2 hrs at 0 °C chemoselectively provided the trifluoroacetamide dienol **169** in 81% yield. The Ley-Griffith conditions to oxidise the primary alcohol, as previously discussed, proceeded in quantitative yield, and the aldehyde was subjected to the modified Takai conditions to construct trifluoroacetamide vinylboronic ester **170** in 84% yield.



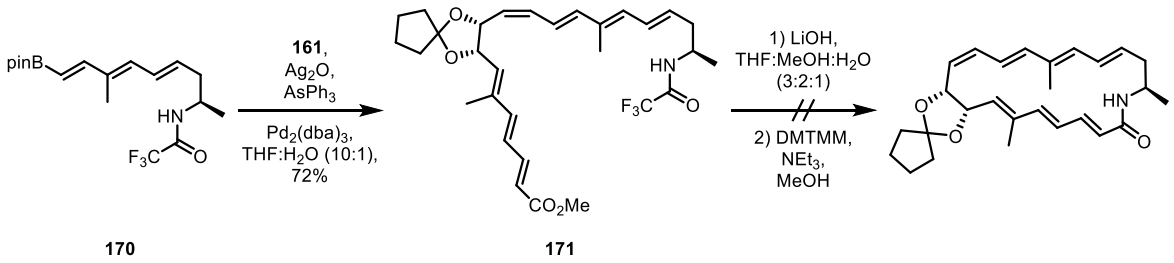
134 **169** **170**

Scheme 3.8. Construction of the trifluoroacetamide vinylboronic ester **170**.

With the trifluoroacetamide boronic ester **170** in hand, the Suzuki cross-coupling was re-tested. **170** was subjected to the Suzuki cross-coupling conditions with triphenylarsine and trienoate **161**, which very pleasingly proceeded smoothly to afford the full-length protected linear heronamide analogue **171** in 72% yield (Scheme 3.9). The hydrolysis of the ester and amide in **171** required the addition of methanol to the aqueous solution; the resulting amino acid proved difficult to extract from the basic aqueous mixture,

so the mixture was diluted with pH 7 phosphate buffer, and the amino acid was extracted from the neutral pH mixture with chloroform.

Conditions to attempt the cyclisation were again taken from the total synthesis of incednine from Toshima and co-workers, which employed DMTMM as the macrolactamisation agent.[94] DMTMM was shown by Tani and co-workers to activate carboxylic acids in the presence of amines, forming amide bonds in high yields with α,β-unsaturated acids which provided further confidence in use of the coupling agent.[121] Unfortunately, in our hands, no macrolactam product was observed by NMR analysis of the crude reaction mixture, and no recovery of the starting material was possible.

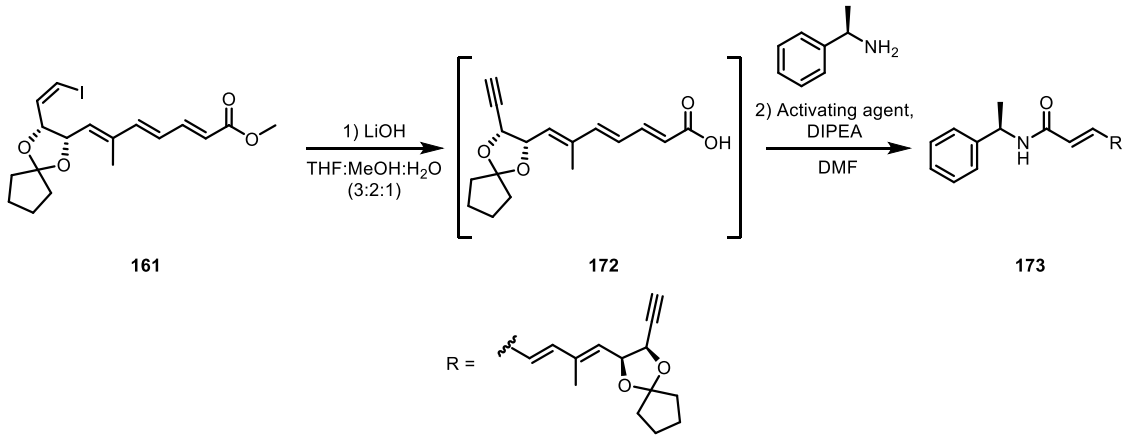


Scheme 3.9. Suzuki cross-coupling and attempted macrocyclisation.

3.7 Amide coupling study

As the macrocyclisation had proved troublesome, a step back was taken to study amide bond formation in the context of the trienoate system. The full-length trienoate **161** was therefore hydrolysed using lithium hydroxide to furnish the acid intermediate **172**, accompanied by elimination of the vinyl iodide to an alkyne. Amide coupling conditions were then screened with carboxylic acid **172** and (*S*)-α-methylbenzylamine, as shown in Table 3.1, using DIPEA as the base and DMF as the solvent. Entry 1 uses the reagent diethylphosphoryl cyanide (DEPC) as the acid activating agent; DEPC was first used for amide couplings by Yamada and co-workers in 1976, and is proposed to couple *via* the acyl

cyanide.[122] Under these conditions, amide **173** was isolated in a low yield of 23%. Entry 2 shows the highest yield of 70% with the reagent (benzotriazole-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP), which has previously been tested to form macrocyclic peptides by Xu and co-workers.[123] The most common amide coupling reagents with the carbodiimide EDCI and *N*-hydroxybenzotriazole (HOBt) were also tried, as shown in entry 3, but provided a lower yielding result (53%).[124-125] The azabenzotriazole HATU was also attempted (entry 4), however, starting material remained and the reaction mixture was not purified further.[126]

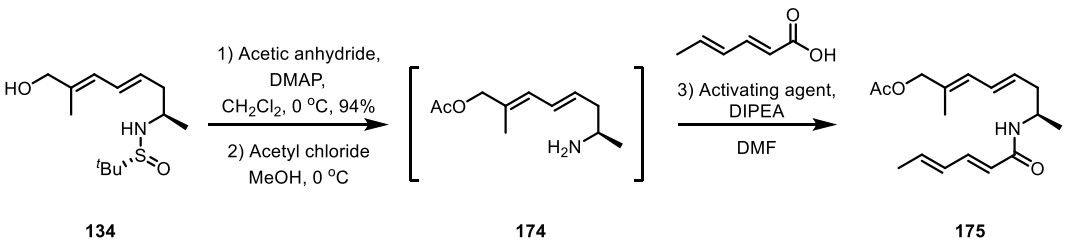


161 **172** **173**

Table 3.1. Amide coupling study with trienoate **161**.

Entry	Activating agent	Yield (% over two steps)
1	DEPC	23
2	PyBOP	70
3	EDCl, HOBt	53
4	HATU	Starting material remaining

Another model study was conducted to test which agent would be best at activating an α,β-unsaturated carboxylic acid with amine fragment **174**. The alcohol in sulfinamide **134** was first acetylated using acetic anhydride and DMAP in 94% yield to alleviate any chemoselectivity issues in the study.[127] Dry HCl (acetyl chloride and methanol) was employed to remove the Ellman auxiliary to afford the amine intermediate **174**. Table 3.2 shows its coupling with sorbic acid to form amide **175**. Entry 1 shows a moderate yield of 48%, compared to 23% in Table 3.1, when using DEPC as the activating agent. Entry 2 has a significantly lower yielding PyBOP reaction when related to Table 3.1 with 23% compared to 70%. EDCI and HOBt (entry 3) also showed a decrease in yield, from 53% to 39%. With HATU (entry 4), the product was isolated in 23% yield.



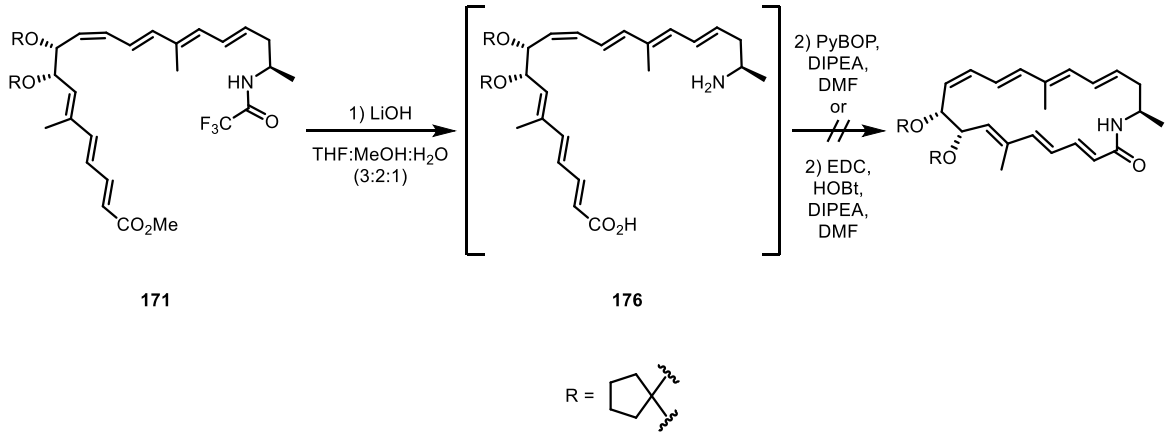
134 **174** **175**

Table 3.2. Amide coupling study with amine **174**.

Entry	Activating agent	Yield (% over two steps)
1	DEPC	48
2	PyBOP	23
3	EDCl, HOBt	39
4	HATU	23

3.8 Ring closure attempt and cyclopentylidene acetal deprotection study

Taking all things into consideration from Table 3.1 and 3.2, PyBOP was selected as a suitable activating agent since it had provided the highest yield of 70% for the carboxylic acid, as well as being easy to use, with simple purification. Full-length linear protected heronamide analogue **171** was hydrolysed with lithium hydroxide to provide amino acid intermediate **176** (Scheme 3.10). The macrocyclisation was attempted on a 9 μmol scale using PyBOP; however, disappointingly, no product or starting material was observed. EDCI and HOBt provided moderate yields in both Table 3.1 and 3.2, so an attempt to cyclise amino acid **176** with EDCI and HOBt was tried on a 9 μmol scale, but to no fruition. This led to the strong belief that the cyclopentylidene acetal protecting group was not flexible enough to allow the correct conformation to be adopted. The need for an appropriate conformation in the precursor, enabling favourable preorganisation to take place, is essential.[128]

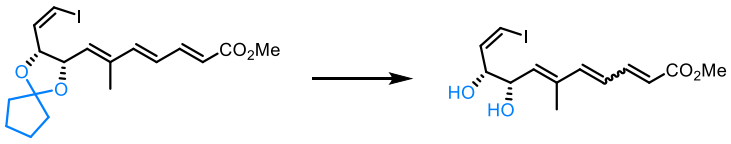


Scheme 3.10. Amide coupling attempt of amino acid intermediate **176**.

As described earlier, the cyclopentylidene acetal ought to be deprotected under milder conditions then a normal acetonide. Keeping in mind the synthetic route, the optimal place to deprotect the cyclopentylidene acetal and potentially replace it with acyclic

protecting groups would be the trienoate **161**, which would develop conditions for the flexibility to deprotect at a different stage if necessary. The highly conjugated system discouraged us from the use of 'standard' HCl conditions to avoid any isomerisation of the double bonds.

Table 3.3 describes the study that was conducted to identify conditions for this deprotection. Entry 1 employs Amberlyst 15, a sulfonic acid cation exchange resin that can be regenerated for multiple uses, with which Suzuki *et al.* showed the removal of an acetonide dimethyl acetal in the formal synthesis of (+)-isolaurepinnacin.[129] Monitoring of the reaction by TLC revealed decomposition of the starting material of around 6 hrs reaction time. Although the reaction did not reach completion (as other experiments suggested prolonged reaction times led only to decomposition), at this point the mixture was filtered and worked up, then purified *via* silica gel column chromatography, to afford the diol **177** in 46% yield (87% BRSM). Boron trichloride (entry 2) is a strong Lewis acid that is rarely used to remove acetals, but the success of Ye and co-workers using it on 2',3'-isopropylidene-uridine gave us some confidence to attempt it.[130] Unfortunately, within five minutes of adding BCl_3 into the mixture of trienoate **161** in dry dichloromethane, the substrate decomposed and no recovery of starting material or desired product was possible. Oishi and co-workers reported a slow addition of HF in acetonitrile at room temperature to achieve isopropylidene acetal deprotection, but after 1 hr an indistinguishable mix of isomerised products was observed in the crude analysis.[131] However, to our delight, on reducing the reaction time to 15 min, cooling the reaction to 0 °C, the deprotected diol **177** was isolated in an excellent 83% yield as a 7:1 (*E*:*Z*) mixture.

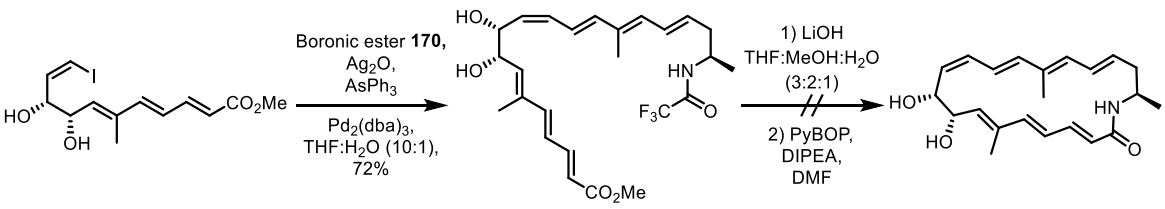


161 177

Table 3.3. Deprotection study of the cyclopentylidene acetal

Entry	Conditions	Result
1	Amberlyst 15, MeOH:H_2O (20:1)	46% (87% BRSM)
2	BCl_3, CH_2Cl_2	Polymerisation
3	MeCN:HF (5:1), 0 °C	83% (7:1, *E*:*Z*)

Diol **177** is an interesting substrate for macrocyclisation, as the flexibility at C8 and C9 could potentially help place the molecule in the right conformer and likely mimics the natural cyclisation substrate; however, there is a potential risk of oligomerisation, but a dilute reaction mixture could help avoid oligomer issues. As such, diol **177** was Suzuki cross-coupled with boronic ester **170** in 72% yield to provide full-length trifluoroacetamide **178**. **178** was then hydrolysed with lithium hydroxide, and macrocyclisation was attempted on an 8 μmol scale using PyBOP / DIPEA, but again, unfortunately, no product was observed.

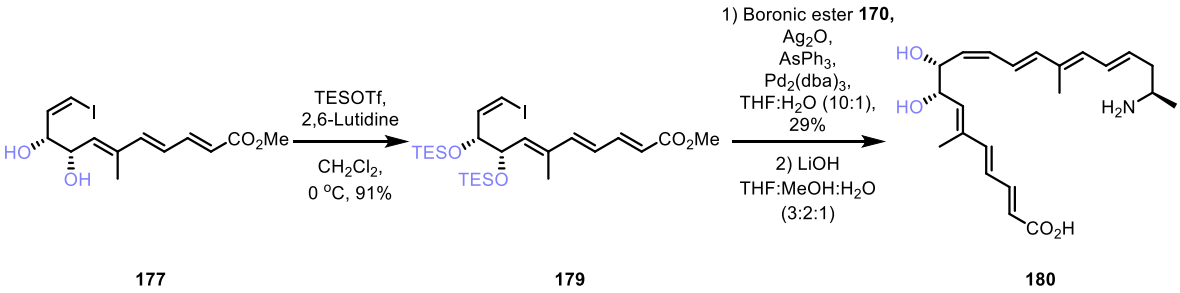


177 178

Scheme 3.11. Macrocyclisation attempt with free diol **178**.

3.9 Construction of silyl ether protected C1-C11

Theorising that the issue lay with having free alcohols, we therefore decided to protect the diol with silyl ethers. This would retain conformational flexibility at C8/C9 while negating the possible lactonisation or oligomerisation. Diol **177** was TES protected using TESOTf and 2,6 lutidine at 0 °C, forming *bis*-silyl protected trienoate **179** in 91% yield (Scheme 3.12).[132] However, **179** was Suzuki cross-coupled with boronic ester **170** to form the TES protected full-length heronamide analogue in a low 29% yield; this could be due to the basicity of the solution cleaving the silyl ethers, but before optimising the cross-coupling conditions the molecule was carried forward to see if the amide bond formation could be possible. Regrettably, under hydrolysis using lithium hydroxide, the silyl ethers were removed and the free diol **180** was observed on analysis of the crude reaction mixture.

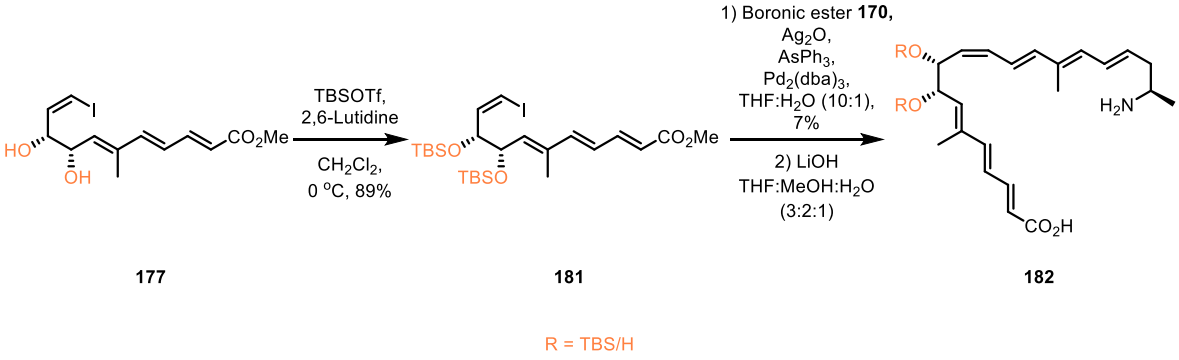


177 179 180

Scheme 3.12. Suzuki cross-coupling with TES protected diol **179**.

A TBS ether should be more resistant to basic conditions;[133] however, as the protecting groups become bulkier (TES<TBS), the protection of a 1,2 diol can become increasingly difficult due to steric hindrance. TBS protection of diol **177** was attempted using the TBSOTf, and proceeded smoothly in 20 mins to form TBS-protected trienoate **181** in 89% yield (Scheme 3.13). **181** was subjected to the Suzuki cross-coupling conditions with boronic ester **170** forming the TBS protected full-length heronamide analogue in a very poor 7% yield, with unreacted deprotected diol **177** observed. Nonetheless, the TBS protected

full-length heronamide analogue was carried forward to see if it would survive hydrolysis conditions. From crude analysis and mass spectrometry, it unfortunately appeared that once again some loss of the silyl ethers (**182**) occurred using lithium hydroxide.



Scheme 3.13. Suzuki cross-coupling with TBS protected diol **181**.

3.10 Summary

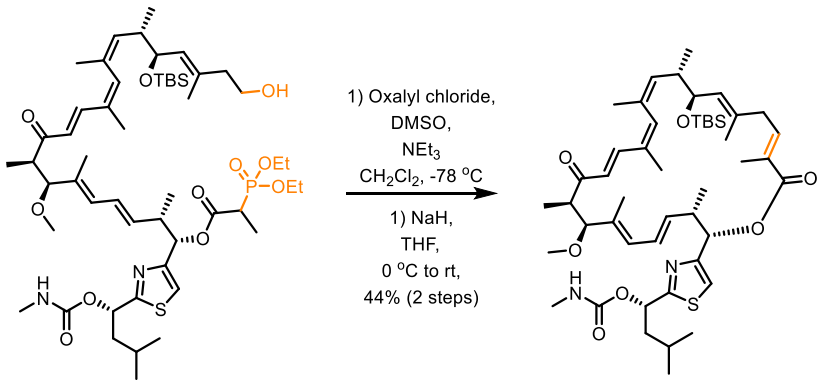
Significant advances towards a scalable synthesis of the heronamide core were achieved by switching the 'direction' of the C11–C12 cross-coupling. The C1-C11 southern fragment was prepared in 10 steps with a 10% overall yield, and the northern C12-C20 fragment was constructed in 9 steps with a 46% overall yield. Suzuki cross-coupling proceeded in a high yield of 72%; however, many issues emerged with the macrolactamisation. Alternative protecting group did not survive the hydrolysis conditions, and the cyclisation did not proceed with an unprotected diol. Without being able to achieve macrolactamisation with the cyclopentylidene acetal, silyl ethers, or free diol, a rethink of the synthetic route or order of events seemed necessary. This strategy evolution forms the focus of the next chapter.

4. Horner-Wadsworth-Emmons Ring-Closing Strategy

4.1 Previous total syntheses using an HWE ring-closing strategy

As our macrolactamisation attempts to prepare the C1-C20 core had proven unsuccessful, we decided at this stage to evaluate other cyclisation methods. Our attention was drawn to an intramolecular HWE reaction, a ring-closing strategy that had proved to be useful for other natural products such as archazolid A, wortmannilactone C, and marinisporolide C.[134-136]

Menche *et al*. successfully used a ring-closing HWE reaction *en route* to synthesising the 24-membered macrocycle archazolid A, as shown in Scheme 4.0.[134] Swern oxidation of alcohol **183** generate the aldehyde, and NaH mediated deprotonation to the phosphorus ylide. This successfully cyclised to give the α,β-unsaturated lactone **184** in a respectable yield of 44% over two steps.

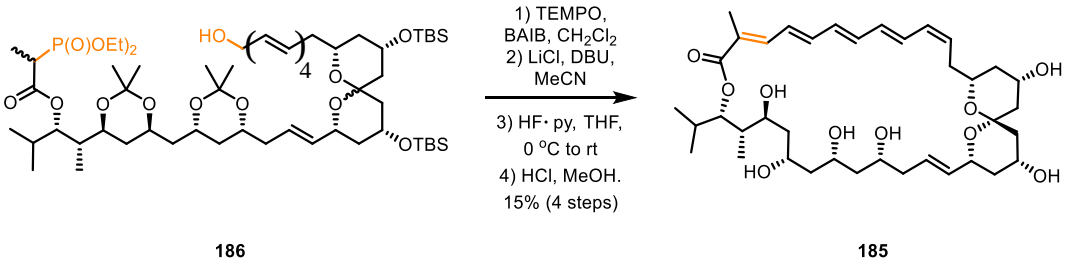


183 **184**

Scheme 4.0. HWE ring-closing reaction in the total synthesis of archazolid A.[133]

The total synthesis of marinisporolide C **185** (Scheme 4.1), accomplished by Dias and de Lucca, used an intramolecular HWE reaction to close the 30-membered ring after attempts at macrolactonisation failed.[135, 137] The authors performed an intramolecular HWE

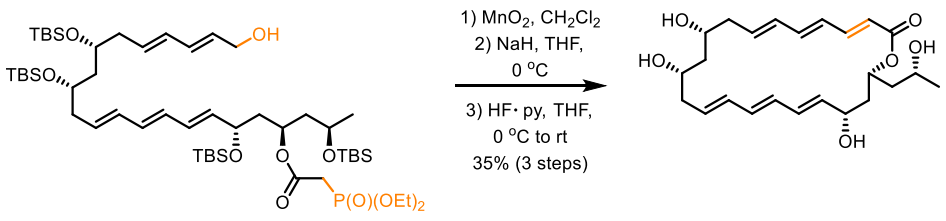
using the Masamune-Roush modification of LiCl/DBU after oxidising alcohol **186** in the endgame towards marinisporolide C.[138] The use of a strong organic base (DBU) and LiCl as a Lewis acid enabled the cyclisation to proceed relatively smoothly, and following deprotection constructed marinisporolide C in 15% yield over four steps .



186 **185**

Scheme 4.1. Endgame synthesis of marinisporolide C.[134]

Cossy and co-workers described a convergent synthesis of wortmannilactone **187** that employed an HWE olefination for the 22-membered ring cyclisation strategy (Scheme 4.2).[136] Following oxidation of the allylic alcohol **187** to the aldehyde with MnO_2, the resulting aldehyde was treated with a cooled solution of NaH in THF to effect cyclisation. Upon deprotection, wortmannilactone C **188** was synthesised in 35% over three steps.



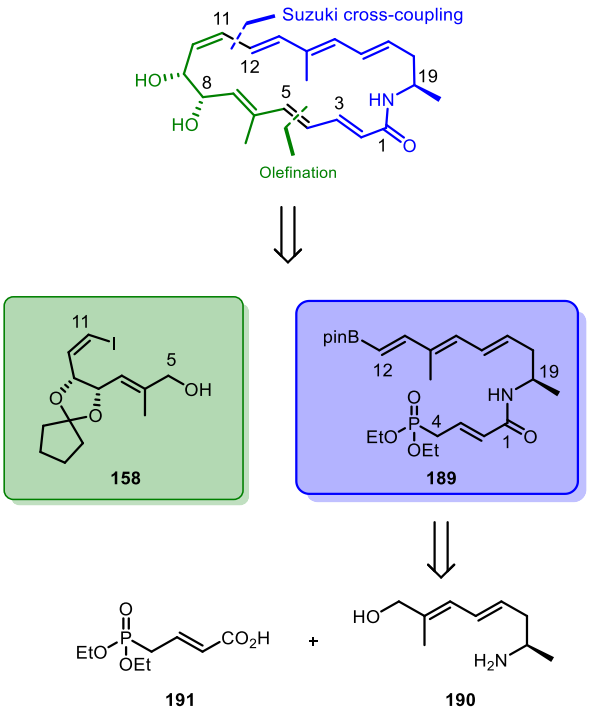
188 **187**

Scheme 4.2. Endgame HWE reaction in the total synthesis of wortmannilactone C.[135]

4.2 Revised retrosynthesis for HWE ring closing strategy

These literature precedents (among others) for the synthesis of large ring polyene natural products using HWE olefinations gave us confidence that this might be a good

endgame strategy in our synthesis of the heronamide core. A revised retrosynthesis of the core was envisioned as shown in Scheme 4.3, by a reordering of coupling events of the constituent fragments. The Suzuki cross-coupling would now use previously synthesised (*Z*)-vinyl iodide **158**, and boronic ester **189** with the HWE phosphonate already in place. Boronic ester **189** in turn derives from a chemoselective amide coupling using previously-synthesised free amine **190** and acid **191**.

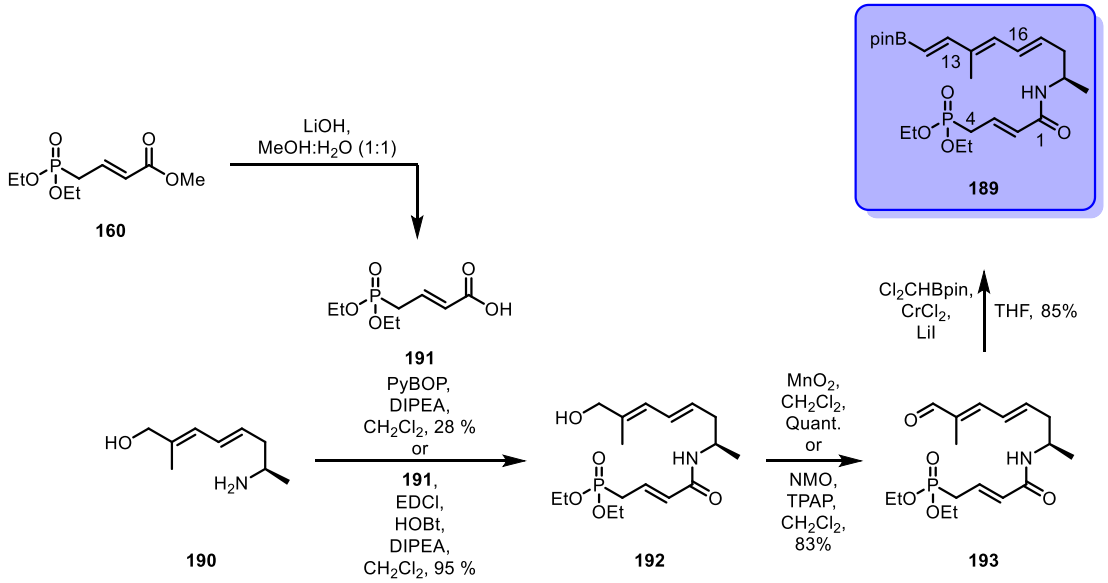


Scheme 4.3. Revised retrosynthesis towards the heronamide core.

4.3 Revised synthesis of amide 189, Suzuki cross-coupling of fragments and attempted cyclisation

Taking advantage of the nucleophilicity of amines in comparison to alcohols, free amine **190** was subjected to amide coupling conditions to form amido phosphonate **192** (Scheme 4.4). Ester **160** was hydrolysed to acid **191** in 83% yield, and coupled with the free amine **190** using PyBOP (28% yield). As the PyBOP conditions could not be optimised

further, other reagents were explored, such as EDCI / HOBt. Initial attempts adding all reagents at once led to a much improved 77% yield of amide product. The reaction was optimised further to a 95% yield by pre-stirring acid **191** (1.00 equiv.) with DIPEA, EDCI and HOBt in CH_2Cl_2 for 5 mins, and then slowly adding a slight excess of a solution of free amine **190** (1.05 equiv.) in CH_2Cl_2. Amido phosphonate **192** was oxidised to aldehyde **193** in 83% yield using Ley-Griffith conditions, or in quantitative yield using manganese dioxide. The previously discussed modified Takai conditions allowed the vinyl boronic ester to be installed, affording vinylboronic ester coupling partner **189** in 85% yield.[78]



Scheme 4.4. Preparation of boronic ester Suzuki cross-coupling precursor **189**.

Vinylboronic ester **189** was coupled with iodoalcohol **158** as shown in Table 4.0. Different ligand/catalyst systems were screened at 31 °C (the room temperature of the lab due to building cooling failures!) to see which ligand would offer the optimal yield for synthesising allylic alcohol **194**. Tetrakis(triphenylphosphine)palladium(0) (entry 1) required the longest time for the reaction to reach completion of the conditions tested, with an overnight reaction duration that provided a meagre 21% yield. Entries 2 and 3 show the

use of the electron-rich phosphorous ligands tri(2-furyl)phosphine (TFP) and tris(4-methoxyphenyl)phosphine with $Pd_2(dba)_3$ as catalyst; surprisingly, these cross-coupled with low yields of 16% after 8 h. At this temperature, degraded boronic ester was often seen as a major by-product. The previously discussed $AsPh_3$ and $Pd_2(dba)_3$ conditions (entry 4) also gave a poor yield of 33% at this temperature; however, when conducted at a lower temperature of 22 °C (entry 5), a pleasing yield of 70% was obtained. These reaction conditions were used going forward and conducted at the lower 'room temperature' conditions.

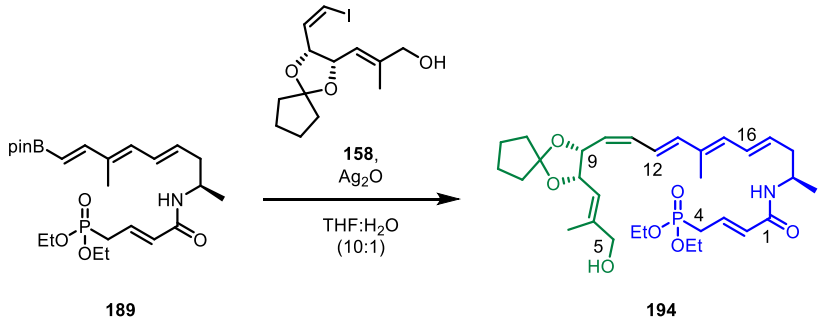


Table 4.0. Ligand screen for Suzuki cross-coupling iodoalcohol **158**

Entry	Ligand/Catalyst	Yield (%)
1[a]	$Pd(PPh_3)_4$	21
2[a]	TFP/$Pd_2(dba)_3$	16
3[a]	Tris(4-methoxyphenyl) phosphine/$Pd_2(dba)_3$	16
4[a]	$AsPh_3$/$Pd_2(dba)_3$	33
5[b]	$AsPh_3$/$Pd_2(dba)_3$	70

[a]Performed at 31 °C [b]Performed at 22 °C

This coupling completes the full-length carbon skeleton. Allylic alcohol **194** would now need to be oxidised prior to cyclisation, for which several conditions were tested (Table 4.1). MnO_2 was first used to oxidise the allylic alcohol **194** to form aldehyde **195** since it

requires minimal purification, but unfortunately only degradation was observed (Entry 1). Swern conditions (Entry 2) formed **195** in 57% yield; however, upon scaling up the reaction, the product appeared to undergo double bond isomerisation. Entry 3 shows a Dess-Martin oxidation using K_2CO_3 to neutralise the acetic acid and prevent isomerisation of the conjugated system. The reaction was performed at 0 °C and afforded aldehyde **195** in 54% yield which, importantly, was reproducible upon scale up. These struggles to oxidise the allylic alcohol post Suzuki cross-coupling led to the attempt of Suzuki cross-coupling with iodoaldehyde **159**, which directly produced aldehyde **195** in 37% yield. An HWE macrocyclisation was attempted with aldehyde **195** on a 35 μmol scale in a dilute THF solution (0.02 M). Aldehyde **195** was treated with NaH at −20 °C, and slowly warmed to room temperature, under which conditions trace cyclised product (**196**) was observed.

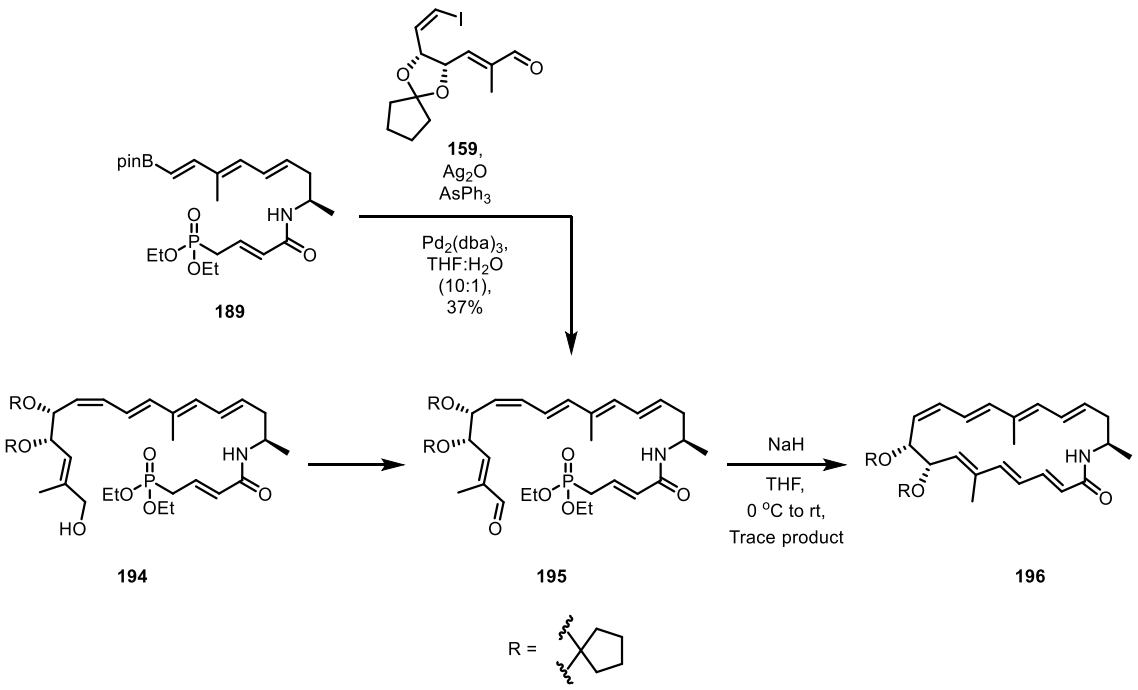


Table 4.1. Oxidation of allylic alcohol **194**.

Entry	Conditions	Yield (%)
1	MnO_2, CH_2Cl_2	Degradation
2	DMSO, Oxalyl chloride, NEt_3, CH_2Cl_2, −78 °C	57
3	DMP, K_2CO_3, CH_2Cl_2, 0 °C	54

A trace of what could be the macrocyclic product was observed by HRMS (Figure 4.0), the mass error being within 0.2 ppm. However, there was insufficient product to be definitively observed by ^{1}H NMR spectroscopy. Different non-nucleophilic strong bases − LDA and LHMDS − were tried to see if the cyclisation yield would increase. Dilute solutions of aldehyde **195** was cooled to −78 °C in THF, and freshly made LDA or LHMDS was added dropwise; with no product was observed with these strong bases at −78 °C after 2 hrs, the mixtures were slowly brought to room temperature overnight, but still only trace product was observed with most of the material being degraded phosphonate. This raised the key

question of whether the cyclopentylidene acetal is flexible enough to allow the cyclisation to take place.

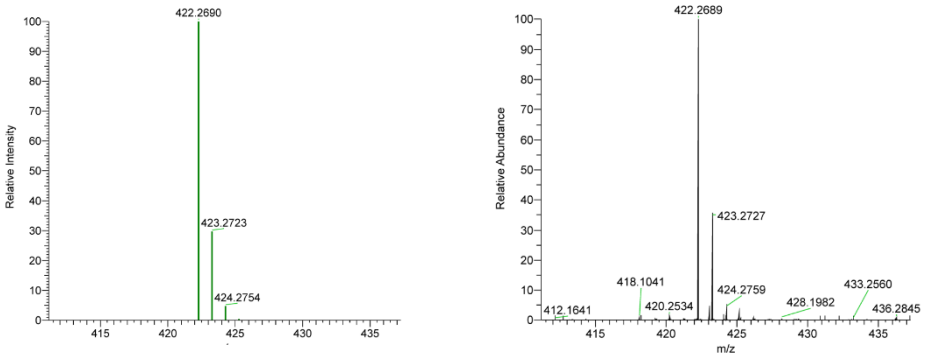
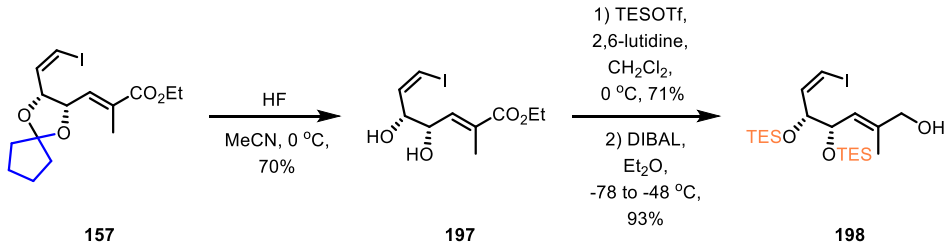


Figure 4.0. Theoretical HRMS spectrum (left) and found (right) of cyclised product.

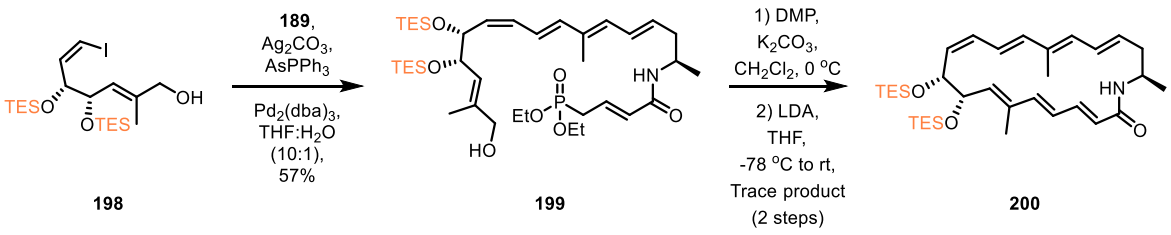
4.4 TES protection of diols and attempted cyclisation

With the cyclopentylidene acetal potentially preventing adoption of the required conformation in order for the cyclisation to proceed, we proposed that a silyl ether would confer sufficient flexibility for the HWE to ensue. The optimal stage to change the protecting group was at ester **157**, which was deprotected using HF to form diol **197** in 70% yield (Scheme 4.5). The diol was *bis*-TES protected in 71% yield, and the ester reduced with DIBALH to afford allylic alcohol **198** in 93% yield.



Scheme 4.5. Synthesis of silyl protected iodoalcohol **198**.

Iodoalcohol **198** was coupled with boronic ester **189** using the Suzuki cross-coupling conditions with a slight change in the base (Scheme 4.6). Previously, when silyl ether **179** and **181** were Suzuki cross-coupled using Ag_2O as the base, the TES and TBS groups appeared susceptible to cleavage, leading to dramatically lower yields. Pleasingly, changing the base to silver carbonate when cross-coupling TES-protected allylic alcohol **198** generated full-length allylic phosphonate **199** in 57% yield. This was followed by a DMP oxidation with minimal purification that enabled set up of two small-scale − 26 μmol − attempted cyclisations with NaH and LDA as base. No observable product in **200** appeared using NaH, however, when using LDA, trace product was observed by mass spectrometry which provided some optimism in the new protecting group.



Scheme 4.6. Suzuki cross-coupling and attempted cyclisation with silyl ethers.

The Suzuki cross-coupling was scaled up from 45 μM to 0.21 mmol in order to provide sufficient material for the cyclisation; however, this appeared to create issues with the Suzuki coupling. When attempting the coupling on larger scale, *no* product was observed by ^{1}H NMR spectroscopy of the crude reaction mixture and, unfortunately, there was insufficient time or material to investigate a solution to overcome this issue.

4.5 Summary

Boronic ester **189** was constructed in 9 steps with an overall yield of 54% with the phosphonate in place for a macro-HWE cyclisation. The facile synthesis of these coupling

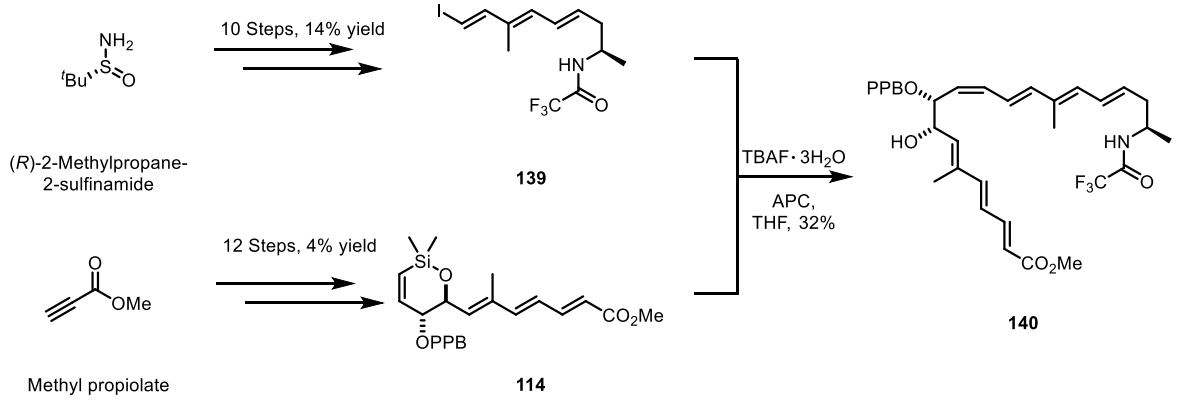
partners allowed sufficient material for a screening of different ligands for a Suzuki cross-coupling, and led to identifying high yielding Suzuki cross-coupling reaction conditions. The full-length carbon skeleton was subjected to various HWE reaction conditions and led to trace product being detecting by HRMS. The protecting groups were changed to the TES silyl ether in an attempt to enhance the cyclisation yield, but still the putative desired product was only observed by mass spectrometry. The Suzuki cross-coupling of the silyl ether were scaled up to ensure enough cyclised material could be isolated, but upon scale up, the Suzuki cross-coupling failed.

5. Conclusion and future work

5.1 Conclusion

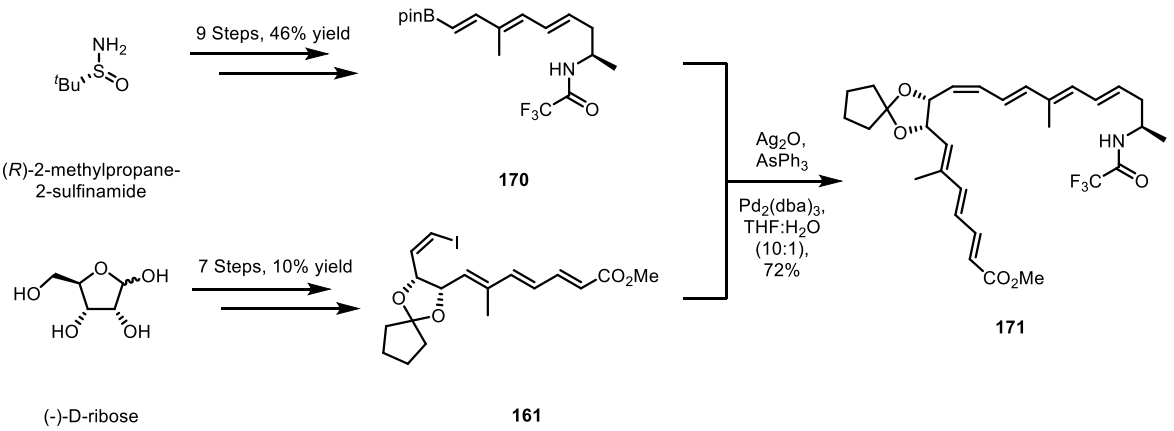
Several routes have been developed towards the heronamide natural product core which allow for side chain variation and potential glycosylation of the diols. Studying these two modifications will provide further insight to the heronamide structure-activity relationship for biological activity.

Using cyclic siloxane methodology developed by the Anderson group, various coupling partners were synthesised: cyclic siloxane C1-C11 **114** in 12 steps with a 4% overall yield and (*E*)-vinyliodide C12-C20 **139** in 10 steps with a 14% overall yield (Scheme 5.0). These successfully underwent Hiyama cross-coupling to prepare PPB-protected C1-C20 acyclic skeleton **140** in 32% yield. When this compound was subjected to hydrolysis conditions, deprotection was achieved but the subsequent amide coupling did not take place. Unfortunately, this synthetic route had issues in scaling up due to sensitivity of the cyclic siloxanes towards silica gel column chromatography and longer reaction times. A new synthetic route was needed to make large amounts of material to test amide coupling conditions.



Scheme 5.0. Synthesis of C1-20 acyclic skeleton **140** *via* cyclic siloxane **114**.

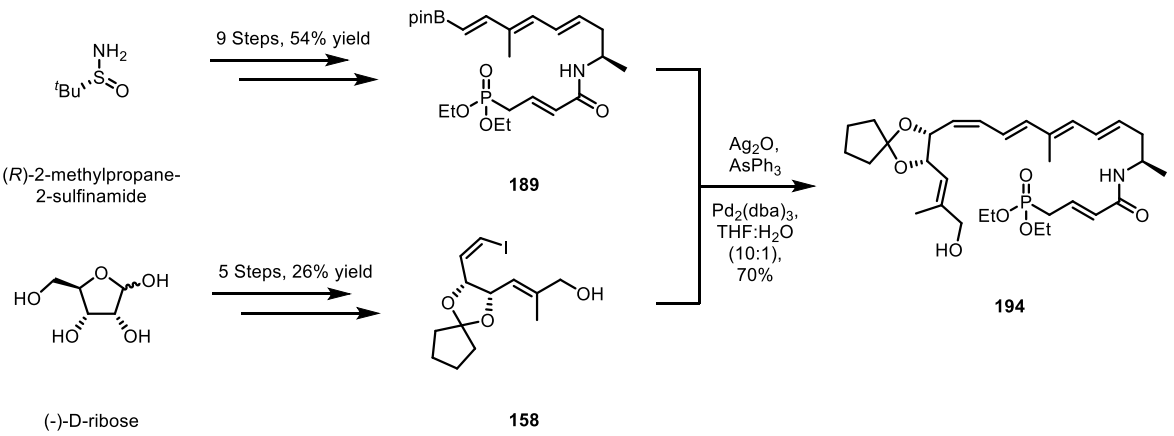
The C11-C12 disconnection was altered from using a Hiyama cross-coupling to a Suzuki cross-coupling, and, as such, the fragments were synthesised. As shown in Scheme 5,2, C1-C11 (*Z*)-vinyl iodide **161** was constructed in 7 steps with a 10% overall yield, and the C12-C20 boronic ester **170** was synthesised in 9 steps with a 46% overall yield. These fragments were Suzuki cross-coupled to generate the C1-C20 cyclopentylidene acetal **171** in 72% yield. The ester and amide in this acyclic skeleton were hydrolysed, but when subjected to amide coupling conditions, unfortunately no product was observed. The cyclopentylidene protecting group was changed to silyl ethers − TES and TBS – and still, no product could be detected. This led to thinking the amide coupling should occur prior to the cyclisation, and the macrocyclisation proceed *via* an HWE olefination.



Scheme 5.1. Synthesis of C1-20 acyclic skeleton **171** *via* trienoate **161**.

Fortunately, the macrocyclisation using the HWE strategy did not require design of a new synthetic route; all that was necessary was to reorder a few key steps. The synthesis of C1-C4/C12-C20 boronic ester **189**, as shown in Scheme 5.2, was achieved in 9 steps with a 54% overall yield, and the C5-C11 (*Z*)-vinyl iodide in 26% overall yield. These fragments were Suzuki cross-coupled in 70% yield to form the C1-C4 / C5-C20 allylic alcohol **194**, which was oxidised to the aldehyde. The HWE macrocyclisation was attempted, but only

trace product was observed by HRMS. The cyclopentylidene acetal was changed to TES ethers, and still, only trace cyclised product was observed by mass spectrometry.



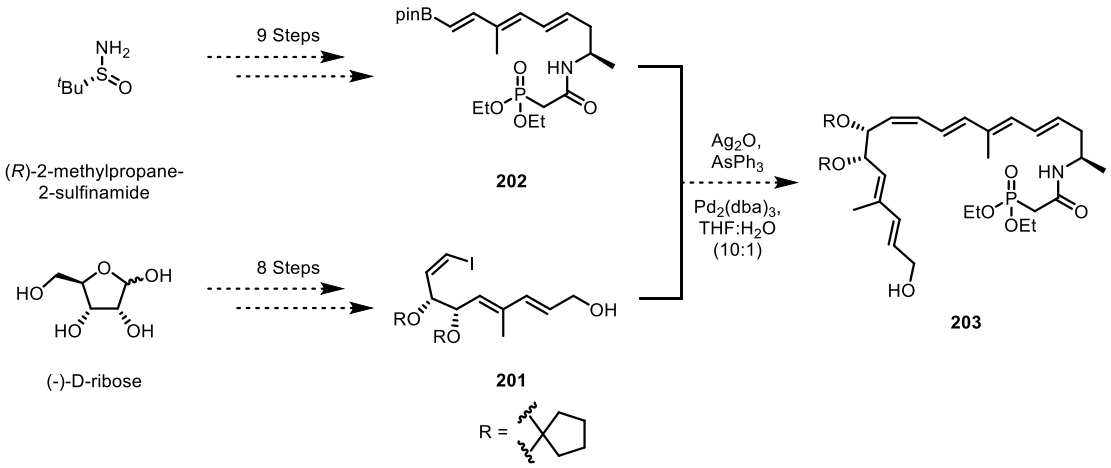
Scheme 5.2. Synthesis of allylic phosphonate **194** *via* iodoalcohol **158**.

The acyclic heronamide core was made in the longest linear sequence of 10 steps with an overall yield of 38% and requires just two more steps – HWE cyclisation and HF deprotection – for completion. This is in comparison to a longest linear sequence of 24 steps with a 0.1% overall yield of the previously synthesised heronamide C from Kanoh and co-workers. If this route can be optimised and successfully cyclised, the late-stage side chain variation will add three more steps to the longest linear sequence but will enable significant diversity in this biologically-important region of the molecule.

5.2 Future work

The synthetic route with the most promise lies in the construction of fragments C1-C4 / C12-C20 boronic ester **189** and C5-C11 (*Z*)-vinyl iodide **158** with ring-closing *via* an HWE olefination, as shown in Scheme 5.2; however, there have been issues in the cyclisation and a small alteration can potentially make the cyclisation proceed. Scheme 5.3 illustrates the cyclisation using C3-C11 (*Z*)-vinyl iododiene **201** and C1-C2/C12-C20 phosphonate vinylboronic ester **202** to hopefully allow more flexibility for the right

conformation to proceed with ease. If needed, this can also allow using the LiCl/DBU Masamune-Roush conditions or the $Ba(OH)_2$ Paterson conditions.[138-139]



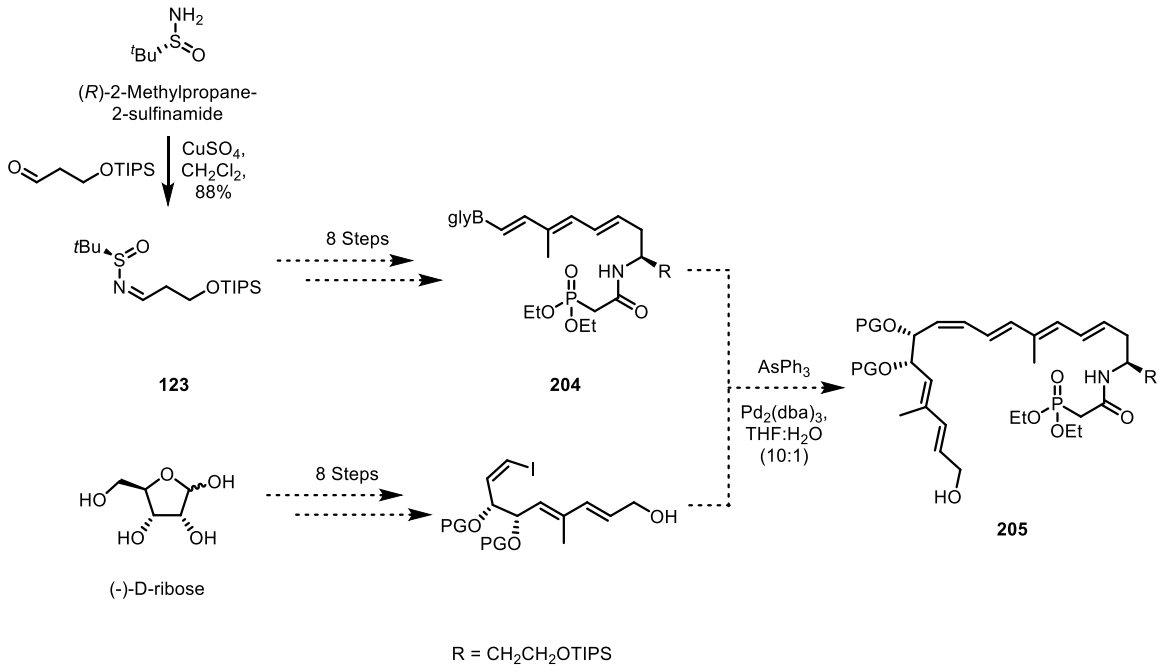
Scheme 5.3. Synthesis of C1-C2, C3-C20 phosphonate **203** *via* iododiene **201**.

If the cyclisation does not proceed with the cyclopentylidene acetal intact, then a modification to silyl ethers is swiftly accessible. The Suzuki cross-coupling with the silyl ethers will need a small adjustment to the reaction conditions to ensure a higher yield. Previously, when using our Suzuki cross-coupling conditions with the bases Ag_2O or Ag_2CO_3 while having a TES ether, it was shown that the silyl ethers were too labile and could not survive. C1-C2/C12-C20 boronic ester **202** can be hydrolysed prior to coupling, as this would remove the necessity of the base in the conditions.

An alternative would be to modify the Takai pinacol boronic ester reagent. Instead of refluxing the boronic acid with pinacol, a switch to ethylene glycol will make the glycol boronic ester and homologating with the modified Takai conditions will make the vinyl glycol boronic ester.[78] The benefit of a glycol ester in comparison to a pinacol ester was shown by Denmark and co-workers in their elucidation of the role of boronic esters in the Suzuki cross-coupling.[97] As shown in Scheme 5.4, the palladium-boron complex is able to

be formed without needing to hydrolyse the glycol boronic ester. This would remove the necessity of a stoichiometric amount of base and can be investigated quickly.

Once the cyclisation has been established, applying this methodology in combination with Part II student Alistair Sterling's findings (Scheme 2.21) will enable manipulation of the side chain at a late stage. Sulfinamine **123** is made in high yields and a *dr* >20:1 with a TIPS protected alcohol that is primed for functionalisation. The glycol boronic ester will be used in the modified Takai olefination to make glycolboronic ester **204**. Once successfully Suzuki cross-coupled and cyclised, an oxidation to remove the TIPS to make the aldehyde will allow different groups to be attached, and the biological aspects of the project to be further studied.



Scheme 5.4. Synthesis of C1-C2, C3-C20 phosphonate **205** for side chain manipulation.

6. Experimental

6.1 General Experimental

Reactions: Unless otherwise stated, all reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen.

Solvents and reagents: Solvents and commercially available reagents were dried and purified before use where appropriate using standard procedures. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), methanol (MeOH), acetonitrile (MeCN), toluene (PhMe), diisopropylamine (DIPA) were obtained dry and oxygen free from solvent dispenser units having passed through an activated alumina column under nitrogen., Unless otherwise noted, petroleum ether refers to the fraction of light petroleum ether boiling at 40-60 °C.

Chromatography: Thin layer chromatography was performed using Merck DC Kieselgel 60 F254 plates and visualised by either UV fluorescence (λ 254 nm) or stained and heated using vanillin, phosphomolybdic acid (PMA) or potassium permanganate. Flash column chromatography was carried out on Macherey-Nagel Kieselgel 60M (230-400 mesh) under positive pressure.

Optical rotation: Optical rotations were recorded on a Perkin-Elmer 241 or 341 polarimeter with a 1 dm path length cell (using the sodium D line, 589 nm). Specific rotations ($[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$) are given in deg dm^2g^{-1}. Concentration (*c*) is reported in g/100 mL.

Enantiomeric excess: Enantiomeric excess (*ee*) was determined by HPLC on an Agilent 1200 series running in normal phase under UV (210-254 nm) detection using a ZORBAX RX-SIL (150 mm × 4.6 mm ID) as the analytical column. Chiral analysis was carried out on a DAICEL CHIRALPAK®-IA or IB (250 mm × 4.6 mm ID).

Infrared spectra: Infrared spectra were recorded on a Bruker Tensor 27 Fourier FT-IR spectrometer, and the samples were prepared as a thin film on a diamond/ZnSe PIKE

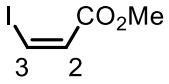
Miracle ATR module. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}). Only selected, characteristic IR absorption data are reported for each compound.

NMR spectra: Proton (^{1}H), carbon (^{13}C), and fluorine (^{19}F) spectra were recorded on a Bruker DPX200 (200/50 MHz), Bruker AVIII400 (400/100 MHz), or a Bruker AVIII500 (500/125 MHz). Chemical shifts (δ_H, δ_C, and δ_F) are reported in parts per million (ppm), referenced to the residual peak stated ($CDCl_3$ (δ = 7.26/77.2), C_6D_6 (δ = 7.16/128.1), THF-d_8 (δ = 1.72/67.2) with signal splitting recorded as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sex), septet (sept) and multiplet (m). Coupling constants (*J*) are reported to the nearest 0.5 Hz.

Mass spectra: High resolution mass spectra (HRMS) were recorded by the Departmental Mass Spectrometry Service, University of Oxford using a Bruker Daltonics microTOF spectrometer (resolution = 5000 FWHM). High resolution values are calculated to 4 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm.

6.2 Experimental procedures

Methyl (*Z*)-3-iodoacrylate, 206

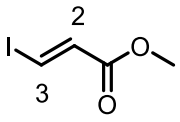


To a solution of methyl propiolate (5.30 mL, 60.0 mmol, 1.0 equiv.) in acetic acid (20 mL) was added sodium iodide (18.0 g, 120 mmol, 2.0 equiv.) and the mixture was stirred at 70 °C for 16 hrs. The solution was cooled to room temperature, diluted with Et_2O (45 mL), and aqueous 1 N NaOH (150 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo* to afford **206** as a dark brown liquid (12.7 g, 60.0 mmol, quant. yield).[31]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47 (1H, d, J = 9.0 Hz, 3-*H*), 6.91 (1H, d, J = 9.0 Hz, 2-*H*), 3.78 (3H, S, OC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.0, 129.5, 95.2, 51.7; **HRMS** (ESI^+) calc. for $C_4H_6O_2I$ ($[M+H]^+$): 212.9407; found 212.9409.

All physical and spectroscopic data are in accordance with data reported by Piers *et al*.[140]

Methyl (*E*)-3-iodoacrylate, 62



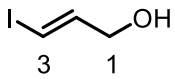
To a solution of iodide **206** (8.4 g, 40 mmol, 1.00 equiv.) in PhMe (14 mL) was added HI (1.1 mL, 55 wt. % in H_2O, 4.8 mmol, 0.12 equiv.) and the solution was stirred at 80 °C for 16 hrs. The reaction mixture was cooled to room temperature and diluted with

Et_2O (25 mL) and H_2O (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ (100 mL), sat. aqueous $Na_2S_2O_3$ (100 mL) and then brine (20 mL). The organic layer was dried over $MgSO_4$ and then concentrated *in vacuo* to afford **62** as pale yellow crystals (4.7 g, 22 mmol, 56% yield).[31]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.83 (1H, d, J = 15.0 Hz, 3-*H*), 6.82 (1H, d, J = 15.0 Hz, 2-*H*), 3.70 (3H, s, OC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 164.8, 136.2, 99.8, 52.1; **HRMS** (ESI^+) calc. for $C_4H_6IO_2$ ($[M+H]^+$): 212.9407; found: 212.9413.

All physical and spectroscopic data are in accordance with data reported by Garrais *et al*.[31]

(*E*)-3-iodoprop-2-en-1-ol, 64

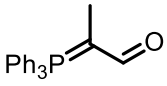


To a solution of $LiAlH_4$ (25 mL, 4 M in Et_2O, 100 mmol, 1.3 equiv.) in Et_2O (120 mL) cooled to −78 °C was added a solution of ester **62** (16 g, 77 mmol, 1.0 equiv.) in Et_2O (15 mL) dropwise. The completion of the reaction was monitored by TLC. After 2 hrs, the reaction mixture was warmed to at 0 °C and quenched with a slow addition of H_2O (3.8 mL) and aqueous NaOH (15 wt. %, 3.8 mL). When bubbling ceased, H_2O (11.4 mL) was added to finish quenching the reaction mixture and the solution was stirred for 15 min at room temperature. $MgSO_4$ was added and stirred for another 15 min. The resulting suspension was filtered through Celite® and concentrated *in vacuo*. Purification by distillation (90 °C, 11 mbar) afforded **64** (8.7 g, 50 mmol, 65% yield) as a clear liquid.[141]

***R*$_f$** 0.46 (petroleum ether:EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.70 (1H, dt, *J* = 14.5, 5.5 Hz, 2-*H*), 6.40 (1H, dt, *J* = 14.5, 1.5 Hz, 3-*H*), 4.10 (2H, td, *J* = 5.5, 1.5 Hz, 1-H_2), 1.72 – 1.57 (1H, broad s, O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 144.8, 76.8, 65.3.

All spectroscopic data are in accordance with data reported by Rossi *et al*.[141]

2-(Triphenylphosphaneylidene)propanal, **70**



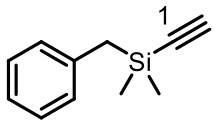
To a solution of sodium hydride (3.30 g, 60 % in mineral oil, 82.4 mmol, 3.0 equiv.) in THF (80 mL) cooled to 0 °C was added ethyltriphenylphosphonium bromide (10.2 g, 27.5 mmol, 1.0 equiv.) and the reaction mixture was brought to room temperature. After stirring for 16 hrs, the solution was cooled to 0 °C and ethyl formate (5.56 mL, 68.8 mmol, 2.5 equiv.) was added dropwise. The mixture was stirred for 2 hrs at 0 °C and then brought to room temperature to stir for 2 hrs. It was quenched by a slow addition of HCl (30 mL, 1 M) at 0 °C, and then brought to room temperature. The mixture was adjusted to pH 8 (indicated by pH indicator paper) using aqueous NaOH (6 M), and the resulting solution was diluted with CH_2Cl_2 (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (2 × 100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by dissolving in minimal CH_2Cl_2 and followed by precipitating ylide **70** (5.7 g, 17.9 mmol, 65%), using Et_2O, as a white solid.

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^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.81 (1H, d, *J* = 6.5 Hz, C*H*O), 7.72 – 7.65 (3H, m, Ar*H*), 7.63 – 7.51 (12H, m, Ar*H*), 1.87 (3H, d, *J* = 13.5 Hz, CH_3).

All spectroscopic data are in accordance with data reported by Hena and Kiyooka.[142]

Benzyl(ethynyl)dimethylsilane, **61**



A solution of benzylmagnesium chloride was prepared from slow addition of benzyl chloride (16.0 mL in a dropping funnel, 139 mmol, 1.00 equiv.) and Et_2O (100 mL in a different dropping funnel) to an excess of magnesium turnings (4.74 g, 195 mmol, 1.40 equiv.) in Et_2O (20 mL). The reaction mixture was stirred at reflux for 2 hrs. After cooling to room temperature, the Grignard solution was added dropwise to dimethyldichlorosilane (24.0 mL, 199 mmol, 1.43 equiv.) in Et_2O (20 mL). The resulting mixture was stirred at reflux for 2 hrs then at room temperature for 16 hrs. The solvent and excess of dimethyldichlorosilane were removed *in vacuo*. The residue was dissolved in anhydrous Et_2O, filtered under N_2 atmosphere and the salt was washed with anhydrous Et_2O. The filtrate was concentrated *in vacuo* to afford 21.0 g of crude benzylchlorodimethylsilane that was used without further purification.[58]

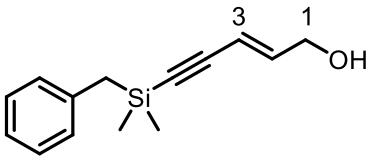
To a solution of crude benzylchlorodimethylsilane (21.6 g, 117 mmol, 1.0 equiv.) in THF (240 mL) at 0 °C was added a solution of ethynylmagnesium bromide (304 mL, 0.5 M in THF, 152 mmol, 1.3 equiv.) over 45 min. The reaction mixture was warmed to room temperature, stirred for 16 hrs, cooled to 0°C, quenched with sat. aqueous NH_4Cl (50 mL) and diluted with Et_2O (200 mL) and water (200 mL). The aqueous layer was extracted twice with Et_2O (100 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography

(Et_2O:petroleum ether, 1:25) afforded **61** (15.5 g, 88.9 mmol, 64% yield over 2 steps,) as a pale yellow oil.[57]

R_f 0.65 (petroleum ether:Et_2O, 96:4); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 – 7.20 (2H, m, Ar*H*), 7.14 – 7.01 (3H, m, Ar*H*), 2.42 (1H, s, 2-*H*), 2.23 (2H, s, SiCH_2Ar), 0.16 (6H, s, ArCH$_2$Si(*CH*$_3$)$_2$C≡CH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.7, 128.5, 128.4, 124.6, 94.5, 88.7, 26.0, -2.2.

All spectroscopic data are in accordance with data reported by Trost *et al.*[57]

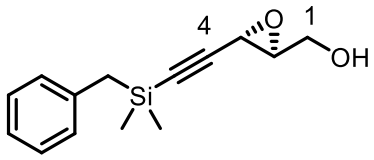
(*E*)-5-(Benzyldimethylsilyl)pent-2-en-4-yn-1-ol, 65



To a degassed (N_2 bubbling, 15 min) solution of iodide **64** (2.17 g, 11.8 mmol, 1.0 equiv.) and alkyne **61** (2.06 g, 11.8 mmol, 1.0 equiv.) in THF (45 mL) was added copper iodide (225 mg, 1.18 mmol, 0.10 equiv.) and *bis*(triphenylphosphine)palladium dichloride (83.0 mg, 0.118 mmol, 1.0 mol%). The mixture was further degassed (N_2 bubbling, 15 min) and diisopropylamine (13.3 mL, 94.4 mmol, 8.0 equiv.) was added dropwise. The resulting mixture was sonicated for 1 hr and left to stir for 16 hrs. The reaction mixture was quenched with sat. aqueous NH_4Cl (40 mL) and diluted with CH_2Cl_2 (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 9:1 to 8:2) afforded enyne **65** (2.12 g, 9.21 mmol, 78% yield) as a brown viscous oil.

***R*$_f$** 0.36 (petroleum ether:EtOAc, 8:2); **IR ν_{max}** (thin film) /cm^{-1} 3339, 1494, 1251; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.23 (2H, m, Ar*H*), 7.14 – 6.99 (3H, m, Ar*H*), 6.31 (1H, dt, *J* = 16.0, 5.0 Hz, 3-*H*), 5.78 (1H, dt, *J* = 16.0, 2.0 Hz, 2-*H*), 4.22 (2H, td, *J* = 5.5, 2.0 Hz, 1-*H*), 2.23 (2H, s, SiCH_2Ar), 1.49 (1H, t, *J* = 5.5 Hz, O*H*), 0.15 (6H, s, ArCH_2Si(CH_3)$_2$C≡CH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 143.4, 139.0, 128.5, 128.3, 124.5, 110.3, 104.4, 93.8, 63.0, 26.3, -2.0; **HRMS** (ESI$^+$) calc. for $C_{14}H_{19}OSi$ ([M+H]$^+$): 231.1205; found 231.1232.

((2*S*,3*S*)-3-((Benzyldimethylsilyl)ethynyl)oxiran-2-yl)methanol, 66



Asymmetric Procedure: 4 Å molecular sieves were added to a round-bottom flask and activated by heating under vacuum. The flask was allowed to reach room temperature, charged with N_2 and CH_2Cl_2 (100 mL) was added. The reactor was then cooled to −30 °C and titanium tetraisopropoxide (4.7 mL, 16 mmol, 0.5 equiv.) was added while stirring. The solution was allowed to stir for 20 min at −30 °C, and L-(+)-diethyltartrate (3.2 mL, 19. mmol, 0.6 equiv.) was added dropwise at −30 °C. After stirring for 30 min, enyne **65** (7.1 g, 31 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) was added dropwise. The resulting solution was stirred for 50 min at −30 °C, and *tert*-butyl hydroperoxide (21 mL, 5.5 M solution in decane over 4 Å molecular sieves, 115 mmol, 3.7 equiv.) was added dropwise. After stirring at −30 °C for 5 days, the resulting solution was diluted with EtOAc (5 mL) and sat. aqueous Na_2SO_4 (16 mL, 1 mL per mmol of titanium tetraisopropoxide) was added. The resulting biphasic mixture was stirred at room temperature for 4 hrs and filtered through Celite®. The Celite® was washed several times with EtOAc. The solid residue was then transferred to a round-bottom flask, refluxed for 15 min in EtOAc (50 mL) and filtered over Celite®. The combined

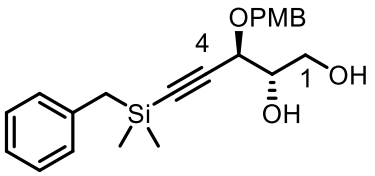
filtrates were concentrated *in vacuo*. Purification by column chromatography (SiO_2, petroleum ether:Et_2O, 9:1) afforded epoxide **66** (4.9 g, 20 mmol, 65% yield) as a yellow oil.

$[\alpha]_D^{25}$ +30.3 (c 0.617, $CHCl_3$) ; Enantiomeric excess was determined by **HPLC**: 88% ee (CHIRALPAK® 1A, 1.3 mL / min, 2.5% IPA / hexanes), Rt: (*S*) 10.111, Rt: (*R*) 10.735.

Non-Asymmetric Procedure: To a solution of enyne **65** (67 mg, 0.29 mmol, 1.0 equiv.) stirred in CH_2Cl_2 (0.6 mL) at 0 °C was added m-CPBA (100 mg, washed with pH 7.5 potassium phosphate buffer and recrystallised after concentration under N_2, 0.59 mmol, 2.0 equiv.). After stirring for 2 h, the solution was diluted with CH_2Cl_2 (3 mL), allowed to warm to room temperature and sat. aqueous $NaHCO_3$ (5 mL) cooled to 0 °C was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with $NaSO_4$ and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 3:1) afforded epoxide (±)-**104** (51 mg, 0.21 mmol, 71% yield).

R_f 0.45 (petroleum ether / EtOAc, 7:3); **IR ν_{max}** (thin film) /cm^{-1} 3425, 1057; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.23 (2H, m, Ar*H*), 7.13 – 7.03 (3H, m, Ar*H*), 3.96 (1H, ddd, *J* = 13.0, 5.0, 2.0 Hz, 1-$H_A$$H_B$), 3.72 (1H, ddd, *J* = 13.0, 8.0, 3.0 Hz, 1-$H_A$$H_B$), 3.45 (1H, d, *J* = 2.0 Hz, 3-*H*), 3.32 (1H, dt, *J* = 3.0, 2.0 Hz, 2-*H*), 2.21 (2H, s, SiCH_2Ar), 1.57 (1H, broad s, *OH*), 0.14 (6H, s, $ArCH_2Si(CH_3)_2C{\equiv}CH$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.6, 128.5, 128.4, 124.6, 102.4, 88.8, 60.2, 60.2, 42.8, 26.0, -2.3; **HRMS** (ESI^+) calc. for $C_{14}H_{19}O_2Si$ ($[M+H]^+$): 247.1154; found 247.1191

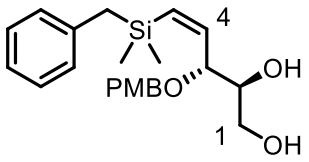
(2*S*,3*R*)-5-(Benzyldimethylsilyl)-3-((4-methoxybenzyl)oxy)pent-4-yne-1,2-diol, 67



To a solution of epoxide **66** (580 mg, 2.4 mmol, 1.0 equiv.) in toluene (2.3 mL) was added europium (III) trfluoromethanesulfonate (260 mg, 0.43 mmol, 0.18 equiv.) and 2,6-di-*tert*-butyl-4-methylpyridine (88 mg, 0.43 mmol, 0.18 equiv.) . The resulting mixture was heated to 40 °C under inert atmosphere. PMBOH (0.79 mL, 6.4 mmol, 2.7 equiv.) was added the solution was stirred for 4 days at 40 °C. Concentration *in vacuo* and purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 9:1 to 4:1 to elute PMBOH first, then 3:1) afforded **67** (750 mg, 2.0 mmol, 89% yield) as a yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −96.7 (c 1.06 $CHCl_3$); ***Rf*** 0.53 (petroleum ether / EtOAc, 1:1); **IR ν_{max}** (thin film) /cm^{-1} 3340, 2380, 1720, 1250; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.31 – 7.26 (2H, m, OCH_2 Ar*H*), 7.24 (2H, m, OCH_2 Ar*H*), 7.17 – 7.09 (3H, m, $SiCH_2$ Ar*H*), 6.94 – 6.88 (2H, m, $SiCH_2$ Ar*H*), 4.75 (1H, d, *J* = 11.0 Hz, O*CH*$_2$Ar), 4.43 (1H, d, *J* = 11.0 Hz, O*CH*$_2$Ar), 4.24 (1H, d, *J* = 4.5 Hz, 3-*H*), 3.92 – 3.85 (1H, m, 2-*H*), 3.84 (3H, s, ArO*CH*$_3$), 3.81 – 3.67 (2H, m, 1-*H*), 2.60 (1H, d, *J* = 7.0 Hz, 2-O*H*), 2.26 (2H, s, SiC*H*$_2$Ar), 0.22 (6H, s, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.6, 138.8, 130.0, 129.2, 128.4, 128.4, 124.7, 114.0, 102.7, 92.4, 72.8, 71.6, 71.1, 63.2, 55.4, 26.2, -1.9; **HRMS** (ESI^+) calc. for $C_{22}H_{28}O_4SiNa$ ($[M+Na]^+$): 407.1655; found 407.1640.

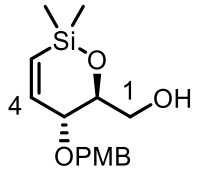
(*Z*)-5-(Benzyldimethylsilyl)-3-((4-methoxybenzyl)oxy)pent-4-ene-1,2-diol, 68



To a flame-dried round-bottom flask containing Pd/$CaCO_3$ (61 mg, 5 wt. % on $CaCO_3$, 0.03 mmol, 5.0 mol%) was evacuated and backfilled with N_2, then toluene (6.1 mL) was added. The flask was evacuated and backfilled with H_2 three times. A solution of diol **67** (230 mg, 0.58 mmol, 1.0 equiv.) and quinoline (34 µL, 0.29 mmol, 0.5 equiv.) in cyclohexene (0.61 mL) was added to the stirring mixture. The hydrogenation was monitored by TLC and after 10 min the reaction mixture was filtered through Celite® and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (SiO_2, petroleum ether:EtOAc, 4:1) afforded **68** (150 mg, 0.37 mmol, 64% yield) as a yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +2.04 (c 0.167, $CHCl_3$); $\boldsymbol{Rf}$ 0.54 (petroleum ether / EtOAc, 1:1); **IR ν_{max}** (thin film) /cm^{-1} 3415, 1248, 1036; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24 – 7.16 (4H, m, $SiCH_2$ Ar*H*), 7.11 – 7.05 (1H, m, $SiCH_2$ Ar*H*), 7.03 – 6.98 (2H, m, OCH_2 Ar*H*), 6.90 – 6.84 (2H, m, OCH_2 Ar*H*), 6.28 (1H, dd, *J* = 14.5, 9.5 Hz, 4-*H*), 5.96 (1H, d, *J* = 14.5, 1.0 Hz, 5-*H*), 4.48 (1H, d, *J* = 11.0 Hz, OCH_2Ar), 4.20 (1H, d, *J* = 11.0 Hz, OCH_2Ar), 4.09 (1H, ddd, *J* = 9.5, 5.0, 1.0 Hz, 3-*H*), 3.80 (3H, s, ArOCH_3), 3.75 (1H, m, 1-*H*), 3.66 (1H, m, 1-*H*), 3.49 (1H, dtd, *J*=6.5, 5.0, 4.0 Hz, 2-*H*), 2.36 (1H, dd, *J* = 6.5, 2.5 Hz, 2-O*H*), 2.16 (2H, d, *J* = 1.0 Hz, SiCH_2Ar), 1.62 – 1.56 (1H, m, 1-O*H*), 0.13 (3H, s, Si(CH_3)$_2$), 0.10 (3H, s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.5, 146.0, 139.5, 135.1, 130.0, 129.4, 128.4, 128.4, 124.5, 114.3, 80.9, 73.2, 70.6, 63.3, 55.4, 26.7, -1.3, -1.4; **HRMS** (ESI^+) calc. for $C_{22}H_{30}O_4SiNa$ ($[M+Na]^+$): 409.1806; found 409.1811.

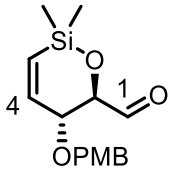
((5*R*,6*S*)-5-((4-Methoxybenzyl)oxy)-2,2-dimethyl-5,6-dihydro-2*H*-1,2-oxasilin-6-yl)methanol, **59**



To a round-bottom flask containing crude alkene **68** (0.53 mmol, 1.00 equiv.) in THF (1.06 mL) was added TBAF·3H_2O (0.66 mL, 1 M in THF, 0.66 mmol, 1.25 equiv.). After stirring for 3 hrs, the solution was diluted with CH_2Cl_2 (3 mL) and washed with aqueous HCl (1 N, 3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 3:2) afforded cyclic siloxane **59** (100 mg, 0.34 mmol, 64% yield) as a pale-yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −108 (c 1.05, $CHCl_3$); ***Rf*** 0.58 (petroleum ether / EtOAc, 3:2); **IR ν_{max}** (thin film) /cm^{-1} 1729, 1251; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 (2H, m, Ar*H*), 6.92 – 6.85 (2H, m, Ar*H*), 6.80 (1H, dd, *J* = 14.5, 2.0 Hz, 4-*H*), 5.84 (1H, dd, *J* = 14.5, 2.0 Hz, 5-*H*), 4.62 (1H, d, *J* = 11.0 Hz, OCH_2Ar), 4.50 (1H, d, *J* = 11.0 Hz, OCH_2Ar), 4.00 (1H, dt, *J* = 9.0, 2.0 Hz, 3-*H*), 3.84 – 3.81 (1H, m, 1-*H*), 3.80 (3H, s, ArOCH_3), 3.79 – 3.75 (1H, m, 1-*H*), 3.73 – 3.63 (1H, m, 2-*H*), 2.17 (1H, dd, *J* = 7.5, 5.0 Hz, 1-O*H*), 0.20 (3H, s, Si(CH_3)$_2$), 0.18 (3H, s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.5, 149.4, 130.0, 129.8, 127.3, 114.0, 74.9, 74.5, 71.6, 64.3, 55.4, -0.5, -0.8; **HRMS** (ESI^-) calc. for $C_{15}H_{21}O_4Si$ ($[M-H]^-$): 293.1204; found 294.1205.

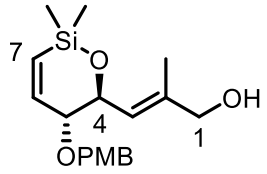
(5*R*,6*R*)-5-((4-Methoxybenzyl)oxy)-2,2-dimethyl-5,6-dihydro-2*H*-1,2-oxasiline-6-carbaldehyde, 69



To a solution of $SO_3 \cdot py$ (150 mg, 0.95 mmol, 3.5 equiv.) in CH_2Cl_2 (1 mL) at 0 °C was added DMSO (0.26 mL, 3.7 mmol, 13.6 equiv.) dropwise. After stirring for 30 min at 0 °C, a solution of alcohol **59** (80. mg, 0.27 mmol, 1.0 equiv.) and DIPEA (0.29 mL, 1.4 mmol, 5.0 equiv.) in CH_2Cl_2 (0.36 mL) was added dropwise. After stirring at 0 °C for 30 min, the solution was added poured into aqueous HCl (1 N, 5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with H_2O (20 mL) and brine (2 × 75 mL) then dried over Na_2SO_4 and concentrated *in vacuo* to afford aldehyde **69** as a yellow oil. Aldehyde **69** was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.70 (1H, d, *J* = 1.0 Hz, 1-*H*), 7.27 (1H, m, Ar*H*), 7.23 (1H, m, Ar*H*), 6.92 – 6.84 (2H, m, Ar*H*), 6.79 (1H, dd, *J* = 14.5, 3.0 Hz, 4-*H*), 5.96 (1H, dd, *J*=14.5, 1.5 Hz, 5-*H*), 4.61 (1H, d, *J* = 11.0 Hz, OC*H*$_2$Ar), 4.51 (1H, d, *J* = 11.0 Hz, OC*H*$_2$Ar), 4.36 (1H, dd, *J* = 7.5, 1.0 Hz, 2-*H*), 4.14 (1H, ddd, *J* = 7.5, 3.0, 1.5 Hz, 3-*H*), 3.80 (3H, s, ArOC*H*$_3$), 0.25 (3H, s, Si((C*H*$_3$)$_2$), 0.25 (3H, s, Si((C*H*$_3$)$_2$); **HRMS** (ESI^+) calc. for $C_{15}H_{20}O_4Si$ ($[M+Na]^+$): 315.1023; found 315.1021.

(*E*)-3-((5*R*,6*S*)-5-((4-Methoxybenzyl)oxy)-2,2-dimethyl-5,6-dihydro-2*H*-1,2-oxasilin-6-yl)-2-methylprop-2-en-1-ol, **72**



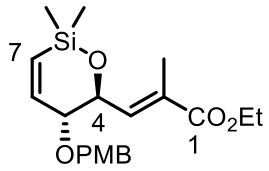
To a solution of crude aldehyde **69** (1.7 mmol, 1.00 equiv.), in toluene (11.7 mL) was added 2-(triphenyl-l5-phosphanylidene)propanal (720 mg, 2.3 mmol, 1.35 equiv.). After stirring at 80 °C for 16 hrs, the reaction was concentrated *in vacuo* and dissolved in minimal amount of Et_2O. Triphenylphosphine oxide was triturated with pentane and the mixture was filtered. This process was repeated and the resulting solution concentrated. The crude aldehyde was used in the next step without further purification.

To a solution of crude aldehyde (347 mg, 1.04 mmol, 1.00 equiv.) in methanol (10 mL) at 0 °C was added sodium borohydride (39.0 mg, 1.04 mmol, 1.00 equiv.) portion wise. After stirring for 50 min, H_2O (5 mL) and Et_2O (10 mL) were added and the solution was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 3:2) afforded **72** (210 mg, 0.629 mmol, 37% yield over 3 steps) as a yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −40.4 (c 0.417, $CHCl_3$); ***Rf*** 0.13 (petroleum ether/EtOAc, 3:2); **IR ν_{max}** (thin film) /cm^{-1} 3387, 2994, 2956, 1612, 1035, 846; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 – 7.19 (2H, m, Ar*H*), 6.90 – 6.84 (2H, m, Ar*H*), 6.81 – 6.73 (1H, m, 6-*H*), 5.91 – 5.85 (1H, m, 7-*H*), 5.49 (1H, dd, *J* = 8.5, 2.0, 3-*H*), 4.62 – 4.56 (1H, m, 5-*H*), 4.55 (1H, d, *J* = 11.5 Hz, OCH_2Ar),

4.48 (1H, d, *J* = 11.5 Hz, OC*H*$_2$Ar), 4.03 (2H, s, 1-*H*), 3.84 (1H, dt, *J* = 8.5, 2.0 Hz, 4-*H*), 3.79 (3H, s, ArOC*H*$_3$), 1.73 (3H, s, 2-C*H*$_3$), 0.23 (3H, *s*, Si(C*H*$_3$)$_2$) 0.18 (3H, *s*, Si(C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.4, 149.5, 140.1, 130.3, 129.8, 128.1, 125.2, 113.8, 71.9, 70.9, 68.2, 65.1, 55.4, 14.5, -0.4, -0.8; **HRMS** (ESI^+) calc. for $C_{18}H_{26}O_4SiNa$ ($[M+Na]^+$): 357.1493; found 357.1494.

Ethyl (*E*)-3-((5*R*,6*S*)-5-((4-methoxybenzyl)oxy)-2,2-dimethyl-5,6-dihydro-2*H*-1,2-oxasilin-6-yl)-2-methylacrylate, 77

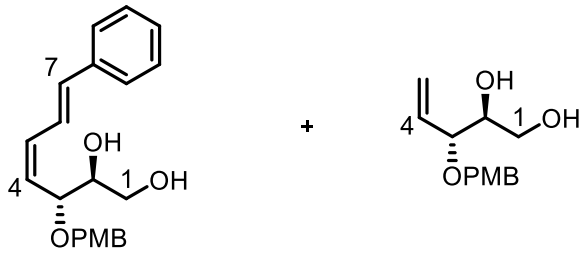


To a solution of crude aldehyde **69** (0.34 mmol, 1.0 equiv.), in toluene (3.4 mL) was added 2-(triphenyl-I5-phosphanylidene)propanal (160 g, 0.34 mmol, 1.0 equiv.). After stirring at 80 °C for 2 hrs, the reaction mixture was concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:Et_2O, 4:1) afforded α,β-unsaturated ester **77** (90 mg, 0.24 mmol, 70% yield over 2 steps) as a pale oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −71.1 (c 1.33, $CHCl_3$); ***Rf*** 0.27 (petroleum ether:Et_2O, 9:1); **IR ν_{max}** (thin film) /cm^{-1} 1711, 1658, 1250, 1175, 1128; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.20 (2H, d, *J* = 8.0 Hz, Ar*H*), 6.87 – 6.81 (2H, m, Ar*H*), 6.78 (1H, dd, *J* = 14.5, 2.0 Hz, 6-*H*), 6.68 (1H, dd, *J* = 8.5, 2.0 Hz, 3-*H*), 5.90 (1H, dd, *J* = 14.5, 2.0 Hz, 7-*H*), 4.60 (1H, t, *J* = 8.5 Hz, 5-*H*), 4.54 (1H, d, *J* = 11.0 Hz, OC*H*$_2$Ar), 4.46 (1H, d, *J* = 11.0 Hz, OC*H*$_2$Ar), 4.32 – 4.16 (2H, m, $CO_2CH_2CH_3$), 3.89 (1H, dt, *J* = 8.5, 2.0 Hz, 4-*H*), 3.80 (3H, d, *J* = 1.5 Hz, ArOC*H*$_3$), 1.91 (3H, s, 1-C*H*$_3$), 1.31 (3H, td, *J* = 7.0, 1.5 Hz, $CO_2CH_2CH_3$), 0.24 (3H, s, Si((C*H*$_3$)$_2$), 0.19

(3H, s, Si((C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 168.0, 159.4, 149.1, 140.0, 131.4, 129.9, 129.8, 128.2, 113.9, 71.9, 71.2, 60.8, 55.4, 14.4, 13.5, -0.4, -0.8; **HRMS** (ESI^+) calc. for $C_{20}H_{28}O_5SiNa$ ($[M+Na]^+$): 399.1598; found 399.1599.

(2*S*,3*R*,4*Z*,6*E*)-3-((4-Methoxybenzyl)oxy)-7-phenylhepta-4,6-diene-1,2-diol, **78**



78 **78'**

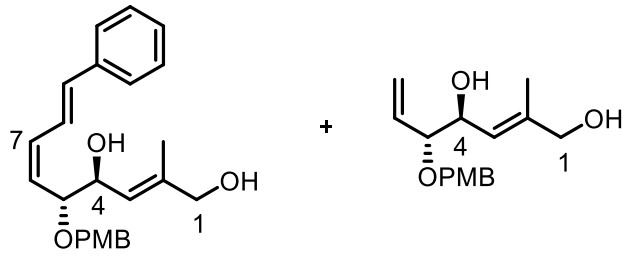
To a vial containing cyclic siloxane **59** (20 mg, 68 μmol, 1.0 equiv.), β-bromostyrene (10 μL, 82 μmol, 1.2 equiv.), and allylpalladium(II) chloride dimer (1.2 mg, 3.4 μmol, 5.0 mol%) under N_2 atmosphere was added TBAF·3H_2O (0.21 mL, 1 M in THF, 0.21 mmol, 3.0 equiv.). After stirring for 8 hrs in the dark, the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2, petroleum ether:EtOAc, 1:1) afforded diols **78** and **78'** (16 mg, 49 μmol, 72% yield) in a 7:1 ratio as a yellow oil.

78: ***Rf*** 0.12 (petroleum ether:EtOAc, 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.44 – 7.37 (2H, m, Ar*H*), 7.37 – 7.35 (2H, m, Ar*H*), 7.35-7.33 (1H, m, Ar*H*), 7.32-7.30 (1H, m, OCH_2 Ar*H*), 7.29 – 7.26 (1H, m, OCH_2 Ar*H*), 7.25 – 7.20 (2H, m, OCH_2 Ar*H*), 6.87 – 6.85 (1H, m, 6-*H*), 6.62 (1H, d, 15.5 Hz, 7-*H*), 6.53 (1H, tt, *J* = 11.0, 1.0 Hz, 5-*H*), 5.49 (1H, ddt, *J* = 11.0, 9.5, 1.0 Hz, 4-*H*), 4.61 (1H, dd, *J* = 11.5, 4.5 Hz, OC*H*$_2$Ar), 4.51 (1H, ddd, *J* = 9.5, 4.5, 1.1 Hz, 3-*H*), 4.33 (1H, dd, *J* = 11.5, 4.5 Hz, OC*H*$_2$Ar), 3.79 (3H, s, ArOC*H*$_3$), 3.75-3.73 (1H, m, 2-*H*), 3.70 (2H, m, 1-*H*) 2.46 (1H, d, *J* = 5.5 Hz, 2-O*H*), 1.75 (1H, dt, *J* = 8.0, 4.5 Hz, 1-O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.5, 136.8, 135.7, 134.9, 129.9, 129.8, 128.8, 128.3,

127.8, 126.8, 123.3, 114.0, 75.8, 73.5, 70.2, 63.5, 55.4; **HRMS** (ESI^+) calc. for $C_{21}H_{24}O_4Na$ ($[M+Na]^+$): 363.1567; found 363.1564.

78': ***Rf*** 0.12 (petroleum ether:EtOAc, 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.28 (2H, m, OCH_2Ar*H*), 6.91 – 6.88 (2H, m, OCH_2 Ar*H*), 6.53 – 6.39 (2H, m, 5-*H*), 5.77 (H, dd, *J* = 15.5, 8.0 Hz, 4-*H*), 4.63 – 4.56 (1H, m, OCH_2Ar), 4.32 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 4.02 (1H, dd, *J* = 8.0, 4.5 Hz, 3-*H*), 3.81 (3H, s, $ArOCH_3$), 3.77 (1H, m, 2-*H*), 3.71 (2H, m, 1-*H*); **HRMS** (ESI^+) calc. for $C_{13}H_{18}O_4Na$ ($[M+NA]^+$): 261.1103; found 261.1122.

(2*E*,4*S*,5*R*,6*Z*,8*E*)-5-((4-Methoxybenzyl)oxy)-2-methyl-9-phenylnona-2,6,8-triene-1,4-diol, **79**



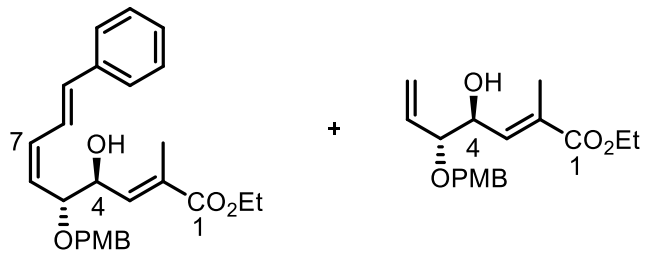
79 **79'**

To a vial containing cyclic siloxane **72** (14 mg, 42 μmol, 1.0 equiv.), β-bromostyrene (6.5 μL, 50 μmol, 1.2 equiv.), and allylpalladium(II) chloride dimer (0.80 mg, 2.1 μmol, 5.0 mol%) under N_2 atmosphere was added TBAF·$3H_2O$ (0.13 mL, 1 M in THF, 0.13 mmol, 3.0 equiv.). After stirring for 8 hrs in the dark, the reaction mixture was concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 1:1) afforded allylic alcohols **79** and **79'** (8 mg, 23 μmol, 53% yield) in a 3.8:1ratio as a yellow oil.

79: ***Rf*** 0.12 (petroleum ether:EtOAc, 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.36 – 7.32 (4H, m, OCH_2Ar*H*), 7.26 (5H, m, Ar*H*), 6.87 (1H, m, 8-*H*), 6.60 (1H, d, *J* = 15.5 Hz, 9-*H*), 6.49 (1H, td, *J* = 11.0, 1.0 Hz, 7-*H*), 5.53 – 5.49 (1H, m, 3-*H*), 5.49 – 5.46 (1H, m, 6-*H*), 4.63 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 4.54 – 4.48 (1H, m, 4-*H*), 4.41 (1H, ddd, *J* = 9.5, 4.0, 1.0 Hz, 5-*H*), 4.36 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 3.99 (2H, s, 1-*H*), 3.79 (3H, s, $ArOCH_3$), 2.36 (1H, d, *J* = 5.0 Hz, 4-O*H*), 1.71 (3H, s, 2-CH_3), 1.34 (1H, broad s, 1-O*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.4, 139.9, 136.9, 135.1, 134.4, 131.6, 129.8, 128.8, 128.2, 127.7, 126.7, 123.7, 123.4, 114.0, 76.3, 70.2, 69.9, 68.3, 55.4, 14.5; **HRMS** (ESI^+) calc. for $C_{24}H_{28}O_4Na$ ($[M+Na]^+$) : 403.1880; found 403.1880.

79': ***Rf*** 0.12 (petroleum ether/EtOAc, 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.43 (2H, td, *J* = 6.8, 6.2, 2.6 Hz, OCH_2Ar*H*), 6.92 (2H, m, OCH_2Ar*H*), 6.47 – 6.40 (2H, m, 7-*H*), 5.83 – 5.73 (1H, m, 5-*H*), 5.47 – 5.28 (1H, m, 3-*H*), 4.62 – 4.59 (1H, m, OCH_2Ar), 4.53 (1H, m, 4-*H*), 4.35 – 4.33 (1H, m, OCH_2Ar), 4.04 (2H, m, 1-*H*), 3.95 – 3.91 (1H, m, 5-*H*), 3.83 (3H, *s*, $ArOCH_3$), 1.73 (3H, s, 2-CH_3); **HRMS** (ESI^+) calc. for $C_{16}H_{22}O_4Na$ ($[M+Na]^+$): 301.1410; found 301.1411.

Ethyl (2*E*,4*S*,5*R*,6*Z*,8*E*)-4-hydroxy-5-((4-methoxybenzyl)oxy)-2-methyl-9-phenylnona-2,6,8-trienoate, 93



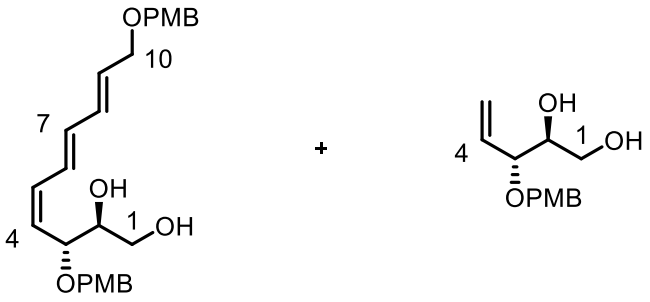
93 **207**

To a vial containing cyclic siloxane **77** (15 mg, 40 μmol, 1.0 equiv.), β-bromostyrene (6.1 μL, 48 μmol, 1.2 equiv.), and allylpalladium(II) chloride dimer (0.73 mg, 2.0 μmol, 5.0 mol%) under N_2 atmosphere was added TBAF·$3H_2O$ (0.12 mL, 1 M in THF, 0.12 mmol, 3.0 equiv.). After stirring for 8 hrs in the dark, the reaction mixture was concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 4:1) afforded α,β-unsaturated esters **93** and **207** (14 mg, 34 μmol, 85% yield) in a 5:1 ratio as a yellow oil.

93: ***Rf*** 0.33 (petroleum ether:EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39 – 7.33 (4H, m, Ar*H*), 7.29 (3H, m, OCH_2Ar*H*, Ar*H*), 6.92 – 6.88 (2H, m, OCH_2Ar*H*), 6.85 (1H, d, *J* = 11.5 Hz, 8-*H*), 6.75 – 6.70 (1H, m, 3-*H*), 6.64 (1H, d, *J* = 15.5 Hz, 9-*H*), 6.52 (1H, t, *J* = 11.0 Hz, 7-*H*), 5.46 (1H, t, *J* = 10.0 Hz, 6-*H*), 4.67 (1H, d, *J* = 11.5 Hz, 5-O*CH*$_2$Ar), 4.55 (1H, dd, *J* = 8.5, 4.5 Hz, 4-*H*), 4.52 – 4.46 (1H, m, 5-*H*), 4.38 (1H, d, *J* = 11.5 Hz, 5-O*CH*$_2$Ar), 4.20 – 4.13 (2H, m, O*CH*$_2$$CH_3$), 3.83 (3H, s, OCH_2ArO*CH*$_3$), 1.90 (3H, s, 2-C*H*$_3$), 1.31 – 1.26 (3H, m, $CO_2CH_2CH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.5, 138.5, 136.9, 135.6, 134.8, 131.0, 129.9, 129.8, 128.8, 128.3, 127.1, 126.8, 126.8, 123.4, 114.0, 75.9, 70.7, 70.0, 60.9, 55.4, 14.3, 13.4; **HRMS** (ESI^+) calc. for $C_{26}H_{31}O_5$ ($[M+H]^+$): 423.2172; found 423.2176.

207: ***Rf*** 0.33 (petroleum ether/EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.44 (2H, m, OCH_2Ar*H*), 6.94 – 6.88 (2H, m, OCH_2Ar*H*), 6.64 (1H, m, 3-*H*), 6.47 (2H, m, 7-*H*), 5.74 (1H, dd, *J* = 15.4, 8.4 Hz, 6-*H*), 4.62 (1H, d, *J* = 7.4 Hz, O*CH*$_2$Ar), 4.57 (1H, m, 4-*H*), 4.43 (1H, m, O*CH*$_2$Ar), 4.22 (2H, dt, *J* = 10.5, 4.5 Hz, O*CH*$_2$$CH_3$), 4.02 – 3.97 (1H, m, 5-*H*), 3.84 (3H, s, OCH_2ArO*CH*$_3$), 1.89 (3H, s, 2-C*H*$_3$), 1.33 (3H, m, *J* = 7.1 Hz, OCH_2C*H*$_3$).). **HRMS** (ESI^+) calc. for $C_{18}H_{25}O_5$ ($[M+H]^+$): 321.1702; found 321.1728.

(2*S*,3*R*,4*Z*,6*E*,8*E*)-3,10-*Bis*((4-methoxybenzyl)oxy)deca-4,6,8-triene-1,2-diol, **89**



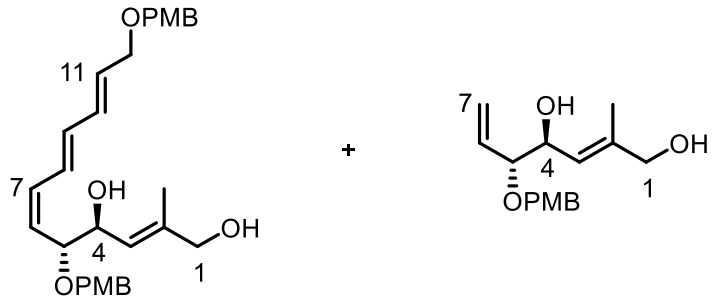
89 **78'**

To a vial containing cyclic siloxane **59** (20 mg, 68 μmol, 1.0 equiv.), 1-((((2*E*,4*E*)-5-bromopenta-2,4-dien-1-yl)oxy)methyl)-4-methoxybenzene (23 mg, 82 μmol, 1.2 equiv.) and allylpalladium(II) chloride dimer (1.2 mg, 3.4 μmol, 5.0 mol%) under N_2 atmosphere was added TBAF·$3H_2O$ (0.21 mL, 1 M in THF, 0.21 mmol, 3.0 equiv.). After stirring for 8 hrs in the dark, the reaction mixture was concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 1:1) afforded diols **89** and **78'** (15 mg, 37 μmol, 53% yield) in a 6.6:1 ratio as a yellow oil.

89*: Rf* 0.12 (petroleum ether:EtOAc, 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.31 – 7.23 (2H, m, 10-OCH_2 Ar*H*, 3-OCH_2 Ar*H*), 7.24 – 7.15 (2H, m, 10-OCH_2 Ar*H*, 3-OCH_2 Ar*H*), 6.92 – 6.83 (4H , m, 10-OCH_2 Ar*H*, 3-OCH_2 Ar*H*), 6.42 – 6.25 (4H, m, 5-*H*. 6-*H*, 7-*H*, 8-*H*), 5.88 (1H , ddt, *J* = 14.5, 9.0, 4.0 Hz, 9-*H*), 5.47 – 5.38 (1H, m, 4-*H*), 4.55 (1H, d, *J* = 11.5 Hz, 3-O*CH*$_2$Ar), 4.46 (2H, s, 10-O*CH*$_2$Ar), 4.41 (1H, dd, *J* = 9.5, 5.0 Hz, 3-*H*), 4.28 (1H, d, *J* = 11.5 Hz, 3-O*CH*$_2$Ar), 4.06 (2H, d, *J* = 4.0 Hz. 10-*H*), 3.81 (3H, s, OCH_2ArO*CH*$_3$), 3.80 (3H, s, OCH_2ArO*CH*$_3$), 3.74 (1H, d, *J* = 6.2 Hz, 2-*H*), 3.72 – 3.64 (2H, m, 1-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.5, 159.3, 135.2, 134.4, 132.2, 131.9, 130.3, 129.9, 129.8, 129.5, 128.1,

127.2, 114.0, 113.9, 76.1, 73.4, 72.1, 70.4, 70.1, 63.5, 55.4, 29.8; **HRMS** (ESI^+) calc. for $C_{26}H_{32}O_6Na$ ($[M+Na]^+$): 463.2097; found 463.2114.

(2*E*,4*S*,5*R*,6*Z*,8*E*,10*E*)-5,12-*Bis*((4-methoxybenzyl)oxy)-2-methyldodeca-2,6,8,10-tetraene-1,4-diol, **92**



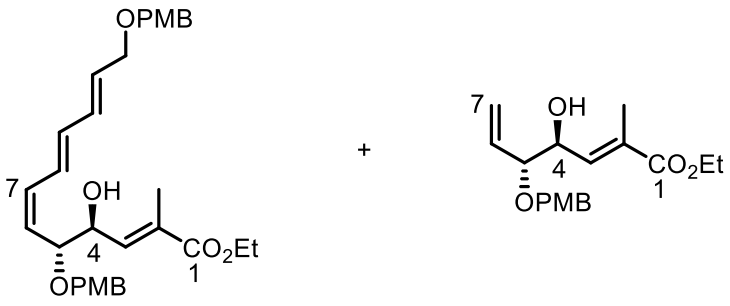
92 **79'**

To a vial containing cyclic siloxane **72** (14 mg, 42 μmol, 1.0 equiv.), 1-((((2*E*,4*E*)-5-bromopenta-2,4-dien-1-yl)oxy)methyl)-4-methoxybenzene (14 mg, 50 μmol, 1.2 equiv.) and allylpalladium(II) chloride dimer (0.80 mg, 2.1 μmol, 5.0 mol%) under N_2 atmosphere was added TBAF·$3H_2O$ (0.13 mL, 1 M in THF, 0.13 mmol, 3.0 equiv.). After stirring for 8 hrs in the dark, the reaction mixture was concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 1:1) afforded allylic alcohols **92** and **79'** (7 mg, 14 μmol, 34% yield) in a 7.5:1 ratio as a yellow oil.

92: ***Rf*** 0.12 (petroleum ether:EtOAc, 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.25 (4H, q, *J* = 9.0, 8.0 Hz, OCH_2 Ar*H*), 6.88 (4H, dt, *J* = 9.0, 3.0 Hz, OCH_2 Ar*H*), 6.39 – 6.23 (2H, m, 9-*H*, 10-*H*), 5.83 (2H, m, 7-*H*, 8-*H*), 5.47 (2H, m, 3-*H*, 11-*H*), 5.42 – 5.27 (1H, m, 6-*H*), 4.58 (1H, dd, *J* = 11.5, 8.0 Hz, 5-OCH_2ArCH_3), 4.51 – 4.39 (3H, m, 4-*H*, 12-OCH_2Ar), 4.34 – 4.26 (1H, m, 5-OCH_2ArCH_3), 4.06 (2H, d, *J* = 6.0 Hz, 12-*H*), 4.00 (2H, d, *J* = 10.0 Hz, 1-

H), 3.81 (3H, s, OCH_2ArCH_3), 3.80 (3H, s, OCH_2ArCH_3), 1.69 (3H, s, 2-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 155.6, 139.8, 139.0, 136.4, 134.7, 134.6, 133.9, 132.2, 129.7, 129.6, 128.9, 128.0, 127.9, 123.4, 123.3, 114.0, 83.0, 77.4, 72.1, 70.2, 70.0, 68.2, 55.4, 29.8, 14.4; **HRMS** (ESI^+) calc. for $C_{29}H_{36}O_6Na$ ($[M+Na]^+$): 503.2401; found 503.2403.

Ethyl (2*E*,4*S*,5*R*,6*Z*,8*E*,10*E*)-4-hydroxy-5,12-*bis*((4-methoxybenzyl)oxy)-2-methyldodeca-2,6,8,10-tetraenoate, 94



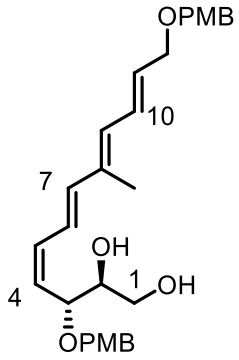
94 **207**

To a vial containing cyclic siloxane **77** (15 mg, 40 μmol, 1.0 equiv.), 1-((((2*E*,4*E*)-5-bromopenta-2,4-dien-1-yl)oxy)methyl)-4-methoxybenzene (14 mg, 50 μmol, 1.2 equiv.) and allylpalladium(II) chloride dimer (0.70 mg, 2.0 μmol, 5.0 mol%) under N_2 atmosphere was added TBAF·$3H_2O$ (0.12 mL, 1 M in THF, 0.12 mmol, 3.0 equiv.). After stirring for 8 hrs in the dark, the reaction mixture was concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 4:1) afforded α,β-unsaturated esters **94** and **207** (10 mg, 20 μmol, 50% yield) in a 9:1 ratio as a yellow oil.

94: ***Rf*** 0.34 (petroleum ether:EtOAc, 3:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.31 – 7.15 (4H, m, OCH_2ArH), 6.88 (4H, dd, *J* = 8.5, 6.5 Hz, OCH_2ArH), 6.66 (1H, dt, *J* = 8.5, 1.5 Hz, 3-*H*), 6.30 (4H, m, 7-*H*, 8-*H*, 9-*H*, 10-*H*), 5.91 – 5.82 (1H, m, 11-*H*), 5.43 – 5.32 (1H, m, 6-

H), 4.58 (1H, d, *J* = 11.5 Hz, 5-O*CH*$_2$Ar), 4.46 (3H, m, 12-OC*H*$_2$*Ar*, 4-*H*), 4.37 (1H, dd, *J* = 9.5, 4.4 Hz, 5-*H*), 4.30 (1H, d, *J* = 11.5 Hz, 5- OC*H*$_2$Ar), 4.18 (2H,qd, *J* = 7.0, 3.5 Hz, OC*H*$_2$CH$_3$), 4.06 (2H, d, *J* = 6.0 Hz, 12-*H*), 3.81 (3H, s, OCH$_2$Ar*CH*$_3$), 3.80 (3H, s, OCH$_2$Ar*CH*$_3$), 1.84 (3H, s, 2-C*H*$_3$), 1.32 – 1.21 (3H, m, CO$_2$CH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 167.8, 159.5, 138.5, 135.6, 135.1, 134.4, 132.2, 131.8, 131.0, 130.4, 130.0, 129.7, 129.6, 127.3, 127.3, 125.2, 114.0, 77.2, 76.2, 72.1, 70.6, 70.1, 66.9, 60.9, 55.4, 14.4, 13.4; **HRMS** (ESI$^+$) calc. for $C_{31}H_{38}O_7Na$ ([M+Na]$^+$): 545.2515; found 545.2428.

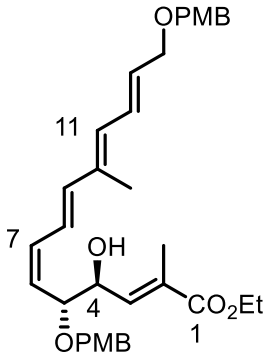
(2*S*,3*R*,4*Z*,6*E*,8*E*,10*E*)-3,12-*Bis*((4-methoxybenzyl)oxy)-8-methyldodeca-4,6,8,10-tetraene-1,2-diol, 90



To a vial containing cyclic siloxane **59** (17 mg, 58 μmol, 1.0 equiv.), 1-((((2*E*,4*E*,6*E*)-7-iodo-5-methylhepta-2,4,6-trien-1-yl)oxy)methyl)-4-methoxybenzene (26 mg, 70 μmol, 1.2 equiv.) and allylpalladium(II) chloride dimer (1.0 mg, 2.9 μmol, 5.0 mol%) under N_2 atmosphere was added TBAF·3H$_2$O (0.17 mL, 1 M in THF, 0.17 mmol, 3.0 equiv.). After stirring for 8 hrs in the dark, the reaction mixture was concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 1:1) afforded **90** (22 mg, 48 μmol, 82% yield) as a yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −3.92 (c 0.375, $CHCl_3$); ***Rf*** 0.12 (petroleum ether:EtOAc, 3:2); **IR ν_{max}** (thin film) /cm^{-1} 3429, 2933, 1612, 1248, 1063; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.26 – 7.07 (4H, m, OCH_2ArH), 6.78 (4H, t, *J* = 8.5 Hz, OCH_2ArH), 6.52 (1H, dd, *J* = 15.0, 11.5 Hz, 10-*H*), 6.41 – 6.29 (2H, m, 6-*H*, 7-*H*), 6.28 – 6.24 (1H, m, 5-*H*), 6.06 (1H, d, *J* = 11.5 Hz, 9-*H*), 5.78 (1H, dt, *J* = 15.0, 6.0 Hz, 11-*H*), 5.29 (1H, t, *J* = 10.0 Hz, 4-*H*), 4.47 (1H, d, *J* = 11.5 Hz, 3-OCH_2Ar), 4.40 – 4.31 (3H, m, 12-OCH_2Ar, 3-*H*), 4.20 (1H, d, *J* = 11.5 Hz, 3-OCH_2Ar), 3.99 (2H, d, *J* = 6.0 Hz, 12-*H*), 3.71 (3H, s, OCH_2ArCH_3), 3.70 (3H, s, OCH_2ArCH_3), 3.69 – 3.61 (1H, m, 2-*H*), 3.60 (2H, d, *J* = 8.0 Hz, 1-*H*), 1.74 (3H, s, 8-CH_3); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 159.9, 140.5, 135.4, 135.0, 132.6, 132.3, 131.0, 130.5, 129.9, 129.7, 129.5, 128.2, 127.9, 123.3, 114.2, 114.2, 76.0, 74.1, 72.2, 70.4, 70.1, 63.8, 54.8, 12.7, 1.4; **HRMS** (ESI^+) calc. for $C_{29}H_{36}O_6Na$ ($[M+Na]^+$): 503.2404; found 503.2405.

Ethyl (2*E*,4*S*,5*R*,6*Z*,8*E*,10*E*,12*E*)-4-hydroxy-5,14-*bis*((4-methoxybenzyl)oxy)-2,10-dimethyltetradeca-2,6,8,10,12-pentaenoate, 95

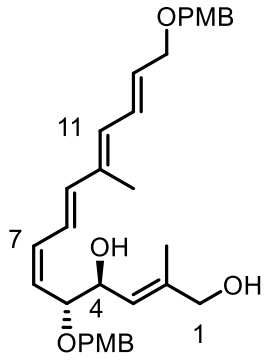


To a vial containing cyclic siloxane **77** (15 mg, 40 μmol, 1.0 equiv.), 1-((((2*E*,4*E*,6*E*)-7-bromo-5-methylhepta-2,4,6-trien-1-yl)oxy)methyl)-4-methoxybenzene (16 mg, 48 μmol, 1.2 equiv.) and allylpalladium(II) chloride dimer (0.8 mg, 2.0 μmol, 5.0 mol%) under N_2 atmosphere was added TBAF·$3H_2O$ (0.12 mL, 1 M in THF, 0.12 mmol, 3.0 equiv.). After stirring for 8 hrs in the dark, the reaction mixture was concentrated *in*

vacuo. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 4:1) afforded **95** (11 mg, 20 μmol, 50% yield) as a yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −5.12 (c 0.18, $CHCl_3$); ***Rf*** 0.33 (petroleum ether:EtOAc, 3:1); **IR** $\boldsymbol{\nu_{max}}$ (thin film) /cm^{-1} 2979, 2354, 1752, 1512, 1247, 1117; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.29 – 7.21 (4H, m, OCH_2Ar*H*), 7.12 (1H, d, *J* = 8.5 Hz, 3-*H*), 6.84 – 6.75 (4H, m, OCH_2Ar*H*), 6.71 – 6.60 (1H, m, 12-*H*), 6.45 (1H, dd, *J* = 15.0, 11.0 Hz, 8-*H*), 6.33 – 6.19 (2H, m, 7-*H*, 9-*H*), 6.10 (1H, d, *J* = 11.5 Hz, 11-*H*), 5.83 (1H, dt, *J* = 14.5, 6.0 Hz, 13-*H*), 5.42 (1H, t, *J* = 10.0 Hz, 6-*H*), 4.55 (3H, m, 4-*H*, 5-O*CH₂Ar*), 4.51 – 4.44 (1H, m, 5-*H*), 4.38 (2H, s, 14-O*CH₂Ar*), 4.24 (1H, d, *J* = 11.5 Hz, 5-O*CH₂*Ar), 3.98 (4H, m, 14-*H*, O*CH₂*CH_3), 3.31 (3H, s, OCH_2Ar*CH₃*), 3.30 (3H, s, OCH_2Ar*CH₃*), 1.96 – 1.91 (3H, m, 2-C*H₃*), 1.67 (3H, s, 10-C*H₃*), 0.93 (3H, td, *J* = 7.0, 2.0 Hz, OCH_2C*H₃*); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 167.5, 159.9, 159.8, 140.5, 139.8, 137.7, 135.3, 135.1, 132.7, 132.3, 131.0, 130.8, 129.9, 129.5, 127.9, 127.3, 123.2, 114.2, 114.2, 76.3, 72.2, 71.1, 70.4, 69.9, 60.6, 54.8, 30.1, 14.2, 13.5, 12.6; **HRMS** (ESI^+) calc. for $C_{34}H_{42}O_7Na$ ($[M+Na]^+$): 585.2823; found 585.2820.

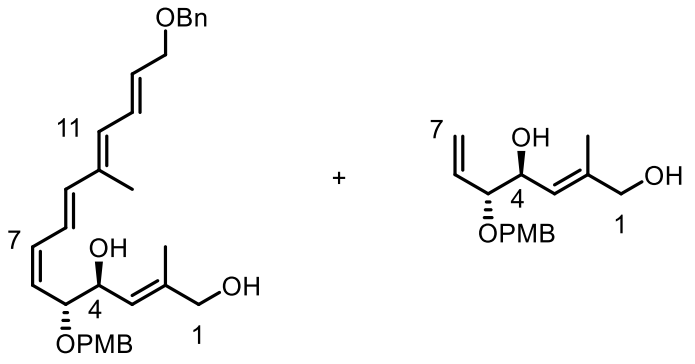
(2*E*,4*S*,5*R*,6*Z*,8*E*,10*E*,12*E*)-5,14-*Bis*((4-methoxybenzyl)oxy)-2,10-dimethyltetradeca-2,6,8,10,12-pentaene-1,4-diol, 91



To a vial containing cyclic siloxane **72** (14 mg, 42 μmol, 1.0 equiv.), 1-((((2*E*,4*E*,6*E*)-7-bromo-5-methylhepta-2,4,6-trien-1-yl)oxy)methyl)-4-methoxybenzene (16 mg, 50 μmol, 1.2 equiv.) and allylpalladium(II) chloride dimer (0.8 mg, 2.1 μmol, 5.0 mol%) under N_2 atmosphere was added TBAF·$3H_2O$ (0.13 mL, 1 M in THF, 0.13 mmol, 3.0 equiv.). After stirring for 8 hrs in the dark, the reaction mixture was concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 1:1) afforded **91** (12 mg, 23 μmol, 55% yield) as a yellow oil.

$[\alpha]_D^{25}$ −9.80 (c 0.50, $CHCl_3$); ***Rf*** 0.12 (petroleum ether:EtOAc, 3:2); **IR ν_{max}** (thin film) /cm^{-1} 3416, 2924, 1690, 1513, 1248, 1002; **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.24 (4H, t, *J* = 9.0 Hz, OCH_2Ar*H*), 6.88 – 6.74 (4H, m, OCH_2Ar*H*), 6.73 – 6.60 (1H, m, 12-*H*), 6.58 – 6.49 (1H, m, 8-*H*), 6.34 (1H, t, *J* = 11.0 Hz, 7-*H*), 6.27 (1H, d, *J* = 15.0 Hz, 9-*H*), 6.12 (1H, d, *J* = 11.0 Hz, 11-*H*), 5.83 (1H, dt, *J* = 15.5, 6.0 Hz, 13-*H*), 5.73 (1H, d, *J* = 8.5 Hz, 3-*H*), 5.57 (1H, t, *J* = 10.0 Hz, 6-*H*), 4.61 (3H, m, 4-*H*, 5-O*CH$_2$Ar*), 4.52 (1H, m, 5-*H*), 4.38 (2H, s, 14-O*CH$_2$Ar*), 4.32 (1H, dd, *J* = 11.5, 5.0 Hz, 5-O*CH$_2$Ar*), 3.97 (2H, d, *J* = 6.0 Hz, 14-*H*), 3.75 (2H, s, 1-*H*), 3.31 (6H, s, OCH_2Ar*CH$_3$*, OCH_2Ar*CH$_3$*), 1.70 (3H, s, 10-C*H$_3$*), 1.54 (3H, s, 2-C*H$_3$*); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 159.9, 140.2, 139.3, 135.7, 135.4, 134.6, 132.5, 132.2, 131.1, 130.8, 129.9, 129.7, 129.5, 124.3, 124.0, 123.6, 119.3, 114.2, 83.6, 77.1, 72.2, 70.4, 70.0, 68.0, 54.8, 30.1, 14.3, 12.7; **HRMS** (ESI^+) calc. for $C_{32}H_{40}O_6Na$ ($[M+Na]^+$): 543.2717; found 543.2720.

(2*E*,4*S*,5*R*,6*Z*,8*E*,10*E*,12*E*)-14-(Benzyloxy)-5-((4-methoxybenzyl)oxy)-2,10-dimethyltetradeca-2,6,8,10,12-pentaene-1,4-diol, 97



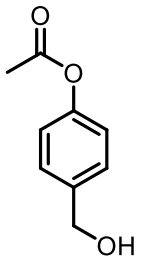
97 **79'**

To a vial containing cyclic siloxane **72** (100 mg, 0.299 mmol, 1.0 equiv.), ((((2*E*,4*E*,6*E*)-7-bromo-5-methylhepta-2,4,6-trien-1-yl)oxy)methyl)benzene (105 mg, 0.359 mmol, 1.2 equiv.) and allylpalladium(II) chloride dimer (5.50 mg, 15.0 μmol, 5.0 mol%) under N_2 atmosphere was added TBAF·$3H_2O$ (0.9 mL, 1 M in THF, 0.897 mmol, 3.0 equiv.). After stirring for 8 hrs in the dark, the reaction mixture was concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether / EtOAc, 1:1) afforded **97** and **79'** (73 mg, 0.16 mmol, 53% yield) in a 6.6:1 ratio as a yellow oil.

97: ***Rf*** 0.12 (petroleum ether:EtOAc, 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 – 7.17 (5H, m, OCH_2Ar*H*), 7.17 – 7.10 (2H, m, OCH_2Ar*H*), 6.78 (2H, dd, *J* = 8.5, 4.0 Hz, OCH_2Ar*H*), 6.54 (1H, dd, *J* = 15.0, 11.5 Hz, 12-*H*), 6.36 – 6.21 (3H, m, 7-*H*, 8-*H*, 9-*H*), 6.06 (1H, d, *J* = 11.5 Hz, 11-*H*), 5.88 – 5.65 (1H, m, 13-*H*), 5.39 (1H, d, *J* = 8.5 Hz, 3-*H*), 5.35 – 5.19 (1H, m, 6-*H*), 4.50 (1H, dd, *J* = 11.5, 3.0 Hz, 5-OC*H₂Ar*), 4.45 (2H, s, 14-OC*H₂Ar*), 4.38 (1H, dt, *J* = 9.0, 4.0 Hz, 4-*H*), 4.29 – 4.19 (3H, m, 5-*H*, 5-OC*H₂Ar*), 4.03 (2H, d, *J* = 6.0 Hz, 14-*H*), 3.91 (2H, d, *J* = 9.0 Hz, 1-*H*), 3.71 (3H, d, *J* = 2.0 Hz, OCH_2ArCH_3), 1.74 (3H, s, 10-C*H₃*), 1.59 (3H, s, 2-C*H₃*);**^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.4, 140.9, 140.0, 139.7, 135.5,

134.7, 132.1, 131.2, 130.2, 129.8, 129.6, 129.1, 127.9, 127.8, 127.1, 123.6, 123.1, 113.9, 83.0, 72.4, 70.7, 70.3, 70.1, 69.9, 55.4, 14.5, 12.8; **HRMS** (ESI^+) calc. for $C_{31}H_{37}O_5$ ($[M-H]^-$):489.2646; found 489.2638.

4-(Hydroxymethyl)phenyl acetate, 103

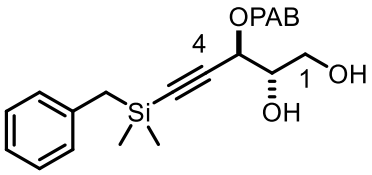


To a solution of 4-hydroxybenzyl alcohol (7.5 g, 60 mmol, 1.0 equiv.) and NEt_3 (8.4 mL, 60 mmol, 1.0 equiv.) in EtOAc (100 mL) 0 °C, was added a solution of acetyl chloride (5.1 mL, 72 mmol, 1.2 equiv.) in EtOAc (50 mL) dropwise. After stirring for 5 hrs at 0 °C, the reaction was filtered and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 1:0 to 0:1) afforded PABOH **103** (6.2 g, 37 mmol, 62% yield).[143]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.12 – 7.01 (2H, m, Ar*H*), 4.67 (2H, s, ArCH_2OH), 2.30 (3H, s, ArOCO(CH_3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 169.7, 150.2, 138.6, 128.2, 121.8, 64.9, 21.3; **HRMS** (ESI^+) calc. for $C_9H_{10}O_3Na$ ($[M+Na]^+$): 189.0522; found 189.0522.

All spectroscopic data are in accordance with data reported by Nägele *et al.*[143]

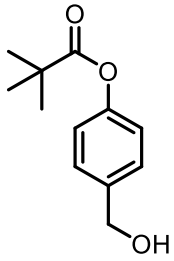
4-(((1-(Benzyldimethylsilyl)-4,5-dihydroxypent-1-yn-3-yl)oxy)methyl)phenyl acetate, 105



To a solution of epoxide (±)-**104** (180 mg, 0.73 mmol, 1.0 equiv.) in toluene (4.7 mL) was added europium (III) trfluoromethanesulfonate (79 mg, 0.13 mmol, 0.18 equiv.) and 2,6-di-*tert*-butyl-4-methylpyridine (27 mg, 0.13 mmol, 0.18 equiv.). The resulting mixture was heated to 40 °C under inert atmosphere. PABOH (0.28 mL, 2.0 mmol, 2.7 equiv.) was added at this temperature and the solution was stirred for 3 days. Concentration *in vacuo* and purification by flash SiO_2 column chromatography (petroleum ether / EtOAc, 3:1 to 3:2) afforded diol (±)-**105** (130 mg, 2.1 mmol, 48% yield) as a yellow oil.

Rf 0.21 (petroleum ether:EtOAc, 3:2); **IR ν_{max}** (thin film) /cm^{-1} 3060, 3025, 2177, 1751, 1119, 1056; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.32 (2H, d, *J* = 9.0 Hz, OCH_2ArH), 7.23 (2H, dd, *J* = 8.0, 7.0 Hz, OCH_2ArH), 7.14 – 7.05 (5H, m, $SiCH_2ArH$), 4.76 (1H, d, *J* = 11.5 Hz, OCH_2Ar)), 4.46 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 4.24 (1H, d, *J* = 4.5 Hz, 3-*H*), 3.85 (1H, dd, *J* = 10.5, 4.0 Hz, 2-*H*), 3.76 (2H, dd, *J* = 8.0, 4.0 Hz, 1-*H*), 2.30 (3H, s, $ArOCOCH_3$), 2.22 (2H, s, $SiCH_2Ar$), 0.19 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 169.6, 150.5, 138.8, 134.8, 129.3, 128.4, 128.4, 124.7, 121.8, 102.4, 92.6, 77.0, 76.8, 72.9, 71.9, 70.7, 63.1, 26.1, 21.2, -1.9; **HRMS** (ESI^+) calc. for $C_{23}H_{28}O_5NaSi$ ($[M+Na]^+$): 435.1598; found 435.1594.

4-(Hydroxymethyl)phenyl pivalate, 107

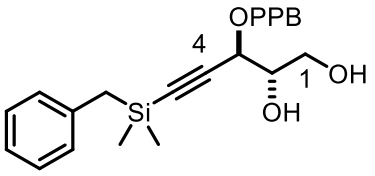


To a solution of 4-hydroxybenzyl alcohol (6.2 g, 50 mmol, 1.0 equiv.) and NEt_3 (10 mL, 75 mmol, 1.5 equiv.) in THF (50 mL) was added pivaloyl chloride (6.8 ml, 55 mmol, 1.1 equiv.) dropwise. After stirring for 1 hr, the solution was cooled to 0 °C and reaction was quenched with H_2O (20 mL). The solution was diluted with Et_2O (75 mL), the organic layer separated, and the aqueous layer was extracted with Et_2O (3 × 75 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 3:1) afforded PPBOH **107** (6.9 g, 33 mmol, 66% yield) as a clear and colourless solid.[144]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 (2H, dt, *J* = 8.5, 3.0 Hz, Ar*H*), 7.07 – 6.97 (2H, m, Ar*H*), 4.63 (2H, dd, *J* = 8.0, 4.0 Hz, ArC*H*$_2$OH), 1.35 (9H, s, ArOCOC(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 177.4, 150.5, 138.4, 128.1, 121.6, 64.7, 39.2, 27.2; **HRMS** (ESI^+) calc. for $C_{12}H_{16}O_3Na$ ($[M+Na]^+$): 231.0992; found 231.0994.

All spectroscopic data are in accordance with data reported by Odyniec *et al.*[144]

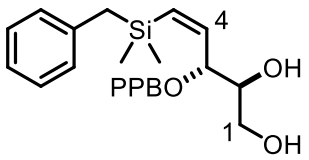
4-((((3*R*,4*S*)-1-(Benzyldimethylsilyl)-4,5-dihydroxypent-1-yn-3-yl)oxy)methyl)phenyl pivalate, 108



To a solution of epoxide (±)-**104** (290 mg, 1.2 mmol, 1.0 equiv.) in toluene (7.4 mL) was added europium (III) trifluoromethanesulfonate (130 mg, 0.21 mmol, 0.18 equiv.) and 2,6-di-*tert*-butyl-4-methylpyridine (43 mg, 0.21 mmol, 0.18 equiv.). The resulting mixture was heated to 40 °C under inert atmosphere. PPBOH (650 mg, 3.1 mmol, 2.7 equiv.) was added at this temperature and the solution was stirred for 6 days. Concentration *in vacuo* and purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 3:1 to 3:2) afforded diol (±)-**108** (410 mg, 0.90 mmol, 78% yield) as a yellow oil.

Rf 0.29 (petroleum ether:EtOAc, 3:2); **IR ν_{max}** (thin film) /cm^{-1} 3394, 2966, 1750, 1505, 1198, 1117, 836; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35 – 7.29 (2H, m, OCH_2ArH), 7.23 (2H, dd, *J* = 8.0, 7.0 Hz, OCH_2ArH), 7.13 – 7.02 (5H, m, $SiCH_2ArH$), 4.76 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 4.46 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 4.23 (1H, d, *J* = 4.5 Hz, 3-*H*), 3.84 (1H, dd, *J* = 11.0, 4.5 Hz, 2-*H*), 3.73 (2H, d, *J* = 11.0 Hz, 1-*H*), 2.56 (1H, bs, 2-O*H*), 2.23 (2H, s, $SiCH_2Ar$), 1.36 (9H, s, $ArOCOC(CH_3)_3$, 0.19 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 177.2, 151.0, 138.8, 134.5, 129.3, 128.5, 128.4, 124.7, 121.7, 102.5, 92.6, 72.9, 71.8, 70.8, 63.1, 39.2, 27.3, 26.1, -1.9; **HRMS** (ESI^+) calc. for $C_{26}H_{34}O_5SiNa$ ($[M+Na]^+$): 477.2068; found 477.2065.

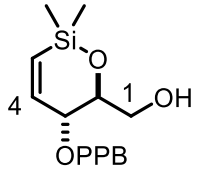
4-((((3*R*,4*S*,*Z*)-1-(Benzyldimethylsilyl)-4,5-dihydroxypent-1-en-3-yl)oxy)methyl)phenyl pivalate, 109



To a flame-dried round-bottom flask containing Pd/$CaCO_3$ (956 mg, 5 wt. % on $CaCO_3$, 0.451 mmol, 5.0 mol%), the flask was evacuated and backfilled with N_2, then toluene (90 mL) was added. The flask was evacuated and backfilled with H_2 three times. A solution of alkyne (±)-**108** (4.10 g, 9.02 mmol, 1.0 equiv.) and quinolone (0.500 mL, 4.51 mmol, 0.5 equiv.) in cyclohexene (0.45 mL) was added to the stirring mixture. The hydrogenation was monitored by TLC and after 2 hr 24 min the reaction mixture was filtered through Celite® and concentrated *in vacuo* affording alkene (±)-**109** as a yellow oil which was carried to the next step without further purification.

Rf 0.29 (petroleum ether:EtOAc, 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.29 – 7.23 (2H, m, OCH_2ArH), 7.20 – 7.16 (2H, m, OCH_2ArH), 7.06-7.03 (5H, m, $SiCH_2ArH$), 6.28 (1H, dd, *J* = 14.5, 9.5 Hz, 4-*H*), 5.98 (1H, dd, *J* = 14.5, 1.0 Hz, 5-*H*), 4.52 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 4.26 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 3.82 – 3.64 (3H, m, 3-*H*, 1-*H*), 3.53 (1H, s, 2-*H*), 2.18 (2H, s, $SiCH_2Ar$) 1.36 (9H, s, $ArOCOC(CH_3)_3$), 0.13 (6H, s, $Si(CH_3)_2$).

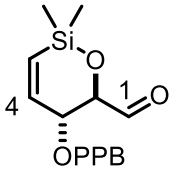
4-((((5*R*,6*S*)-6-(Hydroxymethyl)-2,2-dimethyl-5,6-dihydro-2*H*-1,2-oxasilin-5-yl)oxy)methyl)phenyl pivalate, 110



To a round-bottom flask containing alkene (±)-**109** (8.24 g, 18.0 mmol, 1.00 equiv.) in THF (150 mL) was added TBAF·$3H_2O$ (22.5 mL, 22.5 mmol, 1.25 equiv., 1 M solution in THF) dropwise. After stirring for 1 h 50 min, the solution was diluted with CH_2Cl_2 (100 mL) and washed with aqueous HCl (1 N, 100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (180 mL), PPTS (904 mg, 3.60 mmol, 20 mol%) was added and the reaction mixture was stirred for 16 hrs at room temperature. The solution was diluted with CH_2Cl_2 (100 mL) and washed with H_2O (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 1:1) afforded cyclic siloxane (±)-**110** (5.19 g, 14.2 mmol, 79% yield) as a pale-yellow oil.

Rf 0.58 (petroleum ether:EtOAc, 3:2); **IR ν_{max}** (thin film) /cm^{-1} 3441, 2971, 2874, 1751, 1613, 1508, 1278, 1198, 1117, 844; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38 – 7.31 (2H, m, Ar*H*), 7.07 – 7.00 (2H, m, Ar*H*), 6.80 (1H, dd, *J* = 14.5, 1.5 Hz, 4-*H*), 5.85 (1H, dd, *J* = 14.5, 2.5 Hz, 5-*H*), 4.68 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 4.57 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 4.05 – 3.99 (1H, m, 3-*H*), 3.89 – 3.77 (1H, m, 2-*H*), 3.70 (2H, d, *J* = 11.5 Hz, 1-*H*), 2.16 (1H, broad, 1-O*H*), 1.35 (9H, s, ArOCOC(CH_3)$_3$), 0.21 (3H, s, Si(CH_3)$_2$), 0.19 (3H, s, Si(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 177.2, 150.8, 149.2, 135.3, 129.1, 127.5, 121.7, 75.0, 74.6, 71.3, 64.1, 39.2, 27.2, -0.5, -0.8; **HRMS** (ESI^+) calc. for $C_{19}H_{28}O_5SiNa$ ($[M+Na]^+$): 387.1598; found 387.1599.

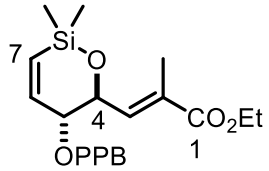
4-((((5*R*,6*R*)-6-Formyl-2,2-dimethyl-5,6-dihydro-2*H*-1,2-oxasilin-5-yl)oxy)methyl)phenyl pivalate, 115



To a solution of $SO_3 \cdot py$ (2.83 g, 17.8 mmol, 3.50 equiv.) in CH_2Cl_2 (20 mL) at 0 °C was added DMSO (4.90 mL, 69.2 mmol, 13.6 equiv.) dropwise. After stirring for 30 min at 0 °C, a solution of alcohol (±)-**110** (1.86 g, 5.09 mmol, 1.00 equiv.) and DIPEA (4.40 mL, 25.4 mmol, 5.00 equiv.) in CH_2Cl_2 (5.5 mL) was added dropwise. After stirring at 0 °C for 30 min, the solution was poured into aqueous HCl (1 N, 25 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (75 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford aldehyde (±)-**115** as a yellow oil. Aldehyde (±)-**115** was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.72 (1H, d, *J* = 1.0 Hz, 1-*H*), 7.43 – 7.30 (2H, m, Ar*H*), 7.09 – 6.97 (2H, m, Ar*H*), 6.80 (1H, dd, *J* = 14.5, 3.0 Hz, 4-*H*), 5.99 (1H, dd, *J* = 14.5, 1.5 Hz, 5-*H*), 4.65 (1H, d, *J* = 11.5 , OCH_2Ar)), 4.61 (1H, d, *J* = 11.5 , OCH_2Ar), 4.40 (1H, dd, *J* = 7.5, 1.0 Hz, 2-*H*), 4.17 (1H, ddd, *J* = 7.5, 3.0, 1.5 Hz, 3-*H*), 1.35 (9H, s, ArOCOC(CH_3)$_3$), 0.27 (6H, s, Si((CH_3)$_2$).

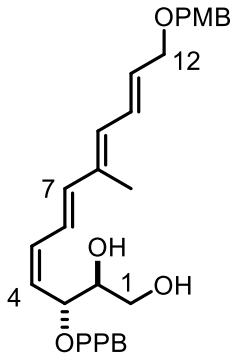
Ethyl (*E*)-3-((5*R*,6*S*)-2,2-dimethyl-5-((4-(pivaloyloxy)benzyl)oxy)-5,6-dihydro-2*H*-1,2-oxasilin-6-yl)-2-methylacrylate, 208



To a solution of crude (aldehyde (±)-**115** (0.10 mmol, 1.0 equiv.), in toluene (1 mL) was added carbethoxyethylidene)triphenylphosphorane (43 mg, 0.12 mmol, 1.2 equiv.). After stirring at 80 °C for 1.5 h, the reaction mixture was concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:Et_2O, 1:1) afforded cyclic siloxane (±)-**208** (9.0 mg, 0.020 mmol, 20% yield over 2 steps) as a pale-yellow oil.

Rf 0.4 (petroleum ether:Et_2O, 4:1); **IR ν_{max}** (thin film) /cm^{-1} 2977, 1752, 1712, 1251, 1115, 848; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 – 7.26 (2H, m, Ar*H*), 7.01 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.79 (1H, dd, *J* = 14.5, 2.0 Hz, 7-*H*), 6.69 (1H, dd, *J* = 8.5, 1.5 Hz, 3-*H*), 5.92 (1H, dd, *J* = 14.5, 2.0 Hz, 6-*H*), 4.66 – 4.58 (2H, m, 4-*H*, OCH_2Ar), 4.52 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 4.21 (2H, qd, *J* = 7.0, 1.8 Hz, $CO_2CH_2CH_3$), 3.90 (1H, dt, *J* = 8.0, 2.0 Hz, 5-*H*), 1.91 (3H, d, *J* = 1.0 Hz, 1-CH_3), 1.35 (9H, s, ArOCOC(CH_3)$_3$), 1.30 (3H, t, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 0.24 (3H, s, Si((CH_3)$_2$), 0.20 (3H, s, Si((CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 168.0, 150.8, 148.8, 139.9, 135.3, 131.5, 130.9, 129.2, 128.5, 121.6, 71.6, 71.2, 60.9, 39.2, 30.5, 29.9, 27.3, 14.4, 13.5, 1.2, -0.4, -0.8; **HRMS** (ESI^+) calc. for $C_{24}H_{35}O_6Si$ ($[M+H]^+$): 447.2197; found 447.2198.

4-((((2*S*,3*R*,4*Z*,6*E*,8*E*,10*E*)-12-(4-methoxybenzyl)oxy)-1,2-dihydroxy-8-methyldodeca-4,6,8,10-tetraen-3-yl)oxy)methyl)phenyl pivalate, 112

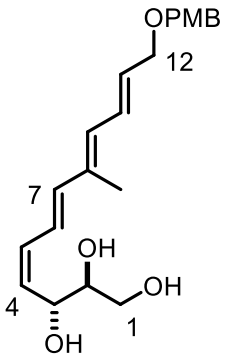


To a vial containing (±)-**110** (50 mg, 0.14 mmol, 1.0 equiv.), 1-((((2*E*,4*E*,6*E*)-7-bromo-5-methylhepta-2,4,6-trien-1-yl)oxy)methyl)-4-methoxybenzene (52 mg, 0.18 mmol, 1.2 equiv.) and allylpalladium(II) chloride dimer (2.5 mg, 50 μmol, 5.0 mol%) under N_2 atmosphere was added TBAF·$3H_2O$ (0.41 mL, 1 M in THF, 0.41 mmol, 3.0 equiv.). After stirring for 16 hrs in the dark, the reaction mixture was concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 1:1) afforded tetraene (±)-**112** (29 mg, 55 μmol, 39% yield) as a yellow oil.

Rf 0.12 (petroleum ether:EtOAc, 3:2); **IR ν_{max}** (thin film) /cm^{-1} 2979, 970; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.34 – 7.27 (4H, m, Ar*H*), 7.06 – 6.99 (2H, m, Ar*H*), 6.94 - 6.85 (2H, m, Ar*H*), 6.63 (1H, dd, *J* = 15.0, 11.5 Hz, 10-*H*) 6.50 – 6.42 (1H, m, 5-*H*), 6.42 – 6.35 (2H, m, 6-*H*, 7-*H*), 6.17 (1H, d, *J* = 11.5 Hz, 9-*H*), 5.95 – 5.87 (1H, m, 11-*H*), 5.40 (1H, t, *J* = 10.0 Hz, 4-*H*), 4.62 (1H, d, *J* = 12.0 Hz, 3-OC*H*$_2$Ar), 4.54 (2H, s, 12-OC*H*$_2$Ar), 4.50 – 4.45 (1H, m, 3-*H*), 4.36 (1H, d, *J* = 12.0 Hz, 3-OC*H*$_2$Ar), 4.13 (2H. dd, *J* = 6.5, 1.5 Hz, 12-*H*), 3.83 – 3.66 (6H, m, 1-*H*, 2-*H*, OCH_2ArCH_3), 1.85 (3H, d, *J* = 1.1 Hz, 8-C*H*$_3$), 1.36 (12H, s, $ArOCOC(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 150.9, 140.8, 138.3, 135.5, 135.4, 135.3, 132.4, 131.4, 129.1, 129.0, 128.6, 127.9, 127.8, 126.8, 122.5, 121.7, 76.4, 73.5, 72.4, 70.7,

70.0, 63.4, 39.2, 27.3, 26.0, 12.9; **HRMS** (ESI^+) calc. for $C_{33}H_{42}O_7Na$ ($[M+Na]^+$): 573.2823; found 573.2820.

(2*S*,3*R*,4*Z*,6*E*,8*E*,10*E*)-12-((4-Methoxybenzyl)oxy)-8-methyldodeca-4,6,8,10-tetraene-1,2,3-triol, 113

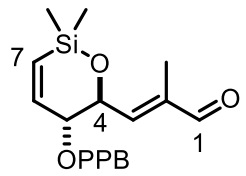


To a vial containing (±)-**112** (10 mg, 18 μmol, 1.0 equiv.) in anhydrous MeOH (0.2 mL) under N_2 atmosphere at 0 °C was added NaMeOH (1 μL, 2 M solution in MeOH, 19 μmol, 1.1 equiv.). After stirring for 1 hr in the dark, NaMeOH (36 μL, 2 M solution in MeOH, 72 μmol, 4.0 equiv.) and stirred further for 16 hrs at room temperature. The solution was diluted with CH_2Cl_2 (5 mL) and quenched with H_2O (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers was dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Purification by flash SiO_2 column chromatography (petroleum ether:EtOAc, 1:1) afforded triol (±)-**113** (5.0 mg, 14 μmol, 79% yield) as a yellow oil.

Rf 0.2 (MeOH:CH_2Cl_2, 1:19); **IR ν_{max}** (thin film) /cm^{-1} 3088, 3029, 1658, 1207, 1027; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.22 (2H, d, *J* = 8.0 Hz, Ar*H*), 6.88 (2H, d, *J* = 8.0 Hz, Ar*H*), 6.48-6.30 (2H, m, 5-*H*, 10-*H*), 6.28 – 6.16 (2H, m, 6-*H*, 7-*H*), 5.98-5.90 (1H, m, 9-*H*), 5.89-5.80 (1H, m, 11-*H*), 5.42- 5.35 (1H, m, 4-*H*), 4.63 (2H, s, OC*H*$_2$Ar), 4.0 (2H, d, *J* = 1.0 Hz,

12-*H*), 3.93 – 3.77 (4H, m, 3-H, OCH_2ArCH_3), 3.66 – 3.60 (3H, m, 1-*H*, 2-*H*), 1.79 (3H, s, 8-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C, 147.0, 142.0, 136.6, 133.2, 129.7, 128.2, 128.0, 127.8, 119.1, 115.4, 115.4, 110.7, 51.1, 40.2, 29.9, 27.3, 16.9, 14.3, 1.2; **HRMS** (ESI^+) calc. for $C_{21}H_{28}O_5Na$ ($[M+Na]^+$): 383.1829; found 383.1827

4-((((5*R*,6*S*)-2,2-Dimethyl-6-((*E*)-2-methyl-3-oxoprop-1-en-1-yl)-5,6-dihydro-2*H*-1,2-oxasilin-5-yl)oxy)methyl)phenyl pivalate, 116

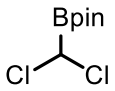


To a solution of crude aldehyde (±)-**115** (0.288 mmol, 1.0 equiv.) in toluene (5 mL) was added 2-(triphenyl-l5-phosphanylidene)propanal (138 mg, 0.432 mmol, 1.5 equiv.). After stirring at 30 °C for 16 hrs, the reaction mixture was diluted with Et_2O (5 mL) and H_2O was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was diluted with Et_2O (8 mL) and pentane (45 mL), filtered to remove the resulting precipitating triphenylphosphine oxide, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:Et_2O, 4:1) afforded cyclic silane (±)-**116** (95 mg, 0.236 mmol, 82% yield over 2 steps) as a pale-yellow oil.

Rf 0.36 (petroleum ether:Et_2O, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H δ 9.43 (1H, s, 1-*H*), 7.24 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.00 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.82 (1H, dd, *J* = 14.5, 2.0 Hz, 6-*H*), 6.34 (1H, dd, *J* = 8.0, 1.5 Hz, 3-*H*), 5.95 (1H, dd, *J* = 14.5, 2.0 Hz, 7-*H*), 4.75 (1H, dd, *J* = 8.0 Hz, 4-*H*), 4.61 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 4.46 (1H, d, *J* = 11.5 Hz, OCH_2Ar),

3.93 (1H, dt, *J* = 8.0, 2.0 Hz, 5-*H*), 1.81 (3H, d, *J* = 1.5 Hz, 2-C*H*$_3$), 1.35 (9H, s, ArOCOC(C*H*$_3$)$_3$), 0.26 (3H, s, Si((C*H*$_3$)$_2$), 0.21 (3H, s, Si((C*H*$_3$)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 168.0, 152.3, 147.9, 137.8, 132.2, 130.8, 130.4, 128.3, 123.3, 118.7, 80.0, 53.6, 33.2, 32.9, 23.7, 16.8, 5.7, 2.5, 1.9; **HRMS** (ESI$^+$) calc. for $C_{22}H_{30}O_5SiNa$ ([M+Na]$^+$): 425.1760; found 425.1765

2-(Dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 117



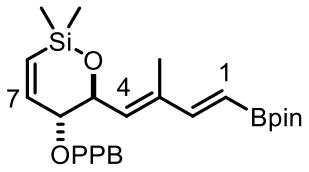
To a solution of CH_2Cl_2 (5.0 mL, 78 mmol, 1.0 equiv.) in THF (100 mL) at −100 °C (MeOH/N_2 (l)) was added a solution of *n*-BuLi (31 mL, 2.5 M in hexanes, 77 mmol, 1.0 equiv.) dropwise over 40 min. After stirring for 40 min at −100 °C, trimethyl borate (8.8 mL, 78 mmol 1.0 equiv.) was added quickly and the reaction mixture was stirred further for 40 min at −100 °C. The mixture was warmed to room temperature and quenched with aqueous HCl (5 M, 30 mL). The organic layer was separated and the aqueous layer was extracted EtOAc (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield (dichloromethyl)boronic acid as a pale-yellow oil.

(Dichloromethyl)boronic acid was dissolved in benzene (25 mL), and pinacol (1.2 g, 9.0 mmol, 0.9 equiv.) and $MgSO_4$ (1.2 g, 9.3 mmol, 1.0 equiv.) were added. After stirring for 48 hrs at reflux, the solution was allowed to cool to room temperature and concentrated. The pale yellow solution was fractionally distilled (68 °C, 1.5 mbar) to yield boronic ester **117** (6.2 g, 55 mmol, 71% yield over 2 steps) as a colourless oil.[145]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.35 (1H, s, C*H*Cl_2BpinH), 1.33 (12H, s, $CHCl_2$Bpin*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 85.9, 24.6.

All spectroscopic data are in accordance with data reported by Benoit *et al*.[145]

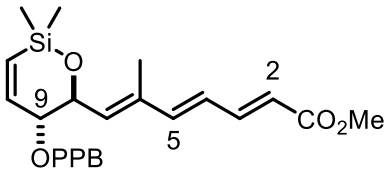
4-((((5*R*,6*S*)-2,2-Dimethyl-6-((1*E*,3*E*)-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)buta-1,3-dien-1-yl)-5,6-dihydro-2*H*-1,2-oxasilin-5-yl)oxy)methyl)phenyl pivalate, 118



A Schlenk flask containing chromium(II) chloride (408 mg, 3.32 mmol, 8.00 equiv.) was activated *in vacuo* by heat until the chromium (II) chloride was free flowing. Upon cooling to room temperature, the flask was filled with N_2 and THF (4.1 mL) was added. The resulting grey suspension was stirred for 30 min, upon which the resulting suspension turning mint green. A solution of aldehyde (±)-**116** (167 mg, 0.415 mmol, 1.00 equiv.) and boronic ester **117** (411 mg, 1.95 mmol, 4.70 equiv.) in THF (2.1 mL) was added slowly *via* syringe, followed by addition of a solution of LiI (222 mg, 1.66 mmol, 4.00 equiv.) in THF (2.0 mL). After stirring for 16 hrs, the solution was diluted with H_2O (10 mL) and ethylenediaminetetraacetic acid disodium salt dihydrate was added and stirred vigorously for 30 min. The solution was diluted Et_2O (15 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (5 × 20 mL) and the combined organic layers were washed with brine (15 mL). The organic layers are then dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:Et_2O, 4:1) afforded cyclic silane (±)-**118** (199 mg, 0.382 mmol, 92% yield) as a bright yellow oil.

Rf 0.15 (petroleum ether:Et_2O, 4:1); **IR ν_{max}** (thin film) /cm^{-1} 2917, 1752, 1732, 1608, 1252; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.29 – 7.24 (2H, m, Ar*H*), 7.08 (1H, dd, *J* = 18.0, 1.0 Hz, 2-*H*), 7.00 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.76 (1H, dd, *J* = 14.5, 2.5 Hz, 7-*H*), 5.91 (1H, dd, *J* = 14.5, 2.0 Hz, 4-*H*), 5.75 – 5.71 (1H, m, 8-*H*), 5.61 (1H, dd, *J* = 18.0, 1.0 Hz, 1-*H*), 4.70 (1H, dd, *J* = 8.5, 8.0 Hz, 6-*H*), 4.55 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 4.51 (1H, d, *J* = 11.5 Hz, OCH_2Ar), 3.83 (1H, dt, *J* = 7.8, 2.2 Hz, 5-*H*), 1.83 (3H, d, *J* = 1.2 Hz, 3-CH_3), 1.35 (9H, s, ArOCOC(CH_3)$_3$), 1.30 – 1.22 (12H, m, Bpin*H*), 0.24 (3H, s, Si((CH_3)$_2$), 0.18 (3H, s, Si((CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 177.2, 153.8, 150.7, 148.9, 138.5, 135.7, 135.6, 129.1, 128.9, 121.5, 83.3, 71.7, 71.5, 39.2, 29.8, 27.3, 25.0, 24.9, 12.8, 1.2, -0.3, -0.6; **HRMS** (ESI^+) calc. for $C_{29}H_{43}O_6BSiNa$ ($[M+Na]^+$): 549.2812; found 549.2811.

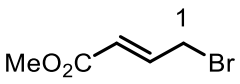
Methyl (2*E*,4*E*,6*E*)-7-((5*R*,6*S*)-2,2-dimethyl-5-((4-(pivaloyloxy)benzyl)oxy)-5,6-dihydro-2*H*-1,2-oxasilin-6-yl)-6-methylhepta-2,4,6-trienoate, 114



To a solution of boronic ester (±)-**118** (180 mg, 0.34 mmol, 1.1 equiv.) in THF:H_2O (1.4:0.34 mL) was added vinyl iodide **62** (66 mg, 0.31 mmol, 1.0 equiv.), Pd(dppf)Cl_2 (23 mg, 0.031 mmol, 0.1 equiv), and Tl_2CO_3 (290 mg, 0.62 mmol, 2.0 equiv.). After stirring for 16 hrs in the dark, the solution was filtered through Celite®, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (petroleum ether:Et_2O, 4:1) afforded trienoate (±)-**114** (79 mg, 0.15 mmol, 47% yield) as a yellow oil.

Rf 0.25 (petroleum ether:Et_2O, 4:1); **IR ν_{max}** (thin film) /cm^{-1} 2985, 1733, 1600, 1249, 1207; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.40 – 7.31 (1H, m, 3-*H*), 7.25 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.98 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.79 (1H, dd, *J* = 14.6, 2.0 Hz, 10-*H*), 6.59 (1H, dd, *J* = 15.4, 0.8 Hz, 5-*H*), 6.41 – 6.30 (1H, m, 4-*H*), 5.95 – 5.88 (2H, m, 2-*H*, 11-*H*), 5.65 (1H, d, *J* = 8.4 Hz, 7-*H*), 4.65 (1H, t, *J* = 8.4 Hz, 8-*H*), 4.60 (1H, d, *J* = 11.7 Hz, OCH_2Ar), 4.48 (1H, d, *J* = 11.7 Hz, OCH_2Ar), 3.86 (1H, dt, *J* = 8.3, 2.1 Hz, 9-*H*), 3.75 (3H, s, 1-CO_2CH_3), 1.85 (3H, d, *J* = 1.2 Hz, 6-CH_3), 1.35 (9H, s, ArOCOC(CH_3)$_3$), 0.24 (3H, s, Si((CH_3)$_2$), 0.19 (3H, s, Si((CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.7, 149.1, 145.2, 145.2, 137.2, 136.5, 135.4, 129.2, 128.5, 128.2, 126.2, 121.6, 120.6, 78.0, 71.6, 71.3, 51.7, 27.3, 13.4, -0.4, -0.7; **HRMS** (ESI^+) calc. for $C_{27}H_{36}O_6SiNa$ ($[M+Na]^+$): 507.2179; found 507.2194.

Methyl (*E*)-4-bromobut-2-enoate, 209

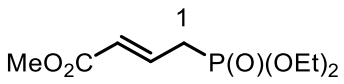


To a solution of methyl crotonate (16 mL, 150 mmol, 1.0 equiv.) and benzoyl peroxide (1.8 g, 7.5 mmol, 5.0 mol%) in benzene (150 mL), was added NBS (29 g, 170 mmol, 1.1 equiv.). After stirring for 16 hr at reflux, the solution was filtered, concentrated *in vacuo*, and dissolved in Et_2O (200 mL). The organic layer was washed with water (2 × 100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash SiO_2 column chromatography (petroleum ether:EtOAc, 20:1) affording bromine **209** (22 g, 120 mmol, 82% yield) as a brown oil.[146]

Rf 0.15 (petroleum ether:EtOAc, 19:1); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.01 (1H, dt, *J* = 15.0, 7.5 Hz, 2-*H*), 6.03 (1H, dt, *J* = 15.0, 1.5 Hz, 3-*H*), 4.01 (2H, dd, *J* = 7.5, 1.5 Hz, 1-*H*), 3.76 (3H, s, CO_2CH_3).

All spectroscopic data are in accordance with data reported by Kosobokov *et al*.[147]

Methyl (*E*)-4-(dimethoxyphosphoryl)but-2-enoate, 160

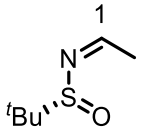


A solution of compound **209** (22 g, 120 mmol, 1.00 equiv.) and triethyl phosphite (1.8 g, 7.5 mmol, 1.1 equiv.) was stirred neat for 16 hrs at 120 °C. The solution was cooled to room temperature and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (MeOH / CH_2Cl_2, 1:99) afforded phosphonate **160** (29 g, 120 mmol, 99% yield) as a yellow oil.[148]

Rf 0.3 (MeOH:CH_2Cl_2, 2.5:97.5); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 6.89 (1H, dt, *J* = 15.5, 8.0 Hz, 2-*H*), 5.96 (1H, d, *J* = 15.5, 3-*H*), 4.19 – 4.04 (4H, m, P(OC*H*$_2$CH$_3$)$_2$), 3.74 (3H, s, CO_2CH_3), 2.74 (2H, ddd, *J* = 23.0, 8.0, 1.5 Hz, 1-*H*), 1.45 – 1.20 (6H, m, P(OCH$_2$C*H*$_3$)$_2$).

All spectroscopic data are in accordance with data reported by Baeckström *et al*.[148]

(*R*,*E*)-*N*-Ethylidene-2-methylpropane-2-sulfinamide, 129

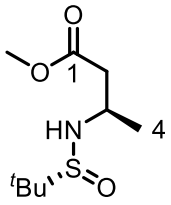


To a solution of (*R*)-(+)-2-methyl-2-propanesulfinamide (10 g, 83 mmol, 1.0 equiv.) and anhydrous $CuSO_4$ (40 g, 250 mmol, 3.0 equiv.) in CH_2Cl_2 (136 mL), was added acetaldehyde (9.3 mL, 170 mmol, 2.0 equiv.). After stirring for 24 hrs, acetaldehyde (9.3 mL, 170 mmol, 2.0 equiv.) was added again and the solution was stirred further for 48 hrs. The resulting suspension was filtered through Celite® and concentrated. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 1:1) afforded imine **129** (12 g, 83 mmol, quantitative) as a colourless oil.[149]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.08 (1H, d, *J* = 5.0 Hz, 1-*H*), 2.23 (3H, d, *J* = 5.0 Hz, 2-*H*), 1.19 (9H, s, SOC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 166.1, 56.7, 22.6, 22.5, 22.5.

All spectroscopic data are in accordance with data reported by Ruan *et al*.[149]

Methyl (*R*)-3-(((*R*)-tert-butylsulfinyl)amino)butanoate, 130



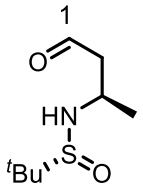
To a solution of DIPA (13.1 mL, 92.5 mmol, 1.25 equiv.) in THF (120 mL) at 0 °C, was added *n*-BuLi (38.5 mL, 2.5 M solution in hexanes, 96.2 mmol, 1.30 equiv.) dropwise. After stirring for 15 min, the solution was cooled to −78 °C and MeOAc (0.970 mL, 12.2 mmol, 1.20 equiv.) was added dropwise. After stirring for 30 min, a solution of $TiCl(O^iPr)_3$ (46.0 mL, 192 mmol, 2.60 equiv.) in THF (40 mL) was added slowly by cannulation. After stirring for 45 min, a solution of imine **129** (10.9 g, 74.0 mmol, 1.00 equiv.) in THF (20 mL) was added dropwise. Upon stirring for 3 hrs at −78 °C, aqueous NH_4Cl (120 mL) was

added to quench the reaction and the mixture was brought to room temperature. The mixture was then diluted with H_2O (50 mL) and EtOAc (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 1:1) afforded ester **130** (13.7 g, 62.0 mmol, 84% yield) as a white solid.[84]

Rf 0.53 (MeOH:CH_2Cl_2, 2.5:97.5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.16 – 4.09 (1H, m, N*H*), 3.84 – 3.71 (1H, m, 3-*H*), 3.69 (3H, d, *J* = 1.5 Hz, OCH_3), 2.73 – 2.50 (2H, m, 2-*H*), 1.26 (3H, dd, *J* = 6.5, 1.5 Hz, 4-*H*), 1.20 (9H, s, SOC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 172.2, 55.6, 51.8, 48.6, 42.0, 22.7, 21.6.; **HRMS** (ESI^+) calc. for $C_9H_{20}NO_3S$ ($[M+H]^+$): 222.1158; found 222.1158.

All spectroscopic data are in accordance with data reported by Tang and Ellman.[84]

(*R*)-2-Methyl-*N*-((*R*)-4-oxobutan-2-yl)propane-2-sulfinamide, 131



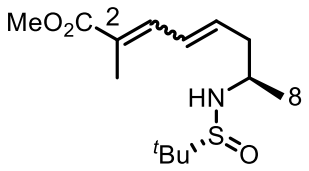
To a solution of ester **130** (3.00 g, 13.6 mmol, 1.00 equiv.) in PhMe (136 mL) at −78 °C, DIBALH (26.3 mL, 1 M solution in hexanes, 26.3 mmol, 1.80 equiv.) at −78 °C was added dropwise along the wall of the round-bottom flask *via* cannula. The reaction mixture was stirred for 15 min, after which it was quenched slowly with MeOH (6 mL). The

solution was warmed to 0 °C, aqueous NaOH (15 wt. %, 1.05 mL) was added and stirred for 15 min. H_2O (3.15 mL) was added and the mixture was warmed to room temperature. After stirring for 20 min, $MgSO_4$ was added and stirred for 15 min. The resulting suspension was filtered through Celite® and concentrated. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 1:1) afforded aldehyde **131** (2.20 g, 11.6 mmol, 85% yield) as a colourless waxy solid.

Rf 0.5 (MeOH:CH_2Cl_2, 97.5:2.5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.78 (1H, t, *J* = 1.5 Hz, 1-*H*), 3.84 (1H, q, *J* = 6.5 Hz, 3-*H*), 3.71 (1H, ddd, *J* = 12.0, 5.5, 1.5 Hz, N*H*), 2.80 (2H, dt, *J* = 5.5, 1.5 Hz, 2-*H*), 1.31 (3H, dd, *J* = 6.5, 1.0 Hz, 4-*H*), 1.20 (9H, d, *J* = 1.0 Hz, SOC(C*H*$_3$)$_3$); **HRMS** (ESI$^+$) calc. for $C_8H_{17}NO_2SNa$ ([M+Na]$^+$): 214.0878; found 214.0854.

All spectroscopic data are in accordance with data reported by Christian Kuper.[55]

Methyl (*R*,3*E*,5*E*)-8-(((*R*)-*tert*-butylsulfinyl)amino)-3-methylnona-3,5-dienoate, 132

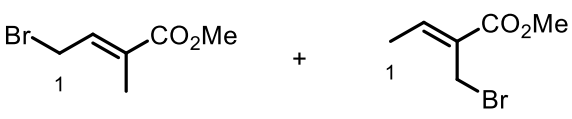


To a suspension of NaH (1.44 g, 60% in mineral oil, 36.0 mmol, 2.00 equiv.) in THF (240 mL) at 0 °C, a solution of phosphonate (13.5 g, 70% pure, 37.8 mmol, 2.10 equiv.), azeotroped with toluene (3 × 30 mL) prior to addition, in THF (24 mL) was added dropwise. After stirring for 30 min, the solution was cooled to −10 °C and a solution of aldehyde **131** (3.44 g, 18.0 mmol, 1.00 equiv.) in THF (30 mL) was added dropwise. The resulting deep

red solution was stirred for 16 hrs at room temperature, and benzaldehyde (3.70 mL, 36.0 mmol, 2.00 equiv.) was added dropwise at 0 °C to quench the excess phosphonate. The mixture was stirred for 6 hrs at room temperature, after which it was diluted with EtOAc (100 mL) and H_2O (60 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ (150 mL) and brine (150 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 1:1) afforded dienoate **132** (5.07 g, 17.6 mmol, 98% yield) as a colourless oil as a 5:1, *E*:*Z* ratio.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −16.1 (C 0.75, $CHCl_3$); ***Rf*** 0.48 (MeOH:CH_2Cl_2, 2.5:97.5); **IR ν_{max}** (thin film) /cm^{-1} 2980, 1711, 1638, 1364, 1025; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.16 (1H, dt, *J* = 11.0, 1.0 Hz, 3-*H*), 6.43 (1H, dd, *J* = 15.0, 11.0 Hz, 4-*H*), 6.02 (1H, dt, *J* = 15.0, 7.5 Hz, 5-*H*), 3.75 (3H, s, OC*H*$_3$), 3.59 – 3.44 (1H, m, 7-*H*), 3.18 (1H, d, *J* = 5.0 Hz, N*H*), 2.43 (2H, dd, *J* = 7.5, 6.0 Hz, 6-*H*), 1.94 (3H, d, *J* = 1.5 Hz, 2-C*H*$_3$), 1.19 (12H, s, SOC(C*H*$_3$)$_3$, 8-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 169.1, 137.3, 134.6, 132.5, 126.9, 63.8, 55.6, 52.0, 50.6, 42.1, 36.9, 21.3, 16.2, 12.8; **HRMS** (ESI^+) calc. for $C_{14}H_{26}NO_3S$ ($[M+H]^+$): 288.1628; found 288.1628.

Methyl (*E*)-4-bromo-2-methylbut-2-enoate, 210



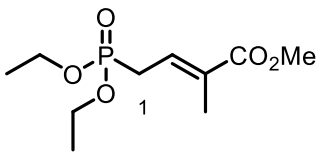
210 **211**

To a solution of methyl tiglate (19.0 mL, 158 mmol, 1.00 equiv.) in CCl_4 (89 mL), was added NBS (28.0 g, 158 mmol, 1.00 equiv.). After stirring for 16 hrs at reflux, the solution was filtered through Celite®, concentrated *in vacuo*, and purified by flash SiO_2 column chromatography (pentane:Et_2O, 19:1) affording title bromides **210** and **211** (27.1 g, 123 mmol, 89% yield) in a 1.6:1 ratio as a brown oil.[150]

Rf 0.15 (EtOAc:petroleum ether,1:19); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 6.92 (1H, tq, *J* = 8.5, 1.0 Hz, 2-*H*), 4.03 (2H, dd, *J* = 8.5, 1.0 Hz, 1-*H*), 3.76 (3H, s, OC*H*$_3$), 1.92 (3H, s, 3-C*H*$_3$).

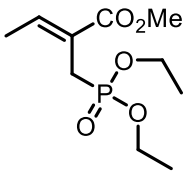
All physical and spectroscopic data are in accordance with data reported by Orsini and Pelizzoni.[150]

Methyl (*E*)-4-(diethoxyphosphoryl)-2-methylbut-2-enoate, 121



121

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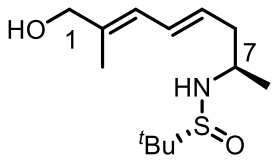
212

A solution of bromide **210** and **211** (12.0 g, 62.2 mmol, 1.00 equiv.) and triethyl phosphite (11.2 mL, 65.3 mmol, 1.05 equiv.) was stirred for 16 hrs at 120 °C. The solution was brought to room temperature and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (MeOH:CH_2Cl_2, 1:99) afforded compounds **121** and **212** (12.0 g, 48.0 mmol, 77% yield) in a 2.5:1 ratio.[151]

Rf 0.33 (MeOH:CH_2Cl_2, 2.5:97.5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.75 (1H, tdd, *J* = 8.0, 7.0, 1.5 Hz, 2-*H*), 4.17 – 4.00 (4H, m, (OC*H*$_2$CH$_3$)$_2$), 3.74 (3H, s, OC*H*$_3$), 2.74 (2H, ddd, *J* = 23.5, 8.0, 1.5 Hz, 1-*H*), 1.95 – 1.83 (3H, m, 3-C*H*$_3$), 1.34 – 1.29 (6H, m, (OCH$_2$C*H*$_3$)$_2$).

All spectroscopic data are in accordance with data reported by Kitahara *et al*.[151]

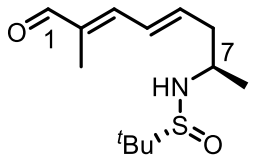
(*R*)-*N*-((*R*,4*E*,6*E*)-8-Hydroxy-7-methylocta-4,6-dien-2-yl)-2-methylpropane-2-sulfinamide, 134



To a solution of ester **132** (1.0 g, 3.5 mmol, 1.0 equiv.) in THF (35 mL) at −78 °C, $LiAlH_4$ (1.1 mL, 4 M solution in Et_2O, 4.2 mmol, 1.2 equiv.) at −78 °C was added dropwise along the wall of the round-bottom flask. After stirring for 40 min, H_2O (0.16 mL) was slowly added to quench the reaction mixture and the solution was warmed to 0 °C. Aqueous NaOH (15 wt. %, 0.16 mL) was added and stirred for 15 min. H_2O (0.48 mL) was added to finish the quench. The mixture was then warmed to room temperature and stirred for 20 min. $MgSO_4$ was added and stirred for 15 min. The resulting suspension was filtered through Celite® and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (MeOH:CH_2Cl_2, 1:99) afforded alcohol **134** (0.75 g, 2.9 mmol, 83% yield) as a colourless waxy semi-solid.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −26.4 (c 1.73, $CHCl_3$); ***Rf*** 0.56 (MeOH:CH_2Cl_2, 1:19); **IR ν_{max}** (thin film) /cm^{-1} 2837, 1670, 1504, 1293, 1251, 1127, 1029, 753; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.36 (1H, dd, *J* = 15.0, 11.0 Hz, 4-*H*), 6.05 (1H, dt, *J* = 11.0, 1.0 Hz, 3-*H*), 5.64 (1H, dt, *J* = 15.0, 7.5 Hz, 5-*H*), 4.06 (2H, s, 1-*H*), 3.46 (1H, qd, *J* = 7.0, 4.5 Hz, 7-*H*), 3.24 (1H, d, *J* = 4.5 Hz, N*H*), 2.34 (2H, q, *J* = 7.0 Hz, 6-*H*), 1.81 – 1.75 (3H, m, 2-CH_3), 1.19 (12H, s, SOC(CH_3)$_3$, 8-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 136.6, 129.9, 129.4, 124.6, 68.6, 55.5, 50.4, 41.9, 22.7, 21.2, 14.3; **HRMS** (ESI^+) calc. for $C_{13}H_{25}NO_2SNa$ ($[M+Na]^+$): 282.1498; found 282.1499.

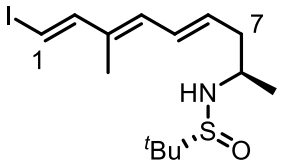
(*R*)-2-Methyl-*N*-((*R*,4*E*,6*E*)-7-methyl-8-oxoocta-4,6-dien-2-yl)propane-2-sulfinamide, 135



To a solution of alcohol **134** (181 mg, 0.699 mmol, 1.0 equiv.) in CH_2Cl_2 (7 mL), was added TPAP (12.3 mg, 0.035 mmol, 5.0 mol%) and NMO (327 mg, 2.79 mmol, 4.0 equiv.). After stirring for 1 hr, the solution was loaded directly onto silica and purified by flash SiO_2 column chromatography (pentane:EtOAc, 1:1) which afforded aldehyde **135** (174 mg, 0.678 mmol, 97% yield) as a white waxy semi-solid.

Rf 0.7 (MeOH:CH_2Cl_2, 1:19); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.40 (1H, s, 1-*H*), 6.81 (1H, dt, *J* = 11.0, 1.5 Hz, 3-*H*), 6.59 (1H, ddt, *J* = 15.0, 11.0, 1.5 Hz, 4-*H*), 6.18 (1H, dt, *J* = 15.0, 7.5 Hz, 5-*H*), 3.57 – 3.43 (1H, m, 7-*H*), 2.47 (2H, ddt, *J* = 7.5, 4.0, 2.0 Hz, 6-*H*), 1.81 (3H, d, *J* = 1.0 Hz, 2-CH_3), 1.17 (12H, s, SOC(CH_3)$_3$, 8-*H*); **HRMS** (ESI^+) calc. for $C_{13}H_{23}NO_2SNa$ ($[M+Na]^+$): 257.1450; found 257.1414

(*R*)-*N*-((*R*,4*E*,6*E*,8*E*)-9-Iodo-7-methylnona-4,6,8-trien-2-yl)-2-methylpropane-2-sulfinamide, 136



A Schlenk flask containing chromium(II) chloride (552 mg, 4.49 mmol, 5.00 equiv.) was activated *in vacuo* by heat until chromium (II) chloride was free flowing. After reaching room temperature, the flask was filled with N_2 and THF (11.3 mL) and the resulting grey suspension was stirred for 30 min. Upon the resulting suspension turning mint green, a solution of iodoform (707 mg, 1.79 mmol, 2.00 equiv.) in THF (5.0 mL) was added and stirred until the resulting suspension turned deep red. A solution of aldehyde **135** (231 mg, 0.900 mmol, 1.00 equiv.) in THF (8.3 mL) was added slowly. After stirring for 16 hrs, the solution was diluted with H_2O (30 mL) and stirred vigorously for 10 min. The solution was diluted with EtOAc (50 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (5 × 50 mL) and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 1:1) afforded triene **136** (141 mg, 0.37 mmol, 41% yield) as a bright yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −18.1 (c 0.73, $CHCl_3$); ***Rf*** 0.58 (MeOH:CH_2Cl_2, 1:19); **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.99 (1H, d, *J* = 14.5 Hz, 2-*H*), 6.33 (1H, dd, *J* = 15.0, 11.0 Hz, 5-*H*), 5.97 (1H, d, *J* = 14.5 Hz, 1-*H*), 5.73 (1H, d, *J* = 11.0 Hz, 4-*H*), 5.55 – 5.43 (1H, m, 6-*H*), 3.31 (1H, m, 8-*H*), 3.07 (1H, s, N*H*), 2.18 – 2.06 (2H, m, 7-*H*), 1.47 (3H, s, 3-CH_3), 1.02 (9H, s, SOC(CH_3)$_3$), 0.97

(3H, d, *J* = 6.0 Hz, 9-*H*); **^{13}C NMR** (101 MHz, C_6D_6) δ_C 149.7, 134.5, 132.3, 132.1, 130.1, 75.5, 55.0, 50.5, 41.8, 22.5, 21.3, 11.9; **HRMS** (ESI^+) calc. for $C_{14}H_{25}INOS$ ($[M+H]^+$): 382.0702; 382.0688.

(Dibromomethylene)triphenyl-l5-phosphane, 213

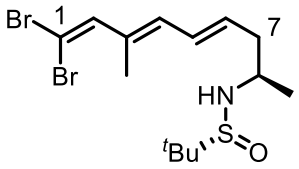
$[Ph_3PCHBr_2]Br \cdot CH_3CN$

To a solution of triphenylphosphine (5.25 g, 20.0 mmol, 2.0 equiv.) in CH_2Cl_2 (50 mL) was added tetrabromomethane (3.32g, 10.0 mmol, 1.0 equiv.). After stirring for 30 min, water (50 mL) was added, the layers separated, and the aqueous layer with CH_2Cl_2 (1 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by dissolving in CH_3CN (50 mL), followed by sonication for 30 min. The mixture was filtered, and the solids were washed with CH_3CN to provide ylide **213** (3.40 g, 6.10 mmol, 61% yield) as a white solid.[152]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.37 (1H, d, *J* = 2.5 Hz, C*H*Br_2), 8.20 – 8.09 (6H, m, Ar*H*), 7.84 – 7.77 (3H, m, Ar*H*), 7.74 – 7.65 (6H, m, Ar*H*), 1.99 (3H, s, C*H*$_3$CN); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 135.7 (d, *J* = 3.1 Hz), 135.1 (d, *J* = 9.7 Hz), 130.4 (d, *J* = 12.8 Hz), 116.5 (d, *J* = 88.8 Hz), 29.8 (d, *J* = 47.5 Hz), 2.06; **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 32.8.

All physical and spectroscopic data are in accordance with data reported by Schmidt *et al*.[152]

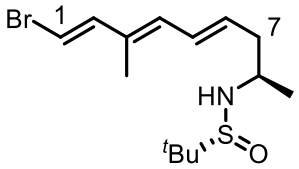
(*R*)-*N*-((*R*,4*E*,6*E*)-9,9-Dibromo-7-methylnona-4,6,8-trien-2-yl)-2-methylpropane-2-sulfinamide, 137



A flask containing ylide **213** (903 mg, 1.60 mmol, 2.20 equiv.), was evacuated and backfilled with N_2 (3×). THF (1.6 mL) and Potassium *t*-butoxide (1.60 mL, 1 M THF, 1.60 mmol, 2.00 equiv.) were added. After stirring for 40 min, a solution of aldehyde **135** (190 mg, 0.740 mmol, 1.00 equiv.) and THF (1.6 mL) was added. Upon further stirring for 3 hrs in the dark, the reaction was loaded directly onto silica. Purification by flash SiO_2 column chromatography (MeOH:CH_2Cl_2, 1:19) was used to afford gem-dibromo triene **137** (240 mg, 0.580 mmol, 79% yield) as brown oil.

Rf 0.52 (MeOH:CH_2Cl_2, 1:19); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.99 (1H, s, 2-*H*), 6.44 – 6.36 (1H, m, 5-*H*), 6.19 (1H, dd, *J* = 11.0, 1.0 Hz, 4-*H*), 5.79 (1H, dt, *J* = 15.0, 7.5 Hz, 6-*H*), 3.51 – 3.46 (1H, m, 8-*H*), 3.24 (1H, d, *J* = 5.0 Hz, N*H*), 2.37 (2H, t, *J* = 7.0 Hz, 7-*H*), 2.03 (3H, d, *J* = 1.5 Hz, 3-CH_3), 1.19 (9H, s, SOC(CH_3)$_3$), 1.18 (3H, d, *J* = 1.5 Hz, 9-*H*).

(*R*)-*N*-((*R*,4*E*,6*E*,8*E*)-9-Bromo-7-methylnona-4,6,8-trien-2-yl)-2-methylpropane-2-sulfinamide, 138

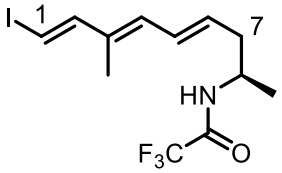


To a solution of gem-dibromo triene **137** (230 mg, 0.580 mmol, 1.0 equiv.) in NEt_3 (410 µL, 2.90 mmol, 5.0 equiv.), was added dimethyl phosphite (1.1 mL, 11.6 mmol, 20

equiv.) slowly. After stirring for 16 hrs in the dark, the solution was concentrated *in vacuo* and purification by flash SiO_2 column chromatography (pentane: EtOAc, 1:1) was used to yield (*E*)-vinlybromo triene **138** (154 mg, 0.460 mmol, 79% yield) as a yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −17.8 (c 0.64, $CHCl_3$); ***Rf*** 0.86 (MeOH:CH_2Cl_2, 1:19); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.74 (1H, d, *J* = 13.5 Hz, 2-*H*), 6.42 (1H, dd, *J* = 15.0, 11.0 Hz, 5-*H*), 6.27 (1H, d, *J* = 13.5 Hz, 1-*H*), 6.03 (1H, d, *J* = 11.0 Hz, 4-*H*), 5.76 (1H, dt, *J* = 15.0, 7.5 Hz, 6-*H*), 3.48 (1H, d, *J* = 7.0 Hz, 8-*H*), 2.43 – 2.32 (2H, m, 7-*H*), 1.84 – 1.81 (3H, m, 3-CH_3), 1.19 (12H, s, SOC(CH_3)$_3$, 9-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 140.7, 133.6, 132.6, 132.0, 131.4, 129.7, 55.6, 50.4, 42.2, 22.7, 21.3, 15.6; **HRMS** (ESI^+) calc. for $C_{14}H_{25}{}^{79}BrNOS$ ($[M+H]^+$): 334.0840; found 334.0821.

2,2,2-Trifluoro-*N*-((*R*,4*E*,6*E*,8*E*)-9-iodo-7-methylnona-4,6,8-trien-2-yl)acetamide, 139



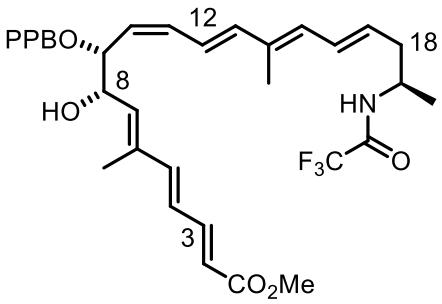
To a solution of iodide **136** (32 mg, 0.090 mmol, 1.0 equiv.) in MeOH (0.18 mL) at 0 °C, was added a solution of acetyl chloride (13 µL, 0.17 mmol, 2.0 equiv.) in MeOH (0.18 mL) dropwise. After stirring for 15 min, CH_2Cl_2 (1 mL) was added and then concentrated *in vacuo* to almost dryness and repeated twice to azeotrope the HCl. The free amine was used in the next step without further purification.

To the solution of crude free amine in CH_2Cl_2 (0.36 mL) at 0 °C, pyridine (28 µL, 0.36 mmol, 4.0 equiv.) and then TFAA (18 µL, 0.12 mmol, 1.5 equiv.) were added dropwise. After stirring for 2 hrs at 0 °C, the solution was quenched with sat. aqueous NH_4Cl (5 mL).

The mixture was diluted with EtOAc (3 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (EtOAc:Pentane, 1:9) afforded trifluoroacetamide **139** (17 mg, 0.046 mmol, 51% yield) as an off-white oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +21.1 (c 0.68, $CHCl_3$) ***Rf*** 0.61 (MeOH:CH_2Cl_2, 1:19); **^{1}H NMR** (400 MHz, C_6D_6) δ_H 6.97 (1H, d, *J* = 14.5 Hz, 2-*H*), 6.09 – 6.01 (1H, m, 5-*H*), 5.99 (1H, d, *J* = 14.5 Hz, 1-*H*), 5.64 (1H, d, *J* = 11.0 Hz, 4-*H*), 5.35 (1H, s, N*H*), 5.25 (1H, dt, *J* = 15.0, 7.5 Hz, 6-*H*), 3.73 (1H, dt, *J* = 14.0, 7.0 Hz, 8-*H*), 1.70 (2H, t, *J* = 7.0 Hz, 7-*H*), 1.42 (3H, d, *J* = 1.0 Hz, 3-C*H*$_3$), 0.58 (3H, dd, *J* = 6.5, 1.5 Hz, 9-*H*); **^{13}C NMR** (101 MHz, C_6D_6) (CF_3 resonance not observed) δ_C 149.5, 134.8, 131.6, 131.1, 129.6, 128.2, 127.9, 75.9, 45.8, 39.3, 19.2, 11.8; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -75.8; **HRMS** (ESI^+) calc. for $C_{12}H_{15}F_3INO$ ($[M+Na]^+$): 396.0048; found 396.0030.

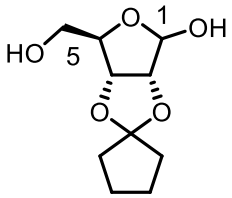
Methyl (2*E*,4*E*,6*E*,8*S*,9*R*,10*Z*,12*E*,14*E*,16*E*,19*R*)-8-hydroxy-6,14-dimethyl-9-((4-(pivaloyloxy)benzyl)oxy)-19-(2,2,2-trifluoroacetamido)icosa-2,4,6,10,12,14,16-heptaenoate, 140



To a vial containing cyclic siloxane (±)-**114** (6.0 mg, 12 μmol, 1.0 equiv.), iodide **139** (5.0 mg, 13 μmol, 1.1 equiv.) and allylpalladium(II) chloride dimer (0.20 mg, 0.60 μmol, 5.0 mol%) under a N_2 atmosphere was added TBAF·$3H_2O$ (36 μl, 1 M in THF, 0.036 mmol, 3.0 equiv.). After stirring for 16 hrs in the dark, the reaction mixture was concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 4:1) afforded **140** (2.5 mg, 3.7 mmol, 31% yield) as a yellow oil as a 1:1 *dr*.

Rf 0.23 (Pentane:EtOAc, 2:1); **^{1}H NMR** (400 MHz, C_6D_6) δ_H 7.41 (1H, dd, *J* = 15.0, 11.0 Hz, 3-*H*), 7.19 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.04 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.47 (1H, ddd, *J* = 15.5, 11.0, 5.5 Hz, 12-*H*), 6.36 (1H, d, *J* = 11.0 Hz, 13-*H*), 6.33 – 6.20 (4H, m, 16-*H*, 15-*H*, 11-*H*, 5-*H*), 6.06 (1H, d, *J* = 11.0 Hz, 4-*H*), 6.01 (1H, d, *J* = 11.2, 2-*H*), 5.88 (1H, d, *J* = 15.5 Hz, 10-*H*), 5.73 (1H, d, *J* = 8.5 Hz, 7-*H*), 5.47 (1H, t, *J* = 10.0 Hz, 17-*H*), 5.35-5.33 (1H, m, N*H*), 4.61 (1H, dt, *J* = 8.5, 4.5 Hz, 8-*H*), 4.57 – 4.52 (1H, m, 9-OCH_2Ar), 4.45 (1H dd, *J* = 9.1, 4.2 Hz, 9-*H*), 4.29 – 4.21 (1H, m, 9-OCH_2Ar), 3.81 (1H, dq, *J* = 12.9, 6.7 Hz, 19-*H*), 3.45 (3H, s, OCH_3), 1.72 (2H, d, *J* = 2.4 Hz, 18-*H*), 1.58 (3H, d, *J* = 1.1 Hz, 6-CH_3), 1.38 – 1.35 (3H, m, 14-CH_3), 1.23 (9H, s, ArOCOC(CH_3)$_3$), 1.72 (3H, t, *J* = 6.5 Hz, 20-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C [1 mg of material proved insufficient to obtain qualitative ^{13}C spectrum]; **HRMS** (ESI^+) calc. for $C_{37}H_{46}F_3NO_7Na$ ($[M+Na]^+$): 696.3119; found 696.3119.

(3a'*R*,6'*R*,6a'*R*)-6'-(Hydroxymethyl)tetrahydrospiro[cyclopentane-1,2'-furo[3,4-d][1,3]dioxol]-4'-ol, 153

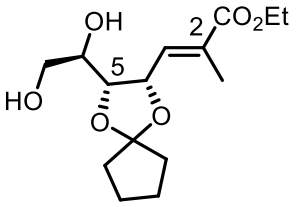


To a solution of (-)-D-Ribose (5.0 g, 33 mmol, 1.0 equiv.) and cyclopentanone (75 mL) in DMF (75 mL) at 0 °C, was added conc. H_2SO_4 (1.0 mL). After stirring for 4 hrs at room temperature, the solution was cooled to 0 °C and solid $NaHCO_3$ was added until the reaction reached pH 7 (indicated by pH paper). The mixture was filtered through Celite® and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 1:1) afforded sugar **153** (5.4 g, 25 mmol, 76% yield) as a yellow viscous liquid.

Rf 0.41 (1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.46 – 5.40 (1H, m, 1-*H*), 4.83 – 4.74 (1H, m, 3-*H*), 4.52 (1H, d, *J* = 6.0 Hz, 2-*H*), 4.43 (1H, q, *J* = 3.0 Hz, 4-*H*), 3.80 – 3.69 (2H, m, 5-*H*), 1.95 – 1.89 (2H, m, cyclopentylidene*H*), 1.68 (6H, tt, *J* = 8.0, 4.5 Hz, cyclopentylidene*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 121.9, 102.9, 87.7, 86.8, 81.7, 63.8, 35.8, 35.8, 23.8, 23.3.

All spectroscopic data are in accordance with data reported by Hirano *et al*.[101]

Ethyl (*E*)-3-((2*S*,3*R*)-3-((*R*)-1,2-dihydroxyethyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-2-methylacrylate, 144



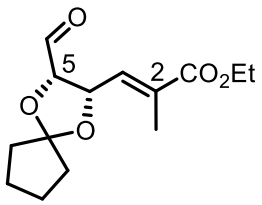
To a solution of cyclopentylidene **153** (2.0 g, 9.2 mmol, 1.0 equiv.) in CH_2Cl_2 (9.2 mL), was added ethyl 2-(triphenylphosphoranylidene)propionate (9.6 g, 28 mmol, 3.0 equiv.). After stirring for 3 days, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and cooled to 0 °C. Benzaldehyde (2.3 mL, 23 mmol, 2.5 equiv.) was added slowly and stirred for 8 hrs at room temperature. The solution was concentrated *in vacuo* and the residue was diluted with Et_2O (30 mL) and pentane (250 mL). The mixture was filtered to remove the resulting precipitating triphenylphosphine oxide, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 3:2) afforded alkene **144** (1.5 g, 5.2 mmol, 56% yield) as a pale-yellow oil.

Rf 0.25 (EtOAc:Pentane, 1:1); **IR ν_{max}** (thin film) /cm^{-1} 3208, 1718; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.75 (1H, dq, *J* = 9.0, 1.5 Hz, 3-*H*), 4.94 (1H, dd, *J* = 9.0, 6.5 Hz, 4-*H*), 4.21-4.14 (3H, m, 5-*H*, $CO_2CH_2CH_3$), 3.87 – 3.64 (3H, m, 6-*H*, 7-*H*), 2.01 – 1.88 (7H, m, 2-CH_3, cyclopentylidene*H*), 1.82 – 1.63 (6H, m, cyclopentylidene*H*), 1.30 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 135.7, 119.5, 78.5, 74.3, 70.1, 64.6, 61.1, 37.3, 36.8, 23.9, 23.3, 14.4, 13.3; **HRMS** (ESI^+) calc. for $C_{15}H_{24}O_6Na$ ($[M+Na]^+$): 323.1466; found 323.1466.

Preparation of sodium periodate adsorbed on silica

$NaIO_4$ (12.9 g, 60.0 mmol) was dissolved in water (25 mL) at 70 °C followed by addition of silica (50.0 g). The resulting slurry was vigorously shaken after which water was removed *in vacuo*.[104]

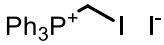
Ethyl (*E*)-3-((2*S*,3*S*)-3-formyl-1,4-dioxaspiro[4.4]nonan-2-yl)-2-methylacrylate, 155



To a solution of protected sugar **144** (300. mg, 0.999 mmol, 1.00 equiv.) in CH_2Cl_2 (5 mL), was added silica supported sodium periodate (2.00 g). After stirring for 30 min, the reaction mixture was diluted with Et_2O (10 mL), filtered through Celite®, and then concentrated *in vacuo*. Aldehyde **155** (263 mg, 0.979 mmol, 98% yield) was isolated as a pale-yellow oil and used in the next step without further purification.

Rf 0.82 (Pentane:EtOAc, 3:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.51 (1H, d, *J* = 3.5 Hz, 6-*H*), 6.62 (1H, dq, *J* = 8.0, 1.5 Hz, 3-*H*), 5.07 – 4.98 (1H, m, 4-*H*), 4.39 (1H, dd, *J* = 7.5, 3.5 Hz, 5-*H*), 4.25 – 4.11 (2H, m, 5-OC*H*$_2$CH$_3$), 2.20 – 1.98 (2H, m, cyclopentylidene*H*), 1.88 (3H, dd, *J* = 1.5, 1.0 Hz, 2-C*H*$_3$), 1.82 – 1.70 (6H, m, cyclopentylidene*H*), 1.28 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 199.5, 166.7, 133.6, 132.9, 121.6, 81.9, 75.6, 61.2, 36.8, 36.7, 24.1, 23.2, 14.3, 13.7; **HRMS** (ESI^+) calc. for $C_{14}H_{20}O_5Na$ ($[M+Na]^+$): 291.1208l; found 291.1229.

(Iodomethyl)triphenylphosphonium iodide, 156

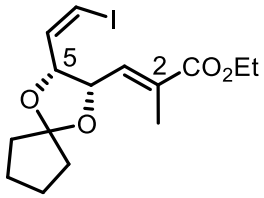


To a solution of triphenylphosphine (60.1 g, 229 mmol, 1.00 equiv.) in benzene (100 mL) was added diiodomethane (24.2 mL, 99%, contains stabilizer, 298 mmol, 1.30 equiv.). After stirring for 16 hrs at reflux in the dark, the crude product was purified by filtration. The white crystals were washed with PhMe (3 × 80 mL) and dried *in vacuo* to yield iodide salt **156** (96.0 g, 181 mmol, 79% yield) as a white solid.[153]

^{1}H NMR (200 MHz, DMSO-d_6) δ_H 8.06 – 7.75 (9H, m, Ar*H*), 7.33 – 7.09 (6H, m, Ar*H*), 5.07 (2H, d, J = 8.5 Hz, CH_2I).

All spectroscopic data are in accordance with data reported by Goundry *et al.*[153]

Ethyl (*E*)-3-((2*S*,3*R*)-3-((*Z*)-2-iodovinyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-2-methylacrylate, 157

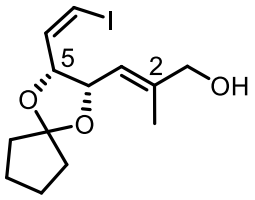


To a solution of ylide **156** (230 mg, 0.44 mmol, 3.0 equiv.) in THF (3 mL) at 0 °C, was added NaHMDS (0.22 mL, 2 M solution in THF, 0.44 mmol, 3.0 equiv.) dropwise. After stirring for 30 min, the reaction mixture was cooled to −78 °C and a solution of aldehyde **155** (39 mg, 0.15 mmol, 1.0 equiv.) in THF (1.8 mL) was added dropwise. The solution was allowed to reach room temperature slowly, and after stirring for 16 hrs in the dark, the solution was cooled to 0 °C. The reaction was quenched with sat. aqueous $NaHCO_3$ (10 mL) and the mixture was diluted with Et_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers

were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:Et_2O, 4:1) afforded alkene **157** (43 mg, 0.11 mmol 76% yield) as a pale-yellow oil.

Rf 0.7 (Pentane:Et_2O, 4:1); **IR ν_{max}** (thin film) /cm^{-1} 2925, 1716, 1619, 1261; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.57 (1H, dd, *J* = 8.5, 1.5 Hz, 3-*H*), 6.47 (1H, dd, *J* = 8.0, 1.0 Hz, 7-*H*), 6.24 (1H, t, *J* = 8.0 Hz, 6-*H*), 4.98 (1H, dd, *J* = 8.5, 6.5 Hz, 4-*H*), 4.87 (1H, ddd, *J* = 8.0, 6.5, 1.0 Hz, 5-*H*), 4.19 (2H, qd, *J* = 7.0, 3.5 Hz, $CO_2CH_2CH_3$), 2.01 – 1.95 (2H, m, cyclopentylidene*H*), 1.90 (3H, d, *J* = 1.5 Hz, 2-CH_3), 1.83 – 1.80 (2H, m, cyclopentylidene*H*), 1.74 – 1.68 (4H, m, cyclopentylidene*H*), 1.29 (3H, t, *J* = 7.1 Hz, OCH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.4, 137.1, 135.9, 131.7, 119.9, 85.7, 81.4, 74.8, 61.0, 37.4, 36.9, 24.0, 23.3, 14.4, 13.6. **HRMS** (ESI^+) calc. for $C_{15}H_{21}IO_4Na$ ($[M+Na]^+$): 415.0377; found 415.0378.

(*E*)-3-((2*S*,3*R*)-3-((*Z*)-2-Iodovinyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-2-methylprop-2-en-1-ol, 158

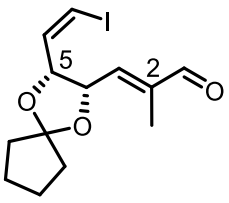


To a solution of ester **157** (409 mg, 1.04 mmol, 1.00 equiv.) in THF (4.2 mL) at −90 °C, DIBALH (2.61 mL, 1 M solution in hexanes, 2.61 mmol, 2.50 equiv.) was added dropwise along the wall of the round-bottom and warmed to −78 °C. After stirring for 20 min the solution was warmed to –46 °C and stirred further for 30 min. Upon completion of the reaction H_2O (0.1 mL) was slowly added to quench the reaction mixture and the solution

was warmed to 0 °C. Aqueous NaOH (15 wt. %, 0.1 mL) was added, stirred for 15 min and H_2O (0.26 mL) was added to finish the quench. The mixture was then warmed to room temperature and stirred for 20 min. $MgSO_4$ was added and stirred further for 15 min. The resulting suspension was filtered through Celite® and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (EtOAc:pentane, 1:4) afforded alcohol **158** (304 mg, 0.868 mmol, 83% yield) as a clear and colourless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −98.0 (C 0.67, $CHCl_3$); ***Rf*** 0.21 (Pentane:Et_2O, 4:1); **IR ν_{max}** (thin film) /cm^{-1} 3334, 2974, 1652, 1047 ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.44 (1H, dd, *J* = 8.0, 1.0 Hz, 7-*H*), 6.27 (1H, t, *J* = 8.0 Hz, 6-*H*), 5.41 (1H, dq, *J* = 9.0, 1.5 Hz, 3-*H*), 4.94 (1H, dd, *J* = 9.0, 6.5 Hz, 4-*H*), 4.79 (1H, ddd, *J* = 8.0, 6.5, 1.0 Hz, 5-*H*), 4.02 (2H, dd, *J* = 6.5, 1.5 Hz, 1-*H*), 1.99 – 1.90 (2H, m, cyclopentylidene*H*), 1.85 – 1.79 (2H, m, cyclopentylidene*H*), 1.75 (3H, d, *J* = 1.4 Hz, 2-C*H*$_3$)), 1.70 (4H, dddd, *J* = 7.5, 5.4, 3.2, 1.1 Hz, cyclopentylidene*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 141.4, 138.0, 119.8, 119.2, 84.9, 81.1, 74.6, 68.0, 37.5, 37.0, 24.0, 23.3, 14.5; **HRMS** (ESI^+) calc. for $C_{13}H_{20}IO_3$ ($[M+H]^+$): 351.0457; found 351.0447.

(*E*)-3-((2*S*,3*R*)-3-((*Z*)-2-Iodovinyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-2-methylacrylaldehyde, 159

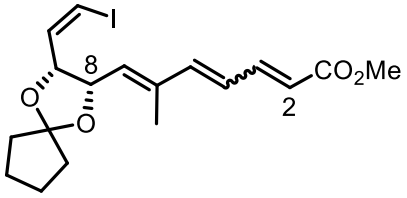


To a solution of alcohol **158** (100 mg, 0.29 mmol, 1.0 equiv.) in CH_2Cl_2 (0.6 mL), was added DMP (130 mg, 0.31 mmol, 1.1 equiv.). After stirring for 30 min, pentane (2 mL) was added, then filtered to remove the resulting precipitating triphenylphosphine oxide, and

concentrated *in vacuo*. Aldehyde **159** (98 mg, 0.28 mmol, 97% yield) was isolated as a clear and colourless oil and was used in the next step without further purification.

Rf 0.76 (Pentane:Et_2O, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.41 (1H, s, 1-*H*), 6.48 (1H, dd, *J* = 8.0, 1.0 Hz, 7-*H*), 6.38 – 6.13 (2H, m, 6-*H*, 3-*H*), 5.13 (1H, dd, *J* = 8.5, 6.5 Hz, 4-*H*), 4.93 (1H, ddd, *J* = 7.5, 6.5, 1.0 Hz, 5-*H*), 2.05 – 1.93 (2H, m, cyclopentylidene*H*), 1.84 (2H, d, *J* = 1.0 Hz, cyclopentylidene*H*), 1.81 (3H, d, *J* = 1.5 Hz, 2-C*H*$_3$), 1.78 – 1.67 (4H, m, cyclopentylidene*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 194.4, 146.9, 141.6, 136.9, 120.3, 85.9, 81.5, 74.5, 37.4, 36.9, 24.0, 23.3, 10.3; **HRMS** (ESI^+) calc. for $C_{13}H_{17}IO_3Na$ ($[M+Na]^+$): 371.0115; found 371.0118.

Methyl (2*E*,4*E*,6*E*)-7-((2*S*,3*R*)-3-((*Z*)-2-Iodovinyl)-1,4-dioxaspiro[4.4]nonan-2-yl)-6-methylhepta-2,4,6-trienoate, 161

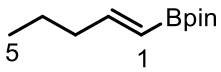


To a suspension of NaH (19 mg, 60% in mineral oil, 0.79 mmol, 2.0 equiv.) in THF (3 mL) at 0 °C, was added a solution of phosphonate **160** (210 mg, 70% pure, 0.83 mmol, 2.1 equiv.), which had been azeotroped with toluene (3 × 30 mL), in THF (1.8 mL) dropwise. After stirring for 30 min, the solution was cooled to −10 °C and a solution of aldehyde **159** (75 mg, 0.40 mmol, 1.0 equiv.) in THF (1.8 mL) was added dropwise. The resulting deep red solution was stirred for 1 hr at room temperature and in the dark, and the solution was diluted with Et_2O (10 mL) and H_2O (5 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were

washed with sat. aqueous $NaHCO_3$ (15 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:Et_2O, 9:1) afforded trienoate **161** (65 mg, 0.15 mmol, 38% yield) as a clear and colourless oil as a 5:1, *E*:*Z* ratio.

$[\alpha]_D^{25}$ −98.2 (C 0.50, $CHCl_3$); ***Rf*** 0.68 (Pentane:Et_2O, 4:1); **IR ν_{max}** (thin film) /cm^{-1} 2954, 1715, 1618, 1434, 1270; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39 – 7.29 (1H, m, 3-*H*), 6.54 (1H, dd, *J* = 15.5, 1.0 Hz, 5-*H*), 6.45 (1H, dd, *J* = 8.0, 1.0 Hz, 11-*H*), 6.37 – 6.28 (1H, m, 4-*H*), 6.24 (1H, t, *J* = 8.0 Hz, 10-*H*), 5.92 (1H, d, *J* = 15.0 Hz, 2-*H*), 5.56 (1H, d, *J* = 9.0 Hz, 7-*H*), 5.03 (1H, dd, *J* = 9.0, 6.5 Hz, 8-*H*), 4.83 (1H, ddd, *J* = 8.0, 6.5, 1.0 Hz, 9-*H*), 3.75 (3H, s, OCH_3), 2.00 – 1.92 (2H, m, cyclopentylidene*H*), 1.87 (3H, d, *J* = 1.0 Hz, 7-CH_3), 1.82 (2H, qd, *J* = 4.5, 1.5 Hz, cyclopentylidene*H*), 1.74 – 1.67 (4H, m, cyclopentylidene*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 145.0, 144.3, 137.7, 137.5, 131.2, 126.5, 121.0, 119.5, 85.3, 81.4, 75.0, 51.7, 37.4, 37.0, 30.4, 24.0, 23.3, 13.4; **HRMS** (ESI^+) calc. for $C_{18}H_{23}IO_4Na$ ($[M+Na]^+$): 453.0533; found 453.0535.

(*E*)-4,4,5,5-Tetramethyl-2-(pent-1-en-1-yl)-1,3,2-dioxaborolane, 162



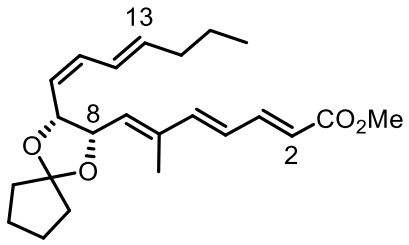
A round-bottom flask containing butenylboronic acid (200 mg, 1.76 mmol, 1.00 equiv.), pinacol (207 mg, 1.76 mmol, 1.00 equiv.), and $MgSO_4$ (530 mg, 4.40 mmol, 2.50 equiv.) was evacuated and backfilled with N_2 (3×). CH_2Cl_2 (1.76 mL) was added and the mixture was stirred for 16 hrs. The solution was then diluted with CH_2Cl_2, filtered, washed with CH_2Cl_2, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography

(petroleum ether:Et_2O, 9:1) afforded pinacol boronic ester **162** (165 mg, 0.845 mmol, 48% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.63 (1H, d, *J* = 18.0 Hz, 2-*H*), 5.42 (1H, d, *J* = 18.0 Hz, 1-*H*), 2.17 – 2.07 (2H, m, 3-*H*), 1.50 – 1.39 (2H, m, 4-*H*), 1.26 (12H, s, Bpin*H*), 0.90 (3H, t, *J* = 7.5 Hz, 5-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 154.7, 83.1, 38.1, 24.9, 21.5, 13.9.

All spectroscopic data are in accordance with data reported by D'Annibale *et al.*[154]

Methyl (2*E*,4*E*,6*E*)-7-((2*S*,3*R*)-3-((1*Z*,3*E*)-hepta-1,3-dien-1-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)-6-methylhepta-2,4,6-trienoate, 163

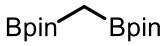


To a solution of trienoate **161** (10 mg, 0.023 mmol, 1.0 equiv.), boronic ester **162** (6.0 mg, 0.026 mmol, 1.2 equiv.), Ag_2O (27 mg, 0.12 mmol, 5.0 equiv.), and Ph_3As (9.0 mg, 0.028 mmol, 1.2 equiv.) in THF:H_2O (1.0 mL:0.1 mL, 10:1), was added $Pd_2(dba)_3$ (3.0 mg, 0.0035 mmol, 15 mol%). After stirring for 2 hrs in the dark, the solution was filtered through Celite® and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:Et_2O, 4:1) afforded diene **163** (5.5 mg, 0.015 mmol, 64% yield) as a yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −94.2 (c 0.91, $CHCl_3$); ***Rf*** 0.63 (Pentane:Et_2O, 4:1); **IR ν_{max}** (thin film) /cm^{-1} 2956, 1717, 1618, 1333,1239, 997; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H δ 7.36 – 7.28 (1H, m, 3-*H*),

6.56 (1H, d, *J* = 15.5 Hz, 5-*H*), 6.35 – 6.20 (2H, m, 4-*H*, 12-*H*), 6.11 (1H, t, *J* = 11.0 Hz, 11-*H*), 5.90 (1H, d, *J* = 15.5 Hz, 2-*H*), 5.74 (1H, dt, *J* = 14.5, 7.0 Hz, 13-*H*), 5.65 (1H, d, *J* = 9.0 Hz, 7-*H*), 5.25 – 5.18 (1H, m, 10-*H*), 5.02 (1H, ddd, *J* = 9.0, 6.5, 1.0 Hz, 9-*H*), 4.93 (1H, dd, *J* = 9.0, 6.5 Hz, 8-*H*), 3.75 (3H, s, OC*H*$_3$), 2.12 – 2.02 (2H, m, 14-*H*), 1.96 (2H, td, *J* = 7.0, 6.5, 1.9 Hz, cyclopentylidene*H*), 1.84 – 1.77 (5H, m, 6-C*H*$_3$, cyclopentylidene*H*), 1.73 – 1.67 (4H, m, cyclopentylidene*H*), 1.45 – 1.36 (2H, m, 15-*H*), 0.89 (3H, t, *J* = 7.5 Hz, 16-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.6, 145.1, 144.7, 138.3, 133.1, 132.5, 126.0, 125.0, 123.4, 120.7, 118.9, 75.4, 74.9, 51.7, 42.5, 37.7, 37.1, 35.1, 24.0, 23.4, 22.4, 13.8, 13.1; **HRMS** (ESI^+) calc. for $C_{23}H_{32}O_4Na$ ($[M+Na]^+$): 395.2193; found 395.2194.

***Bis*(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane, 165**

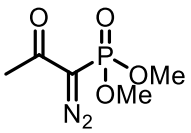


A Schlenk tube containing copper iodide (11 mg, 0.058 mmol, 0.10 equiv.), lithium methoxide (55 mg, 1.4 mmol, 2.5 equiv.), bis(pinacolato)diboron (320 mg, 1.3 mmol, 2.2 equiv.) was evacuated and filled with N_2 (3×). A solution of DMF (2 mL) and dibromomethane (0.040 mL, 0.58 mmol, 1.0 equiv.) was added and stirred for 16 hrs at 40 °C. The solution was then diluted with EtOAc, filtered through silica, washed with EtOAc, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 9:1) afforded boronic ester **165** (120 mg, 44 mmol, 76% yield) as a white solid.[110]

^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.16 (24H, d, *J* = 5.5 Hz, Bpin*H*), 0.29 (2H, s, C*H*$_2$).

All physical and spectroscopic data are in accordance with data reported by Zhang *et al*.[110]

Dimethyl (1-diazo-2-oxopropyl)phosphonate, 166

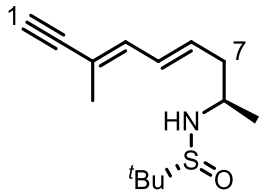


To a suspension of NaH (38 mg, 60% in mineral oil, 0.95 mmol, 1.0 equiv.) in PhMe:THF (3.2 mL, 5:1) at 0 °C, was added dimethyl acetylmethylphosphonate (0.14 mL, 1.05 mmol, 1.1 equiv.) dropwise. After stirring for 20 min, the solution was warmed to room temperature and a solution of 4-aceteamidobenznesulfonyl azide (230 mg, 0.95 mmol, 1.0 equiv.) in THF (0.9 mL) was added dropwise. The reaction was stirred for 16 hrs and subsequently the reaction was filtered through Celite®. The reaction was concentrated *in vacuo* and purified by flash SiO_2 column chromatography (pentane:EtOAc, 2:3) to afford diazophosphonate **166** (180 mg, 0.94 mmol, 99% yield) as a bright yellow oil.[155]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.87 (3H, s, P(O)(OC*H*$_3$)$_2$), 3.81 (3H, s, P(O)(OC*H*$_3$)$_2$), 2.27 (3H, s, C(O)(C*H*$_3$)); **HRMS** (ESI$^+$) calc. for $C_5H_{10}N_2O_4P$ ([M+H]$^+$): 193.0373; found 193.0376.

All spectroscopic data are in accordance with data reported by Kalhor-Monfared *et al.*[155]

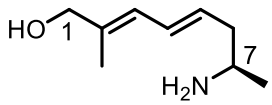
(*R*)-2-methyl-*N*-((*R*,4*E*,6*E*)-7-methylnona-4,6-dien-8-yn-2-yl)propane-2-sulfinamide, 167



To a solution of diazophophonate **166** (630 μL, 2.69 mmol, 2.30 equiv.) in THF (12 mL) at −78 °C, was added NaOMe (126 mg, 2.34 mmol, 2.00 equiv.). After stirring for 45 min, a solution of aldehyde **135** (300 mg, 1.17 mmol, 1.00 equiv.) in THF (12 mL) was added slowly and the solution was stirred for 16 hrs in the dark at room temperature. The solution was then diluted with EtOAc (30 mL) and H_2O (20 mL) was added to quench the reaction mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (MeOH:CH_2Cl_2, 1:39) afforded alkyne **167** (173 mg, 0.679 mmol, 58% yield) as yellow oil.

Rf 0.64 (MeOH:CH_2Cl_2, 1:19); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.47 – 6.32 (2H, m, 4-*H*, 5-*H*), 5.72 (1H, dt, *J* = 14.5, 7.5 Hz, 6-*H*), 3.48 (1H, qd, *J* = 6.5, 5.0 Hz, 8-*H*), 3.19 (1H, d, *J* = 5.0 Hz, N*H*), 2.93 (1H, s, 1-*H*), 2.38 (2H, t, *J* = 7.0 Hz, 7-*H*), 1.90 (3H, dd, *J* = 4.0, 1.4Hz, 3-CH_3), 1.21 – 1.15 (12H, s, SOC(CH_3)$_3$, 9-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 136.7, 132.0, 129.6, 129.5, 117.0, 87.3, 55.6, 50.5, 41.9, 22.7, 21.2, 17.5; **HRMS** (ESI^+) calc. for $C_{14}H_{23}NOSNa$ ($[M+Na]^+$): 276.1393; found 276.1394.

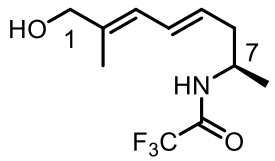
***(R,2E,4E)*-7-Amino-2-methylocta-2,4-dien-1-ol, 190**



To a solution of alcohol **134** (150 mg, 0.58 mmol, 1.0 equiv.) in MeOH (2 mL) at 0 °C, was added acetyl chloride (82 µL, 1.2 mmol, 2.0 equiv.) dropwise. After stirring for 30 min, the solution was quenched H_2O (3 mL), and the pH of the solution was adjusted to pH 3 (indicated by pH paper) using aqueous 3 N HCl. The mixture was diluted with $CHCl_3$ (2 mL) and the organic layer was separated. The aqueous layer was washed with $CHCl_3$ (2 × 3 mL), and the aqueous layer was adjusted to pH 12 (indicated by pH paper) using aqueous 6 N NaOH. The aqueous layer was then extracted with $CHCl_3$ (3 × 5 mL) and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* yielding amine **190** (90 mg, 0.58 mmol, quant. yield) as a white waxy semisolid.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −0.82 (c 0.64, $CHCl_3$); ***Rf*** 0.0 (MeOH:CH_2Cl_2, 1:19); **IR ν_{max}** (thin film) /cm^{-1} 3339, 2912, 1446, 971; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.32 (1H, ddt, *J* = 15.0, 11.0, 1.5 Hz, 4-*H*), 6.04 (1H, ddt, *J* = 11.0, 2.5, 1.5 Hz, 3-*H*), 5.65 (1H, dt, *J* = 15.0, 7.5 Hz, 5-*H*), 4.05 (2H, s, 1-*H*), 3.02 – 2.92 (1H, m, 7-*H*), 2.25 – 2.02 (2H, m, 6-*H*), 1.83 – 1.75 (3H, s, 2-C*H*$_3$), 1.08 (3H, d, *J* = 6.3 Hz, 8-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 136.0, 131.4, 128.7, 124.8, 68.5, 47.0, 43.8, 23.7, 14.3; **HRMS** (ESI^+) calc. for $C_9H_{18}NO$ ($[M+H]^+$): 156.1383; found 156.1382.

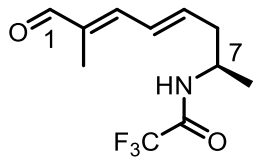
2,2,2-Trifluoro-*N*-((*R*,4*E*,6*E*)-8-hydroxy-7-methylocta-4,6-dien-2-yl)acetamide, 169



To a solution of amine **134** (148 mg, 0.954 mmol, 1.00 equiv.) and NEt_3 (470 µL, 3.34 mmol, 3.50 equiv.) in CH_2Cl_2 (3.0 mL) at 0 °C, was added a solution of TFAA (0.150 mL, 1.05 mmol, 1.10 equiv.) in CH_2Cl_2 (0.6 mL) over 1 hr *via* syringe pump. After stirring further for 1 hr at 0 °C, another solution of TFAA (0.150 mL, 1.05 mmol, 1.10 equiv.) in CH_2Cl_2 (0.5 mL) was added over 1 hr *via* syringe pump. Upon completion of the addition, the solution was quenched with sat. aqueous NH_4Cl (5 mL). The mixture was diluted with EtOAc (3 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (MeOH:CH_2Cl_2, 1:99) was used to yield alcohol **169** (193 mg, 0.768 mmol, 81% yield) as an off white semi-solid.

Rf 0.58 (MeOH:CH_2Cl_2, 1:19); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.34 (1H, dd, *J* = 15.0, 11.0 Hz, 4-*H*), 6.04 (2H, d, *J* = 11.0 Hz, 3-*H*, N*H*), 5.60 (1H, dt, *J* = 15.0, 7.5 Hz, 5-*H*), 4.11 (3H, d, *J* = 13.5 Hz, 7-*H*, 1-*H*), 2.36 (2H, t, *J* = 7.5 Hz, 6-*H*), 1.77 (3H, t, *J* = 1.0 Hz, 2-C*H*$_3$), 1.24 (3H, d, *J* = 6.5 Hz, 8-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 156.4, 137.1, 130.1, 127.7, 124.2, 116.0 (q, J_{CF} = 288.2 Hz), 68.4, 46.2, 39.3, 33.8, 19.8; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -76.0; **HRMS** (ESI^+) calc. for $C_{11}H_{16}F_3NO_2Na$ ($[M+Na]^+$): 274.1031; found 274.1107.

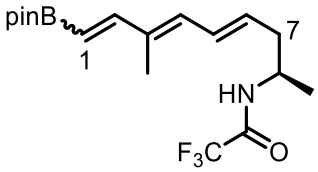
2,2,2-Trifluoro-*N*-((*R*,4*E*,6*E*)-7-methyl-8-oxoocta-4,6-dien-2-yl)acetamide, 214



To a solution of alcohol **169** (53 mg, 0.21 mmol, 1.0 equiv.) in CH_2Cl_2 (2.1 mL), was added TPAP (3.9 mg, 0.011 mmol, 5.0 mol%) and NMO (98 mg, 0.84 mmol, 4.0 equiv.). After stirring for 1 hr, the solution was loaded directly onto silica and purified by flash SiO_2 column chromatography (MeOH:CH_2Cl_2, 1:99) afforded aldehyde **214** (52 mg, 0.21 mmol, quant. yield) as a white waxy semisolid.

Rf 0.35 (EtOAc:pentane, 1:4); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 9.44 (1H, s, 1-*H*), 6.82 (1H, dd, *J* = 11.0, 1.5 Hz, 3-*H*), 6.70 – 6.44 (1H, m, 4-*H*), 6.13 (2H, dt, *J* = 14.5, 7.5 Hz, 5-*H*, N*H*), 4.22 (1H, dd, *J* = 14.5, 7.5 Hz, 7-*H*), 2.50 (2H, t, *J* = 7.5 Hz, 6-*H*), 1.84 (3H, d, *J* = 1.5 Hz, 2-C*H*$_3$), 1.30 (3H, d, *J* = 6.5 Hz, 8-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 195.1, 156.5, 147.8, 138.6, 137.5, 129.2, 115.9 (q, J_{CF} = 287.9), 46.0, 39.9, 29.8, 20.0, 9.5; **^{19}F NMR** (377 MHz, $CDCl_3$) δ_F -76.0; **HRMS** (ESI^+) calc. for $C_{11}H_{15}F_3NO_2$ ($[M+H]^+$): 250.1055; found 250.1087.

2,2,2-Trifluoro-*N*-((*R*,4*E*,6*E*,8*E*)-7-methyl-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nona-4,6,8-trien-2-yl)acetamide, 170

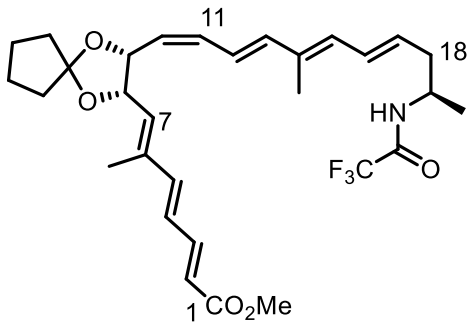


A Schlenk flask containing chromium(II) chloride (205 mg, 1.67 mmol, 8.00 equiv.) was activated *in vacuo* by heat until the chromium (II) chloride was free flowing. After

reaching room temperature, the flask was filled with N_2 and THF (2.1 mL) and the resulting grey suspension was stirred for 30 min. Upon the resulting suspension turning mint green, a solution of aldehyde **214** (52 mg, 0.209 mmol, 1.0 equiv.) and boronic ester **117** (88.0 mg, 0.418 mmol, 2.00 equiv.) in THF (1.1 mL) was added slowly *via* syringe, followed by a slow addition of a solution of LiI (112 mg, 0.835 mmol, 4.00 equiv.) in THF (1.1 mL). After stirring for 16 hrs in the dark, the solution was diluted with H_2O (10 mL) and ethylenediaminetetraacetic acid disodium salt dihydrate was added and stirred vigorously for 30 min. The solution was diluted Et_2O (5 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (5 × 20 mL) and the combined organic layers were washed with brine (30 mL). The organic layers are then dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:Et_2O, 4:1) afforded boronic ester **170** (65.5 mg, 0.176 mmol, 84% yield, 20:1 (*E*:*Z*)) as a maroon oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +52.1 (c 3.10, $CHCl_3$); ***Rf*** 0.45 (EtOAc:Pentane, 1:4); **IR ν_{max}** (thin film) /cm^{-1} 3304, 2917, 1677, 1634, 1184,1157; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.05 (1H, dd, *J* = 18.0, 1.0 Hz, 2-*H*), 6.51 – 6.40 (1H, m, 5-*H*), 6.19 (1H, d, *J* = 11.0 Hz, 4-*H*), 6.07 (1H, d, *J* = 8.0 Hz, N*H*), 5.71 (1H, dt, *J* = 15.0, 7.5 Hz, 6-*H*), 5.60 (1H, d, *J* = 18.0 Hz, 1-*H*), 4.12 (1H, dq, *J* = 8.0, 6.5 Hz, 8-*H*), 2.40 (2H, ddd, *J* = 8.0, 6.0, 1.5 Hz, 7-*H*), 1.85 (3H, d, *J* = 1.0 Hz, 3-C*H*$_3$), 1.28 (12H, s, Bpin*H*), 1.25 (3H, d, *J* = 6.5 Hz, 9-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 171.4, 153.8, 136.0, 133.8, 130.9, 130.4, 128.5, 121.3 (q, J_{CF} = 287.9), 104.3, 83.3, 46.2, 39.5, 24.9, 19.9, 12.1; **HRMS** (ESI^+) calc. for $C_{18}H_{27}BF_3NO_3Na$ ($[M+Na]^+$): 397.1929; found 396.1934.

Methyl (2*E*,4*E*,6*E*)-6-methyl-7-((2*S*,3*R*)-3-((*R*,1*Z*,3*E*,5*E*,7*E*)-5-methyl-10-(2,2,2-trifluoroacetamido)undeca-1,3,5,7-tetraen-1-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)hepta-2,4,6-trienoate, 171

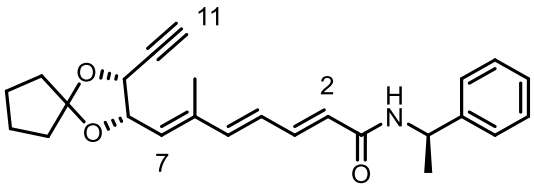


To a solution of trienoate **161** (40 mg, 0.093 mmol, 1.0 equiv.), boronic ester **170** (42 mg, 0.11 mmol, 1.2 equiv.), Ag_2O (110 mg, 0.47 mmol, 5.0 equiv.), and Ph_3As (34 mg, 0.11 mmol, 1.2 equiv.) in THF:H_2O (0.42 mL: 0.040 mL, 10:1), was added $Pd(dba)_2$ (8.0 mg, 0.014 mmol, 15 mol%). After stirring for 2 hrs in the dark, the solution was filtered through Celite® and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 4:1) afforded ester **171** (37 mg, 0.067 mmol, 72% yield) as a neon yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +33 (c 0.63 , $CHCl_3$); ***Rf*** 0.47 (Pentane:EtOAc, 4:1); **IR ν_{max}** (thin film) /cm^{-1} 2928, 1704, 1258, 1090; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.40 – 7.34 (1H, m, 3-*H*), 6.65 (2H, m, 5-*H*, 11-*H*), 6.58 (1H d, *J* = 16.0 Hz, 13-*H*), 6.49 – 6.32 (3H, m, 4-*H*, *12*-*H*, 16-*H*), 6.32 – 6.25 (1H, m, N*H*), 6.06 (1H, d, *J* = 11.0 Hz, 15-*H*), 5.93 (1H, d, *J* = 15.5 Hz, 2-H), 5.85 (1H, dd, *J* = 21.5, 8.5 Hz, 7-*H*), 5.73 (1H, dt, *J* = 15.0, 7.5 Hz, 17-*H*), 5.59 (1H, dd, *J* = 16.0, 2.0 Hz, 10-*H*), 4.96 – 4.85 (2H, m, 8-*H*, 9-*H*), 4.27 – 3.97 (1H, m, 19-*H*), 3.75 (3H, s, OC*H*$_3$), 2.41 (2H, t, *J* = 7.0 Hz, 18-*H*), 1.89 (3H, dd, *J* = 4.0, 1.0 Hz, 6-C*H*$_3$), 1.82 – 1.75 (5H, m, 14-C*H*$_3$, cyclopentylidene*H*), 1.70 (6H, h, *J* = 5.3, 4.2 Hz, cyclopentylidene*H*), 1.25 (3H, d,

J = 6.6 Hz, 20-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.7, 167.5, 147.1, 145.1, 144.7, 138.0, 134.0, 133.9, 133.0, 131.9, 130.9, 130.4, 128.8, 128.6, 127.5, 126.5, 120.5 (q, J_{CF} = 191.7 Hz), 70.0, 51.7, 46.2, 39.4, 37.6, 37.1, 23.7, 23.5, 19.7, 13.3, 12.1; **^{19}F NMR** (377 MHz, $CDCl_3$) δ_F -75.9; **HRMS** (ESI^-) calc. for $C_{30}H_{37}F_3NO_5$ ($[M-H]^-$): 548.2618; found 548.2618.

(2*E*,4*E*,6*E*)-7-((2*S*,3*R*)-3-Ethynyl-1,4-dioxaspiro[4.4]nonan-2-yl)-6-methyl-N-((*R*)-1-phenylethyl)hepta-2,4,6-trienamide, 173

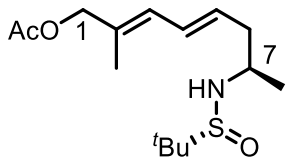


To a solution of trieneoate **161** (61 mg, 0.14 mmol, 1.0 equiv.) in THF:MeOH:H_2O (3:2:1, 0.36 mL), was added $LiOH \cdot H_2O$ (59 mg, 1.4 mmol, 10 equiv.). After stirring for 1 hr, the solution was diluted with $CHCl_3$ (5 mL) and H_2O was added (2 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford crude acid **172** which was carried to the next step without further purification.

To a solution of (*S*)-α-methylbenzylamine (4.0 µL, 33 µmol, 1.0 equiv.), crude acid **172** (11 mg, 36 µmol, 1.1 equiv.), DIPEA (12 µL, 66 µmol, 2.0 equiv.) in DMF (1.6 ml), was added PyBOP (34 mg, 66 µmol, 2.0 equiv.). After stirring for 16 hrs in the dark, sat. aqueous $NaHCO_3$ (10 mL) and EtOAC (5 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 4 mL). The combined organic layers were washed with brine (3 × 50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 2:1) afforded amide **173** (9 mg, 20 µmol, 70% yield) as a yellow oil.

Rf 0.35 (Pentane:EtOAc, 2:1); **IR ν_{max}** (thin film) / cm^{-1} 3284, 3030, 1732, 1650, 1538, 1335, 1107, 998, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.27 (3H, d, *J* = 4.5 Hz, Ar*H*), 7.20 (3H, d, *J* = 6.0 Hz, Ar*H*, 3-*H*), 6.53 (1H, d, *J* = 15.5 Hz, 5-*H*), 6.26 (1H, dd, *J* = 15.5, 11.0 Hz, 4-*H*), 5.87 – 5.74 (2H, m, 2-*H*, 7-*H*), 5.67 (1H, d, *J* = 8.0 Hz, N*H*), 5.22 – 5.11 (1H, m, NHC*H*(CH_3)Ar), 4.78 (1H, dd, *J* = 8.5, 6.0 Hz, 8-*H*), 4.69 (1H, d, *J* = 2.0 Hz, 9-*H*), 2.44 (1H, d, *J* = 2.0 Hz, 11-*H*), 1.81 (3H, d, *J* = 1.0 Hz, 6-C*H*$_3$), 1.75 – 1.68 (4H, m, cyclopentylidene*H*), 1.63 (4H, tdd, *J* = 6.5, 4.5, 2.0 Hz, cyclopentylidene*H*), 1.46 (3H, d, *J* = 7.0 Hz, NHCH(C*H*$_3$)Ar); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.1, 143.1, 141.2, 138.6, 129.7, 128.8, 127.6, 126.8, 126.4, 124.2, 120.2, 79.5, 76.2, 74.7, 68.9, 49.0, 37.5, 37.2, 23.5, 21.8, 13.3; **HRMS** (ESI^+) calc. for $C_{25}H_{29}NO_3Na$ ($[M+Na]^+$): 414.2045; found 414.2023.

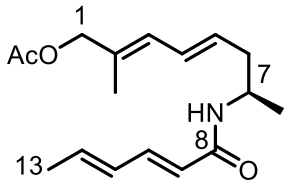
(*R*,2*E*,4*E*)-2-Methyl-7-(2,2,2-trifluoroacetamido)octa-2,4-dien-1-yl acetate, 215



To a solution of DMAP (24.0 mg, 0.200 mmol, 0.100 equiv.) and alcohol **134** (519 mg, 2.00 mmol, 1.00 equiv.) in CH_2Cl_2 (7 mL) at 0 °C, was added acetic anhydride (280 µL, 3.00 mmol, 1.50 equiv.) dropwise. After stirring for 30 min, the solution was quenched with sat. aqueous $NaHCO_3$ (10 mL). The mixture was diluted with EtOAc (3 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (MeOH:CH_2Cl_2, 1:49) was used to yield protected alcohol **215** (567 mg, 1.88 mmol, 94% yield) as an off white waxy semi-solid.

Rf 0.54 (MeOH:CH_2Cl_2, 1:19); **IR ν_{max}** (thin film) /cm^{-1} 3027, 1737, 1659, 1228, 1048; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.45 – 6.33 (1H, m, 4-*H*), 6.04 (1H, d, *J* = 11.0 Hz, 3-*H*), 5.79 – 5.60 (1H, m, 5-*H*), 4.52 (2H, d, *J* = 8.5 Hz, 1-*H*), 3.46 (1H, q, *J* = 6.5 Hz, 7-*H*), 2.45 – 2.28 (2H, m, 6-*H*), 2.08 (3H, d, *J* = 1.0 Hz, OC(O)C*H*$_3$), 1.77 (3H, m, 2-C*H*$_3$), 1.18 (3H, d, *J* = 3.5 Hz, 8-*H*); **HRMS** (ESI^+) calc. for $C_{15}H_{27}NO_3SNa$ ($[M+H]^+$): 324.1609; found 324.1636.

(*R*,2*E*,4*E*)-7-((2*E*,4*E*)-Hexa-2,4-dienamido)-2-methylocta-2,4-dien-1-yl acetate, 175

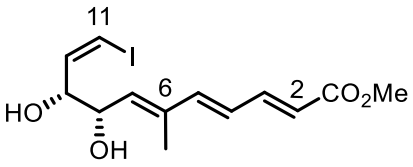


To a solution of amine **174** (30 mg, 0.15 mmol, 1.0 equiv.), sorbic acid (19 mg, 0.17 mmol, 1.1 equiv.), DIPEA (52 µl, 0.30 mmol, 2.0 equiv.) in DMF (7.6 mL), was added DEPC (43 µl, 0.30 mmol, 3.0 equiv.). After stirring for 16 hrs in the dark, sat. aqueous $NaHCO_3$ (10 ml) was added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 4 mL), brine (3 × 50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 2:1) afforded amide **175** (21 mg, 72 µmol, 48% yield) as a yellow oil.

Rf 0.22 (Pentane:EtOAc, 2:1); **IR ν_{max}** (thin film) /cm^{-1} 2982, 1714, 1645, 1240, 1037; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.15 (1H, ddd, *J* = 15.5, 10.0, 6.0 Hz, 10-*H*), 6.33 – 6.24 (2H, m, 4-*H*, 11-*H*), 6.17 – 5.98 (2H, m, 3-*H*, 12-*H*), 5.76 – 5.61 (2H, m, 5-*H*, 9-*H*), 5.37 (1H, d, *J* = 8.5 Hz, N*H*), 4.50 (2H, d, *J* = 12.5 Hz, 1-*H*), 4.22 – 4.07 (1H, m, 7-*H*), 2.42 – 2.23 (2H, m, 6-*H*), 2.08 (3H, d, *J* = 2.5 Hz, 1-OC(O)C*H*$_3$), 1.82 (3H, d, *J* = 6.0 Hz, 13-C*H*$_3$), 1.76 (3H, dd, *J* = 5.0, 1.0 Hz, 2-C*H*$_3$), 1.16 (3H, dd, *J* = 6.5, 3.5 Hz, 7-C*H*$_3$); **^{13}C NMR** (101 MHz,

$CDCl_3$) 171.0, 165.7, 133.1, 131.0, 130.8, 128.8, 128.3, 127.9, 121.8, 69.8, 45.1, 39.9, 34.6, 21.1, 20.4, 18.7, 14.5; **HRMS** (ESI^+) calc. for $C_{17}H_{25}NO_3Na$ ($[M+Na]^+$): 314.1727; found 314.1726.

Methyl (2*E*,4*E*,6*E*,8*S*,9*R*,10*Z*)-8,9-dihydroxy-11-iodo-6-methylundeca-2,4,6,10-tetraenoate, 177

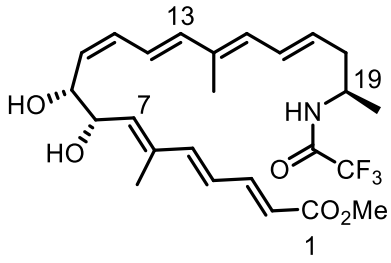


To a solution of trienoate **161** (191 mg, 0.444 mmol, 1.00 equiv.) in MeCN (2.5 mL) at 0 °C, was added hydrofluoric acid (0.5 mL, 48% aqueous) dropwise. After stirring for 20 min in the dark, sat. aqueous $NaHCO_3$ (5 mL) was added slowly to until pH 7 (indicated by pH paper) was reached and diluted with EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 1:1) afforded trieneoate **177** (134 mg, 0.369 mmol, 83% yield) as a pale waxy semi-solid.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −28.0 (c 1.73, $CHCl_3$); ***Rf*** 0.29 (Pentane:EtOAc, 1:1); **IR ν_{max}** (thin film) /cm^{-1} 3398, 2980, 1714, 1616, 1435, 1242, 1143, 772; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.33 (1H, ddd, *J* = 15.5, 11.0, 1.0 Hz, 3-*H*), 6.56 (1H, dd, *J* = 15.5, 1.0 Hz, 5-*H*), 6.50 (1H, dd, *J* = 8.0, 1.0 Hz, 11-*H*), 6.39 – 6.28 (2H, m, 10-*H*, 4-*H*), 5.92 (1H, d, *J* = 15.5 Hz, 2-*H*), 5.70 (1H, d, *J* = 9.0 Hz, 7-*H*), 4.68 (1H, dd, *J* = 9.0, 3.5 Hz, 8-*H*), 4.52 (1H, ddd, *J* = 8.0, 3.5, 1.0 Hz, 9-*H*), 3.75 (3H, s, OCH_3), 2.48 (1H, bs, 9-O*H*), 2.32 (1H, s, 8-O*H*), 1.87 (3H, d, *J* = 1.2 Hz, 6-

C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) 167.6, 144.9, 144.5, 139.0, 137.7, 132.9, 126.7, 121.0, 85.5, 76.9, 70.1, 51.7, 13.3; **HRMS** (ESI^+) calc. for $C_{13}H_{17}IO_4Na$ ($[M+Na]^+$): 387.0064; found 387.0063.

Methyl (2*E*,4*E*,6*E*,8*S*,9*R*,10*Z*,12*E*,14*E*,16*E*,19*R*)-8,9-dihydroxy-6,14-dimethyl-19-(2,2,2-trifluoroacetamido)icosa-2,4,6,10,12,14,16-heptaenoate, 178

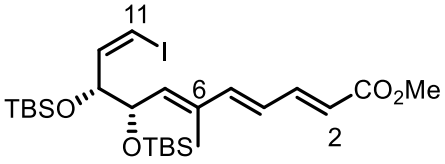


To a solution of trienoate **177** (12 mg, 33 µmol, 1.0 equiv.), boronic ester **170** (15 mg, 40 µmol, 1.2 equiv.), Ag_2O (40 mg, 0.17 mmol, 5.0 equiv.), and Ph_3As (12 mg, 40 µmol, 1.2 equiv.) in THF:H_2O (0.16 mL:20 µL, 10:1), was added $Pd(dba)_2$ (3.0 mg, 5.0 µmol, 15 mol%). After stirring for 2 hrs in the dark, the solution was filtered through Celite® and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 1:1) afforded ester **178** (10 mg, 21 µmol, 63% yield) as a neon yellow oil.

Rf 0.21 (Pentane:EtOAc, 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 (1H, s, 3-*H*), 6.53 – 6.12 (6H, m, 4-*H*, 5-*H*, 11-*H*, 12-*H*, 15-*H*, 16-*H*), 6.03 (1H, d, *J* = 11.1 Hz, 13-*H*), 5.85 (1H, dd, *J* = 15.5, 4.0 Hz, 2-*H*), 5.63 (2H, m, 7-*H*, 17-*H*), 5.38 – 5.29 (1H, m, 10-*H*), 4.62 (1H, td, *J* = 8.5, 8.0, 3.5 Hz, 8-*H*), 4.54 – 4.41 (1H, m, 9-*H*), 4.06 (1H, p, *J* = 6.5 Hz, 19-*H*), 3.68 (3H, s, OC*H*$_3$), 2.33 (2H, t, *J* = 7.0 Hz, 18-*H*), 1.80 (3H, d, *J* = 1.0 Hz, 6-C*H*$_3$), 1.77 (3H, d, *J* = 1.0 Hz, 14-C*H*$_3$), 1.17 (3H, s, 20-*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) (CF_3 resonance not observed) δ_C 177.6, 160.8, 145.0, 144.6, 144.3, 140.2, 139.8, 139.0, 137.7, 134.7, 133.0,

132.2, 130.7, 129.6, 126.7, 121.1, 117.3, 73.6, 57.0, 51.7, 46.2, 39.6, 29.8, 13.3, 12.8; **^{19}F NMR** (377 MHz, MeOD) δ_F -77.3; **HRMS** (ESI$^+$) calc. for $C_{25}H_{32}F_3NO_5Na$ ([M+Na]$^+$): 506.2125; found 506.2123.

Methyl (2*E*,4*E*,6*E*,8*S*,9*R*,10*Z*)-8,9-*bis*((*tert*-butyldimethylsilyl)oxy)-11-iodo-6-methylundeca-2,4,6,10-tetraenoate, 181

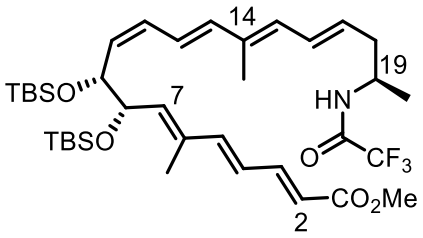


To a solution of diol **177** (20 mg, 55 µmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) at 0 °C, 2,6-lutidine (50 µL, 0.44 mmol, 8.0 equiv.) and was added TBSOTf (50 µL, 0.22 mmol, 4.0 equiv.) dropwise. After stirring for 20 min in the dark, the solution was diluted with Et_2O (2 mL) and sat. aqueous $NaHCO_3$ (5 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:Et_2O, 19:1) afforded trieneoate **181** (29 mg, 49 µmol, 89% yield) as a pale-yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −23.4 (c 1.09 , $CHCl_3$); ***Rf*** 0.9 (Et_2O:Pentane, 1:4); **IR ν_{max}** (thin film) /cm^{-1} 1722, 1653 **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.41 – 7.31 (1H, m, 3-*H*), 6.61 – 6.55 (1H, m, 5-*H*), 6.37 – 6.26 (2H, m, 11-*H*, 4-*H*), 6.14 (1H, t, *J* = 8.0 Hz, 10-*H*), 5.90 (1H, d, *J* = 15.0 Hz, 2-*H*), 5.64 (1H, d, *J* = 9.0 Hz, 7-*H*), 4.44 (1H, dd, *J* = 9.0, 5.0 Hz, 8-*H*), 4.30 (1H, ddd, *J* = 8.0, 5.0, 1.0 Hz, 9-*H*), 3.75 (3H, s, OC*H*$_3$), 1.81 (3H, J, d, *J* = 1.0 Hz, 6-C*H*$_3$), 0.86 (9H, s, OTBS*H*), 0.84 (9H, s, OTBS*H*), 0.05 (6H, s, OTBS*H*), 0.04 (6H, s, OTBS*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.7, 145.5, 145.4, 142.0, 137.9, 134.4, 125.6, 120.2, 82.9, 79.1,

72.6, 51.6, 26.0, 25.9, 18.3, 18.2, 13.4, -4.2, -4.3, -4.4, -4.5; **HRMS** (ESI^+) calc. for $C_{25}H_{45}IO_4Si_2Na$ ($[M+Na]^+$): 615.1793; found 615.1792

Methyl (2*E*,4*E*,6*E*,8*S*,9*R*,10*Z*,12*E*,14*E*,16*E*,19*R*)-8,9-*bis*((*tert*-butyldimethylsilyl)oxy)-6,14-dimethyl-19-(2,2,2-trifluoroacetamido)icosa-2,4,6,10,12,14,16-heptaenoate, 216

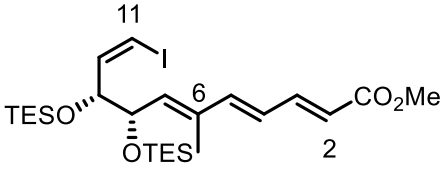


To a solution of trienoate **181** (26 mg, 44 µmol, 1.0 equiv.), boronic ester **170** (20 mg, 0.11 mmol, 1.2 equiv.), Ag_2O (100 mg, 0.22 mmol, 5.0 equiv.), and Ph_3As (32 mg, 0.11 mmol, 1.2 equiv.) in THF:H_2O (0.40 mL:40 µl, 10:1), was added $Pd(dba)_2$ (7.0 mg, 13 µmol, 15 mol%). After stirring for 3 hrs in the dark, the solution was filtered through Celite® and concentrated *in vacuo.* Purification by flash SiO_2 column chromatography (pentane: EtOAc, 4:1) afforded ester **216** (2.0 mg, 3.1 µmol, 7% yield) as a neon yellow oil.

Rf 0.19 (Pentane:Et_2O, 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.33 (1H, m, 3-*H*), 6.56 (1H, d, *J* = 15.2 Hz, 5-*H*), 6.46 (2H, m, 12-*H*, 15-*H*), 6.37 – 6.27 (2H, m, 4-*H*, 16-*H*), 6.23 (1H, d, *J* = 15.4 Hz, 13-*H*), 6.16 (1H, bs, N*H*), 6.10 (1H, q, *J* = 10.9 Hz, 11-*H*), 5.90 (1H, m, 2-*H*), 5.67 (1H, m, 17-*H*), 5.62 (1H, d, *J* = 9.4 Hz, 7-*H*), 5.40 – 5.29 (1H, m, 10-*H*), 4.46 – 4.39 (1H, m, 9-*H*), 4.37 – 4.28 (1H, m, 8-*H*), 4.13 (1H, dt, *J* = 13.9, 6.6 Hz, 19-*H*), 3.75 (3H, s, OC*H*$_3$), 2.40 (2H, t, *J* = 7.0 Hz, 18-*H*), 1.82 (6H, s, 6-C*H*$_3$, 14-C*H*$_3$), 1.25 (3H, s, 20-*H*), 0.82 (18H, d, *J* = 1.2 Hz, TBS*H*), -0.02 (12H, dd, *J* = 5.7, 2.9 Hz, TBS*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 168.9, 167.8, 145.7, 145.5, 139.8, 139.1, 138.4, 135.2, 134.2, 132.6, 131.0,

130.9, 130.5, 125.3, 124.5, 120.0, 117.4 (q, J_{CF} = 221.8 Hz), 73.6, 73.2, 51.6, 46.2, 39.5, 29.9, 25.9, 19.9, 18.3, 13.4, 12.8, -4.3, -4.5, -4.6; **HRMS** (ESI^+) calc. for $C_{37}H_{61}F_3NO_5Si_2$ ($[M+H]^+$): 712.4035; found 712.4045.

Methyl (2*E*,4*E*,6*E*,8*S*,9*R*,10*Z*)-11-iodo-6-methyl-8,9-*bis*((triethylsilyl)oxy)undeca-2,4,6,10-tetraenoate, 179

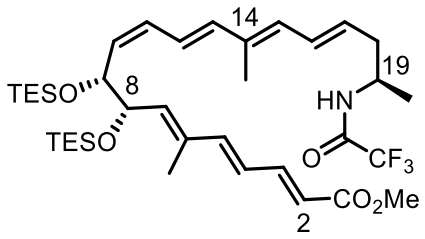


To a solution of diol **177** (35 mg, 97 µmol, 1.0 equiv.) in CH_2Cl_2 (1.1 ml) at 0 °C, was added 2,6-lutidine (0.10 mL, 0.86 mmol, 8.0 equiv.) and TESOTf (0.10 mL, 0.43 mmol, 4.0 equiv.) dropwise. After stirring for 10 min in the dark, the solution was diluted with Et_2O (2 mL) and sat. aqueous $NaHCO_3$ (5 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:Et_2O, 19:1) afforded trieneoate **179** (52 mg, 88 µmol, 91% yield) as a pale-yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −21.1 (c 1.00 , $CHCl_3$); ***Rf*** 0.75 (Pentane:Et_2O, 4:1); **IR ν_{max}** (thin film) /cm^{-1} 1740, 1661, 1455; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35 (1H, dd, *J* = 15.0, 11.0 Hz, 3-*H*), 6.57 (1H, d, *J* = 15.5 Hz, 5-*H*), 6.38 – 6.25 (2H, m, 4-*H*, 11-*H*), 6.16 (1H, t, *J* = 8.5 Hz, 10-*H*), 5.90 (1H, d, *J* = 15.0 Hz, 2-*H*), 5.66 (1H, d, *J* = 9.0 Hz, 7-*H*), 4.46 (1H, dd, *J* = 8.5, 4.5 Hz, 8-*H*), 4.32 (1H, dd, *J* = 8.5, 4.5 Hz, 9-*H*), 3.74 (3H, s, OCH_3), 1.81 (3H, d, *J* = 1.0 Hz, CH_3), 0.93 (18H, t, *J* = 8.0 Hz, OTES*H*), 0.66 – 0.44 (12H, m, OTES*H*); **^{13}C NMR** (101 MHz, $CDCl_3$)

δ_C 167.7, 145.5, 145.4, 141.9, 137.7, 134.3, 125.5, 120.2, 82.6, 72.3, 51.6, 13.3, 6.9, 6.9, 6.6, 5.0, 5.0; **HRMS** (ESI^+) calc. for $C_{25}H_{45}IO_4Si_2Na$ ($[M+Na]^+$): 615.1799; 615.1779.

Methyl (2*E*,4*E*,6*E*,8*S*,9*R*,10*Z*,12*E*,14*E*,16*E*,19*R*)-6,14-dimethyl-8,9-*bis*((triethylsilyl)oxy)-19-(2,2,2-trifluoroacetamido)icosa-2,4,6,10,12,14,16-heptaenoate, 217

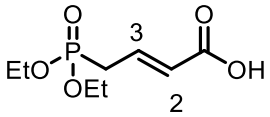


To a solution of trienoate **179** (52 mg, 88 µmol, 1.0 equiv.), boronic ester **170** (39 mg, 0.11 mmol, 1.2 equiv.), Ag_2O (200 mg, 0.44 mmol, 5.0 equiv.), and Ph_3As (32 mg, 0.11 mmol, 1.2 equiv.) in THF:H_2O (0.80 mL:80 µL, 10:1), was added $Pd(dba)_2$ (7.0 mg, 13 µmol, 15 mol%). After stirring for 3 hrs in the dark, the solution was filtered through Celite® and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 4:1) afforded ester **217** (18 mg, 26 µmol, 29% yield) as a neon yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +47.2 (c 1.64, $CHCl_3$)**;** ***Rf*** 0.72 (Pentane:EtOAc, 4:1); **IR ν_{max}** (thin film) /cm^{-1} 3312, 2954, 1700, 1616, 1262, 1092, 964, 726; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39 – 7.28 (1H, m, 3-*H*), 6.55 (1H, d, *J* = 15.0 Hz, 5-*H*), 6.51 – 6.38 (1H, m, 12-*H*), 6.35 – 6.17 (3H, m, 4-*H*, 13-*H*, 16-*H*), 6.15 – 6.04 (2H, m, 11-*H*, 15-*H*), 5.89 (1H, d, *J* = 15.5 Hz, 2-*H*), 5.66 (2H, dd, *J* = 13.0, 8.5 Hz, 7-*H*, 17-*H*), 5.41 – 5.30 (1H, m, 10-*H*), 4.46 (1H, dd, *J* = 9.0, 5.0 Hz, 9-*H*), 4.38 (1H, dd, *J* = 9.0, 5.0 Hz, 8-*H*), 4.17 – 4.09 (1H, m, 19-*H*), 3.75 (3H, s, OCH_3), 2.40 (2H, t, *J* = 7.0 Hz, 18-*H*), 1.84 (3H, s, 14-CH_3), 1.82 (3H, s, 6-CH_3), 1.25 (3H, d, *J* =

6.6 Hz, 20-*H*), 0.90 (18H, td, *J* = 8.0, 2.5 Hz, OTES*H*), 0.53 (12H, qd, *J* = 8.0, 2.5 Hz, OTES*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.8, 156.4, 145.7, 145.5, 138.8, 138.4, 135.1, 134.1, 133.9, 132.3, 131.1, 130.9, 130.3, 125.3, 124.3, 120.0, 116.5 (q, J_{CF} = 231.6), 73.4, 73.0, 51.6, 46.2, 39.5, 19.9, 13.3, 12.7, 6.9, 6.8, 5.1, 5.0; **HRMS** (ESI^-) calc. for $C_{37}H_{59}F_3NO_5Si_2$ ($[M-H]^-$): 710.3878; found 710.3900.

(*E*)-4-(Diethoxyphosphoryl)but-2-enoic acid, 191

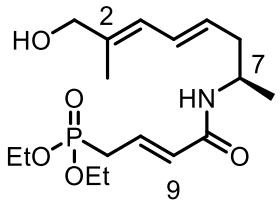


To a solution of phosphonate **160** (300 mg, 1.27 mmol, 1.0 equiv.) in MeOH (4 mL), was added aqueous LiOH (4.20 mL, 3 M solution in H_2O, 12.7 mmol, 10.0 equiv.). After stirring for 2 hrs, the solution was diluted with H_2O (10 mL) and CH_2Cl_2 (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the organic layers were discarded. Subsequently, the aqueous layer was taken to pH 3 (indicated by pH paper) using aqueous 6 N HCl, and $CHCl_3$ (10 mL) was added to the aqueous layer. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. No further purification was necessary to afford acid **191** (234 mg, 1.05 mmol, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.07 – 6.83 (1H, m, 3-*H*), 5.97 (1H, dd, *J* = 15.5, 5.0 Hz, 12-*H*), 4.24 – 4.04 (4H, m, P(O)(OC*H*$_2$CH$_3$)$_2$), 2.78 (2H, ddd, *J* = 23.0, 8.0, 1.4 Hz, 4-*H*), 1.33 (6H, t, *J* = 7.0 Hz, P(O)(OCH$_2$C*H*$_3$)$_2$).

All spectroscopic data are in accordance with data reported by Aoki *et al*.[156]

Diethyl ((*E*)-4-(((*R*,4*E*,6*E*)-8-hydroxy-7-methylocta-4,6-dien-2-yl)amino)-4-oxobut-2-en-1-yl)phosphonate, 192

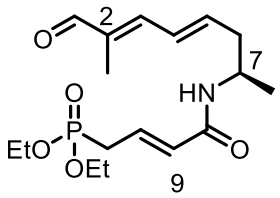


To a solution of acid **191** (252 mg, 1.14 mmol, 1.10 equiv.), EDCI (218 mg, 1.14 mmol, 1.00 equiv.), and HOBt (154 mg, 1.14 mmol, 1.00 equiv.) in CH_2Cl_2 (18 mL), was added DIPEA (400 μL, 2.27 mmol, 2.00 equiv.). After stirring for 5 min, a solution of amine **190** (185 mg, 1.19 mmol, 1.05 equiv.) in CH_2Cl_2 (5 mL) was added slowly. The reaction was stirred for 2 hrs and H_2O (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL) was added. The combined organic layers were washed with aqueous 1 M HCl (10 mL), sat. aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (CH_2Cl_2:MeOH, 49:1) afforded amide **192** (387 mg, 1.08 mmol, 95% yield) as a yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +20.1 (c 0.636, $CHCl_3$); ***Rf*** 0.16 (MeOH:CH_2Cl_2, 1:19); **IR ν_{max}** (thin film) /cm^{-1} 2910, 1670, 1504, 1294, 1127, 1029, 752; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.69 (1H, dd, *J* = 15.5, 8.0 Hz, 10-*H*), 6.35 – 6.23 (H, m, 4-*H*), 6.03 (1H, d, *J* = 11.0 Hz, 3-*H*), 5.94 (1H, dd, *J* = 15.5, 5.0 Hz, 9-*H*), 5.62-5.59 (2H, m, 5-*H*, N*H*), 4.18 – 4.01 (7H, m, 1-*H*, 7-*H*, P(O)(OCH_2CH_3)$_2$), 2.70 (2H, ddd, J_{HP} = 22.5, J_{HH} = 8.0, 1.0 Hz, 11-*H*), 2.31 (2H, t, *J* = 7.0 Hz, 6-*H*), 1.77 (3H, d, *J* = 1.5 Hz, 2-CH_3), 1.32 (6H, t, *J* = 7.1 Hz, P(O)(OCH_2CH_3)$_2$), 1.17 (3H, d, *J* = 6.5 Hz, 7-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 164.4, 149.8, 136.4, 132.6 (d,

J_{CP} = 13.0 Hz), 129.3 (d, J_{CP} = 11.5 Hz), 128.7, 124.7, 68.6, 62.5 (d, J_{CP} = 8.5 Hz), 45.2, 40.0, 30.3 (d, J_{CP} = 139.5 Hz), 20.4, 16.6 (d, J_{CP} = 6.0 Hz), 14.3; **HRMS** (ESI^+) calc. for $C_{17}H_{30}NO_5PNa$ ($[M+Na]^+$): 382.1754; found 382.1753.

Diethyl ((*E*)-4-(((*R*,4*E*,6*E*)-7-methyl-8-oxoocta-4,6-dien-2-yl)amino)-4-oxobut-2-en-1-yl)phosphonate, 193

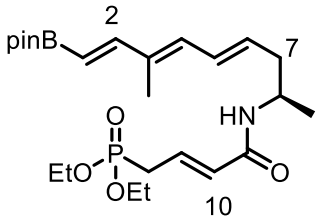


To a solution of amide **192** (7.0 mg, 19 µmol, 1.0 equiv.) in CH_2Cl_2 (0.2 mL), was added MnO_2 (34 mg, 0.39 mmol, 20.0 equiv.). After stirring in the dark for 35 min, the solution filtered over Celite® and concentrated *in vacuo* affording aldehyde **193** (7.0 mg, 19 µmol, quant. yield), and carried to the next step without further purification.

$[\alpha]_D^{25}$ +17.1 (c 0.636, $CHCl_3$); ***Rf*** 0.36 (MeOH:CH_2Cl_2, 1:19); **IR ν_{max}** (thin film) /cm^{-1} 3002, 1634, 1503, 1293, 1128, 1041, 828; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.42 (1H, d, *J* = 2.8 Hz, 1-*H*), 6.81 (1H, d, *J* = 11.0 Hz, 3-*H*), 6.73 (1H, dd, *J* = 15.5, 8.0 Hz, 10-*H*), 6.63 – 6.50 (1H, m, 4-*H*), 6.18 (1H, dd, *J* = 15.0, 7.5 Hz, 5-*H*), 5.94 (1H, dd, *J* = 15.5, 5.0 Hz, 9-*H*), 5.45 (1H, s, N*H*), 4.28 – 4.18 (1H, m, 7-*H*), 4.17 – 4.03 (4H, m, P(O)(OC*H*$_2$CH$_3$)$_2$), 2.70 (2H, dd, J_{HP} = 23.5, J_{HH} = 7.0 Hz, 11-*H*), 2.45 (2H, q, *J* = 7.5 Hz, 6-*H*), 1.83 (3H, s, C*H*$_3$), 1.32 (6H, td, *J* = 7.0, 2.0 Hz, P(O)(OCH$_2$C*H*$_3$)$_2$), 1.23 – 1.19 (3H, m, 7-C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 195.2, 164.4, 148.4, 140.4, 137.0, 133.1 (d, J_{CP} = 11.0 Hz), 128.6, 128.4 (d, J_{CP} = 13.5 Hz), 62.4 (d, J_{CP} = 8.5 Hz), 45.0, 40.6, 30.2 (d, J_{CP} = 139.0 Hz), 20.6,

16.6 (d, J_{CP} = 5.6 Hz), 9.6; **HRMS** (ESI^+) calc. for $C_{17}H_{29}NO_5P$ ($[M+H]^+$): 358.1778; found 358.1778

Diethyl ((*E*)-4-(((*R*,4*E*,6*E*,8*E*)-7-methyl-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nona-4,6,8-trien-2-yl)amino)-4-oxobut-2-en-1-yl)phosphonate, 189

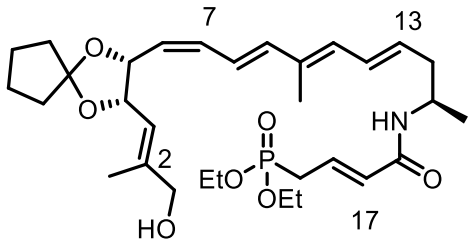


A Schlenk flask containing chromium(II) chloride (896 mg, 7.30 mmol, 8.00 equiv.) was activated *in vacuo* by heat until the chromium (II) chloride was free flowing. After reaching room temperature, the flask was filled with N_2 and THF (9.1 mL) was added and the resulting grey suspension was stirred for 30 min. Upon the resulting suspension turning mint green, a solution of aldehyde **193** (326 mg, 0.910 mmol, 1.00 equiv.) and *gem* dichloroboronic ester **117** (385 mg, 1.82 mmol, 2.00 equiv.) in THF (6.1 mL) was added slowly *via* syringe, followed by addition of a solution of LiI (488 mg, 3.65 mmol, 4.00 equiv.) in THF (3.1 mL). After stirring for 16 hrs in the dark, the solution was diluted with $CHCl_3$ (15 mL) and H_2O (30 mL) was added. The organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (5 × 40 mL) and the combined organic layers were washed with brine (50 mL). The organic layers are then dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (MeOH:CH_2Cl_2, 97:3) afforded boronic ester **189** (373 mg, 0.770 mmol, 85% yield, 10:1 (*E*:*Z*)) as a maroon oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +30.3 (c 0.273, $CHCl_3$); ***Rf*** 0.15 (MeOH:CH_2Cl_2, 1:19); **IR ν_{max}** (thin film) /cm^{-1} 3004, 2837, 1597, 1503, 1293, 1250, 1177, 1126, 1028, 828, 754; **^{1}H NMR** (400 MHz,

$CDCl_3$) δ_H 6.98 (1H, d, *J* = 18.1 Hz, 2-*H*), 6.63 (1H, dd, *J* = 15.3, 7.9 Hz, 11-*H*), 6.36 (1H, ddt, *J* = 15.0, 11.1, 1.3 Hz, 5-*H*), 6.12 (1H, d, *J* = 11.2 Hz, 4-*H*), 5.98 – 5.86 (1H, m, 10-*H*), 5.69 (1H, dt, *J* = 14.9, 7.5 Hz, 6-*H*), 5.50 (1H, d, *J* = 18.0 Hz, 1-*H*), 4.13 – 3.93 (5H, m, 7-*H*, P(O)(OCH_2CH$_3$)$_2$), 2.71 – 2.56 (2H, m, 12-*H*), 2.37 – 2.18 (2H, m, 6-*H*), 1.77 (3H, d, *J* = 1.1 Hz, 3-CH_3), 1.27 – 1.22 (6H, m, P(O)(OCH$_2$CH_3)$_2$), 1.21 (6H, d, *J* = 2.7 Hz, Bpin*H*), 1.16 (6H, s, Bpin*H*), 1.11 (3H, d, *J* = 6.7 Hz, 7-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 164.3, 153.9, 136.7, 135.0, 134.4, 132.6, 132.3 (d, J_{CP} = 11.0 Hz), 129.7, 128.7 (d, J_{CP} = 13.5 Hz), 83.1, 75.0, 62.4 (d, J_{CP} = 6.5 Hz), 45.1, 40.1, 30.0 (d, J_{CP} = 139.0 Hz), 24.8, 20.2, 16.4 (d, J_{CP} = 6.0 Hz), 12.0; **HRMS** (ESI$^+$) calc. for $C_{24}H_{41}BNO_6PNa$ ([M+Na]$^+$): 504.2659; found 504.2658.

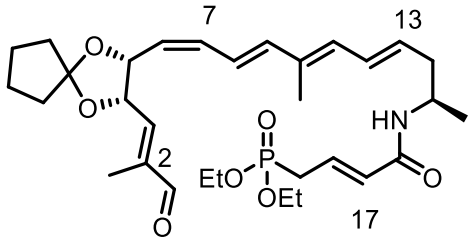
Diethyl ((*E*)-4-(((*R*,4*E*,6*E*,8*E*,10*Z*)-11-((2*R*,3*S*)-3-((*E*)-3-hydroxy-2-methylprop-1-en-1-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)-7-methylundeca-4,6,8,10-tetraen-2-yl)amino)-4-oxobut-2-en-1-yl)phosphonate, 194



To a solution of iodide **158** (30 mg, 87 µmol, 1.0 equiv.), boronic ester **189** (50 mg, 0.10 mmol, 1.2 equiv.), Ag_2O (100 mg, 0.43 mmol, 5.0 equiv.), and Ph_3As (32 mg, 0.10 mmol, 1.2 equiv.) in THF:H_2O (0.55 mL:55 µL, 10:1), was added $Pd_2(dba)_3$ (12 mg, 0.013 mmol, 15 mol%). After stirring for 2 hrs in the dark, the solution was filtered through Celite® and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (MeOH:CH_2Cl_2, 1:49) afforded tetraene **194** (35 mg, 61 µmol, 70% yield) as a neon yellow oil.

$[\alpha]_D^{25}$ +29.3 (c 0.727, $CHCl_3$); ***Rf*** 0.35 (MeOH:CH_2Cl_2, 1:19); **IR ν_{max}** (thin film) /cm^{-1} 1683, 1646, 1635, 1119; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.72 (1H, dt, *J* = 15.5, 8.0 Hz, 18-*H*), 6.52 – 6.36 (2H, m, 8-*H*, 12-*H*), 6.32 – 6.15 (2H, m, 7-*H*, 9-*H*), 6.07 (1H, d, *J* = 11.0 Hz, 11-*H*), 5.92 (1H, dd, *J* = 15.5, 5.0 Hz, 17-*H*), 5.76 – 5.65 (1H, m, 13-*H*), 5.52 – 5.44 (2H, m, 3-*H*, N*H*), 5.44 – 5.33 (1H, m, 6-*H)*, 5.05 – 4.99 (1H, m, 5-*H*), 4.87 (1H, dd, *J* = 9.0, 6.0 Hz, 4-*H*), 4.21 – 4.04 (5H, m, 15-*H*, P(O)(OC$H_2$$CH_3$)$_2$), 3.98 (2H, s, 1-*H*), 2.69 (2H, dd, J_{HP} = 22.5, J_{HH} = 8.0 Hz, 19-*H*), 2.34 (2H, dd, *J* = 17.5, 7.0 Hz, 14-*H*), 1.99 – 1.90 (4H, m, cyclopentylidene*H*), 1.86 (3H, s, 10-CH_3), 1.81 (4H, d, *J* = 6.8 Hz, cyclopentylidene*H*), 1.70 (3H, dd, *J* = 8.0, 4.5 Hz, 2-CH_3), 1.34 – 1.27 (6H, m, P(O)(OCH_2CH_3)$_2$), 1.17 (3H, d, *J* = 6.5 Hz, 15-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 164.3, 140.6, 139.9, 134.0, 133.8, 132.7 (d, J_{CP} = 11.0 Hz), 132.4, 131.3, 128.8, 128.6 (d, J_{CP} = 13.5 Hz), 122.6, 120.8, 118.6, 75.1, 74.7, 68.1, 62.4 (d, J_{CP} = 6.5 Hz), 45.2, 40.2, 37.8, 37.2, 30.2 (d, J_{CP} = 139.2 Hz), 29.8, 23.9, 23.4, 20.4, 16.6 (d, J_{CP} = 6.0 Hz), 14.3, 12.8; **HRMS** (ESI^+) calc. for $C_{31}H_{48}NO_7PNa$ ($[M+Na]^+$): 600.3061; found 600.3061.

Diethyl ((*E*)-4-(((*R*,4*E*,6*E*,8*E*,10*Z*)-7-methyl-11-((2*R*,3*S*)-3-((*E*)-2-methyl-3-oxoprop-1-en-1-yl)-1,4-dioxaspiro[4.4]nonan-2-yl)undeca-4,6,8,10-tetraen-2-yl)amino)-4-oxobut-2-en-1-yl)phosphonate, 195

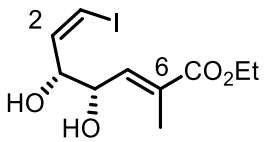


To a solution of alcohol **194** (9.0 mg, 16 µmol, 1.0 equiv.) and K_2CO_3 (6.0 mg, 48 µmol, 3.0 equiv.) in CH_2Cl_2 (0.2 mL), was added DMP (10 mg, 23 µmol, 1.5 equiv.). After stirring for 45 min, the solution was loaded directly on SiO_2 to purification by flash SiO_2

column chromatography (MeOH:CH_2Cl_2, 1:49) affording aldehyde **195** (5.0 mg, 8.6 µmol, 54% yield) as a neon yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +32.1 (c 0.455, $CHCl_3$); ***Rf*** 0.56 (MeOH:CH_2Cl_2, 1:19); **IR** $\boldsymbol{\nu_{max}}$ (thin film) /cm^{-1} 1729, 1672, 1633, 1051; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.41 (1H, s, 1-*H*), 6.72 (1H, dd, *J* = 15.5, 8.0 Hz, 18-*H*), 6.51 – 6.33 (2H, m, 8-*H*, 12-*H*), 6.31 – 6.15 (2H, m, 7-*H*, 9-*H*), 6.09 (1H, d, *J* = 11.5 Hz, 11-*H*), 5.97 – 5.86 (1H, m, 17-*H*), 5.72 (1H, dt, *J* = 15.0, 7.5 Hz, 13-*H*), 5.37 (1H, d, *J* = 8.0 Hz, 3-*H*), 5.28 (1H, dd, *J* = 11.0, 9.0 Hz, 6-*H*), 5.17 (1H, ddd, *J* = 9.0, 6.5, 1.1 Hz, 4-*H*), 5.05 (1H, dd, *J* = 9.0, 6.5 Hz, 5-*H*), 4.20 – 4.04 (5H, m, 15-*H*, P(O)(OC*H*$_2$$CH_3$)$_2$), 2.70 (2H, ddd, J_{HP} = 23.0, J_{HH} = 7.5, 1.5 Hz, 19-*H*), 2.41 – 2.27 (2H, m, 14-*H*), 2.01 (4H, td, *J* = 7.0, 6.5, 3.0 Hz, cyclopentylidene*H*), 1.91 – 1.84 (3H, m, 2-C*H*$_3$), 1.78 – 1.67 (7H, m, cyclopentylidene*H*, 10-CH_3), 1.31 (6H, td, *J* = 7.0, 1.0 Hz, P(O)(OCH$_2$C*H*$_3$)$_2$), 1.25 (3H, s, 15-C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 194.5, 164.3, 148.2, 140.9, 140.9, 133.8, 133.0, 132.8 (d, J_{CP} = 11.0 Hz), 131.7, 129.9, 128.6 (d, J_{CP} = 13.4 Hz), 124.0, 121.8, 119.7, 75.3, 62.4 (d, J_{CP} = 7.2 Hz), 45.3, 40.2, 37.6, 37.0, 30.3 (d, J_{CP} = 139.0 Hz), 29.8, 24.0, 23.4, 22.8, 20.4, 16.6 (d, J_{CP} = 6.0 Hz), 12.8, 9.9; **HRMS** (ESI^+) calc. for $C_{31}H_{46}NO_7PNa$ ($[M+Na]^+$): 598.2904; found 598.2899.

Ethyl (2*E*,4*S*,5*R*,6*Z*)-4,5-dihydroxy-7-iodo-2-methylhepta-2,6-dienoate, 197

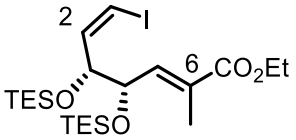


To a solution of ester **157** (477 mg, 1.36 mmol, 1.00 equiv.) in MeCN (23 mL) at 0 °C, was added hydrofluoric acid (4.5 mL, 48%) dropwise. After stirring for 15 min in the dark, sat. aqueous $NaHCO_3$ (80 mL) was added slowly to minimise bubbling and diluted

with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (pentane:EtOAc, 1:1) afforded diol **197** (308 mg, 0.945 mmol, 83% yield) as a pale waxy semi-solid.

$[\alpha]_D^{25}$ −11.0 (c 1.83, $CHCl_3$); ***Rf*** 0.24 (EtOAc:pentane, 1:1); **IR** ν_{max} (thin film) /cm^{-1} 3238, 1697, 1651, 1047; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.70 – 6.58 (1H, m, 5-*H*), 6.60 – 6.45 (1H, m, 1-*H*), 6.33 (1H, d, *J* = 8.0 Hz, 2-*H*), 4.65 (1H, dd, *J* = 8.5, 3.5 Hz, 4-*H*), 4.59 – 4.45 (1H, m, 3-*H*), 4.21 (2H, ddd, *J* = 7.0, 5.5, 2.0 Hz, OC*H*$_2$$CH_3$), 1.91 (3H, t, *J* = 1.5 Hz, 6-C*H*$_3$), 1.30 (3H, td, *J* = 7.0, 5.5 Hz, OCH_2C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.5, 143.3, 138.8, 137.1, 85.8, 80.5, 70.2, 61.1, 14.4; **HRMS** (ESI^+) calc. for $C_{10}H_{15}IO_4Na$ ($[M+Na]^+$): 348.9913; found 348.9898.

Ethyl (2*E*,4*S*,5*R*,6*Z*)-7-iodo-2-methyl-4,5-*bis*((triethylsilyl)oxy)hepta-2,6-dienoate, 220

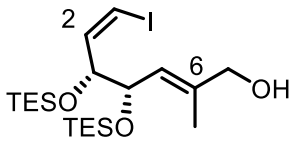


To a solution of diol **197** (278 mg, 0.850 mmol, 1.00 equiv.) in CH_2Cl_2 (8.6 mL) at 0 °C, 2,6-lutidine (800 µL, 6.80 mmol, 8.00 equiv.) and was added TESOTf (760 µL, 3.40 mmol, 4.00 equiv.) dropwise. After stirring for 15 min, the solution was diluted with Et_2O (5 mL) and sat. aqueous $NaHCO_3$ (15 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by

flash SiO_2 column chromatography (pentane:Et_2O, 19:1) afforded TES ether **220** (335 mg, 0.600 mol, 71% yield) as a pale-yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −19.0 (c 0.42, $CHCl_3$); ***Rf*** 0.9 (pentane); **IR** $\boldsymbol{\nu_{max}}$ (thin film) /cm^{-1} 1715, 1654, 1609, 1088; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.68 – 6.51 (1H, m, 5-*H*), 6.40 – 6.26 (1H, m, 1-*H*), 6.18 (1H, t, *J* = 8.0 Hz, 2-*H*), 4.42 (1H, dd, *J* = 9.0, 4.5 Hz, 4-*H*), 4.33 (ddd, *J* = 8.0, 4.5, 1.0 Hz, 3-*H*), 4.26 – 4.14 (2H, m, OC*H*$_2$CH$_3$), 1.86 (3H, dd, *J* = 1.5, 1.0 Hz, 6-C*H*$_3$), 1.28 (2H, td, *J* = 7.0, 2.0 Hz, OCH$_2$C*H*$_3$), 0.98 – 0.85 (18H, m, TES*H*), 0.57 – 0.45 (12H, m, TES*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 167.8, 146.7, 141.6, 141.3, 128.7, 83.0, 60.8, 14.4, 13.5, 7.0, 6.5, 5.0; **HRMS** (ESI^+) not found.

(2*E*,4*S*,5*R*,6*Z*)-7-iodo-2-methyl-4,5-*bis*((triethylsilyl)oxy)hepta-2,6-dien-1-ol, 198

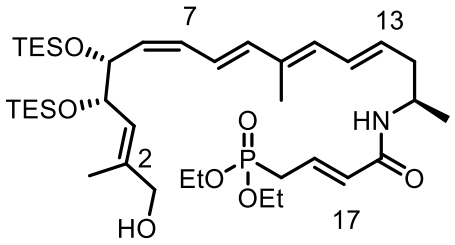


To a solution of ester **220** (243 mg, 0.438 mmol, 1.00 equiv.) in Et_2O (4.4 mL) at −78 °C, was added DIBALH (1.1 mL, 1 M solution in hexanes, 1.10 mmol, 2.50 equiv.) dropwise along the wall of the round-bottom. After stirring for 20 min the solution was warmed to −48 °C and stirred further for 30 min. Upon completion of the reaction H_2O (0.04 mL) was slowly added to quench the reaction mixture and the solution was warmed to 0 °C. Aqueous NaOH (15 wt. %, 0%, mL) was added and stirred for 15 min. H_2O (0.11 mL) was added to finish the quench. The mixture was then warmed to room temperature and stirred for 20 min. $MgSO_4$ was added and stirred further for 15 min. The resulting suspension was filtered through Celite® and concentrated. Purification by flash SiO_2 column

chromatography (EtOAc:pentane, 1:4) afforded alcohol **198** (209 mg, 0.407 mmol, 93% yield) as a clear and colourless oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ −14.6 (c 5.50, $CHCl_3$)***; Rf*** 0.4 (EtOAc:Pentane, 1:9); **IR ν_{max}** (thin film) /cm^{-1} 2954, 1670, 1608, 1097, 1005; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.61 (1H, dd, *J* = 14.5, 6.5 Hz, 2-*H*), 6.25 (1H, dd, *J* = 14.5, 1.0 Hz, 1-*H*), 5.35 (1H, dd, *J* = 9.0, 1.5 Hz, 5-*H*), 4.20 (1H, dd, *J* = 9.0, 6.0 Hz, 4-*H*), 4.01 (2H, d, *J* = 3.0 Hz, 7-*H*), 3.91 (1H, td, *J* = 6.0, 1.0 Hz, 3-*H*), 1.68 (3H, d, *J* = 1.5 Hz, 6-C*H*$_3$), 0.92 (18H, td, *J* = 8.0, 520 Hz, TES*H*), 0.55 (12H, qd, *J* = 8.0, 2.0 Hz, TES*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 147.1, 137.2, 126.4, 79.0, 72.5, 68.5, 14.6, 6.9, 6.9, 5.1, 5.0; **HRMS** (ESI^+) calc. for $C_{20}H_{41}IO_3Si_2Na$ ($[M+Na]^+$): 535.1531; 535.1533.

Diethyl ((*E*)-4-(((2*R*,4*E*,6*E*,8*E*,10*Z*,12*R*,13*S*,14*E*)-16-hydroxy-7,15-dimethyl-12,13-*bis*((triethylsilyl)oxy)hexadeca-4,6,8,10,14-pentaen-2-yl)amino)-4-oxobut-2-en-1-yl)phosphonate, 199



To a solution of iodide **198** (23 mg, 45 µmol, 1.0 equiv.), boronic ester **189** (22 mg, 45 µmol, 1.0 equiv.), Ag_2CO_3 (37 mg, 0.14 mmol, 3.0 equiv.), and Ph_3As (17 mg, 54 µmol, 1.2 equiv.) in THF:H_2O (0.5 mL:50 µL, 10:1), was added $Pd_2(dba)_3$ (6.0 mg, 6.8 µmol, 15 mol%). After stirring for 7 hrs in the dark, the solution was filtered through Celite® and concentrated *in vacuo*. Purification by flash SiO_2 column chromatography (MeOH:CH_2Cl_2, 1:49) afforded tetraene **199** (19 mg, 26 µmol, 57% yield) as a neon yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ +34.2 (c 1.73, $CHCl_3$); ***Rf*** 0.44 (MeOH:CH_2Cl_2, 1:19); **IR ν_{max}** (thin film) /cm^{-1} 3296, 3043, 2876, 2358, 1671, 1629; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.71 (1H, dq, *J* = 15.5, 8.0 Hz, 18-*H*), 6.42 (1H, dd, *J* = 15.0, 11.0 Hz, 12-*H*), 6.29 – 6.17 (3H, m, 7-*H*, 8-*H*, 9-*H*), 6.04 (1H, d, *J* = 11.0 Hz, 11-*H*), 5.92 (1H, dd, *J* = 15.5, 5.0 Hz, 17-*H*), 5.69 (2H, 1H, ddt, *J* = 18.0, 15.0, 7.0 Hz, 6-*H*, 13-*H*), 5.44 (1H, d, *J* = 8.0 Hz, N*H*), 5.38 (1H, d, *J* = 9.0 Hz, 3-*H*), 4.23 (1H, dd, *J* = 9.0, 5.5 Hz, 4-*H*), 4.10 (5H, dt, *J* = 7.0, 4.5 Hz, 15-*H*, (P(O)OC*H*$_2$$CH_3$)$_2$), 4.00 (3H, d, *J* = 9.5 Hz, 1-*H*, 5-*H*), 2.69 (2H, dd, *J* = 23.0, 7.0 Hz, 19-*H*), 2.33 (2H, dd, *J* = 18.0, 7.0 Hz, 14-*H*), 1.86 (3H, s, 10-C*H*$_3$), 1.68 (3H, s, 2-C*H*$_3$), 1.31 (6H, td, *J* = 7.1, 1.8 Hz, (P(O)OCH$_2$C*H*$_3$)$_2$), 1.17 (3H, d, *J* = 6.5 Hz, 15-C*H*$_3$), 0.91 (18H, td, *J* = 8.0, 2.5 Hz, TES*H*), 0.54 (12H, dd, *J* = 8.0, 5.5 Hz, TES*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 164.3, 136.5, 134.5, 134.1, 132.7 (d, J_{CP} = 11.5 Hz), 131.8, 131.6, 131.0, 130.1, 129.5, 128.6 (d, J_{CP} = 13.5 Hz), 128.1, 127.1, 73.2, 68.7, 62.4 (d, J_{CP} = 6.5 Hz), 45.3, 40.2, 30.2 (d, J_{CP} = 139.0 Hz), 29.8, 20.4, 16.6 (d, J_{CP} = 6.0 Hz), 14.6, 12.8, 7.0, 6.9, 5.1, 5.0; **HRMS** (ESI^+) calc. for $C_{38}H_{70}NO_7PSi_2Na$ ($[M+Na]^+$): 762.4321; found 762.4313.

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