Total synthesis of the marine toxin phorboxazole A using palladium(II)-mediated intramolecular alkoxycarbonylation for tetrahydropyran synthesis

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The potent antitumor agent phorboxazole A was synthesized from six subunits comprising C1-C2 (**115**), C3-C8 (**98**), C9-C19 (**74**), C20-C32 (**52**), C33-C41 (**84**) and C42-C46 (**85**). Tetrahydropyrans B and C containing cis-2,6-disubstitution were fabricated via palladium(II)-mediated intramolecular alkoxycarbonylation which, in the case of tetrahydropyran C, was carried out with catalytic palladium(II) 10 and *p*-benzoquinone as the stoichiometric re-oxidant. Tetrahydropyran D was obtained by a stereoselective tin(IV)-catalyzed coupling of a C9 aldehyde with an allylsilane, and the C19-C20 connection was made using a completely stereoselective Wittig-Schlosser (*E*) olefination. Coupling of the oxazole C32 methyl substituent with the intact C33-C46 δ-lactone **3** was accompanied by elimination of the vinyl bromide to a terminal alkyne, but the C32-C33 linkage was implemented successfully with **83** 15 and C33-C41 lactone **84**. The C42-C46 segment of the side chain was then appended via Julia-Kocienski olefination. The macrolide portion of phorboxazole A was completed by means of an Ando-Still-Gennari intramolecular (*Z*)-selective olefination at C2-C3 which required placement of a (dimethoxyphosphinyl)acetate moiety at C24. Final deprotection led to phorboxazole A via a route in which the longest linear sequence is 37 steps and the overall yield is 0.36%.
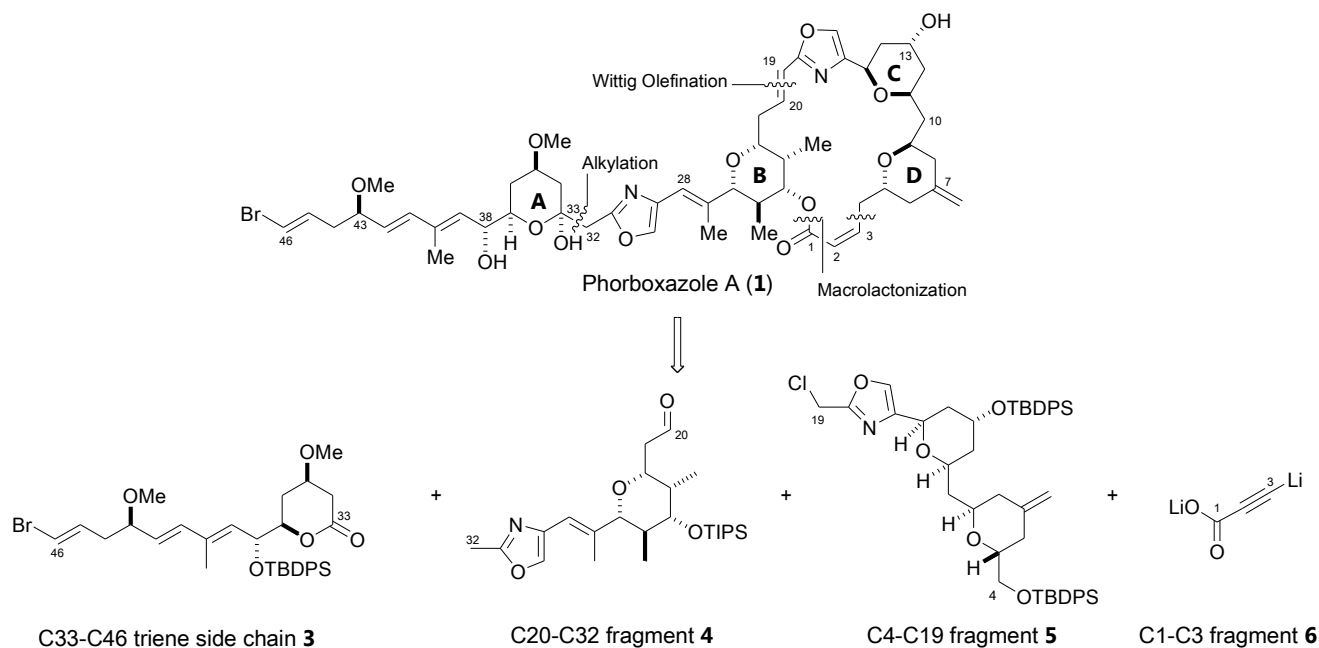
20 ## Introduction

Phorboxazole A (**1**) and its C-13 epimer phorboxazole B (**2**) were isolated in small quantity by Molinski and coworkers from a species of marine sponge of the genus *Phorbas* sp. found in the 25 Indian Ocean.[1] A combination of extensive NMR measurements, derivatization, and degradation studies established the structure and absolute configuration of phorboxazoles A and B which were found to possess an unprecedented carbon skeleton consisting of a highly oxygenated 21-membered macrolactone ring bearing a 30 sixteen-carbon side chain.[2] Three tetrahydropyrans and an oxazole are embedded in the macrolactone portion while a second oxazole and a fourth tetrahydropyran in the form of a cyclic hemiacetal are present in the side chain. Phorboxazole A, with tumor cell growth inhibition in the sub-nanomolar range, is 35 among the most potent cytotoxic agents yet discovered. *In vitro* tests in the National Cancer Institute's panel of 60 human tumor cell lines showed that phorboxazole A inhibited the growth of colon tumor cells HCT-116 and HT29 at GI_{50} 4.36 x 10^{-10} and 3.31 x 10^{-10}, respectively. Cellular bioassays established that 40 phorboxazole A arrests the cell cycle at the S phase and does not affect tubulin polymerization or interfere with the integrity of microtubules. The exact mechanism of action remains unknown but a structure-activity relationship study with phorboxazole A analogues indicated that both the macrolide portion and side

45 chain are essential for activity, suggesting a bimodal interaction of the molecule with key cellular components.[3] The novel structure, potent activity and scarcity in nature of phorboxazoles A and B have combined to make their synthesis an inviting objective.[4-6] There has also been strong interest in the design 50 and synthesis of biologically active phorboxazole A analogues.[7]

Results and Discussion

Our approach to phorboxazole A was conceptualized from four subunits: (i) a C33-C46 side chain component **3**, (ii) a C20-C32 aldehyde **4** containing tetrahydropyran B and an oxazole, (iii) a 55 C4-C19 portion **5** containing tetrahydropyrans C and D as well as a second oxazole, and (iv) a three-carbon unit such as **6** corresponding to C1-C3 (Scheme 1). Connection of side chain **3** with fragment **4** would be made via deprotonation at the C32 methyl group of **4** followed by addition of the resultant anion to 60 the lactone carbonyl of **3,** a coupling tactic employed in Evans' synthesis of phorboxazole B.[5a] A modified Wittig olefination was programmed for linkage of C19 with C20 as an (*E*) double bond. The script for the C1-C3 portion of **1** initially specified its introduction as the dianion of a propiolate, with semi-reduction of 65 the alkyne and macrolactonization completing the synthesis. As events unfolded, this finale had to be abandoned and a different end game was devised.[8]

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Scheme 1 Retrosynthetic analysis of phorboxazole A

Synthesis of the C33-C46 side chain 3

Synthesis of **3** began from commercially available diethyl D-tartrate (**7**) as a C36-C39 platform from which chain extension could be deployed independently from each ester (Scheme 2). The vicinal diol of **7** was first converted to an acetonide and the pair of ethyl esters was reduced to diol **8**. Monosilylation of **8**[9] followed by tosylation of **9** gave **10**, and a Finkelstein reaction of the latter provided iodide **11**. Homologation of **11** with potassium cyanide afforded nitrile **12** which was reduced to aldehyde **13**. Asymmetric allylation[10] of aldehyde **13** gave (*S*) homoallylic alcohol **14** in good yield and excellent diastereoselectivity (dr 96:4). After conversion of **14** to its methyl ether **15**, the terminal double bond was cleaved by ozonolysis to provide aldehyde **16**. Acid catalyzed methanolysis of the acetonide was followed by spontaneous cyclization to afford cyclic acetal **17**. In order to effect selective oxidation of diol **17**, the primary alcohol was protected with *tert*-butylchlorodimethylsilane and the secondary alcohol of **18** was masked as its *tert*-butyldiphenylsilyl ether **19**. Selective deprotection of the primary alcohol and subsequent Swern oxidation of **20** then gave aldehyde **21**.

Several methods were explored with **21** for introducing the (*E*)-trisubstituted double bond at C39-C40. Triethyl 2-phosphonopropionate reacted with **21** to give an acceptable yield of α,β-unsaturated ester **22** but with an unfavourable (*E/Z*) ratio of 1:2. Fortunately, it was found that **21** reacted with ylide **23** to give a nearly quantitative yield of ester **22** with excellent stereoselectivity favouring the desired (*E*) isomer (Scheme 3).[11] The ester was reduced to primary alcohol **24** which was oxidized to aldehyde **25**, and Horner-Wadsworth-Emmons olefination of **25** with triethyl phosphonoacetate (**26**) cleanly provided (*E,E*)-dienoate **27**. The latter was converted via alcohol **28** to aldehyde **29** by a reduction-oxidation sequence analogous to that used with **22**. Asymmetric allylation[10] of **29** gave homoallylic alcohol **30** (dr>20:1) in good yield, and the hydroxyl group was methylated to furnish triene ether **31**.
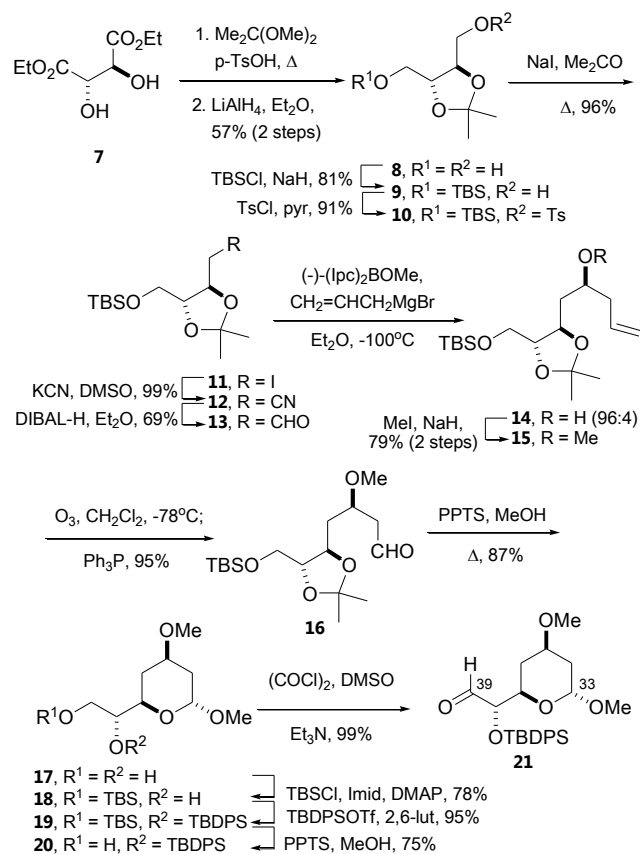

Scheme 2 Synthesis of C33-C39 subunit from diethyl tartrate

Oxidative cleavage of the terminal olefin of **31** was initially plagued by competing hydroxylation of the internal diene, but

this could be avoided by using catalytic osmium tetraoxide and stoichiometric sodium periodate under carefully controlled conditions.[12] This protocol resulted in an acceptable yield of aldehyde **32**. The aldehyde was advanced to (E)-vinyl bromide **33** by a Takai reaction[13] with bromoform and chromous chloride, but halogen exchange during the reaction generated variable quantities of the (E)-chloroalkene from which separation of pure **33** was tedious. A solution to this problem was found in a subsequent Takai reaction that produced the (E)-bromoalkene exclusively (vide infra).
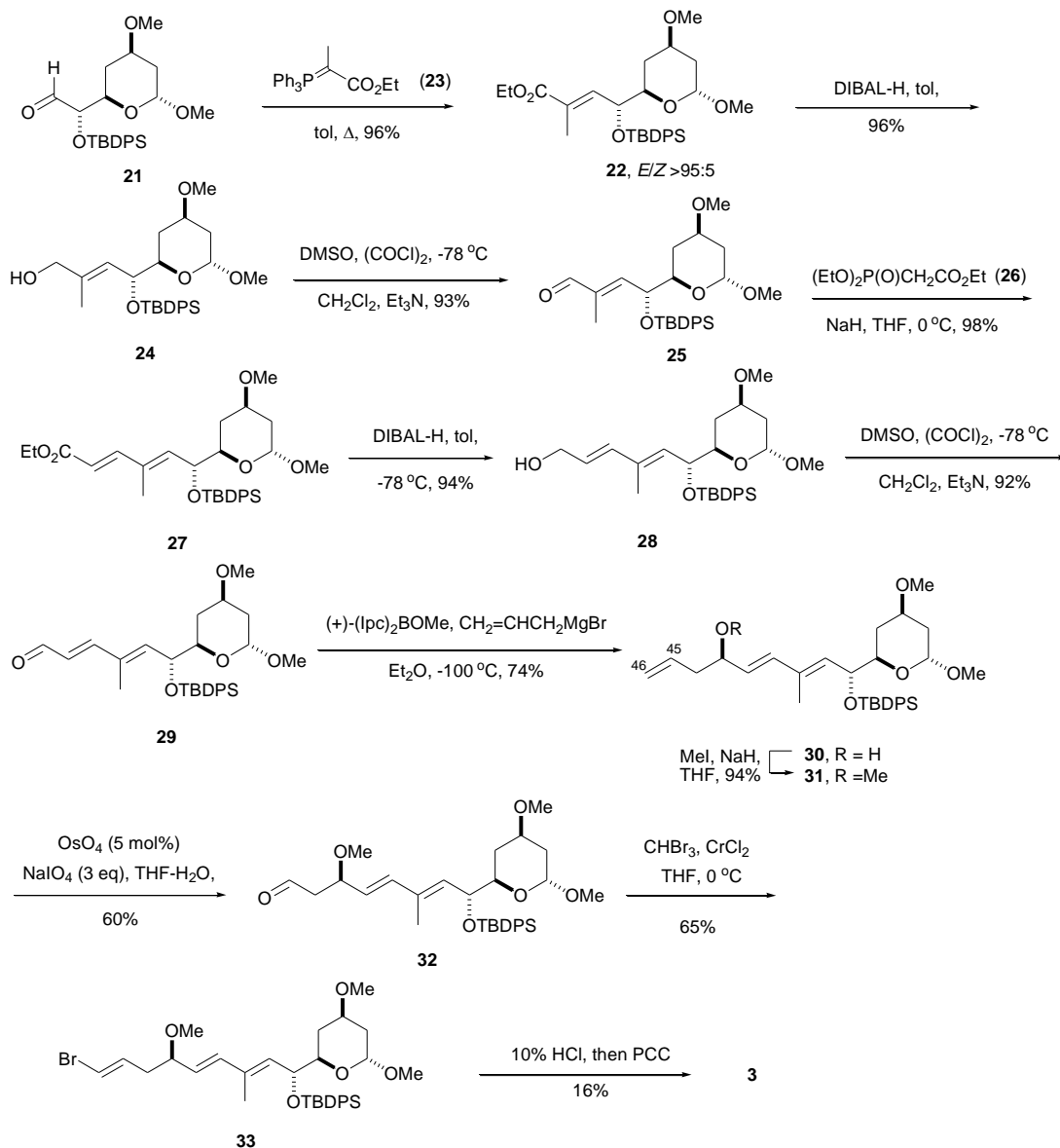
Scheme 3 Synthesis of C33-C46 side chain **3** from aldehyde **21**

From **33**, there remained only the seemingly straightforward task of converting the methyl acetal to a δ-lactone in order to reach **3** (Scheme 3). However, attempted hydrolysis of acetal **33** under acidic conditions produced an intractable mixture that appeaed to result from elimination of methanol from the side chain to give an unstable conjugated tetraene. This outcome indicated that a path to **3** would be needed that avoided acidic reagents for generating the lactone carbonyl from a precursor bearing the methoxy triene unit. In a previous study, we found that a thiophenyl acetal can serve as a convenient surrogate for a δ-lactone due to its facile hydrolytic cleavage in the presence of silver ion and in situ oxidation of the resultant hemiacetal.[14] We returned to **20** to exploit this tactic and found that treatment of this methyl acetal with trimethylsilylthiophenol and zinc iodide as described by Hanessian[15] gave a 2:1 mixture of thioacetal anomers, **34α** and **34β**, in good yield (Scheme 4). The anomers were separated by chromatography, but in order to simplify spectral interpretation of subsequent intermediates only the major anomer **34α** was carried forward.

Thiophenyl acetal **34α** was advanced to triene **35** by a nine-step sequence analogous to that used to take **20** to **31** (Scheme 4. When **35** was exposed to silver nitrate-catalyzed hydrolysis, a mixture of anomeric hemiacetals was produced which yielded a single δ-lactone **36** upon oxidation with Ley's reagent.[16] Oxidative cleavage of the terminal olefin of **36** under conditions used with **31** gave aldehyde **37** but a conventional Takai reaction of **37** with chromous chloride and bromoform again produced the terminal (E)-chloroalkene as a troublesome by-product.[17]

Modified conditions using chromous bromide, prepared by reduction of chromium(III) bromide with lithium aluminium hydride and used *in situ*,[13] solved this problem and led to the C33-C46 side chain of **1**, albeit in modest yield due to partial destruction of the lactone. A robust protecting group for the oxygen function at C38 of **3** was considered essential for subsequent coupling of this fragment with other phorboxazole subunits and the *tert*-butyldiphenylsilyl ether of **3** was left in place until a final stage of the synthesis for this purpose.
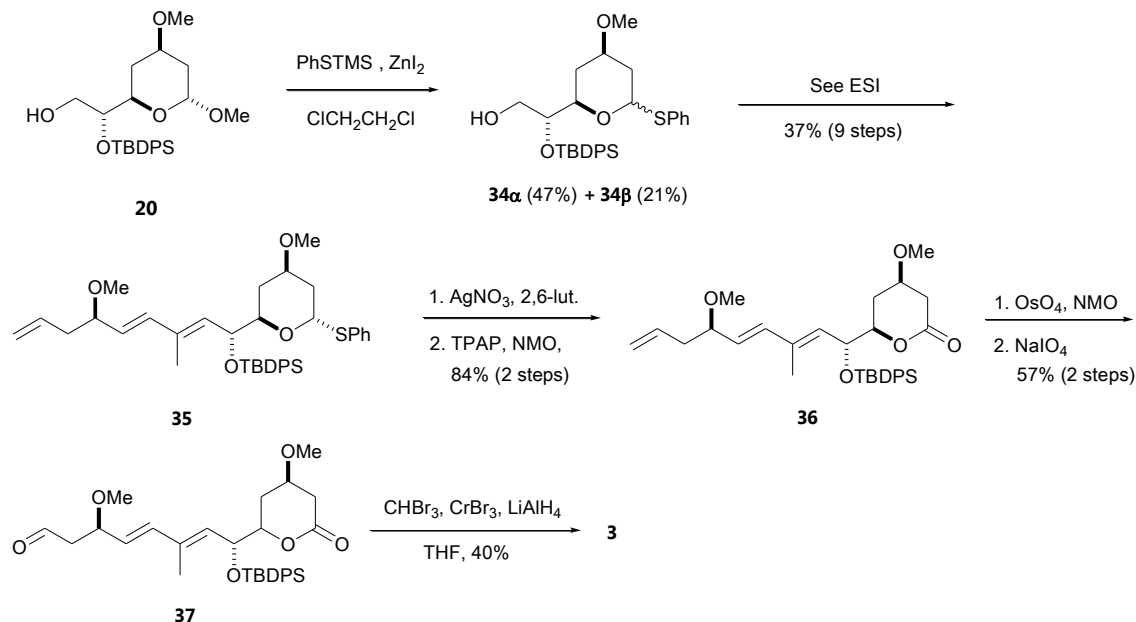

Scheme 4 Completion of phorboxazole A side chain **3** from thioacetal **34α**

Synthesis of the C20-C32 subunit 4

Synthesis of this segment of the phorboxazole macrocycle presented an opportunity to explore a route to the embedded tetrahydropyran B via intramolecular palladium(II)-mediated alkoxycarbonylation that would expand the scope of the method and measure its stereoselectivity.[18] Although the method has been demonstrated in the context of tetrahydrofuran synthesis,[19] its application to the construction of tetrahydropyrans has received relatively little attention.[20] In the present case, the outcome leading from a hex-1-en-6-ol to the pentasubstituted tetrahydropyran of **4** was known[21] but many features of the reaction, including its mechanism, were obscure. Two observations were noted in a previous exercise that portended problems for the present study. First, it was seen that the palladium(II) species was reduced to inactive palladium(0), presumably by carbon monoxide, during the reaction so that many successive additions of the palladium salt were necessary to drive the reaction to completion. Second, intramolecular alkoxycarbonylation was critically dependent on the nature of the solvent, an alcohol alone being inadequate for success of the reaction. Later studies, particularly those directed toward tetrahydropyran C of **1**, clarified these issues (vide infra), but with acquisition of **4** as the immediate objective synthesis of its acyclic precursor became our next task.

Synthesis of **4** began from the known methyl 2-methyl-4-oxazolecarboxylate (**38**),[22] prepared by a modification of Cornforth's method.[23] Reduction of **38** to aldehyde **39** followed by Wittig olefination with 2-(triphenylphosphoranylidene)propionaldehyde (**40**) yielded unsaturated aldehyde **41** exclusively as the (*E*) isomer (Scheme 5). Asymmetric crotylation[24] of **41** with (-)-(*Z*)-crotyldiisopinylcampheylborane afforded homoallylic alcohol **42** with an anti:syn ratio of >96:4 according to ^{13}C NMR. The
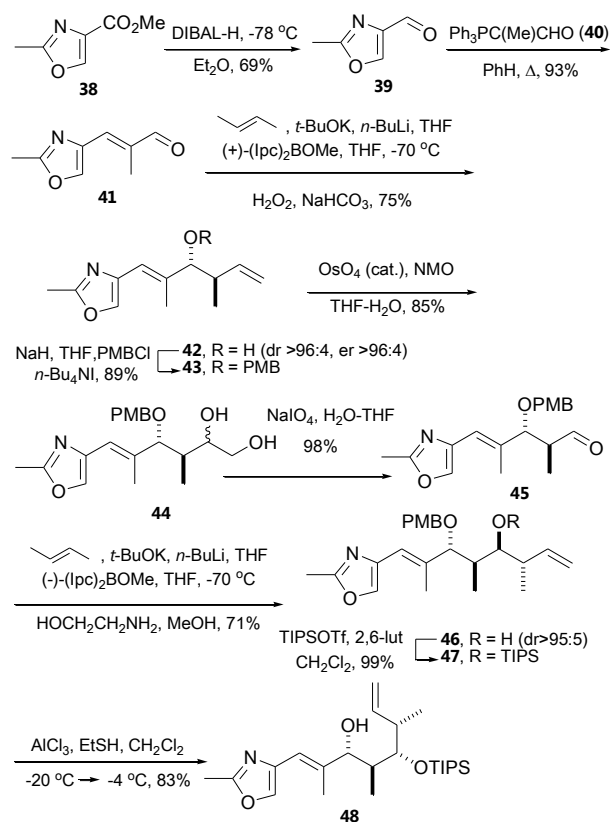
Scheme 5 Synthesis of tetrahydropyran B precursor **48** from oxazole **38**

enantiomeric ratio of the major anti isomer was also >96:4, as measured by analysis of its Mosher ester using ^{19}F NMR.[25] These data in combination with precedent established by Brown[24] allow confident assignment of absolute configuration to **42** as (25R,26R). Etherification of **42** with *p*-methoxybenzyl chloride in the presence of tetra-*n*-butylammonium iodide afforded **43** which underwent oxidative cleavage of the terminal olefin via diol **44** to furnish aldehyde **45**. A second asymmetric crotylation, in this case with the (Z)-crotyldiisopinylcampheylborane enantiomeric with that used on aldehyde **41**, gave homoallylic alcohol **46** with a C23-C24

anti:syn ratio >95:5 and an enantiomeric ratio > 96:4 by Mosher ester analysis. Alcohol **46** was protected as its triisopropylsilyl ether **47** without incident, but cleavage of the *p*-methoxybenzyl ether with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone unexpectedly led to an α,β-unsaturated ketone resulting from oxidation of the allylic alcohol after ether scission. The problem was solved by removing the *p*-methoxybenzyl group from **47** with ethanethiol and aluminium chloride[26] in a process that furnished alkoxycarbonylation substrate **48** in good yield.
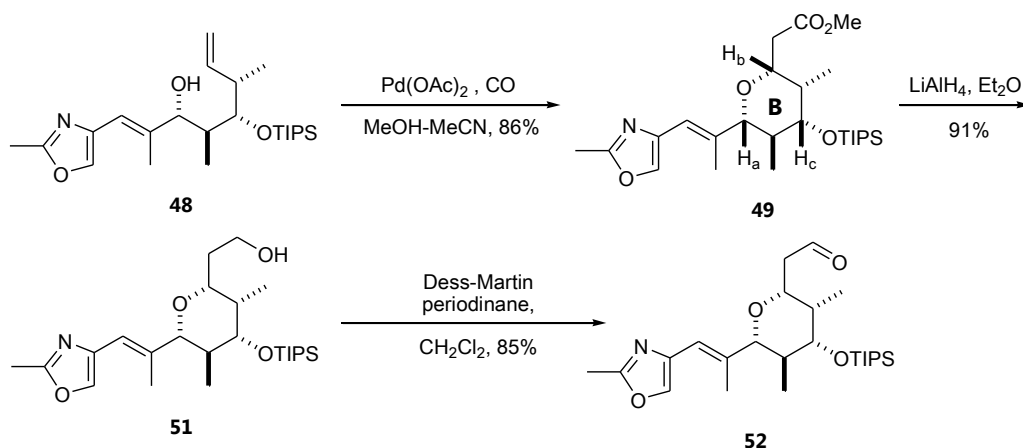
Scheme 6 Intramolecular alkoxycarbonylation of alkenol **48** to form tetrahydropyran B

Initial attempts to cyclize **48** in the presence of palladium(II) chloride and methanol under an atmosphere of carbon monoxide took several days and gave a disappointing yield of **49** but two observations resulted in a marked improvement in efficiency and rate. First, it was found that palladium(II) acetate was superior to other palladium salts in promoting the reaction; second, inclusion of acetonitrile as a co-solvent with methanol greatly retarded reduction of palladium(II) to palladium (0) (Scheme 6). Although alkoxycarbonylation of **48** still required addition of three equivalents of palladium(II) acetate, tetrahydropyran **49** was produced as the sole stereoisomer in high yield. The configuration of **49** was established by nuclear Overhauser

experiments which proved that protons H$_a$, H$_b$, and H$_c$ were axial and confirmed that all five stereocenters in this tetrahydropyran correspond in absolute configuration to C22-C26 of phorboxazole A. A mechanism involving a tightly complexed π-palladium(II) species configured as in **50** (Scheme 7) which collapses to tetrahydropyran **51** is believed to be responsible for the high level of stereoselectivity in the conversion of **48** to **49**. In preparation for coupling of **49** with a fragment representing C9-C19 of **1**, the ester was reduced and the resultant alcohol **52** was oxidized to aldehyde **4**.
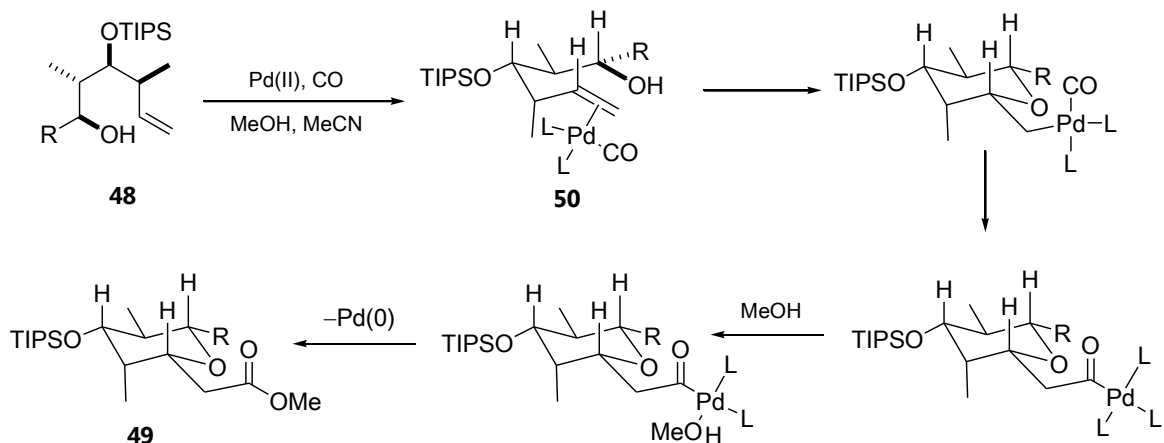
Scheme 7 Proposed mechanism of intramolecular palladium(II)-mediated alkoxycarbonylation of **48**

## Synthesis of a C10-C19 subunit and its coupling to C20-C32

Connection of C19 to C20 was programmed via a modified Schlosser-Wittig (*E*)-olefination[27] along lines demonstrated for 2-halomethyloxazoles by Panek[28] and applied by Evans in his synthesis of phorboxazole B (**2**).[5a] The partner needed for aldehyde **52** was therefore one bearing a phosphonium substituent at C19, and for this purpose chloromethyloxazole **53** was prepared by the method of Hermitage[29] and was reduced to aldehyde **54** (Scheme 8). The aldehyde was reacted with (+)-allyldiisopinylcampheylborane[10] to give (*R*) homoallylic alcohol **55** in which the e.r. was >20:1 as measured from the ^{13}C NMR spectrum of its Mosher ester.[25] After protection of **55** as its *tert*-butyldimethylsilyl ether **56**, oxidative scission of the terminal alkene gave aldehyde **57**. The latter was subjected to a second asymmetric allylation with (+)-allyldiisopinylcampheylborane which produced syn alcohol **58** accompanied by *ca* 8% of its anti isomer. Purified alcohol **58** was protected as its *tert*-butyldiphenylsilyl ether **59**, from which the *tert*-butyldimethylsilyl ether was cleaved selectively[30] to afford alkenol **60**.
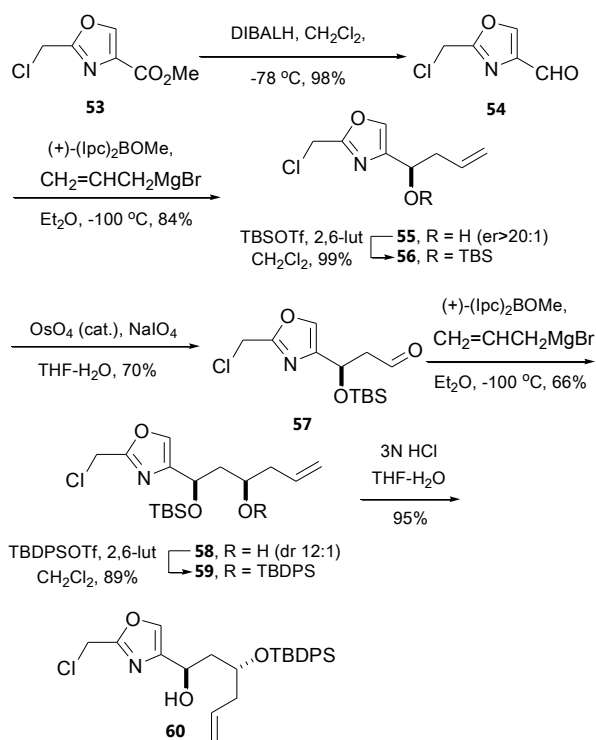
Scheme 8 Synthesis of tetrahydropyran C precursor **60** from oxazole **53**

In the belief that the activated chlorine substituent of **60** was unlikely to survive exposure to palladium reagents, elaboration of tetrahydropyran C by alkoxycarbonylation of this substrate was deferred until after its coupling to **52**. Chloromethyloxazole **60** was therefore converted to phosphonium salt **61** with tri-*n*-butylphosphine, and the ylide prepared with 1,8-diazabicyclo[5.4.0]undec-7-ene was reacted with aldehyde **52** in an olefination that provided alkene **62** in excellent yield and with exclusive (*E*) configuration of the C19-C20 double bond as determined by ^{1}H NMR (Scheme 9). Alkoxycarbonylation of **62**

again required an excess of palladium(II) acetate and gave, in addition to the desired bistetrahydropyran **63**, ester **64** resulting from methoxycarbonylation of the terminal alkene without participation by the C15 hydroxy group (Scheme 10). This unsatisfactory result left us without a practical route to the C10-C19 portion of **1** and prompted a search for conditions that would afford a viable entry to this domain. For this exercise, we returned to alkenol **60.**
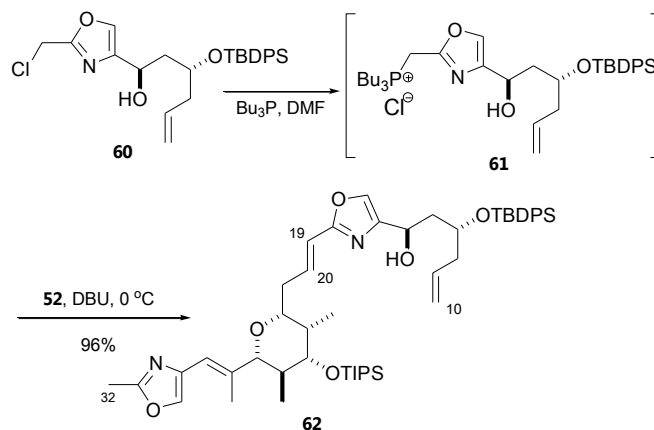
**Scheme 9** Wittig coupling of **60** with **52** to yield C10-C32 subunit **62**
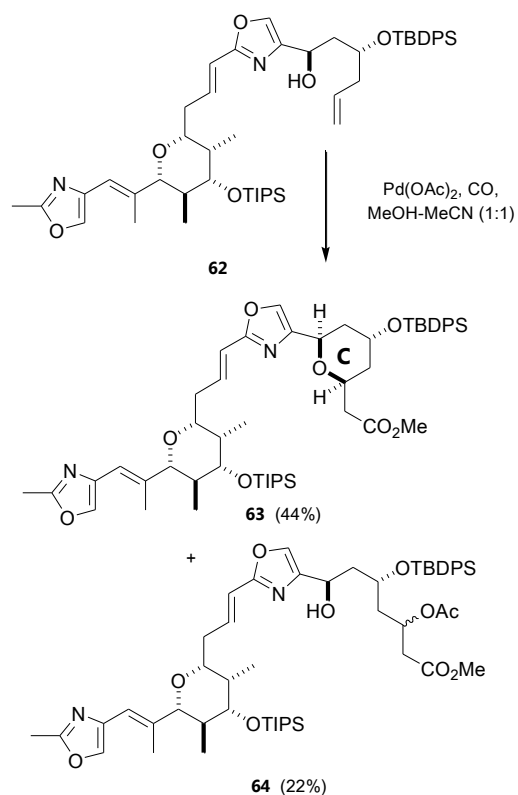
Scheme 10 Intramolecular alkoxycarbonylation of C10-C32 to form tetrahydropyran C

Alkoxycarbonylation studies and improved preparation of the C9-C19 fragment

A comprehensive study of the reaction of **60** with carbon monoxide and methanol in the presence of various palladium(II) salts revealed that the chlorine substituent could survive most alkoxycarbonylation conditions. However, the yield of **65** was generally low even with a large excess of the palladium(II) salt (Table 1, entry 1). When palladium(II) chloride was used in the reaction, a further complication arose in the form of γ-lactone **66** resulting from silyl ether cleavage followed by carbonylation and cyclization (Table 1, entries 2 and 3). We assumed that excess palladium(II) chloride was responsible for unmasking the silyl ether of **60,** and in order to suppress this aberrant process alkoxycarbonylation protocols that employed catalytic palladium(II) salts were investigated. It has been shown by Murahashi that tetrahydrofurans can be prepared by intramolecular alkoxylation of 4-pentenols using catalytic palladium(II) chloride with copper(II) chloride as the stoichiometric oxidant[31] and the process was extended to intramolecular alkoxycarbonylation by Semmelhack,[19c] but those conditions with **60** again produced γ-lactone **66** as a major by-product (Table 1, entry 4). However, a report by Marshall that *p*-benzoquinone could serve as the stoichiometric oxidant for intramolecular alkoxycarbonylation of a 5-hexynol catalyzed by palladium(II) chloride[32] suggested that reexamination of **60** as a substrate with this precedent could be fruitful. In fact, exposure of **60** to 10 mol% of palladium(II) chloride-acetonitrile complex and 5.5 equivalents of *p*-benzoquinone in methanol-acetonitrile under a carbon monoxide atmosphere gave **65** in a reproducible yield of *ca* 60% (Table 1, entry 5) with stereoselectivity in favour of the (11*S*,15*R*) isomer >10:1. The syn relationship between protons at C11 and C15 was established by a nuclear Overhauser experiment. Formation of **66** was not observed under these conditions. This outcome permitted the preparation of **65** on a scale approximating 1 g and greatly facilitated our progress toward **1**.
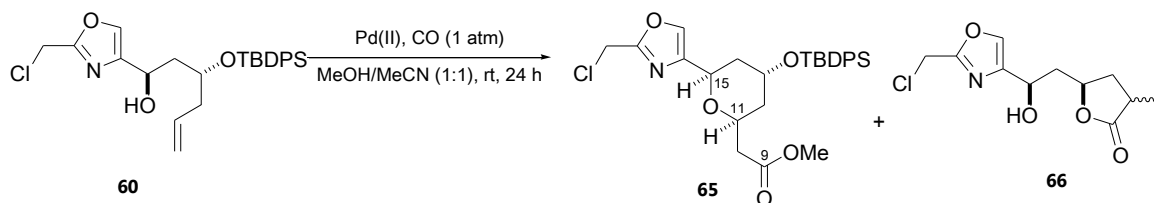
Table 1 Intramolecular alkoxycarbonylation of **60** using stoichiometric and catalytic palladium(II) salts

entry	Pd(II) salt	equivs	stoichiometric oxidant	equivs	yield (%)	
					65	**66**
1	Pd(OAc)$_2$	3	none	-	41	0
2	PdCl$_2$	3	none	-	20	46
3	PdCl$_2$(MeCN)$_2$	3	none	-	23	51
4	PdCl$_2$(MeCN)$_2$	10 mol%	CuCl$_2$	4	21	33
5	PdCl$_2$(MeCN)$_2$	10 mol%	*p*-benzoquinone	5.5	58[a]	0

[a] 17% of **60** was recovered.

Synthesis of the C4-C8 fragment, its coupling with C9-C19 and assembly of a C4-C32 subunit

Synthesis of the phorboxazole moiety comprising C4-C8 is summarized in Scheme 11. (*S*)-(-)-Glycidol (**67**) was protected as its *tert*-butyldiphenylsilyl ether **68** which was reacted with lithium trimethylsilylacetylide to give alkynol **69**. The trimethylsilyl group was removed selectively from **69**, and the resultant alkyne **70** was treated with bromo-9-borabicyclo[3.3.1]nonane[33] to yield vinyl bromide **71**. The latter was converted to bis-silyl ether **72** and then cross-coupled[34] with trimethylsilylmethylmagnesium chloride in the presence of a catalytic quantity of 1,3-bis(diphenylphosphino)propanenickel(II) chloride.[35] This sequence furnished allylsilane **73** in an overall yield of 69% for the six steps from **67**.
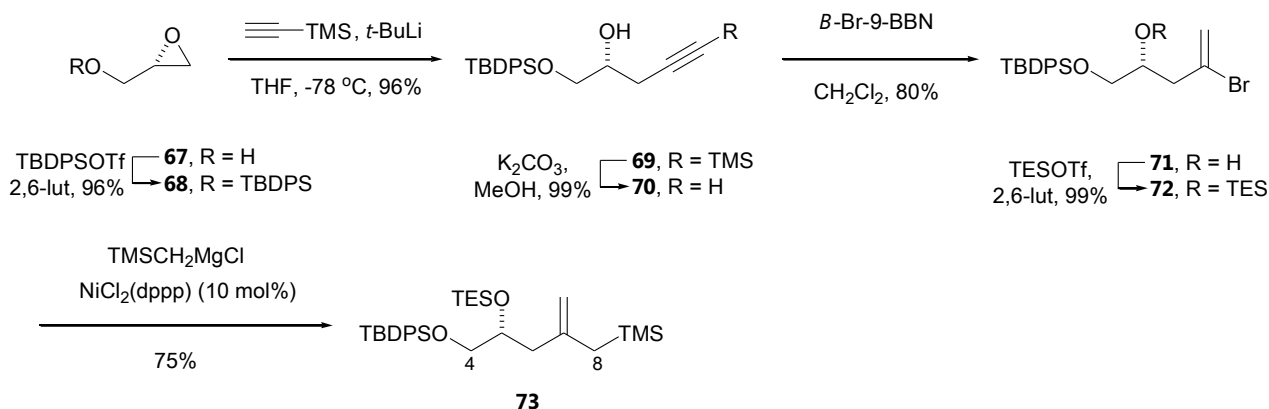
Scheme 11 Synthesis of C4-C8 subunit **73** from (S)-glycidol
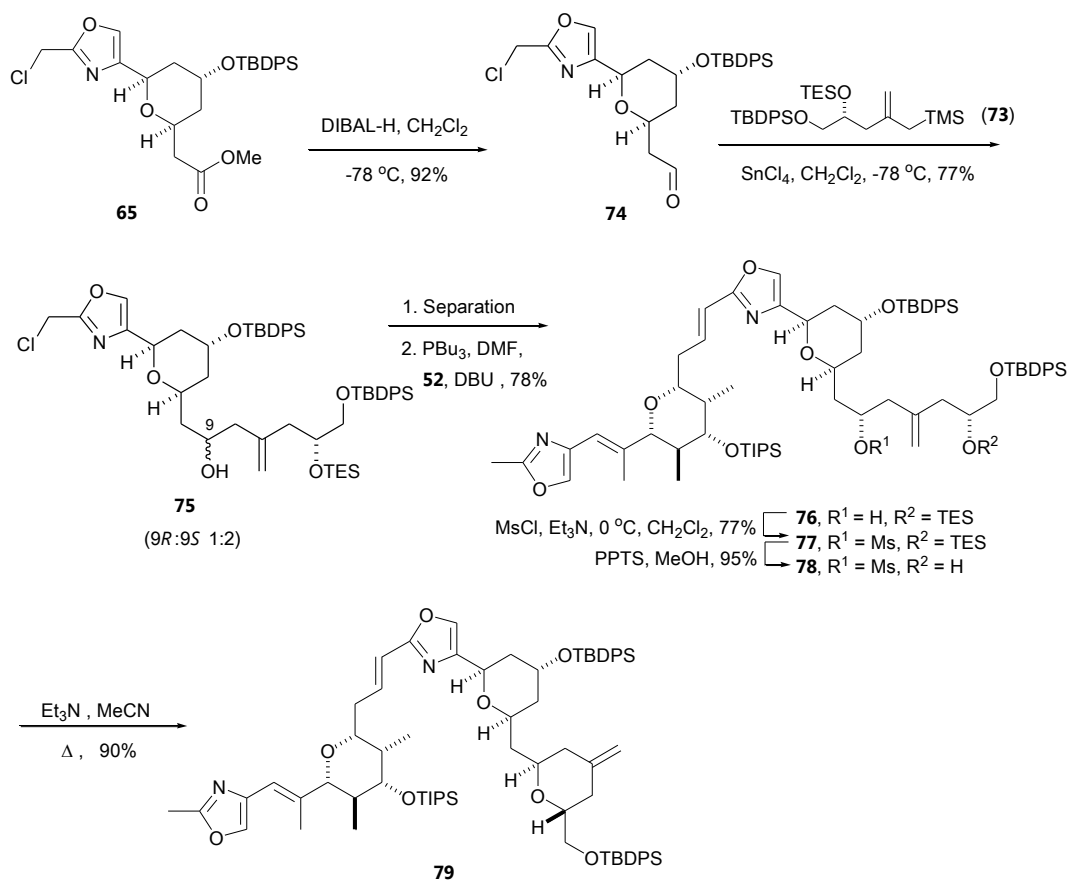
Scheme 12 Assembly of C4-C32 domain from **73,74** and **52**

Aldehyde **74** required for reaction with **73** was obtained by reduction of ester **65** with diisobutylaluminium hydride, but when **73** and **74** were exposed to boron trifluoride etherate the desired homoallylic alcohol was obtained in less than 20% yield. However, when stannic chloride was used as catalyst under Dias' conditions,[36] **75** was produced in good yield as a separable 2:1 mixture of C9 alcohols (Scheme 12). The configuration of these stereoisomeric alcohols was determined by preparing their (*R*) and (*S*) Mosher esters and using Kakisawa's model for assigning absolute configuration to the secondary esters.[37] This analysis established that the major, less polar isomer of **75** possessed (9*S*) configuration. In the hope that separation of C9 stereoisomers of **75** could be avoided, the mixture was oxidized to a ketone and the C5 silyl ether was cleaved in the expectation that reduction of the resultant cyclic hemiacetal would produce the required (9*R*) configuration of tetrahydropyran D. Although a cyclic hemiacetal (not depicted) was formed and was reduced to a tetrahydropyran with triethylsilane in the presence of a Lewis acid, the reduction was accompanied by saturation of the C7 exo methylene substituent.[38]

This result necessitated a change in our strategy for constructing tetrahydropyran D and led to a plan involving displacement of a leaving group at C9 of **75** by the C5 hydroxy substituent. It was recognized that this approach risked sacrificing the chlorine substituent in **75**, and to avoid this mishap the order of subunit assembly was reversed. Thus, instead of coupling C29-C46 with a C4-C19 segment, connection of **75** to C20-C46 would be completed first and tetrahydropyran D would be fabricated after this linkage was in place. The major (9*S*) stereoisomer of **75** was separated from the mixture and was reacted sequentially with tri-

n-butylphosphine, 1,8-diazabicyclo[5.4.0]undecen-7-ene and aldehyde **52** to give olefin **76**. This alcohol was converted to its mesylate **77,** the C5 silyl ether was cleaved with acidic methanol, and alcohol **78** was treated with triethylamine to furnish **79** in 54% overall yield for the four steps from (9*S*)-**75**. With acquisition of the C4-C32 portion of phorboxazole A in the form of **79**, it appeared that advance towards the C4-C46 domain of **1** along lines drafted in Scheme 1 would be straightforward. However, this proved to be a false hope that required further revisions to the synthesis plan as described below.

Coupling of C20-C32 with C33-C46

As a prelude to assembling the complete C4-C46 segment of **1**, we first investigated the union of lactone **3** with a simpler partner **80** which was prepared by silylation of alcohol **52**. A similar coupling was carried out by Pattenden[4e] and Evans[5a] in their phorboxazole syntheses, but in our hands treatment of **80** with lithium diethylamide followed by **3** gave, in addition to the expected product **81**, the terminal alkyne **82** in nearly equal quantity (Scheme 13). Separation of the two products was accomplished by preparative thin-layer chromatography and an attempt was made to convert alkyne **82** to (*E*)-vinyl bromide **81** along lines used by Smith as the final step in his synthesis of **1**.[4b] Although reaction of **82** with silver nitrate and *N*-bromosuccinimide gave a bromoalkyne in good yield, subsequent palladium(II)-catalyzed stannylation failed to produce the desired (*E*)-vinylstannane. Our attempt to repair this deviant C32-C33 coupling was therefore abandoned.
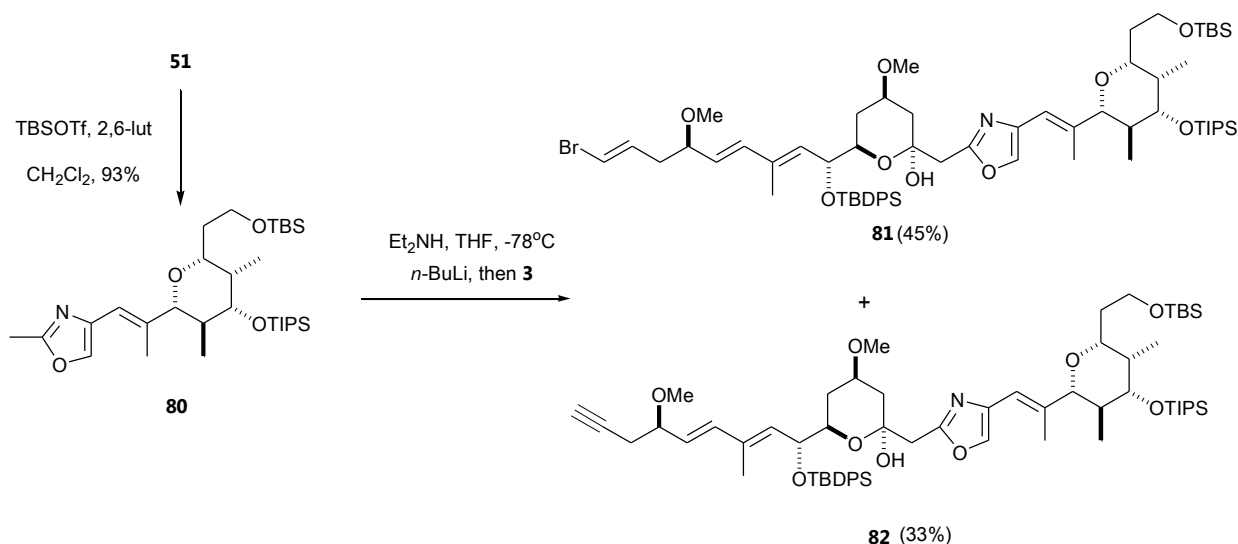
Scheme 13 Coupling of oxazole **80** with lactone **3**

Formation of terminal alkyne **82** along with **81** is due to difficulty in controlling the precise quantity of base needed to deprotonate **80** for linkage with **3**,[39] and in order to recast the C32-C33 union in a way that would avoid generating an alkyne an additional disconnection at C41-C42 was introduced into the synthesis plan. In this modification, a C42-C46 fragment would be installed after coupling C20-C32 unit **83** with lactone **84** and

Julia-Kocienski olefination[40] with known sulfone **85**[4d] along lines employed by Williams[4d,f] and Lin[5b] would be used for the C41-C42 conjunction (Scheme 14). A further revision, made for reasons that became apparent later when a free alcohol in tetrahydropyran B was needed for macrocyclization, was replacement of the C24 triisopropylsilyl ether of **80** by a *p*-methoxybenzyl ether in **83**.
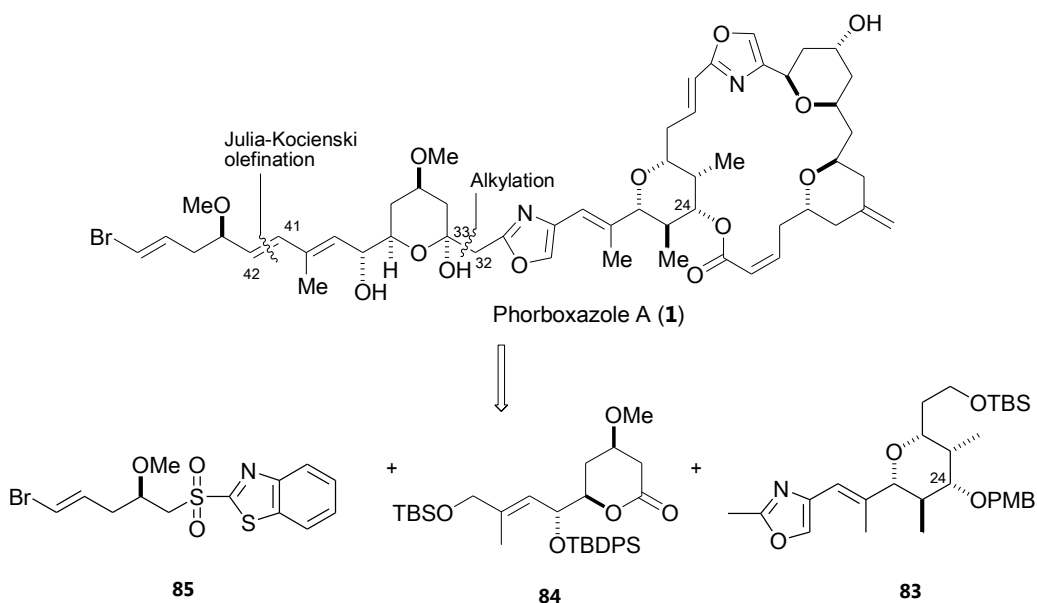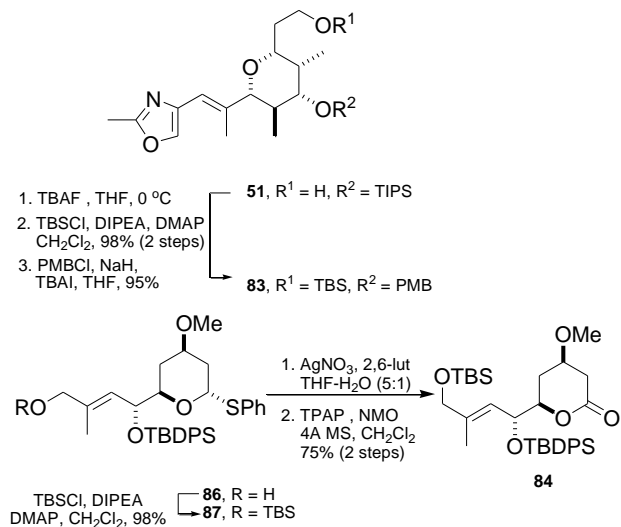

Scheme 14 Revised route to phorboxazole A using C41-C42 olefination

Oxazole **83** and lactone **84** were obtained from fragments synthesized previously en route to C20-C32 and C33-C46 subunits, respectively (Scheme 15). First, alcohol **86** was prepared from **34α** by oxidation to an aldehyde, Wittig olefination with ylide **23** and reduction of the resultant ester. After conversion of **86** to the primary *tert*-butyldimethylsilyl ether **87**, the phenylthio acetal was hydrolyzed and the resulting hemiacetal was oxidized to lactone **84**. In a parallel sequence, the triisopropylsilyl ether of **52** was cleaved to produce a diol in which the primary alcohol was selectively masked as the

corresponding *tert*-butyldimethylsilyl ether. The latter was then reacted with *p*-methoxybenzyl chloride and tetra-*n*-butylammonium iodide to give **83**. In contrast to the coupling of **80** with **3**, condensation of the C32 anion of **83** with lactone **84** proceeded cleanly and in excellent yield to afford **88** as a single hemiacetal stereoisomer (Scheme 16). The two *tert*-butyldimethylsilyl ethers of **88** were cleaved and the allylic alcohol of diol **89** was selectively oxidized with manganese dioxide to afford α,β-unsaturated aldehyde **90**. After protection of **90** as silyl ether **91**, Julia-Kocienski olefination of this

aldehyde with sulfone **85** furnished the fully funtionalized C20-C46 segment **92** of phorboxazole A containing the requisite C41-C42 (*E*) olefin. Unmasking the remaining *tert*-butyldimethylsilyl ether gave primary alcohol **93** and set the stage for coupling to the C3-C19 subunit.
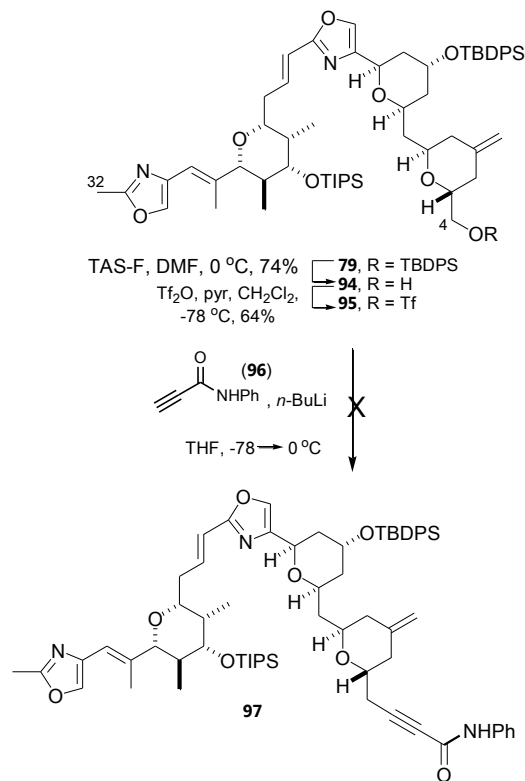

1. TBAF , THF, 0 °C
2. TBSCl, DIPEA, DMAP CH₂Cl₂, 98% (2 steps)   ⌐ **51**, R¹ = H, R² = TIPS
3. PMBCl, NaH, TBAI, THF, 95%   └→ **83**, R¹ = TBS, R² = PMB

1. AgNO₃, 2,6-lut THF-H₂O (5:1)
2. TPAP , NMO 4A MS, CH₂Cl₂ 75% (2 steps)

TBSCl, DIPEA DMAP, CH₂Cl₂, 98%   ⌐ **86**, R = H
    └→ **87**, R = TBS

Scheme 15 Synthesis of oxazole **83** and lactone **84**

Et₂NH, THF, -78 °C, *n*-BuLi, then **84**   96%

83

MnO₂, CH₂Cl₂   84%

p-TsOH, MeOH 99%   ⌐ **88** R¹ = R² = TBS, R³ = H
    └→ **89** R¹ = R² = H, R³ = Me

85, NaHMDS, THF, -78 °C, 98%

TBSCl, Imid CH₂Cl₂,86%   ⌐ **90**, R = H
    └→ **91**, R = TBS

p-TsOH MeOH, 92%   ⌐ **92**, R = TBS
    └→ **93**, R = H
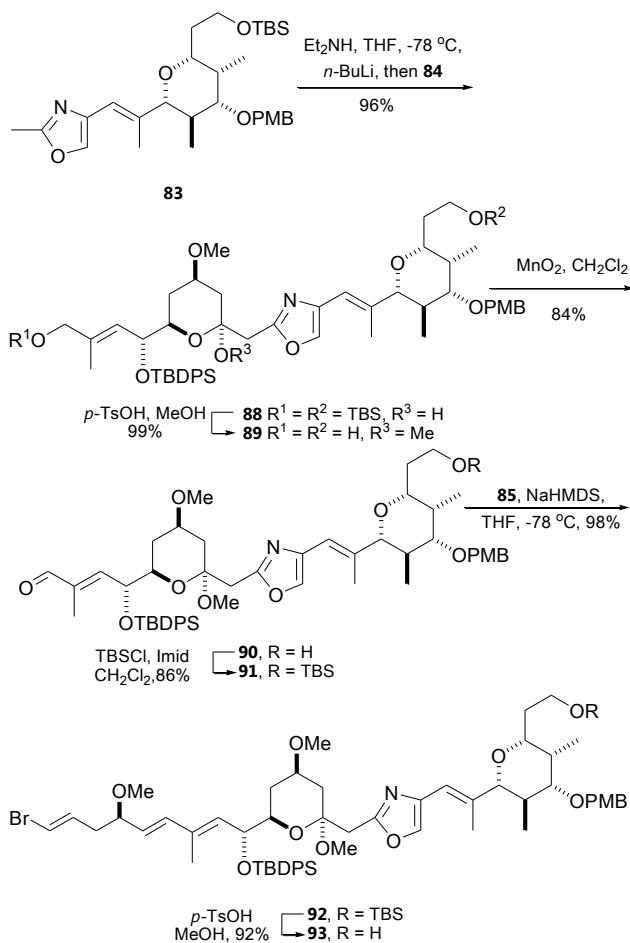
Scheme 16 Synthesis of C20-C46 domain from oxazole **83**, lactone **84**, and sulfone **85**

Coupling of C20-C46 with C3-C19

The end-game strategy for **1** initially envisioned attachment of the C20-C46 sector **93** to (9*S*)-**75** followed by homologation of the assembled C4-C46 domain with alkynoate **6**. Features of this plan were developed in Evans' route to phorboxazole B (**2**),[4a] but to ensure its applicability to **1** the simpler C4-C32 subunit **79** was used as a test substrate for this sequence. Selective cleavage of the primary *tert*-butyldiphenylsilyl ether of **79** was accomplished with tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F)[30] and the resulting primary alcohol **94** was advanced to triflate **95** (Scheme 17). However, attempts to replicate the blueprint outlined in Scheme 1 by displacing the triflate from **95** with alkynoate nucleophiles, including the dianion of *N*-phenylpropiolamide (**96**), resulted in extensive decomposition with no evidence for the formation of **97**. This result caused us to reconsider our planned conclusion of the synthesis via macrolactonization and led to a final revision in which intramolecular olefination to form the C2-C3 (*Z*) double bond would close the macrocycle. This realignment required two significant modifications to previously synthesized intermediates. First, an additional carbon representing C3 as an aldehyde had to be introduced into the precursor for **1**; second, a C1-C2 fragment that could initiate olefination would need to be positioned at the C24 hydroxy group. The first requirement was met by allylsilane **98**, a one-carbon homologue of **73**.

TAS-F, DMF, 0 °C, 74%   ⌐ **79**, R = TBDPS
Tf₂O, pyr, CH₂Cl₂, -78 °C, 64%   ⌐ **94**, R = H
    └→ **95**, R = Tf

(**96**) NHPh , *n*-BuLi
THF, -78 → 0 °C

97

Scheme 17 Attempted homologation of C4-C32 subunit with **96** via triflate **95**

The route to **98** began with conversion of 1,3-propanediol to its mono-*tert*-butyldiphenylsilyl ether and oxidation to aldehyde **99** (Scheme 18). Asymmetric allylation[10] of **99** afforded (*R*) homoallylic alcohol **100** with er >96:4 as measured from the ¹⁹F NMR spectrum of its Mosher ester.[25] After protection of this alcohol as its triethylsilyl ether **101**, ozonolytic cleavage of the

vinyl group gave aldehyde **102** which was condensed with diazaphosphonate **103**[41] to give alkyne **104**. Exposure of this alkyne to *B*-bromo-9-borabicyclo[3.3.1]nonane[33] resulted in partial cleavage of the triethylsilyl ether, and in order to avoid handling a mixture the triethylsilyl ether of **104** was cleaved selectively with acidic methanol and the pure alkynol **105** was

brominated to yield bromoalkene **106**. The latter was reprotected as **107** and was reacted with (trimethylsilylmethyl)magnesium chloride in the presence of Kumada's nickel(II) catalyst[35] to give **98** in an overall yield of 34% for the ten steps from 1,3-propanediol.
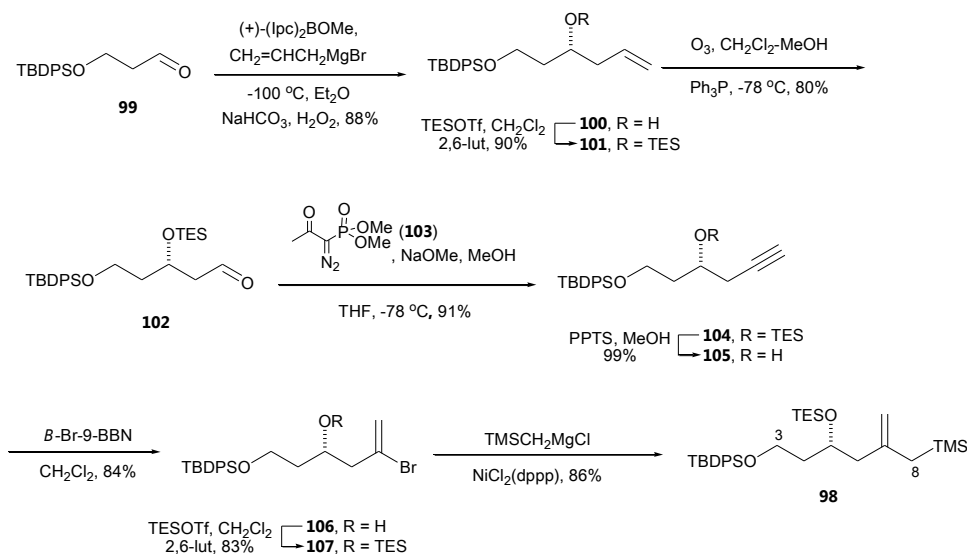
**Scheme 18** Synthesis of C3-C8 subunit **98** from propanal **99**

The condensation of aldehyde **74** with allylsilane **98** in the presence of stannic chloride gave the expected 2:1 mixture of C9 homoallylic alcohols in which the major component **108** was assigned (9*S*) configuration by NMR comparison with **75** of known configuration (Scheme 19). After separation from its minor (9*R*) diastereomer, **108** was coupled with aldehyde **109**, obtained by oxidation of **93**, using the olefination method previously employed with **75**. The C9 alcohol of the resultant (*E*) alkene **110** was converted to mesylate **111**, the C5 triethylsilyl ether of **111** was cleaved, and the liberated alcohol **112** was treated with triethylamine in acetonitrile to deliver **113**. This sequence completed the four tetrahydropyran rings of phorboxazole A and produced a C3-C46 assemblage that housed all but two of the carbons needed for the final target.
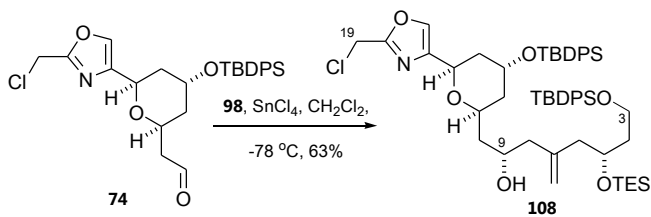
Scheme 19 Assembly of C3-C19 domain from **74** from allylsilane **98**
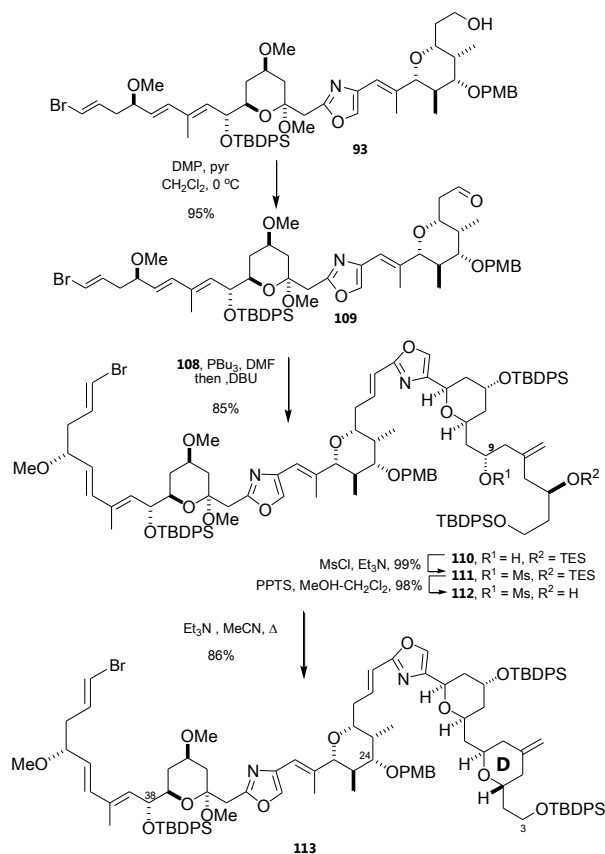
Scheme 20 Assembly of C3-C46 sector and tetrahydropyran D from aldehyde **109** and C3-C19 subunit **108**

Macrocyclization and completion of the synthesis

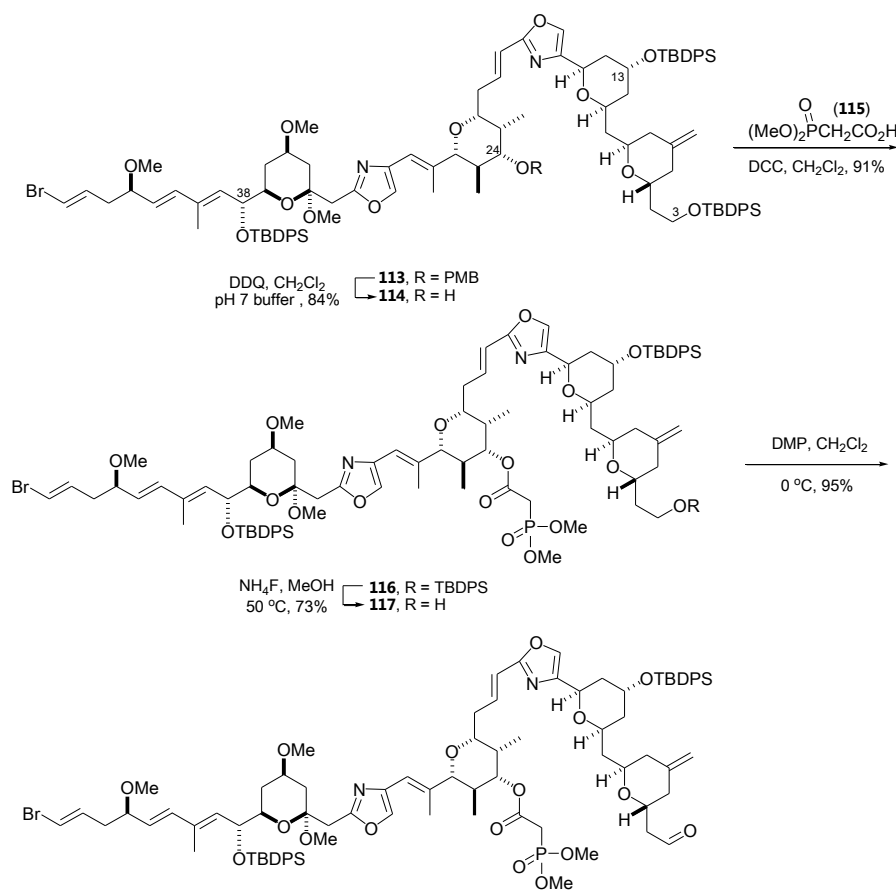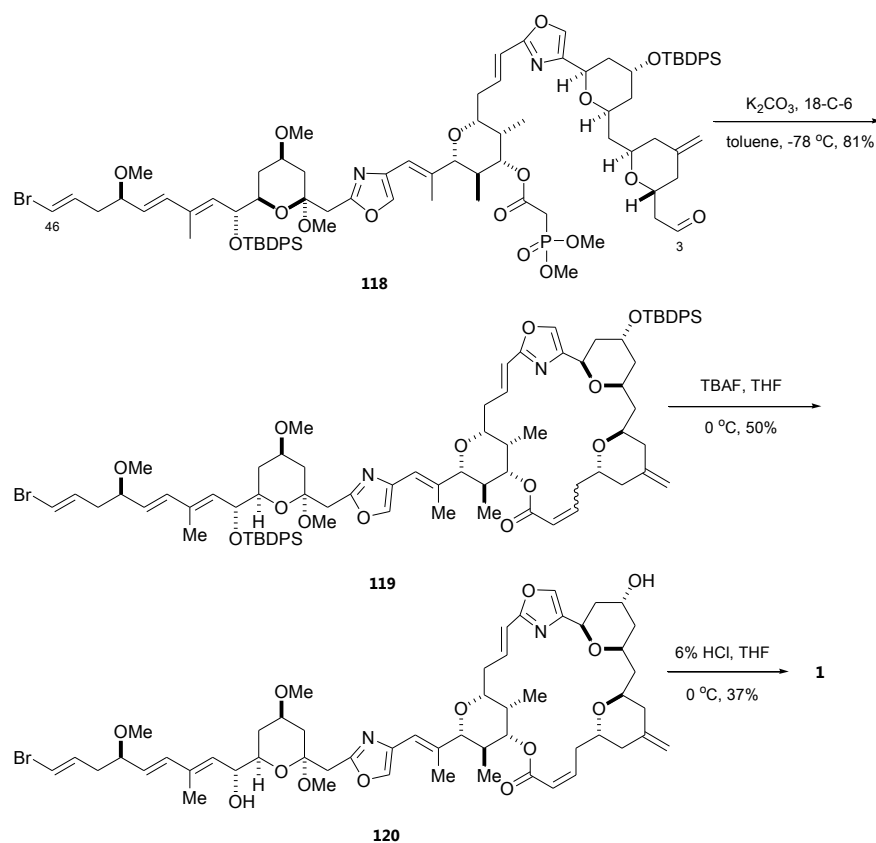Of the six completed syntheses of phorboxazoles,[4,5] all except that of Evans[5a] employed intramolecular Gennari-Still olefination[42] to close the macrolactone. A modification of this approach that held appeal for us was the prospect of setting (Z) configuration at the C2-C3 alkene of **1** using an intramolecular variant of Ando's phosphonate methodology,[43] and this move became the pivotal gambit in our end-game strategy. First, the *p*-methoxybenzyl ether was cleaved with buffered 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (Scheme 21) but the C24 hydroxy group of **114** proved to be too sterically hindered to react with (diphenoxyphosphinyl)acetic acid under Ando's conditions. Fortunately, esterification of **114** with (dimethoxyphosphinyl)acetic acid (**115**) in the presence of *N,N*-dicyclohexylcarbodiimide as described by Williams[4d] afforded phosphonate **116** in high yield. In a previous study,[44] we had shown that a primary *tert*-butyldiphenylsilyl ether can be cleaved selectively with ammonium fluoride in methanol at 50 °C,[45] and

application of this protocol to **116** led efficiently to alcohol **117**. Oxidation of **117** then furnished macrocyclization precursor **118**. Intramolecular condensation of **118** under conditions described by Williams[4d] produced the expected lactone **119** in high yield as an inseparable 3.5:1 mixture of C2-C3 olefin isomers in which the desired (Z) alkene predominated (Scheme 22). The mixture was reacted with tetra-*n*-butylammonium fluoride to cleave both silyl ethers, and diol **120** was obtained as the pure (2Z) olefin isomer after chromatography. Final acidic hydrolysis of the C33 methyl acetal then gave phorboxazole A (**1**). Although a sample of natural phorboxazole A was not available, the identity of our synthesized material was established by comparison of its ^{1}H NMR spectrum with that published for **1**[2a] and also by correspondence of its ^{13}C NMR spectrum with data recorded in the literature.[4d]

Scheme 21 Synthesis of macrolactonization precursor **118** from C3-C46 segment **113**

Scheme 22 Intramolecular olefination of C1-C46 sector **118** leading to phorboxazole A (**1**)

Conclusion

A synthesis of phorboxazole A was completed in which the longest linear sequence is 37 steps and the overall yield is 0.36%. Previous routes to **1** have overall yields that fall in the range 0.3%[4e] to 4.8%[4f] and are characterized by a longest linear sequence that is uniformly 30 to 38 steps   A distinguishing feature of our route is application of intramolecular palladium(II)-mediated alkoxycarbonylation for fabrication of two of the four tetrahydropyrans of the molecule, along with the finding that this ring construction can be made catalytic in the metal. The scarcity of natural phorboxazole A, together with its extraordinary potency as an antitumor agent, puts a heavy premium on synthesis for studies of its biological properties and a modular route such as that described above is probably the most realistic means for acquiring phorboxazoles and their analogues in sufficient quantity for future research.

Experimental

General

Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying reagents immediately prior to use. Tetrahydrofuran and ether were distilled from sodium and benzophenone under an argon atmosphere. Toluene, diisopropylethylamine, triethylamine, pyridine and dichloromethane were distilled from calcium hydride under argon. All solvents used for routine isolation of products and chromatography were reagent grade. Moisture- and air-sensitive reactions were carried out under an atmosphere of argon. Reaction flasks were flame dried under a stream of argon gas, and glass syringes were oven dried at 120 °C prior to use.

Unless otherwise stated, concentration under reduced pressure refers to a rotary evaporator at water aspirator pressure. Residual solvent was removed by vacuum pump at a pressure less than 0.25 mm of mercury.

Analytical thin-layer chromatography (TLC) was conducted using E. Merck precoated plates (0.2 mm layer thickness of silica gel 60 F-254). Compounds were visualized by ultraviolet light and/or by heating the plate after dipping in a 3-5% solution of phosphomolybdic acid in ethanol, 10% ammonium molybdate in water, a 1% solution of vanillin in 0.1 M sulfuric acid in methanol or 2.5% *p*-anisaldehyde in 88% ethanol, 5% water, 3.5% concentrated sulfuric acid, and 1% acetic acid. Flash chromatography was carried out using silica gel (230-400 mesh ASTM or 40 μm particle size). Optical rotations were measured with a polarimeter at ambient temperature using a 0.9998 dm cell with 1 mL capacity. Infrared (IR) spectra were recorded on a FT-IR spectrometer. Proton nuclear magnetic resonance (NMR) spectra were measured at either 300 or 400 MHz and carbon-13 spectra were measured at 75 or 100 MHz. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale. ^{1}H NMR spectral data are reported in the order : chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad),

coupling constant (*J*, in hertz) and number of protons. NMR analysis of (*R*) and (*S*) Mosher esters of alcohol mixtures from asymmetric reactions was carried out using ^{1}H, ^{13}C and ^{19}F signals, and absolute configurational assignments were made using Kakisawa's method[37] with these esters.

Chemical ionization (CI) high- and low-resolution mass spectra (HRMS and MS) were obtained using a source temperature of 120 °C and methane gas as the ionizing source. Perfluorokerosene was used as a reference. Electron impact (EI) mass spectra (HRMS and MS) were obtained at 70 eV. Fast atom bombardment (FAB) mass spectra were measured using a MS-50 spectrometer.

((4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)dimethanol (8).

To a solution of lithium aluminium hydride (4.16 g, 0.109 mol) in ether (80 mL) was added a solution of (4*S*,5*S*)-diethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (15.75 g, 65.24 mmol) in ether (40 mL) dropwise over 40 min. The mixture was refluxed for 24 h, then was cooled to 0~5 °C and cautiously treated with water (4.2 mL), 4N aqueous sodium hydroxide solution (4.2 mL), and water (12.6 mL). The mixture was stirred at room temperature until the unreacted lithium aluminium hydride had completely decomposed, then was filtered through a Büchner funnel and the collected solid was extracted with tetrahydrofuran. The combined extract was dried (Na$_2$SO$_4$), and concentrated under reduced pressure, and the residual oil was purified by flash chromatography to give **8** (7.78 g, 73%) as a colourless oil. The spectral data matched those reported for **8**.[46]

((4*R*,5*R*)-5-((*tert*-Butyldimethylsilanyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (9).

To a suspension of hexane-washed sodium hydride (1.36 g, 33.9 mmol) in tetrahydrofuran (50 mL) was added **8** (5.50 g, 33.9 mmol) and the mixture was stirred for 45 min, at which time a white precipitate had formed. *tert*-Butyldimethylsilyl chloride was added and vigorous stirring was continued for 10 h. The mixture was poured into ethyl acetate (250 mL), washed with 10% aqueous potassium carbonate (50 mL) and brine (50 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel to give **9** (7.60 g, 81%) as a colourless oil: $[\alpha]_D^{23}$ -16.3 (c 7.5, CHCl$_3$); IR (neat) 3471, 2986, 2930, 2858, 1472, 1463, 1370, 1254, 1217, 1167, 1082, 1004, 837, 778, 675 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.00 (dd, *J* = 5, 8 Hz, 1H), 3.92 – 3.89 (m, 2H), 3.82 – 3.64 (m, 3H), 2.38 (dd, *J* = 5, 8 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 109.5, 80.5, 78.4, 64.1, 63.1, 27.4, 27.3, 26.2, 18.7, -5.1; MS (CI) *m/z* 277 (M+H)$^+$, 261, 245, 220, 219, 187, 161, 143, 131, 117, 89; HRMS (CI) *m/z* 277.1833 (calcd for C$_{13}$H$_{29}$O$_4$Si: 277.1835).

((4R,5R)-5-((*tert*-Butyldimethylsilanyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate (10).

A solution of **9** (1.323 g, 4.79 mmol) and *p*-toluenesulfonyl chloride (1.37 g, 7.17 mmol) in pyridine (5 mL) was stirred for 16 h at 0 °C and then was diluted with water and extracted with ethyl acetate (20 mL x 3). The combined extract was washed with aqueous sodium bicarbonate solution (30 mL) and brine (20 mL), and dried (Na$_2$SO$_4$). The solvents were removed under reduced pressure and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 5:1) to give **10** (1.88 g, 91%) as a colourless oil: $[\alpha]_D^{23}$ +6.6 (c 5, CHCl$_3$); IR (neat) 2986, 2930, 2857, 1598, 1471, 1462, 1369, 1253, 1178, 1095, 983, 838, 780, 665, 555 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.81 (d, J = 8 Hz, 2H), 7.34 (d, J = 8 Hz, 2H), 4.26 – 4.18 (m, 1H), 4.14 – 4.05 (m, 2H), 3.87 – 3.81 (m, 1H), 3.78 (dd, J = 4, 10 Hz, 1H), 3.64 (dd, J = 6, 10 Hz, 1H), 2.45 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.3, 133.2, 130.2, 128.4, 110.4, 77.6, 76.9, 70.1, 63.7, 27.3, 27.2, 26.2, 22.0, 18.6, -5.1; MS (CI) *m/z* 431 (M+H)$^+$, 415, 373, 355, 315, 271, 259, 229, 201, 173, 143; HRMS (CI) *m/z* 431.1916 (calcd for C$_{20}$H$_{35}$O$_6$SSi: 431.1924).

tert-Butyl(((4*R*,5*S*)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)dimethylsilane (11).

A solution of **10** (8.07 g, 18.7 mmol) and sodium iodide (8.43 g, 56.2 mmol) in acetone (50 mL) was heated under reflux for 30 h. The solvent was evaporated, water (50 mL) was added, and the resulting solution was extracted with ether (50 mL x 3). The combined extract was dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 12:1) to give **11** (7.00 g, 96%) as a colourless oil: $[\alpha]_D^{23}$ +2.8 (c 5.0, CHCl$_3$); IR (neat) 2986, 2954, 2929, 2857, 1471, 1370, 1253, 1137, 1091, 1005, 938, 838, 778, 675 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.92 – 3.78 (m, 3H), 3.76 – 3.68 (m, 1H), 3.42 (dd, *J* = 5, 10, 1H), 3.31 (dd, *J* = 5, 10, 1H), 1.56 (s, 3H), 1.47 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 109.9, 81.5, 78.3, 64.1, 27.9, 27.7, 26.3, 18.7, 7.3, -5.0; MS (CI) *m/z* 387 (M+H)$^+$, 371, 313, 285, 271, 241, 184, 143, 117, 75; HRMS (CI) *m/z* 387.0855 (calcd for C$_{13}$H$_{28}$IO$_3$Si: 387.0853).

2-((4*R*,5*R*)-5-((*tert*-Butyldimethylsilanyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acetonitrile (12).

A solution of **11** (0.118 g, 0.199 mmol) and potassium cyanide (0.032 g, 0.49 mmol) in dimethyl sulfoxide (0.7 mL) was stirred for 3 d at room temperature. Water (15 mL) was added to the mixture and the resulting solution was extracted with ethyl acetate (10 mL x 3). The combined extract was washed with brine (10 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel to give **12** (0.056 g, 99%) as a colourless oil: $[\alpha]_D^{23}$ +7.1 (c 1.1, CHCl$_3$); IR (neat) 2988, 2955, 2930, 2858, 2253, 1472, 1372, 1253, 1143, 1088, 1006, 972, 837, 779, 671 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.09 – 4.03 (m, 1H), 3.91 – 3.84 (m, 2H), 3.65 (ddd, *J* = 2, 5, 10 Hz, 1H), 2.81 (dd, *J* =4, 17 Hz, 1H), 2.64 (dd, *J* =4, 17 Hz, 1H), 1.44 (s, 3H), 1.38 (s, 3H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 117.1, 110.4, 79.7, 75.0, 63.7, 27.4, 26.2, 22.4, 18.6, -5.1.; MS (CI) *m/z* 286 (M+H)$^+$, 267, 228, 170, 156, 140, 117, 97, 73; HRMS (CI) *m/z* 286.1835 (calcd for C$_{14}$H$_{28}$NO$_3$Si: 286.1839).

2-((4*R*,5*R*)-5-((*tert*-Butyldimethylsilanyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (13).

To a solution of **12** (0.287g, 1.00 mmol) in ether (3 mL) at –78 °C was added slowly neat diisobutylaluminium hydride (0.197 mL, 1.1 mmol). The mixture was stirred at -78 °C for 2 h, after which it was transferred to a pre-cooled (0 °C) saturted solution of potassium sodium tartrate. The mixture was stirred, the layers were separated and the aqueous layer was extracted with ether (10 mL x 3). The combined extract was dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 10:1) to yield **13** (202 mg, 69%) as a colourless oil: $[\alpha]_D^{23}$ +2.2 (c 5, CHCl$_3$); IR (neat) 2987, 2955, 2930, 2858, 1730, 1472, 1380, 1254, 1086, 837, 778 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.80 (dd, *J* = 2, 2 Hz, 1H), 4.35 (ddd, *J* = 4, 8, 8

Hz, 1H), 3.83 (dd, *J* = 4, 10 Hz, 1H), 3.73 (ddd, *J* = 4, 6, 8 Hz, 1H), 3.66 (dd, *J* = 6, 10 Hz, 1H), 2.75 (ddd, *J* = 2, 4, 17 Hz, 1H), 2.66 (ddd, *J* = 2, 8, 17 Hz, 1H), 1.39 (s, 3H), 1.38 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 200.4, 190.7, 80.7, 74.6, 63.8, 47.5, 27.5, 27.2, 26.2, 18.7, -5.1; MS (CI) *m/z* 287 (M-H)$^+$, 273, 245, 231, 213, 173, 155, 145, 115; HRMS (CI) *m/z* 287.1676 (calcd for C$_{14}$H$_{27}$O$_4$Si : 287.1679).

(*S*)-1-((4*R*,5*R*)-5-((*tert*-Butyldimethylsilanyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-2-ol (14).

To a solution of (-)-*B*-methoxydiisopinocampheyl -borane (1.98 g, 6.26 mmol) in ether (7 mL) at 0 ^{o}C was added allylmagnesium bromide (1.0M solution in hexane, 5.36 mL) and the solution was allowed to warm to room temperature. After 1 h, the solution was cooled to –100 ^{o}C and a solution of **13** (0.967 g, 3.35 mmol) in ether (10 mL) was added slowly. The solution was allowed to warm to –78 ^{o}C over 1 h and then to 0 ^{o}C. After 1 h, 30% hydrogen peroxide (1.37 mL) and 4N aqueous sodium hydroxide (0.68 mL) were added and the mixture was stirred for 8 h. The mixture was diluted with water (10 mL) and extracted with ether (20 mL x 3), and the combined extract was dried (Na$_2$SO$_4$) and concentrated. The residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 20:1) to yield a mixture of **14** and isopinylcampheol (1.53 g) as a colourless oil. This mixture was used in the next step without further purification. Data for **14**: IR (neat) 3482, 3073, 2929, 2858, 1469, 1372, 1253, 1216, 1084, 913, 836, 777 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.83 (ddd, *J* = 7, 10, 17 Hz, 1H), 5.17 – 5.07 (m, 2H), 4.15 – 4.01 (m, 1H), 3.98 – 3.87 (m, 1H), 3.87 – 3.64 (m, 3H), 2.36 – 2.20 (m, 2H), 1.94 – 1.77 (m, 2H), 1.41 (s, 3H), 1.38 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 135.1, 118.2, 117.9, 109.0, 81.6, 80.9, 79.7, 77.6, 77.2, 70.9, 68.6, 64.1, 63.9, 42.4, 40.1, 39.5, 27.7, 27.3, 26.3, 18.7, -5.0, -5.1; MS (CI) *m/z* 331 (M+H)$^+$, 316, 315, 273, 255, 215, 197, 145, 123, 89, 75; HRMS (CI) *m/z* 331.2300 (calcd for C$_{17}$H$_{35}$O$_4$Si : 331.2305).

tert-Butyl(((4*R*,5*R*)-5-((*S*)-2-methoxypent-4-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)dimethylsilane (15).

To a stirred solution of **14** containing isopinylcampheol (32 mg, 0.097 mmol) in tetrahydrofuran (1.2 mL) was added hexane-washed sodium hydride (12 mg, 0.30 mmol) and the mixture was heated under reflux for 1 h. The mixture was cooled to room temperature and methyl iodide was added dropwise. The resulting solution was heated at reflux for 1.5 h, cooled to 0 ^{o}C, diluted with water (1 mL) and extracted with ether (5 mL x 3). The combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was purified by column chromatography on silica gel to yield **15** (26 mg, 79% from **13**) as a colourless oil: $[\alpha]_D^{23}$ +2.5 (c 6.6, CHCl$_3$); IR (neat) 3077, 2984, 2930, 2858, 1472, 1378, 1369, 1253, 1216, 1137, 1095, 913, 837, 777 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.82 (ddd, *J* = 7, 10, 17 Hz, 1H), 5.13 – 5.06 (m, 2H), 4.06 (ddd, *J* = 3, 8, 9 Hz, 1H), 3.78 – 3.71 (m, 2H), 3.70 – 3.61 (m, 1H), 3.52 – 3.44 (m, 1H), 3.38 (s, 3H), 2.33 – 2.29 (m, 2H), 1.74 (ddd, *J* = 3, 9, 14 Hz, 1H), 1.63 (ddd, *J* = 4, 9, 14 Hz, 1H), 1.40 (s, 3H), 1.38 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 134.8, 117.6, 108.9, 82.0, 77.6, 75.9, 63.9, 57.4, 38.9, 38.8, 27.8, 27.4, 26.3, 18.8, -4.9; MS (CI) *m/z* 345 (M+H)$^+$, 331, 289, 257, 231, 199, 171, 169, 125, 113, 75; HRMS (CI) *m/z* 345.2459 (calcd for C$_{18}$H$_{37}$O$_4$Si : 345.2461).

(*R*)-4-((4*R*,5*R*)-5-((*tert*-Butyldimethylsilanyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-methoxybutanal (16).

Ozone was passed into a solution of **15** (0.362 g, 1.05 mmol) in dichloromethane (12 mL) at -78 ^{o}C until a light blue color persisted. Triphenylphosphine (1.38 g, 5.26 mmol) was added and the solution was warmed to room temperature and stirred for 30 min. The mixture was concentrated and the residual oil was purified by flash chromatography on silica gel to give **16** (0.346 g, 95%) as a colourless oil: $[\alpha]_D^{23}$ +9.0 (c 2.6, CHCl$_3$); IR (neat) 2985, 2954, 2930, 2858, 1727, 1472, 1463, 1379, 1253, 1216, 1087, 1005, 837, 778 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.80 (dd, *J* = 2, 2 Hz, 1H), 4.00 (ddd, *J* = 2, 8, 10 Hz, 1H), 3.92 (dddd, *J* = 5, 5, 7, 8 Hz, 1H), 3.80 – 3.74 (m, 1H), 3.69 – 3.61 (m, 2H), 3.38 (s, 3H), 2.69 (ddd, *J* = 2, 5, 16 Hz, 1H), 2.62 (ddd, *J* = 2, 7, 16 Hz, 1H), 1.96 (ddd, *J* = 2, 8, 14 Hz, 1H), 1.62 (ddd, *J* = 5, 10, 14 Hz, 1H), 1.37 (s, 3H), 1.35 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 201.7, 109.2, 81.5, 76.1, 74.7, 63.8, 57.7, 49.2, 39.1, 27.7, 27.3, 26.3, 18.7, -5.0, -5.1; MS (CI) *m/z* 347 (M+H)$^+$, 329, 303, 287, 255, 245, 213, 197, 173, 143, 129, 85, 73; HRMS (CI) *m/z* 347.2249 (calcd for C$_{17}$H$_{35}$O$_5$Si : 347.2254).

(*R*)-1-((2*R*,4*R*,6*R*)-4,6-Dimethoxytetrahydro-2*H*-pyran-2-yl)ethane-1,2-diol (17).

A solution of **16** (52 mg, 0.15 mmol) and pyridinium *p*-toluenesulfonate (2 mg) in methanol (2 mL) was heated under reflux for 12 h and was concentrated. The residual oil was purified by flash chromatography on silica gel (dichloromethane:methanol 95:5) to yield **17** (27 mg, 87%) as a colourless oil: $[\alpha]_D^{23}$ -87.5 (c 1.19, CHCl$_3$); IR (neat) 3420, 2930, 2829, 1456, 1374, 1205, 1121, 1046, 1005, 966, 888 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.90 (d, *J* = 3 Hz, 1H), 3.84 – 3.61 (m, 5H), 3.34 (s, 3H), 3.32 (s, 3H), 2.61 (d, *J* = 5 Hz, 1H), 2.23 – 2.13 (m, 2H), 2.03 – 1.98 (m, 1H), 1.49 – 1.28 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 99.7, 74.2, 72.3, 69.2, 64.2, 55.9, 55.1, 36.3, 33.7; MS (CI) *m/z* 207 (M+H)$^+$, 197, 175, 156, 143, 117, 113, 87, 71; HRMS (CI) *m/z* 207.1230 (calcd for C$_9$H$_{19}$O$_5$: 207.1233).

(*R*)-2-(*tert*-Butyldimethylsilanyloxy)-1-((2*R*,4*R*,6*R*)-4,6-dimethoxytetrahydro-2*H*-pyran-2-yl)ethanol (18).

Imidazole (18.8 mg, 0.276 mmol), *tert*-butyldimethylsilyl chloride (41 mg, 0.28 mmol) and 4-*N*,*N*-dimethylaminopyridine (2 mg) were added sequentially to a solution of **17** (26 mg, 0.13 mmol) in dimethylformamide (1 mL). After 12 h, the solution was poured into saturated aqueous sodium bicarbonate (5 mL) and extracted with ether (5mL x 3). The combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 5:1) to yield **18** (31.0 mg, 78%) as a colourless oil: $[\alpha]_D^{23}$ - 39.6 (c 0.66, CHCl$_3$); IR (neat) 3473, 2955, 2930, 2858, 2362, 1472, 1362, 1254, 1123, 1053, 1003, 967, 837, 776 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.89 (d, *J* = 3 Hz, 1H), 3.82 (ddd, *J* = 2, 4, 12 Hz, 1H), 3.70 – 3.55 (m, 4H), 3.32 (s, 3H), 3.30 (s, 3H), 2.44 (d, *J* = 5 Hz, 1H), 2.13 (dddd, *J* = 2, 3, 4, 13 Hz, 1H), 2.01 – 1.96 (m, 1H), 1.48 – 1.38 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 99.6, 74.3, 72.7, 67.7, 64.0, 55.8, 55.0, 36.4, 33.7, 26.2, 18.6, -5.0; MS (CI) *m/z* 321 (M+H)$^+$, 313, 289.1, 257.1, 239.1, 213, 199, 173, 145, 117, 89, 75; HRMS (CI) *m/z* 319.19409 (M$^+$ – H) (calcd for C$_{15}$H$_{31}$O$_5$Si : 319.19408).

(*R*)-5-((2*R*,4*R*,6*R*)-4,6-Dimethoxytetrahydro-2*H*-pyran-2-yl)-2,2,8,8,9,9-hexamethyl-3,3-diphenyl-4,7-dioxa-3,8-disiladecane (19).

A solution of **18** (282 mg, 0.879 mmol) in dichloromethane (7.5 mL) at 0 ^{o}C was treated with 2,6-lutidine

(0.32 mL, 2.6 mmol) and *tert*-butyldiphenylsilyl trifluoromethanesulfonate (529 mg, 1.32 mmol). The solution was stirred at 0 °C for 30 min and at room temperature for 5 h, and the reaction was quenched with saturated sodium bicarbonate solution. After addition of dichloromethane (25 mL), the pH of the aqueous phase was adjusted to *ca.* 7.0 with 1M hydrochloric acid. The aqueous phase was extracted with dichloromethane (20 mL x 3), and the combined extract was dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 15:1) to yield **19** (471 mg, 96%) as a colourless oil: $[\alpha]_D^{23}$ –50.3 (c 0.95, CHCl$_3$); IR (neat) 3069, 3045, 2955, 2930, 2894, 2857, 2826, 1472, 1427, 1389, 1361, 1303, 1256, 1204, 1191, 1123, 1111, 1050, 1006, 972, 939, 927, 898, 836, 776, 739, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74 – 7.70 (m, 4H), 7.44 – 7.33 (m, 6H), 4.86 (d, J = 3 Hz, 1H), 3.77 – 3.67 (m, 3H), 3.59 – 3.45 (m, 2H), 3.29 (s, 3H), 3.19 (s, 3H), 2.12 – 2.04 (m, 1H), 1.90 – 1.82 (m, 1H), 1.46 – 1.18 (m, 2H), 1.06 (s, 9H), 0.79 (s, 9H), -0.11 (s, 3H), -0.15 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 136.4, 134.6, 134.3, 130.1, 129.9, 128.0, 127.8, 99.3, 76.2, 73.4, 67.7, 63.7, 55.7, 54.8, 36.7, 33.2, 27.5, 26.3, 20.0, 18.6, -1.0, -5.2; MS (CI) *m/z* 501 (M – t-Bu)$^+$, 469, 437, 385, 345, 313, 261, 199, 147, 113, 89; HRMS (CI) *m/z* 501.2490 (calcd for C$_{27}$H$_{41}$O$_5$Si$_2$: 501.2493, M – t-Bu).

(R)-2-(*tert*-Butyldiphenylsilanyloxy)-2-((2R,4R,6R)-4,6-dimethoxytetrahydro-2*H*-pyran-2-yl)ethanol (20). A solution of **19** (57 mg, 0.096 mmol) and pyridinium *p*-toluenesulfonate (1.2 mg, 4.8 μmol) in methanol (5 mL) was heated at reflux for 3 h. The solution was poured into a saturated sodium bicarbonate solution and extracted with ether (5 mL x 3), and the combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 3:1) to give **20** (34 mg, 75%) as a colourless oil: $[\alpha]_D^{23}$ –35.8 (c 0.75, CHCl$_3$); IR (neat) 3462, 2930, 2856, 1472, 1427, 1362, 1261, 1112, 1049, 822, 776, 740, 703 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74 – 7.67 (m, 4H), 7.47 – 7.35 (m, 6H), 4.79 (d, J = 3 Hz, 1H), 3.84 (dt, J = 5, 5 Hz, 1H), 3.72 (ddd, J = 2, 4, 12 Hz, 1H), 3.71 – 3.60 (m, 2H), 3.57 – 3.46 (m, 1H), 3.31 (s, 3H), 3.12 (s, 3H), 2.13 – 2.03 (m, 2H), 1.80 (bs, 1H), 1.45 – 1.25 (m, 2H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 136.4, 136.1, 134.2, 133.7, 130.4, 130.3, 128.2, 99.5, 74.4, 72.9, 69.9, 64.1, 55.8, 55.0, 36.6, 32.3, 27.5, 19.8; MS (CI) *m/z* 413 (M – OMe)$^+$, 355, 323, 303, 271, 245, 213, 199, 163, 135, 113, 91; HRMS (CI) *m/z* 413.2138 (calcd for C$_{24}$H$_{33}$O$_4$Si : 413.2148, M – OMe).

(S)-2-(*tert*-Butyldiphenylsilanyloxy)-2-((2R,4R,6R)-4,6-dimethoxytetrahydro-2*H*-pyran-2-yl)acetaldehyde (21). A solution of dimethyl sulfoxide (47 μL, 0.66 mmol) in dichloromethane (2 mL) at –78 °C was treated with oxalyl chloride (29 μL, 0.33 mmol) and after 15 min a solution of **20** (98 mg, 0.22 mmol) in dichloromethane (1 mL) was added. After a further 15 min, triethylamine (92 μL, 0.66 mmol) was added and the solution was warmed to –10 °C over1 h, then warmed to room temperature for 30 min. The solution was poured into a mixture of ether (5 mL) and saturated ammonium chloride solution (5 mL), and the aqueous layer was separated and extracted with ether (5 mL x 3). The combined extract was washed with saturated sodium bicarbonate solution (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel

(hexane:ethyl acetate 6:1) to give **21** (97 mg, 99%) as a colourless oil: $[\alpha]_D^{23}$ –93.9 (c 0.59, CHCl$_3$); IR (neat) 2957, 2932, 2896, 2858, 2830, 1736, 1472, 1428, 1376, 1258, 1114, 1047, 969, 921, 890, 822, 741, 703 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.65 (d, J = 1 Hz, 1H), 7.69 – 7.63 (m, 4H), 7.44 – 7.26 (m, 6H), 4.82 (d, J = 3 Hz, 1H), 4.06 (d, J = 1, 3 Hz, 1H), 3.91 (dt, J = 12, 3 Hz, 1H), 3.59 – 3.49 (m, 1H), 3.25 (s, 3H), 3.12 (s, 3H), 2.11 – 2.05 (m, 1H), 1.78 – 1.72 (m, 1H), 1.48 – 1.36 (m, 2H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 203.8, 136.3, 133.2, 130.5, 128.2, 99.6, 79.9, 72.5, 70.2, 55.7, 55.1, 36.4, 33.1, 27.4, 19.9; MS (CI) *m/z* 441 (M - H)$^+$; HRMS (CI) *m/z* 441.2099 (calcd for C$_{25}$H$_{33}$O$_5$Si : 441.2097, M - H).

(R,E)-Ethyl 4-(*tert*-butyldiphenylsilanyloxy)-4-((2R,4R,6R)-4,6-dimethoxytetrahydro-2*H*-pyran-2-yl)-2-methylbut-2-enoate (22). To a solution of **21** (10.2 mg, 23 μmol) in toluene (1.5 mL) was added **23** (25 mg, 69 μmol) and the solution was heated at 100 °C for 12 h under argon. The solution was concentrated under reduced pressure and the crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 12:1) to give **22** (11.7 mg, 96%) as a colourless oil: $[\alpha]_D^{23}$ –71.1 (c 0.52, CHCl$_3$); IR (neat) 2957, 2931, 2894, 2857, 2829, 1714, 1472, 1428, 1237, 1112, 1049, 970, 822, 740, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.73 – 7.60 (m, 4H), 7.42 – 7.25 (m, 6H), 6.62 (dq, J = 1, 9 Hz, 1H), 4.83 (d, J = 3 Hz, 1H), 4.46 (dd, J = 6, 9 Hz, 1H), 4.17 – 4.07 (m, 2H), 3.72 (ddd, J = 2, 6, 12 Hz, 1H), 3.63 – 3.52 (m, 1H), 3.31 (s, 3H), 3.22 (s, 3H), 2.14 – 2.08 (m, 1H), 2.00 – 1.94 (m, 1H), 1.34 (d, J = 1 Hz, 3H), 1.26 (t, J = 7 Hz, 3H), 1.44 – 1.16 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 167.9, 139.8, 136.4, 134.1, 133.9, 130.1, 130.0, 129.9, 128.0, 127.8, 99.4, 73.0, 72.6, 71.5, 60.9, 55.8, 54.9, 36.4, 32.8, 27.8, 19.8, 14.6, 13.2; MS (CI) *m/z* 495 (M – OMe)$^+$, 437, 377, 353, 279, 239, 199, 113, 87; HRMS (CI) *m/z* 495.2564 (calcd for C$_{29}$H$_{39}$O$_5$Si : 495.2567, M$^+$-OMe).

(R,E)-4-(*tert*-Butyldiphenylsilanyloxy)-4-((2R,4R,6R)-4,6-dimethoxytetrahydro-2*H*-pyran-2-yl)-2-methylbut-2-en-1-ol (24). To a solution of **22** (92 mg, 0.18 mmol) in toluene (0.5 mL) at -78 °C was added diisobutylaluminium hydride (75 μL, 0.44 mmol, 0.25M solution in toluene) and the mixture was stirred for 1 h at –78 °C. Saturated Rochelle salt solution (1 mL) and ethyl acetate (2 mL) were added, and the mixture was allowed to warm to room temperature and was stirred for 2 h. The organic layer was separated, the aqueous layer was extracted with ethyl acetate (5 mL x 3) and the combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 4:1) to give **24** (81.8 mg, 96%) as a colourless oil: $[\alpha]_D^{23}$ -46.4 (c 2.56, CHCl$_3$); IR (neat) 3448, 3071, 3048, 2957, 2931, 2895, 2857, 2822, 1472, 1427, 1370, 1303, 1260, 1204, 1157, 1112, 1066, 1049, 969, 908, 823, 740, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 – 7.70 (m, 4H), 7.47 – 7.35 (m, 6H), 5.32 (dq, J = 9, 1 Hz, 1H), 4.92 (d, J = 3 Hz, 1H), 4.51 (dd, J = 6, 9 Hz, 1H), 3.73 (d, J = 13 Hz, 1H), 3.68 (d, J = 13 Hz, 1H), 3.75 – 3.59 (m, 2H), 3.35 (s, 3H), 3.33 (s, 3H), 2.20 – 2.16 (m, 1H), 2.02 – 1.98 (m, 1H), 1.49 – 1.42 (m, 1H), 1.25 – 1.10 (m, 1H), 1.16 (d, J = 1 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 138.2, 136.5, 135.3, 134.3, 130.0, 129.9, 127.9, 127.7, 125.0, 99.4, 73.2, 72.6, 72.0, 68.4, 55.9, 54.9, 36.4, 33.1, 30.1, 27.4, 19.8, 14.4; MS (CI) *m/z* 453 (M - OMe)$^+$, 409, 395, 363, 339, 311, 253, 199, 165, 135, 113, 87;

HRMS (CI) *m/z* 453.2457 (calcd for $C_{27}H_{37}O_4Si$: 453.2461, M$^+$ - OMe).

(*R,E*)-4-(*tert*-Butyldiphenylsilanyloxy)-4-((2*R*,4*R*,6*R*)-4,6-dimethoxytetrahydro-2*H*-pyran-2-yl)-2-methylbut-2-enal (25). A solution of dimethyl sulfoxide (8.3 μL, 0.12 mmol) in dichloromethane (1 mL) at −78 °C was treated with oxalyl chloride (5.1 μL, 0.059 mmol), and after 15 min a solution of **24** (19 mg, 0.039 mmol) in dichloromethane (1.5 mL) was added. After a further 15 min, triethylamine (16 μL, 0.12 mmol) was added and the solution was warmed to −10 °C over 1 h, then warmed to room temperature for 0.5 h. The solution was poured into a mixture of ether (5 mL) and saturated ammonium chloride solution (5 mL) and the aqueous layer was separated and extracted with ether (5 mL x 3). The combined extract was washed with saturated sodium bicarbonate solution (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 6:1) to yield **25** (17.6 mg, 93%) as a colourless oil: $[\alpha]_D^{23}$ −63.6 (c 2.4, CHCl$_3$); IR (neat) 3071, 3045, 2954, 2931, 2895, 2857, 2828, 1693, 1472, 1427, 1377, 1260, 1203, 1112, 1071, 1048, 999, 972, 910, 822, 803, 740, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.47 (s, 1H), 7.74 − 7.62 (m, 4H), 7.49 − 7.33 (m, 6H), 6.36 (dq, *J* = 9, 1 Hz, 1H), 4.85 (d, *J* = 3 Hz, 1H), 4.68 (dd, *J* = 5, 9 Hz, 1H), 3.79 (ddd, *J* = 2, 5, 12 Hz, 1H), 3.66 − 3.58 (m, 1H), 3.34 (s, 3H), 3.21 (s, 3H), 2.18 − 2.13 (m, 1H), 2.08 − 2.04 (m, 1H), 1.46 − 1.24 (m, 2H), 1.34 (d, *J* = 1 Hz, 3H), 1.12 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 195.3, 151.8, 140.0, 136.3, 133.9, 133.5, 130.4, 128.1, 128.0, 99.5, 72.9, 72.2, 71.4, 55.9, 54.9, 36.4, 32.7, 27.4, 19.8, 9.9; MS (CI) *m/z* 451 (M - OMe)$^+$, 425, 393, 361, 338, 309, 281, 263, 231, 199, 163, 145, 113, 87; HRMS (CI) *m/z* 451.2308 (calcd for $C_{27}H_{35}O_4Si$: 451.2305, M$^+$ - OMe).

(*R*,2*E*,4*E*)-Ethyl 6-(*tert*-butyldiphenylsilanyloxy)-6-((2*R*,4*R*,6*R*)-4,6-dimethoxy tetrahydro-2*H*-pyran-2-yl)-4-methylhexa-2,4-dienoate (26). To a slurry of hexane-washed sodium hydride (8 mg, 0.197 mmol) in tetrahydrofuran (1.5 mL) at 0 °C was added **27** (39.2 μL, 0.197 mmol) and the mixture was stirred for 0.5 h. A solution of **25** (47.7 mg, 0.0988 mmol) in tetrahydrofuran (1 mL) was added and the mixture was allowed to warm to room temperature and was stirred for 1 h. The reaction was quenched with water (1 mL) and the mixture was extracted with ether (3 mL x 3). The combined extract was washed with brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 9:1) to afford **26** (52.4 mg, 96%) as a colourless oil: $[\alpha]_D^{23}$ -148.5 (c 0.57, CHCl$_3$); IR (neat) 2958, 2930, 2890, 2857, 2824, 1714, 1622, 1472, 1427, 1366, 1305, 1269, 1173, 1111, 1068, 1048, 976, 822, 740 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.73 − 7.60 (m, 4H), 7.40 − 7.31 (m, 6H), 7.15 (dd, *J* = 1, 16 Hz, 1H), 5.80 (d, *J* = 9 Hz, 1H), 5.70 (d, *J* = 16 Hz, 1H), 4.83 (d, *J* = 3 Hz, 1H), 4.50 (dd, *J* = 6, 9 Hz, 1H), 4.21 (q, *J* = 7 Hz, 2H), 3.69 (ddd, *J* = 2, 6, 12 Hz, 1H), 3.60 − 3.55 (m, 1H), 3.30 (s, 3H), 3.23 (s, 3H), 2.14 − 2.09 (m, 1H), 1.97 − 1.93 (m, 1H), 1.31 (t, *J* = 7 Hz, 3H), 1.26 (d, *J* = 1 Hz, 3H), 1.42 − 1.09 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.6, 149.0, 139.5, 136.4, 134.7, 134.2, 134.1, 130.1, 127.9, 127.8, 118.0, 99.4, 73.0, 72.6, 71.7, 60.7, 55.9, 54.9, 36.4, 32.9, 27.4, 19.8, 14.7, 13.0; MS (CI) *m/z* 552 (M)$^+$ 520, 495, 463, 437, 403, 379, 349, 321, 305, 265, 227, 199, 145, 113, 87; HRMS (FAB) *m/z* 552.2897 (calcd for $C_{32}H_{44}O_6Si$: 552.2907).

(*R*,2*E*,4*E*)-6-(*tert*-Butyldiphenylsilanyloxy)-6-((2*R*,4*R*,6*R*)-4,6-dimethoxytetra hydro-2*H*-pyran-2-yl)-4-methylhexa-2,4-dienol (28). To a solution of **26** (52.4 mg, 0.0947 mmol) in toluene (2 mL) at -78 °C was added diisobutylaluminium hydride (1.5 mL, 0.280 mmol, 0.187M solution in toluene) and the solution was stirred for 1 h at −78 °C. Saturated Rochelle salt solution (1 mL) and ethyl acetate (2 mL) were added, and the mixture was allowed to warm to room temperature and was stirred for 2 h. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (5 mL x 3). The combined extract was washed with brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 4:1) to yield **28** (45.4 mg, 94%) as a colourless oil: $[\alpha]_D^{23}$ −111.4 (c 0.42 , CHCl$_3$); IR (neat) 3435, 2954, 2929, 2890, 2856, 2822, 1472, 1427, 1260, 1203, 1157, 1112, 1066, 1048, 967, 909, 822, 739, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74 − 7.60 (m, 4H), 7.43 − 7.28 (m, 6H), 6.10 (dd, *J* = 1, 16 Hz, 1H), 5.63 (dt, *J* = 16, 6 Hz, 1H), 5.44 (d, *J* = 9 Hz, 1H), 4.83 (d, *J* = 3 Hz, 1H), 4.47 (dd, *J* = 6, 9 Hz, 1H), 4.16 (d, *J* = 6 Hz, 2H), 3.69 (ddd, *J* = 2, 6, 12 Hz, 1H), 3.60 − 3.52 (m, 1H), 3.30 (s, 3H), 3.22 (s, 3H), 2.13 − 2.07 (m, 1H), 1.97 − 1.91 (m, 1H), 1.24 (d, *J* = 1 Hz, 3H), 1.42 − 1.08 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 136.5, 136.4, 136.2, 135.3, 134.5, 134.4, 131.8, 129.9, 129.8, 127.8, 127.7, 99.4, 73.2, 72.7, 71.9, 66.3, 64.2, 55.8, 54.9, 36.4, 33.0, 30.1, 27.4, 19.8, 13.3; MS (CI) *m/z* 510 (M)$^+$, 453, 421, 365, 348, 289, 229, 199, 145, 113, 87; HRMS (CI) *m/z* 510.2796 (calcd for $C_{30}H_{42}O_5Si$: 510.2802, M$^+$).

(*R*,2*E*,4*E*)-6-(*tert*-Butyldiphenylsilanyloxy)-6-((2*R*,4*R*,6*R*)-4,6-dimethoxytetra hydro-2*H*-pyran-2-yl)-4-methylhexa-2,4-dienal (29). A solution of dimethyl sulfoxide (19 μL, 0.27 mmol) in dichloromethane (2 mL) at −78 °C was treated with oxalyl chloride (11.7 μL, 0.133 mmol) and after 15 min a solution of **28** (45.4 mg, 0.089 mmol) in dichloromethane (1 mL) was added. After a further 15 min, triethylamine (37 μL, 0.27 mmol) was added and the solution was warmed to −10 °C for 1 h, then was warmed to room temperature for 0.5 h. The solution was poured into a mixture of ether (5 mL) and saturated ammonium chloride solution (5 mL), and the aqueous layer was separated and extracted with ether (5 mL x 3). The combined extract was washed with saturated sodium bicarbonate solution (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 6:1) to give **29** (41.5 mg, 92%) as a colourless oil: $[\alpha]_D^{23}$ −163.8 (c 0.32, CHCl$_3$); IR (neat) 3065, 3045, 2954, 2930, 2894, 2856, 2822, 1682, 1631, 1605, 1427, 1374, 1260, 1203, 1112, 1068, 969, 910, 822, 803, 740, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.56 (d, *J* = 8 Hz, 1H), 7.75 − 7.63 (m, 4H), 7.46 − 7.33 (m, 6H), 6.95 (d, *J* = 16 Hz, 1H), 6.01 (dd, *J* = 8, 16 Hz, 1H), 5.92 (d, *J* = 9 Hz, 1H), 4.86 (d, *J* = 3 Hz, 1H), 4.57 (dd, *J* = 5, 9 Hz, 1H), 3.76 (ddd, *J* = 2, 5, 12 Hz, 1H), 3.65 − 3.59 (m, 1H), 3.35 (s, 3H), 3.25 (s, 3H), 2.18 − 2.14 (m, 1H), 2.05 − 2.01 (m, 1H), 1.35 (d, *J* = 1 Hz, 3H), 1.46 − 1.19 (m, 2H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.4, 157.1, 141.7, 136.4, 136.3, 135.1, 134.1, 133.8, 130.2, 128.7, 128.0, 127.9, 99.5, 73.0, 72.4, 71.6, 55.9, 54.9, 36.4, 32.9, 27.4, 19.8, 13.1; MS (CI) *m/z* 509 (M+H)$^+$, 491, 452, 419, 387, 364, 335, 305, 277, 229, 199, 161, 145, 113; HRMS (CI) *m/z* 509.2720 (calcd for $C_{30}H_{41}O_5Si$: 509.2723, M+H).

tert-Butyl((1R,2E,4E,6R)-1-((2R,4R,6R)-4,6-dimethoxytetrahydro-2H-pyran-2-yl)-6-hydroxy-3-methylnona-2,4,8-trienyloxy)diphenylsilane (30). To a solution of (+)-B-methoxydiisopinocampheylborane (152 mg, 0.480 mmol) in ether (1.5 mL) at 0 °C was added via syringe allylmagnesium bromide (0.285 mL, 0.285 mmol, 1.0M solution in ether) and the solution was allowed to warm to room temperature. After 1 h, the solution was cooled to –78 °C and a solution of **29** (41.5 mg, 81 μmol) in ether (1 mL) was added slowly. The solution was allowed to warm to –15 °C and after 1 h 30% hydrogen peroxide (130 μL) and 4N aqueous sodium hydroxide (65 μL) were added. The mixture was stirred overnight, diluted with water (1 mL) and extracted with ether (2 mL x 3). The combined extract was dried (Na$_2$SO$_4$) and concentrated, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 9:1) to give **30** (32.8 mg, 73%) as a colourless oil: $[\alpha]_D^{23}$ -107.6 (c 0.23, CHCl$_3$); IR (neat) 3441, 3071, 2958, 2929, 2894, 2856, 2822, 1427, 1374, 1299, 1260, 1203, 1111, 1066, 1048, 967, 910, 822, 803, 739, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74 – 7.59 (m, 4H), 7.43 – 7.27 (m, 6H), 6.08 (d, J = 16 Hz, 1H), 5.86 – 5.73 (m, 1H), 5.47 (dd, J = 7, 16 Hz, 1H), 5.42 (d, J = 10 Hz, 1H), 5.19 – 5.12 (m, 2H), 4.83 (d, J = 3 Hz, 1H), 4.48 (dd, J = 6, 9 Hz, 1H), 4.18 (q, J = 6 Hz, 1H), 3.66 (ddd, J = 2, 6, 12 Hz, 1H), 3.60 – 3.51 (m, 1H), 3.30 (s, 3H), 3.24 (s, 3H), 2.37 – 2.23 (m, 2H), 2.14 – 2.08 (m, 1H), 1.97 – 1.92 (m, 1H), 1.63 (bs, 1H), 1.21 (d, J = 1 Hz, 3H), 1.46 – 1.08 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 136.5, 136.4, 135.4, 134.6, 134.4, 131.7, 130.8, 129.9, 129.8, 127.8, 127.7, 118.7, 99.4, 73.2, 72.8, 72.2, 71.9, 55.8, 54.9, 42.5, 36.4, 33.0, 27.4, 19.8, 13.3; MS (CI) m/z 519 (M – OMe)$^+$ 493, 461, 443, 405, 388, 336, 322, 289, 239, 213, 199, 145, 113, 87; HRMS (CI) m/z 519.2939 (calcd for C$_{32}$H$_{43}$O$_4$Si : 519.2931, M – OMe).

tert-Butyl((1R.2E,4E,6R)-1-(2R,4R,6R)-4,6-dimethoxytetrahydro-2H-pyran-2-yl)-6-methoxy-3-methylnona-2,4,8-trienyloxy)diphenylsilane (31). To a stirred solution of **30** (32.8 mg, 59 μmol) in tetrahydrofuran (2.5 mL) was added hexane-washed sodium hydride (15 mg, 0.37 mmol) and the suspension was heated under reflux for 1 h. The solution was cooled to room temperature and methyl iodide (37 μL, 0.59 mmol) was added. The solution was heated under reflux for 1.5 h, cooled to 0 °C, diluted with water (1 mL) and extracted with ether (3 mL x 3). The combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 19:1) to give **31** (30 mg, 89%) as a colourless oil: $[\alpha]_D^{23}$ –99.1 (c 0.15, CHCl$_3$); IR (neat) 3071, 2954, 2929, 2894, 2855, 2822, 1463, 1427, 1374, 1260, 1203, 1111, 1066, 1049, 967, 911, 822, 803, 739, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74 – 7.60 (m, 4H), 7.43 – 7.26 (m, 6H), 6.00 (d, J = 16 Hz, 1H), 5.77 (ddt, J = 17, 10, 7 Hz, 1H), 5.40 (d, J = 9 Hz, 1H), 5.29 (dd, J = 8, 16 Hz, 1H), 5.12 – 5.04 (m, 2H), 4.85 (d, J = 3 Hz, 1H), 4.48 (dd, J = 6, 9 Hz, 1H), 3.71 – 3.53 (m, 3H), 3.30 (s, 3H), 3.25 (s, 3H), 3.22 (s, 3H), 2.42 – 2.20 (m, 2H), 2.17 – 2.09 (m, 1H), 2.00 – 1.90 (m, 1H), 1.20 (d, J = 1 Hz, 3H), 1.42 – 1.08 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 137.2, 136.5, 136.4, 135.4, 135.0, 134.6, 134.3, 131.5, 129.9, 129.8, 128.9, 127.8, 127.6, 117.2, 99.4, 82.4, 73.2, 72.7, 71.9, 56.6, 55.8, 54.9, 40.7, 36.4, 33.1, 27.4, 19.8, 13.3; MS (CI) m/z 533 (M – OMe)$^+$ 507, 475, 419, 388, 335, 299, 239, 199, 145, 113, 85; HRMS (CI) m/z 533.3073 (calcd for C$_{33}$H$_{45}$O$_4$Si : 533.3087, M – OMe).

(3R,4E,6E,8R)-8-(tert-Butyldiphenylsilanyloxy)-8-((2R,4R,6R)-4,6-dimethoxytetra hydro-2H-pyran-2-yl)-3-methoxy-6-methylocta-4,6-dienal (32). To a solution of **31** (34.1 mg, 60.4 μmol) in tetrahydrofuran-water (1:1, 6 mL) were added osmium tetraoxide (0.04M in H$_2$O, 75.4 μL, 5 mol %) and sodium periodate (26 mg, 121 μmol) and the mixture was stirred at room temperature for 20 h under argon. The mixture was diluted with water (5 mL) and extracted with ether (5 mL x 3), and the combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 7:1) to furnish **32** (18.3 mg, 54%) as a colourless oil: $[\alpha]_D^{23}$ -65.3 (c 0.19, CHCl$_3$); IR (neat) 2954, 2920, 2850, 1727, 1463, 1427, 1375, 1111, 1067, 1048, 968, 822, 804, 740, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.76 (dd, J = 1, 3 Hz, 1H), 7.73 – 7.60 (m, 4H), 7.43 – 7.29 (m, 6H), 6.08 (d, J = 16 Hz, 1H), 5.44 (d, J = 9 Hz, 1H), 5.30 (dd, J = 8, 16 Hz, 1H), 4.85 (d, J = 3 Hz, 1H), 4.49 (dd, J = 6, 9 Hz, 1H), 4.10 (dt, J = 8, 4 Hz, 1H), 3.69 (ddd, J = 2, 6, 12 Hz, 1H), 3.64 – 3.53 (m, 1H), 3.31 (s, 3H), 3.24 (s, 3H), 3.22 (s, 3H), 2.68 (ddd, J = 3, 8, 16 Hz, 1H), 2.50 (ddd, J = 2, 5, 16 Hz, 1H), 2.17 – 2.09 (m, 1H), 2.00 – 1.92 (m, 1H), 1.22 (d, J = 1 Hz, 3H), 1.45 – 1.20 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 201.2, 137.9, 136.4, 135.0, 134.5, 132.6, 130.0, 129.8, 127.8, 127.7, 127.2, 99.4, 73.1, 72.6, 71.9, 56.7, 55.8, 54.9, 49.9, 36.3, 33.0, 30.1, 27.4, 19.8, 13.3; MS (CI) m/z 534 (M$^+$ – MeOH) 476, 421, 390, 360, 336, 289, 252, 199, 183, 135, 113; HRMS (CI) m/z 534.2795 (calcd for C$_{32}$H$_{42}$O$_5$Si : 534.2802, M – MeOH).

((1R,2E,4E,6R,8E)-9-Bromo-1-((2R,4R,6R)-4,6-dimethoxytetrahydro-2H-pyran-2-yl)-6-methoxy-3-methylnona-2,4,8-trienyloxy)(tert-butyl)diphenylsilane (33).

To a suspension of chromium(II) chloride (304 mg, 2.47 mmol) in tetrahydrofuran (17 mL) at 0 °C was added a solution of **32** (80.9 mg, 0.143 mmol) and bromoform (75 μL, 0.86 mmol) in tetrahydrofuran (1 mL). The suspension was allowed to warm to room temperature and was stirred for 12 h, then was diluted with water (10 mL) and extracted with ether (10 mL x 3). The combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the resulting oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 15:1) to yield **33** (59.8 mg, 65%) as a colourless oil: $[\alpha]_D^{23}$ -61.0 (c 0.15, CHCl$_3$); IR (neat) 2950, 2928, 2855, 2818, 1623, 1472, 1427, 1363, 1261, 1111, 1066, 1048, 968, 937, 909, 822, 803, 739, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74 – 7.60 (m, 4H), 7.43 – 7.30 (m, 6H), 6.25 – 6.10 (m, 0.5H), 6.13 (d, J = 8 Hz, 1H), 6.01 (d, J = 16 Hz, 1H), 5.92 – 5.76 (m, 0.5H), 5.42 (d, J = 9 Hz, 1H), 5.24 (dd, J = 8, 16 Hz, 1H), 4.86 (d, J = 3 Hz, 1H), 4.49 (dd, J = 6, 9 Hz, 1H), 3.72 – 3.40 (m, 3H), 3.31 (s, 3H), 3.25 (s, 3H), 3.21 (s, 3H), 2.50 – 2.20 (m, 2H), 2.17 – 2.09 (m, 1H), 1.99 – 1.92 (m, 1H), 1.42 – 1.32 (m, 1H), 1.21 (d, J = 1 Hz, 3H), 1.20 – 1.10 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 137.8, 136.5, 135.2, 134.6, 134.3, 132.1, 129.9, 129.8, 128.2, 127.8, 127.7, 99.4, 81.6, 73.2, 72.7, 71.9, 56.6, 55.8, 54.9, 36.4, 33.1, 30.1, 27.4, 19.8, 13.3; MS (CI) m/z 610 (M$^+$ – MeOH) 541, 499, 453, 422, 336, 299, 213, 199, 113, 87; HRMS (CI) m/z 610.2109 (calcd for C$_{33}$H$_{43}$O$_4$^{79}BrSi : 610.2114, M – MeOH).

(4R,6R)-6-((1R,2E,4E,6R,8E)-9-Bromo-1-(tert-butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4,8-trienyl)-4-methoxytetrahydropyran-2-one (3). From 33. To a solution of **33** (29 mg, 46 μmol) in tetrahydrofuran (14 mL) was

added 10% hydrochloric acid (5.7 mL) and the mixture was heated for 13 h at 61-65 °C. The mixture was cooled to room temperature, diluted with ether (10 mL) and washed with saturated sodium bicarbonate solution (10 mL x 3). The separated organic layer was dried and concentrated under reduced pressure and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 5:1) to give a hemiacetal that was used immediately for the next reaction.

To a solution of the hemiacetal obtained above in dichloromethane (3 mL) was added pyridinium chlorochromate (100 mg, 0.46 mmol), sodium acetate (30 mg, 0.37 mmol) and 4A molecular sieves, and the mixture was stirred for 2 h at room temperature. The mixture was filtered through a short column of silica gel to give **3** (4.5 mg, 16%) as a colourless oil: $[\alpha]_D^{23}$ -23.4 (c 0.22, CHCl$_3$); IR (neat) 3065, 2954, 2926, 2854, 1743, 1625, 1462, 1427, 1360, 1235, 1110, 998, 968, 937, 822, 800, 741, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65 – 7.58 (m, 4H), 7.42 – 7.27 (m, 6H), 6.17 – 6.11 (m, 1H), 6.05 (d, J = 14 Hz, 1H), 6.00 (d, J = 16 Hz, 1H), 5.44 (d, J = 9 Hz, 1H), 5.29 (dd, J = 8, 16 Hz, 1H), 4.62 (dd, J = 5, 9 Hz, 1H), 4.16 (ddd, J = 3, 5, 12 Hz, 1H), 3.68 – 3.61 (m, 1H), 3.56 (dt, J = 13, 6 Hz, 1H), 3.32 (s, 3H), 3.21 (s, 3H), 2.85 (ddd, J = 1, 6, 17 Hz, 1H), 2.39 (dd, J = 8, 17 Hz, 1H), 2.37 – 2.17 (m, 3H), 1.40 – 1.32 (m, 1H), 1.27 (d, J = 1 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.8, 136.9, 136.3, 135.9, 133.8, 129.9, 129.7, 129.5, 128.6, 127.7, 127.5, 106.4, 81.0, 79.7, 72.4, 70.7, 56.3, 56.0, 39.1, 36.8, 29.9, 27.0, 19.4, 13.0; MS (CI) m/z 569 (M$^+$ – t-Bu), 537, 497, 453, 407, 375, 319, 283, 239, 199, 187, 135; HRMS (CI) m/z 569.1368 (calcd for C$_{29}$H$_{34}$O$_5$^{79}BrSi : 569.1359, M – t-Bu).

(R)-2-(tert-Butyldiphenylsilanyloxy)-2-((2R,4R,6S)-4-methoxy-6-(phenylthio) tetrahydro-2H-pyran-2-yl)ethanol (34α). To a solution of **20** (207 mg, 0.466 mmol) in 1,2-dichloroethane (6 mL) at 0 °C were added zinc iodide (287 mg, 0.899 mmol) and trimethyl(phenylthio)silane (264 μL, 1.39 mmol). The mixture was allowed to warm to room temperature and was stirred for 5 h, then was diluted with ether (20 mL) and washed with 10% hydrochloric acid (10 mL). The organic layer was separated, washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 10 : 1) to give **34α** (113 mg, 47%) as a colourless oil: $[\alpha]_D^{23}$ -167.2 (c 0.75, CHCl$_3$); IR (neat) 3470, 3070, 3049, 2956, 2930, 2890, 2856, 1584, 1472, 1427, 1362, 1260, 1111, 1067, 997, 950, 853, 822, 740, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74 – 7.67 (m, 5H), 7.47 – 7.35 (m, 10H), 5.73 (d, J = 5 Hz, 1H), 4.28 (ddd, J = 2, 3, 12 Hz, 1H), 3.79 (dt, J = 5, 4 Hz, 1H), 3.67 – 3.46 (m, 3H), 3.34 (s, 3H), 2.37 – 2.31 (m, 1H), 2.07 – 2.01 (m, 1H), 1.84 (ddd, J = 6, 12, 13 Hz, 1H), 1.55 – 1.40 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 136.4, 136.2, 136.1, 135.3, 134.2, 133.6, 131.6, 130.4, 130.3, 129.4, 128.2, 127.5, 85.1, 74.6, 73.6, 70.5, 64.0, 55.8, 37.5, 33.0, 27.6, 19.9; MS (CI) m/z 413 (M – SPh)$^+$ 381, 323, 303, 257, 225, 179, 111, 79; HRMS (CI) m/z 413.2135 (calcd for C$_{24}$H$_{33}$O$_4$Si : 413.2148, M – SPh). There was also obtained **34β** (52 mg, 21%) as a colourless oil.

tert-Butyl((1R,2E,4E,6R)-6-methoxy-1-((2R,4R,6S)-4-methoxy-6-(phenylthio) tetrahydro-2H-pyran-2-yl)-3-methylnona-2,4,8-trienyloxy)diphenylsilane (35). To a solution of (4R,5E,7E,9R)-9-(tert-butyldiphenylsilanyloxy)-9-((2R,4R,6S)-4-methoxy-6-(phenylthio)tetrahydro-2H-pyran-2-yl)-7-methylnona-1,5,7-trien-4-ol obtained from **34α** (21.0 mg, 33 μmol) in tetrahydrofuran (2.5 mL) was added hexane-washed

sodium hydride (13 mg, 0.33 mmol) and the mixture was heated at reflux for 1 h. The solution was cooled to room temperature, methyl iodide (21 μL, 0.33 mmol) was added and the solution was heated at reflux for 1.5 h. The mixture was cooled to 0 °C, diluted with water (1 mL) and extracted with ether (5 mL x 3). The combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 19:1) to give **35** (21.4 mg, 89%) as a colourless oil: $[\alpha]_D^{23}$ –174.4 (c 2.2, CHCl$_3$); IR (neat) 3071, 2956, 2924, 2854, 1463, 1428, 1361, 1260, 1111, 966, 911, 821, 804, 740, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.70 – 7.60 (m, 4H), 7.40 – 7.15 (m, 11H), 5.99 (d, J = 16 Hz, 1H), 5.85 – 5.72 (m, 1H), 5.70 (d, J = 5 Hz, 1H), 5.45 (d, J = 9 Hz, 1H), 5.29 (dd, J = 8, 16 Hz, 1H), 5.14 – 5.05 (m, 2H), 4.51 (dd, J = 5, 9 Hz, 1H), 4.27 (ddd, J = 2, 5, 12 Hz, 1H), 3.66 – 3.55 (m, 2H), 3.36 (s, 3H), 3.22 (s, 3H), 2.42 – 2.21 (m, 3H), 2.14 – 2.05 (m, 1H), 1.82 (ddd, J = 6, 12, 17 Hz, 1H), 1.40 – 1.20 (m, 1H), 1.18 (d, J = 1 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 137.3, 136.4, 136.4, 135.8, 135.3, 135.0, 134.5, 134.3, 131.9, 131.6, 130.0, 129.8, 129.1, 128.9, 127.9, 127.7, 127.3, 117.3, 85.6, 82.4, 73.6, 72.7, 72.2, 56.6, 55.9, 40.7, 37.6, 33.4, 27.5, 19.8, 13.2; MS (CI) m/z 643 (M + H)$^+$, 611, 579, 533, 501, 469, 419, 355, 323, 277, 245, 199, 179, 111, 75; HRMS (CI) m/z 643.3280 (calcd for C$_{39}$H$_{51}$O$_4$SiS : 643.3277, M + H).

(4R,6R)-6-((1R,2E,4E,6R)-1-(tert-Butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4,8-trienyl)-4-methoxytetrahydropyran-2-one (36). To a solution of **35** (42.5 mg, 66 μmol) in tetrahydrofuran-water (5:1, 6 mL) was added silver nitrate (231 mg, 1.36 mmol) and 2,6-lutidine (268 μL, 0.230 mmol) and the solution was stirred for 3 h at room temperature. The solution was diluted with water (5 mL) and the aqueous layer was separated and extracted with ethyl acetate (5 mL x 3). The combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was passed through a column of silica gel (hexane:ethyl acetate 4:1) to give the pure hemiacetal as a colourless oil. This material was used immediately in the next reaction.

To a solution of the hemiacetal obtained above in dichloromethane (5 mL) was added tetra-n-propylammonium perruthenate (3.8 mg, 11 μmol), 4-methylmorpholine N-oxide (45 mg, 0.38 mmol) and 4A molecular sieves and the mixture was stirred for 3 h at room temperature. The mixture was filtered through silica gel (hexane:ethyl acetate 4:1) to give pure **36** (30.4 mg, 84%) as a colourless oil: $[\alpha]_D^{23}$ –55.3 (c 0.55, CHCl$_3$); IR (neat) 3071, 2928, 2855, 2814, 1748, 1472, 1427, 1360, 1234, 1110, 998, 967, 914, 822, 741, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.74 – 7.60 (m, 4H), 7.43 – 7.26 (m, 6H), 6.02 (d, J = 16 Hz, 1H), 5.77 (ddt, J = 17, 11, 7 Hz, 1H), 5.45 (d, J = 9 Hz, 1H), 5.36 (dd, J = 8, 16 Hz, 1H), 5.12 – 5.05 (m, 2H), 4.62 (dd, J = 5, 9 Hz, 1H), 4.20 – 4.14 (m, 1H), 3.72 – 3.57 (m, 2H), 3.34 (s, 3H), 3.23 (s, 3H), 2.87 (ddd, J = 1, 5, 17 Hz, 1H), 2.41 (dd, J = 8, 17 Hz, 1H), 2.34 – 2.21 (m, 3H), 1.60 – 1.50 (m, 1H), 1.28 (d, J = 1 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.1, 136.8, 136.7, 136.3, 134.9, 133.9, 133.7, 130.3, 130.0, 129.9, 129.4, 128.1, 127.8, 117.3, 82.2, 80.1, 72.8, 71.2, 56.7, 56.4, 40.6, 37.2, 30.3, 30.1, 27.4, 19.8, 15.7, 13.4; MS (CI) m/z 549 (M + H)$^+$ 517, 485, 459, 419, 363, 321, 289, 239, 199, 179, 137, 79; HRMS (CI) m/z 549.3019 (calcd for C$_{33}$H$_{45}$O$_5$Si : 549.3036, M + H).

(3R,4E,6E,8R)-8-(*tert*-Butyldiphenylsilanyloxy)-3-methoxy-8-((4R)-4-methoxy-6-oxotetrahydro-2*H*-pyran-2-yl)-6-methylocta-4,6-dienal (37). To a solution of **36** (24.1 mg, 44 μmol) in tetrahydrofuran-water (1:1, 4.39 mL, 0.01M) was added osmium tetraoxide (0.001M in *tert*-butanol, 176 μL, 0.4 mol %) and sodium periodate (28.2 mg, 132 μmol) and the mixture was stirred at room temperature for 20 h under argon. The mixture was diluted with water (5 mL) and extracted with ether (5 mL x 3), and the combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (hexane: EtOAc 5:1) to give **37** (13.7 mg, 57%) as a colourless oil: IR (neat) 3069, 2925, 2854, 1734, 1463, 1427, 1361, 1235, 1156, 1110, 998, 969, 822, 800, 741, 703 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.76 (t, *J* = 2 Hz, 1H), 7.74 – 7.60 (m, 4H), 7.43 – 7.26 (m, 6H), 6.09 (d, *J* = 16 Hz, 1H), 5.49 (d, *J* = 8 Hz, 1H), 5.37 (dd, *J* = 8, 16 Hz, 1H), 4.64 (dd, *J* = 5, 9 Hz, 1H), 4.21 – 4.09 (m, 2H), 3.72 – 3.63 (m, 1H), 3.35 (s, 3H), 3.25 (s, 3H), 2.88 (dd, *J* = 5, 17 Hz, 1H), 2.53 (dd, *J* = 2, 5 Hz, 1H), 2.50 – 2.28 (m, 4H), 1.60 – 1.50 (m, 1H), 1.28 (d, *J* = 1 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ ; MS (ES) *m/z* 568 (M$^+$ + NH$_4$); HRMS (ES) *m/z* 568.3049 (calcd for C$_{32}$H$_{46}$NO$_6$Si : 568.3094, M + NH$_4$).

(4R,6R)-6-((1R,2E,4E,6R,8E)-9-Bromo-1-(*tert*-butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4,8-trienyl)-4-methoxytetrahydropyran-2-one (3). From 37. Chromium(III) bromide monohydrate was placed in a flame-dried flask which was heated at 130 °C for 24 h. During this period, the colour of the chromium(III) bromide hydrate changed from black to the dark green colour of anhydrous chromium(III) bromide. To this anhydrous chromium(III) bromide (467 mg, 1.60 mmol) at 0 °C was added tetrahydrofuran (7 mL) which caused a change in colour from green to dark brown. A solution of lithium aluminium hydride (0.80 mL, 0.8 mmol, 1M solution in tetrahydrofuran) was added dropwise, during which the colour of the solution changed from brown to bright green. To this solution were added **37** (57 mg, 93 μmol) and bromoform (70 μL, 0.801 mmol) and the mixture was stirred for 12 h at 50 °C. The mixture was diluted with water (10 mL) and extracted with ether (10 mL x 3), and the combined extract was washed with brine (5 mL), dried and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 8:1) to furnish **3** (23.4 mg, 40%), identical with material obtained from **33**.

2-Methyloxazole-4-carboxaldehyde (39). To a solution of **38** (756 mg, 5.40 mmol) in ether (100mL) at −78 °C under argon was added diisobutylaluminium hydride (1.0M, 10.8 mL, 10.8 mmol) in one portion. The mixture was allowed to warm to room temperature and stirred for 3 h. Methanol (2.0 mL) was added and the mixture was diluted with dichloromethane (100 mL) and washed with saturated aqueous sodium potassium tartrate solution (100 mL). The organic phase was dried (MgSO$_4$) and concentrated under reduced pressure to give **39** (332 mg, 61%) as a colourless oil: IR (film) 2959, 2931, 1701, 1458, 1260, 1016, 797 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.53 (s,3H) , 8.16 (s, 1H), 9.89 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.74, 140.9, 144.5, 163.0, 183.8; MS (CI) *m/z* 112 (M+H)$^+$, 95, 84, 69; HRMS (CI) *m/z* 112.0401, calcd for C$_5$H$_6$NO$_2$ *m/z* 112.0399.

(1E)-2-Methyl-3-(2-methyloxazol-4-yl)prop-2-enal (41). A solution of **39** (2.23 g, 20.1 mmol) and **40** (7.025 g, 22.1 mmol) in benzene (300 mL) was heated at 80 °C for 18 h. Benzene was removed under reduced pressure and ether (200 mL) was added

to the residue. The mixture was filtered, the filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 2:1) to give **41** (2.82 g, 93%) as a colourless oil: IR (film) 3128, 3058, 2974, 2931, 2838, 2728, 1701, 1686, 1663, 1637, 1630, 1597, 1414, 1380, 1360, 1327, 1286, 1218, 1172, 1109, 1030, 975, 904, 844, 791 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.07 (s, 3H), 2.50 (s, 3H), 7.05 (s, 1H), 7.81 (s, 1H), 9.52 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 11.0, 13.8, 137.4, 137.8, 138.5, 139.7, 161.7, 194.3.

(3R,4R,1E)-2,4-Dimethyl-1-(2-methyloxazol-4-yl)hexa-1,5-dien-3-ol (42). To a solution of potassium *tert*-butoxide (2.98 g, 26.4 mmol) in dry tetrahydrofuran (27 mL) at -78 °C was added *trans*-2-butene (5 mL) followed dropwise by *n*-butyllithium (2.6M solution in hexanes, 10.2 mL, 26.4 mmol). The mixture was stirred for 15 min at -45 °C and was cooled to -78 °C, after which a solution of (+)-*B*-methoxydiisopinylcampheylborane (8.29 g, 26.4 mmol) in dry tetrahydrofuran (30 mL) was added dropwise. The mixture was stirred for 30 min and boron trifluoride etherate (4.1 mL, 35.1 mmol) was added, followed by a solution of **41** (2.67 g, 17.7 mmol) in tetrahydrofuran (25 mL). The mixture was stirred for 6 h at -78 °C and a saturated aqueous solution of sodium bicarbonate (52 mL) and 30% hydrogen peroxide (10.7 mL) were added. The resulting mixture was allowed to warm to room temperature and was stirred for 16 h. The phases were separated and the organic phase was washed with water (25 mL). The aqueous phase was extracted with ether (3 x 25 mL), and the combined extract was washed with brine (25 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate:hexanes:triethylamine 100:200:3) to yield **42** (2.44 g, 67%) as a pale yellow oil: $[\alpha]_D^{23}$ +14.3 (c 0.78, CHCl$_3$); IR (film) 3359, 3174, 3077, 2970, 2929, 2870, 1668, 1638, 1584, 1452, 1383, 1318, 1222, 1107, 1010 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.93 (d, *J* = 7 Hz, 3H), 1.89 (s, 3H), 2.28 (bs, 1H), 2.36 (m, 1H), 2.43 (s, 3H), 3.82 (d, *J* = 8 Hz, 1H), 5.13 (ddd, *J* = 1, 2, 10 Hz, 1H), 5.15 (ddd, *J* = 1, 2, 17 Hz, 1H), 5.78 (ddd, *J* = 8, 10, 17 Hz, 1H), 6.22 (m, 1H), 7.47 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.7, 14.0, 16.7, 42.2, 81.0, 116.5, 117.5, 135.4, 137.7, 139.7, 140.6, 160.6; MS (EI) *m/z* 208 (M+H)$^+$, 190, 174, 152, 124, 110, 84; HRMS (CI) *m/z* 207.1257, calcd for C$_{12}$H$_{17}$NO$_2$ *m/z* 207.1259.

4-[(3R,4R,1E)-3-(4-Methoxybenzyloxy)-2,4-dimethylhexa-1,5-dienyl]-2-methyloxazole (43). To a solution of **42** (400 mg, 1.93 mmol) in dry tetrahydrofuran (15 mL) was added sodium hydride (60% suspension in mineral oil, 175 mg, 4.29 mmol), and the suspension was stirred for 40 min at reflux. After the mixture had cooled to room temperature, *p*-methoxybenzyl chloride (0.45 mL, 3.25 mmol) and tetra-*n*-butylammonium iodide (25 mg) were added. The mixture was stirred under argon at reflux for 6 h and at room temperature for 10 h. A saturated aqueous solution of ammonium chloride (2.5 mL) and water (10 mL) were added and the mixture was extracted with dichloromethane (3 x 25 mL). The combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate:hexanes 1:4 with 1% triethylamine) to yield **43** (565 mg, 89 %) as a colourless oil: $[\alpha]_D^{23}$ +42.5 (c 3.67, CHCl$_3$); IR (film) 3071, 2961, 2932, 2860, 2836, 1613, 1586, 1513, 1457,

1302, 1248, 1108, 1072, 1036, 917, 821, 635 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.87 (d, J = 7 Hz, 3H), 1.90 (d, J = 1 Hz, 3H), 2.46 (s, 3H), 2.46 (m, 1H), 3.50 (d, J = 9 Hz, 1H), 3.78 (s, 3H), 4.19 (d, J = 12 Hz, 1H), 4.45 (d, J = 12 Hz, 1H), 5.02 (ddd, J = 1, 2, 10 Hz, 1H), 5.07 (ddd, J = 1, 2, 17 Hz, 1H), 5.92 (ddd, J = 7, 10, 17 Hz, 1H), 6.20 (m, 1H), 6.85 (m, 2H), 7.23 (m, 2H), 7.52 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.7, 13.7, 16.5, 40.2, 55.0, 69.7, 88.6, 113.5, 113.8, 119.0, 129.2, 130.6, 135.4, 137.6, 138.1, 141.6, 158.9, 160.6; MS (CI) m/z 328 (M+H)$^+$, 281, 273, 137, 121, 84; HRMS (CI) m/z 328.1908, calcd for C$_{20}$H$_{26}$NO$_3$ m/z 328.1913.

(3R,4R,5E)-4-(4-Methoxybenzyloxy)-3,5-dimethyl-6-(2-methyloxazol-4-yl)hex-5-ene-1,2-diol (44). To a solution of **43** (5.21 g, 15.9 mmol) in tetrahydrofuran (125 mL) and water (4.7 mL) at 0 °C was added osmium tetraoxide (0.2M solution in *tert*-butanol, 3.04 mL, 0.63 mmol) followed by an aqueous solution of *N*-methylmorpholine-*N*-oxide (60 %, 2.45 g, 19.3 mmol). The mixture was stirred for 10 h at room temperature, ether (300 mL) was added, and the organic phase was separated and washed with water (100 mL) and brine (90 mL). The aqueous phase was extracted with dichloromethane (2 x 100 mL) and the combined organic extract was dried (Na$_2$SO$_4$) and concentrated. The residual oil was purified by flash chromatography on silica gel (ethyl acetate:ethanol:triethylamine 95:5:1) to give **44** (4.80 g, 84 %) as a colourless oil (1:1 mixture of diastereomers): IR (film) 3419, 2962, 2933, 2870, 1613, 1585, 1514, 1457, 1385, 1302, 1248, 1175, 1108, 1061, 1035 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.67 (two d, J = 7 Hz, 3H), 1.83 (two s, 3H), 1.96 (m, 1H), 2.39 (s, 3H), 3.06 (s, 1H), 3.48-3.59 (m, 3H), 3.68 (s, 3H), 3.71 (m, 1H), 4.13 (d, J = 11 Hz, 1H), 4.38 (two d, J = 11 Hz, 1H), 4.68 (s, 1H), 6.18 (two s, 1H), 6.78 (two d, J = 9 Hz, 2H), 7.17 (d, J = 9 Hz, 2H), 7.49 (two s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 11.4, 12.7, 12.9, 13.2, 13.4, 37.4, 37.5, 54.9, 64.1, 64.5, 69.6, 69.8, 72.5, 75.7, 86.9, 90.0, 113.6, 113.7, 119.2, 120.3, 129.2, 129.3, 129.4, 129.8, 135.5, 135.6, 136.6, 137.1, 137.2, 137.3, 158.9, 159.1, 160.6, 160.7; MS (FAB) m/z 362 (M+H)$^+$, 307, 224, 164, 154, 121, 107, 89; HRMS (FAB) m/z 362.1971, calcd for C$_{20}$H$_{28}$NO$_5$ m/z 362.1968.

(2S,3R,4E)-3-(4-Methoxybenzyloxy)-2,4-dimethyl-5-(2-methyloxazol-4-yl)pent-4-enal (45). To a solution of **44** (1.88 g, 5.20 mmol) in tetrahydrofuran (20 mL) and water (50 mL) was added sodium metaperiodate (1.35 g, 6.40 mmol) and the solution was stirred for 30 min at room temperature. The mixture was extracted with dichloromethane (3 x 40 mL) and the combined extract was dried (Na$_2$SO$_4$) and concentrated to give pure **45** (1.67 g, 98%) as a colourless oil: $[\alpha]_D^{23}$ +62.4 (c 1.05, CHCl$_3$); IR (film) 2965, 2933, 2855, 2837, 1726, 1613, 1586, 1514, 1457, 1284, 1174, 1109, 1064, 1034, 820 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.80 (d, J = 7 Hz, 3H), 1.93 (d, J = 1 Hz, 3H), 2.48 (s, 3H), 2.67 (ddt, J = 3, 7, 10 Hz, 1H), 3.80 (s, 3H), 3.93 (d, J = 10, 1H), 4.20 (d, J = 11 Hz, 1H), 4.46 (d, J = 11 Hz, 1H), 6.27 (m, 1H), 6.86 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H), 7.56 (s, 1H); 9.70 (d, J = 3, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 10.9, 13.1, 13.8, 48.6, 55.2, 69.7, 85.3, 113.8, 120.5, 129.5, 129.8, 135.8, 136.0, 137.3, 159.2, 161.0, 204.2; MS (EI) m/z 330 (M+H)$^+$, 311, 272, 255, 231, 208, 193, 164, 121, 91, 78; HRMS (EI) m/z 330.17002, calcd for C$_{19}$H$_{24}$NO$_4$ m/z 330.17053.

(3S,4S,5R,6R,7E)-6-(4-Methoxybenzyloxy)-3,5,7-trimethyl-8-(2-methyloxazol-4-yl)octa-1,7-dien-4-ol (46). To a solution of potassium *tert*-butoxide (2.62 g, 23.2 mmol) in dry tetrahydrofuran (21 mL) at -78 °C was added *trans*-2-butene (ca. 8 mL, excess) followed dropwise by *n*-butullithium (1.6M solution in hexanes, 14.2 mL, 23.2 mmol). The mixture was stirred for 15 min at -45 °C and was cooled to –78 °C. A solution of (–)-*B*-methoxydiisopinylcampheylborane (7.32 g, 23.2 mmol) in dry tetrahydrofuran (32 mL) was added dropwise, and after 30 min boron trifluoride etherate (3.61 mL, 31.1 mmol) was added followed by a solution of **45** (4.15 g, 12.6 mmol) in tetrahydrofuran (21 mL). The mixture was stirred for 19 h at -78 °C and the reaction was quenched with methanol (12 mL) and 2-aminoethanol (36 mL). The mixture was allowed to warm to room temperature and was stirred for 3 h, after which dichloromethane (200 mL) and water (80 mL) were added. The phases were separated, the organic phase was washed with water (50 mL) and brine (50 mL), and the aqueous phase was extracted with dichloromethane (2 x 50 ml). The combined extract was dried (Na$_2$SO$_4$) and concentrated to give a crude product containing a 6.1:1 mixture of diastereomers (determined by ^{13}C NMR). Flash chromatography of the mixture on silica gel (ethyl acetate:hexanes:triethylamine 33:66:1) gave pure **46** (2.55 mg, 53 %) as a pale yellow oil: $[\alpha]_D^{23}$ +37.6 (c 3.73, CDCl$_3$); IR (film) 3385, 2970, 2932, 2872, 1652, 1615, 1586, 1559, 1514, 1457, 1381, 1302, 1248, 1173, 1108, 1068, 1036, 918, 821 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.78 (d, J = 7 Hz, 3H), 0.93 (d, J = 7 Hz, 3H), 1.90 (d, J = 1 Hz, 3H), 1.93 (m, 1H), 2.16 (s, 1H), 2.23 (m, 1H), 2.46 (s, 3H), 3.71 (d, J = 9 Hz, 1H), 3.78 (s, 3H), 3.86 (d, J = 8 Hz, 1H), 4.20 (d, J = 11 Hz, 1H), 4.45 (d, J = 11 Hz, 1H), 5.04 (dd, J = 2, 10 Hz, 1H), 5.09 (dd, J = 2, 17 Hz, 1H), 5.80 (ddd, J = 9, 10, 17 Hz, 1H), 6.28 (s, 1H), 6.85 (d, J = 9 Hz, 2H), 7.23 (d, J = 9 Hz, 2H), 7.52 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 9.7, 13.7, 13.9, 16.7, 36.7, 42.0, 55.1, 70.2, 72.9, 86.8, 113.7, 115.1, 118.6, 129.3, 130.4, 135.5, 137.7, 137.8, 142.4, 159.0, 160.7; MS (EI) m/z 385 (M$^+$), 368, 330, 284, 272, 264, 249, 193, 172, 164, 148, 140, 121, 77; HRMS (EI) m/z 385.2257, calcd for C$_{23}$H$_{31}$NO$_4$ m/z 385.2253.

4-[(3R),(4S),(5S),(6S),(1E)-3-(4-Methoxybenzyloxy)-2,4,6-triisopropylsilanyl oxyocta-1,7-dienyl]-2-methyloxazole (47). To a solution of **46** (130 mg, 338 μmol) in dry dichloromethane (9 mL) at 0 °C was added 2,6-lutidine (94 μL, 810 μmol), followed by triisopropylsilyl triflate (110 μL, 407 μmol). The solution was stirred for 2 h at room temperature and dichloromethane (10 mL) was added. The solution was washed with brine (15 mL), dried (Na$_2$SO$_4$) and concentrated and the residue was purified by flash chromatography on silica gel (ethyl acetate:hexanes:triethylamine 25:75:1) to give **47** (142 mg, 99%) as a colourless oil: $[\alpha]_D^{23}$ –12.6 (c 4.20, CHCl$_3$); IR (film) 2962, 2942, 2891, 2866, 1653, 1616, 1586, 1514, 1463, 1457, 1383, 1248, 1108, 1041, 1012, 992, 917, 883, 820, 677 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.81 (d, J = 7 Hz, 3H), 0,99 (d, J = 7 Hz, 3H), 1.10 (m, 21H), 1.71 (m, 1H), 1.91 (d, J = 1Hz, 3H), 1.93 (m, 1H), 2.40 (dd, J = 16,6 Hz, 1H), 2.45 (s, 3H), 2.63 (dd, J = 16,8 Hz, 1H), 3.49 (d, J = 10 Hz, 1H), 3.67 (s, 3H), 3.68 (m, 1H), 3.94 (ddd, J = 2, 17 Hz, 1H), 6.18 (s, 1H), 5.59 (ddd, J = 8, 6, 2 Hz, 1H), 6.11 (s, 1H), 6.80 (d, J = 9 Hz, 2H), 7.47 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 6.3, 13.0, 14.0, 14.1, 14.5, 18.4 (x 2), 35.1, 38.3, 39.2, 51.9, 74.8, 77.7, 89.0, 118.8, 135.8, 138.0, 138.1, 160.8, 172.0; MS (CI) m/z 479 (M$^+$), 448, 436, 404, 378,

355, 305, 285, 273, 243, 164, 131, 121; HRMS (CI) *m/z* 479.3072, calcd for $C_{25}H_{45}NO_5Si$ *m/z* 479.3067.

4-[(3R,4S,5S,6S,1E)-3-Hydroxy-2,4,6-trimethyl-5-triisopropylsilanyloxyocta-1,7-dienyl]-2-methyloxazole (48). To a solution of **47** (255 mg, 481 µmol) in dry dichloromethane (4 mL) was added ethanethiol (140 µL, 1.88 mmol) and the mixture was cooled to –20 ˚C under argon. A solution of anhydrous aluminium trichloride (52.7 mg, 383 µmol) in dichloromethane (8 mL) was added dropwise, and the mixture was stirred for 30 min at -5 ˚C. Additional quantities of anhydrous aluminum trichloride (19.8 mg, 144 µmol) were added after 1 h and 2 h, and the mixture was stirred at –5 °C for 2h. A saturated aqueous solution of sodium bicarbonate (7 mL), aqueous sodium potassium tartrate solution (2M, 7 mL), and water (3 mL) were added, and the mixture was stirred for an additional 20 min at room temperature. The phases were separated, the aqueous layer was extracted with dichloromethane (3 x 20 mL), and the combined extract was washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by flash chromatography on silica gel (ethyl acetate:hexanes:triethylamine 20:80:1) to give **48** (101 mg, 90%) as a pale yellow oil: $[\alpha]_D^{23}$ –51.2 (c 4.40, CHCl₃); IR (film) 3327, 3080, 3049, 2926, 2865, 2721, 1638, 1585, 1462, 1453, 1385, 1319, 1237, 1217, 1103, 1043, 933, 913, 883, 736, 635 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.72 (d, *J* = 7 Hz, 3H), 1.06 (m, 24H), 1.82 (s, 3H), 1.92 (m, 1H), 2.42 (s, 3H), 2.56 (m, 1H), 3.01 (s, 3H), 4.15 (m, 2H), 5.01 (d, *J* = 11 Hz, 1H), 5.08 (d, *J* = 17 Hz, 1H), 5.98 (ddd, *J* = 7, 11, 17 Hz, 1H), 6.18 (s, 1H), 7.48 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 12.9, 13.1, 13.2, 13.7, 17.2, 18.2, 18.3, 39.6, 42.2, 77.4, 80.4, 114.2, 117.8, 135.3, 137.8, 140.7, 141.3, 160.6; MS (FAB) *m/z* 504 (M⁺), 404, 378, 306, 241, 230, 215, 190, 157, 152, 131, 115, 103, 87; HRMS (FAB) *m/z* 422.3092, calcd for $C_{24}H_{44}NO_3Si$ *m/z* 422.3091.

(2R,3S,4R,5S,6R)-3,5-Dimethyl-6-[(1E)-1-methyl-2-(2-methyloxazol-5-yl)vinyl]-4-triisopropylsilanyloxytetrahydropyran-2-yl}acetic acid methyl ester (49). To a solution of **48** (973 mg, 2.3 mmol) in methanol (20 mL) under carbon monoxide at room temperature was added a solution of palladium(II) acetate (911 mg, 3.85 mmol) in acetonitrile (40 mL) and methanol (20 mL) and the mixture was stirred at room temperature for 20 h, at which time an additional quantity of palladium(II) acetate (427 mg, 1.8 mmol) was added. The black suspension was stirred for a further 24 h and was filtered through a short pad of silica. The filter pad was washed with a mixture of ether and ethanol (10:1) and the filtrate was concentrated under reduced pressure to give crude **49** (1.29 g). Flash chromatography of this material on silica gel (toluene:methanol 20:1) gave pure **49** (947 mg, 86%) as a colourless oil: $[\alpha]_D^{23}$ +14.1 (c 1.19, CHCl₃); IR (neat) 3161, 2945, 2891, 2867, 1743, 1587, 1462, 1437, 1382, 1311, 1266, 1244, 1194, 1175, 1106, 1081, 1066, 1031, 998, 981, 883, 807, 677, 635 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.81 (d, *J* = 7 Hz, 3H), 0.99 (d, *J* = 7 Hz, 3H), 1.09 (m, 21H), 1.71 (m, 1H), 1.91 (d, *J* = 1 Hz, 3H), 1.93 (m, 1H), 2.40 (dd, *J* = 6, 16 Hz, 1H), 2.45 (s, 3H), 2.63 (dd, *J* = 8, 16 Hz, 1H), 3.49 (d, *J* = 10 Hz, 1H), 3.67 (s, 3H), 3.68 (m, 1H), 3.94 (ddd, *J* = 2, 6, 8 Hz, 1H), 6.18 (s, 1H), 7.47 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 6.3, 13.0, 14.0, 14.1, 14.5, 18.4, 18.4, 35.1, 38.3, 39.2, 51.9, 74.8, 77.7, 89.0, 118.8, 135.8, 138.0, 138.1, 160.8, 172.0; MS (CI) *m/z* 479 (M⁺), 448,

436, 404, 378, 355, 305, 285, 273, 243, 164, 131, 121; HRMS (CI) *m/z* 479.3072, calcd for $C_{26}H_{45}NO_5Si$ *m/z* 479.3067.

(2R,3S,4R,5S,6R)-3,5-Dimethyl-6-[(1E)-1-methyl-2-(2-methyloxazol-5-yl)vinyl]-4-triisopropylsilanyloxytetrahydropyran-2-ylethanol (51). To a suspension of lithium aluminium hydride (100 mg, 2.67 mmol) in ether (20 mL) at 0 °C was added dropwise a solution of **49** (1.28 g, 2.67 mmol) in ether (10 mL), and the mixture was stirred for 3 h at 10 °C. The reaction was quenched by careful addition of water (0.6 mL) and aqueous sodium hydroxide (15 %, 0.16 mL) and the mixture was stirred at room temperature for 30 min. The suspension was filtered through Celite, the collected solid was washed with tetrahydrofuran (400 mL), and the filtrate was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate:hexanes 1:1) to give **51** (947 mg (79 %) as a colourless oil: $[\alpha]_D^{23}$ +24.5 (c 0.55, CDCl₃); IR (film) 3384, 2944, 2927, 2891, 2867, 1653, 1586, 1462, 1457, 1387, 1362, 1312, 1159, 1109, 1084, 1065, 1030, 920, 882, 808, 676 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.82 (d, *J* = 7 Hz, 3H), 1.02 (d, *J* = 7 Hz, 3H), 1.09 (m, 21H), 1.48 (m, 1H), 1.68-1.86 (m, 2H), 1.92 (d, *J* = 1 Hz, 3H), 1.98 (m, 1H), 2.45 (s, 3H), 2.66 (s, 1H), 3.51 (d, *J* = 10 Hz, 1H), 3.63-3.78 (m, 4H), 6.19 (s, 1H), 7.49 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 6.9, 13.3, 14.2, 14.3, 14.6, 18.6, 18.7, 35.3, 35.5, 40.6, 62.7, 77.6, 78.0, 79.8, 89.4, 119.2, 136.1, 138.1, 161.1; MS (FAB) *m/z* 452 (M+H)⁺, 408, 390, 350, 306, 277, 245, 215, 187, 164, 157, 152, 136, 115, 87, 75, 59; HRMS (FAB) *m/z* 452.3195, calcd for $C_{25}H_{46}NO_4Si$ *m/z* 452.3196.

(2R,3S,4R,5S,6R)-3,5-Dimethyl-6-[(1E)-1-methyl-2-(2-methyloxazol-5-yl)vinyl]-4-triisopropylsilanyloxytetrahydropyran-2-ylacetaldehyde (52).
To a solution of **51** (95 mg, 214 µmol) in dichloromethane (8 mL) at 0 °C was added a solution of Dess-Martin periodinane (120 mg, 282 µmol) in dichloromethane (17 mL) and the solution was stirred for 3 h at room temperature. The solution was poured into a saturated aqueous solution of sodium bicarbonate (40 mL) containing sodium thiosulfate (10 g) and the mixture was stirred for 15 min. The phases were separated and the organic phase was washed with saturated aqueous sodium bicarbonate (30 mL), water (35 ml) and brine (35 ml), then was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate:hexanes 1:1) to give **52** (82 mg, 85 %) as a colourless oil: $[\alpha]_D^{23}$ +28.8 (c 2.73, CHCl₃); IR (film) 3149, 2962, 2891, 2724, 1728, 1586, 1462, 1383, 1312, 1240, 1112, 1031, 997, 807, 678, 636 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.81 (d, *J* = 7 Hz, 3H), 0.98 (d, *J* = 7 Hz, 3H), 1.07 (s, 21H), 1.74 (m, 1H), 1.84 (m, 1H), 1.90 (s, 3H), 2.37 (dd, *J* = 3, 17 Hz, 1H), 2.42 (s, 3H), 2.70 (ddd, *J* = 1, 7, 17 Hz, 1H), 3.48 (d, *J* = 10 Hz, 1H), 3.69 (dd, *J* = 5, 10 Hz, 1H), 4.00 (dd, *J* = 3, 9 Hz, 1H), 6.16 (s, 1H), 7.47 (s, 1H), 9.74 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 6.8, 13.3, 14.2, 14.3, 14.7, 18.6, 18.7, 35.4, 39.9, 47.3, 73.7, 77.9, 89.4, 119.1, 136.0, 138.1, 161.0, 201.7; MS (FAB) *m/z* 450 (M+H)⁺, 350, 306, 269, 243, 215, 199, 157, 115, 87, 59; HRMS (FAB) *m/z* 450.3034, calcd for $C_{25}H_{44}NO_4Si$ *m/z* 450.3040.

2-Chloromethyloxazole-4-carboxaldehyde (54). To a solution of **53** (840 mg, 4.78 mmol) in dichloromethane (50 mL) at –78 °C was added dropwise diisobutylaluminium hydride (1.0M in

dichloromethane, 9.56 mL, 9.56 mmol) and the mixture was stirred for 3 h at –78 °C. The reaction was quenched with methanol (20 mL), and the mixture was allowed to warm to room temperature and diluted with dichloromethane (100 mL). The solution was washed with saturated aqueous sodium potassium tartrate solution (100 mL), dried (MgSO₄), and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (hexanes:ethyl acetate 3:1) to give **54** (680 mg, 98%) as a colourless oil: IR (film) 3145, 2846, 1700, 1559, 1117, 997, 793 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.65 (s, 2H), 8.30 (s, 1H), 9.92 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) 35.6, 141.4, 145.6, 160.8, 184.0; MS (CI) m/z 145 (M+H)⁺, 125, 110, 97, 84, 70; HRMS (CI) m/z 144.9932, calcd for $C_5H_4NO_2{}^{35}Cl$ m/z 144.9900.

(3R)-3-(2-Chloromethyloxazol-4-yl)-3-hydroxybut-1-ene (55).
To a solution of (+)-B-methoxydiisopinylcampheylborane (1.26 g, 3.87 mmol) in dry ether (15 mL) under argon at 0°C was added allylmagnesium bromide (1.0M solution in ether, 3.30 mL, 3.30 mmol) dropwise. The mixture was allowed to warm to room temperature and was stirred for 1 h. The solvent was removed under vacuum and the residue was extracted with *n*-pentane (4 x 30 mL). The resulting suspension was filtered under argon through a Schlenk tube and the filtrate was concentrated under vacuum. The residue was dissolved in ether (20 mL), the solution was cooled to –100°C and a solution of **54** (280 mg, 1.93 mmol) in ether (20 mL) at -78 °C was added. The mixture was stirred at –100°C for 1h and the reaction was quenched with methanol (0.1 mL). The mixture was allowed to warm to room temperature, after which aqueous sodium hydroxide (2N, 1.5 mL) and 30% hydrogen peroxide (3.0 mL) were added and the mixture was stirred for 10 h. The mixture was washed with brine (40 mL), the organic layer was separated and dried (MgSO₄), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 3:1) to give **55** (306 mg, 84%) as a colourless oil in which the enantiomeric ratio was determined to be >20:1 from the ¹³C NMR spectrum of its Mosher ester: $[\alpha]_D^{23}$ +9.0 (c 1.44, CHCl₃); IR (film) 3431, 2909, 1642, 1569, 1432, 924, 798 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.59 (ddd, J = 5, 8, 14 Hz, 1H), 2.64 (ddd, J = 1, 5, 7 Hz, 1H) 2.69 (bs, 1 H) 4.58 (s, 2H), 4.72 (dd, J = 6, 9 Hz, 1H), 5.16 (dd, J = 1, 9 Hz, 1H), 5.19 (d, J = 17 Hz, 1H), 5.81 (m, 1H), 7.56 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 36.1, 41.1, 66.7, 119.4, 133.9, 136.3, 144.2, 159.7; MS (CI) m/z 187 (M+H)⁺, 170, 161, 148, 146, 110, 84; HRMS (CI) m/z 187.0398, calcd for $C_8H_{10}NO_2{}^{35}Cl$ m/z 187.0400.

(4R)-4-(Chloromethyloxazol-4-yl)-4-*tert*-butyldimethylsilanyl-oxybut-1-ene (56). To an ice-cold solution of **55** (295 mg, 1.57 mmol) and 2,6-lutidine (0.37 mL, 3.1 mmol) in dichloromethane (3 mL) under argon was added *tert*-butyldimethylsilyl triflate (0.54 mL, 2.4 mmol) and the solution was allowed to warm to room temperature during 1 h. The solution was poured into an ice-cold saturated aqueous solution of sodium bicarbonate (10 mL) and the mixture was extracted with hexanes (5 x 10 mL). The combined extract was dried (MgSO₄) and concentrated under reduced pressure, and the residue was purified by chromatography on silica gel (ethyl acetate:hexanes 2:1) to give **56** (469 mg, 99%) as a colourless oil: $[\alpha]_D^{23}$ +6.3 (c 2.23, CHCl₃); IR (film) 2955, 2930, 2857, 1569, 1258, 1100, 914, 836, 777 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.02 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 2.51 (ddd, J = 1, 5, 7 Hz, 2H), 4.58 (s, 2H), 4.76 (dd, J = 5, 5 Hz, 1H), 5.05 (d, J = 11 Hz, 1H), 5.06 (d, J =

17 Hz, 1H), 5.79 (dddd, J = 7, 7, 11, 17 Hz, 1H), 7.49 (d, J = 1 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ -4.4, -2.6, 18.6, 26.1, 26.2, 36.3, 42.4, 68.9, 118.0, 134.4, 136.6, 145.8, 159.1; MS (CI) m/z 302(M+H)⁺, 286, 244, 189, 147, 117, 75; HRMS (CI) m/z 302.1336, calcd for $C_{14}H_{25}NO_2{}^{35}ClSi$ m/z 302.1343.

(3R)-3-(2-Chloromethyloxazol-4-yl)-3-*tert*-butyldimethylsilanyl-oxypropanal (57). To a solution of **56** (468 mg, 1.55 mmol) in tetrahydrofuran (40 mL) and water (40 mL) was added osmium tetroxide (2.5% solution in *tert*-butanol, 2.04 mL, 0.16 mmol) followed by sodium periodate (1.33 g, 6.20 mmol). After 3 h, the reaction was quenched with a saturated aqueous solution of sodium thiosulfate (350 mL), and after a further 30 min brine (500 mL) was added. The mixture was extracted with ether (5 x 100 mL) and the combined extract was dried (MgSO₄) and concentrated under reduced pressure to give **57** (330 mg, 70%) as a colourless oil: $[\alpha]_D^{23}$ +27.3 (c 1.24, CHCl₃); IR (film) 2930, 2858, 1727, 1259, 1106, 838, 779 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.08 (d, J = 20 Hz, 6H), 0.89 (s, 9H), 2.86 (dddd, J = 2, 6, 16, 20 Hz, 2H), 4.58 (s, 2H), 5.24 (ddd, J = 1, 6, 6 Hz, 1H), 7.56 (d, J = 1 Hz, 1 H), 9.79 (t, J = 2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ -4.7, -4.4, 18.4, 26.1, 36.1, 50.9, 64.7, 136.7, 144.7, 159.7, 200.9; MS (CI) m/z 304 (M+H)⁺, 288, 246, 172, 143, 108, 84, 75; HRMS (CI) m/z 304.1140, calcd for $C_{13}H_{23}NO_3Si{}^{35}Cl$ m/z 304.1136.

(4R,6R)-6-(2-Chloromethyloxazol-4-yl)-6-*tert*-butyldimethyl-silanyloxy-4-hydroxyhex-1-ene (58). To a solution of (+)-B-methoxydiisopinylcampheylborane (726 mg, 2.29 mmol) in ether (10 mL) at 0 °C was added allylmagnesium bromide (2.0 mL, 2.0 mmol) and the mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum and the residue was extracted with *n*-pentane (4 x 10 mL), The resulting suspension was filtered under argon through a Schlenk tube and pentane was removed from the filtrate under vacuum. The residue was dissolved in ether (20 mL), the solution was cooled to –100°C and a solution of **57** (346 mg, 1.14 mmol) in ether (20 mL) at –78 °C was added via cannula. The mixture was stirred at –100 °C for 1 h and the reaction was quenched with methanol (1.0 mL). The mixture was allowed to warm to room temperature and was treated with aqueous sodium hydroxide (2N, 1.0 mL) and 30% hydrogen peroxide (2.0 mL). The mixture was stirred for 10 h and was extracted with ether (4 x 10 mL), and the extract was washed with brine (20 mL), dried (MgSO₄) and concentrated under reduced pressure to give crude **58** as a 12:1 mixture of diastereomers. The crude material was purified by flash column chromatography on silica gel (ethyl acetate:hexanes 1:2) to give **58** (249 mg, 66%) as a colourless oil: $[\alpha]_D^{23}$ +31.2 (c 1.39, CHCl₃); IR (film) 3420, 2929, 2359, 1258, 1096, 837, 778 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ -0.05 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.89 (m, 2H), 2.23 (t, J = 6 Hz, 2H), 3.03 (b, 1H), 3.82 (dddd, J = 1, 6, 7, 9 Hz, 1H), 4.56 (d, J = 1 Hz, 2H), 4.92 (t, J = 6 Hz, 1H), 5.07 (dd, J = 1, 9 Hz, 1H), 5.08 (dd, J = 1, 17 Hz, 1H), 5.81 (dddd, J = 7, 7, 9, 17 Hz, 1H), 7.51 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ -4.6, -4.3, 18.4, 26.1, 36.1, 42.3, 44.5, 68.1, 69.2, 118.0, 135.1, 136.5, 145.5, 159.3; MS (CI) m/z 346 (M+H)⁺, 310, 288, 196, 145, 110; HRMS (CI) m/z 346.1599, calcd for $C_{16}H_{29}NO_3{}^{35}ClSi$ m/z 346.1605.

(4R,6R)-6-(2-Chloromethyloxazol-4-yl)-6-*tert*-butydimethyl-silanyloxy-4-*tert*-butyldiphenylsilanyloxyhex-1-ene (59). To an ice-cold solution of **58** (30 mg, 0.09 mmol) and 2,6-lutidine (20 μL, 0.18 mmol) in dichloromethane (1 mL) under argon was

added *tert*-butyldiphenylsilyl triflate (52 mg, 0.14 mmol) and the mixture was stirred at room temperature for 6 h. The mixture was poured into an ice-cold saturated aqueous solution of sodium bicarbonate (10 mL) and was extracted with hexanes (5 x 10 mL). The combined extract was dried (MgSO$_4$) and concentrated under reduced pressure, and the residue was purified by chromatography on silica gel (ethyl acetate:hexanes 1:3) to give **59** (45.0 mg, 89%) as a colourless oil: $[\alpha]_D^{23}$ +14.1 (c 1.82, CHCl$_3$); IR (film) 3073, 2955, 2893, 2857, 1427, 1257, 1111, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ -0.10 (s, 3H), 0.00 (s, 3H), 0.81 (s, 9H), 1.04 (s, 9H), 2.00 (td, J = 4, 8 Hz, 2H), 2.20 (m, 2H), 3.85 (td, J = 6, 12 Hz, 1H), 4.52 (s, 2H), 4.78 (t, J = 7 Hz, 1H), 4.90 (dd, J = 2, 17 Hz, 1H), 4.96 (dt, J = 1, 12 Hz, 1H), 5.71 (dddd, J = 7, 7, 10, 17 Hz, 1H), 7.10 (s, 1H), 7.55 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ -4.5, -4.2, 18.5, 19.8, 26.2, 27.0, 36.3, 41.6, 44.3, 53.8, 65.7, 70.3, 117.7, 127.9, 128.1, 129.9, 130.1, 134.6, 134.7, 135.2, 135.6, 136.4, 136.5, 145.2, 158.9; MS (CI) *m/z* 584 (M+H)$^+$,568, 526, 492, 260, 199, 135; HRMS (CI) *m/z* 584.2780, calcd for C$_{32}$H$_{47}$NO$_3$^{35}ClSi$_2$ *m/z* 584.2783.

(4R,6R)-6-(2-Chloromethyloxazol-4-yl)-6-hydroxy-4-*tert*-butyldiphenylsilanyloxy hex-1-ene (60). To a solution of **59** (40 mg, 0.07 mmol) in tetrahydrofuran (15 mL) was added hydrochloric acid (3N, 3 mL) and the mixture was stirred for 10 h at room temperature. The mixture was cooled to 0 °C and solid sodium bicarbonate was added in small portions until gas evolution had subsided. The aqueous layer was extracted with ether (4 x 10 mL) and the combined extract was dried (MgSO$_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexanes:ethyl acetate 3:1) to give **60** (31 mg, 95%) as a colourless oil: $[\alpha]_D^{23}$ +12.7 (c 1.00, CHCl$_3$); IR (film) 3389, 2930, 2857, 1427, 1111, 702, 610 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.07 (s, 9H), 2.10 (m, 4H), 4.05 (ddd, J = 4, 7, 12 Hz, 1H), 4.55 (s, 2H), 4.79 (dd, J = 2, 17 Hz, 1H), 4.87 (dd, J = 4, 9 Hz, 1H), 4.92 (dd, J = 2, 12 Hz, 1H), 5.56 (dddd, J = 7, 7, 12, 17 Hz, 1H), 7.55 (m, 11H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 14.3, 19.7, 27.4, 42.3, 42.7, 66.7, 73.6, 118.1, 128.0, 128.2, 130.2, 130.3, 134.2, 136.3, 144.7, 159.4; MS (CI) *m/z* 470 (M+H)$^+$, 452, 412, 334, 269, 199, 139, 78; HRMS (CI) *m/z* 470.1914, calcd for C$_{26}$H$_{33}$NO$_3$^{35}ClSi *m/z* 470.1918.

(1R,3R)-3-(*tert*-butyldiphenylsilanyloxy)-1-(2-((*E*)-3-((2*R*,3*S*,4*S*,5*S*,6*R*)-3,5-dimethyl-6-((*E*)-1-(2-methyloxazol-4-ylprop-1-en-2-yl)-4-(triisopropylsilanyloxy)tetrahydro-2*H*-pyran-2-yl)prop-1-enyl)oxazol-4-yl)hex-5-en-1-ol (62). To a solution of **60** (86 mg, 0.18 mmol) in dimethylformamide (5 mL) under argon at room temperature was added tri-*n*-butylphosphine (0.23 mL, 0.90 mmol) and the mixture was stirred at room temperature for 3 h, then was cooled to 0 °C. A solution of **52** (164 mg, 0.36 mmol) in dimethylformamide (5 mL) was added via followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (3.6 mL, 0.18 mmol), and the solution was stirred at 0 °C for 30 min. The mixture was diluted with ethyl acetate (25 mL), and the reaction was quenched with saturated aqueous ammonium chloride (10 mL). The phases were separated, the aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined extract was washed with water (20 mL) and brine (20 mL), dried (MgSO$_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes-ethyl acetate 3:1) to afford **62** (152 mg, 96%) as a colourless oil: $[\alpha]_D^{23}$ +23.8 (c 1.26, CHCl$_3$); IR (film) 3331, 2930, 2865, 1735, 1587, 1463, 1428, 736 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.85 (d, J = 7 Hz, 3H), 1.05 (m, 33H), 1.75 (m, 1H), 1.90 (m, 2H), 1.94 (s, 3H), 2.10 (m, 4H), 2.33 (ddd, J = 3, 6, 7 Hz, 1H), 2.44 (s, 3H), 2.55 (ddd, J = 3, 6, 7 Hz, 1H), 3.31 (b, 1H), 3.46 (d, J = 10 Hz, 1H), 3.54 (t, J = 1 Hz, 1H), 3.62 (dd, J = 4, 10 Hz, 1H), 4.05 (ddd, J =3, 4, 7 Hz, 1H), 4.79 (dd, J = 2, 17 Hz, 1H), 4.85 (dd, J = 3, 9 Hz, 1H), 4.90 (dd, J = 2, 10 Hz, 1H), 5.56 (dddd, J = 7, 7, 10, 17 Hz, 1H), 6.19 (s, 1H), 6.29 (d, J = 16 Hz, 1H), 6.65 (dddd, J = 6, 8, 16 Hz, 1H), 7.24 (s, 1H), 7.50 (s, 1H), 7.54 (m, 10H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 6.5, 13.3, 13.5, 14.2, 14.4, 15.1, 18.2, 18.6, 18.7, 19.7, 27.4, 30.1, 35.6, 3.8, 39.7, 42.3, 42.8, 66.8, 73.5, 78.2, 89.3, 118.1, 118.6, 118.9, 128.0, 128.2, 130.2, 130.3, 133.8, 134.4, 136.0, 136.3, 136.8, 138.2, 138.6, 144.6, 161.0, 161.5; MS (FAB) *m/z* 867 (M$^+$), 809, 731, 611, 541, 472, 350, 309, 239, 199, 135, 87; HRMS (FAB) *m/z* 867.5206, calcd for C$_{51}$H$_{75}$N$_2$O$_6$Si$_2$ *m/z* 867.5164.

Methyl 2-((2*S*,4*R*,6*S*)-4-(*tert*-butyldiphenylsilanyloxy)-6-(2-((*E*)-3-((2*R*,3*S*,4*S*,5*S*,6*R*)-3,5-dimethyl-6-((*E*)-1-(2-methyloxazol-4-yl)prop-1-en-2-yl)-4-(triisopropylsilanyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (63). T*o* a solution of **62** (29 mg, 0.07 mmol) in anhydrous methanol (3 mL) under a carbon monoxide atmosphere was added a solution of palladium(II) acetate (15 mg, 0.14 mmol) in anhydrous acetonitrile (6 mL) and anhydrous methanol (3 mL). The initial orange colour of the solution turned black after 15 min at room temperature. Progress of the reaction was monitored by thin-layer chromatography and an additional quantity of palladium(II) acetate (15.1 mg, 0.14 mmol) in anhydrous acetonitrile (1.5 mL) and anhydrous methanol (1.5 mL) was added every 24 h during 6 d (total 90.6 mg, 0.84 mmol, 12 equiv) of palladium (II) acetate). The mixture was concentrated under reduced pressure, the residue was taken up in ether (20 mL) and the suspension was filtered through a short column of silica, eluting with ether. The eluent was concentrated under reduced pressure and the residue was purified by chromatography on silica gel (hexanes:ethyl acetate 3:1) to furnish **63** (14 mg, 44%) as a colourless oil: $[\alpha]_D^{23}$ +44.8 (c 1.10, CHCl$_3$); IR (film) 2930, 2865, 1740, 1462, 1427, 1110, 1084, 1066, 738, 703 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.88 (d, J = 7 Hz, 3H), 0.95 (m, 33H), 1.80, (m, 6H), 1.88 (s, 3H), 2.15 (m, 1H), 2.40 (m, 2H), 2.50 (s, 3H), 2.54 (m, 1H), 2.67 (dd, J = 7, 15 Hz, 1H), 3.58 (M, 4H), 3.67 (s, 3H), 3.97 (m, 1H), 4.30 (s, 1H), 4.57 (ddq, J = 7, 10, 10 Hz, 1H), 5.06 (d, J = 10 Hz, 1H), 6.19 (s, 1H), 6.33 (d, J = 16 Hz, 1H), 6.64 (ddd, J = 7, 8, 16 Hz, 1H), 7.55 (m, 12H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 6.5, 14.2, 14.4, 14.7, 18.7, 19.7, 27.3, 27.4, 30.0, 35.6, 37.8, 38.4, 39.6, 41.0, 41.5, 52.0, 53.8, 66.0, 68.0, 69.6, 78.2, 89.3, 118.8, 119.0, 128.1, 130.2, 134.3, 134.7, 136.0, 136.1, 136.2, 138.2, 138.6, 142.9, 161.0, 161.4, 171.8; MS (FAB) *m/z* 925 (M$^+$), 867, 667, 625, 367, 327, 239, 197, 135, 87; HRMS (FAB) *m/z* 925.5219, calcd for C$_{53}$H$_{77}$N$_2$O$_8$Si$_2$ *m/z* 925.5219.

There was also obtained **64** (7 mg, 22%) as a mixture of two diastereomers: IR (film) 3385, 2945, 2865, 1739, 1457, 1436, 1110, 705 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.85 (d, J = 7Hz, 1H), 1.10 (m, 33H), 1.93 (s, 3H), 2.00 (m, 6H), 2.28 (m, 1H), 2.45 (s, 3H), 2.55 (ddd, J = 4, 7, 8 Hz, 1H), 2.80 (m, 2H), 3.55 (m, 10H), 4.00 (t, J = 6 Hz, 1H), 4.79 (m, 1H), 6.18 (s, 1H), 6.27 (dd, J = 4, 16 Hz, 1H), 6.65 (m, 1H), 7.19 (2s, 1H), 7.50 (s, 1H), 7.55 (m, 10H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 6.5, 13.3, 14.2, 14.4, 14.7, 18.6, 18.7, 19.7, 27.4, 35.6, 36.2, 36.8, 37.9, 39.3, 39.7, 52.1, 70.2, 78.2, 89.3, 118.4, 118.9, 128.1, 130.2, 133.9, 136.0, 136.3, 138.6, 161.0, 161.5, 172.2, 172.4, 175.4, 175.6; MS (FAB) 985 (M$^+$), 927, 849, 729, 427, 367, 327, 239, 199, 135, 87; HRMS (FAB) *m/z* 985.5422, calcd for C$_{55}$H$_{81}$N$_2$O$_{10}$Si$_2$ *m/z* 985.5430.

Methyl 2-((2S,4R,6R)-4-(tert-butyldiphenylsilanyloxy)-6-(2-(chloromethyl)oxazol-4-yl)tetrahydro-2H-pyran-2-yl)acetate (65). To a mixture of **60** (112 mg , 0.238 mmol), dichlorobis(acetonitrile)palladium(II) (6.2 mg, 24 □mol, 10 mol%) and sublimed *p*-benzoquinone (12.9 mg, 0.119 mmol) under carbon monoxide at room temperature were added methanol (6 mL) and acetonitrile (6 mL), and the mixture was stirred at room temperature for 2 h. Over the next 10 h, further additions of *p*-benzoquinone (13 mg, 0.12 mmol, 0.5 equivalent) in methanol-acetonitrile (1:1, 2 mL) were made to the mixture at regular intervals until the reaction was complete (total of 5.5 equivalents of *p*-benzoquinone). After 11 h, the solution was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane:ethyl acetate 12:1) to produce **65** (72 mg, 58%) as a colourless oil: $[\alpha]_D^{23}$ +13.4 (c 2.10, CHCl$_3$); IR (film) 2930, 2857, 1740, 1428, 1112, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.55 (s, 1H), 7.54 (m, 10 H), 4.58 (s, 2H), 4.56 (m, 1H), 4.30 (s, 1H), 3.67 (s, 3H), 2.64 (dd, J = 15, 7 Hz, 1H), 2.37 (dd, J = 16, 6 Hz, 1H), 1.80 (m, 4H), 1.11 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 171.7, 159.4, 159.2, 143.0, 141.2, 137.7, 136.9, 136.2, 136.1, 134.3, 134.2, 130.2, 128.1, 69.6, 68.7, 67.9, 67.7, 66.2, 65.9, 52.0, 41.5, 41.0, 40.4, 38.4, 37.8, 36.8, 36.3, 36.1, 27.3, 19.7, 19.5; MS (CI) *m/z* 528 (M$^+$), 492, 470, 436, 367, 327, 307, 254, 225, 199, 183, 153; HRMS (CI) *m/z* 528.1977 (calcd for C$_{28}$H$_{35}$NO$_5$Si^{35}Cl: 528.1973). There was also recovered **60** (19 mg, 17%).

(R)-tert-Butyldiphenylsilanylglycidol (68). To a solution containing (S)-(-)-glycidol (0.1 mL, 1.51 mmol), imidazole (205 mg, 3.02 mmol) and 4-*N*,*N*-dimethylaminopyridine (18 mg, 0.15 mmol) in dry dimethylformamide (10 mL) at room temperature was added *tert*-butyldimethylsilyl triflate (0.39 mL, 1.51 mmol) and the mixture was stirred for 3 h. To the solution was added *n*-pentane (40 mL) and water (30 mL), and the aqueous layer was separated and extracted with pentane (2 x 20 mL). The combined extract was dried (MgSO$_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 3:1) to give **68** (436 mg, 93%) as a colourless oil: $[\alpha]_D^{23}$ +8.7 (c 1.90, CHCl$_3$), lit^{47} $[\alpha]_D^{25}$ +2.40 (c 9.07 CHCl$_3$); IR (film) 3071, 3050, 2930, 2858, 1472, 1428, 1113, 918, 824, 703 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.06 (s, 9H), 2.62 (dd, J = 7, 12 Hz, 1H), 2.75 (dd, J = 4, 7 Hz, 1H), 3.13 (m, 1H), 3.72 (dd, J = 5, 12 Hz, 1H), 3.86 (dd, J = 3, 12 Hz, 1H), 7.40 (m, 6H), 7.75 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 19.7, 27.2, 44.9, 52.7, 64.8, 128.2, 130.2, 133.7, 136.0, 136.1.

(4R)-5-tert-Butyldiphenylsilanyloxy-4-hydroxy-1-trimethylsilyl -pentyne (69). To a solution of trimethylsilylacetylene (0.16 mL, 1.1 mmol) in tetrahydrofuran (10 mL) at –78 °C under argon was added *tert*-butyllithium (1.23M in hexane, 0.89 mL, 1.1 mmol). After 10 min, boron trifluoride etherate (0.15 mL, 1.2 mmol) was added followed by a solution of **68** (230 mg, 0.74 mmol) in tetrahydrofuran (2 mL). The mixture was stirred at -78 °C for 1 h and at 0 °C for 20 min. A saturated aqueous solution of ammonium chloride (1 mL) was added and the mixture was extracted with ethyl acetate (3 x 5 mL). The combined extract was washed with brine (10 mL), dried (MgSO$_4$), and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 3:1) to give **69** (291 mg, 96%) as a colourless oil: $[\alpha]_D^{23}$ + 11.4 (c 1.30, CHCl$_3$); IR (film) 3565,

3445, 3306, 3071, 2931, 2858, 2176, 1472, 1427, 1113, 703 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.14 (s, 9H), 1.08 (s, 9H), 2.55 (d, J = 2 Hz, 2H), 3.74 (m, 2H), 3.89 (m, 1H), 7.45 (m, 6H), 7.73 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 0.3, 0.5, 0.8, 19.4, 19.8, 20.1, 25.2, 27.4, 28.5, 30.5, 66.9, 70.7, 87.5, 103.2, 127.9, 128.3, 128.5, 130.2, 130.6, 133.2, 136.0; HRMS (CI) *m/z* 410.2105, calcd for C$_{24}$H$_{34}$O$_2$Si$_2$ *m/z* 410.2097.

(4R)-5-tert-Butyldiphenylsilanyloxy-4-hydroxypentyne (70). To a solution of **69** (89 mg, 0.22 mmol) in methanol (10 mL) was added solid potassium carbonate and the mixture was stirred at room temperature for 3 h. Ether (20 mL) and water (20 mL) were added, the phases were separated and the aqueous phase was extracted with ethyl acetate (3x10 mL). The combined extract was washed with brine (10 mL), dried (MgSO$_4$), and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 3:1) to give **70** (74 mg, 98%) as a colourless oil: $[\alpha]_D^{23}$ +6.2 (c 1.50, CHCl$_3$); IR (film) 3565, 3445, 3306, 3071, 2931, 2858, 1472, 1427, 1113, 703 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.08 (s, 9H), 1.97 (t, J = 2 Hz, 1H), 2.47 (dd, J = 7, 3 Hz, 1H), 2.52 (d, J = 6 Hz, 1H), 3.74 (m, 2H), 3.89 (m, 1H), 7.45 (m, 6H), 7.73 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 19.7, 23.6, 27.2, 66.7, 70.6, 70.9, 128.2, 130.3, 133.4, 136.0; HRMS (CI) *m/z* 398.1696, calcd for C$_{26}$H$_{26}$O$_2$Si *m/z* 398.1702.

(4R)-2-Bromo-4-hydroxy-5-tert-butyldiphenylsilanyloxypentene (71). To a solution of **70** (27 mg, 0.08 mmol) in dichloromethane (5 mL) at 0 °C under argon was added 9-bromo-9-borabicyclo[3.3.1]nonane (1.0M solution in dichloromethane, 0.40 mL, 0.40 mmol) and the mixture was allowed to warm to room temperature overnight. The solution was cooled to 0 °C, ethanolamine (0.1 mL) and methanol (1 mL) were added, and the mixture was diluted with ether (5 mL). The solution was washed with a saturated aqueous solution of sodium potassium tartrate (5 mL) and the phases were separated. The organic layer was dried (MgSO$_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 5:1) to give **71** (28 mg, 80%) as a colourless oil: $[\alpha]_D^{23}$ +4.7 (c 1.0, CHCl$_3$); IR (film) 3583, 3445, 3071, 2929, 2857, 1428, 1112, 701, 608, cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.10 (s, 9H), 2.50 (d, J = 2 Hz, 1H), 2.65 (m, 2H), 3.62 (dd, J = 7, 10 Hz, 1H), 3.77 (dd, J = 7, 12 Hz, 1H), 5.55 (s, 1H), 5.73 (s, 1H), 7.45 (m, 6H), 7.73 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 19.7, 27.0, 27.3, 45.5, 67.1, 70.0, 119.7, 128.1, 128.3, 130.1, 130.5, 133.4, 135.2, 136.0; MS (CI) *m/z* 419 (M+H)$^+$, 389, 349, 347, 311, 309, 241, 199, 181, 163, 135, 117, 91; HRMS (CI) *m/z* 390.1008, calcd for C$_{20}$H$_{32}$OSi^{79}Br *m/z* 390.1015.

(4R)-2-Bromo-4-triethylsilanyloxy-5-tert-butyldiphenylsilanyloxy-1-pentene (72). To a solution of **71** (14 mg, 0.03 mmol) in dichloromethane (5 mL) at 0 °C was added 2,6-lutidine (11 μL, 0.10 mmol) and triethylsilyl triflate (15 μL, 0.07 mmol). The mixture was allowed to warm to room temperature and stirred for 1h, then was poured into an ice-cold saturated aqueous solution of sodium bicarbonate (5 mL). The phases were separated, the aqueous layer was extracted with *n*-pentane (4 x 10 mL), and the combined organic extract was dried (MgSO$_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 3:1) to give **72** (16 mg, 100%) as a colourless oil: $[\alpha]_D^{23}$

+12.7 (c 1.44, CHCl$_3$); IR (film) 2955, 2875, 1427, 1112, 1075, 739, 701 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.60 (m, 6H), 1.05 (m, 9H), 1.17 (s, 9H), 2.55 (dd, J = 15, 7 Hz, 1H), 3.01 (dd, J = 12, 7 Hz, 1H), 3.67 (m, 2H) ,4.05 (m, 1H), 5.45 (s, 1H), 5.67 (s, 1H), 7.45 (m, 6H), 7.72 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 5.2, 6.8, 7.2, 19.6, 27.2, 30.1, 47.2, 67.4, 71.0, 119.6, 127.8, 128.1, 129.7, 130.0, 131.6, 133.9, 135.5, 136.0; HRMS (CI) m/z 532.1834, calcd for C$_{27}$H$_{41}$BrO$_2$Si$_2$ m/z 532.1828.

(4R)-4-Triethylsilanyloxy-5-$tert$-butyldiphenylsilanyloxy-2-trimethylsilylmethyl-1-pentene (73). To a solution of trimethylsilylmethyl-magnesium chloride (1.0M solution in ether, 50 μL, 0.1 mmol) in tetrahydrofuran (3 mL) was added a solution of **72** (16 mg, 33 μmol) in tetrahydrofuran (2 mL) followed by 1,3-bis(diphenylphos phino)propanenickel(II) chloride (4 mg, 7 μmol) and the mixture was heated at reflux for 3 h. After cooling to room temperature, the reaction was quenched with a saturated aqueous solution of ammonium chloride (1 mL). Ether (5 mL) was added, the layers were separated and the organic phase was dried (MgSO$_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 10:1) to give **73** (6.4 mg, 40%) as a colourless oil: $[\alpha]_D^{23}$ +12.3 (c 1.2, CHCl$_3$); IR (film) 3071, 2955, 2876, 1427, 1113, 701 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.02 (s, 9H), 0.55 (m, 6H), 0.10 (s, 9H), 0.91 (m, 9H), 1.15 (s, 9H), 1.56 (m, 2H), 2.05 (dd, J = 14, 7 Hz, 1H), 2.38 (dd, J = 14, 5 Hz, 1H), 3.60 (m, 2H), 3.88 (m, 1H), 4.57 (s, 1H), 4.65 (s, 1H), 7.45 (m, 6H), 7.73 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ -2.7, -1.0, 1.4, 5.3, 7.3, 19.6, 27.3, 27.5, 29.6, 30.1, 43.7, 68.0, 72.5, 110.4, 128.0, 130,0, 134.0, 134.2, 136.0, 144.5; HRMS (CI) m/z 572.3498, calcd for C$_{36}$H$_{52}$O$_2$Si$_3$ m/z 572.3506.

2-((2S,4R,6R)-4-($tert$-Butyldiphenylsilanyloxy)-6-(2-(chloromethyl)oxazol-4-yl)tetrahydro-2H-pyran-2-yl)acetaldehyde (74). To a solution of **65** (58 mg, 0.11 mmol) in dichloromethane (10 mL) under argon at –78 °C was added dropwise diisobutylaluminium hydride (1.0M in dichloromethane, 0.22 mL, 0.22 mmol) and the mixture was stirred for 3 h at –78 °C. The reaction was quenched with methanol (5 mL), and the mixture was allowed to warm to room temperature and was diluted with dichloromethane (20 mL). The solution was washed with saturated aqueous potassium sodium tartrate solution (20 mL), dried (MgSO$_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 3:1) to give **74** (50 mg, 92%) as a colourless oil: $[\alpha]_D^{23}$ +32.4 (c 1.02, CHCl$_3$); IR (film) 3095, 2930, 2857, 1710, 1428, 1112, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.81 (t, J = 2 Hz, 1H), 7.72 – 7.66 (m, 4H), 7.57 (s, 1H), 7.47 – 7.28 (m, 6 H), 5.12 (dd, J = 2, 12 Hz, 1H), 4.72 – 4.62 (m, 1H), 4.60 (s, 2H), 4.36 (t, J = 3 Hz, 1H), 2.67 (dd, J = 2, 8 Hz, 0.5H), 2.62 (dd, J = 2, 8 Hz, 0.5H), 2.48 (dd, J = 2, 5 Hz, 0.5H), 2.42 (dd, J = 2, 5 Hz, 0.5H), 2.00 – 1.90 (m, 1H), 1.84 – 1.73 (m, 1H), 1.66 – 1.56 (m, 1H), 1.50 – 1.36 (m, 1H), 1.13 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 201.4, 159.5, 142.8, 137.6, 136.9, 136.3, 136.2, 136.1, 134.3, 134.1, 130.3, 128.2, 77.8, 77.5, 77.2, 68.4, 68.3, 67.9, 66.3, 66.1, 65.8, 49.9, 49.6, 40.6, 38.6, 37.8, 36.7, 36.3, 36.1, 27.5, 27.4, 19.7; MS (FAB) m/z 498 (M$^+$ + H), 484, 410, 392, 337, 297, 239, 197, 154, 135, 89; HRMS (FAB) m/z 498.1859 (calcd for C$_{27}$H$_{33}$O$_4$N^{35}ClSi: 498.1867, M$^+$ + H).

(2S,6R)-7-($tert$-Butyldiphenylsilanyloxy)-1-((2R,4R,6R)-4-($tert$-butyldiphenylsilanyloxy)-6-(2-(chloromethyl)oxazol-4-yl)tetrahydro-2H-pyran-2-yl)-4-methylene-6-

(triethylsilanyloxy)heptan-2-ol (75). To a solution of **73** (37 mg, 68 μmol) in dichloromethane (2 mL) at –78 °C was added tin tetrachloride (1.0M solution in dichloromethane, 55 μL, 55 μmol) and the solution was stirred at –78 °C for 30 min. A solution of **74** (13.6 mg, 27.3 μmol) in dichloromethane (0.5 mL) was added and the mixture was stirred for 1 h at –78 °C. The reaction was quenched with saturated sodium bicarbonate solution (2 mL) and the mixture was extracted with dichloromethane (10 mL x 3). The combined extract was dried (Na$_2$SO$_4$) and concentrated under reduced pressure and the resulting oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 20:1 to 10:1) to give **72** (20.4 mg, 77%) as a colourless oil: IR (neat) 3507, 3071, 3049, 2954, 2931, 2875, 2858, 1471, 1427, 1361, 1265, 1237, 1185, 1112, 1007, 896, 822, 739, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71 – 7.67 (m, 8H), 7.55 (s, 1H), 7.48 – 7.38 (m, 12H), 5.09 (d, J = 10 Hz, 1H), 4.95 (d, J = 10 Hz, 2H), 4.60 (s, 2H), 4.52 – 4.48 (m, 1H), 4.34 (m, 1H), 4.10 – 4.02 (m, 1H), 3.87 – 3.84 (m, 1H), 3.59 (dd, J = 5, 10 Hz, 1H), 2.90 (brs, 1H), 2.52 (dd, J = 5, 14 Hz, 1H), 2.27 – 2.18 (m, 3H), 1.94 (d, J = 10 Hz, 1H), 1.77 – 1.42 (m, 6H), 1.13 (s, 9H), 1.07 (s, 9H), 0.89 (t, J = 8 Hz, 9H), 0.51 (q, J = 8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.3, 144.1, 143.3, 136.6, 136.2, 136.1, 136.0, 136.0, 134.4, 134.3, 134.0, 133.9, 130.4, 130.2, 130.1, 128.1, 128.1, 115.6, 115.5, 72.8, 70.5, 67.9, 67.7, 66.9, 66.3, 66.2, 45.9, 42.4, 40.8, 38.8, 38.2, 36.3, 34.1, 33.2, 32.0, 30.7, 30.1, 27.5, 27.3, 23.3, 23.1, 19.7, 19.6, 15.7, 14.6, 7.3, 5.3; MS (ES) m/z 988 (M + Na)$^+$; HRMS (ES) m/z 988.4522 (calcd for C$_{55}$H$_{76}$NO$_6$Si$_3$ClNa : 988.4567, M + Na).

(2S,6R)-7-($tert$-Butyldiphenylsilanyloxy)-1-((2R,4R,6R)-4-($tert$-butyldiphenylsilanyloxy)-6-(2-(((E)-3-((2R,3S,4S,5S,6R)-3,5-dimethyl-6-((E)-1-(2-methyloxazol-4-yl)prop-1-en-2-yl)-4-(triisopropylsilanyloxy)tetrahydro-2H-pyran-2-yl)prop-1-enyl)oxazol-4-yl)tetrahydro-2H-pyran-2-yl)-4-methylene-6-(triethylsilanyloxy)heptan-2-ol (76). To a solution of **75** (8.2 mg, 8.5 μmol) in dimethylformamide (1.5 mL) under argon at room temperature was added tri-n-butylphosphine (13 μL, 0.052 mmol) and the solution was stirred for 4 h. A solution of **52** (8.8 mg, 20 μmol) in dimethylformamide (1 mL) containing 1,8-diazabicyclo[5.4.0]undec-7-ene (1.7 μL, 11 μmol) was added and the mixture was stirred at room temperature for 1 h, then was diluted with ethyl acetate (5 mL). Saturated aqueous ammonium chloride (5 mL) was added, the phases were separated and the aqueous phase was extracted with ethyl acetate (5 mL x 3). The combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 15:1) to give **76** (9.1 mg, 78%) as a colourless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.67 – 7.63 (m, 8H), 7.48 (s, 1H), 7.44 – 7.29 (m, 13H), 6.62 (ddd, J = 6, 8, 16 Hz, 1H), 6.32 (d, J = 16 Hz, 1H), 6.19 (s, 1H), 5.03 (d, J = 11 Hz, 1H), 4.90 (d, J = 6 Hz, 2H), 4.46 (brs, 1H), 4.30 (brs, 1H), 4.05 – 4.00 (m, 1H), 3.85 – 3.80 (m, 1H), 3.66 – 3.43 (m, 5H), 2.60 – 2.45 (m, 2H), 2.44 (s, 3H), 2.38 – 2.10 (m, 5H), 2.05 – 1.85 (m, 3H), 1.92 (d, J = 1 Hz, 3H), 1.80 – 1.45 (m, 5H), 1.09 – 0.97 (m, 45H), 0.85 (t, J = 8 Hz, 9H), 0.47 (q, J = 8 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 161.4, 161.0, 144.1, 143.3, 138.6, 138.2, 136.5, 136.2, 136.0, 134.4, 134.4, 134.0, 133.9, 130.1, 130.0, 128.1, 119.0, 118.8, 115.4, 89.3, 78.2, 72.7, 70.5, 68.1, 67.7, 66.9, 66.2, 45.7, 42.3, 40.9, 39.6, 38.7, 38.1, 36.8, 35.6, 30.1, 27.5, 27.3, 19.7, 19.6, 18.7, 18.6, 14.8, 14.4, 14.2, 13.3, 7.3, 6.5, 5.2.

(2S,6R)-7-($tert$-Butyldiphenylsilanyloxy)-1-((2S,4R,6R)-4-($tert$-butyldiphenylsilanyloxy)-6-(2-(((E)-3-((2R,3S,4S,5S,6R)-3,5-

dimethyl-6-((E)-1-(2-methyloxazol-4-yl)prop-1-en-2-yl)-4-(triisopropylsilanyloxy)tetrahydro-2H-pyran-2-yl)prop-1-enyl)oxazol-4-yl)tetrahydro-2H-pyran-2-yl)-4-methylene-6-(triethylsilanyloxy)heptan-2-yl methanesulfonate (77). To a solution of **76** (9.0 mg, 6.6 μmol) and triethylamine (11 μL, 79 μmol) in dichloromethane (1.5 mL) under argon at 0 °C was added methanesulfonyl chloride (3 μL, 39 μmol) and the solution was stirred at room temperature for 3 h. Saturated sodium bicarbonate solution (3 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (5 mL x 3) and the combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 7:1) to give **77** (7.3 mg, 77%) as a colourless oil: $[\alpha]_D^{23}$ +34.8 (c 0.70, CHCl$_3$); IR (neat) 2929, 2865, 1361, 1174, 1111, 911, 740, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.68 – 7.63 (m, 8H), 7.48 (s, 1H), 7.43 – 7.33 (m, 13H), 6.62 (ddd, J = 6, 8, 15 Hz, 1H), 6.31 (d, J = 16 Hz, 1H), 6.19 (s, 1H), 5.04 – 4.89 (m, 4H), 4.32 – 4.22 (m, 2H), 3.84 – 3.76 (m, 1H), 3.61 (dd, J = 4, 10 Hz, 1H), 3.55 – 3.41 (m, 5H), 3.00 (s, 3H), 2.65 – 2.20 (m, 5H), 2.44 (s, 3H), 2.13 (dd, J = 7, 14 Hz, 1H), 2.00 – 1.40 (m, 7H), 1.92 (d, J = 1 Hz, 3H), 1.09 – 0.97 (m, 45H), 0.84 (t, J = 8 Hz, 9H), 0.45 (q, J = 8 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 161.3, 161.0, 143.1, 141.8, 138.5, 138.2, 136.6, 136.1, 136.0, 134.7, 134.5, 134.2, 134.0, 133.9, 130.2, 130.0, 128.1, 128.1, 119.0, 118.8, 116.9, 89.3, 79.4, 78.2, 77.6, 72.3, 68.1, 68.0, 67.8, 66.3, 66.1, 43.3, 41.6, 40.9, 39.7, 39.0, 38.3, 38.1, 36.8, 35.6, 30.1, 27.5, 27.2, 19.7, 19.6, 18.7, 18.6, 14.8, 14.4, 14.2, 13.3, 7.3, 6.5, 5.2; MS (ES) m/z 1463 (M$^+$ + Na); HRMS (ES) m/z 1463.7571 (calcd for C$_{81}$H$_{120}$N$_2$O$_{11}$SSi$_4$Na : 1463.7588, M + Na).

(2S,6R)-7-(tert-Butyldiphenylsilanyloxy)-1-((2S,4R,6R)-4-(tert-butyldiphenylsilanyloxy)-6-(2-((E)-3-((2R,3S,4S,5S,6R)-3,5-dimethyl-6-((E)-1-(2-methyloxazol-4-yl)prop-1-en-2-yl)-4-(triisopropylsilanyloxy)tetrahydro-2H-pyran-2-yl)prop-1-enyl)oxazol-4-yl)tetrahydro-2H-pyran-2-yl)-6-hydroxy-4-methyleneheptan-2-yl methanesulfonate (78). To a solution of **77** (7.0 mg, 4.9 μmol) in methanol (1 mL) was added pyridinium p-toluenesulfonate (4.3 mg, 17 μmol) and the solution was stirred at room temperature for 1 h. Saturated sodium bicarbonate (3 mL) was added, the phases were separated and the aqueous phase was extracted with dichloromethane (5 mL x 3). The combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 3:1) to yield **78** (6.1 mg, 95%) as a colourless oil: $[\alpha]_D^{23}$ +39.8 (c 0.69, CHCl$_3$); IR (neat) 3371, 2927, 2858, 1360, 1173, 1111, 911, 740, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.69 – 7.67 (m, 8H), 7.52 (s, 1H), 7.45 – 7.37 (m, 13H), 6.65 (ddd, J = 6, 8, 16 Hz, 1H), 6.32 (d, J = 16 Hz, 1H), 6.21 (s, 1H), 5.09 – 5.04 (m, 1H), 4.97 (d, J = 10 Hz, 1H), 4.93 (d, J = 10 Hz, 2H), 4.35 (brs, 1H), 4.29 (t, J = 11 Hz, 1H), 3.91 (brs, 1H), 3.67 – 3.62 (m, 2H), 3.57 – 3.47 (m, 3H), 3.04 (s, 3H), 2.70 – 2.48 (m, 4H), 2.48 (s, 3H), 2.30 – 2.20 (m, 3H), 2.08 – 1.24 (m, 8H), 1.96 (d, J = 1 Hz, 3H), 1.12 (s, 9H), 1.11 (m, 21H), 1.08 (s, 9H), 1.04 (d, J = 7 Hz, 3H), 0.85 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.4, 161.0, 142.9, 141.8, 138.5, 138.2, 136.8, 136.1, 136.0, 134.6, 134.5, 134.2, 133.6, 130.2, 128.2, 128.2, 119.0, 118.7, 116.7, 89.3, 79.1, 78.2, 70.6, 68.3, 68.1, 67.9, 66.1, 43.1, 40.9, 40.1, 39.7, 38.9, 38.3, 37.9, 36.8, 35.6, 30.1, 27.5, 27.3, 19.7, 19.7, 18.7, 18.6, 14.8, 14.4, 14.3, 13.3, 6.5; MS (ES) m/z 1327

(M$^+$ + H); HRMS (ES) m/z 1327.6895 (calcd for C$_{75}$H$_{107}$N$_2$O$_{11}$SSi$_3$: 1327.6903, M + H).

4-((2R,4R,6R)-4-(tert-Butyldiphenylsilanyloxy)-6-(((2R,6R)-6-((tert-butyldiphenylsilanyloxy)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)methyl)tetrahydro-2H-pyran-2-yl)-2-((E)-3-((2R,3S,4S,5S,6R)-3,5-dimethyl-6-((E)-1-(2-methyloxazol-4-yl)prop-1-en-2-yl)-4-(triisopropylsilanyloxy)tetrahydro-2H-pyran-2-yl)prop-1-enyl)-2-methyloxazole (79). To a solution of **78** (22.1 mg, 16.6 μmol) in acetonitrile (6.5 mL) was added triethylamine (232 μL, 1.66 mmol) and the solution was heated at reflux for 20 h, then was concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 9:1) to give **79** (18.8 mg, 92%) as a colourless oil: $[\alpha]_D^{23}$ +29.4 (c 0.60, CHCl$_3$); IR (neat) 3070, 2928, 2857, 1463, 1427, 1387, 1107, 1031, 883, 822, 740, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70 – 7.65 (m, 8H), 7.52 (s, 1H), 7.45 – 7.34 (m, 13H), 6.66 (ddd, J = 6, 8, 16 Hz, 1H), 6.36 (d, J = 16 Hz, 1H), 6.22 (s, 1H), 5.02 (d, J = 11 Hz, 1H), 4.82 (s, 1H), 4.75 (s, 1H), 4.23 (brs, 1H), 4.20 – 4.16 (m, 1H), 4.01 – 3.99 (m, 1H), 3.90 – 3.86 (m, 1H), 3.73 (dd, J = 5, 10 Hz, 1H), 3.67 – 3.62 (m, 2H), 3.55 (t, J = 6 Hz, 1H), 3.49 (d, J = 10 Hz, 1H), 2.57 – 2.18 (m, 5H), 2.48 (s, 3H), 2.05 (dd, J = 5, 13 Hz, 1H), 2.00 – 1.24 (m, 8H), 1.96 (d, J = 1 Hz, 3H), 1.10 (m, 21H), 1.08 (s, 9H), 1.05 (s, 9H), 1.04 (d, J = 7 Hz, 3H), 0.85 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.4, 161.0, 143.4, 142.3, 138.6, 138.3, 136.4, 136.2, 136.1, 136.0, 134.6, 134.4, 134.2, 134.0, 130.1, 130.0, 128.1, 128.1, 119.0, 118.9, 110.8, 89.3, 78.2, 72.2, 70.2, 69.7, 68.0, 66.2, 66.0, 39.6, 39.5, 39.0, 38.7, 38.2, 37.3, 36.8, 35.6, 30.1, 27.4, 27.3, 19.7, 19.7, 18.7, 18.6, 14.8, 14.4, 14.3, 13.3, 6.5; MS (ES) m/z 1253 (M$^+$ + Na); HRMS (ES) m/z 1231.7048 (calcd for C$_{74}$H$_{103}$N$_2$O$_8$Si$_3$: 1231.7022, M + H).

4-((E)-2-((2R,3S,4S,5S,6R)-6-(2-(tert-Butyldimethylsilanyloxy)ethyl)-3,5-dimethyl-4-(triisopropylsilanyloxy)tetrahydro-2H-pyran-2-yl)prop-1-enyl)-2-methyloxazole (80). To a solution of **51** (12 mg, 27 μmol) in dichloromethane (2 mL) was added tert-butyldimethylsilyl trifluoromethanesulfonate (9 μL, 39 μmol) and 2,6-lutidine (6 μL, 51 μmol) and the solution was stirred at room temperature for 1 h. The solution was poured into saturated aqueous sodium bicarbonate (5 mL) and extracted with ether (5 mL x 3), and the combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 5 : 1) to yield **80** (14 mg, 93%) as a colourless oil: $[\alpha]_D^{23}$ -26.6 (c 0.24 CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 (s, 1H), 6.20 (s, 1H), 3.70 – 3.63 (m, 4H), 3.44 (d, J = 10 Hz, 1H), 2.48 (s, 3H), 1.94 (d, J = 1 Hz, 3H), 1.90 – 1.70 (m, 3H), 1.60 – 1.50 (m, 1H), 1.15 – 1.05 (m, 21H), 1.00 (d, J = 7 Hz, 3H), 0.92 (s, 9H), 0.84 (d, J = 7 Hz, 3H), 0.07 (d, J = 4 Hz, 6H); HRMS (EI) m/z 349.3977, calcd for C$_{31}$H$_{59}$NO$_4$Si$_2$ 349.3983.

(2S,4R,6R)-6-((1R,2E,4E,6R,8E)-9-Bromo-1-(tert-butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4,8-trienyl)-2-((4-((E)-2-((2R,3S,4S,5S,6R)-6-(2-(tert-butyldimethylsilanyloxy)ethyl)-3,5-dimethyl-4-(triisopropylsilanyloxy)tetrahydro-2H-pyran-2-yl)prop-1-enyl)oxazol-2-yl)methyl)-4-methoxytetrahydro-2H-pyran-2-ol (81). A flask containing a solution of **50** (24.2 mg, 43 μmol) and diethylamine (27 μL, 261 μmol) in tetrahydrofuran (400 μL) was cooled to −78 °C and n-butyllithium (2.30M solution in hexane,

24 μL, 56 μmol) was added dropwise via syringe. The colour of the solution, which turned bright yellow, was stirred for 20 min at –78 °C and a solution of **3** (15.9 mg, 25 μmol) in tetrahydrofuran (250 μL) at –78 °C was added dropwise via syringe. The solution turned dark yellow, and after 1 h the reaction was quenched with water (1 mL) and the mixture was extracted with ether (5 mL x 3). The combined extract was washed with brine (5 mL), dried and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 20:1 to 15:1) to produce **81** (18.2 mg, 45%) as a colourless oil: $[\alpha]_D^{23}$ +20.2 (c 0.82, CHCl$_3$); IR (neat) 3381, 2928, 2894, 2864, 1463, 1428, 1388, 1361, 1252, 1084, 1028, 833, 808, 775, 740, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.61 – 7.56 (m, 4H), 7.40 – 7.27 (m, 6H), 7.42 (s, 1H), 6.18 (s, 1H), 6.20 – 5.80 (m, 2H), 5.40 – 5.15 (m, 3H), 5.15 – 4.95 (brs, 1H), 4.45 – 4.35 (m, 1H), 4.00 – 3.90 (m, 1H), 3.70 – 3.50 (m, 7H), 3.45 – 3.25 (m, 1H), 3.34 (s, 3H), 3.22 (s, 3H), 3.02 (d, J = 15 Hz, 1H), 2.95 (d, J = 15 Hz, 1H), 2.50 – 2.40 (m, 1H), 2.35 – 2.15 (m, 2H), 2.10 – 2.00 (m, 1H), 1.88 (s, 3H), 1.90 – 1.50 (m, 5H), 1.43 (s, 3H), 1.15 – 1.05 (m, 21H), 0.98 (d, J = 7 Hz, 3H), 0.95 (s, 9H), 0.87 (s, 9H), 0.80 (d, J = 6 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 160.4, 139.4, 138.2, 138.0, 136.4, 136.3, 135.8, 135.3, 135.2, 134.6, 134.3, 132.1, 130.1, 129.9, 129.8, 127.8, 127.6, 127.2, 125.9, 119.2, 118.2, 96.9, 89.2, 81.9, 81.1, 80.8, 78.5, 77.6, 75.3, 73.8, 73.4, 72.4, 70.3, 60.3, 56.9, 56.6, 56.0, 40.9, 40.2, 39.8, 37.6, 36.5, 35.7, 32.5, 30.7, 30.1, 27.3, 26.3, 26.2, 19.6, 18.7, 18.6, 14.9, 14.5, 13.3, 13.2, 6.7, -5.0; MS (ES) m/z 1192 (M + H)$^+$; HRMS (ES) m/z 1192.5850 (calcd for C$_{64}$H$_{103}$^{79}BrNO$_9$Si$_3$: 1192.6124, M + H).

There was also obtained (2S,4R,6R)-2-((4-((E)-2-((2R,3S,4S,5S,6R)-6-(2-(*tert*-butyldimethylsilanyloxy)ethyl)-3,5-dimethyl-4-(triisopropylsilanyloxy)tetrahydro-2H-pyran-2-yl)prop-1-enyl)oxazol-2-yl)methyl)-6-((1R,2E,4E,6R)-1-(*tert*-butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4-dien-8-ynyl)-4-methoxytetrahydro-2H-pyran-2-ol (**82**, 13.3 mg, 33%) as a colourless oil: IR (neat) 3381, 3312, 2928, 2865, 2123, 1575, 1463, 1427, 1388, 1361, 1253, 1093, 1028, 969, 882, 834, 776, 740, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.65 – 7.57 (m, 4H), 7.45 (s, 1H), 7.43 – 7.27 (m, 6H), 6.17 (s, 1H), 6.04 (d, J = 16 Hz, 1H), 5.39 – 5.31 (m, 2H), 4.41 (dd, J = 6, 9 Hz, 1H), 3.99 – 3.94 (m, 1H), 3.76 – 3.57 (m, 7H), 3.44 – 3.41 (m, 1H), 3.36 (s, 3H), 3.29 (s, 3H), 3.05 (d, J = 15 Hz, 1H), 2.97 (d, J = 15 Hz, 1H), 2.46 – 2.43 (m, 2H), 2.28 (dd, J = 4, 12 Hz, 1H), 2.19 (s, 1H), 2.13 – 2.05 (m, 1H), 2.00 (t, J = 3 Hz, 1H), 1.95 – 1.68 (m, 5H), 1.90 (s, 3H), 1.65 – 1.52 (m, 2H), 1.15 – 1.05 (m, 21H), 1.00 (d, J = 7 Hz, 3H), 0.97 (s, 9H), 0.89 (s, 9H), 0.82 (d, J = 6 Hz, 3H), 0.04 (s, 3H), 0.01 (s, 3H); HRMS (ES) m/z 1112.6754 (calcd for C$_{64}$H$_{102}$NO$_9$Si$_3$: 1112.6862, M + H).

(R,E)-5-((2R,4R)-4-Methoxy-6-(phenylthio)tetrahydro-2H-pyran-2-yl)-2,2,7,10,10,11,11-heptamethyl-3,3-diphenyl-4,9-dioxa-3,10-disiladodec-6-ene (87).

To a solution of **86** (20 mg, 36 μmol) in dichloromethane (2.7 mL) at room temperature was added a *tert*-butyldimethylsilyl chloride (25.4 mg, 0.169 mmol), N,N-diisopropylethylamine (50 μL, 0.287 mmol) and 4-(N,N-dimethylamino)pyridine (0.4 mg). After 12 h, the solution was poured into saturated aqueous. sodium bicarbonate (5 mL) and extracted with ether (5 mL x 3). The combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 10 : 1) to yield **87** (24 mg, 98%) as a colourless oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 – 7.30 (m, 4H), 7.25 – 7.13 (m, 8H), 7.12 – 7.08 (m, 3H), 5.71 (d, J = 5 Hz, 1H), 5.48 (dd, J = 1, 9 Hz, 1H), 4.47 (dd, J = 6, 9 Hz, 1H), 4.31 – 4.25 (m, 1H), 3.83 (d, J = 15 Hz, 1H), 3.79 (d, J = 15 Hz, 1H), 3.66 – 3.56 (m, 1H), 3.38 (s, 3H), 2.41 – 2.35 (m, 1H), 2.19 – 2.14 (m, 1H), 1.83 (ddd, J = 6, 12, 17 Hz, 1H), 1.40 – 1.20 (m, 1H), 1.06 (s, 9H), 1.04 (d, J = 1 Hz, 3H), 0.92 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); HRMS (ES) m/z 676.3431, calcd for C$_{39}$H$_{56}$O$_4$SSi$_2$ 676.3438.

(4R,6R)-6-((R,E)-2,2,7,10,10,11,11-Heptamethyl-3,3-diphenyl-4,9-dioxa-3,10-disiladodec-6-en-5-yl)-4-methoxytetrahydropyran-2-one (84). To a solution of **87** (24 mg, 35 μmol) in tetrahydrofuran-water (5:1, 3 mL) was added silver nitrate (90 mg, 0.53 mmol) and 2,6-lutidine (124 μL, 1.07 mmol), and the mixture was stirred for 18 h at room temperature. The solution was diluted with water (5 mL) and extracted with ethyl acetate (5 mL x 3), and the combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 10:1) to give a hemiacetal. To a solution of the hemiacetal in dichloromethane (3 mL) was added tetra-n-propylammonium perruthenate (2.5 mg, 7.1 μmol), 4-methylmorpholine N-oxide (258 mg, 2.20 mmol) and 4□ molecular sieves, and the mixture was stirred for 1 h at room temperature. The solution was filtered through a column of silica gel (hexane:ethyl acetate 4:1 as eluent) to produce **84** (15.6 mg, 75%) as a colourless oil: $[\alpha]_D^{23}$ -9.8 (c 0.55, CHCl$_3$); IR (neat) 2954, 2929, 2891, 2856, 1747, 1471, 1427, 1361, 1250, 1192, 1111, 1006, 837, 777, 740, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.67 – 7.59 (m, 4H), 7.42 – 7.28 (m, 6H), 5.47 (dd, J = 1, 9 Hz, 1H), 4.55 (dd, J = 5, 9 Hz, 1H), 4.15 (ddd, J = 3, 5, 12 Hz, 1H), 3.79 (t, J = 15 Hz, 2H), 3.66 – 3.58 (m, 1H), 3.32 (s, 3H), 2.87 (dd, J = 2, 6 Hz, 0.5H), 2.82 (dd, J = 2, 6 Hz, 0.5H), 2.40 – 2.31 (m, 2H), 1.55 – 1.41 (m, 1H), 1.10 (s, 3H), 1.03 (s, 9H), 0.87 (s, 9H), 0.00 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.7, 139.7, 135.9, 133.6, 129.8, 129.6, 127.6, 127.4, 120.5, 79.8, 77.2, 72.5, 70.5, 67.2, 56.0, 36.9, 29.7, 29.6, 27.0, 25.9, 19.3, 18.3, 13.8, -5.3, -5.4; MS (ES) m/z 605 (M + Na)$^+$; HRMS (ES) m/z 605.3054 (calcd for C$_{33}$H$_{50}$O$_5$Si$_2$^{23}Na : 605.3095, M + Na).

(2R,3R,4S,5R,6R,E)-2-(2-(*tert*-Butyldimethylsilanyl)ethyl)-3,5-dimethyl-6-(1-(2-methyloxazol-4-yl)prop-1-en-2-yl)tetrahydro-2H-pyran-4-ol. To a solution of **51** (26 mg, 58 mmol) in tetrahydrofuran (3 mL) at room temperature was added a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1.0M, 0.12 mL, 0.12 mmol). After 2 h, the reaction was quenched with saturated aqueous ammonium chloride (5 mL) and most of the tetrahydrofuran was removed under reduced pressure. The remaining liquid was extracted with ethyl acetate (5 mL x 3) and the combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (dichlorormethane:methanol 9:1) to give a diol (17 mg) that was carried forward without further purification. To a stirred solution of the diol (39 mg, 0.13 mmol) in dichloromethane (4 mL) was added *tert*-butyldimethylsilyl chloride (45 mg, 0.298 mmol), N,N-diisopropylethylamine (150 μL, 0.861 mmol) and 4-(N,N-dimethylamino)pyridine (1 mg). After 12 h, the solution was poured into saturated aqueous sodium bicarbonate (10 mL) and extracted with ether (10 mL x 3). The combined extract was washed with brine (10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel (hexane:ethyl acetete 5 : 1) to yield **87** (54 mg, 98%) as a colourless oil: ^{1}H NMR (400 MHz,

CDCl$_3$) δ 7.52 (s, 1H), 6.21 (s, 1H), 3.71 – 3.61 (m, 3H), 3.54 – 3.42 (m, 2H), 2.49 (s, 3H), 1.93 (d, J = 1 Hz, 3H), 1.90 – 1.59 (m, 5H), 0.97 (d, J = 7 Hz, 3H), 0.90 (s, 9H), 0.87 (d, J = 6 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); HRMS (ES) m/z 409.2630, calcd for C$_{22}$H$_{39}$NO$_4$Si 409.2648

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4-((*E*)-2-((2*R*,3*R*,4*S*,5*S*,6*R*)-6-(2-(*tert*-Butyldimethylsilanyloxy)ethyl)-4-(4-methoxybenzyloxy)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)prop-1-enyl)-2-methyloxazole (83). To a solution of **87** (174 mg, 0.424 mmol) in tetrahydrofuran (9 mL) was added sodium hydride (62 mg, 1.55 mmol, 60% suspension in mineral oil) and the mixture was heated at reflux for 1.5 h. After the mixture had cooled to room temperature, *p*-methoxybenzyl chloride (98 μL, 0.72 mmol) and tetra-*n*-butylammonium iodide (78 mg, 0.21 mmol) were added, and the mixture was heated at reflux for 4.5 h. After the mixture had cooled to room temperature, the reaction was quenched with saturated ammonium chloride solution (5 mL) and the mixture was extracted with ether (10 mL x 3). The combined extract was washed with brine (10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 15:1) to give **83** (215 mg, 95%) as a colourless oil: $[\alpha]_D^{23}$ +40.2 (c 0.70, CHCl$_3$); IR (neat) 2954, 2927, 2854, 1612, 1585, 1513, 1462, 1386, 1302, 1248, 1172, 1093, 1035, 971, 834, 776 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 (s, 1H), 7.32 (d, J = 9 Hz, 2H), 6.92 (d, J = 9 Hz, 2H), 6.20 (s, 1H), 4.62 (d, J = 11 Hz, 1H), 4.33 (d, J = 11 Hz, 1H), 3.84 (s, 3H), 3.73 –3.70 (m, 2H), 3.62 – 3.58 (m, 1H), 3.46 (d, J = 10 Hz, 1H), 3.24 (dd, J = 5, 10 Hz, 1H), 2.48 (s, 3H), 2.15 – 2.10 (m, 1H), 1.92 (s, 3H), 1.90 – 1.80 (m, 2H), 1.70 – 1.60 (m, 1H), 1.00 (d, J = 7 Hz, 3H), 0.93 (s, 9H), 0.85 (d, J = 6 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.6, 159.2, 138.3, 137.9, 135.5, 130.7, 129.4, 118.6, 113.8, 89.0, 83.5, 74.6, 69.6, 59.9, 55.3, 36.1, 34.3, 33.3, 29.7, 26.0, 18.4, 15.3, 14.2, 14.1, 13.8, 13.8, 6.1, -5.3; MS (ES) m/z 530 (M + H)$^+$; HRMS (ES) m/z 530.3313 (calcd for C$_{30}$H$_{48}$NO$_5$Si : 530.3302, M + H).

(2*S*,4*R*,6*R*)-2-((4-((*E*)-2-((2*R*,3*R*,4*S*,5*S*,6*R*)-6-(2-(*tert*-Butyldimethylsilanyloxy)ethyl)-4-(4-methoxybenzyloxy)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)prop-1-enyl)oxazol-2-yl)methyl)-6-((*R*,*E*)-2,2,7,10,10,11,11-heptamethyl-3,3-diphenyl-4,9-dioxa-3,10-disiladodec-6-en-5-yl)-4-methoxytetrahydro-2*H*-pyran-2-ol (88). To a solution of **83** (20.1 mg, 38 μmol) and diethylamine (23 μL, 226 μmol) in tetrahyrofuran (350 μL) at –78 °C was added dropwise *n*-butyllithium (2.46M solution in hexane, 20 μL, 49 μmol) during which the solution turned bright yellow. After 25 min, a solution of **84** (10.6 mg, 18.2 μmol) in tetrahydrofuran (175 μL) at –78 °C was added via syringe over 10 min (5 μL/30 sec) during which the colour of the mixture faded to a light brownish-yellow. After 40 min, the reaction was quenched with water (1 mL) and the mixture was extracted with ether (10 mL x 3). The combined extract was washed with brine (10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 9:1) to give **88** (19.4 mg, 96%) as a colourless oil: $[\alpha]_D^{23}$ +39.7 (c 0.86, CHCl$_3$); IR (neat) 3372, 2955, 2928, 2856, 1613, 1576, 1513, 1462, 1428, 1361, 1249, 1090, 1035, 836, 776, 740, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60 – 7.56 (m, 4H), 7.39 (s, 1H), 7.36 – 7.26 (m, 8H), 6.86 (d, J = 9 Hz, 2H), 6.11 (s, 1H), 5.28 (d, J = 8 Hz, 1H), 4.81 (s, 1H), 4.57 (d, J = 11 Hz, 1H), 4.28 (d, J = 11 Hz, 1H), 4.32 – 4.27 (m, 1H), 3.93 – 3.85 (m, 1H), 3.79 (s, 3H), 3.73 – 3.64 (m, 5H), 3.57 – 3.52 (m, 1H), 3.39 (d, J = 10 Hz, 1H) 3.32 (s, 3H), 3.18 (dd, J = 5, 10 Hz, 1H), 2.97 (d, J = 16 Hz, 1H), 2.91 (d, J = 16 Hz, 1H), 2.24 – 2.18 (m, 1H), 2.10 – 2.02 (m, 2H), 1.90 – 1.75 (m, 3H), 1.84 (s, 3H), 1.60 – 1.50 (m, 2H), 1.05 – 0.90 (m, 15H), 0.87 (s, 9H), 0.86 (s, 9H), 0.78 (d, J = 6 Hz, 3H), 0.01 (s, 6H), -0.02 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.0, 159.2, 138.6, 137.7, 136.0, 136.0, 135.5, 134.4, 134.3, 130.8, 129.4, 129.4, 129.3, 127.3, 127.2, 122.8, 118.1, 113.8, 96.5, 89.0, 83.5, 74.7, 73.5, 73.1, 71.9, 69.6, 67.6, 60.0, 55.6, 55.3, 40.6, 40.0, 36.2, 34.3, 33.3, 32.0, 30.3, 29.7, 26.9, 26.0, 25.9, 19.2, 18.4, 18.3, 14.2, 13.8, 13.6, 6.1, -5.2, -5.3; MS (ES) m/z (M$^+$ + H) 1112; HRMS (ES) m/z 1112.6499 (calcd for C$_{63}$H$_{98}$NO$_{10}$Si$_3$: 1112.6461, M$^+$ + H).

(2*S*,4*R*,6*R*)-6-((*R*,*E*)-1-(*tert*-Butyldiphenylsilanyloxy)-4-hydroxy-3-methylbut-2-enyl)-2-((4-((*E*)-2-((2*R*,3*R*,4*S*,5*S*,6*R*)-6-(2-hydroxyethyl)-4-(4-methoxybenzyloxy)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)prop-1-enyl)oxazol-2-yl)methyl)-4-methoxytetrahydro-2*H*-pyran-2-ol (89). To a solution of **88** (34.3 mg, 30.8 μmol) in methanol (5 mL) was added *p*-toluenesulfonic acid monohydrate (5.9 mg, 30.8 μmol) and the solution was stirred for 1 h. A saturated solution of sodium bicarbonate (3 mL) was added, most of the methanol was evaporated under reduced pressure and the remaining liquid was extracted with ethyl acetate (10 mL x 3). The combined extract was washed with brine (10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the resulting oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 1:3) to give **89** (28.0 mg, 99%) as a colourless oil: $[\alpha]_D^{23}$ +14.6 (c 0.50, CHCl$_3$); IR (neat) 3377, 2959, 2930, 2856, 1576, 1513, 1457, 1428, 1361, 1247, 1110, 1090, 1035, 823, 756, 703 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, J = 8 Hz, 2H), 7.71 (d, J = 8 Hz, 2H), 7.56 (s, 1H), 7.46 – 7.27 (m, 8H), 6.92 (d, J = 9 Hz, 2H), 6.26 (s, 1H), 5.27 (dd, J = 1, 9 Hz, 1H), 4.62 (d, J = 11 Hz, 1H), 4.53 (dd, J = 6, 9 Hz, 1H), 4.34 (d, J = 11 Hz, 1H), 3.85 (s, 3H), 3.83 – 3.79 (m, 2H), 3.72 – 3.54 (m, 5H), 3.55 (d, J = 10 Hz, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 3.26 (dd, J = 5, 10 Hz, 1H), 3.07 (d, J = 15 Hz, 1H), 2.30 – 2.28 (m, 1H), 2.20 – 1.87 (m, 5H), 1.94 (d, J = 1 Hz, 3H), 1.62 – 1.31 (m, 3H), 1.17 (d, J = 1 Hz, 3H), 1.09 (s, 9H), 1.04 (d, J = 7 Hz, 3H), 0.87 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.3, 159.2, 138.0, 137.8, 137.7, 136.1, 136.1, 134.8, 133.9, 130.6, 129.6, 129.5, 129.4, 127.5, 127.3, 124.4, 119.1, 113.8, 99.9, 89.2, 82.9, 78.9, 77.3, 73.5, 72.2, 69.7, 67.9, 64.4, 62.1, 55.7, 55.3, 47.9, 39.2, 35.6, 35.1, 35.0, 33.2, 32.1, 30.7, 29.7, 27.0, 19.3, 19.1, 14.1, 13.7, 6.3; MS (ES) m/z (M$^+$ + H), 898; HRMS (ES) m/z 920.4745 (calcd for C$_{52}$H$_{71}$NO$_{10}$Si : 920.4770, M$^+$ + Na).

(*R*,*E*)-4-(*tert*-Butyldiphenylsilanyloxy)-4-((2*R*,4*R*,6*S*)-6-((4-((*E*)-2-((2*R*,3*R*,4*S*,5*S*,6*R*)-6-(2-hydroxyethyl)-4-(4-methoxybenzyloxy)-3,5-dimethyltetrahydro-2*H*-pyran-2-yl)prop-1-enyl)oxazol-2-yl)methyl)-4,6-dimethoxytetrahydro-2*H*-pyran-2-yl)-2-methylbut-2-enal (90). To a solution of **89** (28.0 mg, 30.8 μmol) in dichloromethane (6.5 mL) was added freshly prepared manganese dioxide (75 mg, 0.86 mmol) and the suspension was stirred vigorously for 2 h. The suspension was loaded on to a column of silica gel which was flushed with hexane:ethyl acetate (1:1) to yield **90** (23.6 mg, 84%) as a colourless oil: $[\alpha]_D^{23}$ +4.4 (c 0.50, CHCl$_3$); IR (neat) 3456, 2959, 2930, 2857, 1692, 1613, 1577, 1513, 1462, 1428, 1385, 1361, 1247, 1107, 1091, 1034, 822, 755, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.17 (s, 1H), 7.68 (d, J = 8 Hz, 2H), 7.58 (d, J = 8 Hz, 2H), 7.45 (s, 1H), 7.42 – 7.30 (m, 8H), 6.86 (d, J = 9 Hz, 2H),

6.23 (dd, J = 1, 9 Hz, 1H), 6.16 (s, 1H), 4.67 (dd, J = 6, 9 Hz, 1H), 4.56 (d, J = 11 Hz, 1H), 4.28 (d, J = 11 Hz, 1H), 3.79 (s, 3H), 3.77 – 3.73 (m, 2H), 3.67 – 3.42 (m, 3H), 3.27 (s, 3H), 3.15 (s, 3H), 3.27 – 3.13 (m, 2H), 2.94 (d, J = 15 Hz, 1H), 2.58 (brs, 1H), 2.25 – 2.15 (m, 1H), 2.10 – 1.80 (m, 5H), 1.86 (d, J = 1 Hz, 3H), 1.57 – 1.30 (m, 3H), 1.30 (d, J = 1 Hz, 3H), 1.06 (s, 9H), 0.98 (d, J = 7 Hz, 3H), 0.81 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.8, 159.2, 158.9, 150.8, 139.9, 137.9, 137.8, 136.2, 135.9, 135.8, 133.4, 133.1, 130.6, 130.1, 129.4, 127.8, 127.6, 118.9, 113.8, 100.0, 89.2, 82.9, 78.9, 77.3, 73.1, 72.8, 71.6, 69.7, 62.0, 55.7, 55.3, 47.9, 39.1, 35.4, 35.1, 35.0, 33.2, 31.6, 29.7, 26.9, 19.3, 14.1, 13.7, 9.7, 6.3; MS (ES) m/z (M$^+$ + H) 896; HRMS (ES) m/z 896.4769 (calcd for C$_{52}$H$_{70}$NO$_{10}$Si : 896.4820, M$^+$ + H).

(R,E)-4-((2R,4R,6S)-6-((4-((E)-2-((2R,3R,4S,5S,6R)-6-(2-(tert-Butyldimethylsilanyloxy)ethyl)-4-(4-methoxybenzyloxy)-3,5-dimethyltetrahydro-2H-pyran-2-yl)prop-1-enyl)oxazol-2-yl)methyl)-4,6-dimethoxytetrahydro-2H-pyran-2-yl)-4-(tert-butyldiphenylsilanyloxy)-2-methylbut-2-enal (91). To a solution of **90** (23.6 mg, 26.3 μmol) in dichloromethane (5 mL) was added tert-butyldimethylsilyl chloride (15.3 mg, 0.102 mmol) and imidazole (9.3 mg, 0.137 mmol) and the solution was stirred at room temperaure for 12 h, after which it was poured into saturated aqueous sodium bicarbonate (10 mL) and extracted with ether (10 mL x 3). The combined extract was washed with brine (10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the the crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 5:1) to yield

91 (22.8 mg, 86%) as a colourless oil: $[\alpha]_D^{23}$ +9.0 (c 0.42, CHCl$_3$); IR (neat) 2954, 2929, 2856, 1694, 1613, 1577, 1513, 1462, 1428, 1387, 1248, 1092, 1036, 835, 777, 741, 703 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.17 (s, 1H), 7.68 (d, J = 8 Hz, 2H), 7.57 (d, J = 8 Hz, 2H), 7.45 (s, 1H), 7.42 – 7.25 (m, 8H), 6.83 (d, J = 9 Hz, 2H), 6.23 (dd, J = 1, 9 Hz, 1H), 6.14 (s, 1H), 4.67 (dd, J = 6, 9 Hz, 1H), 4.56 (d, J = 11 Hz, 1H), 4.28 (d, J = 11 Hz, 1H), 3.79 (s, 3H), 3.68 – 3.62 (m, 3H), 3.55 – 3.52 (m, 2H), 3.39 (d, J = 10 Hz, 1H), 3.27 (s, 3H), 3.16 (s, 3H), 3.20 – 3.16 (m, 2H), 2.94 (d, J = 15 Hz, 1H), 2.23 – 2.17 (m, 1H), 2.10 – 1.95 (m, 2H), 1.86 (d, J = 1 Hz, 3H), 1.81 – 1.76 (m, 2H), 1.40 – 1.12 (m, 3H), 1.29 (d, J = 1 Hz, 3H), 1.06 (s, 9H), 0.94 (d, J = 7 Hz, 3H), 0.87 (s, 9H), 0.80 (d, J = 6 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.9, 159.2, 158.9, 150.8, 139.9, 138.5, 138.1, 136.1, 135.9, 135.8, 133.4, 133.1, 130.8, 130.1, 130.1, 129.4, 127.8, 127.7, 118.4, 113.8, 100.1, 89.0, 83.5, 74.7, 73.1, 72.8, 71.7, 69.6, 60.0, 55.6, 55.3, 47.9, 39.1, 36.1, 35.4, 34.3, 33.3, 31.6, 26.9, 26.0, 19.3, 18.4, 14.3, 13.8, 9.7, 6.1, -5.3; MS (ES) m/z (M$^+$ + H) 1171; HRMS (ES) m/z 1010.5634 (calcd for C$_{58}$H$_{84}$NO$_{10}$Si$_2$: 1010.5601, M$^+$ + H).

2-(((2S,4R,6R)-6-((1R,2E,4E,6R,8E)-9-Bromo-1-(tert-butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4,8-trienyl)-2,4-dimethoxytetrahydro-2H-pyran-2-yl)methyl)-4-((E)-2-((2R,3R,4S,5S,6R)-6-(2-(tert-butyldimethylsilanyloxy)ethyl)-4-(4-methoxybenzyloxy)-3,5-dimethyltetrahydro-2H-pyran-2-yl)prop-1-enyl)oxazole (92). To a solution of **91** (23.0 mg, 22.8 μmol) and **85** (21.4 mg, 56.9 μmol) in tetrahydrofuran (1 mL) at –78 °C was added dropwise sodium bis(trimethylsilyl)amide (1M soluton in tetrahydrofuran, 55 μL, 55 μmol,) over 3 min. The mixture was stirred at –78°C for 0.5 h, then warmed to 0 °C for 15 min, and finally stirred at room temperature for 0.5 h. The reaction was quenched with pH 7 buffer solution (10 mL) and the mixture was extracted with ether (10 mL x 3). The combined extract was washed with brine

(10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 7:1) to give

92 (26.9 mg, 99%) as a colourless oil: $[\alpha]_D^{23}$ -21.3 (c 0.28, CHCl$_3$); IR (neat) 2928, 2855, 1614, 1578, 1513, 1462, 1427, 1387, 1361, 1248, 1103, 1035, 834, 777, 741, 703 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 (dd, J = 1, 8 Hz, 2H), 7.61 (dd, J = 1, 8 Hz, 2H), 7.50 (s, 1H), 7.38 – 7.25 (m, 8H), 6.86 (d, J = 9 Hz, 2H), 6.17 (s, 1H), 6.13 (dd, J = 7, 14 Hz, 1H), 6.05 (d, J = 14 Hz, 1H), 5.96 (d, J = 16 Hz, 1H), 5.34 (d, J = 9 Hz, 1H), 5.20 (dd, J = 8, 16 Hz, 1H), 4.56 (d, J = 11 Hz, 1H), 4.50 (dd, J = 7, 9 Hz, 1H), 4.28 (d, J = 11 Hz, 1H), 3.79 (s, 3H), 3.68 – 3.65 (m, 2H), 3.59 – 3.52 (m, 4H), 3.40 (d, J = 10 Hz, 1H), 3.28 (s, 3H), 3.26 (s, 3H), 3.20 (s, 3H), 3.33 – 3.17 (m, 2H), 2.94 (d, J = 15 Hz, 1H), 2.27 – 2.18 (m, 3H), 2.07 – 2.02 (m, 1H), 1.88 (d, J = 1 Hz, 3H), 1.83 – 1.62 (m, 3H), 1.60 – 1.11 (m, 4H), 1.17 (d, J = 1 Hz, 3H), 1.04 (s, 9H), 0.94 (d, J = 7 Hz, 3H), 0.88 (s, 9H), 0.81 (d, J = 6 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.2, 138.4, 138.0, 137.3, 136.1, 136.0, 136.0, 134.9, 134.2, 133.9, 131.6, 130.8, 129.6, 129.4, 129.4, 127.7, 127.4, 127.2, 118.6, 113.8, 106.3, 99.9, 89.0, 83.5, 81.1, 74.7, 73.5, 73.5, 72.5, 69.6, 60.0, 56.2, 55.7, 55.3, 48.0, 39.2, 36.7, 36.1, 35.5, 34.4, 33.3, 32.3, 29.7, 27.0, 26.0, 19.4, 18.4, 14.3, 13.8, 13.0, 6.1, -5.3; MS (ES) m/z (M$^+$ + H) 1171; HRMS (ES) m/z 1071.5600 (calcd for C$_{64}$H$_{94}$^{79}BrNO$_{10}$Si$_2$: 1071.5507, M$^+$ + H).

2-((2R,3S,4S,5R,6R)-6-((E)-1-(2-(((2S,4R,6R)-6-((1R,2E,4E,6R,8E)-9-Bromo-1-(tert-butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4,8-trienyl)-2,4-dimethoxytetrahydro-2H-pyran-2-yl)methyl)oxazol-4-yl)prop-1-en-2-yl)-4-(4-methoxybenzyloxy)-3,5-dimethyltetrahydro-2H-pyran-2-yl)ethanol (93). To a solution of **92** (27.3 mg, 23.3 μmol) in methanol (5 mL) was added p-toluenesulfonic acid monohydrate (4.4 mg, 23 μmol) and the solution was stirred for 45 min. A saturated solution of sodium bicarbonate (3 mL) was added, methanol was partially evaporated under reduced pressure and the remaining liquid was extracted with ethyl acetate (10 mL x 3). The combined organic extract was washed with brine (10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 1:1) to afford

93 (22.6 mg, 92%) as a colourless oil: $[\alpha]_D^{23}$ -27.1 (c 0.24, CHCl$_3$); IR (neat) 3109, 2928, 2855, 1614, 1585, 1513, 1461, 1427, 1362, 1247, 1106, 1035, 822, 742, 703 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 (dd, J = 1, 8 Hz, 2H), 7.60 (dd, J = 1, 8 Hz, 2H), 7.49 (s, 1H), 7.40 – 7.25 (m, 8H), 6.86 (d, J = 9 Hz, 2H), 6.19 (s, 1H), 6.13 (dd, J = 7, 14 Hz, 1H), 6.05 (d, J = 14 Hz, 1H), 5.96 (d, J = 16 Hz, 1H), 5.34 (d, J = 9 Hz, 1H), 5.20 (dd, J = 8, 16 Hz, 1H), 4.56 (d, J = 11 Hz, 1H), 4.50 (dd, J = 7, 9 Hz, 1H), 4.29 (d, J = 11 Hz, 1H), 3.79 (s, 3H), 3.79 – 3.74 (m, 2H), 3.65 (d, J = 10 Hz, 1H), 3.59 – 3.51 (m, 4H), 3.27 (s, 3H), 3.26 (s, 3H), 3.20 (s, 3H), 3.33 – 3.17 (m, 2H), 2.93 (d, J = 15 Hz, 1H), 2.54 (brs, 1H), 2.29 – 2.18 (m, 3H), 2.06 – 1.80 (m, 5H), 1.88 (d, J = 1 Hz, 3H), 1.60 – 1.20 (m, 2H), 1.17 (d, J = 1 Hz, 3H), 1.04 (s, 9H), 0.98 (d, J = 7 Hz, 3H), 0.81 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 159.2, 137.8, 137.7, 137.4, 136.2, 136.1, 136.0, 135.9, 135.8, 134.9, 134.3, 133.9, 131.6, 130.6, 129.6, 129.4, 129.4, 127.7, 127.4, 127.2, 119.0, 113.8, 106.3, 99.9, 89.2, 82.9, 81.1, 79.0, 73.5, 73.4, 72.5, 69.7, 62.1, 56.2, 55.7, 55.3, 48.0, 39.2, 35.5, 35.1, 35.0, 33.2, 32.3, 29.7, 27.0, 19.4, 14.1, 13.7, 13.0, 6.3; MS (ES) m/z (M$^+$ + H) 1056; HRMS (ES) m/z 1056.4657 (calcd for C$_{58}$H$_{79}$^{79}BrNO$_{10}$Si : 1056.4594, M$^+$ + H).

((2R,6R)-6-(((2R,4R,6R)-4-(*tert*-Butyldiphenylsilanyloxy)-6-(2-((*E*)-3-((2R,3S,4S,5S,6R)-3,5-dimethyl-6-((*E*)-1-(2-methyloxazol-4-yl)prop-1-en-2-yl)-4-(triisopropylsilanyloxy)tetrahydro-2H-pyran-2-yl)prop-1-enyl)oxazol-4-yl)tetrahydro-2H-pyran-2-yl)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)methanol (94). To a solution of **79** (10.9 mg, 8.9 µmol) in dimethylformamide (6 mL) at 0 °C was added tris(dimethylamino)sulfur (trimethylsilyl)difluoride (34.0 mg, 123 µmol) and the solution was stirred for 48 h at 0 °C. Phosphate buffer (pH 7.2, 1 mL) was added and the mixture was extracted with ether (1 mL x 3). The combined extract was dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 1:1 to ethyl acetate only) to give **94** (5.1 mg, 74%) as a colourless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.69 – 7.63 (m, 4H), 7.49 (s, 1H), 7.44 – 7.35 (m, 7H), 6.65 (ddd, *J* = 6, 8, 16 Hz, 1H), 6.32 (d, *J* = 16 Hz, 1H), 6.18 (s, 1H), 5.00 (d, *J* = 10 Hz, 1H), 4.78 (s, 1H), 4.72 (s, 1H), 4.30 (brs, 1H), 4.25 – 4.09 (m, 2H), 3.92 – 3.83 (m, 1H), 3.72 – 3.40 (m, 5H), 2.60 – 1.35 (m, 14H), 2.44 (s, 3H), 1.92 (d, *J* = 1 Hz, 3H), 1.08 (m, 30H), 1.00 (d, *J* = 7 Hz, 3H), 0.81 (d, *J* = 7 Hz, 3H); HRMS (ES) *m/z* 980.5797, calcd for C$_{57}$H$_{84}$N$_2$O$_8$Si$_2$ 980.5766.

((2R,6R)-6-(((2R,4R,6R)-4-(*tert*-Butyldiphenylsilanyloxy)-6-(2-((*E*)-3-((2R,3S,4S,5S,6R)-3,5-dimethyl-6-((*E*)-1-(2-methyloxazol-4-yl)prop-1-en-2-yl)-4-(triisopropylsilanyloxy)tetrahydro-2H-pyran-2-yl)prop-1-enyl)oxazol-4-yl)tetrahydro-2H-pyran-2-yl)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)methyl trifluoromethanesulfonate (95). To a solution of **94** (4.9 mg, 4.9 µmol) in dichloromethane (2 mL) at –78 °C was added pyridine (2 µL, 12 µmol) and trifluoromethanesulfonic anhydride (2.5 µL, 15 µmol). The solution was stirred for 1 h at –78 °C, a saturated solution of sodium bicarbonate (1 mL) was added and the mixture was warmed to room temperature. The mixture was extracted with ether (1 mL x 3) and the combined extract was dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 5:1) to give **95** (5.6 mg, 64%) as a colourless oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.74 – 7.64 (m, 4H), 7.49 (s, 1H), 7.43 – 7.37 (m, 7H), 6.64 (ddd, *J* = 6, 8, 16 Hz, 1H), 6.32 (d, *J* = 16 Hz, 1H), 6.18 (s, 1H), 5.01 (d, *J* = 11 Hz, 1H), 4.86 (s, 1H), 4.80 (s, 1H), 4.42 (d, *J* = 5 Hz, 2H), 4.30 (brs, 1H), 4.22 – 4.02 (m, 2H), 3.63 – 3.43 (m, 4H), 2.59 – 1.35 (m, 14H), 2.44 (s, 3H), 1.92 (d, *J* = 1 Hz, 3H), 1.08 (m, 30H), 1.00 (d, *J* = 7 Hz, 3H), 0.81 (d, *J* = 7 Hz, 3H).

3-(*tert*-Butyldiphenylsilanyloxy)propanal (99). To a solution of 1,3-propanediol (4.18 g, 55 mmol) in dichloromethane (50 mL) was added *tert*-butyldiphenylsilyl chloride (5 mL, 19.5 mmol) and *N,N*-diisopropylethylamine (10 mL, 71.7 mmol) and the solution was stirred for 12 h, after which it was diluted with water (50 mL). The mixture was extracted with ethyl acetate (50 mL x 3) and the combined extract was washed with brine (25 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 2:1) to give 3-(*tert*-butyldiphenylsilanyloxy)propanol (6.14 g, 99%) which was used immediately for the next reaction.

To a solution of dimethyl sulfoxide (0.913 mL, 12.9 mmol) in dichloromethane (22 mL) at –78 °C was added oxalyl chloride (0.56 mL, 6.45 mmol), and after 25 min a solution of the alcohol obtained above (1.35 g, 4.29 mmol) in dichloromethane (8 mL)

was added. After a further 25 min, triethylamine (1.79 mL, 12.9 mmol) was added and the solution was allowed to warm slowly to –10 °C over 1 h, then was warmed to room temperature for 0.5 h. The solution was poured into a mixture of ether (25 mL) and saturated ammonium chloride solution (25 mL) and the aqueous layer was separated and extracted with ether (25 mL x 3). The combined extract was washed with saturated sodium bicarbonate solution (25 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 15 : 1) to yield **99** (1.34 g, 99%) as a colourless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.80 (t, *J* = 2 Hz, 1H), 7.65 – 7.61 (m, 4H), 7.42 – 7.34 (m, 6H), 4.00 (t, *J* = 6 Hz, 1H), 2.59 (dt, *J* = 6, 2 Hz, 1H), 1.01 (s, 9H). This aldehyde is unstable and was used immediately for the next reaction.

(R)-1-(*tert*-Butyldiphenylsilanyloxy)hex-5-en-3-ol (100). To a solution of (+)-*B*-methoxydiisopinocampheylborane (3.21 g, 10.15 mmol) in ether (25 mL) at 0 °C was added allylmagnesium bromide (1.0M solution in hexane, 8.6 mL) and the mixture was allowed to warm to room temperature. The solvent was removed under vacuum, the residue was extracted with pentane (10 mL x 4) and the resulting suspension was filtered under argon through a Schlenk tube. Pentane was removed from the filtrate under vacuum, the residue was dissolved in ether (25 mL) and the solution was cooled to –100°C. To this solution was added a solution of **99** (1.34 g, 4.29 mmol) in ether (25 mL) at –78 °C and the mixture was stirred at –100 °C for 1 h, after which the reaction was quenched with methanol (1.0 mL). The mixture was allowed to warm to room temperature, then was treated with saturated sodium bicarbonate solution (10 mL) and 30% hydrogen peroxide (5 mL) and was stirred for 10 h. The mixture was extracted with ether (25 mL x 3), and the combined extract was washed with brine (20 mL), dried (MgSO$_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 25:1) to yield **100** (1.52 g, 88%) as a colourless oil with enantiomeric ratio >96:4 by Mosher ester analysis of its ^{19}F NMR spectrum: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.65 – 7.61 (m, 4H), 7.42 – 7.34 (m, 6H), 5.83 (ddt, *J* = 7, 10, 17 Hz, 1H), 5.12 – 5.05 (m, 2H), 3.95 – 3.90 (m, 1H), 3.88 – 3.80 (m, 2H), 3.20 (d, *J* = 3 Hz, 1H), 2.27 – 2.22 (m, 2H), 1.73 – 1.68 (m, 2H), 1.03 (s, 9H); HRMS (EI) *m/z* 354.2003, calcd for C$_{22}$H$_{30}$O$_2$Si 354.2015.

(S)-5-(*tert*-Butyldiphenylsilanyloxy)-3-(triethylsilanyloxy)pentanal (102). To a solution of **100** (99 mg, 0.28 mmol) in dichloromethane (9 mL) at 0 °C were added 2,6-lutidine (0.097 mL, 0.837 mmol) and triethylsilyl trifluoromethanesulfonate (95 µL, 0.42 mmol), and the solution was stirred at 0 °C for 30 min and at room temperature for 5 h. The reaction was quenched with saturated sodium bicarbonate solution, dichloromethane (10 mL) was added and the pH of the aqueous phase was adjusted to *ca.* 7.0 with 1M hydrochloric acid. The aqueous phase was extracted with dichloromethane (10 mL x 3), and the combined extract was dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 40:1) to give **101** (117 mg, 90%) as a colourless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.63 (m, 4H), 7.39 (m, 6H), 5.78 (ddt, *J* = 17, 10, 7 Hz, 1H), 4.99 (m, 2H), 3.94 (m, 1H), 3.69 (m, 2H), 2.20 (m, 2H), 1.66 (m, 2H), 1.02 (s, 9H), 0.91 (t, *J* = 8 Hz, 9H), 0.55 (q, *J* = 8 Hz, 6H).

Ozone was passed through a solution of **101** (50.1 mg, 0.107 mmol) in dichloromethane (5 mL) at 0 °C until a light blue color persisted. Triphenylphosphine (140 mg, 0.534 mmol) was added

and the mixture was warmed to room temperature and was stirred for 30 min. The mixture was concentrated and the residue was purified by flash chromatography on silica gel (hexane:ethyl acetate 10:1) to yield **102** (39.9 mg, 80%) as a colourless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.80 (t, J = 2 Hz, 1H), 7.68 – 7.64 (m, 4H), 7.45 – 7.28 (m, 6H), 4.46 (tt, J = 6, 6 Hz, 1H), 3.81 – 3.66 (m, 2H), 2.63 – 2.47 (m, 2H), 1.91 – 1.68 (m, 2H), 1.07 (s, 9H), 0.94 (t, J = 8 Hz, 9H), 0.60 (q, J = 8 Hz, 6H). This aldehyde was unstable and was used immediately for the next reaction.

(*R*)-9,9-Diethyl-2,2-dimethyl-3,3-diphenyl-7-(prop-2-ynyl)-4,8-dioxa-3,9-disilaundecane (104). A freshly prepared solution of sodium methoxide (75 mL, 1M solution in methanol) was added to a solution of **103** (178 mg, 0.924 mmol) in tetrahydrofuran (10 mL) at –78 °C, and after 5 min neat **102** (174 mg, 0.370 mmol) was added. The solution was stirred for 10 min at –78 °C, then was warmed to room temperature. After 30 min, the reaction was quenched with saturated ammonium chloride solution (5 mL) and the aqueous phase was separated and extracted with ether (10 mL x 3). The combined extract was dried (MgSO$_4$), filtered, and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane:ethyl acetate 20:1) to yield **104** (154 mg, 90%) as a colourless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.68 (m, 4H), 7.36 (m, 6H), 4.09 (m, 1H), 3.76 (m, 2H), 2.37 (m, 2H), 2.00 (t, J = 3 Hz, 1H), 1.89 (m, 1H), 1.75 (m, 1H), 1.06 (s, 9H), 0.96 (t, J = 8 Hz, 9H), 0.62 (q, J = 8 Hz, 6H); HRMS (EI) *m/z* 466.2739, calcd for C$_{28}$H$_{42}$O$_2$Si$_2$ 466.2723.

(*S*)-5-Bromo-1-(*tert*-butyldiphenylsilanyloxy)hex-5-en-3-ol (106). To a solution of **104** (196 mg, 0.42 mmol) in methanol (5 mL) was added pyridinium *p*-toluenesulfonate (5 mg) and the solution was stirred for 2 h, then was concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 15:1) to give **105** (148 mg, 99%) as a colourless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.67 (m, 4H), 7.42 – 7.25 (m, 6H), 4.08 (m, 1H), 3.87 (m, 2H), 3.41 (d, J = 3 Hz, 1H), 2.42 (m, 2H), 2.02 (t, J = 3 Hz, 1H), 1.80 (m, 2H), 1.05 (s, 9H). This material was used immediately for the next reaction.

To a solution of **105** (148 mg, 0.42 mmol) in dichloromethane (5 mL) at 0 °C under argon was added 9-bromo-9-borabicyclo[3.3.1]nonane (1.0M solution in dichloromethane, 2 mL, 2 mmol). The mixture was allowed to warm to room temperature and was stirred overnight, then was cooled to 0 °C and ethanolamine (0.5 mL) and methanol (2 mL) were added. The mixture was diluted with ether (10 mL) and was washed with a saturated aqueous solution of sodium potassium tartrate (10 mL). The phases were separated and the organic layer was dried (MgSO$_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate 30:1) to yield **106** (153 mg, 84%) as a colourless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.66 (m, 4H), 7.46 – 7.28 (m, 6H), 5.70 (d, J = 1 Hz, 1H), 5.53 (d, J = 1 Hz, 1H), 4.28 (m, 1H), 3.91 (m, 2H), 3.23 (brs, 1H), 2.71 – 2.50 (m, 2H), 1.81 (m, 2H), 1.07 (s, 9H).

(*R*)-9,9-Diethyl-2,2-dimethyl-3,3-diphenyl-7-(2-((trimethylsilyl)methyl)allyl)-4,8-dioxa-3,9-disilaundecane (98). To a solution of **106** (153 mg, 0.353 mmol) in dichloromethane (7 mL) at 0 °C were added 2,6-lutidine (0.21 mL, 1.81 mmol) and triethylsilyl trifluoromethanesulfonate (0.21 mL, 0.93 mmol). The solution was stirred at 0 °C for 30 min and at room temperature for 5 h, and the reaction was quenched with saturated sodium bicarbonate solution. The aqueous phase was

separated and was extracted with dichloromethane (10 mL x 3), and the combined extract was dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 40:1) to yield **107** (161 mg, 83%) as a colourless oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66 (m, 4H), 7.33 – 7.25 (m, 6H), 5.57 (s, 1H), 5.41 (d, J = 1 Hz, 1H), 4.23 (m, 1H), 3.71 (m, 2H), 2.53 (m, 2H), 1.82 (m, 1H), 1.64 (m, 1H), 1.03 (s, 9H), 0.91 (t, J = 8 Hz, 9H), 0.58 (q, J = 8 Hz, 6H). This material was carried forward immediately to the next reaction.

To a solution of (trimethylsilyl)methylmagnesium chloride (1.0M solution in ether, 0.69 mL, 0.69 mmol) in tetrahydrofuran (12 mL) was added a solution of **107** (252 mg, 0.46 mmol) in tetrahydrofuran (2 mL) followed by [1,3-bis(diphenylphosphino)propane]nickel(II) chloride (25 mg, 46 μmol) and the mixture was heated at reflux for 12 h. After cooling to room temperature, the reaction was quenched with saturated ammonium chloride solution (15 mL) and ether (15 mL) was added. The phases were separated and the organic phase was dried (MgSO$_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane:ethyl acetate 200:1) to give **98** (220 mg, 86%) as a colourless oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.66 (m, 4H), 7.37 (m, 6H), 4.58 (d, J = 10 Hz, 2H), 4.10 (m, 1H), 3.73 (m, 2H), 2.17 (dd, J = 6, 13 Hz, 1H), 2.05 (dd, J = 7, 13 Hz, 1H), 1.78 (m, 1H), 1.59 (m, 1H), 1.52 (s, 2H), 1.04 (s, 9H), 0.92 (t, J = 8 Hz, 9H), 0.57 (q, J = 8 Hz, 6H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 144.6, 136.0, 134.5, 134.4, 129.9, 128.0, 110.3, 68.5, 61.2, 47.2, 40.3, 27.5, 27.3, 19.6, 7.4, 5.5, -1.0; HRMS (ES) *m/z* 596.3888, calcd for C$_{35}$H$_{60}$O$_2$Si$_3$ 598.3901.

(*R*)-8-(*tert*-Butyldiphenylsilanyloxy)-1-((2*R*,4*R*,6*R*)-4-(*tert*-butyldiphenylsilanyloxy)-6-(2-(chloromethyl)oxazol-4-yl)tetrahydro-2*H*-pyran-2-yl)-4-methylene-6-(triethylsilanyloxy)octan-2-ol (108). To a solution of **98** (117 mg, 0.211 mmol) in dichloromethane (7 mL) at –78 °C was added tin tetrachloride (1.0M solution in dichloromethane, 188 μL, 188 μmol) and the solution was stirred at –78 °C for 30 min. A solution of **74** (45.8 mg, 92 μmol) in dichloromethane (2.5 mL) was added and the mixture was stirred for 1 h at –78 °C. The reaction was quenched with saturated sodium bicarbonate solution (2 mL) and the mixture was extracted with dichloromethane (10 mL x 3). The combined extract was dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 20:1 to 10:1) to give **108** (56.8 mg, 63%) as a colourless oil: $[\alpha]_D^{23}$ +10.1 (c 0.98, CHCl$_3$); IR (neat) 3477, 3070, 2953, 2927, 2855, 1471, 1427, 1238, 1110, 894, 822, 739, 701 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.67 – 7.65 (m, 8H), 7.52 (s, 1H), 7.43 – 7.36 (m, 12H), 5.05 (d, J = 10 Hz, 1H), 4.88 (d, J = 5 Hz, 2H), 4.57 (s, 2H), 4.48 – 4.40 (m, 1H), 4.32 (s, 1H), 4.09 – 4.02 (m, 2H), 3.76 – 3.67 (m, 2H), 2.77 (brs, 1H), 2.22 – 2.16 (m, 4H), 2.00 – 1.85 (m, 2H), 1.80 – 1.35 (m, 6H), 1.10 (s, 9H), 1.04 (s, 9H), 0.90 (t, J = 8 Hz, 9H), 0.55 (q, J = 8 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 159.3, 144.3, 143.3, 136.6, 136.1, 136.0, 134.4, 134.3, 130.2, 130.0, 128.1, 128.0, 115.3, 77.6, 70.5, 68.7, 67.9, 66.7, 66.1, 61.1, 45.5, 44.3, 42.6, 40.2, 38.7, 38.1, 36.2, 32.3, 30.7, 30.1, 29.8, 27.5, 27.3, 23.1, 19.7, 19.6, 15.7, 14.5, 7.3, 5.4; MS (ES) *m/z* (M + Na)$^+$ 1002; HRMS (ES) *m/z* 1002.4739 (calcd for C$_{56}$H$_{78}$ClNO$_6$Si$_3$Na : 1002.4723, M + Na).

2-((2*R*,3*S*,4*S*,5*R*,6*R*)-6-((*E*)-1-(2-(((2*S*,4*R*,6*R*)-6-((1*R*,2*E*,4*E*,6*R*,8*E*)-9-Bromo-1-(*tert*-butyldiphenylsilanyloxy)-

6-methoxy-3-methylnona-2,4,8-trienyl)-2,4-dimethoxytetrahydro-2H-pyran-2-yl)methyl)oxazol-4-yl)prop-1-en-2-yl)-4-(4-methoxybenzyloxy)-3,5-dimethyltetrahydro-2H-pyran-2-yl)acetaldehyde (109).

To a solution of **93** (6.0 mg, 5.5 μmol) in dichloromethane (1.6 mL) under argon at room temperature was added Dess-Martin periodinane (4.9 mg, 12 μmol) and the solution was stirred at room temperature for 1 h. The solution was poured into an ice-cold mixture of saturated aqueous sodium bicarbonate (1 mL) containing sodium thiosulfate (0.5 g) and was extracted with ethyl acetate (2 mL x 3). The combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 9:1) to give

109 (5.7 mg, 95%) as a colourless oil: $[\alpha]_D^{23}$ -21.3 (c 0.18, CHCl$_3$); IR (neat) 2929, 2855, 1727, 1615, 1513, 1457, 1428, 1361, 1247, 1106, 1034, 822, 741, 703 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.75 (t, J = 2 Hz, 1H), 7.72 (dd, J = 1, 8 Hz, 2H), 7.60 (dd, J = 1, 8 Hz, 2H), 7.40 (s, 1H), 7.40 – 7.27 (m, 8H), 6.87 (d, J = 9 Hz, 2H), 6.18 (s, 1H), 6.13 (dd, J = 7, 14 Hz, 1H), 6.05 (d, J = 14 Hz, 1H), 5.96 (d, J = 16 Hz, 1H), 5.33 (d, J = 9 Hz, 1H), 5.20 (dd, J = 8, 16 Hz, 1H), 4.56 (d, J = 11 Hz, 1H), 4.50 (dd, J = 7, 9 Hz, 1H), 4.30 (d, J = 11 Hz, 1H), 4.01 – 3.97 (m, 1H), 3.79 (s, 3H), 3.79 – 3.74 (m, 2H), 3.59–3.50 (m, 3H), 3.27 (s, 3H), 3.25 (s, 3H), 3.20 (s, 3H), 3.29 – 3.17 (m, 1H), 2.94 (d, J = 15 Hz, 1H), 2.74 (ddd, J = 2, 9, 17 Hz, 1H), 2.41 (ddd, J = 2, 5, 17 Hz, 1H), 2.29 – 2.10 (m, 4H), 1.89 – 1.78 (m, 2H), 1.87 (d, J = 1 Hz, 3H), 1.37 –1.19 (m, 2H), 1.17 (d, J = 1 Hz, 3H), 1.04 (s, 9H), 0.97 (d, J = 7 Hz, 3H), 0.80 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 201.3, 159.3, 140.5, 137.9, 137.7, 137.4, 136.3, 136.2, 136.1, 136.0, 136.0, 134.9, 134.3, 133.9, 131.6, 130.4, 129.6, 129.4, 129.4, 127.7, 127.4, 127.2, 119.0, 113.9, 113.9, 106.3, 99.9, 89.2, 82.7, 81.1, 73.5, 73.2, 72.5, 69.8, 56.2, 55.6, 55.3, 48.0, 47.0, 39.2, 35.5, 34.3, 33.1, 32.3, 27.0, 19.4, 14.1, 13.7, 13.0, 6.2; MS (ES) m/z (M$^+$ + H) 1054; HRMS (ES) m/z 1054.4500 (calcd for C$_{58}$H$_{77}$^{81}BrNO$_{10}$Si : 1054.4490, M$^+$ + H).

(2S,6R)-1-((2R,4R,6R)-6-(2-((E)-3-((2R,3S,4S,5R,6R)-6-((E)-1-(2-(((2S,4R,6R)-6-((1R,2E,4E,6R,8E)-9-Bromo-1-(tert-butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4,8-trienyl)-2,4-dimethoxytetrahydro-2H-pyran-2-yl)methyl)oxazol-4-yl)prop-1-enyl)-4-(4-methoxybenzyloxy)-3,5-dimethyltetrahydro-2H-pyran-2-yl)prop-1-enyl)oxazol-4-yl)-4-(tert-butyldiphenylsilanyloxy)tetrahydro-2H-pyran-2-yl)-8-(tert-butyldiphenylsilanyloxy)-4-methylene-6-(triethylsilanyloxy)octan-2-ol (110). To a solution of **108** (55.0 mg, 56 μmol) in dimethylformamide (2 mL) under argon at room temperature was added tri-n-butylphosphine (98 μL, 392 μmol) and the mixture was stirred at room temperature for 3 h. A solution of **109** (21.7 mg, 20.6 μmol) in dimethylformamide (0.5 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3.7 μL, 24.7 μmol) were added and the mixture was stirred at room temperature for 1 h, then was diluted with ethyl acetate (5 mL). Saturated aqueous ammonium chloride (5 mL) was added, the phases were separated and the aqueous phase was extracted with ethyl acetate (5 mL x 3). The combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 15:1 to 4:1) to afford **110** (34.5 mg, 85%) as a colourless oil: $[\alpha]_D^{23}$ +3.8 (c 0.32, CHCl$_3$); IR (neat) 3519, 2929, 2856, 1513, 1457, 1428, 1361, 1247, 1106, 1035, 969, 822,

741, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.73 (dd, J = 1, 8 Hz, 2H), 7.66 – 7.60 (m, 10H), 7.51 (s, 1H), 7.40 – 7.25 (m, 21H), 6.86 (d, J = 9 Hz, 2H), 6.63 (ddd, J = 6, 8, 15 Hz, 1H), 6.34 (d, J = 16 Hz, 1H), 6.21 (s, 1H), 6.14 (dd, J = 7, 14 Hz, 1H), 6.06 (d, J = 14 Hz, 1H), 5.97 (d, J = 16 Hz, 1H), 5.35 (d, J = 9 Hz, 1H), 5.21 (dd, J = 8, 16 Hz, 1H), 5.03 (d, J = 11 Hz, 1H), 4.85 (d, J = 9 Hz, 2H), 4.56 (d, J = 11 Hz, 1H), 4.51 (dd, J = 7, 9 Hz, 1H), 4.45 (m, 1H), 4.31 (s, 1H), 4.27 (d, J = 11 Hz, 1H), 4.10 –3.95 (m, 2H), 3.78 (s, 3H), 3.71 (m, 2H), 3.59 – 3.48 (m, 4H), 3.47 (d, J = 10 Hz, 1H), 3.28 (s, 3H), 3.26 (s, 3H), 3.21 (s, 3H), 3.31 – 3.16 (m, 2H), 2.95 (d, J = 15 Hz, 1H), 2.89 (brs, 1H), 2.56 (m, 1H), 2.38 (m, 1H), 2.31 – 2.12 (m, 9H), 1.91 (d, J = 1 Hz, 3H), 1.90 – 1.20 (m, 11H), 1.18 (d, J = 1 Hz, 3H), 1.08 (s, 9H), 1.05 (s, 9H), 1.02 (s, 9H), 0.98 (d, J = 7 Hz, 3H), 0.88 (t, J = 8 Hz, 9H), 0.82 (d, J = 6 Hz, 3H), 0.54 (q, J = 8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.1, 159.4, 144.0, 143.1, 138.2, 138.1, 137.5, 136.3, 136.2, 135.9, 135.8, 135.8, 135.1, 134.4, 134.3, 134.3, 134.1, 134.1, 134.1, 131.8, 130.8, 130.0, 130.0, 129.8, 129.6, 129.5, 127.9, 127.9, 127.8, 127.6, 127.4, 119.0, 118.9, 115.0, 114.0, 106.5, 100.1, 89.3, 83.4, 81.3, 77.5, 73.7, 73.6, 72.7, 70.3, 70.0, 68.4, 67.8, 66.6, 66.0, 60.9, 56.4, 55.8, 55.5, 48.2, 45.2, 44.2, 42.2, 40.0, 39.4, 38.5, 37.8, 36.6, 35.7, 33.8, 33.5, 32.5, 29.9, 27.3, 27.2, 27.1, 19.6, 19.5, 19.3, 14.4, 14.0, 13.2, 7.1, 5.2; HRMS (MALDI) calcd for C$_{108}$H$_{139}$N$_2$O$_{15}$Si$_3$^{79}BrNa (M – TES + H + Na, ^{79}Br)$^+$ 1889.8617, found 1889.8559.

(2S,6R)-1-((2S,4R,6R)-6-(2-((E)-3-((2R,3S,4S,5R,6R)-6-((E)-1-(2-(((2S,4R,6R)-6-((1R,2E,4E,6R,8E)-9-Bromo-1-(tert-butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4,8-trienyl)-2,4-dimethoxytetrahydro-2H-pyran-2-yl)methyl)oxazol-4-yl)prop-1-en-2-yl)-4-(4-methoxybenzyloxy)-3,5-dimethyltetrahydro-2H-pyran-2-yl)prop-1-enyl)oxazol-4-yl)-4-(tert-butyldiphenylsilanyloxy)tetrahydro-2H-pyran-2-yl)-8-(tert-butyldiphenylsilanyloxy)-4-methylene-6-(triethylsilanyloxy)octan-2-yl methanesulfonate (111). To a solution of **110** (31.1 mg, 15.6 μmol) in dichloromethane (5 mL) at 0 °C were added triethylamine (48 μL, 344 μmol) and methanesulfonyl chloride (8 μL, 103 μmol) and the solution was allowed to warm to room temperature. After 1.5 h, a saturated aqueous solution of sodium bicarbonate (3 mL) was added, the phases were separated and the aqueous phase was extracted with dichloromethane (5 mL x 3). The combined extract was washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 9:1 to 3:1) to give **111** (32.2 mg, 99%) as a colourless oil: $[\alpha]_D^{23}$ +5.0 (c 0.40, CHCl$_3$); IR (neat) 2929, 2856, 1513, 1462, 1427, 1360, 1247, 1173, 1105, 1035, 970, 910, 822, 741, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.73 (dd, J = 1, 8 Hz, 2H), 7.66 – 7.60 (m, 10H), 7.51 (s, 1H), 7.44 (s, 1H), 7.41 – 7.29 (m, 18H), 7.26 (d, J = 9 Hz, 2H), 6.86 (d, J = 9 Hz, 2H), 6.62 (ddd, J = 6, 8, 15 Hz, 1H), 6.33 (d, J = 16 Hz, 1H), 6.21 (s, 1H), 6.14 (dd, J = 7, 14 Hz, 1H), 6.05 (d, J = 14 Hz, 1H), 5.97 (d, J = 16 Hz, 1H), 5.34 (d, J = 9 Hz, 1H), 5.21 (dd, J = 8, 16 Hz, 1H), 5.03 (m, 1H), 4.96 (d, J = 11 Hz, 1H), 4.88 (s, 2H), 4.56 (d, J = 11 Hz, 1H), 4.51 (dd, J = 6, 9 Hz, 1H), 4.25 (m, 3H), 4.01 (m, 1H), 3.78 (s, 3H), 3.68 (m, 2H), 3.58 – 3.44 (m, 5H), 3.28 (s, 3H), 3.25 (s, 3H), 3.20 (s, 3H), 3.31 – 3.15 (m, 2H), 2.99 (s, 3H), 2.94 (d, J = 15 Hz, 1H), 2.60 – 2.10 (m, 10H), 1.90 (d, J = 1 Hz, 3H), 2.00 – 1.20 (m, 12H), 1.18 (d, J = 1 Hz, 3H), 1.08 (s, 9H), 1.04 (s, 9H), 1.01 (s, 9H), 0.98 (d, J = 7 Hz, 3H), 0.87 (t, J = 8 Hz, 9H), 0.82 (d, J = 6 Hz, 3H), 0.51 (q, J = 8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.1, 159.3,

142.9, 141.8, 138.2, 138.1, 137.5, 136.3, 136.2, 135.9, 135.8, 135.8, 135.1, 134.6, 134.4, 134.3, 134.1, 134.1, 134.0, 131.8, 130.8, 130.0, 130.0, 129.8, 129.6, 129.5, 127.9, 127.8, 127.8, 127.6, 127.4, 119.0, 118.9, 116.3, 114.0, 106.5, 100.1, 89.3, 83.4, 81.3, 79.0, 77.4, 73.6, 72.7, 70.0, 68.5, 67.9, 67.7, 65.9, 60.9, 60.6, 56.4, 55.8, 55.5, 48.2, 44.6, 43.2, 40.8, 40.1, 39.4, 38.7, 38.2, 37.8, 36.8, 36.6, 35.7, 33.8, 33.5, 32.5, 31.7, 29.9, 27.3, 27.2, 27.1, 21.2, 19.6, 19.5, 19.3, 14.4, 14.0, 13.2, 7.1, 5.2; MS (ES) m/z 2059 (M$^+$ + H); HRMS (ES) m/z 2058.9288 (calcd for $C_{115}H_{155}N_2O_{17}SSi_4Br$: 2058.9307, M$^+$).

(2S,6R)-1-((2S,4R,6R)-6-(2-((E)-3-((2R,3S,4S,5R,6R)-6-((E)-1-(2-(((2S,4R,6R)-6-((1R,2E,4E,6R,8E)-9-Bromo-1-(tert-butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4,8-trienyl)-2,4-dimethoxytetrahydro-2H-pyran-2-yl)methyl)oxazol-4-yl)prop-1-en-2-yl)-4-(4-methoxybenzyloxy)-3,5-dimethyltetrahydro-2H-pyran-2-yl)prop-1-enyl)oxazol-4-yl)-4-(tert-butyldiphenylsilanyloxy)tetrahydro-2H-pyran-2-yl)-8-(tert-butyldiphenylsilanyloxy)-6-hydroxy-4-methyleneoctan-2-yl methanesulfonate (112). To a solution of **111** (32.0 mg, 15.6 μmol) in methanol (5 mL) was added pyridinium p-toluenesulfonate (2.2 mg, 8.8 μmol) and the solution was stirred at room temperature for 1.5 h. The solution was concentrated under reduced pressure and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 9:1 to 1:1) to give **112** (29.7 mg, 98%) as a colourless oil: $[\alpha]_D^{23}$ +8.3 (c 0.30, CHCl₃); IR (neat) 3504, 2959, 2856, 1513, 1462, 1427, 1360, 1248, 1173, 1105, 1035, 970, 910, 822, 756, 742, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl₃) δ 7.72 (dd, J = 1, 8 Hz, 2H), 7.64 − 7.59 (m, 10H), 7.50 (s, 1H), 7.43 (s, 1H), 7.42 − 7.30 (m, 18H), 7.27 (d, J = 9 Hz, 2H), 6.85 (d, J = 9 Hz, 2H), 6.60 (ddd, J = 6, 8, 15 Hz, 1H), 6.32 (d, J = 16 Hz, 1H), 6.20 (s, 1H), 6.13 (dd, J = 7, 14 Hz, 1H), 6.05 (d, J = 14 Hz, 1H), 5.96 (d, J = 16 Hz, 1H), 5.33 (d, J = 9 Hz, 1H), 5.20 (dd, J = 8, 16 Hz, 1H), 5.07 (m, 1H), 4.93 (m, 3H), 4.55 (d, J = 11 Hz, 1H), 4.50 (dd, J = 6, 9 Hz, 1H), 4.35 − 4.22 (m, 3H), 4.12 − 4.00 (m, 1H), 3.85 − 3.79 (m, 3H), 3.77 (s, 3H), 3.59 − 3.43 (m, 4H), 3.27 (s, 3H), 3.25 (s, 3H), 3.20 (s, 3H), 3.32 − 3.15 (m, 2H), 3.01 (s, 3H), 2.93 (d, J = 15 Hz, 1H), 2.62 − 2.10 (m, 10H), 1.89 (d, J = 1 Hz, 3H), 2.00 − 1.20 (m, 12H), 1.17 (d, J = 1 Hz, 3H), 1.07 (s, 9H), 1.04 (s, 9H), 1.01 (s, 9H), 0.97 (d, J = 7 Hz, 3H), 0.81 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl₃) δ 161.1, 159.3, 142.8, 141.8, 138.2, 138.1, 137.5, 136.3, 136.3, 136.2, 135.9, 135.7, 135.0, 134.5, 134.3, 134.2, 134.0, 134.0, 133.3, 133.2, 131.8, 130.8, 129.8, 129.6, 129.5, 128.0, 128.0, 127.8, 127.6, 127.4, 119.0, 118.8, 116.5, 114.0, 106.5, 100.1, 89.3, 83.4, 81.2, 78.9, 77.4, 73.7, 72.7, 70.0, 69.6, 68.0, 67.6, 65.9, 63.4, 60.6, 56.3, 55.8, 55.5, 48.1, 44.4, 42.8, 40.6, 39.3, 38.7, 38.5, 38.2, 37.8, 36.8, 36.6, 35.7, 33.8, 33.5, 32.4, 31.7, 29.9, 27.2, 27.1, 27.0, 21.2, 19.6, 19.5, 19.2, 14.4, 14.0, 13.2, 5.9; HRMS (ES) m/z 1945.8572 (calcd for $C_{109}H_{142}N_2O_{17}SSi_3Br$: 1945.8520, M + H).

2-(((2S,4R,6R)-6-((1R,2E,4E,6R,8E)-9-Bromo-1-(tert-butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4,8-trienyl)-2,4-dimethoxytetrahydro-2H-pyran-2-yl)methyl)-4-((E)-2-((2R,3R,4S,5S,6R)-6-((E)-3-(4-((2R,4R,6R)-4-(tert-butyldiphenylsilanyloxy)-6-(((2R,6R)-6-(2-(tert-butyldiphenylsilanyloxy)ethyl)-4-methylenetetrahydro-2H-pyran-2-yl)methyl)tetrahydro-2H-pyran-2-yl)oxazol-2-yl)allyl)-4-(4-methoxybenzyloxy)-3,5-dimethyltetrahydro-2H-pyran-2-yl)prop-1-enyl)oxazole (113). To a solution of **112** (29.7 mg, 15.3 μmol) in acetonitrile (7 mL) was added triethylamine (0.85 mL, 6.1 mmol) and the solution was heated at reflux for 24 h. The solution was concentrated under reduced

pressure and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 10:1 to 5:1) to give **113** (24.2 mg, 86%) as a colourless oil: $[\alpha]_D^{23}$ -3.4 (c 0.41, CHCl₃); IR (neat) 2930, 2856, 1513, 1471, 1427, 1360, 1248, 1106, 1035, 969, 822, 741, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl₃) δ 7.73 (dd, J = 1, 8 Hz, 2H), 7.66 − 7.60 (m, 10H), 7.51 (s, 1H), 7.42 − 7.31 (m, 19H), 7.26 (d, J = 9 Hz, 2H), 6.86 (d, J = 9 Hz, 2H), 6.61 (ddd, J = 6, 8, 16 Hz, 1H), 6.34 (d, J = 16 Hz, 1H), 6.21 (s, 1H), 6.14 (dd, J = 7, 14 Hz, 1H), 6.06 (d, J = 14 Hz, 1H), 5.97 (d, J = 16 Hz, 1H), 5.34 (d, J = 9 Hz, 1H), 5.21 (dd, J = 8, 16 Hz, 1H), 4.99 (d, J = 12 Hz, 1H), 4.70 (d, J = 3 Hz, 2H), 4.56 (d, J = 11 Hz, 1H), 4.51 (dd, J = 6, 9 Hz, 1H), 4.25 (m, 2H), 4.14 (m, 1H), 3.96 (m, 2H), 3.78 (s, 3H), 3.75 − 3.50 (m, 5H), 3.46 (d, J = 10 Hz, 1H), 3.28 (s, 3H), 3.26 (s, 3H), 3.21 (s, 3H), 3.29 (m, 2H), 3.16 (m, 1H), 2.94 (d, J = 15 Hz, 1H), 2.56 (m, 1H), 2.40 − 2.10 (m, 8H), 1.88 (d, J = 1 Hz, 3H), 2.00 − 1.20 (m, 13H), 1.18 (d, J = 1 Hz, 3H), 1.08 (s, 9H), 1.05 (s, 9H), 1.01 (s, 9H), 0.98 (d, J = 7 Hz, 3H), 0.83 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl₃) δ 160.9, 159.2, 143.1, 142.4, 138.0, 137.9, 137.4, 136.1, 136.0, 135.8, 135.7, 135.6, 135.6, 134.9, 134.2, 134.2, 134.1, 134.0, 134.0, 133.9, 131.6, 130.6, 129.8, 129.7, 129.6, 129.4, 129.4, 127.6, 127.6, 127.4, 127.2, 118.8, 118.8, 113.8, 110.1, 106.3, 99.9, 89.1, 83.3, 81.1, 73.5, 73.4, 72.5, 69.8, 69.3, 69.1, 68.9, 67.6, 65.9, 60.7, 56.2, 55.6, 55.3, 48.0, 39.7, 39.2, 38.5, 37.8, 36.7, 36.4, 35.5, 33.6, 33.3, 32.3, 32.0, 30.1, 29.7, 29.4, 27.1, 27.0, 26.9, 22.7, 19.4, 19.3, 19.2, 14.2, 14.2, 13.8, 13.0, 5.8; HRMS (ES) m/z 1849.8639 (calcd for $C_{108}H_{138}N_2O_{14}Si_3Br$: 1849.8582, M + H).

(2R,3R,4S,5R,6R)-2-((E)-1-(2-(((2S,4R,6R)-6-((1R,2E,4E,6R,8E)-9-Bromo-1-(tert-butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4,8-trienyl)-2,4-dimethoxytetrahydro-2H-pyran-2-yl)methyl)oxazol-4-yl)prop-1-en-2-yl)-6-((E)-3-(4-((2R,4R,6R)-4-(tert-butyldiphenylsilanyloxy)-6-(((2R,6R)-6-(2-(tert-butyldiphenylsilanyloxy)ethyl)-4-methylenetetrahydro-2H-pyran-2-yl)methyl)tetrahydro-2H-pyran-2-yl)oxazol-2-yl)allyl)-3,5-dimethyltetrahydro-2H-pyran-4-ol (114). 2,3-Dichloro-5,6-dicyanobenzoquinone (15.0 mg, 66 μmol) was added to a solution of **113** (24.7 mg, 13.3 μmol) in dichloromethane (5 mL) containing pH 7 buffer (0.5 mL) at room temperature and the mixture was stirred vigorously for 2 h. The reaction was quenched with saturated aqueous sodium bicarbonate (3 mL) and the mixture was diluted with dichloromethane and poured into a saturated aqueous sodium bicarbonate–brine solution (6 mL). The aqueous phase was separated and was extracted with dichloromethane (10 mL x 3), and the combined extract was dried (MgSO₄) and concentrated under reduced pressure. The residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 5:1 to 1:1) to give **114** (19.5 mg, 84%) as a colourless oil: $[\alpha]_D^{23}$ -6.4 (c 0.32, CHCl₃); IR (neat) 3444, 2930, 2856, 1472, 1428, 1257, 1106, 1052, 822, 741, 702 cm^{-1}; ^{1}H NMR (400 MHz, CDCl₃) δ 7.73 (dd, J = 1, 8 Hz, 2H), 7.66 − 7.59 (m, 10H), 7.51 (s, 1H), 7.42 − 7.26 (m, 19H), 6.59 (ddd, J = 6, 8, 16 Hz, 1H), 6.32 (d, J = 16 Hz, 1H), 6.21 (s, 1H), 6.13 (dd, J = 7, 14 Hz, 1H), 6.05 (d, J = 14 Hz, 1H), 5.97 (d, J = 16 Hz, 1H), 5.34 (d, J = 9 Hz, 1H), 5.21 (dd, J = 8, 16 Hz, 1H), 4.97 (d, J = 13 Hz, 1H), 4.70 (s, 2H), 4.51 (dd, J = 7, 9 Hz, 1H), 4.25 (s, 1H), 4.15 (m, 1H), 3.95 (m, 2H), 3.71 − 3.43 (m, 8H), 3.32 − 3.18 (m, 2H), 3.28 (s, 3H), 3.26 (s, 3H), 3.21 (s, 3H), 2.94 (d, J = 15 Hz, 1H), 2.55 (m, 1H), 2.40 − 2.15 (m, 7H), 1.82 (d, J = 1 Hz, 3H), 2.02 − 1.20 (m, 14H), 1.18 (d, J = 1 Hz, 3H), 1.07 (s, 9H), 1.04 (s, 9H), 1.01 (s, 9H), 0.97 (d, J = 7 Hz, 3H), 0.84 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl₃) δ

160.8, 159.2, 143.1, 142.4, 137.9, 137.8, 137.3, 136.1, 136.0, 135.8, 135.7, 135.6, 135.6, 134.9, 134.2, 134.1, 134.0, 134.0, 133.9, 133.9, 131.6, 129.7, 129.7, 129.5, 129.4, 127.6, 127.6, 127.4, 127.2, 118.7, 110.1, 106.3, 99.9, 88.8, 81.1, 77.2, 73.5, 72.5, 69.3, 69.1, 68.8, 67.6, 65.9, 60.7, 56.2, 55.6, 48.0, 39.7, 39.2, 39.2, 38.5, 37.9, 36.6, 36.1, 35.5, 34.6, 32.3, 29.7, 29.3, 27.1, 27.0, 26.9, 19.4, 19.3, 19.2, 14.3, 13.4, 13.0, 5.5; HRMS (MALDI) calcd for $C_{100}H_{129}N_2O_{13}Si_3{}^{79}BrNa$ (M + Na, $^{79}Br)^+$ 1751.7907, found 1751.7878.

(2*R*,3*R*,4*S*,5*S*,6*R*)-2-((*E*)-1-(2-(((2*S*,4*R*,6*R*)-6-((1*R*,2*E*,4*E*,6*R*,8*E*)-9-Bromo-1-(*tert*-butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4,8-trienyl)-2,4-dimethoxytetrahydro-2*H*-pyran-2-yl)methyl)oxazol-4-yl)prop-1-en-2-yl)-6-((*E*)-3-(4-((2*R*,4*R*,6*R*)-4-(*tert*-butyldiphenylsilanyloxy)-6-(((2*R*,6*R*)-6-(2-(*tert*-butyldiphenylsilanyloxy)ethyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)methyl)tetrahydro-2*H*-pyran-2-yl)oxazol-2-yl)allyl)-3,5-dimethyltetrahydro-2*H*-pyran-4-yl 2-(dimethoxyphosphoryl)acetate (116). To a solution of 114 (19.5 mg, 11.3 μmol) and dimethylphosphonoacetic acid (115, 6.8 mg, 40 μmol) in dichloromethane (4.5 mL) was added dicyclohexylcarbodiimide (6.5 mg, 32 μmol) and the mixture was stirred at room temperature for 20 h. The mixture was concentrated under reduced pressure and the crude residue was purified by flash chromatography on silica gel (hexane:ethyl acetate 2:1 to 1:1 to ethyl acetate only) to yield 116 (21.2 mg, 91%): $[\alpha]_D^{23}$ -9.7 (c 0.30, CHCl₃); IR (neat) 2922, 2856, 1734, 1463, 1428, 1361, 1264, 1105, 1035, 886, 822, 805, 755, 742, 703 cm^{-1}; ^{1}H NMR (400 MHz, CDCl₃) δ 7.73 (dd, J = 1, 8 Hz, 2H), 7.66 – 7.60 (m, 10H), 7.52 (s, 1H), 7.42 – 7.27 (m, 19H), 6.56 (ddd, J = 6, 8, 16 Hz, 1H), 6.30 (d, J = 16 Hz, 1H), 6.22 (s, 1H), 6.13 (dd, J = 7, 14 Hz, 1H), 6.05 (d, J = 14 Hz, 1H), 5.97 (d, J = 16 Hz, 1H), 5.34 (d, J = 9 Hz, 1H), 5.21 (dd, J = 8, 16 Hz, 1H), 4.96 (d, J = 11 Hz, 1H), 4.75 (dd, J = 5, 11 Hz, 1H), 4.70 (d, J = 3 Hz, 2H), 4.51 (dd, J = 7, 9 Hz, 1H), 4.25 (s, 1H), 4.17 – 4.11 (m, 1H), 3.96 (m, 2H), 3.80 (d, J = 2 Hz, 3H), 3.77 (d, J = 2 Hz, 3H), 3.73 – 3.42 (m, 8H), 3.28 (s, 3H), 3.25 (s, 3H), 3.21 (s, 3H), 2.99 (d, J = 22 Hz, 2H), 2.94 (d, J = 16 Hz, 1H), 2.55 (m, 1H), 2.35 – 2.16 (m, 7H), 1.93 (d, J = 1 Hz, 3H), 2.11 – 1.20 (m, 14H), 1.18 (d, J = 1 Hz, 3H), 1.07 (s, 9H), 1.04 (s, 9H), 1.00 (s, 9H), 0.99 (d, J = 7 Hz, 3H), 0.76 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl₃) δ 165.3, 165.2, 160.9, 159.4, 143.3, 142.6, 138.0, 137.5, 137.3, 136.5, 136.3, 136.2, 136.0, 135.9, 135.7, 135.7, 135.2, 135.0, 134.4, 134.3, 134.3, 134.1, 134.1, 134.0, 134.0, 131.8, 129.9, 129.9, 129.7, 129.6, 127.8, 127.8, 127.6, 127.4, 119.3, 119.1, 110.3, 106.4, 100.1, 88.9, 81.2, 80.4, 73.7, 73.7, 72.6, 69.5, 69.2, 69.0, 67.8, 66.0, 64.5, 60.8, 56.3, 55.8, 53.3, 53.3, 48.1, 39.8, 39.3, 39.3, 38.6, 38.0, 36.8, 36.2, 35.7, 35.5, 34.3, 34.1, 33.0, 32.4, 32.3, 27.2, 27.1, 27.0, 19.6, 19.5, 19.4, 14.4, 13.4, 13.2, 6.3; HRMS (MALDI) calcd for $C_{104}H_{136}N_2O_{17}PSi_3{}^{79}BrNa$ (M + Na, $^{79}Br)^+$ 1901.7976, found 1901.7960.

(2*R*,3*R*,4*S*,5*S*,6*R*)-2-((*E*)-1-(2-(((2*S*,4*R*,6*R*)-6-((1*R*,2*E*,4*E*,6*R*,8*E*)-9-Bromo-1-(*tert*-butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4,8-trienyl)-2,4-dimethoxytetrahydro-2*H*-pyran-2-yl)methyl)oxazol-4-yl)prop-1-en-2-yl)-6-((*E*)-3-(4-((2*R*,4*R*,6*R*)-4-(*tert*-butyldiphenylsilanyloxy)-6-(((2*R*,6*R*)-6-(2-hydroxyethyl)-4-methylenetetrahydro-2*H*-pyran-2-yl)methyl)tetrahydro-2*H*-pyran-2-yl)oxazol-2-yl)allyl)-3,5-dimethyltetrahydro-2*H*-pyran-4-yl 2-(dimethoxyphosphoryl)acetate (117). Ammonium fluoride (127 mg, 3.43 mmol) was added to a

solution of 116 (18.9 mg, 10.0 μmol) in methanol (3 mL) and the solution was stirred at 50 °C for 5 h. The reaction was quenched with saturated ammonium chloride solution and the mixture was extracted with ethyl acetate (20 mL x 3). The extract was washed with brine, dried (Na₂SO₄), and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 1:2 to ethyl acetate only) to give 117 (12.2 mg, 73%) as a colourless oil: $[\alpha]_D^{23}$ -11.9 (c 0.57, CHCl₃); IR (neat) 3456, 2927, 2855, 1734, 1463, 1428, 1362, 1270, 1105, 1035, 883, 805, 755, 703 cm^{-1}; ^{1}H NMR (400 MHz, CDCl₃) δ 7.72 (dd, J = 1, 8 Hz, 2H), 7.66 – 7.60 (m, 7H), 7.52 (s, 1H), 7.43 – 7.26 (m, 12H), 6.57 (ddd, J = 6, 8, 16 Hz, 1H), 6.30 (d, J = 16 Hz, 1H), 6.22 (s, 1H), 6.13 (dd, J = 7, 14 Hz, 1H), 6.05 (d, J = 14 Hz, 1H), 5.96 (d, J = 16 Hz, 1H), 5.34 (d, J = 9 Hz, 1H), 5.21 (dd, J = 8, 16 Hz, 1H), 4.97 (d, J = 11 Hz, 1H), 4.77 – 4.69 (m, 3H), 4.51 (dd, J = 7, 9 Hz, 1H), 4.29 (s, 1H), 4.14 (m, 1H), 3.94 (m, 1H), 3.80 (d, J = 2 Hz, 3H), 3.77 (d, J = 2 Hz, 3H), 3.67 – 3.51 (m, 7H), 3.33 – 3.18 (m, 2H), 3.28 (s, 3H), 3.25 (s, 3H), 3.21 (s, 3H), 2.99 (d, J = 22 Hz, 2H), 2.94 (d, J = 16 Hz, 1H), 2.82 (brs, 1H), 2.53 (m, 1H), 2.38 – 2.16 (m, 7H), 1.93 (d, J = 1 Hz, 3H), 2.13 – 1.30 (m, 14H), 1.18 (d, J = 1 Hz, 3H), 1.08 (s, 9H), 1.04 (s, 9H), 0.98 (d, J = 7 Hz, 3H), 0.76 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl₃) δ 165.1, 161.0, 159.3, 142.6, 141.9, 137.8, 137.3, 137.2, 136.3, 136.1, 136.0, 135.8, 135.8, 135.4, 134.9, 134.4, 134.2, 133.9, 133.9, 131.6, 129.8, 129.8, 129.6, 129.4, 127.7, 127.7, 127.4, 127.2, 119.1, 118.7, 110.4, 106.3, 99.9, 88.7, 81.1, 80.2, 77.0, 73.5, 73.5, 72.5, 70.5, 70.0, 69.8, 67.3, 65.9, 60.2, 56.2, 55.6, 53.2, 53.1, 48.0, 40.0, 39.2, 39.2, 38.7, 37.5, 36.2, 36.0, 35.5, 35.4, 34.2, 32.9, 32.2, 32.2, 27.1, 27.0, 19.4, 19.4, 14.3, 13.2, 13.0, 6.1; HRMS (MALDI) calcd for $C_{88}H_{118}N_2O_{17}PSi_2{}^{79}BrNa$ (M + Na, $^{79}Br)^+$ 1663.6769, found 1663.6782.

(2*R*,3*R*,4*S*,5*S*,6*R*)-2-((*E*)-1-(2-(((2*S*,4*R*,6*R*)-6-((1*R*,2*E*,4*E*,6*R*,8*E*)-9-Bromo-1-(*tert*-butyldiphenylsilanyloxy)-6-methoxy-3-methylnona-2,4,8-trienyl)-2,4-dimethoxytetrahydro-2*H*-pyran-2-yl)methyl)oxazol-4-yl)prop-1-en-2-yl)-6-((*E*)-3-(4-((2*R*,4*R*,6*R*)-4-(*tert*-butyldiphenylsilanyloxy)-6-(((2*R*,6*R*)-4-methylene-6-(2-oxoethyl)tetrahydro-2*H*-pyran-2-yl)methyl)tetrahydro-2*H*-pyran-2-yl)oxazol-2-yl)allyl)-3,5-dimethyltetrahydro-2*H*-pyran-4-yl 2-(dimethoxyphosphoryl)acetate (118). To a solution of 117 (12.2 mg, 7.4 μmol) in dichloromethane (4 mL) at 0 °C was added Dess-Martin periodinane (12.3 mg, 29 μmol) and the solution was allowed to warm to room temperature and was stirred for 1 h. The mixture was poured into an ice-cold solution of saturated sodium bicarbonate (1 mL) containing sodium thiosulfate (0.5 g) and was extracted with ethyl acetate (2 mL x 3). The combined extract was washed with brine (5 mL), dried (Na₂SO₄) and concentrated under reduced pressure, and the residual oil was purified by flash chromatography on silica gel (hexane:ethyl acetate 1:2) to give 118 (11.6 mg, 95%) as a colourless oil: $[\alpha]_D^{23}$ -12.1 (c 0.43, CHCl₃); IR (neat) 2955, 2929, 2856, 1732, 1463, 1428, 1266, 1104, 1035, 755, 703 cm^{-1}; ^{1}H NMR (400 MHz, CDCl₃) δ 9.68 (t, J = 2 Hz, 1H), 7.72 (dd, J = 1, 8 Hz, 2H), 7.65 – 7.59 (m, 7H), 7.52 (s, 1H), 7.42 – 7.26 (m, 12H), 6.57 (ddd, J = 6, 8, 16 Hz, 1H), 6.30 (d, J = 16 Hz, 1H), 6.22 (s, 1H), 6.13 (dd, J = 7, 14 Hz, 1H), 6.05 (d, J = 14 Hz, 1H), 5.96 (d, J = 16 Hz, 1H), 5.34 (d, J = 9 Hz, 1H), 5.20 (dd, J = 8, 16 Hz, 1H), 4.98 (d, J = 11 Hz, 1H), 4.77 – 4.73 (m, 3H), 4.50 (dd, J = 6, 9 Hz, 1H), 4.32 – 4.26 (bs, 2H), 4.15 (m, 1H), 3.97 (m, 1H), 3.80 (d, J = 2 Hz, 3H), 3.77 (d, J = 2 Hz, 3H), 3.63 – 3.49 (m, 5H), 3.28 (m, 1H), 3.27 (s, 3H), 3.25 (s, 3H), 3.20 (s, 3H),

2.99 (d, $J = 22$ Hz, 2H), 2.94 (d, $J = 16$ Hz, 1H), 2.58 – 2. 16 (m, 10H), 1.93 (d, $J = 1$ Hz, 3H), 2.14 – 1.20 (m, 12H), 1.18 (d, $J = 1$ Hz, 3H), 1.07 (s, 9H), 1.04 (s, 9H), 0.98 (d, $J = 7$ Hz, 3H), 0.76 (d, $J = 6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 200.9, 165.0, 160.8, 159.2, 142.8, 141.4, 140.9, 137.8, 137.3, 137.1, 136.3, 136.0, 136.0, 135.7, 135.7, 135.2, 134.8, 134.3, 134.1, 133.8, 133.8, 131.6, 129.7, 129.7, 129.5, 129.4, 127.6, 127.6, 127.4, 127.2, 119.1, 118.8, 111.2, 106.2, 99.8, 88.7, 81.0, 80.2, 77.0, 73.5, 72.4, 69.7, 69.3, 67.4, 67.0, 65.8, 60.4, 56.1, 55.6, 53.1, 53.1, 47.9, 39.7, 39.1, 39.1, 38.9, 38.7, 38.3, 37.7, 36.0, 35.5, 35.3, 34.2, 32.8, 32.2, 32.2, 27.0, 26.9, 19.3, 19.3, 14.2, 14.2, 13.2, 13.0, 6.1; HRMS (MALDI) calcd for C$_{88}$H$_{116}$N$_2$O$_{17}$PSi$_2$^{79}BrNa (M + Na, ^{79}Br)$^+$ 1661.6620, found 1661.6626.

13,38-Bis(*O-tert*-butyldiphenylsilanyl)-33-(*O*-methyl)phorboxazole A (119). A suspension of potassium carbonate (11.7 mg, 0.085 mmol) and 18-crown-6 (104 mg, 0.393 mmol) in toluene (6 mL) was stirred at room temperature for 3 h, then was cooled to –78 °C and a solution of **118** (11.6 mg, 7.07 μmol) in toluene (3 mL) was added via syringe. The mixture was slowly warmed to room temperature and was stirred for 62 h. The mixture was washed with brine (5 mL x 2), the brine washes were extracted with ethyl acetate (2 mL x 3) and the combined extract was dried (MgSO4), filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane:ethyl acetate 3:1) to give **119** (8.7 mg, 81%) as a 3.5:1 (*Z:E*) mixture of C2 olefin isomers: ^{1}H NMR (400 MHz, CDCl$_3$, major isomer) δ 7.74 – 7.71 (m, 2H), 7.67 – 7.60 (m, 7H), 7.52 (s, 1H), 7.44 – 7.27 (m, 12H), 6.70 (ddd, $J = 6, 8, 16$ Hz, 1H), 6.28 (d, $J = 16$ Hz, 1H), 6.25 (s, 1H), 6.13 (dd, $J = 7, 14$ Hz, 1H), 6.05 (d, $J = 14$ Hz, 1H), 5.96 (d, $J = 16$ Hz, 1H), 5.90 (bs, 1H), 5.34 (d, $J = 9$ Hz, 1H), 5.21 (dd, $J = 8, 16$ Hz, 1H), 5.01 (brs, 1H), 4.89 (d, $J = 12$ Hz, 1H), 4.82 – 4.75 (m, 1H), 4.63 (s, 1H), 4.53 – 4.48 (m, 2H), 4.31 (s, 1H), 4.21 – 4.07 (m, 3H), 4.00 – 3.95 (m, 1H), 3.60 – 3.52 (m, 5H), 3.28 (s, 3H), 3.26 (s, 3H), 3.21 (s, 3H), 2.95 (d, $J = 15$ Hz, 1H), 2.75 (d, $J = 12$ Hz, 1H), 2.58 – 2.49 (m, 1H), 2.48 – 1.04 (m, 20H), 1.93 (d, $J = 1$ Hz, 3H), 1.18 (d, $J = 1$ Hz, 3H), 1.06 (s, 9H), 1.04 (s, 9H) 0.96 (d, $J = 7$ Hz, 3H), 0.76 (d, $J = 6$ Hz, 3H); HRMS (MALDI) calcd for C$_{86}$H$_{109}$N$_2$O$_{13}$Si$_2$^{79}BrNa (M + Na, ^{79}Br)$^+$ 1535.6549, found 1535.6544.

33-*O*-Methylphorboxazole A (120). To a solution of **119** (5.6 mg, 3.7 μmol) in tetrahydrofuran (0.6 mL) at 0 °C was added tetra-*n*-butylammonium fluoride (1M solution in tetrahydrofuran, 74 μL, 74 μmol) and the solution was stirred at room temperature for 20 h. The mixture was filtered through a short pad of silica gel, using ethyl acetate-methanol (15:1) as eluent, and the filtrate was concentrated under vacuum. The crude residue was purified by flash chromatography on silica gel (hexane:ethyl acetate 1:1 to 1:3 to ethyl acetate only) to afford pure **120** (1.9 mg, 50%): ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55 (s, 1H), 7.40 (s, 1H), 6.67 (ddd, $J = 6, 10, 16$ Hz, 1H), 6.30 – 6.13 (m, 4H), 6.07 (d, $J = 14$ Hz, 1H), 5.91 (m, 2H), 5.49 (m, 2H), 4.97 (s, 1H), 4.73 (dd, $J = 4, 10$ Hz, 1H), 4.60 (s, 1H), 4.50 (dd, $J = 4, 11$ Hz, 1H), 4.38 (m, 2H), 4.17 – 3.94 (m, 3H), 3.65 – 3.41 (m, 8H), 3.32 (s, 3H), 3.29 (s, 3H), 3.26 (m, 3H), 3.23 (s, 3H), 3.09 (d, $J = 15$ Hz, 1H), 2.69 (d, $J = 12$ Hz, 1H), 2.46 – 0.80 (m, 20H), 1.83 (d, $J = 1$ Hz, 3H), 1.17 (d, $J = 1$ Hz, 3H), 0.95 (d, $J = 7$ Hz, 3H), 0.76 (d, $J = 6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 165.6, 161.4, 159.0, 144.4, 142.1, 141.7, 137.9, 137.4, 137.3, 137.2, 136.3, 134.2, 133.8, 130.0, 129.0, 121.0, 119.3, 110.2, 106.4, 100.1, 89.2, 81.1, 79.4, 78.0, 73.5, 73.1, 72.9, 71.1, 69.1, 68.6, 66.9, 64.5, 56.3, 55.7, 52.9, 48.2, 41.3, 39.2, 39.2, 39.0, 39.0, 37.0, 35.6, 35.0, 34.4, 32.9,

32.6, 31.8, 30.5, 21.2, 14.3, 13.5, 13.3; HRMS (MALDI) calcd for C$_{54}$H$_{73}$N$_2$O$_{13}$^{79}BrK (M + K, ^{79}Br)$^+$ 1075.3903, found 1075.3928.

Phorboxazole A (1). To a solution of **120** (1.9 mg, 1.8 μmol) in tetrahydrofuran (1 mL) at 0 °C was added dropwise hydrochloric acid (6%, 0.4 mL), and after 10 min the mixture was warmed to room temperature and was stirred for 4 d. The mixture was cooled to 0°C, treated dropwise with saturated sodium bicarbonate solution (1 mL) and was extracted with ether (1 mL x 3). The combined extract was dried (Na2SO4), filtered and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane:ethyl acetate 1:3 to ethyl acetate only, then methanol:dichlorormethane 1:19) to give **1** (0.7 mg, 37%) as an off-white solid: [α]$_D^{23}$ +43.7 (c 0.12 MeOH), lit^1 [α]$_D$ +44.8 (c 1.0 MeOH); ^{1}H NMR (400 MHz, CDCl3) δ 7.55 (s, 1H), 7.40 (s, 1H), 6.67 (ddd, $J = 6, 10, 16$ Hz, 1H), 6.29 – 6.14 (m, 4H), 6.08 (d, $J = 14$ Hz, 1H), 5.91 (m, 2H), 5.47 (dd, $J = 8, 16$ Hz, 1H), 5.34 (d, $J = 9$ Hz, 1H), 5.27 (d, $J = 2$ Hz, 1H), 4.97 (s, 1H), 4.72 (dd, $J = 4, 10$ Hz, 1H), 4.60 (s, 1H), 4.50 (dd, $J = 4, 11$ Hz, 1H), 4.38 (s, 1H), 4.30 (t, $J = 8$ Hz, 1H), 4.17 – 3.95 (m, 3H), 3.81 – 3.70 (m, 2H), 3.65 – 3.42 (m, 4H), 3.34 (s, 3H), 3.22 (s, 3H), 3.14 (d, $J = 16$ Hz, 1H), 3.06 (d, $J = 16$ Hz, 1H), 2.69 (d, $J = 12$ Hz, 1H), 2.55 – 2.20 (m, 9H), 2.08 – 1.78 (m, 8H), 1.96 (d, $J = 1$ Hz, 3H), 1.79 (d, $J = 1$ Hz, 3H), 1.74 – 1.57 (m, 2H), 1.47 – 1.11 (m, 3H), 0.95 (d, $J = 7$ Hz, 3H), 0.75 (d, $J = 6$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl3) δ 165.7, 161.4, 160.1, 144.5, 142.0, 141.7, 138.0, 137.7, 137.5, 137.4, 136.0, 134.2, 133.8, 133.8, 129.7, 128.8, 121.0, 119.3, 118.5, 110.2, 106.4, 96.7, 89.2, 81.1, 79.3, 78.0, 73.5, 73.0, 72.5, 71.0, 69.1, 68.6, 66.9, 64.4, 56.3, 55.8, 41.3, 40.5, 39.7, 39.3, 39.0, 39., 94220, 37.0, 35.0, 34.4, 33.1, 32.6, 31.7, 30.5, 14.2, 13.5, 13.4, 6.0; HRMS (MALDI) calcd for C$_{53}$H$_{71}$N$_2$O$_{13}$^{79}BrNa (M + Na, ^{79}Br)$^+$ 1045.3984, found 1045.4032.

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Notes and references

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