A Synthesis of (+)-Herboxidiene A

Nicholas D. Smith[a], Philip J. Kocienski*[a], and Stephen D. A. Street[b]

[a]Department of Chemistry, The University, Southampton, SO17 1BJ, UK

[b]Pfizer Central Research, Sandwich, Kent, CT13 9NJ, UK.

Fax +44 (01703) 678825; E-mail pjk1@soton.ac.uk

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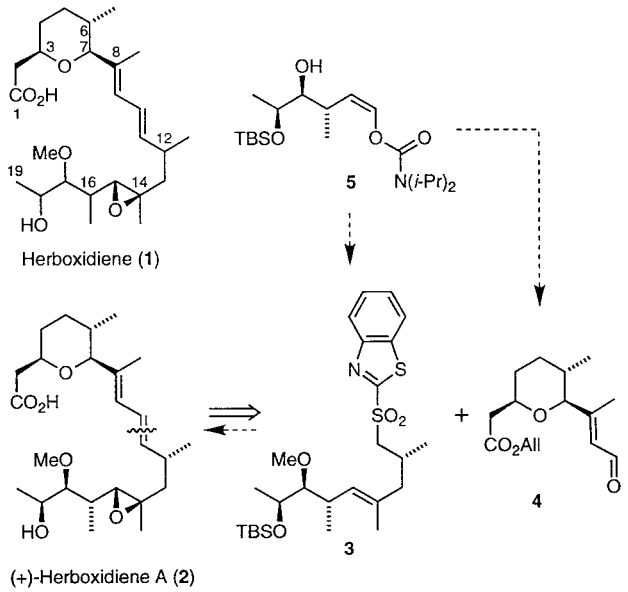
Dedicated to Professor Sylvestre Julia on the occasion of his retirement

Key steps in a stereoselective synthesis of Herboxidiene A, a diastereoisomer of the natural herbicide Herboxidiene, include a Hoppe homoaldol reaction, a copper(I)-mediated 1,2-metallate rearrangement, and a one-pot synthesis of a diene fragment from condensation of a lithiated benzothiazolyl sulfone and an aldehyde.

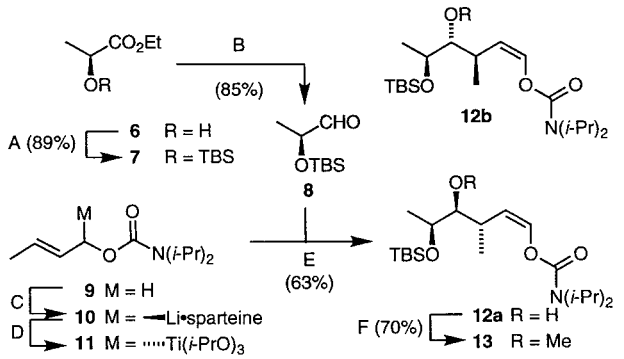
In 1992 a Monsanto group[1] isolated Herboxidiene from the fermentation broth of *Streptomyces* sp. A7847. At 7 g/acre, Herboxidiene inhibited the growth of broadleaf annual weeds such as oilseed rape, wild buckwheat, morning glory, and hemp sesbania but phytotoxicity towards wheat was not detected. Extensive spectroscopic and degradation experiments established the gross structure of Herboxidiene as **1**, and although the relative stereochemistry of the 5 stereogenic centres contained in the oxirane and oxane rings was ascertained by NMR spectroscopy, the relative stereochemistry at C12, C16, C17 and C18 eluded assignment by the Monsanto group. Despite the sparse stereochemical evidence for the natural product we launched a synthetic effort to establish structure-activity relationships between the natural product and its diastereoisomers (Note 1). We now report a synthesis of (+)-Herboxidiene A (**2**), a notional target chosen as a vehicle to explore new fragment linkage reactions. A notable economy in our approach, outlined in Scheme 1, derives from the versatility of enol carbamate **5**:



Scheme 1

it served as the starting material in the construction of both the C11–C19 fragment **3** and the C1–C10 fragment **4** thereby accounting for 5 of the 9 stereogenic centres found in the target. As an added bonus, the enol carbamate moiety of **5** played a crucial role in the chain extension reactions required to fashion fragments **3** and **4**.

Synthesis of enol carbamate fragment **5** (Scheme 2). Hoppe and co-workers[2-4] showed that metallation of crotyl carbamate **9** with BuLi in the presence of (–)-sparteine results in precipitation of a single diastereomeric complex **10** having the (*S*)-configuration (Notes 2 and 3). Transmetallation with Ti(*i*-PrO)$_4$ (inversion of configuration)[5] led to formation of an orange-coloured solution containing the configurationally stable complex **11** to which was added aldehyde **8**.[6] The resultant diastereoselective homoaldol reaction occurred with high facial discrimination to give a mixture of two separable diastereoisomeric *anti*-adducts **12a,b** in 72% yield (d.r. = 7:1) along with recovered aldehyde (8%) (Notes 4 and 5). On a 20-30 mmol scale, the diastereoselectivity depended on the rate of addition of the Ti(*i*-PrO)$_4$. Rapid addition recommended in the published procedure[5] resulted in a d.r. of only 4:1 owing to the increase in temperature which results when the large volume of Ti(*i*-PrO)$_4$ [cooled to –35°C (Note 6)] is added *rapidly* to the reaction mixture at –80°C. The increase in temperature and its less efficient dissipation allows racemisation of **10** with attendant loss of diastereoselectivity. The sequence ended with *O*-



Scheme 2. *Reagents and Conditions:*

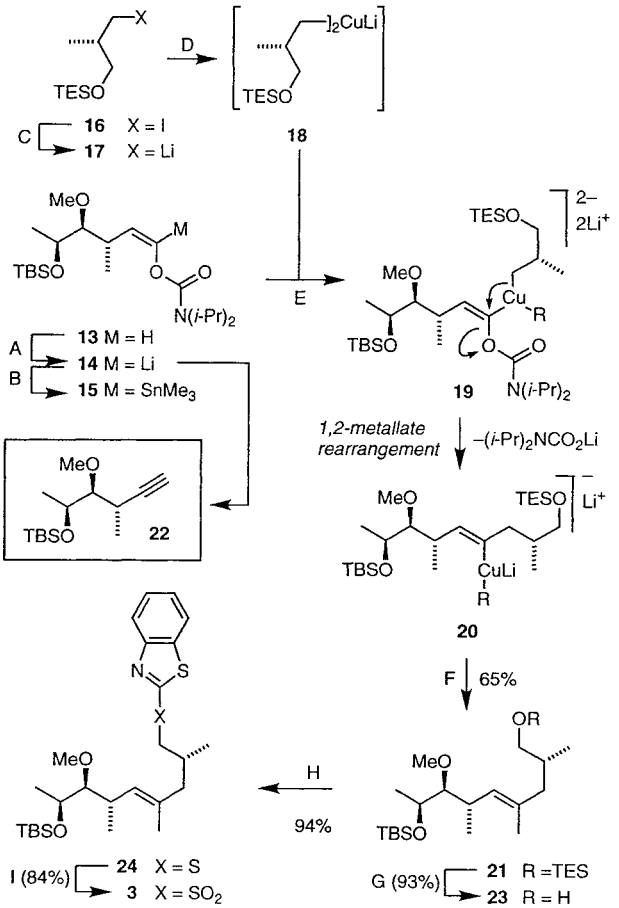
A	89%	TBSCl, DMAP, imidazole / CH_2Cl_2, r.t., 2 h
B	85%	DIBALH / PhMe-CH_2Cl_2, –80°C, 35 min
C	—	BuLi, (–)-sparteine / cyclohexane-pentane, –80°C, 3 h
D	—	Ti(*i*-PrO)$_4$ / pentane, –80°C, 20 min
E	63%	aldehyde **8**, –80°C (1.5 h)→ r.t (1 h)
F	70%	4-Me-2,6-di-*t*-Bupyr, MeOTf / PhMe, 70°C, 10 h

6 steps: 33.4% overall yield

methylation of **12a** with MeOTf and the hindered base 2,6-di-*tert*-butyl-4-methylpyridine to give methyl ether **13** in 70% yield.

Synthesis of C11–C19 fragment 3 (Scheme 3). The prime strategic goal in our synthesis of fragment **3** from enol carbamate **5** was the use of a 1,2-metallate rearrangement to transform the (*Z*)-enol carbamate moiety into a trisubstituted alkene stereoselectively.[7,8] Metallation of **13** with *t*-BuLi at –80°C efficiently and rapidly furnished the lithiated enol carbamate **14** whose instability (*vide infra*) was circumvented by conversion to the corresponding alkenylstannane **15** (95%). Stannane **15** was easily purified by chromatography and could be stored.

The key 1,2-metallate rearrangement was part of a four stage sequence which began with halogen-lithium exchange of iodide **16** by treatment with 1.7 equivalents of *t*-BuLi at –80°C.[9,10] In the second stage, the homocuprate **18** was formed by addition of a solution of CuBr•SMe_2 in SMe_2 to the alkyllithium **17** at –65°C and allowing the reaction mixture to warm to 0°C. In the third stage, a solution of alkenylstannane **15** was added to a 1:1 mixture of cuprate **18** and its alkyllithium precursor **17** at –35°C resulting in transmetallation[11] to the requisite higher order cuprate **19**. On slow warming to –10°C, the 1,2-metallate rearrangement occurred whereupon the resultant alkenylcuprate **20** was alkylated with MeI/HMPA (stage four). After column chromatography to remove the organotin residues, ^{1}H NMR analysis of the crude mixture indicated the presence of three inseparable products: the desired trisubstituted alkene (*E*)-**21** (56%), the geometric isomer (*Z*)-**21** (8%) and the terminal alkyne **22** (12%). Treatment of the mixture with HF•pyridine selectively removed the triethylsilyl ether groups allowing isolation of the products by column chromatography. Pure alcohol (*E*)-**23** was obtained in 52% yield along with mixed fractions containing the (*Z*)-isomer (41%) giving a total yield for the deprotection of 93%.

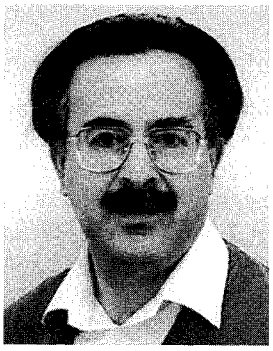


Scheme 3. *Reagents and Conditions:*

A	—	*t*-BuLi / THF, –85°C, 50 min
B	95%	Me_3SnCl, –85°C, 80 min→rt
C	—	*t*-BuLi / Et_2O-pentane, –80°C
D	—	CuBr•SMe_2, SMe_2-THF
E	—	add alkenyl stannane **15**, –35→0°C
F	65%	MeI, HMPA / THF, –20°C
G	93%	HF•pyridine / pyridine-THF, 0°C→rt, 1 h
H	94%	2-mercaptobenzothiazole, Ph_3P, DEAD / THF, rt,30 min
I	84%	Mo(VI), H_2O_2 / EtOH-H_2O, 0°C→rt, 5 h, rt, 24 h

9 steps, 45.3% overall

Biographical Sketch

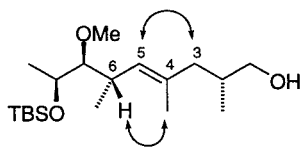


Philip Kocienski obtained his PhD degree from Brown University in 1971 under Professor Joseph Ciabattonito with a thesis on the chemistry of cyclopropenes. After three years as a post-doctoral fellow with Professor George Büchi at the Massachusetts Institute of Technology he moved to the State University of New York at Binghamton as assistant professor of chemistry. In 1976 he moved to Leeds University to work with Professor Basil Lythgoe on the synthesis of Vitamin D. In 1979 he was appointed Brotherton research lecturer at Leeds University where he investigated new synthetic methods based on organosulfur and organosilicon chemistry. In 1980 he was made a lecturer at Leeds and in 1983 he was awarded the Hickinbottom Fellowship. He received the Pfizer Academic Award in 1983 and 1986.

Since his appointment to the chair of organic chemistry at Southampton University in 1985, Prof Kocienski's research has focused on the synthesis of natural products and the design of new synthetic methods with a particular emphasis being placed on the application of organometallic reactions. In recognition of his achievements in organic synthesis, Professor Kocienski was awarded the Tilden Medal (1992) and the Simonsen Medal (1996) of the Royal Society of Chemistry. He was Glaxo Professor from 1989-1994 at Southampton and he has also held visiting professorships in Germany (BASF Professor at Kaiserslautern), France (Orsay, Marseilles, Caen, Rouen) and Spain (Santiago di Compostela).

During a survey of experimental parameters aimed at optimising the 1,2-metallate rearrangement we noted that reproducibility of both the yield and stereoselectivity was critically dependent on reaction conditions. Thus, (1) cuprates derived from *freshly* recrystallised CuBr•SMe_2 gave a higher ratio of the desired (*E*)-isomer (8:1) compared to cuprates derived from CuCN (3:1); (2) 3 equivalents of alkyllithium **17** with respect to Cu(I) were required for good mass conversion; (3) slow addition of *cold* alkenylstannane (see experimental section) was necessary to achieve (*E*):(*Z*) = 8:1; and (4) the optimum temperature window for the rearrangement was between –35 and –15°C (Note 7).

The stereochemistry of the trisubstituted alkene in **23** was confirmed by NOESY studies summarised in Scheme 4. Significant enhancements were observed between C3H and C5H (3.9% average) and C6H and C4Me (7.6% average). Conversely, no C3H↔C6Me or C5H↔C4Me interactions consistent with (*Z*)-stereochemistry were observed.

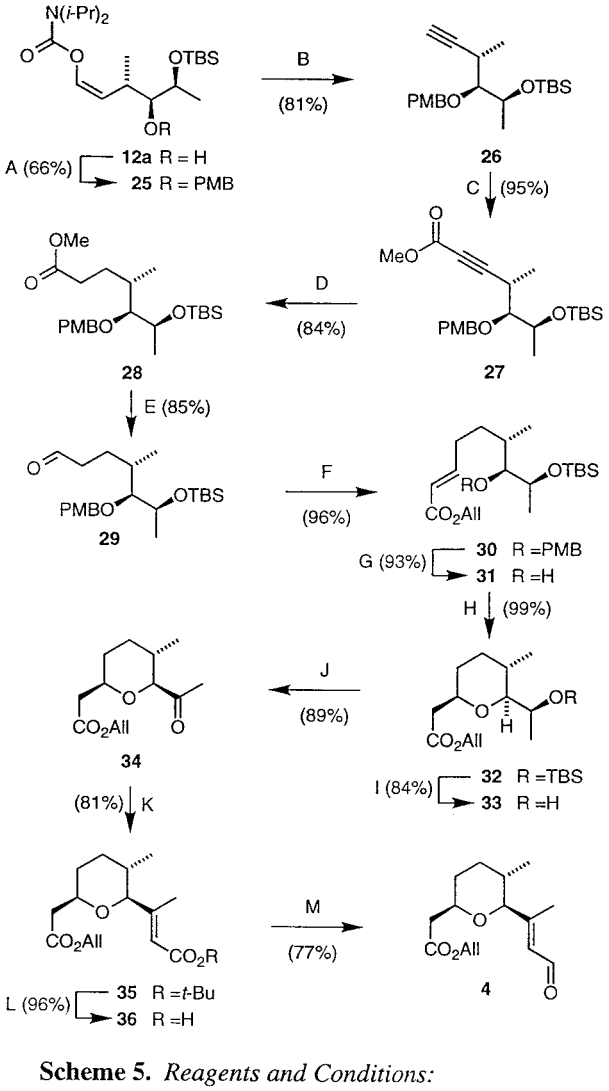


Irradiate	Observe	n.O.e.
C3H	C5H	4.4%
C5H	C3H	3.4%
C6H	C4Me	6.4%
C4Me	C6H	8.8%

Scheme 4

To complete the synthesis of fragment **3**, pure **(*E*)-23**. was converted to the benzothiazole thioether under Mitsunobu conditions[12] using sulfanylbenzothiazole, triphenylphosphane and DEAD to give **24** in 94% yield (Scheme 3). Finally, oxidation of the thioether of **24** to sulfone **3** was achieved in 84% yield (Note 8) using aqueous hydrogen peroxide and a molybdenum(VI) catalyst.[13]

Synthesis of the C1-C10 fragment 4 (Scheme 5). The instability of the lithiated enol carbamate that complicated our synthesis of the C11-C20 fragment **3** was turned to our advantage in the construction of the C1-C10 fragment **4**. Thus metallation of enol carbamate derivative **25** with *t*-BuLi at –20°C resulted in α-elimination to a vinylidene carbene which underwent a FritschButtenburgWiechell rearrangement[14-16] to the terminal alkyne **26** in 81% yield (Note 9). Lithiation of alkyne **26** followed by treatment with methyl chloroformate gave alkynyl ester **27** in 95% yield. Sequential reduction of both the alkyne function (step D) and the ester function (step E) in **27** gave aldehyde **29** in 71% yield for the two steps. Chain extension of aldehyde **29** with the sodium derivative of allyl diethylphosphonoacetate led to exclusive formation of the (*E*)-allyl ester **30** in 96% yield. In order to create the oxane ring, the *p*-methoxybenzyloxy protecting group was removed (93%) using DDQ/H2O[17,18] and the alcohol **31** treated with 1.1 equivalents of *t*-BuOK at –65°C. Quenching of the reaction mixture with water at the same temperature gave a nearly quantitative yield of **32** having all three ring substituents in the requisite equatorial position (Note 10).



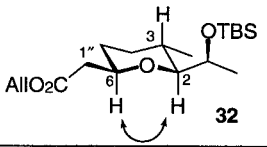
Scheme 5. *Reagents and Conditions:*

A	66%	PMBO–C(=NH)CCl_3,TMSOTf / Et_2O, r.t.
B	81%	*t*-BuLi / Et_2O, –20°C
C	95%	(a) BuLi / THF, –80°C; (b) $ClCO_2Me$
D	84%	H_2 (1 atm), Pd–C / EtOAc, r.t.
E	85%	DIBALH / CH_2Cl_2, –80°C
F	96%	$(EtO)_2P(=O)CH_2CO_2All$, NaH / THF, –10°C
G	93%	DDQ / CH_2Cl_2–H_2O, r.t.
H	99%	*t*-BuOK / THF, –65°C
I	84%	TBAF, 4Å MS / THF, r.t.
J	89%	PCC, 4ÅMS / CH_2Cl_2, r.t.
K	81%	$(EtO)_2P(=O)CH_2CO_2Bu^t$, NaH / THF, 0°C→ r.t.
L	96%	TFA, PhSMe / CH_2Cl_2
M	78%	(a) $[Me_2N{=}CHCl]Cl$ / THF–MeCN; (b) $LiAlH(OBu^t)_3$

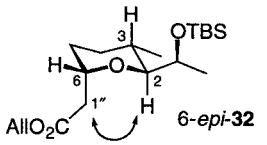
13 steps: 14.3% overall yield

Proof that the cyclisation reaction leading to the oxane ring (step H) is thermodynamically controlled was gleaned by lowering of the reaction temperature to –85°C. Two cyclisation products were now generated in the ratio 10:1 with the major product being the desired all equatorial isomer **32**. The minor isomer (6-*epi*-**32**) was separated and treated with *t*-BuOK at –65°C whereupon complete isomerisation to **32** occurred. Since the major isomer **32** is formed rapidly and the isomerisation of 6-*epi*-**32** is slow at –85°C, **32** must also be the kinetic product of the cyclisation. The stereochemistry at C2 and C3 of **32** and its 6-*epi* diastereoisomer was assigned from $J_{H2\text{-}H3}$ of 9.6 Hz

consistent with a *trans*-diaxial disposition (Note 11). The results from NOESY experiments summarised in Scheme 6 were used to assign the stereochemistry of the C6 side chain.



Irradiate	Observe	n.O.e.
C6H	C2H	8.1%
C2H	C6H	9.5%
C2H	C1″H	0

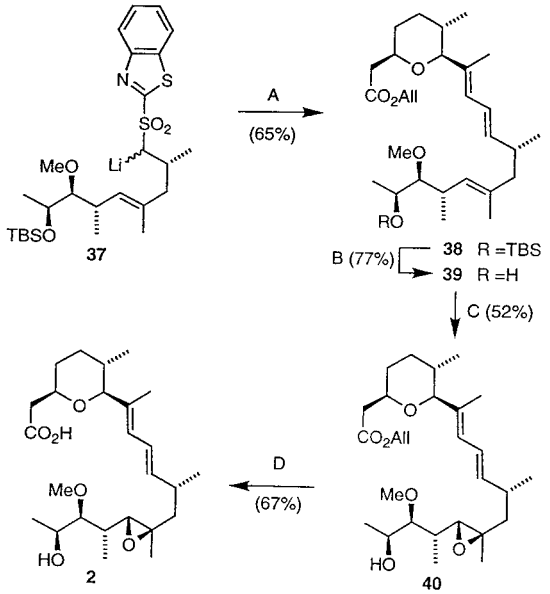


Irradiate	Observe	n.O.e.
C1″H	C2H	3.1%
C2H	C1″H	3.6%
C6H	C2H	0

Scheme 6

To complete the synthesis of the C1-C10 fragment **4**, the *tert*-butyldimethylsilyl group of **32** was removed with TBAF (84%) and the alcohol thus exposed oxidised with pyridinium chlorochromate activated by powdered 4Å molecular sieves.[19,20] Chain extension of ketone **34** using the sodium derivative of *tert*-butyl diethylphosphonoacetate gave unsaturated ester **35** in 81% yield with an (*E*):(*Z*) selectivity of 15:1. Selective removal of the *tert*-butyl group with trifluoroacetic acid and thioanisole gave the free acid **36** in 96% yield. Finally, selective reduction of **36** to aldehyde **4** was achieved in 77% yield by prior activation of the acid with Vilsmeier's reagent[21] followed by reduction with $LiAlH(O\textit{t}\text{-}Bu)_3$.

Union of fragments 3 and 4 (Scheme 7). Construction of the (*E,E*)-diene in Herboxidiene A was accomplished by a new one-pot olefination reaction recently reported by Sylvestre Julia and his colleagues.[22,23] This valuable procedure involved slow addition of LDA to a THF solution of sulfone **3** at –80°C to give a yellow solution of the sulfone anion **37**. After stirring for 1 h, a precooled solution of aldehyde **4** in THF was added to the reaction mixture and stirred for 1.5 h before being warmed to room temperature. After an aqueous workup and purification by column chromatography, the desired (*E,E*)-diene **38** was isolated in 65% yield along with a further 6% of a 1:1 mixture of two isomeric dienes. Removal of the TBS ether from **38** with HF•pyridine gave the alcohol **39** in 77% yield. Highly selective hydroxyl-directed epoxidation of the alkene with $VO(acac)_2$ (4 mol%) and *tert*-butyl hydroperoxide (10 equiv)[24-26] then gave the epoxide **40** as a single diastereoisomer in 52% yield (Note 12). Finally, deprotection of the allyl ester using $Pd(PPh_3)_4$ and morpholine[27] completed the synthesis of Herboxidiene A. A comparison of the ^1H and ^{13}C NMR spectra of our synthetic product with the data reported for natural Herboxidiene (Tables 1 and 2) were similar—especially in the region encompassing C1-C10—but the significant differences in the C11-C19 region clearly indicated that our synthetic material was a diastereoisomer of Herboxidiene.



Scheme 7. *Reagents and Conditions:*

A 65% aldehyde **4** / THF, –78°C
B 77% HF•pyr / THF-pyridine, r.t.
C 52% $VO(acac)_2$, *t*-BuOOH / CH_2Cl_2, 0°C
D 67% $Pd(PPh_3)_4$, morpholine / THF, r.t.

4 steps: 17.4% overall yield

Table 1. ^1H NMR Data for Herboxidiene and Herboxidiene A

	Herboxidiene[b]			Herboxidiene A[c]		
Position[a]	*d*	mult.	*J*(Hz)	*d*	mult.	*J*(Hz)
C2-H_A	2.25	dd	14.1, 7.5	2.48-2.63	m	—
C2-H_B	2.45	dd	14.1, 6.6	2.48-2.63	m	—
C3-H	3.76	m	—	3.74-3.84	m	—
C4-H_A	1.68-1.86	m	—	1.56-1.72	m	—
C4-H_B	1.30	m	—	1.22-1.50	m	—
C5-H_A	1.68-1.86	m	—	1.81-1.93	m	—
C5-H_B	1.12-1.26	m	—	1.22-1.50	m	—
C6-H	1.55	m	—	1.56-1.72	m	—
C6-Me	0.66	d	6.6	0.73	d	6.6
C7-H	3.34	d	9.9	3.42	d	9.9
C8–Me	1.68	s	—	1.72	s	—
C9–H	5.90	d	11.1	5.95	d	10.8
C10–H	6.29	dd	15.0, 10.8	6.22	dd	15.1, 10.8
C11–H	5.45	dd	15.0, 9.0	5.61	dd	15.1, 7.6
C12–H	2.44	m	—	2.31-2.45	m	—
C12–Me	1.03	d	6.6	1.03	d	6.6
C13–H_A	1.91	dd	13.1, 4.3	1.81-1.93	m	—
C13–H_B	1.12-1.26	m	m	1.22-1.50	m	—
C14–Me	1.27	s	—	1.27	s	—
C15–H	2.65	d	9.6	2.79	d	9.3
C16–H	1.45	m	—	1.56-1.72	m	—
C16–Me	0.83	d	6.9	1.08	d	7.2
C17–H	2.96	dd	6.0, 4.5	2.97	dd	6.2, 3.3
C18–H	3.78	dq	6.6, 6.3	3.96	dq	6.4, 6.2
C19–H	1.11	d	6.6	1.21	d	6.2
OMe	3.52	s	—	3.58	s	—

[a] See structure **1** for numbering scheme
[b] Recorded in MeOD
[c] Recorded in $CDCl_3$

Table 2. ^{13}C NMR Data for Herboxidiene and Herboxidiene A

	Herboxidiene	Herboxidiene A	
Position[a]	δ_C[b]	δ_C[b]	δ_C[c]
C1	179.8	Not observed	173.6
C2	46.4	47.6	46.0
C3	77.0	76.0	74.0
C4	33.1	33.2	31.6
C5	33.7	33.8	32.1
C6	33.5	33.8	32.4
C6-Me	18.2	18.3	17.7
C7	92.2	92.4	91.1
C8	136.5	136.3	133.8
C8–Me	12.1	12.6	12.2
C9	129.5	129.7	129.3
C10	126.6	125.9	124.1
C11	140.5	141.6	140.9
C12	36.5	36.9	35.8
C12–Me	22.7	21.7	20.7
C13	48.1	43.2	41.2
C14	62.6	62.5	59.6
C14–Me	16.8	17.8	17.2
C15	67.8	65.5	63.8
C16	36.4	35.9	34.3
C16–Me	11.7	15.2	14.6
C17	88.6	92.0	90.1
C18	69.8	70.7	68.9
C19	19.9	20.4	19.8
OMe	61.9	60.9	61.9

[a] See structure **1** for numbering scheme
[b] Recorded in MeOD
[c] Recorded in $CDCl_3$

In conclusion, we have shown that the Herboxidiene skeleton can be constructed from ethyl (*S*)-lactate, methyl (*R*)-3-hydroxy-2-methylpropionate, (*E*)-crotyl alcohol, allyl diethylphosphonoacetate, and *tert*-butyl diethylphosphonoacetate—all cheap commercial starting materials. Furthermore, the ready availability of ethyl (*R*)-lactate and methyl (*S*)-3-hydroxy-2-methylpropionate together with the metal-dependent stereochemistry of the Hoppe homoaldol reaction suggests that most if not all the stereochemical permutations encompassed by C11-C19 could be prepared with only minor alterations to our route. The connective synthesis of the C14-C15 trisubstituted alkene gives further testimony to the value of 1,2-metallate rearrangements for the stereoselective synthesis of elaborate polyketide chains.[28-30] Finally, our synthesis provides only the second example of the new "one-pot" Julia olefination in complex fragment linkage chemistry which promises to have broad application in natural product synthesis.[31]

Notes

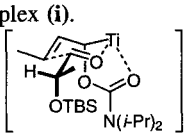
1. The Monsanto study narrowed the structure of natural Herboxidiene to one of 64 possible diastereoisomers. The stereochemical ambiguity is concentrated in the fragment encompassing C11-C19.

2. Deprotonation of carbamate **9** with butyllithium in the presence of (–)-sparteine gave a configurationally labile mixture of the complexes (*S*)-**10** and (*R*)-**10**. After 20 to 60 min of rapid stirring, (*S*)-**10** began to crystallise out of the equilibrium mixture as a fine white precipitate. Continued stirring for a further 2 h produced a thick white paste which requires mechanical stirring.

3. An X-ray structure of a (carbamoyloxy)allyllithium-sparteine complex provides proof of stereochemistry.[32]

4. The diastereoselectivity, though modest, is nevertheless an impressive demonstration of the high level of reagent control in the homoaldol reaction since titanium reagent **11** and aldehyde **8** are a mismatched pair.

5. The configuration assigned to the major enol carbamate **12a** is predicted from Hoppe's work.[5] Carbamate **12b** results from transmetallation of the small quantity of (*R*)-**10** present in the equilibrium mixture. The (*Z*)-*anti* stereochemistry arises from allylmetallation of complex **(i)**.



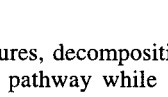
(i)

6. The solution of Ti(*i*-PrO)$_4$ was precooled to minimise temperature changes—and hence racemisation—during addition. Below –35°C, the Ti(*i*-PrO)$_4$ is insoluble in the hydrocarbon solvent.

7. At lower temperatures, decomposition to the acetylene **22** was the major reaction pathway while at higher temperatures poorer stereoselectivity was observed.

8. In addition to **3**, approximately 10% of the secondary alcohol resulting from removal of the *tert*-butyldimethylsilyl protecting group under these reaction conditions was isolated.

9. Strict temperature control was crucial in this transformation in order to minimise competing elimination to the enyne **(ii)**.

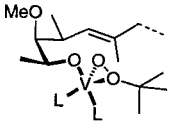


(ii)

10. For other examples of thermodynamically controlled intramolecular conjugate additions to oxane rings see Hori's synthesis of Tetronomycin[33] and Nicolaou's synthesis of Brevetoxin B.[34]

11. The *trans*-diaxial disposition of C2H and C3H incidentally provides independent verification of the *anti* stereochemistry of the Hoppe homoaldol reaction.

12. The assignment of stereochemistry in **40** required that epoxidation occurred through intermediate **(iii)** in which (1) the coordination geometry of V^{5+} is trigonal bipyramidal; (2) the carbon skeleton adopts a *pseudo*-chair conformation; (3) steric interactions between the substituents and vanadium ligands are minimised; and (4) breakage of the peroxide bond occurs from the backside along the axis of the O–O bond.[35] Similar factors are known to govern the epoxidation stereochemistry of homoallylic alcohols.[36] Hydroxyl-directed epoxidation of homo- and *bis*-homoallylic alcohols has been reviewed.[37]



(iii)

For a description of general experimental details including spectroscopic information and solvent purification see reference (31). ^1H NMR spectra were recorded in Fourier Transform mode on Jeol GX-270 (270 MHz) or Bruker AM 300 (300 MHz)

spectrometers. All spectra were obtained in $CDCl_3$ solution as stated and the chemical shift values are reported as values in p.p.m. relative to residual chloroform (δ = 7.27) as internal standard unless otherwise stated. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, app = apparent and br = broad. Coupling constants (J) are reported in Hz. ^{13}C NMR spectra were recorded on a Jeol GX-270 (67.5 MHz), or a Bruker AM 360 (90 MHz) spectrometer. All spectra were obtained in $CDCl_3$ solution unless otherwise stated and the chemical shift values are reported as values in p.p.m. relative to residual chloroform (δ = 77.2) as internal standard. The multiplicities refer to the signals in the off-resonance spectra and were elucidated using the Distortionless Enhancement by Polarisation Transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Multiplicities are described using the following abbreviations: 0 = singlet (due to quarternary carbon), 1 = doublet (methyne), 2 = triplet (methylene), 3 = quartet (methyl). The numbering scheme used to assign the signals in compounds **38**, **39**, **40**, and **2** is based upon structure **1**. NMR assignments were made with the aid of both ^1H–^1H and ^1H–^{13}C correlation spectroscopy for compounds **3**, **12a**, **23**, **28**, **30**, **31**, **32** and **38**; ^1H–^1H correlation spectroscopy only for compounds **12b**, **13**, **15**, **24–35**, **39**, **40**. The assignments for all other compounds were made by inference.

Ethyl (*S*)-2-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}propanoate (7):
To a solution of imidazole (25.5 g, 375 mmol) and DMAP (915 mg, 7.5 mmol) in CH_2Cl_2 (310 mL) at 0°C was added (*S*)-ethyl lactate (28.3 mL, 250 mmol). A solution of *tert*-butyldimethylsilyl chloride (41.5 g, 275 mmol) in CH_2Cl_2 (50 mL) was added to the colourless mixture to give a white precipitate. The mixture was warmed to r.t. and stirred for 2 h, whereupon it was diluted with CH_2Cl_2 (100 mL) and shaken with H_2O (200 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and the residue purified by chromatography (silica gel, hexanes:Et_2O = 96:4) to give TBS ether **7** (52 g, 224 mmol, 90%) as a colourless oil; $[\alpha]_D$ –30.0 (c = 2.5 in $CHCl_3$).

IR (film): ν = 2933 (s), 2859 (s), 1754 (s), 1471 (m), 1255 (s), 1146 (s), 834 (s), 779 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 4.31 (1H, q, J = 6.8 Hz), 4.18 (2H, dq, J = 3.9, 7.2 Hz), 1.40 (3H, d, J = 6.8 Hz), 1.28 (3H, t, J = 7.2 Hz), 0.91 (9H, s), 0.10 (3H, s), 0.07 (3H, s).

^{13}C NMR (75 MHz): δ = 174.2 (0), 68.6 (1), 60.8 (2), 25.8 (3, 3C), 21.4 (3), 18.4 (0), 14.3 (3), –4.8 (3), –5.3 (3).

LRMS (CI mode, NH_3): m/z = 250 [$(M+NH_4)^+$, 35%], 233 [$(M+H)^+$, 100%], 217 (25), 175 (50), 159 (25).

(*S*)-2-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}propanal (8):
To a solution of ester **(II)** (23.2 g, 100 mmol) in CH_2Cl_2 (200 mL) in a 500 ml RB flask fitted with coolable dropping funnel and internal thermometer at –80°C was added precooled (*ca.* –60°C) DIBALH (1.5M in toluene, 70 mL, 105 mmol) over 20 min maintaining the internal temperature at –80°C. The colourless solution was stirred at –80°C for 35 min and then added via cannula to a rapidly stirring mixture of sodium potassium tartrate (89 g, 315 mmol) dissolved in ice/H_2O (500 mL) and CH_2Cl_2 (200 mL). The emulsion was stirred rapidly for 2 h to give two separate layers. The organic layer was separated and the aqueous layer washed with Et_2O (3 x 300 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and the residue purified by chromatography (silica gel, hexanes:Et_2O = 96:4) to give aldehyde **8** (16.1 g, 85 mmol, 85%) as a colourless oil; $[\alpha]_D$ –13.0 (c = 2.3 in $CHCl_3$).

IR (film): ν = 2934 (s), 2870 (s), 1741 (s), 1374 (s), 1258 (s), 1137 (s), 1010 (s), 837 (s), 779 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 9.62 (1H, d, J = 1.4 Hz), 4.10 (1H, dq, J = 1.2, 6.8 Hz), 1.28 (3H, d, J = 6.8 Hz), 0.92 (9H, s), 0.11 (3H, s), 0.10 (3H, s).

^{13}C NMR (75 MHz): δ = 204.3 (1), 74.0 (1), 25.9 (3, 3C), 18.6 (3), 18.3 (0), –4.6 (3), –4.7 (3).

LRMS (CI mode, NH_3): m/z = 206 [$(M+NH_4)^+$, 57%], 189 [$(M+H)^+$, 55%], 173 (25), 159 (55), 131 (100).

The Hoppe homoaldol reaction.
To freshly distilled (–)-sparteine (5.16 g, 22 mmol) in a 250 ml RB flask fitted with a mechanical stirrer and dropping funnel with cooling finger was added crotyl carbamate **9** (4.38 g, 22 mmol) in pentane (27 mL) via cannula. Cyclohexane (4 mL) was added and the mixture cooled to –80°C. BuLi (14.4 mL, 23 mmol) was added over 90 seconds with rapid stirring whereupon a white precipitate formed after 1 h. The mixture was stirred for a further 2 h after which a precooled (–40°C) solution of Ti(O*i*Pr)$_4$ in pentane (47 mL) was added dropwise down the cold flask wall over 20 min to give an orange solution. The mixture was stirred at –80°C for 50 min whereupon aldehyde **8** (3.77 g, 20 mmol) in pentane (9 mL) was added dropwise. The orange solution was stirred at –80°C for a further 90 min and then warmed to r.t. and stirred for 1 h. The yellow solution was diluted with Et_2O (100 mL) and shaken with HCl (2M, 160 mL) and H_2O (160 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 150 mL). The combined organic layers were shaken with saturated $NaHCO_3$ (100 mL), dried ($MgSO_4$), concentrated *in vacuo*, and the residue purified by chromatography (silica gel, hexanes:Et_2O = 90:10) to give:

(1Z,3S,4S,5S)-1-[(N,N-Diisopropylcarbamoyl)oxy]-5-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-4-hydroxy-3-methylhex-1-ene **(12a)** (4.89 g, 12.6 mmol, 63%) as a colourless oil; $[\alpha]_D$ +29.2 (c = 2.8 in $CHCl_3$).

IR (film): ν = 3507 (br m), 2963 (s), 2858 (s), 1710 (s), 1438 (s), 1308 (s), 1135 (s), 1061 (s), 836 (s), 777 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 7.05 (1H, dd, J = 6.6, 0.8 Hz, H1), 4.87 (1H, dd, J = 9.9, 6.6 Hz, H2), 4.05 (1H, br s, C<u>H</u>Me$_2$), 3.84 (1H, br. s, C<u>H</u>Me$_2$), 3.70 (1H, dq, J = 6.2, 6.4 Hz, H5), 3.19 (1H, ddd, J = 6.2, 3.9, 3.3 Hz, H4), 2.79 (1H, ddq, J = 9.9, 3.9, 6.0 Hz, H3), 2.52 (1H, dd, J = 3.3, 0.8 Hz, OH), 1.24 (12H, d, J = 6.8 Hz, 2 x CHMe$_2$), 1.12 (3H, d, J = 6.0 Hz, C5-Me), 1.12 (3H, d, J = 6.4 Hz, H6), 0.89 (9H, s, CMe$_3$), 0.08 (6H, s, SiMe$_2$).

^{13}C NMR (75 MHz): δ = 152.8 (0, C=O), 135.1 (1, C1), 111.6 (1, C2), 79.2 (1, C4), 70.1 (1, C5), 46.6 (1, <u>C</u>Me$_2$), 45.7 (1, <u>C</u>Me$_2$), 32.0 (1, C3), 25.8 (3, 3C, CMe$_3$), 21.5 (3, 2C, C<u>Me</u>$_2$), 20.4 (3, 2C, C<u>Me</u>$_2$), 20.1 (3, C6), 18.5 (3, C3-Me), 18.0 (0, <u>C</u>Me$_3$), –4.1 (3, SiMe$_2$), –4.9 (3, SiMe$_2$).

LRMS (CI mode, NH_3): m/z = 388 [$(M+H)^+$, 80%], 243 (45), 200 (20), 128 (100).

HRMS (CI mode, NH_3): Found, $(M+H)^+$, 388.2863. $C_{20}H_{41}NO_4Si$+H requires M, 388.2883.

and *(1Z,3R,4R,5S)-1-[(N,N-Diisopropylcarbamoyl)oxy]-5-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-4-hydroxy-3-methylhex-1-ene* **(12b)** (660 mg, 1.7 mmol, 9%) as a colourless oil; $[\alpha]_D$ +13.4 (c = 1.3 in $CHCl_3$).

IR (film): ν = 3480 (br s), 2961 (s), 2858 (s), 1694 (s), 1435 (s), 1371 (s), 1303 (s), 1256 (s), 1211 (s), 1137 (s), 1062 (s), 1013 (s), 836 (s), 779 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 7.09 (1H, dd, J = 6.3, 0.7 Hz, H1), 4.78 (1H, dd, J = 9.2, 6.5 Hz, H2), 4.14 (1H, br s, C<u>H</u>Me$_2$), 3.93 (1H, dq, J = 3.7, 6.3 Hz, H5), 3.79 (1H, br s, C<u>H</u>Me$_2$), 3.36 (1H, dd, J

= 3.7, 8.4 Hz, H4), 2.69–2.82 (1H, m, H3), 2.37 (1H, m, OH), 1.26 (12H, br s, 2 x $CHMe_2$), 1.12 (3H, d, J = 6.3 Hz, H6), 1.00 (3H, d, J = 7.0 Hz, C3-Me), 0.90 (9H, s, CMe_3), 0.09 (3H, s, $SiMe_2$), 0.08 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 153.1 (0, C=O), 135.4 (1, C1), 113.5 (1, C2), 76.5 (1, C4), 69.6 (1, C5), 47.0 (1, $\underline{C}Me_2$), 45.7 (1, $\underline{C}Me_2$), 32.6 (1, C3), 25.9 (3, 3C, $C\underline{Me}_3$), 21.6 (3, 2C, $C\underline{Me}_2$), 20.5 (3, 2C $C\underline{Me}_2$), 18.2 (0, $\underline{C}Me_3$), 17.4 (3, C6), 16.4 (3, C7), –4.4 (3, $SiMe_2$), –4.7 (3, $SiMe_2$).

LRMS (Electrospray mode): m/z = 410 [(M+Na)$^+$, 100%], 388 (15).

(1*Z*,3*S*,4*S*,5*S*)-1-[(*N*,*N*-Diisopropylcarbamoyl)oxy]-5-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-4-methoxy-3-methylhex-1-ene (13):

To a solution of alcohol **12a** (4.54 g, 12 mmol) in toluene (50 mL) in a 250 ml RB flask was added 2,6-di-*tert*-butyl-4-methylpyridine (14.8 g, 72 mmol) in toluene (70 mL) *via* cannula. A reflux condenser was fitted and MeOTf (5.4 mL, 48 mmol) was added and the reaction mixture heated at 75°C for 10 h to give a white precipitate suspended in a pink solution. The mixture was then cooled to r.t. and NH_4OH (d = 0.88, 5 mL, 120 mmol) was added to give a white precipitate. After stirring for 1 h, CH_2Cl_2 (100 mL) was added and the mixture shaken with HCl (2M, 216 mL) and H_2O (100 mL). The organic layer was separated and the aqueous layer washed with CH_2Cl_2 (3 x 150 mL). The combined organic layers were shaken with sat $NaHCO_3$ (100 mL), dried ($MgSO_4$), concentrated *in vacuo*, and the yellow residue purified by chromatography (silica gel, hexanes:Et_2O = 96:4) to give methyl ether **13** (3.36 g, 8.4 mmol, 70%) as a colourless oil: $[\alpha]_D$ +17.1 (c = 1.6 in $CHCl_3$).

IR (film): ν = 2964 (s), 1711 (s), 1439 (s), 1373 (s), 1305 (s), 1159 (s), 1108 (s), 1057 (s), 835 (s), 771 (s) cm^{-1}.

^1H NMR (300 MHz): δ = 7.00 (1H, dd, J = 6.6, 0.7 Hz, H1), 4.84 (1H, dd, J = 9.9, 6.6 Hz, H2), 4.07 (1H, br s, $C\underline{H}Me_2$), 3.81 (1H, br s, $C\underline{H}Me_2$), 3.77 (1H, dq, J = 6.6, 6.3 Hz, H5), 3.49 (3H, s, OMe), 2.91 (1H, ddq, J = 9.9, 3.3, 7.0 Hz, H3), 2.83 (1H, dd, J = 7.0, 3.3 Hz, H4), 1.24 (12H, d, J = 7.0 Hz, $CH\underline{Me}_2$), 1.10 (3H, d, J = 7.0 Hz, C3-Me), 1.07 (3H, d, J = 6.3 Hz, H6), 0.90 (9H, s, CMe_3), 0.08 (3H, s, $SiMe_2$), 0.06 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 153.0 (0, C=O), 134.6 (1, C1), 112.2 (1, C2), 89.7 (1, C4), 70.7 (1, C5), 61.3 (3, OMe), 46.8 (1, $\underline{C}Me_2$), 45.8 (1, $\underline{C}Me_2$), 31.8 (1, C3), 26.1 (3, 3C, $C\underline{Me}_3$), 21.6 (3, 2C, $C\underline{Me}_2$), 20.5 (3, 2C, $C\underline{Me}_2$), 20.1 (3, C6), 19.2 (3, C3-Me), 18.2 (0, $\underline{C}Me_3$), –4.5 (3, $SiMe_2$), –4.6 (3, $SiMe_2$).

LRMS (CI mode, NH_3): m/z = 419 [(M+NH_4)$^+$, 5%], 402 [(M+H)$^+$, 70%], 344 (5), 203 (10), 128 (100).

(1*E*,3*S*,4*S*,5*S*)-1-[(*N*,*N*-Diisopropylcarbamoyl)oxy]-5{[(1,1-dimethylethyl)dimethylsilyl]oxy}-4-methoxy-3-methyl-1-(trimethylstannyl)hex-1-ene (15):

To a solution of enol carbamate **13** (3.41 g, 8.5 mmol) in THF (35 mL) at –85°C was added *t*-BuLi (6.1 mL, 9.4 mmol) dropwise over 3 min to give a yellow solution. The mixture was stirred at –85°C for 50 min whereupon a precooled solution (–30°C) of Me_3SnCl in THF (10 mL) was added via cannula down onto the cold flask wall. The yellow solution was stirred at –85°C for 80 min and then warmed to r.t. The mixture was diluted with Et_2O (30 mL) and shaken with H_2O (60 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 60 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo*, and the pale yellow residue purified by chromatography (silica gel, hexanes:Et_2O = 97:3) to give stannane **15** (4.54 g, 8.0 mmol, 95%) as a colourless oil: $[\alpha]_D$ +8.3 (c = 1.2 in $CHCl_3$).

IR (film): ν = 2966 (s), 1687 (s), 1438 (s), 1374 (s), 1304 (s), 1255 (s), 1159 (s), 1107 (s), 1055 (s), 834 (s), 772 (s) cm^{-1}.

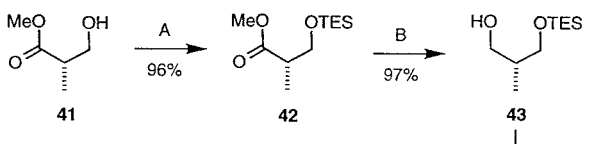
^1H NMR (300 MHz): δ = 5.01 (1H, d, $J_{H,H}$ = 9.2 Hz, $J_{Sn,H}$ = 32.7 Hz, H2), 4.43 (1H, br s, $C\underline{H}Me_2$), 3.82 (1H, br s, $C\underline{H}Me_2$), 3.78 (1H, dq, J = 6.6, 6.3 Hz, H5), 3.49 (3H, s, OMe), 2.99 (1H, ddq, J = 10.3, 3.3, 7.0 Hz, H3), 2.80 (1H, dd, J = 7.0, 3.3 Hz, H4), 1.24 (12H, br s, 2 x CMe_2), 1.08 (3H, d, J = 7.0 Hz, C3-Me), 1.07 (3H, d, J = 6.3 Hz, H6), 0.90 (9H, s, $C\underline{Me}_3$), 0.14 (9H, s, $J_{Sn,H}$ = 56.3, 54.1 Hz, $SnMe_3$), 0.08 (3H, s, $SiMe_2$), 0.07 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 155.0 (0, C=O), 154.6 (0, C1), 126.0 (1, $J_{Sn,C}$ = 68 Hz, C2), 89.8 (1, C4), 70.8 (1, C5), 61.3 (3, OMe), 46.6 (1, $\underline{C}Me_2$), 45.6 (1, $\underline{C}Me_2$), 33.0 (1, $J_{Sn,C}$ = 33 Hz, C3), 26.1 (3, 3C, $C\underline{Me}_3$), 21.6 (3, 2C, $C\underline{Me}_2$), 20.6 (3, 2C,$C\underline{Me}_2$), 20.3 (3, C6), 19.0 (3, C3-Me), 18.3 (0, $\underline{C}Me_3$), –4.5 (3, $SiMe_2$), –4.5 (3, $SiMe_2$), –6.4 (3, 3C, $SnMe_3$, $J_{Sn,C}$ = 380, 362 Hz).

LRMS (CI mode, NH_3): m/z = 566 [(M(^{119}Sn)+H)$^+$, 100%], 550 (40), 402 (20), 294 (15), 128 (45).

HRMS (EI mode): Found, (M)$^{+\bullet}$, 564.2516. $C_{24}H_{50}NO_4SiSn$ requires M, 564.2531.

Iodoalkane **16** was prepared in standard steps as shown in Scheme 8.



Scheme 8. *Reagents and Conditions:*

A 96% TESCl, DMAP, imidazole / CH_2Cl_2, r.t.
B 97% DIBALH / PhMe, –78°C
C 93% I_2, PPh_3, imidazole / CH_2Cl_2, r.t.

3 steps: 86.6%

Methyl (*S*)-2-Methyl-3-[(triethylsilyl)oxy]propanoate (42):

Methyl (*S*)-3-hydroxy-2-methylpropanoate (**41**) (4.73 g, 40 mmol) was added to a solution of imidazole (3.54 g, 52 mmol) in CH_2Cl_2 (30 mL) and the mixture cooled to 0°C. Triethylsilyl chloride (7.4 mL, 44 mmol) was added followed by DMAP (98 mg, 0.8 mmol) and the mixture warmed to r.t. and stirred for a further 2 h. CH_2Cl_2 (20 mL) was added and the mixture shaken with H_2O (20 mL). The CH_2Cl_2 layer was separated and the aqueous layer washed with CH_2Cl_2 (3 x 10 mL); the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to leave a colourless oil. This was purified by liquid chromatography (silica gel, hexanes:Et_2O = 97:3) to leave ester **42** (9.11 g, 39.2 mmol, 98%) as a colourless oil: $[\alpha]_D$ +14.2 (c = 1 in $CHCl_3$).

IR (film): ν = 2955 (s), 2912 (s), 2879 (s), 1743 (s), 1461 (s), 1242 (s), 1096 (s), 1012 (m), 810 (m), 743 (s), 671 (w) cm^{-1}.

^1H NMR (270 MHz): δ = 3.80 (1H, dd, J = 9.8, 6.9 Hz), 3.68 (3H, s), 3.63 (1H, dd, J = 9.7, 6.2 Hz), 2.59–2.72 (1H, m), 1.14 (3H, d, J = 7.2 Hz), 0.94 (9H, t, J = 7.8 Hz), 0.60 (6H, q, J = 7.8 Hz).

^{13}C NMR (75 MHz): δ = 175.6 (0), 65.1 (2), 51.6 (3), 42.7 (1), 13.7 (3), 6.8 (3, 3C), 4.4 (2, 3C).

LRMS (CI mode, NH_3): m/z = 233 [(M+H)$^+$, 100%], 203 (25), 132 (15).

(*R*)-2-Methyl-3-[(triethylsilyl)oxy]propanol (43):

To a solution of ester **42** (8.89 g, 38.3 mmol) in toluene (100 mL) at –78°C was added DIBALH (1.5M in toluene, 54 mL, 80 mmol) dropwise over 10 min and the colourless solution stirred for a further 50 min. The mixture was then warmed to –30°C and

transferred via cannula to a rapidly stirring solution of potassium sodium tartrate (68 g, 241 mmol) dissolved in ice/H_2O (230 mL). The emulsion was stirred rapidly for 1 h to give two separate layers. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (3 x 30 mL); the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to leave a colourless oil. This was purified by liquid chromatography (silica gel, hexanes:Et_2O = 75:25) to leave alcohol **43** (7.57 g, 37.0 mmol, 97%) as a colourless oil: $[\alpha]_D$ +11.0 (c = 1 in $CHCl_3$).

IR (film): ν = 3360 (br s), 2956 (s), 1459 (s), 1415 (m), 1239 (m), 1090 (s), 1040 (s), 804 (s), 746 (s), 670 (m) cm^{-1}.

^1H NMR (270 MHz): δ = 3.73 (1H, dd, J = 9.9, 4.6 Hz), 3.55–3.65 (2H, m), 3.55 (1H, dd, J = 9.9, 8.1 Hz), 3.06 (1H, br s, OH), 1.88 - 2.02 (1H, m), 0.96 (9H, t, J = 7.9 Hz), 0.83 (3H, d, J = 6.9 Hz), 0.61 (6H, q, J = 8.0 Hz).

^{13}C NMR (75 MHz): δ = 68.7 (2), 68.6 (2), 37.3 (1), 13.3 (3), 6.9 (3, 3C), 4.5 (2, 3C).

LRMS (CI mode, NH_3): m/z = 205 [(M+H)$^+$, 100%], 132 (12), 35 (25).

(*S*)-1-Iodo-2-methyl-3-[(triethylsilyl)oxy]propane (16):
To a solution of imidazole (13.9 g, 204 mmol) and triphenylphosphane (19.7 g, 75 mmol) in CH_2Cl_2 (200 mL) at 0°C was added I_2 (19.02 g, 75 mmol). A solution of **43** (13.9 g, 68 mmol) in CH_2Cl_2 (70 mL) was then added over 10 min and the mixture warmed to r.t., covered in foil and stirred for a further 20 h. The mixture was shaken with $Na_2S_2O_3$ (5%, 200 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 200 mL); the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to leave a colourless oil. Hexanes (300 mL) was added and the resulting white precipitate was removed by filtration. The filtrate was concentrated *in vacuo* and purified by liquid chromatography (silica gel, hexanes:Et_2O = 99:1) followed by short path distillation (bp 52–56 °C, 0.1 mmHg,) to give iodide **16** (19.8 g, 63.0 mmol, 93%) as a colourless oil: $[\alpha]_D$ +6.0 (c = 1 in $CHCl_3$).
IR (film): ν = 2957 (s), 2877 (s), 1457 (s), 1417 (s), 1239 (m), 1101 (s), 1007 (s), 801 (s), 744 (s), 674 (m) cm^{-1}.

^1H NMR (270 MHz): δ = 3.52 (1H, dd, J = 10.0, 5.0 Hz, H3), 3.41 (1H, dd, J = 10.0, 7.1 Hz, H3), 3.33 (1H, dd, J = 9.5, 5.0 Hz, H1), 3.26 (1H, dd, J = 9.5, 5.6 Hz, H1), 1.61–1.68 (1H, m, H2), 0.97 (9H, t, J = 7.9 Hz, TES), 0.96 (3H, d, J = 6.8 Hz, H4), 0.61 (6H, q, J = 7.9 Hz, TES).

^{13}C NMR (75 MHz): δ = 66.6 (2, C3), 37.6 (2, C1), 17.5 (1, C2), 14.0 (3, C4), 7.0 (3, TES), 4.6 (2, TES).

LRMS (CI mode, NH_3): m/z = 332 [(M+NH_4)$^+$, 10%], 315 [(M+H)$^+$, 35%] 230 (10), 132 (100).

HRMS (CI mode, NH_3): Found, (M+H)$^+$, 315.0679. $C_{10}H_{23}IOSi$+H requires M, 315.06412.

Synthesis of Alkene 21 via 1,2-Metallate Rearrangement:
t-BuLi (1.50M in hexanes, 3.7 mL, 5.6 mmol) was added dropwise over 15 min to a solution of iodoalkane **16** (1.04 g, 3.3 mmol) in Et_2O (4.2 mL) and pentane (3.3 mL) at –80°C. After 10 min, the cloudy solution was warmed to 0°C in an ice bath and THF (0.45 mL, 5.6 mmol) was added in one portion. After 50 min, the mixture was cooled to –65°C and a solution of freshly recrystallised CuBr•SMe_2 (226 mg, 1.1 mmol) in dimethyl sulfide (2 mL) was added to give a bright yellow solution. The mixture was allowed to warm to –15°C over 80 min to give a colourless solution, which was then warmed to 0°C and stirred for a further 20 min. The mixture was cooled to –35°C and a solution of alkenylstannane **15** (565 mg, 1.0 mmol) in Et_2O (5.2 mL) was added down the cold flask wall over 10 min. The cloudy solution was allowed to warm to –10°C over 90 min and then warmed to 0°C and stirred for a further 1 h. The light brown solution was then cooled to –65°C where upon anhyd HMPA (0.4 mL, 2.2 mmol) and MeI (0.62 mL, 10 mmol) were added simultaneously. The resulting yellow solution was allowed to warm to –20°C over 1 h and then warmed to r.t. and stirred for a further 1 h. The mixture was then diluted with Et_2O (25 mL) and shaken with sat NH_4Cl (25 mL) and NH_3 (10%, 25 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 20 mL); the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to leave a colourless oil. Liquid chromatography (silica gel, hexanes:Et_2O = 98.5:1.5) gave a colourless oil (323 mg) containing three inseparable components whose yield was determined by ^1H NMR spectroscopy: [(*E*)-**21**] (255 mg, 0.56 mmol, 56%); [(*Z*)-**21**] (36 mg, 0.08 mmol, 8%); and **22** (32 mg, 0.12 mmol, 12%).

Removal of the Triethylsilyl Protecting Group from (*E*)-21 and (*Z*)-21 with HF•Pyridine:
The inseparable mixture of [(*E*)-**21**], [(*Z*)-**21**] and **22** (1.17 g, 2.5 mmol) was dissolved in anhyd pyridine (2 mL, 25 mmol) and THF (50 mL) and cooled to 0°C. HF•pyridine (0.72 mL, 25 mmol) was added in one portion and the green solution warmed to r.t. and stirred for 1 h. The mixture was then diluted with Et_2O (20 mL) and shaken with sat $NaHCO_3$ (80 mL) until effervescence ceased. The organic layer was separated and the aqueous layer washed with Et_2O (3 x 50 mL); the combined organic layers were then washed with HCl (2M, 12.7 mL, 25 mmol) and H_2O (15 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 20 mL). The combined organic layers were then shaken with sat $NaHCO_3$ (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown oil which was purified by liquid chromatography (silica gel, hexanes:Et_2O = 80:20) to give pure *(4E,2R,6S,7S,8S)-8-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}-1-hydroxy-7-methoxy-2,4,6-trimethylnon-4-ene* [(*E*)-**23**] (445 mg, 1.29 mmol, 52%) as a colourless oil: $[\alpha]_D$ +4.9 (c = 1.1 in $CHCl_3$).

IR (film): ν = 3381 (br, s), 2956 (s), 1462 (s), 1380 (s), 1253 (s), 1166 (s), 1106 (s), 1039 (s), 988 (s), 932 (s), 834 (s), 776 (s) cm^{-1}.

^1H NMR (300 MHz): δ = 5.21 (1H, dd, J = 9.9, 0.7 Hz, H5), 3.78 (1H, dq, J = 6.3, 6.6 Hz, H8), 3.46 (3H, s, OMe), 3.39–3.52 (2H, m, H1), 2.81 (1H, dd, J = 6.3, 4.8 Hz, H7), 2.62 (1H, ddq, J = 9.9, 4.8, 7.0 Hz, H6), 2.00–2.10 (1H, m, H3), 1.70–1.92 (2H, m, H3, H2), 1.61 (3H, d, J = 1.5 Hz, C4-Me), 1.08 (3H, d, J = 6.6 Hz, C9-Me), 1.01 (3H, d, J = 7.0 Hz, C2-Me), 0.91 (9H, s, CMe_3), 0.87 (3H, d, J = 6.3 Hz, C6-Me), 0.08 (3H, s, $SiMe_2$), 0.07 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 133.1 (0, C4), 128.4 (1, C5), 90.1 (1, C7), 70.4 (1, C8), 68.5 (2, C1), 60.9 (3, OMe), 44.8 (2, C3), 34.1 (1, C6), 33.9 (1, C2), 26.0 (3, 3C, CMe_3), 19.9 (3, C9), 18.7 (3, C6-Me), 18.2 (0, $\underline{C}Me_3$), 17.0 (3, C2-Me), 16.2 (3, C6-Me1), –4.5 (3, $SiMe_2$), –4.6 (3, $SiMe_2$).

LRMS (CI mode, NH_3): m/z = 362 [(M+NH_4)$^+$, 7%], 345 [(M+H)$^+$, 100%], 313 (15), 203 (40), 181 (45).

HRMS (CI mode, NH_3): Found, (M+H)$^+$, 345.2809. $C_{19}H_{41}O_3Si$+H requires M, 345.2825.

and pure *(3S,4S,5S)-5-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}-4-methoxy-3-methylhex-1-yne* (**22**): (67 mg) as a colourless oil: $[\alpha]_D$ +17.7 (c = 1.3 in $CHCl_3$).

IR (film): ν = 3312 (m), 2932 (s), 2858 (s), 1465 (s), 1377 (s), 1254 (s), 1111 (s), 989 (s), 934 (s), 834 (s), 777 (s), 630 (s) cm^{-1}.

^1H NMR (300 MHz): δ = 4.00 (1H, dq, J = 6.5, 6.6 Hz, H5), 3.55 (3H, s, OMe), 2.84 (1H, dd, J = 6.5, 3.7 Hz, H4), 2.71 (1H, ddq, J = 3.7, 2.2, 7.4 Hz, H3), 2.08 (1H, d, J = 2.2 Hz, H1), 1.29 (3H, d,

J = 7.4 Hz, C3-Me), 1.17 (3H, d, J = 6.6 Hz, H6), 0.90 (9H, s, CMe_3), 0.10 (6H, s, $SiMe_3$).

^{13}C NMR (75 MHz): δ = 88.3 (1, C1), 85.7 (0, C2), 70.3 (1, C5), 69.9 (1, C4), 61.4 (3, OMe), 27.8 (1, C3), 25.9 (3, 3C, $C\underline{Me}_3$), 19.9 (3, C3-Me), 18.5 (3, C6), 18.1 (0, $\underline{C}Me_3$), –4.5 (3, $SiMe_2$), –4.7 (3, $SiMe_2$).

LRMS (CI mode, NH_3): m/z = 274 [$(M+NH_4)^+$, 10%], 257 [$(M+H)^+$, 100%], 199 (15), 106 (25).

In addition a fraction consisting of a mixture of (*E*) and (Z)-**23** (350 mg, 1.0 mmol, 41%) was obtained.

2-{[(4*E*,2*R*,6*S*,7*S*,8*S*)-8-{[(1,1-Dimethylethyl)dimethylsilyl]-oxy}-7-methoxy-2,4,6-trimethylnon-4-enyl]thio}benzothiazole (24):

2-Sulfanylbenzothiazole (220 mg, 1.30 mmol) and triphenylphosphane (259 mg, 0.99 mmol) were weighed into a RB flask and dissolved in THF (6 mL). The yellow solution was cooled to 0°C and a solution of (*E*)-**23** (227 mg, 0.66 mmol) in THF (2 mL) was added via cannula. Diethyl azodicarboxylate (0.16 mL, 1.20 mmol) was added dropwise over 5 min and the mixture warmed to r.t. and stirred for 30 min. The mixture was then diluted with Et_2O (10 mL) and shaken with H_2O (10 mL) and brine (10 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to a volume of approximately 6 mL. Hexane (30 mL) was added and the precipitate formed was removed by filtration through Celite. The filtrate was concentrated *in vacuo* to a colourless oil. This was purified by liquid chromatography (silica gel, hexanes:Et_2O = 97:3) to leave thioether **24** (306 mg, 0.62 mmol, 94%) as a colourless oil: $[\alpha]_D$ +10.3 (c = 1.6 in $CHCl_3$).

IR (film): ν = 2957 (s), 1461 (s), 1429 (s), 1378 (s), 1253 (s), 1107 (s), 995 (s), 834 (s), 776 (s), 756 (s), 671 (m) cm^{-1}.

^1H NMR (300 MHz): δ = 7.83–7.86 (1H, m, BT), 7.74–7.77 (1H, m, BT), 7.38–7.44 (1H, m, BT), 7.26–7.32 (1H, m, BT), 5.26 (1H, d, J = 10.1 Hz, H5), 3.76 (1H, dq, J = 6.6, 6.5 Hz, H8), 3.49 (3H, s, OMe), 3.48 (1H, dd, J_{AB} = 13.1 Hz, J = 4.8 Hz, H1), 3.04 (1H, dd, J_{AB} = 12.9 Hz, J = 7.7 Hz, H1), 2.82 (1H, dd, J = 6.6, 3.7 Hz, H7), 2.63 (1H, ddq, J = 10.1, 3.7, 6.6 Hz, H6), 2.09–2.24 (2H, m, H2, H3), 1.92–2.04 (1H, m, H3), 1.64 (3H, d, J = 1.1 Hz, C5-Me), 1.07 (3H, d, J = 6.6 Hz, H9), 1.03 (2 x 3H, d, J = 6.6 Hz, C2-Me, C6-Me), 0.88 (9H, s, CMe_3), 0.06 (3H, s, $SiMe_2$), 0.01 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 167.7 (0, BT), 153.5 (0, BT), 135.3 (0, BT), 132.2 (0, C4), 128.9 (1, C5), 126.1 (1, BT), 124.2 (1, BT), 121.5 (1, BT), 121.0 (1, BT), 90.3 (1, C7), 71.0 (1, C8), 61.4 (3, OMe), 47.2 (2, C3), 40.4 (2, C1), 34.3 (1, C6), 31.5 (1, C2), 26.1 (3, 3C, $C\underline{Me}_3$), 20.3 (3, C9), 19.3 (3, C2-Me), 18.9 (3, C6-Me), 18.2 (0, $\underline{C}Me_3$), 16.1 (3, C4-Me), –4.5 (3, $SiMe_2$), –4.6 (3, $SiMe_2$).

LRMS (EI mode): m/z = 493 [$(M)^{+\bullet}$, 20%], 446 (15), 330 (55), 203 (80), 73 (100).

HRMS (EI mode): Found, $(M)^{+\bullet}$, 493.2514. $C_{26}H_{43}NO_2S_2Si$ requires M, 493.2505.

2-{[(4*E*,2*R*,6*S*,7*S*,8*S*)-8-{[(1,1-Dimethylethyl)dimethylsilyl]-oxy}-7-methoxy-2,4,6-trimethylnon-4-enyl]sulfonyl}benzo-thiazole (3):

To a solution of thioether **24** (160 mg, 0.32 mmol) in EtOH (3 mL) at 0°C under Ar was added a solution of $Mo_7O_{24}(NH_4)_6{\bullet}4H_2O$ (37 mg, 0.03 mmol) in H_2O_2 (30% w/v in H_2O, 0.17 mL, 1.5 mmol). The mixture was allowed to warm to r.t. over 5 h and stirred for a further 24 h. The mixture was then diluted with Et_2O (3 mL) and shaken with H_2O (3 mL) and brine (3 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to leave a yellow oil. This was purified by liquid chromatography (silica gel, hexanes:Et_2O = 85:15) to leave sulfone **3** (143 mg, 0.27 mmol, 84%) as a colourless oil: $[\alpha]_D$ +10.0 (c = 0.6 in $CHCl_3$).

IR (film): ν = 3447 (m), 2958 (s), 1472 (s), 1381 (s), 1327 (s), 1255 (s), 1109 (s), 987 (s), 836 (s), 764 (s), 631 (s) cm^{-1}.

^1H NMR (300 MHz): δ = 8.19–8.23 (1H, m, BT), 8.00–8.04 (1H, m, BT), 7.57–7.68 (2H, m, BT), 5.22 (1H, d, J = 9.9 Hz, H5), 3.72 (1H, dq, J = 6.6, 6.3 Hz, H8), 3.52 (1H, dd, J_{AB} = 14.4 Hz, J = 4.0 Hz, H1), 3.43 (3H, s, OMe), 3.29 (1H, dd, J_{AB} = 14.4 Hz, J = 8.8 Hz, H1), 2.79 (1H, dd, J = 6.3, 4.0 Hz, H7), 2.55–2.66 (1H, m, H6), 2.41–2.51 (1H, m, H2), 2.13 (1H, dd, J_{AB} = 13.7 Hz, J = 7.3 Hz, H3), 2.01 (1H, dd, J_{AB} = 13.4 Hz, J = 7.2 Hz, H3), 1.54 (3H, d, J = 1.5 Hz, C4-Me), 1.10 (3H, d, J = 6.6 Hz, C2-Me), 1.03 (3H, d, J = 6.3 Hz, H9), 0.98 (3H, d, J = 6.6, C6-Me), 0.87 (9H, s, CMe_3), 0.04 (3H, s, $SiMe_2$), 0.00 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 166.9 (0, BT), 152.9 (0, BT), 136.9 (0, BT), 131.2 (0, C4), 130.3 (1, C5), 128.1 (1, BT), 127.8 (1, BT), 125.6 (1, BT), 122.5 (1, BT), 89.8 (1, C7), 70.6 (1, C8), 61.0 (3, OMe), 60.4 (2, C1), 47.7 (2, C3), 34.1 (1, C6), 26.7 (1, C2), 26.0 (3, 3C, $C\underline{Me}_3$), 20.0 (3, C9), 20.0 (3, C2-Me), 18.8 (3, C6-Me), 18.2 (0, $\underline{C}Me_3$), 15.7 (3, C4-Me), –4.5 (3, $SiMe_2$), –4.6 (3, $SiMe_2$).

LRMS (EI mode): m/z = 525 [$(M)^{+\bullet}$, 3%], 468 (20), 424 (25), 362 (40), 203 (100), 73 (90).

HRMS (EI mode): Found, $(M)^{+\bullet}$, 525.2424. $C_{26}H_{43}NO_4S_2Si$ requires M, 525.2403.

(1*Z*,3*S*,4*S*,5*S*)-1-[(*N*,*N*-Diisopropylcarbamoyl)oxy]-5-{[(1,1-dimethylethyl)dimethylsilyl]oxy}-4-[(4-methoxyphenyl)methoxy]-3-methylhex-1-ene (25):

To a solution of enol carbamate **12a** (4.54 g, 12 mmol) and 4-methoxybenzyl trichloroacetimidate (5.0 mL, 24 mmol) in Et_2O (120 mL) at 0°C was added a solution of TMSOTf in Et_2O (0.5M, 80 µL). The colourless solution was warmed to r.t. and stirred for 20 min, after which a further portion of 4-methoxybenzyloxy-trichloroacetimidate (1.8 mL, 8.4 mmol) was added as required by TLC. After a further 2 h, the mixture was diluted with Et_2O (50 mL) and shaken with sat $NaHCO_3$ (30 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to a white suspension which was filtered through Celite, washing with hexanes and concentrated. Filtration of the resultant white suspension gave a colourless oil which was purified by chromatography (silica gel, hexanes:Et_2O = 91:9) to give PMB ether **25** (4.02 g, 7.9 mmol, 66%) as a colourless oil: $[\alpha]_D$ +10.2 (c = 2.2 in $CHCl_3$).

IR (film): ν = 2959 (s), 2857 (s), 1712(s), 1613 (m), 1514 (s), 1464 (m), 1371 (s), 1304 (s), 1249 (s), 1062 (s), 833 (s), 776 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 7.27–7.30 (2H, m, Ar), 7.01 (1H, dd, J = 6.6, 0.8 Hz, H1), 6.86–6.89 (2H, m, Ar), 4.93 (1H, dd, J = 9.9, 6.5 Hz, H2), 4.75 (1H, d, J_{AB} = 11.1 Hz, $C\underline{H}_2Ar$), 4.50 (1H, d, J_{AB} = 11.1 Hz, $C\underline{H}_2Ar$), 4.09 (1H, br s, $CHMe_2$), 3.86 (1H, dq, J = 6.6, 6.2 Hz, H5), 3.84 (1H, br s, $CHMe_2$), 3.81 (3H, s, OMe), 3.11 (1H, dd, J = 6.6, 3.5 Hz, H4), 2.97 (1H, ddq, J = 9.9, 3.5, 7.0 Hz, H3), 1.24 (12H, d, J = 6.8 Hz, 2 x $CHMe_2$), 1.12 (3H, d, J = 6.2 Hz, H6), 1.04 (3H, d, J = 7.0 Hz, C3-Me), 0.89 (9H, s, CMe_3), 0.05 (3H, s, $SiMe_2$), 0.04 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 159.0 (0, Ar), 153.1 (0, C=O), 134.4 (1, C1), 131.7 (0, Ar), 129.2 (1, Ar), 113.7 (1, Ar), 112.8 (1, C2), 86.9 (1, C4), 74.0 (2, $\underline{C}H_2Ar$), 70.8 (1, C5), 55.4 (3, OMe), 46.8 (1, $\underline{C}Me_2$), 45.8 (1, $\underline{C}Me_2$), 31.5 (1, C3), 26.1 (3, 3C, $C\underline{Me}_3$), 21.7

(3, 2C, CH$\underline{Me}_2$), 20.6 (3, 2C, CH$\underline{Me}_2$), 20.0 (3, C6), 19.5 (3, C3-Me), 18.2 (0, $\underline{C}Me_3$), –4.4 (3, $SiMe_2$), –4.5 (3, $SiMe_2$).

LRMS (CI mode, NH_3): *m/z* = 525 [$(M+NH_4)^+$, 10%], 508 [$(M+H)^+$, 10%], 363 (65), 231 (10), 121 (100).

(3*S*,4*S*,5*S*)-5-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}-4-[(4-methoxyphenyl)methoxy]-3-methylhex-1-yne (26):
To a solution of enol carbamate **25** (4.4 g, 8.7 mmol) in Et_2O (85 mL) at –25°C was added *t*-BuLi (1.54M in hexanes, 11.3 mL, 17.3 mmol) over 15 min to give a brown solution. The mixture was stirred at –20°C for 30 min and then quenched at –20°C by the addition of H_2O (20 mL). The mixture was warmed to r.t., diluted with Et_2O (30 mL) and shaken. The organic layer was separated and the aqueous layer washed with Et_2O (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and the residue purified by chromatography (silica gel, hexanes:Et_2O = 97:3) to give alkyne **26** (2.57 g, 7.1 mmol, 81%) as a colourless oil: $[\alpha]_D$ +12.2 (*c* = 2.5 in $CHCl_3$).

IR (film): ν = 3309 (m), 2932 (s), 2857 (s), 1613 (m), 1514 (m), 1464 (s), 1250 (s), 1172 (s), 1110 (s), 1038 (s), 776 (s), 630 (s) cm^{-1}.

^1H NMR (300 MHz): δ = 7.28–7.33 (2H, m, Ar), 6.86–6.89 (2H, m, Ar), 4.73 (1H, d, J_{AB} = 11.8 Hz, C$\underline{H}_2$Ar), 4.64 (1H, d, J_{AB} = 11.0 Hz, C$\underline{H}_2$Ar), 4.03 (1H, dq, *J* = 5.9, 6.6 Hz, H5), 3.82 (3H, s, OMe), 3.12 (1H, dd, *J* = 5.9, 4.4 Hz, H4), 2.77 (1H, ddq, *J* = 4.4, 2.2, 6.6 Hz, H3), 2.08 (1H, d, *J* = 2.2 Hz, H1), 1.20 (3H, d, *J* = 6.6 Hz, H6), 1.17 (3H, d, *J* = 7.4 Hz, C3-Me), 0.90 (9H, s, CMe_3), 0.07 (3H, s, $SiMe_2$), 0.05 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 159.3 (0, Ar), 131.1 (0, Ar), 129.8 (1, Ar), 113.8 (1, Ar), 86.6 (0, C2), 84.8 (1, C4), 74.0 (2, CH_2Ar), 70.4 (1, C5), 69.7 (1, C1), 55.4 (3, OMe), 27.6 (1, C3), 26.1 (3, 3C, C$\underline{Me}_3$), 19.8 (3, C6), 18.8 (3, C7), 18.2 (0, $\underline{C}Me_3$), –4.3 (3, $SiMe_2$), –4.7 (3, $SiMe_2$).

LRMS (CI mode, NH_3): *m/z* = 380 [$(M+NH_4)^+$, 3%], 363 [$(M+H)^+$, 3%], 255 (5), 159 (10), 121 (100).

HRMS (CI mode, NH_3): Found, $(M+H)^+$, 363.2354. $C_{21}H_{35}O_3Si$+H requires M, 363.2355.

Methyl (4*S*,5*S*,6*S*)-6-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}-5-[(4-methoxyphenyl)methoxy]-4-methylhept-2-ynoate (27):
To a solution of alkyne **26** (2.0 g, 5.5 mmol) in THF (40 mL) at –85°C was added BuLi (1.6 M in hexanes, 3.8 mL, 6.1 mmol) over 12 min to give a pale yellow solution. The mixture was stirred at –80°C for 40 min whereupon freshly distilled $ClCO_2Me$ (0.85 mL, 11 mmol) was added dropwise over 1 min. The reaction mixture was allowed to warm to –35°C over 45 min and then warmed to r.t. and stirred for 90 min. The mixture was diluted with Et_2O (30 mL) and shaken with H_2O (40 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and the residue purified by chromatography (silica gel, hexanes:Et_2O = 91:9) to give alkynyl ester **27** (2.19 g, 5.2 mmol, 95%) as a colourless oil: $[\alpha]_D$ +18.9 (*c* = 1.7 in $CHCl_3$).

IR (film): ν = 2954 (s), 2857 (s), 2236 (s), 1715 (s), 1613 (m), 1514 (m), 1463 (s), 1382 (s), 1252 (s), 1173 (s), 1110 (s), 834 (s), 777 (s) cm^{-1}.

^1H NMR (300 MHz): δ = 7.28–7.34 (2H, m, Ar), 6.86–6.91 (2H, m, Ar), 4.71 (1H, d, J_{AB} = 11.4 Hz, C$\underline{H}_2$Ar), 4.62 (1H, d, J_{AB} = 11.0 Hz, C$\underline{H}_2$Ar), 3.98 (1H, dq, *J* = 5.2, 6.6 Hz, H6), 3.82 (3H, s, CO_2Me), 3.77 (3H, s, OMe), 3.20 (1H, dd, *J* = 5.2, 5.1 Hz, H5), 2.96 (1H, dq, *J* = 5.1, 7.4 Hz, H4), 1.24 (3H, d, *J* = 7.4 Hz, C4-Me), 1.20 (3H, d, *J* = 6.6 Hz, H7), 0.89 (9H, s, CMe_3), 0.06 (3H, s, $SiMe_2$), 0.03 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 159.3 (0, Ar), 154.5 (0, C1), 130.7 (0, Ar), 129.8 (1, 2C, Ar), 113.8 (1, 2C, Ar), 92.0 (0, C2), 84.4 (1, C5), 74.0 (0, C2), 73.8 (2, $\underline{C}H_2Ar$), 69.5 (1, C6), 55.4 (3, OMe), 52.7 (3, OMe), 27.9 (1, C4), 26.0 (3, 3C, C$\underline{Me}_3$), 19.2 (3, C4-Me), 18.2 (0, $\underline{C}Me_3$), 17.8 (3, C7), –4.3 (3, $SiMe_2$), –4.6 (3, $SiMe_2$).

LRMS (CI mode, NH_3): *m/z* = 438 [$(M+NH_4)^+$, 45%], 421 [$(M+H)^+$, 5%], 159 (10), 121 (100).

HRMS (EI mode): Found, $(M)^{+\bullet}$, 420.2300. $C_{23}H_{36}O_5Si$ requires M, 420.2332.

Methyl (4*S*,5*S*,6*S*)-6-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}-5-[(4-methoxyphenyl)methoxy]-4-methylheptanoate (28):
A stirred solution of alkynyl ester **27** (1.98 g, 4.7 mmol) in EtOAc (35 mL) was hydrogenated at 1 atm over Pd on carbon (5%, 500 mg, 0.23 mmol). After 2 h H_2 (240 mL, 10.7 mmol) was absorbed. The mixture was filtered through Celite, concentrated *in vacuo* and the residue purified by chromatography (silica gel, hexanes:Et_2O = 91:9) to give saturated ester **28** (1.67 g, 3.9 mmol, 84%) as a colourless oil: $[\alpha]_D$ –15.1 (*c* = 1.7 in $CHCl_3$).

IR (film): ν = 2955 (s), 2894 (s), 1740 (s), 1613 (m), 1514 (m), 1463 (s), 1301 (s), 1249 (s), 1172 (s), 1094 (s), 1038 (s), 987 (m) cm^{-1}.

^1H NMR (300 MHz): δ = 7.26–7.30 (2H, m, Ar), 6.86–6.90 (2H, m, Ar), 4.69 (1H, d, J_{AB} = 11.0 Hz, C$\underline{H}_2$Ar), 4.49 (1H, d, J_{AB} = 11.0 Hz, C$\underline{H}_2$Ar), 4.01 (1H, dq, *J* = 5.9, 6.3 Hz, H6), 3.82 (3H, s, CO_2Me), 3.67 (3H, s, OMe), 3.04 (1H, dd, *J* = 5.9, 5.5 Hz, H5), 2.40 (1H, ddd, *J* = 15.5, 9.5, 5.5 Hz, H2), 2.26 (1H, ddd, *J* = 15.9, 9.6, 7.0 Hz, H2), 1.91 (1H, dddd, *J* = 13.3, 9.9, 7.0, 3.3 Hz, H3), 1.70–1.82 (1H, m, H4), 1.46–1.58 (1H, m, H3), 1.17 (3H, d, *J* = 6.3 Hz, H7), 0.95 (3H, d, *J* = 6.6 Hz, C4-Me), 0.90 (9H, s, CMe_3), 0.08 (3H, s, $SiMe_2$), 0.05 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 174.7 (0, C1), 159.1 (0, Ar), 131.6 (0, Ar), 129.2 (1, 2C, Ar), 113.8 (1, 2C, Ar), 87.5 (1, C5), 73.8 (2, CH_2Ar), 70.1 (1, C6), 55.4 (3, CO_2Me), 51.6 (3, OMe), 33.6 (1, C4), 31.9 (2, C2), 26.9 (2, C3), 26.1 (3, 3C, C$\underline{Me}_3$), 19.8 (3, C7), 18.2 (0, $\underline{C}Me_3$), 17.0 (3, C4-Me), –4.3 (3, $SiMe_2$), –4.5 (3, $SiMe_2$).

LRMS (CI mode, NH_3): *m/z* = 442 [$(M+NH_4)^+$, 5%], 425 [$(M+H)^+$, 3%], 241 (5), 159 (10), 121 (100).

(4*S*,5*S*,6*S*)-6-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}-5-[(4-methoxyphenyl)methoxy]-4-methylheptanal (29):
A 50 ml RB flask fitted with an internal thermometer was charged with ester **28** (1.36 g, 3.2 mmol) in CH_2Cl_2 (16 mL). The mixture was cooled to –80°C and DIBALH (1.5M in toluene, 2.3 mL, 3.5 mmol) added over 15 min maintaining the internal temperature at –80°C. The colourless solution was stirred at –80°C for 50 min and then added via cannula to a rapidly stirring mixture of sodium potassium tartrate (2.71 g, 9.6 mmol) dissolved in ice/H_2O (70 mL) and CH_2Cl_2 (50 mL). The emulsion was stirred rapidly for 2 h to give two separate layers. The organic layer was separated and the aqueous layer washed with Et_2O (3 x 70 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and the residue purified by chromatography (silica gel, hexanes:Et_2O = 88:12) to give aldehyde **29** (1.07 g, 2.7 mmol, 85%) as a colourless oil: $[\alpha]_D$ –20.4 (*c* = 1.5 in $CHCl_3$).

IR (film): ν = 2932 (s), 2857 (s), 1726 (s), 1613 (m), 1514 (s), 1463 (m), 1301 (m), 1249 (s), 1172 (m), 1095 (s), 834 (s), 776 (m) cm^{-1}.

^1H NMR (300 MHz): δ = 9.75 (1H, t, *J* = 1.9 Hz, H1), 7.25–7.29 (2H, m, Ar), 6.86–6.91 (2H, m, Ar), 4.69 (1H, d, J_{AB} = 11.0 Hz, C$\underline{H}_2$Ar), 4.47 (1H, d, J_{AB} = 11.0 Hz, C$\underline{H}_2$Ar), 4.03 (1H, dq, *J* = 5.5, 6.3 Hz, H6), 3.82 (3H, s, OMe), 3.04 (1H, dd, *J* = 5.9, 5.5 Hz, H5), 2.47 (1H, dddd, *J* = 16.9, 9.6, 5.5, 1.5 Hz, H2), 2.38 (1H,

dddd, J = 16.9, 8.8, 6.6, 1.8 Hz, H2), 1.92 (1H, dddd, J = 13.2, 9.6, 6.2, 3.3 Hz, H3), 1.71–1.84 (1H, m, H4), 1.44–1.57 (1H, m, H3), 1.18 (3H, d, J = 6.6 Hz, H7), 0.95 (3H, d, J = 6.6 Hz, C4-Me), 0.91 (9H, s, CMe_3), 0.08 (3H, s, $SiMe_2$), 0.06 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 203.2 (0, C1), 159.2 (0, Ar), 131.4 (0, Ar), 129.3 (1, 2C, Ar), 113.8 (1, 2C, Ar), 87.3 (1, C5), 73.7 (2, CH_2Ar), 69.8 (1, C6), 55.4 (3, OMe), 41.8 (2, C2), 33.6 (1, C4), 26.1 (3, 3C, CMe_3), 24.3 (2, C3), 19.7 (3, C7), 18.2 (0, CMe_3), 17.1 (3, C4-Me), –4.3 (3, $SiMe_2$), –4.5 (3, $SiMe_2$).

LRMS (CI mode, NH_3): m/z = 412 [$(M+NH_4)^+$, 20%], 274 (15), 257 (70), 121 (100).

Prop-2-enyl (2*E*,6*S*,7*S*,8*S*)-8-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}-7-[(4-methoxyphenyl)methoxy]-6-methylnon-2-enoate (30):

NaH (60% dispersion in oil, 130 mg, 3.2 mmol) was weighed into a 50 ml RB flask, washed with pentane (3 x 3 mL) and dried under a stream of Ar. THF (25 mL) was added and the suspension cooled to –10°C whereupon allyl diethylphosphonoacetate (0.74 mL, 3.5 mmol) was added. After completion of effervescence, the mixture was stirred at 0°C for 10 min to give a colourless solution. The mixture was cooled to –25°C whereupon a solution of aldehyde **29** (1.07 g, 2.7 mmol) in THF (7 mL) at –25°C was added dropwise via cannula. The mixture was allowed to warm to –10°C over 30 min and then warmed to r.t. The mixture was then diluted with Et_2O (20 mL) and shaken with brine (30 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and the yellow residue purified by chromatography (silica gel, hexanes:Et_2O = 93:7) to give ester **30** (1.24 g, 2.6 mmol, 96%) as a colourless oil: $[\alpha]_D$ –7.6 (c = 1.5 in $CHCl_3$).

IR (film): ν = 2955 (s), 2857 (s), 1724 (s), 1654 (s), 1613 (s), 1514 (s), 1463 (s), 1361 (s), 1259 (s), 1171 (s), 1095 (s), 987 (s), 937 (s), 835 (s), 775 (s) cm^{-1}.

^1H NMR (300 MHz): δ = 7.25–7.28 (2H, m, Ar), 7.00 (1H, dt, J = 15.8, 7.0 Hz, H3), 6.86–6.91 (2H, m, Ar), 5.97 (1H, ddt, J = 17.3, 10.7, 5.5 Hz, $CH{=}CH_2$), 5.85 (1H, dt, J = 15.4, 1.5 Hz, H2), 5.37 (1H, ddt, J = 17.3, 1.8, 1.5 Hz, $CH{=}CH_AH_B$), 5.26 (1H, ddt, J = 10.3, 1.5, 1.1 Hz, $CH{=}CH_AH_B$), 4.70 (1H, d, J_{AB} = 11.4 Hz, CH_2Ar), 4.65 (2H, ddd, J = 4.0, 1.5, 1.1 Hz, $OCH_2{-}CH{=}CH_2$), 4.47 (1H, d, J_{AB} = 11.4 Hz, CH_2Ar), 4.00 (1H, dq, J = 5.5, 6.3 Hz, H8), 3.82 (3H, s, OMe), 3.02 (1H, dd, J = 5.9, 5.5 Hz, H7), 2.24–2.34 (1H, m, H4), 2.05–2.16 (1H, m, H4), 1.65–1.78 (2H, m, H6, H5), 1.28–1.40 (1H, m, H5), 1.16 (3H, d, J = 6.3 Hz, H9), 0.96 (3H, d, J = 7.0 Hz, C6-Me), 0.90 (9H, s, CMe_3), 0.08 (3H, s, $SiMe_2$), 0.05 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 166.5 (0, C1), 159.1 (0, Ar), 150.4 (1, C3), 132.6 (1, $CH{=}CH_2$), 131.5 (0, Ar), 129.3 (1, 2C, Ar), 121.0 (1, C2), 118.2 (2, $CH{=}CH_2$), 113.8 (1, 2C, Ar), 87.4 (1, C7), 73.6 (2, CH_2Ar), 69.9 (1, C8), 65.0 (2, $OCH_2{-}CH{=}CH_2$), 55.4 (3,OMe), 33.8 (1, C6), 30.3 (2, C5), 30.0 (2, C4), 26.1 (3, 3C, CMe_3), 19.7 (3, C9), 18.2 (0, CMe_3), 17.1 (3, C6-Me), –4.3 (3, $SiMe_2$), –4.5 (3, $SiMe_2$).

LRMS (CI mode, NH_3): m/z = 494 [$(M+NH_4)^+$, 15%], 257 (45), 159 (15), 121 (100).

HRMS (EI mode): Found, $(M)^{+\bullet}$, 476.2915. $C_{27}H_{44}O_5Si$ requires M, 476.2958.

Prop-2-enyl (2*E*,6*S*,7*S*,8*S*)-8-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}-7-hydroxy-6-methylnon-2-enoate (31):

DDQ (727 mg, 3.2 mmol) was added to a rapidly stirring solution of PMB ether **30** (1.09 g, 2.3 mmol) in CH_2Cl_2 (20 mL) and H_2O (1.1 mL) at r.t. The dark green suspension was stirred for 20 min to give a brown mixture which was filtered through Celite. The filtrate was concentrated *in vacuo* to leave a black solid. This was dissolved in CH_2Cl_2 (2 mL) and hexanes (20 mL) and again filtered through Celite. The filtrate was shaken vigourously with saturated $Na_2S_2O_5$ (6 x 20 mL), dried ($MgSO_4$), concentrated *in vacuo*, and the residue purified by chromatography (silica gel, hexanes:Et_2O = 87:13) to give alcohol **31** (762 mg, 2.1 mmol, 93%) as a colourless oil: $[\alpha]_D$ –4.6 (c = 1.0 in $CHCl_3$).

IR (film): ν = 3554 (br m), 2956 (s), 2858 (s), 1724 (s), 1654 (s), 1463 (s), 1363 (s), 1256 (s), 1168 (s), 1063 (s), 993 (s), 944 (s), 837 (s), 777 (s) cm^{-1}.

^1H NMR (300 MHz): δ = 7.01 (1H, dt, J = 15.8, 6.9 Hz, H3), 5.96 (1H, ddt, J = 16.9, 10.3, 5.9 Hz, $CH{=}CH_2$), 5.87 (1H, dt, J = 15.4, 1.5 Hz, H2), 5.34 (1H, ddt, J = 16.9, 1.6, 1.6 Hz, $CH{=}CH_AH_B$), 5.24 (1H, ddt, J = 10.7, 1.5, 1.1 Hz, $CH{=}CH_AH_B$), 4.64 (2H, ddd, J = 5.9, 1.6, 1.1 Hz, $CH_2{-}CH{=}CH_2$), 3.90 (1H, dq, J = 3.3, 6.3 Hz, H8), 3.00 (1H, ddd, J = 7.3, 7.0, 3.7 Hz, H7), 2.27–2.41 (1H, m, H4), 2.28 (1H, d, J = 7.3 Hz, OH), 2.09–2.23 (1H, m, H4), 1.79 (1H, dddd, J = 13.2, 9.9, 6.6, 2.3 Hz, H5), 1.49–1.63 (1H, m, H6), 1.37 (1H, dddd, J = 14.4, 9.6, 9.6, 5.2 Hz, H5), 1.17 (3H, d, J = 6.3 Hz, H9), 0.92 (3H, d, J = 6.6 Hz, C6-Me), 0.89 (9H, s, CMe_3), 0.10 (3H, s, $SiMe_2$), 0.08 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 166.4 (0, C1), 150.2 (1, C3), 132.5 (1, C2), 121.1 (1, $CH{=}CH$), 118.1 (2, $CH{=}CH_2$), 79.8 (1, C7), 68.6 (1, C8), 65.0 (2, $CH_2{-}CH{=}CH_2$), 35.0 (1, C6), 30.1 (2, C5), 29.9 (2, C4), 25.9 (3, 3C, CMe_3), 21.1 (3, C9), 18.1 (0, CMe_3), 16.4 (3, C6-Me), –3.8 (3, $SiMe_2$), –4.7 (3, $SiMe_2$).

Electrospray MS: m/z = 379 [$(M+Na)^+$, 100%], 357 (15).

HRMS (CI mode, NH_3): Found, $(M+H)^+$, 357.2426. $C_{19}H_{37}O_4Si+H$ requires M, 357.2461.

Prop-2-enyl (2*S*,3*S*,6*R*)-2-[({[1′-(1,1-Dimethylethyl)dimethylsilyl]oxy}ethyl)-3-methyloxan-6-yl]ethanoate (32):

To a solution of alcohol **31** (209 mg, 0.58 mmol) in THF (6 mL) in a 25 ml RB flask at –65°C was added *t*-BuOK (0.64 mL, 0.64 mmol) over 1 min down the cold flask wall. The resulting yellow solution was stirred at –65 °C for 1 h and then quenched by the addition of H_2O (1 mL). The mixture was warmed to r.t. and diluted with Et_2O (10 mL) and shaken with brine (15 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and the pale yellow residue purified by chromatography (silica gel, hexanes:Et_2O = 96:4) to give oxane **32** (204 mg, 0.57 mmol, 99%) as a colourless oil: $[\alpha]_D$ +8.5 (c = 1.5 in $CHCl_3$).

IR (film): ν = 2930 (s), 2856 (s), 1742 (s), 1461 (s), 1373 (s), 1254 (s), 1195 (s), 1162 (s), 1088 (s), 1010 (s), 957 (m), 836 (s), 774 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 5.91 (1H, ddt, J = 17.1, 10.5, 5.5 Hz, $CH{=}CH_2$), 5.32 (1H, ddt, J = 17.3, 1.5, 1.5 Hz, $CH{=}CH_ACH_B$), 5.24 (1H, ddt, J = 10.7, 1.5, 1.5 Hz, $CH{=}CH_ACH_B$), 4.60 (2H ddd, J = 5.5, 1.5, 1.5 Hz, $CH_2{-}CH{=}CH_2$), 3.93 (1H, dq, J = 2.6, 6.3 Hz, CHOTBS), 3.66–3.75 (1H, m, H6), 2.83 (1H, dd, J = 9.6, 2.6 Hz, H2), 2.58 (1H, dd, J = 15.1, 7.1 Hz, $CH_AH_BCO_2All$), 2.42 (1H, dd, J = 15.1, 5.5 Hz, $CH_AH_BCO_2All$), 1.73–1.81 (1H, m, H4), 1.56–1.71 (2H, m, H5, H3), 1.18–1.37 (2H, m, H4, H5), 1.13 (3H, d, J = 6.3 Hz, TBSOCH-Me), 0.88 (9H, s, CMe_3), 0.87 (3H, d, J = 7.0 Hz, C3-Me), 0.05 (3H, s, $SiMe_2$), 0.05 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 171.4 (0, C=O), 132.4 (1, $CH{=}CH_2$), 118.1 (2, $CH{=}CH_2$), 86.6 (1, C2), 74.6 (1, C6), 69.3 (1, TBSO-CH-Me), 65.1 (2, $CH_2CH{=}CH_2$), 41.7 (2, CH_2CO_2All), 33.1 (2, C4), 31.8 (2, C5), 30.5 (1, C3), 26.0 (3, 3C, CMe_3), 19.1 (3, TBSO-CH-Me), 18.2 (0, CMe_3), 17.7 (3, C3-Me), –3.8 (3, $SiMe_2$), –4.7 (3, $SiMe_2$).

Electrospray MS: *m/z* = 379 [(M+Na)$^+$, 100%], 357 (10).

HRMS (CI mode, NH_3): Found, (M+H)$^+$, 357.2437. $C_{19}H_{37}O_4Si$+H requires M, 357.2461.

When the above cyclisation was conducted at –85°C, a 10:1 mixture of oxane **32** and its C6 epimer was obtained: *(2S,3S,6S)-2-({[1-(1,1-Dimethylethyl)dimethylsilyl]oxy}ethyl)-3-methyl-6-(3-oxa-2-oxohex-5-enyl)oxane* (6-*epi*-**32**) as a colourless oil: $[\alpha]_D$ +25.5 (*c* = 0.8 in $CHCl_3$).

IR (film): ν = 2932 (s), 2858 (s), 1741 (s), 1462 (s), 1370 (s), 1253 (m), 1170 (s), 1108 (s), 1011 (m), 836 (s), 775 (m) cm^{-1}.

^{1}H NMR (270 MHz): δ = 5.93 (1H, ddt, *J* = 16.9, 10.3, 5.5 Hz, C<u>H</u>=CH$_2$), 5.32 (1H, ddt, *J* = 17.3, 1.5, 1.5 Hz, CH=CH$_A$C<u>H</u>$_B$), 5.24 (1H, ddt, *J* = 10.3, 1.5, 1.5 Hz, CH=C<u>H</u>$_A$CH$_B$), 4.59 (2H ddd, *J* = 5.5, 1.5, 1.5 Hz, C<u>H</u>$_2$-CH=CH$_2$), 4.47–4.55 (1H, m, H6), 3.93 (1H, dq, *J* = 2.2, 6.3 Hz, C<u>H</u>OTBS), 3.10 (1H, dd, *J* = 8.8, 2.6 Hz, H2), 2.85 (1H, dd, *J* = 14.3, 9.2 Hz, CH$_A$<u>H</u>$_B$CO$_2$All), 2.42 (1H, dd, *J* = 14.3, 5.9 Hz, C<u>H</u>$_A$H$_B$CO$_2$All), 1.64–1.90 (3H, m, H5, H4, H3), 1.44–1.53 (1H, m, H5), 1.26–1.39 (1H, m, H4), 1.13 (3H, d, *J* = 6.3 Hz, TBSOCH-<u>Me</u>), 0.92 (3H, d, *J* = 6.3 Hz, C3-Me), 0.89 (9H, s, CMe$_3$), 0.06 (6H, s, SiMe$_2$).

^{13}C NMR (75 MHz): δ = 171.3 (0, C=O), 132.4 (1, <u>C</u>H=CH$_2$), 118.5 (2, CH=<u>C</u>H$_2$), 89.5 (1, C2), 69.6 (1, C6), 69.2 (1, TBSO-<u>C</u>H-Me), 65.4 (2, <u>C</u>H$_2$CH=CH$_2$), 37.3 (2, <u>C</u>H$_2$CO$_2$All), 30.5 (1, C3), 28.2 (2, C4), 27.5 (2, C5), 26.1 (3, 3C, C<u>Me</u>$_3$), 19.6 (3, TBSO-CH-<u>Me</u>), 18.3 (3, C3-Me), 18.3 (0, <u>C</u>Me$_3$), –3.7 (3, SiMe$_2$), –4.9 (3, SiMe$_2$).

Electrospray LRMS: *m/z* = 379 [(M+Na)$^+$, 100%], 357 (10).

Prop-2-enyl (2*S*,3*S*,6*R*)-[2-(1′-Hydroxyethyl)-3-methyloxan-6-yl]ethanoate (33):

To a suspension of powdered molecular sieves (4Å, 50 mg) and TBS ether **32** (178 mg, 0.5 mmol) in THF (10 mL) at 0°C was added TBAF (1.1M in THF, 0.91 mL, 1 mmol). A further equal portion of TBAF was added after 2 h and stirring continued for a further 5 h. The mixture was diluted with Et_2O (10 mL) and shaken with brine (15 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) concentrated *in vacuo*, and the yellow residue purified by chromatography (silica gel, hexanes:Et_2O = 80:20) to give alcohol **33** (101 mg, 0.42 mmol, 84%) as a colourless oil: $[\alpha]_D$ +5.7 (*c* = 0.7 in $CHCl_3$).

IR (film): ν = 3455 (br s), 2830 (s), 2852 (s), 1737 (s), 1650 (m), 1456 (s), 1375 (s), 1277 (s), 1082 (s), 1007 (s), 895 (m), 816 (m) cm^{-1}.

^{1}H NMR (270 MHz): δ = 5.91 (1H, ddt, *J* = 17.2, 10.4, 5.8 Hz, C<u>H</u>=CH$_2$), 5.32 (1H, ddt, *J* = 17.2, 1.5, 1.6 Hz, CH=CH$_A$C<u>H</u>$_B$), 5.24 (1H, ddt, *J* = 10.4, 1.4, 1.2 Hz, CH=C<u>H</u>$_A$CH$_B$), 4.60 (2H ddd, *J* = 5.8, 1.6, 1.2 Hz, C<u>H</u>$_2$-CH=CH$_2$), 3.83 (1H, dq, *J* = 1.4, 6.6 Hz, C<u>H</u>OTBS), 3.76–3.87 (1H, m, H6), 2.79 (1H, dd, *J* = 9.9, 1.4 Hz, H2), 2.55 (1H, dd, *J* = 14.9, 8.2 Hz, CH$_A$<u>H</u>$_B$CO$_2$All), 2.45 (1H, dd, *J* = 14.9, 4.9 Hz, C<u>H</u>$_A$H$_B$CO$_2$All), 1.78–1.90 (1H, m, H4), 1.62–1.76 (2H, m, H5, H3), 1.22–1.42 (2H, m, H4, H5), 1.20 (3H, d, *J* = 6.6 Hz, TBSOCH-<u>Me</u>), 0.87 (3H, d, *J* = 6.6 Hz, C3-Me).

^{13}C NMR (75 MHz): δ = 171.1 (0, C=O), 132.3 (1, <u>C</u>H=CH$_2$), 118.4 (2, CH=<u>C</u>H$_2$), 86.1 (1, C2), 74.6 (1, C6), 66.3 (1, TBSO-<u>C</u>H-Me), 65.3 (2, <u>C</u>H$_2$CH=CH$_2$), 41.6 (2, <u>C</u>H$_2$CO$_2$All), 32.5 (2, C4), 31.7 (2, C5), 30.7 (1, C3), 20.8 (3, TBSO-CH-<u>Me</u>), 17.4 (3, C3-Me).

LRMS (CI mode, NH_3): *m/z* = 260 [(M+NH$_4$)$^+$, 30%], 243 [(M+H)$^+$, 100%], 225 (40), 139 (20).

Prop-2-enyl (2*S*, 3*S*, 6*R*)-[2-(1′-Oxoethyl)-3-methyloxan-6-yl]-ethanoate (34):

Activated powdered molecular sieves (4Å, 4.35 g) were added to a solution of alcohol **33** (2.1 g, 8.7 mmol) in CH_2Cl_2 (90 mL) at r.t. under Ar. To the suspension was added PCC (3.75 g, 17.4 mmol). The black mixture was stirred for 1 h and then filtered through silica gel. The filtrate was concentrated *in vacuo* and purified by chromatography (silica gel, hexanes: Et_2O = 90:10) to give ketone **34** (1.86 g, 7.7 mmol, 89%) as a colourless oil: $[\alpha]_D$ –80.5 (*c* = 2 in $CHCl_3$).

IR (film): ν = 2931 (s), 2876 (s), 1738 (s), 1649 (m), 1457 (m), 1421 (m), 1357 (s), 1275 (s), 1190 (s), 1084 (s), 1021 (s), 931 (m), 756 (m) cm^{-1}.

^{1}H NMR (270 MHz): δ = 5.91 (1H, ddt, *J* = 17.2, 10.4, 5.6 Hz, C<u>H</u>=CH$_2$), 5.31 (1H, ddt, *J* = 17.1, 1.6, 1.6 Hz, CH=CH$_A$C<u>H</u>$_B$), 5.23 (1H, ddt, *J* = 10.4, 1.6, 1.4 Hz, CH=C<u>H</u>$_A$CH$_B$), 4.60 (2H ddd, *J* = 5.6, 1.6, 1.4 Hz, C<u>H</u>$_2$-CH=CH$_2$), 3.81 (1H, dddd, *J* = 9.9, 7.7, 5.2, 2.2 Hz, H6), 3.42 (1H, d, *J* = 10.2 Hz, H2), 2.61 (1H, dd, *J* = 15.3, 7.7 Hz, CH$_A$<u>H</u>$_B$CO$_2$All), 2.58 (1H, dd, *J* = 15.3, 5.2 Hz, C<u>H</u>$_A$H$_B$CO$_2$All), 2.15 (3H, s, Me-C=O), 1.84–1.93 (1H, m, H4), 1.67–1.76 (1H, m, H5), 1.46–1.63 (1H, m, H3), 1.24–1.46 (2H, 2 x m, H4, H5), 0.83 (3H, d, *J* = 6.6 Hz, C3-Me).

^{13}C NMR (75 MHz): δ = 207.8 (0, Me-<u>C</u>=O), 170.7 (0, C=O), 132.1 (1, <u>C</u>H=CH$_2$), 118.1 (2, CH=<u>C</u>H$_2$), 90.0 (1, C2), 73.8 (1, C6), 65.1 (2, <u>C</u>H$_2$CH=CH$_2$), 41.3 (2, <u>C</u>H$_2$CO$_2$All), 32.2 (2, C4), 31.8 (1, C3), 31.0 (2, C5), 25.8 (3, <u>Me</u>-C=O), 16.9 (3, C3-Me).

LRMS (CI mode, NH_3): *m/z* = 258 [(M+NH$_4$)$^+$, 100%], 241 [(M+H)$^+$, 70%], 197 (40), 139 (15).

1,1-Dimethylethyl (*E*)-3-Methyl-3-[(2*S*,3*S*,6*R*)-3-methyl-6-{[(prop-2-enyloxy)carbonyl]methyl}oxan-2-yl]propenoate (35):

To a suspension of NaH [60%, 216 mg, 9 mmol, washed with pentane (3 x 3 mL)] in THF (17 mL) at 0°C was added *t*-butyl diethylphosphonoacetate (2.3 mL, 9.9 mmol). After completion of effervescence, the mixture was stirred at 0°C for 10 min, whereupon ketone **34** (1.09 g, 4.5 mmol) in THF (7 mL) was added dropwise via cannula. The mixture was warmed to r.t. and stirred for 2 h. The mixture was then diluted with Et_2O (20 mL) and shaken with brine (60 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) concentrated *in vacuo*, and the residue purified by chromatography (silica gel, hexanes:Et_2O = 92:8) to give ester **35** (1.23 g, 3.6 mmol, 81%) as a colourless oil: $[\alpha]_D$ +13.0 (*c* = 1 in $CHCl_3$).

IR (film): ν = 2929 (s), 2853 (s), 1740 (s), 1712 (s), 1651 (m), 1456 (m), 1366 (s), 1239 (s), 1146 (s), 1072 (s), 929 (m), 866 (m) cm^{-1}.

^{1}H NMR (270 MHz): δ = 5.90 (1H, ddt, *J* = 17.4, 10.4, 5.4 Hz, C<u>H</u>=CH$_2$), 5.69 (1H, m, =CH-CO$_2$), 5.30 (1H, ddt, *J* = 17.4, 1.6, 1.5 Hz, CH=CH$_A$C<u>H</u>$_B$), 5.21 (1H, ddt, *J* = 10.4, 1.6, 1.3 Hz, CH=C<u>H</u>$_A$CH$_B$), 4.59 (2H ddd, *J* = 5.6, 1.5, 1.3 Hz, C<u>H</u>$_2$-CH=CH$_2$), 3.74–3.85 (1H, m, H6), 3.36 (1H, d, *J* = 9.7 Hz, H2), 2.61 (1H, dd, *J* = 15.1, 7.0 Hz, CH$_A$<u>H</u>$_B$CO$_2$All), 2.44 (1H, dd, *J* = 15.1, 6.1 Hz, C<u>H</u>$_A$H$_B$CO$_2$All), 2.09 (3H, d, *J* = 1.4 Hz, =C-Me), 1.82–1.92 (1H, m, H4), 1.65–1.76 (1H, m, H5), 1.45–1.62 (1H, m, H3), 1.47 (9H, s, CMe$_3$), 1.21–1.42 (2H, 2 x m, H4, H5), 0.74 (3H, d, *J* = 6.6 Hz, C3-Me).

^{13}C NMR (75 MHz): δ = 171.0 (0, <u>C</u>O$_2$All), 166.2 (0, <u>C</u>O$_2$Bu^t), 155.0 (0, Me<u>C</u>=C), 132.2 (1, <u>C</u>H=CH$_2$), 120.3 (1, <u>C</u>CO$_2$Bu^t), 118.1 (2, CH=<u>C</u>H$_2$), 90.0 (1, C2), 79.9 (0, <u>C</u>Me$_3$), 74.1 (1, C6), 65.1 (2, <u>C</u>H$_2$CH=CH$_2$), 41.5 (2, <u>C</u>H$_2$CO$_2$All), 32.6 (1, C3), 32.3 (2, C4), 31.5 (2, C5), 28.4 (3, 3C, C<u>Me</u>$_3$), 17.7 (3, C3-Me), 14.3 (3, =C-<u>Me</u>).

LRMS (CI mode, NH_3): *m/z* = 356 [$(M+NH_4)^+$, 70%], 339 [$(M+H)^+$, 5%], 300 (50), 283 (100), 264 (80), 237 (25).

HRMS (CI mode, NH_3): Found, $(M+NH_4)^+$, 356.2443. $C_{19}H_{30}O_5$+NH_4 requires M, 356.2437.

(*E*)-3-Methyl-3-[(2*S*,3*S*,6*R*)-3-methyl-6-{[(prop-2-enyloxy)-carbonyl]methyl}oxan-2-yl]propenoic Acid (36):
TFA (2.8 mL, 36 mmol) was added dropwise over 10 min to a solution of ester **35** (1.22 g, 3.6 mmol) and thioanisole (4.1 mL, 36 mmol) in CH_2Cl_2 (36 mL) at 0°C. The colourless solution was warmed to r.t. and stirred for 6 h. The mixture was then concentrated *in vacuo* and purified by chromatography (silica gel, hexanes:Et_2O = 50:50) to give carboxylic acid **36** (976 mg, 3.5 mmol, 96%) as a colourless oil: $[\alpha]_D$ +14.8 (*c* = 1.6 in $CHCl_3$).

IR (film): ν = 3100 (br s), 2932 (s), 1693 (s), 1435 (m), 1256 (m), 1073 (s), 1024 (m), 929 (m), 723 (m) cm^{-1}.

^1H NMR (270 MHz): δ = 5.91 (1H, ddt, *J* = 17.4, 10.4, 5.4 Hz, C<u>H</u>=CH_2), 5.80 (1H, d, *J* = 1.4 Hz, =CH-CO_2), 5.30 (1H, ddt, *J* = 17.4, 1.5, 1.6 Hz, CH=CH_AC<u>H</u>$_B$), 5.21 (1H, ddt, *J* = 10.2, 1.4, 1.4 Hz, CH=C<u>H</u>$_A$$CH_B$), 4.59 (2H ddd, *J* = 5.4, 1.6, 1.4 Hz, C<u>H</u>$_2$-CH=CH_2), 3.76–3.87 (1H, m, H6), 3.43 (1H, d, *J* = 9.7 Hz, H2), 2.60 (1H, dd, *J* = 15.2, 7.2 Hz, CH_A<u>H</u>$_B$$CO_2$All), 2.45 (1H, dd, *J* = 15.2, 5.8 Hz, C<u>H</u>$_A$$H_B$$CO_2$All), 2.14 (3H, d, *J* = 1.4 Hz, =C-Me), 1.82–1.92 (1H, m, H4), 1.65–1.76 (1H, m, H5), 1.45–1.62 (1H, m, H3), 1.23–1.45 (2H, 2 x m, H4, H5), 0.75 (3H, d, *J* = 6.6 Hz, C3-Me).

^{13}C NMR (75 MHz): δ = 172.2 (0, CO_2H), 171.2 (0, <u>C</u>O_2All), 159.8 (0, Me<u>C</u>=C), 132.2 (1, <u>C</u>H=CH_2), 118.2 (2, CH=<u>C</u>H_2), 117.7 (1, <u>C</u>CO_2H), 89.8 (1, C2), 74.1 (1, C6), 65.3 (2, <u>C</u>H_2CH=CH_2), 41.5 (2, <u>C</u>$H_2$$CO_2$All), 32.8 (1, C3), 32.3 (2, C4), 31.5 (2, C5), 17.6 (3, C3-Me), 14.8 (3, =C-<u>Me</u>).

LRMS (CI mode, NH_3): *m/z* = 300 [$(M+NH_4)^+$, 45%], 283 [$(M+H)^+$, 100%], 264 (50).

HRMS (CI mode, NH_3): Found, $(M+NH_4)^+$, 300.1818. $C_{15}H_{22}O_5$+NH_4 requires M, 300.1811.

Prop-2-enyl (2*S*,3*S*,6*R*)-2-{[(*E*)-3-Oxo-1-methylpropenyl]-3-methyloxan-6-yl}ethanoate (4):
Freshly distilled oxalyl chloride (0.26 mL, 3 mmol) was added dropwise to a solution of DMF (81µL, 1.05 mmol) in CH_2Cl_2 (2 mL) at 0°C. The resulting white suspension was stirred at 0°C for 1 h whereupon the solvent and excess oxalyl chloride were removed *in vacuo*. The remaining white solid was suspended in THF (2.5 mL) and MeCN (1.5 mL) and cooled to –35°C. A solution of carboxylic acid **36** (282 mg, 1 mmol) and anhyd pyridine (85µL, 1.05 mmol) in THF (2.5 mL) was added via cannula and the mixture stirred at –35°C for 1 h. The mixture was cooled to –80°C and a suspension of CuI (19 mg, 0.1 mmol) in THF (1.5 mL) was added. $LiAlH(Ot\text{-}Bu)_3$ (1M in THF, 2.1 mL, 2.1 mmol) was then added over 8 min and the mixture stirred at –80°C for 25 min. The mixture was quenched at –80°C by the simultaneous addition of HCl (1M, 10 mL) and Et_2O (10 mL). The mixture was then warmed to r.t. and diluted with Et_2O (30 mL) and shaken with H_2O (30 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 40 mL). The combined organic layers were shaken with sat $NaHCO_3$ (40 mL), dried ($MgSO_4$), concentrated *in vacuo*, and the residue purified by chromatography (silica gel, hexanes:Et_2O = 80:20) to give aldehyde **4** (205 mg, 0.77 mmol, 77%) as a colourless oil: $[\alpha]_D$ +47.0 (*c* = 0.6 in $CHCl_3$).

IR (film): ν = 2923 (s), 2853 (s), 1738 (s), 1676 (s), 1456 (m), 1276 (m), 1191 (m), 1072 (s), 929 (m) cm^{-1}.

^1H NMR (270 MHz): δ = 10.06 (1H, d, *J* = 7.9 Hz, CHO), 5.88–5.94 (1H, m, =CH-CHO), 5.90 (1H, ddt, *J* = 17.2, 10.4, 5.5 Hz, C<u>H</u>=CH_2), 5.29 (1H, ddt, *J* = 17.2, 1.6, 1.6 Hz, CH=CH_AC<u>H</u>$_B$), 5.20 (1H, ddt, *J* = 10.4, 1.6, 1.3 Hz, CH=C<u>H</u>$_A$$CH_B$), 4.58 (2H ddd, *J* = 5.6, 1.6, 1.3 Hz, C<u>H</u>$_2$-CH=CH_2), 3.83 (1H, dddd, *J* = 10.6, 7.7, 5.2, 2.1 Hz, H6), 3.49 (1H, d, *J* = 9.9 Hz, H2), 2.59 (1H, dd, *J* = 15.2, 7.2 Hz, CH_A<u>H</u>$_B$$CO_2$All), 2.46 (1H, dd, *J* = 15.2, 7.2 Hz, C<u>H</u>$_A$$H_B$$CO_2$All), 2.14 (3H, d, *J* = 1.6 Hz, =C-Me), 1.84–1.96 (1H, m, H4), 1.66–1.77 (1H, m, H5), 1.46–1.62 (1H, m, H3), 1.23–1.45 (2H, 2 x m, H4, H5), 0.75 (3H, d, *J* = 6.8 Hz, C3-Me).

^{13}C NMR (75 MHz): δ = 191.6 (1, CHO), 170.9 (0, CO_2), 160.1 (0, Me<u>C</u>=C), 132.2 (1, <u>C</u>H=CH_2), 128.8 (1, =<u>C</u>H-CHO), 118.2 (2, CH=<u>C</u>H_2), 89.2 (1, C2), 74.1 (1, C6), 65.2 (2, <u>C</u>H_2CH=CH_2), 41.4 (2, <u>C</u>$H_2$$CO_2$All), 32.6 (1, C3), 32.3 (2, C4), 31.5 (2, C5), 17.6 (3, C3-Me), 13.2 (3, =C-<u>Me</u>).

LRMS (CI mode, NH_3): *m/z* = 284 [$(M+NH_4)^+$, 35%], 267 [$(M+H)^+$, 100%], 237 (25), 122 (30).

HRMS (CI mode, NH_3): Found, $(M+H)^+$, 267.1575. $C_{15}H_{22}O_4$+H requires M, 267.1596.

Prop-2-enyl (2*S*,3*S*,6*R*)-{[(1*E*,3*E*,7*E*,11*S*,10*S*,9*R*,5*R*)-11-{[(1,1-Dimethylethyl)dimethylsilyl]oxy}-10-methoxy-1,5,7,9-tetramethyldodeca-1,3,7-trienyl]-3-methyloxan-6-yl}-ethanoate (38):
A solution of LDA in THF (0.72M , 0.74 mL, 0.53 mmol) was added dropwise to a solution of sulfone **3** (254 mg, 0.48 mmol) in THF (9 mL) at –80°C. The resulting deep yellow solution was stirred at –80°C for 1 h whereupon a precooled (–80°C) solution of aldehyde **4** (113 mg, 0.42 mmol) in THF (2.3 mL) was added via cannula. The mixture was stirred at –80°C for a further 90 min and then warmed to r.t. and stirred for 30 min. The yellow solution was diluted with Et_2O (20 mL) and shaken with brine (20 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and the residue purified by chromatography (silica gel, hexanes:Et_2O = 96:4) to give diene **38** (157 mg, 0.27 mmol, 65%) as a colourless oil: $[\alpha]_D$ +64.6 (*c* = 1.0 in $CHCl_3$).

IR (film): ν = 2928 (s), 2856 (s), 1740 (s), 1455 (s), 1378 (s), 1254 (s), 1189 (s), 1108 (s), 1066 (s), (s), 930 (s), 833 (s), 775 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 6.20 (1H, dd, *J* = 15.1, 10.7 Hz, H10), 5.87–5.93 (1H, m, H9), 5.88 (1H, ddt, *J* = 17.2, 10.4, 5.6 Hz, C<u>H</u>=CH_2), 5.57 (1H, dd, *J* = 15.0, 7.2 Hz, H11), 5.31 (1H, ddt, *J* = 17.2, 1.6, 1.5 Hz, CH=CH_A<u>H</u>$_B$), 5.20 (1H, ddt, *J* = 10.4, 1.4, 1.3 Hz, CH=C<u>H</u>$_A$$H_B$), 5.18 (1H, d, *J* = 8.3 Hz, H15), 4.58 (2H, ddd, *J* = 5.6, 1.4, 1.4 Hz, CH_2-CH=CH_2), 3.72–3.82 (1H, m, H3), 3.73 (1H, dq, *J* = 6.6, 6.4 Hz, H18), 3.47 (3H, s, OMe), 3.32 (1H, d, *J* = 9.9 Hz, H7), 2.79 (1H, dd, *J* = 6.8, 3.9 Hz, H17), 2.61 (1H, dd, *J* = 15.2, 6.4 Hz, CH_A<u>H</u>$_B$C=O), 2.53–2.63 (1H, m, H16), 2.43 (1H, dd, *J* = 15.2, 6.8 Hz, C<u>H</u>$_A$$H_B$C=O), 2.31–2.44 (1H, m, H12), 2.05 (1H, dd, *J* = 13.0, 6.2 Hz, H13), 1.88 (1H, dd, *J* = 13.0, 8.1 Hz, H13), 1.80–1.88 (1H, m, H5), 1.70 (3H, d, *J* = 1.0 Hz, C8-Me), 1.64–1.70 (1H, m, H4), 1.61 (3H, d, *J* = 1.5 Hz, C14-Me), 1.47–1.54 (1H, m, H6), 1.15–1.44 (2H, m, H4, H5), 1.04 (3H, d, *J* = 6.4 Hz, H19), 1.00 (3H, d, *J* = 7.0 Hz, C16-Me), 0.93 (3H, d, *J* = 6.8 Hz, C12-Me), 0.91 (9H, s, CMe_3), 0.70 (3H, d, *J* = 6.6 Hz, C6-Me), 0.09 (3H, s, $SiMe_2$), 0.07 (3H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 171.2 (0, C1), 140.8 (1, C11), 134.3 (0, C8), 132.8 (0, C14), 132.3 (1, <u>C</u>H=CH_2), 128.6 (1, C9), 128.0 (1, C15), 123.9 (1, C10), 118.1 (2, CH=<u>C</u>H_2), 90.7 (1, C7), 90.3 (1, C17), 74.0 (1, C3), 70.9 (1, C18), 65.1 (2, <u>C</u>H_2-CH=CH_2), 61.4 (3, OMe), 47.5 (2, C13), 41.7 (2, C2), 35.2 (1, C12), 34.2 (1, C16), 32.5 (2, C4), 32.4 (1, C6), 31.8 (2, C5), 26.1 (3, 3C, C<u>Me</u>$_3$), 20.1 (3, C19), 19.6 (3, C12-<u>Me</u>), 18.9 (3, C16-<u>Me</u>), 18.3 (0, <u>C</u>Me_3), 17.9 (3, C6-<u>Me</u>), 16.3 (3, C14-<u>Me</u>), 12.3 (3, C8-<u>Me</u>), –4.4 (3, $SiMe_2$), –4.5 (3, $SiMe_2$).

LRMS (CI mode, NH_3): *m/z* = 594 [$(M+NH_4)^+$, 70%], 576 [$(M+H)^+$, 50%], 291 (100), 283 (80), 159 (40).

HRMS (EI mode): Found, $(M)^{+\bullet}$, 576.4205. $C_{34}H_{60}O_5Si$ requires M, 576.4210.

Prop-2-enyl (2*S*,3*S*,6*R*)-{[(1*E*,3*E*,7*E*,11*S*,10*S*,9*R*,5R)-11-Hydroxy-10-methoxy-1,5,7,9-tetramethyldodeca-1,3,7-trienyl]-3-methyloxan-6-yl}ethanoate (39):

HF•pyridine (0.24 mL, ca. 8.0 mmol) was added dropwise to a solution of TBS ether **38** (90 mg, 0.16 mmol) in THF (8 mL) in a polypropylene flask at r.t. The mixture was stirred for 24 h whereupon Et_2O (10 mL) was added and the mixture shaken with H_2O (20 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) concentrated *in vacuo*, and the pale yellow residue purified by chromatography (silica gel, hexanes:Et_2O = 70:30) to give **39** (57 mg, 0.12 mmol, 77%) as a colourless oil: $[\alpha]_D$ +68.9 (*c* = 1.1 in $CHCl_3$).

IR (film): ν = 3479 (br m), 2925 (s), 1740 (s), 1453 (s), 1377 (s), 1190 (s), 1101 (s), 1019 (s), 968 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 6.14 (1H, dd, *J* = 15.1, 11.0 Hz, H10), 5.87–5.94 (1H, m, H9), 5.88 (1H, ddt, *J* = 17.3, 10.4, 5.5 Hz, C<u>H</u>=CH_2), 5.48 (1H, dd, *J* = 15.1, 8.1 Hz, H11), 5.29 (1H, ddt, *J* = 17.3, 1.8, 1.5 Hz, CH=CH_A<u>H_B</u>), 5.19 (1H, ddt, *J* = 10.3, 1.8, 1.1 Hz, CH=C<u>H_A</u>H_B), 5.10 (1H, d, *J* = 9.9 Hz, H15), 4.57 (2H, ddd, *J* = 5.5, 1.5, 1.5 Hz, <u>CH_2</u>-CH=CH_2), 3.73–3.82 (1H, m, H3), 3.59 (1H, dq, *J* = 6.6, 6.3 Hz, H18), 3.54 (3H, s, OMe), 3.32 (1H, d, *J* = 9.5 Hz, H7), 2.76 (1H, dd, *J* = 7.2, 3.7 Hz, H17), 2.62 (1H, dd, *J* = 15.1, 5.9 Hz, CH_A<u>H_B</u>C=O), 2.49–2.60 (1H, m, H16), 2.42 (1H, dd, *J* = 15.1, 7.0 Hz, C<u>H_A</u>H_BC=O), 2.30–2.40 (1H, m, H12), 1.99 (1H, dd, *J* = 11.4, 5.9 Hz, H13), 1.94 (1H, dd, *J* = 11.4, 6.4 Hz, H13), 1.78–1.87 (1H, m, H5), 1.69 (3H, d, *J* = 0.5 Hz, C8-Me), 1.65–1.73 (1H, m, H4), 1.55 (3H, d, *J* = 1.1 Hz, C14-Me), 1.47–1.62 (1H, m, H6), 1.14–1.40 (2H, m, H4, H5), 1.04 (3H, d, *J* = 6.3 Hz, H19), 1.02 (3H, d, *J* = 7.7 Hz, C16-Me), 0.95 (3H, d, *J* = 6.6 Hz, C12-Me), 0.69 (3H, d, *J* = 6.6 Hz, C6-Me).

^{13}C NMR (75 MHz): δ = 171.2 (0, C1), 140.9 (1, C11), 134.1 (0, C8), 133.2 (0, C14), 132.3 (1, <u>C</u>H=CH_2), 129.0 (1, C9), 127.7 (1, C15), 124.1 (1, C10), 118.1 (2, CH=<u>C</u>H_2), 90.7 (1, 2C, C7, C17), 74.0 (1, C3), 69.4 (1, C18), 65.1 (2, <u>C</u>H_2-CH=CH_2), 61.9 (3, OMe), 48.0 (2, C13), 41.5 (2, C2), 35.5 (1, C12), 34.6 (1, C16), 32.4 (2, C4), 32.3 (1, C6), 31.8 (2, C5), 20.5 (3, C19), 20.0 (3, C12-<u>Me</u>), 18.5 (3, C16-<u>Me</u>), 17.8 (3, C3-<u>Me</u>), 16.3 (3, C14-<u>Me</u>), 12.3 (3, C8-<u>Me</u>).

LRMS (CI mode, NH_3): *m/z* = 480 [$(M+NH_4)^+$, 10%], 463 [$(M+H)^+$, 50%], 291 (100), 95 (65).

HRMS (CI mode, NH_3): Found, $(M+NH_4)^+$, 480.3714. $C_{28}H_{46}O_5$+NH_4 requires M, 480.3689.

Prop-2-enyl (2*S*,3*S*,6*R*)-{[(1*E*,3*E*,11*S*,10*S*,9*R*,8*R*,7*R*,5R)-7,8-Epoxy-11-hydroxy-10-methoxy-1,5,7,9-tetramethyldodeca-1,3-dienyl]-3-methyloxan-6-yl}ethanoate (40):

$VO(acac)_2$ (0.4 mg, 0.002 mmol) was added to a solution of alkene **39** (23 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) at 0°C. To the resulting blue solution was added *t*-BuO_2H (5.5M in decane, 18 µL, 0.1 mmol) to give a dark brown solution. The mixture was monitored by TLC, more $VO(acac)_2$ and *t*-BuO_2H being added as required. After 26 h, CH_2Cl_2 (3 mL) was added and the mixture was shaken with brine (5 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 x 5 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*, and the pale yellow residue purified by chromatography (silica gel, hexanes:Et_2O = 50:50) to give oxirane **40** (12 mg, 0.03 mmol, 52%) as a colourless oil: $[\alpha]_D$ +36.8 (*c* = 1 in $CHCl_3$).

IR (film): ν = 3472 (br m), 2926 (s), 1736 (s), 1457 (s), 1384 (s), 1192 (s), 1100 (s), 1019 (s), 733 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 6.22 (1H, ddd, *J* = 15.3, 10.7, 1.0 Hz, H10), 5.89 (1H, ddt, *J* = 17.2, 10.4, 5.6 Hz, C<u>H</u>=CH_2), 5.87–5.92 (1H, m, H9), 5.57 (1H, dd, *J* = 15.1, 7.5 Hz, H11), 5.30 (1H, ddt, *J* = 17.2, 1.6, 1.5 Hz, CH=CH_A<u>H_B</u>), 5.19 (1H, ddt, *J* = 10.4, 1.5, 1.4 Hz, CH=C<u>H_A</u>H_B), 4.57 (2H, ddd, *J* = 5.6, 1.4, 1.2 Hz, <u>CH_2</u>-CH=CH_2), 3.96 (1H, dq, *J* = 6.4, 6.2 Hz, H18), 3.73–3.83 (1H, m, H3), 3.58 (3H, s, OMe), 3.33 (1H, d, *J* = 9.9 Hz, H7), 2.96 (1H, dd, *J* = 6.4, 3.1 Hz, H17), 2.79 (1H, d, *J* = 9.3 Hz, H15), 2.62 (1H, dd, *J* = 15.1, 6.6 Hz, CH_A<u>H_B</u>C=O), 2.43 (1H, dd, *J* = 15.1, 6.6 Hz, C<u>H_A</u>H_BC=O), 2.30–2.42 (1H, m, H12), 1.88 (1H, dd, *J* = 13.7, 6.4 Hz, H13), 1.78–1.84 (1H, m, H5), 1.70 (3H, d, *J* = 1.2 Hz, C8-Me), 1.46–1.78 (3H, m, H16, H4, H6), 1.26 (3H, s, C14-Me), 1.20–1.44 (3H, m, H13, H4, H5), 1.21 (3H, d, *J* = 6.4 Hz, 19), 1.08 (3H, d, *J* = 7.2 Hz, C16-Me), 1.02 (3H, d, *J* = 6.8 Hz, C12-Me), 0.70 (3H, d, *J* = 6.6 Hz, C6-Me).

^{13}C NMR (75 MHz): δ = 171.1 (0, C1), 140.0 (1, C11), 135.0 (0, C8), 132.3 (1, <u>C</u>H=CH_2), 128.2 (1, C9), 124.3 (1, C10), 118.0 (2, CH=<u>C</u>H_2), 90.6 (1, C7), 90.1 (1, C17), 74.1 (1, C3), 68.9 (1, C18), 65.0 (2, <u>C</u>H_2-CH=CH_2), 63.8 (1, C15), 61.9 (3, OMe), 59.5 (0, C14), 46.1 (2, C2), 41.6 (2, C13), 35.2 (1, C12), 34.3 (1, C16), 32.5 (2, C5), 32.4 (1, C6), 31.8 (2, C4), 20.7 (3, C12-<u>Me</u>), 19.8 (3, C19), 17.8 (3, C6-<u>Me</u>), 17.2 (3, C14-<u>Me</u>), 14.6 (3, C16-<u>Me</u>), 12.3 (3, C8-<u>Me</u>).

LRMS (CI mode, NH_3): *m/z* = 496 [$(M+NH_4)^+$, 100%], 478 [$(M+H)^+$, 30%], 461 (45), 291 (45), 129 (60).

HRMS (CI mode, NH_3): Found, $(M+NH_4)^+$, 496.3646. $C_{28}H_{46}O_6$+NH_4 requires M, 496.3638.

(2*S*,3*S*,6*R*)-{[(1*E*,3*E*,11*S*,10*S*,9*R*,8*R*,7*R*,5R)-7,8-Epoxy-11-hydroxy-10-methoxy-1,5,7,9-tetramethyldodeca-1,3-dienyl]-3-methyloxan-6-yl}ethanoic Acid (2):

To a solution of allyl ester **40** (10 mg, 0.021 mmol) in THF (0.5 mL) at r.t. was added $Pd(PPh_3)_4$ (4.8 mg, 0.004 mmol) followed by anhyd morpholine (18 µL, 0.21 mmol). After 5 h, the mixture was diluted with Et_2O (2 mL) and shaken with H_2O (3 mL) and HCl (2M, 0.1 mL, 0.21 mmol). The organic layer was separated and the aqueous layer washed with EtOAc (5 x 4 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), concentrated *in vacuo*, and the residue purified by chromatography (silica gel, $CHCl_3$:MeOH = 95:5) to give Herboxidiene A **(2)** (6 mg, 0.014 mmol, 67%) as a colourless oil: $[\alpha]_D$ +35.3 (*c* = 0.3 in $CHCl_3$).

IR (film): ν = 3425 (br m), 3190 (br m), 2967 (s), 2365 (s), 1719 (s), 1457 (s), 1378 (s), 1308 (s), 1255 (s), 1199 (s), 1155 (s), 1070 (s), 968 (s), 885 (m), 797 (m), 756 (s), 700 (m) cm^{-1}.

LRMS (CI mode, NH_3): *m/z* = 439 [$(M+H)^+$, 25%], 421 (100), 389 (75), 251 (80), 143 (75), 123 (100).

HRMS (CI mode, NH_3): Found, $(M+NH_4)^+$, 456.2231. $C_{25}H_{42}O_6$+NH_4 requires M, 456.3325.

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