A synthesis of herboxidiene

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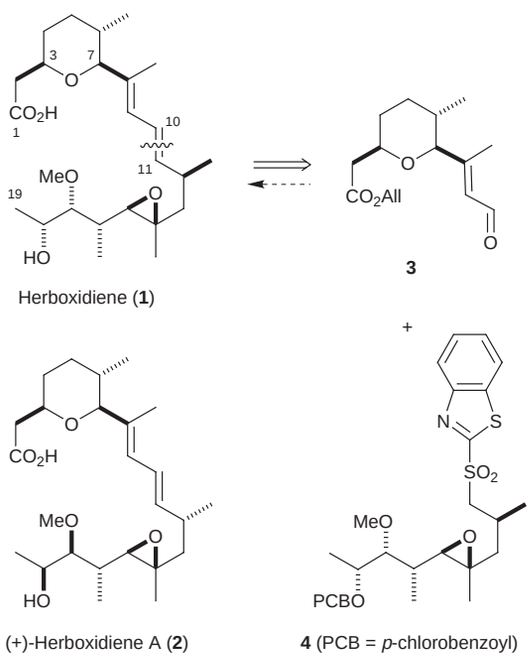
Received (in Cambridge) 6th January 1999, Accepted 3rd February 1999

The natural herbicide herboxidiene was constructed from two key fragments using a modified Julia olefination based on the benzothiazolyl sulfone activator. Key steps in the synthesis of the C1–C10 oxane fragment were (a) a modified Julia olefination using a 1-phenyl-1*H*-tetrazolyl sulfone as activator and (b) an intramolecular addition of an alkoxide to an α,β-unsaturated ester. Key steps in the synthesis of the C11–C19 polyketide fragment were (a) a directed aldol reaction using a camphor-10,2-sultam as auxiliary; (b) an Ireland–Claisen rearrangement and (c) a hydroxy-directed epoxidation.

Introduction

Screening of microbial fermentation broths for herbicidal activity led to the discovery of a metabolite from *Streptomyces* sp. A7847 which displays exceptional phytotoxicity towards a broad range of broadleaf weeds such as oilseed rape (*Brassica napus*), wild buckwheat (*Polygonum convolvulus*), morning glory (*Ipomoea* sp.) and hemp sesbania (*Sesbania exaltata*).[1] At doses of 35 g hectare^{-1} 90% inhibition of the aforementioned weeds was observed and as little as 7 g hectare^{-1} secured a 75% inhibition; however, even at doses of 5.6 kg hectare^{-1}, the active agent, herboxidiene (**1**),† was innocuous towards wheat (*Triticum aestivum*). Early structural studies established the polyketide nature of the metabolite, its connectivity and the relative configuration of 5 of the 9 stereogenic centres.[2] A full assignment of the relative and absolute stereochemistry was reported by a Novartis group in 1997 through a combination of selective degradation of the natural product and asymmetric synthesis of the respective fragments and their conclusions corroborated by X-ray analysis.[3] The potent herbicidal activity of herboxidiene and the recent discovery that it up-regulates gene expression of low density lipoprotein receptors[4] has spurred interest in its total synthesis. Our first approach to herboxidiene and its analogues was launched before the complete stereochemistry had been assigned and culminated in herboxidiene A (**2**), a diastereoisomer differing from the natural product at C12, C17 and C18.[5] Asymmetric syntheses of major fragments have also been recorded by the Banwell[6–8] and Novartis[3] groups. We now report the first total synthesis of herboxidiene (**1**) based on the union of the benzothiazolyl sulfone **4** and the aldehyde **3** (Scheme 1) using a modified Julia olefination.[9,10] Our synthesis also incorporates the first synthetic application of a new variant of the modified Julia olefination based on the use of 1-phenyl-1*H*-tetrazol-5-yl sulfones.[11]



Scheme 1

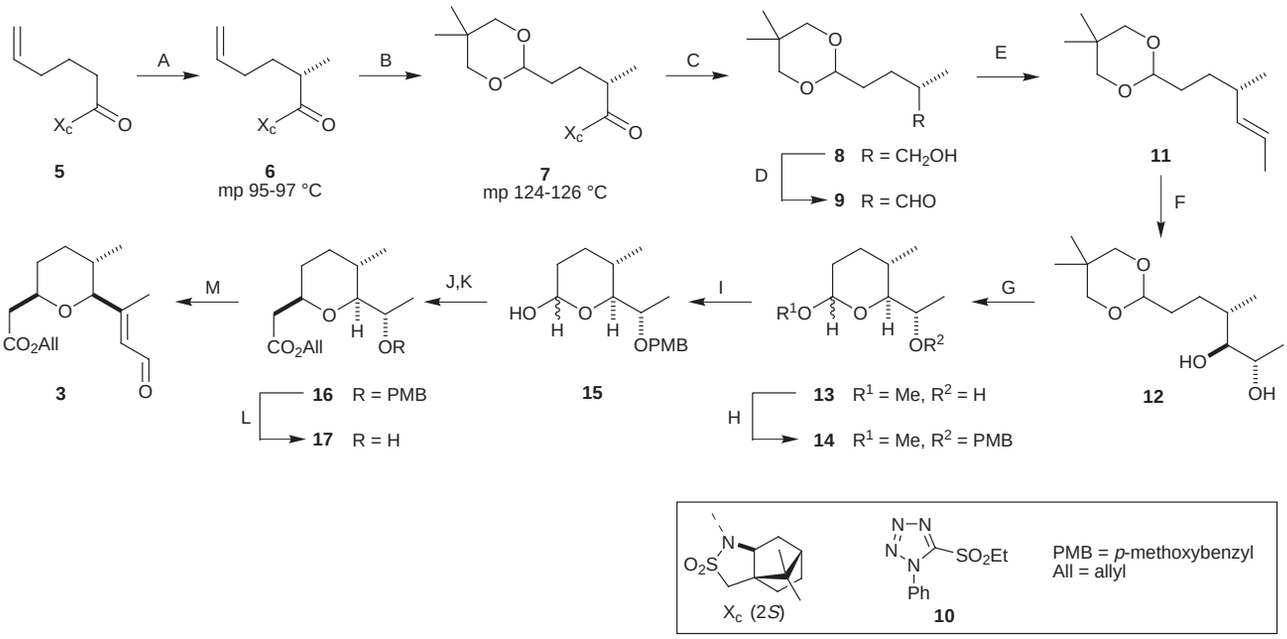
Results and discussion

Synthesis of the C1–C10 aldehyde fragment 3

Our previous synthesis of aldehyde **3**[5] was substantially modified in the quest for a more practical route. α-Alkylation of the hex-5-enoyl bornane-10,2-sultam **5** (Scheme 2) afforded the alkylation product **6** with excellent stereoselectivity.[12] A simple recrystallisation yielded analytically pure product with no detectable isomeric contaminants in 80% yield. Ozonolysis of **6** in MeOH–CH_2Cl_2 (1 : 3) yielded a mixture of the corresponding aldehyde (minor) and dimethyl acetal (major) after reductive work-up and the mixture was converted to the crystalline acetal **7** on treatment with 2,2-dimethylpropane-1,3-diol in the presence of *p*-TsOH. Acetal **7** again only needed recrystallisation to yield pure product in 72% overall yield from **6**. Alcohol **8** derived from reductive removal of the chiral auxiliary was the most sensitive intermediate in the entire synthesis owing to easy acid-catalysed intramolecular transacetalisation but with due care, it could be purified by distillation and oxidised to the corresponding aldehyde **9** in 96% yield.

The next step of the sequence required a 2-carbon chain extension of aldehyde **9** with concomitant generation of the *trans*-alkene **11**. We chose this and a later transformation (*vide infra*) as vehicles for displaying the advantages of the modified Julia olefination in fragment linkage reactions. Recent detailed studies have revealed that the yield and stereoselectivity of the modified Julia olefination is sensitive to the base used to deprotonate the sulfone and solvent polarity.[13–15] A noteworthy new development is the discovery[11] that 1-phenyl-1*H*-tetrazolyl

† The IUPAC name for herboxidiene is: 2-[3,4,5,6-tetrahydro-5-methyl-6-(7,8-epoxy-11-hydroxy-10-methoxy-1,5,7,9-tetramethyldodec-1,3-dienyl)-2*H*-pyran-2-yl]ethanoic acid.



Scheme 2 *Reagents and conditions:*

A 80% (a) BuLi, THF, −80 °C, 2 h; (b) MeI, DMPU, −80 °C→rt, 12 h
B 72% (a) O_3, MeOH–CH_2Cl_2 (1:3), −78 °C, 2 h; (b) Me_2S, −78 °C→rt, 12 h; (c) 2,2-dimethylpropane-1,3-diol, *p*-TsOH, PhMe, Δ (−H_2O), 12 h
C 93% $LiAlH_4$, Et_2O, rt, 12 h
D 96% Pyr·SO_3, Et_3N, DMSO, rt, 30 min
E 93% sulfone **10**, KHMDS, DME, −60 °C, 45 min
F 83% AD-mix α, $MeSO_2NH_2$, *t*-BuOH–H_2O (2:3), 0 °C, 18 h
G 73% TsOH, MeOH, rt, 3 d, α:β = 3:1
H 93% (a) KHMDS, THF, 0 °C, 20 min; (b) PMBCl, TBAI, 0 °C→rt, 24 h
I 74% AcOH–THF–H_2O (3:2:2), 65 °C, 2 h, α:β = 3:2
J 82% allyl diethylphosphonoacetate, Cs_2CO_3, THF, Δ, 18 h
K 89% *t*-BuOK, THF, −65 °C, 10 min, pure *cis* isomer
L 95% DDQ, H_2O–CH_2Cl_2 (1:15), rt, 30 min
M 54% 4 steps (see ref. 5).

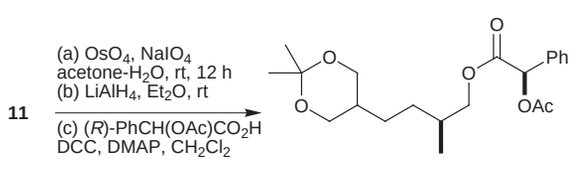
sulfones can give superior yields and stereoselectivity for the synthesis of simple alkenes compared with the benzothiazolyl sulfones advocated by Julia.[9,10] In the case at hand, addition of potassium hexamethyldisilazide (KHMDS) to a mixture of sulfone **10** and aldehyde **9** in 1,2-dimethoxyethane (DME) at −60 °C gave a 93% yield of the alkene **11** with good stereoselectivity (*E*:*Z* = 93:7). A highly stereoselective Sharpless asymmetric dihydroxylation[16] returned the diol **12** together with an inseparable minor diastereoisomer (dr = 93:7) in 83% yield. The identical dr for the last two steps indicates there was no racemisation in the Julia olefination.‡

As a prelude to another 2-carbon chain extension, we required deprotection of acetal **12** to the corresponding aldehyde (or its cyclic lactol congener). Unfortunately all attempts to achieve a mild hydrolysis failed.§ We therefore resorted to a detour beginning with slow methanolysis of the acetal **12** at room temperature in the presence of *p*-TsOH to give an inseparable mixture of 2 major anomeric acetals **13** (α:β = 3:1) in 73% yield. After protection of the remaining free hydroxy group as its *p*-methoxybenzyl ether **14**, the acetals were then hydrolysed with aqueous acetic acid to a mixture of anomeric lactols **15**. The requisite 2-carbon chain extension was accomplished using a Horner–Wadsworth–Emmons reaction with allyl diethylphosphonoacetate in the presence of caesium carbonate whereupon the intermediate unsaturated ester underwent ring closure to a mixture of 2 isomeric oxaneacetic esters (dr = 2:3) in which the desired isomer **16** was the minor component. Protracted heating of the mixture with caesium carbonate led to no change in ratio suggesting that the oxanes were the products of a kinetically controlled conjugate addition.¶ However, on treatment with potassium *tert*-butoxide at −65 °C, the mixture isomerised rapidly and efficiently to give the desired isomer **16** as the exclusive product.‖ At this stage, a chromatographic purification removed all minor diastereoisomeric impurities accrued since the Julia olefination 7 steps previous to give the oxaneacetic ester **16** in 73% overall yield from **15** and 28% overall from aldehyde **9**. To complete the sequence, oxidative cleavage of the *p*-methoxybenzyl ether with DDQ[17] gave alcohol **17** which was converted to the desired fragment **3** in four further steps as described previously.[5]

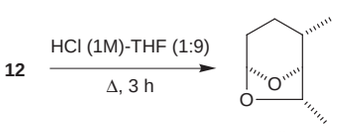
Synthesis of the C11–C19 sulfone fragment 4

Construction of sulfone **4** began with a highly stereoselective

‡ Further proof that the modified Julia olefination proceeded without racemisation was gleaned by oxidative cleavage of alkene **11** according to the following sequence. Comparison of the ^1H and ^{13}C NMR spectra of the mandelate **37** with a sample prepared from partially racemised olefin revealed a dr of ≥94:6.

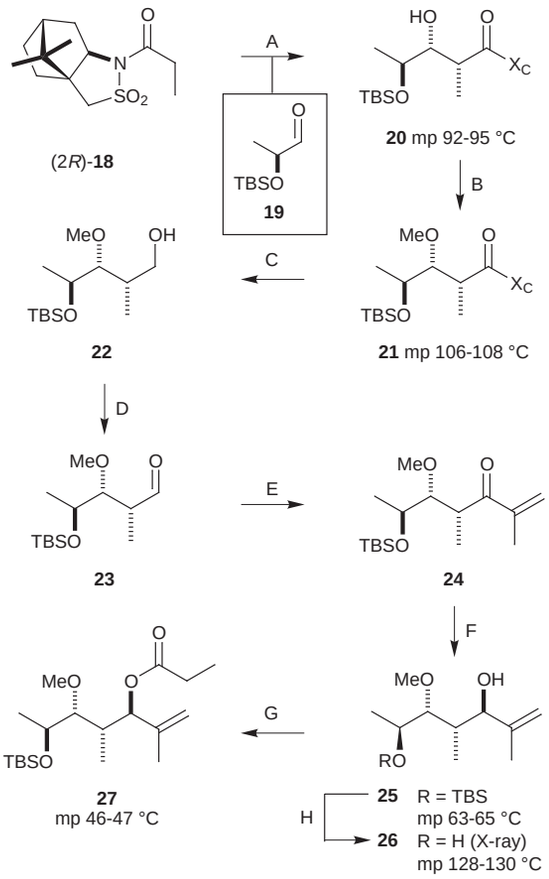


§ Under strongly acidic conditions (1 M HCl in THF, reflux, 3 h), cyclodehydration occurred to give a pleasant smelling, volatile bicyclic acetal **38**.



¶ Banwell and co-workers[29] showed that under non-equilibrating conditions, the stereochemistry of oxaneacetic esters formed by the intramolecular Michael addition of O-nucleophiles to tethered acrylates is a kinetic process whose stereochemistry is governed by the double bond geometry of the acrylate.

‖ The equilibration of oxaneacetic esters with alkoxide bases was reported by Maurer and co-workers in 1979[30] and has been used by others.[5,31,32]



Scheme 3 *Reagents and conditions:*

A	75%	(a) Et_2BOTf, CH_2Cl_2, −5 °C; (b) *i*-Pr_2NEt, 30 min; (c) **19**, −78 °C, 3 h
B	90%	MeOTf, proton sponge®, PhMe, 80 °C, 24 h
C	99%	$LiAlH_4$, Et_2O, 0 °C, 15 min
D	91%	Dess–Martin periodinane, CH_2Cl_2, 0 °C→rt, 2 h
E	80%	(a) CH_2=C(Me)MgBr, Et_2O, 0 °C, 1 h; (b) DMP, CH_2Cl_2, rt, 4 h
F	75%	$LiAlH_4$, LiI, Et_2O, −100 °C, 1 h
G	97%	$(EtCO)_2O$, DMAP, pyridine, rt, 16 h
H	72%	TBAF·$3H_2O$, THF, rt, 15 min.

boron-mediated aldol reaction between propionyl sultam **18** and the (*S*)-aldehyde **19** (Scheme 3).[12,18] Adduct **20** was obtained enantiopure in 75% yield after a single recrystallisation from hexanes as befits the conjunction of a matched pair. To effect methylation of the aldol **20**, a combination of proton sponge® [1,8-bis(dimethylamino)naphthalene] and methyl triflate was employed. These conditions represent a cheap hybrid formulation of two other costly mild methylation procedures popularised by Evans:[19] (a) methyl triflate (inexpensive) with 1,6-di-*tert*-butyl-4-methylpyridine (very expensive) and, (b) trimethyloxonium tetrafluoroborate (expensive) with proton sponge® (inexpensive). Methyl triflate and proton sponge® are compatible partners and produced the methylated adduct **21** in 90% yield with no trace of retroaldolisation.

Following reductive removal of the chiral auxiliary the alcohol **22** was oxidised with the Dess–Martin periodinane[20,21] to afford aldehyde **23** in excellent yield. Addition of isopropenylmagnesium bromide to aldehyde **23** was not stereoselective giving a mixture of allylic alcohols (*syn : anti* = 57 : 43) which was immediately oxidised to enone **24** in 80% overall yield. Reduction of enone **24** at −100 °C with lithium aluminium hydride in the presence of lithium iodide[22] was stereoselective affording a solid product which, according to NMR spectroscopic analysis, was a mixture of diastereoisomers (dr = 85 : 15). After recrystallisation of the solid product and careful chromatography of the residual mother liquors, a combined yield of 75% of enantiopure **25** was obtained. A single crystal X-ray

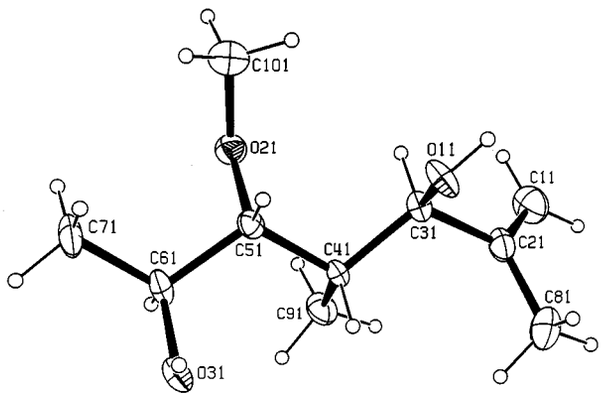


Fig. 1 X-Ray crystal structure of the diol **26**.

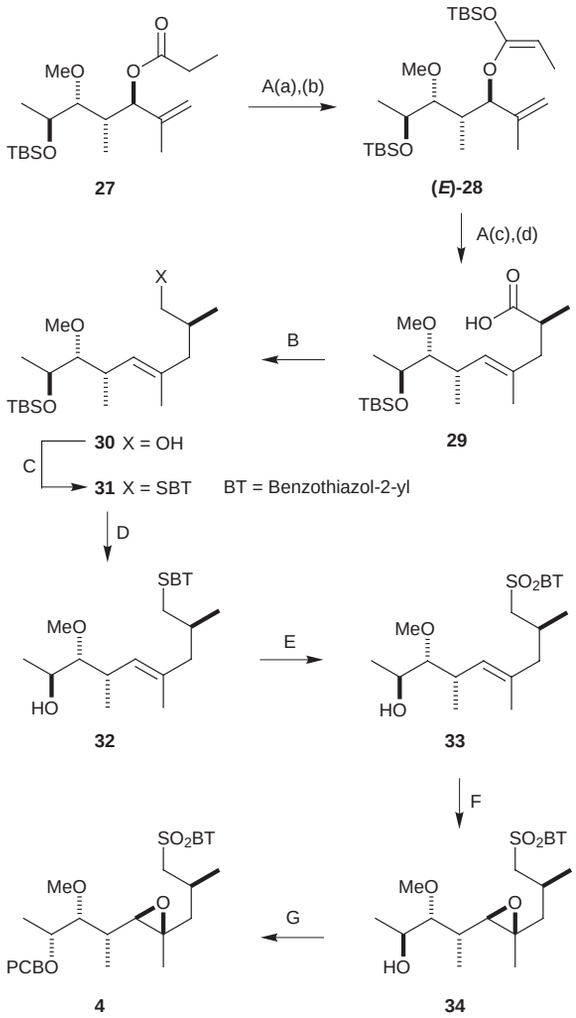
analysis of the corresponding diol **26** (Fig. 1) revealed that the reduction had proceeded with 1,3-*anti*-stereoselectivity.** Finally, esterification of the pure alcohol under standard conditions then afforded the propionate ester **27** in 97% yield.

Like Banwell before us,[7] we chose the chirality transfer inherent in the well-organised chair transition state typical of the Ireland–Claisen rearrangement[23] to introduce the C14–C15 trisubstituted alkene and the stereogenic centre at C12. Thus, the lithium enolate of propionate ester **27** (Scheme 4) was treated with TBSCl in hexanes followed by DMPU†† to give (*E*)-silyl ketene acetal **28.** Rearrangement of **28** followed by acid hydrolysis of the intermediate silyl esters lead to the formation of a diastereoisomeric mixture of carboxylic acids in 68% yield (dr = 86 : 14). After reduction to the corresponding alcohols, the diastereoisomers were easily separated by flash chromatography and the major isomer **30** subjected to a Mitsunobu reaction with 2-mercaptobenzothiazole[24] to give the thioether **31** in good yield. Oxidation of the thioether **31** to the corresponding sulfone by ammonium heptamolybdate tetrahydrate [$(NH_4)_6Mo_7O_{24}·4H_2O$] catalysis[25] required over 48 h for complete conversion. Furthermore, attempted TBS deprotection of the resulting sulfone with TBAF·$3H_2O$ lead to complete decomposition: only benzothiazolone was isolated in 86% yield. Simply reversing the order of the aforementioned steps solved both problems. TBS deprotection of the thioether **31** with TBAF·$3H_2O$ occurred in excellent yield with no detectable decomposition and the sulfur atom of the resulting alcohol **32** was then rapidly converted to the sulfone **33** *via* treatment with ammonium heptamolybdate tetrahydrate and H_2O_2 in EtOH.

The directed epoxidation reaction used in our synthesis of herboxidiene A[5] was redeployed for the oxidation of olefin **33**. The reactivity of an olefinic alcohol towards $VO(acac)_2$ catalysed epoxidation depends on the proximity of the hydroxy group to the alkene.[26] As a consequence, the oxidation of bishomoallylic alcohol **33** was extremely slow at sub-ambient temperatures and low catalyst loadings. Unfortunately, conducting the epoxidation in toluene at 60 °C [3 mol% $VO(acac)_2$, 1.5 equiv. *tert*-butyl hydroperoxide (TBHP)] resulted in ring closure to a tetrahydrofuran in 63% yield. Alternatively the reaction could be hurried at 0 °C if repeated portions of catalyst (total 40 mol%) were added but then acetates of the product **34** and starting material **31** were also formed. Success was eventually achieved using just 1 mol% of catalyst in a cold (−8 °C) solution of the olefin **33** in CH_2Cl_2 with addition of TBHP *via* a syringe pump over 48 h. After the addition was complete, the oxidation was allowed a further 24 h whereupon

** The chelation-controlled reduction of β-alkoxy ketones lacking a substituent on the intervening carbon using LiI–$LiAlH_4$ occurs with *syn*-stereoselectivity.[22]

†† The use of DMPU to assist enolate silylation at low temperature by TBSCl does not affect the enolate geometry.[33]



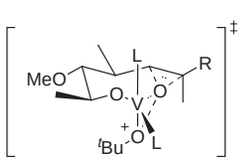
Scheme 4 *Reagents and conditions:*

A 68% (a) LDA, THF, −78 °C, 30 min; (b) TBSCl, DMPU; (c) −78 °C→Δ, 1 h; (d) aq. HCl
B 90% $LiAlH_4$, Et_2O, 0 °C, 10 min
C 99% BTSH, Ph_3P, DIAD, THF, 0 °C→rt, 2 h
D 98% TBAF·$3H_2O$, THF, rt, 32 h
E 88% Mo(VI), H_2O_2, H_2O–EtOH, rt, 24 h
F 69% $VO(acac)_2$, TBHP, CH_2Cl_2, −8 °C, 72 h
G 74% (a) Ph_3P, DMAD, THF, 0 °C; (b) PCBOH, 0 °C→rt, 3 h.

oxirane **34** was obtained in 69% yield as a *single diastereoisomer* together with 26% of recovered starting material **33**.‡‡ Concomitant oxidation of the thioether and olefin in **32** was also achieved with MCPBA to yield 46% of the epoxysulfone **34** directly (dr = 85 : 15).

To complete the synthesis of the fragment **4**, all that remained was to invert the stereogenic centre at C18 and to protect the resultant hydroxy group. Reasoning that an ester function would be a sufficiently robust protecting group for the imminent Julia olefination, a Mitsunobu reaction was the logical choice for the inversion operation.[27] Initial experiments employed the standard Mitsunobu conditions: *viz.*, a mixture

‡‡ The model **39** we used to predict the stereochemistry of the hydroxy-directed epoxidation was based on earlier work by Sharpless[34] and Mihelich.[35]



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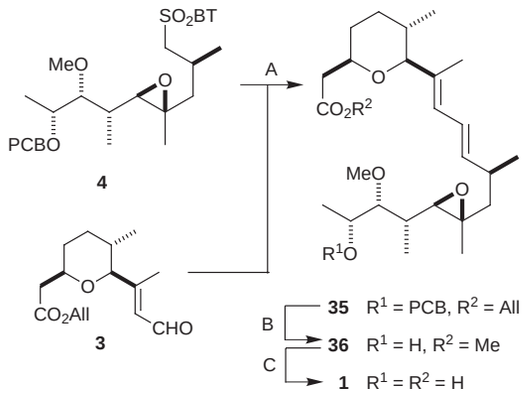


Scheme 5 *Reagents and conditions:*

A 81% (a) LDA, THF, −78 °C, 15 min; (b) **3**, −78 °C→−20 °C, 1.5 h
B 72% K_2CO_3, MeOH, Δ, 2 h
C 84% K_2CO_3, H_2O–MeOH (1 : 4), Δ, 1 h.

of the alcohol **34**, triphenylphosphine and *p*-chlorobenzoic acid (PCBOH) in THF at 0 °C was treated with either diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) and allowed to warm. Although these simple experiments afforded the desired ester **4**, yields were low to moderate (23–66%) and the product was very difficult to separate from the hydrazodicarboxylate by-product. To solve the purification problem the azodicarboxylate component was changed to the rarely used dimethyl congener which gives a water soluble hydrazodicarboxylate derivative but now significant quantities of acylated hydrazine adducts were formed and the yield of the product ester **4** was disappointing (30%). These problems were circumvented by forming the adduct between triphenylphosphine and dimethyl azodicarboxylate (DMAD)[28] in THF at 0 °C. The alcohol **34** was then added followed by the slow portionwise addition of the PCBOH. With the new protocol, ester **4** was produced rapidly in good yield (74%) and was easily separated from the hydrazodicarboxylate by-product by aqueous extraction.

Completion of synthesis—union of sulfone 4 and aldehyde 3

The one-pot Julia reaction between sulfone **4** and the aldehyde **3** (Scheme 5) yielded 81% of the protected herboxidiene derivative **35** with excellent selectivity (10*E* : *Z* = 91 : 9). Although direct double deprotection of **35** was possible by simple saponification, we favoured a two step deprotection protocol *via* the previously reported methyl ester of herboxidiene **36**[2] because separation of minor impurities and the (10*Z*)-isomer from allyl ester **35** by chromatography proved very difficult, as was direct purification of herboxidiene itself.§§ However, purification of the methyl ester **36** was straightforward and the high field ^1H and ^{13}C NMR spectra of our synthetic material compared favourably with the data reported by Isaac.[2] Finally, hydrolysis of pure methyl ester **36** with potassium carbonate in aqueous methanol gave herboxidiene in 84% yield.

Comparison of ^1H and ^{13}C NMR spectroscopic data for our synthetic herboxidiene with the data for the natural material reported by Isaac[2] revealed significant discrepancies in the C1–C3 region (see Tables 1 and 2). However, the sodium salt of our synthetic material (prepared by treatment with Na_2CO_3 in CD_3OD) provided ^1H and ^{13}C NMR data in complete agreement with those of Isaac. Therefore, the data reported for natural herboxidiene likely pertains to a carboxylate derivative rather than the free acid.

In conclusion, we have completed the first total synthesis of (+)-herboxidiene which features two variants of the modified

§§ Herboxidiene was not separable from *p*-chlorobenzoic acid or its minor (10*Z*)-isomer by simple flash chromatography.

Table 1 ^{1}H NMR data for natural and synthetic herboxidiene (**1**)

	Natural herboxidiene[a]			Synthetic herboxidiene[b]		
Position	δ	Multiplicity	J/Hz	δ	Multiplicity	J/Hz
$H2_A$	2.45	dd	14.1, 6.6	2.46	dd	15.6, 7.2
$H2_B$	2.25	dd	14.1, 7.5	2.38	dd	15.3, 5.7
H3	3.76	m	—	3.80–3.70	m	—
$H4_A$	1.86–1.68	m	—	1.90–1.82	m	—
$H4_B$	1.30	m	—	1.40–1.22	m	—
$H5_A$	1.86–1.68	m	—	1.74–1.65	m	—
$H5_B$	1.26–1.12	m	—	1.40–1.22	m	—
H6	1.55	m	—	1.60–1.43	m	—
C6-Me	0.66	d	6.6	0.68	d	6.6
H7	3.34	d	9.9	3.34	d	9.9
C8-Me	1.68	s	—	1.69	s	—
H9	5.90	d	11.1	5.92	d	10.8
H10	6.29	dd	15.0, 10.8	6.30	dd	15.0, 10.8
H11	5.45	dd	15.0, 9.0	5.47	dd	15.0, 9.1
H12	2.44	m	—	2.50–2.38	m	—
C12-Me	1.03	d	6.6	1.04	d	6.7
$H13_A$	1.91	dd	13.1, 4.3	1.92	dd	13.4, 4.3
$H13_B$	1.26–1.12	m	—	1.18	dd	13.0, 11.2
C14-Me	1.27	s	—	1.28	s	—
H15	2.65	d	9.6	2.65	d	9.4
H16	1.45	m	—	1.60–1.43	m	—
C16-Me	0.83	d	6.9	0.83	d	6.9
H17	2.96	dd	6.0, 4.5	2.97	dd	6.1, 4.3
H18	3.78	dq	6.6, 6.3	3.78	quintet	6.4
H19	1.11	d	6.6	1.10	d	6.4
OMe	3.52	s	—	3.52	s	—

[a] Recorded in CD_3OD at 300 MHz (data taken from ref. 2). [b] Recorded in CD_3OD at 360 MHz.

Table 2 ^{13}C NMR data for natural and synthetic herboxidiene (**1**)

Position	Natural[a] δ	Synthetic[b] δ	$\Delta\delta$	Position	Natural[a] δ	Synthetic[b] δ	$\Delta\delta$
C1	179.8	175.3	−4.5	C12	36.5	36.6	+0.1
C2	46.4	42.3	−4.1	C12-Me	22.7	22.7	0.0
C3	77.0	75.5	−1.5	C13	48.1	48.1	0.0
C4	33.1	32.8	−0.3	C14	62.6	62.6	0.0
C5	33.7	33.4	−0.3	C14-Me	16.8	16.8	0.0
C6	33.5	33.4	−0.1	C15	67.8	67.9	+0.1
C6-Me	18.2	18.1	−0.1	C16	36.4	36.4	0.0
C7	92.2	92.2	0.0	C16-Me	11.7	11.5	−0.2
C8	136.5	136.2	−0.3	C17	88.6	88.5	−0.1
C8-Me	12.1	12.1	0.0	C18	69.8	69.9	+0.1
C9	129.5	129.6	+0.1	C19	19.9	19.8	−0.1
C10	126.6	126.5	−0.1	OMe	61.9	61.9	0.0
C11	140.5	140.7	+0.2				

[a] Recorded in CD_3OD at 75 MHz (data taken from ref. 2). [b] Recorded in CD_3OD at 90 MHz.

Julia olefination in key fragment linkage reactions. We have shown that, depending on the nature of the olefinic linkage, variation of the heterocyclic sulfone can be used to optimise yield and stereoselectivity. Thus, in the case at hand, the benzothiazolyl sulfone unit is superior for the construction of the conjugated (*E,E*)-diene moiety whereas a 1-phenyl-1*H*-tetrazol-5-yl sulfone gave high yields and *trans*-selectivity in the construction of a simple alkene.

Experimental

For a description of general experimental details including spectroscopic information and solvent purification see reference 5. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM 360 or Aspect 400 spectrometers with chemical shift values being reported in ppm relative to residual chloroform ($\delta_H = 7.27$ or $\delta_C = 77.2$) as internal standard unless otherwise stated. All coupling constants (J) are reported in Hertz (Hz). The multiplicities in the ^{13}C NMR spectra 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 quaternary carbon), 1 = doublet (methine), 2 = triplet (methylene), 3 = quartet (methyl). For the sake of consistency, all NMR assignments refer to herboxidiene numbering. 5-Mercapto-1-phenyl-1*H*-tetrazole and 2-mercapto-1,3-benzothiazole were obtained from Aldrich.

(2*S*)-*N*-(Hex-5-enoyl)bornane-10,2-sultam 5

To a mechanically stirred suspension of sodium hydride (6.0 g, 60 wt%, 150 mmol) in PhMe (125 ml) at rt under N_2 was added dropwise a solution of (2*S*)-bornane-10,2-sultam (25 g, 116 mmol) in PhMe (250 ml) over 30 min. The mixture was stirred for a further 1 h before being treated dropwise with hex-5-enoyl chloride[36] (17.4 g, 131 mmol) in PhMe (125 ml) over 30 min and then allowed to stir overnight. The reaction mixture was then quenched by the addition of sat. aqueous NH_4Cl (100 ml) and the layers shaken and then separated. The aqueous phase was extracted with Et_2O (2 × 50 ml) and the combined organic extracts washed successively with NaOH (1 M, 2 × 20 ml), brine (40 ml), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was purified by column chromatography eluting

with 30% Et_2O in hexanes to yield the desired product contaminated by hex-5-enoic acid. The impurity was subsequently removed by dissolving the material in Et_2O (250 ml), washing with sat. aqueous $NaHCO_3$ (4 × 75 ml), drying ($MgSO_4$) and then concentrating *in vacuo* to yield the pure unsaturated acyl sultam **5** (34.0 g, 109 mmol, 94%) as a clear oil: bp (Kugelrohr oven) 250 °C/0.2 mmHg, $[\alpha]_D$ +91.8 (*c* 1.02, $CHCl_3$); ν_{max}(film)/cm^{-1} 2962s, 1701s, 1457m, 1414m, 1385m, 1335s, 1269s, 1238s, 1212s, 1112m, 1083m, 1057m, 1039m, 989m, 912m, 771m; δ_H(360 MHz, $CDCl_3$) 5.78 (1H, ddt, *J* 17.0, 10.3, 6.7, H3), 5.02 (1H, dq, *J* 17.1, 1.7, CH=CH_ZH$_E$), 4.96 (1H, ddt, *J* 10.2, 1.9, 1.1, CH=CH$_Z$$H_E$), 3.85 (1H, dd, *J* 7.3, 5.3, CHN), 3.49 (1H, d, *J* 13.8, CH_AH$_B$SO$_2$), 3.42 (1H, d, *J* 13.8, CH$_A$$H_BSO_2$), 2.78–2.63 (2H, m), 2.15–2.03 (4H, m), 1.95–1.83 (3H, m), 1.77 (2H, quintet, *J* 7.5), 1.44–1.30 (2H, m), 1.14 and 0.96 (3H each, s, CMe_2); δ_C(90 MHz, $CDCl_3$) 171.9 (0), 137.8 (1), 115.5 (2), 65.3 (1), 53.1 (2), 48.5 (0), 47.9 (0), 44.8 (1), 38.6 (2), 34.9 (2), 33.0 (2), 32.9 (2), 26.6 (2), 23.7 (2), 21.0 (3), 20.0 (3); *m*/*z* (EI mode) 311 (92%), 257 (31), 135 (100), 97 (47), 69 (69) (Found: C, 61.62; H, 8.05; N, 4.51. $C_{16}H_{25}NO_3S$ requires C, 61.70; H, 8.09; N, 4.50%).

(2*S*)-*N*-[(*S*)-2-Methylhex-5-enoyl]bornane-10,2-sultam 6

To a stirred solution of the acyl sultam **5** (15.6 g, 50.2 mmol) in anhydrous THF (250 ml) at −80 °C (internal temperature) under N_2 was added BuLi (21.7 ml, 2.31 M in hexanes, 50.1 mmol) *via* a syringe-pump over 1 h. After the addition was complete, the reaction mixture was stirred at −80 °C for a further 1 h before being treated dropwise with a solution of methyl iodide (9.4 ml, 21.4 g, 151 mmol) in anhydrous dimethylpropylene urea (DMPU, 18.2 ml, 19.3 g, 151 mmol) over 25 min. The reaction mixture was then allowed to warm slowly to −60 °C, stirred for 1 h and then allowed to warm to rt overnight. After this time the mixture was diluted with H_2O (200 ml) and Et_2O (200 ml) and the layers shaken and then separated. The aqueous phase was then extracted with Et_2O (3 × 50 ml) and the combined organic extracts washed successively with H_2O (3 × 50 ml), brine (50 ml), dried ($MgSO_4$) and then concentrated *in vacuo* to yield 16.0 g of a white solid. The solid was further purified by recrystallisation (50 ml cyclohexane) to yield the methylated adduct **6** (13.0 g, 40.0 mmol, 80%) as a white solid: mp 95–97 °C; $[\alpha]_D$ +98.0 (*c* 1.09, $CHCl_3$); ν_{max}(film)/cm^{-1} 2935m, 1685s, 1327s, 1272m, 1220m, 1134m, 1057m, 534m; δ_H(360 MHz, $CDCl_3$) 5.81 (1H, ddt, *J* 17.0, 10.3, 6.7, H3), 5.02 (1H, dq, *J* 17.2, 1.8, CH=CH_ZH$_E$), 4.95 (1H, dm, *J* 10.2, CH=CH$_Z$$H_E$), 3.90 (1H, t, *J* 6.3, CHN), 3.51 (1H, d, *J* 13.8, CH_AH$_B$SO$_2$), 3.44 (1H, d, *J* 13.8, CH$_A$$H_BSO_2$), 3.09 (1H, sextet, *J* 6.8, H6), 2.13–2.02 (4H, m), 1.97–1.84 (4H, m), 1.50–1.32 (3H, m), 1.22 (3H, d, *J* 6.9, C6-Me), 1.16 and 0.98 (3H each, s, CMe_2); δ_C(90 MHz, $CDCl_3$) 176.1 (0), 138.2 (1), 114.8 (2), 65.1 (1), 53.2 (2), 48.4 (0), 47.8 (0), 44.7 (1), 39.9 (1), 38.5 (2), 32.9 (2), 32.0 (2), 31.5 (2), 26.5 (2), 20.9 (3), 19.9 (3), 19.0 (3); *m*/*z* (EI mode) 325 (46%), 271 (100), 214 (17), 191 (22), 135 (88), 111 (50), 93 (23), 83 (99), 67 (18), 55 (78), 41 (52) (Found: C, 62.76; H, 8.41; N, 4.27. $C_{17}H_{27}NO_3S$ requires C, 62.74; H, 8.36; N, 4.30%).

(2*S*)-*N*-[(*S*)-4-(5,5-Dimethyl-1,3-dioxan-2-yl)-2-methylbutanoyl]bornane-10,2-sultam 7

Ozone was bubbled through a stirred solution of the olefin **6** (5.64 g, 17.4 mmol) in CH_2Cl_2 (100 ml) and MeOH (30 ml) at −78 °C for 2 h. After this time the ozone flow was stopped and N_2 bubbled through the cold solution for 10 min to remove excess ozone. Dimethyl sulfide (30 ml) was then added and the mixture allowed to warm slowly to rt overnight. All solvent was then removed *in vacuo* to yield 8.33 g of an oily residue which was subsequently dissolved in PhMe (100 ml). Following a negative starch–iodide paper test, the solution was treated with 2,2-dimethylpropane-1,3-diol (1.90 g, 18.3 mmol) and a catalytic quantity of *p*-TsOH·H_2O (*ca*. 10 mg). The mixture was then stirred at reflux overnight with removal of water using a Dean–Stark apparatus. The cooled reaction mixture was diluted with Et_2O (100 ml) and washed successively with sat. aqueous $NaHCO_3$ (50 ml), H_2O (4 × 30 ml) and brine (30 ml). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to yield 7.25 g of a crude solid which was recrystallised (30 ml cyclohexane) to yield the pure dioxane product **7** (5.20 g, 12.6 mmol, 72%) as a white solid: mp 124–126 °C; $[\alpha]_D$ +75.0 (*c* 1.11, $CHCl_3$); ν_{max}(film)/cm^{-1} 2956s, 1692s, 1328s, 1133m, 1113m, 547m, 536m; δ_H(360 MHz, $CDCl_3$) 4.43 (1H, t, *J* 4.9, H3), 3.89 (1H, t, *J* 6.3, CHN), 3.58 (2H, d, *J* 11.0, CH_AH$_B$O), 3.49 (1H, d, *J* 13.7, CH_AH$_B$SO$_2$), 3.43 (1H, d, *J* 13.8, CH$_A$$H_BSO_2$), 3.41 (2H, d, *J* 11.3, CH$_A$$H_B$O), 3.08 (1H, sextet of m, 6.8, H6), 2.08–2.03 (2H, m), 1.97–1.82 (4H, m), 1.75–1.48 (3H, m), 1.44–1.30 (2H, m), 1.22 (3H, d, *J* 6.9, C6-Me), 1.17 and 0.70 (3H each, s, acetal CMe_2), 1.15 and 0.97 (3H each, s, bornane CMe_2); δ_C(90 MHz, $CDCl_3$) 176.0 (0), 101.8 (1), 77.2 (2), 77.2 (2), 65.1 (1), 53.2 (2), 48.4 (0), 47.8 (0), 44.7 (1), 39.9 (1), 38.5 (2), 32.9 (2), 32.3 (2), 30.2 (0), 26.9 (2), 26.5 (2), 23.1 (3), 22.0 (3), 20.9 (3), 20.0 (3), 19.1 (3); *m*/*z* (CI mode, NH_3) 431 (100%), 414 (26), 350 (16), 250 (14), 233 (49) (Found: C, 60.84; H, 8.49; N, 3.28. $C_{21}H_{35}NO_5S$ requires C, 60.99; H, 8.53; N, 3.39%).

(2*S*)-4-(5,5-Dimethyl-1,3-dioxan-2-yl)-2-methylbutan-1-ol 8

To a stirred suspension of lithium aluminium hydride (0.81 g, 21.3 mmol) in anhydrous Et_2O (50 ml) at rt under N_2 was added dropwise a solution of the acyl sultam **7** (3.50 g, 8.47 mmol) in anhydrous Et_2O–THF (3 : 1) over 10 min. The resultant mixture was then allowed to stir at rt overnight. After this time the reaction was quenched by the dropwise addition of 20% KOH (50 ml) and then stirred vigorously for 1 h. The biphasic mixture was then filtered through a pad of Celite and the residue washed well with Et_2O (3 × 10 ml). The layers of the filtrate and combined washings were then separated and the organic phase washed successively with 20% KOH (5 × 20 ml), H_2O (20 ml) and brine (20 ml). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to yield essentially pure alcohol **8** (1.59 g, 7.87 mmol, 93%) as a clear oil: bp (Kugelrohr oven) 170 °C/0.3 mmHg; $[\alpha]_D$ −7.3 (*c* 1.05, $CHCl_3$); ν_{max}(film)/cm^{-1} 3424br s, 2954s, 2870s, 1472m, 1394m, 1116s, 1078m, 1042m, 1018s; δ_H(360 MHz, $CDCl_3$) 4.43 (1H, t, *J* 4.9, H3), 3.61 (2H, d, *J* 11.2, Me_2CCH_AH$_B$O), 3.52 (1H, dd, *J* 10.6, 5.9, H7$_A$), 3.45 (1H, dd, *J* 10.6, 6.2, H7$_B$), 3.43 (2H, d, *J* 11.4, Me_2CCH$_A$$H_B$O), 1.78–1.49 (4H, m), 1.27 (1H, dddd, *J* 12.8, 10.3, 7.3, 5.1), 1.20 and 0.72 (3H each, s, CMe_2), 0.93 (3H, d, *J* 6.7, C6-Me); δ_C(90 MHz, C_6D_6) 103.3 (1), 77.6 (2C, 2), 68.1 (2), 36.4 (1), 33.2 (2), 30.5 (0), 28.1 (2), 23.6 (3), 22.1 (3), 17.4 (3); *m*/*z* (CI+ mode, NH_3) 220 (100%), 203 (3), 133 (17), 122 (64), 116 (44). The alcohol is unstable under mildly acidic conditions: appreciable decomposition was noted after just 30 min in $CDCl_3$.

(2*S*)-4-(5,5-Dimethyl-1,3-dioxan-2-yl)-2-methylbutanal 9

A biphasic mixture of the alcohol **8** (860 mg, 4.26 mmol) and triethylamine (3.55 ml, 2.58 g, 25.5 mmol) in anhydrous DMSO (20 ml) at rt under N_2 was treated portionwise with sulfur trioxide–pyridine complex (2.03 g, 12.8 mmol) and stirred vigorously for 30 min. The mixture was then poured into 10% aqueous $NaHSO_4$ (200 ml), stirred for 10 min and then extracted with CH_2Cl_2 (4 × 50 ml). The combined organic extracts were then washed successively with H_2O (2 × 50 ml) and brine (50 ml) and then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then further purified by column chromatography eluting with 20% Et_2O in hexanes to yield the aldehyde **9** (816 mg, 4.08 mmol, 96%) as a clear oil: bp (Kugelrohr oven) 140 °C/0.3 mmHg; $[\alpha]_D$ +12.8 (*c* 1.07, $CHCl_3$); ν_{max}(film)/cm^{-1} 2956s, 2848s, 1726s, 1472m, 1394m, 1120s, 1018m, 984m; δ_H(360 MHz, $CDCl_3$) 9.62 (1H, d, *J* 1.8, H7), 4.43 (1H, t, *J* 4.8,

H3), 3.59 (2H, d, *J* 11.1, C$H_A$$H_B$O), 3.41 (2H, d, *J* 11.1, CH$_A$-H_BO), 2.36 (1H, sextet of d, *J* 6.9, 1.7, H6), 1.92–1.82 (1H, m), 1.75–1.60 (2H, m), 1.55–1.44 (1H, m), 1.18 and 0.72 (3H, s, CMe_2), 1.10 (3H, d, *J* 7.0, C6-Me); δ_C(90 MHz, $CDCl_3$) 204.9 (1), 101.7 (1), 77.2 (2C, 2), 46.1 (1), 32.2 (2), 30.2 (0), 24.7 (2), 23.1 (3), 21.9 (3), 13.4 (3); *m*/*z* (CI mode, NH_3) 218 (100%), 201 (10) (Found: C, 65.81; H, 9.99. $C_{11}H_{20}O_3$ requires C, 65.97; H, 10.07%).

5-Ethylsulfonyl-1-phenyl-1*H*-tetrazole 10

To a suspension of powdered potassium hydroxide (3.3 g, 58.9 mmol) in EtOH (100 ml) was added 1-phenyl-1*H*-tetrazole-5-thiol (Aldrich, 10 g, 56.2 mmol) and the resulting mixture stirred at reflux for 1 h. After this time ethyl bromide (4.4 ml, 6.42 g, 58.9 mmol) was added dropwise and the reaction stirred at reflux for a further 18 h. The solvent was then removed *in vacuo* and the residue partitioned between H_2O (100 ml) and Et_2O (100 ml). The layers were then separated and the organic phase washed successively with sat. $NaHCO_3$ (2 × 75 ml) and brine (75 ml). After drying ($MgSO_4$) the solvent was removed *in vacuo* to yield essentially pure 5-ethylthio-1-phenyl-1*H*-tetrazole (9.86 g, 47.9 mmol, 86%) as a brown oil. A mechanically stirred suspension of the thioether (9.86 g, 47.9 mmol) and $NaHCO_3$ (20 g, 238 mmol) in CH_2Cl_2 (200 ml) was treated portionwise with 3-chloroperoxybenzoic acid (41.0 g, 50 wt%, 119 mmol) and stirred vigorously for 18 h. After this time the reaction mixture was poured into sat. $NaHCO_3$–$Na_2S_2O_3$ (200 ml) and stirred vigorously for 3 h. The layers were then separated and the aqueous phase extracted with CH_2Cl_2 (2 × 50 ml). The combined organic extracts were then washed with sat. $NaHCO_3$ (3 × 75 ml), brine (75 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 40–55% Et_2O in hexanes to yield 5-ethylsulfonyl-1-phenyl-1*H*-tetrazole (**10**, 8.33 g, 35.0 mmol, 73%) as a white solid: mp 70-71 °C (10% EtOAc–hexanes) (lit. 37 mp 73–74 °C; CAS No. 3206-46-0); δ_H(360 MHz, $CDCl_3$) 7.71–7.65 (2H, m), 7.64–7.55 (3H, m), 3.75 (2H, q, *J* 7.4), 1.52 (3H, t, *J* 7.4); δ_C(90 MHz, $CDCl_3$) 153.2 (0), 133.1 (0), 131.6 (1), 129.8 (2C, 1), 125.2 (2C, 1), 50.9 (2), 7.0 (3).

5,5-Dimethyl-2-[(*E*,3*S*)-3-methylhex-4-enyl]-1,3-dioxane 11

To a stirred solution of the aldehyde **9** (3.82 g, 19.1 mmol) and sulfone **10** (5.95 g, 25.0 mmol) in anhydrous 1,2-dimethoxyethane (80 ml) at −60 °C (bath temperature) under N_2 was added dropwise *via* a cannula a solution of potassium hexamethyldisilazane (KHMDS, 7.0 g, 80 wt%, 28.1 mmol) in anhydrous DME (40 ml) over 45 min. After this time H_2O (10 ml) was added and the mixture stirred vigorously whilst warming to rt. The mixture was then diluted with Et_2O (150 ml) and H_2O (80 ml) and the layers shaken and then separated. The aqueous phase was then extracted with Et_2O (3 × 50 ml) and the combined organic extracts washed successively with H_2O (3 × 50 ml) and brine (50 ml). The organic phase was then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 0–10% Et_2O in hexanes to yield the olefin **11** (3.76 g, 17.7 mmol, 93%, *E*:*Z* = 93:7) as a clear oil: $[\alpha]_D$ +7.2 (*c* 1.01, $CHCl_3$); ν_{max}(film)/cm^{-1} 2956s, 1454m, 1394m, 1122s, 1044m, 1020s, 966s; δ_H(360 MHz, $CDCl_3$) 5.40 (1H, ddq, *J* 15.2, 6.2, 0.7, H8), 5.26 (1H, ddq, *J* 15.2, 7.6, 1.3, H7), 4.39 (1H, t, *J* 5.1, H3), 3.60 (2H, d, *J* 9.9, C$H_A$$H_B$O), 3.42 (2H, d, *J* 10.6, CH$_A$$H_B$O), 2.04 (1H, septet, *J* 7.0, H6), 1.63 (3H, dm, *J* 6.3, C8-Me), 1.70–1.52 (2H, m), 1.44–1.27 (2H, m), 1.19 and 0.72 (3H each, s, CMe_2), 0.96 (3H, d, *J* 6.7, C6-Me); δ_C(90 MHz, $CDCl_3$) 137.1 (1), 123.5 (1), 102.6 (1), 77.4 (2C, 2), 36.9 (1), 33.0 (2), 31.3 (2), 30.3 (0), 23.1 (3), 22.0 (3), 21.0 (3), 18.1 (3); *m*/*z* (CI mode, NH_3) 230 (100%), 213 (25), 126 (36), 96 (86), 79 (26) (Found: C, 73.36; H, 11.13. $C_{13}H_{24}O_2$ requires C, 73.54; H, 11.39%).

(2*S*,3*S*,4*S*)-6-(5,5-Dimethyl-1,3-dioxan-2-yl)-4-methylhexane-2,3-diol 12

To a mechanically stirred solution of AD-mix α[38] (25.0 g) in *t*-BuOH (70 ml) and H_2O (80 ml) was added methanesulfonamide (1.70 g, 17.9 mmol). The mixture was then cooled to 0 °C and a solution of the olefin **11** (3.76 g, 17.7 mmol, *E*:*Z* = 93:7) in *t*-BuOH (10 ml) added. The reaction was then stirred vigorously at 0 °C for 24 h. Solid Na_2SO_3 (26 g) was added and the mixture allowed to stir for 1 h whilst being allowed to warm to rt. The biphasic system was then extracted with CH_2Cl_2 (4 × 50 ml) and the combined organic extracts washed successively with KOH (2 M, 60 ml) and brine (50 ml). The organic phase was then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography eluting with Et_2O to yield the diol **12** (3.62 g, 14.7 mmol, 83%, dr ~ 93:7) as a clear oil: $[\alpha]_D$ −13.5 (*c* 0.48, $CHCl_3$); ν_{max}(film)/cm^{-1} 3424br s, 2954s, 1472s, 1334s, 1120s, 1042m, 1018m, 984m; δ_H(360 MHz, $CDCl_3$) 4.41 (1H, t, *J* 7.6, H3), 3.85 (1H, quintet, *J* 6.0, H8), 3.60 (2H, d, *J* 11.1, C$H_A$$H_B$O), 3.42 (2H, d, *J* 11.0, CH$_A$$H_B$O), 3.13 (1H, t, *J* 5.2, H7), 2.40–2.15 (2H, m, OH), 1.80–1.52 (4H, m), 1.37–1.28 (1H, m), 1.20 (3H, d, *J* 6.3, C8-Me), 1.18 and 0.72 (3H each, s, CMe_2), 0.96 (3H, d, *J* 6.8, C6-Me); δ_C(90 MHz, $CDCl_3$) 102.6 (1), 79.9 (1), 77.3 (2C, 2), 67.9 (1), 35.0 (1), 32.2 (2), 30.3 (0), 25.1 (2), 23.1 (3), 21.9 (3), 20.2 (3), 16.7 (3); *m*/*z* (CI mode, NH_3) 264 (36%), 247 (71), 160 (11), 143 (21), 122 (100), 105 (22) (Found: $(M + H)^+$, 247.1911. $C_{13}H_{27}O_4$ requires *M* 247.1909).

(2*S*,3*S*,6*S*)-2-[(1*S*)-1-Hydroxyethyl]-6-methoxy-3-methyloxane 13α and (2*S*,3*S*,6*R*)-2-[(1*S*)-1-hydroxyethyl]-6-methoxy-3-methyloxane 13β

A solution of the diol **12** (3.62 g, 14.7 mmol) and *p*-TsOH·H_2O (40 mg) in MeOH (60 ml) was stirred at rt for 3 d. After this time the mixture was diluted with Et_2O (100 ml) and shaken with sat. $NaHCO_3$ (100 ml). The layers were then separated and the aqueous phase extracted with Et_2O (4 × 20 ml). The combined organic extracts were then washed with brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 40% Et_2O in hexanes to yield the methyl glycoside **13** (1.88 g, 10.8 mmol, 73%, α:β = 3:1) as a white solid: mp 36–40 °C; bp (Kugelrohr oven) 100 °C/0.3 mmHg; $[\alpha]_D$ +101.8 (*c* 0.50, $CHCl_3$); ν_{max}(film)/cm^{-1} 3474br s, 2930s, 1458m, 1374m, 1233m, 1211m, 1158m, 1129m, 1047m, 1026m, 997m, 964m, 908m; δ_H(360 MHz, $CDCl_3$) 4.77 (1H*α*, t, *J* 2.4, H3), 4.33 (1H*β*, dd, *J* 9.7, 2.1, H3), 4.00–3.90 (1H, m, H8), 3.50 (3H*β*, s, OMe), 3.34 (3H*α*, s, OMe), 3.17 (1H*α*, dd, *J* 9.4, 0.8, H7), 2.86 (1H*β*, dd, *J* 9.8, 1.5, H7), 2.00–1.39 (5H, m), 1.29 (3H*β*, d, *J* 6.6, C8-Me), 1.27 (3H*α*, d, *J* 6.5, C8-Me), 0.88 (3H*α*, d, *J* 6.5, C6-Me), 0.87 (3H*β*, d, *J* 6.5, C6-Me); δ_C(90 MHz, $CDCl_3$) *α* 98.5 (1), 77.2 (1), 66.3 (1), 54.5 (3), 30.7 (1), 30.1 (2), 26.9 (2), 20.8 (3), 17.7 (3); *β* 103.7 (1), 84.2 (1), 66.5 (1), 56.2 (3), 31.6 (2), 31.4 (2), 30.5 (1), 20.8 (3), 16.9 (3); *m*/*z* (CI mode, NH_3) 192 (75%), 160 (100), 143 (75), 96 (22), 79 (40) (Found: C, 62.04; H, 10.22. $C_9H_{18}O_3$ requires C, 62.04; H, 10.41%).

(2*S*,3*S*,6*S*)-6-Methoxy-2-[(1*S*)-1-(4-methoxybenzyloxy)ethyl]-3-methyloxane 14α and (2*S*,3*S*,6*R*)-6-methoxy-2-[(1*S*)-1-(4-methoxybenzyloxy)ethyl]-3-methyloxane 14β

A stirred solution of potassium hexamethyldisilazide (KHMDS, 1.88 g, 80 wt%, 7.54 mmol) in anhydrous THF (45 ml) under N_2 at 0 °C was treated dropwise with a solution of the alcohol **13**α,β (1.01 g, 5.80 mmol, α,β = 3:1) in anhydrous THF (15 ml). After complete addition the mixture was stirred for 20 min; neat *p*-methoxybenzyl chloride (PMBCl, 1.02 ml, 1.18 g, 7.56 mmol) was then added dropwise. A small portion of tetrabutylammonium iodide (TBAI, 60 mg) was added and the mixture allowed to warm to rt and stirred for 24 h. The reaction

mixture was then partitioned between Et_2O (40 ml) and brine (50 ml). The layers were then shaken and separated and the aqueous layer extracted with Et_2O (3 × 10 ml). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was then purified by column chromatography eluting with 20–50% Et_2O in hexanes to yield the ether **14**α,β (1.58 g, 5.37 mmol, 93%, α,β = 3 : 1) as a clear oil: $[\alpha]_D$ +103.1 (*c* 0.52, $CHCl_3$); ν_{max}(film)/cm^{-1} 2932s, 1613m, 1514s, 1458m, 1373m, 1302m, 1248s, 1172m, 1128s, 1057s, 1035s, 998m, 906m, 821m; δ_H(360 MHz, $CDCl_3$) 7.27 (2H, d, *J* 8.7, Ar), 6.85 (2H, d, *J* 8.6, Ar), 4.78 (1Hα, d, *J* 3.1, H3), 4.64 (1H, d, *J* 11.8, C$H_A$$H_B$Ar), 4.34 (1Hβ, *J* 11.9, C$H_A$$H_B$Ar), 4.33 (1Hα, d, *J* 11.8, C$H_A$$H_B$Ar), 4.21 (1Hβ, dd, *J* 9.6, 2.0, H3), 3.78 (3H, s, MeOAr), 3.65 (1H, dq, *J* 6.3, 1.6, H8), 3.47 (3Hβ, s, OMe), 3.32 (3Hα, s, OMe), 3.19 (1Hα, dd, *J* 10.1, 1.6, H7), 2.87 (1Hβ, dd, *J* 9.6, 2.1, H7), 1.93–1.61 (3H, m), 1.55–1.36 (2H, m), 1.27 (3Hβ, d, *J* 6.4, C8-Me), 1.27 (3Hα, d, *J* 6.4, C8-Me), 0.64 (3H, d, *J* 6.6, C6-Me); δ_C(90 MHz, $CDCl_3$) *α* 159.2 (0), 130.9 (0), 129.8 (2C, 1), 113.7 (2C, 1), 98.6 (1), 77.1 (1), 71.8 (1), 70.4 (2), 55.3 (3), 54.5 (3), 30.4 (1), 29.9 (2), 27.2 (2), 17.4 (3), 15.5 (3); *β* 159.2 (0), 131.0 (0), 129.7 (2C, 1), 113.7 (2C, 1), 104.0 (1), 83.9 (1), 72.4 (1), 70.1 (2), 56.0 (3), 55.3 (3), 31.7 (2), 31.5 (2), 30.2 (1), 16.6 (3), 15.3 (3); *m*/*z* (CI mode, isobutane) 312 (100%), 280 (14), 155 (37), 138 (55), 121 (36) (Found: C, 69.22; H, 8.98. $C_{17}H_{26}O_4$ requires C, 69.36; H, 8.90%).

(2*S*,3*S*,6*S*)-6-Hydroxy-2-[(1*S*)-1-(4-methoxybenzyloxy)ethyl]-3-methyloxane 15α and (2*S*,3*S*,6*R*)-6-hydroxy-2-[(1*S*)-1-(4-methoxybenzyloxy)ethyl]-3-methyloxane 15β

A solution of the methyl glycoside **14**α,β (1.73 g, 5.88 mmol, α : β = 3 : 1) in AcOH–THF–H_2O (3 : 2 : 2, 30 ml) was stirred at 65 °C for 2 h. The cooled mixture was diluted with Et_2O (40 ml) and H_2O (20 ml). The layers were then shaken and separated and the aqueous phase extracted with Et_2O (3 × 15 ml). The combined organic extracts were successively washed with H_2O (4 × 15 ml), sat. $NaHCO_3$ (3 × 15 ml), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was purified by column chromatography eluting with 40% Et_2O in hexanes to afford some recovered starting material (311 mg, 1.06 mmol, 18%) and the lactol **15**α,β (1.22 g, 4.36 mmol, 74%, α : β = 1.4 : 1) as a clear oil: $[\alpha]_D$ +73.1 (*c* 0.54, $CHCl_3$); ν_{max}(film)/cm^{-1} 3405br m, 2930s, 2855s, 1612m, 1514s, 1459m, 1376m, 1247s, 1173m, 1112m, 1035s, 1001s, 821m; δ_H(360 MHz, $CDCl_3$) 7.28 (2Hβ, d, *J* 8.6, Ar), 7.27 (2Hα, d, *J* 8.6, Ar), 6.87 (2H, d, *J* 8.7, Ar), 5.40 (1Hα, m, H3), 4.64 (1Hβ, d, *J* 11.8, C$H_A$$H_B$Ar), 4.64 (1Hα, d, *J* 11.8, C$H_A$$H_B$Ar), 4.67–4.60 (1Hβ, signal obscured, H3), 4.36 (1Hβ, d, *J* 11.8, C$H_A$$H_B$Ar), 4.35 (1Hα, d, *J* 11.8, C$H_A$$H_B$Ar), 3.81 (3H, s, OMe), 3.70–3.60 (1H, m, H8), 3.46 (1Hα, dd, *J* 10.3, 2.0, H7), 2.97 (1Hβ, dd, *J* 9.4, 2.0, H7), 2.80–2.65 (1Hβ, br s, OH), 2.32–2.23 (1Hα, br s, OH), 1.92–1.65 (3H, m), 1.60–1.33 (2H, m), 1.28 (3Hβ, d, *J* 6.4, C8-Me), 1.23 (3Hα, d, *J* 6.4, C8-Me), 0.68 (3Hα, d, *J* 6.4, C6-Me), 0.66 (3Hβ, d, *J* 6.4, C6-Me); δ_C(90 MHz, $CDCl_3$) *α* 159.3 (0), 130.9 (0), 129.8 (2C, 1), 113.7 (2C, 1), 91.9 (1), 77.2 (1), 72.0 (1), 70.4 (2), 55.4 (3), 30.7 (1), 30.1 (2), 26.5 (2), 17.6 (3), 15.7 (3); *β* 159.3 (0), 130.9 (0), 129.8 (2C, 1), 113.8 (2C, 1), 97.2 (1), 84.3 (1), 72.3 (1), 70.3 (2), 55.4 (3), 33.8 (2), 31.6 (2), 30.0 (1), 16.7 (3), 15.5 (3); *m*/*z* (CI mode, NH_3) 298 (100%), 280 (19), 155 (27), 138 (44), 121 (34) (Found: $(M + NH_4)^+$, 298.2013. $C_{16}H_{24}O_4 + NH_4$ requires *M* 298.2018).

Prop-2-enyl {(2*S*,3*S*,6*R*)-2-[(1*S*)-1-(4-methoxybenzyloxy)ethyl]-3-methyloxan-6-yl}ethanoate 16

A stirred suspension of the lactol **15**α,β (1.22 g, 4.36 mmol, α : β = 1.4 : 1) and caesium carbonate (2.90 g, 8.90 mmol) in anhydrous THF (20 ml) under N_2 was treated with allyl diethylphosphonoacetate (1.85 ml, 2.07 g, 8.77 mmol) and heated at reflux overnight. The cooled reaction mixture was partitioned between Et_2O (40 ml) and H_2O (20 ml) and the aqueous phase extracted (3 × 10 ml Et_2O). The combined organic extracts were washed with brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then purified by column chromatography eluting with 40% Et_2O in hexanes to afford 1.30 g of tetrahydropyran isomers **16** (*cis* : *trans* = 4 : 6, 82%). A solution of the isomers (1.30 g, 3.59 mmol) in anhydrous THF (30 ml) at −65 °C under N_2 was then treated dropwise with a solution of potassium *tert*-butoxide (485 mg, 4.33 mmol) in anhydrous THF (10 ml). After stirring for 10 min, sat. NH_4Cl (2 ml) was added and the mixture allowed to warm to rt. The reaction mixture was then partitioned between Et_2O (40 ml) and H_2O (20 ml) and the aqueous phase extracted with Et_2O (3 × 10 ml). The combined organic extracts were washed with brine (15 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 20% Et_2O in hexanes to yield the pure *cis* tetrahydropyran **16** (1.15 g, 3.18 mmol, 73% overall) as a clear oil: $[\alpha]_D$ +29.8 (*c* 0.60, $CHCl_3$); ν_{max}(film)/cm^{-1} 2928s, 1738s, 1613m, 1514s, 1456m, 1372m, 1302m, 1276m, 1248s, 1194m, 1170m, 1084m, 1036m; δ_H(360 MHz, $CDCl_3$) 7.27 (2H, d, *J* 8.6, Ar), 6.86 (2H, d, *J* 8.7, Ar), 5.92 (1H, ddt, *J* 17.2, 10.4, 5.7, CH_2CH=CH_2), 5.31 (1H, dq, *J* 17.2, 1.5, CH_2CH=C$H_Z$$H_E$), 5.22 (1H, dq, *J* 10.4, 1.3, CH_2CH=CH_ZH_E), 4.63 (1H, d, *J* 11.9, C$H_A$$H_B$Ar), 4.58 (2H, dt, *J* 5.7, 1.3, CH_2CH=CH_2), 4.33 (1H, d, *J* 11.9, C$H_A$$H_B$Ar), 3.80 (3H, s, OMe), 3.70 (1H, dddd, *J* 11.2, 8.5, 5.6, 3.0, H3), 3.61 (1H, dq, *J* 6.4, 2.1, H8), 2.84 (1H, dd, *J* 9.5, 3.1, H7), 2.68 (1H, dd, *J* 15.3, 8.1, $H2_A$), 2.43 (1H, dd, *J* 15.3, 5.3, $H2_B$), 1.85–1.75 (2H, m), 1.62 (1H, ddt, *J* 12.9, 4.2, 2.1), 1.39 (1H, tdd, *J* 12.9, 11.1, 3.7, $H4_{ax}$), 1.28–1.15 (1H, signal obscured), 1.20 (3H, d, *J* 6.4, C8-Me), 0.63 (3H, d, *J* 6.3, C6-Me); δ_C(90 MHz, $CDCl_3$) 171.5 (0), 159.3 (0), 132.4 (1), 131.1 (0), 129.8 (2C, 1), 118.2 (2), 113.8 (2C, 1), 86.5 (1), 75.3 (1), 72.2 (1), 70.2 (2), 65.2 (2), 55.4 (3), 41.4 (2), 33.0 (2), 31.7 (2), 30.4 (1), 17.2 (3), 15.3 (3); *m*/*z* (CI mode, NH_3) 380 (100%), 121 (36) (Found: $M^{+\bullet}$, 362.2095. $C_{21}H_{30}O_5$ requires *M* 362.2093).

Prop-2-enyl {(2*S*,3*S*,6*R*)-2-[(1*S*)-1-hydroxyethyl]-3-methyloxan-6-yl}ethanoate 17

A vigorously stirred solution of the PMB ether **16** (508 mg, 1.40 mmol) in a mixture of CH_2Cl_2 (30 ml) and H_2O (2 ml) at rt was treated with 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone (470 mg, 2.07 mmol) and the resulting brown mixture stirred for 30 min. Anhydrous $MgSO_4$ (*ca*. 20 g) was then added and the mixture stirred for a further 10 min. The thick suspension was filtered and the filtrate concentrated *in vacuo*. The resulting residue was purified by column chromatography eluting with 30% Et_2O in hexanes to yield the alcohol **17** (321 mg, 1.33 mmol, 95%) as a clear oil: $[\alpha]_D$ +7.8 (*c* 0.97, $CHCl_3$) [lit. 5 $[\alpha]_D$ +5.7 (*c* 0.7, $CHCl_3$)]; ^1H and ^{13}C NMR in complete agreement with that previously reported.[5]

(2*R*)-*N*-[(2*R*,3*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-2-methylpentanoyl]bornane-10,2-sultam 20

To a stirred solution of triethylborane (32.0 ml, 1.0 M in hexanes, 32.0 mmol) at rt under N_2 was added dropwise triflic acid (2.83 ml, 4.80 g, 32.0 mmol). Evolution of ethane was noted and the temperature of the reaction mixture rose to 38 °C. The mixture was then stirred for 15 min before being cooled to −10 °C and treated dropwise with (2*R*)-*N*-propanoylbornane-10,2-sultam[18] (**18**, 4.34 g, 16.0 mmol) in anhydrous CH_2Cl_2 (60 ml) at such a rate that the internal temperature did not rise above −5 °C. After 5 min diisopropylethylamine (5.90 ml, 4.40 g, 33.9 mmol) was added dropwise and the reaction stirred for 30 min at −5 °C before cooling to −78 °C. The neat aldehyde **19**[5] (9.14 g, 48.6 mmol) was added dropwise and stirring continued for 3 h. The reaction mixture was quenched by the addition of sat. NH_4Cl (50 ml), allowed to warm to rt and diluted with Et_2O (100 ml). The layers were separated and the aqueous phase extracted with Et_2O (3 × 30 ml). The combined organic

extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield 15.2 g of a crude oil. The residue was purified by column chromatography eluting with 20% Et_2O in hexanes followed by recrystallisation (hexanes) to yield the aldol **20** (5.50 g, 12.0 mmol, 75%) as a white solid: mp 92–95 °C; $[\alpha]_D$ −65.8 (*c* 1.20, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3517br, 2967s, 1680m, 1335s, 1139m; δ_H(400 MHz, $CDCl_3$) 3.86 (1H, dd, *J* 5.9, 5.9, CHN), 3.80–3.71 (2H, m, H17, H18), 3.47 (1H, d, *J* 13.8, CH_AH$_B$SO$_2$), 3.40 (1H, d, *J* 13.8, CH$_A$$H_BSO_2$), 3.36 (1H, dq, *J* 7.1, 4.2, H16), 2.04–1.99 (2H, m), 1.91–1.82 (3H, m), 1.42–1.36 (1H, m), 1.35–1.29 (1H, m), 1.27 (3H, d, *J* 7.1, H19), 1.17 (3H, d, *J* 5.9, C16-Me), 1.15 and 0.96 (3H each, s, CMe_2), 0.90 (9H, s, CMe_3), 0.09 and 0.08 (3H each, s, $SiMe_2$); δ_C(100 MHz, $CDCl_3$) 176.7 (0), 75.0 (1), 68.1 (1), 64.7 (1), 53.0 (2), 48.3 (0), 47.7 (0), 44.5 (1), 40.4 (1), 38.2 (2), 32.8 (2), 26.4 (2), 25.8 (3, 3C), 20.7 (3), 19.8 (3), 19.1 (3), 17.9 (0), 12.9 (3), −4.2 (3), −5.0 (3); *m*/*z* (CI mode, NH_3) 460 (12%), 442 (4), 328 (100), 289 (3), 272 (3), 245 (5) (Found: C, 57.51; H, 8.98; N, 2.97. $C_{22}H_{41}NO_5SSi$ requires C, 57.48; H, 8.99; N, 3.05%).

(2*R*)-*N*-[(2*R*,3*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-methoxy-2-methylpentanoyl]bornane-10,2-sultam 21

To a stirred solution of the aldol **20** (12.1 g, 26.4 mmol) and 1,8-bis(dimethylamino)naphthalene (proton sponge®, 17.0 g, 79.4 mmol) in anhydrous PhMe (100 ml) at rt under N_2 was added methyl triflate (9.0 ml, 13.1 g, 79.6 mmol). The resulting mixture was heated to 80 °C and stirred for 24 h whereupon the suspension was allowed to cool to rt, treated with conc. NH_4OH (15 ml) and then stirred for 30 min. The biphasic mixture was diluted with CH_2Cl_2 (100 ml) and H_2O (50 ml) and the layers shaken well and then separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 30 ml) and the combined organic extracts washed successively with HCl (2 M, 4 × 50 ml) and brine (50 ml). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography eluting with 20% Et_2O in hexanes to yield the methyl ether **21** (11.3 g, 23.9 mmol, 90%) as a white solid: mp 106–108 °C (hexanes); $[\alpha]_D$ −74.9 (*c* 0.39, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2971m, 1691m, 1342s, 1142m, 1107s, 776m; δ_H(400 MHz, $CDCl_3$) 3.84 (1H, dd, *J* 7.5, 5.1, CHN), 3.79 (1H, dq, *J* 6.4, 2.6, H18), 3.52 (3H, s, OMe), 3.46 (1H, dd, *J* 8.4, 2.6, H17), 3.45 (1H, d, *J* 13.6, CH_AH$_B$SO$_2$), 3.39 (1H, d, *J* 14.0, CH$_A$$H_BSO_2$), 3.07 (1H, dq, *J* 8.3, 7.0, H16), 2.04 (1H, dd, *J* 13.7, 7.8), 1.98 (1H, dm, *J* 14.0), 1.93–1.81 (3H, m), 1.42–1.36 (1H, m), 1.35–1.29 (1H, m), 1.27 (3H, d, *J* 7.0, H19), 1.12 and 0.94 (3H each, s, CMe_2), 1.11 (3H, d, *J* 6.1, C16-Me), 0.87 (9H, s, CMe_3), 0.06 and 0.02 (3H each, s, $SiMe_2$); δ_C(100 MHz, $CDCl_3$) 174.7 (0), 85.5 (1), 70.1 (1), 64.9 (1), 61.2 (3), 53.1 (2), 48.3 (0), 47.7 (0), 44.6 (1), 42.4 (1), 38.3 (2), 32.7 (2), 26.4 (2), 25.8 (3, 3C), 20.8 (3), 19.9 (3), 17.9 (0), 17.3 (3), 15.7 (3), −4.7 (3, 2C); *m*/*z* (CI mode, NH_3) 474 (4%), 342 (100), 310 (1), 278 (2) (Found: C, 58.34; H, 9.12; N, 2.92. $C_{23}H_{43}NO_5SSi$ requires C, 58.31; H, 9.15; N, 2.96%).

(2*S*,3*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-methoxy-2-methylpentan-1-ol 22

A solution of the acyl sultam **21** (2.03 g, 4.3 mmol) in anhydrous Et_2O (20 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.50 g, 13.2 mmol) in Et_2O (10 ml) at 0 °C under N_2. After 15 min the reaction was quenched by the careful addition of sat. NH_4Cl (10 ml) and stirred vigorously for 10 min. The mixture was filtered through a Celite pad and the residue washed well with Et_2O (3 × 5 ml). The layers of the filtrate and combined washings were then separated and the aqueous layer extracted with Et_2O (2 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 40% Et_2O in hexanes to yield (2*R*)-bornane-10,2-sultam (0.87 g, 4.05 mmol, 94%) as a white solid and the alcohol **22** (1.11 g, 4.24 mmol, 99%) as a clear oil: $[\alpha]_D$ +25.5 (*c* 1.07, $CHCl_3$); ν_{max}(film)/cm^{-1} 3410br, 2941s, 1476m, 1385m, 1265m, 1110s, 1065m, 836s, 776s; δ_H(400 MHz, $CDCl_3$) 3.84 (1H, dq, *J* 6.1, 6.1, H18), 3.62–3.54 (2H, m, H15), 3.47 (3H, s, OMe), 3.07 (1H, dd, *J* 6.0, 3.5, H17), 1.99 (1H, dddq, *J* 6.8, 6.8, 5.6, 3.4, H16), 1.19 (3H, d, *J* 6.1, H19), 0.89 (3H, d, *J* 7.1, C16-Me), 0.85 (9H, s, CMe_3), 0.05 and 0.03 (3H each, s, $SiMe_2$); δ_C(100 MHz, $CDCl_3$) 87.2 (1), 69.0 (1), 66.3 (2), 60.3 (3), 36.8 (1), 25.8 (3, 3C), 20.4 (3), 18.0 (0), 11.3 (3), −4.2 (3), −4.8 (3); *m*/*z* (CI mode, NH_3) 606 (31%), 492 (100), 263 (48), 131 (19), 117 (21) (Found: C, 59.57; H, 11.41. $C_{13}H_{30}O_3Si$ requires C, 59.49; H, 11.52%).

(2*S*,3*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-3-methoxy-2-methylpentanal 23

A stirred solution of the alcohol **22** (6.80 g, 26.0 mmol) in anhydrous CH_2Cl_2 (120 ml) at 0 °C under N_2 was treated in one portion with Dess–Martin reagent[20,21] (13.4 g, 31.6 mmol). The resulting solution was allowed to warm to rt and stirred for 2 h whereupon the reaction mixture was poured into sat. $Na_2S_2O_3$–$NaHCO_3$ (200 ml) and stirred vigorously for 30 min. The biphasic system was diluted with Et_2O (100 ml) and the layers shaken and then separated. The aqueous phase was then extracted with Et_2O (2 × 20 ml) and the combined organic extracts washed with sat. $NaHCO_3$ (4 × 30 ml), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was purified by column chromatography eluting with 10% Et_2O in hexanes) to yield the aldehyde **23** (6.15 g, 23.7 mmol, 91%) as a clear oil: $[\alpha]_D$ −7.5 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2932s, 1728s, 1472m, 1258m, 1114s, 1004m, 940m, 836s, 812m, 776m; δ_H(360 MHz, $CDCl_3$) 9.81 (1H, s, H15), 3.76 (1H, quintet, *J* 6.3, H18), 3.47 (1H, dd, *J* 7.1, 3.0, H17), 3.34 (3H, s, OMe), 2.78 (1H, dq, *J* 7.2, 3.0, H16), 1.25 (3H, d, *J* 6.0, H19), 1.04 (3H, d, *J* 7.0, C16-Me), 0.88 (9H, s, CMe_3), 0.08 and 0.06 (3H each, s, $SiMe_2$); δ_C(90 MHz, $CDCl_3$) 204.8 (1), 84.9 (1), 68.7 (1), 59.7 (3), 48.3 (1), 25.9 (3, 3C), 20.9 (3), 18.0 (0), 7.6 (3), −3.9 (3), −4.8 (3); *m*/*z* (CI mode, NH_3) 278 (100%), 261 (48), 249 (16).

(4*R*,5*R*,6*S*)-2,4-Dimethyl-6-(*tert*-butyldimethylsilyloxy)-5-methoxyhept-1-en-3-one 24

A stirred suspension of magnesium (2.7 g, 113 mmol) in anhydrous Et_2O (130 ml) at rt under N_2 was provided with 1 crystal of re-sublimed iodine. The brown mixture was then treated with one quarter of a solution of 2-bromopropene (10 g, 82.6 mmol) in anhydrous Et_2O (20 ml). The resultant suspension was heated to reflux until the brown colour had dissipated and Grignard formation had initiated. The remainder of the solution of bromide was then added at such a rate as to maintain a gentle reflux (*ca*. 30 min). After the complete addition the cloudy solution of prop-2-enylmagnesium bromide was heated at reflux for an additional 2.5 h before being cooled to 0 °C. A solution of the freshly prepared aldehyde **23** (6.15 g, 23.7 mmol) in anhydrous Et_2O (50 ml) was then added dropwise over 10 min and the reaction mixture stirred at 0 °C for 1 h. H_2O (50 ml) was then added cautiously followed by 1 M HCl (50 ml) and the biphasic mixture stirred for 10 min. The layers were then separated and the aqueous phase extracted (3 × 30 ml Et_2O). The combined organic extracts were then washed with sat. $NaHCO_3$ (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 10% Et_2O in hexanes) to afford a mixture of allylic alcohols (6.51 g, 21.6 mmol, 91%, dr = 57:43 in favour of the *syn* isomer). The alcohols (6.37 g, 21.1 mmol) were then dissolved in anhydrous CH_2Cl_2 (100 ml) and the resulting solution treated with Dess–Martin reagent[20,21] (DMP, 11.0 g, 25.9 mmol) and stirred at rt under N_2 for 4 h. After this time the mixture was poured into sat. $Na_2S_2O_3$–$NaHCO_3$ (100 ml) and stirred vigorously for 1 h. The biphasic mixture was then diluted with Et_2O (100 ml) and the layers separated. The aqueous phase was

extracted (3 × 30 ml Et_2O) and the combined organic extracts washed with brine (30 ml), dried ($MgSO_4$) and then concentrated *in vacuo*. The crude ketone was then further purified *via* column chromatography (eluting with 5% Et_2O in hexanes) to yield pure **24** (5.58 g, 18.6 mmol, 88%, 80% from **23**) as a clear oil: $[\alpha]_D$ −35.2 (*c* 1.02, $CHCl_3$); ν_{max}(film)/cm^{-1} 2956s, 2931s, 2858s, 1676s, 1462m, 1380m, 1257s, 1115s, 1058m, 932s, 835s, 776s; δ_H(360 MHz, $CDCl_3$) 5.97 (1H, m, $H13_E$), 5.80 (1H, m, $H13_Z$), 3.66 (1H, quintet, *J* 6.0, H18), 3.52 (1H, dq, *J* 6.9, 5.1, H16), 3.37–3.34 (1H, signal obscured, H17), 3.35 (3H, s, OMe), 1.88 (3H, m, C14-Me), 1.13 (3H, d, *J* 6.1, H19), 1.09 (3H, d, *J* 6.8, C16-Me), 0.88 (9H, s, CMe_3), 0.06 and 0.05 (3H each, s, $SiMe_2$); δ_C(90 MHz, $CDCl_3$) 205.3 (0), 143.8 (0), 124.9 (2), 87.6 (1), 69.4 (1), 60.6 (3), 41.4 (1), 26.0 (3C, 3), 19.8 (3), 18.3 (3), 18.1 (0), 11.8 (3), −4.2 (3), −4.7 (3); *m*/*z* (CI mode, isobutane) 301 (100%), 285 (3), 269 (5), 243 (16), 169 (63) (Found: C, 63.73; H, 10.53. $C_{16}H_{32}O_3Si$ requires C, 63.95; H, 10.73%).

(3*R*,4*S*,5*R*,6*S*)-2,4-Dimethyl-6-(*tert*-butyldimethylsilyloxy)-5-methoxyhept-1-en-3-ol 25

To a stirred solution of anhydrous lithium iodide (25.0 g, 187 mmol) in anhydrous Et_2O (200 ml) at −30 °C under N_2 was added the enone **24** (5.58 g, 18.6 mmol) in anhydrous Et_2O (20 ml). The resulting mixture was stirred vigorously for 20 min and then further cooled to −95 °C (internal temperature). A solution of lithium aluminium hydride (20 ml, 1.0 M in Et_2O, 20 mmol) was then added dropwise *via* a syringe pump over 30 min. The reaction mixture was then quenched by the careful addition of MeOH (20 ml) followed by H_2O (50 ml) and then allowed to warm to rt. The biphasic system was then filtered through a Celite pad and the residue washed well (3 × 50 ml Et_2O). The layers of the filtrate and combined washings were then separated and the aqueous phase extracted (2 × 20 ml Et_2O). The combined organic extracts were then washed successively with H_2O (2 × 50 ml), brine (50 ml), dried ($MgSO_4$) and then concentrated *in vacuo*. The resulting crude solid product (5.22 g, *ca*. 93%, dr (C15) = 85:15) was then further purified *via* recrystallisation (5% H_2O–EtOH 30 ml) to afford 3.46 g of the title compound **25** as a white crystalline solid: mp 63–65 °C. The mother liquor was concentrated *in vacuo* and the residue (1.65 g) further purified *via* column chromatography (eluting with 7% Et_2O in hexanes) to yield an additional 0.76 g of pure product as a white solid (desired isomer is the less polar component). The above procedure yielded in total 4.22 g of diastereoisomerically pure **25** (14.0 mmol, 75%): $[\alpha]_D$ +9.2 (*c* 1.07, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3444br s, 2953s, 2858s, 1655m, 1373m, 1257m, 1115s, 1086m, 1043m, 993m, 934s, 899m, 835s, 810m, 772s; δ_H(360 MHz, $CDCl_3$) 5.06 (1H, m, $H13_E$), 4.92 (1H, m, $H13_Z$), 3.95 (1H, d, *J* 7.4, H15), 3.81 (1H, quintet, *J* 6.2, H18), 3.46 (3H, s, OMe), 3.30 (1H, dd, *J* 6.9, 2.0, H17), 2.66–2.59 (1H, m, OH), 2.08 (1H, ddq, *J* 7.2, 7.1, 1.9, H16), 1.68 (3H, s, C14-Me), 1.22 (3H, d, *J* 6.1, H19), 0.88 (3H, d, *J* 7.1, C16-Me), 0.87 (9H, s, CMe_3), 0.07 and 0.05 (3H each, s, $SiMe_2$); δ_C(90 MHz, $CDCl_3$) 146.7 (0), 112.8 (2), 85.4 (1), 79.3 (1), 68.9 (1), 59.9 (3), 35.7 (1), 26.0 (3C, 3), 21.1 (3), 18.1 (0), 17.5 (3), 11.3 (3), −3.9 (3), −4.7 (3); *m*/*z* (CI mode, NH_3) 303 (100%), 285 (13), 253 (8), 132 (7), 96 (28) (Found: C, 63.48; H, 11.26. $C_{16}H_{34}O_3Si$ requires C, 63.52; H, 11.33%).

(3*R*,4*S*,5*R*,6*S*)-2,4-Dimethyl-5-methoxyhept-1-en-3,6-diol 26

A stirred solution of the silyl ether **25** (100 mg, 0.33 mmol) in anhydrous THF (5 ml) at rt under N_2 was treated with tetrabutylammonium fluoride trihydrate (520 mg, 1.65 mmol). After stirring for 15 min the mixture was partitioned between EtOAc (20 ml) and H_2O (20 ml) and the layers shaken and then separated. The aqueous phase was extracted (3 × 10 ml EtOAc) and the combined organic extracts washed with brine (10 ml), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 50% EtOAc in hexanes) to yield the diol **26** (45 mg, 0.24 mmol, 72%) as a white solid: mp 128–130 °C (EtOAc); $[\alpha]_D$ +3 (*c* 0.34, $CHCl_3$); ν_{max}(film)/cm^{-1} 3328m, 2926m, 1460m, 1097s, 1018s, 902m, 733 (m); δ_H(360 MHz, $CDCl_3$) 5.07 (1H, m, $H13_E$), 4.94 (1H, m, $H13_Z$), 4.03 (1H, quintet, *J* 6.2, H18), 3.99 (1H, d, *J* 7.0, H15), 3.47 (3H, s, OMe), 3.36 (1H, dd, *J* 5.8, 2.1, H17), 2.67–2.60 (1H, m, OH), 2.05 (1H, quintet of d, *J* 7.1, 2.0, H16), 1.98–1.90 (1H, m, OH), 1.70 (3H, s, C14-Me), 1.25 (3H, d, *J* 6.4, H19), 0.98 (3H, d, *J* 7.1, C16-Me); δ_C(90 MHz, $CDCl_3$) 146.6 (0), 113.0 (2), 84.0 (1), 79.4 (1), 67.2 (1), 58.9 (3), 35.5 (1), 19.6 (3), 17.7 (3), 11.9 (3) (Found: $(M + H)^+$, 189.1490. $C_{10}H_{21}O_3$ requires *M*, 189.1491).

Crystal data. $C_{10}H_{20}O_3$, *M* = 188.26, crystallises fom ethyl acetate as extremely fine needles which invariably shattered on cutting. Finally data were collected at 20 °C an uncut crystal of dimensions 3.0 × 0.15 × 0.02 mm and a beam diameter of 0.80 mm. Monoclinic, space group $P2_1$, *a* = 7.3028(10), *b* = 19.019(3), *c* = 8.1976(12) Å, *β* = 90.816(12)°, *V* = 1138.5(3) $Å^3$, *Z* = 4, *μ*(Mo-K*α*) = 0.079 mm^{-1}. The intensities of 3957 reflections were corrected for 25% crystal decomposition and for variations in the irradiated volume (correction factors 1.000–0.921).[39–41] Averaging gave 3115 unique reflections (Rint = 0.049); of these 1620 were deemed observed [$I > 2\sigma(I)$]. Final agreement indices were $R[I > 2\theta(I)] = 0.054$ and wR_2(all data) = 0.14 and in the final difference map $|\Delta\rho| < 0.24$ e $Å^{-3}$. The absolute configuration of the model could not be reliably determined and was therefore assigned from the known absolute stereochemistry of atoms C4*n*, C5*n* and C6*n* (*n* = 1,2). Scattering factors and dispersion corrections were those incorporated in the least squares refinement program SHELXL97 and the WINGX package was used for other calculations.[42,43]

Full crystallographic details, excluding structure factor tables, have been deposited in the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/303.

(3*R*,4*S*,5*R*,6*S*)-2,4-Dimethyl-6-(*tert*-butyldimethylsilyloxy)-5-methoxyhept-1-en-3-yl propionate 27

A stirred solution of the alcohol **26** (4.0 g, 13.2 mmol) in anhydrous pyridine (30 ml) at rt under N_2 was treated with propionic anhydride (3.4 ml, 3.45 g, 26.5 mmol) followed by 4-(dimethylamino)pyridine (30 mg, 0.25 mmol) and then stirred for 16 h. The mixture was then diluted with Et_2O (250 ml) and the organic phase washed successively with 2 M HCl (5 × 50 ml) and sat. $NaHCO_3$ (2 × 50 ml). The ethereal liquor was then dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 5% Et_2O in hexanes) to yield the ester **27** (4.60 g, 12.8 mmol, 97%) as a clear oil which later crystallised upon standing: mp 46–47 °C; bp (Kugelrohr oven) 160 °C/0.8 mmHg; $[\alpha]_D$ −5.1 (*c* 0.60, $CHCl_3$); ν_{max}(film)/cm^{-1} 2932s, 2858m, 1740s, 1463m, 1361m, 1257m, 1185s, 1108s, 1003m, 958m, 926m, 835s, 775m; δ_H(360 MHz, $CDCl_3$) 5.11 (1H, d, *J* 10.0, H15), 5.04 (1H, m, $H13_E$), 4.96 (1H, quintet, *J* 1.7, $H13_Z$), 3.74 (1H, dq, *J* 7.7, 6.0, H18), 3.38 (3H, s, OMe), 2.99 (1H, dd, *J* 7.8, 1.5, H17), 2.36 (2H, dq, *J* 7.7, 1.4, H12), 2.23 (1H, ddq, *J* 10.0, 7.1, 1.5, H16), 1.66 (3H, br s, C14-Me), 1.22 (3H, d, *J* 6.1, H19), 1.16 (3H, t, *J* 7.5, C12-Me), 0.89 (9H, s, CMe_3), 0.75 (3H, d, *J* 7.1, C16-Me), 0.07 and 0.05 (3H each, s, $SiMe_2$); δ_C(90 MHz, $CDCl_3$) 173.8 (0), 142.1 (0), 115.8 (2), 84.7 (1), 79.5 (1), 69.0 (1), 60.9 (3), 34.9 (1), 28.2 (2), 25.9 (3C, 3), 21.2 (3), 18.1 (0), 17.3 (3), 9.5 (3), 9.4 (3), −3.7 (3), −4.8 (3); *m*/*z* (CI mode, NH_3) 376 (100%), 359 (15), 285 (70), 277 (25), 253 (15), 188 (10), 132 (10), 96 (30)

(Found: C, 63.72; H, 10.61. $C_{19}H_{38}O_4Si$ requires C, 63.64; H, 10.68%).

(*E*,2*S*,6*S*,7*R*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)-7-methoxy-2,4-6-trimethylnon-4-enoic acid 29

To a stirred solution of diisopropylamine (0.65 ml, 0.47 g, 4.6 mmol) in anhydrous THF (10 ml) at 0 °C under N_2 was added dropwise *n*-butyllithium (1.85 ml, 2.27 M in hexanes, 4.2 mmol). The resulting solution of lithium diisopropylamide was stirred for 5 min and then further cooled to −78 °C. A solution of the ester **27** (1.0 g, 2.79 mmol) in anhydrous THF (5 ml) was then added continuously down the cold flask side-wall over 5 min whilst the base solution was vigorously stirred. The clear reaction mixture was stirred for 30 min and then treated dropwise with *tert*-butyldimethylsilyl chloride (TBSCl, 3.0 ml, 1.03 M in hexanes, 3.1 mmol) followed by anhydrous dimethylpropylene urea (DMPU, 4 ml). After stirring for 5 min the solution was allowed to warm to rt (cold bath removed) and then heated at reflux for 1 h. The colourless mixture was then allowed to cool to rt, treated with 2 M HCl (10 ml) and stirred vigorously for 30 min. The layers were then separated and the aqueous phase extracted with CH_2Cl_2 (5 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 25–50% Et_2O in hexanes) to yield the acid **29** (835 mg, 82 wt% (contaminated by TBSOH), 1.91 mmol, 68%, dr (C12) Å 6:1 determined by integration of OMe resonances in the ^{1}H NMR (360 MHz, $CDCl_3$): δ_{major} = 3.52, δ_{minor} = 3.50) as a clear oil. An analytical sample of the acid free from TBSOH was obtained by repeated chromatography, but diastereoisomers were not separated: $[a]_D$ −0.8 (*c* 0.51, $CHCl_3$); ν_{max}(film)/cm^{-1} 2957s, 2930s, 2857s, 1709s, 1462m, 1255m, 1104m, 835m, 775m; δ_H(360 MHz, $CDCl_3$) 5.06 (1H, dm, *J* 9.2, H15), 3.83 (1H, dq, *J* 6.2, 3.5, H18), 3.52 (3H, s, OMe), 2.86 (1H, dd, *J* 7.8, 3.6, H17), 2.70–2.59 (1H, m, H12), 2.50–2.38 (2H, m, H16, $H13_B$), 2.05 (1H, dd, *J* 13.5, 8.4, $H13_A$), 1.60 (3H, d, *J* 1.2, C14-Me), 1.12 (3H, d, *J* 6.9, C12-Me), 1.09 (3H, d, *J* 6.2, H19), 0.95 (3H, d, *J* 6.6, C16-Me), 0.89 (9H, s, CMe_3), 0.04 (6H, s, $SiMe_2$); δ_C(90 MHz, $CDCl_3$) 182.8 (0), 131.2 (1), 131.2 (0), 90.3 (1), 70.4 (1), 61.5 (3), 44.0 (2), 37.9 (1), 35.2 (1), 26.0 (3C, 3), 18.2 (0), 17.8 (3), 17.0 (3), 16.4 (3), 15.8 (3), −4.3 (3), −4.7 (3); *m*/*z* (CI mode, NH_3) 375 (31%), 358 (34), 327 (9), 227 (100), 212 (18), 195 (15), 172 (10) (Found: $M^{+\bullet}$, 358.2538. $C_{19}H_{38}O_4Si$ requires *M* 358.2539).

(*E*,2*S*,6*S*,7*R*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)-7-methoxy-2,4,6-trimethylnon-4-en-1-ol 30

A stirred suspension of lithium aluminium hydride (0.35 g, 9.2 mmol) in anhydrous Et_2O (15 ml) at 0 °C under N_2 was treated dropwise with a solution of the acid **29** (1.64 g, 82 wt%, 3.76 mmol, dr (C12) Å 6:1) in anhydrous Et_2O (5 ml). A vigorous reaction ensued and after stirring for 10 min the reaction mixture was quenched by the careful addition of sat. NH_4Cl (10 ml). The biphasic system was then filtered through a Celite pad and the residue washed well (4 × 10 ml Et_2O). The layers of the combined washings and filtrate were then separated and the aqueous phase extracted (10 ml Et_2O). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 30% Et_2O in hexanes) to yield the alcohol **30** (1.17 g, 3.40 mmol, 90%, dr (C12) ≈ 6:1) as a clear oil.

The two diastereoisomers (at C12) can be separated as follows: 1.0 g of **30** (dr (C12) > 4:1) was loaded onto a silica column (id 7 cm, depth 12 cm) and eluted with 15% Et_2O in hexanes taking a pre-fraction of 2.2 l followed by 20 ml fractions to yield in order of elution, 303 mg of mixed material (dr ≈ 3:1) followed by 590 mg of pure material (dr ≥ 95:5).

(*E*,2*S*,6*S*,7*R*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)-7-methoxy-2,4,6-trimethylnon-4-en-1-ol **30**. $[a]_D$ +1.5 (*c* 0.62, $CHCl_3$); ν_{max}(film)/cm^{-1} 3365br m, 2956s, 2929s, 2857s, 1461m, 1256m, 1103m, 1047m, 836m, 775m; δ_H(360 MHz, $CDCl_3$) 5.00 (1H, dm, *J* 10.0, H15), 3.85 (1H, dq, *J* 6.2, 3.4, H18), 3.52 (3H, s, OMe), 3.48 (1H, dd, *J* 10.5, 5.8, $H11_A$), 3.41 (1H, dd, *J* 10.6, 5.9, $H11_B$), 2.86 (1H, dd, *J* 7.7, 3.4, H17), 2.42 (1H, ddq, *J* 9.9, 8.0, 6.7, H16), 2.11 (1H, dd, *J* 12.2, 5.1, $H13_A$), 1.88–1.79 (1H, m, H12), 1.79–1.70 (2H, m, $H13_B$, OH), 1.58 (3H, d, *J* 1.3, C14-Me), 1.08 (3H, d, *J* 6.2, H19), 0.95 (3H, d, *J* 6.6, C16-Me), 0.87 (9H, s, CMe_3), 0.84 (3H, d, *J* 6.5, C12-Me), 0.03 (6H, s, $SiMe_2$); δ_C(90 MHz, $CDCl_3$) 133.0 (0), 130.0 (1), 90.4 (1), 70.4 (1), 68.6 (2), 61.5 (3), 44.5 (2), 35.3 (1), 33.8 (1), 26.0 (3C, 3), 18.1 (0), 17.6 (3), 17.2 (3), 16.7 (3), 16.0 (3), −4.3 (3), −4.7 (3); *m*/*z* (CI mode, isobutane) 345 (100%), 313 (45), 213 (82), 181 (34) (Found: C, 66.07; H, 11.61. $C_{19}H_{40}O_3Si$ requires C, 66.22; H, 11.70%).

(*E*,2*R*,6*S*,7*R*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)-7-methoxy-2,4,6-trimethylnon-4-en-1-ol **12-epi-30**. $[a]_D$ +6.9 (*c* 0.58, $CHCl_3$); ν_{max}(film)/cm^{-1} 3373br m, 2955s, 2928s, 2857s, 1462m, 1382m, 1256m, 1102s, 1047s, 932m, 835m, 775m; δ_H(360 MHz, $CDCl_3$) 5.02 (1H, d, *J* 9.9), 3.84 (1H, dq, *J* 6.0, 3.5), 3.53 (3H, s), 3.50 (1H, dd, *J* 10.5, 5.6), 3.41 (1H, dd, *J* 10.5, 6.0), 2.87 (1H, dd, *J* 7.7, 3.5), 2.47 (1H, ddq, *J* 9.6, 7.3, 7.3), 2.10 (1H, dd, *J* 12.1, 5.1), 1.90–1.74 (2H, m), 1.60 (3H, m), 1.51 (1H, br s), 1.11 (3H, d, *J* 6.2), 0.97 (3H, d, *J* 6.6), 0.92 (9H, s), 0.90–0.87 (3H, m), 0.05 (6H, s, $SiMe_2$); δ_C(90 MHz, $CDCl_3$) 132.8 (0), 130.1 (1), 90.4 (1), 70.3 (1), 68.5 (2), 61.4 (3), 44.3 (2), 35.2 (1), 33.9 (1), 26.0 (3C, 3), 18.2 (0), 17.9 (3), 17.1 (3), 16.7 (3), 16.3 (3), −4.2 (3), −4.7 (3); *m*/*z* (CI mode, NH_3) 344 (3%), 287 (4), 255 (12), 229 (3), 203 (100), 181 (34), 159 (40), 123 (39), 89 (43), 73 (96), 69 (41) (Found: $M^{+\bullet}$, 344.2744. $C_{19}H_{40}O_3Si$ requires *M* 344.2747).

2-{[(*E*,2*S*,6*S*,7*R*,8*S*)-8-(*tert*-Butyldimethylsilyloxy)-7-methoxy-2,4,6-trimethylnon-4-enyl]thio}-1,3-benzothiazole 31

To a stirred solution of the alcohol **30** (1.47 g, 4.27 mmol) in anhydrous THF (25 ml) at rt under N_2 was added 2-mercapto-1,3-benzothiazole (BTSH, 0.86 g, 5.15 mmol) and triphenylphosphine (1.34 g, 5.11 mmol). The resulting solution was cooled to 0 °C and diisopropyl azodicarboxylate (DIAD, 1.10 ml, 1.13 g, 5.59 mmol) added dropwise. The cooling bath was then removed and the mixture allowed to stir for 2 h. After this time the solvent was removed *in vacuo* and the residue further purified *via* column chromatography (eluting with 3% EtOAc in hexanes) to yield the sulfide **31** (2.08 g, 4.21 mmol, 99%) as a clear oil: $[a]_D$ +0.3 (*c* 0.65, $CHCl_3$); ν_{max}(film)/cm^{-1} 2956s, 2928s, 2894s, 2856s, 1461s, 1428s, 1255m, 1103m, 995m, 836m, 775m, 755m; δ_H(360 MHz, $CDCl_3$) 7.86 (1H, dm, *J* 8.1), 7.75 (1H, dm, *J* 8.0), 7.41 (1H, ddd, *J* 8.5, 7.3, 1.3), 7.29 (1H, ddd, *J* 8.1, 7.4, 1.2), 5.06 (1H, dm, *J* 9.9, H15), 3.87 (1H, dq, *J* 6.2, 3.4, H18), 3.54 (3H, s, OMe), 3.45 (1H, dd, *J* 12.9, 5.3, $H11_A$), 3.12 (1H, dd, *J* 12.9, 7.5, $H11_B$), 2.88 (1H, dd, *J* 7.9, 3.4, H17), 2.47 (1H, ddq, *J* 9.9, 7.8, 6.7, H16), 2.27–2.10 (2H, m, H12, $H13_A$), 1.93 (1H, dd, *J* 12.8, 8.0, $H13_B$), 1.62 (3H, d, *J* 1.2, C14-Me), 1.11 (3H, d, *J* 6.2, H19), 1.03 (3H, d, *J* 6.5, C12-Me), 1.00 (3H, d, *J* 6.6, C16-Me), 0.90 (9H, s, CMe_3), 0.05 (6H, s, $SiMe_2$); δ_C(90 MHz, $CDCl_3$) 167.6 (0), 153.4 (0), 135.3 (0), 132.2 (0), 130.7 (1), 126.1 (1), 124.2 (1), 121.5 (1), 121.0 (1), 90.3 (1), 70.4 (1), 61.5 (3), 47.2 (2), 40.4 (2), 35.3 (1), 31.5 (1), 26.0 (3C, 3), 19.4 (3), 18.2 (0), 17.7 (3), 17.2 (3), 16.1 (3), −4.3 (3), −4.7 (3); *m*/*z* (CI mode, NH_3) 493 (10%), 446 (6), 436 (4), 330 (47), 203 (97), 159 (33), 123 (63), 73 (100) (Found: $M^{+\bullet}$, 493.2508. $C_{26}H_{43}NO_2S_2Si$ requires *m*/*z* 493.2505) (Found: C, 63.36; H, 8.84; N, 2.82. $C_{26}H_{43}NO_2S_2Si$ requires C, 63.23; H, 8.78; N, 2.84%).

(*E*,2*S*,6*S*,7*R*,8*S*)-1-(1,3-Benzothiazol-2-ylthio)-7-methoxy-2,4,6-trimethylnon-4-en-8-ol 32

A stirred solution of the silyl ether **31** (631 mg, 1.28 mmol)

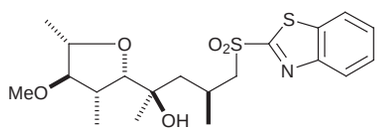
in anhydrous THF (15 ml) at rt under N_2 was treated with TBAF·$3H_2O$ (2.0 g, 6.3 mmol) and the resulting clear mixture stirred for 28 h. After this time TLC analysis indicated incomplete consumption of the silyl ether; additional TBAF·$3H_2O$ (0.5 g, 1.6 mmol) was then added and the reaction stirred for a further 4 h. The solution was then partitioned between Et_2O (30 ml) and H_2O (30 ml) and the layers shaken well and then separated. The aqueous phase was extracted with Et_2O (3 × 15 ml) and the combined organic extracts washed with brine (20 ml), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 30% EtOAc in hexanes) to yield the alcohol **32** (475 mg, 1.25 mmol, 98%) as a clear oil: $[a]_D$ −22.1 (*c* 1.00, $CHCl_3$); ν_{max}(film)/cm^{-1} 3441br s, 2979s, 2829s, 1458s, 1427s, 1239m, 1126m, 1096s, 994s, 904m, 756s, 727s; δ_H(360 MHz, $CDCl_3$) 7.85 (1H, dm, *J* 8.1), 7.75 (1H, dm, *J* 8.0), 7.40 (1H, ddd, *J* 8.2, 7.3, 1.3), 7.28 (1H, ddd, *J* 8.0, 7.4, 1.2), 5.07 (1H, dm, *J* 9.9, H15), 3.84 (1H, m, H18), 3.53 (3H, s, OMe), 3.44 (1H, dd, *J* 12.9, 5.1, $H11_A$), 3.09 (1H, dd, *J* 12.9, 7.4, $H11_B$), 2.96 (1H, dd, *J* 8.2, 3.8, H17), 2.51 (1H, ddq, *J* 9.8, 8.2, 6.7, H16), 2.23–2.09 (2H, m, H12, $H13_A$), 1.98–1.89 (2H, m, $H13_B$, OH), 1.63 (3H, d, *J* 1.3, C14-Me), 1.14 (3H, d, *J* 6.4, H19), 1.05 (3H, d, *J* 6.7, C12-Me), 1.01 (3H, d, *J* 6.5, C16-Me); δ_C(90 MHz, $CDCl_3$) 167.6 (0), 153.4 (0), 135.3 (0), 132.6 (0), 130.1 (1), 126.1 (1), 124.2 (1), 121.5 (1), 121.0 (1), 89.6 (1), 69.4 (1), 61.6 (3), 47.0 (2), 40.3 (2), 35.7 (1), 31.5 (1), 19.4 (3), 17.7 (3), 17.5 (3), 16.2 (3); *m*/*z* (EI mode) 379 (3%), 332 (14), 290 (18), 248 (7), 223 (6), 208 (10), 167 (73), 123 (100%), 89 (41), 81 (37) (Found: C, 63.13; H, 7.62; N, 3.61. $C_{20}H_{29}NO_2S_2$ requires C, 63.28; H, 7.70; N, 3.69%).

(*E*,2*S*,6*S*,7*R*,8*S*)-1-(1,3-Benzothiazol-2-ylsulfonyl)-7-methoxy-2,4,6-trimethylnon-4-en-8-ol 33

To a stirred solution of the sulfide **32** (870 mg, 2.30 mmol) in EtOH (20 ml) at rt was added dropwise a yellow solution of ammonium molybdate tetrahydrate (280 mg, 0.23 mmol) in aqueous hydrogen peroxide (2.6 g, 30 wt%, 22.9 mmol). The resultant mixture was stirred vigorously for 24 h and then partitioned between Et_2O (30 ml) and H_2O (20 ml). The layers were shaken and then separated and the aqueous phase extracted (3 × 10 ml Et_2O). The combined organic extracts were washed with H_2O (2 × 20 ml), dried ($MgSO_4$) and then concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 40% EtOAc in hexanes) to yield the sulfone **33** (835 mg, 2.03 mmol, 88%) as a clear oil: $[a]_D$ −24.0 (*c* 1.09, $CHCl_3$); ν_{max}(film)/cm^{-1} 3447br s, 2962s, 2929s, 1472m, 1458m, 1318m, 1146m, 1097m, 763m, 731m, 632m; δ_H(360 MHz, $CDCl_3$) 8.19 (1H, dm, *J* 7.8), 8.01 (1H, dm, *J* 8.11), 7.63 (1H, ddd, *J* 8.1, 7.2, 1.4), 7.58 (1H, ddd, *J* 7.9, 7.2, 1.4), 5.02 (1H, dm, *J* 9.9, H15), 3.79 (1H, dq, *J* 6.4, 3.8, H18), 3.58 (1H, dd, *J* 14.4, 3.7, $H11_A$), 3.50 (3H, s, OMe), 3.23 (1H, dd, *J* 14.4, 8.7, $H11_B$), 2.92 (1H, dd, *J* 8.0, 3.8, H17), 2.50–2.39 (2H, m, H16, H12), 2.07 (1H, ddd, *J* 13.4, 7.9, 1.1, $H13_A$), 1.98 (1H, dd, *J* 13.6, 6.8, $H13_B$), 2.0–1.80 (1H, br, OH), 1.49 (3H, d, *J* 1.3, C14-Me), 1.10 (6H, d, *J* 6.4, C12-Me, H19), 1.01 (3H, d, *J* 6.7, C16-Me); δ_C(90 MHz, $CDCl_3$) 166.7 (0), 152.8 (0), 136.8 (0), 131.6 (0), 131.3 (1), 128.2 (1), 127.8 (1), 125.5 (1), 122.5 (1), 89.4 (1), 69.2 (1), 61.4 (3), 60.0 (2), 47.4 (2), 35.5 (1), 26.6 (1), 20.2 (3), 17.6 (3), 17.5 (3), 15.9 (3); *m*/*z* (CI mode, isobutane) 412 (100%), 380 (26), 362 (42), 322 (54) (Found: $(M + H)^+$, 412.1614. $C_{20}H_{30}NO_4S_2$ requires *M* 412.1616) (Found: C, 58.17; H, 7.15; N, 3.42. $C_{20}H_{29}NO_4S_2$ requires C, 58.36; H, 7.10; N, 3.40%).

(2*S*,4*R*,5*R*,6*S*,7*R*,8*S*)-1-(1,3-Benzothiazol-2-ylsulfonyl)-4,5-epoxy-7-methoxy-2,4,6-trimethylnon-8-ol 34

A stirred solution of the hydroxy olefin **33** (519 mg, 1.26 mmol) in anhydrous CH_2Cl_2 (10 ml) at −8 °C under N_2 was treated with vanadyl bis(acetylacetonate) (3.4 mg, 13 μmol) followed by the slow addition of a solution of *tert*-butyl hydroperoxide (TBHP, 0.71 ml, 5.32 M in isooctane, 3.8 mmol) in anhydrous CH_2Cl_2 (9 ml) *via* a syringe pump over 48 h. After the complete addition of the stoichiometric oxidant the colourless solution was allowed to stir for a further 24 h at −8 °C. After this time the mixture was diluted with Et_2O (20 ml) and H_2O (20 ml) and the layers shaken well and then separated. The aqueous phase was then extracted (2 × 10 ml) and the combined organic extracts washed with brine (10 ml), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 35–60% EtOAc in hexanes) to afford in order of elution: the tetrahydrofuran by-product **40** (25 mg, 0.06 mmol, 5%), recovered starting material



40

33 (136 mg, 0.33 mmol, 26%) and the epoxide **34** (373 mg, 0.87 mmol, 69%) all as clear oils. ^{1}H and ^{13}C NMR analysis revealed the latter compound to be a single diastereoisomer.

(2*S*,4*R*,5*R*,6*S*,7*R*,8*S*)-1-(1,3-Benzothiazol-2-ylsulfonyl)-4,5-epoxy-7-methoxy-2,4,6-trimethylnon-8-ol **34**. $[a]_D$ −4.0 (*c* 1.98, $CHCl_3$); ν_{max}(film)/cm^{-1} 3452br s, 2966s, 2932s, 1471m, 1318s, 1148s, 1097s, 763m; δ_H(360 MHz, $CDCl_3$) 8.18 (1H, dm, *J* 7.6), 8.01 (1H, dm, *J* 7.5), 7.66–7.56 (2H, m), 3.94 (1H, quintet, *J* 5.8, H18), 3.61 (1H, dd, *J* 14.2, 4.7, $H11_A$), 3.48 (3H, s, OMe), 3.34 (1H, dd, *J* 14.3, 7.9, $H11_B$), 3.06 (1H, t, *J* 5.0, H17), 2.61 (1H, d, *J* 9.5, H15), 2.62–2.50 (1H, m), 2.08–2.00 (1H, m), 1.80 (1H, dd, *J* 14.2, 7.3, $H13_A$), 1.67–1.55 (1H, m), 1.59 (1H, dd, *J* 14.2, 7.4, $H13_B$), 1.27 (3H, s, C14-Me), 1.22 (3H, d, *J* 6.8, H19), 1.20 (3H, d, *J* 6.5, C12-Me), 1.01 (3H, d, *J* 6.9, C16-Me); δ_C(90 MHz, $CDCl_3$) 166.6 (0), 152.7 (0), 136.8 (0), 128.2 (1), 127.9 (1), 125.5 (1), 122.5 (1), 86.6 (1), 68.1 (1), 64.9 (1), 60.5 (3), 60.3 (2), 60.2 (0), 45.4 (2), 34.7 (1), 26.1 (1), 20.9 (3), 19.1 (3), 16.4 (3), 11.8 (3); *m*/*z* (CI mode, isobutane) 428 (11%), 410 (15), 378 (100), 322 (14), 298 (12), 213 (14), 136 (27) (Found: $(M + H)^+$, 428.1561. $C_{20}H_{30}NO_5S_2$ requires *M*, 428.1565) (Found: C, 56.19; H, 6.84; N, 3.23. $C_{20}H_{29}NO_5S_2$ requires C, 56.18; H, 6.84; N, 3.28%).

(2*S*,3*S*,4*R*,5*S*)-3,5-Dimethyl-2-[(1*R*,3*S*)-4-(1,3-benzothiazol-2-ylsulfonyl)-1,3-dimethyl-1-hydroxybutyl]-4-methoxyoxolane **40**. δ_H(360 MHz, $CDCl_3$) 8.22 (1H, dm, *J* 7.5 Hz), 8.03 (1H, dm, *J* 7.9 Hz), 7.68–7.55 (2H, m), 3.80 (1H, dq, *J* 6.7, 2.6 Hz), 3.57 (1H, dd, *J* 14.3, 6.7 Hz), 3.57 (1H, d, *J* 4.6 Hz), 3.48 (1H, dd, *J* 14.3, 6.0 Hz), 3.29 (3H, s), 3.08 (1H, d, *J* 2.5 Hz), 2.73–2.60 (1H, m), 2.20–2.10 (2H, m), 1.77 (1H, dd, *J* 14.1, 3.4 Hz), 1.65 (1H, dd, *J* 14.2, 8.8 Hz), 1.31 (3H, d, *J* 6.6 Hz), 1.28 (3H, d, *J* 6.8 Hz), 1.27 (3H, s), 1.03 (3H, d, *J* 7.4 Hz); δ_C(90 MHz, $CDCl_3$) 166.9 (0), 152.8 (0), 136.8 (0), 128.2 (1), 127.8 (1), 125.6 (1), 122.5 (1), 95.1 (1), 85.6 (1), 79.8 (1), 73.3 (0), 62.1 (2), 56.9 (3), 42.9 (2), 40.2 (1), 26.2 (3), 25.3 (1), 22.3 (3), 20.7 (3), 15.0 (3).

(1*R*,2*R*,3*R*,4*R*,5*R*,7*S*)-8-(1,3-Benzothiazol-2-ylsulfonyl)-4,5-epoxy-2-methoxy-1,3,5,7-tetramethyloctyl 4-chlorobenzoate 4

A solution of triphenylphosphine (393 mg, 1.50 mmol) in anhydrous THF (3 ml) at 0 °C under N_2 was treated with neat dimethyl azodicarboxylate[28] (207 mg, 1.42 mmol) and the resultant colourless suspension stirred for 5 min. A solution of the alcohol **34** (304 mg, 0.71 mmol) in anhydrous THF (3 ml) was then added dropwise and the mixture stirred for a further 5 min. One third of a solution of *p*-chlorobenzoic acid (138 mg, 0.88 mmol) in anhydrous THF (1.8 ml) was then added dropwise and the cooling bath removed. After 1 h a further one third of the acid solution was added, followed by the remainder after a subsequent hour. The reaction was then stirred for a final 1 h

period after complete addition of the acid component and then worked-up as follows: the mixture was diluted with EtOAc (20 ml) and washed successively with sat. $NaHCO_3$ (15 ml), H_2O (4 × 10 ml) and brine (10 ml). The resulting organic phase was dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 20% EtOAc in hexanes) to afford the *p*-chlorobenzoate **4** (297 mg, 0.52 mmol, 74%) as a white foam: $[\alpha]_D$ −17.3 (*c* 1.60, $CHCl_3$); ν_{max}(film)/cm^{-1} 2964s, 2933s, 1712s, 1594m, 1472m, 1459m, 1321s, 1273s, 1148s, 1090s, 1015m, 760m, 730m, 632m; δ_H(360 MHz, $CDCl_3$) 8.19 (1H, dm, *J* 7.2), 8.02 (1H, dm, *J* 7.6), 7.99 (2H, d, *J* 8.7), 7.65 (1H, ddd, *J* 7.3, 7.3, 1.4), 7.60 (1H, ddd, *J* 7.3, 7.3, 1.4), 7.40 (2H, d, *J* 8.7), 5.29 (1H, quintet, *J* 6.6, H18), 3.61 (1H, dd, *J* 14.2, 4.7, $H11_A$), 3.51 (3H, s, OMe), 3.37 (1H, dd, *J* 6.8, 4.2, H17), 3.34 (1H, dd, *J* 14.2, 7.9, $H11_B$), 2.65 (1H, d, *J* 9.3, H15), 2.64–2.51 (1H, m, H16), 1.80 (1H, dd, *J* 14.1, 7.3, $H13_A$), 1.62 (1H, dd, *J* 14.1, 7.5, $H13_B$), 1.63–1.52 (1H, m, H12), 1.30 (3H, d, *J* 6.5, H19), 1.27 (3H, s, C14-Me), 1.24 (3H, d, *J* 6.7, C12-Me), 1.02 (3H, d, *J* 6.9, C16-Me); δ_C(90 MHz, $CDCl_3$) 166.6 (0), 165.2 (0), 152.7 (0), 139.4 (0), 136.8 (0), 131.1 (2C, 1), 129.2 (0), 128.8 (2C, 1), 128.3 (1), 127.9 (1), 125.5 (1), 122.5 (1), 84.5 (1), 73.1 (1), 64.6 (1), 61.5 (3), 60.3 (2), 59.9 (0), 45.5 (2), 35.0 (1), 26.1 (1), 20.9 (3), 16.8 (3), 16.4 (3), 10.8 (3); *m*/*z* (CI mode, NH_3) 583 (8%), 548 (23), 378 (67), 213 (92), 136 (100) (Found: $(M + H)^+$, 566.1433. $C_{27}H_{33}ClNO_6S_2$ requires *M*, 566.1438).

18*O*-(4-Chlorobenzoyl)herboxidiene allyl ester 35

To a stirred solution of the sulfone **4** (331 mg, 0.58 mmol) in anhydrous THF (6 ml) at −78 °C under N_2 was added dropwise a solution of freshly prepared lithium diisopropylamide (LDA, 1.3 ml, 0.41 M in THF, 0.53 mmol) and the resulting deep yellow solution stirred for 15 min. A solution of the enal **3** (131 mg, 0.49 mmol, prepared in 4 steps from **17** as previously described[5]) in anhydrous THF (2 ml) was then added dropwise. The colour of the reaction mixture lightened. The mixture was stirred for 30 min at −78 °C and then allowed to warm slowly to −20 °C over 1 h. The resulting colourless solution was then quenched by the addition of sat. NH_4Cl (2 ml) and allowed to warm to rt with vigorous stirring. After further dilution with EtOAc (15 ml) and H_2O (15 ml) the layers were well shaken and separated. The aqueous phase was then extracted (3 × 5 ml EtOAc) and the combined organic extracts washed with brine (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 15% EtOAc in hexanes) to yield the diene **35** (246 mg, *ca*. 0.40 mmol, 81%) as a clear oil. ^{1}H NMR analysis indicated the presence of a small quantity of the associated 10*Z* isomer together with other minor impurities (<5%). Conversion to the methyl ester **36** as outlined below facilitated purification and enabled accurate measurement of the *E*:*Z* ratio for the olefination step as 91:9 in favour of the natural 10*E* geometry. Repeated chromatography (eluting with 20% Et_2O in hexanes) provided a good purity sample of **35** for characterisation purposes: $[\alpha]_D$ −25 (*c* 0.4, $CHCl_3$); ν_{max}(film)/cm^{-1} 2927m, 1720s, 1091m; δ_H(360 MHz, $CDCl_3$) 8.00 (2H, d, *J* 8.7, Ar), 7.41 (2H, d, *J* 8.7, Ar), 6.22 (1H, dd, *J* 15.0, 10.9, H10), 5.94–5.82 (1H, m, CH_2CH=CH_2), 5.88 (1H, dm, *J* 10.4, H9), 5.42 (1H, dd, *J* 15.0, 8.9, H11), 5.30 (1H, dm, *J* 17.9, CH_2CH=CH_ZH_E), 5.27 (1H, quintet, *J* 6.9, H18), 5.20 (1H, dm, *J* 10.5, CH_2CH=CH_ZH_E), 4.58 (2H, d, *J* 5.5, CH_2CH=CH_2), 3.83–3.74 (1H, m, H3), 3.52 (3H, s, OMe), 3.37 (1H, dd, *J* 6.9, 3.9, H17), 3.31 (1H, d, *J* 9.9, H7), 2.62 (1H, d, *J* 9.7, H15), 2.61 (1H, dd, *J* 15.1, 6.5, $H2_A$), 2.43 (1H, dd, *J* 15.2, 6.5, $H2_B$), 2.47–2.34 (1H, m, H12), 1.91 (1H, dd, *J* 13.5, 4.6, $H13_A$), 1.88–1.80 (1H, m, $H5_A$), 1.72–1.65 (1H, m, $H4_A$), 1.69 (3H, s, C8-Me), 1.57–1.46 (2H, m, H6, H16), 1.40–1.15 (3H, m, $H4_B$, $H5_B$, $H13_B$), 1.29 (3H, d, *J* 6.5, H19), 1.24 (3H, s, C14-Me), 1.03 (3H, d, *J* 6.6, C12-Me), 0.88 (3H, d, *J* 6.9, C16-Me), 0.64 (3H, d, *J* 6.6, C6-Me); δ_C(90 MHz, $CDCl_3$) 171.2 (0), 165.3 (0), 139.4 (1), 139.4 (0), 135.3 (0), 132.3 (1), 131.2 (2C, 1), 129.3 (0), 128.8 (2C, 1), 128.3 (1), 125.3 (1), 118.0 (2), 90.8 (1), 84.7 (1), 74.0 (1), 73.3 (1), 66.0 (1), 65.1 (2), 61.5 (3), 60.9 (0), 47.1 (2), 41.6 (2), 35.4 (1), 35.2 (1), 32.4 (2), 32.2 (1), 31.8 (2), 22.3 (3), 17.7 (3), 16.8 (3), 16.8 (3), 12.0 (3), 10.8 (3); *m*/*z* (CI mode, NH_3) 616 (0.6%), 460 (2), 361 (4), 304 (16), 290 (24), 227 (46), 183 (15), 139 (100), 95 (41) (Found: M^+, 616.3169. $C_{35}H_{49}ClO_7$ requires *M*, 616.3167).

Herboxidiene methyl ester 36

A stirred suspension of the benzoate **35** (223 mg, 0.36 mmol) and potassium carbonate (100 mg, 0.72 mmol) in anhydrous MeOH (5 ml) was heated at reflux for 2 h. The mixture was allowed to cool to rt and subsequently diluted with EtOAc (20 ml) and H_2O (10 ml). The layers were then shaken and separated and the aqueous phase extracted with EtOAc (3 × 5 ml). The combined organic extracts were washed with brine (5 ml), dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 35% EtOAc in hexanes) to yield the pure methyl ester **36** (117 mg, 0.26 mmol, 72%) as a clear oil. The 10*E*:*Z* ratio of this material reflected that of the starting material [*E*:*Z* = 91:9, determined by integration of the H11 resonance in the ^{1}H NMR spectrum; δ_{H11} (10*E*) = 5.44 (1H, dd, *J* 15.0, 8.7), δ_{H11} (10*Z*) = 5.21 (1H, t, *J* 10.0)]. The pure natural isomer could be isolated by subsequent careful column chromatography eluting with 20% EtOAc in hexanes, the 10*E* isomer being the less polar component. ^{1}H and ^{13}C NMR data were in complete agreement with those previously reported by Isaac *et al*.[2] DEPT data and proton resonance coupling constants were not reported by Isaac and so are listed here: $[\alpha]_D$ +0.9 (*c* 0.66, $CHCl_3$); ν_{max}(film)/cm^{-1} 3501br m, 2954s, 2925s, 2849m, 1740s, 1455m, 1067m; δ_H(360 MHz, $CDCl_3$) 6.24 (1H, dd, *J* 15.0, 10.8, H10), 5.90 (1H, d, *J* 11.0, H9), 5.45 (1H, dd, *J* 14.9, 8.8, H11), 3.90–3.83 (1H, m, H18), 3.82–3.73 (1H, m, H3), 3.67 (3H, s, CO_2Me), 3.55 (3H, s, OMe), 3.33 (1H, d, *J* 9.8, H7), 2.98 (1H, t, *J* 5.3, H17), 2.60 (1H, dd, *J* 15.2, 6.2, $H2_A$), 2.60–2.53 (1H, m, OH), 2.56 (1H, d, *J* 9.7, H15), 2.45–2.37 (1H, m, H12), 2.41 (1H, dd, *J* 15.2, 6.7, $H2_B$), 1.90 (1H, dd, *J* 13.6, 4.7, $H13_A$), 1.88–1.81 (1H, m, $H5_A$), 1.71 (3H, s, C8-Me), 1.70–1.50 (3H, m, $H4_A$, H6, H16), 1.40–1.20 (3H, m, $H4_B$, $H5_B$, $H13_B$), 1.29 (3H, s, C14-Me), 1.19 (3H, d, *J* 6.4, H19), 1.05 (3H, d, *J* 6.7, C12-Me), 0.88 (3H, d, *J* 6.9, C16-Me), 0.67 (3H, d, *J* 6.6, C6-Me); δ_C(90 MHz, $CDCl_3$) 172.0 (0), 139.4 (1), 135.4 (0), 128.3 (1), 125.4 (1), 90.8 (1), 87.8 (1), 74.0 (1), 68.4 (1), 66.2 (1), 61.5 (0), 61.5 (3), 51.7 (3), 47.1 (2), 41.5 (2), 35.5 (1), 35.3 (1), 32.4 (2), 32.3 (1), 31.8 (2), 22.2 (3), 19.2 (3), 17.8 (3), 16.7 (3), 12.1 (3), 12.0 (3); *m*/*z* (CI mode, NH_3) 452 (28%), 434 (9), 351 (12), 305 (10), 278 (22), 265 (19), 237 (12), 211 (11), 197 (15), 173 (44), 157 (42), 129 (100), 123 (55), 95 (56), 69 (50) (Found: M^+, 452.3136. $C_{26}H_{44}O_6$ requires *M*, 452.3138).

Herboxidiene 1

A solution of the methyl ester **36** (16 mg, 35 μmol) in MeOH (2 ml) was treated with an aqueous solution of potassium carbonate (24 mg, 174 μmol in 0.5 ml H_2O) and the resultant mixture stirred at reflux for 1 h whereupon the reaction was allowed to cool and diluted with EtOAc (10 ml) and H_2O (5 ml). The aqueous layer was then acidified to pH 2–3 by the careful addition of HCl (2 M, *ca*. 0.5 ml) and the layers shaken well and then separated. The aqueous phase was extracted with EtOAc (4 × 5 ml) and the combined organic extracts washed with brine (5 ml), dried (Na_2SO_4) and then concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 7% MeOH in CH_2Cl_2) to yield herboxidiene (**1**, 13 mg, 30 μmol, 84%) as a clear oil. ^{1}H and ^{13}C NMR data recorded in CD_3OD are listed in Tables 1 and 2 respectively. ν_{max}(film)/cm^{-1} 3470br w, 2962s, 2919s,

2849m, 1731m, 1456m, 1068m; *m*/*z* (EI mode) 438 (10%), 420 (4), 337 (7), 293 (7), 251 (58), 183 (18), 173 (34), 129 (85), 95 (100), 69 (82) (Found: M^+, 438.2980. $C_{25}H_{42}O_6$ requires *M*, 438.2981).

Acknowledgements

We thank Rhône-Poulenc Rorer for a CASE studentship.

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Paper 9/00185I