Total synthesis of milbemycin E: synthesis of the C(11)–C(25) fragment

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Treatment of 2-methylpropanal with the (*E*)-but-2-enyl(diisopinocampheyl)borane 9 prepared from (+)-α-pinene gives the *anti*- and *syn*-products 10 and 11, ratio 88 : 12, from which the major *anti*-isomer 10 is separated by preparative GLC. Hydroboration–oxidation of its *tert*-butyldimethylsilyl ether 14 gives the primary alcohol 15 which has been converted into the bromide 16 and iodide 17. The propenyl(diisopinocampheyl)borane 23 prepared from (−)-α-pinene reacts with the aldehyde 22 prepared from (*S*)-malic acid to give the *anti*- and *syn*-1,3-diol derivatives 24 and 25, ratio 86 : 14, and the *anti*-product 24 has been taken through to the epoxide 31. Sequential alkylation of 1,3-dithiane with the iodide 17 and the epoxide 31 gives the 2,2-dialkyl-1,3-dithiane 33 which is converted into the spiroacetal 4 by treatment with dilute aqueous hydrogen fluoride. After protection, ozonolysis gives the aldehyde 43 which has been condensed with the ylide 34 to give the α,β-unsaturated ester 44. This has been reduced and converted into the iodide 46 which has been used to alkylate the chiral oxazolidinone 39 to give the required C(11)–C(25) fragment 48 of milbemycin E 1 after reductive removal of the chiral auxiliary. This has been converted into the phosphonium salt 2 ready for Wittig coupling with the hydroxybutenolide 3 for the assembly of the milbemycin nucleus.

The milbemycins and avermectins are an important group of macrolides with potent and useful biological activities.[1] We are developing a convergent approach to these compounds based on the use of a Wittig reaction between a phosphorane corresponding to the C(11)–C(25) fragment and an aldehyde corresponding to the C(1)–C(10) fragment as the key convergent step.[2] As applied to a synthesis of milbemycin E **1**, this would involve the Wittig reaction between the spiroacetal-containing phosphonium salt **2** and the hydroxybutenolide **3**.[3] We previously described a synthesis of milbemycin spiroacetals from methyl α-D-glucopyranoside.[4] We now report an alternative synthesis of these spiroacetals using chiral allylboranes and aldehydes to prepare homoallylic alcohols as developed by H. C. Brown,[5] and the completion of a synthesis of the phosphonium salt **2**.[6] The accompanying papers describe a synthesis of the hydroxybutenolide **3** and the completion of a synthesis of milbemycin E **1**.

The present approach to spiroacetals is based on the alkylation of 1,3-dithiane with an alkyl halide **7** and an epoxide **6** to give the protected triol **5**.[7] The use of other acyl carbanion equivalents was briefly investigated but was not successful. Deprotection of the dialkylated dithiane **5** gave the spiroacetal **4** which was taken through to the phosphonium salt **2**.

Results and discussion

Methoxy(diisopinocampheyl)borane **8** was prepared by hydroboration of (+)-α-pinene, equilibration with an excess of (+)-α-pinene to optimize its optical purity, followed by methanolysis of the diisopinocampheylborane so obtained.[8] Treatment of the methoxyborane **8** with the organometallic reagent generated by treatment of (*E*)-but-2-ene with butyllithium and potassium *tert*-butoxide gave (*E*)-but-2-enyl(diisopinocampheyl)borane **9** which was reacted *in situ* with 2-methylpropanal followed by oxidative cleavage of the chiral auxiliary to give *anti*- and *syn*-2,4-dimethylhex-5-en-3-ol **10** and **11**, yield 80%, ratio 88 : 12 (Scheme 1).[5] The major diastereoisomer **10** was separated by preparative GLC, and shown to correspond to an enantiomeric excess of >80% by treatment with Mosher's (*S*)-acid chloride[9] which gave the two diastereoisomers **12** and **13** which could be distinguished by ^{1}H NMR spectroscopy.

Protection of the *anti*-alcohol **10** using *tert*-butyldimethylsilyl trifluoromethanesulfonate[10] gave the silyl ether **14** which was hydroborated using borane–tetrahydrofuran to give the primary alcohol **15** after oxidation. The alcohol was converted into the bromide **16** and iodide **17** using carbon tetrabromide[11] and triphenylphosphine, and iodine, imidazole and triphenylphosphine, in good yield.[12]

Dimethyl (*S*)-malate **18** was reduced to methyl (*S*)-3,4-dihydroxybutanoate **19** following the literature procedure,[13] and the diol protected as its acetonide **20** (Scheme 2). Further reduction gave the alcohol **21** which was oxidized to the aldehyde **22**. Reactions of this aldehyde with achiral Grignard reagents were not stereoselective and so it was necessary to use a chiral reagent to control the stereoselectivity of addition to the aldehyde group. This was achieved using the prop-2-enyl(diisopinocampheyl)borane **23** prepared as described by Brown from (−)-α-pinene.[14] Reaction of the borane **23** with the aldehyde **22** gave, after oxidative removal of the auxiliary, a mixture of the 1,3-*anti*- and 1,3-*syn*-products **24** and **25**, ratio 86 : 14, whose spectroscopic and optical rotation data agreed with those reported in the literature.[15] This mixture of alcohols was not separated on a preparative scale, rather the mixture was protected using (2-trimethylsilylethoxy)methyl chloride (SEM chloride) to give the (2-trimethylsilylethoxy)methyl ether **26** containing *ca.* 10% of its *syn*-diastereoisomer.[16] Ozonolysis gave the aldehyde **27**, but attempts to generate a Grignard reagent from the bromide **16** and add it to the aldehyde **27** were not successful, in that complex mixtures of products were obtained. As an alternative procedure for the coupling of the aldehyde **27** and alkyl halides **16** or **17**, the aldehyde was converted into its trimethylsilylated cyanohydrin **28**. However, attempts to deprotonate this cyanohydrin and alkylate it using either the bromide **16** or iodide **17** were not successful.

At this point it was decided to develop the chemistry of the acetal-containing end of the (2-trimethylsilylethoxy)methyl ether **26**. Selective hydrolysis of the acetonide gave the diol **29**

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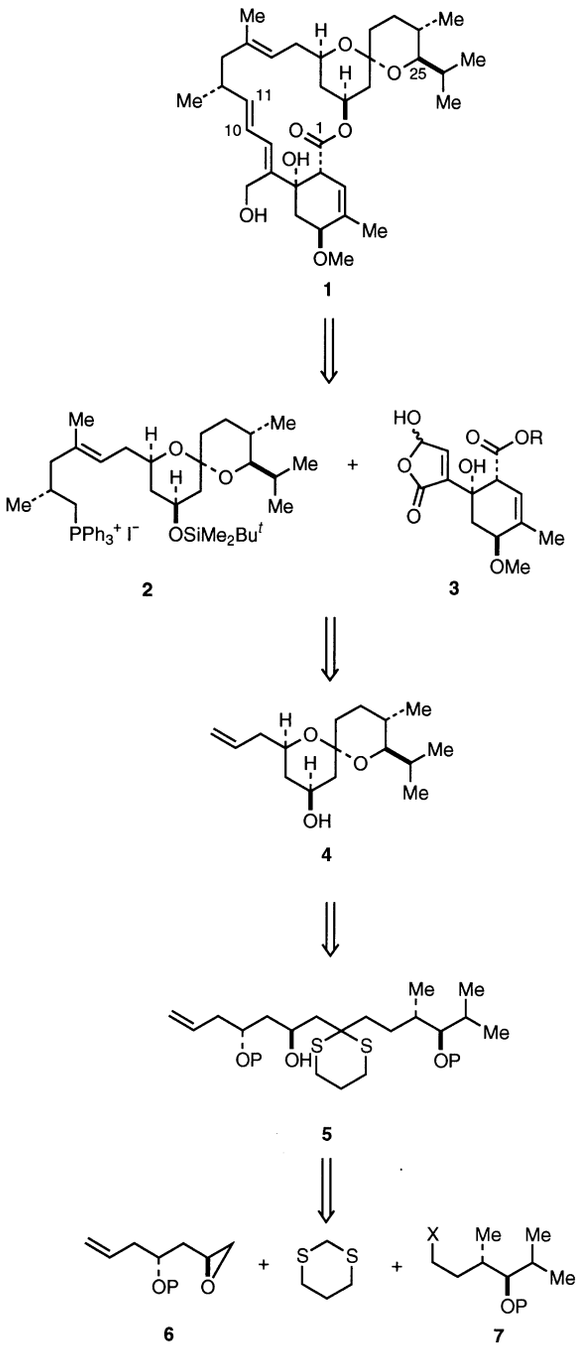
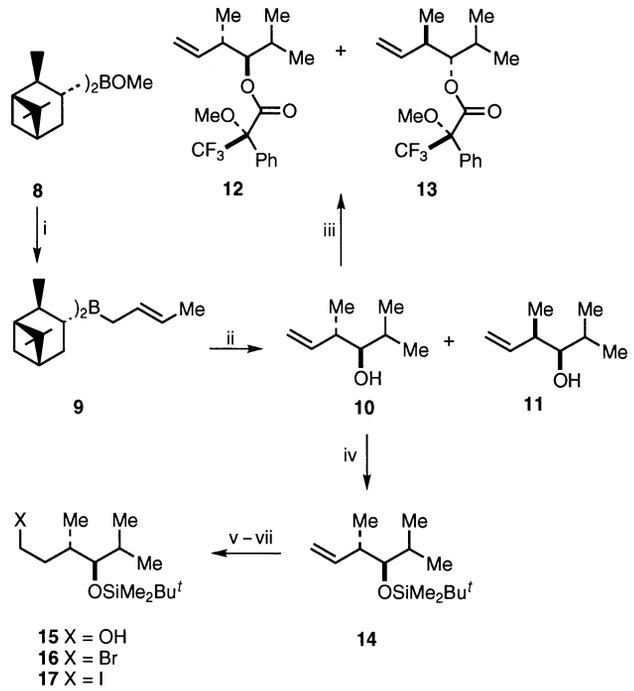




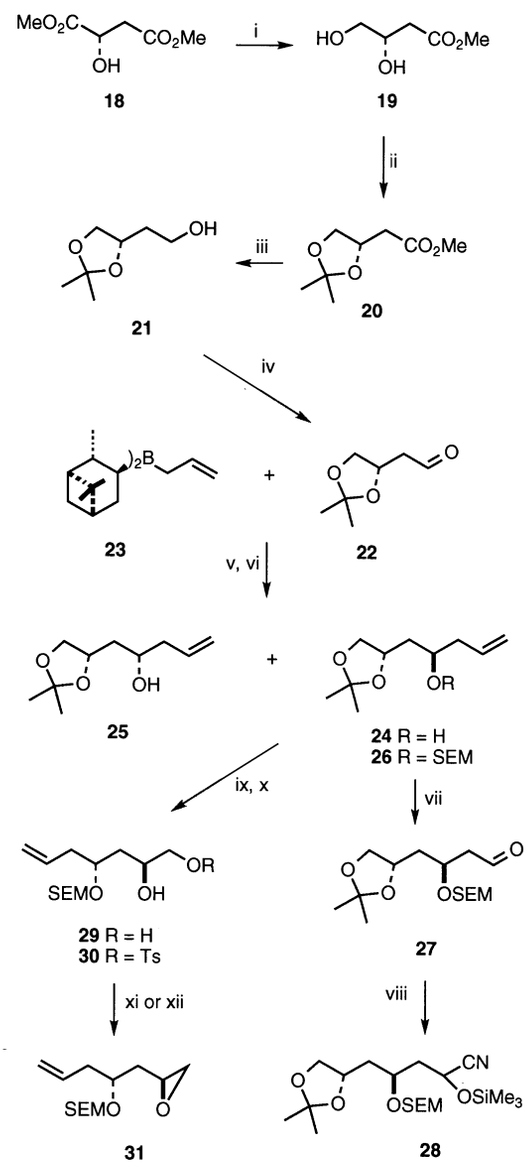
Scheme 1 *Reagents:* i, (*E*)-but-2-ene, butyllithium, potassium *tert*-butoxide, then boron trifluoride–diethyl ether; ii, 2-methylpropanal, then sodium hydroxide, hydrogen peroxide (80%; **10**:**11** = 88:12); iii, (*S*)-2-methoxy-2-trifluoromethyl-2-phenylacetyl chloride, pyridine (67%); iv, *tert*-butyldimethylsilyl trifluoromethanesulfonate, 2,6-lutidine (95%); v, borane in tetrahydrofuran, then sodium hydroxide, hydrogen peroxide (85%); vi, triphenylphosphine, carbon tetrabromide (83%); vii, triphenylphosphine, imidazole, iodine 99%)

which was converted into the toluene-*p*-sulfonate **30**. Treatment with potassium carbonate in methanol then gave the epoxide **31** which was also obtained directly from the diol **29** using diethyl diazodicarboxylate and triphenylphosphine in anhydrous *N*,*N*-dimethylformamide.[17] The next phase of the work involved alkylation of 1,3-dithiane with the alkyl iodide **16** and then with the epoxide **31**.

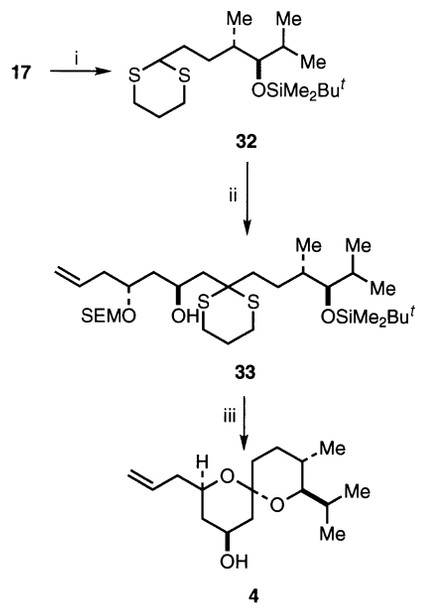
Alkylation of 1,3-dithiane using the iodide **17** was achieved using butyllithium as base to give the 2-alkyldithiane **32** in a yield of 87% (Scheme 3). For the second alkylation using epoxide **31**, *tert*-butyllithium was found to be a suitable base, and the 2,2-dialkyldithiane **33** was isolated in an excellent yield (97%). It was intended at this stage to deprotect the hydroxy groups of the intermediate **33**, and then to investigate hydrolysis of the dithiane and spiroacetal formation. However, it was found that all these transformations can be accomplished in a single step, since treatment of **33** with dilute aqueous hydrogen fluoride in acetonitrile gave the spiroacetal **4** directly (87%). This spiroacetal was identified on the basis of spectroscopic data, and was identical with a sample which had been prepared earlier from methyl α-D-glucopyranoside,[4] although, in our hands, the convergent synthesis reported here is more amenable to scale-up than that reported earlier from the glucose derivative, and has since been applied to synthesise more complex spiroacetals and the intact C(11)–C(25) fragments of avermectins.[18]

It remained to develop the chemistry of the spiroacetal side-chain to complete a synthesis of the required phosphonium salt **2**. The sequence devised by Baker in his synthesis of milbemycin β_3, which uses the stereoselective alkylation of a chiral oxazolidinone to introduce the remaining chiral centre, was selected as the most appropriate at this stage.[19] To get a feel for the reactions involved, the aldehyde **27** was condensed with the stabilized phosphorane **34** to give the (*E*)-alkene **35** which was reduced using diisobutylaluminium hydride to the alcohol **36** (Scheme 4). This was converted into the bromide **37** and iodide **38**, and the latter was found to react effectively with the lithium enolate of oxazolidinone **39**[20] to give the alkylated oxazolidinone **40**. This appeared to be a single diastereoisomer, its structure being assigned by analogy with the stereoselectivity expected for alkylation of the (*Z*)-enolate of the oxazolidinone **39**. Reduction using lithium aluminium hydride then gave the alcohol **41** which, by ^{1}H and ^{13}C NMR spectroscopy, appeared to be essentially a single diastereoisomer.

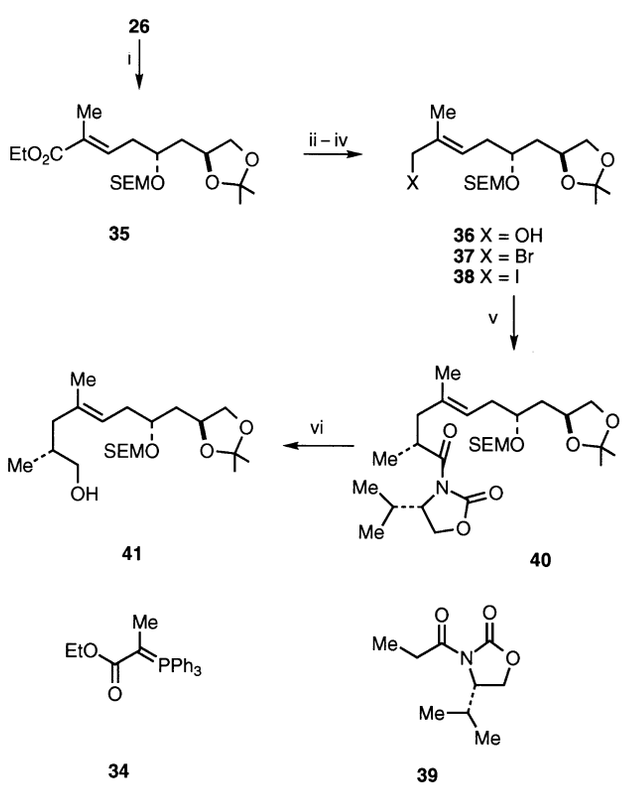
This sequence was used to convert the spiroacetal **4** into the phosphonium salt **2** (Scheme 5). The spiroacetal was protected as its *tert*-butyldimethylsilyl ether **42** which was converted into the aldehyde **43** by ozonolysis followed by a reductive work-up. Wittig condensation with the phosphorane **34** gave the α,β-unsaturated ester **44** which was reduced to the alcohol **45** using diisobutylaluminium hydride. This alcohol was converted into the iodide **46** as before, and the iodide used to alkylate the enolate of the chiral oxazolidinone **39**.[20] The product from this reaction appeared by NMR spectroscopy to be essentially a single diastereoisomer, and was assigned the structure **47** by



Scheme 2 *Reagents:* i, sodium borohydride, borane–dimethyl sulfide complex; ii, dimethoxypropane, toluene-*p*-sulfonic acid; iii, lithium aluminium hydride (94%); iv, oxalyl chloride, dimethyl sulfoxide (96%); v, **23**, then hydrogen peroxide, sodium hydroxide (**24**, 61%; **25**, 11%); vi, (2-trimethylsilylethoxy)methyl chloride, *N*,*N*-diisopropylethylamine (100%); vii, ozone, methanol, −78 °C, then dimethyl sulfide (82%); viii, sodium metabisulfite, sodium cyanide, then trimethylsilyl chloride, triethylamine (64%); ix, aqueous hydrogen chloride (84%); x, toluene-*p*-sulfonyl chloride, triethylamine, 4-dimethylaminopyridine (64%); xi, diethyl azodicarboxylate, triphenylphosphine, *N*,*N*-dimethylformamide (77% from **29**); xii, anhydrous potassium carbonate, methanol (92% from **30**)



Scheme 3 *Reagents:* i, 1,3-dithiane, butyllithium (87%); ii, *tert*-butyllithium, **31** (97%); iii, hydrogen fluoride, aqueous acetonitrile (87%)



Scheme 4 *Reagents:* i, ozone, dimethyl sulfide, then **34** (90%); ii, diisobutylaluminium hydride (99%); iii, triphenylphosphine, carbon tetrabromide (79%); iv, iodine, triphenylphosphine, imidazole; v, lithium enolate of **39** (70% from **36**); vi, lithium aluminium hydride (67%)

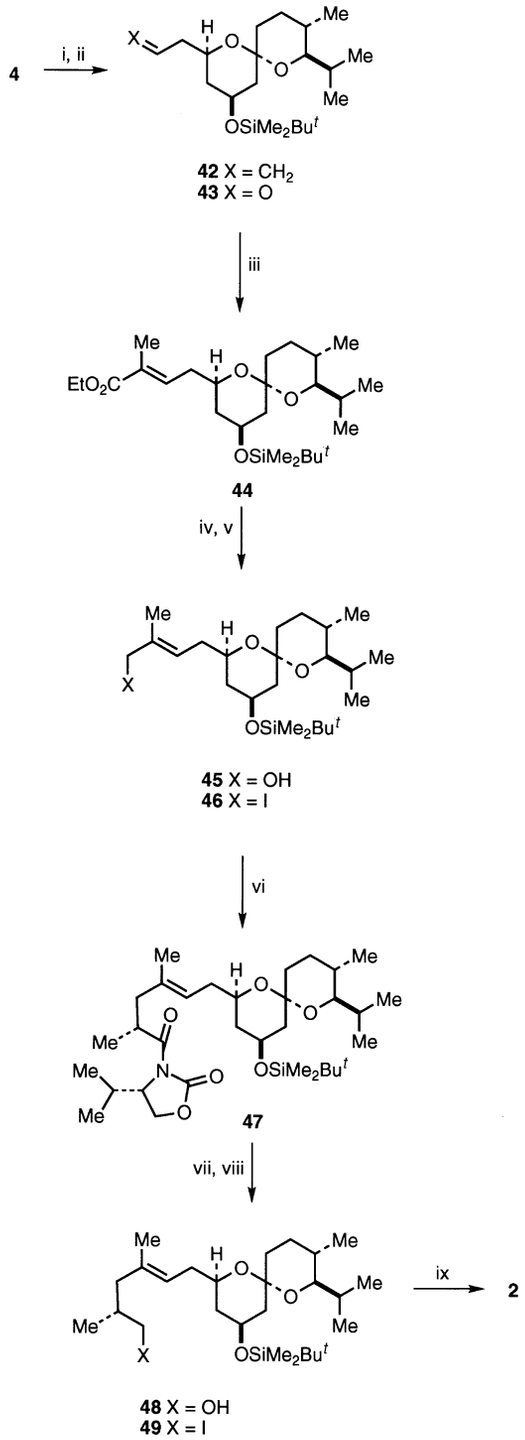
analogy with the literature. Reduction gave the alcohol **48** which was converted into the phosphonium salt **2** by way of the iodide **49**.

The structures of the later intermediates in this synthesis were assigned by analogy with the literature and were consistent with their spectroscopic data. The incorporation of the phosphonium salt **2** into a synthesis of milbemycin E **1**, which was found to be identical with the natural product, confirmed the stereochemical assignments.[3]

This work provides a convergent synthesis of the spiroacetal **4** and procedures for the conversion of this spiroacetal into the phosphonium salt **2** corresponding to the C(11)–C(25) fragment of milbemycin E **1**. The accompanying papers describe a synthesis of the C(1)–C(10) fragment of non-aromatic β-milbemycins and a total synthesis of milbemycin E **1**.

Experimental

For general experimental details see the first paper in this series.[2] Dimethyl (*S*)-malate **18** (30 g, 0.181 mol) was reduced using borane–dimethyl sulfide and sodium borohydride as reported in the literature[13] and the crude product converted into methyl (*S*)-3,4-isopropylidenedioxybutanoate **20** (25.5 g, 79%), bp 54–56 °C/0.5 mmHg, using 2,2-dimethoxypropane and toluene-*p*-sulfonic acid. Reduction using lithium aluminium hydride gave (*S*)-3,4-isopropylidenedioxybutanol **21** (17.3 g, 94%), bp 101–102 °C/15 mmHg (lit.,[21] 55–56 °C/0.05 mmHg); $[\alpha]_D$ −1.07 (*c*



Scheme 5 *Reagents:* i, *tert*-butyldimethylsilyl chloride, imidazole (91%); ii, ozone, dimethyl sulfide; iii, **34** (69% from **42**); iv, diisobutylaluminium hydride (99%); v, iodine, triphenylphosphine, imidazole; vi, lithium enolate of **39** (87% from **45**); vii, lithium aluminium hydride (99%); viii, iodine, triphenylphosphine, imidazole (89%); ix, triphenylphosphine, acetonitrile (84%)

2.54, MeOH) [lit.,[21] −1.29 (*c* 4.6, MeOH)]. Oxidation using oxalyl chloride and dimethyl sulfoxide gave the aldehyde **22**[13] (16.4 g, 96%) which was used directly in the reaction with the propenylborane **23**.

(3*R*,4*S*)-2,4-Dimethylhex-5-en-3-ol 10

Butyllithium in tetrahydrofuran (2 M; 62.5 cm^3, 0.125 mol) was added to a stirred solution of potassium *tert*-butoxide (14.0 g, 0.125 mol) and (*E*)-but-2-ene (22.5 cm^3, 0.25 mol) in tetrahydrofuran (35 cm^3) at −78 °C and the mixture stirred at −45 °C for 10 min. The solution was cooled to −78 °C and methoxy(diisopinocampheyl)borane **8** in ether [1 M; 0.15 mol; from (+)-α-pinene] was added dropwise. After stirring the mixture for 30 min at −78 °C, boron trifluoride–diethyl ether (20 cm^3, 0.167 mol) was added dropwise followed by a solution of 2-methylpropanal (16.1 cm^3, 0.175 mol) in ether (50 cm^3). The mixture was stirred at −78 °C for 3 h, aqueous sodium hydroxide (3 M; 91.2 cm^3, 0.275 mol) and aqueous hydrogen peroxide (30%; 37.5 cm^3) were added and the reaction was heated under reflux for 1 h. After cooling, the aqueous layer was separated and extracted with ether (150 cm^3) and the combined organic layers washed with water (150 cm^3) and brine (150 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was distilled and the fraction boiling from 50–75 °C/25 mmHg was collected. Chromatography, using light petroleum–ethyl acetate 15:1 as eluent, gave the *anti*- and *syn*-alcohols **10** and **11** (12 g, 80%), ratio 88:12, as a mixture of diastereoisomers. Preparative GLC using a 15% polyethylene glycol adipate (PEGA) on Chromosorb A (60–85 mesh) column, 15 ft × 0.375 in, 110 °C, afforded the *title compound* **10** (60–70%), $[\alpha]_D$ −17.96 (*c* 1.7, $CHCl_3$) (Found: $M^+ + NH_4$, 146.1546. $C_8H_{20}NO$ requires *M*, 146.1545); ν_{max}/cm^{-1} 3700–3100, 3070, 1639, 1460, 1384, 1368, 1085, 995 and 912; δ_H 5.79 (1 H, m, 5-H), 5.12 (2 H, m, 6-H_2), 3.10 (1 H, ddd, *J* 5, 5.5, 4.5, 3-H), 2.34 (1 H, m, 4-H), 1.76 (1 H, m, 2-H), 1.47 (1 H, d, *J* 4.5, OH), 1.01 (3 H, d, *J* 6.6, 4-CH_3) and 0.97 and 0.93 (each 3 H, d, *J* 6.8, CH_3); δ_C 140.5 (d), 115.8 (t), 79.5 (d), 41.4 (d), 30.5 (d), 19.8 (q), 17.0 (q) and 16.4 (q); *m/z* (CI) 146 ($M^+ + NH_4$, 100%), 128 (M^+, 18) and 111 (41). In addition, a small amount of (3*R*,4*R*)-2,4-dimethylhex-5-en-3-ol **11** (10%) was obtained, $[\alpha]_D$ −6.72 (*c* 1.4, $CHCl_3$); ν_{max}/cm^{-1} 3700–3120, 3070, 1644, 1460, 1383, 1368, 998, 981, 967 and 912; δ_H 5.80 (1 H, m, 5-H), 5.12 (2 H, m, 6-H_2), 3.19 (1 H, m, 3-H), 2.40 (1 H, m, 4-H), 1.76 (1 H, m, 2-H), 1.40 (1 H, br s, OH), 1.03 (3 H, d, *J* 6.5, 4-CH_3), 0.96 and 0.94 (each 3 H, d, *J* 6, CH_3); δ_C 142.2 (d), 114.6 (t), 79.5 (d), 40.6 (d), 30.4 (d), 19.5 (q), 16.8 (q) and 13.6 (q); *m/z* (CI) 146 ($M^+ + NH_4$, 100%), 128 (M^+, 35) and 111 (45).

(*S*)-(−)-2-Methoxy-2-trifluoromethyl-2-phenylacetyl chloride (51 μl, 0.3 mmol) was added to a solution of the alcohol **10** (35 mg, 0.27 mmol) in carbon tetrachloride–pyridine (20 drops of a 1:1 mixture). The mixture was stirred at room temperature for 12 h and water (1 cm^3) was added. The mixture was diluted with ether (20 cm^3), washed with aqueous hydrogen chloride (0.1 M; 5 cm^3), saturated aqueous sodium hydrogen carbonate (5 cm^3), water (5 cm^3) and brine (5 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue afforded the ester **12** (63 mg, 67%); ν_{max}/cm^{-1} 3080, 1750, 1640, 1450, 1260, 1170, 1120, 1080, 1015, 995 and 720; δ_H 7.59 (2 H, m, ArH), 7.41 (3 H, m, ArH), 5.65 (1 H, m, 5-H), 5.01–4.89 (3 H, m, 3-H and 6-H_2), 3.53 (3 H, s, OCH_3), 2.53 (1 H, m, 4-H), 1.97 (1 H, m, 2-H), 0.97 (3 H, d, *J* 7, CH_3) and 0.92 and 0.88 (each 3 H, d, *J* 6.7, CH_3); *m/z* (CI) 362 ($M^+ + NH_4$, 67%), 189 (88) and 128 (36).

(3*S*,4*R*)-4-*tert*-Butyldimethylsilyloxy-3,5-dimethylhex-1-ene 14

tert-Butyldimethylsilyl trifluoromethanesulfonate (36.6 cm^3, 158 mmol) was added dropwise to a solution of the alcohol **10** (13.5 g, 105 mmol) and 2,6-lutidine (2,6-dimethylpyridine) (39.4 cm^3, 264 mmol) in dichloromethane (40 cm^3) at 0 °C. The mixture was stirred at room temperature for 2 h before being diluted with ether (80 cm^3) and washed with aqueous hydrogen chloride (30 cm^3), water (30 cm^3) and brine (30 cm^3). After drying ($MgSO_4$) the mixture was concentrated under reduced pressure. Distillation of the residue gave the *title compound* **14** (24.1 g, 95%), bp 103–105 °C/20 mmHg, $[\alpha]_D$ 0 (*c* 0.95, $CHCl_3$) (Found: $M^+ + H$, 243.2154. $C_{14}H_{31}OSi$ requires *M*, 243.2144); ν_{max}/cm^{-1} 3070, 1640, 1460, 1385, 1360, 1255, 1095, 1050, 1000, 910, 860, 835 and 770; δ_H 5.91 (1 H, m, 2-H), 4.97 (2 H, m, 1-H_2), 3.28 (1 H, dd, *J* 4.0, 6.5, 4-H), 2.37 (1 H, m, 3-H), 1.75 (1 H, m, 5-H), 1.01 (3 H, d, *J* 7, CH_3), 0.92 [9 H, s, $SiC(CH_3)_3$], 0.88 and 0.87 (each 3 H, d, *J* 7, CH_3) and 0.03 [6

H, s, $Si(CH_3)_2$]; *m/z* (CI) 243 ($M^+ + H$, 18%), 187 (30), 128 (27) and 111 (100).

(3*S*,4*R*)-4-*tert*-Butyldimethylsilyloxy-3,5-dimethylhexanol 15

Borane in tetrahydrofuran (1.0 M; 108 cm^3, 108 mmol) was added dropwise to a stirred solution of the alkene **14** (23.7 g, 98 mmol) in tetrahydrofuran (50 cm^3) at 0 °C and the mixture stirred at room temperature until all the alkene had been consumed (TLC). The mixture was cooled to 0 °C and aqueous sodium hydroxide (3 M; 36 cm^3, 108 mmol) and aqueous hydrogen peroxide (30%; 48 cm^3, 360 mmol) were added dropwise such that the reaction temperature did not exceed 35 °C. On completion of the addition the reaction was heated under reflux for 1 h, cooled to room temperature and the aqueous layer extracted with ether (2 × 50 cm^3). The organic extracts were washed with brine (50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Distillation of the residue gave the *title compound* **15** (22 g, 85%), bp 95–96 °C/0.65 mmHg, $[\alpha]_D$ 0 (*c* 1.13, $CHCl_3$) (Found: $M^+ + H$, 261.2241. $C_{14}H_{33}O_2Si$ requires *M*, 261.2250); ν_{max}/cm^{-1} 3600–3100, 1460, 1265, 1095, 1051, 1005, 835 and 770; δ_H 3.72 and 3.63 (each 1 H, m, 1-H), 3.25 (1 H, dd, *J* 4, 6, 4-H), 2.0 (1 H, br s, OH), 1.76 (3 H, m, 2-H_2 and 3-H), 1.53 (1 H, m, 5-H), 0.96 (3 H, d, *J* 7, CH_3), 0.93 [9 H, s, $SiC(CH_3)_3$], 0.91 and 0.87 (each 3 H, d, *J* 7, CH_3) and 0.08 [6 H, s, $Si(CH_3)_2$]; *m/z* (CI) 261 ($M^+ + H$, 100%).

(3*S*,4*R*)-1-Bromo-4-*tert*-butyldimethylsilyloxy-3,5-dimethylhexane 16

Triphenylphosphine (5.24 g, 20 mmol) in dichloromethane (27 cm^3) was added to a cooled solution of the alcohol **15** (5.13 g, 19.7 mmol) and carbon tetrabromide (6.63 g, 20.0 mmol) in dichloromethane (85 cm^3) at a rate such that the temperature did not exceed 0 °C. The mixture was stirred at 0 °C until all starting material had been consumed (TLC). Silica gel was added and the slurry concentrated under reduced pressure. Chromatography of the residue, using light petroleum as eluent, gave the bromide **16** (5.27 g, 83%). A small sample was distilled using a Kugelrohr to give the *title compound* **16**, bp 89–90 °C/1 mmHg, $[\alpha]_D$ −14.77 (*c* 1.04, $CHCl_3$) (Found: $M^+ - C_4H_9$, 265.0623. $C_{10}H_{12}{}^{79}BrOSi$ requires *M*, 265.0624); ν_{max}/cm^{-1} 1470, 1465, 1387, 1361, 1260, 1050, 1008, 840, 775 and 670; δ_H 3.55 and 3.39 (each 1 H, m, 1-H), 3.24 (1 H, dd, *J* 5, 6, 4-H), 2.07 (1 H, m), 1.75 (3 H, m), 0.92 [9 H, s, $SiC(CH_3)_3$], 0.91 (9 H, overlapping d, 3 × CH_3) and 0.08 [6 H, s, $Si(CH_3)_2$]; *m/z* (EI) 281 (14%), 279 (14), 211 (22), 209 (22) and 185 (64).

(3*S*,4*R*)-4-*tert*-Butyldimethylsilyloxy-1-iodo-3,5-dimethylhexane 17

A solution of the alcohol **15** (2.25 g, 8.65 mmol), triphenylphosphine (9.12 g, 34.7 mmol), imidazole (2.36 g, 34.7 mmol) and iodine (6.59 g, 26.0 mmol) in benzene (400 cm^3) was heated at 80 °C for 45 min. After cooling, saturated aqueous sodium hydrogen carbonate (400 cm^3) was added, and the resulting solution stirred for 10 min. Iodine was added until the organic layer remained coloured on prolonged stirring. The excess of the iodine was removed by the addition of saturated aqueous sodium thiosulfate. After extraction of the aqueous layer with ether (2 × 50 cm^3), the organic extracts were washed with water (75 cm^3) and brine (75 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give a mixture of the iodide **17** and triphenylphosphine oxide. The latter was removed by filtration through a short column of silica gel eluting with petrol. Concentration of the filtrate afforded the *title compound* **17** (3.2 g, 99%) (Found: $M^+ - C_4H_9$, 313.0485. $C_{10}H_{22}IOSi$ requires *M*, 313.0486); ν_{max}/cm^{-1} 1470, 1460, 1387, 1360, 1250, 1185, 1045, 1005, 835 and 775; δ_H 3.38 (1 H, m, 1-H), 3.26 (1 H, br t, *J* 5, 4-H), 3.24 (1 H, m, 1-H′), 2.09 (1 H, m), 1.76 (2 H, m), 1.61 (1 H, m), 0.91 [12 H, m, CH_3 and $SiC(CH_3)_3$], 0.9 and 0.88 (each 3 H, d, *J* 5, CH_3) and 0.07 [6 H, s, $Si(CH_3)_2$]; *m/z* (EI) 327 (32%), 313 (17) and 257 (64).

(3*S*)-3,4-Isopropylidenedioxybutanal 22

A solution of dimethyl sulfoxide (20.4 cm^3, 238 mmol) in dichloromethane (45 cm^3) was added dropwise to a cooled solution of oxalyl chloride (15.5 cm^3, 178 mmol) in dichloromethane (225 cm^3) at −78 °C. After 5 min, a solution of the alcohol **21** (17.3 g, 119 mmol) in dichloromethane (120 cm^3) was added dropwise followed, after 15 min, by triethylamine (83 cm^3, 595 mmol) and the resultant mixture was stirred at −78 °C for 15 min, before being allowed to warm to room temperature. After stirring at this temperature for 20 min the mixture was partitioned between benzene, ether and water (4:1:1; 600 cm^3). The aqueous layer was extracted with ether (100 cm^3) and the organic fractions washed with brine (50 cm^3), dried ($MgSO_4$–K_2CO_3) and concentrated under reduced pressure to afford the title compound **22** (16.4 g, 96%) which was used without further purification; δ_H 9.80 (1 H, t, *J* 2, 1-H), 4.54 (1 H, quintet, *J* 6, 3-H), 4.20 (1 H, dd, *J* 6, 7, 4-H), 3.59 (1 H, dd, *J* 6, 7, 4-H′), 2.76 (2 H, m, 2-H_2) and 1.43 and 1.39 (each 3 H, s, CH_3).

(4*R*,6*S*)-4-Hydroxy-6,7-isopropylidenedioxyhept-1-ene 24

Prop-2-enylmagnesium bromide (1.52 M in ether; 85.5 cm^3, 130 mmol) was added dropwise to a solution of methoxydiisopinocampheylborane [1 M in ether; 150 mmol; from (*S*)-(−)-α-pinene] at −78 °C. The reaction mixture was stirred at −78 °C for 20 min and allowed to warm to room temperature. The resulting suspension was cooled to −78 °C and the aldehyde **22** (15.8 g, 110 mmol) in ether (75 cm^3) was added dropwise. After 1 h at −78 °C, the reaction was allowed to attain ambient temperature, aqueous sodium hydroxide (3 M; 116 cm^3, 350 mmol) and aqueous hydrogen peroxide (30%; 45 cm^3, 400 mmol) were added and the mixture heated under reflux for 1 h. After cooling, the aqueous layer was extracted with ether (150 cm^3) and the organic extracts were washed with water (100 cm^3) and brine (100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using gradient elution (light petroleum, ethyl acetate, benzene) gave the less polar (4*S*)-diastereoisomer **25** (1.3 g, 11%), $[\alpha]_D$ +11.5 (*c* 1.12, $CHCl_3$); δ_H 5.79 (1 H, m, 2-H), 5.09 (2 H, m, 1-H_2), 4.23 (1 H, m, 6-H), 4.06 (1 H, dd, *J* 8, 6, 7-H), 3.82 (1 H, m, 4-H), 3.54 (1 H, dd, *J* 8, 7, 7-H′), 3.1 (1 H, s, OH), 2.23 (2 H, m, 3-H_2), 1.66 (2 H, m, 5-H_2) and 1.39 and 1.33 (each 3 H, s, CH_3); δ_C 134.7 (d), 117.8 (t), 109.4 (s), 75.5 (d), 70.0 (d), 69.6 (t), 41.7 (t), 39.5 (t), 26.7 (q) and 25.6 (q); followed by the title compound **24** (7.4 g, 61%), $[\alpha]_D$ −8.0 (*c* 0.26, $CHCl_3$) [lit., −8.5 (*c* 2.6, $CHCl_3$)] (Found: $M^+ + H$, 187.1334. $C_{10}H_{19}O_3$ requires *M*, 187.1334); ν_{max}/cm^{-1} 3610–3200, 3080, 1640, 1380, 1370, 1245, 1215, 1158, 1055, 915, 877 and 826; δ_H 5.83 (1 H, m, 2-H), 5.14 (2 H, m, 1-H_2), 4.34 (1 H, m, 6-H), 4.10 (1 H, dd, *J* 9, 6.5, 7-H), 3.91 (1 H, m, 4-H), 3.59 (1 H, dd, *J* 9, 7.5, 7-H′), 2.29 (2 H, m, 3-H_2), 1.73 (2 H, m, 5-H_2) and 1.43 and 1.38 (each 3 H, s, CH_3); δ_C 134.6 (d), 118.3 (t), 108.8 (s), 73.6 (d), 69.5 (t), 67.8 (d), 42.2 (t), 39.4 (t), 26.8 (q) and 25.5 (q); *m/z* (CI) 204 ($M^+ + NH_4$, 13%) and 187 ($M^+ + H$, 100).

(4*R*,6*S*)-6,7-Isopropylidenedioxy-4-(2-trimethylsilylethoxymethoxy)hept-1-ene 26

(2-Trimethylsilylethoxy)methyl chloride (10.6 cm^3, 59.7 mmol) was added dropwise to the alcohol **24** (7.4 g, 39.4 mmol) and *N*,*N*-diisopropylethylamine (17.3 cm^3, 99.5 mmol) in dichloromethane (60 cm^3) at 0 °C, and the mixture stirred at room temperature for 16 h. The reaction was diluted with ether (100 cm^3) and quenched with water (30 cm^3). The aqueous layer was extracted with ether (2 × 50 cm^3) and the organic extracts washed with water (30 cm^3) and brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using light petroleum–ether as eluent gave the *title compound* **26** (12.6 g, 100%), $[\alpha]_D$ −13.8 (*c* 0.4, $CHCl_3$) (Found: $M^+ + NH_4$, 334.2409. $C_{16}H_{36}NO_4Si$ requires *M*, 334.2414); ν_{max}/cm^{-1} 3080, 1640, 1378, 1368, 1250, 1214, 1160, 1153, 1105, 1055, 1030, 995, 937, 917, 860 and 835; δ_H 5.71 (1 H, m, 2-H), 5.00 (2 H, m,

1-H_2), 4.77 and 4.75 (each 1 H, d, *J* 7, O*H*CHO), 4.12 (1 H, m, 6-H), 3.96 (1 H, dd, *J* 6, 8, 7-H), 3.75 (1 H, m, 4-H), 3.53 [2 H, m, CH_2CH$_2$Si(CH$_3$)$_3$], 3.43 (1 H, t, *J* 7.5, 7-H′), 2.24 (2 H, m, 3-H_2), 1.68 and 1.56 (each 1 H, m, 5-H), 1.30 and 1.25 (each 3 H, s, CH_3), 0.86 [2 H, m, CH_2Si(CH$_3$)$_3$] and −0.07 [9 H, s, Si(CH$_3$)$_3$]; *m/z* (CI) 334 (M^+ + NH_4, 1%).

(3*S*,5*S*)-5,6-Isopropylidenedioxy-3-(2-trimethylsilylethoxymethoxy)hexanal 27

Ozone was bubbled through a solution of the alkene **26** (3.24 g, 10.3 mmol) in methanol (100 cm^3) at −78 °C until a blue colour persisted. The reaction vessel was flushed with oxygen, dimethyl sulfide (10.54 cm^3, 144 mmol) was added and the reaction was allowed to warm slowly to room temperature. After 1 h, the solution was concentrated under reduced pressure, and the residue dissolved in ether (100 cm^3), washed with water (30 cm^3) and brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue gave the *title compound* **27** (2.65 g, 82%), $[\alpha]_D$ +8.33 (*c* 1.37, $CHCl_3$); ν_{max}/cm^{-1} 1725, 1478, 1469, 1247, 1215, 1155, 1096, 1054, 1028, 937, 920, 860 and 835; δ_H 10.01 (1 H, t, *J* 2.7, 1-H), 4.97 (2 H, s, OCH_2O), 4.46 (2 H, m, 3-H and 5-H), 4.29 (1 H, dd, *J* 5, 7, 6-H), 3.83 [3 H, m, 6-H′ and OCH_2CH$_2$Si(CH$_3$)$_3$], 2.90 (2 H, m, 2-H_2), 2.03 (2 H, m, 4-H_2), 1.63 and 1.58 (each 3 H, s, CH_3), 0.86 [2 H, m, CH_2Si(CH$_3$)$_3$] and 0.25 [9 H, s, Si(CH$_3$)$_3$]; *m/z* (CI) 336 (M^+ + NH_4, 5%), 318 (M^+, 3) and 289 (100).

(4*S*,6*S*)-2-Trimethylsilyloxy-6,7-isopropylidenedioxy-4-(2-trimethylsilylethoxymethoxy)heptanenitrile 28

Sodium metabisulfite (300 mg, 3.2 mmol) in water (4 cm^3) was added to the aldehyde **27** (1.0 g, 3.14 mmol) and the resultant suspension shaken for 20 min. After stirring at room temperature for 1 h, the mixture was cooled to 0 °C and sodium cyanide (154 mg, 3.14 mmol) in water (3 cm^3) was added at such a rate that the temperature did not exceed 35 °C. The mixture was extracted with benzene (4 × 10 cm^3) and the organic fractions were washed with aqueous sodium hydrogen sulfite, dried ($MgSO_4$) and concentrated under reduced pressure to yield the cyanohydrin (1.06 g, 98%). This was dissolved in tetrahydrofuran (10 cm^3) and trimethylsilyl chloride (0.80 cm^3, 6.3 mmol) and triethylamine (1.10 cm^3, 7.0 mmol) were added. The resulting suspension was stirred at room temperature for 16 h then filtered and the filter cake washed with anhydrous benzene. Concentration of the filtrate under reduced pressure gave the product (830 mg, 64%) which was purified by Kugelrohr distillation, bp 150 °C/0.1 mmHg, to give the *title compound* **28** as a mixture of epimers at C(1); ν_{max}/cm^{-1} 1380, 1370, 1250, 1102, 1054, 1028 and 843; δ_H 4.58 (3 H, m), 4.09 (1 H, m), 3.97 (1 H, m, 7-H), 3.86 and 3.77 (each 0.5 H, m), 3.54 [2 H, m, CH_2-CH$_2$Si(CH$_3$)$_3$], 3.41 (1 H, m, 7-H′), 1.97 (2 H, m, 3-H_2), 1.68 (2 H, m, 5-H_2), 1.31 and 1.25 (each 3 H, s, CH_3), 0.88 [2 H, m, CH_2Si(CH$_3$)$_3$], 0.14 and 0.13 [each 4.5 H, s, Si(CH$_3$)$_3$] and −0.06 [9 H, s, Si(CH$_3$)$_3$].

(2*S*,4*R*)-4-(2-Trimethylsilylethoxymethoxy)hept-6-ene-1,2-diol 29

Aqueous hydrogen chloride (1 M; 120 cm^3) was added to the acetonide **26** (37.9 g, 0.119 mol) in tetrahydrofuran (660 cm^3) and the mixture stirred for 12 h at room temperature. Ethyl acetate (300 cm^3) was added, the layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 200 cm^3). The organic extracts were washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (2:1) as eluent gave the starting material **26** (3.2 g, 8%), followed by the *title compound* **29** (23.4 g, 71%) (Found: M^+ + H, 277.1846. $C_{13}H_{29}O_4Si$ requires *M*, 277.1835); ν_{max}/cm^{-1} 3540–3190, 3080, 1640, 1251, 1102, 1056, 1028, 917, 860 and 835; δ_H 5.77 (1 H, m, 6-H), 5.08 (2 H, m, 7-H_2), 4.79 (2 H, s, OCH_2O), 3.94 (2 H, m, 2-H and 4-H), 3.63 [3 H, m, 1-H and OCH_2CH$_2$Si(CH$_3$)$_3$], 3.45 (1 H, dd, *J* 6.5, 10.5, 1-H′), 2.93 (2 H, br s, 2 × OH), 2.33 (2 H, m, 5-H_2), 1.58 (2 H, m, 3-H_2), 0.95 [2 H, m, CH_2Si(CH$_3$)$_3$] and 0.03 [9 H, s, Si(CH$_3$)$_3$]; *m/z* (CI) 294 (M^+ + NH_4, 34%), 277 (M^+ + H, 97), 247 (25), 231 (61) and 213 (100).

(2*S*,4*R*)-2-Hydroxy-4-(2-trimethylsilylethoxymethoxy)hept-6-en-1-yl toluene-*p*-sulfonate 30

Toluene-*p*-sulfonyl chloride (3.8 g, 19.9 mmol) in dichloromethane (20 cm^3) was added to the diol **29** (5 g, 18.1 mmol), triethylamine (12.6 cm^3, 90 mmol) and 4-dimethylaminopyridine (220 mg, 1.8 mmol) in dichloromethane (55 cm^3) at 0 °C. The mixture was stirred at 0 °C for 12 h then diluted with ether (100 cm^3) and quenched with water (10 cm^3). The aqueous layer was separated, extracted with ether (3 × 50 cm^3) and the organic extracts washed with brine (40 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (4:1) as eluent gave the *title compound* **30** (5.0 g, 64%); ν_{max}/cm^{-1} 3580–3220, 3070, 1640, 1600, 1364, 1248, 1189, 1175, 1095, 1055, 1026, 973, 860, 834 and 665; δ_H 7.80 and 7.35 (each 2 H, d, *J* 9.5, ArH), 5.75 (1 H, m, 6-H), 5.08 (2 H, m, 7-H_2), 4.69 (2 H, s, OCH_2O), 4.09 (1 H, m, 2-H), 3.98 (2 H, m, 1-H_2), 3.86 (1 H, m, 4-H), 3.60 [2 H, m, OCH_2CH$_2$Si(CH$_3$)$_3$], 2.47 (3 H, s, ArCH_3), 2.23 (2 H, m, 5-H_2), 1.82 (1 H, br s, OH), 1.54 (2 H, m, 3-H_2), 0.95 [2 H, m, CH_2Si(CH$_3$)$_3$] and 0.03 [9 H, s, Si(CH$_3$)$_3$]; *m/z* (CI) 330 (100%) and 313 (22).

(4*R*,6*S*)-6,7-Epoxy-4-(2-trimethylsilylethoxymethoxy)hept-1-ene 31

Diethyl diazodicarboxylate (7.44 cm^3, 47.3 mmol) was added dropwise to the diol **29** (8.7 g, 31.5 mmol) and triphenylphosphine (12.4 g, 47.3 mmol) in dimethylformamide (160 cm^3) and the solution heated at 80 °C for 60 h. After cooling to room temperature, the reaction mixture was partitioned between ether (250 cm^3) and water (250 cm^3). The aqueous layer was extracted with ether (2 × 100 cm^3) and the organic extracts washed with water (50 cm^3) and brine (50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Trituration in ether–light petroleum removed triphenylphosphine oxide and diethyl hydrazinodicarboxylate. Concentration of the mother liquor under reduced pressure and chromatography of the residue gave the *title compound* **31** (6.3 g, 77%), $[\alpha]_D$ −25.4 (*c* 1.16, $CHCl_3$) (Found: C, 60.8; H, 10.4. $C_{13}H_{26}O_3Si$ requires C, 60.4; H, 10.15%. Found: M^+ + NH_4, 276.1999. $C_{13}H_{30}NO_3Si$ requires *M*, 276.1995); ν_{max}/cm^{-1} 3070, 3040, 1639, 1248, 1098, 1054, 1030, 860 and 835; δ_H 5.80 (1 H, m, 2-H), 5.10 (2 H, m, 1-H_2), 4.76 and 4.74 (each 1 H, d, *J* 7, O*H*CHO), 3.89 (1 H, m, 4-H), 3.65 [2 H, m, OCH_2CH$_2$Si(CH$_3$)$_3$], 3.04 (1 H, m, 6-H), 2.80 (1 H, t, *J* 5, 7-H), 2.50 (1 H, dd, *J* 5, 2.5, 7-H′), 2.37 (2 H, m, 3-H_2), 1.68 (2 H, m, 5-H_2), 0.95 [2 H, m, CH_2Si(CH$_3$)$_3$] and 0.02 [9 H, s, Si(CH$_3$)$_3$]; δ_C 134.3 (d), 117.4 (t), 93.7 (t), 74.5 (d), 65.2 (t), 49.5 (d), 47.3 (t), 39.4 (t), 37.7 (t), 18.1 (t) and −1.5 (q); *m/z* (CI) 275 (M^+ + NH_4, 2%).

Alternatively, anhydrous potassium carbonate (3.3 g, 23.7 mmol) was added to a solution of the toluene-*p*-sulfonate **30** (4.95 g, 11.5 mmol) in methanol (75 cm^3), and the mixture stirred at room temperature for 4 h. The reaction mixture was then filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in ether (75 cm^3) and the ether solution washed with water (25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (8:1) as eluent gave the epoxide **31** (2.72 g, 92%).

2-[(3*S*,4*R*)-4-*tert*-Butyldimethylsilyloxy-3,5-dimethylhexyl]-1,3-dithiane 32

Butyllithium (1.6 M in hexane; 11.9 cm^3, 18.9 mmol) was added dropwise to 1,3-dithiane (3.8 g, 22.8 mmol) in tetrahydrofuran (40 cm^3) at −40 °C and the solution stirred for 2 h. The iodide

17 (4.2 g, 11.4 mmol) in tetrahydrofuran (20 cm^3) was added and the solution stirred at −20 °C for 14 h. Saturated aqueous ammonium chloride (20 cm^3) and ether (60 cm^3) were added. The aqueous layer was extracted with ether (3 × 25 cm^3) and the organic extracts washed with water (30 cm^3) and brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether–light petroleum as eluent gave the alkylated dithiane **32** (3.54 g, 87%). A small sample was distilled using a Kugelrohr, bp 120–121 °C/0.05 mmHg) to give the *title compound* **32**, $[\alpha]_D$ −6.1 (*c* 0.61, $CHCl_3$) (Found: C, 59.8; H, 10.8; S, 17.85. $C_{18}H_{38}OS_2Si$ requires C, 59.9; H, 10.55; S, 17.7%. Found: $M^+ + H$, 363.2210. $C_{18}H_{39}OS_2Si$ requires *M*, 363.2212); ν_{max}/cm^{-1} 1460, 1250, 1045, 835 and 770; δ_H 4.01 (1 H, t, *J* 6.5, 2-H), 3.23 (1 H, t, *J* 4.5, 4′-H), 2.84 (4 H, m, 4-H_2 and 6-H_2), 2.13 (1 H, m), 1.92–1.54 (6 H, m), 1.27 (1 H, m), 0.91 [9 H, s, $SiC(CH_3)_3$], 0.90 (3 H, d, *J* 7, CH_3), 0.88 and 0.87 (each 3 H, d, *J* 6, CH_3) and 0.05 [6 H, s, $Si(CH_3)_2$]; δ_C 81.2 (d), 47.9 (d), 37.2 (d), 33.7 (t), 30.9 (d), 30.4 (2 × t), 29.2 (t), 26.0 (q), 20.9 (q), 18.3 (q), 18.3 (s), 18.1 (q), 16.6 (q), −3.8 (q) and −4.0 (q); *m/z* (EI) 361 ($M^+ - H$, 2%), 347 (15), 319 (17) and 305 (100).

(2′*R*,4′*R*,3″*S*,4″*R*)-2-[2-Hydroxy-4-(2-trimethylsilylethoxymethoxy)hept-6-enyl]-2-(4-*tert*-butyldimethylsilyloxy-3,5-dimethylhexyl)-1,3-dithiane 33

tert-Butyllithium (1.67 M in pentane; 16.4 cm^3, 27.4 mmol) and tetramethylethylenediamine (8.25 cm^3, 54.5 mmol) were added to the 2-alkyldithiane **32** (27.4 mmol) in tetrahydrofuran (90 cm^3) at −20 °C, and the solution stirred for 2 h. The epoxide **31** (3.53 g, 13.7 mmol) in tetrahydrofuran (25 cm^3) was added. After 1 h at −20 °C, the reaction was allowed to warm to −5 °C and was then quenched by the addition of water (30 cm^3). After dilution with ether (150 cm^3), separation and extraction of the aqueous layer with ether (2 × 75 cm^3), the organic extracts were washed with water (50 cm^3) and brine (50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether as eluent gave the *title compound* **33** (8.2 g, 97%), $[\alpha]_D$ −10.8 (*c* 0.81, $CHCl_3$) (Found: M^+, 620.3791. $C_{31}H_{64}O_4S_2Si_2$ requires *M*, 620.3785); ν_{max}/cm^{-1} 3580–3280, 3080, 1640, 1471, 1463, 1252, 1097, 1055, 1027, 920, 860 and 838; δ_H 5.83 (1 H, m, 6′-H), 5.09 (2 H, m, 7′-H_2), 4.76 (2 H, s, OCH_2O), 4.21 (1 H, m, 2′-H), 3.92 (1 H, m, 4′-H), 3.66 [3 H, m, $OCH_2CH_2Si(CH_3)_3$ and OH], 3.26 (1 H, t, *J* 4.5, 4″-H), 2.86 (4 H, m, 4-H_2 and 6-H_2), 2.34 (2 H, t, *J* 4.5, 5-H_2), 2.31–1.20 (12 H, m), 0.99 [2 H, m, $CH_2Si(CH_3)_3$], 0.94–0.86 (18 H, m, 3 × CH_3 and $SiC(CH_3)_3$], 0.07 and 0.05 (each 3 H, s, $SiCH_3$) and 0.03 [9 H, s, $Si(CH_3)_3$]; *m/z* (CI) 621 ($M^+ + H$, 7%) and 503 (100).

(2*R*,4*S*,6*R*,8*R*,9*S*)-4-Hydroxy-8-isopropyl-9-methyl-2-prop-2-enyl-1,7-dioxaspiro[5.5]undecane 4

Hydrogen fluoride (40% in water; 4.4 cm^3) was added to the 2,2-dialkyldithiane **33** (7.26 g, 11.7 mmol) in aqueous acetonitrile (55 cm^3) and the solution stirred at room temperature for 4 h. Ethyl acetate (100 cm^3) and water (30 cm^3) were added, the mixture separated and the aqueous layer extracted with ethyl acetate. The organic extracts were washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (7:1) as eluent gave the *title compound* **4** (2.74 g, 87%), $[\alpha]_D$ +78.0 (*c* 0.82, $CHCl_3$) (Found: C, 71.3; H, 10.6. $C_{16}H_{28}O_3$ requires C, 71.6; H, 10.5%); ν_{max}/cm^{-1} 3480–3120, 1640, 1378, 1005 and 977; δ_H 5.86 (1 H, m, 2′-H), 5.07 (2 H, m, 3′-H_2), 4.13 (1 H, m, 4-H), 3.61 (1 H, m, 2-H), 3.04 (1 H, dd, *J* 2, 9.5, 8-H), 2.30 and 2.21 (each 1 H, m, 1′-H), 1.98 (2 H, m, 3-H_{eq} and 5-H_{eq}), 1.87 (1 H, d of septets, *J* 2, 7, 1″-H), 1.69–1.41 (6 H, m, 9-H, 10-H_2, 11-H_2 and OH), 1.26 (1 H, dd, *J* 11, 12, 5-H_{ax}), 1.14 (1 H, q, *J* 12, 3-H_{ax}), 0.94 and 0.82 (each 3 H, d, *J* 7, CH_3) and 0.80 (3 H, d, *J* 6, CH_3); δ_C 135.3 (d), 116.7 (t), 97.3 (s), 78.0 (d), 67.5 (d), 64.9 (d), 44.9 (t), 40.4 (t), 40.1 (t), 35.6 (t), 31.5 (d), 28.0 (d), 28.0 (t), 20.6 (q), 17.2 (q) and 13.9 (q); *m/z* (CI) 268 ($M^+ + H$, 100%).

Ethyl (5*R*,7*S*,2*E*)-7,8-isopropylidenedioxy-2-methyl-5-(2-trimethylsilylethoxymethoxy)oct-2-enoate 35

Ozone was bubbled through the alkene **26** (2.0 g, 6.28 mmol) in methanol (50 cm^3) at −78 °C until the appearance of a blue colour indicated an excess of ozone. After flushing with oxygen, dimethyl sulfide (7.2 cm^3, 88 mmol) was added and the reaction allowed to warm slowly to room temperature. After 1 h at room temperature the solution was concentrated under reduced pressure. The residue was dried azeotropically with benzene, then dissolved in benzene (60 cm^3) and the stabilised ylide **34** (3 g, 7.64 mmol) was added. The solution was stirred at room temperature for 16 h, concentrated under reduced pressure and chromatography of the residue gave the *title compound* **35** (2.3 g, 90%), $[\alpha]_D$ −11.57 (*c* 0.98, $CHCl_3$); ν_{max}/cm^{-1} 1709, 1646, 1378, 1368, 1249, 1028, 861 and 837; δ_H 6.80 (1 H, br t, *J* 7.5, 3-H), 4.74 and 4.72 (each 1 H, d, *J* 7, O*H*CHO), 4.2 (3 H, m, OCH_2CH_3 and 7-H), 4.05 (1 H, dd, *J* 6, 8, 8-H), 3.92 (1 H, m, 5-H), 3.63 [2 H, m, $OCH_2CH_2Si(CH_3)_3$], 3.52 (1 H, t, *J* 7.5, 8-H′), 2.47 (2 H, t, *J* 6.5, 4-H_2), 1.85 (3 H, d, *J* 1, 2-CH_3), 1.70 (2 H, m, 6-H_2), 1.39 and 1.34 (each 3 H, s, CH_3), 1.29 (3 H, t, *J* 7, OCH_2CH_3), 0.94 [2 H, m, $CH_2Si(CH_3)_3$] and 0.02 [9 H, s, $Si(CH_3)_3$]; δ_C 167.7 (s), 137.1 (s), 129.7 (s), 108.5 (s), 93.0 (t), 73.9 (d), 73.1 (d), 69.8 (t), 65.8 (t), 60.4 (t), 39.2 (t), 34.3 (t), 26.9 (q), 25.7 (q), 18.0 (t), 14.2 (q), 12.6 (q) and −1.5 (q); *m/z* 387 ($M^+ - 15$).

(5*R*,7*S*,2*E*)-7,8-Isopropylidenedioxy-2-methyl-5-(2-trimethylsilylethoxymethoxy)oct-2-enol 36

Diisobutylaluminium hydride (1 M in tetrahydrofuran; 7.97 cm^3, 7.97 mmol) was added to the unsaturated ester **35** (1.43 g, 3.56 mmol) in tetrahydrofuran (17 cm^3) at −78 °C and the mixture stirred at −78 °C for 2 h and then at room temperature for 1 h. After cooling to −78 °C, methanol (1.76 cm^3) was added and the solution stirred at room temperature for 1 h. Water (1.00 cm^3) was added and the resultant gelatinous precipitate stirred with Celite until a granular solid was obtained. After filtration through a Celite bed and washing the filter cake with ethyl acetate, concentration of the filtrate under reduced pressure gave the *title compound* **36** (1.27 g, 99%), $[\alpha]_D$ −15.24 (*c* 0.93, $CHCl_3$) (Found: C, 59.6; H, 10.3. $C_{18}H_{36}O_5Si$ requires C, 59.95, H, 10.5%); ν_{max}/cm^{-1} 3570–3240, 1378, 1369, 1250, 1058, 1030, 862 and 838; δ_H 5.46 (1 H, br t, *J* 7, 3-H), 4.75 and 4.69 (each 1 H, d, *J* 7.5, O*H*CHO), 4.20 (1 H, m, 7-H), 4.05 (1 H, dd, *J* 6, 8, 8-H), 4.02 (2 H, br s, 1-H_2), 3.83 (1 H, m, 5-H), 3.64 [2 H, m, $OCH_2CH_2Si(CH_3)_3$], 3.52 (1 H, t, *J* 7.5, 8-H), 2.32 (2 H, m, 4-H_2), 1.7 (2 H, m, 6-H_2), 1.68 (3 H, s, 2-CH_3), 1.39 and 1.34 (each 3 H, s, CH_3), 0.95 [2 H, m, $CH_2Si(CH_3)_3$] and 0.03 [9 H, s, $Si(CH_3)_3$]; *m/z* 361 ($M^+ + H$), 360 (M^+) and 345 ($M^+ - 15$).

(5*R*,7*S*,2*E*)-7,8-Isopropylidenedioxy-2-methyl-5-(2-trimethylsilylethoxymethoxy)oct-2-enyl bromide 37

Triphenylphosphine (445 mg, 2.81 mmol) in dichloromethane (1.5 cm^3) was added to the alcohol **36** (540 mg, 1.5 mmol) and carbon tetrabromide (548 mg, 1.65 mmol) in dichloromethane (3 cm^3) at such a rate that the temperature did not exceed 0 °C and the mixture stirred at 0 °C until all the alcohol had been consumed (TLC). Silica gel was added and the slurry evaporated under reduced pressure. Chromatography of the residue using light petroleum–ether (6:1) gave the *title compound* **37** (503 mg, 79%), $[\alpha]_D$ −13.07 (*c* 0.96, $CHCl_3$); ν_{max}/cm^{-1} 1377, 1368, 1246, 1210, 1154, 1096, 1051, 1026, 858 and 833; δ_H 5.65 (1 H, m, 3-H), 4.74 and 4.70 (each 1 H, d, *J* 5.5, O*H*CHO), 4.21 (1 H, m, 7-H), 4.06 (1 H, dd, *J* 6, 8, 8-H), 3.98 (2 H, s, 1-H_2), 3.84 (1 H, m, 5-H), 3.63 [2 H, m, $OCH_2CH_2Si(CH_3)_3$], 3.52 (1 H, t, *J* 8, 8-H′), 2.33 (2 H, m, 4-H_2), 1.79 (3 H, s, 2-CH_3), 1.68 (2 H, m, 6-H_2), 1.41 and 1.36 (each 3 H, s, CH_3), 0.96 [2 H, m, $CH_2Si(CH_3)_3$] and 0.05 [9 H, s, $Si(CH_3)_3$]; *m/z* 409, 407 ($M^+ - 15$).

(5*R*,7*S*,2*E*)-7,8-Isopropylidenedioxy-2-methyl-5-(2-trimethylsilylethoxymethoxy)oct-2-enyl iodide 38

Iodine (608 mg, 2.4 mmol) was added to the allylic alcohol **36** (360 mg, 1.0 mmol), triphenylphosphine (522 mg, 1.96 mmol) and imidazole (152 mg, 1.22 mmol) in acetonitrile–ether (2:3; 4 cm^3) at 0 °C. The mixture was stirred at 0 °C for 30 min, diluted with ether (4 cm^3) and washed with saturated aqueous sodium thiosulfate (3 cm^3), aqueous copper(II) sulfate (3 cm^3) and water (3 cm^3). After being dried ($MgSO_4$) and concentrated under reduced pressure at 0 °C, the slurry was suspended in 1:1 pentane–ether and filtered through a short plug of silica. Concentration of the filtrate at 0 °C gave the iodide **38** which was dissolved in tetrahydrofuran and used immediately in the next step or stored at −20 °C in the dark; δ_H 5.73 (1 H, t, *J* 7.6, 3-H), 4.74 and 4.70 (each 1 H, d, *J* 7, O*H*CHO), 4.21 (1 H, m, 7-H), 4.06 (1 H, dd, *J* 6, 8, 8-H), 3.95 (2 H, s, 1-H_2), 3.83 (1 H, m, 5-H), 3.64 [2 H, m, OCH_2CH_2Si(CH_3)$_3$], 3.53 (1 H, t, *J* 8, 8-H′), 2.26 (2 H, m, 4-H_2), 1.81 (3 H, s, 2-CH_3), 1.68 (2 H, m, 6-H_2), 1.41 and 1.36 (each 3 H, s, CH_3), 0.96 [2 H, m, CH_2Si(CH_3)$_3$] and 0.04 [9 H, s, Si(CH_3)$_3$].

(4*S*)-3-[(2*R*,7*R*,9*S*,4*E*)-2,4-Dimethyl-9,10-isopropylidenedioxy-7-(2-trimethylsilylethoxymethoxy)dec-4-enoyl]-4-isopropyloxazolidin-2-one 40

Lithium diisopropylamide (2.86 mmol) in tetrahydrofuran (5 cm^3) was generated at 0 °C, cooled to −78 °C and the oxazolidinone **39** (504 mg, 2.72 mmol) in tetrahydrofuran (5 cm^3) was added. After 45 min, the iodide **38** (640 mg, 1.36 mmol) in tetrahydrofuran (3 cm^3) was added and the solution was allowed to warm to −15 °C and stirred at this temperature for 14 h whereupon it was quenched by the addition of water (5 cm^3) and diluted with ether (15 cm^3). The aqueous layer was separated, extracted with ether (3 × 15 cm^3) and the organic extracts washed with water (15 cm^3) and brine (15 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue, using light petroleum–ether (2:1) as eluent, gave the *title compound* **40** (504 mg, 70%), $[\alpha]_D$ + 24.6 (*c* 1.18, $CHCl_3$) (Found: C, 61.75; H, 9.55; N, 2.65. $C_{27}H_{49}NO_7Si$ requires C, 61.45; H, 9.35; N, 2.65%); ν_{max}/cm^{-1} 1779, 1700, 1387, 1369, 1301, 1248, 1207, 1057, 1028, 861 and 838; δ_H 5.21 (1 H, t, *J* 7, 5′-H), 4.76 and 4.70 (each 1 H, d, *J* 7, O*H*CHO), 4.46 (1 H, m, 4-H), 4.24 (2 H, m, 5-H_2), 4.05 (1 H, dd, *J* 6, 8, 10′-H), 3.98 (1 H, m, 9′-H), 3.77 (1 H, m, 7′-H), 3.63 [2 H, t, *J* 8.5, OCH_2CH_2Si(CH_3)$_3$], 3.51 (1 H, t, *J* 7.5, 10′-H′), 2.53 (1 H, dd, *J* 5.5, 13, 3′-H), 2.28 (3 H, m, 2′-H and 6′-H_2), 1.99 (1 H, dd, *J* 9, 13, 3′-H′), 1.67 [3 H, m, (CH_3)$_2$C*H* and 8′-H_2], 1.67 (3 H, s, 4-CH_3), 1.39 and 1.34 (each 3 H, s, CH_3), 1.06 (3 H, d, *J* 6.5, 2′-CH_3), 0.94 [2 H, m, CH_2Si(CH_3)$_3$], 0.90 and 0.86 (each 3 H, d, *J* 7, CH_3) and 0.02 [9 H, s, Si(CH_3)$_3$]; *m/z* (CI) 545 (M^+ + NH_4, 15%), 410 (100).

(2*R*,7*R*,9*S*,4*E*)-2,4-Dimethyl-9,10-isopropylidenedioxy-7-(2-trimethylsilylethoxymethoxy)dec-4-enol 41

The oxazolidinone **40** (568 mg, 1.08 mmol) in ether (4 cm^3) was added to a suspension of lithium aluminium hydride (41 mg, 1.08 mmol) in ether (2 cm^3) at 0 °C. After stirring at this temperature for 3 h, the reaction was quenched by the addition of water (41 μl), 15% aqueous sodium hydroxide (41 μl) and water (123 μl). After filtering, the filtrate was concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (3:1) as eluent gave the *title compound* **41** (290 mg, 67%), $[\alpha]_D$ −15.3 (*c* 0.72, $CHCl_3$) (Found: C, 59.6; H, 10.3. $C_{21}H_{42}O_5Si$ requires C, 59.7; H, 10.05%); ν_{max}/cm^{-1} 3590–3180, 1378, 1368, 1249, 1213, 1152, 1100, 1053, 1030, 858 and 834; δ_H 5.20 (1 H, t, *J* 7, 5-H), 4.75 and 4.70 (each 1 H, d, *J* 7, O*H*CHO), 4.21 (1 H, m, 9-H), 4.05 (1 H, dd, *J* 6, 8, 10-H), 3.79 (1 H, m, 7-H), 3.64 [2 H, t, *J* 8.5, OCH_2CH_2Si(CH_3)$_3$], 3.51 (1 H, t, *J* 5.5, 10-H′), 3.44 (2 H, m, 1-H_2), 2.28 (3 H, m), 2.09 (1 H, m), 1.71 (4 H, m, 8-H_2 and 2-H and OH), 1.63 (3 H, s, 4-CH_3), 1.39 and 1.34 (each 3 H, s, CH_3), 0.95 [2 H, m, CH_2Si(CH_3)$_3$], 0.86 (3 H, d, *J* 6, 2-CH_3) and 0.03 [9 H, s, Si(CH_3)$_3$]; δ_C 136.5 (s), 121.3 (d), 108.6 (s), 93.8 (t), 74.6 (d), 73.4 (d), 69.6 (t), 68.2 (t), 65.3 (t), 44.4 (t), 38.8 (t), 33.5 (d), 33.2 (t), 29.9 (q), 25.7 (q), 17.9 (t), 16.5 (q), 16.0 (q) and −1.7 (q); *m/z* (CI) 420 (M^+ + NH_4, 12%), 403 (M^+ + H, 10) and 227 (100).

(2*R*,4*S*,6*R*,8*R*,9*S*)-4-*tert*-Butyldimethylsilyloxy-9-methyl-8-isopropyl-2-prop-2-enyl-1,7-dioxaspiro[5.5]undecane 42

tert-Butyldimethylsilyl chloride (6.2 g, 41.5 mmol) in anhydrous dimethylformamide (5 cm^3) was added to the spiroacetal **4** (7.4 g, 27.6 mmol) and imidazole (4.7 g, 69.0 mmol) in dimethylformamide (10 cm^3) and the solution stirred at room temperature for 16 h. Water (50 cm^3) and ether (50 cm^3) were added and the layers separated. The aqueous layer was extracted with ether (3 × 50 cm^3) and the organic extracts washed with water (25 cm^3) and brine (25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether–light petroleum as eluent gave the *title compound* **42** (9.58 g, 91%), $[\alpha]_D$ +68.4 (*c* 0.95, $CHCl_3$); ν_{max}/cm^{-1} 1641, 1462, 1385, 1254, 1189, 1131, 1088, 1068, 1008, 981, 910, 872, 836 and 775; δ_H 5.87 (1 H, m, 2′-H), 5.06 (2 H, m, 3′-H_2), 4.13 (1 H, m, 4-H), 3.57 (1 H, m, 2-H), 3.03 (1 H, dd, *J* 2, 9.5, 8-H), 2.25 (2 H, m, 1′-H_2), 1.86 (3 H, m, 1″-H, 3-H_{eq} and 5-H_{eq}), 1.54 (5 H, m, 9-H, 10-H_2 and 11-H_2), 1.30 (1 H, dd, *J* 11, 12, 5-H_{ax}), 1.18 (1 H, q, *J* 11.5, 3-H_{ax}), 0.95 (3 H, d, *J* 7, CH_3), 0.90 [9 H, s, SiC(CH_3)$_3$], 0.82 (3 H, d, *J* 7, CH_3), 0.79 (3 H, d, *J* 6.5, 9-CH_3) and 0.07 [6 H, s, Si(CH_3)$_2$]; *m/z* (CI) 383 (M^+ + H, 36%), 325 (11) and 251 (100).

Ethyl (2*E*)-4-[(2*R*,4*S*,6*R*,8*R*,9*S*)-4-*tert*-butyldimethylsilyloxy-9-methyl-8-isopropyl-1,7-dioxaspiro[5.5]undecan-2-yl]-2-methylbut-2-enoate 44

Following the procedure outlined above for the synthesis of the ester **35**, the alkene **42** (7.08 g, 18.5 mmol) gave, after chromatography using light petroleum–ether (12:1) as eluent, the *title compound* **44** (5.5 g, 69%), $[\alpha]_D$ +49.7 (*c* 1.24, $CHCl_3$) (Found: M^+ − C_4H_9, 411.2558. $C_{22}H_{39}O_5Si$ requires *M*, 411.2557); ν_{max}/cm^{-1} 1712, 1654, 1461, 1387, 1260, 1251, 1082, 1008, 981, 873, 836 and 777; δ_H 6.88 (1 H, dt, *J* 1.5, 7.5, 3-H), 4.19 (2 H, q, *J* 7, OC$H_2$$CH_3$), 4.14 (1 H, m, 4′-H), 3.63 (1 H, m, 2′-H), 3.00 (1 H, dd, *J* 2, 9.5, 8′-H), 2.33 (2 H, m, 4-H_2), 1.84 (3 H, m, 1″-H, 3′-H_{eq} and 5′-H_{eq}), 1.85 (3 H, d, *J* 1, 2-CH_3), 1.63 (1 H, m, 10′-H_{ax}), 1.48 (4 H, m, 9′-H, 10′-H_{eq} and 11′-H_2), 1.28 (5 H, m, 5′-H_{ax}, 3′-H_{ax} and OCH_2CH_3), 0.94 (3 H, d, *J* 7, CH_3), 0.90 [9 H, s, SiC(CH_3)$_3$], 0.81 (3 H, d, *J* 7, CH_3), 0.76 (3 H, d, *J* 6, 9′-CH_3) and 0.06 [6 H, s, Si(CH_3)$_2$]; δ_C 168.3 (s), 138.8 (d), 129.1 (s), 97.3 (s), 78.1 (d), 67.0 (d), 65.6 (d), 60.3 (t), 45.3 (t), 41.2 (t), 35.5 (t), 34.8 (t), 31.3 (t), 31.3 (d), 28.1 (d), 28.0 (t), 25.8 (q), 20.8 (q), 17.2 (q), 14.1 (q), 13.9 (q), 12.4 (q) and −4.9 (q); *m/z* (CI) 469 (M^+ + H, 39%), 411 (21) and 337 (100).

(2*E*)-4-[(2*R*,4*S*,6*R*,8*R*,9*S*)-4-*tert*-Butyldimethylsilyloxy-9-methyl-8-isopropyl-1,7-dioxaspiro[5.5]undecan-2-yl]-2-methylbut-2-enol 45

Following the procedure outlined above for the synthesis of the alcohol **36**, the ester **44** (3.0 g, 6.4 mmol) gave, after chromatography using light petroleum–ether (4:1) as eluent, the *title compound* **45** (2.7 g, 99%), $[\alpha]_D$ +44.1 (*c* 1.06, $CHCl_3$) (Found: M^+ − C_4H_9, 369.2493. $C_{20}H_{37}O_4Si$ requires *M*, 369.2491); ν_{max}/cm^{-1} 3560–3150, 1460, 1385, 1255, 1217, 1188, 1163, 1132, 1086, 1068, 1010, 982, 871, 836 and 775; δ_H 5.50 (1 H, m, 3-H), 4.12 (1 H, m, 4′-H), 4.03 (2 H, br s, 1-H_2), 3.56 (1 H, m, 2′-H), 3.01 (1 H, dd, *J* 2, 9.5, 8′-H), 2.22 (2 H, m, 4-H_2), 1.86 (3 H, m, 1″-H, 3′-H_{eq} and 5′-H_{eq}), 1.69 (3 H, d, *J* 1, 2-CH_3), 1.65 (1 H, m, 10′-H_{ax}), 1.47 (4 H, m, 9′-H, 10′-H_{eq} and 11′-H_2), 1.30 (1 H, dd, *J* 11, 12, 5′-H_{ax}), 1.19 (1 H, q, *J* 11.5. 3′-H_{ax}), 0.94 (3 H, d, *J* 7, CH_3), 0.90 [9 H, s, SiC(CH_3)$_3$], 0.82 (3 H, d, *J* 6.5, CH_3), 0.77 (3 H, d, *J* 6, 9′-CH_3), 0.07 [6 H, s, Si(CH_3)$_2$]; δ_C 136.6 (s), 122.4 (d), 97.3 (s), 78.0 (d), 68.9 (t), 67.7 (d), 65.7 (d), 45.4 (t),

41.0 (t), 35.6 (t), 33.6 (t), 31.4 (d), 28.1 (t), 28.1 (d), 25.8 (q), 20.8 (q), 18.1 (s), 17.3 (q), 13.9 (q), 13.7 (q) and −4.9 (q); *m/z* (CI) 444 ($M^+ + NH_4$, 50%) and 427 ($M^+ + H$, 100).

(4*S*)-3-{(2*R*,4*E*)-6-[(2*R*,4*S*,6*R*,8*R*,9*S*)-4-*tert*-Butyldimethylsilyloxy-9-methyl-8-isopropyl-1,7-dioxaspiro[5.5]undecan-2-yl]-2,4-dimethylhex-4-enoyl}-4-isopropyloxazolidin-2-one 47

Following the procedure outlined for the synthesis of **40**, the alcohol **45** (1.01 g, 2.37 mmol) was converted *via* the iodide **46** to the *title compound* **47** (1.23 g, 87%), $[\alpha]_D$ +60.2 (*c* 1.04, $CHCl_3$) (Found: $M^+ - C_4H_9$, 536.3406. $C_{29}H_{50}NO_6Si$ requires *M*, 536.3407); ν_{max}/cm^{-1} 1781, 1699, 1458, 1384, 1298, 1244, 1200, 1117, 1082, 1006, 978, 859, 833 and 772; δ_H 5.27 (1 H, t, *J* 7, 5′-H), 4.46 (1 H, m, 4-H), 4.26 (1 H, t, *J* 9, 5-H), 4.24 (1 H, dd, *J* 3.5, 9, 5-H′), 4.16 (1 H, m, 4″-H), 3.98 (1 H, m), 3.52 (1 H, m, 2″-H), 3.02 (1 H, dd, *J* 2, 9.5, 8″-H), 3.52 (1 H, dd, *J* 5.5, 13), 2.27 (2 H, m), 2.09 (1 H, m), 2.0 (1 H, dd, *J* 9, 13), 1.82 (3 H, m), 1.67 (3 H, s, 4′-CH_3), 1.63 (1 H, m), 1.45 (4 H, m), 1.29 (1 H, dd, *J* 11, 12, 5″-H_{ax}), 1.15 (1 H, q, *J* 11.5, 3″-H_{ax}), 1.07 (3 H, d, *J* 7, CH_3), 0.96 (3 H, d, *J* 7, CH_3), 0.92 (3 H, d, *J* 4, CH_3), 0.89 [9 H, s, $SiC(CH_3)$], 0.85 and 0.81 (each 3 H, dd, *J* 7, CH_3), 0.77 (3 H, d, *J* 6, CH_3) and 0.06 [6 H, s, $Si(CH_3)_2$]; *m/z* (CI) 611 ($M^+ + NH_4$, 12%), 594 ($M^+ + H$, 16) and 462 (100).

(2*R*,4*E*)-6-[(2*R*,4*S*,6*R*,8*R*,9*S*)-4-*tert*-Butyldimethylsilyloxy-9-methyl-8-isopropyl-1,7-dioxaspiro[5.5]undecan-2-yl]-2,4-dimethylhex-4-enol 48

Following the procedure outlined for the synthesis of alcohol **41**, the oxazolidinone **47** (2.51 g, 476 mmol) was reduced to the *title compound* **48** (1.94 g, 99%), $[\alpha]_D$ +49.8 (*c* 0.86, $CHCl_3$) (Found: $M^+ - C_4H_9$, 411.2926. $C_{23}H_{43}O_4Si$ requires *M*, 411.2930); ν_{max}/cm^{-1} 3540–3140, 1458, 1383, 1250, 1184, 1124, 1086, 1066, 1008, 980, 870, 834 and 772; δ_H 5.27 (1 H, t, *J* 7, 5-H), 4.11 (1 H, m, 4′-H), 3.5 (3 H, m, 1-H_2 and 2′-H), 3.03 (1 H, dd, *J* 2, 9.5, 8′-H), 2.16 (3 H, m, 3-H and 6-H_2), 1.76 (4 H, m, 3-H′, C*H*Me_2, 3′-H_{eq} and 5′-H_{eq}), 1.65 (3 H, s, 4-CH_3), 1.62 (2 H, m, 2-H), 1.5 (5 H, m, 9′-H, 10′-H_2 and 11′-H_2), 1.30 (1 H, dd, *J* 11, 12, 5′-H_{ax}), 1.20 (1 H, q, *J* 11.5, 3′-H_{ax}), 0.95 (3 H, d, *J* 6, 2-CH_3), 0.89 [12 H, CH_3 and $SiC(CH_3)_3$], 0.82 (3 H, d, *J* 7, CH_3), 0.78 (3 H, d, *J* 6, 9′-CH_3) and 0.07 [6 H, s, $Si(CH_3)_2$]; δ_C 135.7 (s), 122.4 (d), 97.3 (s), 77.7 (d), 68.4 (t), 68.1 (d), 65.8 (d), 45.4 (t), 44.4 (t), 41.0 (t), 35.5 (t), 34.1 (t), 33.6 (d), 31.5 (d), 28.1 (d), 28.0 (t), 25.8 (q), 20.8 (q), 18.1 (s), 17.2 (q), 16.6 (q), 6.0 (q), 13.9 (q) and −4.9 (q); *m/z* (CI) 469 ($M^+ + H$, 24%), 411 ($M^+ - 57$, 3) and 337 (100).

(2*R*,4*E*)-6-[(2*R*,4*S*,6*R*,8*R*,9*S*)-4-*tert*-Butyldimethylsilyloxy-9-methyl-8-isopropyl-1,7-dioxaspiro[5.5]undecan-2-yl]-2,4-dimethylhex-4-enyl iodide 49

Iodine (321 mg, 1.27 mmol) was added to the alcohol **48** (246 mg, 0.53 mmol), triphenylphosphine (281 mg, 1.04 mmol) and imidazole (81 mg, 1.16 mmol) in acetonitrile–ether (2:3; 3 cm^3) at 0 °C. The mixture was stirred at 0 °C for 30 min, and then diluted with ether (10 cm^3), washed with saturated aqueous sodium thiosulfate (5 cm^3), aqueous copper(II) sulfate (5 cm^3) and water (5 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ether (20:1) as eluent gave the *title compound* **49** (274 mg, 89%), $[\alpha]_D$ +36.7 (*c* 0.4, $CHCl_3$); ν_{max}/cm^{-1} 1457, 1383, 1250, 1184, 1128, 1084, 1065, 1007, 980, 870, 834 and 772; δ_H 5.31 (1 H, t, *J* 6.5, 5-H), 4.13 (1 H, m, 4′-H), 3.55 (1 H, m, 2′-H), 3.24 (1 H, dd, *J* 4.5, 9.5, 1-H), 3.10 (1 H, dd, *J* 6, 9.5, 1-H′), 3.05 (1 H, dd, *J* 2, 9.5, 8′-H), 2.19 (2 H, m, 6-H_2), 2.07 (1 H, dd, *J* 7.5, 13.5, 3-H), 1.85 (4 H, m, 3-H′, C*H*Me_2, 3-H_{eq} and 5-H_{eq}), 1.64 (2 H, m, 9′-H and 2-H), 1.61 (3 H, s, 4-CH_3), 1.46 (4 H, m, 10′-H_2 and 11′-H_2), 1.30 (1 H, dd, *J* 11, 12, 5′-H_{ax}), 1.19 (1 H, q, *J* 11.5, 3′-H_{ax}), 0.97 (3 H, d, *J* 6, CH_3), 0.96 (3 H, d, *J* 7, CH_3), 0.90 [9 H, s, $SiC(CH_3)_3$], 0.82 (3 H, d, *J* 7, CH_3), 0.79 (3 H, d, *J* 6, CH_3) and 0.07 [6 H, s, $Si(CH_3)_2$]; *m/z* (CI) 579 ($M^+ + H$, 29%) and 447 (100).

(2*R*,4*E*)-6-[(2*R*,4*S*,6*R*,8*R*,9*S*)-4-*tert*-Butyldimethylsilyloxy-9-methyl-8-isopropyl-1,7-dioxaspiro[5.5]undecan-2-yl]-2,4-dimethylhex-4-enyl(triphenyl)phosphonium iodide 2

A solution of triphenylphosphine (186 mg, 0.75 mmol) and the iodide **49** (274 mg, 0.47 mmol) in acetonitrile (0.9 cm^3) was heated under reflux for 72 h, diluted with acetonitrile (10 cm^3) and washed with light petroleum until only the phosphonium salt remained in the acetonitrile layer (TLC). After drying ($MgSO_4$), the acetonitrile solution was concentrated under reduced pressure to give the *title compound* **2** (336 mg, 84%) as a foam which was used without further purification; ν_{max}/cm^{-1} 1587, 1438, 1383, 1253, 1185, 1109, 1084, 1062, 1007, 978, 867, 844, 775 and 635; δ_H 7.92–7.62 (15 H, m, ArH), 5.24 (1 H, t, *J* 7, 5-H), 4.09 (1 H, m, 4′-H), 3.74 (1 H, m, 2′-H), 3.52 (2 H, m, 1-H_2), 2.95 (1 H, br d, *J* 5.5, 8′-H), 2.05 (4 H, m, 3-H_2 and 6-H_2), 1.76 (4 H, m, 2-H, C*H*Me_2, 3′-H_{eq} and 5′-H_{eq}), 1.53 (1 H, m, 9′-H), 1.37 (4 H, m, 10′-H_2, 11′-H_2), 1.39 (3 H, s, 4-CH_3), 1.24 (1 H, dd, *J* 10.5, 12, 5′-H_{ax}), 1.13 (1 H, q, *J* 11, 3-H_{ax}), 0.94 (3 H, d, *J* 6, 2-CH_3), 0.88 (3 H, d, *J* 7, CH_3), 0.86 [9 H, s, $SiC(CH_3)_3$], 0.78 and 0.71 (each 3 H, d, *J* 6, CH_3) and 0.05 [6 H, s, $Si(CH_3)_2$]; *m/z* (FAB) 713 (M^+, 45%).

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