Pergamon

Tetrahedron, Vol. 53, No. 27, pp. 9377-9392, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00590-5

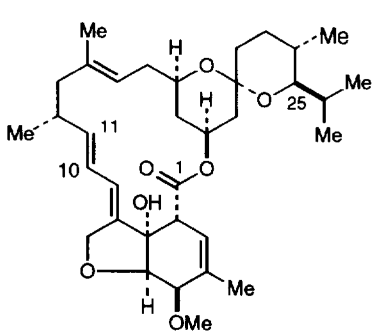
A Convergent Synthesis of the C(11)-C(25) Fragment of the Aglycone of Avermectin A_{2b}

Eric Menager, Eric Merifield, Mark Smallridge and Eric J. Thomas*

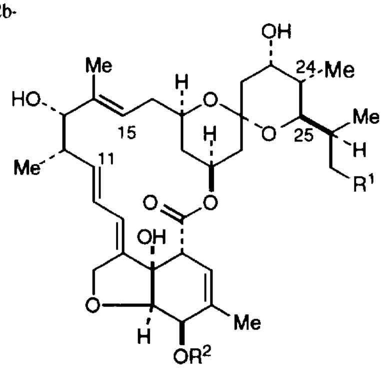
The Department of Chemistry, The University of Manchester, Manchester, M13 9PL, U.K.

Abstract: Oxidation of the mixture of products obtained by treatment of (*S*)-2-methylbutanal **8** with the *E*-but-2-enyldi-isopinocampheylborane prepared from (+)-pinene gave a mixture of homoallylic alcohols from which the major isomer **9** was isolated by chromatography. Oxidation with vanadylacetoacetate and *tert*-butyl hydroperoxide gave the epoxides **12** and **13**, ratio 80 : 20. Following procedures developed in a synthesis of the model spiroacetal **19**, 1,3-dithiane was alkylated, firstly using the epoxide **12**, and then, after protection of the product **21** so obtained as its acetonide **23**, using the epoxide **25**, to give the 2,2-dialkylated 1,3-dithiane **25**. Deprotection was accompanied by cyclisation to give the spiroacetal **28**. Spiroacetal **29** was similarly prepared and taken through to the C(11)-C(25) fragment **38** of the aglycone of avermectin A_{2b} **3**. © 1997 Elsevier Science Ltd.

The development of efficient syntheses of the milbemycins and avermectins is an important objective for synthetic organic chemists because of the biological activity of these compounds.[1] We have described syntheses of milbemycins, including milbemycin G **1**, in which the key convergent step, forming the C(10)-C(11) bond, is a Wittig reaction.[2-4] We now report full details of syntheses of the C(15)-C(25) fragments of the aglycones of avermectin B_{2a} and A_{2b} **2** and **3**.[5] These syntheses feature the Brown asymmetric allylation of aldehydes which is used to prepare homoallylic alcohols with stereogenic centres corresponding to C(24) and C(25) of the avermectins.[6] Transition metal directed epoxidation[7] then gives hydroxy-epoxides which are used to alkylate 1,3-dithiane.[8] Further dithiane alkylation, deprotection and spiroacetalisation give the required spiroacetals.[9] The allylborane chemistry is also used to introduce the stereogenic centres at C(12) and C(13) in the C(11)-C(25) fragment of the aglycone of avermectin A_{2b}.



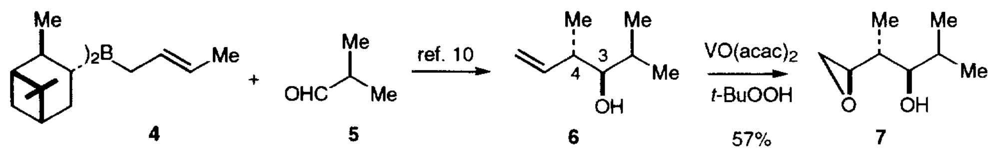
1



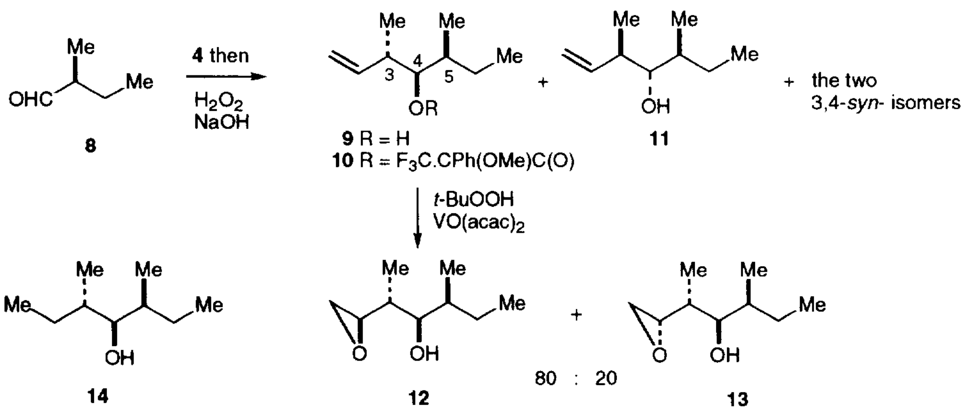
2 R^1 = Me, R^2 = H
3 R^1 = H, R^2 = Me

RESULTS AND DISCUSSION

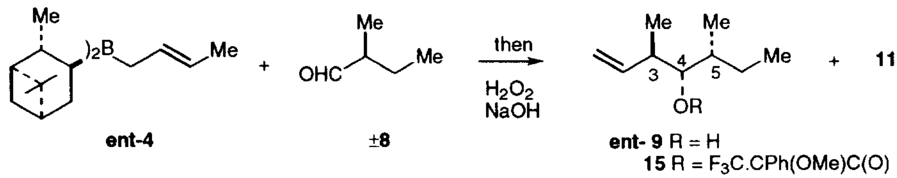
The (*E*)-but-2-enyldi-isopinocampheylborane **4** is known to react with 2-methylpropanal **5** to give the (3*R*,4*S*)-2,4-dimethylhex-5-en-3-ol **6** in a 60-70% isolated yield (e.e. ≥ 80%) after oxidative removal of the chiral auxiliary and separation of the minor 3,4-*syn*-diastereoisomer.[10] The 3,4-*anti*-stereoselectivity (3,4-*anti* : 3,4-*syn* = 88 : 12) is determined by the (*E*)-geometry of the butenylborane and the absolute configuration is controlled by the chirality of the ligands on boron.[6] The epoxidation of aliphatic homoallylic alcohols using *tert*-butylhydroperoxide catalysed by vanadyl acetoacetate is known to be stereoselective in favour of *syn*-hydroxyepoxides,[7] and the application of this procedure to the alkenol **6** gave a mixture of epoxides from which the (3*R*,4*R*,5*R*)-isomer **7** could be isolated as a single diastereoisomer (57%).



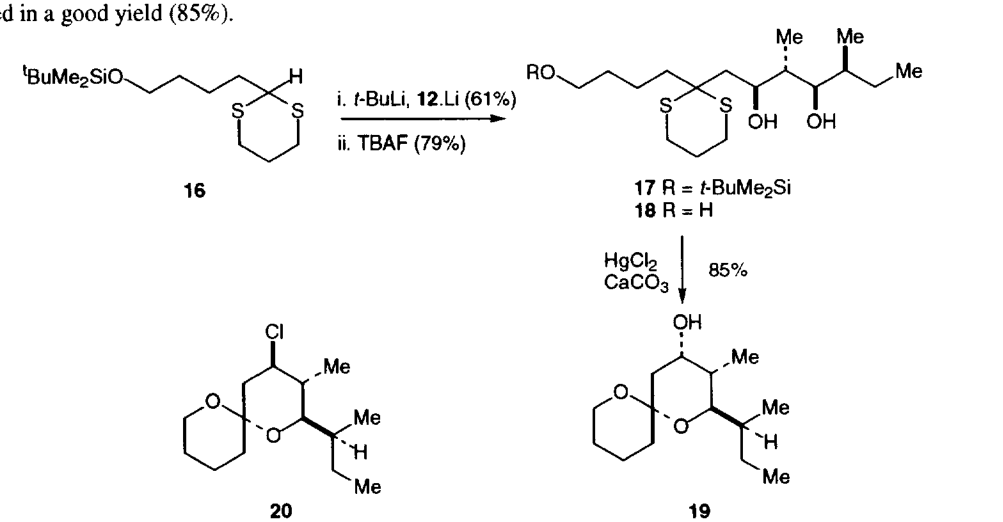
For the synthesis of the aglycone of avermectin B_{2a} **2**, this sequence was carried out starting with (*S*)-2-methylbutanal. The question here was whether the additional stereogenic centre in the aldehyde would affect significantly the stereoselectivity of either the allylation or epoxidation steps. Treatment of (*S*)-2-methylbutanal **8**[11] with the (*E*)-but-2-enyldi-isopinocampheylborane **4** prepared from (+)-pinene followed by oxidation using alkaline hydrogen peroxide gave a mixture of the 3,5-dimethylhept-1-en-4-ols **9** and **11** together with the two 3,4-*syn*-diastereoisomers, combined yield 65%, ratio (GLC) 76 : 9 : 2 : 13, from which the major product, the 3,4-*anti*-4,5-*syn*-diastereoisomer **9**, was isolated in a 41% yield by chromatography.[6] Epoxidation of **9** using *tert*-butyl hydroperoxide and vanadyl acetoacetate was stereoselective and gave the *syn*- and *anti*-hydroxyepoxides **12** and **13**, ratio 80 : 20, which were also separated by chromatography.[7]



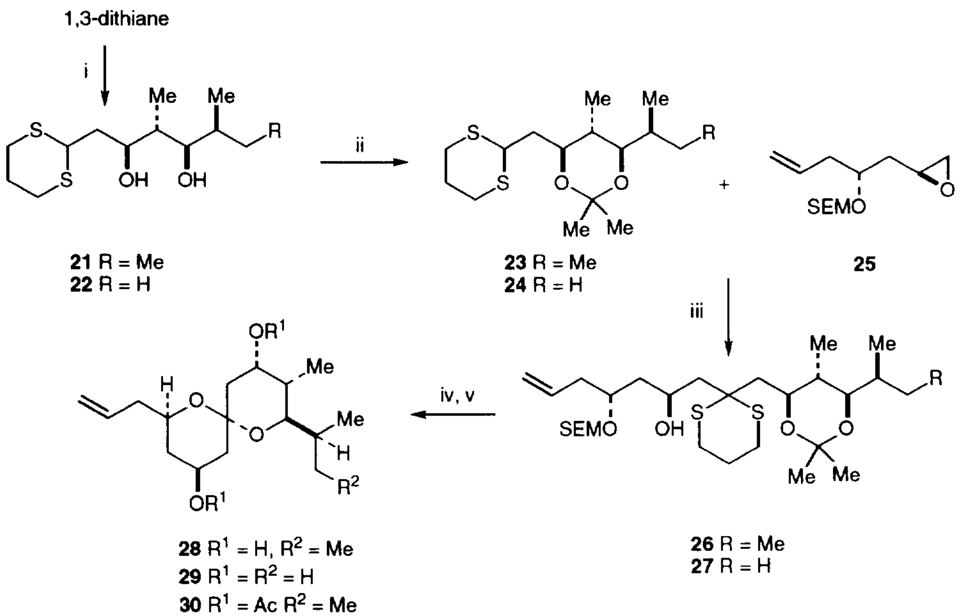
The 3,4-*anti*-4,5-*syn*-stereochemistry was assigned to the major isomer from the allylborane reaction since the 3,4-*anti*-configuration was expected to be introduced by the (*E*)-geometry of the but-2-enylborane and the absolute stereochemistry at C(3) and C(4) would be controlled by the use of (+)-pinene as the chiral auxiliary.[6] This assignment was consistent with the formation of a product on hydrogenation which was optically active and which contained two methyl doublets and two methyl triplets in its ^{1}H NMR spectrum and was therefore identified as the chiral 3,5-dimethylheptan-4-ol **14** rather than one of its meso-diastereoisomers. The reaction of racemic 2-methylbutanal **±8** with the but-2-enyldi-isopinocampheylborane **ent-4** prepared from (-)-pinene gave two major products identified as the 3,4-*anti*-4,5-*syn*-hept-1-en-4-ol **ent-9** and its 3,4-*anti*-4,5-*anti*-diastereoisomer **11** on the basis of the stereoselectivity expected for a reaction of the (*E*)-but-2-enylborane prepared from (-)-pinene. This confirmed which of the minor products from the reaction of the (*S*)-aldehyde **8** with the borane **4** was the 3,4-*anti*-4,5-*anti*-isomer **11**. The other minor products from this reaction must have been the 3,4-*syn*-isomers but it was not established which was which. By comparison of the (*S*)-Mosher's derivatives **10** and **15** prepared from the alcohols **9** and **ent-9**,[12] their optical purities were shown to be *ca.* 92% and 54%, respectively. The slightly lower than expected[6] stereoselectivity in this reaction of (*S*)-2-methylbutanal with the allylborane **4** may be due minor racemisation of the aldehyde.



Model studies using the 1,3-dithiane **16** were carried out to develop conditions for the synthesis of spiroacetals. Using *tert*-butyllithium, the dithiane **16** was alkylated using the hydroxyepoxide **12**, which had been deprotonated using butyllithium, to give the 2,2-dialkyl-1,3-dithiane **17** (61%). Desilylation gave the trihydroxydithiane **18**, but preliminary attempts to hydrolyse the dithiane and form the spiroacetal using mercury(II) chloride gave mixtures of products containing both the hydroxyspiroacetal **19** and a chlorospiroacetal provisionally identified as **20**, formed perhaps by reaction of the initially formed hydroxyspiroacetal **19** with hydrogen chloride released during the reaction. To avoid this side-reaction, the dithiane hydrolysis was repeated in the presence of calcium carbonate[13] and the hydroxyspiroacetal **19** was isolated in a good yield (85%).



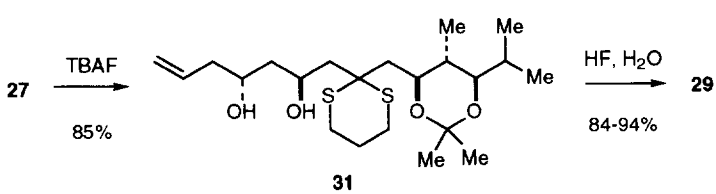
In order to prepare the spiroacetal fragment of avermectin A_{2b} **2**, 1,3-dithiane was alkylated using the hydroxyepoxide **12**, and the product **21** protected as its acetonide **23**. This was deprotonated using *tert*-butyllithium, and the lithiated dithiane alkylated using the epoxide **25**[10] to give the 2,2-dialkyl-1,3-dithiane **26**, the addition of hexamethylphosphoric triamide being required for efficient alkylation in this case. Finally on treatment with pyridine-hydrogen fluoride complex in aqueous acetonitrile, the dialkyldithiane **26** gave the spiroacetal **28** in a 58% yield. The structure of the spiroacetal was assigned on the basis of spectroscopic data obtained for the spiroacetal and its bis-acetate **30** which confirmed that one of the hydroxyl groups was equatorial and the other was axial in line with the proposed structure. This sequence was repeated starting with the epoxide **7** to give the spiroacetal **29**, aqueous hydrogen fluoride being used for small-scale cyclisations in this case.



Scheme 1 Synthesis of spiroacetals

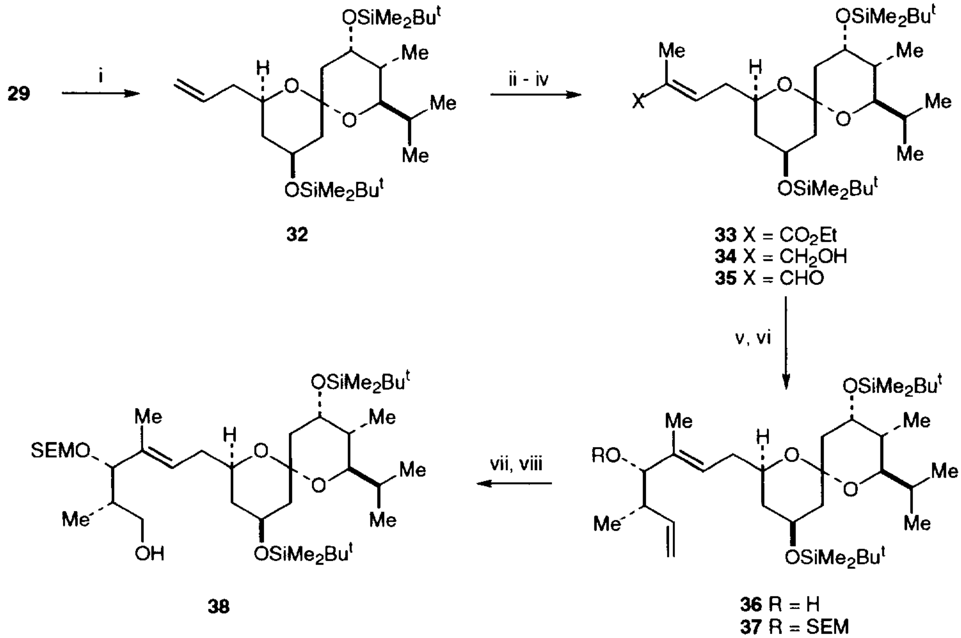
Reagents: i, BuLi, **7** or **12** (**21**, 48%; **22**, 78%); ii, $Me_2C(OMe)_2$,TsOH, acetone (**23**, 88%; **24**, 87%); iii, *t*-BuLi, HMPA, **25** (**26**, 53%; **27**, 80%); iv, HF - py or HF, aq. MeCN (**28**, 58%; **29**, 65%); v, Ac_2O, DMAP, Et_3N (100%).

For larger-scale work a two-step deprotection-spirocyclisation was found to give better overall yields. Treatment of the protected tetra-ol **27** with tetrabutylammonium fluoride gave the diol **31** (85%) which was converted into the spiroacetal **29** using aqueous hydrogen fluoride in acetonitrile (*ca.* 90%).



Having prepared the spiroacetals **28** and **29** which correspond to the C(15)-C(25) fragments of the aglycones of avermectins B_{2a} and A_{2b} **2** and **3**, respectively, preliminary investigations were carried out into the completion of a synthesis of the intact C(11)-C(25) fragment of **3**.

Protection of the spiroacetal **29** using *tert*-butyldimethylsilyl trifluoromethanesulfonate gave the bis-silyl ether **32** which was ozonolysed and the crude aldehyde condensed with 1-ethoxycarbonylethylidene-triphenylphosphorane to give the αβ-unsaturated ester **33**. Reduction gave the alcohol **34** which was oxidised to the aldehyde **35**, and the aldehyde coupled with the (*E*)-but-2-enyldi-isopinocampheylborane **4** prepared from (+)-pinene followed by oxidation using alkaline hydrogen peroxide to give the homoallylic alcohol **36**.[6] Minor diastereoisomers were expected but not detected in the product from this reaction. Alcohol **36** was converted into its trimethylsilylethoxymethoxy (SEM) ether **37** and the terminal double-bond cleaved selectively using osmium tetraoxide and lead(IV) acetate with reduction using sodium borohydride to give the alcohol **38** which corresponds to the C(11)-C(25) component of the aglycone of avermectin A_{2b} **3**.



Scheme 2 Synthesis of the C(11)-C(25) fragment of avermectin A_{2b}

Reagents i, *t*-$BuMe_2SiOTf$, 2,6-lutidine (75%); ii, O_3, MeOH, -78 °C, Me_2S, $EtO_2C.CMe{=}PPh_3$ (86%); iii, DIBAL-H (94%); iv, DMSO, $(COCl)_2$, Et_3N (93%); v, **4**, -78 °C, 3 h, NaOH, H_2O_2 (73%); vi, SEMCl, *i*-Pr_2NEt (97%); vii, OsO_4, py, then $Na_2S_2O_5$ (68%); viii, $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, then $NaBH_4$, EtOH (88%).

This work shows that the convergent approach used to prepare spiroacetals for a milbemycin synthesis[10] can also be applied to provide access to the more complex spiroacetals required for the synthesis of an avermectin. It features the stereoselective synthesis of homoallylic alcohols using alk-2-enylboranes prepared from di-isopinocampheylborane both for the stereoselective synthesis of the relatively simple starting materials **6** and **9** and for the development of the more complex intermediate **36**. It remains to convert the primary alcohol

38 into the corresponding phosphonium salt ready for a Wittig reaction to complete the assembly of the intact aglycone **3** of avermectin A_{2b}.

EXPERIMENTAL

Melting points were determined on a Buchi 510 apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 297 and 1710 spectrometers as liquid films unless otherwise stated. Low and high resolution mass spectra were taken on VG Micromass ZAB 16F and Kratos Concept mass spectrometers using the chemical ionisation mode (CI) unless otherwise stated. NMR spectra were recorded on Bruker WA 300 and Bruker AC-300 spectrometers. Optical rotations were measured at 20 °C and are given in units of 10^{-1} deg cm^2g^{-1}. Flash chromatography was carried out using Merck silica gel 60 (40 - 63 μm, 230 - 400 mesh) or May and Baker Sorbsil C60 silica gel (40 - 60 μm). All solvents were dried and distilled before use. Light petroleum refers to the fraction boiling in the range 40 - 60 °C. Ether refers to diethyl ether.

2-(4-*tert*-Butyldimethylsilyloxybutyl)-1,3-dithiane **16** (1.41 g, 96%), υ_{max} / cm^{-1} 1250, 1095, 830 and 770; δ_H 4.07 (1 H, t, *J* 7.5, 2-H), 3.63 (2 H, m, 4'-H_2), 2.89 (4 H, m, 4-H_2 and 6-H_2), 2.15 (1 H, m, 5-H), 1.85 (3 H, overlapping m, 1'-H_2 and 5-H), 1.58 (4 H, m, 2'-H_2 and 3'-H_2), 0.92 [9 H, s, $SiC(CH_3)_3$] and 0.07 [6 H, s, $Si(CH_3)_2$]; *m/z* (EI) 249 (M^+ - 57, 100%); was obtained by silylation of the corresponding alcohol using *tert*-butyldimethylsilyl chloride and imidazole in tetrahydrofuran, the alcohol in turn being prepared from tetrahydropyran-2-ol and propane-1,3-dithiol.

(S)-2-Methylbutanal 8

Sodium dichromate (70 g, 235 mmol) and sulfuric acid (98%, 56 cm^3) in water (410 cm^3) were added to (*S*)-2-methylbutanol (75 cm^3, 0.7 mol) at 95 °C over 30 min, and the mixture warmed to 140 °C for 15 min. The volatile products were collected as they distilled out during both the addition and warming stages of the reaction, and the organic phase of the distillate was then separated, dried ($MgSO_4$), and fractionally distilled through a 20 cm column packed with glass helices. The distillate was dried ($MgSO_4$) to give (*S*)-2-methylbutanal **8** (30-35%), b.p 90-92 °C (lit.[11] 90-92 °C), $[\alpha]_D$ +28.1 (*c* 1 in $CHCl_3$) [lit.[11] 34.5 (neat)] which was dried by stirring over 4A sieves overnight then distilled from them before use; υ_{max} / cm^{-1} 1725, 1460, 1380, 1170, 970, 900 and 770.

(3S,4R,5S)- and (3R,4S,5S)-3,5-dimethylhept-1-en-4-ols 9 and 11

(*S*)-2-Methylbutanal **8** (18.8 cm^3, 0.175 mol) in ether (24 cm^3) was added to (*E*)-but-2-enyldi-isopinocampheylborane **4** [0.127 mol; prepared from (+)-pinene] in tetrahydrofuran, and the mixture stirred at -70 °C for 3 h. Aqueous sodium hydroxide (96 cm^3; 3 M) was added followed by aqueous hydrogen peroxide (45 cm^3; 30%). The mixture was heated under reflux for 1 h before being cooled. The organic layer was washed with water (100 cm^3), brine (100 cm^3), and dried ($MgSO_4$). Concentration under reduced pressure gave a residue which was chromatographed using light petroleum - ether as eluant to give, after isolation of additional product by preparative GLC of mixed fractions on a PEG column at 130 °C (4.57 m), the (3*S*,4*R*,5*S*)-isomer of the *title compound* **9** (7 g, 41%), $[\alpha]_D$ -6.3 (*c* 1.1, $CHCl_3$); υ_{max} /cm^{-1} 3450, 3075, 1640, 1460, 1375, 1235, 1130, 1090, 995, 960 and 910 ; δ_H 5.79 (1 H, m, 2-H), 5.16 (2 H, m, 1-H_2), 3.23 (1 H, dd, *J* 7.5, 5, 4-H), 2.3 (1

H, m, 3-H), 1.62 (3 H, m, 6-H_2 and OH), 1.32 (1 H, m, 5-H), 1.0 (3 H, d, *J* 7, 3-CH_3), 0.93 (3 H, t, *J* 7, 7-H_3) and 0.9 (3 H, d, *J* 7, 5-CH_3); *m/z* (CI) 160 (M^++ 18, 100%) and 125 (14).

10% Palladium on charcoal (57 mg) was added to the alkenol **9** (102 mg, 0.72 mmol) in ethanol (5 cm^3) and the mixture stirred under an atmosphere of hydrogen for 24 h at room temperature. After filtration through celite, the filtrate was concentrated under reduced pressure. Chromatography of the residue using light petroleum - ether as eluant gave the 3,5-dimethylheptan-4-ol **14** (50 mg, 49%), $[\alpha]_D$ -8.8 (*c* 0.3, $CHCl_3$); υ_{max} /cm^{-1} 3390, 1460, 1380, 1260, 1150, 1100, 990, 955 and 805; δ_H 3.22 (1 H, dd, J 7.5, 2.5, 4-H), 1.07-1.78 (7 H, overlapping m), 0.93 (6 H, overlapping t, *J* 8, 1-H_3 and 7-H_3) and 0.85 (6 H, overlapping d, *J* 7, 3-CH_3 and 5-CH_3).

Following the above procedure but using racemic 2-methylbutanal **±8** (2.2 cm^3, 20 mmol) and (*E*)-but-2-enyldi-isopinocampheylborane **ent-4** [30 mmol; prepared from (-)-pinene] gave a mixture of products which were separated by preparative GLC on a PEG column at 130 °C (4.57 m) to give the (3*R*,4*S*,5*R*)-3,5-dimethylhept-1-en-4-ol **ent-9** (0.53 g, 19%), $[\alpha]_D$ +3.7 (*c* 1.1, $CHCl_3$) followed by the (3*R*,4*S*,5*S*)-isomer of the *title compound* **11**, $[\alpha]_D$ +8.4 (*c* 1.2, $CHCl_3$); υ_{max} /cm^{-1} 3350, 3080, 1640, 1000 and 910 ; δ_H 5.82 (1 H, m, 2-H), 5.13 (2 H, m, 1-H_2), 3.16 (1 H, t, *J* 7.5, 4-H), 2.42 (1 H, m, 3-H), 1.46 (3 H, m, 6-H_2 and OH), 1.2 (1 H, m, 5-H) and 0.98 (9 H, m, 7-H_3, 3-CH_3 and 5-CH_3); *m/z* (CI) 160 (M^+ + 18, 100%).

(*S*)-Methoxytrifluoromethylphenylacetyl chloride (0.29 mmol) and pyridine (0.3 cm^3, 3.7 mmol) were added to the alcohol **9** (32 mg, 0.23 mmol) in dichloromethane (1 cm^3) and the mixture stirred for 72 h at room temperature. Water (1 cm^3) was added and the mixture was extracted with ether (2 x 10 cm^3). The ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum - ether (20 : 1) as eluant, gave the ester **10** (33 mg, 44%); υ_{max} /cm^{-1} 3075, 1740, 1640, 1255, 1175, 1110, 1010, 920, 760 and 720; δ_H 7.59 (2 H, m, ArH), 7.43 (3 H, m, ArH), 5.69 (1 H, m, 2-H), 4.99 (3 H, 1-H_2 and 4-H), 3.53 (3 H, s, OCH_3), 2.54 (1 H, m, 3-H), 1.72 (1-H, m, 5-H), 1.38 and 1.23 (each 1 H, m, 6-H), 1.0 (3 H, d, *J* 7, 3-CH_3), 0.92 (3 H, t, *J* 7, 7-H_3) and 0.89 (3 H, d, *J* 6, 5-CH_3); δ_F -72.96 (5%), and -73.08 (95%); *m/z* (CI) 376 (M^++ 18, 59%) and 189 (100).

Following the same procedure, the alcohol **ent-9** (39.5 mg, 0.28 mmol) gave the ester **15** (46 mg, 46%); υ_{max} /cm^{-1} 3075, 1740, 1640, 1260, 1165, 1015, 995, 920 and 720; δ_H 7.58 (2 H, m, ArH), 7.39 (3 H, m, ArH), 5.68 (1 H, m, 2-H), 4.8 (3 H, 1-H_2 and 4-H), 3.55 (3 H, s, OCH_3), 2.56 (1 H, m, 3-H), 1.71 (1-H, m, 5-H), 1.26 (2 H, m, 6-H_2), 1.0 (3 H, d, *J* 7, CH_3), 0.88 (3 H, t, *J* 7, 7-H_3) and 0.84 (3 H, d, *J* 7, CH_3); δ_F -72.97 (75%) and -73.09 (25%); *m/z* (CI) 376 (M^+ + 18, 28%) and 189 (100).

(3R,4R,5R)-5,6-Epoxy-2,4-dimethylhexan-3-ol **7** *and*
(2R,3R,4R,5S)-1,2-Epoxy-3,5-dimethylheptan-4-ol **12**

Anhydrous *tert*-butyl hydroperoxide in toluene (3 M; 40 cm^3, 120 mmol) was added dropwise to a solution of the alkenol **16** (10 g, 78.1 mmol) and $VO(acac)_2$ (0.6 g, 2.3 mmol) in dichloromethane (700 cm^3) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 24 h. Aqueous sodium sulphite (10%; 30 cm^3) was added and the mixture stirred a further 30 min before being washed with water. The aqueous layer was extracted with ether and the organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum - ether (8 : 1) as the eluant gave the *title compound* **7** (6.4 g, 57 %), $[\alpha]_D$ -1.2 (*c* 2.1, $CHCl_3$);υ_{max} /cm^{-1} ($CHCl_3$) 3500, 1465, 1410, 1390, 1365, 1260, 1230, 1130, 1090, 990, 950, 912, 880, 835 and 810; δ_H 3.37 (1 H, dd, *J* 7, 4.5, 3-H), 2.94 (1

H, m, 5-H), 2.74 (1 H, t, *J* 4.5, 6-H), 2.46 (1 H, dd, *J* 5, 3, 6-H'), 2.3 (1 H, s, OH), 1.85 (1 H, m, 2-H), 1.39 (1 H, sex, J 7.5, 4-H) and 0.98, 0.94 and 0.87 (each 3 H, d, *J* 7, CH_3); *m/z* (CI) 162 (M^+ + 18, 43%), 145 (M^+ + 1) and 127 (100).

Following this procedure, the alkenol **9** gave the *title compound* **12** (1.9 g, 72%), $[\alpha]_D$ +9 (*c* 1, in $CHCl_3$); υ_{max} /cm^{-1} 3450, 1460, 1375, 1260, 990, 955, 910, 865 and 820; δ_H 3.61 (1 H, dd, *J* 2.5, 7.5, 4-H), 2.97 (1 H, m, 2-H), 2.8 (1 H, dd, J 4, 5, 1-H), 2.52 (1 H, dd, *J* 2.5, 5, 1-H'), 1.68 (1 H, br s, OH), 1.4 and 1.55 (each 2 H, m), 0.96 (3 H, t, *J* 7, 7-H_3), 0.94 (3 H, d, *J* 7, CH_3) and 0.87 (3 H, d, *J* 7.5, CH_3); *m/z* (CI) 176 (M^++ 18, 100%); followed by the (2*S*,3*R*,4*R*,5*S*)-epoxide **13** (380 mg, 14%), $[\alpha]_D$ +13.6 (*c* 0.9, in $CHCl_3$); υ_{max} /cm^{-1} 3460, 1260, 1130, 1035, 990, 960, 910, 870 and 820; δ_H 3.43 (1 H, dd, *J* 2.5, 7.5, 4-H), 3.02 (1 H, m, 2-H), 2.85 (1 H, t, *J* 5, 1-H), 2.75 (1 H, dd, *J* 2.5, 5, 1-H'), 1.95 (1 H, br s, OH), 1.71, 1.55, 1.44 and 1.34 (each 1 H, m), 0.95 (3 H, d, *J* 7, CH_3), 0.93 (3 H, t, *J* 7, 7-H_3) and 0.85 (3 H, d, *J* 7.5, CH_3); *m/z* (CI) 176 (M^+ + 18, 48%), 159 (M^+ + 1, 100) and 141 (92).

2-[(2S,3S,4R,5S)-2,4-Dihydroxy-3,5-dimethylheptyl]-2-(4-tert-butyldimethylsilyloxybutyl)-1,3-dithiane ***17***

tert-Butyllithium (1.25 M in pentane; 2.9 cm^3, 3.6 mmol) and *N,N,N',N'*-tetramethylethylenediamine (1.1 cm^3, 7.3 mmol) were added to to a solution of the dithiane **16** (0.93 g, 3.0 mmol) in tetrahydrofuran (5 cm^3) at -20 °C, and the solution stirred for 2 h. In a separate flask, butyllithium (1.65 M in hexane; 0.7 cm^3, 1.2 mmol) was added to a solution of the epoxide **12** (152 mg, 1.0 mmol) in tetrahydrofuran (1 cm^3), and this solution was then transferred to the solution of the lithium salt of dithiane **16** using a syringe. The temperature of the reaction mixture was maintained at -20 °C during the addition, then allowed to warm to 0 °C, and stirred for 16 h. Water (4 cm^3) and ether (100 cm^3) were added, and the mixture washed with dilute aqueous hydrogen chloride (0.1 M; 50 cm^3), water (2 x 50cm^3), and brine (50 cm^3). The washings were extracted with ether (2 x 50 cm^3), and the organic extracts dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue, using light petroleum - ether (6 : 1) as eluant, gave the recovered dithiane **16** (634 mg) followed by the *title compound* **17** (271 mg, 61%), $[\alpha]_D$ -8.04 (*c* 1.1, $CHCl_3$) (Found M^+, 464.2814. $C_{23}H_{48}O_3S_2Si$ requires *M*, 464.2814); υ_{max} /cm^{-1} 3380, 1460, 1250, 1095, 835 and 775; δ_H 4.19 (1 H, br s, exch. D_2O, OH), 4.02 (1 H, t, *J* 7.5, 2'-H), 3.65 (2 H, t, *J* 5, 4''-H_2), 3.56 (1 H, dd, *J* 10, 2.5, 4'-H), 3.0 and 2.78 (each 2 H, m), 2.37 (1 H, dd, J 10, 15, 1'-H), 2.02 (5 H, m), 1.27- 1.75 (9 H, m), 0.9 [18 H, m, $SiC(CH_3)_3$, 3'-CH_3, 5'-CH_3, and 7-H_3] and 0.07 [6 H, s, $Si(CH_3)_2$]; *m/z* (EI) 464 (M^+, 16%).

2-[(2S,3S,4R,5S)-2,4-Dihydroxy-3,5-dimethylheptyl]-2-(4-hydroxybutyl)-1,3-dithiane ***18***

Tetrabutylammonium fluoride (1 M in tetrahydrofuran; 1.7 cm^3, 1.7 mmol) was added dropwise to a solution of the silyl ether 25 (383 mg, 0.83 mmol) in tetrahydrofuran (4 cm^3) at 0 °C. The mixture was allowed to warm to ambient temperature and stirred for 5 h. Water (4 cm^3) was added and the mixture extracted with ethyl acetate (3 x 20 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate - light petroleum (3 : 2) as eluant gave the *title compound* **18** (227 mg, 79%), $[\alpha]_D$ -14.7 (*c* 1, MeOH); υ_{max} /cm^{-1} 3360, 1455, 1065, 1030 and 755; δ_H 4.14 (1 H, dd, *J* 10, 5, 4'-H), 4.03 (1 H, br s, OH), 3.69 (2 H, m, 4''-H_2), 3.49 (1 H, m, 2'-H), 3.23 (1 H, br s, OH), 3.01 and 2.7 (each 2 H, m), 2.35 (1 H, dd, *J* 15, 7.5, 1'-H), 1.18 - 2.15 (14 H, overlapping m), 0.93 (3 H, t, *J* 7, 7'-H_3) and 0.78 and 0.79 (each 3 H, d, *J* 7, CH_3); *m/z* (CI) 243 (100%) and 225 (31).

(2R,3S,4S,6S)-3-Methyl-2-[(S)-1-methylpropyl]-1,7-dioxaspiro[5,5]undecan-4-ol ***19***

The trihydroxydithiane **18** (207 mg, 0.59 mmol), mercury(II) chloride (351 mg, 2.4 mmol), and calcium carbonate (430 mg, 4.3 mmol) were stirred in tetrahydrofuran (8 cm^3) for 24 h at room temperature. Ether (30 cm^3) was added and the mixture filtered through celite, washed with water (30 cm^3) and brine (30 cm^3), and concentrated under reduced pressure. Chromatography of the residue using light petroleum - ether (5 : 1) as eluant gave the *title compound* **19** (121 mg, 85%), $[\alpha]_D$ +85.1 (*c* 1.0, $CHCl_3$); υ_{max} /cm^{-1} 3500, 1380, 1212, 1190, 1135, 1120, 1080, 1045, 1020, 1010, 990 and 830; δ_H 3.55 - 3.8 (5 H, overlapping m, 2-H, 4-H, 8-H_2, and OH), 1.95 (1 H, dd, *J* 15, 2.5, 5-H_{eq}), 1.83 (1 H, m), 1.43 - 1.68 (10 H, overlapping m), 0.98 (3 H, t, *J* 6, CH_2CH_3) and 0.92 and 0.88 (each 3 H, d, *J* 6, CH_3); *m/z* (CI) 243 (M^+ + 1, 100%) and 225 (37).

In the absence of the calcium carbonate, a mixture of products was obtained from which (2*R*,3*R*,4*R*,6*S*)-4-chloro-3-methyl-2-[(*S*)-1-methylpropyl]-1,7-dioxaspiro[5,5]undecane **20** (14%) was isolated by chromatography; υ_{max} /cm^{-1} 1385, 1180, 1160, 1090, 1050, 1040 and 1000; δ_H 4.06 (1 H, m, 4-H), 3.6 (2 H, m, 8-H_2), 3.34 (1 H, dd, *J* 10, 2.5, 2-H), 2.23 (1H, dd, *J* 12.5, 5, 5-H_{eq}), 1.4 - 1.93 (11 H, overlapping m), 1.04 (3 H, d, *J* 7.5, CH_3), 0.97 (3 H, t, *J* 7.5, CH_3) and 0.88 (3 H, d, *J* 7.5, CH_3); *m/z* 262 (M^+, 27%), 260 (M^+, 100) and 224 (19).

2-[(2S,3S,4R,5S)-2,4-Dihydroxy-3,5-dimethylheptyl]-1,3-dithiane ***21*** *and*
2-[(2S,3S,4R)-2,4-Dihydroxy-3,5-dimethylhexyl]-1,3-dithiane ***22***

Butyllithium (1.6 M in hexane; 14.15 cm^3, 22.63 mmol) was added to 1,3-dithiane (1.8 g, 15.1 mmol) in tetrahydrofuran (24 cm^3) at -40 °C and the solution stirred for 2 h. The epoxide **12** (1.19 g, 7.53 mmol) in tetrahydrofuran (6 cm^3) was added at -20 °C, and after 18 h at this temperature, saturated aqueous ammonium chloride (25 cm^3) and ether (50 cm^3) were added. The aqueous layer was extracted with ether (2 x 30 cm^3) and the organic extracts washed with brine (30 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ethyl acetate (2 : 1) as eluant, gave recovered epoxide **12** (447 mg, 38%), followed by the *title compound* **21** (0.97 g, 48%), $[\alpha]_D$ -15.8 (c 0.45, $CHCl_3$); ν_{max} /cm^{-1} 3380, 1459, 1422, 1388, 1275, 1146, 1002, 987, 959 and 912; δ_H 4.36 (1 H, dd, *J* 4.5, 10, 2-H), 3.98 (1 H, m, 2'-H), 3.56 (1 H, dd *J* 2.5, 10, 4'-H), 3.10 - 2.64 (4 H, m, 4-H_2 and 6-H_2), 2.19 - 1.79 (6 H, overlapping m, 5-H_2, 1'-H_2, and 2 x OH), 1.68 (1 H, m, 3'-H), 1.56 (1 H, m, 5'-H), 1.35 (2 H, m, 6'-H_2), 0.93 (3 H, t, *J* 7.5, 7'-H_3), and 0.85 and 0.78 (each 3 H, d *J* 6, 3'-CH_3 and 5'-CH_3); *m/z* (CI) 279 (M^+ + 1, 46%), 278 (M^+, 18), 260 (18), 171 (91) and 153 (100).

Following this procedure, 1,3-dithiane (15.97 g, 0.133 mol) and the epoxide **7** (6.39 g, 44.3 mmol) gave the *title compound* **22** (9.1 g, 78 %) (Found: C, 54.75; H, 9.05; S, 24.2. $C_{12}H_{24}O_2S_2$ requires C, 54.5; H, 9.15; S, 24.25%); υ_{max} /cm^{-1} ($CHCl_3$) 3440, 1425, 1275, 1140, 980, 920 and 910; δ_H 4.34 (1 H, dd, *J* 10, 4.45, 2-H), 3.98 (1 H, m, 2'-H), 3.73 (1 H, br s, OH), 3.42 (1 H, d, *J* 9, 4'-H), 2.9 (4 H, m, 4-H_2 and 6-H_2), 2.58 (1 H, br s, OH), 2.17 - 1.81 (5 H, m), 1.67 (1 H, m, 5'-H) and 0.99, 0.86 and 0.81 (each 3 H, d, *J* 7, CH_3); *m/z* (EI) 264 (M^+, 30%) and 246 (50).

2-[(2S,3S,4R,5S)-3,5-Dimethyl-2,4-di-O-isopropylidinedioxyheptyl]-1,3-dithiane ***23*** *and*
2-[(2S,3S,4R)-3,5-Dimethyl-2,4-di-O-isopropylidinedioxyhexyl]-1,3-dithiane ***24***

The 2-dihydroxyheptyl-1,3-dithiane **21** (288 mg, 1.04 mmol) and toluene *p*-sulphonic acid (9 mg, 0.052 mmol) were dissolved in acetone and 2,2-dimethoxypropane (1 : 1; 3.36 cm^3) and the mixture stirred at room temperature for 9 h. Ether (15 cm^3) was added, and the solution washed with water (5 cm^3), dried (K_2CO_3) and concentrated under reduced pressure. Chromatography of the residue gave the *title compound* **23** (219 mg, 88%) as a low melting oily solid, m.p. 32-34 °C (benzene), $[\alpha]_D$ -14.36 (*c* 1.18, $CHCl_3$) (Found: C, 60.45; H, 9.4. $C_{16}H_{30}O_2S_2$ requires C, 60.35; H, 9.5%); ν_{max} /cm^{-1} 1378, 1252, 1200, 1188, 1154, 1027, 953, 910, 833; δ_H 4.27 (1 H, dd *J* 4, 11.5, 2-H), 3.74 (1 H, dt *J* 2.5, 10, 2'-H), 3.46 (1 H, dd *J* 2.5, 10, 4'-H), 2.89 (4 H, m, 4-H_2 and 6-H_2), 2.1 (2 H, m, 5-H and 1'-H), 1.90 (1 H, m, 5-H'), 1.77 (1 H, ddd *J* 4, 10, 12.5, 1'-H'), 1.55 (1 H, m, 3'-H), 1.48 - 1.25 (3 H, overlapping m, 5'-H and 6'-H_2), 1.43 and 1.35 (each 3 H, s, CH_3), 0.87 (3 H, t *J* 6.5, 7'-H_3), 0.83 (3 H, d *J* 6, CH_3) and 0.75 (3 H, d *J* 6.5, CH_3); *m/z* (CI) 319 (M^++ 1, 91%), 261 (100) and 243 (25).

Following this procedure, the dihydroxyalkyl-1,3-dithiane **22** (9 g, 34.1 mmol) gave the *title compound* **24** (9.1 g, 87 %), $[\alpha]_D$ -21.5 (*c* 1.18, $CHCl_3$); (Found: C, 59.2; H, 9.0; S, 20.8. $C_{15}H_{28}S_2O_2$ requires C, 59.15; H, 9.25, S, 21.05 %); υ_{max} /cm^{-1} ($CHCl_3$) 1425, 1390, 1380, 1355, 1280, 1250, 1200, 1185, 1163, 1072, 1050, 1030, 1010, 953, 922, 905, 850 and 660 ; δ_H 5.24 (1 H, dd, *J* 11.5, 3.5, 2-H), 3.75 (1 H, dt, *J* 2, 10, 2'-H), 3.32 (1 H, dd, *J* 10, 2, 4'-H), 2.97 - 2.78 (4 H, m, 4-H_2 and 6-H_2), 2.08 (2 H, m, 5-H and 1'-H), 1.90 (2 H, m, 5-H' and 3'-H), 1.75 (1H, ddd, *J* 14, 10, 3.5, 1'-H'), 1.37 (1 H, m, 5'-H), 1.40 and 1.35 (each 3 H, s, CH_3) and 0.94, 0.83 and 0.74 (each 3 H, d, *J* 7, CH_3); *m/z* (CI) 305 (M^+ + 1, 90%) and 247 (100).

2-[(2S,3S,4R,5S)-3,5-Dimethyl-2,4-di-O-isopropylidinedioxyheptyl]-2-[(2S,4R)-2-hydroxy-4-(2-trimethylsilylethoxy)methoxyhept-6-enyl]-1,3-dithiane ***26*** *and*
2-[(2S,3S,4R)-3,5-Dimethyl-2,4-di-O-isopropylidinedioxyhexyl]-2-[(2S,4R)-2-hydroxy-4-(2-trimethylsilylethoxy)methoxyhept-6-enyl]-1,3-dithiane ***27***

tert Butyllithium (1.55 M in pentane; 0.43 cm^3, 0.66 mmol) and hexamethylphosphoric diamide (0.23 cm^3, 1.33 mmol) were added to a solution of the 2-alkyldithiane **23** (204 mg, 0.64 mmol) in tetrahydrofuran (2 cm^3) at -20 °C and the solution stirred at -20 °C for 2 h. The epoxide **25** (83 mg, 0.32 mmol) in tetrahydrofuran (2 cm^3) was added *via* a cannula and the reaction allowed to warm to -10 °C. After 4 h, water (2 cm^3) and ether (10 cm^3) were added, and the aqueous layer extracted with ether (3 x 5 cm^3). The organic extracts were washed with water (2 x 5 cm^3) and brine (5 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using gradient elution, light petroleum : ether (8:1 to 2:1) gave recovered 2-alkyldithiane **23** (96 mg, 47%) and the *title compound* **26** (99 mg, 53%); ν_{max} /cm^{-1} 3460, 1639, 1251, 1174, 1092, 1056, 1028, 919, 862, 838 and 728 ; δ_H 5.81 (1 H, m, 6'-H), 5.07 (2 H, m, 7'-H_2), 4.73 and 4.74 (each 1 H, d, *J* 9, OHC*H*O), 4.21 (1 H, m, 2'-H), 3.92 (1 H, m, 4'-H), 3.81 (1 H, dt, *J* 5.5, 10, 2"-H), 3.67 [2 H, m, OC*H*$_2$.$CH_2Si(CH_3)_3$], 3.47 (1 H, dd *J* 1.5, 10, 4"-H), 2.95 and 2.75 (each 2 H, m, 4-H_2 and 6-H_2), 2.27-1.8 (8 H,m), 1.72 (1 H, br s, OH), 1.62-1.24 (6 H, m), 1.41 and 1.34 (each 3 H, s, CH_3), 0.97 [2 H, m, C*H*$_2Si(CH_3)_3$), 0.87 (3 H, t, *J* 7, 6"-H_3), 0.81 (3 H, d, *J* 5.5, CH_3), 0.79 (3 H, d, *J* 5, CH_3), 0.04 [9 H, m, $Si(CH_3)_3$); m/z (FI) 576 (M^+).

Following this procedure, the 2-alkyl-1,3-dithiane **24** (1.67 g, 5.5 mmol) and the epoxide **25** (0.73 g, 2.84 mmol) gave the *title compound* **27** (1.27 g, 80 %), $[\alpha]_D$ -20.3 (*c* 1.5, $CHCl_3$) (Found: C, 59.75; H, 9.9; S, 11.7. $C_{28}H_{54}O_5S_2Si$ requires C, 59.75; H, 9.65; S, 11.4%); ν_{max} /cm^{-1} ($CHCl_3$) 3460, 2960, 1640, 1380, 1250, 1175, 1100, 1055, 1020, 920, 860, 835 and 695 ; δ_H 5.82 (1 H, m, 6'-H), 5.06 (2 H, m, 7'-H_2), 4.72 and 4.74 (each 1 H, d, J 7, OHC*H*O), 4.20 (1 H, m, 2'-H), 3.91 (1 H, m, 4'-H), 3.78 (1 H, dd, *J* 10, 7, 2"-H), 3.68 [3 H, m, $OCH_2CH_2Si(CH_3)_3$ and OH], 3.33 (1 H, dd, *J* 10, 2, 4"-H), 2.98 and 2.74 (each 2 H, m, SCH_2), 2.4 - 1.8 (9 H, m), 1.6 - 1.3 (3 H, m), 1.39 and 1.34 (each 3 H, s, CH_3), 1.0 -1.91 [2 H, m, $CH_2Si(CH_3)_3$], 0.93, 0.83 and 0.8 (each 3 H, d, *J* 7, CH_3) and 0.02 [9 H, s, $Si(CH_3)_3$]; *m/z* (CI), 563 (M^+ + 1, 18%), 562 (M^+, 15).

(2R,3S,4S,6R,8R,10S)-3-Methyl-2-[(S)-1-methylpropyl]-8-(prop-2-enyl)-1,7-dioxaspiro[5,5]undecane-4,10-diol **28** *and*
(2R,3S,4S,6R,8R,10S)-3-Methyl-2-(1-methylethyl)-8-(prop-2-enyl)-1,7-dioxaspiro-[5,5]undecane-4,10-diol **29**

Hydrogen fluoride-pyridine complex (1.92 cm^3) was added dropwise to the dialkyldithiane **26** (60 mg, 0.104 mmol) in anhydrous acetonitrile (4.5 cm^3). After 1 h at room temperature, the mixture was partitioned between ethyl acetate (10 cm^3) and water (5 cm^3). The aqueous layer was extracted with ethyl acetate (3 x 5 cm^3), and the organic extracts washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether (1 : 1) as eluant, gave the *title compound* **28** (18 mg, 58%), $[\alpha]_D$ +42.5 (*c* 1.20, $CHCl_3$) (Found: C, 68.8; H, 10.1. $C_{17}H_{30}O_4$ requires C, 68.4, H, 10.15%); ν_{max} /cm^{-1} 3600, 3460, 3080, 1640, 1455, 1380, 1152, 1133, 1122, 1079, 1034, 988, 962, 922, 900 and 880 ; δ_H 5.80 (1 H, m, 2"-H), 5.13 (2 H, m, 3"-H_2), 4.10 (1 H, m, 10-H), 3.74 (1 H, dq, *J* 10.5, 3, 4-H), 3.70 (1 H, m, 8-H), 3.57 (1 H, d, *J* 10.5, 4-OH), 3.42 (1 H, dd, *J* 2, 10.7, 2-H), 2.25 (2 H, m, 1"-H_2), 1.97 (3 H, m, 5-Heq, 9-Heq and 11-Heq), 1.65 (1 H, dd, *J* 3.4, 14, 5-Hax), 1.61 (1 H, s, 10-OH), 1.58 (1 H, m, 3-H), 1.51 (1 H, m, 1'-H), 1.39 (2 H, m, 2'-H_2), 1.32 (1 H, dd, *J* 12, 11, 11-Hax), 1.19 (1 H, q, *J* 11.5, 9-Hax), 0.94 (3 H, t, *J* 7.5, 3'-H_3), 0.89 (3 H, d, *J* 7, 3-CH_3) and 0.83 (3 H, d, J 7, 1'-CH_3); *m/z* (CI) 299 (M^+, 67%) and 281 (100).

Aqueous hydrogen fluoride (60% v/v; 6.4 cm^3) was added dropwise to a solution of the dithiane **27** (8.5 g, 15.1 mmol) in acetonitrile (121 cm^3). After 4 h at room temperature, the reaction mixture was poured into ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate (x 3) and the organic extracts were washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate : light petroleum (gradient elution) gave the *title compound* **29** (2.8 g, 65 %), $[\alpha]_D$ +57.9 (*c* 2.2, $CHCl_3$) (Found: C, 67.55; H, 9.65. $C_{16}H_{28}O_4$ requires C, 67.5; H, 9.9 %; Found: M^+ + H, 285.2058. $C_{16}H_{29}O_4$ requires *M*, 285.2066); ν_{max} /cm^{-1} ($CHCl_3$) 3600, 3500, 1640, 1385, 1240, 1150, 1130, 1080, 1010, 980, 960, 920 and 885 ; δ_H 5.78 (1 H, m, 2"-H), 5.12 (2 H, m, 3"-H_2), 4.12 (1 H, m, 10-H), 3.79 (1 H, dq *J* 10.5, 3.5, 4-H), 3.68 (1 H, m, 8-H), 3.55 (1 H, d, *J* 10.5, 4-OH), 3.3 (1 H, dd, *J* 10.5, 2, 2-H), 2.24 (2 H, m, 1"-H_2), 1.98 (3 H, m, 5-Heq, 9-Heq and 11-Heq), 1.85 (1 H, m, 1'-H), 1.64 (1 H, dd, *J* 14.5, 3, 5-Hax), 1.63 (1 H, br s, OH), 1.53 (1 H, m, 3-H), 1.33 (1 H, dd, *J* 11, 11.5, 11-Hax), 1.18 (1 H, q, *J* 11.5, 9-Hax) and 1.0, 0.99 and 0.84 (each 3 H, d, *J* 7, CH_3); δ_C 13.6, 13.8, 20.6, 27.9, 29.6, 36.0, 40.2, 41.0, 44.4, 64.2, 68.3, 69.9, 72.2, 99.3, 117.8 and 134.4; *m/z* (CI), 285 (M^+ + 1, 30%) and 267 (100).

(2R,3S,4S,6R,8R,10S)-4,10-Diacetoxy-3-methyl-2-[(S)-1-methylpropyl]-8-(prop-2-enyl)-1,7-dioxaspiro-[5,5]undecane **30**

Acetic anhydride (0.27 mmol) was added to the dihydroxyspiroacetal **28** (16.1 mg, 0.054 mmol), triethylamine (0.54 mmol) and 4-dimethylaminopyridine (1 mg, 8 μmol) in dichloromethane (0.5 cm^3) and the mixture stirred at room temperature until all the starting material had been consumed (TLC). Ether (5 cm^3) and water (1.5 cm^3) were added and the aqueous layer was extracted with ether (3 x 5 cm^3). The organic extracts were washed with water (3 cm^3) and brine (3 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using light petroleum : ether (4:1) as eluant, gave the *title compound* **30** (21 mg, 100%); ν_{max} /cm^{-1} 1720, 1640, 1458, 1370, 1255, 1181, 1022, 995, 968 and 918; δ_H 5.91 (1 H, m, 2"-H), 5.12 (1 H, m, 10-H), 5.06 (2 H, m, 3"-H_2), 4.91 (1 H, q, *J* 3.5, 4-H), 3.72 (1 H, m, 8-H), 3.66 (1 H, dd, *J* 2, 10.5, 2-H), 2.27 and 2.18 (each 1 H, m, 1"-H), 2.10 (1 H, dd, *J* 14, 2.5, 5-Heq), 2.05 and 2.02 (each 3 H, s, CH_3CO_2), 2.10 (1 H, m, 11-Heq), 1.94 (1 H, ddd, *J* 1.8, 5, 12, 9-Heq), 1.75 (1 H, m, 3-H), 1.61 (1 H, dd, *J* 4, 15, 5-Hax), 1.48 (1 H, m, 1'-H), 1.40 (2 H, m, 2'-H_2), 1.38 (1 H, t, *J* 12, 11-Hax), 1.16 (1 H, q, *J* 12, 9-Hax), 0.93 (3 H, t, *J* 7.5, 3'-H_3) and 0.86 and 0.84 (each 3 H, d, *J* 6.5, CH_3); δ_C 171.2, 170.4, 135.0, 116.7, 97.2, 71.6, 71.0, 68.8, 67.5, 41.1, 40.1, 38.7, 36.4, 35.3, 34.1, 27.4, 21.3, 21.3, 13.1, 12.5 and 11.2; *m/z* (CI) 323 (52%) and 263 (100).

2-[(2S,3S,4R)-3,5-Dimethyl-2,4-di-O-isopropylidinedioxyhexyl]-2-[(2S,4R)-2,4-dihydroxyhept-6-enyl]-1,3-dithiane 31

Tetrabutylammonium fluoride (1 M in tetrahydrofuran; 2.66 cm^3, 2.66 mmol) was added to a solution of the silyl ether **27** (368 mg, 0.65 mmol) in tetrahydrofuran (4 cm^3) at room temperature and the mixture stirred at 50 °C for 60 h. Water (5 cm^3) was added and the mixture extracted with ether (3 x 20 cm^3). The combined wextracts were washed with brine (2 x 15 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue usine ether - light petroleum as eluent (gradient elution) gave the *title compound* **31** (240 mg, 85%), $[\alpha]_D$ +2.64 (*c* 0.91, $CHCl_3$) (Found: C, 61.0; H, 9.5; S, 14.9; M, 432.2372. $C_{22}H_{40}O_4S_2$ requires C, 61.05; H, 9.3; S, 14.85%; *M*, 432.2368); ν_{max} /cm^{-1} 3439, 3410, 3372, 1427, 1381, 1254, 1201, 1175, 1084 and 994; δ_H 5.89 (1 H, m, 6'-H), 5.14 (2 H, m, 7'-H_2), 4.40 (1 H, m, 2'-H), 4.06 (2 H, m, 4'-H and 2"-H), 3.87 (1 H, t, *J* 9, OH), 3.37 (1 H, dd, *J* 10, 2, 4"-H), 3.25 (1 H, br s, OH), 3.07 and 2.76 (each 2 H, m), 2.58-1.85 (9 H, m), 1.64 (2 H, m), 1.32 (1 H, m), 1.41 and 1.33 (each 3 H, s, CH_3), and 0.95, 0.85 and 0.84 (each 3 H, d, *J* 6.5, CH_3); δ_c 12.2, 14.2, 19.4, 20.0, 24.9, 26.1, 26.6, 28.2, 29.6, 30.1, 35.1, 42.0, 42.8, 43.3, 51.4, 67.1, 68.2, 70.6, 76.5, 97.5, 117.2, 135.1; *m/z* (EI) 432 (M^+, 20).

Aqueous hydrogen fluoride (60% v/v, 2 cm^3) was added dropwise to the dialkyldithiane 31 (2.57 g, 5.94 mmol) in acetonitrile (10 cm^3) and the mixture stirred for 7 days before being diluted with ethyl acetate (20 cm^3) and neutralised with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (4 x 30 cm^3) and the combined organic extracts washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate - light petroleum (gradient elution) gave the spiroacetal **29** (1.33 g, 90%).

(Ethyl (2E)-4-[(2R,4S,6R,8R,9S,10S)-4,10-Di-tert-butyldimethylsilyloxy-9-methyl-8-(1-methylethyl)-1,7-dioxaspiro[5,5]undecan-2-yl]-2-methylbut-2-enoate 33

tert-Butyldimethylsilyl trifluoromethanesulfonate (4.7 cm^3, 20.5 mol) was added to the spiroacetal **29** (2 g, 7.04 mmol) and 2,6-lutidene (4.11 cm^3) in dichloromethane (50 cm^3) at 0 °C. After 3 h at room temperature, the reaction mixture was diluted with ether and washed with water. The aqueous solution was extracted with ether and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (1 : 99) as eluant, gave the *silyl ether* **32** (2.7 g, 75 %), $[\alpha]_D$ +79.9 (*c*

1.05, $CHCl_3$); υ_{max} /cm^{-1} 1470, 1460, 1385, 1360, 1255, 1190, 1175, 1130, 1070, 1005, 980, 910, 860 and 840; δ_H 5.93 (1 H, m, 2"-H), 5.00 (2 H, m, 3"-H_2), 4.09 (1 H, m, 10-H), 3.83 (1 H, m, 4-H), 3.62 (1 H, m, 8-H), 3.51 (1 H, dd, *J* 10, 2.5, 2-H), 2.3 and 2.15 (each 1 H, m, 1"-H), 1.8 (4 H, m, 5-Heq, 9-Heq, 11-Heq and 1'-H), 1.53 (2 H, m, 5-Hax and 3-H), 1.2 (2 H, m, 9-Hax and 11-Hax), 0.97 (3 H, d, *J* 7, CH_3), 0.89 [18 H, s, 2 x $SiC(CH_3)_3$], 0.82 and 0.8 (each 3 H, d, *J* 6.5, CH_3) and 0.04 [12 H, s, 2 x $Si(CH_3)_2$]; *m/z* (Cl) 513 (M^+ + 1, 5%) and 455 (10).

Ozone was passed through a solution of the silylether **32** (210 mgs, 0.41 mmmol) in methanol (10 cm^3) at -78 °C for 1 hour. The solution was then purged with oxygen, dimethylsulphide (0.3 cm^3) was added, and the reaction allowed to warm up slowly to room temperature. After 90 min at room temperature, the reaction mixture was concentrated under reduced pressure and dried by distillation with benzene. The residue was dissolved in benzene (5 cm^3) and (1-ethoxycarbonylethylidene)(triphenylphosphorane) (210 mgs, 0.62 mmol) added. After 24 h, the reaction mixture was concentrated under reduced pressure, and chromatography of the residue using ether : light petroleum (1 : 50) as eluant, gave the *title compound* **33** (210 mg, 86 %), $[\alpha]_D$ +63 (*c* 0.5, $CHCl_3$) (Found: C, 64.8; H, 11.0. $C_{32}H_{62}O_6Si_2$ requires C, 64.7; H, 10.85%); υ_{max} /cm^{-1} ($CHCl_3$) 1700, 1650, 1470, 1460, 1385, 1360, 1255, 1170, 1130, 1070, 1020, 1005, 980, 870 and 835; δ_H 6.87 (1 H, td, *J* 7, 1.5, 3-H), 4.15 (3 H, m, CH_2CH_3 and 4'-H), 3.82 (1 H, q, *J* 3, 10'-H), 3.71 (1 H, m, 2'-H), 3.56 (1 H, dd, *J* 10, 2.5, 8'-H), 2.26 (2 H, m, 4-H_2), 1.82 (3 H, s, 2-CH_3), 1.79 (4 H, m, 11'-H_{eq}, 3'-Heq, 5'-Heq, and 1"-H), 1.54 (1 H, dd, *J* 14, 4, 11'-Hax), 1.54 (1 H, m, 9'-H), 1.29 (3 H, t, CH_3CH_2), 1.26 (2 H, m, 5'-H_{ax} and 3'-H_{ax}), 0.98 (3 H, d, *J* 8, CH_3), 0.89 and 0.87 [each 9 H, s, $SiC(CH_3)_3$], 0.83 and 0.81 (each 3 H, d, *J* 6.5, CH_3) and 0.06 and 0.01 [each 6 H, s, $Si(CH_3)_2$]; *m/z* (Cl) 599 (M^+ + 1, 5%).

(2E)-4-[(2R,4S,6R,8R,9S,10S)-4,10-Di-tert-butyldimethylsilyloxy-9-methyl-8-(1-methylethyl)-1,7-dioxaspiro[5,5]undecan-2-yl]-2-methylbut-2-enol ***34***

Di-isobutylaluminium hydride (1 M in hexane; 7.6 cm^3, 7.6 mmol) was added dropwise to the ester (2.03 g, 3.4 mmol) in tetrahydrofuran (40 cm^3) at -78 °C. After 1 h, the reaction was allowed to warm to room temperature and stirred for a further hour. The mixture was cooled to -78 °C, methanol (1.7 cm^3) was added, and the mixture allowed to warm to room temperature. After 1 h, water (0.95 cm^3) and celite were added, and the mixture filtered through a celite bed which was washed thoroughly with dichloromethane. Concentration under reduced pressure and chromatography of the residue using ether : light petroleum gave the *title compound* **34** (1.78 g, 94 %), $[\alpha]_D$ +66.0 (*c* 1.3, $CHCl_3$); υ_{max} /cm^{-1} ($CHCl_3$) 3600, 3450, 1470, 1460, 1385, 1360, 1265, 1190, 1170, 1130, 1070, 1020, 1005, 980, 865 and 835 ; δ_H 5.52 (1 H, t, 3-H), 4.08 (1 H, m, 4'-H), 4.01 (2 H, s, 1-H_2), 3.83 (1 H, q, *J* 3, 10'-H), 3.60 (1 H, m, 2'-H) 3.52 (1 H, dd, *J* 10, 2, 8'-H), 2.19 (2 H, m, 4-H_2), 1.79 (4 H, m, 11'-H_{eq}, 3'-H_{eq}, 5'-H_{eq} and 1"-H), 1.66 (3 H, s, 2-CH_3), 1.55 (1 H, m, 9'-H), 1.52 (1 H, dd, *J* 14, 4, 11'-H_{ax}), 1.40 (1 H, br s, OH), 1.28 (1 H, t, *J* 12, 5'-H_{ax}, 1.14 (1 H, q, *J* 11.5, 3'-H_{ax}), 0.96 (3 H, s, *J* 7, CH_3), 0.88 [18 H, s, 2 x $SiC(CH_3)_3$], 0.82 (3 H, d, *J* 6.5, CH_3), 0.79 (3 H, d, *J* 6, CH_3), 0.58 [6 H, s, $Si(CH_3)_2$] and 0.05 and 0.02 (each 3 H, s, $SiCH_3$); *m/z* 557 (M^++ 1, 15%) and 425 (100).

(3S,4S,5E)-7-[(2R,4S,6R,8R,9S,10S)-4,10-Di-tert-butyldimethylsilyloxy-9-methyl-8-(1-methylethyl)-1,7-dioxaspiro[5,5]undecan-2-yl]-3,5-dimethylhepta-1,5-diene-4-ol ***36***

Dimethylsulphoxide (0.54 cm^3) was added dropwise to oxalyl chloride (0.32 cm^3) in dichloromethane (10 cm^3) at -78 °C. After 10 min, a solution of the alcohol **34** (1.78 g, 3.2 mmol) in dichloromethane (5 cm^3) was added, and the mixture maintained at -78 °C for 20 min. Triethylamine (2.09 cm^3) was added, and the reaction mixture allowed to attain room temperature and stirred for 20 min. Ether (50 cm^3) was added and the solution washed with water (2 x 25 cm^3). The aqueous washings were extracted with ether (2 x 50 cm^3), and the organic extracts dried ($MgSO_4$) and concentrated under reduced pressure to give the aldehyde **35** (1.66 g, 93 %) which was used without further purification; δ_H 9.4 (1 H, s, 1-H), 6.71 (1 H, t, 3-H), 4.11 (1 H, m, 4'-H), 3.84 (1 H, m, 10'-H), 3.74 (1 H, m, 2'-H), 3.52 (1 H, dd, *J* 10, 2, 8'-H), 2.45 (2 H, t, *J* 6.5, 4-H_2), 1.81 (4 H, m, 11'-H_{eq}, 3'-H_{eq}, 5'-H_{eq}, and 1''-H), 1.74 (3 H, s, 2-CH_3), 1.57 (1 H, dd, *J* 14, 4, 11'-H_{ax}), 1.56 (1 H, m, 9'-H), 1.25 (2 H, m, 3'-H_{ax} and 5'-H_{ax}), 0.94 (3 H, d, *J* 7, CH_3), 0.89 and 0.87 each [9 H, s,$SiC(CH_3)_3$], 0.82 and 0.8 (each 3 H, d, *J* 7, CH_3), 0.06 [6 H, s, $Si(CH_3)_2$] and 0.04 and 0.02 (each 3 H, s, $SiCH_3$).

Butyllithium (1.6 M in tetrahydrofuran; 2.5 cm^3, 4 mmol) was added to potassium *tert*-butoxide (0.45 g, 4 mmol) and (*E*)-but-2-ene (2 cm^3) in tetrahydrofuran (2 cm^3) at -78 °C. The mixture was stirred at -45 °C for 10 min, cooled to -78 °C and methoxydi-isopinocampheylborane [1 M in ether; 4.8 mmol; prepared from (+)-α-pinene] was added. After 30 min, boron trifluoride etherate (0.64 cm^3, 5 mmol) was added followed by the aldehyde **35** (1.8 g, 3.2 mmol) in ether (5 cm^3). The mixture was stirred at -78 °C for 3 h, and aqueous sodium hydroxide (3 M; 2.9 cm^3, 8.8 mmol) and aqueous hydrogen peroxide (30%; 1.2 cm^3) were added. The mixture was allowed to attain room temperature, and heated under reflux for 1 h. After cooling, the layers were separated and the aqueous layer was extracted with ether. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue gave recovered aldehyde **35** (0.4 g) and the *title compound* **36** (1.1 g, 73 % based on recovered starting material), $[\alpha]_D$ +46 (*c* 1.1, $CHCl_3$); υ_{max} /cm^{-1} 3300, 1597, 1462, 1385, 1255, 1174, 1131, 1070, 1023, 867, 836 and 775 ; δ_H 5.73 (1 H, m, 2-H), 5.51 (1 H, t, *J* 7, 6-H), 5.15 (2 H, m, 1-H_2), 4.07 (1 H, m, 4'-H), 3.82 (1 H, q, *J* 3, 10'-H), 3.68 (1 H, dd, *J* 8.5, 2, 8'-H), 3.59 (1 H, m, 2'-H), 3.52 (1 H, dd, *J* 10, 2.5, 4-H), 2.32 (2 H, m, 3-H and 7-H), 2.15 (1 H, m, 7-H'), 1.77 (4 H, m, 11'-H_{eq}, 3'-H_{eq}, 5'-H_{eq} and 1''-H), 1.62 (3 H, s, 5-CH_3), 1.55 (1 H, m, 9'-H), 1.53 (1 H, dd, *J* 14, 3.5, 11'-H_{ax}), 1.21 (3 H, m, 5'-H_{ax}, 3'-H_{ax} and OH), 0.96 (3 H, d, *J* 7, CH_3), 0.89 [21 H, m, 2 x $SiC(CH_3)_3$ and CH_3], 0.82 and 0.90 (each 3 H, d, CH_3), 0.05 [6 H, s, $Si(CH_3)_2$] and 0.06 and 0.02 (each 3 H, s, $SiCH_3$); *m/z* (Cl) 611 (M^+ + 1) and 593.

(3S,4S,5E)-7-[(2R,4S,6R,8R,9S,10S)-4,10-Di-tert-butyldimethylsilyloxy-9-methyl-8-(1-methylethyl)-1,7-dioxaspiro[5,5]undecan-2-yl]-3,5-dimethyl-4-(2-trimethylsilylethoxymethoxy)hepta-1,5-diene 37

Trimethylsilylethoxymethyl chloride (0.75 cm^3, 4.2 mmol) was added to the alcohol (1 g, 1.64 mmol) and di-isopropylethylamine (1.5 cm^3, 8.6 mmmol) in dichloromethane (25 cm^3) at 0 °C, and the reaction stirred for 24 h at room temperature when TLC indicated complete consumption of starting material. The reaction mixture was poured into ether and washed with water. The aqueous layer extracted with ether, and the organic extracts washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue gave the *title compound* **37** (1.18 g, 97 %), $[\alpha]_D$ +13.5 (*c* 1.2, $CHCl_3$); υ_{max} /cm^{-1} 1641, 1463, 1385, 1251, 1174, 1131, 1098, 1071, 1027, 918, 862, 836 and 775 ; δ_H 5.83 (1 H, m, 2-H), 5.44 (1 H, m, 6-H), 5.04 (2 H, m, 1-H_2), 4.5 and 4.57 (each 1 H, d, *J* 7, OHC*H*O), 4.06 (1 H, m, 4'-H), 3.77 - 3.25 (6 H, m), 2.34 (2 H, m, 3-H and 7-H), 2.15 (1 H, m, 7-H'), 1.76 (4 H, m, 11'-H_{eq}, 3'-H_{eq}, 5-H_{eq} and 1''-H), 1.51 (2 H, m, 9'-H and 11'-H_{ax}), 1.52 (3 H, s, 5-CH_3), 1.28 (1 H, t, *J* 11, 5'-H_{ax}), 1.11 (1 H, q, *J* 11, 3'-H_{ax}), 1.0 - 0.75 (32 H, m) and 0.05 (21 H, br s, 7 x $SiCH_3$); *m/z* (Cl) 758 (M^+ + 18, 10%) and 741 (M^++ 1, 20).

(3S,4S,2E)-6-[(2R,4S,6R,8R,9S,10S)-4,10-Di-tert-butyldimethylsilyloxy-9-methyl-8-(1-methylethyl)-1,7-dioxaspiro[5,5]undecan-2-yl]-2,4-dimethyl-3-(2-trimethylsilylethoxymethoxy)hex-4-en-1-ol **38**

Osmium tetroxide (70 mgs, 0.28 mmol) in pyridine (3 cm^3) was added to the alkene **37** (200 mg, 0.27 mmol) in pyridine (2 cm^3) at -20 °C and the mixture stirred at -20 °C for 1 h. Aqueous sodium metabisulphite (20%; 3 cm^3) was added and the mixture stirred for 30 min before dichloromethane and water were added.The aqueous layer was extracted with dichloromethane and the organic extracts were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (30 : 70) gave a mixture of epimeric diols (142 mg, 68 %), $[\alpha]_D$ +11.9 (*c* 1.2, $CHCl_3$); υ_{max} /cm^{-1} 3415, 1462, 1385, 1362, 1252, 1175, 1131, 1070, 1024, 919, 863, 836 and 775; δ_H 5.5 (1 H, m, 6-H), 4.53 and 4.59 (each 1 H, d, *J* 7, OHC*H*O), 4.03 (1 H, m, 4'-H), 3.9-3.4 (9 H, m), 2.26 and 2.17 (each 1 H, m, 7-H), 1.92 (1 H, m, 3-H), 1.78 (4 H, 11'-H_{eq}, 3'-H_{eq}, 5'-H_{eq} and 1"-H), 1.55 (3 H, s, 5-CH_3), 1.55 (2 H, m, 9'-H and 11'-H_{ax}), 1.28 (1 H, m, 5'-H_{ax}), 1.23 (2 H, br s, 2 x OH), 1.1 (1 H, m, 3'-H_{ax}), 0.88 and 0.86 each [9 H, s, $SiC(CH_3)_3$], 0.95 (3 H, d, *J* 7, CH_3), 0.8 [2 H, m, $CH_2Si(CH_3)_3$], 0.82, 0.78 and 0.63 (each 3 H, d, *J* 7, CH_3) and 0.1 - 0.00 (21 H, 3 x s, 7 x $SiCH_3$); *m/z* (CI) 792 (M^+ + 18).

Lead tetraacetate (78 mg, 0.18 mmol) was added to the diols (132 mg, 017 mmol) and sodium carbonate (180 mg, 1.7 mmol) in dichloromethane (5 cm^3) at 0 °C. After 30 min, no starting material remained (TLC), and the reaction mixture was filtered through a mixture of celite and sodium sulphate, the solids being washed thoroughly with dichloromethane. The organic solution was concentrated under reduced pressure and the residue was dissolved in ethanol (5 cm^3). Sodium borohydride (7 mgs, 0.18 mmol) was added, and after stirring at room temperature for 30 min, the mixture was poured into water and extracted with ether. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether : light petroleum (30 : 70) as eluant, gave the *title compound* **38** (110 mg, 88%); υ_{max} /cm^{-1} 1602, 1471, 1385, 1253, 1189, 1127, 1058, 1008, 982, 838 and 779 ; δ_H 5.5 (1 H, m, 5-H), 4.59 and 4.54 (each 1 H, d, *J* 7, OHC*H*O), 4.06 (1 H, m, 4'-H), 3.9-3.4 (8 H, m), 2.3 and 2.19 (each 1 H, m 6-H), 1.91 (1 H, m, 2-H), 1.87 - 1.68 (4 H, 11'-H_{eq}, 3'-H_{eq}, 5'-H_{eq}, and 1"-H), 1.55 (3 H, s, 4-CH_3), 1.55 (2 H, m, 9'-H and 11'-H_{ax}), 1.3 (1 H, m, 5'-H_{ax}), 1.28 (1 H, s, OH), 1.1 (1 H, q, 3'-H_{ax}), 0.95 (3 H, d *J* 7, CH_3), 0.88 ad 0.86 each [9 H, s, $SiC(CH_3)_3$], 0.82, 0.78 and 0.72 (each 3 H, d, *J* 7, CH_3) and 0.01 (21 H, s, 7 x $SiCH_3$).

ACKNOWLEDGEMENTS

We thank the EPSRC (SERC) for post-doctoral support (to E.M. and M.S.) and for a studentship (to P.G.S.).

REFERENCES

1. Davies, H. G.; Green, R. H., *Chem. Soc. Rev.*, **1991**, *20*, 211-269; Davies, H. G.; Green, R. H., *Chem. Soc. Rev.*, **1991**, *20*, 271-339.
2. Bailey, S.; Teerawutgulrag, A.; Thomas, E. J., *J. Chem. Soc., Chem. Commun.*, **1995**, 2519-2520; Bailey, S.; Teerawutgulrag, A.; Thomas, E. J., *J. Chem. Soc., Chem. Commun.*, **1995**, 2521-2522.
3. Steel, P. G.; Mills, O. S.; Parmee, E. R.; Thomas, E. J., *J. Chem. Soc., Perkin Trans. I*, **1997**, 391-400; Parmee, E. R.; Steel, P. G.; Thomas, E. J., *J. Chem. Soc., Chem. Commun.*, **1989**, 1250-1253.

4. Hughes, M. J.; Thomas, E. J., *J. Chem. Soc., Perkin Trans. I*, 1993, 1493-1505; Parmee, E. R.; Mortlock, S. V.; Stacey, N. A.; Thomas, E. J.; Mills, O. S., *J. Chem. Soc., Perkin Trans. I*, **1997**, 381-390.
5. Springer, J. P.; Arison, B. H.; Hirschfield, J. M.; Hoogsteen, K., *J. Am. Chem. Soc.*, **1981**, *103*, 4221-4224.
6. Brown, H. C.; Bhat, K. S., *J. Am. Chem. Soc.*, **1986**, *108*, 293-294; Brown, H. C.; Bhat, K. S., *J. Am. Chem. Soc.*, **1986**, *108*, 5919-5923; Brown, H. C.; Jadhav, P. K., *J. Org. Chem.*, **1984**, *49*, 4089-4091; Brown, H. C.; Desai, M. C.; Jadhav, P. K., *J. Org. Chem.*, **1982**, *47*, 5065-5069; Brown, H. C.; Joshi, N. N., *J. Org. Chem.*, **1988**, *53*, 4059-4062.
7. Mihelich, E. D.; Daniels, K.; Eickhoff, D. J., *J. Am. Chem. Soc.*, **1981**, *103*, 7690-7692.
8. Redlich, H.; Schneider, B.; Francke, W., *Tetrahedron Lett.*, **1980**, *21*, 3009-3012; Redlich, H.; Schneider, B., *Leibigs Ann, Chem.*, **1983**, 412-424; Redlich, H.; Schneider, B.; Hoffmannn, R. W.; Geueke, K.-J., *Leibigs Ann. Chem.*, **1983**, 393-411.
9. Preliminary communication: Merifield, E.; Steel, P. G.; Thomas, E. J., *J. Chem. Soc., Chem. Commun.*, **1987**, 1826-1828.
10. Steel, P. G.; Thomas, E. J., *J. Chem. Soc., Perkin Trans. I*, **1997**, 371-380.
11. Badin, E. J.; Pacsu, E., *J. Am. Chem. Soc.*, **1945**, *67*, 1352-1353; Kirmse, W.; Arold, H., *Chem. Ber.*, **1971**, *104*, 1800-1806.
12. Dale, J. A.; Dull, D. L.; Mosher, H. S., *J. Org. Chem.*, **1969**, *34*, 2543-2549.
13. Corey, E. J.; Erickson, B. W. *J. Org. Chem.*, **1971**, *36*, 3553-3560.

(*Received in UK* 21 *April* 1997; *revised* 20 *May* 1997; *accepted* 22 *May* 1997)