Chemistry of Bis-spiroacetals: [1] Synthesis of *cis*- and *trans*-1-(2-Methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-2-yl)methanol

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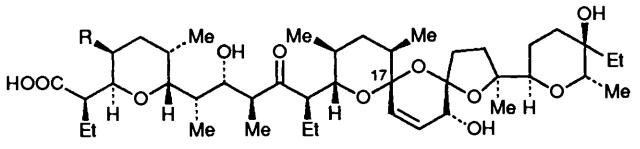
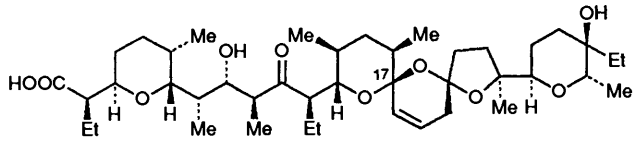
The synthesis of the *cis* and *trans* isomers of the bis-spiroacetal **25** is described, establishing methodology for the preparation of the polyether antibiotic *epi*-17-deoxy-(*O*-8)-salinomycin **3**. The hydroxymethyl group at C-2 of **25**, which provides an important 'handle' for elaboration of the right hand side of the molecule, was introduced by S_N2 displacement of the hindered iodide **24** using potassium superoxide in dimethyl sulphoxide (DMSO) in the presence of 18-crown-6. Barton-type cyclization of the iodohydrin **10** provided the iodo-bis-spiroacetal **24** with the *trans* isomers **24a**, **24b** favoured over the *cis* isomers **24c**, **24d** by 3:1. The key iodohydrin **10** was prepared in high yield by reaction of the epoxide **9** with LiI catalysed by $BF_3{\cdot}Et_2O$. The epoxide **9**, in turn, was prepared by condensation of the highly functionalised acetylene **6**, derived from lactonic acid **11**, with δ-valerolactone.

The polyether antibiotics salinomycin **1**,[2] narasin A **2**,[3] *epi*-17-deoxy-(*O*-8)-salinomycin **3**,[4] noboritomycin,[5] CP44,661[6] and

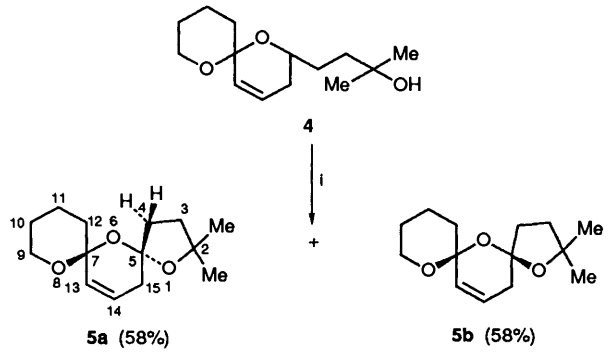


Salinomycin **1**; R = H
Narasin A **2**; R = Me



epi -17-Deoxy-(*O*-8)-salinomycin **3**

X-14766 A[7] provide interesting synthetic targets due to the presence of the 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene ring system. Recent synthetic approaches to this heterocycle have focused on the addition of acetylide ions to δ-valerolactones followed by acid catalysed cyslisation[8] and the oxidative rearrangement of a 2-furyl ketone.[9] Our synthetic effort,[10] however, has concentrated on the oxidative cyclisation of a hydroxy spiroacetal to a bis-spiroacetal (Scheme 1). We



5a (58%) **5b** (58%)

Scheme 1 *Reagents*: i, $PhI(OAC)_2$ (3 quiv.); I_2 (2 equiv.), cyclohexane, *hv*, 24 h

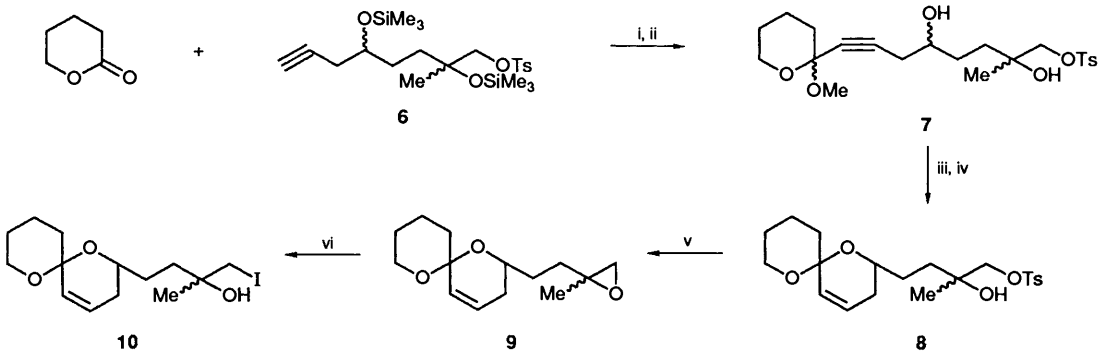
now report[1] the introduction of a suitable functional group, CH_2X, at C-2 which will facilitate further elaboration of the right hand side of this molecule. This problem needed addressing before the Barton-type methodology could be applied to the synthesis of the natural products themselves.

In our initial work[10] involving the cyclisation of spiroacetal **4** to the bis-spiroacetal **5** using iodobenzene diacetate and iodine in cyclohexane under photolytic conditions, we reported a 53% yield of the *trans* bis-spiroacetal **5a**. Careful optimization of the reaction conditions by maintaining the reaction mixture at 15 °C under a nitrogen atmosphere gave a 58% yield of the *trans* isomer **5a** together with the minor *cis* isomer **5b** in 23% yield. The ^1H NMR spectra of these two isomers allowed ready assignment of the stereochemistry. Thus, 4-H, resonating at δ 2.59–2.70 in the *trans* isomer, is significantly deshielded due to its close proximity to *O*-8 of the A ring. This same proton in the *cis* isomer **5b** resonates further upfield as part of the multiplet at δ 1.48–2.19.

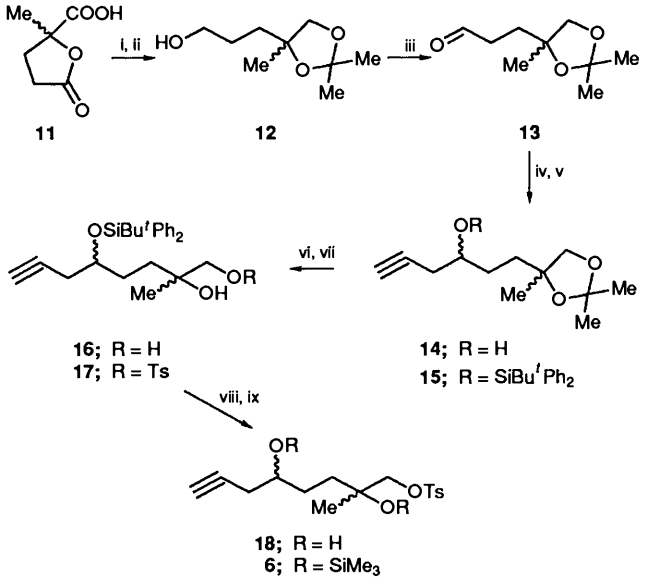
Our previous route[10] to bis-spiroacetal **5** did not allow the possibility of controlling the absolute stereochemistry at C-2 required for the natural product. It was envisaged that nucleophilic opening of epoxide **9** would provide potential cyclization precursors which could be converted into bis-spiroacetals with the desired functionality at C-2. Hence, in the present work, a synthesis of the epoxide **9** was required which would also allow the introduction of the methyl group in a stereoselective manner.

To this end, the epoxide **9** was synthesised from δ-valerolactone and the highly functionalised acetylene **6** (Scheme 2). The key acetylene **6** in turn, was derived from the lactonic acid **11** (Scheme 3) which itself can be prepared in optically active form—a requirement for the natural product work—by simply effecting a 'classical' resolution using Mori's procedure.[11]

In the present case, the racemic lactonic acid **11** was converted into the alcohol **12** following literature procedure and then oxidised in 78% yield using dimethyl sulphoxide (DMSO) activated with trifluoroacetic anhydride at −65 °C to the aldehyde **13**. Addition of the aldehyde **13** to the Grignard reagent of prop-2-ynyl bromide in the presence of mercuric chloride gave the acetylene **14** in 81% yield as a 1:1 mixture of diastereoisomers. After protection of the secondary alcohol **14** as a *tert*-butyldiphenylsilyl ether **15** the acetonide was liberated



Scheme 2 *Reagents:* i, BuLi, −78 °C, 0.5 h then δ-valerolactone, 0.5 h; ii, MeOH, Amberlite, IR-120 resin, room temp., 18 h, 76%; iii, H_2, Lindlar catalyst, hexane–EtOAc; iv, pyridinium toluene-*p*-sulphonate, CH_2Cl_2, room temp., 10 min, 91%; v, NaH, THF, room temp., 4 h, 94%; vi, LiI, BF_3·Et_2O, THF, −50 °C, 5 h, 96%



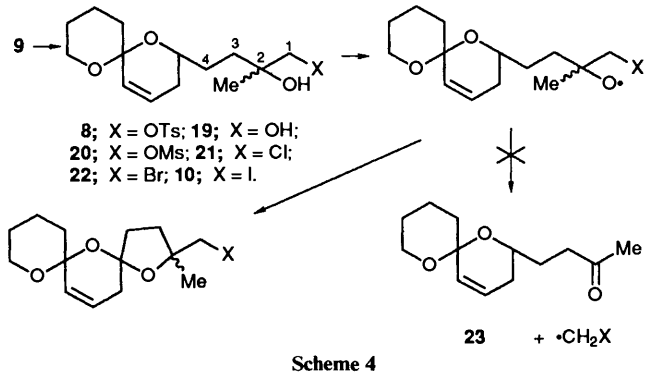
Scheme 3 *Reagents:* i, $LiAlH_4$, Et_2O, room temp., 18 h; ii, acetone, *p*-TSA, 18 h; iii, DMSO, TFAA, CH_2Cl_2, −65 °C, NEt_3, 68%; iv, Mg, prop-2-ynyl bromide, Et_2O, 81%; v, Bu^tPh_2SiCl, imidazole, CH_2Cl_2, 24 h, 96%; vi, Amberlite IR-120 resin, MeOH, 24 h, 81%; vii, TsCl, pyridine, 18 h, 84%; viii, 2% HF in MeCN, 12 h, 96%; ix, TMS–imidazole, CH_2Cl_2, 6 h, 95%

using methanol and Amberlite IR-118 resin to give the diol **16** which then underwent selective tosylation on the primary alcohol to give the tosylate **17** in 84% yield.

Whilst the acetylene **17** possessed all the functionality required for conversion into the epoxide **9**, further manipulation of protecting groups was required. It was preferable to replace the robust *tert*-butyldiphenysilyl ether as a trimethylsilyl ether at this stage as it proved difficult to remove after the lithium acetylide addition had taken place. Thus, the *tert*-butyldiphenylsilyl ether **17** was deprotected using 2% hydrofluoric acid in acetonitrile and the resultant diol **18** reprotected as the bis-trimethylsilyl ether **6** using *N*-trimethylsilylimidazole in 95% yield. Tetrabutylammonium fluoride was found to be unsuitable to remove the silyl group as this converted the tosylate-alcohol into an epoxide which was then incompatible with the subsequent acetylide addition.

Despite the presence of the tosylate group, the acetylene **6** upon treatment with butyllithium at −78 °C for 1 h underwent nucleophilic addition to δ-valerolactone providing the methoxyacetal **7** in 76% yield after treatment with acidic methanol. Hydrogenation of the acetylene over Lindlar catalyst to the *cis* alkene followed by acid catalysed cyclisation using a catalytic quantity of pyridinium toluene-*p*-sulphonate (PPTS) in dichloromethane afforded the spiroacetal-tosylate **8** in 91% yield. Finally, intramolecular displacement of the tosylate using sodium hydride in tetrahydrofuran afforded the epoxide **9** in 94% yield.

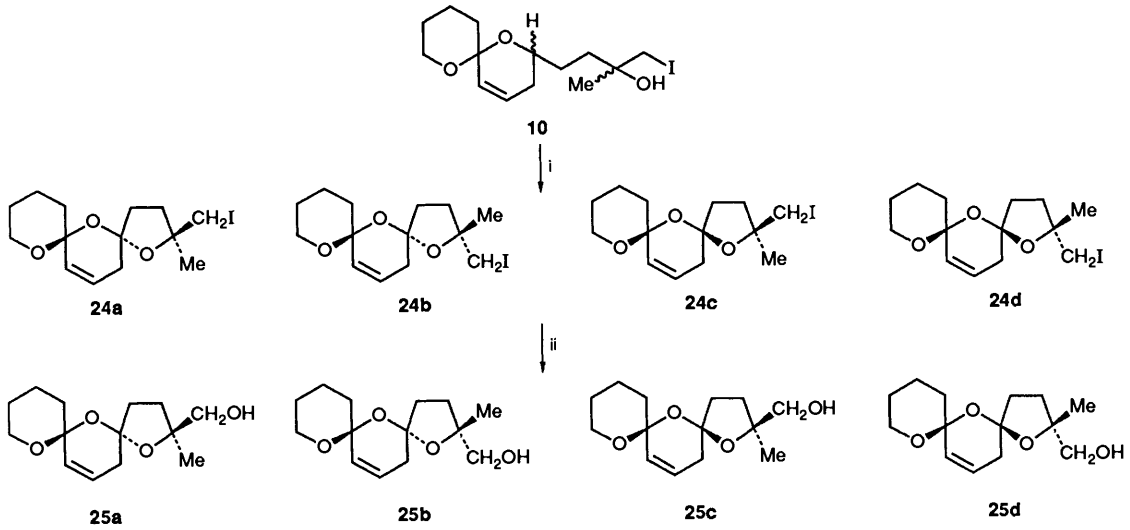
Having devised a synthesis of the epoxide **9** which allows for introduction of a methyl group with an *S* configuration as required for the synthesis of salinomycin, attention was then turned to putting in place suitable functionality at C-2 of the bis-spiroacetal which would provide a 'handle' to extend the right hand side of the molecule. Nucleophilic opening of the epoxide **9** allowed the introduction of various substituents at C-1 of the corresponding hydroxy spiroacetals **8**, **10**, **19**, **20**, **21** and **22** which had the potential upon Barton-type cyclisation to a bis-spiroacetal to provide such a 'handle'. The choice of substituent at C-1 of the hydroxy spiroacetal, however, was limited by the prerequisite that it must be compatible with the cyclisation reaction and not facilitate the competitive fragmentation to the methyl ketone **23** (Scheme 4).



Scheme 4

Attempts to effect oxidative cyclisation of hydroxy spiroacetals **8**, **19**, **20**, **21** and **22** where X = OTs, OH, OMs, Cl and Br respectively, using the same conditions which were successfully applied to the dimethylspiroacetal **4** were unsuccessful. However, spirocyclisation of the iodohydrin **10** afforded the desired iodo bis-spiroacetal **24** (Scheme 5). Treatment of the epoxide **9** with an excess of lithium iodide and boron trifluoride–diethyl ether in tetrahydrofuran at −50 °C afforded the iodohydrin **10** in 96% yield as a 1:1 mixture of two diastereoisomers that were not separated (Scheme 2). Although this is a new method for halohydrin formation, halohydrins have been noted as by products in Lewis acid-catalysed cuprate reactions where a halide salt is present.[12]

Conversion of iodohydrin **10** into the key iodo bis-spiroacetal **24** was achieved using (diacetoxyiodo)benzene (2.7 equiv.) and iodine (1.6 equiv.) in cyclohexane upon irradiation with two 270 W tungsten filament lamps for 24 h, ensuring the reaction



Note: All compounds are racemic although one one enantiomer is indicated

24a:**24b**:**24c**:**24d** = 3:3:1:1

Scheme 5 *Reagents:* i, $PhI(OAc)_2$ (3 equiv.), I_2 (2 equiv.), cyclohexane, *hv*, 24 h, 76%; ii, KO_2, 18-crown-6, DMSO, room temp., 81%

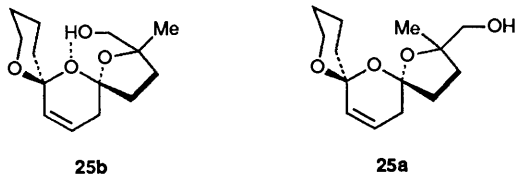


Fig. 1

mixture was kept cool in a water bath with rigorous exclusion of oxygen. The iodo-bis-spiroacetal **24** was isolated in 76% yield as a 3:3:1:1 mixture of isomers **24a**:**24b**:**24c**:**24d**. The two *trans*-isomers **24a**, **24b** were then separated from the two *cis*-isomers **24c**, **24d** by flash chromatography. The *trans*-isomers **24a**, **24b** were readily distinguished from their ^1H NMR spectra by the characteristic deshielding of 4-H resonsating at δ 2.66–2.75 in **24a**, **b** relative to the *cis*-isomers **24c**, **d** where this proton resonated as part of the multiplet at δ 1.82–2.33.

Whilst the *trans*-iodides **24a**, **24b** were readily separable from the *cis*-iodides **24c**, **24d**, separation of the individual *trans*-iodides (*i.e.* **24a** from **24b**) and the individual *cis*-iodides (*i.e.* **24c** from **24d**) was not possible. However, conversion of the iodide into an alcohol allowed separation of the individual isomers.

S_N2 Displacement of the iodide **24** proved to be a difficult process owing to the steric hindrance of the neopentyl-like configuration. Success was finally realised with an excess of potassium superoxide in DMSO–tetrahydrofuran (THF) for 2 d using 18-crown-6 to enhance the nucleophilicity of the superoxide anion. Thus, the *trans*-iodides **24a**, **24b** were converted into *trans*-alcohols **25a**, **25b** in 81% yield which were readily separated by flash chromatography owing to their differing R_f values. This is a consequence of the ability of the hydroxy group in the favoured conformation of isomer **25b** to participate in intramolecular hydrogen bonding to the oxygen atom of the neighbouring spiroacetal ring (Fig. 1). The methyl group in isomer **25a** resonated at δ 1.47 and was deshielded relative to the methyl group at δ 1.20 in isomer **25b** owing to it being 1,3-*syn* to the C–O bond of the central ring (Fig. 1).

In a similar fashion the *cis-iodides* **24c**, **24d** were converted into the *cis*-alcohols **25c**, **25d** and the individual isomers separated by flash chromatography. In this case the methyl group at δ 1.37 in isomer **25d** was also deshielded relative to the methyl group at δ 1.11 in isomer **25c** as previously observed for the *trans*-isomers. Difficulties, however, were encountered in the conversion of the *cis*-iodides **24c**, **24d** into the *cis*-alcohols **25c**, **25d** owing to the ready equilibration of the *cis*-iodides to the *trans*-iodides **24a**, **24b**.

In summary, the successful synthesis of the *trans*-alcohol **25** which has the same stereochemistry as that present in the bis-spiroacetal moiety of the polyether antibiotic *epi*-17-deoxy-(*O*-8)-salinomycin **3** has been achieved starting from the lactonic acid **11** and δ-valerolactone. This provides an excellent framework for the synthesis of this portion of the natural product. The work herein described overcomes two problems associated with our earlier studies: (i) the introduction of the methyl group at C-2 of the bis-spiroacetal with the required *S* configuration by incorporation of a resolution step into the present synthesis of epoxide **9** and (ii) the introduction of a suitable 'handle' at C-2 in the form of an iodide or an hydroxy group which allows elaboration of the right hand side of the molecule.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Pye Unicam SP3-200S spectrophotometer as Nujol mulls between sodium chloride discs. ^1H NMR spectra were recorded in the solvents stated using tetramethylsilane as internal standard on either a Hitachi R-1200 or a JEOL GX270 spectrometer, *J* values are given in Hz. Mass spectra and accurate mass measurements were recorded on a AEI MS9 spectrometer with an ionisation potential of 70 eV. Microanalyses were performed by the Microanalytical laboratory, University of Otago. Solvents were purified and dried according to the method of Perrin, Perrin and Armarego.[13] Column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh) with the solvents described according to the method of Still *et al.*[14] Compounds were visualised on TLC by UV fluorescence or by spraying with vanillin in methanolic sulphuric acid.

2,2-Dimethyl-1,6,8-trioxadispiro[4.1.5.3]*pentadec-13-ene* **5**.—A solution of the hydroxy spiroacetal **4**[10] (700 mg, 2.9 mmol), ground iodine (1.48 g, 5.8 mmol) and iodobenzenediacetate (1.86 g, 5.8 mmol) in cyclohexane (35 cm^3) was purged with nitrogen and irradiated with two 250 W tungsten filament lamps, the temperature of the reaction mixture being carefully maintained < 15 °C. After 12 h, the reaction mixture was diluted

with ether (200 cm^3) and then washed with 10% aqueous sodium thiosulphate (50 cm^3), water (50 cm^3) and brine (20 cm^3) and dried (K_2CO_3). The solvent was removed at reduced pressure to afford crude bis-spiroacetal **5** as a mixture of diastereoisomers which were separated by flash chromatography, using hexane–ethyl acetate (9:1) as eluent, to give:

(a) the *trans* isomer **5a** (403 mg, 58%) as a colourless oil for which the ^{13}C and ^1H NMR data were in agreement with that reported previously;[10] (b) the cis-*isomer* **5b** (161 mg, 23%) as a colourless oil (Found: M^+, 238.1578. $C_{14}H_{22}O_3$ requires *M*, 238.1569); ν_{max}(film)/cm^{-1} 3035 (w, =CH), 2943, 2875 (s, CH) and 1655 (w, C=C); δ_H(270 MHz; $CDCl_3$) 1.15 (3 H, s, Me), 1.39 (3 H, s, Me), 1.48–2.19 (11 H, m, 3-H, 3-H′, 4-H, 4-H′, 10_{ax}-H, 10_{eq}-H, 11_{ax}-H, 11_{eq}-H, 12_{ax}-H, 12_{eq}-H and 15-H), 2.37 (1 H, ddd, $J_{15,15}$ 16.9, $J_{15,14}$ 2.8 and $J_{15,13}$ 2.3, 15-H′), 3.61 (1 H, m, 9_{eq}-H), 4.03 (1 H, ddd, $J_{9ax,9eq}$ 11.5, $J_{9ax,10ax}$ 11.5 and $J_{9ax,10eq}$ 2.8, 9_{ax}-H), 5.71 (1 H, ddd, $J_{13,14}$ 10.2, $J_{13,15}$ 2.8 and $J_{13,15}$ 1.1, 13-H) and 5.86 (1 H, ddd, $J_{14,13}$ 10.2, $J_{14,15}$ 5.9 and $J_{14,15}$ 2.2, 14-H); δ_C(67.8 MHz; $CDCl_3$) 18.7, 25.2 (t, C-10 and C-11), 28.1 (q, Me), 28.9 (q, Me), 35.1, 36.5, 37.1, 39.0 (t, C-3, C-4, C-12 and C-15), 61.3 (t, C-9), 82.9 (s, C-2), 93.6 (s, C-7), 104.2 (s, C-5), 124.1 (d, C-13) and 130.2 (d, C-14); *m/z* 238 (M^+, 42%), 151 ($C_9H_{11}O_2$, 29), 124 ($C_8H_{12}O$, 100) and 75 (70).

Tetrahydro-2-methyl-5-oxofuran-2-carboxylic Acid **11**.—Acetic acid (43 cm^3) was dissolved in water (65 cm^3) neutralised to pH 6 with sodium hydroxide (21.5 g) and cooled to 0 °C. Levulinic acid (2-oxopentanoic acid) (250 g, 2.2 mol) and a solution of sodium cyanide (108 g, 2.2 mol) in water (150 cm^3) were added simultaneously over a period of 1 h. The resulting brown solution was stirred at room temperature for 0.5 h after which concentrated hydrochloric acid (560 cm^3) was added and the mixture heated at reflux for 4 h. After concentration by distillation at reduced pressure the precipitated salts were filtered off, the filter cake washed with acetone and the washings added to the filtrate to further precipitate inorganic salts. The procedure was repeated several times after which the solvent was removed at reduced pressure to afford a brown oil which was distilled *in vacuo* to give the title compound **11** (220 g, 75%) as a colourless oil which solidified on cooling, b.p. 148–150 °C/0.02 mmHg (lit.,[15] b.p. 163–167 °C/1.5 mmHg). Recrystallisation from hexane–ether gave a colourless crystalline solid, m.p. 72–73 °C (lit.,[16] m.p. 72–73.5 °C).

3-(2,2,4-*Trimethyl*-1,3-*dioxolan*-4-*yl*)*propan*-1-*ol* **12**.—The title compound was prepared from compound **11** according to the procedure described by Mori,[11] in 85% yield, b.p. 72–74 °C/0.2 mmHg (lit.,[11] b.p. 83 °C/0.4 mmHg).

3-(2,2,4-*Trimethyl*-1,3-*dioxolan*-4-*yl*)*propanal* **13**.—A solution of dry DMSO (1.88 g, 24 mmol) in dry dichloromethane (12 cm^3) under nitrogen was cooled to −65 °C and a solution of trifluoroacetic anhydride (3.8 g, 18 mmol) in dry dichloromethane (6 cm^3) was added dropwise, the temperature not being allowed to exceed −60 °C. The resulting white slurry was stirred for 10 min at this temperature after which a solution of compound **12** (2.09 g, 12 mmol) in dry dichloromethane (6 cm^3) was slowly added to it. After being stirred for 15 min the solution was warmed to −20 °C and dry triethylamine (3 g, 30 mmol) was added to it. The reaction was warmed to room temperature, diluted with water (5 cm^3) and extracted with dichloromethane (2 × 80 cm^3). The organic extract was washed with water (2 × 30 cm^3) and brine (50 cm^3), dried (K_2CO_3) and evaporated at reduced pressure. Purification of the residue by flash chromatography, using hexane–ethyl acetate (9:1) as eluent, afforded the *title compound* **13** (1.61 g, 78%) as a colourless liquid, b.p. (Kugelrohr) 55 °C/17 mmHg (Found: C, 62.8; H, 9.4%. $C_9H_{16}O_3$ requires C, 62.6; H, 9.1%); ν_{max}(film)/cm^{-1} 3005, 2940 (s, CH), 2880 (m, HCO), 2723 (w, HCO) and 1730 (s, C=O); δ_H(270 MHz; $CDCl_3$) 1.28 (3 H, s, 4′-Me), 1.38 (6 H, s, 2 × 2′-Me), 1.79–2.02 [2 H, m, $CH_2C(Me)O$], 2.53–2.59 (2 H, m, CH_2CHO), 3.75 (1 H, d, *J* 8.6, CH_AH_BO), 3.79 (1 H, d, *J* 8.6, CH_AH_BO) and 9.80 (1 H, t, *J* 1, CHO); δ_C(67.8 MHz; $CDCl_3$) 25.0 (q, 4′-Me), 27.1 (q, 2′-Me), 27.2 (q, 2′-Me), 32.0 (t, C-3), 39.2 (t, C-2), 74.3 (t, C-5′), 80.2 (s, C-4′), 109.6 (s, C-2′) and 201.7 (d, C-1); *m/z* 157 (M − Me, 1%), 115 ($C_6H_{11}O_2$, 3), 97 (C_6H_9O, 3), 72 (C_4H_8O, 4), 57 (5), 44 (5), 43 (100), 42 (17) and 41 (19).

1-(2,2,4-*Trimethyl*-1,3-*dioxolan*-4-*yl*)*hex*-5-*yn*-3-*ol* **14**.—A solution of prop-2-ynyl bromide (80% w/v solution in toluene; 1.95 cm^3, 13 mmol) was slowly added to a suspension of activated magnesium turnings (430 mg, 17.5 mmol) and mercuric chloride (*ca.* 5 mg) in dry diethyl ether (15 cm^3) cooled to 0 °C under nitrogen. After initiation of the reaction by gentle heating, the reaction mixture was cooled to 0 °C and stirred for 0.5 h. A solution of compound **13** (1.5 g, 8.7 mmol) in dry ether (30 cm^3) was added to the grey suspension and the reaction mixture stirred at room temperature for 1 h. After quenching with saturated aqueous ammonium chloride (10 cm^3), the mixture was extracted with ethyl acetate (80 cm^3), washed with water (2 × 20 cm^3) and brine (50 cm^3) and dried (K_2CO_3). After removal of solvent at reduced pressure the residue was purified by flash chromatography, using hexane–ethyl acetate (1:1) as eluent, to give the *title compound* **14** as a 1:1 mixture of diastereoisomers (1.56 g, 81%) [Found: C, 65.8; H, 8.5%; $M^+ + H$ (CI, CH_4), 255.1593. $C_{14}H_{22}O_4$ requires C, 66.1; H, 8.7%; *M*H, 255.1596]; ν_{max}(film)/cm^{-1} 3650–3150 (br s, OH), 3300 (s, ≡CH), 2995, 2940, 2880 (s, CH) and 2120 (w, C≡C); δ_H(270 MHz; $CDCl_3$) 1.28, 1.29 (3 H, s, 4′-Me), 1.38 (6 H, s, 2 × 2′-Me), 1.52–1.83 (4 H, m, 2 × CH_2), 2.06 (1 H, m, ≡CH), 2.36–2.42 (2 H, m, $C{\equiv}CCH_2$), 2.59–2.95 (1 H, br s, OH) and 3.71–3.81 (3 H, m, CH_2O and *CH*OH); δ_C(67.8 MHz; $CDCl_3$) 24.8 (q, 4′-Me), 27.1–27.4 (q, 2′-Me), 31.0 (t, C-1), 35.7 (t, C-2), 36.3 (t, C-4), 69.9–70.8 (d, C-6 and C-3), 74.4 (t, C-5′), 80.9, 81.0 (s, C-4′ and C-5) and 109.5 (s, C-2′); *m/z* 197 (M − Me, 3%), 115 ($C_6H_{11}O_2$, 18), 97 (C_6H_9O, 12), 72 (C_4H_8O, 27), 69 (15), 59 (23), 57 (26), 43 (100) and 41 (24).

3-tert-*Butyldiphenylsilyloxy*-1-(2,2,4-*trimethyl*-1,3-*dioxolan*-4-*yl*)*hex*-5-*yne* **15**.—A solution of the alcohol **14** (720 mg, 3.4 mmol), imidazole (360 mg, 5.3 mmol) and *tert*-butyldiphenylsilyl chloride (1.02 g, 3.7 mmol) in dry dichloromethane (10 cm^3) under nitrogen was stirred for 8 h at room temperature. Water (0.2 cm^3) was added and the reaction mixture extracted with ether (3 × 50 cm^3). The organic extract was washed with water (2 × 25 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The resultant residue was purified by flash chromatography using hexane–ethyl acetate (9:1) as eluent to afford the *silyl ether* **15** (1.38 g, 96%) as a colourless oil; ν_{max}(film)/cm^{-1} 3315 (m, ≡CH), 3074 (w, Ar-H), 2930, 2855 (s, CH), 2120 (w, C≡C) and 1390, 1372 (s, CMe_3); δ_H(270 MHz; $CDCl_3$) 1.06 (9 H, s, Bu^t), 1.18, 1.20 (3 H, s, 4′-Me), 1.32, 1.33, 1.37, 1.38 (6 H, s, 2 × 2′-Me), 1.54–1.64 (4 H, m, 2 × CH_2), 1.92 (1 H, m, ≡CH), 2.30–2.33 (2 H, m, $CH_2C{\equiv}$), 3.61–3.70 (2 H, m, CH_2O), 3.82–3.91 (1 H, m, CHO), 7.25–7.43 (6 H, m, ArH) and 7.66–7.69 (4 H, m, ArH); δ_C(67.8 MHz; $CDCl_3$) 19.3 (s, CMe_3), 24.7 (q, 4′-Me), 26.3 (t, C-1), 27.0 (q, CMe_3 and 2′-Me), 30.5 (t, C-2), 34.7 (t, C-4), 70.2 (d, C-6), 71.3 (d, C-3), 73.9 (t, C-5′), 77.2 (s, C-4′), 80.9 (s, C-5), 109.0 (s, C-2′), 127.6 (d, C-2″), 129.8 (d, C-4″), 133.9 (s, C-1″) and 135.7 (d, C-3″); *m/z* 435 (M − Me, 2%), 335 ($C_{22}H_{27}OSi$, 73), 239 ($C_{16}H_{19}Si$, 5), 221 (56), 199 ($C_{12}H_{11}OSi$, 100), 139 (11), 135 (19) and 119 (19).

5-tert-*Butyldiphenylsilyloxy*-2-*methyloct*-7-*yne*-1,2-*diol* **16**.—A solution of the acetonide **15** (650 mg, 1.44 mmol) in methanol

(30 cm^3) was stirred with Amberlite IR 120 resin for 36 h. Subsequent filtration and evaporation of the solvent at reduced pressure afforded a yellow oil that was purified by flash chromatography, using hexane–ethyl acetate (1:1) as eluent to give the *diol* **16** (450 mg, 76%) as a colourless oil (Found: C, 72.8; H, 8.45. $C_{25}H_{34}O_3Si$ requires C, 73.1; H, 8.45%); ν_{max}(film)/cm^{-1} 3590–3210 (br s, OH), 3309 (m, ≡CH), 2935 (s, CH) and 2115 (w, C≡C); δ_H(270 MHz; $CDCl_3$) 1.07 (9 H, s, Bu^t), 1.08 (3 H, s, Me), 1.46–1.72 (4 H, m, 2 × CH_2), 1.94 (1 H, m, ≡CH), 2.34 (2 H, dd, $J_{6,8}$ 2.2 and $J_{6,5}$ 5.1, CH_2C≡), 3.33–3.37 (2 H, m, CH_2O), 3.87–3.94 (1 H, m, CHO), 7.26–7.44 (6 H, m, ArH) and 7.66–7.70 (4 H, m, ArH); δ_C(67.8 MHz; $CDCl_3$) 19.3 (s, CMe_3), 22.9 (q, 2-Me), 26.2 (t, C-3), 27.0 (q, CMe_3), 29.6 (t, C-4), 33.1 (t, C-6), 69.6 (t, C-1), 70.3 (d, C-8), 71.3 (d, C-5), 72.6 (s, C-2), 81.0 (s, C-7), 127.6 (d, C-2′), 129.8 (d, C-4′), 133.8 (s, C-1′) and 135.9 (d, C-3′); *m/z* 353 (M − Bu^t, 1%), 335 (M − Bu^t − H_2O, 19), 222 ($C_{16}H_{14}OSi$, 6), 199 ($C_{12}H_{11}OSi$), 139 (18), 135 (19), 123 (10), 105 (22) and 77 (C_6H_5, 10).

5-tert-*Butyldiphenylsilyloxy*-2-*hydroxy*-2-*methyloct*-7-*yn*-1-*yl Toluene*-p-*sulphonate* **17**.—A solution of the diol **16** (533 mg, 1.3 mmol) and toluene-*p*-sulphonyl chloride (323 mg, 1.7 mmol) in dry pyridine (6 cm^3) was stirred at room temperature for 22 h under nitrogen. The solution was then diluted with ethyl acetate (100 cm^3) and the organic phase washed with 5% hydrochloric acid (2 × 15 cm^3), water (20 cm^3) and brine (30 cm^3), dried ($MgSO_4$) and evaporated at reduced pressure. Purification of the residue by flash chromatography, using hexane–ethyl acetate (4:1) as eluent, afforded the *tosylate* **17** (640 mg, 84%) as a colourless oil (Found: C, 67.95; H, 7.3; S, 5.7%. $C_{32}H_{40}O_5Si$ requires C, 68.05; H, 7.1; S, 5.7%); ν_{max}(film)/cm^{-1} 3605–3280 (br s, OH), 3285 (m, ≡CH), 2960, 2921, 2848 (s, CH), 2124 (w, C≡C) and 1367, 1178 (s, SO_2O); δ_H(270 MHz; $CDCl_3$) 1.05 (9 H, s, Bu^t), 1.07 (3 H, s, 2-Me), 1.43–1.61 (4 H, m, 2 × CH_2), 1.92 (1 H, t, *J* 2.6, ≡CH), 2.27 (2 H, dd, $J_{6,8}$ 2.6 and $J_{6,5}$ 5.9, CH_2C≡), 2.44 (3 H, s, ArMe), 3.75–3.77 (2 H, m, CH_2O), 3.77–3.86 (1 H, m, CHO), 7.32–7.46 (8 H, m, ArH), 7.75–7.77 (4 H, m, ArH) and 7.79 (2 H, d, *J* 8.5, Ar-H); δ_C(67.8 MHz; $CDCl_3$) 19.3 (s, CMe_3), 21.7 (q, 4′-Me), 23.1 (q, 2-Me), 26.2 (t, C-3), 27.0 (q, CMe_3), 29.2 (t, C-4), 33.0 (t, C-6), 70.4 (d, C-8), 71.1 (d, C-5), 76.2 (t, C-1), 80.8 (s, C-7), 127.6 (d, C-2″), 128.0 (d, C-2′), 129.8 (d, C-4″), 129.9 (d, C-3′), 132.7 (s, C-4′), 133.8 (s, C-1″), 135.9 (d, C-3″) and 145.0 (s, C-1′); *m/z* 489 (M − Bu^t − H_2O, 2%) and 335 (M − Bu^t − TsOH, 34).

2,5-*Dihydroxy*-2-*methyloct*-7-*yn*-1-*yl Toluene*-p-*sulphonate* **18**.—To a solution of the silyl ether **17** (4 g, 7.1 mmol) in acetonitrile (80 cm^3) was added 2% aqueous hydrofluoric acid (5 cm^3) and the mixture stirred for 24 h at room temperature. The solvent was then evaporated at reduced pressure and the residue purified by flash chromatography, using hexane–ethyl acetate (1:1) as eluent, to afford the *diol* **18** (2.19 g, 95%) as a colourless oil; ν_{max}(film)/cm^{-1} 3678–3290 (br s, OH), 3305 (s, ≡CH), 2983, 2961, 2920 (s, CH), 2120 (w, C≡C) and 1355, 1173 (SO_2O); δ_H(270 MHz; $CDCl_3$) 1.14 (3 H, s, 2-Me), 1.45–1.76 (4 H, m, 2 × CH_2), 2.04 (1 H, t, *J* 2.7, ≡CH), 2.31–2.39 (3 H, m, CH_2C≡ and OH), 2.43 (3 H, s, ArMe), 3.71–3.82 (4 H, m, CH_2O, CHO and OH), 7.33 (2 H, d, *J* 8.4, ArH) and 7.77 (2 H, d, *J* 8.4, Ar-H); δ_C(67.8 MHz; $CDCl_3$) 21.6 (q, 4′-Me), 23.2, 23.8 (q, 2-Me), 27.2 (t, C-3), 29.5 (t, C-4), 34.1, 34.2 (t, C-6), 70.0, 70.1 (d, C-5 and C-8), 70.9 (s, C-2), 75.6, 76.2 (t, C-1), 80.6 (s, C-7), 127.9 (d, C-2′), 129.9 (d, C-3′), 132.4 (s, C-4′) and 145.1 (s, C-1′); *m/z* (CI, NH_3) 327 (M^+ + H, 100%), 309 (M − H_2O + H, 41), 269 ($C_{13}H_{17}O_4S$, 43), 155 (M − OTs, 40) and 137 (M − OTs − H_2O, 95). Conversion into the monoacetate derivative afforded an analytical sample (Found: C, 58.5; H, 6.5; S, 8.85. $C_{18}H_{24}O_6S$ requires C, 58.68; H, 6.57; S, 8.70%).

2-*Methyl*-2,5-*bis*(*trimethylsilyloxy*)*oct*-7-*yn*-1-*yl Toluene*-p-*sulphonate* **6**.—A solution of the diol **18** (150 mg, 2.4 mmol) and 1-(trimethylsilyl)imidazole (258 mg, 9.6 mmol) in dry dichloromethane (15 cm^3) was stirred for 7 h under nitrogen. The solvent was then evaporated at reduced pressure and the residue purified by rapid column chromatography on Florisil, using hexane–ethyl acetate (9:1) as eluent, to afford the *silyl ether* **6** (205 mg, 95%) as a colourless oil; ν_{max}(film)/cm^{-1} 3305 (s, ≡CH), 2985, 2950, 2920 (s, CH), 2120 (w, C≡) and 1355, 1173 (s, SO_2O); δ_H(270 MHz; $CDCl_3$) 0.14 (18 H, s, 2 × $SiMe_3$), 1.17 (3 H, s, 2-Me), 1.45–1.76 (4 H, m, 2 × CH_2), 2.01 (1 H, t, *J* 2.8, ≡CH), 2.44–2.47 (2 H, m, CH_2C≡C), 2.46 (3 H, s, ArMe), 3.83 (2 H, s, CH_2O), 4.87–4.90 (1 H, m, CHO), 7.37 (2 H, d, *J* 8.4, Ar-H) and 7.80 (2 H, d, *J* 8.4, Ar-H).

2,5-*Dihydroxy*-2-*methyl*-8-(*tetrahydro*-2-*methoxypyran*-2-*yl*)*oct*-7-*yn*-1-*yl Toluene*-p-*sulphonate* **7**.—To a solution of the acetylene **6** (450 mg, 0.96 mmol) in dry THF (20 cm^3), cooled to −78 °C under nitrogen, was added butyllithium (1.6 mol dm^{-3} solution in hexane; 0.72 ml, 1.15 mmol). After 0.5 h, a solution of δ-valerolactone (120 mg, 1.2 mmol) in dry THF (1 cm^3) was added and the reaction mixture stirred at this temperature for 0.5 h. Upon addition of 10% water in THF (1 cm^3), the mixture was warmed to room temperature and the solution dried (K_2CO_3) and evaporated at reduced pressure. The residue was purified by rapid column chromatography on Florisil, using hexane–ethyl acetate (1:1) as eluent. The lactol thus obtained was dissolved in methanol (80 cm^3) and the solution stirred overnight with Amberlite IR120 resin. The solution was filtered, triethylamine (0.1 cm^3) added to the filtrate and the latter evaporated at reduced pressure. The residue was purified by flash chromatography, using hexane–ethyl acetate (1:1) as eluent, to afford the *methoxyacetal* **7** (320 mg, 76%) as an unstable colourless oil; ν_{max}/cm^{-1} 3690–3285 (brs, OH), 2983, 2961, 2920 (s, CH), 2120 (w, C≡C) and 1355, 1173 (s, SO_2O); δ_H(270 MHz; $CDCl_3$) 1.15 (3 H, s, 2-Me), 1.46–1.86 (10 H, m, 5 × CH_2). 2.35–2.45 (3 H, s, CH_2C≡C and OH), 2.45 (3 H, s, ArMe), 3.37 (3 H, s, OMe), 3.35–3.83 (6 H, m, CHO, 2 × CH_2O and OH), 7.36 (2 H, d, *J* 8.4, Ar-H) and 7.79 (2 H, d, *J* 8.4, ArH); δ_C(67.8 MHz; $CDCl_3$), 19.0, 24.6 (t, C-4′ and C-5′), 21.7 (q, 4″-Me), 23.4, 24.0 (q, 2-Me), 27.5 (t, C-3), 29.7 (t, C-4), 34.2 (t, C-6), 36.6 (t, C-3′), 50.5 (q, OMe), 62.1 (t, C-6′), 70.0 (d, CHO), 70.8 (s, C-2), 75.7, 76.4 (t, C-1), 80.4 (s, C-7), 81.7 (s, C-8), 94.9 (s, C-2′), 128.0 (d, C-2″), 130.0 (d, C-3″), 132.6 (s, C-4″) and 145.0 (s, C-1″); *m/z* 269 (M − OTs, 12%), 236 (M − OTs − OMe, 12), 205 (M − OTs − OMe − H_2O, 56), 172 (TsOH, 79) and 115 ($C_6H_{11}O_2$, 100).

4-(1,7-*Dioxaspiro*[5.5]*undec*-4-*en*-2-*yl*)-2-*hydroxy*-2-*methylbutyl Toluene*-p-*sulphonate* **8**.—A solution of the acetylene **7** (300 mg, 0.68 mmol) in hexane–ethyl acetate (1:1) (150 cm^3) was stirred with Lindlar catalyst (*ca.* 5 mg) under a hydrogen atmosphere. After 1.5 h the solution was filtered and evaporated at reduced pressure, and the residue dissolved in dichloromethane (10 cm^3) and treated with a trace of pyridinium toluene-*p*-sulphonate. After being stirred for 0.25 h at room temperature the mixture was evaporated and the residue purified by flash chromatography using hexane–ethyl acetate (4:1) as eluent to afford *spiroacetal* **8** (272 mg, 91%) as a 1:1 mixture of diastereoisomers in the form of a colourless oil (Found: C, 61.3; H, 7.3; S, 7.75%; M^+, 410.1761. $C_{21}H_{30}O_6S$ requires C, 61.44; H, 7.37; S, 7.81%; M^+, 410.1763); δ_H(270 MHz; $CDCl_3$) 1.17, 1.18 (3 H, s, 2-Me), 1.52–1.94 (12 H, m, 6 × CH_2), 2.45 (3 H, s, ArMe), 2.66 (0.5 H, s, OH), 2.86 (0.5 H, s, OH), 3.60–3.92 (5 H, m, 2 × CH_2O and CHO), 5.60 (1 H, d, *J* 9.9, HC=C), 5.87 (1 H, ddd, $J_{4',5'}$ 9.9 $J_{4',3'}$ 3.6 and $J_{4',3'}$ 3.6, C=C*H*CH_2), 7.36 (2 H, d, *J* 8.4, ArH) and 7.81 (2 H, d, *J* 8.4, ArH); δ_C(67.8 MHz; $CDCl_3$) 18.5, 24.9 (t, C-9′ and C-10′), 21.7

(q, 4″-Me), 23.7, 23.8 (q, 2-Me), 28.9, 29.0, 30.5, 34.2, 34.4, 34.8 (t, C-3, C-4, C-3′ and C-11′), 61.1 (t, C-8′), 67.2 (d, C-2′), 70.8, 70.9 (s, C-2), 76.0 (t, C-1), 94.0, 94.1 (s, C-6′); *m/z* 410 (M^+, 5%), 392 (M − H_2O, 9), 269 ($C_{13}H_{17}O_4S$, 24), 238 (M − TsOH, 8) and 124 ($C_8H_{12}O$, 100).

2-(3,4-*Epoxy*-3-*methylbutyl*)-1,7-*dioxaspiro*[5.5]*undec*-4-*ene* **9**.—To a solution of the tosylate **8** (100 mg, 0.24 mmol) in dry THF (25 cm^3) under nitrogen was added sodium hydride (40% dispersion in mineral oil; 15 mg, 0.25 mmol). After being stirred at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous sodium dihyrogen phosphate (1 cm^3) and extracted with diethyl ether (3 × 25 cm^3). The ethereal extract was washed with brine (10 cm^3), dried (K_2CO_3), and evaporated at reduced pressure to afford a colourless oil (46 mg). This was purified by flash chromatography using hexane–ethyl acetate (9:1) as eluent to give the *epoxide* **9** (54 mg, 94%) as a colourless oil, b.p. (Kugelrohr) 90 °C/17 mmHg (Found: C, 70.2; H, 9.2%; M^+, 238.1536. $C_{14}H_{22}O_3$ requires C, 70.5; H, 9.3%; *M*, 238.1568); ν_{max}(thin film)/cm^{-1} 3040 (=CH), 1660 (C=C), 1270 (CO epoxide), 1010 (CO) 900 and 820 (CO epoxide); δ_H(360 MHz; $CDCl_3$) 1.35 (3 H, s, 3′-Me), 1.48–2.24 (12 H, brm, 6 × CH_2), 2.57–2.78 (2 H, m, CH_2 epoxide), 3.56–3.93 (3 H, m, OCH_2 and CHO), 5.57–5.66 (1 H, m, HC=C) and 5.82–5.95 (1 H, m, C=C*H*CH_2); δ_C(90.6 MHz; $CDCl_3$) 18.6 (t, C-10), 21.1 (q, 3′-Me), 25.2 (t, C-9), 30.8, 31.3, 33.1, 35.1 (t, C-1′, C-2′, C-3 or C-11), 53.6 (t, C-4′), 54.0 (s, C-3′), 60.9 (t, C-8), 66.9 (d, C-2), 93.9 (s, C-6), 127.4 (d, C-5) and 130.7 (d, C-4); *m/z* 238 (M^+, 4%), 124 ($C_8H_{12}O$, 100), 114 ($C_6H_{10}O_2$, 35), 95 (91), 69 (59), 68 (61), 55 (93), 43 (76) and 41 (97).

4-(1,7-*Dioxaspiro*[5.5]*undec*-4-*en*-2-*yl*)-1-*iodo*-2-*methylbutan*-2-*ol* **10**.—To a solution of the epoxide **9** (100 mg, 0.42 mmol) in dry THF (25 cm^3), cooled to −50 °C, was added a solution of anhydrous lithium iodide (72 mg, 0.54 mmol) in dry THF (1.5 cm^3) and boron trifluoride–diethyl ether (0.1 cm^3). After being stirred at this temperature for 5 h the reaction mixture was quenched with saturated aqueous ammonium chloride (1.5 cm^3), and diluted with ether (80 cm^3). The ethereal extract was washed with water (15 cm^3) and brine (15 cm^3), dried ($MgSO_4$) and evaporated at reduced pressure to afford a yellow oil. This was purified by flash chromatography, using hexane–ethyl acetate (1:1) as eluent to give *iodohydrin* **10** (155 mg, 96%) as an inseparable 1:1 mixture of diastereoisomers in the form of a colourless oil (Found: C, 45.9; H, 6.15; I, 34.5%; M^+, 366.0673. $C_{14}H_{23}IO_3$ requires C, 45.91; H, 6.33; I, 34.65; *M*, 366.0692); ν_{max}(film)/cm^{-1} 3600–3315 (brs, OH), 3030 (w, =CH), 2943, 2880, 2830 (s, CH) and 1655 (w, C=C); δ_H(270 MHz; $CDCl_3$) 1.38, 1.39 (3 H, s, Me), 1.54–2.17 (12 H, m, 6 × CH_2), 2.40 (0.5 H, s, OH), 2.53 (0.5 H, s, OH), 3.38, 3.39 (2 H, s, CH_2I), 3.61–3.66 (1 H, m, CHO), 3.80–3.94 (2 H, m, CH_2O), 5.61 (1 H, ddd, $J_{5',4'}$ 9.9 $J_{5',3'}$ 2 and $J_{5',3'}$ 2, =CH) and 5.90 (1 H, ddd, $J_{4',5'}$ 9.9, $J_{4',3'}$ 3.6 and $J_{4',3'}$ 3.6, =C*H*CH_2); δ_C(67.8 MHz; $CDCl_3$) 18.5 (t, C-9′ or C-10′), 22.4, 22.5 (t, C-1), 25.0 (t, C-9′ or C-10′), 25.9 (q, 2-Me), 30.0, 30.5, 34.9, 36.6 (t, C-3, C-3′, C-4 and C-11′), 34.9 (t, C-11′), 36.6 (t, C-1), 61.1 (t, C-8′), 67.1 (d, C-2′), 70.3, 70.4 (s, C-2), 94.0 (s, C-6′), 127.4 (d, C-5′) and 130.3 (d, C-4′); *m/z* 366 (M^+, 4%), 349 (M − OH, 4%), 239 (M − I, 17), 225 (M − CH_2I, 33), 221 (M − I − H_2O, 33), 183 (C_4H_8I, 78) and 124 ($C_8H_{12}O$, 100).

2-*Iodomethyl*-2-*methyl*-1,6,8-*trioxadispiro*[4.1.5.3]*pentadec*-13-*ene* **24**.—A solution of the iodohydrin **10** (450 mg, 1.23 mmol), ground iodine (630 mg, 2.5 mmol) and (diacetoxyiodo)-benzene (780 g, 2.45 mmol) in cyclohexane (230 cm^3) was purged with nitrogen and irradiated with two 250 W tungsten filament lamps. After 18 h, during which time the temperature was kept below 15 °C, the mixture was diluted with ether (150 cm^3). The ethereal extract was washed with 10% aqueous sodium thiosulphate (30 cm^3), water (30 cm^3) and brine (50 cm^3), dried ($MgSO_4$), and evaporated at reduced pressure. The resultant residue was purified by flash chromatography to afford the following.

(a) A 1:1 mixture of the trans *iodide* **24a*** and **24b** (261 mg, 57%) as a colourless oil (Found: M^+, 364.0533. $C_{14}H_{21}IO_3$ requires *M*, 364.0533); ν_{max}(film)/cm^{-1} 3035 (w, =CH), 2945, 2885, 2840 (s, CH) and 1655 (w, C=C); δ_H(270 MHz; $CDCl_3$) 1.44 (3 H, s, Me), 1.67 (3 H, s, Me*), 1.49–1.64 (10 H, m, 10_{ax}-H, 10_{ax}-H*, 10_{eq}-H, 10_{eq}-H*, 11_{eq}-H, 11_{eq}-H*, 12_{ax}-H, 12_{ax}-H*, 12_{eq}-H and 12_{eq}-H*), 172–1.94 (6 H, m, 3-H′, 3-H′*, 4-H′, 4-H′*, 11_{ax}-H and 11_{ax}-H*), 2.11–2.20 (3 H, m, 3-H, 15-H′ and 15-H′*), 2.33 (1 H, m, 3-H*), 2.42–2.56 (2 H, m, 15-H and 15-H*), 2.66–2.75 (2 H, m, 4-H and 4-H*), 3.27 (1 H, d, *J* 10.1, C$H_A$$H_B$I*), 3.30 (1 H, d, *J* 10.1, C$H_A$$H_B$I*), 3.45 (1 H, d, *J* 9.5, C$H_A$$H_B$I), 3.55 (1 H, d, *J* 9.5, C$H_A$$H_B$I), 3.66–3.72 (2 H, m, 9_{eq}-H and 9_{eq}-H*), 3.96–4.06 (2 H, m, 9_{ax}-H and 9_{ax}-H*), 5.58–5.63 (2 H, m, 13-H and 13-H*) and 5.82–5.89 (2 H, m, 14-H and 14-H*); *m/z* 364 (M^+, 72%), 237 (M − I, 46), 223 (M − CH_2I, 16), 124 ($C_8H_{12}O$, 100) and 113 ($C_6H_9O_2$, 21).

(b) A 1:1 mixture of the cis *iodides* **24c** and **24d*** (84 mg, 19%) as a colourless oil (Found: M^+, 364.0535. $C_{14}H_{21}IO_3$ requires *M*, 364.0533); ν_{max}(film)/cm^{-1} 3035 (w, =CH), 2945, 2885, 2840 (s, CH) and 1655 (w, C=C); δ_H(270 MHz; $CDCl_3$) 1.39 (3 H, s, Me), 1.63 (3 H, s, Me*), 1.52–2.42 (24 H, m, 3-H, 3-H*, 3-H′, 3-H′*, 4-H, 4-H*, 4-H′, 4-H′*, 10_{ax}-H, 10_{ax}-H*, 10_{eq}-H, 10_{eq}-H*, 11_{ax}-H, 11_{ax}-H*, 11_{eq}-H, 11_{eq}-H*, 12_{ax}-H, 12_{ax}-H*, 12_{eq}-H and 12_{eq}-H*, 15-H, 15-H*, 15-H′ and 15-H′*), 3.19 (1 H, d, *J* 10.1, C$H_A$$H_B$I*), 3.21 (1 H, d, *J* 10.1, C$H_A$$H_B$I*), 3.36 (1 H, d, *J* 9.5, C$H_A$$H_B$I), 3.46 (1 H, d, *J* 9.5, C$H_A$$H_B$I), 3.62–3.70 (2 H, m, 9_{eq}-H and 9_{eq}-H*), 3.92–4.07 (2 H, m, 9_{ax}-H and 9_{ax}-H*), 5.71–5.78 (2 H, m, 13-H and 13-H*) and 5.86–5.94 (2 H, m, 14-H and 14-H*); *m/z* 364 (M^+, 72%), 237 (M − I, 52), 223 (M − CH_2I, 18), 124 ($C_8H_{12}O$, 100) and 113 ($C_6H_9O_2$, 18).

trans-2-*Hydroxymethyl*-2-*methyl*-1,6,8-*trioxadispiro*[4.1.5.3]-*pentadec*-13-*ene* **25a**, **25b**.—A solution of the *trans* iodides **24a,b** (70 mg, 0.2 mmol) in dry THF (7 cm^3) was added to a solution of potassium superoxide (55 mg, 0.8 mmol) and 18-crown-6 (203 mg, 0.8 mmol) in dry DMSO (5 cm^3) under argon. The mixture was stirred for 18 h after which saturated brine (2 cm^3) was added and the THF evaporated. The residue was extracted with ether (2 × 30 cm^3) and the ethereal extract was washed with brine (20 cm^3), dried (K_2CO_3), and evaporated at reduced pressure. The residual colourless oil was purified by flash chromatography using hexane–ethyl acetate (1:1) as eluent to afford the following.

(a) The trans *alcohol* **25b** (19 mg, 40%) as a colourless oil (Found: M^+, 254.1534. $C_{14}H_{22}O_4$ requires *M*, 254.1518); ν_{max}(film)/cm^{-1} 3600–3115 (brs, OH), 3042 (w, =CH) and 1643 (w, C=C); δ_H(270 MHz; $CDCl_3$) 1.20 (3 H, s, Me), 1.53–1.80 (8 H, m, 3′-H′, 4′-H′, $10'_{ax}$-H, $10'_{eq}$-H, $11'_{ax}$-H, $11'_{eq}$-H, $12'_{ax}$-H and $12'_{eq}$-H), 2.13 (1 H, ddd, $J_{15,15}$ 17.2, $J_{15,14}$ 6.2 and $J_{15,13}$ 1, 15′-H′), 2.52–2.61 (2 H, m, 3′-H and 15′-H), 2.79 (1 H, dd, $J_{4,4}$ 12.1 and $J_{4,3}$ 7.7, 4′-H), 3.40 (1 H, t, *J* 10.6, C$H_A$$H_B$OH), 3.56 (1 H, d, *J* 10.6, OH), 3.64 (1 H, d, *J* 10.6, C$H_A$$H_B$OH), 3.63–3.70 (1 H, m, $9'_{eq}$-H), 4.06 (1 H, ddd, $J_{9ax,9eq}$ 11.9 $J_{9ax,10ax}$ 9.2 and $J_{9ax,10eq}$ 6.1, $9'_{ax}$-H), 5.57 (1 H, ddd, $J_{13,14}$ 10.1, $J_{13,15}$ 3.1 and $J_{13,15}$ 1, 13′-H) and 5.85 (1 H, ddd, $J_{14,13}$ 10.1, $J_{14,15}$ 6.2 and $J_{14,15}$ 2.2, 14′-H); δ_C(67.8 MHz; $CDCl_3$) 24.2 (q, Me), 18.6, 24.9, 30.3, 34.3, 35.9, 36.2 (t, C-3′, C-4′, C-10′, C-11′, C-12′ and C-15′), 61.8 (t, C-9′), 67.7 (t, C-1), 86.3 (s, C-2′), 97.1 (s, C-7′), 106.4 (s, C-5′), 124.9 (d, C-13′) and 129.8 (d, C-14′); *m/z* 254 (M^+, 26%), 237 (M − OH, 10), 223 (M − CH_2OH, 96), 124 ($C_8H_{12}O$, 55) and 99 ($C_5H_7O_2$, 100).

(b) The trans *alcohol* **25a** (20 mg, 41%) as a colourless oil (Found: M^+, 254.1537. $C_{14}H_{22}O_4$ requires *M*, 254.1518);

ν_{max}(film)/cm^{-1} 3600–3120 (brs, OH), 3045 (w, =CH) and 1641 (w, C=C); δ_H(270 MHz; $CDCl_3$) 1.47 (3 H, s, Me), 1.53–2.05 (9 H, m, 3′-H, 3′-H′, 4′-H, 10′$_{ax}$-H, 10′$_{eq}$-H, 11′$_{ax}$-H, 11′$_{eq}$-H, 12′$_{ax}$-H, 12′$_{eq}$-H and OH), 2.15 (1 H, ddd, $J_{15,15}$ 17.0, $J_{15,14}$ 5.7 and $J_{15,13}$ 1.3, 15′-H′), 2.48 (1 H, ddd, $J_{15,15}$ 17.0, $J_{15,14}$ 2.8 and $J_{15,13}$ 2.8, 15′-H), 2.70 (1 H, ddd, $J_{4,4}$ 12.6, $J_{4,3}$ 6.3 and $J_{4,3}$ 4.7, 4′-H), 3.39 (1 H, dd, $J_{HA,HB}$ 11.4 and $J_{HA,OH}$ 6.0, CH_AH$_B$OH), 3.47 (1 H, dd, $J_{HA,HB}$ 11.4 and $J_{HB,OH}$ 6.0, CH$_A$$H_B$OH), 3.65–3.71 (1 H, m, 9′$_{eq}$-H), 4.01 (1 H, ddd, $J_{9ax,9eq}$ 11.1, $J_{9ax,10ax}$ 3.8 and $J_{9ax,10eq}$ 3.8, 9′$_{ax}$-H), 5.60 (1 H, ddd, $J_{13,14}$ 10.1, $J_{13,15}$ 2.8 and $J_{13,15}$ 1.3, 13′-H) and 5.84 (1 H, ddd, $J_{14,13}$ 10.1, $J_{14,15}$ 5.7 and $J_{14,15}$ 2.8, 14′-H); δ_C(67.8 MHz; $CDCl_3$) 25.2 (q, Me), 18.8, 25.2, 33.2, 34.3, 36.3, 36.9 (t, C-3′, C-4′, C-10′, C-11′, C-12′ and C-15′), 61.8 (t, C-9′), 69.3 (t, C-1), 85.1 (s, C-2′), 96.4 (s, C-7′), 107.4 (s, C-5′), 124.8 (d, C-13′) and 129.9 (d, C-14′); *m/z* 254 (M^+, 25), 237 (M − OH, 7), 223 (M − CH_2OH, 100), 124 ($C_8H_{12}O$, 51) and 99 ($C_5H_7O_2$), 100).

cis-2-*Hydroxymethyl*-2-*methyl*-1,6,8-*trioxadispiro*[4.1.5.3]-*pentadec*-13-*ene* **25c**, **25d**.—Using a modification of the procedure described above for the preparation of the *trans* alcohols **25a**, **25b**, in which the THF was omitted, the *cis* alcohols **25c**, **25d** were prepared from the *cis* iodides **24c**, **24d** (70 mg, 2 mmol) to give the following.

(a) cis *alcohol* **25c** (19 mg, 40%) as a colourless oil (Found: M^+, 254.1534. $C_{14}H_{22}O_4$ requires *M*, 254.1518); ν_{max}(film)/cm^{-1} 3600–3115 (brs, OH), 3042 (w, =CH) and 1643 (w, C=C); δ_H(270 MHz; $CDCl_3$) 1.11 (3 H, s, Me), 1.46–2.25 (11 H, m, 3′-H, 3′-H′, 4′-H, 4′-H′, 10′$_{ax}$-H, 10′$_{eq}$-H, 11′$_{ax}$-H, 11′$_{eq}$-H, 12′$_{ax}$-H, 12′$_{eq}$-H and 15′-H), 2.47 (1 H, ddd, $J_{15,15}$ 17.0, $J_{15,14}$ 2.6 and $J_{15,13}$ 2.6, 15′-H′), 3.37 (1 H, dd, $J_{HA,HB}$ 10.8 and $J_{HA,OH}$ 10.8, CH_AH$_B$OH), 3.61 (1 H, d, *J* 10.8, CH$_A$$H_B$OH), 3.66–3.75 (1 H, m, 9′$_{eq}$-H), 3.89–4.05 (1 H, m, 9′$_{ax}$-H), 4.26 (1 H, br d, *J* 10.8, OH), 5.97 (1 H, ddd, $J_{13,14}$ 10.3, $J_{13,15}$ 5.9 and $J_{13,15}$ 2.4, 13′-H) and 6.17 (1 H, ddd, $J_{14,13}$ 10.3, $J_{14,15}$ 2.8 and $J_{14,15}$ 1.1, 14′-H); *m/z* 254 (M^+, 26%), 237 (M − OH, 10), 223 (M − CH_2OH, 96), 124 ($C_8H_{12}O$, 55) and 99 ($C_5H_7O_2$, 100).

(b) The cis *alcohol* **25d** (20 mg, 41%) as colourless prisms, m.p. 80–81 °C (Found: C, 65.6; H, 8.7%; M^+, 254.1530. $C_{14}H_{22}O_4$ requires C, 66.1; H, 8.7%; *M*, 254.1518); ν_{max}(film)/cm^{-1} 3600–3120 (brs, OH), 3045 (w, =CH) and 1640 (w, C=C); δ_H(270 MHz; $CDCl_3$) 1.37 (3 H, s, Me), 1.53–2.18 (9 H, m, 3′-H, 3′-H′, 4′-H, 10′$_{ax}$-H, 10′$_{eq}$-H, 11′$_{ax}$-H, 11′$_{eq}$-H, 12′$_{ax}$-H and 12′$_{eq}$-H), 2.16–2.27 (2 H, m, 4′-H′ and 15′-H), 2.38 (1 H, ddd, $J_{15,15}$ 17.0, $J_{15,14}$ 2.5 and $J_{15,13}$ 2.5, 15′-H′), 2.99 (1 H, s, OH), 3.35 (1 H, d, *J* 11.3, CH_AH$_B$OH), 3.42 (1 H, d, *J* 11.3, CH$_A$$H_B$OH), 3.61–3.68 (1 H, m, 9′$_{eq}$-H), 4.06 (1 H, ddd, $J_{9ax,9eq}$ 11.4, $J_{9ax,10ax}$ 2.9 and $J_{9ax,10eq}$ 2.9, 9′$_{ax}$-H), 5.74 (1 H, ddd, $J_{13,14}$ 10.3, $J_{13,15}$ 2.5 and $J_{13,15}$ 0.9, 13′-H) and 5.89 (1 H, ddd, $J_{14,13}$ 10.3, $J_{14,15}$ 5.7 and $J_{14,15}$ 2.5, 14′-H); δ_C(67.8 MHz; $CDCl_3$) 24.0 (q, Me), 18.7 25.1, 32.6, 34.6, 36.4, 39.3 (t, C-3′, C-4′, C-10′, C-11′, C-12′ and C-15′), 61.5 (t, C-9′), 68.6 (t, C-1), 85.1 (s, C-2′), 93.8 (s, C-7′), 105.0 (s, C-5′), 123.9 (d, C-13′) and 130.2 (d, C-14′); *m/z* 254 (M^+, 26%), 237 (M − OH, 10), 223 (M − CH_2OH, 96), 124 ($C_8H_{12}O$, 55) and 99 ($C_5H_7O_2$, 100).

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