Synthesis of the bis-spiroacetal moiety of the polyether antibiotic CP44,161

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The syntheses of bis-spiroacetals **25a**, **25c** and **40** which constitute the central framework of the polyether antibiotic CP44,161 **4**, are described. The tricyclic bis-spiroacetal ring is formed by oxidative cyclisation of hydroxyspiroacetal **9** which in turn is assembled from lactone **10** and acetylene **11**. The key stereogenic centres in acetylene **11** were assembled using a Sharpless asymmetric dihydroxylation and an Evans asymmetric alkylation of a chiral oxazolidinone. Asymmetric dihydroxylation of alkene **14** using $(DHQ)_2PHAL$ (hydroquinine phthalazine-1,4-diyl diether) led to acetylene **22** which in turn was converted to bis-spiroacetals **25a** and **25c**. Construction of the isomeric acetylene **11** was effected *via* Sharpless asymmetric dihydroxylation of alkene **14** using the pseudo-enantiomeric chiral ligand $(DHQD)_2PHAL$ which in turn led to the formation of bis-spiroacetal **40** with the same configuration at C-2 as that present in antibiotic CP44,161 **4**. Barbier addition of bromide **8** to bis-spiroacetal aldehyde **27** afforded alcohol **28** which was then converted to polyethers **32** and **33** *via* an epoxidation cyclization strategy. This latter reaction sequence demonstrated the feasibility of appending the E ring to the tricyclic bis-spiroacetal BCD ring system of antibiotic CP44,161 **4**.

The polyether antibiotics salinomycin **1**,[1] narasin A **2**,[2] *epi*-17-deoxy-(*O*-8)-salinomycin **3**,[3] noboritomycin,[4] CP44,161 **4**[5] and X-14766A[6] contain a characteristic tricyclic 1,6,8-trioxa-dispiro[4.1.5.3]pentadec-13-ene bis-spiroacetal ring system in which two acetal carbons are linked in a spiro fashion. These polyether antibiotics that contain a bis-spiroacetal moiety play an important role in the poultry industry as coccidiostats and are used as feed additives to improve feed utilisation in cattle, sheep and goats. Whilst the synthesis of polyether ionophores which contain a simpler bicyclic spiroacetal ring system has received significant attention[7] from the synthetic community, the synthesis of these polyether antibiotics that contain a more complex tricyclic bis-spiroacetal has been less explored.[8]

To date there have been three total syntheses of salinomycin **1** which made use of a stereoselective aldol reaction to construct the C9–C10 bond. In the first synthesis by Kishi *et al.*[9] the bis-spiroacetal moiety was formed by assembly of a highly functionalised dithiane which provided a latent carbonyl group for the C21 spiro centre. Yonemitsu and co-workers[10–13] used a "chiral pool" approach to prepare salinomycin **1** from D-glucose, D-mannitol and (*S*)-lactic acid using a strategy wherein the B and E rings were assembled prior to construction of the bis-spiroacetal system by an acid catalysed cyclisation. In the most recent approach to salinomycin **1** by Kocienski and co-workers[14–16] the bis-spiroacetal core was constructed by an elegant oxidative rearrangement of an acylfuran or by hydrolysis of an allenol ether that was used as an acyl anion equivalent.

Whilst the synthetic approaches to salinomycin **1** by Kishi, Yonemitsu and Kocienski, have focused on late assembly of the C ring after appending the D,E rings to the B ring, our synthetic efforts have focused on the construction of a tricyclic bis-spiroacetal core containing the B,C,D rings with the idea of appending the A and E rings at a later stage in the synthesis.[17–19]

Towards this end we reported[19] our model work wherein we studied the appendage of the E ring to a B,C,D fragment using an iodoetherification–ring expansion strategy. Unfortunately the critical silver-assisted ring expansion of the terminal tetrahydrofuran ring to a tetrahydropyran ring proved to be incompatible with the sensitive bis-spiroacetal ring system. Our recent synthetic endeavours[20] have therefore focused on the synthesis of polyether antibiotic CP44,161 **4** which has a tetrahydrofuran as the terminal E ring thereby avoiding the necessity to effect the problematic ring expansion in the presence of a bis-spiroacetal ring system.

Results and discussion

Antibiotic CP44,161 **4** has not been synthesised to date and the bis-spiroacetal ring system has the same stereochemistry as that present in salinomycin **1**. Aside from the aromatic A ring and the five membered E ring in CP44,161 **4**, the main differences between the bis-spiroacetal moieties of these two molecules is the absence of a hydroxy group in the C ring, the presence of an additional methyl group in the D ring, and an ethyl rather than a methyl group in the D ring of antibiotic CP44,161 **4**.

The four possible stereoisomers of the bis-spiroacetal ring system are illustrated (Fig. 1). Diastereomer **A** depicts the stereochemistry adopted by salinomycin **1** and CP44,161 **4** and has three stabilising anomeric effects but exhibits unfavourable 1,3-dipole–dipole interactions. 21-*epi*-Salinomycin and 21-*epi*-CP44,161‡ **B** have only one anomeric effect and is the thermodynamically least stable diastereomer. The 17-*epi*-diastereomer **C** exhibits three anomeric effects and although it exhibits unfavourable 1,3-diaxial interactions between the C17 oxygen atom and the C21 methylene it lacks the unfavourable 1,3-dipole–dipole interactions exhibited by diastereomer **A** and 17-*epi*-21-*epi*-diastereomer **D**.

This qualitative analysis leads to the assumption that 17-*epi*-diastereomer **C** exhibits the most thermodynamically stable configuration. It transpires that in the cyclic structure that

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‡ Note that the numbering system for the bis-spiroacetal ring system present in salinomycin is also used for antibiotic CP44,161 in order to facilitate comparisons between the two compounds.

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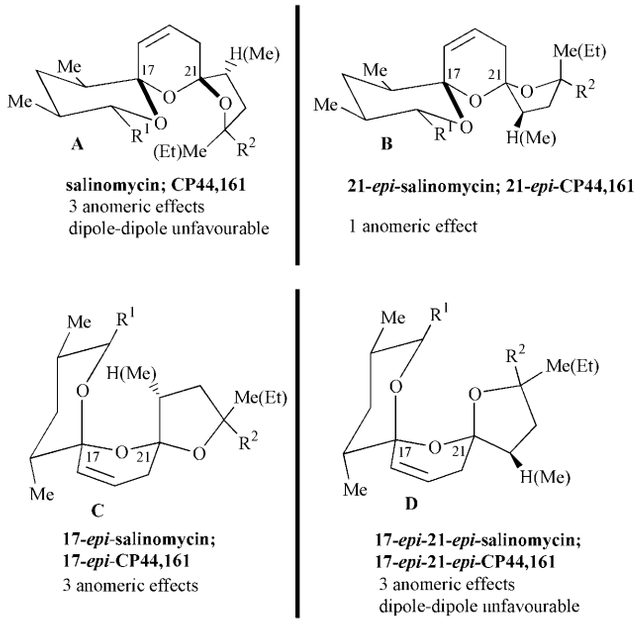


Fig. 1

salinomycin **1** adopts, the repulsive 1,3-dipolar interactions in diastereomer **A** are compensated for by a hydrogen bond between the C9 and C20 hydroxy groups. Bis-spiroacetals whose structures preclude this remote hydrogen bond do not adopt the salinomycin configuration A.

Our synthetic plan (Scheme 1) for the synthesis of CP44,161 **4** is based on the same aldol disconnection initially used by Kishi *et al.*[9] The synthesis of the A ring, namely aldehyde **5**, has already been reported by Kishi *et al.*[21] and Ireland *et al.*[22] in synthetic studies towards lasalocid A. The right hand fragment **6** is formed by addition of the Grignard reagent of bromide **8** to bis-spiroacetal aldehyde **7**. In turn bis-spiroacetal **7** is anticipated to be prepared *via* oxidative cyclisation of bicyclic spiroacetal **9** using methodology previously used in our synthesis of the bis-spiroacetal moiety of *epi*-17-deoxy-(*O*-8)-salinomycin **3**.[17] Further disconnection of bicyclic hydroxyspiroacetal **9** leads to lactone **10** and acetylene **11**.

The synthesis of lactone **10** has already been reported[16,17] hence our initial attention focused on the synthesis of acetylene **11**. The proposed synthesis of acetylene **11** hinged on introduction of the methyl group using an Evans asymmetric alkylation of a chiral oxazolidinone with the oxygen functionality being introduced using Sharpless asymmetric dihydroxylation (Scheme 2). The synthesis of the desired acetylene **11** therefore commenced with the alkylation of propionyloxazolidinone **12** with allyl iodide **13** to form alkene **14** in moderate yield. Based on the Sharpless mnemonic, asymmetric dihydroxylation[23] of the terminal olefin using potassium osmate and $(DHQ)_2PHAL$, was expected to afford diol **16**, however, it actually transpired that lactone **17** produced by cyclisation of the unexpected diol **15**, was in fact formed. Lactone **17** contains the incorrect stereochemistry at C5 to that required for the formation of the desired acetylene **11**. It is unclear why the facial selectivity of dihydroquinine ligands did not follow the Sharpless mnemonic, however, the presence of the chiral oxazolidinone moiety may have been a contributing factor.

The stereochemistry of the lactone **17** isolated from the Sharpless dihydroxylation of alkene **14** using $(DHQ)_2PHAL$ was in fact confirmed by X-ray crystallography in the final stages of our work after lactone **17** had already been converted to acetylene **21** and thence to a bis-spiroacetal. Subsequent re-examination of the Sharpless dihydroxylation of alkene **14** using the complementary $(DHQD)_2PHAL$ (hydroquinidine phthalazine-1,4-diyl diether) ligand (*vide infra*) afforded a mixture of diastereomeric lactones which rendered further synthetic manipulation difficult owing to the production of isomeric product mixtures. It therefore eventuated that we herein report the conversion of lactone **17** to acetylene **21** which demonstrates methodology for the synthesis of close analogues of the bis-spiroacetal moiety of antibiotic CP44,161 **4**. Introduction of the ethyl group with the correct stereochemistry, however, needs further attention.

The synthesis of acetylene **21** from lactone **17** proceeded by reduction with lithium borohydride to afford triol **18** which afforded acetonide **19** after protection of the 1,2-diol. Oxidation of the remaining primary alcohol then afforded aldehyde **20**. Subsequent Grignard addition of prop-2-ynylmagnesium bromide to aldehyde **20** resulted in the formation of alcohol **21** as a 1:1 mixture of diastereomers which were protected as silyl ethers **22** in preparation for their union with lactone **10**.

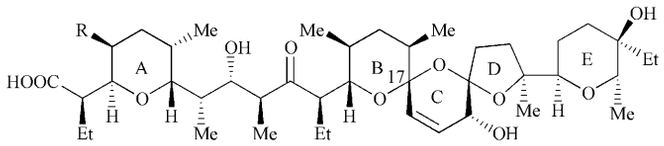
With acetylene **22** and lactone **10** in hand, assembly of the bis-spiroacetal core was effected using methodology previously applied to the synthesis of the bis-spiroacetal moiety of *epi*-17-deoxy-(*O*-8)-salinomycin **3** (Scheme 3). Addition of the lithium acetylide derived from acetylene **22** to lactone **10** followed by treatment of the intermediate lactol with methanol and Amberlite IR 118 resin effected hydrolysis of the acetonide group and formation of more stable methyl acetals as a mixture of diastereomers that were not separated. After protection of the primary hydroxy group as an acetate the resultant acetates **23** were readily purified by flash chromatography. Partial hydrogenation of the alkyne **23** to a *cis*-olefin followed by acid catalysed cyclisation resulted in a 1:1 mixture of spiroacetals **24a** and **24b** (87% yield) that were inseparable by flash chromatography. This initial spirocyclisation is carried out under thermodynamically controlled conditions such that the most stable configuration is afforded at the newly fomed spiro centre owing to maximum stabilisation by the anomeric effect. The two isomers of spiroacetal **24** therefore only differ in the position that the side chain adopts.

Spiroacetals **24a** and **24b** were treated with (diacetoxyiodo)-benzene and iodine to afford a 3.3:1 mixture of tricyclic bis-spiroacetals **25a** and **25c**. The preference for *cis* bis-spiroacetal **25a** in this cyclisation reaction can be attributed to the presence of the additional methyl group in the D ring, which causes unfavourable steric interactions upon formation of the minor *trans* bis-spiroacetal **25b**. *trans* Bis-spiroacetal **25b** therefore undergoes rapid epimerisation at the allylic spirocentre to *cis* bis-spiroacetal **25c**. The presence of the additional methyl group exhibited a marked effect on the stereochemical outcome of the oxidative cyclisation in that the oxidative cyclisation of related spiroacetals which lack this methyl group provided the *trans* isomer as the major product.[17,18]

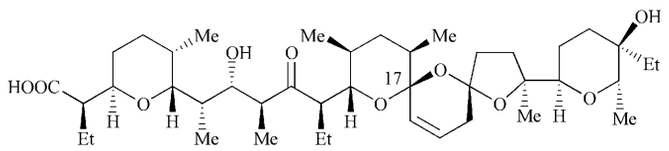
The major bis-spiroacetal **25a** isolated from this oxidative cyclisation has the 17-*epi*-21-*epi*-salinomycin stereochemistry (Fig. 1) whereas the minor *cis* isomer **25c** has the correct bis-spiroacetal stereochemistry for salinomycin **1** and CP44,161 **4**. The proton NMR data support this assignment in that the vinylic protons in bis-spiroacetal **25a** resonate at δ 5.55 (H-13′) and 5.91 (H-14′) respectively, whereas H-14′ in bis-spiroacetal **25c** resonates at δ 5.96 whilst H-13′ resonates further downfield at δ 6.20 with a similar chemical shift to that observed§ for the analogous vinylic proton in antibiotic CP44,161 **4** (H-14′ at δ 5.96 and H-13′ at 6.06).

In previous total syntheses of salinomycin **1** the correct stereochemistry for the bis-spiroacetal ring system was only obtained *via* a thermodynamically controlled cyclisation after the whole carbon skeleton of the natural product had been assembled. Given that it is now well established that long range hydrogen bonding in the final molecule can dramatically alter the position of the bis-spiroacetal equilibrium, it was decided to pursue appendage of the E ring to the major

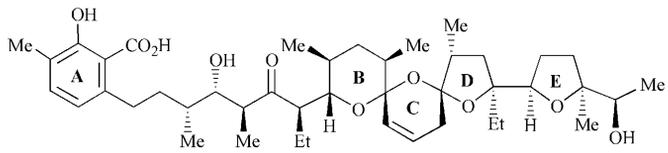
§ We thank Pfizer for a sample of natural CP44,161 **4**.



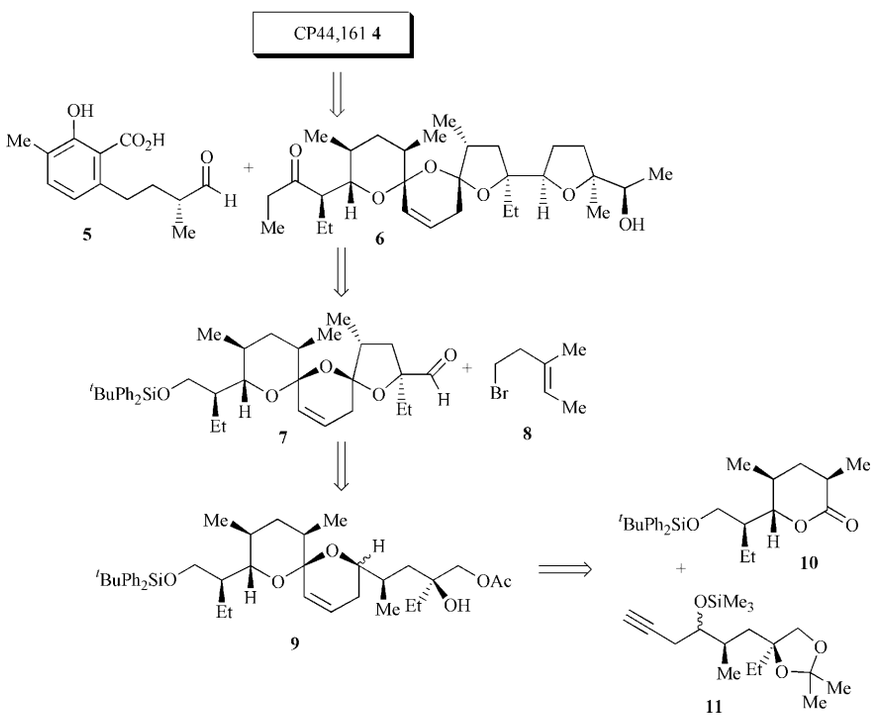
Salinomycin **1** R=H
Narasin A **2** R=Me



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



CP44,161 **4**



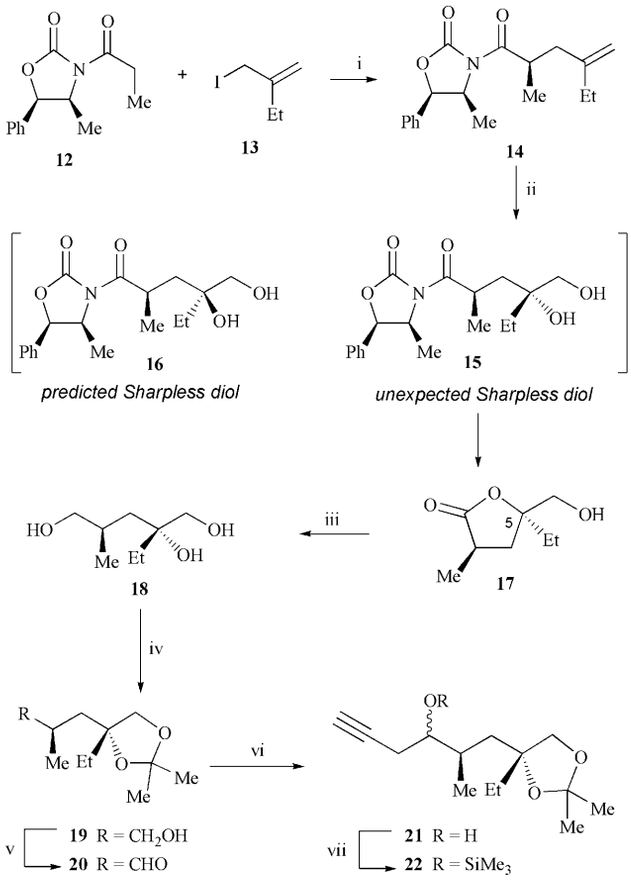
Scheme 1

isomer of the BCD fragment **25a** that we had prepared in the present work.

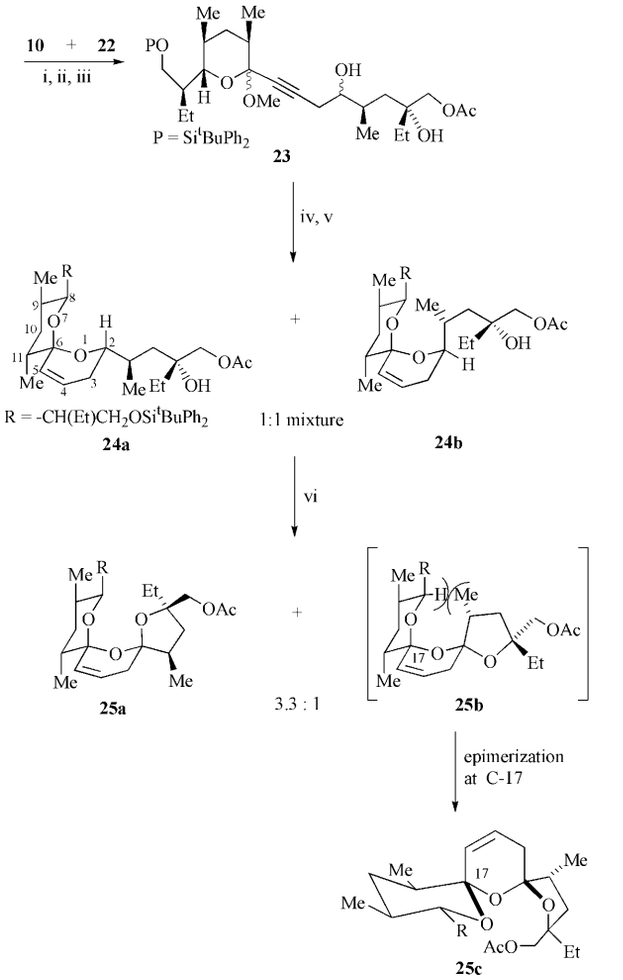
With the bis-spiroacetal ring assembled, hydrolysis of the major *cis* bis-spiroacetal acetate **25a** using potassium carbonate in methanol afforded alcohol **26** in moderate yield. Subsequent oxidation using tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide then afforded aldehyde **27** in preparation for attachment of the terminal tetrahydrofuran E ring *via* acid catalysed cyclisation of a γ-hydroxyepoxide (Scheme 4). Bromide **8** provides the additional carbon atoms for appendage of this E ring.

The key step in the synthesis of bromide **8** involved a Julia reaction of alcohol **38** (Scheme 5) as previously used for the synthesis of a related bromide. Methylation of the anion generated from 2-acetyl-γ-butyrolactone **34** with methyl iodide followed by chloride assisted decarboxylation of lactone **35** afforded chloropentanone **36** in 83% yield. Treatment of chloropentanone **36** with sodium hydroxide resulted in cyclisation to cyclopropyl ketone **37** which upon reduction with lithium aluminium hydride afforded alcohol **38** in 99% yield. Finally, reaction of alcohol **38** with lithium bromide and phosphorus tribromide for 2.5 h followed by treatment with zinc bromide for 2.5 h resulted in the formation of the desired (*E*)-bromide **8** in 50% yield.

Applying methodology established in synthetic approaches to the D and E rings of *epi*-17-deoxy-(*O*-8)-salinomycin **3**,[19] the union of bromide **8** and aldehyde **27** using a Barbier reaction was attempted next. Barbier reaction using an excess of bromide **8** with bis-spiroacetal aldehyde **27** resulted in the successful synthesis of a 4.7 : 1 mixture of *erythro* alcohol **28** and *threo* alcohol **29** in 85% yield (Scheme 4). After separation by flash chromatography the stereochemistry of alcohols **28** and **29** was assigned by comparison with analogous compounds[19] whereby the C*H*OH proton resonated further downfield in the



Scheme 2 *Reagents, conditions and yields*: (i) *n*BuLi, $^{i}Pr_2NH$, THF, 0 °C (55%); (ii) K_2CO_3, $K_3Fe(CN)_6$, $(DHQ)_2PHAL$, K_2OsO_4, $^{t}BuOH$–H_2O, 0 °C (77%); (iii) $LiBH_4$, Et_2O (63%); (iv) acetone, *p*TsOH, room temp. (75%); (v) TPAP, NMO, CH_2Cl_2 (76%); (vi) prop-2-ynyl bromide, Mg, $HgCl_2$, Et_2O (83%); (vii) TMS–imid, CH_2Cl_2 (87%).



Scheme 3 *Reagents, conditions and yields*: (i) *n*BuLi, −78 °C, THF; (ii) MeOH, amberlite resin IR 118; (iii) Ac_2O, NEt_3, CH_2Cl_2 (37% over 3 steps); (iv) H_2, Lindlar, 9:1 pentane–EtOAc; (v) pyridinium toluene-*p*-sulfonate, CH_2Cl_2, room temp. (87% over 2 steps); (vi) $PhI(OAc)_2$, I_2, cyclohexane, *hv* (46%).

erythro alcohols than the corresponding *threo* alcohols. In the present work, H-1′ in *erythro* alcohol **28** resonated as a double doublet at δ 3.59 ($J_{1',2'A}$ 8.0 and $J_{1',2'B}$ 2.5 Hz) whilst this same proton in *threo* alcohol **29** resonated as a double doublet at δ 3.36 ($J_{1',2'A}$ 10.4 and $J_{1',2'B}$ 2.0 Hz).

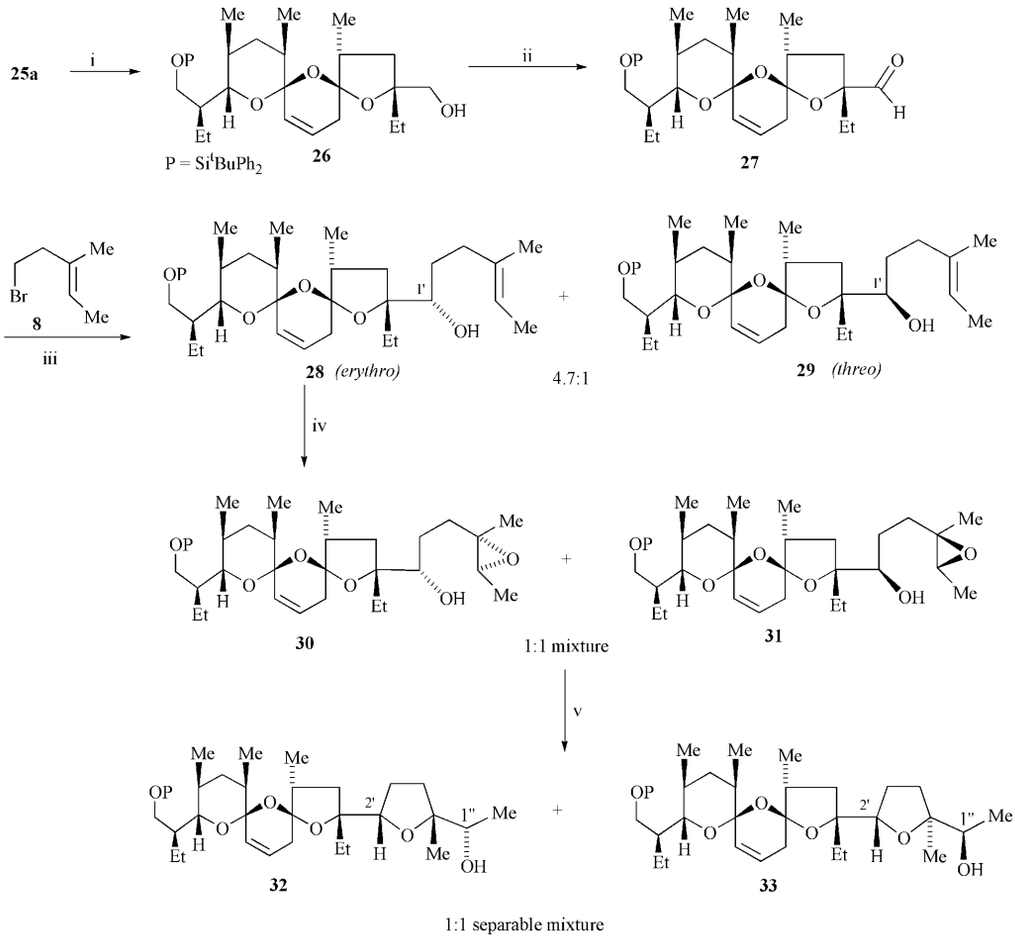
Treatment of *erythro*-alcohol **28** with dimethyldioxirane resulted in an inseparable 1:1 mixture of epoxides **30** and **31** and was confirmed by the characteristic upfield shift of the resonance assigned to H-5′ from δ 5.18 in alcohol **28** to δ 3.84–3.89 in the ^{1}H NMR spectrum of epoxides **30** and **31**. Finally, cyclisation of epoxides **30** and **31** using a catalytic quantity of pyridinium toluene-*p*-sulfonate in dichloromethane at 0 °C afforded a 1:1 mixture of polyethers **32** and **33** in 60% yield. After initial purification by flash chromatography, the individual diastereomers were separated by high performance liquid chromatography.

The stereochemistry of tetrahydrofurans **32** and **33** was confirmed by comparison of their ^{1}H NMR spectra with that observed for related bistetrahydrofurans.[19,24,25] The resonances for H-2′ and H-1″ in *cis* 2,5-disubstituted tetrahydrofurans occur further downfield than the corresponding resonances for *trans* 2,5-disubstituted tetrahydrofurans. In the present case, H-2′ in *cis* 2,5-disubstituted tetrahydrofuran **32** resonated as a double doublet at δ 4.11 ($J_{2',3'A}$ 7.0, $J_{2',3'B}$ 7.0 Hz) whilst this same proton in *trans* 2,5-disubstituted tetrahydrofuran **33** resonated as a multiplet at δ 4.05–4.09. Furthermore, H-1″ in *cis* 2,5-disubstituted tetrahydrofuran **32** resonated as a quartet at δ 3.77 ($J_{1'',2''}$ 6.4 Hz) whilst this same proton was shifted further upfield and resonated as a multiplet at δ_H 3.65–3.72 in *trans* 2,5-disubstituted tetrahydrofuran **33**.

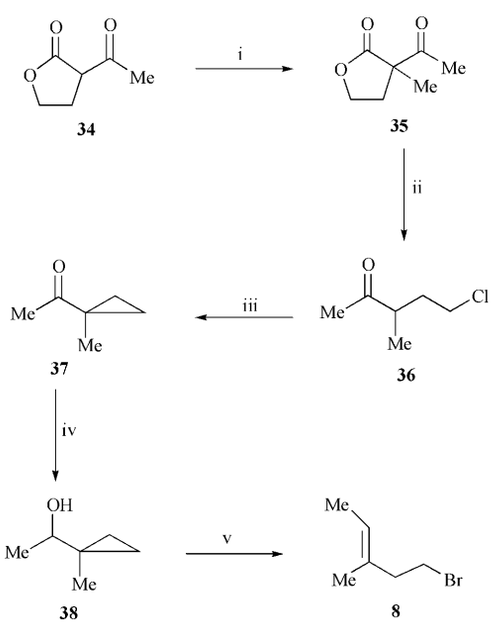
Polyethers **32** and **33** were thus synthesised from aldehyde **27** and bromide **8**. Noteworthy features of the synthetic strategy adopted include the oxidative cyclisation of a bicyclic hydroxyspiroacetal to a bis-spiroacetal which provides *cis* bis-spiroacetal aldehyde **25a** preferentially; the addition of a Grignard reagent derived from bis-homoallylic bromide **8** to a neopentyl-like aldehyde **27**; and acid catalysed cyclisation of a γ-hydroxyepoxide to a disubstituted tetrahydrofuran in the presence of a sensitive bis-spiroacetal.

The synthetic work outlined thus far provides a framework on which to synthesise the bis-spiroacetal moiety of antibiotic CP44,161 **4**. Synthesis of the bis-spiroacetal ring system with the desired (*S*) stereochemistry at C-2 as required for the synthesis of the natural product CP44,161 **4** was next addressed by examining the key Sharpless asymmetric dihydroxylation of alkene **14** using the pseudoenantiomeric $(DHQD)_2PHAL$ ligand (Scheme 6).

Treatment of alkene **14** with potassium osmate and $(DHQD)_2PHAL$ afforded lactone **39** in 76% yield as an 83:17 inseparable mixture with lactone **17** presumably *via* diol **16**. Despite the fact that in this latter case the chirality of the oxazolidinone auxiliary and the Sharpless ligands were clearly "mismatched" lactone **39** (albeit as a mixture containing lactone **17**) was converted to acetylene **11** in a similar manner to that described above for the conversion of lactone **17** to acetylene **22**. Although the production of isomeric mixtures was a difficulty when starting from an isomeric mixture of lactones in the present case, nevertheless, the synthesis of bis-spiroacetal **41** was demonstrated by subjecting lactone **39** to the same synthetic manipulations that were demonstrated above in the conversion of lactone **17** to bis-spiroacetal **25**.



Scheme 4 *Reagents, conditions and yields*: (i) K_2CO_3, MeOH (53%); (ii) TPAP, NMO (80%); (iii) Mg, Et_2O (85%); (iv) dimethyldioxirane, K_2CO_3, acetone, 0 °C (86%); (v) pyridinium toluene-*p*-sulfonate, CH_2Cl_2, 0 °C (60%).



Scheme 5 *Reagents, conditions and yields*: (i) Na, MeOH, benzene, MeI, Δ (83%); (ii) 14.5% HCl, Δ (89%); (iii) NaOH, Δ (58%); (iv) $LiAlH_4$, 0 °C (99%); (v) LiBr, PBr_3, 2,4,6-trimethylpyridine, Et_2O, −50 °C to room temp. then $ZnBr_2$, Et_2O, −40 °C to room temp. (50%).

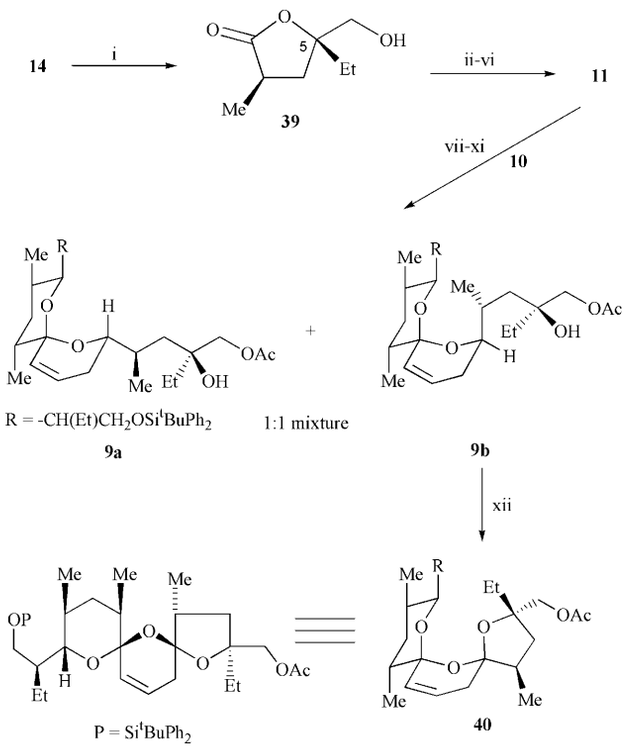
Following a similar procedure to that used for the conversion of acetylene **22** to spiroacetal **24** (Scheme 3) union of acetylene **11** with lactone **10** afforded bicyclic spiroacetal **9** which then underwent oxidative cyclisation to afford bis-spiroacetal **40** with the correct (*S*) stereochemistry at C-2 as present in CP44,161¶ (D, Fig. 1) and would not be converted to the configuration present in CP44,161 **4** (A, Fig. 1) until after appendage of the A and E rings to this central fragment.

In summary our synthetic efforts towards the synthesis of the bis-spiroacetal moiety of the polyether antibiotic CP44,161 **4** has unmasked the subtle differences observed in the key spirocyclisation reaction when a simple methyl group is introduced onto the terminal tetrahydrofuran ring of the bis-spiroacetal ring system present in salinomycin **1**. The syntheses of bis-spiroacetals **25** and **40** reported herein provide a framework on which to construct antibiotic CP44,161 **4** and analogues thereof whereby further modification is possible as exemplified by the conversion of bis-spiroacetal **25** to tetracycle **33**.

Experimental

Mps were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600 Fourier Transform IR spectrophotometer as thin films between sodium chloride plates. Absorption spectra are expressed in wavenumbers (cm^{-1}) with the following abbreviations: s = strong, m = medium, w = weak and br = broad. ^1H NMR spectra were recorded on a Bruker AC 200 (200 MHz) or a Bruker DRX 400 (400 MHz) spectrometer at ambient temperature. All *J*-values are given in Hz. Chemical shifts are expressed in parts per million downfield shift from tetramethylsilane as an internal standard, and reported as position (δ_H), relative integral, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = double doublet, ddd = double double

¶ Note that the numbering system for the bis-spiroacetal ring system present in salinomycin is also used for antibiotic CP44,161 in order to facilitate comparisons between the two compounds.



Scheme 6 *Reagents, conditions and yields*: (i) K_2CO_3, $K_3Fe(CN)_6$, $(DHQD)_2PHAL$, K_2OsO_4, ^tBuOH–H_2O, 0 °C (76%); (ii) $LiBH_4$, Et_2O; (iii) acetone, *p*TsOH, room temp.; (iv) TPAP, NMO, CH_2Cl_2; (v) prop-2-ynyl bromide, Mg, $HgCl_2$, Et_2O; (vi) TMS–imid, CH_2Cl_2; (vii) ^nBuLi, −78 °C, THF; (viii) MeOH, amberlite resin IR 118; (ix) Ac_2O, NEt_3, CH_2Cl_2; (x) H_2, Lindlar catalyst, 9 : 1 pentane–EtOAc; (xi) pyridinium toluene-*p*-sulfonate, CH_2Cl_2, room temp.; (xii) $PhI(OAc)_2$, I_2, cyclohexane.

doublet, t = triplet, q = quartet, m = multiplet, qt = quartet of triplets) and assignment. ^{13}C NMR spectra were recorded on a Bruker AC 200 (50.3 MHz) or a Bruker DRX 400 (100.5 MHz) spectrometer at ambient temperature with complete proton decoupling. Chemical shifts are expressed in parts per million downfield shift from tetramethylsilane as an internal standard and reported as position (δ_C), multiplicity (aided by DEPT135, DEPT 90, COSY and HETCOR experiments) and assignment. Low resolution mass spectra were recorded on a VG70-250S, a VG70-SD or an AEI model MS902 double focusing magnetic sector mass spectrometer operating with an ionisation potential of 70 eV (EI, DEI, CI and DCI). High resolution mass spectra were recorded at nominal resolution of 5000 or 10 000 as appropriate. Major fragments are given as percentages relative to the base peak and assigned where possible. Ionisation methods employed were either electron impact or chemical ionisation with ammonia or methane as reagent gas (CI). Low resolution chemical ionisation mass spectra were also recorded on a Hewlett Packard 5989A mass spectrometer using ammonia as reagent gas with the sample dissolved in methanol. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Thin layer chromatography (TLC) was performed using 0.2 mm thick precoated silica gel plates (Merck Kieselgel 60 F_{254} or Riedel-de Haen Kieselgel S F_{254}). Compounds were visualised by ultraviolet fluorescence or by staining with iodine or vanillin in methanolic sulfuric acid. When NMR data are reported for isomeric mixtures, resonances for the minor isomer are denoted by an asterisk (*). 2-(Chloromethyl)but-1-ene was prepared from 2-ethylprop-2-en-1-ol[26] using the chlorination procedure described by Johnson *et al.*[27]

2-(Iodomethyl)but-1-ene 13

2-(Chloromethyl)but-1-ene (8.16 g, 78 mmol) was added dropwise to a solution of sodium iodide (14 g, 94 mmol) in acetone (100 ml). The reaction was stirred for 16 h at room temperature then filtered and the filtrate concentrated under reduced pressure. The residue was partitioned between hexane and water and the organic phase dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue distilled in a short path distillation apparatus (20 Torr, 75 °C) to give the title compound **13** (4.28 g, 28%) as an unstable pale brown liquid that was used immediately upon preparation; δ_H (200 MHz; $CDCl_3$) 1.07 (3H, t, *J* 7.4, CH_3), 2.28 (2H, qt, *J* 7.4 and *J* 1.0, CH_2CH_3), 3.94 (2H, s, CH_2I), 4.91–4.93 (1H, m, $=CH_AH_B$), 5.22–5.23 (1H, m, $=CH_AH_B$).

(2′*R*,4*S*,5*R*)-(−)-3-(2′-Methyl-4′-ethyl-1′-oxopent-4′-enyl)-4-methyl-5-phenyloxazolidin-2-one 14

To a solution of diisopropylamine (1.06 g, 10.5 mmol) in dry tetrahydrofuran (25 ml), cooled to 0 °C under nitrogen, was added *n*-butyllithium (6.4 ml of a 1.5 M solution in hexane, 9.62 mmol). After stirring at 0 °C for 15 min, the reaction mixture was cooled to −78 °C, whereupon a solution of (4*S*,5*R*)-(−)-4-methyl-3-(1′-oxopropyl)-5-phenyloxazolidin-2-one[28,29] (2.04 g, 8.75 mmol) in dry tetrahydrofuran (10 ml) was added. After stirring at −78 °C for 20 min, a solution of freshly distilled iodide **13** (3.43 g, 17.5 mmol) in dry tetrahydrofuran (10 ml) was added dropwise. The reaction mixture was stirred at −78 °C for 2.5 h then allowed to warm to room temperature. After quenching with saturated ammonium chloride solution (10 ml), the reaction mixture was extracted with ethyl acetate (3 × 50 ml) and dried over magnesium sulfate. Removal of the solvent at reduced pressure afforded a yellow oil which was purified by flash chromatography using hexane–ethyl acetate (9 : 1) as eluent to give the *title compound* **14** (1.46 g, 55%) as a colourless oil (Found: C, 71.5; H, 7.6; N, 4.5; M^+, 301.1712. $C_{18}H_{23}O_3N$ requires C, 71.7; H, 7.7; N, 4.7%; M^+, 301.1678); $[a]_D$ −34.4 (*c* 1.0, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3070w (=CH), 2968, 2935, 2877s (CH), 1790s (-OCON), 1694s (-NCOC) and 1646w (C=C); δ_H (400 MHz; $CDCl_3$) 0.85 (3H, d, *J* 6.5, 4-Me), 1.03 (3H, t, *J* 7.4, CH_2CH_3), 1.17 (3H, d, *J* 6.8, 2′-Me), 2.04–2.10 (3H, m, CH_2CH_3 and 3′-H_A), 2.54 (1H, dd, $J_{B,A}$ 14.0, $J_{B,2'}$ 7.2, 3′-H_B), 4.02–4.07 (1H, m, 2′-H), 4.73–4.80 (3H, m, 4-H and 5′-CH_2), 5.65 (1H, d, *J* 7.3, 5-H) and 7.29–7.43 (5H, m, Ar-H); δ_C (100.6 MHz; $CDCl_3$) 12.2, 14.5, 16.9 (CH_3, 4-Me, 2′-Me and CH_2CH_3), 28.5 (CH_2, CH_2CH_3), 35.8 (CH, C-2′), 40.2 (CH_2, C-3′), 54.8 (CH, C-4), 78.7 (CH, C-5), 109.9 (CH_2, C-5′), 123.9 (CH, Ar-C), 128.7 (CH, Ar-C), 133.4 (quat., Ar-C), 148.5 (quat., C-4′), 152.7 (quat., C-2) and 176.8 (quat., C-1′); *m*/*z* (EI) 301 (M^+, 17%), 233 (23), 184 (18), 178 (19) and 160 (25).

(3*R*,5*R*)-(−)-3-Methyl-5-ethyl-5-hydroxymethyltetrahydrofuran-2-one 17

To a suspension of K_2CO_3 (0.42 g, 3.0 mmol), $K_3Fe(CN)_6$ (1.0 g, 3.0 mmol), $(DHQ)_2PHAL$ (40 mg, 0.05 mmol) and $K_2OsO_4 \cdot 2H_2O$ (3 mg, 0.001 mmol) in 1 : 1 *tert*-butanol (2-methylprop-2-ol)–water (10 ml), cooled to 0 °C, was added alkene **14**. After stirring at 0 °C for 30 min, the reaction mixture was quenched with sodium sulfite (2.24 g), allowed to warm to room temperature, then extracted with ethyl acetate (3 × 20 ml) and dried over magnesium sulfate. Removal of the solvent at reduced pressure afforded a pale brown oil which was purified by flash chromatography with hexane–ethyl acetate (2 : 1) as eluent to give the *title compound* **17** (122 mg, 77%) as a colourless oil (Found: C, 60.6; H, 8.6. $C_8H_{14}O_3$ requires C, 60.7; H, 8.9%); $[a]_D$ −17.6 (*c* 1.7, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3640–3077 (br s, OH), 2973, 2937, 2882s (CH) and 1763s (C=O); δ_H (200 MHz; $CDCl_3$) 0.94 (3H, t, *J* 7.5, CH_2CH_3), 1.29 (3H, d, *J* 7.0, 3-Me), 1.69 (2H, q, *J* 7.5, CH_2CH_3), 1.95 (1H, dd, $J_{4A,4B}$ 12.9, $J_{4A,3}$ 9.9, 4-H_A), 2.19 (1H, dd, $J_{4A,4B}$ 12.9, $J_{4B,3}$ 9.9, 4-H_B), 2.69–2.91 (1H, m, 3-H), 3.45 (1H, dd, $J_{1'A,1'B}$ 12.2, $J_{1'A,OH}$ 7.4, 1′-H_A) and 3.75 (1H, dd, $J_{1'A,1'B}$ 12.2, $J_{1'B,OH}$ 4.8, 1′-H_B); δ_C (100.6

MHz; $CDCl_3$) 7.7 (CH_3, 3-Me), 16.0 (CH_3, CH_2CH_3), 28.7 (CH_2, CH_2CH_3), 34.4 (CH_2, C-4), 35.3 (CH, C-3), 66.4 (CH_2, C-1′), 86.7 (quat., C-5) and 179.7 (quat., C-2); *m*/*z* (CI, CH_4) 159 (MH^+).

(3*R*,5*S*)-3-Methyl-5-ethyl-5-hydroxymethyltetrahydrofuran-2-one 39

The above reaction was repeated using $(DHQD)_2PHAL$ instead of $(DHQ)_2PHAL$ to give the *title compound* **39** which contained 17% of lactone **17** in 76% yield; δ_H (200 MHz; $CDCl_3$) 0.94 (3H, t, *J* 7.5, CH_2CH_3), 1.26 (3H, d, *J* 7.3, 3-Me), 1.66–1.76 (3H, m, CH_2CH_3, 4-H_A), 2.43 (1H, dd, $J_{4A,4B}$ 13.0, $J_{4B,3}$ 10.0, 4-H_B), 2.87–3.04 (1H, m, 3-H), 3.58 (1H, d, $J_{1'A,1'B}$ 12.0, 1′-H_A) and 3.72 (1H, d, $J_{1'A,1'B}$ 12.0, 1′-H_B).

(2*R*,4*R*)-(+)-2-Ethyl-4-methylpentane-1,2,5-triol 18

To a solution of lactone **17** (0.83 g, 5.25 mmol) in dry diethyl ether (200 ml) under nitrogen, was added lithium borohydride (0.23 g, 10.5 mmol). After stirring for 1 h the reaction mixture was quenched with water (20 ml). The solvent was removed at reduced pressure and the residue filtered through a plug of silica gel using methanol as eluent. Removal of solvent at reduced pressure afforded a colourless oil that was purified by flash chromatography using ethyl acetate as eluent to give the *title compound* **18** (0.53 g, 63%) as a colourless oil (Found: MH^+ 163.1325. $C_8H_{18}O_3$ requires *M*H, 163.1334); $[a]_D$ +14.6 (*c* 1.3, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3012–3676 (br s OH) and 2964 (br s, CH); δ_H [400 MHz; $(CD_3)_2CO$] 0.84 (3H, t, *J* 7.6, CH_2CH_3), 0.90 (3H, d, *J* 6.9, 4-Me), 1.41 (1H, dd, $J_{3A,3B}$ 14.6, $J_{3A,4}$ 4.2, 3-H_A), 1.49 (1H, dd, $J_{3B,3A}$ 14.6, $J_{3B,4}$ 7.3, 3-H_B), 1.57 (2H, m, CH_2CH_3), 1.82–1.94 (1H, m, 4-H), 3.26–3.46 (4H, m, 2 × CH_2OH) and 3.59 (1H, t, *J* 5.8, OH), 3.90 (1H, s, OH), 4.27 (1H, t, *J* 5.2, OH); δ_C [100.6 MHz; $(CD_3)_2CO$] 8.5 (CH_3, CH_2CH_3), 19.8 (CH_3, 4-Me), 29.7 (CH_2, CH_2CH_3), 31.8 (CH, C-4), 42.2 (CH_2, C-3), 68.1 (CH_2, C-5), 69.3 (CH_2, C-1) and 74.6 (quat., C-2); *m*/*z* (CI, NH_3) 163 (MH^+, 3%).

(2*R*,4′*R*)-(+)-3-(4-Ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropan-1-ol 19

A solution of triol **18** (0.65 g, 4.0 mmol) in acetone (70 ml) was treated with toluene-*p*-sulfonic acid (10 mg, 0.06 mmol). After stirring the reaction mixture for 1 h, potassium carbonate (1.0 g) was added and stirring continued for 10 min. The solvent was removed under reduced pressure, the resultant residue dissolved in ethyl acetate (100 ml) and washed with water (50 ml), saturated potassium carbonate solution (50 ml) and dried over potassium carbonate. Removal of solvent under reduced pressure afforded a colourless oil which was purified by flash chromatography using hexane–ethyl acetate (1:1) as eluent to give the *title compound* **19** (0.60 g, 75%) as a colourless oil (Found: MH^+ 203.1625. $C_{11}H_{22}O_3$ requires *M*H, 203.1647); $[a]_D$ +5.6 (*c* 0.18, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3418s (OH), 2934, 2875s (CH), 1456s, 1369s, 1250s, 1214s and 1052s; δ_H (400 MHz; $CDCl_3$) 0.85 (3H, t, *J* 7.6, CH_2CH_3), 0.89 (3H, d, *J* 6.8, 2-Me), 1.40 (3H, s, 2′-Me), 1.41 (3H, s, 2′-Me), 1.52–1.82 (4H, m, CH_2CH_3 and 3-CH_2), 1.86–1.96 (1H, m, 2-H), 2.74 (1H, br s, OH), 3.37 (1H, dd, $J_{1A,1B}$ 11.2, $J_{1A,2}$ 7.6, 1-H_A), 3.54 (1H, dd, $J_{1B,1A}$ 11.2, $J_{1B,2}$ 3.7, 1-H_B), 3.64 (1H, d, *J* 8.6, 5′-H_A) and 3.90 (1H, d, *J* 8.6, 5′-H_B); δ_C (100.6 MHz; $CDCl_3$) 9.0 (CH_3, CH_2CH_3), 19.3 (CH_3, 2-Me), 26.9 (CH_3, 2′-Me), 27.1 (CH_3, 2′-Me), 29.3 (CH_2, CH_2CH_3), 32.0 (CH, C-2), 43.5 (CH_2, C-3), 68.9 (CH_2, C-1), 73.6 (CH_2, C-5′), 84.1 (quat., C-4′) and 109.5 (quat., C-2′); *m*/*z* (CI, NH_3) 203 (MH^+, 5%).

(2*R*,4′*R*)-3-(4-Ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropanal 20

To a solution of alcohol **19** (0.60 g, 3.0 mmol) in dichloromethane (40 ml) under nitrogen was added *N*-methylmorpholine *N*-oxide (0.53 g, 4.5 mmol) and powdered 4 Å molecular sieves (1.6 g). The mixture was stirred at room temperature for 10 min then cooled to 0 °C and tetra-*n*-propylammonium perruthenate (53 mg, 0.15 mmol) was added. After stirring at room temperature for 2 h the reaction mixture was filtered through Celite and the solvent evaporated to give a colourless oil which was purified by flash chromatography using hexane–ethyl acetate (9:1) as eluent to give the *title compound* **20** (458 mg, 76%) as a colourless oil (Found: MH^+, 201.1483. $C_{11}H_{20}O_3$ requires *M*H, 201.1491); ν_{max} (film)/cm^{-1} 1724 (C=O); δ_H [200 MHz; $(CD_3)_2CO$] 0.86 (3H, t, *J* 7.4, CH_2CH_3), 1.06 (3H, d, *J* 6.9, 2-Me), 1.28 (3H, s, 2′-Me), 1.30 (3H, s, 2′-Me), 1.48–1.78 (4H, m, CH_2CH_3 and 3-CH_2), 2.46–2.55 (1H, m, 2-H), 3.70 (1H, d, *J* 8.6, 5′-H_A), 3.82 (1H, d, *J* 8.6, 5′-H_B) and 9.58 (1H, d, *J* 3.0, CHO); δ_C [50 MHz; $(CD_3)_2CO$] 8.89 (CH_3, CH_2CH_3), 15.8 (CH_3, 2-Me), 27.2 (CH_3, 2′-Me), 27.3 (CH_3, 2′-Me), 30.7 (CH_2, CH_2CH_3), 39.4 (CH, C-2), 43.0 (CH_2, C-3), 73.5 (CH_2, C-5′), 83.9 (quat., C-4′), 109.7 (quat., C-2′) and 204.6 (CH, CHO); *m*/*z* (CI, CH_4) 201 (MH^+, 6%).

(2*R*,3*S*,4′*R*)- and (2*R*,3*R*,4′*R*)-1-(4-Ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylhex-5-yn-3-ol 21

To a suspension of magnesium (11 mg, 0.45 mmol), iodine (1 mg) and mercuric chloride (1 mg) in dry diethyl ether (1 ml) under nitrogen was added a solution of prop-2-ynyl bromide (0.065 ml, 0.45 mmol) in dry diethyl ether (1 ml) dropwise. The reaction mixture was then cooled to 0 °C and a solution of aldehyde **20** (60 mg, 0.30 mmol) in dry diethyl ether (2 ml) added. After stirring at room temperature for 30 min the reaction mixture was quenched with saturated ammonium chloride solution (1 ml), extracted with ethyl acetate (3 × 10 ml), washed with brine (10 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure afforded a yellow oil which was purified by flash chromatography using hexane–ethyl acetate (8:2) as eluent to give the *title compound* **21** (63 mg, 83%) as a colourless oil and as a 1:1 mixture of diastereomers (Found: MH^+, 241.1776. $C_{14}H_{24}O_3$ requires *M*H, 241.1804); δ_H (400 MHz; $CDCl_3$) 0.84–0.97 (6H, m, CH_2CH_3, 2-Me), 1.40 (3H, s, 2′-Me), 1.41 (3H, s, 2′-Me), 1.45–1.81 (4H, m, 2 × CH_2), 1.87–2.04 (2H, m, 2-H and C≡CH), 2.34–2.42 (2H, m, $CH_2C{\equiv}C$) and 3.49–3.97 (3H, m, 3-H, 5′-CH_2); δ_C (100.6 MHz; $CDCl_3$) 8.9, 9.1 (CH_3, CH_2CH_3), 15.4, 18.9 (CH_3, 2-Me), 23.5, 24.7 (CH_2, CH_2CH_3), 26.7–27.3 (CH_3, 2 × 2′-Me), 29.4, 29.7 (CH_2, C-1), 33.1, 34.1 (CH, C-2), 39.9, 42.4 (CH_2, C-4), 69.7, 70.1 (quat., C-5), 71.8, 74.2 (CH_2, C-5′), 73.5 (CH, C-6), 81.3, 81.8 (CH, C-3), 83.9, 84.1 (quat., C-4′) and 109.4, 109.5 (quat., C-2′); *m*/*z* (CI, CH_4) 241 (MH^+, 40%), 183 (20), 143 (40) and 105 (100).

(2*R*,3*S*,4′*R*)- and (2*R*,3*R*,4′*R*)-1-(4-Ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methyl-3-trimethylsilyloxyhex-5-yne 22

To a solution of alcohol **21** (53 mg, 0.22 mmol) in dry dichloromethane (10 ml) under nitrogen was added 1-(trimethylsilyl)-imidazole (0.25 ml, 1.8 mmol). After stirring for 1 h, the reaction mixture was quenched with water (0.5 ml), washed with brine (5 ml) and dried over potassium carbonate. Removal of the solvent at reduced pressure afforded a pale yellow oil which was purified by flash chromatography using hexane–ethyl acetate (9:1) as eluent to give the *title compound* **22** (60 mg, 87%) as a colourless oil (Found: MH^+, 313.22110. $C_{17}H_{32}O_3Si$ requires *M*H, 313.21990); δ_H (400 MHz; $CDCl_3$) 0.13 (9H, s, Me_3Si), 0.87–0.93 (6H, m, CH_2CH_3 and 2-Me), 1.36 (3H, s, 2′-Me), 1.40 (3H, s, 2′-Me), 1.52–1.75 (4H, m, 2 × CH_2), 1.79–1.90 (1H, m, 2-H), 1.94–1.96 (1H, m, C≡CH), 2.29–2.33 (2H, m, $CH_2C{\equiv}C$) and 3.72–3.78 (3H, m, 3-H, 5′-CH_2); δ_C (100.6 MHz; $CDCl_3$) 0.4 (CH_3, $SiMe_3$), 8.7 (CH_3, CH_2CH_3), 15.9, 17.8 (CH_3, 2-Me), 24.0, 24.4 (CH_2, CH_2CH_3), 26.9–27.4 (CH_3, 2 × 2′-Me), 29.7, 30.0 (CH_2, C-1), 34.0, 34.2 (CH, C-2), 38.3, 39.3 (CH_2, C-4), 69.7, 69.8 (quat., C-5), 73.2, 73.3 (CH_2, C-5′), 75.8, 76.1

(CH, C-6 and C-3), 84.1, 84.2 (quat., C-4′) and 109.1 (quat., C-2′); *m/z* (CI, CH_4) 313 (MH^+, 20%), 297 (M − CH_3, 35), 255 (50), 239 (M − $SiCH_3$, 30), 226 (20) and 215 (100).

(2*R*,4*R*,5*S**,2′*S**,3′*R*,5′*S*,6′*S*,1″*S*)- and (2*R*,4*R*,5*R**,2′*S**,3′*R*,5′*S*,6′*S*,1″*S*)-8-{6-[1-(*tert*-Butyldiphenylsilyloxymethyl)-propyl]-2-methoxy-3,5-dimethyltetrahydro-2*H*-pyran-2-yl}-2-ethyl-2,5-dihydroxy-4-methyloct-7-yn-1-yl acetate 23

To a solution of acetylene **22** (58 mg, 0.185 mmol) in dry tetrahydrofuran (5 ml) cooled to −78 °C under nitrogen was added *n*-butyllithium (0.14 ml of a 1.3 M solution in hexane, 0.185 mmol) dropwise. After stirring at −78 °C for 1 h, a solution of lactone **10**[29] (81 mg, 0.185 mmol) in dry tetrahydrofuran (1 ml) was added in one portion. After gradually warming to room temperature over 1.5 h sodium dihydrogen phosphate (10% aqueous solution, 0.5 ml) was added. The reaction mixture was extracted with ethyl acetate (3 × 10 ml), washed with brine (10 ml) and dried over potassium carbonate. Removal of solvent at reduced pressure gave a pale yellow oil which was redissolved in dry methanol (15 ml) and stirred overnight with amberlite IR 118 resin. Removal of the resin by filtration followed by removal of solvent at reduced pressure yielded an orange oil which was purified by flash chromatography using ethyl acetate as eluent to afford a triol (89 mg) as a colourless oil. This was immediately redissolved in dry dichloromethane (10 ml) and treated with dry triethylamine (0.04 ml, 0.272 mmol) and acetic anhydride (0.014 ml, 0.15 mmol) and 4-dimethylaminopyridine (1 mg). The reaction mixture was stirred at room temperature for 1 h, quenched with water (1 ml), extracted with dichloromethane (3 × 10 ml), washed with brine (10 ml) and dried over anhydrous potassium carbonate. Removal of solvent under reduced pressure gave a colourless oil which was purified by flash chromatography using hexane–ethyl acetate (1:1) as eluent to afford the *title compound* **23** (90 mg, 37% over 3 steps) as a colourless oil and as a mixture of diastereomers (Found: MH^+, 695.4311. $C_{41}H_{62}O_7Si$ requires *M*H, 695.4343); ν_{max} (film)/cm^{-1} 3410s (OH), 2241w (C≡C) and 1740 (C=O); δ_H (200 MHz; $CDCl_3$) 0.62 (3H, t, *J* 7.6, 2-CH_2CH_3), 0.75–1.04 (12H, m, 4-Me, 3′-Me, 5′-Me, 1″-CH_2CH_3), 1.05 (9H, s, ^{t}Bu), 1.22–1.90 (12H, m, 4 × CH_2, 4 × CH), 2.10 (3H, s, CH_3CO), 2.21–2.46 (2H, m, $CH_2C{\equiv}C$), 3.36, 3.37, 3.43, 3.44 (3H, s, CH_3O), 3.30–4.02 (6H, m, CH_2OAc, CH_2OSi, 5-H, 6′-H), 7.36–7.41 (6H, m, ArH) and 7.65–7.74 (4H, m, ArH); *m/z* (CI, CH_4) 695 (MH^+, 4%).

(2*R*,4*R*,2′*R*,6′*S*,8′*S*,9′*S*,11′*R*,1″*S*)- and (2*R*,4*R*,2′*S*,6′*S*,8′*S*,9′*S*,11′*R*,1″*S*)-4-{8-[1-(*tert*-Butyldiphenylsilyloxymethyl)-propyl]-9,11-dimethyl-1,7-dioxaspiro[5.5]undec-4-en-2-yl}-2-ethyl-2-hydroxypent-1-yl acetate 24

A solution of methyl acetals **23** (48 mg, 0.069 mmol) in dry pentane (9 ml) and ethyl acetate (1 ml) was stirred with Lindlar catalyst (2 mg) and potassium carbonate (20 mg) at room temperature under a balloon of hydrogen for 1 h. Removal of the catalyst by filtration through a short pad of Celite followed by removal of the solvent at reduced pressure, afforded a colourless oil. This was redissolved in dichloromethane (10 ml) and treated with pyridinium toluene-*p*-sulfonate (1 mg) at room temperature for 0.5 h. Evaporation of the solvent at reduced pressure afforded a pale yellow oil which was purified by flash chromatography using hexane–ethyl acetate (3:1) as eluent to afford the *title compound* **24** (40 mg, 87%) as a mixture of diastereomers (Found: C, 72.0; H, 8.9. $C_{40}H_{60}O_6Si$ requires C, 72.3; H, 9.1%); ν_{max} (film)/cm^{-1} 3446 (OH), 3070w (Ar-H), 3050w (=CH), 2929s, 2856s (C-H) and 1745s (C=O); δ_H (400 MHz; $CDCl_3$) 0.75–0.89 (15H, m, 5 × CH_3), 1.06 (9H, s, ^{t}Bu), 1.20–1.97 (14H, m, 4 × CH, 5 × CH_2), 2.04–2.10 (3H, m, $COCH_3$), 3.07–4.11 (5H, m, CH_2OSi, CH_2OAc, 8′-H), 5.42–5.45 (1H, m, 5′-H), 5.85–5.90 (1H, m, 4′-H), 7.35–7.42 (6H, m, Ar-H) and 7.62–7.71 (4H, m, Ar-H); *m/z* (CI, CH_4) 665 (MH^+, 12%).

(2′*R*,4′*R*,5′*R*,7′*S*,9′*S*,10′*S*,12′*R*,1″*S*)- and (2′*R*,4′*R*,5′*S*,7′*S*,9′*S*,10′*S*,12′*R*,1″*S*)-{9-[1-(*tert*-Butyldiphenylsilyloxymethyl)-propyl]-2-ethyl-4,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-en-2-yl}methyl acetate 25a, 25c

A mixture of spiroacetals **24** (30 mg, 0.045 mmol), iodine (23 mg, 0.09 mmol) and (diacetoxyiodo)benzene (29 mg, 0.09 mmol) in cyclohexane (10 ml) was purged with nitrogen and irradiated with a 500 W tungsten filament lamp keeping the temperature maintained at approximately 20 °C. After 7 h the solution was diluted with ether (20 ml), washed with 10% aqueous sodium thiosulfate (10 ml), water (10 ml), brine (10 ml) and dried over potassium carbonate. The solvent was evaporated under reduced pressure and the resultant oil purified by flash chromatography using hexane–ethyl acetate (9:1) as eluent to afford the following.

(i) *Bis-spiroacetal* **25a** (10 mg, 36%) as a colourless oil (Found: MH^+, 663.4092. $C_{40}H_{58}O_6Si$ requires *M*H, 663.4081); ν_{max} (film)/cm^{-1} 2925s, 2854s (C-H) and 1741s (C=O); δ_H (400 MHz; $CDCl_3$) 0.68 (3H, t, *J* 7.6, 2′-CH_2CH_3), 0.80 (3H, d, *J* 6.7, 4′-Me), 0.82–0.86 (6H, m, 12′-Me, 1″-CH_2CH_3), 0.94 (3H, d, *J* 6.7, 10′-Me), 1.06 (9H, s, *t*-Bu), 1.06–1.10 (2H, m, 1″-CH_2CH_3), 1.26–1.81 (10H, m, 2′-CH_2CH_3, 3′-CH_2, 11′-CH_2, 3 × CHMe, CHEt), 1.93–1.99 (1H, m, 15′-H_A), 2.06 (3H, s, $COCH_3$), 2.26–2.28 (1H, m, 15′-H_B), 3.59 (1H, dd, $J_{A,B}$ 10.2, $J_{A,1''}$ 5.8, CH_ACH_BOSi), 3.68 (1H, dd, $J_{B,A}$ 10.2, $J_{B,1''}$ 7.4, CH_ACH_BOSi), 3.78 (1H, d, $J_{9',10'}$ 11.8, 9′-H), 4.11 (1H, d, $J_{A,B}$ 11.1, CH_ACH_BOAc), 4.14 (1H, d, $J_{B,A}$ 11.1, CH_ACH_BOAc), 5.55 (1H, ddd, $J_{13',14'}$ 10.1, $J_{13',15'A}$ 1.8, $J_{13',15'B}$ 1.8, 13′-H), 5.91 (1H, ddd, $J_{14',13'}$ 10.1, $J_{14',15'A}$ 4.6, $J_{14',15'B}$ 4.5, 14′-H), 7.35–7.39 (6H, m, Ar-H) and 7.64–7.67 (4H, m, Ar-H); δ_C (100.6 MHz; $CDCl_3$) 8.4 (CH_3, 2′-CH_2CH_3), 13.0 (CH_3, 1″-CH_2CH_3), 14.3 (CH_3, 4′-Me), 15.8 (CH_3, 10′-Me), 18.2 (CH_3, 12′-Me), 18.3 (CH_2, 1″-CH_2CH_3), 19.1 (quat., CMe_3), 21.0 (CH_3, $COCH_3$), 27.0 (CH_3, CMe_3), 29.1, 29.7, 36.1, 39.2 (CH_2, 2′-CH_2CH_3, C-3′, C-11′, C-15′), 31.8, 39.9, 44.2, 44.7 (CH, C-1″, C-4′, C-10′, C-12′), 65.2 (CH_2, CH_2OSi), 70.5 (CH_2, C-1), 75.2 (CH, C-9′), 82.5 (quat., C-2′), 97.4 (quat., C-7′), 107.4 (quat., C-5′), 124.9 (CH, C-13′), 127.2 (CH, Ar-C), 129.5 (CH, Ar-C), 130.5 (CH, C-14′), 134.4 (quat., Ar-C), 135.6 (CH, Ar-C), 135.8 (CH, Ar-C) and 171.1 (quat., C=O); *m/z* (CI, CH_4) 663 (MH^+, 80%) and 647 (M − CH_3, 100).

(ii) *Bis-spiroacetal* **25c** (3 mg, 10%) as a colourless oil (Found: MH^+, 663.4087. $C_{40}H_{58}O_6Si$ requires *M*H, 663.4081); δ_H (400 MHz; $CDCl_3$) 0.72–0.89 (15H, m, 5 × CH_3), 1.02 (9H, s, *t*-Bu), 0.96–2.05 (12H, m, 4 × CH_2, 3 × CHMe, CHEt), 2.05 (3H, s, $COCH_3$), 2.16 (1H, dd, $J_{15'A,15'B}$ 17.2, $J_{15'A,14'}$ 5.6, 15′-H_A), 2.34 (1H, ddd, $J_{15'A,15'B}$ 17.2, $J_{15'B,14'}$ 2.8, $J_{15'B,13'}$ 2.8, 15′-H_B), 3.50–3.65 (1H, m, CH_ACH_BOSi), 3.79 (1H, d, $J_{9',10'}$ 10.5, 9′-H), 3.83–4.07 (1H, m, CH_ACH_BOSi), 4.0 (1H, d, $J_{A,B}$ 10.7, CH_ACH_B-OAc), 4.30 (1H, d, $J_{B,A}$ 10.7, CH_ACH_BOAc), 5.96 (1H, ddd, $J_{14',13'}$ 10.4, $J_{14',15'A}$ 5.6, $J_{14',15'B}$ 2.8, 14′-H), 6.20 (1H, dd, $J_{13',14'}$ 10.4, $J_{13',15'B}$ 2.8, 13′-H), 7.33–7.39 (6H, m, Ar-H) and 7.64–7.73 (4H, m, Ar-H); *m/z* (CI, CH_4) 663 (MH^+, 63%) and 647 (M − CH_3, 100).

(2′*S*,4′*R*,5′*R*,7′*S*,9′*S*,10′*S*,12′*R*,1″*S*)-{9-[1-(*tert*-Butyldiphenylsilyloxymethyl)propyl]-2-ethyl-4,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-2-yl}methyl acetate 40

A sample of lactone **39** (which contained 17% of lactone **17**) was converted to bis-spiroacetal **40** using the procedures described above for the conversion of lactone **17** to bis-spiroacetal **25a**. Bis-spiroacetal **40** was isolated as a colourless oil (Found: MH^+, 663.4077. $C_{40}H_{58}O_6Si$ requires *M*H, 663.4081); δ_H (400 MHz; $CDCl_3$) 0.67 (3H, t, *J* 7.6, 2′-CH_2CH_3), 0.81–0.94 (12H, m, 4 × CH_3), 1.05 (9H, s, *t*-Bu), 1.00–2.09 (12H, m, 4 × CH_2, 3 × CHMe, CHEt), 2.06 (3H, s, $COCH_3$), 2.18 (1H, ddd, $J_{15'A,15'B}$ 17.2, $J_{15'A,14'}$ 4.8, $J_{15'A,13'}$ 1.4, 15′-H_A), 2.27 (1H, ddd, $J_{15'A,15'B}$ 17.2, $J_{15'B,14'}$ 4.4, $J_{15'B,13'}$ 2.0, 15′-H_B), 3.57 (1H, dd, $J_{A,B}$ 10.4, $J_{A,1''}$ 6.0, CH_ACH_BOSi), 3.68 (1H, dd, $J_{B,A}$ 10.4, $J_{B,1''}$

7.2, CH_ACH_BOSi), 3.79 (1H, d, $J_{9',10'}$ 10.8, 9′-H), 3.93 (2H, s CH_2OAc), 5.56 (1H, ddd, $J_{13',14'}$ 10.0, $J_{13',15'A}$ 1.6, $J_{13',15'B}$ 1.6, 13′-H), 5.92 (1H, ddd, $J_{14',13'}$ 10.0, $J_{14',15'A}$ 4.8, $J_{14',15'B}$ 4.4, 14′-H), 7.32–7.43 (6H, m, Ar-H) and 7.63–7.67 (4H, m, Ar-H).

(2′*R*,4′*R*,5′*R*,7′*S*,9′*S*,10′*S*,12′*R*,1″*S*)-{9-[1-(*tert*-Butyldiphenylsilyloxymethyl)propyl]-2-ethyl-4,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-2-yl}methanol 26

To a solution of ester **25a** (10 mg, 0.016 mmol) in methanol (3 ml) was added potassium carbonate (10 mg). The mixture was stirred at room temperature under nitrogen for 1.5 h. The suspension was then filtered and the solvent evaporated to give a yellow oil which was purified by flash chromatography using hexane–ethyl acetate (19 : 1) as eluent to afford the *title compound* **26** (5 mg, 53%) as a colourless oil (Found: MH^+, 621.3955. $C_{38}H_{56}O_5Si$ requires *M*H, 621.3975); ν_{max} (film)/cm^{-1} 3443s (OH); δ_H (400 MHz; $CDCl_3$) 0.69 (3H, t, *J* 7.6, 2′-CH_2CH_3), 0.81–0.87 (9H, m, 4′-Me, 12′-Me, 1″-CH_2CH_3), 0.96 (3H, d, *J* 6.0, 10′-Me), 1.06 (9H, s, *t*-Bu), 1.06–1.68 (10H, m, 3 × CH_2, 3 × C*H*Me, C*H*Et), 1.95–2.09 (2H, m, 3'-CH_2), 2.22 (1H, ddd, $J_{15'A,15'B}$ 16.8, $J_{15'A,14'}$ 6.0, $J_{15'A,13'}$ 0.8, 15′-H_A), 2.40 (1H, ddd, $J_{15'A,15'B}$ 16.8, $J_{15'B,14'}$ 2.8, $J_{15'B,13'}$ 2.8, 15′-H_B), 3.37–3.56 (3H, m, CH_2OH, CH_2OH), 3.59 (1H, dd, $J_{A,B}$ 10.0, $J_{A,1''}$ 6.0, CH_ACH_BOSi), 3.70 (1H, dd, $J_{B,A}$ 10.0, $J_{B,1''}$ 7.6, CH_ACH_B-OSi), 3.86 (1H, d, $J_{9',10'}$ 10.4, 9′-H), 5.49 (1H, ddd, $J_{13',14'}$ 10.2, $J_{13',15'B}$ 2.8, $J_{13',15'A}$ 0.8, 13′-H), 5.87 (1H, ddd, $J_{14',13'}$ 10.2, $J_{14',15'A}$ 6.0, $J_{14',15'B}$ 2.8, 14′-H), 7.33–7.43 (6H, m, Ar-H) and 7.64–7.70 (4H, m, Ar-H); *m*/*z* (CI, CH_4) 621 (MH^+, 45%), 603 (M − OH, 100), 543 (M − Ph, 35) and 279 (65).

(2′*R*,4′*R*,5′*R*,7′*S*,9′*S*,10′*S*,12′*R*,1″*S*)-{9-[1-(*tert*-Butyldiphenylsilyloxymethyl)propyl]-2-ethyl-4,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-2-yl}methanal 27

To a solution of alcohol **26** (5 mg 0.008 mmol) in dichloromethane (2 ml) was added *N*-methylmorpholine *N*-oxide (1.4 mg, 0.012 mmol) and powdered 4 Å molecular sieves (2 mg). The mixture was stirred at room temperature for 10 min, cooled to 0 °C then tetra-*n*-propylammonium perruthenate (*ca*. 0.14 mg, 4×10^{-4} mmol) added. The reaction mixture was stirred at room temperature for 3 h, filtered through Celite and the solvent evaporated to give an oil which was purified by flash chromatography using hexane–ethyl acetate (19 : 1) as eluent to give the *title compound* **27** (4 mg, 80%) as an unstable colourless oil (Found: MH^+, 619.3745. $C_{38}H_{54}O_5Si$ requires *M*H, 619.3819); ν_{max} (film)/cm^{-1} 1732s (C=O); δ_H (400 MHz; $CDCl_3$) 0.68 (3H, t, *J* 7.6, 2′-CH_2CH_3), 0.80 (3H, d, *J* 6.7, 10′-Me or 12′-Me), 0.81 (3H, d, *J* 6.5, 10′-Me or 12′-Me), 0.87 (3H, t, *J* 7.5, 1″-CH_2CH_3), 0.92 (3H, d, *J* 6.4, 4′-Me), 1.05 (9H, s, *t*-Bu), 1.17–2.06 (12H, m, 4 × CH_2, 3 × C*H*Me, C*H*Et), 2.31–2.33 (2H, m, 15′-H_A, 15′-H_B), 3.57 (1H, dd, $J_{A,B}$ 10.2, $J_{A,1''}$ 6.0, CH_ACH_BOSi), 3.66 (1H, dd, $J_{B,A}$ 10.2, $J_{B,1''}$ 9.0, CH_ACH_BOSi), 3.67 (1H, d, $J_{9',10'}$ 10.3, 9′-H), 5.57 (1H, ddd, $J_{13',14'}$ 10.1, $J_{13',15'A}$ 2.0, $J_{13',15'B}$ 2.0, 13′-H), 5.92 (1H, ddd, $J_{14',13'}$ 10.1, $J_{14',15'A}$ 4.6, $J_{14',15'B}$ 4.6, 14′-H), 7.35–7.41 (6H, m, Ar-H), 7.63–7.66 (4H, m, Ar-H) and 9.72 (1H, s, CHO); *m*/*z* (CI, CH_4) 619 (MH^+, 26%) and 541 (M − Ph, 28).

2-Acetyl-2-methyl-γ-butyrolactone 35

2-Acetyl-γ-butyrolactone **34** (39.3 g, 307 mmol) in anhydrous benzene (200 ml) was added dropwise to a stirred suspension of sodium metal (8 g, 348 mmol) in benzene (300 ml) containing methanol (1.5 ml) under nitrogen. The reaction mixture was stirred overnight, heated under reflux for 3 h then methyl iodide (115.8 g, 800 mmol) added. The reaction mixture was heated under reflux for 4 h, then left stirring overnight at room temperature. Sodium iodide was removed by filtration and washed several times with ethyl acetate. Evaporation of the combined filtrates afforded a pale yellow oil that was purified by distillation under reduced pressure to afford the title compound **35** (36.2 g, 83%) as a colourless oil, bp 120–122 °C/15 mm Hg (lit.[30] 120–122 °C/15 mmHg).

5-Chloro-3-methylpentan-2-one 36

A mixture of 2-acetyl-2-methyl-γ-butyrolactone **35** (36.2 g, 255 mmol), hydrochloric acid (87 ml of a 32% solution, 761 mmol) and distilled water (103 ml) was carefully heated until all gas evolution had ceased. The reaction mixture was distilled and 100 ml of distillate collected after which water (75 ml) was added and a further 60 ml of distillate collected. The organic layer was separated and the aqueous layer extracted with ether (3 × 100 ml). The combined organic layers were dried over calcium chloride and the solvent evaporated to afford the title compound **36** (30.5 g, 89%) as a colourless oil, bp 69–71 °C/19 mmHg (lit.[30] 70 °C/19 mm Hg).

1-Acetyl-1-methylcyclopropane 37

Chloride **36** (30.5 g, 227 mmol) was added to a solution of sodium hydroxide (14.0 g, 350 mmol) in water (18 ml) and the reaction mixture heated under reflux for 2 h. Water (32 ml) was added and heating continued for an additional 1.5 h before the water–ketone mixture was distilled until all the organic layer was removed from the reaction mixture. The organic layer of the distillate was separated and the aqueous layer saturated with solid potassium carbonate. The aqueous layer was extracted with ether and the combined organic layers dried over magnesium sulfate and then fractionally distilled to afford the title compound **37** (13.0 g, 58%) as a colourless liquid, bp 120–123 °C (lit.[30] bp 121–124 °C).

1-(1′-Methylcyclopropyl)ethanol 38

A solution of ketone **37** (6 g, 61.2 mmol) in anhydrous ether (60 ml) was added dropwise to a stirred mixture of lithium aluminium hydride (2.37 g, 62.5 mmol) in anhydrous ether (215 ml) at 0 °C under nitrogen. The reaction mixture was stirred at this temperature for 2 h then quenched with saturated sodium sulfate (8 ml). The precipitate was filtered off and washed several times with ether. The combined ether extracts were dried over sodium sulfate and the solvent removed at reduced pressure to afford a colourless oil. Further purification by flash chromatography using pentane–ether (4 : 1) as eluent afforded the title compound **38** (6.05 g, 99%) as a colourless oil (Found: M − H^+, 99.0809. $C_6H_{12}O$ requires *M* − H, 99.0804); ν_{max} (film)/cm^{-1} 3354br (OH), 2971s, 2876s, 1454s, 1375s, 1106s, 1073s, 1012s and 927s; δ_H (200 MHz; $CDCl_3$) 0.25–0.42 (4H, m, CH_2) 1.01 (3H, s, 1′-Me), 1.17 (3H, d, $J_{2,1}$ 6.4, H-2), 1.68 (1H, br s, OH) and 3.09 (1H, q, $J_{1,2}$ 6.4, C*H*OH); δ_C (50 MHz; $CDCl_3$) 10.6, 12.3 (CH_2, C-2′, C-3′), 17.1 (CH_3, C-1″), 19.4 (CH_3, C-2), 21.1 (quat., C-1′) and 74.5 (CH, C-1); *m*/*z* (EI) 99 (M − H, 100%), 85 (M − CH_3, 15), 69 (M − CH_3O, 17), 55 (M − C_2H_5O, 20) and 43 (M − CH_3CO, 18).

(*E*)-1-Bromo-3-methylpent-3-ene 8

Alcohol **38** (1.46 g, 14.6 mmol) and 2,4,6-trimethylpyridine (1.98 ml, 14.0 mmol) in anhydrous ether (32 ml) was treated with lithium bromide (3.29 g, 37.9 mmol) at −30 °C. The resultant suspension was cooled to −50 °C and phosphorus tribromide (1.45 ml, 15.3 mmol) added. The reaction mixture was allowed to warm to 0 °C over 1 h and stirred at this temperature for a further 6 h. 2,4,6-Trimethylpyridine (2.3 ml) and water (10 ml) were added and the aqueous layer extracted with ether (4 × 15 ml). The combined organic extracts were washed with saturated sodium bicarbonate (10 ml), brine (10 ml) and dried over sodium sulfate. Removal of solvent afforded the title compound **8** (1.17 g, 50%) as a colourless oil that was used without further purification in the next step (Found: M^+, 162.0052. $C_6H_{11}Br$ requires *M*, 162.0045); ν_{max} (film)/cm^{-1} 2954s, 2919s, 2861s, 1449s, 1384s, 1267s, 1201s, 1138s and

1020s; δ_H (200 MHz; $CDCl_3$) 1.60 (3H, d, $J_{5,4}$ 6.5, H-5), 1.61 (3H, s, H-1′), 2.53 (2H, t, $J_{2,1}$ 7.5, H-2), 3.42 (2H, t, $J_{1,2}$ 7.5, H-1) and 5.32 (1H, q, $J_{4,5}$ 6.5, H-4); δ_C (50 MHz; $CDCl_3$) 13.4 (CH_3, C-5), 15.2 (CH_3, C-1′), 31.7 (CH_2, C-1), 42.9 (CH_2, C-2), 121.2 (CH, C-4) and 132.6 (quat., C-3); *m/z* (CI, CH_4) 163 (MH^+, 100%), 135 (M − C_2H_3, 10) and 119 (M − C_3H_7, 21).

(*E*)-(2*R*,4*R*,5*R*,7*S*,9*S*,10*S*,12*R*,1′*S*,1″*S*)- and (*E*)-(2*R*,4*R*,5*R*,7*S*,9*S*,10*S*,12*R*,1′*R*,1″*S*)-9-[1-(*tert*-Butyldiphenylsilyloxymethyl)propyl]-2-ethyl-2-(1-hydroxy-4-methylhex-4-en-1-yl)-4,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene 28, 29 [*erythro* and *threo*]

A suspension of magnesium powder (100 mg, 4.35 mmol) in ether (0.75 ml) was activated by stirring under argon for 12 h. Bromide **8** (10 mg, 0.06 mmol) was then added to initiate formation of the alkyl metal reagent. To this, the Barbier mixture, a solution of bromide **8** (5 mg, 0.03 mmol) and aldehyde **27** (3.5 mg, 0.006 mmol) in ether (0.5 ml) was added dropwise with gentle heating. The reaction mixture was heated gently under reflux for 2 h, cooled to room temperature then quenched with ice–water (0.5 ml). The mixture was extracted with ether (3 × 10 ml) and dichloromethane (3 × 10 ml) and the combined organic extracts dried over potassium carbonate. The solvent was removed under reduced pressure to afford a yellow oil which was purified by flash chromatography using hexane–ether (20 : 1) containing a trace of triethylamine as eluent to afford the following.

(i) *(E)-(2R,4R,5R,7S,9S,10S,12R,1′S,1″S)-9-[1-(tert-Butyldiphenylsilyloxymethyl)propyl]-2-ethyl-2-(1-hydroxy-4-methylhex-4-en-1-yl)-4,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-ene* **28** [*erythro*] (2.4 mg, 70%) as a colourless oil (Found: MH^+, 703.4739. $C_{44}H_{66}O_5Si$ requires *M*H, 703.4757); ν_{max} (film)/cm^{-1} 3467 (OH), 2928s, 2856s, 1461s, 1428s, 1379s, 1262s (C-O), 1112s (C-O), 1078s (C-O), 955s, 937s and 824s; δ_H (400 MHz; $CDCl_3$) 0.63 (3H, t, $J_{2'',1''}$ 7.6, 2″-Me), 0.82 (3H, d, *J* 6.8, 12-Me), 0.85 (3H, d, *J* 7.2, 10-Me), 0.88 (3H, t, *J* 7.6, 3‴-Me), 0.97 (3H, d, *J* 6.8, 4-Me), 1.00 (3H, d, *J* 6.4, 6′-Me), 1.06 (9H, s, ′Bu), 1.26 (3H, s, 4′-Me), 1.20–2.35 (16H, m, H-3_A, H-3_B, H-4, H-10, H-11_{ax}, H-11_{eq}, H-12, H-$2'_A$, H-$2'_B$, H-$3'_A$, H-$3'_B$, H-$1''_A$, H-$1''_B$, H-1‴, H-$2'''_A$, H-$2'''_B$), 2.23 (1H, dd, J_{gem} 16.8, $J_{15,14}$ 6.4, H-15_A), 2.43 (1H, ddd, J_{gem} 16.8, $J_{15,14}$ 2.8, $J_{15,13}$ 2.8, H-15_B), 3.55 (1H, dd, J_{gem} 10.2, $J_{1''',1''}$ 6.0 Hz, H-$1'''_B$), 3.59 (1H, dd, $J_{1',2'A}$ 8.0, $J_{1',2'B}$ 2.5, H-1′), 3.71 (1H, dd, J_{gem} 10.2, $J_{1''',1''}$ 8.0, H-$1'''_A$), 3.81 (1H, s, OH), 3.87 (1H, d, $J_{9ax,10ax}$ 10.4, H-9_{ax}), 5.18 (1H, q, $J_{5',6'}$ 6.4, H-5′), 5.49 (1H, dd, $J_{13,14}$ 9.9, $J_{13,15}$ 2.2, H-13), 5.87 (1H, ddd, $J_{14,13}$ 9.9, $J_{14,15}$ 6.4, $J_{14,15}$ 3.2, H-14), 7.35–7.39 (6H, m, Ar-H) and 7.64–7.68 (4H, m, Ar-H); *m/z* (LSIMS) 703 (MH^+, 90%), 685 (M − OH, 100), 645 (M − C_4H_9, 38), 589 (M − $C_7H_{13}O$, 73), 460 (M − $C_{14}H_{26}O_3$, 19), 429 (15) and 391 (47).

(ii) *(E)-(2R,4R,5R,7S,9S,10S,12R,1′R,1″S)-9-[1-(tert-Butyldiphenylsilyloxymethyl)propyl]-2-ethyl-2-(1-hydroxy-4-methylhex-4-en-1-yl)-4,10,12-trimethyl-1,6,8-trioxadispiro-[4.1.5.3]pentadec-13-ene* **29** [*threo*] (0.5 mg, 15%) as a colourless oil (Found: MH^+, 703.4739. $C_{44}H_{66}O_5Si$ requires *M*H, 703.4757); ν_{max} (film)/cm^{-1} 3467 (OH), 2928s, 2856s, 1461s, 1428s, 1379s, 1262s (C-O), 1112s (C-O), 1078s (C-O), 955s, (C-O), 937s (C-O) and 824s (C-O-C); δ_H (400 MHz; $CDCl_3$) 0.70 (3H, t, $J_{2'',1''}$ 7.6, 2″-Me), 0.82 (3H, d, *J* 6.8, 12-Me), 0.85 (3H, d, *J* 6.4, 10-Me), 0.86 (3H, t, *J* 7.6, 3‴-Me), 0.96 (3H, d, *J* 5.8, 6′-Me), 0.98 (3H, d, *J* 6.8, 4-Me), 1.06 (9H, s, ′Bu), 1.26 (3H, s, 4′-Me), 1.20–2.10 (16H, m, H-3_A, H-3_B, H-4, H-10, H-11_{ax}, H-11_{eq}, H-12, H-$2'_A$, H-$2'_B$, H-$3'_A$, H-$3'_B$, H-$1''_A$, H-$1''_B$, H-1‴, H-$2'''_A$, H-$2'''_B$), 2.22 (1H, dd, J_{gem} 16.8, $J_{15,14}$ 6.0, H-15_A), 2.40 (1H, ddd, J_{gem} 16.6, $J_{15,14}$ 3.1, $J_{15,13}$ 3.1, H-15_B), 3.36 (1H, dd, $J_{1',2'A}$ 10.4, $J_{1',2'B}$ 2.0, H-1′), 3.60 (1H, dd, J_{gem} 10.0, $J_{1''',1''}$ 6.0, H-$1'''_B$), 3.58–3.63 (1H, m, OH), 3.71 (1H, dd, J_{gem} 10.0, $J_{1''',1''}$ 7.6, H-$1'''_A$), 3.86 (1H, d, $J_{9ax,10ax}$ 10.0, H-9_{ax}), 5.23 (1H, q, $J_{5',6'}$ 5.8, H-5′), 5.49 (1H, dd, $J_{13,14}$ 10.1, $J_{13,15}$ 2.2, H-13), 5.87 (1H, ddd, $J_{14,13}$ 10.1, $J_{14,15}$ 6.3, $J_{14,15}$ 3.3, H-14), 7.33–7.41 (6H, m, Ar-H) and 7.64–7.68 (4H, m, Ar-H); *m/z* (LSIMS) 703 (MH^+, 90%), 685 (M − OH, 100), 645 (M − C_4H_9, 38), 589 (M − $C_7H_{13}O$, 73), 518 (12), 460 (19), 429 (15) and 391 (47).

(2*R*,4*R*,5*R*,7*S*,9*S*,10*S*,12*R*,1′*S*,4′*S*,5′*S*,1″*S*)- and (2*R*,4*R*,5*R*,7*S*,9*S*,10*S*,12*R*,1′*R*,4′*R*,5′*R*,1″*S*)-9-[1-(*tert*-Butyldiphenylsilyloxymethyl)propyl]-2-(4,5-epoxy-1-hydroxy-4-methylhexan-1-yl)-2-ethyl-4,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene 30, 31

Freshly prepared dimethyldioxirane[31] (0.5 ml) was added to a solution of alcohol **28** (2.4 mg, 0.03 mmol) and potassium carbonate (1 mg) in acetone (0.5 ml) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and the solvent removed under reduced pressure to afford a colourless oil. Purification by flash chromatography using hexane–ethyl acetate (20 : 1) containing a trace of triethylamine as eluent to afford a 1 : 1 mixture of *title compounds* **30** and **31** (2.1 mg, 86%) as a colourless oil (Found: MH^+, 719.4713. $C_{44}H_{66}O_6Si$ requires *M*H, 719.4706); ν_{max} (film)/cm^{-1} 3456 (OH), 2947s, 2914s, 2858s, 1458s, 1379s, 1107s (C-O), 1079s (C-O), 1070s (C-O), 955s (C-O), 944s (C-O) and 915s (C-O); δ_H (400 MHz; $CDCl_3$) 0.62, 0.64* (3H, t, $J_{2'',1''}$ 7.6, 2″-Me), 0.83 (3H, d, *J* 6.8, 12-Me), 0.89 (3H, d, *J* 6.8, 10-Me), 0.90 (3H, t, *J* 7.0, 3‴-Me), 1.01 (3H, d, *J* 6.8, 4-Me), 1.06, 1.07* (9H, s, ′Bu), 1.26 (3H, s, 4′-Me), 1.23–1.28 (1H, m, 6′-Me), 1.20–2.35 (16H, m, H-3_A, H-3_B, H-4, H-10, H-11_{ax}, H-11_{eq}, H-12, H-$2'_A$, H-$2'_B$, H-$3'_A$, H-$3'_B$, H-$1''_A$, H-$1''_B$, H-1‴, H-$2'''_A$, H-$2'''_B$), 2.23 (1H, dd, J_{gem} 17.2, $J_{15,14}$ 6.0, H-15_A), 2.43, 2.44* (1H, ddd, J_{gem} 17.4, $J_{15,14}$ 3.1, $J_{15,13}$ 3.1, H-15_B), 3.53–3.60 (2H, m, H-1′, H-$1'''_B$), 3.71, 3.72* (1H, dd, J_{gem} 10.4, $J_{1''',1''}$ 8.0, H-$1'''_A$), 3.81, 3.82* (1H, s, OH), 3.87, 3.91* (1H, d, $J_{9ax,10ax}$ 10.2, H-9_{ax}), 3.84–3.89 (1H, m, H-5′), 5.48, 5.49* (1H, dd, $J_{13,14}$ 10.3, $J_{13,15}$ 2.7, H-13), 5.85–5.89 (1H, m, H-14), 7.33–7.41 (6H, m, Ar-H) and 7.64–7.67 (4H, m, Ar-H); *m/z* (LSIMS) 719 (MH^+, 93%), 701 (M − OH, 100), 661 (M − C_4H_9, 21), 643 (M − $C_3H_7O_2$, 28), 590 (22), 544 (8) and 480 (9).

(2*R*,4*R*,5*R*,7*S*,9*S*,10*S*,12*R*,2′*S*,5′*R*,1″*S*,1‴*S*)- and (2*R*,4*R*,5*R*,7*S*,9*S*,10*S*,12*R*,2′*R*,5′*S*,1″*R*,1‴*S*)-9-[1-(*tert*-Butyldiphenylsilyloxymethyl)propyl]-2-ethyl-4,10,12-trimethyl-2-[5-methyl-5-(1-hydroxyethyl)tetrahydro-2-furyl]-1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-ene 32, 33

Pyridinium toluene-*p*-sulfonate (1 mg) was added to a solution of a 1 : 1 mixture of epoxides **30** and **31** (2 mg, 0.003 mmol) in dichloromethane (0.5 mL) at 0 °C. After stirring for 4 h at room temperature, the solvent was evaporated and the residue purified by flash chromatography using hexane–ethyl acetate (9 : 1) containing a trace of triethylamine as eluent. Further purification by high performance liquid chromatography [Whatman Partisil 5 (4.6 mm ID × 250 mm)] using hexane–ethyl acetate (93 : 7) containing a trace of triethylamine as eluent to afford the following compounds.

(i) *(2R,4R,5R,7S,9S,10S,12R,2′S,5′R,1″S,1‴S)-9-[1-(tert-Butyldiphenylsilyloxymethyl)propyl]-2-ethyl-4,10,12-trimethyl-2-[5-methyl-5-(1-hydroxyethyl)tetrahydro-2-furyl]-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene* **32** (retention time = 36 min) as a colourless oil (0.6 mg, 30%) (Found: MH^+, 719.4684. $C_{44}H_{66}O_6Si$ requires *M*H, 719.4706); ν_{max} (film)/cm^{-1} 3464 (OH), 2938s, 2861s, 1463s, 1393s, 1200s (C-O), 1094s (C-O), 1073s (C-O), 1044s (C-O), 1005s (C-O), 982s (C-O), 943s (C-O) and 890s (C-O); δ_H (400 MHz; $CDCl_3$) 0.67 (3H, t, $J_{2''',1'''}$ 7.6, 2‴-Me), 0.84 (3H, d, *J* 6.0, 12-Me), 0.86 (3H, t, *J* 7.8, 3‴-Me), 0.87 (3H, d, *J* 7.2, 10-Me), 0.98 (3H, d, *J* 6.4, 4-Me), 1.06 (9H, s, ′Bu), 1.09 (3H, d, $J_{2'',1''}$ 6.4, 2″-Me), 1.26 (3H, s, 5′-Me), 1.15–2.50 (16H, m, H-3_A, H-3_B, H-4, H-10, H-11_{ax}, H-11_{eq}, H-12, H-$3'_A$, H-$3'_B$, H-$4'_A$, H-$4'_B$, H-$1'''_A$, H-$1'''_B$, H-1‴, H-$2''''_A$, H-$2''''_B$), 2.14 (1H, dd, J_{gem} 17.0, $J_{15,14}$ 6.2, H-15_A), 2.39 (1H, ddd, J_{gem} 16.4, $J_{15,14}$ 3.0, $J_{15,13}$ 3.0, H-15_B), 3.50 (1H, br s, OH),

3.57 (1H, J_{gem} 10.2, $J_{1''',1'''}$ 5.4, H-1$''''_B$), 3.70 (1H, dd, J_{gem} 10.2, $J_{1''',1'''}$ 8.0, H-1$''''_A$), 3.77 (1H, q, $J_{1'',2''}$ 6.4, H-1″), 3.85 (1H, d, $J_{9ax,10ax}$ 10.8, H-9$_{ax}$), 4.11 (1H, dd, $J_{2',3'a}$ 7.0, $J_{2',3'b}$ 7.0, H-2′), 5.48 (1H, dd, $J_{13,14}$ 9.7, $J_{13,15}$ 2.4, H-13), 5.85 (1H, ddd, $J_{14,13}$ 9.7, $J_{14,15}$ 6.5, $J_{14,15}$ 2.7, H-14), 7.34–7.41 (6H, m, Ar-H) and 7.64–7.67 (4H, m, Ar-H); *m/z* (LSIMS) 719 (MH^+, 100%), 701 (M − OH, 60), 661 (M − C_4H_9, 30), 589 (32), 407 (20) and 309 (22).

(ii) *(2R,4R,5R,7S,9S,10S,12R,2′R,5′S,1″R,1‴S)-9-[1-(tert-Butyldiphenylsilyloxymethyl)propyl]-2-ethyl-4,10,12-trimethyl-2-[5-methyl-5-(1-hydroxyethyl)tetrahydro-2-furyl]-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene* **33** (retention time = 12 min) as a colourless oil (0.6 mg, 30%); ν_{max} (film)/cm^{-1} 3462 (OH), 2934s, 2863s, 1466s, 1389s, 1205s (C-O), 1091s (C-O), 1073s (C-O), 1042s (C-O), 1009s (C-O), 980s (C-O), 942s (C-O) and 892s (C-O); δ_H (400 MHz; $CDCl_3$) 0.68 (3H, t, $J_{2''',1'''}$ 6.4, 2‴-Me), 0.81 (3H, d, *J* 6.4, 12-Me), 0.85 (3H, t, *J* 7.4, 3‴″-Me), 0.89 (3H, d, *J* 7.6, 10-Me), 0.95 (3H, d, *J* 6.8, 4-Me), 1.05 (9H, s, ᵗBu), 1.04–1.06 (3H, m, 2″-Me), 1.25 (3H, s, 5′-Me), 1.11–2.43 (18H, m, H-3A, H-3B, H-4, H-10, H-11$_{ax}$, H-11$_{eq}$, H-12, H-3′A, H-3′B, H-4′A, H-4′B, H-1‴A, H-1‴B, H-1‴″, H-2‴″A, H-2‴″B, H-15A, H-15B), 3.50 (1H, br s, OH), 3.57 (1H, J_{gem} 10.4, $J_{1''',1'''}$ 6.0, H-1$''''_B$), 3.65–3.72 (2H, m, H-1″, H-1$''''_A$), 3.79 (1H, d, $J_{9ax,10ax}$ 9.6, H-9$_{ax}$), 4.05–4.09 (1H, m, H-2′), 5.52 (1H, d, $J_{13,14}$ 10.4, H-13), 5.87–5.92 (1H, m, H-14), 7.33–7.41 (6H, m, Ar-H) and 7.63–7.69 (4H, m, Ar-H); *m/z* (LSIMS) 719 (MH^+, 100%), 701 (M − OH, 63), 661 (M − C_4H_9, 35), 589 (29), 407 (23) and 309 (25).

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