Synthesis of C-2 functionalised 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-enes

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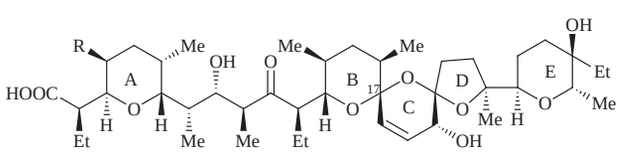
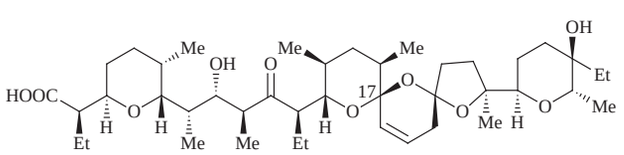
The syntheses of bis-spiroacetals 28 and 44, model systems for the tricyclic bis-spiroacetal moiety of the polyether antibiotic *epi*-17-deoxy-(*O*-8)-salinomycin 3, are described. Introduction of an aldehyde group at C-2 was necessary for further elaboration of the right hand side of the molecule. It was found that the choice of protecting group on the hydroxymethyl substituent (precursor to an aldehyde group) was crucial to the outcome of the key oxidative cyclisation.

The polyether antibiotics salinomycin **1**,[1] narasin A **2**,[2] *epi*-17-deoxy-(*O*-8)-salinomycin **3**,[3] noboritomycin,[4] CP44,161[5] and X-14766A[6] pose a considerable synthetic challenge due to the presence of the rare and complex 1,6,8-trioxadispiro-[4.1.5.3]pentadec-13-ene ring system. Salinomycin **1** and narasin A **2** are commercial agents which are widely used in veterinary medicine as growth promotants for ruminants and as coccidiostats for poultry, however, their parenteral toxicity has prevented their use as clinical antibacterial agents. The X-ray structure of a *p*-iodophenacyl ester derivative of salinomycin revealed the presence of the 1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-ene ring system whose complex stereochemistry has been addressed in several syntheses.



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

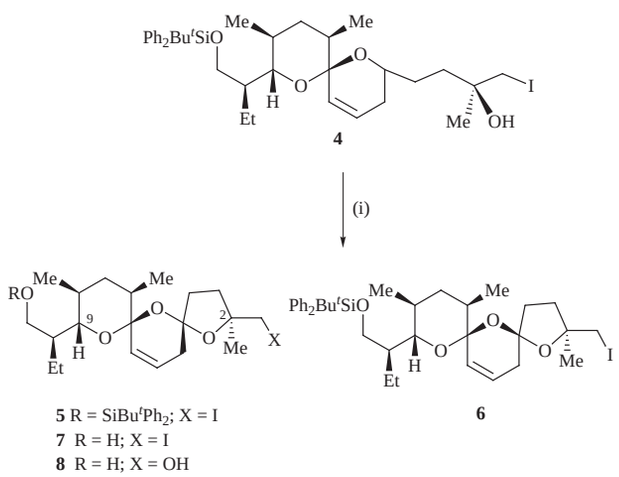


epi-17-Deoxy-(*O*-8)-salinomycin **3**

Kishi *et al.*[7] first reported the synthesis of salinomycin **1** in a lecture in 1982 wherein the bis-spiroacetal unit was assembled *via* addition of an acetylide anion to a lactone followed by acid catalysed cyclisation. A later approach by Yonemitsu and co-workers[8–11] also utilised an acid catalysed cyclisation to assemble the bis-spiroacetal unit with the cyclisation precursor being constructed from starting materials readily available from the chiral pool. More recently, Kocienski and co-workers[12–14] have used the construction of the salinomycin framework for the development of a number of innovative synthetic methods. Thus, the bis-spiroacetal moiety was constructed using an oxidative rearrangement of an acylfuran as demonstrated on simpler model systems[15,16] as well as *via* stereoselective hydrolysis of an allenol ether which 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 towards *epi*-17-deoxy-(*O*-8)-salinomycin **3** 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 D rings at a later stage in the synthesis.

Towards this end we reported[17] a synthesis of iodo bis-spiroacetal **5**,**6** *via* oxidative cyclisation of hydroxy spiroacetal **4** (Scheme 1). Iodide **5** was considered a suitable advanced

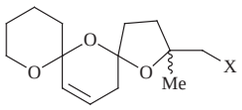


5 R = $SiBu^tPh_2$; X = I
7 R = H; X = I
8 R = H; X = OH

Scheme 1 *Reagents*: (i) $PhI(OAc)_2$ (3 equiv.), I_2 (2 equiv.), cyclohexane, *hv*, 24 h, **5**:**6** 1.7:1, 57%

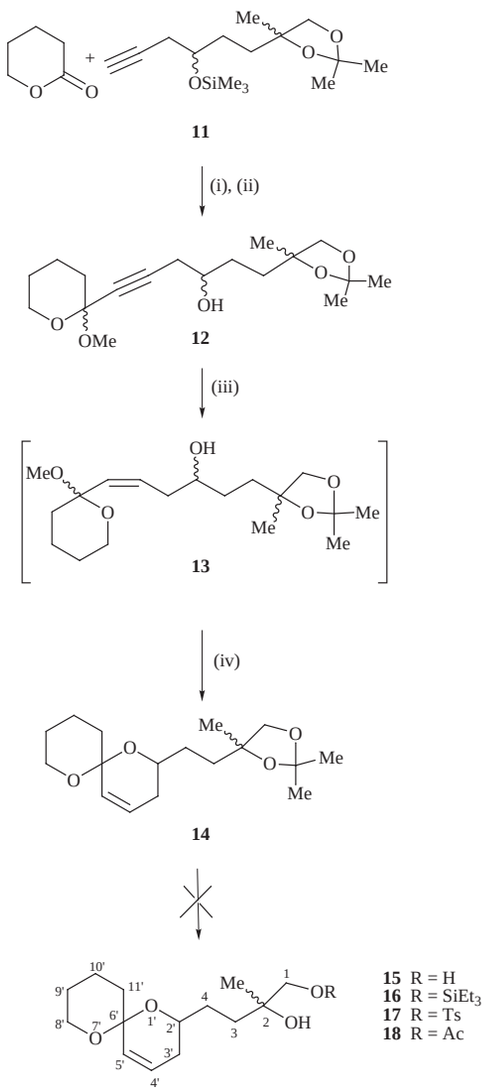
intermediate for the synthesis of *epi*-17-deoxy-(*O*-8)-salinomycin **3** in that it contained an iodomethyl group at C-2 which could be converted into an aldehyde for elaboration of the E ring together with a protected hydroxyethyl group at C-9 which could also be converted to an aldehyde at a later stage in the synthesis when appendage of the A ring was required.

Unfortunately conversion of neopentyl iodide **5** into a hydroxy group required the use of potassium superoxide in dimethyl sulfoxide in the presence of 18-crown-6, conditions which unfortunately resulted in deprotection of the *tert*-butyldimethylsilyl group at C-9 forming alcohol **7** initially, then diol **8**. Despite extensive experimentation alternative conditions for displacement of iodide **5** without affecting the silyl ether were not realized. In order to avoid this unfavourable displacement reaction we have now reexamined the key oxidative cyclisation step on a model system using hydroxy spiroacetals which already have a protected hydroxy group in place. This work has resulted in a more efficient synthesis of bis-spiroacetal **10** than that initially reported[18] *via* iodide **9** and is reported herein.



9 X = I
10 X = OH

Our initial attention[18] focused on the synthesis of bicyclic spiroacetals **15**, **16**, **17** and **18** bearing a hydroxy group at C-1 or a substituent that could be readily transformed into a hydroxy group after oxidative cyclisation of the tertiary hydroxy group. We therefore concentrated on the synthesis of spiroacetal **14** starting from acetylene **11** and δ-valerolactone (Scheme 2) with

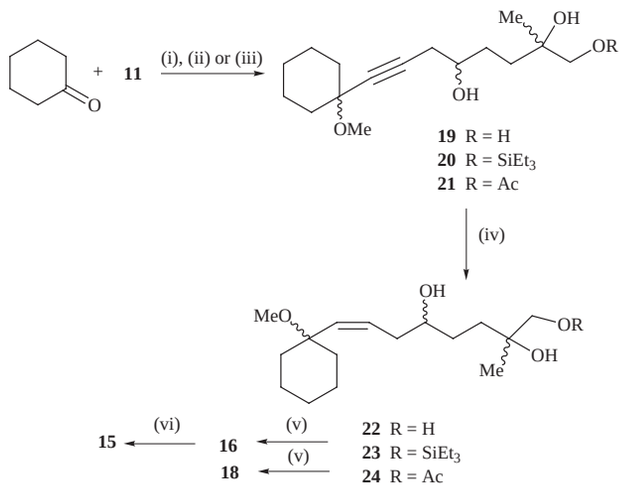


Scheme 2 *Reagents*: (i) Bu^{n}Li, THF, −78 °C, then δ-valerolactone, −78 °C; (ii) MeOH, PPTS, room temp., 15 h, 82%; (iii) H_2, 1 atm, Lindlar catalyst, pentane, room temp., 1 h, 94%; (iv) CSA, CH_2Cl_2, room temp., 0.5 h, 81%

the view that selective protection or functionalisation of the terminal hydroxy group would be possible after removal of the acetonide protecting group.

δ-Valerolactone was added to the lithium acetylide generated from acetylene **11** using butyllithium at −78 °C and the crude mixture treated with methanol and a catalytic quantity of pyridinium toluene-*p*-sulfonate to afford methoxy acetal **12** (82%) with the acetonide group intact. Partial hydrogenation over Lindlar catalyst then afforded alkene **13** (94%) which underwent cyclisation to spiroacetal **14** (81%) using a catalytic quantity of camphorsulfonic acid in dichloromethane at room temperature.

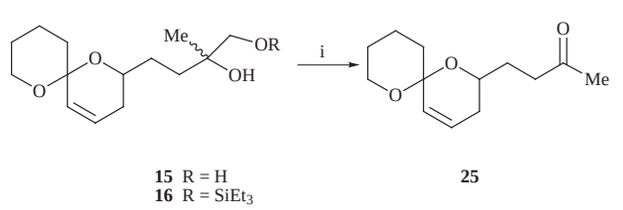
Despite the ease of preparation of spiroacetal acetonide **14**, it was disappointing to find that attempted removal of the acetonide using a range of acid catalysts resulted in destruction of the unsaturated spiroacetal unit. It was therefore decided to remove the acetonide before the spirocyclisation step (Scheme 3).



Scheme 3 *Reagents*: (i) Bu^{n}Li, THF, −78 °C, then δ-valerolactone, −78 °C then MeOH, Amberlite IR 118, room temp., 15 h, 82%; (ii) Et_3SiCl, Et_3N, THF, room temp., 1 h, 69%; (iii) Ac_2O, Et_3N, CH_2Cl_2, room temp., 0.5 h, 64% over 3 steps; (iv) H_2, 1atm, Lindlar catalyst, pentane, room temp., 1 h, 94%; (v) PPTS, CH_2Cl_2, room temp., 0.5 h, 80% (**23**), 78% (**24**) over 2 steps; (vi) Bu$^n{}_4N^+F^-$, THF, room temp., 0.5 h, 94%

Addition of δ-valerolactone to the acetylide derived from acetylene **11** followed by treatment with methanol and Amberlite IR 118 resin resulted in formation of triol **19** wherein hydrolysis of the acetonide had also occurred. Attempts to effect partial hydrogenation of the acetylene were hampered by the difficulties associated with monitoring the reaction, a consequence of the inherent polarity of triol **19**. In order to overcome this problem the primary hydroxy group was protected as a triethylsilyl ether **20** before partial hydrogenation to alkene **23**. Acid catalysed cyclisation then proceeded readily using pyridinium toluene-*p*-sulfonate in dichloromethane affording spiroacetal **16** in 80% yield.

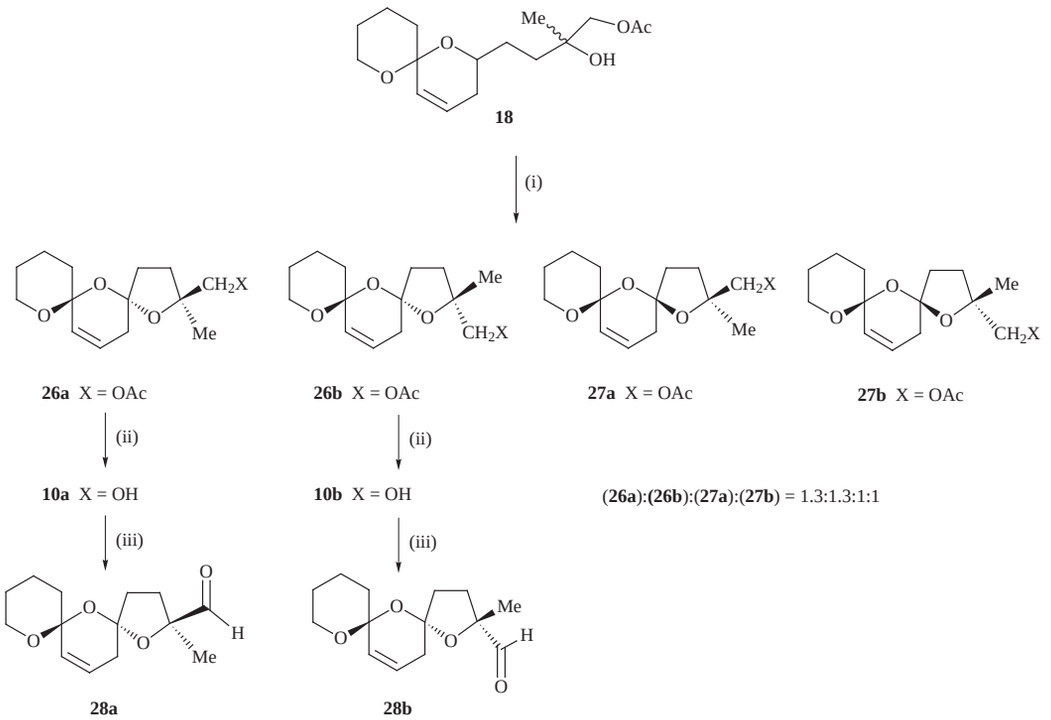
Oxidative cyclisation of hydroxy spiroacetal **15**, prepared from **16** by desilylation using tetrabutylammonium fluoride, using iodobenzene diacetate and iodine with irradiation using a tungsten filament lamp afforded exclusively the fragmentation product, methyl ketone **25** (Scheme 4) in 68% yield. Silyl ether



Scheme 4 *Reagents*: (i) $PhI(OAc)_2$ (3 equiv.), I_2 (2 equiv.), cyclohexane, *hν*, 24 h, 68% (R = H), 73% (R = $SiEt_3$)

16 reacted in a similar fashion affording the methyl ketone in 73% yield. We therefore decided to look at oxidative cyclisation of hydroxy spiroacetals in which the hydroxymethyl group at C-2 was protected or functionalised with an electron withdrawing group and focused on cyclisation of tosylate **17** and acetate **18**.

Tosylate **17** was available to us from our previous work[18] and acetate **18** was prepared in a similar manner to silyl ether **16** (Scheme 3). Triol **19** underwent selective monoacetylation of



Scheme 5 *Reagents*: (i) $PhI(OAc)_2$ (3 equiv.), I_2 (2 equiv.), cyclohexane, *hv*, 24 h, 69%; (ii) K_2CO_3, MeOH, room temp., 85%; (iii) TPAP, NMO, CH_2Cl_2, room temp., 81%. *Note*: All compounds are racemic although only one enantiomer is indicated.

the terminal hydroxy group under standard conditions affording monoacetate **21**. Partial hydrogenation over Lindlar catalyst followed by acid catalysed cyclisation of the resultant alkene **24** afforded spiroacetal acetate **18**. The choice of substituent at C-1 was crucial to the outcome of the subsequent spirocyclisation in that tosylate **17** failed to form a bis-spiroacetal using iodobenzene diacetate and iodine whereas acetate **18** underwent smooth cyclisation to a 1.3 : 1 mixture of bis-spiroacetals **26,27** in 69% yield (Scheme 5). Hydrolysis of the major *trans* bis-spiroacetal acetate **26** (as a 1 : 1 mixture of diastereomers) afforded alcohols **10a** and **10b** which were separable by flash chromatography due to the ability of **10b** to participate in intramolecular hydrogen bonding. Alcohol **10b** was then oxidised cleanly to the aldehyde **28b** in 81% yield and in the same way **10a** was oxidised to **28a**.

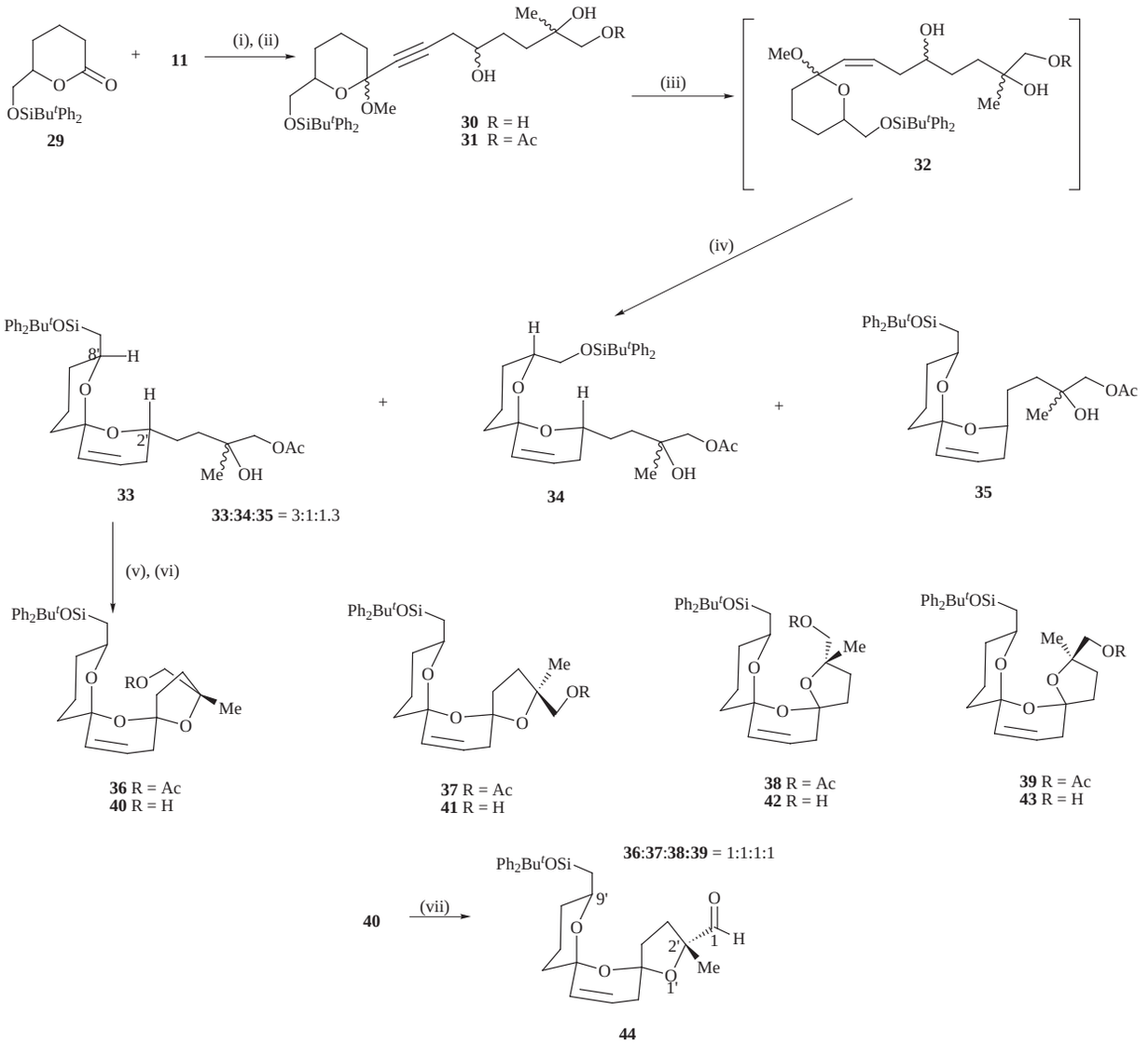
Aldehyde **28** is an important compound for studying the elaboration of the BCD tricyclic bis-spiroacetal unit to incorporate the highly functionalised E ring. The synthesis reported herein is far more efficient than that based on our earlier work wherein the acetonide group in acetylene **11** was converted into a differentially protected triol before coupling to δ-valerolactone. The present work required a detailed understanding of the relative sensitivity of acetonides, tertiary methoxy acetals and unsaturated spiroacetals in order to determine the precise order of events to reach the desired target.

Our attention next focused on the synthesis of aldehyde **44** (Scheme 6) which not only had an aldehyde group at C-2′ for elaboration of the right hand side of the bis-spiroacetal but also contained a protected hydroxymethyl group at C-9′ in preparation for elaboration of the left hand side. Addition of lactone **29**[19] to the lithium acetylide derived from acetylene **11** afforded methoxy acetal **30** after treatment with acidic methanol. Monoacetylation of the primary hydroxy group afforded acetate **31** which underwent partial hydrogenation to alkene **32** which was immediately subjected to acid catalysed cyclisation resulting in formation of a 3 : 1 : 1.3 mixture of bicyclic spiroacetals **33,34,35**.

The presence of the additional protected hydroxymethyl group on the saturated ring of spiroacetals **33,34,35** provided an extra complication in the assignment of stereochemistry for this series of compounds. The major isomer **33** was that wherein the substituents at C-2′ and C-8′ both adopted equatorial positions and the spiro centre adopted the more stable bis-axial configuration. In isomer **33**, both the axial methine protons, 8′ax-H and 2′-ax-H are 1,3-diaxial to O-1′ and O-7′ respectively and resonate in the range δ_H 3.90–3.97. These protons are both deshielded relative to the equatorial methine protons, 8′eq-H and 2′eq-H in isomers **34** and **35** respectively. Spiroacetal **34** is distinguished from **35** by the chemical shift of the methine proton, 2′ax-H which resonates at δ_H 4.10–4.13 and is more deshielded than the analogous proton in **33** due to its close proximity to the silyloxy group.

The major spiroacetal **33** was readily separated by flash chromatography from the more polar inseparable mixture of spiroacetals **34** and **35**. Spiroacetal **33** was then subjected to oxidative cyclisation using iodobenzene diacetate and iodine affording a 1 : 1 : 1 : 1 mixture of bis-spiroacetals **36,37,38,39** in 60% overall yield. Due to the close proximity of H-4′ to O-8′ one of the methylene protons at C-4′ in the *trans* isomers **36,37** was characteristically[17,18] deshielded relative to the same proton in the *cis* isomers **38,39**. Bis-spiroacetal **39** is distinguished from isomer **38** by the chemical shift of the 2′-Me group.[17,18] In isomer **39** 2′-Me is 1,3-*syn* to the C–O bond of the neighbouring ring and is therefore deshielded (δ_H 1.26) relative to 2′-Me in isomer **38** (δ_H 1.15). The two *trans* isomers **36,37** can be distinguished in a similar manner. Thus, 2′-Me in isomer **37** is deshielded relative to that in **36** (δ_H 1.47 for **37** compared with δ_H 1.24 for **36**).

Bis-spiroacetal **39** was the most polar of the bis-spiroacetals **36,37,38,39** and was readily separated by flash chromatography from an inseparable mixture of bis-spiroacetals **36,37,38**. Hydrolysis of the mixture of acetates **36,37,38** under standard conditions afforded alcohols **40,41,42** which allowed initial separation of the more polar alcohol **41** from an inseparable mixture of alcohols **40** and **42**. The lower polarity of alcohols **40** and **42** was attributed to the ability of these isomers to participate in intramolecular hydrogen bonding to O-6′ or O-8′. After further purification bis-spiroacetal **40** was then converted to aldehyde **44** using tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide. Bis-spiroacetal **44**, which bears appropriate functionality at C-2′ and C-9′ in preparation for



Scheme 6 *Reagents*: (i) Bu^{n}Li, THF, −78 °C, then lactone **29**, −78 °C then MeOH, Amberlite IR 118, room temp., 15 h, 37% over two steps; (ii) Ac_2O, Et_3N, CH_2Cl_2, room temp., 70%; (iii) H_2, 1 atm., Lindlar catalyst, pentane, room temp., 1 h; (iv) PPTS, CH_2Cl_2, room temp., 0.5 h, 84% over two steps; (v) $PhI(OAc)_2$ (3 equiv.), I_2 (2 equiv.), cyclohexane, *hv*, 24 h, 60%; (vi) K_2CO_3, MeOH, 90%; (vii) TPAP, NMO, CH_2Cl_2, room temp., 50%

further elaboration of the left and right hand sides of the molecule, is an important model compound for the construction of analogues of *epi*-17-deoxy-(*O*-8)-salinomycin **3** and related polyether antibiotics.

Experimental

Mps were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 200 (200.13 MHz), a Bruker AM 200 (200.13 MHz), a Bruker AM360 (360 MHz), a Bruker AMX 400 (400.13 MHz) or a Bruker DRX 400 (400.12 MHz) spectrometer at ambient temperature. All *J* values are given in Hz. ^{13}C NMR spectra were recorded on a Bruker AC 200 (50.3 MHz), Bruker AM 400 (100.6 MHz), Bruker AMX 400 (100.4 MHz) or a Bruker DRX 400 (100.51 MHz) spectrometer at ambient temperature with complete proton decoupling. Data are expressed in parts per million downfield shift from tetramethylsilane as an internal standard and reported as position (δ_C), multiplicity (aided by DEPT 135 and DEPT 90 experiments) and assignment (aided by COSY and HETCOR experiments). Low resolution mass spectra were recorded on a VG70-250S, a VG70-SD or a 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 (i) electron impact (EI), (ii) desorption electron impact (DEI), (iii) chemical ionisation with ammonia or methane as reagent gas (CI) and (iv) desorption chemical ionisation (DCI) with ammonia as reagent gas. 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 or Riedel-de Haen Kieselgel (both 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.

1-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)-3-trimethylsilyloxyhex-5-yne 11

Chlorotrimethylsilane (200 mg, 1.8 mmol) was added to a mixture of 1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)hex-5-yn-3-ol[18] (382 mg, 1.8 mmol) and dry triethylamine (360 mg, 3.6 mmol) in dry tetrahydrofuran (25 cm^3) at room temperature under nitrogen. The reaction mixture was stirred at room temperature

for 2 h, whereupon a white precipitate formed. Water (3 cm^3) was added and the reaction mixture was extracted with diethyl ether (3 × 30 cm^3). The ethereal extract was washed with water (10 cm^3), brine (10 cm^3) 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–diethyl ether (9:1) as eluent to give the *title compound* **11** (476 mg, 93%) as a colourless oil. $\nu_{max}(CHCl_3)/cm^{-1}$ 3303s (C≡CH), 3053m, 2985s, 2872w (CH), 2305m (C≡C), 1421, 1378, 1261, 1096, 1058 and 980; δ_H(200 MHz; $CDCl_3$) 0.13 (9H, s, Me_3Si), 1.28, 1.29 (3H, s, 4′-Me), 1.38 (6H, s, 2 × 2′-Me), 1.46–1.82 (4H, m, s × CH_2), 1.93 (1H, t, *J* 2.5, C≡CH), 2.21–2.43 (2H, m, $CH_2C{\equiv}C$), 3.66–3.84 (3H, m, CH_2O and CHOSi); δ_C(50 MHz; $CDCl_3$) 0.1 (CH_3, Me_3Si), 24.5 and 24.8 (CH_3, 4′-Me), 27.0, 27.3 (CH_3, 2′-Me), 31.2 (CH_2, C-1), 35.4 (CH_2, C-2), 35.5 (CH_2, C-4), 70.1, 71.0 (CH, C-6 and C-3), 74.1 (CH_2, C-5′), 80.8, 81.2 (quat., C-4′ and C-5) and 109.9 (quat., C-2′); *m*/*z* (EI) 269 (M − CH_3, 11%), 211 (M − $SiMe_3$, 8), 187 (34), 115 ($C_6H_{11}O_2$, 57), 97 (C_6H_9O, 32), 91 (31), 75 (31), 73 ($SiMe_3$, 100), 72 (51), 57 (43) and 55 (28).

6-(Tetrahydro-2-methoxypyran-2-yl)-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)hex-5-yn-3-ol 12

To a solution of **11** (682 mg, 2.4 mmol) in dry tetrahydrofuran (30 cm^3) cooled to −78 °C was added *n*-butyllithium (1.5 cm^3 of a 1.6 M solution in hexanes, 2.4 mmol) dropwise under argon. After stirring at −78 °C for 1 h, a solution of δ-valerolactone (240 mg, 2.4 mmol) in dry tetrahydrofuran (15 cm^3) was added in one portion. After gradually warming to −40 °C over 1.5 h, saturated aqueous sodium dihydrogen phosphate (2 cm^3) was added. The reaction mixture was extracted with diethyl ether (3 × 50 cm^3), washed with brine (30 cm^3) and dried over sodium sulfate. Removal of solvent at reduced pressure gave a colourless oil which was redissolved in dry methanol (30 cm^3) and stirred overnight with a catalytic amount of pyridinium toluene-*p*-sulfonate. Removal of solvent at reduced pressure yielded an orange oil which was purified by flash chromatography using hexane–diethyl ether (1:1) as eluent to give the *title compound* **12** (642 mg, 82%) as a colourless oil; ν_{max}(film)/cm^{-1} 3200–3650 (br s, OH), 2940, 2880s (CH), 2260w (C≡C); δ_H(360 MHz; $CDCl_3$) 1.28, 1.29 (3H, s, 4′-Me), 1.38 (6H, s, 2 × 2′-Me), 1.46–1.93 (10H, m, 5 × CH_2), 2.45 (2H, m, $CH_2C{\equiv}C$), 3.40 (3H, s, OMe), 3.65–3.81 (5H, m, 2 × CH_2O and C*H*OH); δ_C(90.6 MHz; $CDCl_3$) 19.2 (CH_2, C-4″), 24.7 (CH_2, C-5″), 24.9 (CH_3, 4′-Me), 27.1, 27.5 (CH_3, 2′-Me), 31.1, 31.2 (CH_2, C-1 and C-3″), 35.8 (CH_2, C-2), 36.8 (CH_2, C-4), 50.5 (CH_2, OMe), 62.2 (CH_2, C-6″), 70.1, 70.4 (CH, C-3), 80.5, 80.9 (quat., C-5 and C-4′), 82.0 (quat., C-6), 95.1 (quat., C-2″) and 109.4 (quat., C-2′); *m*/*z* (EI) 295 (M − OMe, 2%), 280 (M − OMe − Me, 4), 279 (M − MeOH − Me, 20), 173 ($C_9H_{17}O_2$, 10), 122 ($C_8H_{10}O$, 21), 115 ($C_6H_{11}O_2$, 100), 97 (C_6H_9O, 51), 72 (33), 69 (31), 59 (34), 57 (35) and 43 (66).

(*Z*)-6-(Tetrahydro-2-methoxypyran-2-yl)-1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)hex-5-en-3-ol 13

A solution of **12** (293 mg, 0.9 mmol) in dry pentane (40 cm^3) was stirred with Lindlar catalyst (20 mg) and potassium carbonate (50 mg) at room temperature under a balloon of hydrogen for 1 h with careful monitoring by TLC. Removal of the catalyst by filtration through a short pad of Celite followed by removal of the solvent at reduced pressure, afforded the *title compound* **13** (278 mg, 94%) as a colourless oil, ν_{max}(film)/cm^{-1} 3200–3650 (br s, OH), 3040m (=CH), 2980, 2940, 2880s (CH), 1660w (C=C); δ_H(360 MHz; $CDCl_3$) 1.28 (3H, s, 4′-Me), 1.38 (6H, s, 2 × 2′-Me), 1.42–1.94 (10H, m, 5 × CH_2), 2.27–2.68 (2H, m, $CH_2C{=}C$), 3.17 (3H, s, OMe), 3.43–3.82 (5H, m, 2 × CH_2O and C*H*OH) and 5.15–5.76 (2H, m, HC=CH); *m*/*z* (EI) 296 (M − MeOH, 2%), 281 (M − MeOH − Me, 26), 173 ($C_9H_{17}O_3$, 10), 124 ($C_8H_{12}O$, 24), 115 ($C_6H_{11}O_2$, 100), 97 (68), 72 (39), 69 (51), 57 (38), 55 (40), 43 (72) and 41 (38).

2-[2-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)ethyl]-1,7-dioxaspiro-[5.5]undec-4-ene 14

To a solution of the olefin **13** (294 mg, 1.2 mmol) in dichloromethane (30 cm^3) was added a few crystals of camphorsulfonic acid. After stirring at room temperature for 0.5 h, the solvent was removed at reduced pressure to give a pale yellow oil which was purified by flash chromatography using hexane–diethyl ether (1:1) as eluent to give the *title compound* **14** (288 mg, 81%) as a colourless oil (Found: M^+, 296.1996. $C_{17}H_{28}O_4$ requires *M*, 296.1987); ν_{max}(film)/cm^{-1} 3040m (=CH), 2980, 2940, 2880s (CH), 1660w (C=C); δ_H(360 MHz; $CDCl_3$) 1.28, 1.29 (3H, s, 4″-Me), 1.38 (6H, s, 2 × 2″-Me), 1.48–2.11 (12H, br m, 6 × CH_2), 3.58–3.90 (5H, m, 2 × CH_2O and CHO), 5.57–5.63 (1H, m, HC=C) and 5.83–5.92 (1H, m, =C*H*CH_2); *m*/*z* (EI) 296 (M^+, 7%), 281 (M − Me, 72), 124 ($C_8H_{12}O$, 7), 115 ($C_6H_{11}O_2$, 99), 97 (C_6H_9O, 85), 95 (54), 72 (75), 55 (47), 43 (100) and 41 (45).

2-Methyl-8-(tetrahydro-2-methoxypyran-2-yl)-1-triethylsilyl-oxyoct-7-yn-2,5-diol 20

To a solution of 1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-3-trimethylsilyloxyhex-5-yne **11** (300 mg, 1.06 mmol) in dry tetrahydrofuran (30 cm^3) cooled to −78 °C was added *n*-butyllithium (1.06 cm^3 of a 1.2 M solution in hexanes, 1.27 mmol) dropwise under argon. After stirring for 1 h at −78 °C, a solution of δ-valerolactone (127 mg, 1.27 mmol) in dry tetrahydrofuran (10 cm^3) was added in one portion. After gradually warming to −40 °C over 1.5 h, saturated aqueous sodium dihydrogen phosphate (3 cm^3) was added. The reaction mixture was extracted with ethyl acetate (3 × 50 cm^3), washed with brine (20 cm^3) and dried over potassium carbonate. Removal of solvent at reduced pressure gave a colourless oil which was redissolved in dry methanol (25 cm^3) and stirred overnight with Amberlite IR 118 resin. Removal of Amberlite by filtration followed by removal of solvent at reduced pressure yielded an orange oil which was redissolved in ethyl acetate and dried over potassium carbonate to give a colourless oil. The resultant oil was redissolved in dry tetrahydrofuran (25 cm^3). To this solution was then added triethylamine (2 equiv.) and chlorotriethylsilane (1.2 equiv.) under argon at room temperature. The reaction mixture was stirred at room temperature for 1 h whereupon a white precipitate formed. Water (5 cm^3) was added and the reaction mixture was extracted with ethyl acetate (3 × 40 cm^3). The extract was washed with water (30 cm^3), brine (30 cm^3) and dried over potassium carbonate. Removal of the solvent under reduced pressure gave a pale yellow liquid which was purified by flash chromatography using hexane–ethyl acetate (7:3) as eluent to give the *title compound* **20** (291 mg, 69%) as a colourless oil, $\nu_{max}(CHCl_3)/cm^{-1}$ 3220–3620 (br s, OH), 2956, 2876s (CH), 2220w (C≡C), 1464, 1228, 1144, 1089, 1025; δ_H(200 MHz; $CDCl_3$) 0.63 (6H, m, 3 × CH_3CH_2Si), 0.97 (9H, m, 3 × CH_3CH_2Si), 1.12, 1.13 (3H, s, 2-CH_3) 1.34–1.94 (11H, m, 5 × CH_2 and OH), 2.46 (2H, d, *J* 6.2, $CH_2C{\equiv}C$), 2.71 (1H, br s, OH), 3.38–3.45 (5H, m, CH_3O and CH_2OSi) and 3.72–3.84 (3H, m, CHO and CH_2O); *m*/*z* (CI, CH_4) 400 (MH^+, 2%), 369 (M^+ − MeO, 56), 354 (M^+ − MeO − Me, 41) 237 (100), 219 (54) and 115 ($C_6H_{15}Si$, 36).

4-(1,7-Dioxaspiro[5.5]undec-4-en-2-yl)-1-triethylsilyloxy-2-methylbutan-2-ol 16

A solution of 2-methyl-8-(tetrahydro-2-methoxypyran-2-yl)-1-triethylsilyloxyoct-7-yn-2,5-diol **20** (291 mg, 0.73 mmol) in pentane (40 cm^3) was stirred with Lindlar catalyst (25 mg) and potassium carbonate (150 mg) at room temperature under a balloon of hydrogen for 1 h with careful monitoring by TLC. 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 (25 cm^3) and treated with pyridinium toluene-*p*-sulfonate (5 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 (7:3) as eluent to give the *title compound* **16** (215 mg, 80%) as a (1:1) mixture of diastereomers in the form of a colourless oil (Found: C, 64.85; H, 10.07. $C_{20}H_{38}O_4Si$ requires C, 64.82; H, 10.33%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3300–3590 (br s, OH), 2956, 2876m (CH), 1601w (C=C), 1463, 1396, 1238, 1093, 996; δ_H(200 MHz; $CDCl_3$) 0.63 (6H, m, 3 × CH_3CH_2Si), 0.99 (9H, m, 3 × CH_3CH_2Si), 1.38–2.00 (12H, m, 3′-CH_2, 10′-CH_2, 11′-CH_2, 9′-CH_2, 4-CH_2 and 3-CH_2), 1.18, 1.22 (3H, s, 2-CH_3), 2.56 (0.5H, s, exchangeable on deuteration, OH), 2.58 (0.5H, s, exchangeable on deuteration, OH), 3.39–3.50 (2H, s, CH_2OSi), 3.55–3.67 (1H, m, CHO), 3.78–3.93 (2H, m, 8′-CH_2), 5.61 (1H, dt, $J_{5',4'}$ 9.9, $J_{5',3'}$ 2.0, 5′-H), 5.89 (1H, ddd, $J_{4',5'}$ 9.9, $J_{4',3'}$ 3.6, $J_{4',3'}$ 3.6, 4′-H); δ_C(50 MHz; $CDCl_3$) 4.3 (CH_3, 3 × CH_3CH_2Si), 6.6 (CH_2, 3 × CH_3CH_2Si), 18.5, 25.0, 29.7, 30.8, 34.5, 34.9 (CH_2, C-9′, C-10′, C-11′, C-3′, C-3 and C-4), 22.9, 23.0 (CH_3, 2-Me), 60.8 (CH_2, C-8′), 67.3, 67.5 (CH, C-2′), 69.7, 69.9 (CH_2, C-1), 71.9, 72.0 (quat., C-2), 93.8 (quat., C-6′), 127.6 (CH, C-5′), 130.4 (CH, C-4′); *m/z* (EI) 370 (M^+, 7%), 341 ($M^+ - C_2H_5$, 30), 225 [$M^+ - (C_2H_5)_3SiOCH_2$, 74], 115 [$(C_2H_5)_3Si$, 58], 131 [$(C_2H_5)_3SiO$, 21], 145 [$(C_2H_5)_3SiOCH_2$, 7], 159 (40) and 199 (51).

4-(1,7-Dioxaspiro[5.5]undec-4-en-2-yl)butan-2-one 25

A solution of the alcohol **16** (122 mg, 0.33 mmol), iodine (168 mg, 0.66 mmol), and iodobenzene diacetate (213 mg, 0.66 mmol) in cyclohexane (30 cm^3) was purged with Ar and irradiated with a 500 W tungsten filament lamp. After 5 h, during which time the temperature was maintained at about 20 °C, the solution was diluted with diethyl ether (30 cm^3), washed with 10% aqueous sodium thiosulfate (20 cm^3), water (20 cm^3), brine (20 cm^3) and dried over potassium carbonate. The solvent was evaporated under reduced pressure and the resultant oil purified by flash chromatography using hexane–ethyl acetate (4:1) as eluent to afford the *title compound* **25** (52 mg, 73%) as a colourless oil (Found: C, 69.24; H, 8.62. $C_{13}H_{20}O_3$ requires C, 69.61; H, 8.99%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2945, 2874m (CH), 1711s (C=O), 1601m (C=C), 1357, 1230, 1070; δ_H(200 MHz; $CDCl_3$) 1.52–1.95 (10H, m, 5 × CH_2), 2.17 (3H, s, CH_3CO), 2.45–2.80 (2H, m, CH_2CO), 3.57–3.63 (1H, m, CHO), 3.70–3.89 (2H, m, CH_2O), 5.54–5.62 (1H, m, 5′-H), 5.82–5.91 (1H, m, 4′-H); δ_C(50 MHz; $CDCl_3$) 18.5, 25.0, 29.5, 30.6, 34.9 (CH_2, C-9′, C-10′, C-11, C-3′ and C-4), 29.8 (CH_3, C-1), 40.1 (CH_2, C-3), 60.9 (CH_2, C-8′), 66.2 (CH, C-2′), 93.7 (quat., C-6′), 127.3 (CH, C-5′), 130.3 (CH, C-4′), 200.6 (quat., C=O); *m/z* (CI, CH_4) 225 (MH^+, 100%), 207 ($M - H_2O$, 50), 125 (33) and 101 (24).

4-(1,7-Dioxaspiro[5.5]undec-4-en-2-yl)-2-methylbutane-1,2-diol 15

Tetra-*n*-butylammonium fluoride (0.44 cm^3 of a 1.0 M solution in tetrahydrofuran, 0.44 mmol) was added to a solution of **16** (148 mg, 0.40 mmol) in dry tetrahydrofuran (10 cm^3) at room temperature under argon. After stirring for 30 min, the solvent was evaporated and the oily residue purified by flash chromatography, using hexane–ethyl acetate (1:1) as eluent to afford the *title compound* **15** (96 mg, 94%) as a colourless oil (Found: C, 65.38; H, 9.46. $C_{14}H_{24}O_4$ requires C, 65.58; H, 9.44%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3650–3100 (br s, OH), 3040m (=CH), 2960m, 2880s (CH), 1660w (C=C); δ_H(200 MHz; $CDCl_3$) 1.17, 1.18 (3H, s, 2-Me), 1.42–2.16 (12H, m, 6 × CH_2), 2.90 (2H, br s, 2 × OH), 3.40 (2H, m, CH_2OH), 3.52–4.16 (3H, m, CH_2O and CHO), 5.56 (1H, ddd, $J_{5',4'}$ 9.8, $J_{5',3'}$ 1.9 and $J_{5',3'}$ 1.9, 5′-H), 5.85 (1H, ddd, $J_{4',5'}$ 9.8, $J_{4',3'}$ 3.6 and $J_{4',3'}$ 3.6, 4′-H); δ_C(50 MHz; $CDCl_3$) 18.4, 24.9, 29.4, 30.5, 34.4, 34.8 (CH_2, C-3′, C-9′, C-10′, C-11′, C-3 and C-4), 23.1, 23.3 (CH_3, 2-Me), 61.0 (CH_2, C-8′), 67.3, 67.4 (CH, C-2′), 69.5, 69.7 (CH_2, C-1), 72.4 (quat., C-2), 93.9 (quat., C-6′), 127.6 (CH, C-5′), 130.2 (CH, C-4′); *m/z* (EI) 256 (M^+, 1%), 153 ($C_9H_{13}O_2$, 28), 125 (49), 124 ($C_8H_{12}O$), 155 (44), 101 (55), 95 (61), 85 (41), 83 (41), 69 (55), 55 (54) and 43 (100).

2-Methyl-8-(tetrahydro-2-methoxypyran-2-yl)-2,5-dihydroxyoct-7-yn-1-yl acetate 21

To a solution of 1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-3-trimethylsilyloxylhex-5-yne **11** (826 mg, 2.9 mmol) in dry tetrahydrofuran (80 cm^3) cooled to −78 °C was added *n*-butyllithium (1.52 cm^3 of a 2.1 M in hexanes, 3.2 mmol) dropwise under argon. After stirring at −78 °C for 1 h, a solution of δ-valerolactone (320 mg, 3.2 mmol) in dry tetrahydrofuran (30 cm^3) was added in one portion. After gradually warming to −40 °C over 1.5 h, saturated aqueous sodium dihydrogen phosphate (10 cm^3) was added. The reaction mixture was extracted with ethyl acetate (3 × 50 cm^3), washed with brine (50 cm^3) and dried over potassium carbonate. Removal of solvent at reduced pressure gave a colourless oil which was redissolved in dry methanol (100 cm^3) and stirred overnight with Amberlite IR 118 resin. Removal of Amberlite by filtration followed by removal of solvent at reduced pressure yielded an orange oil which was redissolved in ethyl acetate and dried over potassium carbonate to give a colourless oil.

To a solution of the crude triol **19** in dichloromethane (130 cm^3) at room temperature was added dry triethylamine (2 equiv.) followed by acetic anhydride (1.1 equiv.) and 4-dimethylaminopyridine (3 mg). The reaction mixture was stirred at room temperature for 0.5 h, then quenched with water (10 cm^3), extracted with dichloromethane (3 × 50 cm^3), washed with brine (50 cm^3) and dried over anhydrous potassium carbonate. Removal of the 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* **21** (612 mg, 64%) as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3065–3674 (br s, OH), 2942s (CH), 2247w (C≡C), 1734s (C=O); δ_H(200 MHz; $CDCl_3$) 1.18 (3H, s, 2-CH_3) 1.47–1.87 (10H, m, 5 × CH_2), 2.08 (3H, s, CH_3CO) 2.41–2.58 (2H, m, $CH_2C{\equiv}C$), 2.80 (2H, br s, 2 × OH), 3.36, 3.44 (3H, s, CH_3O), 3.62–3.79 (3H, m, CHO and CH_2O) and 3.95 (2H, s, CH_2OAc).

4-(1,7-Dioxaspiro[5.5]undec-4-en-2-yl)-2-hydroxy-2-methylbutyl acetate 18

A solution of acetate **21** (546 mg, 1.68 mmol) in dry pentane (100 cm^3) and ethyl acetate (10 cm^3) was stirred with Lindlar catalyst (25 mg) and potassium carbonate (150 mg) at room temperature under a balloon of hydrogen for 40 min with careful monitoring by TLC. 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 (100 cm^3) and treated with pyridinium toluene-*p*-sulfonate (5 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 (2:1) as eluent to afford the *title compound* **18** (388 mg, 78%) as a colourless oil (mixture of isomers) (Found: M^+ 298.1780. $C_{16}H_{26}O_5$ requires *M*, 298.1781); $\nu_{max}(CHCl_3)/cm^{-1}$ 3435 (br s, OH), 2946m, 2876m (CH), 1732s (C=O), 1656w (C=C), 1441, 1374, 1244, 1044; δ_H(200 MHz; $CDCl_3$) 1.20 (3H, s, 2-Me), 1.40–2.00 (12H, m, 6 × CH_2), 2.10 (3H, s, CH_3CO), 2.54 (1H, br s, OH), 3.50–3.68 (1H, m, CHO), 3.70–3.90 (2H, m, CH_2O), 4.00 (2H, s, CH_2OAc), 5.58 (1H, m, 5′-H), 5.85 (1H, m, 4′-H); δ_C(50 MHz; $CDCl_3$) 18.5, 24.9, 29.2, 30.6, 34.8, 34.9 (CH_2, C-3′, C-9′, C-10′, C-11′, C-3 and C-4), 20.8 (CH_3, CH_3CO), 23.8, 23.9 (CH_3, 2-Me), 60.9 (CH_2, C-8′), 67.2 (CH, C-2′), 70.9 (CH_2, C-1), 71.1 (quat., C-2), 93.9 (quat., C-6′), 127.4 (CH, C-5′), 130.3 (CH, C-4′), 171.0 (quat., C=O); *m/z* (EI) 298 (M^+, 1%), 225 ($M^+ - CH_3CO_2CH_2$, 9), 207 ($M^+ - CH_3CO_2CH_2 - H_2O$, 5), 43 ($CH_3CO$, 100), 124 (40), 95 (23), 69 (19) and 55 (27).

(2-Methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-2-yl) methyl acetate 26a, 26b, 27a, 27b

A solution of acetate **18** (200 mg, 0.671 mmol), iodine (341 mg, 1.342 mmol), and iodobenzene diacetate (433 mg, 1.34 mmol)

in cyclohexane (40 cm^3) was purged with Ar and irradiated with a 500 W tungsten filament lamp. After 7 h, during which time the temperature was maintained at about 20 °C, the solution was diluted with diethyl ether (50 cm^3), washed with 10% aqueous sodium thiosulfate (30 cm^3), water (30 cm^3) and brine (30 cm^3), and dried over potassium carbonate. The solvent was evaporated under reduced pressure and the resultant oil purified by flash chromatography using hexane–ethyl acetate (7:3) as eluent to afford the following.

(i) *trans* acetates 26a and 26b*. (77 mg, 39%) An inseparable 1:1 mixture of diastereomers in the form of colourless oil; δ_H(200 MHz; $CDCl_3$) 1.19 (3H, s, Me), 1.42 (3H, s, Me*), 1.42–2.15 (20H, 10′-CH_2, 10′-CH_2*, 11′-CH_2, 11′-CH_2*, 12′-CH_2, 12′-CH_2*, 3′-CH_2, 3′-CH_2*, 4′H_A, 4′-H_A*, 15′-H_A and 15′-H_A*), 2.02 (3H, s, MeCO), 2.06 (3H, s, Me*CO), 2.36–2.53 (2H, m, 15′-H_B and 15′-H_B*), 2.55–2.70 (2H, m, 4′-H_B and 4′-H_B*), 3.54–3.67 (2H, 9′$_{eq}$-H and 9′$_{eq}$-H*), 3.83–4.10 (6H, m, 9′$_{ax}$-H, 9′$_{ax}$-H*, 1-CH_2 and 1-CH_2*), 5.48–5.58 (2H, m, 13′-H and 13′-H*), 5.75–5.84 (2H, m, 14′-H and 14′-H*).

(ii) *cis* acetates 27a and 27b*. (58 mg, 30%) An inseparable 1:1 mixture of diastereomers in the form of colourless oil; δ_H(200 MHz; $CDCl_3$) 1.17 (3H, s, Me), 1.34 (3H, s, Me*), 1.40–2.40 (24H, 10′-CH_2, 10′-CH_2*), 11′-CH_2, 11′-CH_2*, 12′-CH_2, 12′-CH_2*, 3′-CH_2, 3′-CH_2*, 4′-CH_2, 4′-CH_2*, 15′-CH_2, 15′-CH_2*), 2.02 (3H, s, MeCO), 2.03 (3H, s, Me*CO), 3.54 3.67 (2H, 9′$_{eq}$-H and 9′$_{eq}$-H*), 3.84–4.19 (6H, m, 9′$_{ax}$-H, 9′$_{ax}$-H*, 1-CH_2 and 1-CH_2*), 5.63–5.74 (2H, m, 13′-H and 13′-H*), 5.78–5.89 (2H, m, 14′-H and 14′-H*).

(2*S,5*S**,7*S**)- and (2*R**,5*S**,7*S**)-(2-Methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-2-yl)methanol 10a,10b [*trans*]**

To a solution of *trans* acetates (1:1 mixture of **26a** and **26b**) (77 mg, 0.26 mmol) in methanol (10 cm^3) was added potassium carbonate (30 mg). The mixture was stirred at room temperature under argon for 1 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 (3:2) as eluent to afford the following.

(i) The *trans* alcohol 10b. (28 mg, 42%) A colourless oil. The spectroscopic data were in agreement with those reported in the literature.[18]

(ii) The *trans* alcohol 10a. (29 mg, 43%) A colourless oil. The spectroscopic data were in agreement with those reported in the literature.[18]

(2*R,5*S**,7*S**)-(2-Methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-2-yl)methanal 28b [*trans*]**

To a mixture of *N*-methylmorpholine *N*-oxide (18 mg, 0.15 mmol) and powdered molecular sieves (4 Å) in dichloromethane (4 cm^3), was added a solution of the *trans* alcohol **10b** (25 mg, 0.1 mmol) in dichloromethane (4 cm^3). The mixture was stirred at room temperature for 10 min, then cooled to 0 °C, and tetra-*n*-propylammonium perruthenate (1.75 mg, 0.005 mmol) was added. The mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through Celite and the solvent evaporated to give an oil which was purified by flash chromatography using hexane–ethyl acetate (4:1) as eluent to give the *title compound* **28b** (20 mg, 81%) as a colourless oil (Found: M^+, 252.1360. $C_{14}H_{20}O_4$ requires *M*, 252.1361); ν_{max}($CHCl_3$)/cm^{-1} 3026w (=CH), 2947m (CH), 1756s (C=O), 1602w (C=C), 1350, 1199, 1093, 997, 940, 890; δ_H(200 MHz; $CDCl_3$) 1.32 (3H, s, Me), 1.45–1.84 (8H, m, 10′-CH_2, 11′-CH_2, 12′-CH_2 and 3′-CH_2), 2.23 (1H, ddd, $J_{15'B,15'A}$ 17.1, $J_{15'B,14'}$ 5.8 and $J_{15'B,13'}$ 1.3, 15′-H_B), 2.45–2.75 (3H, m, 4′-CH_2 and 15′H_A), 3.57–3.67 (1H, m, 9′$_{eq}$-H), 3.71–3.84 (1H, m, 9′$_{ax}$-H), 5.61 (1H, ddd, $J_{13',14'}$ 10.0, $J_{13',15'A}$ 2.9 and $J_{13',15'B}$ 1.2, 13′-H), 5.87 (1H, ddd, $J_{14',13'}$ 10.2, $J_{14',15'A}$ 5.8 and $J_{14',15'B}$ 2.5, 14′-H), 9.81 (1H, s, CHO); δ_C(50 MHz; $CDCl_3$) 18.5, 21.2, 31.6, 33.5, 35.7, 36.4 (CH_2, C-3′, C-4′, C-10′, C-11′, C-12′ and C-15′), 25.0 (CH_3, Me) 61.7 (CH_2, C-9′), 87.7 (quat., C-2′), 96.5 (quat., C-7′), 107.7 (quat., C-5′), 124.5 (CH, C-13′), 139.2 (CH, C-14′), 203.9 (quat., C=O); *m/z* (EI) 252 (M^+, 16%), 223 (M^+ − CHO, 92), 235 (22), 167 (70), 99 (83), 68 (48) and 44 (100).

(2*S,5*S**,7*S**)-(2-Methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-2-yl)methanal 28a [*trans*]**

Using the same procedure described above for the preparation of **28b**, the *title compound* **28a** was prepared as a colourless oil in 81% yield; δ_H(200 MHz; $CDCl_3$) 1.25 (3H, s, Me), 1.45–2.74 (10H, m, 10′-CH_2, 11′-CH_2, 12′-CH_2, 15′-CH_2 and 3′-CH_2), 3.63–3.75 (1H, m, 9′$_{eq}$-H), 3.91–4.07 (1H, m, 9′$_{ax}$-H), 5.63 (1H, ddd, $J_{13',14'}$ 10.0, $J_{13',15'A}$ 1.9 and $J_{13',15'B}$ 1.9, 13′-H), 5.89 (1H, ddd, $J_{14',13'}$ 10.0, $J_{14',15'A}$ 5.1 and $J_{14',15'B}$ 3.0, 14′-H) and 9.59 (1H, s, CHO).

2-Methyl-8-[6-(*tert*-butyldiphenylsilyloxymethyl)tetrahydro-2-methoxypyran-2-yl]oct-7-yne-1,2,5-triol 30

To a solution of 1-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-3-trimethylsilyloxyhex-5-yne **11** (200 mg, 0.704 mmol) in dry tetrahydrofuran (25 cm^3) cooled to −78 °C under nitrogen was added *n*-butyllithium (0.65 cm^3 of a 1.2 M solution in hexane, 0.78 mmol) dropwise. After stirring at −78 °C for 1 h, a solution of 6-(*tert*-butyldiphenylsilyloxymethyl)tetrahydro-2*H*-pyran-2-one **29**[19] (260 mg, 0.704 mmol) in dry tetrahydrofuran (5 cm^3) was added in one portion. After gradually warming to room temperature over 1.5 h sodium dihydrogen phosphate (10% aqueous solution, 3 cm^3) was added. The reaction mixture was extracted with ethyl acetate (3 × 50 cm^3), washed with brine (20 cm^3) and dried over potassium carbonate. Removal of solvent at reduced pressure gave a colourless oil which was redissolved in dry methanol (25 cm^3) and stirred overnight with Amberlite IR 118 resin. Removal of Amberlite 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 the *title compound* **30** (145 mg, 37%) as a colourless oil; ν_{max}(film)/cm^{-1} 3220–3620 (br s, OH), 2932, 2856s (CH), 2243w (C≡C); δ_H(200 MHz; $CDCl_3$) 1.05 (9H, br s, Bu^t), 1.13, 1.26 (3H, s, 2-Me), 1.52–1.96 (12H, m, 5 × CH_2 and 2 × OH), 2.43, 2.49 (2H, d, *J* 6.3 and 6.0, CH_2C≡C), 2.70 (1H, br s, OH), 3.33 (3H, s, CH_3O), 3.37–3.94 (5H, m, CHO, CH_2O and CH_2OSi), 7.35–7.43 (6H, m, ArH) and 7.65–7.70 (4H, m, ArH).

2-Methyl-8-[6-(*tert*-butyldiphenylsilyloxymethyl)tetrahydro-2-methoxypyran-2-yl]-2,5-dihydroxyoct-7-yn-1-yl acetate 31

To a solution of the triol **30** (260 mg, 0.47 mmol) in dichloromethane (60 cm^3) at room temperature was added dry triethylamine (95.1 mg, 0.131 cm^3, 0.94 mmol) followed by acetic anhydride (53.0 mg, 0.049 cm^3, 0.52 mmol) and 4-dimethylaminopyridine (3 mg). The reaction mixture was stirred at room temperature for 1 h, then quenched with water (5 cm^3), extracted with dichloromethane (3 × 10 cm^3), washed with brine (10 cm^3) and dried over anhydrous potassium carbonate. Removal of the 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* **31** (196 mg, 70%) as a colourless oil; ν_{max}(film)/cm^{-1} 3410 (br s, OH), 2932, 2857s (CH), 2242w (C≡C), 1740 (C≡O); δ_H(200 MHz; $CDCl_3$) 1.05 (9H, br s, Bu^t), 1.19, 1.20 (3H, s, 2-Me), 1.54–1.97 (10H, m, 5 × CH_2), 2.09 (3H, s, CH_3CO), 2.44, 2.50 (2H, d, *J*, 5.8, 6.0, CH_2C≡C), 2.59 (1H, br s, OH), 2.68 (1H, br s, OH), 3.33 (3H, s, CH_3O), 3.48–3.81 (4H, m, 2 × CHO, and CH_2OSi), 3.96 (2H, br s, CH_2OCO), 7.36–7.39 (6H, m, ArH) and 7.64–7.70 (4H, m, ArH).

4-{8-(*tert*-Butyldiphenylsilyloxymethyl)-1,7-dioxaspiro[5.5]-undec-4-en-2-yl}-2-methyl-2-hydroxybutyl acetate 33, 34 and 35

A solution of acetate **31** (178 mg, 0.30 mmol) in dry pentane (40 cm^3) and ethyl acetate (5 cm^3) was stirred with Lindlar catalyst (25 mg) and potassium carbonate (150 mg) at room temper-

ature under a balloon of hydrogen for 40 min with careful monitoring by TLC. 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 (25 cm^3) and treated with pyridinium toluene-*p*-sulfonate (5 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 following.

(i) The less polar acetate 33. A colourless oil (Found C, 70.22; H, 8.24%; $C_{33}H_{46}O_6Si$ requires C, 69.93; H, 8.18%); ν_{max}(film)/cm^{-1} 3451 (br s, OH), 3043w (=CH), 2932, 2857s (CH), 1742s (C=O); δ_H(400 MHz; $CDCl_3$) 1.05 (9H, s, Bu^t), 1.21, 1.23 (3H, s, 2-Me), 1.49–1.98 (10H, m, 5 × CH_2), 2.08 (3H, s, CH_3CO), 2.38–2.42 (1H, br m, OH), 3.56 (1H, dd, $J_{B,A}$ 10.4, $J_{B,8'}$ 5.3, CH_AH_BOSi), 3.69 (1H, dd, $J_{A,B}$ 10.4, $J_{A,8'}$ 5.8, CH_AH_BOSi), 3.90–3.97 (2H, m, 8′-H and 2′-H), 3.98–4.01 (2H, m, CH_2OAc), 5.60 (1H, $J_{5',4'}$ 10.0, $J_{5',3'}$ 3.3 and $J_{5',3'}$ 1.6, 5′-H), 5.89 (1H, ddd, $J_{4',5'}$ 10.0, $J_{4',3'}$ 4.8 and $J_{4',3'}$ 2.8, 4′-H), 7.33–7.42 (6H, m, ArH) and 7.67–7.72 (4H, m, ArH); δ_C(100.6 MHz; $CDCl_3$) 19.2 (quat., CMe_3), 20.0 (CH_3, CH_3CO), 24.7 (CH_3, 2-Me), 27.6 (CH_3, CMe_3), 21.6, 27.9, 30.0, 31.3, 35.3, 35.6 (CH_2, C-3′, C-9′, C-10′, C-11′, C-3 and C-4), 67.6 (CH, C-2′), 68.4 (CH, C-1), 71.9 (CH_2, C-1″), 95.2 (quat., C-6′), 127.0 (CH, C-4′) 128.2 (CH, Ar-C), 130.2 (CH, Ar-C), 131.9 (CH, C-5′), 134.5 (quat., Ar-C), 136.4 (CH, Ar-C) and 171.8 (quat., C=O).

(ii) An inseparable (1:1.3) mixture of the polar acetates 34* and 35. A colourless oil; δ_H(400 MHz; $CDCl_3$) 1.04 (9H, s, Bu^t), 1.05 (9H, s, Bu^t*), 1.08 (3H, s, 2-Me), 1.21 (3H, s, 2-Me*), 1.25–1.93 (20H, m, 5 × CH_2, 5 × CH_2*), 2.06 (3H, s, CH_3CO), 2.11 (3H, s, CH_3CO*), 3.52–4.04 (11H, m, CH_2OSi, CH_2OSi*, 8′-H, 8′-H*, 2′-H, CH_2OCO, CH_2OCO*), 4.10–4.13 (1H, m, 2′-H*), 5.54 (1H, d, *J* 10.1, 5′-H*), 5.83 (1H, ddd, $J_{4',5'}$ 10.1, $J_{4',3'}$ 5.3 and $J_{4',3'}$ 2.4, 4′-H*), 5.87–5.91 (1H, m, 4′-H), 5.96 (1H, d, *J* 10.2, 5′-H), 7.33–7.41 (12H, m, 6 × ArH and 6 × ArH*), 7.66–7.69 (8H, m, 4 × ArH and 4 × ArH*).

{9-(*tert*-Butyldiphenylsilyloxymethyl)-2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-2-yl}methyl acetate 36, 37, 38 and 39

A solution of the acetate **33** (146 mg, 0.26 mmol), iodine (131 mg, 0.516 mmol), and iodobenzene diacetate (166 mg, 0.516 mmol) in cyclohexane (20 cm^3) was purged with nitrogen and irradiated with a 500 W tungsten filament lamp. After 5 h, during which time the temperature was maintained at about 20 °C, the solution was diluted with ether (50 cm^3), washed with 10% aqueous sodium thiosulfate (30 cm^3), water (30 cm^3) and brine (30 cm^3), 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) The more polar *cis* acetate 39. A colourless oil (Found: C, 69.97; H, 7.84%; $C_{33}H_{44}O_6Si$ requires C, 70.18; H, 7.85%); ν_{max}(film)/cm^{-1} 3070w, 3043w (=CH), 2934, 2857s (C–H), 1743 (C=O) and 1589w (C≡C); δ_H(400 MHz; $CDCl_3$) 1.05 (9H, s, Bu^t), 1.26 (3H, s, 2′-Me), 1.44–2.14 (10H, m, 3′-CH_2, 4′-CH_2, 10′-CH_2, 11′-CH_2 and 12′-CH_2), 2.05 (3H, s, CH_3CO), 2.19 (1H, ddd, $J_{15'A,15'B}$ 17.0, $J_{15'A,14'}$ 5.8 and $J_{15'A,13'}$ 1.0, 15′-H_A), 2.35 (1H, ddd, $J_{15'B,15'A}$ 17.0, $J_{15'B,14'}$ 2.5 and $J_{15'B,13'}$ 2.5, 15′-H_B), 3.44 (1H, dd, $J_{A,B}$ 9.2 and $J_{A,9'}$ 9.2, CH_AH_BOSi), 3.74 (1H, dd, $J_{B,A}$ 9.2 and $J_{B,9'}$ 4.0, CH_AH_BOSi), 3.81 (1H, d, $J_{A,B}$ 11.0, CH_AH_BOAc), 3.87 (1H, d, $J_{B,A}$ 11.0, CH_AH_BOAc), 4.09–4.16 (1H, m, 9′-H), 5.65 (1H, ddd, $J_{13',14'}$ 10.2, $J_{13',15'B}$ 2.5 and $J_{13'15'A}$ 1.0, 13′-H), 5.84 (1H, ddd, $J_{14',13'}$ 10.2, $J_{14',15'A}$ 5.8 and $J_{14',15'B}$ 2.5, 14′-H), 7.31–7.40 (6H, m, ArH), 7.61–7.65 (4H, m, ArH); δ_C(100.6 MHz; $CDCl_3$) 19.9 (quat., CMe_3), 21.7 (CH_3, CH_3CO), 24.8 (CH_3, 2′-Me), 27.5 (CH_3, CMe_3), 19.0, 27.8, 34.3, 35.4, 35.9, 36.8 (CH_2, C-3′, C-4′, C-10′, C-11′, C-12′, C-15′), 68.4 (CH_2, C-1), 71.7 (CH_2, C-1″), 72.2 (CH, C-9′), 83.4 (quat., C-2′), 97.7 (quat., C-7′), 108.0 (quat., C-5′), 125.3 (CH, C-13′), 128.2 (CH, Ar-C), 130.2 (CH, Ar-C), 130.8 (CH, C-14′), 134.4 (quat., Ar-C), 136.4 (CH, Ar-C) and 171.8 (quat., C=O); *m/z* (CI, CH_4) 565 (M^+, 100%) and 487 (35).

(ii) An inseparable mixture of acetates 36, 37 and 38. δ_H(400 MHz; $CDCl_3$) 1.02–1.06 (3 × 9H, m, Bu^t), 1.15, 1.24, 1.49 (3 × 3H, s, 2′-Me), 1.44–2.94 (3 × 12H, m, 6 × CH_2), 1.96, 2.08 and 2.12 (3 × 3H, s, CH_3CO), 3.48–4.28 (3 × 5H, m, 9′-H, CH_2OSi and CH_2OAc), 5.58–5.70 (3 × 1H, m, 13′-H), 5.83–5.89 (3 × 1H, m, 14′-H), 7.32–7.43 (3 × 6H, m, ArH) and 7.63–7.72 (3 × 4H, m, ArH).

[2′*R**,5*S**,7*S**,9*S**]-{9-(*tert*-Butyldiphenylsilyloxymethyl)-2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-2-yl}-methanol 40

To a solution of the mixture of acetates **36**, **37** and **38** (54 mg, 0.10 mmol) in methanol (10 cm^3) was added potassium carbonate (30 mg). The mixture was stirred at room temperature under nitrogen for 1 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 (2:1) as eluent to afford the following.

(i) The more polar alcohol 41. A colourless oil; δ_H(200 MHz; $CDCl_3$) 1.03 (9H, s, Bu^t), 1.47 (3H, s, 2′-Me), 1.54–2.04 (9H, m, 3′-CH_2, 4′-H_A, 10′-CH_2, 11′-CH_2 and 12′-CH_2), 2.14 (1H, dd, $J_{15'B,15'A}$ 17.0 and $J_{15'B,14'}$ 6.2, 15′-H_B), 2.52 (1H, ddd, $J_{15'A,15'B}$ 17.0, $J_{15'A,14'}$ 2.2 and $J_{15'A,13'}$ 2.8, 15′-H_A), 2.85–2.96 (1H, m, 4′-H_B), 3.35–3.69 (5H, m, CH_2OH, CH_2OSi), 4.10–4.18 (1H, m, 9′-H), 5.62 (1H, ddd, $J_{13',14'}$ 10.1, $J_{13',15'A}$ 2.8 and $J_{13',15'B}$ 0.8, 13′-H), 5.85 (1H, ddd, $J_{14',13'}$ 10.1, $J_{14',15'B}$ 6.2 and $J_{14',15'A}$ 2.2, 14′-H), 7.36–7.41 (6H, m, ArH), 7.68–7.73 (4H, m, ArH).

(ii) A mixture of alcohols 40 and 42. This was further purified by flash chromatography using hexane–ethyl acetate (9:1) to afford *trans*-alcohol **40** as a colourless oil. (Found: MH^+, 523.2866. $C_{31}H_{43}O_5Si$ requires MH^+, 523.2879); ν_{max}(film)/cm^{-1} 3449 (br s, OH), 3041w (=CH), 2934, 2853 (C–H); δ_H(400 MHz; $CDCl_3$) 1.02 (9H, s, Bu^t), 1.19 (3H, s, 2′-Me), 1.49–1.85 (8H, m, 3′-H_B, 4′-H_B, 10′-CH_2, 11′-CH_2 and 12′-CH_2), 2.14 (1H, ddd, $J_{15'B,15'A}$ 17.0, $J_{15'B,14'}$ 6.2 and $J_{15'B,13'}$ 1.0, 15′-H_B), 2.52–2.59 (2H, m, 3′-H_A, 15′-H_A), 2.99 (1H, dd, $J_{4'A,4'B}$ 12.5 and $J_{4'A,3'}$ 7.6, 4′-H_A), 3.42 (1H, t, *J* 10.7, CH_AH_BOH), 3.53–3.64 (4H, m, CH_AH_BOH, CH_2OSi), 4.20–4.27 (1H, m, 9′-H), 5.61 (1H, ddd, $J_{13',14'}$ 10.1, $J_{13',15'}$ 3.2 and $J_{13',15'}$ 1.0, 13′-H), 5.87 (1H, ddd, $J_{14',13'}$ 10.1, $J_{14',15'}$ 6.2 and $J_{14',15'}$ 2.1, 14′-H), 7.34–7.41 (6H, m, ArH), 7.69–7.74 (4H, m, ArH); δ_C(100.6 MHz; $CDCl_3$) 19.9 (quat., CMe_3), 25.0 (CH_3, 2′-Me), 27.5 ($CH_3C$$Me_3$), 19.2, 27.2, 31.4, 35.1, 36.6, 36.7 (CH_2, C-3′, C-4′, C-10′, C-11′, C-12′, C-15′), 68.4 (CH_2, C-1), 68.5 (CH_2, C-1″), 72.2 (CH, C-9′), 87.0 (quat., C-2′), 98.3 (quat., C-7′), 107.2 (quat., C-5′), 125.2 (CH, C-13′), 128.2 (CH, Ar-C), 130.1 (CH, Ar-C), 130.7 (CH, C-14′), 134.5 (quat., Ar-C), 136.4 (CH, Ar-C); *m/z* (CI, CH_4) 523 (MH^+, 100%), 505 (6) and 445 (16).

The instability of alcohol **42** rendered it difficult to isolate.

[2′*R**,5*S**,7*S**9*S**]-{9-(*tert*-Butyldiphenylsilyloxymethyl)-2-methyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-2-yl}-methanal 44

To a solution of the *trans*-alcohol **40** (10 mg, 0.02 mmol) in dichloromethane (2 cm^3) was added *N*-methylmorpholine *N*-oxide (*ca*. 3.6 mg, 0.03 mmol) and powdered molecular sieves (4 Å). The mixture was stirred at room temperature for 10 min then cooled to 0 °C and tetra-*n*-propylammonium perruthenate (*ca*. 0.35 mg, 0.001 mmol) was added. The mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through Celite, and the solvent evaporated to give an oil which was purified by flash chromatography using hexane–ethyl acetate (9:1) as eluent to give the *title compound* **44** (5 mg, 50%) as a colourless oil; ν_{max}(film)/cm^{-1} 3052w (=CH), 2925s, 2854m (CH), 1736m (C=O); δ_H(400 MHz; $CDCl_3$) 1.02 (9H, s, Bu^t), 1.32 (3H, s, 2′-Me), 1.43–1.84 (8H, m, 10′CH_2, 11′-CH_2,

12′-CH_2, 3′-H_B and 4′-H_B), 2.21 (1H, ddd, $J_{15'B,15'A}$ 17.0, $J_{15'B,14'}$ 6.1 and $J_{15,B,13'}$ 0.6, 15′-H_B), 2.47–2.51 (1H, m, 3′-H_A), 2.59 (1H, ddd, $J_{15'A,15'B}$ 17.0, $J_{15'A,14'}$ 2.2 and $J_{15'A,13'}$ 2.6, 15′-H_A), 2.91 (1H, t, J 9.4, 4′-H_A), 3.51 (1H, dd, $J_{A,B}$ 10.5 and $J_{A,9'}$ 4.3, C$H_A$$H_B$OSi), 3.58 (1H, dd, $J_{B,A}$ 10.5 and $J_{B,9'}$ 6.4, $CH_A$$H_B$OSi), 3.90–3.96 (1H, m, 9′-H), 5.63 (1H, ddd, $J_{13',14'}$ 10.1, $J_{13',15'A}$ 2.6 and $J_{13',15'B}$ 0.6, 13′-H), 5.87 (1H, ddd, $J_{14',13'}$ 10.1, $J_{14',15'B}$ 6.1 and $J_{14',15'A}$ 2.2, 14′-H), 7.34–7.41 (6H, m, ArH), 7.68–7.73 (4H, m, ArH), 9.83 (1H, s, CHO); *m*/*z* (CI, CH_4) 521 (M^+, 38%), 443 (7), 425 (1), 347 (1) and 269 (2).

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References

1 H. Kinashi, N. Otake, H. Yonehara, S. Sato and Y. Saito, *Tetrahedron Lett.*, 1973, 4955.
2 J. L. Occolowitz, D. H. Berg, D. H. M. Debono and R. L. Hamill, *Biomed. Mass Spectrosc.*, 1976, **3**, 272.
3 J. W. Westley, J. F. Blount, R. H. Evans and C. Liu, *J. Antibiot.*, 1977, **30**, 610.
4 C. Keller-Julsen, H. D. King, M. Kuhn, H. R. Loosli and A. Von Wartburg, *J. Antibot.*, 1978, **3**, 820.
5 J. Tone, R. Shibatawa, M. Maeda, K. Inoue, S. Nishiyama, M. Ishiguro, W. P. Cullen, J. B. Routien, L. R. Chappell, C. E. Moppett, M. J. Jefferson and W. D. Celmer, 18th Intersociety Conference on Antimicrobial Agents Chemotherapy, Atlanta, GA, Oct 2–4, 1978.
6 J. W. Westley, L. H. Sello, N. Troupe, C. Liu, J. F. Blount, R. G. Pitcher, T. H. Williams and P. A. Miller, *J. Antibiot.*, 1981, **34**, 139.
7 Y. Kishi, S. Hatakeyama and M. D. Lewis, in *Frontiers of Chemistry*, ed. K. J. Laidler, Pergamon, Oxford, 1982, 287.
8 K. Horita, Y. Oikawa and O. Yonemitsu, *Chem. Pharm. Bull.*, 1989, **37**, 1698.
9 K. Horita, S. Nagato, Y. Oikawa and O. Yonemitsu, *Chem. Pharm. Bull.*, 1989, **37**, 1705.
10 K. Horita, Y. Oikawa, S. Nagato and O. Yonemitsu, *Chem. Pharm. Bull.*, 1989, **37**, 1717.
11 K. Horita, S. Nagato, Y. Oikawa and O. Yonemitsu, *Chem. Pharm. Bull.*, 1989, **37**, 1726.
12 R. C. D. Brown and P. J. Kocienski, *Synlett*, 1994, 415.
13 R. C. D. Brown and P. J. Kocienski, *Synlett*, 1994, 417.
14 P. J. Kocienski, R. C. D. Brown, A. Pommier, M. Procter and B. Schmidt, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 9.
15 P. J. Kocienski, Y. Fall and R. Whitby, *J. Chem. Soc.*, *Perkin Trans. 1*, 1989, 841.
16 F. Perron and K. F. Albizati, *J. Org. Chem.*, 1989, **54**, 2044.
17 M. A. Brimble and G. M. Williams, *J. Org. Chem.*, 1992, **57**, 5818.
18 M. A. Brimble, G. M. Williams and R. Baker, *J. Chem. Soc.*, *Perkin Trans. 1*, 1991, 2221.
19 R. J. K. Taylor, K. Wiggins and D. H. Robinson, *Synthesis*, 1990, 589.

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