Synthesis of Talaromycins A, B, C, and E

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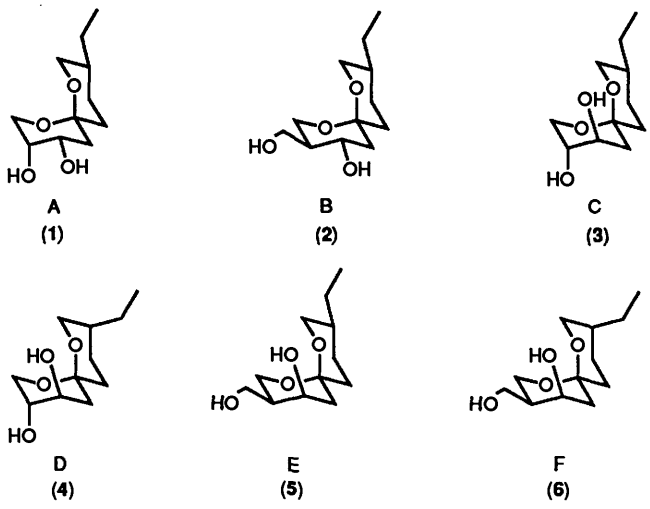
The synthesis of 2,2-diethyl-5-ethynyl-1,3-dioxane (**9**) is reported in an overall yield of 27% from diethyl malonate. Addition of 5-ethyl tetrahydropyran-2-one to the lithium anion of (**9**) gave the hydroxy ketoacetylene (**10**) which was converted in four steps to the olefinic spiroacetals (**19**) and (**20**), which were obtained in a ratio of 2:1. The individual olefinic spiroacetals (**19**) and (**20**) gave access to the (±)-talaromycins A and C, and B and E *via* a chlorohydration, reductive dechlorination, and deprotection sequence.

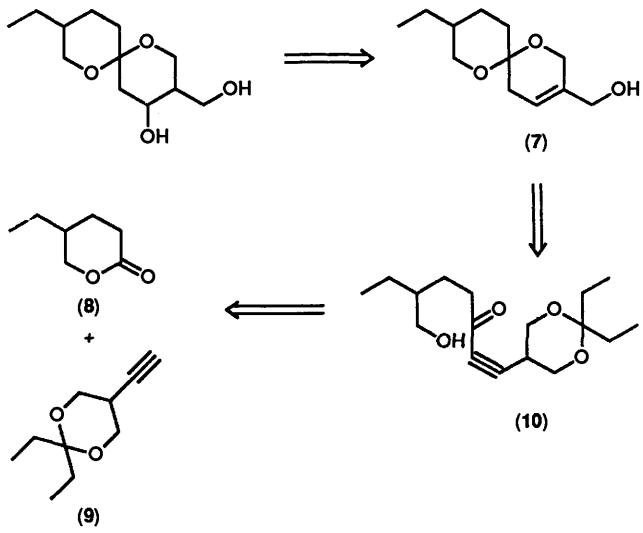
The talaromycins A (**1**) and B (**2**) were isolated from the fungus *Talaromyces stipitatus* which grows on woodshavings based animal feedstuffs, and were identified as avian toxins.[1] Their activity arises through the blockade of outward potassium fluxes in smooth muscle which leads to muscle dysfunction. In a more detailed re-examination of extracts from *Talaromyces stipitatus*,[2] Lynn *et al* isolated four more spiroacetals [talaromycins C–F (**3**)–(**6**)]. The talaromycins have received



considerable synthetic attention; four enantioselective syntheses of talaromycins A and B have been reported[3] along with a number of other racemic syntheses of talaromycins A and B.[4] More recently, two formal syntheses have been reported.[5] Other synthetic studies towards spiroacetals have been reviewed by Kluge[6] and Boivin.[7] An important observation by Lynn *et al.*[2] was the quantitative conversion of talaromycin A into talaromycin B under acid catalysis, reflecting the greater thermodynamic stability associated with all equatorally substituted anomerically stabilised spiroacetals. The greater accessibility of talaromycin B was apparent during the earlier syntheses; talaromycin A syntheses generally required more stringent control of the C-3 hydroxymethyl centre. We report the stereodivergent synthesis of (±)-talaromycins A, B, C, and E from common intermediates.

Syntheses

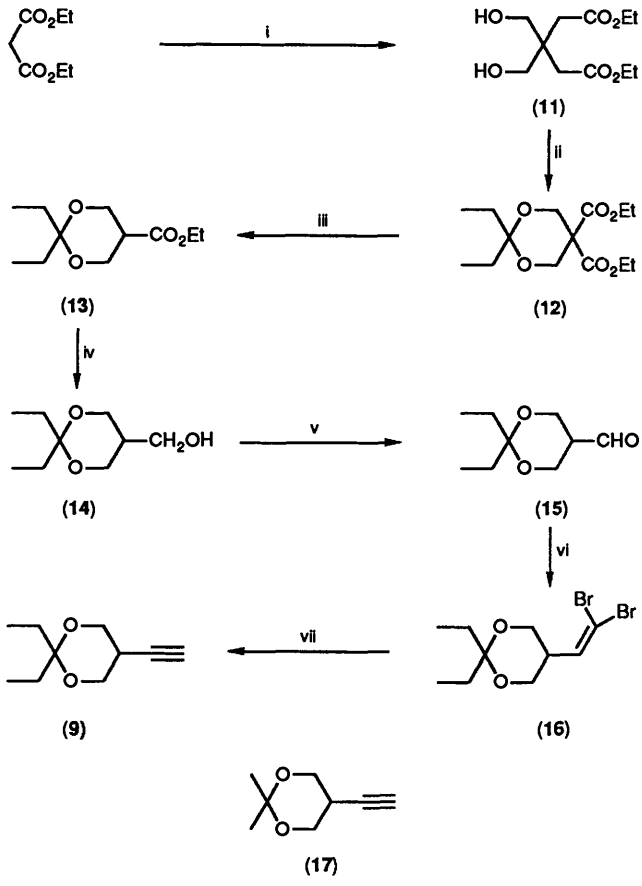
A retrosynthetic analysis (Scheme 1) indicated that the olefinic spiroacetal (**7**) could act as a common key intermediate for synthesis of (±)-talaromycins A, B, C, and E. Synthesis of (**7**) required the availability of the precursor (**10**) followed by acid catalysed spirocyclisation.[8] Formation of (**10**) was envisaged by addition of lactone (**8**) to the lithium anion of the protected diol (**9**).



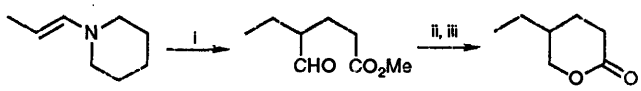
Scheme 1.

The alkyne (**9**) was prepared in 27% overall yield from diethyl malonate (Scheme 2). Alcohol (**14**) was obtained by a synthesis which involved a modification of the route to 2-hydroxymethylpropane-1,3-diol reported by Kaloustian *et al.*[9] Oxidation of the alcohol (**14**) to the aldehyde (**15**) was most efficiently accomplished, in 96% yield, *via* a Swern oxidation[10] [chromium based oxidising agents gave only moderate to poor yields of the aldehyde (**15**)]. The aldehyde (**15**) was transformed *via* the dibromo olefin (**16**) to the alkyne (**9**) in 64% yield using the procedure reported by Corey and Fuchs.[11] Bates *et al.*[12] have independently reported a similar synthesis of the analogous isopropylidene alkyne (**17**). The lactone (**8**) was prepared by a minor modification of the synthesis reported by Kuehne *et al.*[13] (Scheme 3).

With access to gram quantities of the alkyne (**9**) and lactone (**8**) our attention was focussed on the synthesis of spiroacetal (**7**). Addition of the lactone (**8**) to the lithium anion of alkyne (**9**) gave the hydroxy ketoalkyne (**10**) in 79% yield; characteristic absorptions in the IR spectrum at 2 220 cm^{-1} (α,β-unsaturated alkyne) and ν 1 680 cm^{-1} (α,β-unsaturated carbonyl) were observed. Partial hydrogenation to the *Z*-carbon double bond was required to permit spirocyclisation. Studies in these



Scheme 2. *Reagents:* i, K_2CO_3, HCHO, 78%; ii, *p*-TSA, Et_2CO, 91%; iii, NaCl, DMSO H_2O, 79%; iv, $LiAlH_4$, Et_2O, 86%; v, oxalyl chloride, DMSO, Et_3N, 96%; vi, CBr_4, PPh_3, 82%; vii, 2 equiv. BuLi.



Scheme 3. *Reagents:* i, CH_2=$CHCO_2Me$, 82%; ii, $NaBH_4$, MeOH; iii, HCl, 56%.

laboratories[14] have indicated that direct partial hydrogenation of similar ketoalkynes to ketoalkenes in the presence of Lindlar catalyst was frequently accompanied by over-reduction to the saturated ketone.

Consequently, the mixed methoxy ketals (**18**) were formed in 87% yield on treatment of the ketoalkyne (**17**) with dry methanol in the presence of Amberlyst 15 ion exchange resin. These conditions led to the cleavage of the 1,3-dioxane ring in (**10**) to release the 1,3-diol functionality in the mixed methoxyketals (**18**) which were isolated as a 3:1 mixture at the anomeric centre (axial: equatorial, NMR). Partial hydrogenation of the alkyne (**18**) and acid catalysed spirocyclisation gave the olefinic spiroacetals (**7a,b**) as a 2:1 mixture of inseparable diastereomers (pseudoaxial: pseudoequatorial hydroxymethyl group at C-3). The equatorial orientation of the C-9 ethyl group was assigned from the large coupling constants observed between 8-H_a and 9-H_a, $J_{8a,9a}$ = 10.9 Hz for both (**7a**) and (**7b**). The signal corresponding to 8-H_a was a characteristic of subsequent spiroacetals reported in this paper. Separation of the diastereomeric spiroacetals (**7a**) and (**7b**) was required to allow a study of their selective hydration; but protection of the hydroxymethyl group at C-3 was required to prevent spiroacetal equilibration reactions. The t-butyl-dimethylsilyl group[15] was chosen as the protecting group due to the mild conditions required for its introduction, and the non-acidic deprotection conditions. Accordingly the t-BDMS ethers (**19**) and (**20**) were prepared in 84% combined yield after separation by careful flash chromatography.

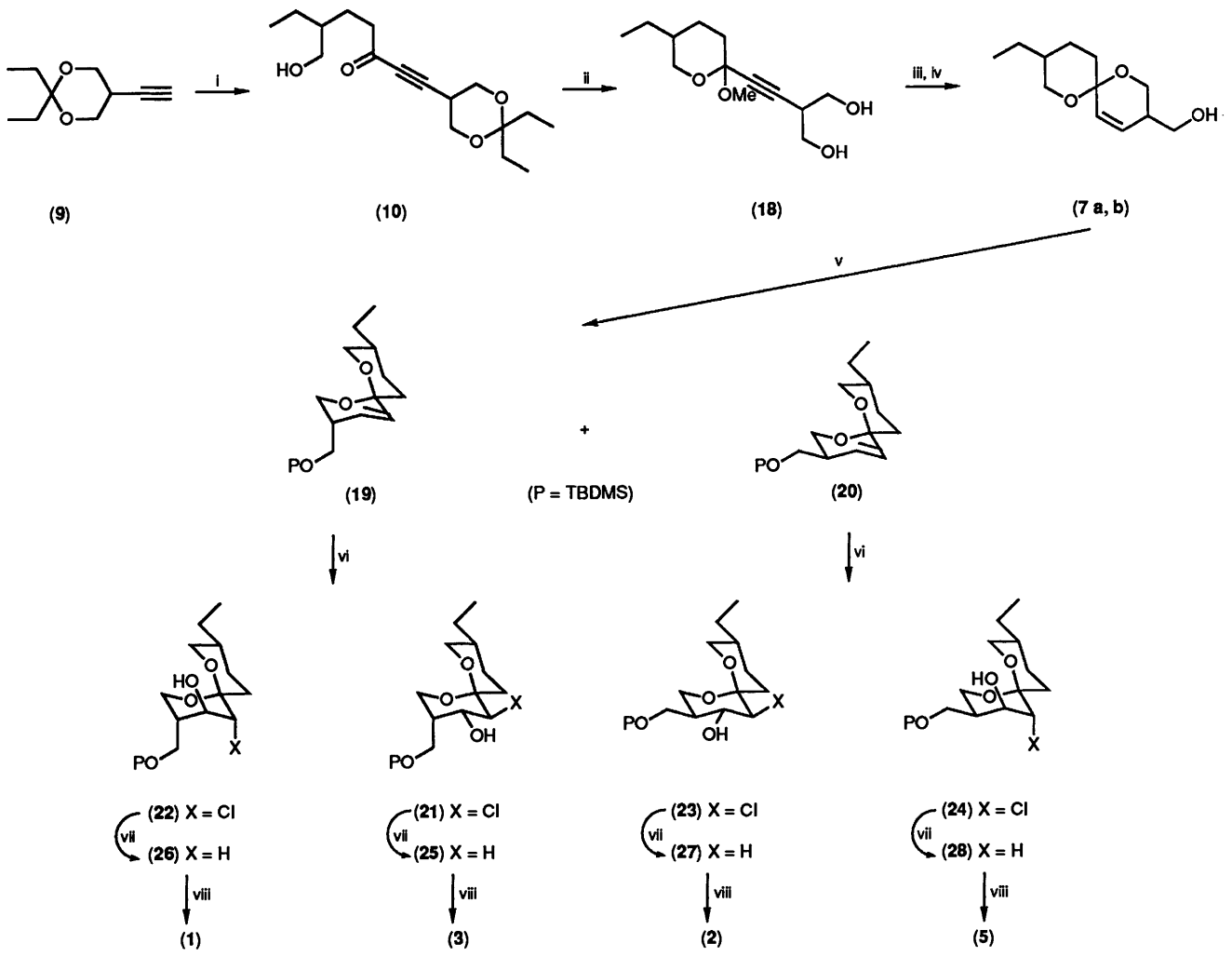
The olefinic spiroacetal (**19**) underwent regioselective chlorohydration to give the diastereomeric chlorohydrins (**21**) and (**22**) in a 1:4 ratio, in 73% combined yield, after separation by flash chromatography. Similarly the olefinic spiroacetal (**20**) gave the *trans*-diequatorial and *trans*-diaxial chlorohydrins (**23**) and (**24**) which were obtained as colourless oils after separation by flash chromatography in a ratio of 1.4:1 in a combined yield of 60%. The *trans*-diaxial coupling between both 3-H_a and 5-H_a with 4-H_a in (**23**) was particularly significant in assigning the stereochemistry of the three contiguous centres C-3 to C-5. The stereochemistry assigned to the chlorohydrins (**21**)–(**24**) were based on analysis of the 360 MHz ^{1}H NMR and 2D spectra. Both *trans*-diaxial chlorohydrins (**22**) and (**24**) exhibited sharp absorptions in their IR spectra, at 3 480 and 3 510 cm^{-1} respectively, indicative of an intra-molecular hydrogen bond between the axial C-4 hydroxyl and the C-7 in the adjacent tetrahydropyran ring, commonly observed in 4-hydroxy-1,7-dioxaspiro[5.5]undecanes. The observed regioselectivity during chlorohydration was in accordance with literature precedence.[16] Reductive dechlorination of the individual chlorohydrins (**21**)–(**24**) gave the corresponding alcohols (**25**)–(**28**) as white crystalline solids in 60–80% yield on purification by flash chromatography (Scheme 4). Finally, deprotection of the t-BDMS ethers (**25**)–(**28**) gave the talaromycins A, B, C, and E; all spectral detail was in accordance with published data. Talaromycin B was obtained as a white crystalline solid, m.p. 129.7–130.5 °C (CH_2Cl_2–hexane) (lit., 127–128 °C), whereas talaromycin A, C, and E were isolated as colourless oils.

Experimental

IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer either as thin films between sodium chloride plates, as solutions in sodium chloride cells (0.1 mm), or as Nujol mulls. ^{1}H NMR spectra were recorded either at 60 MHz on a Hitachi–Perkin-Elmer R-24B spectrometer or at 360 MHz on a Brucker AM 360 spectrometer. Tetramethylsilane (TMS) was used as a standard. ^{13}C NMR spectra were recorded at 90.6 MHz on a Brucker AM 360 spectrometer. Mass spectra and accurate mass measurements were recorded on a Kratos MS30 spectrometer equipped with a Nova-3 computer and DS 505 data system (Kratos) or a VG 7070 spectrometer. An ionisation potential of 70eV was used and major fragmentations are given as percentages of base peak intensity (100%). Chemical ionisation mass spectra were obtained using ammonia as the reagent gas.

Melting points were measured on a Reichert Kofler hot stage melting point apparatus and are uncorrected. Kugelrohr distillations were performed using a Buchi Kugelrohr oven. The temperature of the oven was recorded as the boiling point of the compound. Flash chromatography was performed using Macherey-Nagel Kieselgel 60 (230–400 mesh) silica gel. Analytical TLC (thin layer chromatography) was performed on 0.25 mm precoated silica gel plates (Merck 60F UV_{254}) and compounds were visualised by UV fluorescence, iodine vapour, or by treating with an aqueous solution of potassium permanganate or an acidic methanolic solution of vanillin. Light petroleum refers to the fraction (b.p. 40–60 °C) and ether refers to diethyl ether. Base washed glassware refers to glassware washed with saturated ethanolic potassium hydroxide solution followed by distilled water (to pH 7) and drying.

5,5-Bis(Ethoxycarbonyl)-2,2-diethyl-1,3-dioxane (**12**).—Toluene-*p*-sulphonic acid (2.97 g, 16 mmol) and pentan-3-one (47.4 g, 0.55 mol) were added to a solution of diethyl



Scheme 4. *Reagents:* i, BuLi, THF, −78 °C, (**8**), 78%; ii, MeOH, Amberlyst 15, 100%; iii, H_2/Pd–$CaCO_3$/Pb, MeOH; iv, D,L-Camphorsulphonic acid, CH_2Cl_2, 78%; v, t-BDMSCl, Imidazole, DMF, 84%; vi, t-BuOCl, acetone, H_2O; vii, Bu_3SnH, AIBN, Toluene; viii, Bu_4NF, THF.

bis(hydroxymethyl)malonate (**11**)[17] (110 g, 0.5 mol) in light petroleum (520 ml) and heated to reflux under a Dean and Stark head for 15 h. Azeotropic removal of water (9 ml) and TLC analysis indicated completion of the reaction. On cooling to room temperature the reaction mixture was concentrated to 150 ml (approximately) and diluted with ether (400 ml). The organic phase was washed successively with saturated sodium hydrogen carbonate (180 ml) and brine (180 ml) and dried (Na_2SO_4). Concentration under reduced pressure gave 5,5- *bis(ethoxycarbonyl)*-2,2-*diethyl*-1,3-*dioxane* (**12**) as an oil (144 g, 91%) sufficiently pure for use in the subsequent reaction. An analytical sample was prepared by flash chromatography (Et_2O–light petroleum, 3:7) followed by Kugelrohr distillation, b.p. 74 °C at 0.15 mmHg (Found: C, 58.05; H, 8.30. $C_{14}H_{24}O_6$ requires C, 58.32; H, 8.39%), ν_{max}(thin film) 2 980, 2 950, 2 890, 1 750 (C=O), 1 480, 1 450, 1 260, and 1 110 cm^{-1}; δ_H(60 MHz, $CDCl_3$) 4.24 (4 H, s, 4-H and 6-H), 4.2 (4 H, q, *J* 7 Hz, CH_3CH_2O), 1.74 (4 H, q, *J*, 7 Hz, CH_3CH_2C), 1.25 (6 H, t, *J* 7 Hz, CH_3CH_2O) and 0.84 (6 H, t, *J* 7 Hz, CH_3CH_2C); *m/z* (EI) (Found: M^+ − Et, 259.1182. $C_{12}H_{19}O_6$ requires 259.1157); 259 (M^+ − Et, 76%), 243 (6), 173 (21), 127 (35), 59 (46), and 57 (100).

2,2-*Diethyl*-5-*ethoxycarbonyl*-1,3-*dioxane* (**13**).—Sodium chloride (26.2 g, 0.46 mol) and water (16 ml, 0.89 mol) were added to a solution of 5,5-bis(ethoxycarbonyl)-2,2-diethyl-1,3-dioxane (**12**) (128.6 g, 0.46 mol) in dimethyl sulphoxide (712 ml) and the reaction heated to gentle reflux for 19 h. On cooling to room temperature the reaction was poured into brine (1.5 l), and extracted with ether (4 × 250 ml). The combined organic phase was washed with water (3 × 100 ml) and dried (Na_2SO_4). Concentration under reduced pressure gave 2,2-diethyl-5-ethoxycarbonyl-1,3-dioxane (**13**) (75.6 g, 79%) as an oil, b.p. 75 °C at 0.5 mmHg (Found: C, 61.2; H, 9.35. $C_{11}H_{20}O_4$ requires C, 61.1; H, 9.34%); ν_{max}(thin film) 2 980, 2 950, 2 890, 1 735 (C=O), 1 470, 1 290, 1 160, 1 090, 1 040, and 900 cm^{-1}; δ_H(60 MHz, $CDCl_3$) 4.32–3.95 (6 H, m, 4-H, 6-H and CH_3CH_2O), 2.72 (1 H, m, 5-H), 1.95–1.5 (4 H, m, CH_3CH_2C), 1.25 (3 H, t, *J* 7 Hz, CH_3CH_2O), and 0.87 (6 H, m, CH_3CH_2C); *m/z* (EI) (Found: M^+ − Et, 187.0960. $C_9H_{15}O_4$ requires 187.0970), 187 (64%), 171 (3.5), 142 (6), 113 (8), and 57 (100).

2,2-*Diethyl*-5-*hydroxymethyl*-1,3-*dioxane* (**14**).—A solution of 2,2-diethyl-5-ethoxycarbonyl-1,3-dioxane (**13**) (42.6 g, 197 mmol) in dry ether (460 ml) was added to a suspension of lithium aluminium hydride (2.3 g, 61 mmol) in dry ether (460 ml) under nitrogen at such a rate as to maintain a gentle reflux. On completion of the addition the reaction was maintained at a gentle reflux for 2h. The reaction was cooled in an ice-bath and

portions of water (2.3 ml), sodium hydroxide (2.3 ml; 15%) and water (6.9 ml) were added carefully in a dropwise manner. Stirring was continued until a white precipitate was formed, the reaction mixture was filtered, and the residue washed with ether (2 × 100 ml). The combined organic phase was concentrated under reduced pressure to give 2,2-diethyl-5-hydroxymethyl-1,3-dioxane (**14**) as an oil (29.5 g, 86%), b.p. 60 °C at 0.5 mmHg; ν_{max}(thin film) 3 420 (OH), 2 980, 2 950, 2 880, 1 460, 1 160, 1 090, 1 040, and 900 cm^{-1}; δ_H(60 MHz, $CDCl_3$) 4.12–3.52 (6 H, m, 4-H, 6-H and $CHCH_2OH$), 2.3 (1 H, br s, CH_2OH), 1.96–1.5 (5 H, m, 4-H and CH_3CH_2C), and 0.83 (6 H, t, *J* 7 Hz, CH_3CH_2C); *m/z* (EI) (Found: M^+ − Et, 145.0861. $C_7H_{13}O_3$ requires 145.0865), 145 (53%), 87 (12), and 57 (100).

2,2-*Diethyl*-5-*formyl*-1,3-*dioxane* (**15**).—Dimethyl sulphoxide (12.4 ml, 161 mmol) in dry dichloromethane (36.5 ml) was added to a vigorously stirred solution of oxalyl chloride (8.05 ml, 80.3 mmol) in dry dichloromethane (183 ml) at −70 to −60 °C under nitrogen over a period of 12 min and stirred for a further 4 min. The alcohol, 2,2-diethyl-5-hydroxymethyl-1,3-dioxane (**14**) (12.7 g, 73 mmol) in dry dichloromethane (73 ml) was added dropwise and the reaction mixture stirred for 0.5 h at −70 to −60 °C during which a white opaque solution formed. Dry triethylamine (51 ml) was added dropwise and the reaction mixture stirred for 10 min before warming to room temperature. Water (350 ml) and dichloromethane (350 ml) were added to the reaction mixture and the organic phase separated and the aqueous phase extracted with dichloromethane (1 × 100 ml). The combined organic phase was washed with water (2 × 250 ml), brine (1 × 250 ml) and dried (Na_2SO_4). Concentration under reduced pressure gave 2,2-diethyl-5-formyl-1,3-dioxane (**15**) (12.1 g, 96%) as an oil, b.p. 60–65 °C at 5 mmHg, ν_{max} 2 980, 2 950, 2 880, 1 725 (C=O), 1 465, 1 360, 1 240, 1 160, and 900 cm^{-1}, δ_H(360 MHz, $CDCl_3$) 9.82 (1 H, s, *CHO*), 3.85 (4 H, dd, *J* 3.9 and 12 Hz, 4-H_e and 6-H_e), 3.72 (4 H, dd, *J* 3.9 and 12 Hz, 4-H_a and 6-H_a), 2.23 [1 H, m(5), *J* 3.9 Hz, 5-H], 1.74 (2 H, q, *J* 7.2 Hz, CH_3CH_2C), 1.53 (2 H, q, *J* 7.2 Hz, CH_3CH_2C), 0.78 (3 H, t, *J* 7.2 Hz, CH_3CH_2C), and 0.76 (3 H, t, *J* 7.8 Hz, CH_3CH_2C); δ_C(90.6 MHz; $CDCl_3$), 202.3 (d, CHO), 101.5 (s, C-2), 58.4 (t, C-4 and C-6), 46.4 (d, C-5), 27.9 (t, CH_3CH_2C), 23.7 (t, CH_3CH_2C), 7.6 (q, CH_3CH_3C), and 7.0 (q, CH_3CH_2C).

5-(2,2-*Dibromoethenyl*)-2,2-*diethyl*-1,3-*dioxane* (**16**).—A solution of carbon tetrabromide (51.4 g, 155 mmol) in dry dichloromethane (232 ml) was added dropwise to a solution of triphenylphosphine (81.25 g, 310 mmol) in dry dichloromethane (282 ml) cooled to 0–5 °C under nitrogen. The reaction mixture was stirred for 20 min at 0.5 °C and then cooled to −20 °C. A solution of 2,2-diethyl-5-formyl-1,3-dioxane (**15**) (12.1 g, 70.4 mmol) in dry dichloromethane (282 ml) was added dropwise to the reaction mixture and stirred at −20 °C for 40 min. The reaction mixture was poured into light petroleum (800 ml) and filtered through a pad of Celite. The solid residue was dissolved in dichloromethane (100 ml) and poured into light petroleum (400 ml) at 0 °C and refiltered. The filtrate was concentrated under reduced pressure to give a yellow oil which was purified by dry column chromatography to yield 5-(2,2-dibromoethenyl)-2,2-diethyl-1,3-dioxane (**16**) as an oil (19.04 g, 82%); ν_{max}(thin film) 2 980, 2 950, 2 880, 1 610 (C=C), 1 460, 1 160, 1 090, 900, and 800 cm^{-1}; δ_H(60 MHz, $CDCl_3$) 6.5 (1 H, d, *J* 10.2 Hz, $CH{=}CBr_2$), 4.1–3.5 (4 H, m, 4-H and 6-H), 2.64 (1 H, m, 5-H), 1.7 (4 H, q, *J* 7.2 Hz, CH_3CH_2), and 0.85 (6 H, t, *J* 7.2 Hz, CH_3CH_2).

2,2-*Diethyl*-5-*ethynyl*-1,3-*dioxane* (**9**).—A solution of butyllithium in hexanes (91.8 ml, 128 mmol) was added dropwise to a solution of 5-(2,2-dibromoethenyl)-2,2-diethyl-1,3-dioxane (**16**) (19 g, 58 mmol) in dry tetrahydrofuran (580 ml) at −78 °C under nitrogen, and stirred at this temperature for 1.5 h. The reaction was quenched by the addition of water (250 ml) and the organic phase separated. The aqueous phase was extracted with ether (2 × 100 ml) and the combined organic phase washed with brine (2 × 200 ml) and dried (Na_2SO_4). Concentration under reduced pressure gave 2,2-diethyl-5-ethynyl-1,3-dioxane (**9**) (7.6 g, 78%) as an oil, b.p. 40–45 °C at 2 mmHg (Found: C, 71.1; H, 9.55. $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.59%); ν_{max}(thin film) 3 320 (≡CH), 3 270, 2 980, 2 960, 2 790, 2 120 (C≡C), 1 470, 1 165, 1 140, 1 090, and 900 cm^{-1}; δ_H(360 MHz, $CDCl_3$) 3.82 (2 H, dd, *J* 5 and 11.6 Hz, 4-H_e and 6-H_e), 3.73 (2 H, t, *J* 11.3 Hz, 4-H_a and 6-H_a), 2.72 (1 H, m, 5-H), 2.07 (1 H, d, *J* 2.6 Hz, C≡*CH*), 1.78 (2 H, q, *J* 7.6 Hz, CH_3CH_2C), 1.54 (2 H, q, *J* 7.4 Hz, CH_3CH_2C), 0.82 (3 H, t, *J* 7.4 Hz, CH_3CH_2C), and 0.80 (3 H, t, *J* 7.4 Hz, CH_3CH_2C); δ_C(90.6 MHz, $CDCl_3$) 101.1 (OCO), 80.9 (s, *C*≡CH), 71.4 (d, C≡*C*H), 62.9 (t, C-4 and C-6), 29.8 (t, CH_3CH_2C), 27.8 (d, C-5), 21.6 (t, CH_3CH_2C), 7.8 (q, CH_3CH_2), and 7.0 (q, CH_3CH_2); *m/z* (EI) (Found: M^+ − Et 139.0761. $C_8H_{11}O_2$ requires 139.0759), 139(52%), 104(18), 78(12), 77(10), and 57(100).

2,2-*Diethyl*-5-(6-*ethyl*-7-*hydroxy*-3-*oxohex*-1-*yne*)-1,3-*dioxane* (**10**.—A solution of butyl-lithium in hexanes (3.17 ml, 5.2 mmol) was added dropwise to a solution of 2,2-diethyl-5-ethynyl-1,3-dioxane (**9**) (479.5 mg, 4.7 mmol) in dry tetrahydrofuran (100 ml) at −78 °C under nitrogen and the reaction mixture stirred at this temperature for 2 h. A solution of 5-ethyltetrahydro-2-pyrone[13] (**8**) (602 mg, 4.7 mmol) in dry tetrahydrofuran (10 ml) was added rapidly and the reaction stirred at −78 °C for 2 h. The reaction was quenched by the addition of a saturated solution of sodium dihydrogen orthophosphate (30 ml) and warmed to room temperature. The organic phase was diluted with ethyl acetate (50 ml) and separated from the aqueous layer which was extracted with ethyl acetate (2 × 50 ml). The combined organic phase was washed with brine and dried (Na_2SO_4). Concentration at reduced pressure gave an oil which was purified by flash column chromatography (ether–light petroleum, 9:11) to yield 2,2-diethyl-5-(6-ethyl-7-hydroxy-3-oxohex-1-ynyl)1,3-dioxane (**10**) (1.1 g, 79%) as an oil, b.p. 117 °C at 0.06 mmHg; (Found: C, 69.1; H, 9.4. $C_{17}H_{28}O_4$ requires C, 68.9; H, 9.5%); ν_{max}(thin film) 3 420 (OH), 2 980, 2 950, 2 890, 2 220 (C≡C) conj., 1 680 (C=O) conj., 1 470, 1 165, 1 140, 1 090, and 900 cm^{-1}; δ_H(360 MHz, $CDCl_3$), 3.95–3.8 (4 H, m, 2 × CH_2O), 3.56–3.42 (2 H, m, CH_2O), 2.65–2.5 (2 H, m, 5-H, m, 5-H and OH), 1.88–1.80 (2 H, m, 4′-H), 1.7–1.55 (4 H, m, 5′-H), 1.42–1.15 (4 H, m, 2 × CH_3CH_2), and 0.92–0.82 (9 H, m, 3 × CH_3CH_2); *m/z* (EI) (Found: M^+ − Et, 267.1577. $C_{15}H_{23}O_4$ requires 267.1596), 267 (M^+ − Et, 100%), 181 (16), 163(9), 111(11), and 94(23).

2-(4-*Hydroxy*-3-*hydroxymethylbut*-1-*ynyl*)-5-*ethyl*-2-*methoxytetrahydropyran* (**18**).—The acetylenic ketone (**10**) (1.01 g, 3.4 mmol) and Amberlyst 15 ion exchange resin (50 mg) were stirred in dry methanol (100 ml) under nitrogen for 2.5 h. The reaction mixture was filtered through a pad of Celite and potassium hydrogen carbonate (1:1, v/v) and the pad was washed with dry methanol (2 × 30 ml). Concentration under reduced pressure gave (2α)- and (2β)-anomers of 2-(4′-hydroxy-3′-hydroxymethylbut-1′-ynyl)-5-ethyl-2-methoxytetrahydropyran (**18**), (674 mg, 82%) as a mixture of anomers (1:3 by NMR) which could be separated by flash chromatography (3:2 to 4:1 ethyl acetate–light petroleum); (**18a**) ν_{max}(thin film) 3 620 and 3 440 (OH), 2 980, 2 940, 2 880, 2 260 (C≡C), 1 465, 1 240, 1 160, 1 050, and 900 cm^{-1}; δ_H(360 MHz, $CDCl_3$), 3.85–3.7 (5 H, br m, 6-H_e and 2 × CH_2OH) 3.48–3.4 (1 H, m, 6-H_a), 3.42 (3 H, s, MeO), 3.15 (2 H, br s, 2 × CH_2OH), 2.8 (1 H, quintet, *J* 5.3 Hz, $CH(CH_2OH)_2$), 1.94–182 (2 H, m, 3-H_e and 4-H_e), 1.66 (1 H, ddd, *J* 13.4, 10.3 and 3.3 Hz, 3-H_a), 1.36–1.20 (2 H, m, CH_3CH_2), and 0.88 (3 H, t, *J* 7.4 Hz, CH_3CH_2); δ_C(90.6 MHz,

$CDCl_3$) 96.42 (s, C-2), 84.68 (s, C-5), 80.46 (s, C-6), 67.78 (t, CH_2OH), 63.26 (t, CH_2O), 51.09 (q, OCH_3), 37.15 (d, CH), 35.8 (d, CH), 35.1 (t, CH_2), 25.72 (d, CH_2), 24.04 (d, CH_2), and 11.47 (t, C-11); *m/z* (EI) (Found: M^+ − OMe 211.1318. $C_{12}H_{19}O_3$ requires 211.1334), 211 (M^+ − OMe, 35%), 167(50), 156(49), 133(12), 127(88), 111(22), and 108(100).

(**18b**) (C, 64.60; H, 9.03. $C_{13}H_{22}O_4$ requires C, 64.44; H, 9.15); ν_{max}($CHCl_3$) 3 620 and 3 450 (OH), 3 020, 2 980, 2 950, 2 890, 2 250 (C≡C), 1 470, 1 150, 1 080, 1 040, and 900 cm^{-1}; δ_H(360 MHz, $CDCl_3$), 3.75 (2 H, br s, 2 × CH_2OH), 3.62 (4 H, br s, 10-H and 11-H), 3.5 (1 H, m, 6-H_e), 3.22 (3 H, s, OMe), 3.15 (1 H, t, *J* 10.9 Hz, 6-H_a), 2.67 (1 H, quintet, *J* 5.8 Hz, 9-H), 1.87 (1 H, dt, *J* 10.6 and 3.6 Hz, 3-H_e), 1.76 (1 H, td, *J* 13.0 and 4.4 Hz, 3-H_a), 1.56–1.52 (1 H, m, 4-H_e), 1.43–1.35 (1 H, m, 5-H_a), 1.31 (1 H, qd, *J* 12 and 4.2 Hz, 4-H_a), 1.15–0.96 (2 H, m, 13-H), and 0.78 (3 H, t, *J* 7.4 Hz, 14-H); δ_C(90.6 MHz, $CDCl_3$) 94.25 (s, C-2), 82.49 (s, C-7) 81.38 (s, C-8), 65.95 (t, CH_2), 62.6 (t, CH_2), 50.11 (q, OCH_3), 37.0 (d, CH), 36.26 (t, CH_2), 35.96 (d, CH), 24.87 (t, CH_2), 24.57 (t, CH_2), and 10.81 (q, CH_3CH_2); *m/z* (EI) (Found: M^+ − OMe, 211.1322. $C_{12}H_{19}O_3$ requires 211.1334), 211 (M^+ − OMe, 83%), 181(17), 167(43), 156(58), 133(17), 127(100), 111(23), and 108(91).

(3*S**,6*R**,9*R**)- *and* (3*R**,6*R**,9R*)-9-*Ethyl*-3-*hydroxymethyl*-1,7-*dioxaspiro*[5.5]*undec*-4-*ene* (**7a,b**).—A suspension of acetylenic acetals (**18a,b**) (635 mg, 2.62 mmol), Lindlar's catalyst (52 mg, Pd/$CaCO_3$/Pb) and triethylamine (0.18 ml, 1.3 mmol) in dry methanol (27 ml) was hydrogenated at atmospheric pressure for 3 h. The reaction was filtered through a pad of Celite and the residues washed with methanol (2 × 20 ml). Concentration under reduced pressure gave an oil which was dried (0.08 mmHg, 13 h). Partial spirocyclisation of the crude product was observed during the course of running routine NMR spectra and the crude product was consequently used in the next reaction without any attempt to purify this intermediate. The olefin (636 mg, 2.62 mmol) was dissolved in dry dichloromethane (60 ml) and stirred in the presence of D,L-camphorsulphonic acid (20 mg, 0.087 mmol) under nitrogen for 2.5 h. The reaction was filtered through a pad of Celite and potassium hydrogen carbonate (1:1, v/v) and the pad was washed with dichloromethane (3 × 20 ml). The combined organic phase was concentrated under reduced pressure and the resulting oil was purified by flash chromatography (6.5:3.5, ethyl acetate–light petroleum) to give a 1:2 mixture of (S*S**,6*R**,9*R**)- and (3*R**,6*R**,9*R**)-9-ethyl-3-hydroxymethyl-1,7-dioxaspiro[5.5]undec-4-ene (**7a,b**) as an oil, b.p. 62–64 °C at 0.04 mmHg (434 mg, 78%), ν_{max}(thin film) 3 440 (OH), 3 050, 2 970, 2 940, 2 880, 1 660 (C=C), 1 465, 1 285, 1 245, 1 170, 1 090, 1 020, 910, and 870 cm^{-1}; δ_H(360 MHz, $CDCl_3$), 5.85–5.82 and 5.9 (1 H, m, 4-H), 5.74–5.69 (1 H, m, 5-H), 4.02 and 3.97–3.94 (1 H, m, CH_2O), 3.88–3.74 (2 H, m, CH_2O), 3.65–3.58 (2 H, m, CH_2O including 8-H_e), 3.41 (1 H, t, *J* 10.9 Hz, 8-H_a), 2.62–2.56 and 2.14–2.0 (1 H, m, 3-H), 1.75–1.65 (1 H, br s, OH), 1.74–1.60 (3 H, m, 10-H_a, 10-H_e and 11 H_e), 1.49–1.40 (2 H, m, 9-H_a and 11-H_a), 0.99–0.82 (2 H, m, 13-H), and 0.89 (3 H, t, *J* 7.4 Hz, 14-H); *m/z* (EI) (Found: M^+, 212.1390. $C_{12}H_{20}O_3$ requires 212.1412), 212 (M^+, 4%), 181(12), 143(16), 129(100), 126(92), and 96(47).

(3*S**,6*R**,9*R**)- *and* (3*R**,6*R**,9*R**)-3-[(*t-Butyldimethyl*)*siloxy*]*methyl*-9-*ethyl*-1,7-*dioxaspiro*[5.5]*undec*-4-*ene* (**20**) *and* (**19**).—Imidazole (802 mg, 11.8 mmol) and t-butyldimethylsilyl chloride (887 mg, 5.9 mmol) were added to a solution of the olefinic spiroketals (**7a,b**) (1.0 g, 4.7 mmol) in dry dimethylformamide (5 ml) and stirred under nitrogen at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and dissolved in ether (100 ml). The organic phase was washed with dilute (0.1M) hydrochloric acid (1 × 20 ml), saturated sodium hydrogen carbonate (2 × 20 ml), and brine (1 × 20 ml) and dried (Na_2SO_4). Concentration under reduced pressure gave an oil which was purified by flash chromatography (ether–light petroleum; 1:19 ⟶ 1:9, v/v) to yield (3*S**,6*R**, 9*R**)- and (3*R**,6*R**,9*R**)-3-[(t-butyldimethyl)siloxy]methyl-9-ethyl-1,7-dioxaspiro[5.5]undec-4-ene as colourless oils (**20**) and (**19**) [1.29 g, 84% (combined yield)]: (**20**) R_f 0.18 (1:19, ether–light petroleum), b.p. 97–99 °C at 0.2 mmHg (Found: C, 66.1; H, 10.5. $C_{18}H_{34}O_3Si$ requires C, 66.2; H, 10.5%); ν_{max}(thin film) 3 050 (CH) vinylic, 2 970, 2 940, 2 860, 1 660 (C=C), 1 475, 1 465, 1 260, 1 085, 1 020, 910, 840, and 780 cm^{-1}; δ_H(360 MHz, $CDCl_3$) 5.77 (1 H, d, *J* 10 Hz, 4-H), 5.64 (1 H, dd, *J* 2.6 and 10.4 Hz, 5-H), 3.84 (1 H, dd, *J* 5.7 and 11 Hz, 12-H), 3.57–3.5 (3 H, m, 2 × 8-H and 12-H), 3.45–3.38 (2 H, m, 2 × 2-H), 2.66–2.54 (1 H, m, 3-H_a), 1.74–1.55 (3 H, m, 11-H_e, 10-H_e, 10-H_a), 1.55–1.38 (2 H, m, 9-H_a and 11-H_a), 1.27–1.08 (2 H, m, 3-H_a), 1.74–1.55 (3 H, m, 11-m, 2 × 13-H), 0.88 (3 H, t, *J* 7.2 Hz, 2 × 14-H), 0.87 (9 H, s, Bu^t), and 0.02 (6 H, s, 2 × CH_3Si); δ_C(90.6 MHz, $CDCl_3$), 131.4 (d, C-5), 129.5 (d, C-4), 93.7 (s, 4 × C), 66.0 (t, CH_2O), 64.3 (t, CH_2O), 61.9 (t, CH_2O), 37.9 (d, CH), 36.8 (d, CH), 35.0 (t, CH_2), 26.0 (q, CH_3), 25.5 (t, CH_2), 25.1 (t, CH_2), 11.2 (q, CH_3), and −5.3 (q, CH_3).

(**19**) R_f 0.13 (ether–light petroleum, 1:19), b.p. 97–99 °C at 0.2 mmHg; (Found: C, 66.1; H, 10.5. $C_{18}H_{34}O_3Si$ requires C, 66.2; H, 10.5%); ν_{max}(thin film), 3 040 (CH) vinylic, 2 980, 2 940, 2 860, 1 660 (C=C), 1 470, 1 460, 1 255, 1 100, 1 090, 1 030, 840, and 770 cm^{-1}; δ_H(360 MHz, $CDCl_3$) 5.88 (1 H, dd, *J* 10.1 and 1.2 Hz, 4-H), 5.66 (1 H, d, *J* 10.1 Hz, 5-H), 3.92 (1 H, dd, *J* 3.5 and 11.3 Hz, 2-H_a), 3.78 (1 H, d, *J* 11.3 Hz, 2-H_e), 3.56 (1 H, dd, *J* 2.9 and 10.9 Hz, 8-H_e), 3.55 (2 H, d, *J* 7.5 Hz, 12-H), 3.45 (1 H, t, *J* 10.9 Hz, 8-H_a), 2.04–1.97 (1 H, m, 3-H_e), 1.7–1.5 (3 H, m, 10-H_e, 11-H_e and 10-H_a), 1.45–1.42 (2 H, m, 9-H_a and 11-H_a), 1.24–1.08 (2 H, m, 13-H), 0.89 (9 H, s, Bu^t), 0.88 (3 H, t, *J* 7.4 Hz, 14-H), and 0.04 (6 H, s, 2 × CH_3Si); δ_C(90.6 MHz, $CDCl_3$), 132.2 (d, C-5), 128.6 (d, C-4), 92.8 (s, C-6), 65.9 (t, CH_2O), 63.4 (t, CH_2O), 58.5 (t, CH_2O), 37.7 (d, CH), 36.8 (d, CH), 35.1 (t, CH_2), 26.1 (q, CH_3), 25.5 (t, CH_2), 25.2 (t, CH_2), 18.4 (s, 4′-C), 11.2 (q, CH_3), and −5.3 (q, CH_3Si); *m/z* [Found: 269.1579 (M^+ − Bu^t). $C_{14}H_{25}O_3Si$ requires 269.1573], 269 (7.1%), 183(16), 159(8), 105(13), 91(87), and 77(18).

(3*R**,4*S**,5*S**,6*R**,9*R**)- *and* (3*R**,4*R**,5*R**,6*R**,9*R**)-3-[(*t-Butyldimethyl*)*siloxy*]*methyl*-5-*chloro*-9-*ethyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*ol* (**22**) *and* (**21**).—To the olefinic spiroketal (3*R**,6*R**,9*R**)-3-[(t-butyldimethyl)siloxy]methyl-9-ethyl-1,7-dioxaspiro[5.5]undec-4-ene (**19**) (408 mg, 1.25 mmol) in aqueous acetone (33 ml) (1:10, v/v) was added t-butyl hypochlorite (450 mg, 4.9 mmol) and the reaction stirred at room temperature for 5.5 h. The reaction mixture was concentrated at reduced pressure and taken up in ether (100 ml). The organic phase was washed with water (2 × 15 ml), the aqueous phase being backwashed with ether (20 ml) and the combined organic phase washed with brine (25 ml) and dried (Na_2SO_4). Concentration under reduced pressure gave the diastereoisomeric pair of chlorohydrins (3*R**,4*S**,5*S**, 6*R**, 9*R**) and (3*R**,4*R**,5*R**,6*R**,9*R**)-3-[(t-butyldimethyl)siloxy]-methyl-5-chloro-9-ethyl-1,7-dioxaspiro[5.5]undecan-4-ol (**22**) and (**21**) which were purified by flash chromatography (ether–light petroleum, 1:4) to give (**21**) (71 mg, 14%); R_f 0.28, ν_{max}(thin film) 3 480 (OH), 2 970, 2 940, 2 890, 2 860, 1 465, 1 260, 1 100, 1 050, 1 000, and 840 cm^{-1}; δ_H(360 MHz, $CDCl_3$) 4.19 (1 H, dt, *J* 5.4 and 10.8 Hz, 4-H_a), 4.07 (1 H, dd, *J* 7.0 and 10.1 Hz, 12′-H), 3.79 (1 H, dd, *J* 8.3 and 10.1 Hz, 12-H), 3.72–3.64 (4 H, m, 8-H_e, 2-H_e and 5-H_a), 3.3 (1 H, br d, *J* 4.5 Hz O*H*), 3.22 (1 H, t, *J* 10.9 Hz, 8-H_a), 2.28 (1 H, m, 3-H_e), 2.13 (1 H, dt, *J* 4.8 and 13.3 Hz, 11-H_a), 1.67 (1 H, m, 9-H_a), 1.52 (2 H, m, 11-H_e and 10-H_e), 1.39 (1 H, qd, *J* 4.1 and 12.2 Hz, 10-H_a), 1.19–1.11 (2 H, m, 2 × 13-H), 0.9 (9 H, s, Bu^t), 0.89 (3 H, t, *J* 7.3 Hz, 14-H), and 0.07 (6

H, s, 2 × CH_3Si); *m/z* [Found: 321.1260 (M^+ − Bu^t). $C_{14}H_{26}ClO_4Si$ requires 321.1289], 321 (M^+ − Bu^t, 8.1%), 203(17), 185(13), 161(47), 131(41), 105(20), and 77(100).

(**22**) R_f 0.23 (279 mg, 59%); ν_{max}(thin film), 3 480 (OH), 2 980, 2 960, 2 900, 2 880, 1 480, 1 260, 1 100, 1 010, 850, and 780 cm^{-1}; δ_H(360 MHz, $CDCl_3$) 3.85 (1 H, dd, *J* 5.1 and 12.2 Hz, 12-H), 3.78–3.72 (2 H, m, 2-H_e and 4-H_e), 3.67–3.62 (3 H, m, 5-H_e, 8-H_e and 2-H_a), 3.55 (1 H, dd, *J* 7.7 and 12.2 Hz, 12′-H), 3.5 (1 H, t, *J* 11.3 Hz, 8-H_a), 3.17 (1 H, d, *J* 5.2 Hz OH), 1.97–1.94 (1 H, m, 3-H_e), 1.93 (1 H, dt, *J* 3.7 and 13.7 Hz, 11-H_e), 1.74 (1 H, dt, *J* 4.2 and 13.4 Hz, 11-H_a), 1.66–1.56 (1 H, m, 10-H_e), 1.52–1.43 (1 H, m, 9-H_a), 1.23 (1 H, qd, *J* 12.4 and 4.0 Hz, 10-H_a), 1.16–1.03 (2 H, m, 13-H), 0.87 (9 H, s, Bu^t), 0.86 (3 H, t, *J* 7.4 Hz, 14-H), and 0.02 (6 H, s, 2 × CH_3Si); δ_C(90.6 MHz, $CDCl_3$), 98.7 (s, CH), 70.7 (d, CH), 66.8 (t, CH_2O), 66.1 (s, CH), 61.6 (t, CH_2O), 60.3 (t, CH_2O), 45.0 (d, CH), 36.6 (d, CH), 26.5 (t, CH_2), 25.9 (q, CH_3), 25.1 (t, CH_2), 24.1 (t, CH_2), 11.0 (q, CH_3), and −5.5 (q, CH_3Si); *m/z* (EI) [Found: 321.1278 (M^+ − Bu^t). $C_{14}H_{26}ClO_4Si$ requires 321.1289], 321(15%), 277(10), 161(23), 129(30), 105(33), and 75(100).

(3*S**,4*S**,5*S**,6*R**,9*R**)- *and* (3*S**,4*R**,5*R**,6*R**,9*R**)-3-[(*t-Butyldimethyl*)*siloxy*]*methyl*-5-*chloro*-9-*ethyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*ol* (**24**) *and* (**23**).—Using the procedure described above the olefinic spiroketal (**20**) (3*S**,6*R**,9*R**)-3-[(t-butyldimethyl)siloxy]methyl-9-ethyl-1,7-dioxaspiro[5.5]-undec-4-ene (247 mg, 0.76 mmol) was chlorohydrated to give a mixture (1.4:1) of the chlorohydrins (**23**) and (**24**). Purification by flash chromatography (ether–light petroleum, 3:17) gave (3*S**,4*S**,5*S**,6*R**,9*R**)- and (3*S**,4*R**,5*R**,6*R**,9*R**)-3-[(t-butyldimethyl)siloxy]methyl-5-chloro-9-ethyl-1,7-dioxaspiro-[5.5]undecan-4-ol (**24**) (71 mg, 25%) and (**23**) (100 mg, 35%) respectively as colourless oils (**24**); ν_{max}(thin film) 3 510 (OH), 2 970sh, 2 940, 2 880, 2 860, 1 470, 1 460, 1 110, 1 100, 1 035, 1 010, and 840 cm^{-1}; δ_H(360 MHz, $CDCl_3$), 3.97 (1 H, dd, *J* 2.8 and 10.8 Hz, 4-H_e), 3.85 (1 H, d, *J* 10.8 Hz-OH), 3.79 (1 H, d, *J* 2.7 Hz, 5-H_e), 3.78 (1 H, dd, *J* 11.5 and 5.3 Hz, 12-H), 3.69 (1 H, m, 8-H_e), 3.69 (1 H, dd, *J* 10.4 and 6 Hz, 2-H_e), 3.59 (1 H, t, *J* 11.5 Hz, 12′-H), 3.58 (1 H, t, *J* 10.3 Hz, 2-H_a), 3.33 (1 H, t, *J* 10.9 Hz, 8-H_a), 2.46 (1 H, m, 3-H_a), 2.05 (1 H, dm, *J* 13.1 Hz, 11-H_e), 1.64 (1 H, m, 10-H_e), 1.71–1.39 (3 H, m, 9-H_a, 10-H_a and 11-H_a), 1.42 (2 H, m, 13-H), 0.84 (9 H, s, Bu^t), 0.83 (3 H, t, *J* 7.4 Hz, 14-H), and 0.02 (6 H, s, 2 × CH_3Si); *m/z* (EI) [Found: 321.1259 (M^+ − Bu^t). $C_{14}H_{26}ClO_4Si$ requires 321.1289], 321(16%) 185(7), 161(54), 131(35), and 129(14).

(**23**) ν_{max}(thin film) 2 980 (OH), 2 960, 2 930, 2 880, 2 860, 1 465, 1 250, 1 095, 1 040, 835, and 775 cm^{-1}; δ_H(360 MHz, $CDCl_3$), 3.89 (1 H, t, *J* 9.9 Hz, 4-H_a), 3.75 (1 H, dd, *J* 10.2 and 5.5 Hz), 12-H), 3.70–3.64 (3 H, m, 12′-H, 8-H_e and 2-H_e), 3.53 (1 H, d, *J* 9.7 Hz, 5-H_a), 3.44 (1 H, t, *J* 11.5 Hz, 2-H_a), 3.17 (1 H, t, *J* 11.0 Hz, 8-H_a), 2.9 (1 H, br s, OH), 2.09 (1 H, dt, *J* 12.4 and 4.9 Hz, 11-H_a), 1.94 (1 H, m, 3-H_a), 1.62 (1 H, m, 10-H_e), 1.48 (2 H, m, 11-H_e and 9-H_a), 1.33 (1 H, dq, *J* 12.4 and 3.9 Hz, 10-H_a), 1.14–1.05 (2 H, m, 13-H), 0.85 (3 H, t, *J* 8.4 Hz, 14-H), 0.83 (9 H, s, Bu^t), and 0.33 (6 H, s, 2 × CH_3Si); *m/z* (EI) [Found: 321.1164 (M^+ − Bu^t). $C_{14}H_{26}ClO_4Si$ requires 321.1289] 321(2.4%), 203(100), 185(22), 129(21), 111(13), and 105(10).

(3*S**,4*S**,6*R**,9*R**)-3-[(*t-Butyldimethyl*)*siloxy*]*methyl*-9-*ethyl*-1,7-*dioxaspiro*[5.5]*undecan*-4-*ol* (**27**).—To a solution of the diequatorial chlorohydrin (**23**) (145 mg, 0.382 mmol) in dry toluene (8 ml) was added tributyltin hydride (0.38 ml) and AIBN (10 mg) and the reaction heated to reflux under nitrogen for 3 h. On cooling to room temperature the reaction mixture was concentrated at reduced pressure and purified by flash chromatography to give (3*S**,4*S**,6*R**,9*R**)-3-[t-butyldimethyl)siloxy]methyl-9-ethyl-1,7-dioxaspiro[5.5]undecan-4-ol (**27**) (104 mg, 79%) as a white crystalline solid, m.p. 68.5–70.5 °C; ν_{max}($CHCl_3$) 3 460 (OH), 2 970, 2 940, 2 870, 1 465, 1 380, 1 260, 1 185, 1 090, 1 050, 840, and 780 cm^{-1}; δ_H(360 MHz, $CDCl_3$), 4.02 (1 H, ddd, *J* 10.6 and 5.1 Hz, 4-H_a), 3.72–3.63 (2 H, m, 12-H and 12′-H), 3.55 (1 H, dd, *J* 11.3 and 4.8 Hz, 2-H_e), 3.43 (1 H, m, 8-H_e), 3.27 (1 H, t, *J* 11.4 Hz, 2-H_a), 3.19 (1 H, t, *J* 10.9 Hz, 8-H_a), 2.0 (1 H, dd, *J* 12.8 and 5.1 Hz, 5-H_e), 1.82 (1 H, m, 3-H_a), 1.72–1.54 (3 H, m, 11-H_e, 11-H_a and 10-H_a), 1.44–1.27 (3 H, m, 5-H_a, 9-H_a and 10-H_a), 1.25–1.11 (2 H, m, 13-H), 0.89 (3 H, t, *J* 7.2 Hz, 14-H), 0.81 (9 H, s, Bu^t), and 0.03 (6 H, s, 2 × CH_3Si); *m/z* (EI) 345 (M^+ + H, 23%), 327 (M^+ +H − H_2O, 100), 287 (M^+ − Bu^t, 27), 203(98), 185(26), 165(42), and 127(16).

(3*S**,4*R**,6*R**,9*R**)-3-[(*t-Butyldimethyl*)*siloxy*]*methyl*-9-*ethyl*-1,7-*dioxaspiro*[5.5]*undecan*-4-*ol* (**28**).—Using the procedure described above the diaxial chlorohydrin (**24**) (55 mg, 0.14 mmol) was reduced to (3*S**,4*R**,6*R**,9*R**)-3-[t-butyldimethyl)siloxy]methyl-9-ethyl-1,7-dioxaspiro[5.5]undecan-4-ol (**28**) which was purified by flash chromatography (ether–light petroleum, 1:9) to give (**28**) (35 mg, 72%) as a white crystalline solid, m.p. 41–42.5 °C; ν_{max}($CHCl_3$) 3 520 (OH), 2 970, 2 940, 2 880, 1 460, 1 390, 1 260, 1 180, 1 150, 1 100, 1 020, 840, and 780 cm^{-1}; δ_H(360 MHz, $CDCl_3$), 3.93 (1 H, dddd, *J* 9.9 and 2.75 Hz, 4-H_e), 3.73 (1 H, d, *J* 9.9 Hz, OH), 3.71 (1 H, dd, *J* 11.5 and 5.8 Hz, 12-H), 3.67 (1 H, dd, *J* 10.2 and 5.8 Hz, 2-H_e), 3.60 (1 H, t, *J* 11.7 Hz, 12′-H), 3.61–3.58 (1 H, m, 8-H_e), 3.53 (1 H, dd, *J* 10.2 and 8.4 Hz, 2-H_a), 3.31 (1 H, t, *J* 10.9 Hz, 8-H_a), 1.9 (1 H, m, 3-H_a), 1.89 (1 H, dd, *J* 14 and 3 Hz, 5-H_e), 1.66–1.62 (2 H, m, 5-H_a and 10-He), 1.6–1.52 (2 H, m, 10-H_a and 11-H_e), 1.49–1.38 (2 H, m, 9-H_a and 11-H_a), 1.19–1.1 (2 H, m, 13-H), 0.84 (9 H, s, Bu^t), 0.83 (3 H, t, *J* 7.4 Hz, 14-H), and 0.02 (6 H, s, 2 × CH_3Si); *m/z* (Cl, NH_3) 287 (M^+ − Bu^t, 53%), 243 (10), 195(12), 161(33), 105(28), and 75(100).

(3*R**,4*S**,6*R**,9*R**)-3-[(*t-Butyldimethyl*)*siloxy*]*methyl*-9-*ethyl*-1,7-*dioxaspiro*[5.5]*undecan*-4-*ol* (**25**).—Using the procedure described above the diequatorial chlorohydrin (**21**) (60 mg, 0.16 mmol) was reduced to (3*R**,4*S**,6*R**,9*R**)-3-[(t-butyldimethyl)siloxy]methyl-9-ethyl-1,7-dioxaspiro[5.5]-undecan-4-ol give (**25**) which was purified by flash chromatography (ether–light petroleum, 2:8) to give (**25**) (28 mg, 52%) as a white crystalline solid, m.p. 56–58 °C; ν_{max}($CHCl_3$), 3 440 (OH), 2 970, 2 940, 2 870, 2 870, 1 465, 1 380, 1 260, 1 190, 1 100, 1 080, 905, 840, and 780 cm^{-1}; δ_H(360 MHz, $CDCl_3$), 4.18 (1 H, dddd, *J* 5, 7.1 and 14 Hz, 4-H_a), 4.12 (1 H, t, *J* 10.1 Hz, 12-H), 3.87 (1 H, d, *J* 7.1 Hz, OH), 3.73 (1 H, dd, *J* 10.4 and 5.6 Hz, 12′-H), 3.62 (1 H, dd, *J* 11.6 and 2.6 Hz, 2-H_e), 3.54 (1 H, m, 8-H_e), 3.48 (1 H, d, *J* 11.6 Hz, 2-H_a), 3.09 (1 H, t, *J* 10.9 Hz, 8-H_a), 2.09 (1 H, m, 3-H_e), 1.84 (1 H, dd, *J* 12.9 and 4.9 Hz, 5-H_e), 1.62–1.47 (3 H, m, 5-H_a, 10-H_e and 11-H_e), 1.53–1.35 (3 H, m, 10-H_a, 9-H_a and 11-H_a), 1.12–1.01 (2 H, m, 13-H), 0.9 (9 H, s, Bu^t), 0.86 (3 H, t, *J* 7.2 Hz, 14-H), and 0.09 (6 H, s, 2 × CH_3Si); *m/z* (Found: M^+ − Bu^t, 287.1645. $C_{14}H_{27}O_4Si$ requires 287.1679), 287 (M^+ − Bu^t 8%), 269 (M^+ − Bu^t + H_2O, 13), 157(7), and 127(22).

(3*R**,4*R**,6*R**,9*R**)-3-[(*t-Butyldimethyl*)*siloxy*]*methyl*-9-*ethyl*-1,7-*dioxaspiro*[5.5]*undecan*-*ol* (**26**).—Using the procedure described above the diaxial chlorohydrin (**22**) (200 mg, 0.52 mmol) was reduced to (3*R**,4*R**,6*R**,9*R**)-3-[(t-butyldimethyl)siloxy]methyl-9-ethyl-1,7-dioxaspiro[5.5]undecan-4-ol (**26**) which was purified by flash chromatography (ether–light petroleum, 3:17) to give (**26**) (105 mg, 59%) as a white crystalline solid, m.p. 45–46.5 °C; ν_{max}($CHCl_3$) 3 530 (OH), 2 970, 2 940, 2 870, 1 470, 1 370, 1 260, 1 240, 1 100, 860, 840, and 780 cm^{-1}; δ_H(360 MHz, $CDCl_3$), 4.10 (1 H, d, *J* 9.7 Hz, OH), 3.99 (1 H, dd, *J* 12.1 and 3.3 Hz, 2-H_e), 3.95 (1 H, m, 4-H_e), 3.70 (1 H, dd, *J* 10.1 and 7.7 Hz, 12-H), 3.61 (1 H, dd, *J* 10.9 and 2.0 HZ, 8-H_e), 3.61 (1 H, dd, *J* 10.2 and 8.0 Hz, 12′-H), 3.53 (1 H, d, *J* 12.9

Hz, 2-H_a), 3.31 (1 H, t, *J* 10.9 Hz, 8-H_a), 1.84 (1 H, m, 3-H_e), 1.75 (1 H, dd, *J* 15.0 and 3.1 Hz, 5-H_e), 1.71–1.58 (3 H, m, 11-H_e, 10-H_e and 5-H_e), 1.52–1.36 (3 H, m, 11-H_a, 10-H_a and 9-H_a), 1.18–1.12 (2 H, m, 13-H), 0.88 (9 H, s, Bu^t), 0.87 (3 H, t, *J* 7.4 Hz, 14-H), and 0.05 (6 H, s, 2 × CH_3Si); *m/z* [Found: 287.1669. $C_{14}H_{27}O_4Si$ ($M^+ - Bu^t$) requires 287.1679), 327 ($M^+ - H_2O$, 22%), 287 ($M^+ - Bu^t$, 26), 269(24), 203(21), 185(12), 165(16), 127(34), and 75(100).

(3*S**,4*S**,6*R**,9*R**)-9-*Ethyl*-3-*hydroxymethyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*ol* (**2**) (*Talaromycin B*).—To the spiroketal (**27**) (96.4 mg, 0.28 mmol) in dry THF (2 ml) was added a solution of tetrabutylammonium fluoride in THF (0.7 ml; 1.0M) and stirred at room temperature for 2 h. Concentration of the reaction mixture at reduced pressure afforded the crude product which was purified by column chromatography (silica; methanol–dichloromethane, 3:97) to give talaromycin B (**2**) (51.7 mg, 80%) as white crystals m.p. 129.7–130.5 °C (from CH_2Cl_2–hexane, 1:3) (lit.,[4e] 127–128 °C); ν_{max}($CHCl_3$) 3 420s (OH), 2 960, 2 930, 2 870, 1 470, 1 380, 1 155, 1 090, 1 080, 1 030, and 845 cm^{-1}; δ_H(360 MHz, $CDCl_3$), 4.07 (1 H, dt, *J* 10.6 and 5 Hz, 4-H_a), 3.71 (2 H, d, *J* 5.9 Hz, 12-H), 3.58 (1 H, dd, *J* 11.6 and 1.2 Hz, 2-H_e), 3.51 (1 H, m, 8-H_e), 3.31 (1 H, t, *J* 10.9 Hz, 2-H_a), 3.19 (1 H, t, *J* 10.9 Hz, 8-H_a), 2.72–2.62 (2 H, br s, OH), 1.99 (1 H, dd, *J* 12.6 and 4.9 Hz, 5-H_e), 1.86–1.74 (1 H, m, 3-H_a), 1.62–1.51 (3 H, m, 11-H_e, 11-H_a and 10-H_e), 1.45–1.27 (3 H, m, 10-H_a, 9-H_a and 5-H_a), 1.21–1.11 (2 H, m, 13-H), and 0.88 (3 H, t, *J* 7.5 Hz, 14-H); *m/z* (EI) 231 (M^+ + H, 12%), 218 (M^+ − OH, 26), 183(13), 147(100), 143(53), 129(88), 125(82), 111(39), 96(51), 83(46), and 69(68).

(3*S**,4*R**,6*R**,9*R**)-9-*Ethyl*-3-*hydroxymethyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*ol* (**5**) (*Talaromycin E*).—The spiroketal (**5**) talaromycin E, was prepared from (**28**) (46.3 mg, 0.134 mmol), as described above, in 72% yield and was purified by column chromatography (MeOH–CH_2Cl_2, 2:98) and obtained as a colourless oil; ν_{max}(thin film) 3 500 (OH), 3 360 (OH), 2 960, 2 930, 2 870, 1 465, 1 180, 1 150, 1 090, 1 025, and 860 cm^{-1}; δ_H(360 MHz, $CDCl_3$), 4.05 (2 H, br s, O*H*), 3.81 (1 H, t, *J* 12 Hz, 2-H_e), 3.69 (1 H, dd, *J* 11.2 and 4.5 Hz, 12-H), 3.62 (1 H, dd, *J* 11.2 and 5.4 Hz, 12-H), 3.60–3.54 (1 H, m, 4-H_e), 3.53 (1 H, m, 8-H_e), 3.29–3.22 (2 H, m, 2-H_a and 8-H_a), 1.82 (1 H, d, *J* 14 Hz, 5-H_e), 1.76–1.68 (1 H, m, 3-H_a), 1.61–1.51 (3 H, m, 11-H_e, 5-H_a and 10-H_e), 1.40–1.28 (3 H, m, 9-H_a and 10-H_a and 11-H_a), 1.13–1.0 (2 H, m, 13-H), and 0.8 (3 H, t, *J* 7.1 Hz, 14-H); *m/z* (EI) 231 (M^+ +H, 40%), 213(100), 147(82), 129(87), 126(80), 111(34), 96(30), and 83(36).

(3*R**,4*S**,6*R**,9*R**)-9-*Ethyl*-3-*hydroxymethyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*ol* (**1**) (*Talaromycin A*).—Talaromycin A (**1**) was prepared from (**20**) (18 mg, 0.052 mmol), as described above, in 68% yield, and was purified by column chromatography (MeOH–CH_2Cl_2, 3:97) and obtained as a clear oil; ν_{max}(thin film) 3 350 (OH), 2 980, 2 940, 2 880, 1 460, 1 185, 1 060, 895, and 870 cm^{-1}; δ_H(360 MHz, $CDCl_3$), 4.40 (1 H, dt, *J* 11.7 and 5.8 Hz, 4-H_a), 4.20 (1 H, dd, *J* 11 and 9.0 Hz, 12-H), 3.80 (1 H, dd, *J* 11.0 and 5 Hz, 12′-H), 3.74 (1 H, dd, *J* 11.8 and 2.9 Hz, 2-H_a), 3.58 (1 H, dd, *J* 11.8 and 1.3 Hz, 2-H_e), 3.52 (1 H, m, 8-H_e, 3.19 (1 H, t, *J* 10.9 Hz, 8-H_a), 2.83 (2 H, br s, OH), 2.15 (1 H, m, 3-H_e), 1.89 (1 H, dd, *J* 12.9 and 7.8 Hz, 5-H_e), 1.72 (1 H, t, *J* 12.7 Hz, 5-H_a), 1.71–1.66 (1 H, m, 11-H_e), 1.64–1.60 (1 H, dm, 10-H_e), 1.55–1.31 (3 H, m, 11-H_a, 10-H_a and 9-H_a), 1.21–1.07 (2 H, m, 13-H), and 0.88 (3 H, t, *J* 7.4 Hz, 14-H); *m/z* (CI, NH_3) 231 (M^+ + H, 36%), 213(100), 147(28), 129(22), and 126(15).

(3*R**,4*R**,6*R**,9*R**)-9-*Ethyl*-3-*hydroxymethyl*-1,7-*dioxaspiro*-[5.5]*undecan*-4-*ol* (**3**) (*Talaromycin C*).—Talaromycin C (**3**) was prepared from (**26**) (142 mg, 0.41 mmol), as described above, in 60% yield, and was purified by column chromatography (MeOH–CH_2Cl_2, 2:98) and obtained as a clear oil: ν_{max}(thin film) 3 500–3 300 (OH), 2 960, 2 920, 2 880, 1 465, 1 380, 1 155, 1 080, and 850 cm^{-1}; δ_H(360 MHz, $CDCl_3$), 4.14 (1 H, br d, *J* 8.9 Hz, 4-OH), 3.94 (1 H, dd, *J* 12.1 and 3.0 Hz, 2-H_e), 3.87 (1 H, m, 4-H_e), 3.64 (1 H, dd, *J* 10.7 and 7.8 Hz, 8-H_e), 3.57–3.5 (3 H, m, 2 × 12-H and 2-H_a), 3.23 (1 H, t, *J* 10.7 Hz, 8-H_a), 2.77 (1 H, br s, 12-OH), 1.9–1.88 (1 H, m, 3-H_e), 1.69–1.64 (2 H, m, 5-H_e and 10-H_e), 1.61–1.50 (2 H, m, 11-H_e and 5-H_a), 1.45–1.21 (3 H, m, 11-H_a, 10-H_a and 9-H_a), 1.17–1.0 (2 H, m, 13-H), and 0.80 (3 H, t, *J* 7.6 Hz, 14-H); *m/z* (EI) 231 (M^+ + H, 18%), 213(53), 147(100), 129(83), 111(40), 96(37), 83(39), and 69(49).

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