Supporting Information

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The Changing Faces of Halogenated Marine Natural Products:
Total Synthesis of the Reported Structures of Elatenyne
and an Enyne from Laurencia Majuscula

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Introduction

$^1$H and $^{13}$C NMR spectra were recorded on Bruker DPX-400 or Bruker DRX-500 equipped with an inverse $^{13}$C-$^1$H Cryoprobe, using deuterochloroform as an internal deuterium lock. Chemical shifts are quoted in units of $\delta$ relative to tetramethylsilane ($\delta$=0). Multiplets are indicated as s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; dd, double doublet; m, multiplet; br, broad, etc. Coupling constants $J$ are quoted in Hz. For many of the compounds the $J$ values have been extracted and placed alongside conformational diagrams of the synthetic intermediates. In these instances if the $J$ value carries an asterisk (*) then unambiguous assignment of the proton has not been possible and so the $J$ value may be interchanged with the other $J$ value in the same row (e.g. a row reading: $J^*_{3,4ax}$ 10 $J^*_{7,8ax}$ 11.1, means that the $J_{3,4ax}$ coupling is 10 Hz and the $J_{7,8ax}$ coupling is 11.1 Hz or vice versa); furthermore in some instances it was not possible to assign the 4-C or 8-C protons as axial or equatorial and in these cases the protons are denoted 4-H and 4-H', and 8-H and 8-H'. Where useful, the FID was zero-filled (128 K) and sine-bell shifted (ssb = 30) prior to Fourier Transformation in order to provide baseline-resolved multiplets and easily identifiable coupling constants. Double Quantum Filtered and magnitude COSY and HMQC spectra were typically acquired with 256 slices in $F_1$ and 2048 points in $F_2$ (acquisition time approximately 20 min). $^{13}$C spectra were recorded with proton decoupling; $J$ resolved spin-echo APT or DEPT-135, and in some cases HMQC, were recorded to assist assignment.

Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer calibrated relative to polystyrene absorption at 1630 cm$^{-1}$. The samples were prepared as a thin film or a solution in the solvent indicated.

Mass spectra were recorded by the Mass Spectrometry Service at the University of Cambridge Chemical Laboratory. Microanalyses were carried out by the Microanalytical Service at the University of Cambridge Chemical Laboratory.

Optical specific rotations were measured on a Perkin-Elmer 241 polarimeter and are quoted in units of $^\circ$10$^2$cm$^2$g$^{-1}$. The concentration (c) is expressed in g/0.1 dm$^3$.

Flash chromatography was carried out on silica gel [Merck 9385 Kieselgel 60 (230-400 ASTM)]. Analytical TLC was carried out on 0.25 mm thick plates precoated with Merck Kieselgel F$_{254}$ silica gel and visualised by UV and aqueous potassium permanganate solution or ethanolic phosphomolybdic acid solution. Preparative layer chromatography was carried out on 1 mm thick plates of Merck Kieselgel PF$_{254}$.

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Kugelrohr bulb-to-bulb distillations were carried out using a Büchi GKR-51 machine. Boiling points are oven temperatures.

Dry THF was distilled from potassium in a recycling still using benzophenone ketyl as indicator. Other solvents were purified by standard techniques. Ether refers to diethyl ether. Petroleum ether (PE) refers to the fraction boiling at 40-60 °C.

(2$R$, 2'$R$)-5,5' -Bisacetoxy-octahydro-[2,2']bifuranyl 6

To a stirred solution of the lactone 5 (2.05 g, 12.1 mmol) in DCM (60 mL) at -78 °C was added DIBAL (18.5 mL, of a 1.5 M solution in toluene, 27.7 mmol) dropwise so as to keep the internal temperature below -76 °C. The resulting solution was stirred for 2 h at -78 °C and then pyridine (5.85 mL, 72.4 mmol), a solution of DMAP (5.89 g, 48.2 mmol) in DCM (40 mL) and acetic anhydride (13.7 mL, 144.7 mmol) were added sequentially at a rate to maintain the internal temperature below -76 °C. The reaction mixture was stirred at -78 °C overnight and then allowed to gradually warm to -20 °C over 1 h. The reaction was quenched by the addition of saturated aqueous NH$_4$Cl (50 mL) and was stirred vigorously until a clear two-phase system resulted. The layers were separated and the aqueous layer extracted with DCM (3 × 50 mL). The organic phases were washed with saturated aqueous NaHCO$_3$ (3 × 50 mL), saturated aqueous CuSO$_4$ (50 mL) and were dried (Na$_2$SO$_4$). Purification by flash chromatography (EtOAc:hexane:EtsN, 1:1:0.02) gave the title compounds 6 as a mixture of diastereomers (2.58 g, 10 mmol, 83%), (Found: C, 55.90; H, 7.09%; C$_{12}$H$_{18}$O$_6$ requires C,
55.81; H, 7.02). For characterisation purposes the acetates 6 could be separated by further flash chromatography (EtOAc:hexane, 3:7).

Diastereomer 1: $R_f$ 0.53 (EtOAc:hexane, 1:1); $[\alpha]_D^{20}$ -51.2 (c 0.25, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$=1.83-1.94 (m, 2H), 2.02 (s, 6H; 2 × COCH$_3$), 2.03-2.10 (m, 4H), 2.16-2.23 (m, 2H), 4.21-4.25 (m, 2H; 2-H, 2'-H), 6.31 (dd, $^3$$J$(H, H)=0.9, 4.8 Hz, 2H; 5-H, 5'-H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$=21.7, 25.5, 32.2, 82.0 (2-C, 2'-C), 99.8 (5-C, 5'-C), 171.6 (2 × C=O); IR (film): v 1735 (C=O), 1651; MS (ES): m/z (%):221 Found [M + Na]$^+$ 281.1000 (100), C$_2$H$_5$O$_2$Na requires 281.1001.

Diastereomer 2: $R_f$ 0.44 (EtOAc:hexane, 1:1); $[\alpha]_D^{20}$ -8.8 (c 0.85, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$=1.82-2.18 (m, 8H), 2.03 (s, 3H; COCH$_3$), 2.03 (s, 3H; COCH$_3$), 4.06 (ddd, $^3$$J$(H, H)=4.6, 6.8, 11.4 Hz, 1H; 2-H or 2'-H), 4.28 (dt, $^3$$J$(H, H)=4.6, 8.5 Hz, 1H; 2-H or 2'-H), 6.29-6.32 (m, 1H, 5-H or 5'-H), 6.20-6.22 (m, 1H; 5-H or 5'-H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$=21.7 (two carbons), 24.9, 25.6, 32.1, 32.9, 81.5 (2-C or 2'-C), 83.9 (2-C or 2'-C), 99.1 (5-C or 5'-C), 99.9 (5-C or 5'-C), 170.1 (C=O), 170.8 (C=O); IR (film): v 2959, 1736 (C=O), 1376, 1240, 1093, 1011; MS (ES): m/z (%): Found [M + Na]$^+$ 281.1000 (86), C$_2$H$_5$O$_2$Na req. 281.1001.

Diastereomer 3: $R_f$ 0.38 (EtOAc:hexane, 1:1); $[\alpha]_D^{20}$ +66.7 (c 0.45, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$=1.69-1.80 (m, 2H), 1.95-2.07 (m, 6H), 2.00 (s, 6H; 2 × COCH$_3$), 4.09-4.16 (m, 4H; 2-H, 2'-H), 6.30-6.31 (m, 2H; 5-H, 5'-H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$=21.8, 25.1, 33.1, 84.8 (2-C, 2'-C), 99.5 (5-C, 5'-C), 170.4 (2 × C=O); IR (film): v 2924, 1733 (C=O), 1378, 1240, 1094; MS (ES): m/z (%): Found [M + Na]$^+$ 281.0996 (10), C$_2$H$_5$O$_2$Na req. 281.1001.

(2R, 2'R)-5,5'-Dimethoxy-octahydro-[2,2']bifuranyl 7a and (4aR, 8aR)-2,6-dimethoxy-octahydropyran[3,2-b]pyran 7b

To a stirred solution of a mixture of acetates 6 (6.5 g, 26 mmol) in methanol (350 mL) was added HCl (12.8 mL of a 1.0 M solution in ether, 12.8 mmol) and the resulting solution was stirred. The reaction mixture was concentrated in vacuo and purification by rapid flash chromatography (EtOAc:hexane, 3:7) yielded the title compounds 7 as a mixture of diastereomers (4.76 g, 23.5 mmol, 90%); (Found: C, 59.49; H, 8.85%; C$_{10}$H$_{18}$O$_4$ requires C, 59.39; H, 8.97). For characterisation purposes the acetals 7 could be separated by further careful flash chromatography (EtOAc:hexane, 3:7).

7a Diastereomer 1: $R_f$ 0.31 (EtOAc:hexane, 3:7); $[\alpha]_D^{20}$ -213.8 (c 0.4, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$=1.58-1.64 (m, 2H), 1.80-1.85 (m, 2H), 1.94-2.06 (m, 4H), 3.34 (s, 6H; CH$_3$O), 3.98-4.04 (m, 2H; 2-H, 2'-H), 5.05 (dd, $^3$$J$(H, H)=4.8, 1.4 Hz, 2H; 5-H, 5'-H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$=26.3, 32.3, 55.1 (CH$_3$), 80.3 (2-C, 2'-C), 105.9 (5-C, 5'-C); IR (film): v 2919; MS (ES): m/z (%): Found [M + Na]$^+$ 225.1100 (100), C$_2$H$_5$O$_2$Na requires 225.1103.

7a Diastereomer 2: $R_f$ 0.3 (EtOAc:hexane, 3:7); $[\alpha]_D^{20}$ -31.2 (c 0.33, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$=1.79-2.04 (m, 8H), 3.33 (s, 3H, CH$_3$O), 3.34 (3H, s, CH$_3$O), 3.92-4.03 (m, 2H; 2-H, 2'-H), 4.98 (d, $^3$$J$(H, H)=4.4 Hz, 1H; 5-H), 5.06 (dd, $^3$$J$(H, H)=1.4, 4.8 Hz, 1H; 5'-H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$=25.6 (two carbons), 32.0, 33.0, 54.2 (CH$_3$), 54.5 (CH$_3$), 81.6 (2-C), 82.7 (2'-C), 105.1 (5-C), 105.3 (5'-C); IR (film): v 2901; MS (ES): m/z (%): Found [M + Na]$^+$ 225.1113 (100), C$_2$H$_5$O$_2$Na requires 225.1103.

7a Diastereomer 3: $R_f$ 0.21 (EtOAc:hexane, 3:7); $[\alpha]_D^{20}$ +140.9 (c 0.575, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$=1.61-1.66 (m, 2H), 1.70-1.97 (m, 6H), 3.35 (s, 6H; CH$_3$O), 3.94-4.01 (m, 2H; 2-H, 2'-H), 5.00 (d, $^3$$J$(H, H)=4.3 Hz, 2H; 5-H, 5'-H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$=25.5, 33.0, 54.4 (CH$_3$), 84.9 (2-C, 2'-C), 105.3 (5-C, 5'-C); IR (film): v 2902; MS (ES): m/z (%): Found [M + Na]$^+$ 225.1113 (100), C$_2$H$_5$O$_2$Na requires 225.1103.

7b Diastereomer 1: $R_f$ 0.58 (EtOAc:hexane, 3:7); $[\alpha]_D^{20}$ +603.3 (c 0.3, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$=1.47-1.50 (m, 2H), 1.60-1.64 (m, 2H), 1.93-2.03 (m, 4H), 3.35 (s, 6H; CH$_3$O), 3.71-3.73 (m, 2H; 4a-H, 8a-H), 4.73 (d, $^3$$J$(H, H)=2.6 Hz, 2H; 5-H, 5'-H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$=23.5, 24.2,
54.9 (CH3), 63.0 (4a-C, 8a-C), 98.9 (2-C, 6-C); IR (film): ν = 2938; MS (ES): m/z (%): Found [M + Na]+ 225.1099 (55), C10H18O4Na requires 225.1103.

7b Diastereomer 2: Rf = 0.46 (EtOAc:hexane, 3:7); mp 43-44 °C (from hexane); [α]D = +17.1 (c 0.35, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 1.45-2.13 (m, 8H), 3.35 (s, 3H; CH3O), 3.48 (s, 4H; CH3O, 4a-H or 8a-H), 3.64 (brt, 3J(H, H)=4.0 Hz, 1H; 4a-H or 8a-H), 4.34 (dd, 3J(H, H)= 1.9, 9.4 Hz, 1H; 6-H), 4.72 (brd, 3J(H, H)= 3.1, Hz, 1H; 2-H); 13C NMR (125 MHz, CDCl3): δ = 23.6, 24.3, 26.0, 28.2, 55.0 (CH3), 56.3 (CH3), 62.3 (4a-C or 8a-C), 70.7 (4a-C or 8a-C), 99.0 (2-C or 6-C), 103.5 (2-C or 6-C); IR (film): ν = 3019; MS (ES): m/z (%): Found [M + Na]+ 225.1103 (100), C10H18O4Na requires 225.1103.

(4aR, 8aR)-4,4a,8,8a-Tetrahydropyrano[3,2-b]pyran 8

To a stirred solution of a mixture of acetals 7 (577 mg, 2.86 mmol) in acetonitrile (50 mL) was added sodium iodide (5.14 g, 34.3 mmol) followed by chlorotrimethylsilane (4.35 mL, 37.2 g, 34.2 mmol) dropwise. After stirring for 40 mins hexamethyldisilazane (12.1 mL, 9.72 g, 57.1 mmol) was added rapidly. The reaction mixture was stirred for a further 10 mins and then quenched by the addition of half-saturated aqueous NaHCO3 solution (40 mL) and light petroleum (20 mL) was added. The organic phase was separated and the aqueous phase washed with saturated aqueous Na2S2O3 solution (20 mL), dried (Na2SO4) and the solvent removed in vacuo to yield crude enol ether 8 (394 mg, 2.86 mmol, 100%) as a pale yellow liquid (Note: occasionally the product formed pale yellow crystals).

The crude reaction mixture could be purified Kugelrohr distillation (60 °C, water aspirator) with the distillate being discarded. The residue comprised the title compound as a light yellow liquid (Note: this distillation procedure resulted in significant loss of material); Rf = 0.80 (EtOAc:hexane, 3:7); [α]D = +126.9 (c 0.35, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 2.18 (dddd, 3J(H, H)=1.3, 2.0, 4.8, 17.6 Hz, 2H; 4-H, 8-H), 2.37 (tdd, 3J(H, H)=2.0, 5.8, 17.6 Hz, 2H; 4′-H, 8′-H), 4.14-4.17 (m, 2H; 4a-H, 8a-H), 4.65 (dddd, 3J(H, H)=1.3, 2.0, 4.8, 6.3 Hz, 2H; 3-H, 7-H), 6.39 (td, 3J(H, H)=2.0, 6.3 Hz, 2H; 2-H, 6-H); 13C NMR (125 MHz, CDCl3): δ = 26.2 (4-C, 8-C), 68.4 (4a-C, 8a-C), 97.0 (3-C, 7-C), 143.2 (2-C, 6-C); IR (CDCl3): ν = 3151, 2962, 2901, 1654 (C=C), 1562, 1471, 1361, 1246, 1216, 1094; MS (EI): m/z (%): Found M+ 318.0679 (42), C12H10O2 requires 318.0681.

(2S, 3R, 4aR, 6S, 7R, 8a)-2,6-diallyl-octahydropyrano[3,2-b]pyran-3,7-diol 9 and (2S, 3R, 4aR, 6S, 7R, 8aR)-2,6-diallyl-octahydropyrano[3,2-b]pyran-3,7-diol 10

A 250 ml round-bottomed flask was charged with ether (75 mL). Allylmagnesium chloride (12.9 mL of a 2 M solution in THF, 25.8 mmol) was added followed by 1,4-dioxan (1.09 mL, 1.14 g, 12.9 mmol) and the resulting suspension was stirred at room temperature for a minimum of 1 h to yield a solution of diallylmagnesium and a suspension of magnesium salts which was cooled to -78 °C. A second 250 mL round-bottomed flask was charged with crude enol ether 8 (394 mg, 2.86 mmol). DCM (38 mL) and NaHCO3 (3.8 g) were added. Freshly prepared DMDO (82 mL, of 0.07 M solution in acetonitrile, 5.73 mmol) was added and the reaction mixture was stirred for 10-15 mins. The reaction mixture was concentrated onto the solid NaHCO3 (Note: the solvent must be removed without any external heating). Ethyl acetate (ca. 30 mL) and Na2SO4 were added and the reaction mixture was filtered. The solvent was removed in vacuo and the crude epoxide 9 was briefly dried under high vacuum to give a white crystalline solid; mp 74-76 °C (from EtOAc); [α]D = +122.7 (c 0.55, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 2.20 (brt, 3J(H, H)=2.8 Hz, 4H; 4-H, 4′-H, 8-H, 8′-H), 3.00 (dq, 3J(H, H)=1.3, 2.8 Hz, 2H; 3-H, 7-H), 3.67 (t, 3J(H, H)=2.8 Hz, 2H; 4a-H, 8a-H), 4.91 (d, 3J(H, H)=2.8 Hz, 2H; 2-H, 6-H); 13C NMR (125 MHz, CDCl3): δ = 28.5 (4-C, 8-C), 46.6 (3-C, 7-C), 59.5 (4a-C, 8a-C), 77.3 (2-C, 6-C);
IR (CHCl₃): ν 2927, 1270, 1158, 824, 786; MS (EI): m/z (%): Found M⁺ 170.0579 (45), C₈H₁₀O₄ req. 170.0579.

The crystalline epoxide 9 was dissolved in ether (75 mL) and added dropwise via cannula to the cold (~78 °C) stirring solution of diallylmagnesium. The reaction mixture was allowed to warm to room temperature overnight and was quenched by the addition of 0.5 M HCl (80 mL) and the organic phase separated. The aqueous phase was extracted with EtOAc (2 × 150 mL). The organic phases were washed with NaHCO₃ and dried (MgSO₄). Purification by flash chromatography (EtOAc:PE, 2:1) yielded the inseparable title compounds 10 and epi-10 (~6:1, 414 mg, 1.63 mmol, 57% from 7) as colourless crystals (Note: characterisation is on the mixture of compounds); (Found C, 66.0; H, 8.7%; C₁₄H₂₂O₄ req. C, 66.12; H, 8.72); Rf 0.35 (EtOAc:PE, 1:1); [α]D²⁵ -81.8 (c 0.11, CHCl₃); mp 107-109 °C (from EtOAc/PE);

1H NMR (400 MHz, CDC1₃): 10 δ=1.50 (brd, 3 J (H, H)=4.6 Hz, 2H; 2 × OH), 1.52 (ddd, 3 J (H, H)=3.0, 11.1, 13.3 Hz, 2H; 4-Hₓ, 8-Hₓ), 2.22 (2 × ddd, 3 J (H, H)=3.0, 4.6, 13.3 Hz, 2H; 4-Hᵧ, 8-Hᵧ), 2.33 (dddd, 3 J (H, H)=1.3, 4.4, 6.8, 13.8 Hz, 2H; 2 × CIHCHCH₂), 2.52 (dddd, 3 J (H, H)=1.3, 5.5, 6.8, 13.8 Hz, 2H; 2 × CHHCH₂), 3.13 (dddd, 3 J (H, H)=4.4, 6.8, 11.1 Hz, 2H; 2-H, 6-H), 3.56 (t, 3 J (H, H)=3.0, 2H; 4a-H, 8a-H), 3.70 (tt, 3 J (H, H)=4.6, 11.1 Hz, 2H; 3-H, 7-H), 5.07 (td, 3 J (H, H)=1.3, 10.1 Hz, 2H; 2 × CH=CH₂), 5.13 (td, 3 J (H, H)=1.3, 17.2 Hz, 2H; 2 × CH=CHH₂); 13C NMR (125 MHz, CDC1₃): 10 δ=36.7 (CH₂CH=CH₂), 37.7 (4-C, 8-C), 66.1 (3-C, 7-C), 73.6 (4a-C, 8a-C), 81.0 (2-C, 6-C), 116.7 (CH=CH₂), 135.1 (CH=CH₂); ¹³C NMR (125 MHz, CDC1₃): epi-10 δ=27.8 (CH₂CH=CH₂), 32.7 (4-C), 36.7 (CH₂CH=CH₂), 37.3 (8-C), 63.9 (3-C), 65.3 (7-C or 8a-C), 65.9 (7-C or 8a-C), 73.4 (4a-C), 76.0 (2-C), 80.9 (6-C), 116.9 (CH=CH₂), 116.8 (CH=CH₂), 135.0 (CH=CH₂), 135.2 (CH=CH₂); IR (film): ν 3349 (OH), 2923, 2830, 1642, 1435, 1299, 1103, 1043, 913; MS (EI): m/z (%): Found [M + Na]⁺ 277.1411 (75), C₁₄H₂₂O₄Na req. 277.1416.

(2S, 3R, 4aR, 6S, 7R, 8aR)-2,6-Diallyl-3,7-bis(tbutyldimethylsilanyloxy)octahydropyran[3,2-b]pyran 11 and (2R, 3R, 4aR, 6S, 7R, 8aR)-2,6-diallyl-3,7-bis(tbutyldimethylsilanyloxy)octahydropyran[3,2-b]pyran epi-11

To a stirred solution of (2S and 2R, 3R, 4aR, 6S, 7R, 8aR)-2,6-diallyl-octahydropyran[3,2-b]pyran-3,7-diol 10 and epi-10 (90 mg, 0.354 mmol) in DCM (9 mL) was added triethylamine (741 µL, 537 mg, 5.31 mmol) followed by tbutyldimethylsilyltrifluoromethanesulfonate (651 µL, 749 mg, 2.83 mmol) and the resulting solution stirred at room temperature for 1.5 h. The reaction mixture was quenched with Et₃N (2 mL), diluted with DCM (10 mL) and washed with saturated aqueous NaHCO₃ solution (10 mL). The organic layer was dried (MgSO₄), filtered, concentrated in vacuo, adsorbed onto SiO₂ and purified by flash chromatography (EtOAc:PE, 1:99) to yield the inseparable title compounds 11 and epi-11 (~6:1, 169 mg, 99%) as a colourless oil; Rf 0.93 (EtOAc:PE, 3:7); (Note: characterisation is on the mixture of compounds); [α]D²⁵ -
58.0 (c 0.495, CHCl₃); ¹H NMR (400 MHz, CDCl₃); 11 δ=0.05 (s, 12H; 2 × Si(CH₃)₃), 0.87 (s, 18H; 2 × Si(CH₃)₃), 1.48 (ddd, 3J (H, H)=3.1, 10.9, 13.4 Hz, 2H; 4-Hax, 8-Hax), 2.12 (ddd, 3J (H, H)=3.1, 4.8, 13.4 Hz, 2H; 4-Heq, 8-Heq), 2.15-2.21 (m, 2H; CH/CH=CH₂), 2.49 (ddd, 3J (H, H)=1.6, 7.3, 14.3 Hz, 2H; CH/CH=CH₂), 3.05 (ddd, 3J (H, H)=3.0, 7.3, 9.0, 2H; 2-H, 6-H), 3.49 (t, 3J (H, H)=3.1 Hz, 2H; 4a-H, 8a-H), 3.62 (ddd, 3J (H, H)=4.8, 9.0, 10.9 Hz, 2H; 3-H, 7-H), 5.02 (ddd, 3J (H, H)=1.6, 2.3, 10.3 Hz, 2H; 2 × CH=CHH), 5.06 (ddd, 3J (H, H)=1.6, 2.3, 17.1 Hz, 2H; 2 × CH=CHH), 5.91 (ddd, 3J (H, H)=7.0, 10.3, 17.1 Hz, 2H; 2 × CH=CH₂); ¹H NMR (400 MHz, CDCl₃); epi-11 δ=0.03 (s, 3H; Si(CH₃)₃), 0.04 (s, 3H; Si(CH₃)₃) obscured by major diastereomer), 0.05 (s, 6H; Si(CH₃)₃), 0.86 (s, 9H; 2 × Si(CH₃)₃), 1.46-1.50 (m, 1H; 8-H obscured by major diastereomer), 1.68 (ddd, 3J (H, H)=3.4, 11.7, 13.4 Hz, 1H; 4-Hax), 1.87 (ddd, 3J (H, H)=3.1, 5.0, 13.4 Hz, 1H; 4-Heq), 2.00 (ddd, 3J (H, H)=3.1, 5.1, 13.6 Hz, 1H; 8-H), 2.15-2.20 (m, 1H; CH2CH=CH₂), 2.29 (ddd, 3J (H, H)=1.4, 3.6, 5.0, 15.2 Hz, 1H; CH2CH=CH₂), 2.43 (ddd, 3J (H, H)=7.5, 11.2, 15.2 Hz, 1H; CH₂CH=CH₂), 2.46-2.51 (m, 1H; CH₂CH=CH₂) obscured by major diastereomer), 3.02-3.06 (m, 1H; 6-H obscured by major diastereomer), 3.48-3.49 (m, 1H; 4a-H obscured by major diastereomer), 3.59-3.64 (m, 2H; 8a-H, 7-H obscured by major diastereomer), 3.85 (dt, 3J (H, H)=5.0, 11.2 Hz, 1H; 2-H), 4.20 (td, 3J (H, H)=5.0, 11.7 Hz, 1H; 3-H), 5.01-5.04 (m, 2H; CH=CH₂), 5.05-5.10 (m, 2H; CH=CH₂), 5.82-5.90 (m, 2H; 2 × CH=CH₂); ¹³C NMR (125 MHz, CDCl₃); 11 δ=-4.7 (2 × Si(CH₃)₃), -4.0 (2 × Si(CH₃)₃), 18.0 (2 × Si(CH₃)₃), 25.7 (2 × Si(CH₃)₃), 36.2 (CH₂CH=CH₂), 38.5 (4-C, 8-C), 66.7 (3-C, 7-C), 73.6 (4a-C, 8a-C), 81.5 (2-C, 6-C), 116.1 (CH=CH₂), 135.5 (CH=CH₂); ¹³C NMR (125 MHz, CDCl₃); epi-11 δ=-4.8 (Si(CH₃)₃), -4.7 (Si(CH₃)₃), -4.6 (Si(CH₃)₃), -3.8 (Si(CH₃)₃), 17.8 (Si(CH₃)₃), 18.0 (Si(CH₃)₃), 25.8 (2 × Si(CH₃)₃), 27.6 (CH₂CH=CH₂), 33.3 (4-C), 36.2 (CH₂CH=CH₂), 38.1 (8-C), 64.4 (3-C), 65.2 (8a-C or 7-C), 66.4 (8a-C, 7-C), 73.5 (4a-C), 76.6 (2-C), 81.5 (6-C), 116.1 (CH=CH₂), 116.2 (CH=CH₂), 135.5 (CH=CH₂); IR (film); ν 2956, 1473, 1255, 1255, 1095, 878, 836, 776; MS (ES): m/z (%): Found [M + Na]+ 505.3128 (100), C₂₀H₃₀O₄Si₂Na requires 505.3145.

(2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-Bis-(butyldimethylsilanyloxy)-2,6-bis-(2-hydroxyethyl)-octahydropyrano[3,2-b]pyran 12 and (2R, 3R, 4aR, 6S, 7R, 8aR)-3,7-bis-(butyldimethylsilanyloxy)-2,6-bis-(2-hydroxyethyl)-octahydropyrano[3,2-b]pyran epi-12

Ozone was bubbled through a stirred solution of (2S and 2R, 3R, 4aR, 6S, 7R, 8aR)-2,6-diallyl-3,7-bis(butyldimethylsilanyloxy)-octahydropyrano[3,2-b]pyran 11 and epi-11 (169 mg, 0.351 mmol) at −78 °C in DCM (10 mL) and methanol (10 mL) until the solution became pale blue. The solution was purged with oxygen until colourless and triphenylphosphane (368 mg, 1.402 mmol) added. The reaction mixture was stirred for 2 h then sodium borohydride (80 mg, 2.10 mmol) and the reaction mixture warmed to room temperature for 2 h and stirred for a further 1 h at room temperature. The reaction was quenched by the addition of saturated aqueous NH₄Cl solution (20 mL), the layers separated, and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo and the residue purified by flash chromatography (EtOAc:PE, 15:85) to yield (2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-bis-(butyldimethylsilanyloxy)-2,6-bis-(2-hydroxyethyl)-octahydropyrano[3,2-b]pyran 12 (141 mg, 82%) as large colourless crystals; (Found C, 58.7; H, 10.1%; C₁₅H₂₂O₄ req. C, 58.7; H, 10.3); Rf 0.48 (EtOAc:PE, 3:7); mp 74-74.5 °C (from CHCl₃); [α]D₂⁰ -45.5 (c 0.33, CHCl₃); ¹H NMR (400 MHz, CDCl₃); δ=0.04 (2 × s, 12H; 2Si(CH₃)₃), 0.85 (s, 18H; 2 × Si(CH₃)₃), 1.57 (ddd, 3J (H, H)=3.1, 10.8, 13.6 Hz, 2H; 4-Hax, 8-Hax), 1.77 (ddd, 3J (H, H)=4.5, 7.7, 8.9, 15.1 Hz, 2H; CH/CH₂OH), 2.03 (ddd, 3J (H, H)=3.3, 8.8, 14.6 Hz, 2H; CH/CH₂OH), 2.12 (ddd, 3J (H, H)=3.1, 4.6, 13.6 Hz, 2H; 4-
And (2R, 3R, 4R, 6S, 7R, 8aR)-3,7-bis-(butyldimethylsilanyloxy)-2-(2-hydroxyethyl)-6-(2-triethylsilanyloxy-ethyl)-octahydropyrano[3,2-b]pyran epi-12 (32.5 mg, 18%) as small white crystals; $R_f$ 0.37 (EtOAc:PE, 3:7); mp 95-96 °C (from CHCl₃); $[\alpha]_D^{19}$ -5.6 (c 0.195, CHCl₃); $^1$H NMR (400 MHz, CDCl₃): $\delta$=0.05 (2 x s, 12H; 25(Si(CH₃)₃)), 0.85 (s, 9H; Si(C(H₃)₃)), 0.86 (s, 9H; Si(C(H₃)₃)), 1.54 (ddd, $^3$J(H, H)=$\delta$.6, 10.8, 14.1 Hz, 2H; 4-Hax-Si(CH₃)), 1.69-2.06 (6H, m; 4-Heq-8-Heq, 2 x C₂H₂CH₂OH), 2.47 (br s, 1H; OH), 2.78 (br s, 1H; OH), 3.30 (dt, $^3$J(H, H)=2.0, 9.0 Hz, 1H; 6-H), 3.61 (br dt, $^3$J(H, H)=1.3, 3.6 Hz, 1H; 8a-H), 3.68 (ddd, $^3$J(H, H)=4.8, 9.0, 10.8 Hz, 1H; 7-H), 3.76-3.83 (m, 5H; 2 x CH₂OH, 4a-H), 3.98 (td, $^3$J(H, H)=5.1, 11.2 Hz, 1H; 2-H), 4.18 (dt, $^3$J(H, H)=5.1, 10.8 Hz, 1H; 3-H); $^{13}$C NMR (125 MHz, CDCl₃): $\delta$=4.9 (Si(CH₃)₂), -4.8 (2 x Si(CH₃)₃), -4.7 (Si(CH₃)₃), 17.8, (Si(C(H₃)₃)), 17.9 (2 x Si(C(H₃)₃)), 25.7 (2 x Si(C(H₃)₃)), 33.4 (CH₂), 33.6 (CH₂), 38.0 (CH₂), 61.7 (CH₂), 61.9 (CH₂), 64.2 (3-C), 65.5 (4a-C), 66.4 (7-C), 73.7 (8a-C), 77.0 (2-C), 83.5 (6-C); IR (film): v 3429 (OH), 2955, 2930, 2857, 1473, 1255, 1091, 837, 776; MS (ES): m/z (%): Found [M + Na]$^+$ 513.3052 (100), C₂₅H₄₅O₆Si₂Na req. 513.3044.

(2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-Bis-(butyldimethylsilanyloxy)-2-(2-hydroxyethyl)-6-(2-triethylsilanyloxy-ethyl)-octahydropyrano[3,2-b]pyran 13 and (2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-bis-(butyldimethylsilanyloxy)-2,6-bis-(2-triethylsilanyloxy-ethyl)-octahydropyrano[3,2-b]pyran 12 (60 mg, 0.122 mmol) in DCM (3 mL) at room temperature was added triethylamine (68 µL, 50 mg, 0.490 mmol) followed by dropwise chlorotriethylsilane (21 µL, 19 mg, 0.122 mmol) and the resulting solution stirred for 1.5 h. The reaction mixture was poured into saturated aqueous NaHCO₃ solution (5 mL), extracted with DCM (3 x 2 ml) and the combined organic layers dried (MgSO₄), filtered, concentrated in vacuo and purified by flash chromatography (EtOAc:PE, 5:95) to yield (2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-bis-(butyldimethylsilanyloxy)-2-(2-hydroxyethyl)-6-(2-triethylsilanyloxyethyl)-octahydropyrano[3,2-b]pyran 13 (35 mg, 48%) as a colourless oil; $R_f$ 0.75 (EtOAc:PE, 3:7); $[\alpha]_D^{19}$ -56.3 (c 0.08, CHCl₃); $^1$H NMR (400 MHz, CDCl₃): $\delta$=0.03 (s, 3H; Si(CH₃)₂), 0.04 (s, 3H; Si(CH₃)₂), 0.05 (s, 3H; Si(CH₃)₂), 0.05 (s, 3H; Si(CH₃)₂), 0.59 (q, $^3$J(H, H)=7.7 Hz, 6H; Si(CH₂CH₂SiH₃)), 0.85 (s, 9H; Si(CH₃)₂), 0.86 (s, 9H; Si(CH₃)₂), 0.96 (t, $^3$J(H, H)=7.7 $^3$J(H, H)=5.1, 11.2 Hz, 1H), 1.68-1.77 (m, 1H), 1.98-2.08 (m, 3H), 2.89-2.93 (ddd, $^3$J(H, J)=3.2, 4.8, 13.6 Hz, 1H), 3.12 (dt, $^3$J(H, H)=2.5, 9.5 Hz, 1H; 2-H or 6-H), 3.30 (dt, $^3$J(H, H)=3.1, 9.0 Hz, 1H; 2-H, or 6-H), 3.49 (dt, $^3$J(H, H)=0.8, 3.0 Hz, 1H; 4a-H), 3.53 (ddd, $^3$J(J, H)=4.6, 9.0, 11.0 Hz, 1H; 3-H or 7-H), 3.58 (dt, $^3$J(H, H)=0.8, 3.0 Hz, 1H; 4a-H or 8a-H), 3.66 (ddd, $^3$J(J, H)=5.0, 9.5, 11.0 Hz, 1H; 3-H, 7-H), 3.72-3.76 (m 2H; CH₂Osi), 3.78-3.83 (m, 2H; CH₂OH); $^{13}$C NMR (125 MHz, CDCl₃): $\delta$=4.4 (Si(CH₃)₂), -3.8 (Si(CH₃)₂), 4.9 (Si(CH₂CH₃)₂), 7.2 (Si(CH₂CH₃)₂), 18.1 (Si(C(CH₃)₃)), 26.1 (Si(C(CH₃)₃)), 34.0 (CH₂), 35.7 (CH₂), 38.7 (CH₂), 39.2 (CH₂), 57.0 (CH₂Osi), 59.7 (CH₂OH), 67.2 (3-C or 7-C), 67.7 (3-C or 7-C), 73.7 (4a-C or 8a-C), 74.5 (4a-C or 8a-C), 79.1 (2-C or 6-C), 84.1 (2-C or 6-C); IR (film): v 2957, 1255, 1094, 837, 776,
Recycling: To a stirred solution of (2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-bis-(butyldimethylsilyl oxy)-2,6-bis-(2-triethylsilanyloxyethyl)-octahydropyrano[3,2-b]pyran (15 mg, 0.031 mmol) in methanol (4 mL) was added K$_2$CO$_3$ (30 mg) and the reaction mixture stirred vigorously overnight. The reaction mixture was diluted with saturated aqueous NH$_4$Cl solution (4 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (MgSO$_4$), filtered, concentrated in vacuo and purified by flash chromatography to yield (2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-bis-(butyldimethylsilyl oxy)-2,6-bis-(2-hydroxyethyl)-octahydropyrano[3,2-b]pyran 12 (10.2 mg, 100%) as a colourless oil which was combined with that recovered from the protection reaction and resubjected to the protection reaction above to yield further (2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-bis-(t-butyldimethylsilyloxy)-2-(2-hydroxyethyl)-6-(2-triethylsilanyloxy)-octahydropyrano[3,2-b]pyran 13 (16.4 mg) giving an overall yield of 70% after one recycle.

To a stirred solution of (2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-Bis-(t-butyldimethylsilyloxy)-2-(2-toluene-4-sulfonyloxyethyl)-6-(2-triethylsilanyloxy-ethyl)-octahydropyrano[3,2-b]pyran 14

8
(CH₂CH₂OSi), 38.4 (4-C or 8-C), 38.5 (4-C or 8-C), 59.4 (CH₂CH₂OSi), 67.2 (3-C or 7-C), 67.3 (3-C or 7-C), 67.4 (CH₂CH₂OTs), 73.4 (4a-C), 73.8 (8a-C), 77.5 (6-C), 78.6 (2-C), 127.9, 129.7, 133.2, 144.4; IR (film): 2955, 1364, 1260, 1178, 1093, 836, 778; MS (ES): m/z (%): Found [M + Na]⁺ 781.3996 (100), C₃₇H₇₀O₈SSi₃Na req. 781.3997.

(2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-Bis-(butyldimethylsilanyloxy)-2-ethyl-6-(2-triethylsilanyloxy-ethyl)-octahydropyrano[3,2-b]pyran 15

To a stirred solution of (2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-bis-(butyldimethylsilanyloxy)-6-(2-triethylsilanyloxy-ethyl)-2-(2-toluene-4-sulfonyl oxyethyl)-octahydropyrano[3,2-b]pyran 14 (30 mg, 0.040 mmol) in ether (4 mL) at room temperature was added SuperHydride™ (792 µL of a 1 M solution in THF, 0.79 mmol) and the cloudy solution stirred overnight. The reaction mixture was poured into water (5 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and purified by flash chromatography (EtOAc:PE, 1:9) to yield the title compound 15 (21.3 mg, 91%) as a colourless oil; Rf 0.74 (EtOAc:PE, 1:9); [α]D²⁹⁻52.9 (c 0.365, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 0.04 (s, 6H; Si(CH₃)₂); 0.05 (s, 6H; Si(CH₃)₂); 0.59 (q, 3J (H, H)=7.8 Hz, 6H; Si(CH₂CH₃)₂); 0.86 (s, 9H; Si(CH₃)₃); 0.87 (s, 9H; Si(CH₃)₃); 0.92 (t, 3J (H, H)=7.4 Hz, 3H; CH₃CH₂); 0.96 (t, 3J (H, H)=7.8 Hz, 9H; Si(CH₂CH₃)₃); 1.37-1.53 (m, 4H; CHHCH₃, 8-H, 4-H, CHHCH₂OSi), 1.77 (dd, 3J (H, H)=2.9, 7.4, 14.4 Hz, 1H, CHHCH₃), 2.02-2.14 (m, 3H; 4-H, 8-H, CHHCH₂OSi), 2.91 (dt, 3J (H, H)=2.9, 9.2 Hz, 1H; 2-H), 3.09 (dt, 3J (H, H)=2.5, 9.2 Hz, 1H; 6-H), 3.45 (t, 3J (H, H)=3.3 Hz, 1H; 4a-H or 8a-H), 3.47 (t, 3J (H, H)=3.3 Hz, 1H; 4a-H or 8a-H), 3.57 (ddd, 3J (H, H)=4.8, 9.2, 11.1 Hz, 2H; 3-H, 7-H), 3.69-3.79 (m, 2H; CH₂CH₂OSi); ¹³C NMR (125 MHz, CDCl₃): δ=−4.79 (Si(CH₃)₂), −4.69 (Si(CH₃)₂), −4.19 (Si(CH₃)₂), −4.15 (Si(CH₃)₂), 4.4 (Si(CH₂CH₃)₂), 6.8 (Si(CH₂CH₃)₂), 9.4 (CH₂CH₂C), 17.95 (Si(CH₃)₂), 17.96 (Si(CH₃)₂), 24.6 (CH₂CH₂C), 25.8 (Si(CH₃)₂), 35.3 (CH₂CH₂OSi or 4-C or 8-C), 38.7 (CH₂CH₂OSi or 4-C or 8-C), 38.8 (CH₂CH₂OSi or 4-C or 8-C), 59.5 (CH₂CH₂OSi), 66.9 (3-C or 7-C), 67.5 (3-C or 7-C), 73.66 (4a-C or 8a-C), 73.74 (4a-C or 8a-C), 78.6 (6-C), 83.0 (2-C); IR (film): 2956, 1463, 1254, 1096, 837, 775, 741; MS (ES): m/z (%): Found [M + Na]⁺ 611.3947 (93), C₃₀H₄₅O₇SiNa req. 611.3959. Note: on 51 mg and 140 mg scales the reaction proceeded in 89% and 80% yield respectively.

(2R, 3R, 4aR, 6S, 7R, 8aR)-3,7-Bis-(butyldimethylsilanyloxy)-2-ethyl-6-(2-hydroxyethyl)-octahydropyrano[3,2-b]pyran 16

To a stirred solution of (2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-bis-(butyldimethylsilanyloxy)-2-ethyl-6-(2-triethylsilanyloxy-ethyl)-octahydropyrano[3,2-b]pyran 15 (92.4 mg, 0.157 mmol) in methanol (9 mL) was added K₂CO₃ (180 mg) and the reaction mixture stirred vigorously overnight. The reaction mixture was diluted with saturated aqueous NH₄Cl solution (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and purified by flash chromatography to yield the title compound 16 as a colourless oil (72.8 mg, 98%); Rf 0.72 (EtOAc:PE, 3:7); [α]D²⁹⁻43.9 (c 0.205, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 0.03 (s, 3H Si(CH₃)₂), 0.04 (s, 3H ;Si(CH₃)₂), 0.05 (s, 3H; Si(CH₃)₂), 0.06 (s, 3H; Si(CH₃)₂), 0.85 (s, 9H; Si(CH₃)₂),
0.86 (s, 9H, SiC(CH3)3), 0.93 (t, J(H, H)=7.3 Hz, 3H; CH2CH3), 1.37 (qqd, J(H, H)=7.3, 8.1 Hz, 1H; CHO); 2.72 (ddd, J(H, H)=3.0, 11.0, 13.3 Hz, 1H; 8-Hax), 1.54 (ddd, J(H, H)=3.0, 11.0, 12.9 Hz, 1H; 4-Hax), 1.69-1.75 (m, 1H; CH2HCH2OH), 1.77 (dqd, J(H, H)=3.0, 7.3 Hz, 1H; CHO); 1.99-2.05 (m, 1H; CH2HCH2OH), 2.08 (ddd, J=3.0, 4.8, 12.9 Hz, 1H; 4-Heq), 2.14 (ddd, J(H, H)=3.0, 4.9, 13.3 Hz, 1H; 8-Heq), 2.93 (ddd, J(H, H)=3.0, 8.1, 8.9 Hz, 1H; 2-H), 3.30 (dt, J(H, H)=3.1, 9.0 Hz, 1H; 6-H), 3.51 (dt, J(H, H)=0.8, 3.0 Hz, 1H; 8a-H), 3.56 (ddd, J(H, H)=4.8, 8.9, 11.0 Hz, 1H; 3-H), 3.58 (dt, J(H, H)=0.8, 3.0 Hz, 1H; 4a-H), 3.69 (ddd, J(H, H)=4.9, 9.0, 11.0 Hz, 1H; 7-H), 3.75-3.82 (m, 2H CH2OH); 13C NMR (125 MHz, CDCl3): δ=−4.78 (Si(CH3)2), −4.75 (Si(CH3)2), −4.2 (Si(CH3)2), −4.1 (Si(CH3)2), 19.91 (Si(CH3)2), 21.59 (Si(CH3)2), 23.6 (CH2CH2OH), 26.1 (Si(CH3)2), 26.7 (Si(CH3)2), 27.5 (Si(CH3)2), 33.5 (CH2CH2OH), 38.4 (4-C), 38.8 (8-C), 62.0 (CH2OH), 66.7 (3-C or 7-C), 66.7 (3-C or 7-C), 73.4 (8a-C), 74.2 (4a-C), 83.1 (2-C), 83.7 (6-C); IR (film): 3508, 2935, 2929, 2875, 1463, 1250, 1094, 837, 775; 741; MS (ES): m/z (%): Found [M + Na]+ 497.3115 (100), C24H50O5Si2Na req. 497.3095.

(2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-Bis-(butyldimethylsilanyloxy)-2-ethyl-6-(2-oxyethyl)-octahydropyrano[3,2-b]pyran 17

To a stirred solution of (2R, 3R, 4aR, 6S, 7R, 8aR)-3,7-bis-(butyldimethylsilanyloxy)-6-ethyl-2-(2-hydroxyethyl)-octahydropyrano[3,2-b]pyran 16 (20 mg, 0.042 mmol) in DCM (2 mL) was added NMO (35 mg, 0.295 mmol) and powdered activated 4 Å molecular sieves. The resulting suspension was stirred at room temperature for 10 minutes then TPAP (3 mg, 8.4 μmol) added and the reaction mixture stirred for half an hour then filtered through a short plug of silica washing with DCM to yield the title product 17 (18.9 mg, 95%) as a colourless oil; Rf 0.47 (EtOAc:PE, 1:9); [α]21D = -47.7 (c 1.265, CHCl3); 1H NMR (400 MHz, CDCl3): δ=0.02 (s 3H; Si(CH3)2), 0.03 (s, 3H; Si(CH3)2), 0.04 (s, 3H; Si(CH3)2), 0.66 (s, 3H; Si(CH3)2), 0.85 (s, 18H; 2 × Si(CH3)2), 0.92 (t, J(H, H)=7.4 Hz, 3H; CH2CH3), 1.36 (qqd, J(H, H)=7.4, 8.2, 14.0 Hz, 1H; CH2HCH2OH), 1.49 (ddd, J(H, H)=3.3, 10.9, 13.6 Hz, 1H; 4-Hax), 1.54 (ddd, J(H, H)=3.0, 10.7, 13.1 Hz, 1H; 8-Hax), 1.77 (dqd, J(H, H)=3.0, 7.4, 14.0 Hz, 1H; CH2HCH2OH), 2.07 (ddd, J(H, H)=3.3, 4.7, 13.5 Hz, 1H; 8-Heq), 2.17 (ddd, J(H, H)=3.0, 4.9, 13.2 Hz, 1H; 4-Heq), 2.48 (ddd, J(H, H)=3.1, 8.1, 16.3 Hz, 1H; CH2HCHO), 2.85 (ddd, J(H, H)=3.0, 8.2, 9.1 Hz, 1H; 2-H), 3.52 (dt, J(H, H)=1.0, 3.0 Hz, 1H; 8a-H), 3.53 (ddd, J(H, H)=4.7, 9.1, 10.9 Hz, 1H; 3-H), 3.55 (dt, J(H, H)=1.0, 3.3 Hz, 1H; 4a-H), 3.54 (ddd, J(H, H)=3.7, 8.1, 9.1 Hz, 1H; 6-H), 3.67 (ddd, J(H, H)=4.9, 9.1, 10.7 Hz, 1H; 7-H), 9.78 (dd, J(H, H)=1.9, 3.1 Hz, 1H; CHO); 13C NMR (125 MHz, CDCl3): δ=−4.78 (Si(CH3)2), −4.75 (Si(CH3)2), −4.2 (Si(CH3)2), 9.4 (CH2CH3), 17.86 (Si(CH3)2), 17.92 (Si(CH3)2), 24.6 (CH2CH2), 25.72 (Si(CH3)2), 38.4 (4-C or 8-C), 38.5 (4-C or 8-C), 46.3 (CH2CHO), 66.6 (3-C), 67.0 (7-C), 73.5 (8a-C), 74.1 (8a-C), 77.7 (8-C), 83.1 (2-C), 202.2 (CHO); IR (film): 2930, 1731, 1473, 1256, 1095, 837, 776; MS (ES): m/z (%): Found [M + Na]+ 495.2953 (92), C24H48O8Si2Na req. 495.2938.
(Z, 2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-Bis-(4-butyldimethylsilyl)-1-trimethylsilanyl-propyne (134.5 mg, 0.595 mmol) in THF (1 mL) at −78 °C under nitrogen was added dropwise tBuLi (350 µL of a 1.7 M solution in pentane, 0.595 mmol) and the resulting solution stirred for 1 h. A solution of titanium(IV) isopropoxide (176 µL, 169 mg, 0.595 mmol) in THF (0.5 mL) was added dropwise and the resulting bright yellow solution stirred for 10 minutes. A portion of this solution (1.62 mL) was withdrawn via syringe and discarded. To the remainder (0.120 mmol) was added dropwise a solution of (2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-bis-(4-butyldimethylsilyl)-1-trimethylsilanyl-propyne (18 mg, 0.040 mmol) in THF (0.5 mL, 0.5 mL rinse) and the resulting solution stirred at −78 °C for 30 minutes then the cooling bath was removed and the reaction stirred at room temperature for 30 minutes. The reaction mixture was poured into 0.1 M aqueous HCl (5 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was dissolved in ether (2 mL), cooled to 0 °C and KHMDS (200 mL of a 0.5 M solution in toluene, 0.1 mmol) added dropwise. The resulting dark solution was stirred for 45 minutes, then quenched with saturated aqueous NH₄Cl solution and extracted with ether (3 × 3 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo and the residue purified by flash chromatography (PE→EtOAc:PE, 2:8) to yield the title compound 18 (17.0 mg, 75%) as a yellow oil; 1H NMR (CDCl₃): δ 0.67 (EtOAc:PE, 1:9); 1H NMR (400 MHz, CDCl₃): δ 0.04 (s, 6H; Si(CH₃)₂), 0.06 (s, 3H; Si(CH₃)₂), 0.08 (s, 3H; Si(CH₃)₂), 0.18 (s, 9H; Si(CH₃)₃), 0.86 (s, 9H; Si(CH₃)₃), 0.88 (s, 9H; Si(CH₃)₃), 0.92 (t, J (H, H)=7.5 Hz, 3H; CH₂CH₂), 1.38 (qd, J (H, H)=7.5, 14.1 Hz, 1H; 4-Hax or 8-Hax), 1.50 (dd, J (H, H)=3.0, 10.9, 13.1 Hz, 1H; 4-Hax or 8-Hax), 1.77 (dd, J (H, H)=3.0, 7.5, 14.1 Hz, 1H; CH/CH(CH₃)), 2.09 (dd, J (H, H)=3.0, 4.8, 13.1, 2H; 4-Hax, 8-Hax), 2.34 (dd, J (H, H)=1.8, 6.0, 9.0, 16.2 Hz, 1H; CH/CH(CH₃)=CH=CH), 2.84 (dd, J (H, H)=1.8, 3.4, 7.4, 16.2 Hz, 1H; CH/CH(CH₃)=CH), 2.92 (dd, J (H, H)=3.0, 7.5, 9.0 Hz, 1H; 2-H), 3.09 (dt, J (H, H)=3.4, 9.0 Hz, 1H; 6-H), 3.48 (t, J (H, H)=3.0 Hz, 2H; 4a-H, 8a-H), 3.59 (dd, J (H, H)=4.8, 9.0, 10.9 Hz, 1H; 3-H or 7-H), 3.62 (dd, J (H, H)=4.8, 9.1, 10.9 Hz, 1H; 3-H or 7-H), 5.54 (td, J (H, H)=1.8, 11.0 Hz, 1H; CH₂CH=CH=CH), 6.12 (dd, J (H, H)=6.0, 7.4, 11.0 Hz, 1H; CH₂CH=CH=CH), 13C NMR (125 MHz, CDCl₃): δ −4.4 (Si(CH₃)₃), −4.2 (Si(CH₃)₃), −3.8 (CH₃), −3.6 (Si(CH₃)₃), 0.2 (Si(CH₃)₂), 9.8 (CH₂CH₂), 18.25 (Si(CH₃)₃), 18.30 (Si(CH₃)₃), 25.0 (CH₂CH₂), 26.1 (Si(CH₃)₂), 26.2 (Si(CH₃)₃), 33.3 (CH₂CH=CH₂), 39.0 (4-C, 8-C), 67.2 (3-C or 7-C), 67.7 (3-C or 7-C), 74.0 (4a-C or 8a-C), 74.3 (4a-C or 8a-C), 82.1 (2-C), 83.3 (6-C), 99.0 (C), 102.6 (C), 110.2 (CH₂CH=CH=CH), 142.4 (CH₂CH=CH=CH); IR (film): 2957, 2857, 2154 (alkyne), 1473, 1251, 1095, 838, 775; MS (ES): m/z (%): Found [M + Na⁺] 589.3558 (100), C₃₀H₃₈O₃Si₃Na req. 589.3541.

(Z, 2S, 3R, 4aR, 6S, 7R, 8aR)-2-Ethyl-6-(5′-trimethylsilanyl-pent-2′-en-4′-ynyl)-octahydropyrano[3,2-b]pyran-3,7-diol 19

To a stirred solution of (Z, 2S, 3R, 4aR, 6S, 7R, 8aR)-3,7-bis-(4-butyldimethylsilyl)-1-trimethylsilanyl-propyne (18 mg, 0.35 mmol) in methanol (3 mL) was added PTSA (2 mg) and the resulting solution stirred at room temperature for 22.5 h. The reaction mixture was poured into saturated aqueous NaHCO₃ solution (5 mL) and extracted with EtOAc (4 × 3 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and purified by flash chromatography to yield the title compound 19 (8.7 mg, 74%) as a colourless oil which crystallised on evaporation from chloroform; Rf 0.67.
0.18 (EtOAc:PE, 3:7); mp 114-115 °C (from CHCl3); [α]D2
+161.5 (c 0.13, CHCl3); 1H NMR (400 MHz, CDCl3): δ=0.19 (s, 9H; Si(CH3)3), 0.96 (t, 3 J (H, H)=7.5 Hz, 3H, CH2CH3), 1.31 (d 3 J (H, H)=5.1 Hz, 1H, OH), 1.48-1.57 (m, 3H; 4-Hex, 8-Hex; C(CH3)2), 1.80 (qd, 3 J (H, H)=3.0, 7.5, 15.1 Hz, 1H; CH(CH3)), 2.22 (brm, 1H; OH). 2.22 (dd, 3 J (H, H)=3.0, 4.4, 13.1 Hz, 1H; 4-H eq or 8-H eq), 2.59 (dddd, 3 J (H, H)=1.0, 4.4, 6.1, 14.6 Hz, 1H; CH/CH=CH=CH), 2.85 (dd, 3 J (H, H)=1.2, 4.4, 9.5, 14.6 Hz, 1H; CH/H/CH=CH), 2.97 (dd, 3 J (H, H)=2.8, 7.5, 9.2 Hz, 1H; 2-H), 3.23 (dt, 3 J (H, H)=4.4, 9.2 Hz, 1H; 6-H), 3.55 (dt, 3 J (H, H)=1.1, 3.0 Hz, 1H; 4a-H or 8a-H), 3.56 (dt, 3 J (H, H)=1.0, 3.0 Hz, 1H; 4a-H or 8a-H), 3.62 (ddt, 3 J (H, H)=4.8, 9.2, 11.1 Hz, 1H; 3-H), 3.68 (dd, 3 J (H, H)=4.4, 9.2, 11.5 Hz, 1H; 7-H), 5.63 (td, 3 J (H, H)=1.2, 11.0 Hz, 1H; CH2CH=CH=CH), 6.12 (dd, 3 J (H, H)=6.1, 9.5, 11.0 Hz, 1H; CH2CH=CH=CH); 13C NMR (100 MHz, CDCl3): δ=0.3 (Si(CH3)3), 9.6 (CH3CH2), 24.8 (CH3CH2), 32.7 (CH3CH=CH), 37.0 (4-C or 8-C), 38.3 (4-C or 8-C), 64.9 (7-C), 66.1 (3-C), 73.9 (4a-C or 8a-C), 74.2 (4a-C or 8a-C), 81.1 (C6-C), 82.9 (2-C), 99.9 (C), 102.7 (C), 111.7 (CH2CH=CH), 141.4 (CH2CH=CH); IR (film): 3350, 2960, 2854, 2145 (alkyne), 1251, 1211, 1046, 1013, 843, 760; MS (ES): m/z (%): Found [M + Na]+ 361.1813 (100), C18H30O4SiNa req. 361.1811.

(Z, 2S, 3S, 4aR, 6S, 7S, 8aR)-(3,7-Dibromo-2-ethyl-6-(5-trimethylsilyl-pent-2'-en-4'-ynyl)-octahydropyrano[3,2-b]pyrany 21

To a stirred solution of (Z, 2S, 3R, 4aR, 6S, 7R, 8aR)-2-ethyl-6-(5-trimethylsilyl-pent-2-en-4-ynyl)-octahydropyrano[3,2-b]pyran-3,7-diol 19 (8.7 mg, 0.026 mmol) in DCM (2 mL) was added pyridine (29 µL, 28.5 mg, 0.360 mmol) and triflic anhydride (52 µL, 87.5 mg, 0.308 mmol) and the resulting orange solution stirred at room temperature for 30 minutes. The reaction mixture was quenched with saturated aqueous NaHCO3 solution (5 mL) and DCM (5 mL) and the organic layer washed with saturated aqueous CuSO4 solution (3 mL) and saturated aqueous NaHCO3 solution (3 mL), dried (MgSO4) and filtered through a 5 mm silica plug washing with DCM. The filtrate was concentrated in vacuo to give the crude triflate 20 [Rf 0.79 (EtOAc:PE, 3:7)] as a yellow oil. The triflate was dissolved in toluene (2 mL), tetrabutylammonium bromide (50 mg, 0.154 mmol) was added and the reaction mixture heated to 120 °C for 1 h 45 mins. The resulting solution was cooled to room temperature, filtered through a silica plug washing with DCM, concentrated and purified by flash chromatography (EtOAc:PE, 1:19→2:8) to yield the title compound 21 (1.8 mg, 14%) as an unstable yellow oil; Rf 0.62 (EtOAc:PE, 3:7); 1H NMR (500 MHz, CDCl3): δ=(500 MHz, CDCl3) 0.18 (s, 9H; Si(CH3)3), 0.92 (t, 3 J (H, H)=7.5 Hz, 3H; CH3CH2), 1.62 (qd, 3 J (H, H)=6.8, 7.5, 14.3 Hz, 1H; CHHCH3), 1.80 (qd, 3 J (H, H)=6.8, 7.5, 14.3, 1H; CHHCH3), 2.37 (2dd, 3 J (H, H)=1.8, 4.5, 15.8, 2H; 4-H, 8-H), 2.59-2.65 (m, 3H; CH/HCH=CH, 4-H, 8-H'), 2.80 (dd, 3 J (H, H)=6.8, 7.5, 14.2, 4 J (H, H)=1.5 Hz; CHH/CH=CH), 3.05 (dt, 3 J (H, H)=1.8, 6.8 Hz, 1H; 2-H), 3.31 (1H, dd, 3 J (H, H)=1.8, 6.2, 7.5 Hz, 6-H), 3.53 (td, 3 J (H, H)=1.8, 4.5 Hz, 1H; 4a-H or 8a-H), 3.54 (td, 3 J (H, H)=1.8, 4.5 Hz, 1H; 4a-H or 8a-H), 4.03 (td, 3 J (H, H)=1.8, 4.5 Hz, 1H; 7-H), 4.07 (td, 3 J (H, H)=1.8, 4.5 Hz; 3-H), 5.59 (dd, 3 J (H, H)=1.0, 1.5, 10.9 Hz, 1H; CH2CH=CH=CH), 6.08 (dd, 3 J (H, H)=6.8, 8.0, 10.9 Hz, 1H; CH2CH=CH=CH); δC (125 MHz, CDCl3) -0.09 ((Si(CH3)3)), 9.8 (CH3CH2), 28.5 (CH3CH2), 36.6 (CH2CH=CH), 37.7 (4-C or 8-C), 37.8 (4-C or 8-C), 46.9 (3-C or 7-C), 47.0 (3-C or 7-C), 71.6 (4a-C or 8a-C), 71.9 (4a-C or 8a-C), 78.9 (6-C), 81.2 (2-C), 100.0 (C=C), 102.0 (C=C), 111.9 (CH2CH=CH), 140.5 (CH2CH=CH). Note: The dibromide 21 was unstable and a mass spectrum could not be obtained. However, deprotection provided the enyne 3 which was fully characterised.
**Structural Proof:** Proof of the installation of the bromine atoms in 21 with inversion and hence structural proof for 21 and 3 follows from J-value analysis. In going from the diol 19 to the dibromide 21 the 3-C and 7-C substituents go from being both equatorial to both axial. Hence the corresponding protons in 19 (3-H and 7-H) are axial and have two ‘large’ axial-axial couplings to 2-H (J_{2,3} 9.2 Hz) and 6-H (J_{6,7} 9.2 Hz), and 4-H_{ax} (J_{3,4ax} 11.1 Hz) and 8-H_{ax} (J_{7,8ax} 11.5 Hz), and one ‘small’ axial-equatorial coupling to 4-H_{eq} (J_{3,4eq} 4.8 Hz) and 8-H_{eq} (J_{7,8eq} 4.4 Hz). In the dibromide 21, 3-H and 7-H are now equatorial and consequently experience three ‘small’ equatorial-axial and equatorial-equatorial couplings to their nearest neighbours (J_{3,4} 4.5 Hz, J_{3,4'} 1.8 Hz, J_{2,3} 1.8 Hz; J_{7,8} 4.5 Hz, J_{7,8'} 1.8 Hz, J_{6,7} 1.8 Hz). Moreover, the pattern of J-values seen in 21 and 3 is in excellent agreement with the pattern seen for all of the compounds with the 3-C and 7-C substituents axially oriented (e.g. compounds 25-31 and 4), with the coupling constants in the vicinity of the axially oriented chlorine atom being very similar to those in the vicinity of the axially oriented bromine atoms. For a side-by-side comparison of coupling constants for all of the pyrano[3,2-b]pyrans reported in the paper see Figure S8.

(Z, 2S, 3S, 4aR, 6S, 7S, 8aR)-3,7-Dibromo-2-ethyl-6-(pent-2-en-4-ynyl)-octahydropyrano[3,2-b]pyran 3

To a stirred solution of the silylacetylene 20 (1.5 mg, 3.7 µmol) in THF (2 mL) at –5 °C was added dropwise tetrabutylammonium fluoride (11 µL of a 1 M solution in THF). The resulting solution was stirred for 3 min and poured into saturated ammonium chloride (2 mL) and extracted with EtOAc (4 × 1 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, concentrated in vacuo, and purified by flash chromatography (EtOAc:petroleum ether, 1:4) to give the title compound 3 (1.4 mg, 3.6 µmol, 98%) as a clear and colourless oil; R$_f$ 0.4 (EtOAc:petroleum ether, 3:7); [α]$_d$ 25-25.7 (c 0.07, CH$_2$Cl$_2$); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$=0.91 (t, $^3$J (H, H)=7.5 Hz, 3H, 2-CH$_2$CH$_2$H$_2$), 1.61 (dqd, $^3$J (H, H)=6.7, 7.5, 13.8 Hz, 1H; 2-CH$_2$CH$_2$H$_3$), 1.79 (dqd, $^3$J (H, H)=6.7, 7.5, 13.8 Hz, 1H; 2-CH$_2$CH$_2$H$_3$), 2.36 (td, $^3$J (H, H)=4.4, 15.8 Hz, 1H; 4-H or 8-H), 2.38 (td, $^3$J (H, H)=4.4, 15.8 Hz, 1H; 4-H or 8-H), 2.60 (td, $^3$J (H, H)=1.8, 15.8 Hz, 1H; 4'-H or 8'-H), 2.61 (td, $^3$J (H, H)=1.8, 15.8 Hz, 1H; 4'-H or 8'-H), 2.62 (ddd, $^3$J (H, H)=6.4, 8.0, 14.4, $^4$J (H, H)=1.1 Hz, 1H; CH$_2$CH$_2$CH$_2$=CH), 2.80 (ddd, $^3$J (H, H)=6.9, 7.7, 14.4, $^4$J (H, H)=1.6 Hz, 1H; CH$_2$CH$_2$CH$_2$=CH), 2.94 (dt, $^3$J (H, H)=1.8, 6.7 Hz, 1H; 2-H), 3.10 (dd, $^3$J (H, H)=2.4, $^4$J (H, H)=0.9 Hz, 1H; C≡CH), 3.27 (ddd, $^3$J (H, H)=1.9, 6.4, 7.7 Hz, 1H; 6-H), 3.52 (td, $^3$J (H, H)=1.8, 4.4 Hz, 1H; 4a-H or 8a-H), 3.54 (td, $^3$J (H, H)=1.8, 4.4 Hz, 1H; 4a-H or 8a-H), 4.03 (td, $^3$J (H, H)=1.8, 4.4 Hz, 1H; 7-H), 4.05 (td, $^3$J (H, H)=1.8, 4.4 Hz, 1H; 3-H), 5.55 (ddd, $^3$J (H, H)=10.9, $^4$J (H, H)=1.1, 1.6, 2.4 Hz, 1H; CH$_2$CH$_2$CH$_2$=CH), 6.13 (ddd, $^3$J (H, H)=6.9, 8.0, 10.9, $^5$J (H, H)=0.9 Hz, 1H; CH$_2$CH$_2$=CH); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$=9.4 (CH$_2$CH$_3$), 28.2 (CH$_2$CH$_3$), 36.2 (CH$_2$CH=CH), 37.3 (4-C or 8-C), 37.4 (4-C or 8-C), 46.47 (3-C), 46.52 (7-C), 71.2 (4a-C or 8a-C), 71.4 (4a-C or 8a-C), 78.5 (6-C), 80.1 (C≡CH), 80.8 (2-C), 82.2 (C≡CH), 110.4 (CH$_2$CH=CH), 140.8 (CH$_2$CH=CH); $^{13}$C NMR (125 MHz, C$_6$D$_6$) $\delta$=9.7 (CH$_2$CH$_3$), 28.7 (CH$_2$CH$_3$), 36.7 (CH$_2$CH=CH), 37.3 (4-C or 8-C), 37.4 (4-C or 8-C), 46.42 (3-C or 7-C), 46.44 (3-C or 7-C), 71.3 (4a-C or 8a-C), 71.4 (4a-C or 8a-C), 78.8 (6-C), 80.4 (C≡CH), 80.9 (2-C), 82.7 (C≡CH), 110.6 (CH$_2$CH=CH), 141.3 (CH$_2$CH=CH); IR (film): ν = 3280 (acetylene CH); HRMS (ES): m/z (%): Found [M + Na]$^+$ 412.9716 (20) C$_{13}$H$_{20}^{79}$Br$_2$O$_2$Na requires 412.9728.
(2S, 3R, 4aR, 6S, 7R, 8aR)-2,6-Diallyl-3-hydroxy-7-triethyrsilylanoxy-octahydro-pyra...
Note: for numbering consistency and hence easier comparison of spectroscopic data between compounds all of the chlorinated pyran[3,2-b]pyrans are named and numbered such that the chlorinated carbon is 7-C.

(2S, 3R, 4aR, 6S, 7S, 8aR)-2,6-Diallyl-7-chloro-octahydro-pyrano[3,2-b]pyran-3-ol 24

To a stirred solution of the TES-ether 22 (452 mg, 1.23 mmol) in DCM (20 mL) at 0 °C was added pyridine (0.79 mL, 776 mg, 9.8 mmol) and trifluoromethanesufonic anhydride (0.82 mL, 1.39 g, 4.91 mmol). The reaction mixture was stirred at room temperature for 0.5 h and then quenched by the addition of saturated aqueous NaHCO₃ (30 mL). The organic phase was separated and the aqueous phase was extracted with DCM (2 × 30 mL). The organic phases were washed with saturated aqueous CuSO₄ solution (2 × 30 mL) and dried (MgSO₄). The solvent was removed in vacuo and the crude triflate was briefly dried under high vacuum. Tetrabutylammonium chloride (1.02 g, 3.68 mmol) and toluene (30 mL) were added to the crude triflate and the resulting suspension was placed in a preheated oil bath (120 °C) The reaction mixture was heated at reflux for 2.5 h. The cooled reaction mixture was filtered through a silica gel plug washing with ether. The solvent was removed in vacuo and the residue was dissolved in methanol (30 mL). Amberlyst IR-120 was added and the reaction mixture was stirred overnight. The reaction mixture was filtered and the solvent removed in vacuo. Purification by flash chromatography (EtOAc:PE, 2:1) gave the title compound as a clear and colourless oil (150 mg, 0.55 mmol, 45%); Rf 0.4 (EtOAc); [α]D₂⁰ = -10.5 (c = 0.6 in CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ = 1.61 (ddd, 3J (H, H) = 13.3, 11.0, 3.6, 1H; 4-Ha), 2.15 (dt, 3J (H, H) = 15.5, 4.4 Hz, 1H; 8-H); 2.29 (ddd, 3J (H, H) = 13.3, 4.7, 2.8 Hz, 1H; 4-Ha), 2.40-2.58 (m, 5H; 2 × CH₂CH=CH₂, 8-H'), 3.14 (ddd, 3J (H, H) = 9.2, 5.6, 4.7, 1H; 2-H), 3.45 (ddd, 3J (H, H) = 7.1, 6.8, 1.8 Hz, 1H; 6-H), 3.48 (ddd, 3J (H, H) = 4.4, 2.2, 1.4 Hz; 1H; 8a-H), 3.62-3.64 (m, 1H; 4a-H), 3.81 (ddd, 3J (H, H) = 4.7, 9.2, 11.0 Hz, 1H; 3-H), 3.97 (dt, 3J (H, H) = 4.4, 1.8 Hz, 1H; 7-H), 5.09-5.22 (m, 4H, 2 × CH₂CH=CH₂), 5.81 (ddd, 3J (H, H) = 17.4, 10.2, 7.7, 6.5 Hz, 1H; CH₂CH=CH₂), 6.07 (ddd, 3J (H, H) = 17.3, 10.3, 7.7, 6.6 Hz, 1H; CH₂CH=CH₂); ¹³C NMR (125 MHz, CDCl₃): δ = 37.8 (8-C), 36.7 (CH₂CH=CH₂), 37.6 (CH₂CH=CH₂), 37.9 (4-C), 54.2 (7-C), 65.5 (3-C), 69.9 (8a-C), 75.2 (4a-C), 79.0 (6-C), 80.7 (2-C), 116.7 (CH₂CH=CH₂), 118.0 (CH₂CH=CH₂), 133.5 (CH₂CH=CH₂), 135.1 (CH₂CH=CH₂); IR (film): ν = 3387 (OH), 2918, 2850, 1641 (C=C); HRMS (ES): m/z (%): Found [M + Na]+ 295.1078 (10), C₁₄H₂₁O₃ClNa requires 295.1071.

(2S, 4aR, 6S, 7S, 8aR)-2,6-Diallyl-7-chloro-hexahydro-pyrano[3,2-b]pyran-3-one

To a stirred solution of the alcohol 24 (150 mg, 0.55 mmol) in DCM (10 mL) was added NMO (193 mg, 1.65 mmol) and activated powdered 4 Å molecular sieves. The reaction mixture was stirred for 20 mins and then TPAP (9.6 mg, 30 µmol) was added. The mixture was stirred for 1 h and then filtered through a plug of silica gel washing with EtOAc. Purification by flash chromatography (PE:EtOAc, 2:1) gave the title compound (96 mg, 65%) as a clear and colourless oil; Rf 0.4 (EtOAc:PE, 1:1); [α]D₂⁰ = -70.2 (c = 0.265 in CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ = 2.25 (dt, 3J (H, H) = 15.7, 4.3 Hz, 1H; 8-H), 2.36-2.52 (m, 3H; CH₂CH=CH₂), 2.57-2.63 (m, 1H; CH₂CH=CH₂), 2.58 (dt, 3J (H, H) = 15.7, 2.2 Hz, 1H; 8-H'), 2.68 (dd, 3J (H, H) = 3.8 Hz, 2H, 4-H, 4-H'), 3.51 (dt, 3J (H, H) = 1.6, 6.9 Hz, 1H; 6-H), 3.80 (ddd, 3J (H, H) = 4.0, 2.3, 1.4 Hz, 1H; 8a-H), 3.82 (dd, 3J (H, H) = 7.0, 4.6 Hz, 2-H; 2-H), 3.95-3.99 (m, 2H; 7-H, 4a-H), 5.06 (ddt, 3J (H, H) = 2.1, 3J (H, H) = 10.1, 4J (H, H) = 1.1, 1H; CH₂CH=CH₃H₄), 5.08 (ddt, 3J (H, H) = 2.0, 3J (H, H) = 10.2, 4J (H, H) = 1.0 Hz, 1H; CH₂CH=CH₃H₅), 5.12 (ddt, 3J (H, H) = 2.0, 3J (H, H) = 17.1, 4J (H, H) = 1.6 Hz, 1H; CH₂CH=CH₃H₆), 5.16 (ddt, 3J (H, H) = 2.1, 3J (H, H) = 17.1, 4J (H, H) = 2.6 Hz, 1H; CH₂CH=CH₃H₇), 5.77 (ddd, 3J (H, H) = 17.1, 10.2, 7.9, 6.4 Hz, 1H; CH₂CH=CH₂), 5.93 (ddt, 3J (H, H) = 17.1, 10.2, 6.9, Hz, 1H;
To a stirred solution of (2S,4aR,6S,7S,8aR)-2,6-diallyl-7-chloro-octahydro-pyrano[3,2-b]pyran-3-one (88 mg, 0.33 mmol) in methanol (5 mL) was added sodium borohydride (24 mg, 0.65 mmol). The reaction mixture was stirred for 10 mins and then preabsorbed onto silica gel. Purification by flash chromatography (PE:EtOAc, 1:1) gave the title compound 25 (78 mg, 0.29 mmol, 87%) as a white crystalline solid; Rf 0.5 (EtOAc:PE, 1:1); mp 114-115 °C (from CHCl3); [α]D 26° = -42.2 (c = 0.54 in CHCl3); 1H NMR (500 MHz, CDCl3): δ=1.77 (dt, 3J (H, H)=14.8, 3.5, 1H; 4-H), 2.13 (dt, 3J (H, H)=15.6, 4.3 Hz, 1H; 8-H), 2.27 (dt, 3J (H, H)=14.8, 2.8 Hz, 1H; 4'-H), 2.35-2.54 (m, 5H; 2×CH2CH=CH2, 8'-H), 3.22 (d, 3J (H, H)=11.8 Hz, 1H; OH), 3.24 (t, 3J (H, H)=7.0 Hz, 1H; 2-H), 3.43 (dt, 3J (H, H)=2.0, 7.0 Hz, 1H; 6-H); 3.53-3.56 (m, 2H; 8a-H, 3-H), 3.57-3.59 (br m, 1H; 4a-H); 3.98 (dt, 3J (H, H)=4.3, 2.0 Hz, 1H; 7-H); 5.03 (ddt, 3J (H, H)=2.1, 3.5J (H, H)=10.2, 3.5J (H, H)=1.2 Hz, 1H; CH2CH=CH2cisH), 5.08 (ddt, 3J (H, H)=2.0, 3.5J (H, H)=10.2, 3.5J (H, H)=1.1 Hz, 1H; CH2CH=CH2transH). 13C NMR (125 MHz, CDCl3): δ=35.3 (4-C), 36.3 (CH2CH=CH2), 36.8 (C-8), 37.7 (CH2CH=CH2), 54.2 (7-C), 64.7 (3-C), 70.5 (8a-C), 73.7 (4a-C), 79.7 (6-C), 79.9 (2-C), 116.9 (CH2CH=CH2), 118.2 (CH2CH=CH2), 133.1 (CH2CH=CH2), 134.9 (CH2CH=CH2); IR (film): ν = 3524 (OH), 2920, 1642 (C=O), 1641 (C=O); HRMS (ES): m/z (%): Found [M + Na]+ 273.1259 (90), C14H19O3 requires 273.1257. And the alcohol 24 (10 mg, 36 µmol, 11%).

To a stirred solution of the alcohol 25 (19 mg, 69 µmol) in DCM (1 mL) at -78 °C was added 2,6-lutidine (50 µL, 46 mg, 0.43 mmol) and TESOTf (50 µL, 58 mg, 0.22 mmol). The reaction mixture was allowed to warm to room temperature over 2 h and then quenched by the addition of saturated aqueous NaHCO3. The aqueous phase was extracted with DCM and the combined organic extracts were washed with NaHCO3 and dried (MgSO4). Purification by flash chromatography (PE: EtOAc, 2:1) gave the title compound 26 as a clear and colourless oil (27 mg, 69 µmol, 100%); Rf 0.7 (EtOAc:PE, 1:2); [α]D 26° = -11.0 (c = 0.5 in CHCl3); 1H NMR (500 MHz, CDCl3): δ=0.53-0.65 (m, 6H; Si(CH2CH3)3), 0.98 (t, 3J (H, H)=8.0 Hz, 9H; Si(CH2CH3)3), 1.73 (ddd, 3J (H, H)=14.9, 4.5, 3.6 Hz, 1H; 4-H), 2.10-2.15 (m, 2H; 8-H, 4'-H), 2.28-2.50 (m, 5H; 2×CH2CH=CH2, 8'-H), 3.15 (dt, 3J (H, H)=1.4, 6.8 Hz, 1H; 2-H), 3.35 (dt, 3J (H, H)=2.0, 6.8 Hz, 1H; 6-H), 3.38-3.41 (m, 2H; 8a-H, 4a-H), 3.65 (ddd, 3J (H, H)=3.6, 2.5, 1.4, Hz, 1H; 3-H); 3.90 (dt, 3J (H, H)=4.4, 2.0 Hz, 1H; 7-H), 5.00 (ddd, 3J (H, H)=2.3, 3J (H, H)=10.2, 4J (H, H)=1.3, 1.0 Hz, 1H; CH2CH=CH2cisH), 5.04 (dd, 3J (H, H)=2.1, 3J (H, H)=10.2, 4J (H, H)=1.1 Hz, 1H; CH2CH=CH2transH), 5.08...
(ddt, $J (H, H)=2.3$, $J (H, H)=17.1$, $J (H, H)=1.6$ Hz, 1H; CH$_2$CH=CHOH$_3$), 5.14 (ddt, $J (H, H)=2.1$, $J (H, H)=17.1$, $J (H, H)=1.5$ Hz, 1H; CH$_2$CH=CHOH$_3$), 5.86 (dddt, $J (H, H)=17.1$, 10.2, 7.7, 6.3, Hz, 1H; CH$_2$CH=CHOH$_3$). 13$^C$ NMR (125 MHz, CDC$_3$): $\delta=5.2$ (Si(CH$_2$CH$_3$)$_3$), 6.9 (Si(CH$_2$CH$_3$)$_3$), 36.3 (4-C), 36.4 (8-C), 37.1 (CH$_2$CH=CHOH$_3$), 37.9 (CH$_2$CH=CHOH$_3$), 54.3 (7-C), 64.3 (3-C), 70.5 (8a-C or 4a-C), 70.2 (8a-C or 4a-C), 79.1 (6-C), 80.4 (2-C), 116.2 (CH$_2$CH=CHOH$_3$), 117.4 (CH$_2$CH=CHOH$_3$), 134.4 (CH$_2$CH=CHOH$_3$), 135.8 (CH$_2$CH=CHOH$_3$); IR (film): $\nu = 2947, 2851, 1642$ (C=C); HRMS (ES): m/z (%): Found [M + H]$^+$ 391.1708 (30), C$_{26}$H$_{35}$ClO$_3$Si requires 391.1708.

(2S, 3S, 4aR, 6S, 7S, 8aR)-2,6-Di-(2-oxo-ethyl)-3-triethylsilyloxy-7-chloro-octahydro-pyrano[3,2-b]pyran 27

A mixture of ozone and oxygen was gently bubbled through a stirred solution of the diene 26 (24 mg, 62 µmol) in DCM (5 mL) at -78 °C until the solution became pale blue (ca. 5 mins). The excess ozone was purged from the solution by bubbling oxygen through for a further 3 mins. Triphenylphosphine (95 mg, 0.36 mmol) was added and the resultant solution was allowed to warm to RT overnight. The solvent was removed in vacuo and purification by flash chromatography (PE: EtOAc: 1:1) gave the title compound as a clear and colourless oil 27 (23 mg, 58.8 µmol, 95%); $R_f$ 0.2 (EtOAc:PE: 1:1); [a]$_D^{25}= -2.1$ (c = 0.19 in CHCl$_3$); 1$^H$ NMR (500 MHz, CDC$_3$): $\delta=0.56$ (q, $J (H, H)=8.0$ Hz, 6H; Si(CH$_2$CH$_3$)$_3$), 0.95 (t, $J (H, H)=8.0$ Hz, 9H; Si(CH$_2$CH$_3$)$_3$), 1.82 (dt, $J (H, H)=15.3$, 4.1 Hz, 1H; CH$_2$H$_3$), 2.14 (dt, $J (H, H)=15.3$, 2.3 Hz, 1H; 4-H’), 2.23 (dt, $J (H, H)=15.6$, 4.5 Hz, 1H; 8-H), 2.47 (dt, $J (H, H)=15.6$, 2.0 Hz, 1H; 8-H’), 2.55-2.56 (m, 2H; 2-CH$_2$CHO), 2.68 (dddt, $J (H, H)=17.8$, 5.1, 1.4, 1H; 6-CH$_2$HCHO), 2.92 (dddt, $J (H, H)=17.8$, 7.3, 1.4 Hz, 1H; 6-CH$_2$HCHO), 3.50-3.52 (m, 2H; 8a-H, 4a-H), 3.70-3.71 (m, 1H; 3-H), 3.71 (dddt, $J (H, H)=6.6$, 5.1, 1.7, 1H; 2-H), 4.00 (dddt, $J (H, H)=7.3$, 5.1, 2.0, Hz, 1H; 6-H), 4.02 (dt, $J (H, H)=4.5$, 2.0 Hz, 1H; 7-H), 9.80 (t, $J (H, H)=1.4$ Hz, 1H; 6-CH$_2$HCHO), 9.93 (dd, $J (H, H)=2.4$, 1.9 Hz, 1H; 2-CH$_2$CHO); 13$^C$ NMR (125 MHz, CDC$_3$): $\delta=4.8$ (Si(CH$_2$CH$_3$)$_3$), 6.8 (Si(CH$_2$CH$_3$)$_3$), 35.5 (4-C), 36.6 (8-C), 45.9 (2-CH$_2$CHO), 47.5 (6-CH$_2$CHO) 54.4 (7-C), 65.4 (3-C or 2-C), 70.2 (8a-C or 4a-C), 71.5 (8a-C or 4a-C), 74.1 (6-C), 76.0 (3-C or 2-C), 200.4 (CHO), 203.0 (CHO); IR (film): $\nu = 2851, 1716$ (C=O), 1724 (C=O); HRMS (ES): m/z (%): Found [M + H]$^+$ 391.1707 (5), C$_{18}$H$_{32}$Si$_{18}$ClO$_{3}$Si requires 391.1708.

(2S, 3S, 4aR, 6S, 7S, 8aR)-7-Chloro-2-(2-oxo-ethyl)-3-triethylsilyloxy-6-((E)-5-trimethylsilylpent-2-en-4ynyloxy)-octahydro-pyrano[3,2-b]pyran

The phosphonium salt 3-(trimethylsilyl-2-propynyl)triphenylphosphonium bromide (ex-Aldrich, 54 mg, 119 µmol) was weighed into a dry Schlenk tube and was broken up into a powder with the end of a micro-spatula. A dry stirrer bar was added and the salt was placed under vacuum for 1.5 h with stirring. The vacuum was quenched to Ar and THF (2 mL) was added. The suspension of phosphonium salt was rapidly stirred until a uniform fine suspension was obtained. The salt was cooled to -78 °C and BuLi (74 µL of a 1.6 M solution in hexanes, 119 µmol) was added rapidly. The reaction mixture was stirred at -35 → -30 °C for 30 mins until a blood red solution of ylid was obtained and the
yalid was then re-cooled to -78 °C. In a separate round bottom flask a solution of the bis-aldehyde 27 (16 mg, 41 μmol) in dry THF (2 mL) was prepared and cooled to -78 °C. A solution of the cold ylid (0.68 mL, 41 μmol) was rapidly added to the stirred cold solution of the aldehyde using a gas-tight syringe. The dry ice was removed from the cold bath and a stirrer bar was added. The cold bath (and reaction mixture) were allowed to slowly warm to 0 °C with stirring (ca. 3 h). The reaction mixture was quenched with saturated aqueous NH4Cl and Et2O was added. The aqueous phase was further extracted with ether (2 × 5 mL) and the combined organic extracts dried (MgSO4). Purification by flash chromatography (PE:EtOAc, 3:1) provided the title compound as a clear and colourless oil (9 mg, 19 μmol, 45%) as an approximate 8:1 mixture of (E):(Z) isomers; Rf 0.3 (EtOAc:PE, 1:1); [α]D25 =+14.3 (c = 0.3 in CHCl3); 1H NMR (500 MHz, CDCl3): δ=0.20 (s, 9H; Si(CH3)3), 0.60-0.64 (m, 6H; Si(CH2CH3)3), 0.99 (t, 3J (H, H)=8.0 Hz, 9H; Si(CH2CH3)x), 1.83 (dt, 3J (H, H)=15.2, 4.0 Hz, 1H; 4-H), 2.14-2.22 (m, 2H; 4-H', 8-H), 2.40 (dddd, 3J (H, H)=14.2, 8.1, 6.4, 1.2 Hz, 1H; CH2CH=CH), 2.57 (dt, 3J (H, H)=15.8, 1.9 Hz, 1H; 8-H'), 2.54 (ddt, 3J (H, H)=14.2, 1.6, 7.0 Hz, 1H; CH2CH=CH), 2.57-2.59 (m, 2H; CHCH2CHO), 3.41 (ddd, 3J (H, H)=7.0, 6.4, 1.9 Hz, 1H; 6-H), 3.45 (dt, 3J (H, H)=2.0, 4.0, Hz, 1H; 4a-H), 3.50-3.51 (m, 1H, 8a-H), 3.72-3.74 (m, 2H; 2-H, 3-H), 3.94 (dt, 3J (H, H)=4.5, 1.9 Hz, 1H; 7-H), 5.65 (dt, 3J (H, H)=15.9, 4J (H, H)=1.9 Hz, 1H; CH2CH=CH), 6.20 (dd, 3J (H, H)=15.9, 8.1, 7.0 Hz, 1H; CH2CH=CH=CH), 9.96 (dd, 3J (H, H)=2.4, 1.6 Hz, 1H; CHO); 13C NMR (125 MHz, CDCl3): 18.4 (CHO); IR (film): ν = 2919, 1714 (C=O); HRMS (ES): m/z (%): Found [M + Na]+ 507.2113 (100), C24H41ClO4Si2Na requires 507.2130. And recovered bis-aldehyde (4 mg, 10 μmol, 25%) and bis-enyne (4 mg, 7 μmol, 17%).

(2S, 3S, 4aR, 6S, 7S, 8aR)-7-Chloro-2-(2-hydroxy-ethyl)-3-triethylsilanyloxy-6-((E)-5-trimethylsilanylenpent-2-en-4-ynyl)-octahydro-pyrano[3,2-b]pyran 29

To a stirred solution of the aldehyde 28 (10 mg, 21 μmol) in methanol (2 mL) was added sodium borohydride (3 mg, 135 μmol). The resulting solution was stirred for 10 mins and then quenched by the addition of saturated aqueous NaHCO3. The aqueous phase was extracted with EtOAc, (PE:EtOAc, 3:1) provided the title compound as a clear and colourless oil (10 mg, 21 μmol, 100%); Rf 0.2 (EtOAc:PE, 1:1); [α]D20 =-12.5 (c = 0.16 in CHCl3); 1H NMR (500 MHz, CDCl3): δ=-0.17 (s, 9H; (Si(CH3)3), 0.55-0.63 (m, 6H; Si(CH2CH3)3), 0.97 (t, 3J (H, H)=8.0 Hz, 9H; Si(CH2CH3)x), 1.57 (ddt, 3J (H, H)=14.9, 3.8, 2.7 Hz, 1H; CH2CH2OH), 1.75 (dt, 3J (H, H)=14.9, 3.7 Hz, 4-H); 2.10-2.20 (m, 3H; 4-H', 8-H, CH2CH2OH), 2.37 (dddd, 3J (H, H)=14.2, 8.1, 6.3, 1.2 Hz, 1H; CH2CH=CH), 2.42 (dt, 3J (H, H)=15.7, 2.1 Hz; 8-H), 2.52 (ddt, 3J (H, H)=14.2, 7.1, 1.7 Hz, 1H; CH2CH=CH=CH), 3.11 (dd, 3J (H, H)=8.4, 2.7 Hz, 1H; OH), 3.37 (ddd, 3J (H, H)=7.1, 6.4, 1.8, Hz, 1H; 6-H), 3.40 (ddd, 3J (H, H)=3.7, 2.0, 1.6 Hz, 1H; 4a-H), 3.45 (ddd, 3J (H, H)=5.6, 4.1, 1.5 Hz, 1H; 2-H), 3.46-3.47 (m, 1H; 8a-H), 3.60 (ddd, 3J (H, H)=3.7, 2.4, 1.5 Hz, 1H; 3-H), 3.77 (ddt, 3J (H, H)=10.5, 9.3, 2.7 Hz, 1H; CH/CHOH), 3.84 (ddd, 3J (H, H)=10.7, 8.4, 3.8 Hz, 1H; CH/CHOH), 3.88 (ddd, 3J (H, H)=4.5, 2.1, 1.8 Hz, 1H; 7-H), 5.62 (dt, 3J (H, H)=15.9, 4J (H, H)=1.4 Hz, 1H; CH2CH=CH), 6.17 (ddd, 3J (H, H)=15.9, 8.0, 6.8 Hz, 1H; CH2CH=CH=CH); 13C NMR (125 MHz, CDCl3): δ=-0.09 (Si(CH3)3), 5.1 (Si(CH2CH3)x), 6.9 (Si(CH2CH3)x), 33.9 (CH2CH2OH), 36.1 (4-C), 37.1 (CH2CH=CH, 8-C – accidental equivalence), 54.1 (7-C), 61.6 (CH2OH), 65.4 (3-C), 70.5 (8a-C), 71.7 (4a-C), 78.4 (6-C), 81.2 (2-C), 93.4 (C=C), 103.7 (C=C), 112.5 (CH2CH=CH), 141.0 (CH2CH=CH); IR (film): ν = 3473 (OH), 2954, 2876; HRMS (ES): m/z (%): Found [M + Na]+ 509.2264 (100), C24H43ClO4Si2Na requires 509.2257.
(2S, 3S, 4aR, 6S, 7S, 8aR)-7-Chloro-2-(2-iodo-ethyl)-3-triethylsilanyloxy-6-((E)-5-trimethylsilanyl-pent-2-en-4-ynyl)-octahydro-pyran[3,2-b]pyran 30

To a stirred solution of the alcohol 29 (5 mg, 10.2 µmol), triphenylphosphine (8.1 mg, 31 µmol) and imidazole (2.7 mg, 39 µmol) in ether (1.2 mL) and MeCN (0.4 mL) was added iodine (7.5 mg, 29 µmol). The resulting mixture was stirred for 2 h and then quenched by the addition of saturated aqueous Na2S2O3 solution. The aqueous phase was extracted with ether and the organic phase dried (MgSO4). Purification by flash chromatography (PE:ether, 10:1) gave the title compound as a clear and colourless oil (4.4 mg, 7.38 µmol, 72%). Rf = 0.2 (EtOAc:PE, 1:10); [α]D20 = -22.2 (c = 0.22 in CHCl3); 1H NMR (500 MHz, CDCl3): δ=-0.17 (s, 9H; Si(CH3)3), 0.51-0.63 (m, 6H; Si(CH2CH3)3), 0.96 (t, 3J (H, H)=8.0 Hz, 9H; Si(CH2CH3)3), 1.78 (dt, 3J (H, H)=15.0, 4.0 Hz, 1H; 4-H), 1.78-1.84 (m, 1H; CH2I), 2.11 (dt, 3J (H, H)=15.5, 4.0 Hz, 1H; 7-H), 2.25 (dt, 3J (H, H)=14.3, 8.6, 5.3 Hz, 1H; (CH2CH2I), 2.35 (ddd, 3J (H, H)=14.5, 7.9, 6.5, 1.2 Hz, 1H; C/HCH=CHI), 2.42 (dt, 3J (H, H)=15.0, 2.0 Hz; 8-H'), 2.50 (dddt, 3J (H, H)=14.5, 1.6, 6.9 Hz, 1H; CH/CH=CHI), 2.38 (ddd, 3J (H, H)=8.6, 3.7, 1.2 Hz, 1H; 2-H), 3.33-3.43 (m, 5H; CH2I, 4a-H, 6a-H, 6-H), 3.60 (ddd, 3J (H, H)=4.0, 2.4, 1.2, Hz, 1H; 3-H), 3.87 (dt, 3J (H, H)=4.5, 2.0, Hz, 1H; 7-H), 5.61 (dt, 3J (H, H)=15.9, 4J (H, H)=1.4 Hz, 1H; CH2CH=CHI), 6.17 (ddd, 3J (H, H)=15.9, 8.1, 6.8 Hz, 1H; CH2CH=CHI); 13C NMR (125 MHz, CDCl3); δ=-0.08 (Si(CH3)3), 5.1 (Si(CH2CH3)3), 5.6 (CH2I), 6.9 (Si(CH2CH3)3), 35.8 (CH2CH2I), 36.2 (4-C), 37.0 (8-C), 37.1 (CH2CH=CHI), 54.2 (7-C), 65.1 (3-C), 70.3 (8a-C), 71.9 (4a-C), 78.5 (6-C), 79.3 (2-C), 93.3 (C=C), 103.8 (C=C), 112.4 (CH2CH=CHI), 141.1 (CH2CH=CHI); IR (film): ν =2954, 2874. Note: Satisfactory HRMS data could not be obtained for 30, however full characterisation was obtained on all subsequent compounds. The ESI mass spectrum of 30 corresponds to [M + Na – TESI]+; HRMS (ES): m/z (%): Found [M + Na - TESI]+ 377.1309 (20), C18H27Cl3O3SiNa requires 3771316.

(2S, 3S, 4aR, 6S, 7S, 8aR)-7-Chloro-2-ethyl)-3-hydroxy-6-((E)-5-trimethylsilanyl-pent-2-en-4-ynyl)-octahydro-pyran[3,2-b]pyran 31

To a stirred solution of the iodide 30 (4 mg, 6.7 µmol) was added activated zinc dust. The reaction flask was vacuum purged with argon (3 cycles) and ether (0.3 mL) and methanol (0.3 mL) were added. The reaction mixture was stirred for 2 h and then quenched by the addition of 1 M hydrochloric acid and ether. The organic mixture was stirred for 5 h and then quenched by the addition of 1 M hydrochloric acid and ether. The combined organic extracts were washed with NaHCO3 and dried (MgSO4). Purification by flash chromatography (PE:EtOAc, 3:1) gave the title compound 31 as a clear and colourless oil (2.3 mg, 6.5 µmol, 96%); Rf =0.4 (EtOAc:PE, 1:2); [α]D20 =-13.9 (c = 0.115 in CHCl3); 1H NMR (500 MHz, CDCl3): δ=0.16 (s, 9H; (Si(CH3)3), 0.91 (t, 3J (H, H)=7.5 Hz, 3H; 2-CHCH2CH3), 1.59-1.69 (m, 2H; 2-CHCH2CH3), 1.76 (dt, 3J (H, H)=14.8, 3.5 Hz, 1H; 4-H), 2.12 (dt, 3J (H, H)=15.4, 4.0 Hz, 1H; 8-H), 2.25 (dt, 3J (H, H)=14.8, 2.8 Hz, 1H; 4-H'), 2.40 (ddd, 3J (H, H)=14.3, 8.3, 6.8, 1.3 Hz, 1H; CH2CH=CHI), 2.47 (dt, 3J (H, H)=15.4, 2.0 Hz; 8-H'), 2.52 (ddt, 3J (H, H)=14.3, 1.8, 6.6 Hz, 1H; CH2CH=CHI), 3.08 (dt, 3J (H, H)=0.8, 6.8 Hz, 1H; 2-H), 3.41 (dt, 3J (H, H)=1.8, 6.8 Hz, 1H; 6-H), 3.51 (ddd, 3J (H, H)=4.0, 2.0, 1.6 Hz, 1H; 8a-H). 3.54-3.52 (m, 1H; 3-H), 3.56-
3.54 (m, 1H; 4a-H), 3.94 (dt, 3\( J (H, H) \)=4.0, 2.0, Hz, 1H; 7-H), 5.33 (ddd, 3\( J (H, H) \)=15.8, 4\( J (H, H) \)=1.6, 1.3 Hz, 1H; CH\(_2\) CH=CH), 6.14 (ddd, 3\( J (H, H) \)=15.8, 8.3, 6.6 Hz, 1H; CH\(_2\) CH=CH), \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \)-0.07 ((Si(CH\(_3\))\(_3\)), 9.9 (2-CHCH\(_2\)C\(_3\)), 24.6 (2-CHCH\(_2\)CH\(_3\)), 35.4 (4-C), 36.7 (8-C), 37.0 (CH\(_2\) CH=CH), 54.2 (7-C), 64.7 (3-C), 70.5 (8a-C), 73.9 (4a-C), 78.4 (6-C), 81.7 (2-C), 93.8 (C=\( \equiv \)C), 103.4 (C=\( \equiv \)C), 113.1 (CH\(_2\) CH=CH); IR (film): \( \nu \)= 3529 (OH), 2986, 2921, 2846; HRMS (ES): \( m/z \) (\%): Found [M + Na]\(^{+} \) 379.1476 (90), C\(_{18}\)H\(_{29}\)\(^{35}\)ClO\(_3\)Na requires 379.1472.

\( \alpha \)D\(_{20} \)= -25.0 (c = 0.06 in CHCl\(_3\)); 1H NMR (500 MHz, CDCl\(_3\)):

\( \delta \)= 0.92 (t, \( J (H, H) \)=7.5 Hz, 3H; CHCH\(_2\)C\(_3\)), 1.62-1.72 (m, 2H; 2-CHC\(_2\)H\(_3\)), 1.78 (dt, \( J (H, H) \)=14.8, 3.5 Hz, 1H; 4-H), 2.13 (dt, \( J (H, H) \)=15.6, 4.3, Hz, 1H; 8-H), 2.27 (dt, \( J (H, H) \)=14.9, 2.8 Hz, 1H; 4-H'), 2.42 (dd, \( J (H, H) \)=14.2, 8.2, 6.9, \( J (H, H) =1.3 \) Hz, 1H; CHHCH=CH), 2.49 (dt, \( J (H, H) =15.6, 1.9 \) Hz, 1H; 8-H'), 2.56 (dt, \( J (H, H) =14.9, 6.9, 4 \) Hz, 1H; 8-H'), 2.57 (dt, \( J (H, H) =15.6, 1.3 \) Hz, 1H; 7-H), 3.07 (d, \( J (H, H) =11.8 \) Hz, 1H; OH), 3.10 (dt, \( J (H, H) =0.8, 6.8 \) Hz, 1H; 2-H), 3.44 (dt, \( J (H, H) =1.9, 6.9 \) Hz, 1H; 6-H), 3.52-3.53 (m, 1H; 8a-H), 3.54 (ddd, \( J (H, H) =11.8, 3.5, 2.8 \) Hz, 1H; 3-H), 3.56-3.58 (m, 1H; 4a-H), 3.94 (dt, \( J (H, H) =4.3, 1.9 \) Hz, 1H; 7-H), 5.60 (ddd, \( J (H, H) =15.9, 4 \) Hz, 1H; 2-H), 2.2, 1.8, 1.3 Hz, 1H; CH\(_2\) CH=CH), 6.20 (dd, \( J (H, H) =15.9, 8.2, 6.9 \) Hz, 1H; CH\(_2\) CH=CH); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \)=9.9 (CH\(_2\) CH=CH), 24.7 (2-CHCH\(_3\)), 35.4 (4-C), 36.8 (8-C), 36.9 (CH\(_2\) CH=CH), 54.3 (7-C), 64.7 (3-C), 70.5 (8a-C), 73.9 (4a-C), 76.7 (C=\( \equiv \)C), 79.1 (6-C), 81.6 (2-C), 82.3 (C=\( \equiv \)C), 112.0 (CH\(_2\) CH=CH), 140.7 (CH\(_2\) CH=CH); IR (film): \( \nu \)= 3525 (OH), 3293 (acetylene CH); HRMS (ES): \( m/z \) (\%): Found [M + Na]\(^{+} \) 307.1076 (75), C\(_{15}\)H\(_{21}\)\(^{35}\)ClO\(_3\)Na requires 307.1077.
NMR Spectra

$^1$H NMR (500 MHz, CDCl$_3$) of the pyrano[3,2-b]pyran 3

$^1$H NMR (500 MHz, CDCl$_3$) of the pyrano[3,2-b]pyran 4 (8:1 mixture of (E):(Z) isomers)

*Figure S1.* $^1$H NMR spectra for the pyrano[3,2-b]pyrans 3 and 4.
$^{13}$C NMR (125 MHz, C$_6$D$_6$) of the pyrano[3,2-b]pyran 3

$^{13}$C NMR (125 MHz, CDCl$_3$) of the pyrano[3,2-b]pyran 4 (8:1 mixture of (E):(Z) isomers)

Figure S2. $^{13}$C NMR spectra for the pyrano[3,2-b]pyrans 3 and 4.
Figure S3. $^{13}$C NMR chemical shifts for carbons 8a and 4a for the pyrano[3,2-b]pyrans reported in the paper. When ambiguous, carbon assignments were made on the basis of DEPT, APT, or HMQC experiments. Note: The $^{13}$C NMR spectrum of the parent compound (octahydro-pyrano[3,2-b]pyran) has not been assigned see: R. W. Hoffmann, I. Munster, Liebigs Ann. Chem. 1997, 1143.

*Assignment could be reversed.
Figure S4. $^{13}$C NMR chemical shifts for carbons 8a and 4a for synthetic pyrano[3,2-b]pyrans prepared by the authors in relation to the work reported in the manuscript. When ambiguous, carbon assignments were made on the basis of DEPT, APT, or HMQC experiments.

*assignment could be reversed.
Figure S5. $^{13}$C NMR chemical shifts for carbons 8a and 4a for synthetic pyrano[3,2-b]pyrans prepared by the authors in relation to the work reported in the manuscript. For these compounds the $^{13}$C carbons have not been fully assigned using an HMQC experiment. Nevertheless these compounds all fit the general pattern of $^{13}$C NMR chemical shifts of pyrano[3,2-b]pyrans and [2,2′]-bifuranyls.
Figure S6. $^{13}$C NMR chemical shifts for carbons 2 and 2' for the [2,2']-bifuranyls reported in the paper. When ambiguous, carbon assignments were made on the basis of DEPT, APT, or HMQC experiments. Note: The $^{13}$C NMR spectrum of the parent compound (octahydro[2,2']bifuranyl) has not been assigned see: D. R. Kelly, J. Nally, Tetradedron Lett. 1999, 40, 2209.

*assignment could be reversed.


Figure S7. $^{13}$C NMR chemical shifts for carbons 2 and 2' for the synthetic [2,2']-bifuranyls prepared by the authors in relation to the work reported in the manuscript. When ambiguous, carbon assignments were made on the basis of DEPT, APT, or HMQC experiments. *assignment could be reversed.
**J-Value analysis of pyrano[3,2-b]pyrans**

\[ J_{3,4Ax} = 4.6, \quad J_{3,4eq} = 3.0, \quad J_{4eq, 4a} = 3.1 \]

**10**

\[ J_{3,4Ax} = 10.9, \quad J_{3,4eq} = 4.8, \quad J_{4eq, 4a} = 3.1 \]

**11**

\[ J_{3,4Ax} = 8.9, \quad J_{3,4eq} = 4.6, \quad J_{4eq, 4a} = 3.1 \]

**12**

\[ J_{3,4Ax} = 8.9, \quad J_{3,4eq} = 4.6, \quad J_{4eq, 4a} = 3.1 \]

**13**

\[ J_{3,4Ax} = 8.9, \quad J_{3,4eq} = 4.6, \quad J_{4eq, 4a} = 3.1 \]

**14**

\[ J_{3,4Ax} = 8.9, \quad J_{3,4eq} = 4.6, \quad J_{4eq, 4a} = 3.1 \]

**15**

\[ J_{3,4Ax} = 8.9, \quad J_{3,4eq} = 4.6, \quad J_{4eq, 4a} = 3.1 \]

**16**

\[ J_{3,4Ax} = 8.9, \quad J_{3,4eq} = 4.6, \quad J_{4eq, 4a} = 3.1 \]

**17**

\[ J_{3,4Ax} = 8.9, \quad J_{3,4eq} = 4.6, \quad J_{4eq, 4a} = 3.1 \]

**18**

\[ J_{3,4Ax} = 8.9, \quad J_{3,4eq} = 4.6, \quad J_{4eq, 4a} = 3.1 \]

**Figure S8.** Comparison of J-values for synthesised pyrano[3,2-b]pyrans reported in the paper. (Figure continued on next page).
Figure S8 continued.
X-ray Crystal Structures

Figure 1. X-Ray crystal structure of the bis-epoxide 9.

X-ray Crystallographic Structure Determination of the bis-epoxide 9: Crystal data: C₈H₁₀O₄, \( M_w = 170.2 \), colourless plate 0.46x0.28x0.05mm³, monoclinic \( P2_1 \) (No. 4), \( a=6.4017(2) \), \( b=8.0308(4) \), \( c=7.7826(3)\AA, \beta=110.59(1)°, \ V=374.6(1)\AA^3, \ T = 240(2)K, \ D_X = 1.509 \text{ g cm}^{-3}, \lambda = 0.71073 \AA, \mu = 0.122 \text{ mm}^{-1} \), Nonius Kappa CCD diffractometer equipped with an Oxford Cryosystems Cryostream cooling apparatus, 5.11° < \( \theta < 27.48° \), 2810 measured reflections, 917 independent (\( R_{int}=0.030 \)), 859 with \( I > 4\sigma(I) \). The structure was solved by direct methods (SHELXS-97¹) and refined by least squares (SHELXL-97¹) using Chebyshev weights on \( F_o^2 \) to \( R1 = 0.028, wR2 = 0.071 \ [I > 2\sigma(I)] \), 109 parameters, goodness-of-fit on \( F^2 \) 1.088, residual electron density 0.17 e Å⁻³. The absolute structure was assigned from the known configuration of the starting material. 622 Friedel pairs were averaged for the refinement. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-609011. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Figure 2. X-Ray crystal structure of the chloroalcohol 25.

X-ray Crystallographic Structure Determination of the chloro-alcohol 25: Crystal data: C₁₄H₂₁ClO₃, \( M_w = 272.8 \), colourless block 0.23x0.14x0.10mm³, orthorhombic \( P2_12_12_1 \) (No. 19), \( a=8.9486(8) \), \( b=10.5325(12) \), \( c=16.1990(2) \AA, \ V=1526.8(2)\AA^3, \ T = 260(2)K, \ D_X = 1.187 \text{ g cm}^{-3}, \lambda = 0.71073 \AA, \mu = 0.249 \text{ mm}^{-1} \), Nonius Kappa CCD diffractometer equipped with an Oxford Cryosystems Cryostream cooling apparatus, 3.91° < \( \theta < 22.64° \), 5687 measured reflections, 1992 independent (\( R_{int}=0.054 \)), 1697 with \( I > 4\sigma(I) \). The structure was solved by direct methods (SHELXS-97¹) and refined by least squares (SHELXL-97¹) using Chebyshev weights on \( F_o^2 \) to \( R1 = 0.079, wR2 = 0.206 \ [I > 2\sigma(I)] \), 163 parameters, goodness-of-fit on \( F^2 \) 1.123, residual electron density 0.30 e Å⁻³. The crystals were poor (weakly diffracting) and deteriorated markedly if cooled much below 260K: this is the best of two separate datasets collected from two different crystals. The position of the \(-\text{OH} \) hydrogen atom was not determined but was placed in a reasonable position with SHELXL¹. The absolute structure was assigned from the known configuration of the starting material (weakly confirmed by the Flack parameter: 0.1(4)). Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-609012. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

¹G. M. Sheldrick, SHELXS-97 / SHELXL-97 Program for the Solution of Crystal Structures, University of Göttingen, Göttingen (Germany), 1997.