Stereoselective Synthesis of the Tetrahydropyran Core of Polycavernoside A

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Supporting Information

General experimental details

All commercially available compounds were used without further purification except where stated. All moisture or air sensitive reactions were carried out in oven-dried glassware under a positive pressure of nitrogen using standard syringe/septa techniques. Anhydrous solvents were obtained by passing through a modified Grubbs system of alumina columns, manufactured by Anhydrous Engineering. When stated, DMF was dried sequentially over three portions of 10% w/v 3Å MS beads for 24 h each, and then stored under nitrogen. Petroleum ether is of the 40-60 ^{o}C boiling point range. Routine monitoring of reactions was performed using precoated Merck-Keiselgel 60 F_{254} aluminium backed TLC plates. The spots were visualised by UV_{254} light, or potassium permanganate or Hanessian's stain visualising agents. Flash column chromatography[161] was performed using silica gel (obtained from Fluorochem Ltd.) as the adsorbent.

Melting points were determined on an electrothermal apparatus and are uncorrected. Optical rotations were recorded using with the sodium D line (λ = 589 nm) on a Bellingham and Stanley ADP220 polarimeter and the $[\alpha]_D$ values are quoted in units 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer in the solid or liquid state. ^{1}H and ^{13}C NMR spectra were recorded at using either a Jeol Delta/GX 400 MHz or a Jeol Eclipse 400 MHz spectrometer. ^{19}F NMR spectra were recorded using a Lambda 300 MHz spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) are in Hertz (Hz). Tetramethylsilane was used as the internal reference for proton and carbon chemical shifts. DEPT 135, COSY, HBQC and HMBC NMR spectra were routinely used to definitively assign the signals of ^{1}H and ^{13}C NMR spectra. Electron impact (EI) and chemical ionisation (CI) mass spectra were recorded on a VG Analytical Autospec mass spectrometer. Electrospray (ESI) mass spectra were recorded on a Micromass LCT mass spectrometer or a VG Quattro mass spectrometer.

Methane was the ionisation gas used for chemical ionisation. Elemental analysis was carried out by the microalalysis department at the School of Chemistry, University of Bristol. HPLC was performed using Gilson 712 HPLC system controller software, a Gilson 506c system interface module, a Dynamax UV 1 absorbance detector, a Gilson 881c dynamic mixer, a Gilson 806 manometric module and Gilson 305 pumps.

3-(*tert*-Butyldiphenylsilanyloxy)-propan-1-ol[7a]

n-Butyl lithium (18.5 ml, 46.25 mmol, 2.5 M hexanes) was added to a solution of propane-1,3-diol (3.50 g, 46.00 mmol) in dry THF (75 ml) at –78°C under an argon atmosphere. *tert*-Butylchlorodiphenylsilane (11.96 ml, 46.00 mmol) was then added and the mixture was stirred at –78°C for 15 min, followed by 15 min at r.t, and then refluxed for 24 h. The solvent was then removed *in vacuo* to give an opaque oil which was purified by column chromatography on silica gel, eluting with an increasing proportion of EtOAc/petrol from 5-50% to give the title compound as a white crystalline solid (13.585 g, 94 %); mp: 36-39^{o}C, lit.[7a] 42-44^{o}C; ν_{max} (neat)/cm^{-1} 3291 (OH), 3068, 2929, 2885, 2855, 1472, 1427, 1089; δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s, 3x CH_3), 1.81 (2H, app. quin, *J* 5.6, 2-H_2), 2.38 (1H, br. s, OH), 3.85 (4H, app. t, *J* 5.6, 1-H_2, 3-H_2), 7.37-7.47 (6H, m, 6x Ar-H), 7.66-7.70 (4H, m, 4x Ar-H); δ_C (100 MHz, $CDCl_3$) 19.2 (C-^{t}Bu), 26.9 (3x CH_3), 34.4 (C-2), 61.9, 62.3, {127.8, 129.8, 133.4 and 135.6 (Aromatics)}.

3-(*tert*-Butyldiphenylsilanyloxy)-propanal [7a, 7b]

Dimethylsulfoxide (2.824 ml, 39.8 mmol) was added dropwise to a solution of oxalyl chloride (1.74 ml, 19.9 mmol) in DCM (90 ml) at –78 ^{o}C under a nitrogen atmosphere. After 0.5 h a solution of 3-(tert-butyldiphenylsilanyloxy)-propan-1-ol (3.130 g, 9.95 mmol) in DCM (10 ml) was added dropwise. After a further 45 min triethylamine (11.1 ml, 79.6 mmol) was added and the mixture was allowed to warm to rt over 1 h. Water (100 ml) was added and the layers were separated. The aqueous phase was extracted with DCM (3x 100 ml). The combined organic extracts were washed with water (50 ml) and brine (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow/orange oil which was purified immediately by column chromatography on silica gel, eluting with 10% Et_2O/petrol to give the title compound as a colourless oil (3.107 g, 100%); ν_{max} (neat)/cm^{-1} {3071, 3050, 2959,

2932, 2890, 2858 (CH)}, 2730 (aldehydic CH), 1728 (C=O), 1428, 1112; δ_H (400 MHz, $CDCl_3$) 1.04 (9H, s, 3x CH_3), 2.60 (2H, td, *J* 6.1, 2.2, 2-H_2), 4.02 (2H, t, *J* 6.1, 3-H_2), 7.36-7.46 (6H, m, 6x Ar-H), 7.64-7.68 (4H, m, 4x Ar-H), 9.82 (1H, t, *J* 2.2, 1-H); δ_C (100 MHz, $CDCl_3$) 19.1 (C-^{t}Bu), 26.7 (3x CH_3), 46.4 (C-2), 58.3 (C-3), {127.8, 129.8, 133.2 and 135.5 (Aromatics)}, 201.9 (C-1).

(3*S*,4*R*)-1-(*tert*-Butyl-diphenyl-silanyloxy)-4-methyl-hex-5-en-3-ol 4[8]

E-Butene was condensed into a solution of potassium *tert*-butoxide (8.28 ml, 8.28 mmol, 1.0M solution in THF) in dry THF (12 ml) at –78^{o}C under a nitrogen atmosphere. *n*-Butyl lithium (3.31 ml, 8.28 mmol, 2.5M solution in hexanes) was then added slowly. The resultant yellow solution was warmed to –45 ^{o}C for 15 min then recooled to –78 ^{o}C. A solution of (+)-*B*-methoxydiisopinocampheylborane (2.629 g, 8.31 mmol) in THF (8 ml) was added *via* cannula over 20 min followed by THF washings (4 ml). The mixture was stirred at –78 ^{o}C for 30 min then boron trifluoride etherate (1.36 ml, 11.04 mmol) was added, followed, 15 min later, by a solution of 3-(tert-butyldiphenylsilanyloxy)-propanal in THF (10 ml) *via* cannula over 30 min. The mixture was stirred for 3 h at –78^{o}C, then 3M $NaOH_{aq}$ (15.0 ml, 45.0 mmol) and H_2O_2 (8.0 ml, 82.0 mmol) were added and the mixture refluxed for 1 h. Most of the THF was then removed *in vacuo* and the layers were separated. The aqueous phase was extracted with Et_2O (4x 50 ml). The combined organic extracts were washed with water (50 ml) and brine (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a cloudy oil which was purified by column chromatography on silica gel, eluting with 10% EtOAc/petrol to give alcohol **4** as a colourless oil (2.724 g, 89%); $[\alpha]_D$ –1.5 (*c* 3.7, $CHCl_3$), lit.[9] –1.3 (*c* 4.2, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3429 (OH), {2959, 2931 and 2857 (CH)}, {1472, 1463 and 1428 (C=C)}, 1113; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, d, *J* 8.4, 1'-H_3), 1.05 (9H, s, 3x CH_3), 1.60-1.72 (2H, m, 2-H_2), 2.25 (1H, app. sextet, *J* 6.6, 4-H), 3.72-3.79 (1H, m, 3-H), 3.81-3.91 (2H, m, 1-H_2), 5.02-5.10 (2H, m, 6-H_2), 5.78-5.88 (1H, m, 5-H), 7.34-7.46 (6H, m, 6x Ar-H), 7.66-7.74 (4H, m, 4x Ar-H); δ_C (100 MHz, $CDCl_3$) 15.9 (C-1'), 19.2 (C-^{t}Bu), 26.9 (3x Me), 35.8 (C-2), 44.0 (C-4), 63.3 (C-1), 74.5 (C-3), 115.3 (C-6), {127.8, 129.7, 129.8, 134.9 and 135.7 (C-Ar)}, 140.7 (C-5).

Reaction of 4 with dihydrocinnamalde

Trifluoroacetic acid (0.42 ml, 5.48 mmol) was added to a solution of alcohol **4** (0.361g, 0.55 mmol) and dihydrocinnamaldehyde (0.076 ml, 0.58 mmol) in cyclohexane (20 ml) at rt under a nitrogen atmosphere. The mixture was stirred at rt for 1 h and then quenched with saturated aqueous sodium hydrogen carbonate solution (30 ml). The layers were separated and the aqueous phase was extracted with Et_2O (3x 50 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution (30 ml), water (30 ml) and brine (30 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow oil which was purified by column chromatography on silica gel, eluting with an increasing proportion of EtOAc/petrol from 5-20% to give homoallylic alcohol **5** as a colourless oil (55 mg, 53%); $[\alpha]_D$ +13.6 (*c* 1.7, $CHCl_3$), lit.[10] +15.2 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3379 (OH), 3085, 3062, 3026, 2932, 2857, 1603, 1496, 1454, 969; δ_H (400 MHz, $CDCl_3$) 1.68 (3H, d, *J* 6.6, 7-H_3), 1.76 (2H, dt, *J* 8.3, 7.4, 2-H_2), 2.13 (1H, dtt, *J* 13.9, 7.0, 1.0, 4-*H*H), 2.24-2.32 (1H, m, 4-H*H*), 2.68 (1H, dt, *J* 14.0, 8.3, 1-*H*H), 2.81 (1H, dt, *J* 14.0, 7.4, 1-H*H*), 3.57-3.64 (1H, m, 3-H), 5.45 (1H, dtq, *J* 15.1, 7.1, 1.4, 5-H), 5.60 (1H, dqt, *J* 15.1, 6.8, 1.0, 6-H), 7.16-7.30 (5H, m, 5x Ar-H); δ_C (100 MHz, $CDCl_3$) 18.1 (C-7), 32.2 (C-2), 38.5 (C-1), 40.9 (C-4), 70.3 (C-3), 125.8 (C-Ar), 127.0 (C-5), 128.4 (C-Ar), 128.5 (C-Ar), 129.2 (C-6), 142.3 (C-Ar).

(2*S*, 3*S*, 4*S*, 6*R*)-2-Ethyl-3-methyl-6-(2-phenylethyl)-tetrahydropyran-4-yl trifluoroacetate 8

Trifluoroacetic acid (1.70 ml, 22.05 mmol) was added to a solution of alcohol **5** (120 mg, 0.63 mmol) and propanal (69 µL, 0.95 mmol) in DCM (10 ml) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 4 h and then saturated aqueous sodium hydrogen carbonate solution (40 ml) was added. The layers were separated and the aqueous phase was extracted with DCM (3x 30 ml). The combined organic extracts were washed with brine (30 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil (233 mg) which was purified by column chromatography on silica gel, eluting with 5% EtOAc/*i*-Hexane to give *tetrahydropyran* **8** as a colourless oil (183 mg, 84%)*; $[\alpha]_D^{24}$ +46.7 (*c* 2.4, CH_2Cl_2); ν_{max} (neat)/cm^{-1} {2935 and 2859 (CH)}, 1782 (C=O), 1604, 1496, 1455, 1222, 1167; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.5, 1"-H_3), 1.04 (3H, t, *J* 7.3, 2'-H_3), 1.46 (1H, q, *J* 10.8, 5-H_{ax}), 1.38-1.53 (1H, m, 1'-*H*H), 1.63 (1H, tq, *J* 10.8, 6.5, 3-H), 1.67-1.83

(2H, m, 1'-H*H* and 7-*H*H), 1.90 (1H, dtd, *J* 14.0, 8.4, 4.5, 7-H*H*), 2.04 (1H, ddd, *J* 10.8, 4.9, 1.9, 5-H_{eq}), 2.71 (1H, dt, *J* 13.6, 8.4, 8-*H*H), 2.80 (1H, ddd, *J* 13.6, 8.4, 5.3, 8-H*H*), 2.94 (1H, td, *J* 10.8, 2.7, 2-H), 3.32 (1H, dddd, *J* 10.8, 9.0, 4.5, 1.9, 6-H), 4.74 (1H, td, *J* 10.8, 4.9, 4-H), 7.14-7.31 (5H, m, 5x Ar-H); δ_C (100 MHz, $CDCl_3$) 10.2 (C-2'), 13.1 (C-1'), 26.2, 31.9, 37.4, 37.8, 40.6, 73.7 (C-6), 81.4 (C-4), 81.9 (C-2), 114.0 (q, *J* 284.0, -CF_3), 126.3, 128.8, 128.9, 142.1, 157.6 (q, *J* 41.8, C-ester); δ_F (376 MHz, $CDCl_3$) -75.71; Found (CI): 345.1667 $[MH]^+$ ($C_{18}H_{24}O_3F_3$ requires, 345.1678); *m/z* (CI) 345 ($[MH]^+$, 1), 231 ($[M\text{-}CF_3CO_2]^+$, 11), 173 (100).

* 11 mg (7%) of 2-Ethyl-3-methyl-6-(2'-phenyl-ethyl)-tetrahydropyran-4-ol was also isolated. This was formed by hydrolysis of the labile trifluoroacetate ester upon column chromatography (proven by 2D-TLC).

(-)-Menthone[17]

A solution of (-)-menthol (3.25 g, 20.8 mmol) in dry DCM (60 ml) was added dropwise over 15 min. to the Dess-Martin periodinane (60.0 ml, 28.8 mmol, 15% w/w in DCM) in dry DCM (30 ml) at room temperature under an argon atmosphere. The reaction mixture was stirred for 4 h and was then added to 1M $NaOH_{aq}$ (150 ml). Et_2O (150 ml) was added and the layers were separated. The aqueous phase was extracted with Et_2O (100 ml). The combined organic extracts were washed with water (2x 75 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give (-)-menthone as a colourless oil (3.16 g, 100%) which was used without further purification; $[\alpha]_D$ –25.3 (neat), lit. –25.9 (neat); ν_{max} (neat)/cm^{-1} {2983, 2888 and 2836 (CH)}, 1717 (C=O), 1456, 1367, 1202; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.8, -CH_3), 0.91 (3H, d, *J* 6.6, -CH_3), 1.01 (3H, d, *J* 6.4, 5-CH_3), 1.30-1.42 (2H, m, 3-H_{ax} and 4-H_{ax}), 1.80-1.92 (2H, m, 5-H and 3-H_{eq} or 4-H_{eq}), 1.99 (1H, t, *J* 12.8, 6-H_{ax}), 2.02-2.09 (2H, m, 2-H and 3-H_{eq} or 4-H_{eq}), 2.10-2.19 (1H, m, 1'-H), 2.35 (1H, ddd, *J* 12.8, 3.7, 2.2, 6-H_{eq}); δ_C (100 MHz, $CDCl_3$) 18.7 and 21.2 (2x ^{i}Pr-Me), 22.3 (C-1"), 26.0 (C-1'or C-5), 27.9 (C-3 or C-4), 34.0 (C-3 or C-4), 35.5 (C-1'or C-5), 50.9 (C-6), 56.0 (C-2), 212.4 (C-1).

(+)-(1*R*, 2*S*, 4*R*, 1'*R*)-1-(1-Methylallyl)menthol 9[16]

A solution of crotyl chloride (2.57 g, 28.4 mmol) in dry THF (28 ml) was added dropwise to magnesium turnings (690 mg, 28.4 mmol) in dry THF (58 ml) at room temperature under a nitrogen atmosphere. (Note: the addition of a few crystals of iodine and gentle heating were required to initiate the reaction). When the bubbling had stopped the solution was allowed to cool to room temperature and was then

cooled to 0 ^{o}C. A solution of (-)-menthone (2.58 g, 16.7 mmol) in dry THF (16.7 ml) was added slowly and the mixture was stirred at 0 ^{o}C for 2 h. The reaction was quenched with saturated aqueous ammonium chloride solution (100 ml). Water (50 ml) was added and the biphasic mixture was filtered. The layers were separated and the aqueous phase was extracted with EtOAc (2x 100 ml). The combined organic extracts were washed with brine (100 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow oil (3.63 g), which was purified by column chromatography on silica gel, eluting with 2% EtOAc/petrol to give homoallylic alcohol **9** as a colourless oil (2.37 g, 67%); $[\alpha]_D$ +27.0 (*c* 1.0, $CHCl_3$), lit.[16] +27.4 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3575 (OH), {3077, 2957, 2870 and 2845 (CH)}, 1635, 1458, 1379; δ_H (400 MHz, $CDCl_3$) 0.76-1.01 (2H, m), 0.85 (3H, d, *J* 6.4, 4-CH_3), 0.91 (3H, d, *J* 7.2, 1'-Me), 0.92 (3H, d, *J* 6.8, ^{i}Pr-Me), 0.96 (3H, d, *J* 6.8, ^{i}Pr-Me), 1.22-1.29 (1H, m), 1.35 (1H, ddd, *J* 13.5, 3.7, 2.2), 1.47-1.55 (2H, m), 1.69-1.80 (2H, m), 2.09 (1H, sept.d, *J* 6.8, 1.7, ^{i}Pr-H), 2.59 (1H, quintet, *J* 7.2, 1'-H), 5.09-5.15 (2H, m, 3'-H_2), 5.87 (1H, ddd, *J* 16.6, 10.6, 8.3, 2'-H); δ_C (100 MHz, $CDCl_3$) 15.1, 18.4, 21.0, 23.0, 25.4, 27.9, 30.7, 35.6, 41.9, 45.6, 46.4, 76.6 (C-1), 117.0 (C-3'), 141.2 (C-2').

(-)-(3*S*, 5*E*)-1-Benzyloxyhept-5-en-3-ol 10

p-Toluenesulfonic acid monohydrate (455 mg, 2.39 mmol) was added to a solution of 3-benzyloxypropanal (4.02 g, 24.48 mmol) and alcohol **9** (10.06 g, 47.82 mmol) in dry DCM (250 ml) at room temperature. The mixture was stirred for 22 h and then triethylamine (1 ml) and saturated aqueous sodium hydrogen carbonate solution (250 ml) were added and the mixture was stirred vigorously for 15 min. The layers were separated and the aqueous phase was extracted with DCM (4x 150 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution (200 ml) and brine (200 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil (15.64 g) which was purified by column chromatography on silica gel, eluting with an increasing proportion of EtOAc/petrol from 10-20% to give *homoallylic alcohol* **10** as a colourless oil (5.20 g, 96%); $[\alpha]_D$ –3.5 (*c* 3.4, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3451 (OH), 2914 (CH), 2851 (CH), 1453, 1365, 1102; δ_H (400 MHz, $CDCl_3$) 1.67 (3H, dd, *J* 6.0, 1.1, 7-H_3), 1.71-1.78 (2H, m, 2-H_2), 2.17 (2H, app t, *J* 6.5, 4-H_2), 2.70 (1H, d, *J* 3.1, -OH), 3.64 (1H, ddd, *J* 9.2, 7.5, 5.3, 1-*H*H), 3.71

(1H, dt, *J* 9.2, 5.3, 1-H*H*), 3.77-3.85 (1H, m, 3-H), 4.52 (2H, s, -CH_2Ph), 5.44 (1H, dtd, *J* 15.4, 6.5, 1.1, 5-H), 5.53 (1H, dq, *J* 15.4, 6.0, 6-H), 7.24-7.37 (5H, m, 5x Ar-H); δ_C (100 MHz, $CDCl_3$) 18.4 (C-7), 36.3 (C-2), 41.1 (C-4), 69.3 (C-1), 70.9 (C-3), 73.7 (CH_2Ph), 127.6, 128.0, 128.1, 128.7, 128.8, 138.5 (C-Ar_{ipso}); Found (CI): 221.1537 $[MH]^+$, ($C_{14}H_{21}O_2$ requires, 221.1541); *m/z* (CI) 221 ($[MH]^+$, 7), 203(-H_2O, 6), 143 (-C_6H_6, 8), 129(-C_7H_7, 6), 113(-OBn, 12).

(+)-(2*S*, 3*R*, 4*S*, 6*R*)-6-(2-Benzyloxyethyl)-4-hydroxy-3-methyl-2-ethenyl-tetrahydropyran 11

Trifluoroacetic acid (18.50 ml, 241.5 mmol) was added slowly to a solution of alcohol **10** (1.52 g, 6.9 mmol) and freshly distilled acrolein (1.40 ml, 20.7 mmol) in dry DCM (70 ml) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 3.5 h and then saturated aqueous sodium hydrogen carbonate solution (150 ml) was added and the pH was adjusted to >7 by addition of triethylamine. The layers were separated and the aqueous phase was extracted with DCM (3x 70 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution (100 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil. Potassium carbonate (4.77 g, 34.5 mmol) and methanol (50 ml) were added and the mixture was stirred for 1 h. Volatiles were removed *in vacuo* and then water (150 ml) and DCM (100 ml) were added. The layers were separated and the aqueous phase was extracted with DCM (4x 70 ml). The combined organic extracts were washed with water (70 ml) and brine (70 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil (1.96 g) which was purified by column chromatography on silica gel, eluting with 30% EtOAc/petrol to give *tetrahydropyran* **11** as a colourless oil (1.68 g, 88%); $[\alpha]_D$ +35.1 (*c* 2.2, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3409 (OH), 2920 and 2862 (CH), 1647, 1496, 1454, 1364, 1101, 1051; δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.6, 1”-H), 1.26 (1H, tq, *J* 11.2, 6.6, 3-H), 1.32 (1H, app. q, *J* 11.2, 5-H_{ax}), 1.57 (1H, d, *J* 5.4, -OH), 1.78 (1H, dddd, *J* 14.0, 7.6, 6.1, 4.6, 7-*H*H), 1.88 (1H, ddt, *J* 14.0, 7.8, 5.7, 7-H*H*), 1.97 (1H, ddd, *J* 11.2, 4.6, 1.8, 5-H_{eq}), 3.33-3.43 (2H, m, 2-H and 4-H), 3.57-3.66 (3H, m, 6-H and 8-H_2), 4.50 (2H, s, -CH_2Ph), 5.20 (1H, ddd, *J* 10.5, 1.8, 0.5, 2’-*H*H), 5.25 (1H, ddd, *J* 17.3, 1.8, 1.0, 2’-H*H*), 5.79 (1H, ddd, *J* 17.3, 10.5, 7.3, 1’-H), 7.25-7.36 (5H, m, Ar-H_5); δ_C (100 MHz, $CDCl_3$) 13.0 (C-1”), 36.1 (C-7), 41.0 (C-5), 43.5 (C-3), 66.7 (C-8), 72.3 (C-6), 72.9 (CH_2Ph), 73.6 (C-4), 82.8 (C-2), 117.6 (C-2’), {127.5, 127.6 and 128.3 (C-Ar)},

137.0 (C-1'), 138.5 (C-Ar_{ipso}); Found (EI): 276.1733 $[M]^+$, ($C_{17}H_{24}O_3$ requires, 276.1725); *m/z* (EI) 276 ($[M]^+$, 2).

(+)-(2*S*, 3*R*, 4*S*, 6*R*)-6-(2-Benzyloxyethyl)-4-(*tert*-butyldimethylsilanyloxy)-3-methyl-2-ethenyl-tetrahydropyran 12

Imidazole (116 mg, 1.71 mmol) and DMAP (20 mg, 0.16 mmol) were added to a solution of tetrahydropyran **11** (451 mg, 1.62 mmol) in dry DMF (15 ml) at room temperature under an argon atmosphere. *tert*-Butyldimethylsilyl chloride (260 mg, 1.71 mmol) was added and the mixture was stirred for 7 h. Water (40 ml) and Et_2O (20 ml) were then added. The layers were separated and the aqueous phase was extracted with Et_2O (3x 20 ml). The combined organic extracts were washed with water (20 ml) and brine (20 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless oil which was purified by column chromatography on silica gel, eluting with an increasing proportion of EtOAc/petrol from 3-5% to give *tetrahydropyran* **12** as a colourless oil (634 mg, 100%); $[\alpha]_D$ +44.4 (*c* 1.8, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2929 and 2857 (CH), 1472, 1463, 1362, 1254, 1081; δ_H (400 MHz, $CDCl_3$) 0.05 (3H, s, Si-Me), 0.06 (3H, s, Si-Me), 0.87 (3H, d, *J* 6.6, 1"-H), 0.89 (9H, s, ^{t}Bu), 1.30 (1H, tq, *J* 10.6, 6.6, 3-H), 1.36 (1H, app. q, *J* 10.6, 5-H_{ax}), 1.72-1.89 (3H, m, 5-H_{eq}, 7-H_2), 3.36 (1H, ddd, *J* 10.6, 9.5, 4.6, 4-H), 3.40 (1H, dd, *J* 10.6, 7.4, 2-H), 3.53-3.66 (3H, m, 6-H and 8-H_2), 4.50 (2H, s, -CH_2Ph), 5.18 (1H, ddd, *J* 10.7, 1.9, 0.5, 2'-*H*H), 5.23 (1H, ddd, *J* 17.4, 1.9, 0.8, 2'-H*H*), 5.78 (1H, ddd, *J* 17.4, 10.7, 7.4, 1'-H), 7.24-7.36 (5H, m, Ar-H_5); δ_C (100 MHz, $CDCl_3$) –4.7 (Si-Me), -4.0 (Si-Me), 13.6 (C-1"), 18.0 (C-^{t}Bu), 25.8 (3x Me), 36.2 (C-7), 41.7 (C-5), 43.5 (C-3), 66.8 (C-8), 72.2 (C-6), 73.0 (CH_2Ph), 74.3 (C-4), 82.9 (C-2), 117.3 (C-2'), {127.5, 127.6 and 128.3 (C-Ar)}, 137.4 (C-1'), 138.6 (C-Ar_{ipso}); Found (ESI): 413.2480 $[MNa]^+$, ($C_{23}H_{38}O_3NaSi$ requires, 413.2482); *m/z* (ESI) 413 ($[MNa]^+$, 100).

(+)-(2*S*, 3*S*, 4*S*, 6*R*)-6-(2-Benzyloxyethyl)-4-(*tert*-butyldimethylsilanyloxy)-3-methyl-2-(2-hydroxyethyl)-tetrahydropyran 13

9-BBN (100 ml, 50 mmol, 0.5 M THF) was added to a solution of tetrahydropyran **12** (13.0 g, 33.2 mmol) in dry THF (200 ml) at room temperature under an argon atmosphere. The mixture was stirred for 7 h and then hydrogen peroxide (35 ml, 360 mmol, ~35% w/w) and 3M $NaOH_{aq}$ (65 ml, 195 mmol) were added. The reaction

mixture was stirred for 1 h. The layers were separated and the aqueous phase was extracted with Et_2O (4x 70 ml). The combined organic extracts were washed with water (75 ml) and brine (75 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an opaque oil (19.24 g) which was purified by column chromatography on silica gel, eluting with 20% EtOAc/petrol to give *tetrahydropyran* **13** as a colourless oil (13.4 g, 99%); $[\alpha]_D$ +26.5 (*c* 2.2, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3430 (OH), 2929 and 2857 (CH), 1472, 1253, 1079; δ_H (400 MHz, $CDCl_3$) 0.04 (3H, s, Si-Me), 0.06 (3H, s, Si-Me), 0.88 (3H, d, *J* 6.1, 1"-H), 0.89 (9H, s, ^{t}Bu), 1.29-1.41 (1H, m, 3-H), 1.35 (1H, app. q, *J* 10.9, 5-H_{ax}), 1.62-1.72 (1H, m, 1'-*H*H), 1.73-1.85 (3H, m, 5-H_{eq}, 7-H_2), 1.90 (1H, ddt, *J* 14.7, 6.4, 3.1, 1'-H*H*), 2.98 (1H, dd, *J* 7.1, 3.9, -OH), 3.21 (1H, td, *J* 9.5, 3.1, 2-H), 3.32 (1H, app. td, *J* 10.9, 4.6, 4-H), 3.50-3.61 (3H, m, 6-H and 8-H_2), 3.69-3.82 (2H, m, 2'-H_2), 4.50 (2H, s, -CH_2Ph), 7.26-7.37 (5H, m, Ar-H_5); δ_C (100 MHz, $CDCl_3$) –4.7 (Si-Me), -4.0 (Si-Me), 13.2 (C-1"), 18.0 (C-^{t}Bu), 25.8 (3x Me), 34.7 (C-1'), 36.2 (C-7), 41.7 (C-5), 43.8 (C-3), 61.5 (C-2'), 66.7 (C-8), 72.8 (C-6), 73.1 (CH_2Ph), 73.9 (C-4), 81.9 (C-2), {127.6, 127.7 and 128.34 (C-Ar)}, 138.4 (C-Ar_{ipso}); Found (ESI): 431.2580 $[MNa]^+$, ($C_{23}H_{40}O_4NaSi$ requires, 431.2588); *m/z* (ESI) 431 ($[MNa]^+$, 100).

(+)-(2*S*, 3*S*, 4*S* ,6*R*)-6-(2-Benzyloxyethyl)-4-(*tert*-butyldimethylsilanyloxy)-3-methyl-2-(2-oxoethyl)-tetrahydropyran 14

A solution of tetrahydropyran **13** (10.7 g, 26.3 mmol) in dry DCM (40 ml) was added dropwise over 1 h to the Dess-Martin periodinane (77.0 ml, 36.8 mmol, 15% w/w in DCM) at room temperature under an argon atmosphere. The reaction mixture was stirred for 2 h and was then added to 1M $NaOH_{aq}$ (300 ml). Et_2O (200 ml) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3x 150 ml). The combined organic extracts were washed with water (150 ml) and brine (150 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil (10.8 g) which was purified by column chromatography on silica gel, eluting with an increasing proportion of EtOAc/petrol from 10-12% to give *aldehyde* **14** as a colourless oil (8.6 g, 81%); $[\alpha]_D$ +30.7 (*c* 2.2, $CHCl_3$); ν_{max} (neat)/cm^{-1} {2955, 2929 and 2857 (CH)}, 2725 (aldehydic CH), 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 0.05 (3H, s, Si-Me), 0.06 (3H, s, Si-Me), 0.89 (9H, s, ^{t}Bu), 0.90 (3H, d, *J* 6.8, 1"-H), 1.28-1.39 (1H, m, 3-H), 1.34 (1H, app. q, *J* 14.0, 5-H_{ax}), 1.74 (2H, app. q, *J* 5.4, 7-H_2), 1.83

(1H, ddd, *J* 14.0, 4.9, 1.8, 5-H_{eq},), 2.45 (1H, ddd, *J* 15.8, 9.1, 3.3, 1'-*H*H), 2.59 (1H, ddd, *J* 15.8, 3.4, 1.6, 1'-H*H*), 3.36 (1H, ddd, *J* 14.0, 9.8, 4.9, 4-H), 3.47-3.60 (4H, m, 2-H, 6-H and 8-H_2), 4.45 (1H, d, *J* 12.0, -C*H*HPh), 4.50 (1H, d, *J* 12.0, -CH*H*Ph), 7.26-7.37 (5H, m, Ar-H_5), 9.69 (1H, dd, *J* 3.3, 1.6, 2'-H); δ_C (100 MHz, $CDCl_3$) –4.7 (Si-Me), -4.0 (Si-Me), 13.2 (C-1"), 18.0 (C-^{t}Bu), 25.8 (3x Me), 36.1 (C-7), 41.7 (C-5), 44.0 (C-3), 47.1 (C-1'), 66.4 (C-8), 72.3 (C-2 or C-6), 73.1 (C-4), 73.9 (CH_2Ph), 76.7 (C-2 or C-6), {127.6, 127.7 and 128.4 (C-Ar)}, 138.5 (C-Ar_{ipso}), 202.0 (C-2'); Found (ESI): 429.2418 $[MNa]^+$, ($C_{23}H_{38}O_4NaSi$ requires, 429.2432); *m/z* (ESI) 429 ($[MNa]^+$, 100).

(+)-Methyl (2*S*, 3*S*, 4*S*, 6*R*)-[6-(2-benzyloxy-ethyl)-4-(*tert*-butyldimethyl-silanyloxy)-3-methyl-tetrahydropyran-2-yl]-acetate 16
and
(2*S*, 3*S*, 4*S*, 6*R*)-[6-(2-Benzyloxy-ethyl)-4-(*tert*-butyldimethylsilanyloxy)-3-methyl-tetrahydropyran-2-yl]-acetic acid 15

Pyridinium dichromate (47.8 g, 126.9 mmol) was added to a solution of aldehyde **14** (8.6 g, 21.2 mmol) and dry methanol (5.5 ml, 126.9 mmol) in dry DMF (150 ml) at room temperature under an argon atmosphere. The reaction mixture was stirred for 26 h and then Et_2O (300 ml) was added. The ethereal solution was decanted off and washed with water (200 ml). The aqueous washing was extracted with Et_2O (2x 200 ml) and the combined organic extracts were washed with brine (100 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil (7.6 g) which was purified by column chromatography on silica gel, eluting with an increasing proportion of EtOAc/petrol from 8-50% to give *ester* **16** as a colourless oil (4.26 g, 46%) *acid* **15** as a pale yellow oil (1.24 g, 14%) and recovered aldehyde **14** (2.12 g, 25%); Data for ester **16**: $[\alpha]_D$ +20.6 (*c* 2.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} {2952, 2929, 2889 and 2857 (CH)}, 1744 (C=O), 1437, 1251, 1084; δ_H (400 MHz, $CDCl_3$) 0.04 (3H, s, Si-Me), 0.05 (3H, s, Si-Me), 0.88 (9H, s, ^{t}Bu), 0.90 (3H, d, *J* 6.6, 1"-H), 1.25-1.38 (2H, m, 3-H, 5-H_{ax}), 1.69-1.77 (2H, m, 7-H_2), 1.80 (1H, ddd, *J* 12.7, 4.6, 2.0, 5-H_{eq},), 2.38 (1H, dd, *J* 14.7, 9.6, 1'-*H*H), 2.62 (1H, dd, *J* 14.7, 3.5, 1'-H*H*), 3.35 (1H, ddd, *J* 10.5, 10.0, 4.6, 4-H), 3.46 (1H, td, *J* 9.6, 3.5, 2-H), 3.50-3.57 (3H, m, 6-H and 8-H_2), 3.64 (3H, s, -OMe), 4.45 (1H, d, *J* 11.7, -C*H*HPh), 4.50 (1H, d, *J* 11.7, CH*H*Ph), 7.25-7.37 (5H, m, Ar-H_5); δ_C (100 MHz, $CDCl_3$) –4.6 (Si-Me), -3.9 (Si-Me), 13.3 (C-1"), 18.1 (C-^{t}Bu), 25.9 (3x Me), 36.2 (C-7), 39.4 (C-1'), 41.9 (C-5), 44.1 (C-3),

51.5 (-OMe), 66.9 (C-8), 72.4 (C-6), 73.2 (CH_2Ph), 74.2 (C-4), 78.0 (C-2), {127.5, 127.7 and 128.4 (C-Ar)}, 138.7 (C-Ar_{ipso}), 172.2 (C-2'); Found (ESI): 459.2535 $[MNa]^+$, ($C_{24}H_{40}O_5NaSi$ requires, 459.2537); *m/z* (CI) 437 ($[MH]^+$, 6), 421 ($[- Me]^+$, 8), 405 ($[- OMe]^+$, 4), 305 ($[- OTBS]^+$, 10). Data for acid **15**: δ_H (400 MHz, $CDCl_3$) 0.04 (3H, s, Si-Me), 0.05 (3H, s, Si-Me), 0.88 (9H, s, ^{t}Bu), 0.91 (3H, d, *J* 6.6, 1"-H), 1.22-1.44 (2H, m, 3-H, 5-H_{ax}), 1.71-1.79 (2H, m, 7-H_2), 1.82 (1H, ddd, *J* 12.7, 4.6, 1.7, 5-H_{eq},), 2.45 (1H, dd, *J* 15.4, 9.4, 1'-*H*H), 2.67 (1H, dd, *J* 15.4, 3.1, 1'-H*H*), 3.34 (1H, ddd, *J* 10.6, 9.5, 4.6, 4-H), 3.43 (1H, td, *J* 9.4, 3.1, 2-H), 3.50-3.65 (3H, m, 6-H and 8-H_2), 4.45 (1H, d, *J* 11.8, -C*H*HPh), 4.50 (1H, d, *J* 11.8, -CH*H*Ph), 7.26-7.37 (5H, m, Ar-H_5); δ_C (100 MHz, $CDCl_3$) –4.7 (Si-Me), -4.0 (Si-Me), 13.2 (C-1"), 18.0 (C-^{t}Bu), 25.8 (3x Me), 35.9 (C-7), 38.8 (C-1'), 41.6 (C-5), 43.8 (C-3), 66.7 (C-8), 73.0 (C-6), 73.2 (CH_2Ph), 73.6 (C-4), 77.4 (C-2), {127.6, 127.9 and 128.4 (C-Ar)}, 138.3 (C-Ar_{ipso}), 175.3 (C-2'); Found (ESI): 445.2380 $[MNa]^+$, ($C_{23}H_{38}O_5NaSi$ requires, 445.2380); *m/z* (ESI) 445 ($[MNa]^+$, 100).

(+)-Methyl (2*S*, 3*S*, 4*S*, 6*R*)-[6-(2-benzyloxy-ethyl)-4-(*tert*-butyldimethyl-silanyloxy)-3-methyl-tetrahydropyran-2-yl]-acetate 16

Note: to avoid detonation of diazomethane by static discharge, a diazomethane glassware kit with no ground glass joints was used for this procedure.

A solution of Diazald® (1.00 g, 4.67 mmol) in Et_2O (20 ml) was added dropwise to a solution of KOH (1.00 g, 17.86 mmol) in water (2 ml) and ethanol (8 ml). The mixture was heated to 60 ^oC and the ethereal solution of diazomethane was collected by distillation into a cooled flask (0 ^oC). The diazomethane solution was added slowly to a solution of acid **15** (1.24 g, 2.93 mmol) in Et_2O (25 ml) at 0 ^oC. After stirring for 10 min. excess diazomethane was quenched by addition of AcOH (10 drops). The solution was concentrated *in vacuo* to give *ester* **16** as a pale yellow oil (1.26 g, 99%); Spectral data as above.

(+)-Methyl (2*S*, 3*S*, 4*S*, 6*R*)-[4-(*tert*-butyldimethylsilanyloxy)-6-(2-hydroxy-ethyl)-3-methyl-tetrahydropyran-2-yl]-acetate 17

Pd-C (192 mg, 0.18 mmol, 10% w/w) was added to a solution of **16** (803 mg, 1.84 mmol) in ethanol (25 ml) under a nitrogen atmosphere. A hydrogen filled balloon was attached and the reaction mixture was stirred for 4 h. The mixture was then filtered through a celite® pad and the filtrate was concentrated *in vacuo* to give *alcohol* **17** as a colourless oil (637 mg, 100%); $[\alpha]_D$ +11.7 (*c* 2.3, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3464 (OH), {2953, 2889 and 2856 (CH)}, 1743 (C=O), 1252, 1082; δ_H (400 MHz, $CDCl_3$) 0.05 (3H, s, Si-Me), 0.06 (3H, s, Si-Me), 0.89 (9H, s, ^{t}Bu), 0.91 (3H, d, *J* 6.6, 1"-H), 1.33 (1H, tq, *J* 10.0, 6.6, 3-H), 1.43 (1H, dt, *J* 12.5, 10.9, 5-H_{ax}), 1.62-1.77 (2H, m, 7-H_2), 1.79 (1H, ddd, *J* 12.5, 4.8, 1.8, 5-H_{eq},), 2.41 (1H, dd, *J* 14.9, 10.0, 1'-*H*H), 2.66 (1H, dd, *J* 14.9, 3.0, 1'-H*H*), 3.36 (1H, ddd, *J* 10.9, 10.0, 4.8, 4-H), 3.49 (1H, td, *J* 10.0, 3.0, 2-H), 3.57-3.65 (1H, m, 6-H), 3.69 (3H, s, -OMe), 3.74 (2H, t, *J* 5.4, 8-H_2); δ_C (100 MHz, $CDCl_3$) –4.7 (Si-Me), -4.0 (Si-Me), 13.2 (C-1"), 18.0 (C-^{t}Bu), 25.8 (3x Me), 37.6 (C-7), 38.8 (C-1'), 41.6 (C-5), 43.7 (C-3), 51.8 (-OMe), 61.4 (C-8), 73.6 (C-6), 76.0 (C-4), 78.1 (C-2), 172.3 (C-2'); Found (ESI): 369.2061 $[MNa]^+$, ($C_{17}H_{35}O_5NaSi$ requires, 369.2068); *m/z* (CI) 347 ($[MH]^+$, 35), 331 ($[- Me]^+$, 11), 315 ($[- OMe]^+$, 10), 215 ($[- OTBS]^+$, 90).

(+)-Methyl (2*S*, 3*S*, 4*S*, 6*R*)-[6-(2-benzyloxyethyl)-4-hydroxy-3-methyl-tetrahydropyran-2-yl]-acetate 19

Trifluoroacetic acid (39.5 ml, 532.2 mmol) was added dropwise over 10 min. to a solution of **18** (16.20 g, 53.22 mmol) in dry DCM (160 ml) at 0 ^oC under a nitrogen atmosphere. The mixture was stirred at 0 ^oC for 10 min. and then at room temperature for 1.5 h. Saturated aqueous sodium hydrogen carbonate solution (200 ml) and triethylamine (35.0 ml, 251 mmol) were added and the mixture was stirred for 30 min. The layers were separated and the aqueous phase was extracted with DCM (3x 150 ml). The combined organic extracts were washed with brine (150 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an yellow oil (25.6 g). Potassium carbonate (36.8 g, 266 mmol) and methanol (75 mmol) were added and the mixture was stirred for 1.5 h. Volatiles were removed *in vacuo* and then water (300 ml) and Et_2O (200 ml) were added. The layers were separated and the aqueous phase was extracted with Et_2O (3x 150 ml). The combined organic extracts were washed with water (150 ml) and brine (150 ml), dried over $MgSO_4$, filtered and concentrated *in*

vacuo to give a yellow oil (12.70 g) which was purified by column chromatography on silica gel, eluting with an increasing proportion of EtOAc/petrol from 35-40% to give *tetrahydropyran* **19** as a colourless oil (10.52 g, 62%); $[\alpha]_D$ +10.5 (*c* 2.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3440 (OH), {2949 and 2862 (CH)}, 1740 (C=O), 1496, 1454, 1438; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.6, 1"-H_3), 1.27 (1H, tq, *J* 9.6, 6.6, 3-H), 1.29 (1H, dt, *J* 12.3, 10.5, 5-H_{ax}), 1.68-1.83 (2H, m, 7-H_2), 1.93 (1H, ddd, *J* 12.3, 4.6, 1.6, 5-H_{eq},), 2.40 (1H, dd, *J* 14.7, 9.6, 1'-*H*H), 2.63 (1H, dd, *J* 14.7, 3.4, 1'-H*H*), 3.36 (1H, ddd, *J* 10.5, 9.6, 4.6, 4-H), 3.46 (1H, td, *J* 9.6, 3.4, 2-H), 3.50-3.59 (3H, m, 6-H and 8-H_2), 3.64 (3H, s, -OMe), 4.45 (1H, d, *J* 11.8, -C*H*HPh), 4.50 (1H, d, *J* 11.8, -CH*H*Ph), 7.24-7.37 (5H, m, Ar-H_5); δ_C (100 MHz, $CDCl_3$) 12.7 (C-1"), 36.0 (C-7), 39.0 (C-1'), 41.1 (C-5), 43.8 (C-3), 51.6 (-OMe), 66.7 (C-8), 72.4 (C-6), 73.08 (CH_2Ph), 73.11 (C-4), 77.7 (C-2), {127.5, 127.6 and 128.3 (C-Ar)}, 138.4 (C-Ar_{ipso}), 172.1 (C-2'); Found (CI): 323.1856 $[MH]^+$, ($C_{18}H_{25}O_5$ requires, 323.1858); *m/z* (CI) 323 ($[MH]^+$, 100), 305 (14).

The aqueous phase was acidified to pH 2 and extracted with Et_2O (5x 100 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil which was purified by column chromatography on silica gel, eluting with 75% EtOAc/petrol (+ 0.1% AcOH) to give *acid* **20** as a pale yellow oil (4.58 g, 28%); $[\alpha]_D$ +13.3 (*c* 3.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3391 (OH), {2921 and 2871 (CH)}, 1713 (C=O), 1496, 1454; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 6.6, 1"-H_3), 1.24-1.35 (2H, m, 3-H, 5-H_{ax}), 1.67-1.82 (2H, m, 7-H_2), 1.92 (1H, ddd, *J* 12.4, 4.7, 1.7, 5-H_{eq},), 2.43 (1H, dd, *J* 15.4, 9.4, 1'-*H*H), 2.67 (1H, dd, *J* 15.4, 3.2, 1'-H*H*), 3.34 (1H, ddd, *J* 11.0, 9.9, 4.7, 4-H), 3.42 (1H, td, *J* 9.4, 3.2, 2-H), 3.50-3.62 (3H, m, 6-H and 8-H_2), 4.44 (1H, d, *J* 12.0, -C*H*HPh), 4.48 (1H, d, *J* 12.0, -CH*H*Ph), 7.22-7.35 (5H, m, Ar-H_5); δ_C (100 MHz, $CDCl_3$) 12.7 (C-1"), 35.9 (C-7), 38.7 (C-1'), 40.9 (C-5), 43.5 (C-3), 66.5 (C-8), 72.9 (C-6), 73.0 (C-4), 73.1 (CH_2Ph), 77.4 (C-2), {127.6, 127.8 and 128.4 (C-Ar)}, 138.3 (C-Ar_{ipso}), 175.6 (C-2'); Found (CI): 309.1702 $[MH]^+$, ($C_{17}H_{25}O_5$ requires, 309.1702); *m/z* (CI) 309 ($[MH]^+$, 36), 291 ($[MH^+ - H_2O]$, 32), 273 ($[MH^+ - 2H_2O]$, 7). Acid **20** was methylated with ethereal diazomethane to give ester **19** using the same procedure as described above for the methylation of acid **15**.

(+)-Methyl (2*S*, 3*S*, 4*S*, 6*R*)-[6-(2-benzyloxyethyl)-3-methyl-(4-triisopropyl-silanyloxy)-tetrahydropyran-2-yl]-acetate 21

Triisopropylsilyl trifluoromethanesulfonate (1.23 ml, 4.55 mmol) was added to a solution of **19** (1.00 g, 3.16 mmol) and imidazole (323 mg, 4.74 mmol) in dry DMF (15 ml) at room temperature under an argon atmosphere. The mixture was stirred for 18 h and then water (30 ml) and Et_2O (30 ml) were added. The layers were separated and the aqueous phase was extracted with Et_2O (4x 30 ml). The combined organic extracts were washed with brine (30 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow oil (1.65 g) which was purified by column chromatography on silica gel, eluting with 5% EtOAc/petrol to give *silyl ether* **21** as a colourless oil (1.47 g, 97%); $[\alpha]_D$ +20.5 (*c* 4.1, CH_2Cl_2); ν_{max} (neat)/cm^{-1} {2945, and 2866 (CH)}, 1745 (C=O), 1464, 1091, 883; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.6, 1"-H_3), 1.04-1.08 (3H, m, 3x Si-C*H*), 1.06 (18H, s, 3x SiCH(CH_3)$_2$), 1.32 (1H, tq, *J* 9.7, 6.6, 3-H), 1.35 (1H, dt, *J* 12.5, 11.2, 5-H_{ax}), 1.69-1.80 (2H, m, 7-H_2), 1.91 (1H, ddd, *J* 12.5, 4.6, 1.7, 5-H_{eq},), 2.39 (1H, dd, *J* 14.7, 9.7, 1'-*H*H), 2.63 (1H, dd, *J* 14.7, 3.4, 1'-H*H*), 3.47 (1H, td, *J* 9.7, 3.4, 2-H), 3.49-3.58 (4H, m, 4-H, 6-H and 8-H_2), 3.64 (3H, s, -OMe), 4.45 (1H, d, *J* 12.0, -C*H*HPh), 4.49 (1H, d, *J* 12.0, -CH*H*Ph), 7.26-7.35 (5H, m, Ar-H_5); δ_C (100 MHz, $CDCl_3$) 12.8, 13.3 (C-1"), 17.7, 18.2, 18.3, 36.2 (C-7), 39.3 (C-1'), 42.0 (C-5), 44.5 (C-3), 51.6 (-OMe), 66.8 (C-8), 72.2 (C-6), 73.2 (CH_2Ph), 74.3 (C-4), 77.9 (C-2), {127.5, 127.7 and 128.4 (C-Ar)}, 138.6 (C-Ar_{ipso}), 172.3 (C-2'); Found (CI): 479.3182 $[MH]^+$, ($C_{27}H_{47}O_5Si$ requires, 479.3193); *m/z* (CI) 479 ($[MH]^+$, 36), 447 ($[- Me]^+$, 15), 435 ($[- {}^iPr]^+$, 94), 305 ($[- OTIPS]^+$, 56).

(+)-Methyl (2*S*, 3*S*, 4*S*, 6*R*)-[6-(2-hydroxyethyl)-4-hydroxy-3-methyl-tetrahydropyran-2-yl]-acetate 1

Pd-C (521 mg, 0.49 mmol, 10% w/w) was added to a solution of benzyl ether **21** (1.18 g, 2.46 mmol) in ethanol (40 ml) at room temperature under a nitrogen atmosphere. A hydrogen filled balloon was attached and the reaction mixture was stirred for 15 h. The flask was purged with nitrogen and the mixture was then filtered through a celite® pad. The filtrate was concentrated *in vacuo* to give an opaque oil (1.15 g) which was purified by column chromatography on silica gel, eluting with an increasing proportion of EtOAc/petrol from 15-50% to give alcohol **1** as a colourless oil (947 mg, 99%); $[\alpha]_D$ +15.0 (*c* 1.2, $CHCl_3$), lit.[3] +13.8 (*c* 1.1, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3463, {2945, and 2867 (CH)}, 1743 (C=O), 1464, 883; δ_H (400 MHz,

$CDCl_3$) 0.99 (3H, d, *J* 6.6, 1”-H_3), 1.04-1.08 (3H, m, 3x Si-C*H*), 1.07 (18H, s, 3x SiCH(CH_3)$_2$), 1.35 (1H, tq, *J* 9.9, 6.6, 3-H), 1.45 (1H, dt, *J* 12.3, 11.3, 5-H_{ax}), 1.62-1.80 (2H, m, 7-H_2), 1.89 (1H, ddd, *J* 12.3, 4.6, 1.7, 5-H_{eq},), 2.41 (1H, dd, *J* 14.9, 9.9, 1’-*H*H), 2.67 (1H, dd, *J* 14.9, 3.1, 1’-H*H*), 3.49 (1H, td, *J* 9.9, 3.1, 2-H), 3.52-3.63 (2H, m, 4-H and 6-H), 3.69 (3H, s, -OMe), 3.73 (2H, t, *J* 5.4, 8-H_2); δ_C (100 MHz, $CDCl_3$) 12.8, 13.3 (C-1”), 18.1, 18.2, 18.3, 37.8 (C-7), 38.9 (C-1’), 41.9 (C-5), 44.2 (C-3), 51.8 (-OMe), 61.1 (C-8), 74.0 (C-4), 75.6 (C-6), 78.1 (C-2), 172.3 (C-2’).