A convenient route to enantiomerically pure 2-substituted methyl glycerate derivatives

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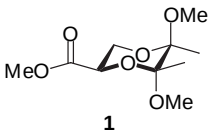


1

Boron trifluoride etherate (10 mL, 81.3 mmol) was added to a stirred solution of D-mannitol (61.9 g, 339.8 mmol), anhydrous trimethyl orthoformate (150 mL, 1.37 mol) and butanedione (63 mL, 717.8 mmol) in MeOH (300 mL) at room temperature, under an atmosphere of argon. After 5h, the reaction mixture was neutralized by the addition of Et_3N (10 mL, 71.74 mmol) and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (1.2 L) and washed with water (600 mL) and brine (300 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was used without further purification. The BDA-diprotected D-mannitol could be purified by recrystallisation from hexane to give a white solid.

Mp 137-138 ºC.

$[\alpha]_D^{27}$ - 222.7 (c = 1.2, $CHCl_3$).

IR: 3452, 2946, 1114 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.07 (2H, ddd, *J* = 11.0 Hz, 6.1 Hz, 3.6 Hz), 3.71 (2H, dd, *J* = 11.3 Hz, 11.3 Hz), 3.64 (2H, dd, *J* = 11.4 Hz, 3.5 Hz), 3.26 (6H, s), 3.25 (6H, s), 2.78 (2H, d, *J* = 6.5 Hz), 1.26 (6H, s), 1.25 (6H, s).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 99.2, 98.0, 69.4, 68.4, 60.9, 48.1, 48.0, 17.8, 17.5.

HRMS (+ESI): *m/z* calcd for $C_{18}H_{34}NaO_{10}$ (MNa^+) 433.2050; found: 433.2040.

Anal. Calcd for $C_{18}H_{34}O_{10}$: C, 52.67; H, 8.35. Found C, 52.57; H, 8.46.

Sodium metaperiodate (95.4 g, 418.5 mmol) was added slowly to a stirred solution of the crude diol in MeOH (350 mL) and water (700 mL) at 0ºC. After stirring overnight at room temperature, sodium hydrogenocarbonate (109.6 g, 1.3 mol) was added, followed by dropwise addition of bromine (26 mL, 507.4 mmol) until a permanent yellow colour remained. Excess bromine was quenched by $Na_2S_2O_3$. The slurry was filtered and the filtrate was extracted with CH_2Cl_2 (2x800 mL). The organic phases were washed with water (400 mL) and brine (400 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by fractional distillation using a Vigreux column (bp 92 ºC/ 0.11 mmHg) to afford **1** as a colourless oil (73.5 g, 314.1 mmol, 46%).

$[\alpha]_D^{25}$ – 158.8 (c = 1.22, $CHCl_3$).

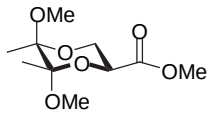
IR: 2953, 1764, 1735 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.53 (1H, dd, *J* = 11.2 Hz, 7.6 Hz), 3.81 (1H, dd, *J* = 11.2 Hz, 11.2 Hz), 3.72-3.68 (4H, m), 3.28 (3H, s), 3.24 (3H, s), 1.35 (3H, s), 1.26 (3H, s).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.1, 99.7, 98.0, 67.1, 59.9, 52.1, 48.3, 48.0, 17.5, 17.4.

HRMS (EI): *m/z* calcd for $C_{10}H_{18}O_6$ (M^+) 234.1103; found: 234.1110.

Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found C, 51.37; H, 7.80.



2

Boron trifluoride-tetrahydrofuran complex (5 mL, 45.3 mmol) was added to a stirred solution of L-ascorbic acid (123.78 g, 702.8 mmol), anhydrous trimethyl orthoformate (160 mL, 1.46 mol) and butanedione (60 mL, 683.7 mmol) in MeOH (300 mL) at room temperature, under an atmosphere of argon. After 5h, the reaction mixture was neutralized by the addition of Et_3N (6.5 mL, 46.63 mmol) and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (1.2 L) and washed with a solution of sodium chloride (400 mL of water and 200 mL of brine). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a white solid (184.4 g). The crude solid was used without further purification.

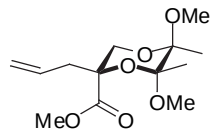
Hydrogen peroxide 35% (100 mL, 1.17 mol) was added slowly (1 h) to a stirred solution of BDA-protected L-ascorbic acid and potassium carbonate (149.3 g, 1.08 mol) in water (550 mL) at ice bath temperature. The mixture was allowed to warm to room temperature and stirred overnight. 10% palladium on activated carbon (500 mg) was added and the mixture was heated to 45 ºC until a negative test to starch iodide paper was obtained (1 h). The reaction mixture was filtered through Celite and the solvent was removed *in vacuo* to give a white powder. Dimethyl sulfate (70 mL, 739.8 mmol) was added to a stirred suspension of the crude potassium carboxylate in acetone (500 mL) at room temperature under an atmosphere of argon. The reaction mixture was stirred at reflux for 2 h and diluted with Et_2O (1.2 L). The organic phase was washed with water (400 mL), saturated aqueous solution of sodium hydrogenocarbonate (400 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a white solid (112.73 g). The crude solid was used without further purification.

Sodium borohydride (24.08 g, 636.5 mmol) was added slowly to a stirred solution of previous crude ester in *iso*propanol (400 mL) at 20 ºC, under an atmosphere of argon. The reaction mixture was heated to 60 ºC for 1 h. Saturated aqueous ammonium chloride (250 mL) and water (500 mL) were slowly added to the solution. The aqueous phase was extracted with CH_2Cl_2 (750 mL, 2x500 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give colourless oil (83.23 g). The crude residue was used without further purification.

Sodium metaperiodate (93.1 g, 408.4 mmol) was added slowly to a stirred solution of the crude diol in MeOH (300 mL) and water (600 mL) at room temperature. After stirring for 2 h, sodium hydrogenocarbonate (112.2 g, 1.33 mol) was added, followed by dropwise addition of bromine (32 mL, 624.5 mmol) until a permanent yellow colour remained. Excess bromine was quenched by $Na_2S_2O_3$. The slurry was filtered and the filtrate was extracted with CH_2Cl_2 (2x800 mL). The organic phases were washed with water (400 mL) and brine (400 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by fractional distillation using a Vigreux column (bp 92 ºC/ 0.11 mmHg) to afford **2** as a colourless oil (60.1 g, 256.8 mmol, 37%).

$[\alpha]_D^{25}$ + 161.5 (c = 1.125, $CHCl_3$).

Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.75. Found C, 51.29; H, 7.76.



3

n-Butyllithium (3.95 mL, 2.5M in hexanes, 9.9 mmol) was added slowly to a stirred solution of diisopropylamine (1.55 mL, 11.1 mmol) in THF (5 mL) at –20 °C to 0 °C. The solution was stirred for an additional 15 min, then added via cannula to a stirred solution of **1** (1.54 g, 6.57 mmol) in THF (35 mL) at –78 °C. After 10 min, allyl iodide (3.0 mL, 32.8 mmol) was added. The reaction mixture was stirred for 30 min, then quenched at –78 °C with saturated NH_4Cl and diluted with Et_2O (50 mL). The organic phase was washed with saturated NH_4Cl (50 mL) and water (50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 9:1) to give **3** as a white solid (1.1 g, 4.01 mmol, 61%).

Mp 68-69 ºC.

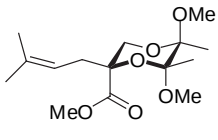
$[\alpha]_D^{26}$ – 124.5 (c = 1.52, $CHCl_3$).

IR: 1735, 1643 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.65-5.53 (1H, m), 5.08-5.04 (2H, m), 4.11 (1H, d, *J* = 11.7 Hz), 3.75 (3H, s), 3.62 (1H, d, *J* = 11.7 Hz), 3.25 (3H, s), 3.22 (3H, s), 2.44 (1H, dd, *J* = 13.7 Hz, 7.7 Hz), 2.37 (1H, dd, *J* = 13.7 Hz, 7.2 Hz), 1.31 (3H, s), 1.27 (3H, s).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 172.9, 130.5, 119.1, 99.7, 98.1, 73.4, 61.8, 51.2, 50.3, 48.1, 42.2, 17.8, 17.7.

HRMS (+ESI): *m/z* calcd for $C_{13}H_{22}NaO_6$ (MNa^+) 297.1314; found: 297.1327.



4

n-Butyllithium (6 mL, 2.5M in hexanes, 15 mmol) was added slowly to a stirred solution of diisopropylamine (2.4 mL, 17.1 mmol) in THF (5 mL) at –20 °C to 0 °C. The solution was stirred for an additional 15 min, then added via cannula to a stirred solution of **1** (2.35 g, 10.05 mmol) in THF (45 mL) at –78 °C. After 20 min, 4-bromo-2-methyl-2-butene (3.5 mL, 30.36 mmol) was added. The reaction mixture was stirred for 30 min, then quenched at –78 °C with saturated NH_4Cl and diluted with Et_2O (50 mL). The organic phase was washed with saturated NH_4Cl (50 mL) and water (50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 4:1) to give **4** as a colourless oil (2.09 g, 6.93 mmol, 69%).

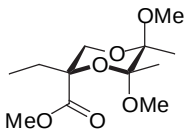
$[\alpha]_D^{25}$ – 95.7 (c = 0.625, $CHCl_3$).

IR: 1741 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.85 (1H, t, *J* = 11.7 Hz), 4.09 (1H, d, *J* = 11.6 Hz), 3.70 (3H, s), 3.55 (1H, d, *J* = 11.6 Hz), 3.22 (3H, s), 3.18 (3H, s), 2.44 (1H, dd, *J* = 11.6 Hz, 8.0 Hz), 2.26 (1H, dd, *J* = 11.6 Hz, 7.2 Hz), 1.63 (3H, s), 1.54 (3H, s), 1.28 (3H, s), 1.23 (3H, s).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 173.0, 135.8, 115.6, 99.6, 98.0, 73.9, 62.0, 51.7, 50.2, 47.9, 36.6, 25.8, 17.74, 17.73, 17.67.

HRMS (+ESI): *m/z* calcd for $C_{15}H_{26}NaO_6$ (MNa^+) 325.1627; found: 325.1636.



6

n-Butyllithium (1.6 mL, 2.5M in hexanes, 4 mmol) was added slowly to a stirred solution of diisopropylamine (670 μL, 4.8 mmol) in THF (3 mL) at –20 °C to 0 °C. The solution was stirred for an additional 15 min, then added via cannula to a stirred solution of **1** (479 mg, 2.05 mmol) in THF (10 mL) at –78 °C. After 10 min, ethyl iodide (820 μL, 10.25 mmol) in HMPA (1 mL) was added. The reaction mixture was stirred for 30 min, then quenched at –78 °C with saturated NH_4Cl and diluted with Et_2O (20 mL). The organic phase was washed with saturated NH_4Cl (20 mL) and water (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 4:1) to give **6** as a colourless oil (320 mg, 1.22 mmol, 60%).

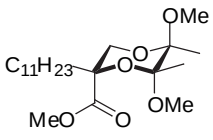
$[\alpha]_D^{25}$ – 90.9 (c = 1.25, $CHCl_3$).

IR: 1739 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.12 (1H, d, *J* = 11.5 Hz), 3.72 (3H, s), 3.53 (1H, d, *J* = 11.5 Hz), 3.20 (3H, s), 3.17 (3H, s), 1.73-1.53 (2H, m), 1.25 (3H, s), 1.22 (3H, s), 0.73 (3H, t, *J* = 7.7 Hz).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 173.2, 99.4, 98.0, 74.0, 61.8, 51.7, 50.2, 47.9, 30.5, 17.7, 17.6, 7.1.

HRMS (+ESI): *m/z* calcd for $C_{12}H_{22}NaO_6$ (MNa^+) 285.1314; found: 285.1319.



7

n-Butyllithium (5 mL, 2.5M in hexanes, 12.5 mmol) was added slowly to a stirred solution of diisopropylamine (2.1 mL, 15 mmol) in THF (5 mL) at –20 °C to 0 °C. The solution was stirred for an additional 15 min, then added via cannula to a stirred solution of **1** (2.08 g, 8.89 mmol) in THF (35 mL) at –78 °C. After 30 min, 1-iodoundecane (6.2 mL, 26.8 mmol) in HMPA (4 mL) was added. The reaction mixture was stirred for 1 h, then quenched at –78 °C with saturated NH_4Cl and diluted with Et_2O (50 mL). The organic phase was washed with saturated NH_4Cl (50 mL) and water (50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 9:1) to give **7** as a colourless oil (1.90 g, 4.9 mmol, 55%).

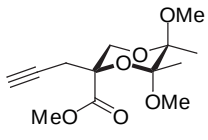
$[\alpha]_D^{25}$ – 210.5 (c = 0.92, $CHCl_3$).

IR: 2923, 1742 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.12 (1H, d, *J* = 11.5 Hz), 3.72 (3H, s), 3.55 (1H, d, *J* = 11.5 Hz), 3.21 (3H, s), 3.18 (3H, s), 1.69-1.49 (2H, m), 1.27-1.10 (24H, m), 0.85-0.81 (3H, m).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 173.0, 99.1, 97.8, 73.5, 61.9, 51.4, 49.9, 47.6, 37.4, 31.6, 29.5, 29.2 (2C), 29.1, 29.0, 28.9, 22.31, 22.27, 17.43, 17.41, 13.7.

HRMS (+ESI): *m/z* calcd for $C_{21}H_{40}NaO_6$ (MNa^+) 411.2723; found: 411.2739.



8

n-Butyllithium (1.2 mL, 2.5M in hexanes, 3 mmol) was added slowly to a stirred solution of diisopropylamine (480 μL, 3.42 mmol) in THF (3 mL) at –20 °C to 0 °C. The solution was stirred for an additional 15 min, then added via cannula to a stirred solution of **1** (470 mg, 2.01 mmol) in THF (10 mL) at –78 °C. After 10 min, propargyl bromide (900 μL, 10.1 mmol) in HMPA

(1 mL) was added. The reaction mixture was stirred for 1 h, then quenched at –78 °C with saturated NH_4Cl and diluted with Et_2O (30 mL). The organic phase was washed with saturated NH_4Cl (30 mL) and water (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 9:1) to give **8** as a white solid (308 mg, 1.13 mmol, 56%). **8** could be recrystallised from hexane.

Mp 102 ºC.

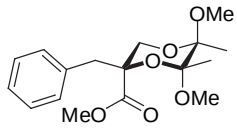
$[\alpha]_D^{25}$ – 159.9 (c = 0.885, $CHCl_3$).

IR: 3263, 1742 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.29 (1H, d, *J* = 11.7 Hz), 3.75 (3H, s), 3.64 (1H, d, *J* = 11.7 Hz), 3.22 (3H, s), 3.16 (3H, s), 2.62 (1H, dd, *J* = 16.5 Hz, 2.8 Hz), 2.41 (1H, dd, *J* = 16.5 Hz, 2.7 Hz), 2.00 (1H, t, *J* = 2.7 Hz), 1.25 (3H, s), 1.23 (3H, s).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.8, 99.8, 98.0, 76.5, 72.6, 72.1, 61.7, 52.0, 50.1, 48.0, 27.6, 17.6, 17.5.

HRMS (+ESI): *m/z* calcd for $C_{13}H_{20}NaO_6$ (MNa^+) 295.1158; found: 295.1159.



9

n-Butyllithium (1.2 mL, 2.5M in hexanes, 3 mmol) was added slowly to a stirred solution of diisopropylamine (480 µL, 3.42 mmol) in THF (3 mL) at –20 °C to 0 °C. The solution was stirred for an additional 15 min, then added via cannula to a stirred solution of **1** (461 mg, 1.97 mmol) in THF (10 mL) at –78 °C. After 10 min, benzyl bromide (1.2 mL, 10.08 mmol) in HMPA (1 mL) was added. The reaction mixture was stirred for 1 h, then quenched at –78 °C with saturated NH_4Cl and diluted with Et_2O (30 mL). The organic phase was washed with saturated NH_4Cl (30 mL) and water (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 9:1) to give **9** as a colourless oil (433 mg, 1.34 mmol, 68%).

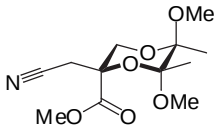
$[\alpha]_D^{25}$ – 118.8 (c = 0.835, $CHCl_3$).

IR: 1739 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22-7.04 (5H, m), 3.95 (1H, d, *J* = 11.6 Hz), 3.69 (1H, d, *J* = 11.6 Hz), 3.61 (3H, s), 3.20 (3H, s), 3.19 (3H, s), 3.00 (1H, d, *J* = 13.3 Hz), 2.91 (1H, d, *J* = 13.3 Hz), 1.32 (3H, s), 1.23 (3H, s).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 172.4, 134.0, 129.7 (2C), 128.0 (2C), 126.9, 99.7, 97.9, 74.2, 61.8, 51.5, 50.1, 47.8, 43.9, 17.64, 17.60.

HRMS (+ESI): *m/z* calcd for $C_{17}H_{24}NaO_6$ (MNa^+) 347.1471; found: 347.1487.



10

n-Butyllithium (1.9 mL, 1.6M in hexanes, 3.04 mmol) was added slowly to a stirred solution of diisopropylamine (480 µL, 3.42 mmol) in THF (3 mL) at –20 °C to 0 °C. The solution was stirred for an additional 15 min, then added via cannula to a stirred solution of **1** (474 mg, 2.02 mmol) in THF (10 mL) at –78 °C. After 10 min, bromoacetonitrile (700 µL, 10.05 mmol) in HMPA (1 mL) was added. The reaction mixture was stirred for 1 h, then quenched at –78 °C with saturated NH_4Cl and diluted with Et_2O (30 mL). The organic phase was

washed with saturated NH_4Cl (30 mL) and water (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 4:1) to give **10** as a colourless oil (308 mg, 1.13 mmol, 56%).

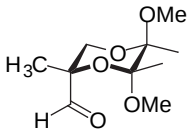
$[\alpha]_D^{25}$ – 111.9 (c = 0.78, $CHCl_3$).

IR: 1741 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.25 (1H, d, *J* = 11.5 Hz), 3.82 (3H, s), 3.77 (1H, d, *J* = 11.5 Hz), 3.27 (3H, s), 3.20 (3H, s), 2.66 (2H, s), 1.31 (3H, s), 1.27 (3H, s).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.9, 114.5, 100.4, 98.1, 70.9, 60.9, 52.8, 50.4, 48.2, 26.0, 17.6, 17.5.

HRMS (+ESI): *m/z* calcd for $C_{12}H_{19}NNaO_6$ (MNa^+) 296.1110; found: 296.1107.



11

Lithium aluminium hydride (52.7 mL, 1M in THF, 52.7 mmol) was added slowly to a stirred solution of **5** (18.43 g, 74.3 mmol) in THF (300 mL) at 0 °C under argon. The mixture was stirred overnight at room temperature. Excess hydride was quenched by successive addition of water (2 mL), 15% aqueous NaOH (2 mL) and water (6 mL). The resulting suspension was filtered through Celite, rinsed with Et_2O, and the solvents were removed in vacuo. The crude residue was used without further purification.

DMSO (10.7 mL, 150.8 mmol) was added dropwise to a stirred solution pf oxalyl chloride (6.3 mL, 72.2 mmol) in CH_2Cl_2 (220 mL) at - 50 °C to -60 °C, under argon. After 2 min, a solution of the crude alcohol (14.39 g) in CH_2Cl_2 (20 mL) was added. After stirring for 15 min, Et_3N (29 mL, 208 mmol) was added. The mixture was stirred for 5 min and then allowed to warm to room temperature. Water (250 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (250 mL). The organic layers were combined, washed with brine (500 mL), 1N HCl solution (500 mL), water (250 mL), saturated $NaHCO_3$ (500 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 9:1) to give **11** as a white solid (9.76 g, 44.8 mmol, 60%). **11** could be recrystallised from hexane.

Mp 63-64 ºC.

$[\alpha]_D^{25}$ – 150.7 (c = 1.265, $CHCl_3$).

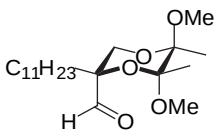
IR: 1725 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.46 (1H, d, *J* = 1.9 Hz), 4.02 (1H, d, *J* = 11.4 Hz), 3.54 (1H, dd, *J* = 11.4 Hz, 1.9 Hz), 3.36 (3H, s), 3.26 (3H, s), 1.35 (3H, s), 1.24 (3H, s), 1.04 (3H, s).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 201.3, 99.8, 97.9, 75.5, 60.9, 50.2, 48.1, 18.5, 17.8, 17.6.

HRMS (+ESI): *m/z* calcd for $C_{10}H_{18}NaO_5$ (MNa^+) 241.1052; found: 241.1043.

Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found C, 54.96; H, 8.33.



12

Lithium aluminium hydride (13.17 mL, 1M in THF, 13.17 mmol) was added slowly to a stirred solution of **7** (6.17 g, 15.9 mmol) in THF (100 mL) at 0 °C under argon. The mixture was stirred overnight at room temperature. Excess hydride was quenched by successive addition of water (0.5 mL), 15% aqueous NaOH (0.5 mL) and water (1.5 mL). The resulting suspension was filtered through Celite, rinsed with Et_2O, and the solvents

were removed in vacuo. The crude residue was used without further purification.

DMSO (2.4 mL, 33.8 mmol) was added dropwise to a stirred solution pf oxalyl chloride (1.4 mL, 16.07 mmol) in CH_2Cl_2 (100 mL) at - 50 °C to -60 °C, under argon. After 2 min, a solution of the crude alcohol (5.26 g) in CH_2Cl_2 (10 mL) was added. After stirring for 15 min, Et_3N (6.5 mL, 46.6 mmol) was added. The mixture was stirred for 5 min and then allowed to warm to room temperature. Water (100 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The organic layers were combined, washed with brine (200 mL), 1N HCl solution (200 mL), water (100 mL), saturated $NaHCO_3$ (200 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 9:1) to give **11** as a pale yellow solid (solidifies on refrigeration, 4.07 g, 11.37 mmol, 71%).

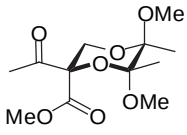
$[\alpha]_D^{26}$ – 73.8 (c = 2.25, $CHCl_3$).

IR: 1725 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.43 (1H, d, *J* = 1.7 Hz), 4.00 (1H, d, *J* = 11.3 Hz), 3.50 (1H, dd, *J* = 11.3 Hz, 1.7 Hz), 3.33 (3H, s), 3.23 (3H, s), 1.50-1.00 (26H, m), 0.85 (3H, t, *J* = 6.8 Hz).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 202.2, 99.5, 98.0, 77.4, 60.0, 50.1, 48.0, 33.5, 31.8, 29.9, 29.48, 29.47, 29.38, 29.22, 29.15, 22.6, 21.6, 17.7, 17.6, 14.0.

HRMS (+ESI): *m/z* calcd for $C_{20}H_{38}NaO_5$ (MNa^+) 381.2617; found: 381.2618.



13

n-Butyllithium (2.7 mL, 2.65M in heptane, 7.2 mmol) was added slowly to a stirred solution of diisopropylamine (1.15 mL, 8.2 mmol) in THF (4 mL) at –20 °C to 0 °C. The solution was stirred for an additional 15 min, then added via cannula to a stirred solution of **1** (1.12 g, 4.78 mmol) in THF (36 mL) at –78 °C. After 10 min, acetyl chloride (1.7 mL, 32.8 mmol) was added. The reaction mixture was stirred for 1 h, then quenched at –78 °C with saturated NH_4Cl and diluted with Et_2O (40 mL). The organic phase was washed with saturated NH_4Cl (40 mL) and water (40 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 4:1) to give **13** as a white solid (754 mg, 2.73 mmol, 57%). **13** could be recrystallised from hexane.

n-Butyllithium (3.8 mL, 2.65M in heptane, 10.07 mmol) was added slowly to a stirred solution of diisopropylamine (1.6 mL, 11.4 mmol) in THF (4 mL) at –20 °C to 0 °C. The solution was stirred for an additional 15 min, then added via cannula to a stirred solution of **1** (1.58 g, 6.75 mmol) in THF (36 mL) at –78 °C. After 10 min, acetic anhydride (3.2 mL, 33.8 mmol) was added. The reaction mixture was stirred for 1 h, then quenched at –78 °C with saturated NH_4Cl and diluted with Et_2O (40 mL). The organic phase was washed with saturated NH_4Cl (40 mL) and water (40 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 4:1) to give **13** as a white solid (1.19 mg, 4.31 mmol, 64%).

Mp 81-83 ºC.

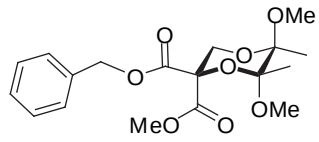
$[\alpha]_D^{25}$ – 90.5 (c = 1.12, $CHCl_3$).

IR: 1750, 1716 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.20 (1H, d, *J* = 11.6 Hz), 3.76 (3H, s), 3.75 (1H, d, *J* = 11.6 Hz), 3.27 (3H, s), 3.20 (3H, s), 2.31 (3H, s), 1.38 (3H, s), 1.27 (3H, s).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 204.7, 168.7, 100.2, 98.2, 80.6, 58.7, 52.7, 50.1, 48.0, 25.3, 17.8 (2C).

HRMS (+ESI): *m/z* calcd for $C_{12}H_{20}NaO_7$ (MNa^+) 299.1107; found: 299.1116.



14

n-Butyllithium (2.9 mL, 2.5M in hexanes, 7.25 mmol) was added slowly to a stirred solution of diisopropylamine (1.1 mL, 7.85 mmol) in THF (4 mL) at –20 °C to 0 °C. The solution was stirred for an additional 15 min, then added via cannula to a stirred solution of **1** (1.12 g, 4.78 mmol) in THF (36 mL) at –78 °C. After 10 min, benzyl chloroformate (3.4 mL, 23.8 mmol) was added. The reaction mixture was stirred for 1 h, then quenched at –78 °C with saturated NH_4Cl and diluted with Et_2O (30 mL). The organic phase was washed with saturated NH_4Cl (30 mL) and water (30 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 9:1) to give **14** as a pale yellow oil (1.08 g, 2.94 mmol, 62%).

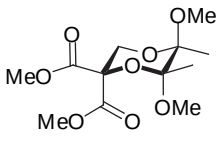
$[\alpha]_D^{25}$ – 55.0 (c = 1.12, $CHCl_3$).

IR: 1749 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35-7.20 (5H, m), 5.22 (1H, d, *J* = 12.3 Hz), 5.07 (1H, d, *J* = 12.3 Hz), 4.28 (1H, d, *J* = 11.4 Hz), 3.80 (1H, d, *J* = 11.4 Hz), 3.67 (3H, s), 3.23 (3H, s), 3.17 (3H, s), 1.38 (3H, s), 1.24 (3H, s).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 168.2, 166.0, 134.9, 128.4 (2C), 128.3, 127.9 (2C), 100.3, 98.1, 75.9, 67.3, 59.3, 52.5, 50.1, 48.0, 17.6, 17.5.

HRMS (+ESI): *m/z* calcd for $C_{18}H_{24}NaO_8$ (MNa^+) 391.1369; found: 391.1365.



15

n-Butyllithium (4.8 mL, 2.5M in hexanes, 12 mmol) was added slowly to a stirred solution of diisopropylamine (1.9 mL, 13.6 mmol) in THF (4 mL) at –20 °C to 0 °C. The solution was stirred for an additional 15 min, then added via cannula to a stirred solution of **1** (1.87 g, 8.0 mmol) in THF (36 mL) at –78 °C. After 10 min, methyl chloroformate (3.1 mL, 40 mmol) was added. The reaction mixture was stirred for 1 h, then quenched at –78 °C with saturated NH_4Cl and diluted with Et_2O (40 mL). The organic phase was washed with saturated NH_4Cl (40 mL) and water (40 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 1:1) to give **15** as a white solid (1.31 g, 4.48 mmol, 56%).

Mp 111-113 ºC.

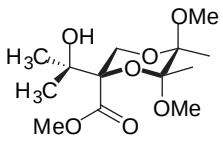
$[\alpha]_D^{25}$ – 61.3 (c = 1.015, $CHCl_3$).

IR: 1743, 1723 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.32 (1H, d, *J* = 11.5 Hz), 3.85 (1H, d, *J* = 11.5 Hz), 3.82 (3H, s), 3.77 (3H, s), 3.28 (3H, s), 3.25 (3H, s), 1.42 (3H, s), 1.29 (3H, s).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 168.6, 167.2, 100.4, 98.2, 76.0, 59.5, 53.2, 52.8, 50.4, 48.2, 17.8, 17.7.

HRMS (+ESI): *m/z* calcd for $C_{12}H_{20}NaO_8$ (MNa^+) 315.1056; found: 315.1058.



16

n-Butyllithium (1.9 mL, 1.6M in hexanes, 3.04 mmol) was added slowly to a stirred solution of diisopropylamine (480 µL, 3.42 mmol) in THF (3 mL) at –20 °C to 0 °C. The solution was stirred for an additional 15 min, then added via cannula to a stirred solution of **1** (477 mg, 2.04 mmol) in THF (10 mL) at –78 °C. After 10 min, acetone (750 µL, 10.09 mmol) was added. The reaction mixture was stirred for 1 h, then quenched at –78 °C with saturated NH_4Cl and diluted with Et_2O (30 mL). The organic phase was washed with saturated NH_4Cl (30 mL) and water (30 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (hexane-EtOAc 4:1) to give **16** as a colourless oil (397 mg, 1.36 mmol, 67%).

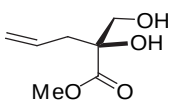
$[\alpha]_D^{25}$ – 124.0 (c = 0.905, $CHCl_3$).

IR: 3500, 1731 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.23 (1H, d, *J* = 11.6 Hz), 4.02 (1H, d, *J* = 11.6 Hz), 3.75 (3H, s), 3.233 (3H, s), 3.227 (3H, s), 2.96 (1H, s), 1.31 (3H, s), 1.24 (3H, s), 1.17 (3H, s), 1.09 (3H, s).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 172.0, 99.4, 97.7, 77.9, 73.2, 59.0, 52.0, 50.5, 48.1, 25.2, 23.1, 17.7, 17.6.

HRMS (+ESI): *m/z* calcd for $C_{13}H_{24}NaO_7$ (MNa^+) 315.1420; found: 315.1413.



17

p-Toluenesulfonic acid monohydrate (178 mg, 0.93 mmol) was added to a stirred solution of **3** (128 mg, 0.46 mmol) in MeOH (10 mL) under argon. The reaction mixture was refluxed for 2 h, neutralized with Et_3N (130 µL, 0.93 mmol) and the solvent was removed under vacuo. The residue was purified by flash chromatography (CH_2Cl_2-acetone 9:1) to give **17** as a colourless oil (70 mg, 0.43 mmol, 94%).

$[\alpha]_D^{25}$ – 30.4 (c = 0.705, CH_3OH).

IR: 3451, 1732, 1642 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 5.76-5.65 (1H, m), 5.02-4.93 (2H, m), 3.64 (1H, d, *J* = 11.2 Hz), 3.64 (3H, s), 3.63 (1H, d, *J* = 11.2 Hz), 2.34 (1H, dd, *J* = 14.0 Hz, 7.6 Hz), 2.25 (1H, dd, *J* = 14.0 Hz, 6.8 Hz).

^{13}C NMR (400 MHz, CD_3OD): δ = 176.3, 133.9, 119.3, 80.4, 68.9, 53.2, 41.4

HRMS (+ESI): *m/z* calcd for $C_7H_{12}NaO_4$ (MNa^+) 183.0633; found: 183.0630.