Supporting Information

for

Efficient, Diastereoselective Chemical Synthesis of a b-Mannopyranosyl Phosphoisoprenoid

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General Procedures. ^{1}H and ^{13}C NMR spectra were run at 500 and 125 MHz, respectively, unless otherwise stated. All solvents were dried and distilled by standard procedures. All reactions were run under a dry argon atmosphere. Triflic anhydride was distilled from phosphorus pentoxide.

General mannosylation protocol: To a stirred solution of sulfoxide (**5**)[1] (111.4 mg, 0.2 mmol) and DTBMP (41 mg, 0.2 mmol) in the chosen solvent (8.0 mL) at -78 °C was added Tf_2O (37.0 µL, 0.22 mmol) and, 5 min later, the solution of the selected tetrabutylammoniumphosphate (0.6 mmol) in the same solvent (2.0 mL) dropwise. The reaction mixture was then stirred at -78 °C for 6 h and then quenched at that temperature with saturated aqueous $NaHCO_3$, washed with brine, dried and concentrated. The products were then separated by chromatography over silica gel.

Dibutylphosphoryl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-a-D-mannopyranoside (7). $[\alpha]_D$ = +24.1° (c = 1.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ: 0.80-0.98 (m, 12H), 1.35-1.47 (m, 4H), 1.60-1.75 (m, 4H), 3.89-4.09 (m, 7H), 4.25 (dd, *J* = 4.6, 10.0 Hz, 1H), 4.31 (t, *J* = 9.6 Hz, 1H), 4.68 (d, *J* = 12.7 Hz, 1H), 4.77 (d, *J* = 12.1 Hz, 1H), 4.85 (d, *J* = 12.1 Hz, 1H), 4.87 (d, *J* = 12.7 Hz, 1H), 5.67 (s, 1H), 5.69 (dd, *J* = 1.7, 7.0 Hz, 1H), 7.30-7.56 (m, 15H); ^{13}C NMR ($CDCl_3$), δ: 14.0, 19.1, 32.5, 32.6, 32.7, 66.2, 68.2, 68.28, 68.33, 68.9, 73.6, 74.2, 75.6, 76.6, 78.9, 97.1 (d, *J* = 7.1 Hz), 102.0, 126.48, 126.50, 127.96, 127.99, 128.1, 128.4, 128.55, 128.60, 128.65, 128.72, 128.76, 128.81, 128.9, 129.4, 137.8, 138.8. HRMS(FAB): Calcd. for $C_{35}H_{45}O_9P$: 641.2880 (MH^+), Found: 641.3051.

Dibutylphosphoryl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-b-D-mannopyranoside (8). $[\alpha]_D$ = -10.4° (c = 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ: 0.93-0.99 (m, 6H), 1.38-1.48 (m, 4H), 1.65-1.76 (m, 4H), 3.47 (dt, *J* =

4.8, 9.9 Hz, 1H), 3.70 (dd, *J* = 3.0, 9.9 Hz, 1H), 3.94 (t, *J* = 10.2 Hz, 1H), 4.02-4.16 (m, 4H), 4.17-4.22 (m, 1H), 4.25 (t, *J* = 9.6 Hz, 1H), 4.33 (dd, *J* = 4.8, 10.3 Hz, 1H), 4.66 (d, *J* = 12.3 Hz, 1H), 4.78 (d, *J* = 12.3 Hz, 1H), 4.91 (d, *J* = 12.1 Hz, 1H), 4.94 (d, *J* = 12.1 Hz, 1H), 5.31 (d, *J* = 7.7 Hz, 1H), 5.64 (s, 1H), 7.28-7.52 (m, 15H); ^{13}C NMR ($CDCl_3$), δ: 13.96, 14.00, 18.98, 19.04, 19.05, 32.49, 32.55, 32.62, 68.3, 68.4, 68.5, 68.6, 68.7, 69.2, 73.2, 75.7, 77.0, 77.1, 78.1, 78.5, 97.4 (d, *J* = 4.0 Hz), 102.0, 126.5, 128.05, 128.14, 128.2, 128.6, 128.7, 128.8, 129.4, 137.7, 138.46, 138.49. HRMS(FAB): Calcd. for $C_{35}H_{45}O_9P$: 641.2880 (MH^+), Found: 641.2978.

Benzyl 2-Cyanoethyl *N,N*-Diisopropylphosphoramidite (10). To a stirred solution of benzyl alcohol (1.03 mL, 10.0 mmol) was added Hunig's base (3.49 mL, 20.0 mmol) followed by 2-cyanoethyl *N,N*-diisopropylchlorophosphoramidite (2.23 mL, 10.0 mmol) after five minutes. The reaction mixture was stirred for 1h at room temperature, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography over silica gel with triethylamine/ethyl acetate/hexane 1/33/66 as the eluent to give the title compound (**10**) (2.90 g, 94%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.20 (t, *J* = 6.5 Hz, 12H), 2.62 (t, *J* = 6.3 Hz, 2H), 3.66 (m, 2H), 3.85 (m, 2H), 4.71 (m, 2H), 7.23-7.38 (m, 5H).

3,7,11,15-Tetramethylhexadecan-1-ol (9). $PtO_2 \cdot H_2O$ (100 mg) and $NaHCO_3$ (2.00g) were added to a solution of phytol, an undetermined mixture of stereoisomers, (2.00g, 6.7 mmol) in THF (25.0 mL) and the reaction mixture was stirred under one atmosphere of H_2 for 20h and then filtered through a Celite pad. The Celite was washed with THF and the filtrate concentrated. The saturated alcohol (**9**)[2] was obtained quantitatively (2.01g) after flash chromatography over silica gel using hexane as eluent. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.85-0.93 (m, 15H), 1.00-1.68 (m, 24H), 3.65-3.73 (m, 2H).

Benzyl 2-Cyanoethyl 3,7,11,15-Tetramethylhexadecylphosphate (12). To a stirred solution of phosphoramidite (**10**) (370 mg, 1.2 mmol) and alcohol (**9**) (299 mg, 1.0 mmol) in acetonitrile (5.0 mL) was added tetrazole (210 mg, 3.0 mmol). The reaction mixture was stirred for 1.5h and then *tert*-butyl hydroperoxide (1.0 mL of 5-6 M solution in decane) was added dropwise. The reaction mixture was stirred for another 1h, concentrated and placed directly on a silica gel column. Elution with ethyl acetate/hexane 1/2 gave the title phosphate (**12**) as an oil (498 mg, 96%). No attempt was made to separate this mixture of diastereomers, which was used as such in the next step. ^{1}H NMR ($CDCl_3$), δ: 0.85-0.95 (m, 15H), 1.03-

1.42 (m, 20H), 1.43-1.50 (m, 1H), 1.52-1.59 (m, 2H), 1.68-1.77 (m, 1H), 2.69 (dt, *J* = 4.0, 6.5 Hz, 2H), 4.06-4.22 (m, 4H), 5.13 (d, *J* = 9.0 Hz, 2H), 7.35-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$), δ: 19.66, 19.7, 19.95, 20.0, 20.1, 20.2, 21.5, 23.0, 23.1, 24.7, 24.9, 25.2, 28.4, 29.7, 30.3, 33.2, 37.46-37.90, 39.8, 62.0 (d, *J* = 4.9 Hz), 67.4 (d, *J* = 6.0 Hz), 70.1 (d, *J* = 5.5 Hz), 116.8, 128.5, 129.2, 136.0 (d, *J* = 6.1 Hz).

TetrabutylammoniumBenzyl 3,7,11,15-Tetramethylhexadecylphosphate (13). To a stirred solution of the phosphate (**12**) (261 mg, 0.5 mmol) in dichloromethane (2.0 mL) was added tetrabutylammonium hydroxide (490 mg of 40% solution in water, 0.75 mmol) in water (2.0 mL). The reaction mixture was stirred vigorously for 1h after which TLC (ethyl acetate/hexane 1/2) indicated complete conversion. The organic phase was separated and the aqueous phase was washed with dichloromethane. The combined organic extracts were dried (Na_2SO_4) and concentrated to give the title salt (**13**) quantitatively as an oil (356 mg). ^{1}H NMR ($CDCl_3$), δ: 0.78-0.87 (m, 15H), 0.92-0.98 (m, 12H), 0.98-1.43 (m, 28H), 1.47-1.54 (m, 2H), 1.56-1.63 (m, 10H), 3.26-3.33 (m, 8H), 3.79-3.90 (m, 2H), 4.92 (d, *J* = 6.0 Hz, 2H), 7.12-7.20 (m, 1H), 7.22-7.28 (m, 2H), 7.39-7.42 (m, 2H); ^{13}C NMR ($CDCl_3$), δ: 13.9-14.1, 19.9-20.1, 23.0, 23.3, 24.8, 24.85, 24.87, 25.2, 28.3, 30.1, 33.2, 37.6-38.0, 38.5-38.6, 39.7, 59.1, 63.7 (d, *J* = 5.5 Hz), 66.9 (d, *J* = 5.0 Hz), 127.1, 127.7, 128.2, 140.7 (d, *J* = 7.9 Hz).

Benzyl 3,7,11,15-Tetramethylhexadecylphosphoryl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-a -D-mannopyranoside (14). A mixture of diastereomers: ^{1}H NMR ($CDCl_3$), δ: 0.85-0.92 (m, 15H), 1.05-1.45 (m, 20H), 1.51-1.59 (m, 2H), 1.63-1.75 (m, 2H), 3.77-4.10 (m, 6H), 4.13+4.23 (4.13, dd, *J* = 4.2, 9.7 Hz; 4.23, dd, *J* = 4.2, 9.7 Hz; 1H), 4.28 (t, *J* = 9.8 Hz, 1H), 4.60-4.67 (m, 2H), 4.71-4.76 (m, 1H), 4.78-4.60 (m, 1H), 5.00-5.05 (m, 1H), 5.08 (d, *J* = 7.2 Hz, 1H), 3.93 (t, *J* = 10.1 Hz, 1H), 4.06-4.18 (m, 2H), 4.22 (t, *J* = 9.7 Hz, 1H), 4.32 (dd, *J* = 4.9, 10.4 Hz, 1H), 5.64+5.66 (5.64, s; 5.66, s; 1H), 5.67-5.71 (m, 1H), 7.23-7.60 (m, 20H); ^{13}C NMR ($CDCl_3$), δ: 19.6-19.7, 20.0, 20.1, 20.2, 23.1, 23.2, 24.7, 24.9, 25.2, 29.7-29.8, 30.0-30.1, 33.2, 37.5-37.9, 39.8, 66.2, 67.16-67.3, 68.75, 68.82, 69.87, 69.91, 73.61, 73.64, 74.1, 74.2, 75.7, 76.5-76.7, 78.8, 97.2-97.3, 102.0, 126.5, 127.4-130.0, 131.8, 132.0, 134.0, 136.0-136.1, 137.0, 137.9, 138.0, 138.9.

Benzyl 3,7,11,15-Tetramethylhexadecylphosphoryl 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-b -D-mannopyranoside (15). Less polar diastereomer: ^{1}H NMR ($CDCl_3$), δ: 10.85-0.92 (m, 15H), 1.05-1.50 (m, 21H), 1.50-1.58 (m, 2H), 1.65-1.75 (m, 1H), 3.41 (dt, *J*=5.0, 10.1 Hz, 1H), 3.67 (dd, *J* = 3.0, 9.9 Hz, 1H), 3.88 (t, *J*=10.2 Hz, 1H), 4.01 (d, *J* = 3.0 Hz, 1H), 4.05-4.13 (m, 2H), 4.23 (t, *J* = 9.7 Hz, 1H), 4.27 (dd, *J* = 5.1, 10.6 Hz, 1H), 4.65 (d, *J* = 12.1 Hz, 1H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.90 (d, *J* = 11.8 Hz, 1H), 4.94 (d, *J* = 11.9 Hz, 1H), 5.13 (dd, *J* = 3.0, 8.0 Hz, 1H), 5.28 (d, *J* = 7.8 Hz, 1H), 5.63 (s, 1H), 7.28-7.53 (m, 20H); ^{13}C NMR ($CDCl_3$), δ: 19.68, 19.74, 20.0, 20.10, 20.2, 20.3, 23.1, 23.2, 24.7, 24.9, 25.2, 28.4, 29.8, 33.2, 37.5-37.9, 40.1, 67.3-67.5, 68.4, 68.6, 69.96, 70.0, 73.2, 75.7, 76.9, 78.0, 78.5, 97.4 (d, *J* = 3.4 Hz), 101.9, 126.3, 128.0, 128.2, 128.3, 128.6, 128.7,128.76, 128.81, 129.0, 129.1, 129.4, 136.1, 136.2, 137.7, 138.4. More polar diastereomer: ^{1}H NMR ($CDCl_3$), δ:0.89-0.91 (m, 15H), 1.05-1.50 (m, 21H), 1.51-1.59 (m, 2H), 1.68-1.77 (m, 1H), 3.44 (dt, *J* = 4.8, 10.0 Hz, 1H), 3.64 (dd, *J* = 2.7, 10.0 Hz, 1H), 3.88 (t, *J* = 2.5 Hz, 1H), 3.93 (t, *J* = 10.1 Hz, 1H), 4.06-4.18 (m, 2H), 4.22 (t, *J* = 9.7 Hz, 1H), 4.32 (dd, *J* = 4.9, 10.4 Hz, 1H), 4.64 (d, *J* = 12.7 Hz, 1H), 4.76 (d, *J* = 12.2 Hz, 1H), 5.07 (d, *J* = 7.4 Hz, 1H), 5.63 (s, 1H), 7.28-7.54 (m, 20H); ^{13}C NMR ($CDCl_3$), δ: 19.7, 19.8, 20.0, 20.1, 20.2, 23.1, 23.2, 24.7, 24.9, 25.2, 28.4, 29.0, 29.7, 33.2, 37.4-37.9, 39.8, 67.5, 68.3, 68.6, 68.7, 69.8, 69.83, 69.96, 70.0, 73.2, 75.7, 76.9, 77.0, 78.0, 78.02, 78.5, 97.4 (d, *J* = 6.4 Hz), 101.9, 126.5, 128.0, 128.1, 128.2, 128.3, 128.3, 128.6, 128.62, 128.7, 128.8, 128.9, 129.0, 129.1, 129.4, 136.0, 136.1, 137.7, 138.5.

Sodium 3,7,11,15-Tetramethylhexadecylphosphoryl b-D-mannopyranoside (4). The protected phosphate (**15**) (33.0 mg, 0.037mmol) was dissolved in THF (2.0 mL) and placed in a three-necked flask equipped with a bubbler, an ammonia inlet and a cold finger condenser. The system was flushed with Ar, the condenser was filled with dry ice/acetone and ammonia was passed through the system until approximately 3 mL had been condensed. To ensuing stirred solution was added Na as small spheres until the color became dark blue. Stirring was then continued for 30 min before quenching with solid $NaHCO_3$ and concentration. The resulting residue was dissolved in a mixture of 1-butanol (30 mL) and water (20 mL). After vigorous agitation, the butanol layer was separated, washed with water three times, and concentrated. The solid residue was placed on a pad of Celite and washed with acetone (25 mL) and then methanol (25 mL). The methanol extract was concentrated to give the title product (**4**) as a white solid (19 mg, 92%). Mp 158 °C (decomp.); ^{1}H NMR (CD_3OD), δ: 0.86-0.95 (m, 15H), 1.07-1.46 (m, 20H), 1.50-1.58 (m, 2H), 1.58-1.63 (m, 1H), 1.64-1.73 (m, 1H), 3.27-3.31 (m, 1H), 3.50 (dd, *J* = 3.0, 9.5 Hz, 1H), 3.56 (t, *J* = 9.5 Hz, 1H), 3.73 (dd, *J* = 5.5, 11.5 Hz, 1H), 3.88 (d, *J* = 11.5 Hz, 1H), 3.92 (d, *J* = 3.0 Hz, 1H), 3.93-3.99 (m, 2H), 5.10 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (CD_3OD), δ: 17.35, 17.41, 17.56, 17.6, 17.7, 20.5, 20.6, 23.0, 23.4, 26.6, 28.2, 31.4, 31.4, 31.5, 35.9-36.5, 38.0, 60.2, 62.9 (d, *J* = 5.0 Hz), 65.6, 70.4 (d, *J* = 5.4 Hz), 72.4, 76.3, 94.5 (d, *J* = 6.0 Hz). Negative ion ESIMS: Calcd. for $C_{26}H_{52}O_9P$ (M-Na^+) 539.3. Found: 539.7.

(1) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321-8348.

(2) Sakata, Y.; Hirano, Y.; Tatemitsu, H.; Misumi, S.; Ochiai, H.; Shibata, H. *Tetrahedron* **1989**, *45*, 4717-4727.