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β-Mannosylation with 4,6-benzylidene protected mannosyl donors without preactivation

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Supporting Information

Experimental Procedure

All reagents were used as purchased without further purification. Dry solvents were taken from a solvent purification system. Glassware were dried for 12 h at 175°C before use. Columns were packed with silica gel 60 (230–400 mesh) as the stationary phase. TLC plates (Merck, 60, F254) were developed by 10% H_2SO_4 in EtOH and heating. ^{13}C-NMR spectra were recorded on a 500 MHz spectrometer equipped with cryo probe. Chemical shifts (d) are reported in ppm relative to the residual solvent signal (d = 7.26 for ^{1}H-NMR and 77.16 for ^{13}C-NMR). High-resolution mass spectral (HRMS) data were obtained on an electrospray (ESI) or a MALDI-TOF mass spectrometer. Optical rotation data were obtained on a Perkin Elmer 341 Polarimeter. NMR assignments were based on COSY and HSQC NMR experiments.

Mannosylation

The general procedures are given below. Changes from these conditions appear from the table (Table 1 and S1). All the donors are known and most of the mannosylation have been chosen in order to compare with literature examples. The data for the new compound **18** is given below.

Typical NIS/TfOH-promoted glycosylation procedure:

A mixture of mannosyl donor (0.10 mmol), glycosyl acceptor (0.15 mmol), and freshly activated powdered molecular sieves (3Å, 100 mg) in CH_2Cl_2 (2mL) was stirred under argon atmosphere for 1 h. The solution was cooled to –78 °C and NIS (0.11 mmol) and TfOH (0.010 mmol) were added. The reaction was slowly allowed to reach 0 °C. Upon completion, the solid was filtered off and the filtrate was washed with 10% Na_2S_2O to remove iodine. The organic layer was separated, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography on silica gel afforded the corresponding glycoside.

Anomeric ratios were measured by comparison of integral intensities of the anomeric protons from ^{1}H-NMR spectra of crude the reaction mixtures.

Pre-activation of sulfoxide:

A mixture of mannosyl donor (ca. 0.10 mmol) and TTBP (2 equiv.) were co-evaporated 3 times with toluene. The dry residue, kept under an argon atmosphere, was then dissolved in CH_2Cl_2 and cooled to -78°C, where Tf_2O was added. After 30 min. the acceptor was added and the temperature was allowed to reach 0C over ca. 2 h where after the reaction was quenched by Et_3N. The crude reaction mixture was diluted by EtOAc, washed with water (3 times) and brine. The organic phase was dries ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford the corresponding glycoside.

Anomeric ratios were measured by comparison of integral intensities of the anomeric protons from ^{1}H-NMR spectra of crude reaction mixtures.

Direct activation of sulfoxide:

Procedure as above, but the acceptor is added before the Tf_2O.

Activation of the trichloroacetimidate:

The mannosyl donor was dried *in vacuo* with the acceptor. The mixture was dissolved in CH_2Cl_2 and freshly activated powdered molecular sieves (3Å, 100 mg) were added followed by stirring at

rt for 30 min. under an argon atmosphere. The reaction mixture was then cooled to -78°C, where the catalyst (and additives, when stated) was added and the reaction progress followed by TLC. The temperature was gradually allowed to increase until all donor had been consumed. The reaction was then quenched by addition of Et_3N, filtered and concentrated *in vacuo*. The anomeric ratio was determined on the crude product, which was purified by flash chromatography.

Methoxyethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**18α**).

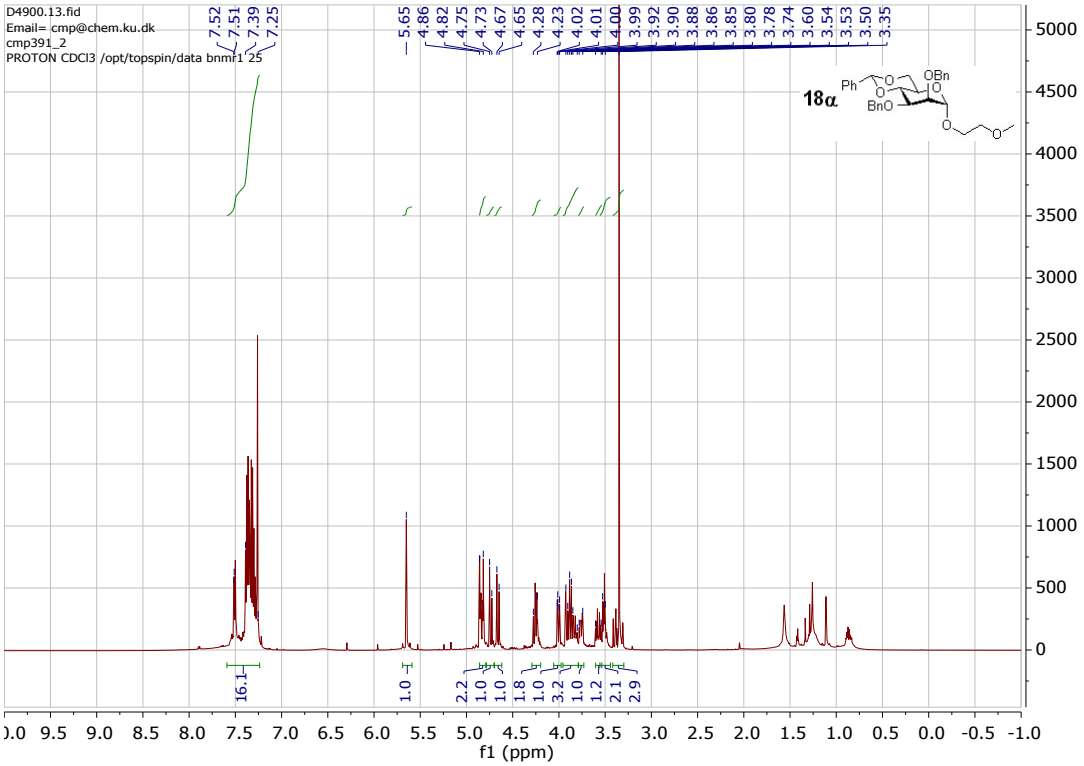
^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.35 (s, 3H, Me), 3.51 (m, 1H, CH2), 3.55 (m, 1H, CH_2), 3.58 (m, 1H, -CH_2), 3.76 (m, 1H, CH_2), 3.83 (ddd, 1H, *J* = 10.2, 9.4, 4.2 Hz H5), 3.88 (dd, 1H, *J* = 10.2, 10.2 Hz, H6), 3.92 (dd, 1H, *J* = 3.2, 1.6 Hz, H2), 4.01 (dd, 1H, *J* = 9.9, 3.2 Hz, H3), 4.34 (dd, 1H, *J* = 10.0, 4.2 Hz, H6'), 4.36 (dd, 1H, J = 9.6, 9.9 Hz, H4), 4.66 (d, 1H, *J* = 12.1 Hz, Bn), 4.73 (d, 1H, *J* = 12.3, Bn), 4.83 (d, 1H, *J* = 12.3, Bn), 4.84 (d, 1H, *J* = 12.1, Bn), 4.86 (d, 1H, *J* = 1.6, H1), 5.65 (s, 1H, PhCH), 7.27-7.56 (m, 15H, ArH). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 59.3 (Me), 64.3 (C5), 66.8 (CH2), 69.0 (C6), 71.6 (CH2), 73.3 (Bn), 73.8 (Bn), 76.5 (C2), 76.7 (C3), 79.4 (C4), 99.7 (C1, J_{CH} = 169.4 Hz), 101.6 (Ph*C*H), 125.5, 126.2, 127.6, 127.9, 128.2, 128.3, 128.4, 128.5, 129.0, 137.8, 138.3, 138.9 (12 Ar C); LC-MS: m/z 507 ($M + H^+$), 524 ($M + H_3O^+$), 529 ($M + Na^+$). HRMS calculated $C_{30}H_{34}O_7H+$ = 507.2377, found: 507.2389

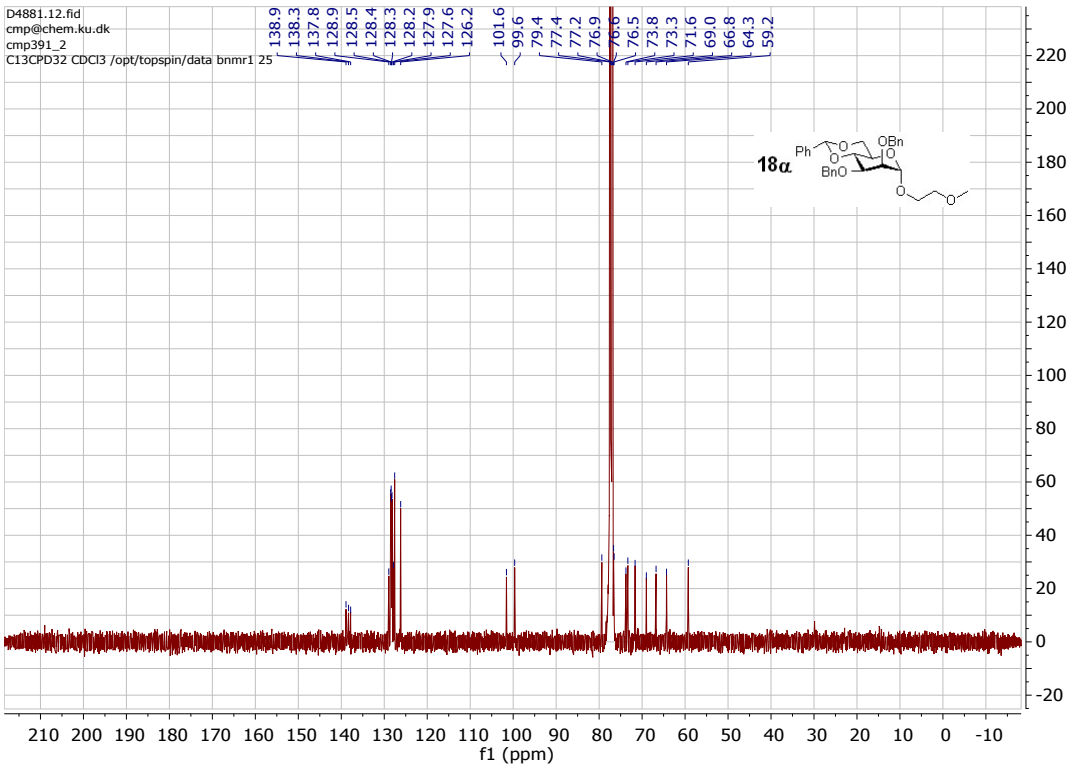
Methoxyethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranoside (**18β**).

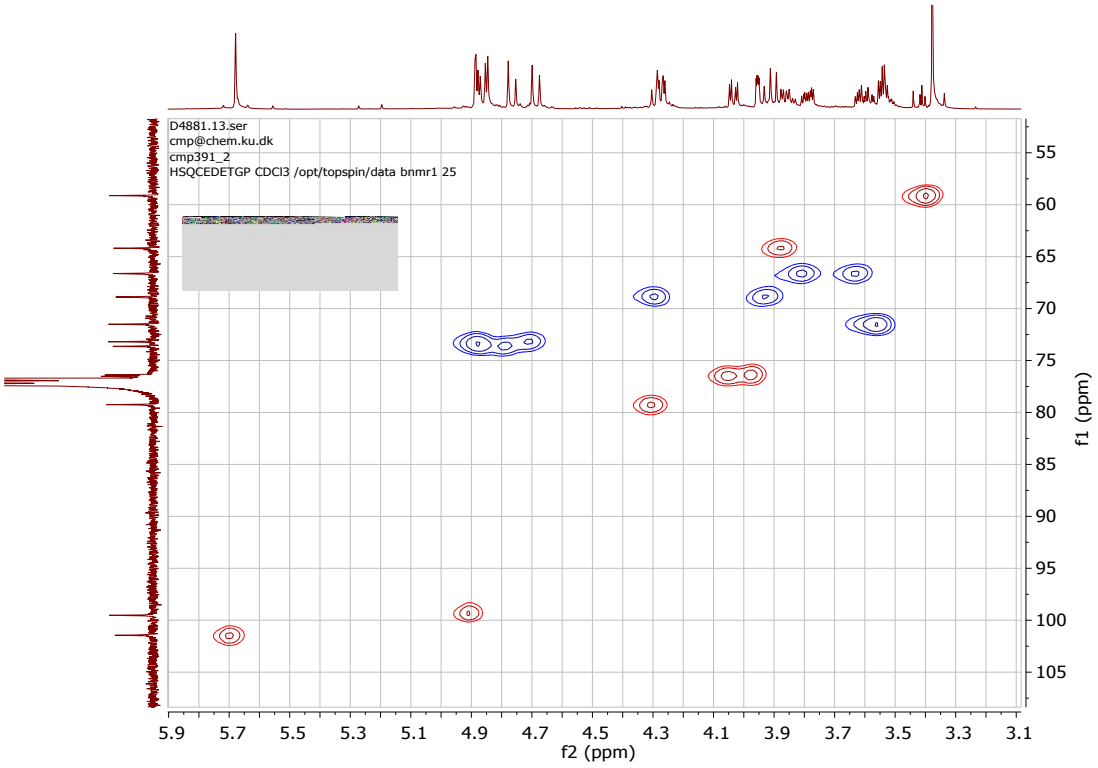
^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.32 (ddd, 1H, *J* = 10.3, 9.9, 5.1 Hz, H5), 3.38 (s, 3H, OMe), 3.75 (m, 3H, CH_2, H3), 3.67 (m, 1H, CH_2), 3.92 (t, 1H, *J* = 10.3 Hz, H6), 3.96 (bd, 1H, *J* = 2.2 Hz, H2), 4.00 (m, 1H, CH_2), 4.19 (t, 1H, *J* = 9.9 Hz, H4), 4.29 (dd, 1H, *J* = 10.3, 5.1 Hz, H6'), 4.51 (bs, 1H, H1), 4.57 (d, 1H, *J* = 12.5 Hz, Bn), 4.66 (d, 1H, *J* = 12.5 Hz, Bn), 4.87 (d, 1H, *J* = 12.2 Hz, Bn), 4.97 (d, 1H, *J* = 12.2 Hz, Bn), 5.60 (s, 1H, PhCH), 7.22-7.50 (m, 15H, ArH); ^{13}C-NMR (126 MHz, $CDCl_3$): δ 59.3 (Me), 67.7 (C5), 68.8 (C6), 69.2 (CH2), 72.0 (CH2), 72.4 (Bn), 74.9 (Bn), 75.9 (C2), 77.9 (C3), 78.8 (C4), 101.6 (PhCH), 102.4 (C1, J_{CH} = 156 Hz), 126.2-129.0 (9 Ar-C), 137.7 (ArC), 138.4 (ArC), 138.6 (ArC); $[\alpha]_D^{25}$ = -50° (c = 1.0 in $CHCl_3$); LC-MS: m/z 507 ($M + H^+$), 524 ($M + H_3O^+$), 529 ($M + Na^+$). HRMS calculated $C_{30}H_{34}O_7H+$ = 529.2197, found: 529.2221

NMR Spectra

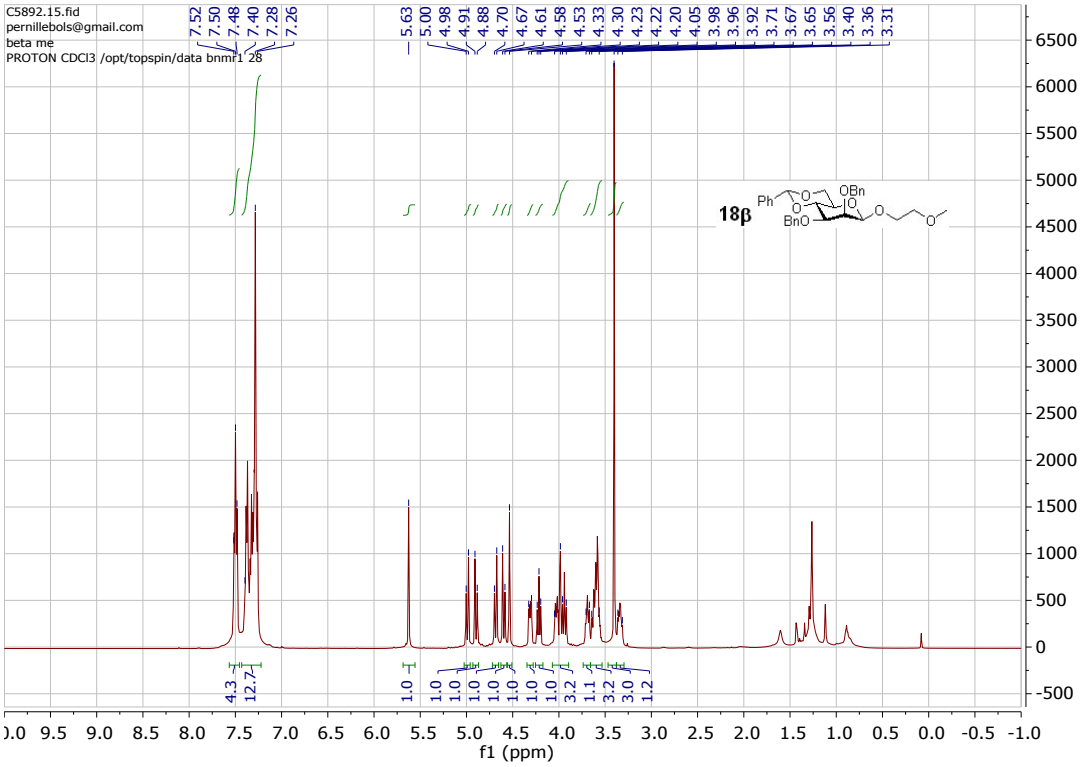
Methoxyethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside.

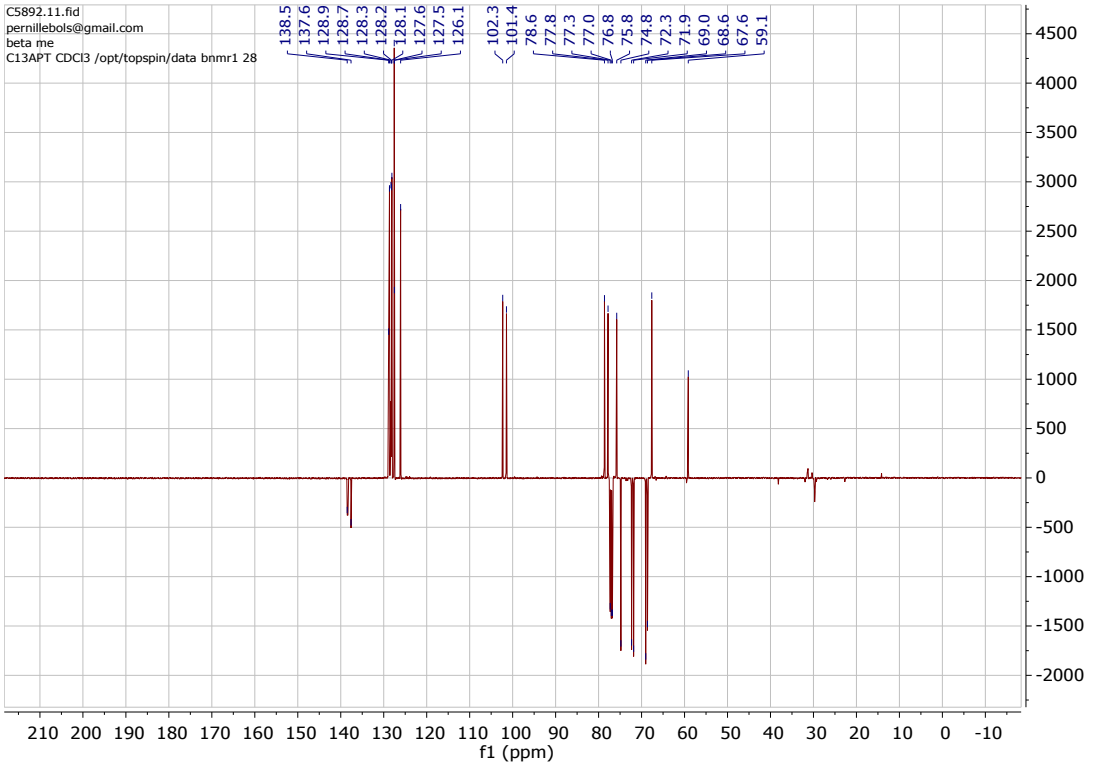






Methoxyethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-mannopyranoside (**18β**).

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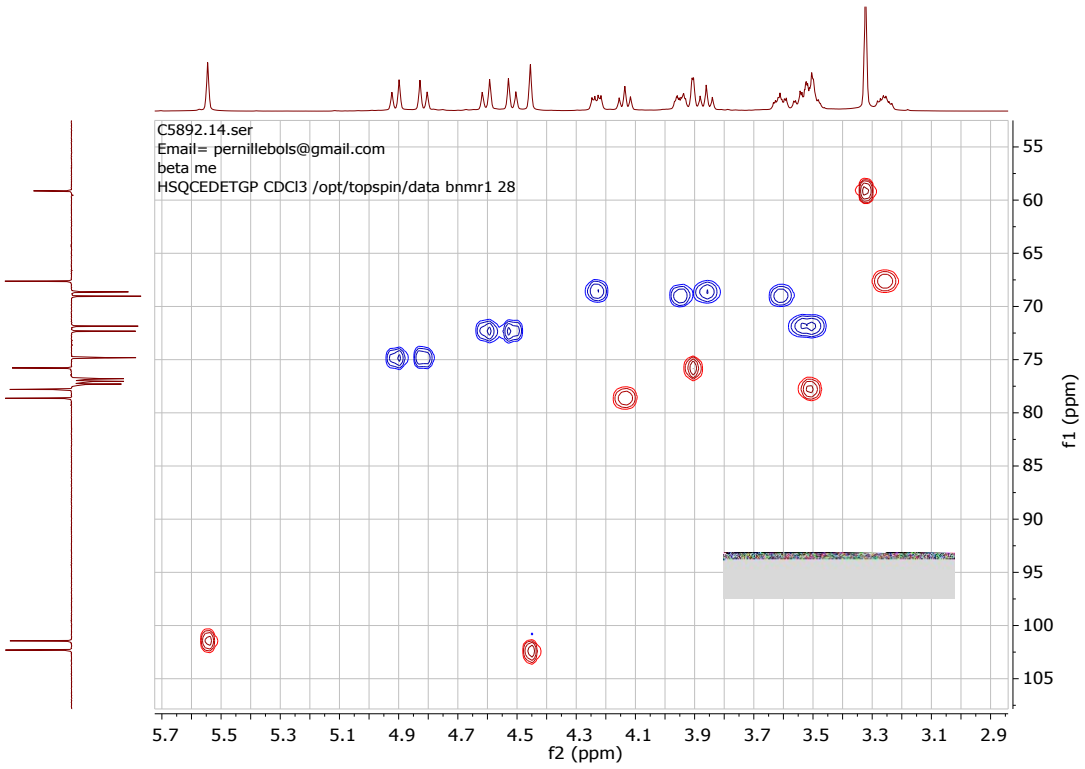
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