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Note

Convergent synthesis of an octasaccharide acceptor corresponding to the reducing terminus of mycobacterial 3-*O*-methylmannose polysaccharide (MMP) [1]

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Abstract

The protected mannose octasaccharide **6** (R = H) was synthesized by imidate coupling of two tetrasaccharide precursors. © 1997 Elsevier Science Ltd.

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As part of a continuing project on the total chemical synthesis of mycobacterial 3-*O*-methylmannose polysaccharide (MMP) [1], which has the unusual property of forming stable complexes with long-chain fatty acids and acyl CoA derivatives [2], we have described the stereocontrolled synthesis of a hexasaccharide glycosyl acceptor [3], and a tetra- and a hexa-saccharide glycosyl donor [4]. We now report a convergent synthesis of the linear methyl (1 → 4)-α-D-mannooctasaccharide acceptor (**6**), which corresponds to the reducing-terminal fragment of MMP. It is also suitably functionalized to serve as a precursor of higher-order structures. See Scheme 1.

Deallylation of the tetrasaccharide (**1**) [4] at room temperature afforded only a low yield in 1:1 MeOH–CH_2Cl_2 [3] as solvent with $PdCl_2$ as catalyst [5,6], but proceeded smoothly upon slight heating (to 35°C) and afforded hemiacetal (**2**) in 82% yield. The desired tetrasaccharide glycosyl imidate (**3**) was then obtained in 92% yield by trichloroacetimidation of **2** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and CCl_3CN [7,8].

Coupling of the tetrasaccharide imidate **3** with the tetrasaccharide acceptor **4** [3] in the presence of triethylsilyl trifluoromethanesulfonate (TESOTf) and powdered molecular sieve 4 Å at −78 °C was complete in 0.5 h, and furnished the protected methyl octasaccharide (**5**) in 45% yield. Its ^1H NMR spectrum showed nine methyl peaks at δ 3.389, 3.350, 3.288, 3.278, 3.188, 3.187, 3.186, 3.180, and 3.178, of which δ 3.389 was assigned to the methyl aglycon (as determined by the NOE-DIFF technique), and the others to 3-*O*-methyl groups. After deacetylation, the target glycosyl mannooctaosyl acceptor **6** was obtained.

All new compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy and/or by elemental analyses. They were also characterized by microanal-

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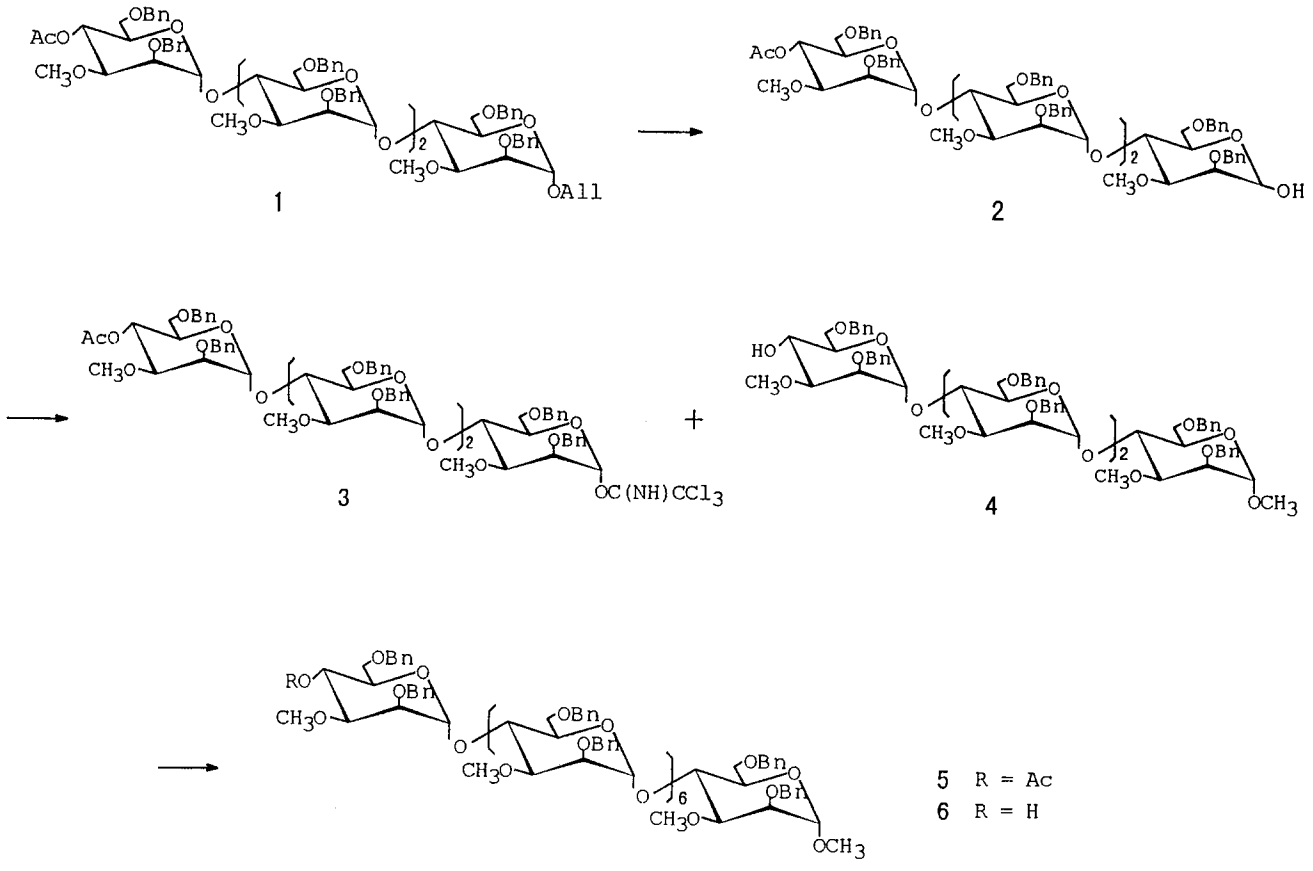

Scheme 1.

ysis. In the case of **5**, however, owing to its hydrophobic nature, a field-desorption mass spectrum (FDMS) was obtained as a further confirmation of composition. The peak appearing at *m/z* 2923 was assigned to the $[M]^+$ ion.

1. Experimental

General methods.—See ref. [3]. Subscripts A–H refer to the individual sugar residues, with A denoting the reducing-end unit.

(4-O-Acetyl-2,6-di-O-benzyl-3-O-methyl-α-D-mannopyranosyl)-[(1 → 4)(2,6-di-O-benzyl-3-O-methyl-α-D-mannopyranosyl)]$_2$-(1 → 4)-2,6-di-O-benzyl-3-O-methyl-D-mannopyranose (**2**).—A mixture of **1** (0.5 g, 0.33 mmol) and $PdCl_2$ (40 mg, 0.23 mmol) in 1:1 MeOH–CH_2Cl_2 (12 mL) was stirred for 4 h with slight heating at 35 °C and filtered through Celite. The filtrate was evaporated and the residue was purified by column chromatography with 1:1 petroleum ether–EtOAc as eluant to furnish **2** as an amorphous solid (mainly the α anomer, 0.4 g, 82%); The data are given for the α anomer only: $[\alpha]_D$ +18.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR: δ 7.52–7.10 (m, 40 H, aromatic H), 5.37–5.21 (m, 4 H, H-1_D,1_C,1_B,1_A), 4.76–4.33 (m, 16 H, 8 PhCH_2), 3.28, 3.20, 3.19, 3.18 (4 s, 12 H, OCH_3-3_D,3_C,3_B,3_A), 2.05 (s, 3 H, CH_3CO); ^{13}C NMR: δ 169.8 (CH_3CO), 139.2–137.9 (aromatic C-1), 128.7–126.6 (aromatic C), 100.0 (C-1_D), 96.2 (C-1_C,1_B), 92.7 (C-1_A), 81.7, 81.5, 81.3, 79.0 (C-3_D,3_C,3_B,3_A), 57.6, 56.7 (OCH_3-3_D,3_C), 56.4 (OCH_3-3_B,3_A), 21.0 (CH_3CO); FDMS: *m/z* 1486 $[M + H]^+$. Anal. Calcd for $C_{86}H_{100}O_{22}$: C, 69.52; H, 6.78. Found: C, 69.40; H, 6.76.

(4-O-Acetyl-2,6-di-O-benzyl-3-O-methyl-α-D-mannopyranosyl)-[(1 → 4)(2,6-di-O-benzyl-3-O-methyl-α-D-mannopyranosyl)]$_2$-(1 → 4)-2,6-di-O-benzyl-3-O-methyl-α-D-mannopyranosyl trichloroacetimidate (**3**).—To a mixture of compound **2** (300 mg, 0.20 mmol) and Cl_3CCN (0.15 mL, 1.5 mmol) in anhyd CH_2Cl_2 (6 mL) at −10 °C was added 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) (25 uL, 0.16 mmol). The mixture was stirred at 0 °C under argon for 2 h. The solvent was removed by evaporation and the residue was purified by column chromatography with 3:2 petroleum ether–EtOAc as eluant to yield **3** as an amorphous solid (302 mg, 92%);

$[\alpha]_D$ +22.7° (*c* 1.5, $CHCl_3$); ^1H NMR: δ 8.65 (s, 1 H, OC(N*H*)CCl_3), 7.60–6.95 (m, 40 H, aromatic H), 6.42 (d, 1 H, $J_{1,2}$ 2.1 Hz, H-1_A), 5.39–5.22 (m, 3 H, H-1_D,1_C,1_B), 4.83–4.32 (m, 16 H, 8 PhCH_2), 3.31, 3.24 (2 s, 6 H, OCH_3-3_D,3_C), 3.22 (s, 6 H, OCH_3-3_B,3_A), 2.07 (s, 3 H, CH_3CO); ^{13}C NMR: δ 169.7 (CH_3CO), 160.5 (*C*=NH), 139.2–138.0 (aromatic C-1), 128.7–126.9 (aromatic C), 99.9 (C-1_D), 96.2 (C-1_C,1_B), 91.5 (C-1_A), 81.6, 81.5, 81.4, 79.0 (C-3_D,3_C,3_B,3_A), 57.6, 56.8, 56.6, 56.4 (OCH_3-3_D,3_C,3_B,3_A), 20.9 (CH_3CO); FDMS: *m/z* 1628 $[M]^+$, 1468 $[M-C_2HCl_3NO]^+$. The compound was used immediately in the next reaction.

Methyl (4-O-acetyl-2,6-di-O-benzyl-3-O-methyl-α-D-mannopyranosyl)-[(1 → 4)-(2,6-di-O-benzyl-3-O-methyl-α-D-mannopyranosyl)]$_6$-(1 → 4)-2,6-di-O-benzyl-3-O-methyl-α-D-mannopyranoside (**5**).—A mixture of compounds **3** (250 mg, 0.15 mmol) and **4** (160 mg, 0.11 mmol) in anhyd CH_2Cl_2 (15 mL) was stirred under argon with powdered molecular sieve 4 Å (1 g) for 0.5 h at room temperature. The solution was cooled to −78 °C and TESOTf (25 uL) was added dropwise. The mixture was stirred for 30 min after which TLC indicated that the reaction was complete. Triethylamine (0.5 mL) was added. The mixture was filtered through Celite, and the filtrate was concentrated. The residue was purified by column chromatography with 3:2 petroleum ether–EtOAc as eluant to yield **5** as an amorphous solid (145 mg, 45%); $[\alpha]_D$ +29.6° (*c* 0.8, $CHCl_3$); ^1H NMR: δ 7.45–7.00 (m, 80 H, aromatic H), 5.43–5.18 (m, 8 H, H-1_H,1_G,1_F,1_E,1_D,1_C,1_B, H-4_H), 4.78 (d, 1 H, $J_{1,2}$ 1.6 Hz, H-1_A), 4.75–4.33 (m, 32 H, 16 PhCH_2), 3.389 (s, 3 H, OCH_3-1_A), 3.350, 3.288, 3.278, 3.188, 3.187, 3.186, 3.180, 3.178 (8 s, 24 H, OCH_3-3_H,3_G,3_F,3_E,3_D,3_C,3_B,3_A), 1.98 (s, 3 H, CH_3CO); ^{13}C NMR: δ 169.9 (CH_3CO), 139.3–138.1 (aromatic C-1), 128.8–126.9 (aromatic C), 101.8, 99.97, 99.89, 99.85, 99.73, 99.07, 98.94 (C-1_H,1_G,1_F,1_E,1_D,1_C,1_B), 96.24 (C-1_A), 82.25,,81.90, 81.60, 81.36, 80.50, 80.29, 79.26 (C-3_H,3_G,3_F,3_E,3_D,3_C,3_B), 78.96 (C-3_A), 57.60, 57.28, 56.99, 56.58, 56.48, 56.27 (OCH_3-3_H,3_G,3_F,3_E,3_D,3_C), 55.56, 55.20 (OCH_3-3_B,3_A), 54.86 (OCH_3-1_A), 21.04 (CH_3CO); FDMS: *m/z* 2923 $[M]^+$. Anal. Calcd for $C_{171}H_{198}O_{42}$: C, 70.21; H, 6.82. Found: C, 70.04; H, 6.73.

Methyl (2,6-di-O-benzyl-3-O-methyl-α-D-mannopyranosyl)-[(1 → 4)-(2,6-di-O-benzyl-3-O-methyl-α-D-mannopyranosyl)]$_6$-(1 → 4)-2,6-di-O-benzyl-3-O-methyl-α-D-mannopyranoside (**6**).—A solution of **5** (80 mg, 27 μmol) in THF (1 mL) and 0.14 N NaOMe–MeOH (1:1, 1.5 mL) was stirred for 3 h at room temperature. Processing and chromatography on silica gel in 1:1 petroleum ether–EtOAc afforded **6** as an amorphous solid (71 mg, 90%); $[\alpha]_D$ +21.5° (*c* 1.0, $CHCl_3$); ^1H NMR: δ 7.40–6.95 (m, 80 H, aromatic H), 5.42–5.16 (m, 7 H, H-1_H,1_G,1_F,1_E,1_D,1_C,1_B), 4.79 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1_A), 4.76–4.32 (m, 32 H, 16 PhCH_2), 3.390 (s, 3 H, OCH_3-1_A), 3.355, 3.296, 3.288, 3.199, 3.197, 3.196, 3.188, 3.178 (8 s, 24 H, OCH_3-3_H,3_G,3_F,3_E,3_D,3_C,3_B,3_A); ^{13}C NMR: δ 139.2–138.2 (aromatic C-1), 128.8–126.8 (aromatic C), 101.6, 99.96, 99.88, 99.83, 99.74, 99.17, 98.96 (C-1_H,1_G,1_F,1_E,1_D,1_C,1_B), 96.23 (C-1_A), 82.24, 81.89, 81.56, 81.35, 80.48, 80.28, 79.26 (C-3_H,3_G,3_F,3_E,3_D,3_C,3_B), 78.95 (C-3_A), 57.60, 57.27, 56.98, 56.56, 56.48, 56.26 (OCH_3-3_H,3_G,3_F,3_E,3_D,3_C), 55.56, 55.21 (OCH_3-3_B,3_A), 54.87 (OCH_3-1_A); FDMS: *m/z* 2882 $[M+H]^+$. Anal. Calcd for $C_{169}H_{196}O_{41}$: C, 70.40; H, 6.85. Found: C, 70.28; H, 6.79.

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