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Note

Stereospecific α-D-mannosylation

Ian L. Scott [a,*], Robert V. Market [a], Russell J. DeOrazio [b], Harold Meckler [b], Timothy P. Kogan [a,1]

[a] *Texas Biotechnology Corporation, 7000 Fannin, Suite 1920, Houston, TX 77030, USA*
[b] *Albany Molecular Research, 21 Corporate Circle, Albany, NY 12203, USA*

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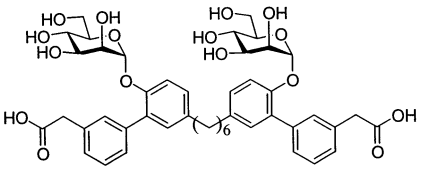
Abstract

The stereospecific formation of α-D-mannosyl glycosidic linkages has been achieved in high yield using tetra-*O*-pivaloyl-α-D-mannopyranosyl fluoride and boron trifluoride diethyl etherate in dichloromethane. Examples of the α-D-mannosylation of primary, secondary, benzylic and phenolic hydroxyl groups are described.

Keywords: Mannosylation; Stereospecific; Glycosyl fluorides

As part of our ongoing research into cell-adhesion antagonists [1], we desired compounds possessing two α-D-mannose units such as 1,6-bis[3-(3-carboxymethylphenyl)-4-(α-D-mannopyranosyloxy)phenyl]hexane (**1**). α-D-Mannosylation is considered to be among the easiest of glycosylation reactions, and when an acetyl group is incorporated at C-2, the reaction is usually considered to be stereospecific [2]. Unfortunately, mannosylation of 1,6-bis[3-(3-carboxymethylphenyl)-4-hydroxyphenyl]hexane (**4**, Scheme 1) using penta-*O*-acetyl-D-mannopyranose catalyzed by $BF_3{\cdot}OEt_2$ [3] gave the desired bis-α-D-mannoside **6a** in 95% yield, but in only 95% purity. This level of purity is insufficient for purposes of pharmaceutical development, and as further purification was impractical at large scale, we elected to look for a stereospecific method of mannosylation.



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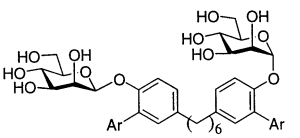

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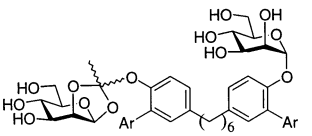

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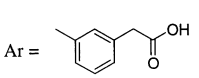

Analysis of the product mixture from glycosylation of the appropriate bis-phenol **4** [1c] with penta-*O*-acetyl-D-mannopyranose by NMR spectroscopy, after extensive HPLC to remove as much of the major component as

* Corresponding author. Present address: Albany Molecular Research, 21 Corporate Circle, Albany, NY 12203, USA. Tel.: +1-518-464-0274.
E-mail address: ians@albmolecular.com (I.L. Scott)
[1] Deceased 27th May 1998. This paper is dedicated to his memory.

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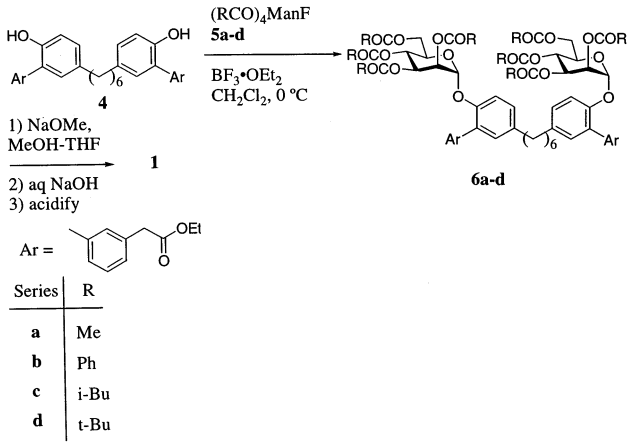
possible[2], revealed the presence of three minor impurities formed in approximately equal amounts. These impurities comprised the mono β anomer **2**[3] and each of the two possible epimeric orthoesters **3**[4] [4a]. As the similarity of the structures of the four components complicated purification of the desired compound to an acceptable level, we elected to develop a more selective glycosylation strategy. We hypothesized that increasing the size of the C-2 protecting/participating group would lead to higher specificity for the α anomer[5]. In order to investigate this hypothesis, we first had to develop a more reactive glycosylating agent. After a brief look at the more commonly used activating groups and Lewis acid catalysts, we selected a combination of the acyl-protected glycosyl fluoride **5a** and $BF_3{\cdot}OEt_2$. Using this system, we observed improvements in both the reaction rate and yield. The percentage purity, as expected, remained unchanged.

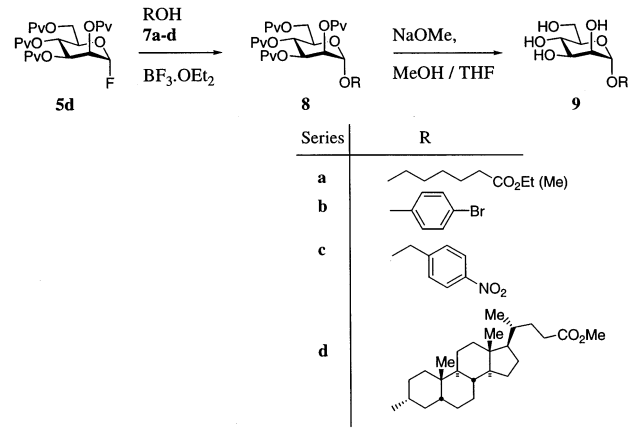
Next, we investigated the effect of changing the size of the acyl protecting groups of the sugar moiety on the stereochemical outcome of the glycosylation (Table 1). Increasing the size of the protecting groups to pivalate on the glycosyl fluoride essentially eliminated the formation of both the β anomer and orthoesters in the formation of **6d**. The major impurity visible by reversed-phase HPLC (after deprotection) was the monoglycoside (0.2%) that was formed by deglycosylation during the cleavage of the pivaloyl groups.

To determine the overall utility of this approach, we extended our studies to the glycosylation of other alcohols using tetra-*O*-pivaloyl-α-D-mannopyranosyl fluoride (Table 2). In each case, the glycosylation yields are given after chromatography: only the α glycoside was observed by either NMR spectroscopy or by HPLC (Scheme 2).



Scheme 1.

Removal of the protecting groups proved initially troublesome due to the high stability of the pivalate group under basic conditions. The preferred conditions that were found involved use of a freshly prepared solution of sodium methoxide in a mixture of methanol and tetrahydrofuran[6]. Under these conditions, the amount of deglycosylation was minimized, and no loss of anomeric purity was observed.



Scheme 2.

Table 1
Mannosylation of **4** [a]

Acyl protecting group	Chemical yield (**1**+**2**+**3**) (%)	Ratio **1**:(**2**+**3**) [b] (%)
Acetate **5a**	95	95:5
Benzoate **5b**	75	98:2
Isobutyrate **5c**	73	97.5:2.5
Pivalate **5d**	91	99.3:0.7

[a] Mannosylation and deprotection reactions were run following the general procedures.

[b] Determined by reversed-phase HPLC after hydrolytic cleavage of all protecting groups.

[2] As the yield suggests, other side products were formed. These were removed by flash chromatography and were not characterized. Other known side reactions include: acyl transfer, disaccharide formation, and C-glycosylation [2c,d,4].

[3] ^{13}C NMR: (100 MHz, $CDCl_3$) δ 96.3 ppm.

[4] ^{13}C NMR: (100 MHz, $CDCl_3$) δ 114.2 and 114.4 ppm.

[5] Similar results have been reported in the formation of α-D-glucopyranosides [5].

[6] The THF was required to increase the solubility of the fully protected glycoside.

Table 2
α-Mannosylation using 2,3,4,6-tetra-*O*-pivaloyl-α-D-mannopyranosyl fluoride (**5d**)

Alcohol	Mannosylation yield (%)	Deprotection yield (%)
4	91	92 [a]
7a	100	85 [b]
7b	100	100
7c	100	92
7d	95 [c]	77

[a] After hydrolysis to **1**.
[b] Methyl ester.
[c] Glycosyl fluoride used as limiting reagent due to coelution of fluoride and product.

In conclusion, we have developed a rapid, clean, high yielding, and stereospecific method for the introduction of α-D-mannosidic linkages [6].

1. Experimental

Preparation of 2,3,4,6-tetra-O-*acetyl*-α-D-*mannopyranosyl fluoride* (**5a**).—To a stirred slurry of D-mannose pentaacetate (100 g, 0.256 mol) in CH_2Cl_2 (10 mL) in a PFE flask was added cold HF–pyridine (100 g). The resulting solution was stirred overnight, sealed, at 40 °C. The solution was poured into a PFE separating funnel containing water (500 mL) and $CHCl_3$ (200 mL) and shaken. The $CHCl_3$ layer was washed with water and satd $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by chromatography (SiO_2, 3:1–2:1 hexanes–EtOAc) gave 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl fluoride (**5a**) (74.06 g, 83%) as a clear oil. The compound's NMR spectrum matched that reported [7].

1,6-Bis[3-(3-ethoxycarbonylmethylphenyl)-4-(2,3,4,6-tetra-O-*acetyl*-α-D-*mannopyranosyloxyphenyl)]hexane* (**6a**).—To an ice-cold solution of **4** (45.4 g, 76 mmol) and 2,3,4,-6-tetra-*O*-acetyl-α-D-mannopyranosyl fluoride (**5a**, 77 g, 220 mmol) in CH_2Cl_2 (400 mL) was added $BF_3{\cdot}OEt_2$ (81.2 mL, 660 mmol) dropwise, and the mixture was stirred at 0 °C for 3 h. The mixture was poured into aq $NaHCO_3$ and extracted with EtOAc. The organic solution was washed with water and satd NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 2:1–3:2–1:1 hexanes–EtOAc) yielded 1,6-bis[3-(3-ethoxycarbonylmethylphenyl)-4-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxyphenyl)]hexane (**6a**, 88.0 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (m, 6 H), 7.27 (m, 2 H), 7.17 (d, 2 H, J 1.5 Hz), 7.07 (m, 4 H), 5.39 (s, 2 H, H-1), 5.27 (m, 6 H), 4.16 (dd, 2 H, $J_{6,6'}$ 12.0 Hz, $J_{5,6}$ 4.7 Hz, H-6), 4.15 (4 H, q, J 7 Hz, CH_2CH_3), 3.94 (dd, 2 H, $J_{5,6'}$ 2.2 Hz, H-6′), 3.79 (ddd, 2 H, $J_{4,5}$ 9.5 Hz, H-5), 3.70 (s, 4 H, CH_2CO_2), 2.58 (t, 4 H, J 7.7 Hz, $ArCH_2CH_2$), 2.13, 2.02, 2.00, and 1.97 (4 s, all 3 H, $COCH_3$), 1.60 (m, 4 H, $ArCH_2CH_2$), 1.36 (m, 4 H, Ar $CH_2CH_2CH_2$), 1.24 (t, 6 H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 20.1, 20.3, 28.7, 31.1, 34.7, 40.8, 60.5, 61.7, 65.5, 68.5, 69.0, 69.2, 96.9, 116.5, 128.3, 128.4, 128.7 , 130.7, 131.2, 132.2, 134.5, 138.3, 151.0, 170.2, 170.3, 170.5, 171.1, 172.3; IR (cm^{-1}): (neat) 1743.

General procedure for the preparation of 2,3,4,6-tetra-O-*acyl*-α-D-*mannopyranosyl fluorides*

2,3,4,6-Tetra-O-*pivaloyl*-α-D-*mannopyranosyl fluoride* (**5d**). To a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl fluoride (**5a**, 74.06 g, 211.4 mmol) in MeOH (1 L) was added K_2CO_3 (0.50 g, 3.6 mmol). The resulting mixture was stirred at room temperature (rt) until the reaction was indicated to be complete by TLC. The solvent was evaporated under reduced pressure, and residual MeOH was removed by co-evaporation of 1,2-dimethoxyethane (3 ×). The residue was dissolved in pyridine (500 mL) and cooled to 0 °C. Pivaloyl chloride (200 mL, 1.62 mol) was added dropwise, followed by 4-dimethylaminopyridine (DMAP, 3.0 g, 27 mmol). The resulting mixture was stirred at 0 °C for 30 min, at rt for 30 min, and then at 70 °C overnight. After cooling to 50 °C, MeOH (50 mL) was added, and the mixture was stirred at 50 °C for 1 h. After cooling to rt, the mixture was diluted with EtOAc, filtered, and washed with additional EtOAc. The combined organic

layers were washed with water, 2 M HCl (2 ×), water, 2 M NaOH, water and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, gradient 30:1–4:1 hexanes–ethyl acetate) to give 2,3,4,6-tetra-*O*-pivaloyl-α-D-mannopyranosyl fluoride (**5d**, 87.48 g, 80%): mp 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.51 (dd, 1 H, $J_{1,F}$ 49.8 Hz, $J_{1,2}$ 1.5 Hz, H-1), 5.55 (t, 1 H, $J_{3,4} = J_{4,5}$ 10 Hz, H-4), 5.39 (m, 2 H), 4.20 (m, 3 H), 1.26, 1.23, 1.15, and 1.11 (4 s, all 9 H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.5, 38.3, 38.4, 38.5, 60.9, 63.8, 67.3 (d, *J* 40 Hz), 68.3, 70.9, 105.1 (d, *J* 224 Hz), 177.1, 177.4, 177.7, 178.6; IR (cm^{-1}): (neat) 1743; CIMS (CH_4) *m*/*z* 519 $[M+1]^+$, 499 $[M-F]^+$. Anal. Calcd for $C_{26}H_{43}FO_9$: C, 60.21; H, 8.36. Found: C, 60.01; H, 8.46.

Preparation of 2,3,4,6-tetra-O-*benzoyl*-α-D-*mannopyranosyl fluoride* (**5b**). Compound **5b** was prepared by the above method: yield (6.91 g, 81%). The compound's NMR spectrum matched that reported [7].

2,3,4,6-Tetra-O-*isobutyryl*-α-D-*mannopyranosyl fluoride* (**5c**). Compound **5c** was prepared by the above method. Yield (2.14 g, 81%): mp 33 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.55 (dd, 1 H, $J_{1,2}$ 1.84 Hz, $J_{1,F}$ 48.7 Hz, H-1), 5.46 (t, 1 H, $J_{3,4} = J_{4,5}$ 10 Hz, H-4), 5.36 (m, 2 H), 4.25, (dd, 1 H, $J_{6,6'}$ 12.4 Hz, $J_{5,6}$ 4.4 Hz, H-6), 4.19 (dd, 1 H, $J_{5,6'}$ 2 Hz, H-6′), 4.16 (ddd,1 H, H-5), 2.64, 2.60, 2.51, and 2.43 (4 septets, all 1 H, *J* 7 Hz, C*H*$(CH_3)_2$), 1.24, 1.21, 1.20, 1.19, 113, 1.11, 1.09, and 1.07 (8 d, all 3 H, *J* 7 Hz, CH(C*H*$_3)_2$)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 18.0, 18.1, 18.2, 18.2, 18.2, 18.2, 18.4, 33.3, 33.4, 60.9, 64.0, 67.1 (d, *J* 39 Hz), 68.1, 70.9 (d, *J* 2 Hz), 105.0 (d, *J* 224 Hz), 176.0, 176.1, 176.1, 176.1; IR (cm^{-1}): (neat) 1743.

General procedure for the preparation of tetra-O-*acyl*-α-D-*mannopyranosides*

4-Bromophenyl tetra-O-*pivaloyl*-α-D-*mannopyranoside* (**8b**). To an ice-cold solution of 4-bromophenol (**7b**, 55.4 mg, 0.32 mmol) and 2,3,4,6-tetra-*O*-pivaloyl-α-D-mannopyranosyl fluoride (**5d**, 0.25 g, 0.48 mmol) in CH_2Cl_2 (1.5 mL) was added $BF_3{\cdot}OEt_2$ (180 μL, 1.5 mmol), and the mixture was stirred at 0 °C for 2 h. The mixture was poured into aq $NaHCO_3$ and extracted with EtOAc. The organic solution was washed with water and satd NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 14:1–9:1 hexanes–EtOAc) yielded 4-bromophenyl 2,3,4,6-tetra-*O*-pivaloyl-α-D-mannopyranoside (**8b**, 0.21 g, 100%) as a white solid: mp 60 °C; ^{1}H NMR (400 MHz, C_6D_6): δ 7.09 and 6.44 (2 d, both 2 H, *J* 9 Hz, Ar), 5.87 (dd, 1 H, $J_{2,3}$ 3.3 Hz, $J_{3,4}$ 10.2 Hz, H-3), 5.76 (t, 1 H, $J_{4,5}$ 10.2 Hz, H-4), 5.66 (dd, 1 H, $J_{1,2}$ 1.9 Hz, H-2), 5.11 (d, 1 H, H-1), 4.16 (dd, 1 H, $J_{5,6}$ 4.6 Hz, $J_{6,6'}$ 12.5 Hz, H-6), 4.06 (dd, 1 H, $J_{5,6'}$ 1.7 Hz, H-6′), 3.96 (ddd, 1 H, H-5), 1.28, 1.19, 1.18, and 1.13 (4 s, each 9 H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.5, 38.4, 38.5, 61.6, 64.7, 68.9, 69.6, 96.1, 115.6, 118.5, 132.8, 155.3, 177.4, 177.7, 177.9, 178.7; IR (cm^{-1}, KBr): 2973, 1737, 1486, 1281, 1150, 1124, 1030, 826; CIMS (CH_4) *m*/*z* 673 $[M+1]^+$, 499. Anal. Calcd for $C_{32}H_{47}BrO_{10}$: C, 57.23; H, 7.05. Found: C, 57.19; H, 6.83.

Ethyl 6-(2,3,4,6-tetra-O-*pivaloyl*-α-*mannopyranosyloxy)hexanoate* (**8a**). Compound **8a** was prepared by the general method except that the reaction was set up at 0 °C and then stored at 4 °C overnight. Yield (0.2 g, 100%): mp 76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46 (t, 1 H, $J_{3,4} = J_{4,5}$ 10.1 Hz, H-4), 5.36 (dd, 1 H, $J_{2,3}$ 3.3 Hz, H-3), 5.22 (dd, 1 H, $J_{1,2}$ 1.8 Hz, H-2), 4.74 (d, 1 H, H-1), 4.19 (dd, 1 H, $J_{5,6}$ 4.4 Hz, $J_{6,6'}$ 12.4 Hz, H-6), 4.12 (q, 2 H, *J* 7.4 Hz, CH_2CH$_3$), 4.11 (dd, 1 H, $J_{5,6'}$1.8 Hz, H-6′), 4.01 (ddd, 1 H, H-5), 3.70 (dt, 1 H, *J* 6.6, 9.9 Hz), 3.48 (m, 2 H), 3.43 (dt, 1 H, *J* 6.6, 9.5 Hz), 2.31 (t, 2 H, *J* 7.5 Hz), 1.63 (m, 4 H), 1.25 (m, 11 H), 1.23, 1.16, and 1.11 (4 s, each 9 H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 24.1, 25.1, 26.5, 26.6, 28.5, 33.7, 38.4, 38.5, 60.0, 61.8, 65.0, 67.9, 69.3, 69.4, 97.8, 174.2, 177.4, 177.8, 178.8; IR (cm^{-1}, KBr): 2971, 1737, 1482, 1285, 1155, 1134, 1077, 1046, 973; CIMS (CH_4) *m*/*z* 499 (100%, $M-O(CH_2)_5CO_2Et)]^+$). Anal. Calcd for $C_{34}H_{58}O_{12}$: C, 61.99; H 8.87. Found: C, 61.82; H, 8.91.

4-Nitrobenzyl 2,3,4,6-tetra-O-*pivaloyl*-α-D-*mannopyranoside* (**8c**). Compound **8c** was prepared by the above method except that the reaction was set up at 0 °C and then stored at

4 °C overnight. Yield (0.20 g, 100%): mp 146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 and 7.51 (2 d, both 2 H, J 9 Hz, Ar), 5.51 (t, 1 H, $J_{3,4} = J_{4,5}$ 10.1 Hz, H-4), 5.41 (dd, 1 H, $J_{2,3}$ 3.3 Hz, H-3), 5.33 (dd, 1 H, $J_{1,2}$ 1.6 Hz, H-2), 4.87 (d, 1 H, H-1), 4.84 and 4.65 (2 d, both 1 H, J 13.2 Hz, PhC*H*H), 4.19 (dd, 1 H, $J_{5,6}$ 4.4 Hz, $J_{6,6'}$ 12.5 Hz, H-6), 4.14 (dd, 1 H, $J_{5,6'}$1.8 Hz, H-6′), 4.05 (ddd, 1 H, H-5), 1.26, 1.24, 1.15, and 1.12 (4 s, each 9 H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.6, 38.4, 38.5, 61.6, 68.0, 69.1, 69.1, 69.3, 97.5, 124.1, 124.1, 144.2, 148.0, 176.6, 177.8, 178.0, 178.7; IR (cm^{-1}, KBr): 2981, 1742, 1524, 1477, 1279, 1129, 1077, 978; CIMS (CH_4) m/z 652 M^+, 499 (100%). Anal. Calcd for $C_{33}H_{49}NO_{12}$: C, 60.82; H 7.58; N, 2.15. Found: C, 60.47; H, 7.42; N, 2.11.

Methyl 3-(2,3,4,6-tetra-O-*pivaloyl*-α-D-*mannopyranosyloxy)lithocholate* (**8d**). Compound **8d** was prepared by the general method except that the reaction was run for 3 h at 0 °C. Yield (0.73 g, 95%): mp 175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (t, 1 H, $J_{3,4} = J_{4,5}$ 10.2 Hz, H-4), 5.40 (dd, 1 H, $J_{2,3}$ 2.9 Hz, H-3), 5.18 (dd, 1 H, $J_{1,2}$ 1.8 Hz, H-2), 4.91 (d, 1 H, H-1), 4.12 (m, 3 H, H-5, 6, and 6′), 3.66 (s, 3 H, CO_2Me), 3.56 (m, 1 H), 2.33 (ddd, 1 H, J 15, 9.9, and 4.7 Hz), 2.22 (ddd, 1 H, J 15, 9.9, and 7.0 Hz), 1.94 (m, 1 H), 1.77 (m, 6 H), 1.5–1.0 (m, 19 H), 1.25 (m, 2 H), 1.25, 1.22, 1.15, and 1.11(4 s, each 9 H, *t*-Bu), 0.91, 0.90, and 0.89(s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 18.5, 21.1, 23.6, 24.4, 26.5, 27.3, 27.4, 28.4, 28.6, 31.2, 32.7, 34.9, 35.6, 36.0, 38.9, 39.0, 39.1, 40.6, 42.3, 42.9, 51.6, 56.2, 56.6, 62.6, 65.7, 69.2, 69.7, 70.5, 78.8, 96.5, 174.9, 177.4, 178.0; IR (cm^{-1}, KBr): 2945, 1743, 1280, 1131, 1072; CIMS (CH_4) m/z 787 [M − (*t*-$BuCO_2H$)]$^+$, 499 (100%). Anal. Calcd for $C_{51}H_{84}O_{12}$: C, 68.89; H 9.52. Found: C, 68.76; H, 9.47.

1,6-Bis[3-(3-ethoxycarbonylmethylphenyl)-4-(2,3,4,6-tetra-O-*pivaloyl*-α-D-*mannopyranosyloxy)phenyl]hexane* (**6d**). Compound **6d** was prepared by the general method except that the reaction was run for 1.5 h at 0 °C. Yield (11.24 g, 91%): mp 133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (m, 6 H), 7.27 (dt, 2 H, J 6.6, 1.8 Hz), 7.17 (d, 2 H, J 1.8 Hz), 7.10 (t, 2 H, J 8 Hz), 7.08 (dd, 2 H, J 8.4 and 2.2 Hz), 5.38 (2 H, t, $J_{3,4} = J_{4,5}$ 10.2 Hz, H-4), 5.36 (d, 2 H, $J_{1,2}$ 1.8 Hz, H-1), 5.32 (dd, 2 H, $J_{2,3}$ 3.2 Hz, H-2), 5.30 (dd, 2 H, H-3), 4.14 (q, 4 H, J 7.0 Hz, OCH_2CH_3), 3.90 (dd, 2 H, (dd, 2 H, $J_{5,6}$ 4.4 Hz, $J_{6,6'}$ 12.4 Hz, H-6), 3.81 (dd, 2 H, $J_{5,6'}$ 1.8 Hz, H-6′), 3.72 and 23.69 (2 d, both 2 H, J 15.0 Hz, $ArCH_2CO_2Et$), 3.55 (ddd, 2 H, H-5), 2.58 (t, 4 H, J 7.7 Hz, $ArCH_2CH_2$–), 1.60 and 1.37 (2 m, both 4 H), 1.24 (t, 6 H, J 7.3 Hz, $CO_2CH_2CH_3$), 1.23, 1.14, 1.10, and 1.10 (4 s, each 9 H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 26.5, 26.6, 28.7, 31.1, 34.8, 38.3, 38.3, 38.4, 40.8, 60.5, 61.4, 64.5, 68.8, 69.1, 69.4, 97.6, 117.3, 128.3, 128.5, 128.8, 128.9, 130.8, 131.1, 132.8, 134.6, 138.5, 138.7, 151.0, 172.3, 177.2, 177.4, 177.7, 178.6; IR (cm^{-1}): (neat) 1736; FABMS m/z 1490 [M − (*t*-$BuCO_2H$)]$^+$, 499. Anal. Calcd for $C_{90}H_{126}O_{24}$: C, 67.90; H 7.98. Found: C, 67.61; H, 7.90.

General deacylation procedure

Preparation of 4-bromophenyl α-D-*mannopyranoside* (**9b**). To an ice-cold solution of 4-bromophenyl 2,3,4,6-tetra-*O*-pivaloyl-α-D-mannopyranoside (**8b**, 0.26 g, 0.39 mmol) in THF (1.2 mL) was added a freshly prepared solution of sodium methoxide (1.1 mL, 0.5 M), prepared from sodium and methanol. The ice-bath was removed, and the solution was stirred at rt overnight. After diluting with methanol (2 mL), sufficient Dowex-50W (H^+) resin was added to give an acidic solution. After removal of the resin by filtration, the solution was neutralized by filtration through a pad of barium carbonate. The solution was concentrated, and the residue was purified by flash chromatography (SiO_2, 4:1 $CHCl_3$–MeOH) to give 4-bromophenyl α-D-mannopyranoside (**9b**, 0.13 g, 100%) as a white solid: mp 209 °C, lit. mp 207–209 °C [8]; ^{1}H NMR (400 MHz, Me_2SO-d_6): δ 7.45 (d, 2 H, $J_{m,p}$ 9 Hz, Ar.), 7.05 (d, 2 H, Ar), 5.36 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1), 4.95 (d, 1 H, $J_{2,OH}$ 4.4 Hz, 2-OH), 4.75 (d, 1 H, $J_{4,OH}$ 5.9 Hz, 4-OH), 4.66 (d, 1 H, $J_{3,OH}$ 6.2 Hz, 3-OH), 4.36 (dd, 1 H, $J_{6',OH}$ 5.9 Hz, $J_{6,OH}$ 6.2 Hz, 6-OH), 3.82 (ddd, 1 H, $J_{2,3}$ 3.1 Hz, 2-H), 3.66 (ddd, 1 H, $J_{3,4}$ 9.2 Hz, 3-H), 3.60 (ddd, 1 H, $J_{5,6}$ 2.2 Hz, $J_{6,6'}$ 11.7 Hz, 6-H), 3.50 (ddd, 1 H, $J_{4,5}$ 9.5 Hz, H-4),

3.45 (ddd, 1 H, $J_{5,6'}$ 5.9 Hz, 6′-H), 3.36 (ddd, 1 H, H-5); ^{13}C NMR (100 MHz, Me_2SO-d_6): δ 61.8, 67.5, 70.7, 71.4, 75.8, 99.8, 114.2, 118.7, 119.8, 132.9, 156.4; IR (cm^{-1}, KBr): 3402, 3277, 2941, 1486, 1239, 1077, 1014, 983, 826; HRMS (MALDI, DHB matrix): Calcd for $C_{12}H_{15}BrO_6$·Na; 356.9933, found 356.9932.

Methyl 6-(α-D-mannopyranosyoxyl)hexanoate (**9a**). Compound **9a** was prepared by the general method. Yield (117 mg, 85%): mp 55 °C; ^{1}H NMR (400 MHz, Me_2SO-d_6, 50 °C): δ 4.59 (d, 1 H, J 1.5 Hz, 1-H), 4.55 (d, 1 H, $J_{4,OH}$ 5.1 Hz, 4-OH), 4.51 (d, 1 H, J 4.4 Hz, OH), 4.35 (d, 1 H, J 5.9 Hz, OH), 4.25 (dd, 1 H, $J_{6',OH}$ 5.8 Hz, $J_{6,OH}$ 6.2 Hz, 6-OH), 3.65 (ddd, 1 H, $J_{5,6}$ 2.4 Hz, $J_{6,6'}$ 11.5 Hz, 6-H), 3.60 (s, 3 H, OMe), 3.60 (m, 3 H, H-2 and OCH_2CH_2), 3.46 (dt, 1 H, $J_{5,6'}$ 5.9 Hz, 6′-H), 3.46 (m, 1 H, H-3), 3.39 (td, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.35 (ddd, 1 H, H-5), 2.30 (t, 2 H, J 7.3 Hz, CH_2CO_2Me), 1.56 and 1.52 (2 quint., both 2 H, J 7.3 Hz, $-CH_2-$), 1.33 (m, 2 H, $-CH_2-$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 25.8, 29.2, 34.0, 51.7, 61.1, 66.4, 67.7, 71.2, 71.8, 72.4, 100.2, 174.3; IR (cm^{-1}, KBr): 3392, 2941, 1737, 1439, 1239, 1135, 1098, 1061, 962, 684. Anal. Calcd for $C_{13}H_{24}O_8$: C, 50.64; H, 7.85. Found: C, 50.40; H, 7.68.

Preparation of 4-nitrobenzyl α-D-mannopyranoside (**9c**). Compound **9c** was prepared by the general method. Yield (0.9 g, 92%): mp 155 °C. The compound's NMR spectrum matched that reported in Ref. [9].

Methyl 3-(α-D-mannopyranosyloxy)lithocholate (**9d**). Compound **9d** was prepared by the general method except that the reaction was run for 19 h at rt. Yield (126 mg, 77%); ^{1}H NMR (400 MHz, Me_2SO-d_6): 4.75 (d, 1 H, J 1.4 Hz, 1-H), 4.60 (d, 1 H, J 4.4 Hz, OH), 4.55 (d, 1 H, J 4.0 Hz, OH), 4.44 (d, 1 H, J 5.8 Hz, OH), 4.30 (t, 1 H, $J_{6,OH}$ and $J_{6',OH}$ 5.9 Hz, 6-OH), 3.62 (dd, 1 H, $J_{6,6'}$ 10.6 Hz, 6-H), 3.58 (s, 3 H, OMe), 3.35–3.57 (m, 6 H), 2.32 (ddd, 1 H, J 15, 9.1, and 5.1 Hz), 2.22 (ddd, 1 H, J 15, 8.0, and 7.0 Hz), 1.91 (d, 2 H, J 7.7 Hz), 1.47–1.87 (m, 8 H), 1.29–1.44 (m, 6 H), 1.14–1.29 (m, 5 H), 0.99–1.14 (m, 4 H), 0.95 (m, 1 H), 0.88 (s, 3 H, Me), 0.87 (d, 3 H, J 7.7 Hz, $CHCH_3$), 0.61 (s, 3 H, Me); ^{13}C NMR (100 MHz, Me_2SO-d_6): δ 12.4, 18.7, 21.0, 23.7, 24.4, 26.6, 27.4, 28.2, 28.6, 30.9, 31.2, 32.8, 34.9, 35.3, 35.7, 35.9, 40.5, 41.9, 42.9, 51.7, 56.5, 62.0, 67.8, 71.4, 71.6, 74.5, 75.9, 98.6, 174.2; IR (cm^{-1}, KBr): 3434, 2941, 2868, 1737, 1449, 1114, 1061, 1025, 972, 684; HRMS (FAB, MNBA matrix): Calcd for $C_{31}H_{52}O_8$ $[M-H]^+$ 553.3742; found 553.3737.

Preparation of 1,6-bis[3-(3-carboxymethylphenyl)-4-(α-D-mannopyranosyloxy)phenyl]hexane (**1**).—Compound **1** was prepared by the general method except that the deacylation reaction was run for 5 h at 0 °C. The precipitate was collected by filtration, washed with a small volume of 2:1 THF–MeOH and acetone, and then dissolved in water. The pH was adjusted to 14 by the addition of NaOH (2 M), and the mixture was stirred at rt until the hydrolysis was complete by TLC. The aqueous solution was acidified using dilute HCl, and the precipitate was collected and dried under high vacuum over P_2O_5. Yield (14.1 g, 91%): mp 106–108 °C, lit. 106–108 °C [1c].

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