Synthesis of Building Blocks for Carba-oligosaccharides: 5a′-Carbamaltose and 5a′-Carbacellobiose, and 5a-Carba-β-D-mannopyranosyl-(1→4)-D-glucopyranose†

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Abstract: Practical synthesis of ether-linked 5a′-carbamaltose and -cellobiose, and the related carbadisaccharide starting from a sole condensate of the 1,2-anhydro-3-*O*-benzyl-4,6-*O*-benzylidene-5a-carba-β-D-mannopyranose and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside is described.

Key words: cyclitols, carbohydrate mimics, pseudo-oligosaccharides, carba-oligosaccharides, ether-linked 5a-carbadisaccharides

In recent years, much attentions have been focused on the chemistry and biochemistry of 5a-carbaoligosaccharides,[1] with extensive synthetic studies carried out.[2] In fact, the imino-linked 5a-carbaoligosaccharide validamycins,[3] and acarbose[4] and modified carba-amino sugar voglibose[5] have been widely used as agricultural antibiotics to control sheath blight of rice plant, and as an effective clinical remedy for treatment of diabetes, respectively. Ether-linked oligosaccharides[6,7] have been shown to act as substrate analogs[7] for some glycosyltransferases involved in oligosaccharide-chain biosynthesis. Because of their stability with regard to various glycosidases in vivo and an expected non-toxic nature for mammals, ether-linked carba-oligosaccharides might be expected to become one of the major subject for development of biologically active carbohydrate mimics as well as useful research tools for glycobiology.

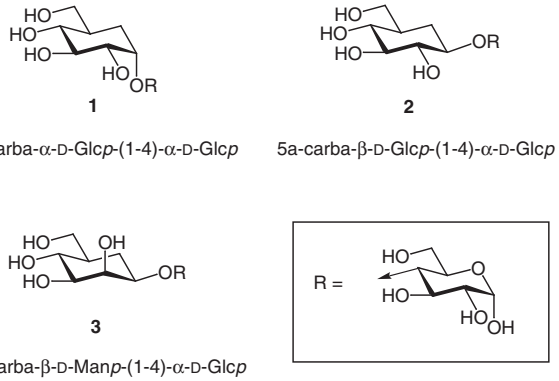


Figure 1

Methyl 5a′-carba-α-maltose has previously been synthesized[8] starting from the coupling product (45%) of 1,2-anhydro-3,4,6-tri-*O*-benzyl-5a-carba-β-D-manno-pyranose[9] (**4**) and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside[10] (**10**), with successful oxidation of the 2′−OH group followed by reduction with $NaBH_4$. However, under the basic conditions required to induce epimerization at the C-1 anomeric position (α→β), the benzyl-protected 5a-carba-hexulopyranose portion was found to be rather unstable, featuring β-elimination to give α,β-unsaturated ketones. Thus there has been a focus on incorporation of the 4′,6′-*O*-benzylidene function (→**5**) into the carba-sugar moiety to hinder this undesired elimination reaction and facilitate smooth configurational inversion at C-1 under basic conditions.

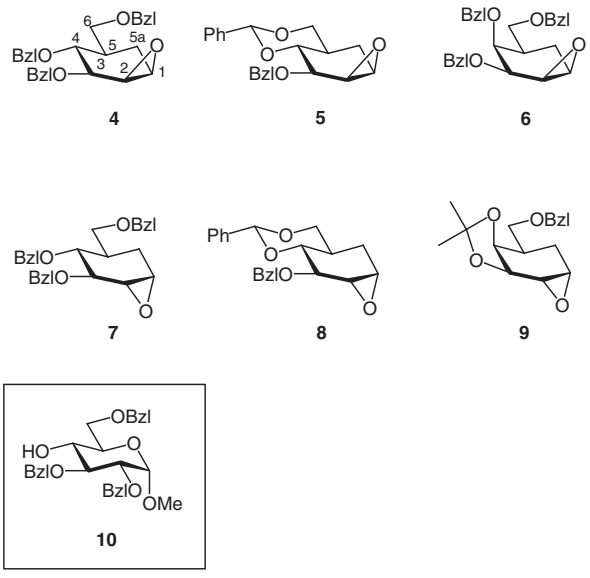
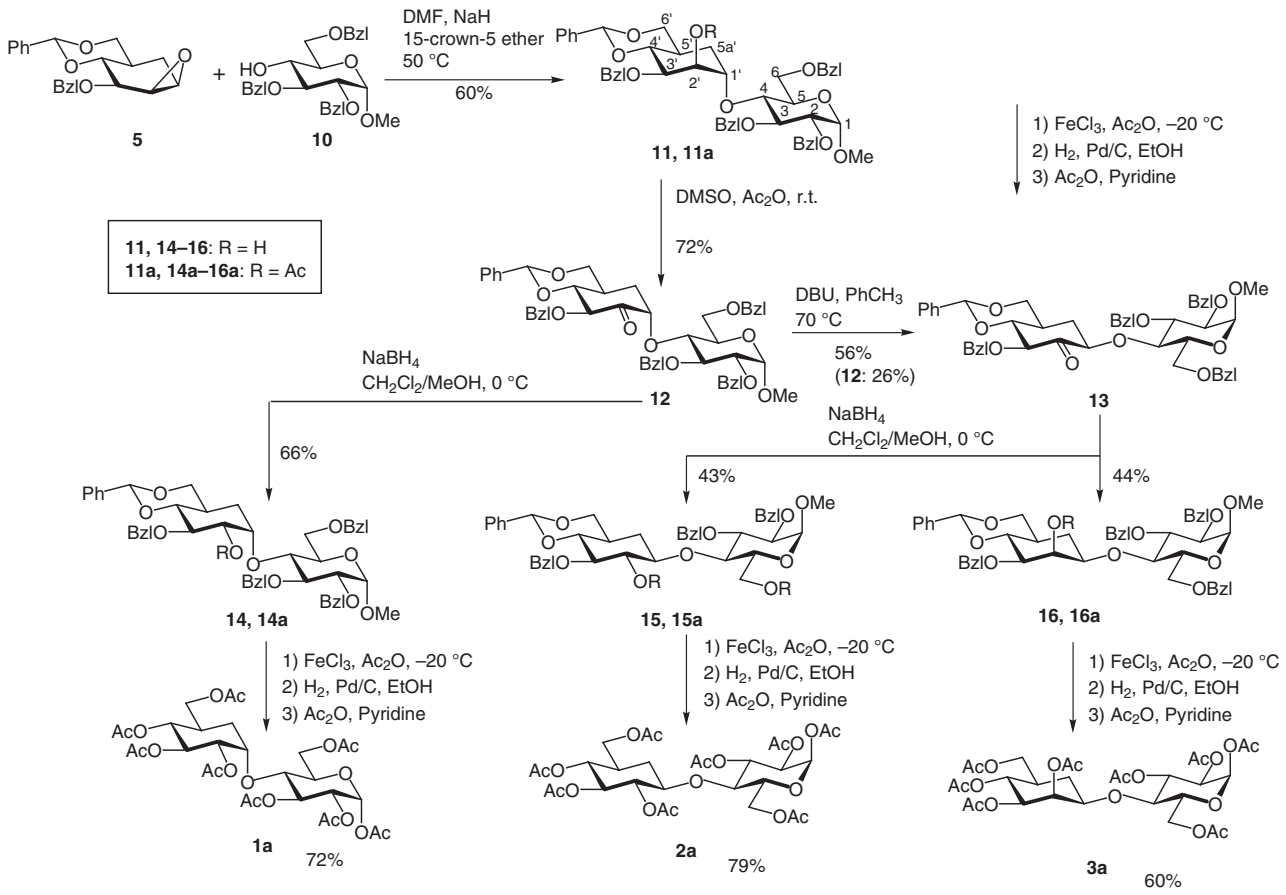


Figure 2

We would like to describe here the established procedure to access carbamaltose, carbacellobiose, and related carbadisaccharides of biological interest, by use of the condensate **11** of 1,2-anhydro-3-*O*-benzyl-4,6-*O*-benzylidene-5a-carba-β-D-mannopyranose (**5**) and the 4-OH unprotected acceptor **10**. Acetolysis of methyl 5a-carba-hexopyranosyl-(1→4)-α-D-glucopyranoside derivatives readily afforded the corresponding 5a′-carbadisaccharide peracetates in high yields. The β-*allo*-type epoxide **6** of this kind has been found to react similarly with methyl



Scheme

2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside to furnish the coupling product (40%).[11] Compound **6** should be a versatile donor for incorporation of 5a-carba-α-galactopyranose residues into oligosaccharide-chains.

Alternatively, attempted direct incorporation of 5a-carba-β-glucose or -β-galactose residue into oligosaccharide-chains has been attempted to generate the donors[12] such as the α-1,2-anhydro-5a-carba-hexopyranose derivatives **7**–**9**, but, under the influence of an oxide anion, all α-epoxides tested underwent elimination reaction at 5a-methylene,[13] giving α,β-unsaturated ketones mainly, and no substitution products are formed.

Coupling of **5** (2 molar equivalents) and an oxide anion generated from **10** by treatment with sodium hydride in DMF was carried out in the presence of 15-crown-5 ether overnight at 50 °C to give the condensate **11**, which, without further purification, was acetylated with acetic anhydride in pyridine to afford the 2′-acetate **11a** (60%). Formation of other condensates was not detected. The 5a-carba-α-*manno* configuration was supported by the ^{1}H NMR spectrum, which revealed a broad doublet (δ = 4.10 ppm, $J_{1',2'} = J_{1',5a'(eq)} = \sim 0$ Hz, $J_{1',5a'(ax)} = 2.6$ Hz) due to 1′-proton.

Compound **11** regenerated from **11a** by Zemplén de-*O*-acetylation[14] was treated with acetic anhydride in DMSO at room temperature to give the ketone **12** (72%). Epimerization at C-1′ was effected by treatment of **12** with DBU in toluene for 1.5 h at 70 °C to afford about a 1:2 equilibrium mixture, which was readily separable by silica gel chromatography to give the 1′-epimer **13** (56%), along with **12** (26%). These ketones are also thought to be potential intermediates for 2-amino-2-deoxy-5a-carbahexopyranosyl-oligosaccharides.

Reduction of **12** with sodium borohydride in CH_2Cl_2/MeOH at 0 °C gave a mixture of new disaccharide derivative **14** (66%), along with **11** (22%). These proved readily separable on a silica gel column and the structure of **14** was established by the ^{1}H NMR spectrum of its 2′-acetate **14a**, with a doublet of doublets (δ = 4.93 ppm, $J_{1',2'} = 3.7$ Hz, $J_{2',3'} = 10.0$ Hz) attributable to the 2′-proton.

Acetolysis[15] of **14a** with acetic anhydride with ferric chloride for 3 h at <−20 °C, followed by hydrogenolysis in the presence of 10% Pd/C under atmospheric pressure of hydrogen and subsequent conventional acetylation, afforded 5a′-carbamaltose octaacetate **1a** in a 72% overall yield. The ^{1}H NMR spectrum supported the proposed structure, demonstrating it to be a 3:1 mixture of the α- and β-anomers.

Similar reduction of **13** with $NaBH_4$ produced, after chromatography, two new disaccharides **15** (43%) and **16** (44%) without selectivity.[16] These were converted into the 2′-acetates **15a** and **16a**, respectively, the assigned structures of which were fully supported by the ^{1}H NMR spectra. Similar acetolysis of **15a** and **16a**, followed by

hydrogenolysis and subsequent acetylation, afforded the respective peracetyl 5a′-carbacellobiose **2a** (α-:β-anomer = 6:1)[17] and 5a-carba-β-D-Man*p*-(1→4)-D-Glc*p* **3a** (α-:β-anomer = 6:1) in 79% and 60% yields, respectively.

The 5a′-carbamaltose and -cellobiose thus obtained have now been assayed for enzyme-inhibitory activity and, interestingly, for possible substrate analogs for amylases and cellulases[18] to furnish unique oligo- and polysaccharides incorporating 5a-carba-D-glucopyranose residues.[19]

Specific rotations: Jasco DIP-370 polarimeter, 1-dm cells. IR spectra: Jasco A-202 or FT-IR-200. ^{1}H NMR spectra: Jeol JNM GSX-270 f.t. (270 MHz) and Jeol Lambda-300 (300 MHz); solvent: $CDCl_3$; internal standard: TMS. TLC: Silica Gel 60 GF (E. Merck, Darmstadt); detection by charring with concd H_2SO_4. Column chromatography: Silica gel 60 K070 (Katayama Chemicals, Osaka) and Wakogel C-300 (silica gel, 300 Mesh, Wako Chemical, Osaka). Organic solutions, after drying (Na_2SO_4), were concentrated <50 °C at diminished pressure.

Methyl (2-*O*-Acetyl-3-*O*-benzyl-4,6-*O*-benzylidene-5a-carba-α-D-mannopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (11a)

To a suspension of 60% NaH (258 mg, 6.45 mmol) in DMF (2.5 mL) was added a solution of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside[10] (**10**, 1.00 g, 2.15 mmol) in DMF (7.5 mL) and 15-crown-5 ether (1.3 mL, 6.5 mmol) at 0 °C, followed by stirring for 1.5 h at r.t. A solution of 1,2-anhydro-3-*O*-benzyl-4,6-*O*-benzylidene-5a-carba-β-D-mannopyranose[9] (**5**, 1.46 g, 4.31 mmol) was added and the mixture was stirred for 15 h at 50 °C. After cooling to 0 °C, the mixture was treated with a small amount of MeOH and then diluted with EtOAc (250 mL). The solution was washed with H_2O (3 × 50 mL), dried, and evaporated to dryness. The residue was treated with acetic anhydride (9 mL) in pyridine (17 mL) for 17 h at 25 °C. After treatment with MeOH, the mixture was evaporated and the residue was chromatographed on a silica gel column (150 g; EtOAc/toluene, 1:20) to give **11a** (1.05 g, 60%) as a white syrup, $[\alpha]_D^{28}$ = +22° (*c* 1.5, $CHCl_3$).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.16 [ddd, 1H, $J_{1',5a'(ax)}$ = 2.6, $J_{5',5a'(ax)} = J_{5a'gem}$ = 14.1 Hz, 5a′(ax)-H], 1.55 [br d, 1H, 5a′ (eq)-H], 1.98 (s, 3H, Ac), 2.14 (m, 1H, 5′-H), 3.36 (s, 3H, OMe), 3.52−3.98 (m, 8H, 2-H, 3-H, 4-H, 5-H, 6,6-CH_2, 4′-H, 6′a-H), 3.87 (br dd, 1H, $J_{2',3'}$ = ~0, $J_{3',4'}$ = 8.9 Hz, 3′-H), 3.95 (dd,1H, $J_{5',6'a}$ = 4.3, $J_{6'gem}$ = 10.9 Hz, 6′b-H), 4.10 [br d, 1H $J_{1',5a'(ax)}$ = 2.6 Hz, 1′-H], 4.60 (m, 1H, 1-H), 4.55 and 4.68 (ABq, J_{gem} = 12.0 Hz), 4.61 (m, 4H), 4.82 and 5.05 (ABq, J_{gem} = 11.4 Hz) (4 × CH_2Ph), 5.59 (s, 1H, C*H*Ph), 5.64 (br s, 1H, 2′-H), 7.20−7.53 (m, 25H, 5 × Ph).

Anal. Calcd for $C_{56}H_{57}O_{11}$ (845.0): C, 72.49; H, 6.68. Found: C, 72.36; H, 6.68.

Methyl (3-O-Benzyl-4,6-O-benzylidene-5a-carba-α-D-*arabino*-hex-2-ulopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (12)

To a solution of **11a** (1.07 g, 1.27 mmol) in MeOH (11 mL) was added 1 M sodium methoxide/MeOH (2 mL) for 17 h at 25 °C. After neutralization with Amberlite IR-120B (H^+), the mixture was evaporated to dryness. The residue was treated with acetic anhydride (3.2 mL) in DMSO (18.6 mL) for 17 h at 25 °C. After treatment with MeOH at 0 °C to destroy excess acetic anhydride, the mixture was diluted with EtOAc (240 mL), washed thoroughly with H_2O, dried, and concentrated. The residue was chromatographed on a silica gel column (90 g; EtOAc/toluene, 1:30) to give **12** (0.72 g, 72%) as a colorless syrup, $[\alpha]_D^{28}$ = −6.3° (*c* 1.1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 [ddd, 1H, $J_{1',5a'(ax)}$ = 2.4, $J_{5',5a'(ax)}$ = 9.5, $J_{5a''gem}$ = 14.4 Hz, 5a′(ax)-H], 1.64 [ddd, 1H, $J_{1',5a'(eq)} = J_{5',5a'(eq)}$ = 2.9 Hz, 5a′(eq)-H], 2.44 (m, 1H, 5′-H), 3.28 (s, 3H, OMe), 3.41−3.65 (m, 7H, 2-H, 3-H, 4-H, 6,6-CH_2, 4′-H, 6′a-H), 3.76 (m, 1H, 5-H), 3.99 (dd, 1H, $J_{5',6'a}$ = 4.4, $J_{6'gem}$ = 11.0 Hz, 6′b-H), 4.16 (d, 1H, $J_{3,4}$ = 9.5 Hz, 3′-H), 4.18 [dd, 1H, $J_{1',5a'(eq)}$ = 2.9 Hz, 1′-H], 4.47 (d, 1H, $J_{1,2}$ = 3.7 Hz, 1-H), 4.40−4.50 (m, 3H) and 4.58−4.65 (m, 5H) (4 × CH_2Ph), 5.45 (s, 1H, C*H*Ph), 7.09−7.47 (m, 25H, 5 × Ph).

Anal. Calcd for $C_{49}H_{52}O_{10}$ (801.0): C, 73.48; H, 6.54. Found: C, 73.26; H, 6.46.

Methyl (3-*O*-Benzyl-4,6-*O*-benzylidene-5a-carba-α-D-manno-(11) and -glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (14)

To a solution of **12** (1.27 g, 1.59 mmol) in CH_2Cl_2/MeOH (10:1, 25 mL) was added $NaBH_4$ (0.40 g, 9.5 mmol), and the mixture was stirred for 1 h at 0 °C. TLC (EtOAc/toluene, 1:4) showed the appearance of two components (R_F = 0.38 and 0.51) and the disappearance of **12** (R_F = 0.58). The mixture was diluted with EtOAc (250 mL), washed with H_2O, dried, and evaporated. The residue was chromatographed on a silica gel column (120 g; EtOAc/hexane, 1:6) to give **11** (0.28 g, 22%) and **14** (0.84 g, 66%) as syrups.

11:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 [m, 1H, 5a′(eq)-H], 1.39 [m, 1H, 5a′(ax)-H], 2.29 (m, 1H, 5′-H), 3.38 (s, 3H, OMe), 3.51−3.99 (m, 10H, 2-H, 3-H, 4-H, 5-H 6,6-CH_2, 3′-H,. 4′-H, 6′,6′-H_2), 4.15 (m, 2H, 1′-H, 2′-H), 4.61 (m, 1H, 1-H), 4.39−4.73 (m, 4H), 4.70 and 4.87 (ABq, J_{gem} = 10.7 Hz), and 4.70−5.05 (ABq, J_{gem} = 10.7 Hz) (4 × CH_2Ph), 5.63 (s, 1H, C*H*Ph), 7.53 (m, 25H, 5 × Ph).

14:

$[\alpha]_D^{18}$ = −9.4° (*c* 0.68, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.71 [ddd, 1H, $J_{1',5a'(ax)}$ = 1.8, $J_{5',5a'(ax)} = J_{5a'gem}$ = 14.0 Hz, 5a′(ax)-H], 1.37 [ddd, 1H, $J_{1',5a'(eq)} = J_{5',5a'(ax)}$ = 2.9 Hz, 5a′(eq)-H], 2.11 (m, 1H, 5′-H), 3.38 (s, 3H, OMe), 3.40−3.47 (m, 3H, 2′-H, 4′-H, 6′b-H), 3.52 (dd, 1H, $J_{2',3'} = J_{3',4'}$ = 9.4 Hz, 3′-H), 3.66−3.71 (m, 4H, 2-H, 3-H, 4-H, 6a-H), 3.90−4.03 (m, 4H, 5-H, 6b-H, 1′-H, 6′a-H), 4.20 and 4.26 (ABq, J_{gem} = 11.0 Hz), 4.55 and 4.66 (ABq, J_{gem} = 11.0 Hz) and 4.48 and 4.68 (ABq, J_{gem} = 12.2 Hz) (3 × CH_2Ph), 4.60 (d, 1H, $J_{1,2}$ = 3.4 Hz, 1-H), 5.52 (s, 1H, C*H*Ph), 7.19−7.50 (m, 25H, 5 × Ph).

Anal. Calcd for $C_{49}H_{54}O_{10}$ (803.0): C, 73.30; H, 6.78. Found: C, 73.22; H, 6.81.

Methyl (2-*O*-Acetyl-3-*O*-benzyl-4,6-*O*-benzylidene-5a-carba-α-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (14a)

Compound **14** (31 mg, 0.039 mmol) was treated with acetic anhydride (0.5 mL) and pyridine (1 mL) for 17 h at 25 °C. The reaction mixture was processed in the usual manner and the product was chromatographed on a silica gel column (3 g; EtOAc/toluene, 1:20) to give **14a** (29 mg, 92%) as a syrup, $[\alpha]_D^{28}$ = +23° (*c* 1.5, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 [ddd, 1H, $J_{1',5a'(ax)}$ = 1.6, $J_{5',5a'(ax)} = J_{5a'gem}$ = 14.8 Hz, 5a′ (ax)-H], 1.84 [ddd, 1H, $J_{1',5a'(eq)} = J_{5',5a'(eq)}$ = 3.5 Hz, 5a′(eq)-H], 2.00 (s, 3H, Ac), 2.15 (m, 1H, 5′-H), 3.38 (s, 3H, OMe), 3.48 (dd, 1H, $J_{3',4'} = J_{4',5'}$ = 11.1 Hz, 4-H), 3.70−3.78 (m, 3H, 2-H, 6-H, 6′b-H), 3.82 (dd, 1H, $J_{5,6a}$ = 2.9, J_{6gem} = 10.3 Hz, 6a-H), 3.89−3.98 (m, 3H, 3-H, 3′-H, 6′a-H), 4.59−4.73 (m, 6H, 1-H, 1′-H, 2 × CH_2Ph), 4.93 (dd, 1H, $J_{1',2'}$ = 3.7, $J_{2',3'}$ = 10.0 Hz, 2′-H), 4.54 and 4.85 (ABq, J_{gem} = 11.6 Hz) and 4.65 and 5.01 (ABq, J_{gem} = 10.7 Hz) (2 × CH_2Ph), 5.59 (s, 1H, C*H*Ph), 7.22−7.72 (m, 25H, 5 × Ph).

Anal. Calcd for $C_{51}H_{56}O_{11}$ (845.0): C, 72.49; H, 6.68. Found: C, 72.24; H, 6.59.

(2,3,4,6-Tetra-*O*-acetyl-5a-carba-α-D-glucopyranosyl)-(1→4)-1,2,3,6-tetra-*O*-acetyl-D-glucopyranose (1a)

To a stirred solution of **14a** (566 mg, 0.70 mmol) in acetic anhydride (17 mL) was added ferric (III) chloride (17 mg, 0.11 mmol) at −20 °C, and the mixture was stirred for a further 3 h at the same temperature. TLC (EtOAc/toluene, 1:2) showed a disappearance of **14a** (R_F = 0.54) and formation of two components (R_F = 0.21 and 0.37). The mixture was diluted with EtOAc (300 mL) and the solution was washed with sat. $NaHCO_3$ and H_2O, dried, and evaporated. The residue was dissolved in EtOH (17 mL), and the solution was hydrogenated in the presence of 10% Pd/C in the presence of two drops of 1 M hydrochloric acid for 17 h at 25 °C. The catalyst was removed by filtration and the filtrate was evaporated. The residue was acetylated in the usual manner and the product was chromatographed on a silica gel column (30 g, acetone/toluene, 1:6) to give an anomeric mixture (343 mg, 72%) of **1a** as a white solid, $[\alpha]_D^{19}$ = +77° (*c* 0.55, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 [m, 1H, 5a′(ax)-H], 1.90−2.16 (s, each 3H, 8 × Ac), 3.71 (dd, 1H, $J_{3,4} = J_{4,5}$ = 9.7 Hz, 4-H), 3.80 (dd, 1H, $J_{5',6'a}$ = 2.8, $J_{6'gem}$ = 11.3 Hz, 6′a-H), 4.01 (m, 1H, 4-H), 4.04 (dd, 1H, $J_{5',6'b}$ = 3.8 Hz, 6′b-H), 4.13 (dd, 1H, $J_{5,6a}$ = 3.4, J_{6gem} = 12.4 Hz, 6a-H), 4.20 (m, 1H, 1′-H), 4.34 (dd, 1H, $J_{5,6b}$ = 2.2 Hz, 6b-H), 4.72 (dd, 1H, $J_{1',2'}$ = 3.2, $J_{2',3'}$ = 10.3 Hz, 2′-H), 4.90 (dd, 1H, $J_{1\alpha,2}$ = 3.7, $J_{2,3}$ = 9.7 Hz, 2-H), 4.91 (m, 1H, 4′-H), 5.24 (dd, 1H, $J_{3',4'}$ = 9.8 Hz, 3′-H), 5.43 (dd, 1H, $J_{3,4}$ = 9.7 Hz, 3-H), 5.66 (d, 1H, $J_{1\beta,2}$ = 8.3 Hz, 1β-H), 6.16 (d, 1H, $J_{1\alpha,2}$= 3.7 Hz1α-H) (α:β ~ 3:1).

Anal. Calcd for $C_{29}H_{40}O_{18}$ (676.6): C, 51.48; H, 5.96. Found: C, 51.63; H, 6.03.

Methyl (3-*O*-Benzyl-4,6-*O*-benzylidene-5a-carba-β-D-*arabino*-hex-2-ulopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (13)

To a solution of **12** (675 mg, 0.84 mmol) in toluene (13 mL) was added DBU (250 mg, 1.68 mmol), and the mixture was stirred for 1.5 h at 70 °C. TLC (EtOAc/toluene, 1:4) revealed the formation of a new component (R_F = 0.33). The reaction mixture was diluted with EtOAc (100 mL), washed with H_2O, dried, and evaporated. The residue was chromatographed on a silica gel column (70 g; EtOAc/toluene, 1:30) to give **12** (178 mg, 26%) and **13** (340 mg, 56%) as syrups.

13:

$[\alpha]_D^{21}$ = −1.8° (*c* 1.1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 [ddd, 1H, $J_{1',5a'(ax)}$ = 12.5, $J_{5',5a'(ax)} = J_{5a'gem}$ = 12.7 Hz, 5a′(ax)-H], 1.66 (m, 1H, 5′-H), 1.79 [ddd, 1H, $J_{1',5a'(eq)}$ = 6.6, $J_{5',5a'(eq)}$ = 3.2 Hz, 5a′(eq)-H], 3.39 (s, 3H, OMe), 3.40 (dd, 1H, $J_{5',6'a}$ = 2.9, $J_{6'gem}$ = 11.7 Hz, 6′a-H), 3.48−3.54 (m, 3H, 2-H, 5-H, 4′-H), 3.81−3.97 (m, 6H, 3-H, 4-H, 6,6-H_2, 3′-H, 6′b-H), 4.21 (dd, 1H, 1′-H), 4.56−4.80 (m, 6H), and 4.60 and 5.09 (ABq, J_{gem} = 11.7 Hz) (4 × CH_2Ph), 5.46 (s, 1H, C*H*Ph), 7.22−7.41 (m, 25H, 5 × Ph).

Anal. Calcd for $C_{49}H_{52}O_{10}$ (801.0): C, 73.48; H, 6.54. Found: C, 73.46; H, 6.47.

Methyl (3-*O*-Benzyl-4,6-*O*-benzylidene-5a-carba-β-D-gluco- (15) and β-D-mannopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (16)

A solution of **13** (1.13 g, 1.4 mmol) in CH_2Cl_2/MeOH (10:1) (23 mL) was treated with $NaBH_4$ (0.36 g, 9.4 mmol) for 2 h at 0 °C. TLC (EtOAc/toluene, 1:4) showed formation of new components (R_F = 0.18 and 0.38) and disappearance of **13** (R_F = 0.50). The reaction mixture was processed as for the preparation of **14**, and the products were chromatographed on a silica gel column (100 g, EtOAc/toluene, 1:10) to give **15** (0.48 g, 43%) and **16** (0.49 g, 44%) as syrups.

15:

$[\alpha]_D^{18}$ = +11° (*c* 0.95, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.71 [ddd, 1H, $J_{1',5a'(ax)} = J_{5',5a'(ax)}$ = 12.0, $J_{5a'gem}$ = 12.9 Hz, 5a′(ax)-H], 1.40 (m, 1H, 5′-H), 1.69 [ddd, 1H, $J_{1',5a'(eq)} = J_{5',5a'(eq)}$ = 3.9 Hz, 5a′(eq)-H], 3.09 (s, 1H, OH), 3.27 (dd, 1H, $J_{2',3'} = J_{3',4'}$ = 10.9 Hz, 3′-H), 3.30 (dd, 1H, $J_{5',6'a}$ = 2.9, $J_{6'gem}$ = 11.2 Hz, 6′a-H), 3.37 (s, 3H, OMe), 3.38−3.46 (m, 3H, 1′-H, 2′-H, 4′-H), 3.51 (dd, 1H, $J_{1,2}$ = 3.8, $J_{2,3}$ = 9.5 Hz, 2-H), 3.66−3.70 (m, 3H, 4-H, 5-H, 6a-H), 3.81 (m, 2H, 3-H, 6′b-H), 4.02 (dd, 1H, $J_{5,6b}$ = 2.4, J_{6gem} = 10.4 Hz, 6b-H), 4.48 and 4.59 (ABq, J_{gem}= 11.5 Hz, CH_2Ph), 4.60 (d, 1H, $J_{1,2}$ = 3.8 Hz, 1-H), 4.60 and 5.07 (ABq, J_{gem} = 11.0 Hz), 4.70 and 4.76 (ABq, J_{gem} = 11.4 Hz), and 4.70 and 4.94 (ABq, J_{gem} = 11.4 Hz) (3 × CH_2Ph), 5.46 (m, 25H, 5 x Ph).

Anal. Calcd for $C_{49}H_{54}O_{10}$ (803.0): C, 73.30; H, 6.78. Found: C, 73.19; H, 6.70.

16:

$[\alpha]_D^{18}$ = +18° (*c* 1.7, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34−1.39 (m, 3H, 5′-H, 5a′, 5a′-CH_2), 2.49 (s, 1H, OH), 3.26 (dd, 1H, $J_{2',3'}$ = 2.4, $J_{3',4'}$ = 9.0 Hz, 3′-H), 3.37 (s, 3H, OMe), 3.64−3.72 (m, 6H, 2-H, 4-H, 5-H, 6a-H, 1′-H, 6′a-H), 3.84−3.95 (m, 4H, 3-H, 6b-H, 4′-H, 6′b-H), 4.21 (br s, 1H, 2′-H), 4.47 and 4.64 (ABq, J_{gem} = 11.5 Hz), and 4.56 and 4.65 (ABq, J_{gem} = 11.9 Hz) (2 × CH_2Ph), 4.61 (d, 1H, $J_{1,2}$ = 3.4 Hz, 1-H), 4.63 and 5.05 (ABq, J_{gem} = 11.0 Hz), and 4.68 and 4.78 (ABq, J_{gem} = 12.5 Hz) (2 × CH_2Ph), 5.53 (s, 1H, C*H*Ph), 7.24−7.50 (m, 25H, 5 × Ph).

Anal. Calcd for $C_{49}H_{54}O_{10}$ (803.0): C, 73.48; H, 6.54. Found: C, 73.37; H, 6.74.

Methyl (2-*O*-Acetyl-3-*O*-benzyl-4,6-*O*-benzylidene-5a-carba-β-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (15a)

Compound **15** (110 mg, 0.14 mmol) was acetylated as for the preparation of **14a**, and the product was chromatographed on a silica gel column (10 g; EtOAc/toluene, 1:15) to give **15a** (102 mg, 88%) as a syrup, $[\alpha]_D^{19}$ = +1.3° (*c* 1.2, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.60 [m, 1H, 5a′(ax)-H], 1.36 (m, 1H, 5′-H), 1.80 [m, 1H, 5a′(eq)-H], 1.82 (s, 3H, Ac), 3.11 (dd, 1H, $J_{5',6'a} = J_{6'gem}$ = 11.3 Hz, 6′a-H), 3.22 [dd, 1H, $J_{1',2'} = J_{1',5a'(ax)}$ = 9.5 Hz, 1′-H], 3.22 (dd, 1H, $J_{2',3'} = J_{3',4'}$ = 9.5 Hz, 3′-H), 3.29 (s, 3H, OMe), 3.35−3.51 (m, 5H, 2-H, 4-H, 5-H, 6a-H, 4′-H), 3.66 (dd, 1H, $J_{2,3} = J_{3,4}$ = 9.3 Hz, 3-H), 3.71 (dd, 1H, $J_{5,6b}$ = 2.9, J_{6gem} = 10.7 Hz, 6b-H), 3.78 (dd, 1H, $J_{5',6'b}$ = 4.2 Hz, 6′b-H), 4.51 (d, 1H, $J_{1,2}$ = 2.9 Hz, 1-H), 4.32, 4.51, 4.53, 4.56, 4.61, 4.70, 4.79, 4.92 (ABq, 2 CH_2Ph), 4.84 (dd, 1H, $J_{1',2'} = J_{2',3'}$ = 9.5 Hz, 2′-H), 5.38 (s, 1H, C*H*Ph), 7.17−7.42 (m, 25H, 5 Ph).

Anal. Calcd for $C_{51}H_{56}O_{11}$ (845.0): C, 72.49; H, 6.68. Found: C, 72.28; H, 6.75.

Methyl (2-*O*-Acetyl-3-*O*-benzyl-4,6-*O*-benzylidene-5a-carba-β-D-mannopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (16a)

Compound **16** (112 mg, 0.14 mmol) was acetylated as for the preparation of **14a**, and the product was chromatographed on a silica gel column (10 g; EtOAc/toluene, 1:15) to give **16a** (115 mg, 97%) as a white syrup, $[\alpha]_D^{28}$ = −7.2° (*c* 1.3, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 [m, 2H, 5′-H, 5a′(ax)-H], 1.62 [m, 2H, 5a′ (eq)-H], 2.12 (s, 3H, Ac), 3.21 (dd, 1H, $J_{2',3'}$ = 2.8, $J_{3',4'}$ = 9.6 Hz, 3′-H), 3.37 (s, 3H, OMe), 3.41−3.81 (m, 10H), 4.60 (m, 1H, 1-H), 4.55−4.66 (m, 4H, 2 × CH_2Ph), 4.42, 4.51, 4.76, and 5.07 (ABq, 4H, 2 × CH_2Ph), 5.51 (s, 1H, C*H*Ph), 5.59 (br s, 1H, 2′-H), 7.23−7.50 (m, 25H, 5 × Ph).

Anal. Calcd for $C_{51}H_{56}O_{11}$ (845.0): C, 72.49; H, 6.68. Found: C, 72.15; H, 6.68.

(2,3,4,6-Tetra-*O*-acetyl-5a-carba-β-D-glucopyranosyl)-(1→4)-1,2,3,6-tetra-*O*-acetyl-D-glucopyranose (2a)

Compound **15a** (462 mg, 0.58 mmol) was treated with ferric chloride (14 mg, 0.09 mmol) in acetic anhydride (14 mL) for 1 h at −20 °C. The reaction mixture was processed as for the preparation of **1a**. The product was then hydrogenolyzed in the presence of 10% Pd/C, and acetylated in the usual manner. The product was chromatographed on a silica gel column (3 g, acetone/toluene, 1:8) to give **2a** (309 mg, 79%) as a white syrup, $[\alpha]_D^{19} = +47°$ (*c* 0.65, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 [m, 1H, 5a′(ax)-H], 1.80 (m, 1H, 5′-H), 1.98, 2.00, 2.02, 2.05, 2.06, 2.08, 2.12, and 2.19 (8s, each 3H, 8 × Ac), 2.25 [m, 1H, 5a′(eq)-H], 3.51 (m, 1H, 1′-H), 3.57 (dd, 1H, $J_{3,4} = J_{4,5} = 9.6$ Hz, 4-H), 3.84 (ddd, 1H, $J_{4,5} = 9.6$, $J_{5,6a} = 2.2$, $J_{5,6b} = 4.8$ Hz, 5-H), 3.88 (dd, 1H, $J_{5',6'a} = 2.9$, $J_{6'gem} = 11.5$ Hz, 6′a-H), 4.04 (dd, 1H, $J_{5',6'b} = 5.1$ Hz, 6′b-H), 4.11 (dd, 1H, $J_{5,6a} = 4.8$, $J_{6gem} = 12.0$ Hz, 6a-H), 4.44 (dd, 1H, $J_{5,6b} = 2.2$ Hz, 6b-H), 4.94−5.04 (m, 4H, 2-H, 2′-H, 3′-H, 4′-H), 5.37 (dd, 1H, $J_{2,3} = J_{3,4} = 9.6$ Hz, 3-H), 6.16 (d, 1H, $J_{1\alpha,2} = 3.7$ Hz, 1α -H), 5.59 (d, 1H, $J_{1\beta,2} = 8.3$ Hz, 1β-H) (α:β ~ 6:1).

Anal. Calcd for $C_{29}H_{40}O_{18}$ (676.6): C, 51.48; H, 5.96. Found: C, 51.37; H, 5.91.

(2,3,4,6-Tetra-O-acetyl-5a-carba-β-D-mannopyranosyl)-(1→4)-1,2,3,6-tetra-*O*-acetyl-D-glucopyranose (3a)

Compound **16** (40 mg, 0.050 mmol) was similarly subjected to acetolysis, hydrogenolysis, and acetylation. The peracetate was obtained by chromatography on a silica gel column (3 g, acetone/toluene, 1:9) to give **3a** (20 mg, 60%) as a white syrup, $[\alpha]_D^{21} = +46°$ (*c* 0.60, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76 [ddd, 1H, $J_{1',5a'(eq)} = J_{5',5a'(eq)} = J_{5a'gem} = 12.6$ Hz, 5a′(ax)-H], 1.82−1.87 [m, 2H, 5′-H, 5a′(eq)-H], 1.97, 2.01, 2.04, 2.09, 2.12, 2.13, 2.14, and 2.17 (8s, each 3H, 8 × Ac), 3.73 (m, 1H, 1′-H), 3.74 (dd, 1H, $J_{3,4} = J_{4,5} = 9.3$ Hz, 4-H), 3.94 (dd, 1H, $J_{5,6a} = 3.7$, $J_{6gem} = 12.0$ Hz, 6a-H), 3.89−4.07 (m, 3H, 5-H, 6′,6′-CH_2). 4.44 (dd, 1H, $J_{5,6b} = 2.0$ Hz, 6b-H), 4.77 (dd, 1H, $J_{2',3'} = 2.8$, $J_{3',4'} = 10.3$ Hz, 3′-H), 4.99 (dd, 1H, $J_{1\alpha,2} = 3.7$, $J_{2,3} = 10.4$ Hz, 2-H), 5.14 (dd, 1H, $J_{4',5'} = 10.3$ Hz, 4′-H), 5.44 (dd, 1H, $J_{3,4} = 9.3$ Hz, 3-H), 5.58 (br s, 1H, 2′-H), 5.68 (d, 1H, $J_{1\beta,2} = 8.5$ Hz, 1β-H), 6.24 (d, 1H, $J_{1\alpha,2} = 3.7$ Hz, 1α-H) (α:β ~ 6:1).

Anal. Calcd for $C_{29}H_{40}O_{18}$ (676.6): C, 51.48; H, 5.96. Found: C, 51.16; H, 5.97.

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