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Synthesis of carbocyclic analogues of the mannosyl trisaccharide: ether- and imino-linked methyl 3,6-bis(5a-carba-α-D-mannopyranosyl)-3,6-dideoxy-α-D-mannopyranosides ☆

Seiichiro Ogawa *, Shin-ichi Sasaki, Hidetoshi Tsunoda

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama, 223, Japan

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Abstract

Carbocyclic analogues **2** and **3** of the "trimannosyl structure **1**", methyl 3,6-bis(5a-carba-α-D-mannopyranosyl)-3,6-dideoxy-α-D-mannopyranosides bonded by way of respective ether and imino linkages, were synthesized. The ether **2** had no inhibitory activity against α-D-mannosidase; in contrast, the imino compound **3** was a mild inhibitor. Furthermore, the inhibitory activity of **4**, related to **3** by introduction of unsaturation between C-5 and C-5a of the carba-sugar moieties, was shown to be somewhat greater.

Keywords: Synthesis; Cyclitols; 5a-Carba-trisaccharides; Glycosidase inhibitors; Neoglycoconjugates

1. Introduction

Carba-sugar analogues of naturally occurring oligosaccharides have so far been used as model compounds for conformational analyses [2] of true oligosaccharides, as substrate analogues for study of enzymic reactions [3], or as potential inhibitors [4] against sugar hydrolases and transferases. In previous papers [1,5], we described a

☆ Synthesis of carba-oligosaccharides related to cell-surface glycans, Part 3. For Part 2, see ref. [1].

* Corresponding author.

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synthesis of 5a-carba-sugar analogues of naturally occurring disaccharides and the branching trisaccharide components of the "trimannosyl core" of glycoproteins. These are all glycosides, the non-reducing ends being composed of the true sugar residues, and some of them were useful as substrates or as model compounds for structural analysis. Since the biological properties of ether-linked 5a-carba-oligosaccharides have not been studied extensively so far, it may be desirable to elaborate a convenient method generally applicable for the introduction of 5a-carba-sugar residues into oligosaccharide chains by way of ether bridges.

Paulsen and von Deyn [6] have reported the first synthesis of four interesting ether-linked 5a-carba-disaccharides by treating the 4- and 6-triflate derivatives of hexopyranoses with the appropriately protected 5a-carba-sugars under basic conditions. According to their method, we require suitable triflate derivatives of hexopyranoses which are reactive toward appropriate nucleophiles. In general, it seemed that it is not always an easy task to prepare such appropriate pairs of acceptor and donor. Therefore, attempts were initially made to construct the ether bond by cleavage of the epoxides, versatile carba-sugar donors, with an oxide anion generated from suitably protected hexopyranose acceptors [7].

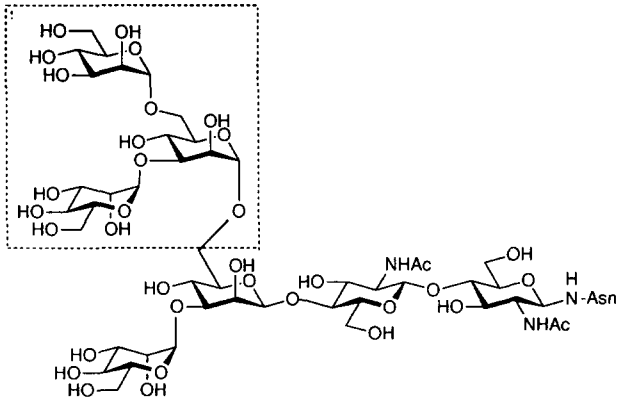
In continuation of the previous work [1], the 5a-carba-sugar analogue of the "trimannosyl structure **1**", methyl 3,6-di-*O*-(5a-carba-α-D-mannopyranosyl)-α-D-mannopyranoside (**2**), part of the common heptasaccharide of *N*-linked sugar chains of high mannose type, was chosen as the target 5a-carba-trisaccharide, expecting it to be a potent inhibitor of α-D-mannosidase and/or transferase GlcNAc II. In addition, in order to evaluate the biological activity of the ether-linked 5a-carba-sugar residues in **2**, the corresponding imino-linked analogues **3** and **4** were also synthesized as reference compounds in a conventional manner.

2. Results and discussion

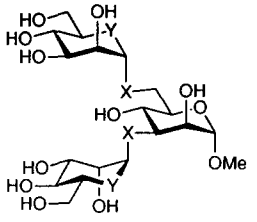
Synthesis of 5-carba-trisaccharide analogues **2–4** and the useful synthetic intermediates **11, 20**, and **26** has been carried out using 1,2-anhydro-3,4,6-tri-*O*-benzyl-5a-carba-β-D-mannopyranose [8] (**6**) as a potential 5a-carba-α-D-mannosyl donor.

Initially, an attempt was made to allow **6** to react with an oxide anion generated from methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside [9] (**7**) by treatment with an excess of sodium hydride in *N,N*-dimethylformamide (DMF). Thus, treatment of 3 molar equiv. of **6** with the oxide anion derived from **7** in the presence of 18-crown-6 ether for 2 h at 70°C gave rise to a single coupling product **8** in 67% yield. The structure of **8** was established by converting it into the acetate **9** (93%), the ^{1}H NMR spectrum ($CDCl_3$) of which revealed a triplet (δ 5.57, J 4.0 Hz) due to the H-2, supporting the *α-manno* configuration of the carba-sugar residue. Opening of the epoxide ring proceeded regioselectively, satisfying the Fürst-Plattner rule as well as being electronically favoured.

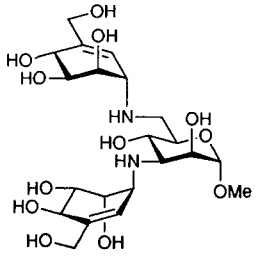
Compound **8** was then protected by benzylation to give the pentabenzyl ether **10** (77%), cleavage of the benzylidene group of which with DIBAL-H in dichloromethane proceeded regioselectively to give the 6-OH-unprotected hexabenzyl ether **11** (88%).



N-Linked sugar chain: higher mannose type



	X	Y
1	O	O
2	O	CH_2
3	NH	CH_2



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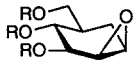
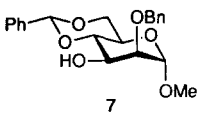
The structure of **11** was confirmed by converting it into the acetate **12** (98%), whose ^{1}H NMR spectrum ($CDCl_3$) showed two doublets of doublets at δ 4.42 (J 11.7, 4.8 Hz) and 4.25 (J 11.7, 3.7 Hz) due to CH_2OAc. The regioselectivity of this reaction may be attributed to the steric effect of the bulky 5a-carba-mannose residue located at C-3.

Introduction of the second carba-mannosyl moiety into C-6 was effected by coupling of 2 molar equiv. of **6** with an oxide anion, generated from **11** by treatment with potassium hydride, in DMF in the presence of 18-crown-6 ether for 1 h at 70°C, giving the coupling product **13** in 60% yield based on consumed **11**. Compound **13** was characterized as the acetate **14** (98%), whose ^{1}H NMR spectrum revealed a triplet (δ 5.57, J 3.0 Hz) due to H-2″, supporting the presence of the α-mannose residue. Deprotection of **13** was first carried out by hydrogenolysis in ethanol in the presence of 10% Pd-C under atmospheric pressure of hydrogen, but the deprotection was not completed even after 3 days. When Pd black was used instead as a catalyst under 3.0 kg/cm^2 of hydrogen, all benzyl groups could be removed within one day. The free trisaccharide **2** thus obtained was isolated as the peracetyl derivative **15** in 82% overall yield. The ^{1}H NMR spectrum of **15** fully supported the structure proposed. Compound **15** was easily converted into **2** (96%) under Zemplén conditions.

Attempted direct coupling of **6** ($\sim$ 2 molar equiv) with a diol, methyl 2,4-di-*O*-benzyl-α-D-mannopyranoside [10], resulted in a preferential attack by the primary oxide anion, affording only the 6-*O*-(5a-carba-α-D-mannopyranosyl) derivative in 65% yield, and formation of the carba-trisaccharide derivative was not observed.



5 R = H
6 R = Bn



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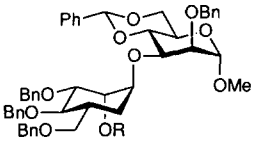
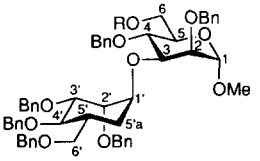
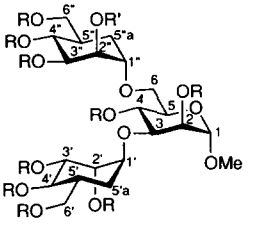


8 R = H
9 R = Ac
10 R = Bn



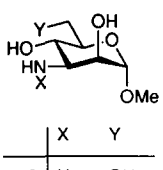
11 R = H
12 R = Ac



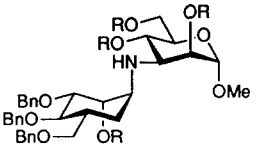
13 R = Bn, R' = H
14 R = Bn, R'= Ac
15 R = R' = Ac

Next, the analogous carba-trisaccharide structures having imino linkages were prepared. Thus, coupling of **6** with methyl 3-amino-3-deoxy-α-D-mannopyranoside [11] (**16**) in 2-propanol in a sealed tube for 6 days at 120°C produced the carba-disaccharide derivative **20** in 95% yield. Acetylation of **20** gave the tetraacetate **21** (94%). In the ^{1}H NMR spectrum of **21**, three signals due to H-3, and coupled H-1′ and H-2′ appeared at δ 3.16 (dd, *J* 2.9, 10.3 Hz), and 2.93 (q, *J* 2.9 Hz) and 5.27 (t, *J* 2.9 Hz), supporting the assigned structure. Then, in order to subject **20** to a displacement reaction at C-6, selective tosylation of 6-OH was envisaged. However, treatment of **20** with 1.9 molar equiv of tosyl chloride in pyridine at −15 to 0°C gave an undesired bicyclic compound **22** in 69% yield through a direct intramolecular attack of the nitrogen function in the intermediate 6-sulfonate. In the ^{1}H NMR spectrum of **22**, a signal due to the anomeric proton appeared as a doublet (*J* 6.2 Hz) at δ 4.59, indicating that the pyranoid ring adopts a flattened $^1C_4$ chair conformation owing to formation of the 3,6-imino bridge. The structure of **22** was further characterized by transforming it into the triacetyl **23** (91%) and hexaacetyl derivatives **24** (~ 100%) in the conventional manner.

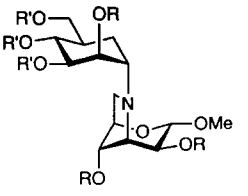
Methyl 3-amino-6-azido-3,6-dideoxy-α-D-mannopyranoside (**18**) was then chosen as the acceptor, the 6-amino function being easily generated after coupling at C-3. Compound **18** was newly prepared from **16** in the sequence of reactions: *N*-protection with the *tert*-butyloxycarbonyl (Boc) group, followed by selective tosylation of the 6-OH (→ **17**, 87%), and azidolysis and successive *N*-deprotection (→ **18**, ~ 90%). Similar coupling of **6** and **18** provided the carba-disaccharide derivative **26** (61%), the structure of which was established by comparing its ^{1}H NMR spectrum with that of **20**. Hydrogenation of **26** with Raney nickel gave the crude amine **27** (82%), which without purification was subjected to further coupling (120°C, 5 days) with **6** to afford the trisaccharide derivative **28** (70%). Acetylation of **28** with acetic anhydride and pyridine at room temperature gave the penta-*N,O*-acetyl derivative **29** (81%). One of the nitrogen



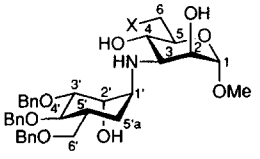
	X	Y
16	H	OH
17	Boc	OTs
18	H	N_3
19	H	NH_2



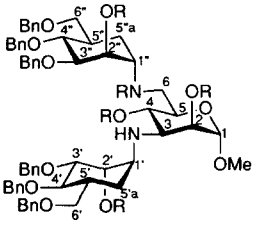
20 R = H
21 R = Ac



22 R = H, R' = Bn
23 R = Ac, R' = Bn
24 R = Ac, R' = Ac
25 R = R' = H



26 X = N_3
27 X = NH_2

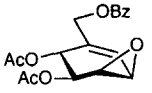


28 R = H
29 R = Ac

functions was shown to be acetylated by the IR spectrum. The ^{1}H NMR spectrum (Me_2SO-d_6) of **29** was then measured at 80°C in order to simplify the complex signal pattern observed at room temperature due to the restricted rotation around the tertiary amido group. Imino functions linking cyclohexane and pyranoid rings have never been acetylated conventionally, as in the acetylation of **20**, conceivably because of steric hindrance. Therefore, the *N*-acetyl group was tentatively assigned to be located at the less hindered 6-imino group. The signals due to C-2 protons of two carba-α-manno-pyranose residues appeared at δ 5.09 (t, *J* 3.4 Hz) and 4.89 (t, *J* 2.9 Hz), supporting the structure proposed. Alternatively, a preparation of **28** was attempted by direct coupling of **6** with methyl 3,6-diamino-3,6-dideoxy-α-D-mannopyranoside [12] (**19**) derived by hydrogenation of **18**. Coupling of 2.2 molar equiv of **6** and **19** in 2-propanol was completed after 9 days at 120°C to give **28** in 72% yield. These results demonstrated that the epoxide **6** should be a useful donor to introduce 5a-carba-α-D-manno-pyranose residues into amino functions of the oligosaccharide chains.

Removal of the benzyl groups of **29** could be readily achieved by hydrogenolysis in the presence of 10% Pd–C and the crude free amine obtained was purified on a column of Dowex 50W-X2 (H^+) resin by elution with ammoniacal methanol, to afford **3** (96%).

Introduction of unsaturation into the carba-sugar moiety, especially between the C-5 and C-5a positions, sometimes increases its biological activity, for example, the enzyme-inhibitory activity of methyl acarviosin derivatives [13]. Therefore, such a trisaccharide **4** containing unsaturated carba-sugar residues was synthesized by use of the other potent carba-sugar donor, 3,4-di-*O*-acetyl-1,2-anhydro-6-*O*-benzoyl-5a-carba-



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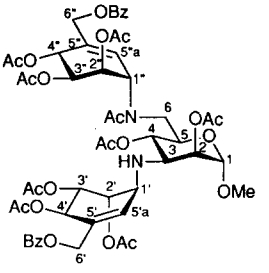

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β-D-*lyxo*-hex-5(5a)-enopyranose [1] [14] (**30**). According to the standard procedure [15], coupling of the diamino sugar **19**, using 2.3 molar equiv of **30**, was carried out in 2-propanol at 50°C for 1 week to give a mixture of products. Partial migration of the acetyl group to the nitrogen function seemed to make the reaction complex. Subsequent acetylation of the mixture gave, after chromatography, the nona-*N,O*-acetyl derivative **31** (34%), the ^{1}H NMR spectrum of which supported the assigned structure, revealing two narrow signals (δ 6.06 and 5.82) due to the alkenic protons [15] at C-5′a and C-5″a. One of the imino groups was acetylated as observed in the case of **29**. On alkaline methanolysis with sodium methoxide, **31** was *N,O*-deacetylated to afford the free carba-trisaccharide **4** (73%). Owing to the small amount of material obtained, this compound was not fully characterized although IR and ^{1}H NMR spectra were in agreement with the suggested structure.

Bioassay.—Only the inhibitory activity against Jack-bean α-D-mannosidase [2] has been assayed to date. The ether-linked compound **2** did not show observable activity at a concentration of 100 μg/mL. On the other hand, the imino-linked trisaccharides **3** and **4** were mild α-D-mannosidase inhibitors, showing 64% (IC_{50} 7.4×10^{-5} mmol/mL) and 91% (IC_{50} 1.4×10^{-5} mmol/mL) inhibition, respectively. The free disaccharide derivative **25** (81%) obtained from **24** also possessed weak inhibition (42%) at 100 μg/mL. These data suggested that the ether-linked carba-sugar analogues of oligosaccharides seem to act not as inhibitors but rather as substrates toward glycohydrolases and/or glycotransferases [16]. Studies along this line are now in progress.

3. Experimental

General methods.—Melting points were determined with a Mel-Temp capillary melting-point apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP-370 polarimeter. ^{1}H NMR spectra were recorded for solutions in $CDCl_3$

[1] For convenience, we here propose a system for naming unsaturated carba-sugars. Thereby, valienamine is named 5a-carba-α-D-*xylo*-hex-5(5a)-enopyranosylamine, the unsaturation being located between C-5 and C-5a, in order to differentiate it from the exo-methylene derivative having unsaturation between C-5 and C-6.

[2] Jack-bean α-D-mannosidase and *p*-nitrophenyl α-D-mannopyranoside (20 mmol) in acetate buffer (100 mmol) at pH 4.5.

(internal Me_4Si) with a Jeol JNM GSX-270 FT (270 MHz) instrument. TLC was performed on Silica Gel 60 GF (E. Merck, Darmstadt) with detection by charring with H_2SO_4. Column chromatography was conducted on Wakogel C-300 (300 Mesh). Organic solutions were dried over anhyd Na_2SO_4 and evaporated at $< 50°C$ under diminished pressure.

*1,2-Anhydro-3,4,6-tri-*O*-benzyl-5a-carba-β-*D*-mannopyranose* (**6**).—To a solution of 1,2-anhydro-5a-carba-β-D-mannopyranose (**5**) [8] (0.775 g, 4.84 mmol) in dry DMF (15 mL) was added 60% NaH (1.2 g, 30 mmol) at 0°C; the mixture was stirred for 30 min, and then BnBr (2.7 mL, 22.7 mmol) was added. The mixture was stirred at room temperature for 1 h and then reaction was quenched by addition of MeOH at 0°C. The mixture was diluted with EtOAc (100 mL), washed with water, dried, and evaporated. The residue was chromatographed (80 g; 1:5 EtOAc–hexane) to give the benyl ether **6** (1.76 g, 85%) as crystals; mp 64–65° (from EtOH), $[\alpha]_D^{25}$ +34° (*c* 1.01, $CHCl_3$); the ^1H NMR spectrum was superimposable on that of the racemate. Anal. Calcd for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02. Found: C, 77.75; H, 6.79.

*Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(3,4,6-tri-*O*-benzyl-5a-carba-α-*D*-mannopyranosyl)-α-*D*-mannopyranoside* (**8**).—To a solution of 35% KH (250 mg, 2.18 mmol) in DMF (0.5 mL) was added a solution of methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**7**; 53.0 mg, 0.142 mmol) in DMF (1 mL), and it was stirred for 1 h at room temperature. To the cooled solution were added the epoxide **6** (128 mg, 0.298 mmol) and 18-crown-6 ether (580 mg, 2.19 mmol) at 0°C, and the mixture was stirred for 2 h at 70°C. After treatment with MeOH (1 mL), the mixture was diluted with EtOAc (30 mL), washed with water thoroughly, dried, and evaporated. The residue was chromatographed (20 g, 1:6 acetone–hexane) to give **8** (74.8 mg, 66%) and recovered **7** (8.2 mg, 16%); $[\alpha]_D^{22}$ +11° (*c* 1.00, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ 5.57 (s, 1 H, PhC*H*), 4.68 (d, 1 H, $J_{1,2}$ 1.1 Hz, H-1), 4.82 and 4.67 (ABq, 2 H, *J* 12.1 Hz), and 4.75 and 4.46 (ABq, 2 H, *J* 11.5 Hz) (PhCH_2), 3.34 (s, 3 H, OMe), 2.51 (s, 1 H, OH), 2.17 (m, 1 H, H-5′), 1.93 [dt, 1 H, $J_{5'a(gem)} = J_{5',5'a(ax)} = 11.7$, $J_{1',5'a(ax)}$ 2.2 Hz, H-5′a(*ax*)], 1.83 [dt, 1 H, $J_{1',5'a(eq)} = J_{5',5'a(eq)} = 2.2$ Hz, H-5′a(*eq*)]. Anal. Calcd for $C_{49}H_{54}O_{10}$: C, 73.30; H, 6.78. Found: C, 73.35; H, 6.88.

*Methyl 3-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-5a-carba-α-*D*-mannopyranosyl)-2-*O*-benzyl-4,6-*O*-benzylidene-α-*D*-mannopyranoside* (**9**).—The alcohol **8** (104 mg, 0.13 mmol) was treated with Ac_2O (0.5 mL) in pyridine (1.5 mL) overnight at room temperature. The mixture was processed in the usual manner and the product was purified by preparative TLC (1:3 EtOAc–hexane) to give the acetate **9** (101 mg, 93%) as a syrup; $[\alpha]_D^{24}$ +11° (*c* 0.76, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ 5.59 (s, 1 H, PhC*H*), 5.57 (t, 1 H, $J_{1',2'} = J_{2',3'} = 4.0$ Hz, H-2′), 4.79 and 4.66 (ABq, 2 H, J_{gem} 12.1 Hz, PhCH_2), 4.69 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1), 4.41 and 4.25 (ABq, 2 H, J_{gem} 12.5 Hz), 4.40 and 4.23 (ABq, 2 H, J_{gem} 10.6 Hz), and 4.39 (s, 2 H) (PhCH_2), 4.10 (t, 1 H, $J_{3',4'} = J_{4',5'} = 9.5$ Hz, H-4′), 3.95 (dd, 1 H, $J_{2,3}$ 2.9, $J_{3,4}$ 9.5 Hz, H-3), 3.74 (dd, 1 H, H-2), 3.48 (dd, 1 H, $J_{5,6}$ 2.7, $J_{6(gem)}$ 9.0 Hz, H-6), 3.35 (s, 3 H, OMe), 2.13 (m, 1 H, H-5′), 2.06 (s, 3 H, Ac). Anal. Calcd for $C_{51}H_{56}O_{11}$: C, 72.49; H, 6.68. Found: C, 72.12; H, 6.54.

*Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-5a-carba-α-*D*-mannopyranosyl)-α-*D*-mannopyranoside* (**10**).—The alcohol **8** (123 mg, 0.154 mmol)

was benzylated as in the preparation of **7** and the product was chromatographed (10 g, 1:3 EtOAc–hexane) to give the pentabenzyl ether **10** (105 mg, 77%); $[\alpha]_D^{25}$ +6° (*c* 1.15, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ 5.33 (s, 1 H, PhC*H*), 4.66 (d, 1 H, $J_{1,2}$ 1.3 Hz, H-1), 4.87 and 4.48 (ABq, 2 H, J_{gem} 11.2 Hz), 4.80 and 4.31 (ABq, 2 H, J_{gem} 11.7 Hz), 4.66 and 4.50 (ABq, 2 H, J_{gem} 12.1 Hz), 4.43 (s, 2 H), and 4.37 and 4.31 (ABq, 2 H, J_{gem} 11.5 Hz) (PhCH_2), 4.24 (dd, 1 H, $J_{2',3'}$ 4.0, $J_{3',4'}$ 9.5 Hz, H-3'), 4.05 (t, 1 H, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4), 3.70 (dd, 1 H, $J_{2,3}$ 2.9 Hz, H-2), 3.58 (dd, 1 H, $J_{6'(gem)}$ 9.5, $J_{5',6'a}$ 5.9 Hz, H-6'a), 3.52 (dd, 1 H, $J_{5',6'b}$ 2.9 Hz, H-6'b), 3.35 (s, 3 H, OMe). Anal. Calcd for $C_{56}H_{60}O_{10}$: C, 75.31; H, 6.77. Found: C, 75.44; H, 6.89.

*Methyl 2,4-di-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-5a-carba-α-*D*-mannopyranosyl)-α-*D*-mannopyranoside* (**11**).—To a solution of **10** (122 mg, 0.137 mmol) in CH_2Cl_2 (3 mL) was added 1.5 M DIBAL-H in toluene (6.0 mL, 0.90 mmol) and the mixture was stirred for 4 h at room temperature. After treatment with MeOH at 0°C, the mixture was treated with aq 10% NaOH (2 mL) for 10 min and the residue was chromatographed (5 g, 1:2 EtOAc–hexane) to give **11** (108 mg, 88%) as a syrup; $[\alpha]_D^{24}$ +32° (*c* 0.90, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ 7.32–7.20 (m, 30 H, 6 Ph), 4.65 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1), 4.90 and 4.51 (ABq, each 1 H, J_{gem} 11.4 Hz), 4.79 and 4.58 (ABq, each 1 H, J_{gem} 11.2 Hz), 4.72 and 4.60 (ABq, each 1 H, J_{gem} 12.1 Hz), 4.67 and 4.41 (ABq, each 1 H, J_{gem} 12.1 Hz), and 4.44 and 4.37 (ABq, each 1 H, J_{gem} 11.4 Hz) (PHCH_2), 3.31 (s, 3 H, OMe), 2.14 (m, 1 H, H-5'), 1.96–1.78 (m, 2 H, H-5'a). Anal. Calcd for $C_{56}H_{62}O_{10}$: C, 75.14; H, 6.98. Found: C, 74.80; H, 6.89.

*Methyl 6-*O*-acetyl-2,4-di-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-5a-carba-α-*D*-mannopyranosyl)-α-*D*-mannopyranoside* (**12**).—Compound **11** (14.3 mg, 0.016 mmol) was treated with Ac_2O (1 mL) and pyridine (1 mL) for 2 h at room temperature. The product was purified by preparative TLC (1:2 EtOAc–hexane) to give the acetate **12** (14.6 mg, 98%) as a syrup; $[\alpha]_D^{20}$ +40° (*c* 0.80, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ 7.32–7.19 (m, 30 H, 6 Ph), 4.69 (d, 1 H, $J_{1,2}$ 2.2 Hz, H-1), 4.89 and 4.79 (ABq, each 1 H, *J* 11.0 Hz), 4.67 and 4.49 (ABq, each 1 H, *J* 11.0 Hz), 4.67 and 4.35 (ABq, each 1 H, *J* 11.7 Hz), 4.60 and 4.41 (ABq, each 1 H, *J* 12.1 Hz), and 4.44 (s, 2 H) (PhCH_2), 4.42 (dd, 1 H, $J_{5,6a}$ 4.8 J_{6gem} 11.7 Hz, H-6a), 4.25 (dd, 1 H, $J_{5,6b}$ 3.7 Hz, H-6b), 3.60 (dd, 1 H, $J_{5',6'a}$ 5.1, $J_{6'(gem)}$ 9.6 Hz, H-6'a), 3.59 (dd, 1 H, $J_{2,3}$ 3.7 Hz, H-2), 3.53 (dd, 1 H, $J_{5',6'b}$ 2.6 Hz, H-6'b), 3.33 (s, 3 H, OMe), 2.16 (m, 1 H, H-5'), 2.05 (s, 3 H, Ac). Anal. Calcd for $C_{58}H_{64}O_{11}$: C, 74.34; H, 6.88. Found: C, 74.24; H, 6.98.

*Methyl 2,4-di-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-5a-carba-α-*D*-mannopyranosyl)-6-*O*-(3,4,6-tri-*O*-benzyl-5a-carba-α-*D*-mannopyranosyl)-α-*D*-mannopyranoside* (**13**).—To a suspension of 35% KH (150 mg, 1.31 mmol) in DMF (0.5 mL) was added a solution of **11** (70.8 mg, 0.079 mmol) in DMF (1 mL) at 0°C under Ar, and it was then stirred for 1 h at room temperature. To this was added a solution of **6** (68.5 mg, 0.159 mmol) and 18-crown-6 ether (340 mg, 1.28 mmol) in DMF (1 mL) at 0°C, and the mixture was stirred for 1 h at 70°C. After treatment with MeOH, it was processed in the usual manner and the crude products were purified by chromatography (10 g, 1:6 EtOAc–toluene) and preparative TLC (1:7 EtOAc–toluene) to give **13** (49.5 mg, 60% based on **11** consumed) and recovered **11** (28 mg); $[\alpha]_D^{24}$ +33° (*c* 1.00, $CHCl_3$); ^1H NMR data (270 MHz, $CDCl_3$): δ 7.29–7.20 (m, 45 H, 9 Ph), 4.89 and 4.51 (ABq, each 1 H, *J* 11.0 Hz), 4.75 and 4.59 (ABq, each 1 H, *J* 11.4 Hz), 4.67 and 4.39 (ABq, each 1

H, J 10.6 Hz), and 4.65 and 4.55 (ABq, each 1 H, J 12.5 Hz) (PhCH_2), 4.65 (d, 1 H, $J_{1,2}$ 1.1 Hz, H-1), 4.57 (s, 2 H), 4.49 and 4.33 (ABq, each 1 H, J_{gem} 12.1 Hz), 4.46 and 4.41 (ABq, each 1 H, J_{gem} 12.1 Hz), and 4.41 (s, 2 H) (PhCH_2), 4.20 (t, 1 H, $J_{1',2'} = J_{2',3'} = 3.1$ Hz, H-2'), 3.28 (s, 3 H, OMe), 2.21–1.98 (m, 2 H, H-5',5'), 1.97–1.81 (m, 2 H, H-5'a,5'a). Anal. Calcd for $C_{84}H_{92}O_{14}$: C, 76.11; H, 7.00. Found: C, 75.97; H, 7.07.

*Methyl 6-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-5a-carba-α-*D*-mannopyranosyl)-2,4-di-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-5a-carba-α-*D*-mannopyranosyl)-α-*D*-mannopyranoside* (**14**).—Compound **13** (24.7 mg, 0.019 mmol) was acetylated with Ac_2O and pyridine conventionally and the product was chromatographed (2 g, 1:3 EtOAc–hexane) to give the acetate (25 mg, 98%) as a syrup; $[\alpha]_D^{20}$ +37° (c 0.91, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.30–7.14 (m, 45 H, 9 Ph), 5.57 (t, 1 H, $J_{1',2'} = J_{2',3'} = 3.3$ Hz, H-2'), 4.91–4.40 (m, 17 H, 8 PhCH_2 and H-1), 4.38 and 4.33 (ABq, each 1 H, J 13.2 Hz, PhCH_2), 3.89 (dd, 1 H, $J_{3',4'}$ 9.5 Hz, H-3'), 3.27 (s, 3 H, OMe), 2.10 (s, 3 H, Ac), 1.94–1.71 (m, 4 H, H-5'a,5'a,5''a,5''a). Anal. Calcd for $C_{86}H_{94}O_{15}$: C, 75.52; H, 6.93. Found: C, 75.82; H, 6.91.

*Methyl 2,4-di-*O*-acetyl-3,6-di-*O*-(2,3,4,6-tetra-*O*-acetyl-5a-carba-α-*D*-mannopyranosyl)-α-*D*-mannopyranoside* (**15**).—A solution of **13** (10.8 mg, 0.0082 mmol) in ethanol (2 mL) containing 1 M HCl (0.1 mL) was hydrogenated in the presence of palladium black (10 mg) in the initial H_2 pressure of 3 kg cm^{-2} overnight at room temperature. The catalyst was removed by filtration and the filtrate was evaporated. The residue was acetylated conventionally and the product was chromatographed (2 g, 1:4 acetone–toluene) to give **15** (6.2 mg, 82%) as a syrup; $[\alpha]_D^{22}$ +26° (c 0.56, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.39 (t, 1 H, $J_{1'',2''} = J_{2'',3''} = 2.9$ Hz, H-2''), 5.31 (t, 1 H, $J_{1',2'} = J_{2',3'} = 3.3$ Hz, H-2'), 5.26 (dd, 1 H, $J_{3'',4''}$ 10.3 Hz, H-3''), 5.25 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 3.7 Hz, H-2), 5.20 (t, 1 H, $J_{3',4'} = J_{4',5'} = 9.9$ Hz, H-4'), 5.18 (t, 1 H, $J_{4'',5''}$ 10.3 Hz, H-4''), 5.13 (t, 1 H, $J_{3,4} = J_{4,5} = 11.4$ Hz, H-4), 5.04 (dd, 1 H, H-3'), 4.68 (d, 1 H, H-1), 4.10 (dd, 1 H, $J_{6''(gem)}$ 9.5, $J_{5'',6''a}$ 4.4 Hz, H-6''a), 4.06 (dd, 1 H, $J_{5',6'a}$ 4.4, $J_{6'(gem)}$ 11.4 Hz, H-6'a), 3.98 (dd, 1 H, $J_{5'',6''b}$ 3.3 Hz, H-6''b), 3.95 (dd, 1 H, $J_{5',6'b}$ 3.7 Hz, H-6'b), 3.87 (dd, 1 H, H-3), 3.75 (ddd, 1 H, $J_{5,6a}$ 3.3, $J_{5,6b}$ 5.5 Hz, H-5), 3.73 (q, 1 H, $J_{1'',5''a} = J_{1'',5''b} = 2.9$ Hz, H-1''), 3.64–3.59 (m, 3 H, H-6,6,1'), 3.38 (s, 3 H, OMe), 2.35–2.00 (m, 2 H, H-5',5'), 2.20, 2.16, 2.13, 2.06, 2.02, 2.01, 1.97, and 1.96 (8 s, 3, 3, 6, 6, 3, 3, 3, and 3 H, 10 Ac). Anal. Calcd for $C_{41}H_{58}O_{24}$: C, 52.67; H, 6.25. Found: C, 52.30; H, 6.60.

*Methyl 3,6-di-*O*-(5a-carba-α-*D*-mannopyranosyl)-α-*D*-mannopyranoside* (**2**).—The deca-*O*-acetyl derivative **15** (9.9 mg) obtained from **13** (14.6 mg, 0.0107 mmol) was treated with 1 M methanolic NaOMe (10 μL) in MeOH (0.5 mL) overnight at room temperature. After neutralization with Amberlite IR-120B (H^+) resin, the mixture was evaporated and the product was chromatographed (1 g, 4:1 MeCN–H_2O) to give **2** (9.1 mg, 96% based on **13**) as a syrup; $[\alpha]_D^{25}$ +7° (c 0.46, MeOH); ^{1}H NMR (270 MHz, D_2O): δ 4.62 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 3.99–3.38 (m, 18 H), 3.27 (s, 3 H, OMe), 2.13–1.40 (m, 6 H).

*Methyl 3-*tert*-butoxycarbonylamino-3-deoxy-6-*O*-*p*-toluenesulfonyl-α-*D*-mannopyranoside* (**17**).—To a solution of methyl 3-amino-3-deoxy-α-*D*-mannopyranoside (**16**; 105 mg, 0.543 mmol) in EtOH (1.5 mL) was added (t-BuOCO)$_2$O (190 μL, 0.827

mmol), and the mixture was stirred for 1 h at room temperature. The mixture was evaporated and the residue was chromatographed (10 g, 1:1 acetone–toluene) to give the *N*-Boc derivative (160 mg, quantitatively), $[\alpha]_D^{26}$ +74° (*c* 0.95, $CHCl_3$). The crude product was dissolved in pyridine (2 mL) and treated with tosyl chloride (160 mg, 0.839 mmol) for 7 h at 0°C. After treatment with MeOH, the mixture was evaporated and the residue was chromatographed (10 g, 1:3 acetone–toluene) to give **17** (210 mg, 87%) as a syrup; $[\alpha]_D^{22}$ +77° (*c* 1.32, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.82–7.32 (m, 4 H, Ph), 5.43 (d, 1 H, $J_{3,NH}$ 7.3 Hz, NH), 4.64 (d, 1 H, $J_{1,2}$ 1.1 Hz, H-1), 4.36 (dd, 1 H, $J_{5,6a}$ 2.2, $J_{6(gem)}$ 11.0 Hz, H-6a), 4.28 (dd, 1 H, $J_{5,6b}$ 5.1 Hz, H-6b), 3.59 (t, 1 H, $J_{3,4} = J_{4,5} = 9.7$ Hz, H-4), 3.35 (s, 3 H, OMe), 2.44 (s, 3 H, Me), 1.43 (s, 9 H, *t*-Bu). Anal. Calcd for $C_{19}H_{29}NO_9S$: C, 50.99; H, 6.53; N, 3.13. Found: C, 50.68; H, 6.95; N, 3.18.

*Methyl 3-amino-6-azido-3,6-dideoxy-α-*D*-mannopyranoside* (**18**).—To a solution of **17** (211 mg, 0.471 mmol) in DMF (1.8 mL) was added a solution of NaN_3 (125 mg, 1.92 mmol) in water (0.2 mL), and it was stirred for 4 h at 100°C. The mixture was evaporated and the residue was chromatographed (5 g, 1:5 acetone–toluene) to give the azide (140 mg, 93%) as a syrup; $[\alpha]_D^{26}$ +97° (*c* 1.1, $CHCl_3$); ν_{max} 3400 cm^{-1} (OH), 2100 (N_3), 1685 (amide); ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.52 (d, 1 H, $J_{3,NH}$ 8.1 Hz, NH), 4.69 (s, 1 H, $J_{1,2}$ ~ 0 Hz, H-1), 3.88–3.73 (m, 3 H, H-2,3,4), 3.63–3.48 (m, 3 H, H-5,6), 3.43 (s, 3 H, OMe), 1.46 (s, 9 H, *t*-Bu).

A mixture of the azide (90.2 mg, 0.283 mmol), trifluoroacetic acid (1 mL), and $CHCl_3$ (1.5 mL) was stirred for 45 min at room temperature, and then evaporated. The product was chromatographed on a column of Dowex 50W-X2 (H^+) resin (10 mL) with H_2O → 1:27 aq ammonia–MeOH as eluent to give the crude amine **18** (62 mg, ~ 90%) as crystals. This compound was used without further purification in the next step.

*Methyl 3-deoxy-3-(3,4,6-tri-*O*-benzyl-5a-carba-α-*D*-mannopyranosylamino)-α-*D*-mannopyranoside* (**20**).—A mixture of **6** (228 mg, 0.530 mmol) and **16** (70.0 mg, 0.362 mmol) in 2-propanol (0.7 mL) was heated in a sealed tube for 6 days at 120°C, and then evaporated. The residue was chromatographed (12 g, 1:1 acetone–toluene) to give **20** (214 mg, 95%) as a syrup; $[\alpha]_D^{22}$ +19.5° (*c* 1.05, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.33–7.23 (m, 15 H, 3 Ph), 4.71 and 4.49 (ABq, each 1 H, J_{gem} 11.4 Hz), and 4.62 and 4.57 (ABq, each 1 H, *J* 11.4 Hz) (PhCH_2), 4.61 (d, 1 H, $J_{1,2}$ 1.1 Hz, H-1), 4.23 (s, 2 H, PhCH_2), 3.96 (t, 1 H, $J_{1',2'} = J_{2',3'} = 3.3$ Hz, H-2'), 3.26 (s, 3 H, OMe), 3.06–3.01 (m, 1 H, H-1'), 2.78 (dd, 1 H, $J_{2,3}$ 2.2, $J_{3,4}$ 9.9 Hz, H-3), 2.22 (m, 1 H, H-5'), 1.92 [ddd, 1 H, $J_{1',5'a(ax)}$ 2.9, $J_{5',5'a(ax)}$ 9.2, $J_{5'(gem)}$ 12.5 Hz, H-5'a(*ax*)], 1.67 [dt, 1 H, $J_{1',5'a(eq)} = J_{5',5'a(eq)} = 2.9$ Hz, H-5'a(*eq*)]. Anal. Calcd for $C_{35}H_{45}NO_9$: C, 67.40; H, 7.27; N, 2.25. Found: C, 66.98; H, 7.69; N, 2.20.

*Methyl 2,4,6-tri-*O*-acetyl-3-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-5a-carba-α-*D*-mannopyranosylamino)-3-deoxy-α-*D*-mannopyranoside* (**21**).—Compound **20** (21 mg, 0.034 mmol) was acetylated conventionally and the product was chromatographed (2 g, 1:4 EtOAc–toluene) to give **21** (25 mg, 94%) as a syrup; $[\alpha]_D^{27}$ +15.6° (*c* 1.25, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.31–7.25 (m, 15 H, Ph), 5.27 (t, 1 H, $J_{1',2'} = J_{2',3'} = 2.9$ Hz, H-2'), 5.06 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 2.9 Hz, H-2), 4.88 (t, 1 H, $J_{3,4} = J_{4,5} = 10.3$ Hz, H-4), 4.83 and 4.46 (ABq, each 1 H, *J* 11.0 Hz, PhCH_2), 4.73 (d, 1 H, H-1), 4.67 and 4.41 (ABq, each 1 H, *J* 11.7 Hz), and 4.65 and 4.51 (ABq, each 1 H, *J* 11.5 Hz)

(PhCH_2), 4.24 (dd, $J_{6(gem)}$ 12.1, $J_{5,6a}$ 5.5 Hz, H-6a), 4.09 (dd, 1 H, $J_{5,6b}$ 2.2 Hz, H-6b), 3.91 (ddd, 1 H, H-5), 3.81 (dd, 1 H, $J_{3',4'}$ 9.0 Hz, H-3'), 3.61 (t, 1 H, $J_{4',5'}$ 9.0 Hz, H-4'), 3.52–3.48 (m, 2 H, H-6'), 3.41 (s, 3 H, OMe), 3.16 (dd, 1 H, H-3), 2.93 (q, 1 H, J 2.9 Hz, H-1'), 2.11, 2.10, 2.09, and 1.97 (4 s, each 3 H, 4 Ac), 2.05–1.99 (m, 1 H, H-5'), 1.87 [dt, 1 H, $J_{5'a(gem)} = J_{5',5'a(ax)} = 13.4$ Hz, H-5'a(*ax*)], 1.42 [dt, 1 H, $J_{5',5'a(eq)}$ 2.9 Hz, H-5'a(*eq*)]. Anal. Calcd for $C_{43}H_{53}NO_{13}$: C, 65.22; H, 6.75; N, 1.77. Found: C, 65.09; H, 7.05; N, 1.71.

Methyl 3,6-dideoxy-3,6-epimino-N-*(3,4,6-tri*-O-*benzyl-5a-carba-α*-D-*mannopyranosyl)-α*-D-*mannopyranoside* (**22**).—To a solution of **20** (238 mg, 0.382 mmol) in pyridine (2 mL) was added tosyl chloride (136 mg, 0.71 mmol) at −15°C, and the mixture was stirred for 7 h at −15°C and overnight at 0°C. After treatment with water (1.5 mL) for 30 min, the mixture was evaporated and the residual product was purified by silica gel chromatography (40 g, 1:4 acetone–toluene) and further by preparative TLC (1:5 EtOH–toluene) to give **22** (160 mg, 69%) as a hygroscopic syrup; $[\alpha]_D^{25}$ +49° (*c* 0.92, $CHCl_3$): ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.38–7.26 (m, 15 H, 3 Ph), 4.59 (d, 1 H, $J_{1,2}$ 6.2 Hz, H-1), 4.53 and 4.49 (2 s, each 2 H), and 4.50 and 4.38 (ABq, each 1 H, J 12.1 Hz) (PhCH_2), 4.19 (t, 1 H, $J_{4,5} = J_{5,6exo} = 3.7$, $J_{5,6endo} \sim 0$ Hz, H-5), 3.60–3.50 (m, 2 H, H-6',6'), 3.54 (s, 3 H, OMe), 3.30 (bt, 1 H, H-3), 3.15 (d, 1 H, $J_{6(gem)}$ 11.5 Hz, H-6endo), 2.90–2.80 (m, 1 H, H-1'), 2.47–2.36 (m, 1 H, H-5'), 1.74–1.47 (m, 2 H, H-5'a,5'a). Anal. Calcd for $C_{35}H_{43}NO_8 \cdot 0.5H_2O$: C, 67.29; H, 6.75; N, 1.91. Found: C, 67.05: H, 6.78; N, 1.89.

Methyl 2,4-di-O-*acetyl*-N-*(2*-O-*acetyl-3,4,6-tri*-O-*benzyl-5a-carba-α*-D-*mannopyranosyl-3,6-dideoxy-3,6-epimino-α*-D-*mannopyranoside* (**23**).—Compound **22** (27.2 mg, 0.382 mmol) was acetylated conventionally and the product was purified by preparative TLC (1:4 acetone–toluene) to give **23** (30 mg, 91%) as a syrup; $[\alpha]_D^{22}$ +49° (*c* 1.37, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.33–7.26 (m, 15 H, 3 Ph), 5.30 (bt, 1 H, H-2'), 4.89 and 4.52 (ABq, each 1 H, J 11.2 Hz, PhCH_2), 4.88 (bt, 1 H, H-4), 4.70 (dd, 1 H, $J_{1,2}$ 7.0, $J_{2,3}$ 1.8 Hz, H-2), 4.66 and 4.45 (2 s, each 2 H, PhCH_2), 4.56 (d, 1 H, H-1), 4.39 (bt, 1 H, H-5), 3.88 (dd, 1 H, $J_{2',3'}$ 2.4, $J_{3',4'}$ 9.5 Hz, H-3'), 3.72 (t, 1 H, $J_{4',5'}$ 9.5 Hz, H-4'), 3.48 (s, 3 H, OMe), 2.93 (dd, 1 H, $J_{5,6exo}$ 3.3, $J_{6(gem)}$ 11.4 Hz, H-6exo), 2.89–2.83 (m, 1 H, H-1'), 2.84 (dd, 1 H, $J_{5,6endo} \sim 0$ Hz, H-6endo), 2.34 (m, 1 H, H-5'), 2.15, 2.13, and 1.99 (3 s, each 3 H, 3 Ac), 1.89–1.67 (m, 2 H, H-5'a). Anal. Calcd for $C_{41}H_{49}NO_{11}$: C, 67.29; H, 6.75; N, 1.91. Found: C, 67.05; H, 6.78; N, 1.89.

Methyl 2,4-di-O-*acetyl-3,6-dideoxy-3,6-epimino*-N-*(2,3,4,6-tetra*-O-*acetyl-5a-carba-α*-D-*mannopyranosyl)-α*-D-*mannopyranoside* (**24**).—A solution of **23** (24.7 mg, 0.0374 mmol) in EtOH (1 mL) was hydrogenated in the presence of 10% Pd–C (10 mg) under atmospheric pressure of H_2 for 2 days at room temperature. The product was acetylated conventionally and purified by chromatography (1:3 acetone–toluene) to give **24** (22 mg, quantitatively) as a syrup; $[\alpha]_D^{23}$ +19° (*c* 1.10, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.46 (t, 1 H, $J_{1',2'} = J_{2',3'} = 2.6$ Hz, H-2'), 5.31 (dd, 1 H, $J_{3',4'} \sim 0$ Hz, H-3'), 5.24 (t, 1 H, $J_{4',5'} \sim 0$ Hz, H-4'), 5.00 (dd, 1 H, $J_{1,2}$ 7.3, $J_{2,3}$ 1.8 Hz, H-2), 4.52 (t, 1 H, $J_{4,5} = J_{5,6exo} = 3.9$, $J_{5,6endo} \sim 0$ Hz, H-5), 4.07 (dd, 1 H, $J_{6'(gem)}$ 11.4, $J_{5',6'a}$ 6.8 Hz, H-6'a), 3.89 (dd, 1 H, $J_{5',6'b}$ 3.7 Hz, H-6'b), 3.71–3.66 (m, 1 H, H-3), 3.53 (s, 3 H, OMe), 3.50 (d, 1 H, $J_{6(gem)}$ 11.9 Hz, H-6endo) 3.04 (dd, 1 H, H-6exo), 2.94 (q, 1 H, $J_{1',5'a(ax)} = J_{1',5'a(eq)} = 2.6$ Hz, H-1'), 2.60–2.40 (m, 1 H, H-5'), 2.18, 2.13, 2.07, 2.06,

2.05, and 2.00 (6 s, each 3 H, 6 Ac), 1.84–1.78 (m, 2 H, H-5'a). Anal. Calcd for $C_{26}H_{37}NO_{14}$: C, 53.15; H, 6.35; N, 2.38. Found: C, 53.22; H, 6.57; N, 2.70.

Methyl N-*(5a-carba-α-*D-*mannopyranosyl)-3,6-dideoxy-3.6-epimino-α-*D-*mannopyranoside* (**25**).—Compound **24** (48.5 mg, 0.825 mmol) was treated with 0.1 M methanolic NaOMe overnight at room temperature. After neutralization with Amberlite IR-120B (H^+) resin, the mixture was evaporated and the residue was chromatographed (1 g, 3:1 $CHCl_3$–MeOH) to give **25** (22.4 mg, 81%) as a syrup; $[\alpha]_D^{25}$ +51° (*c* 0.70, MeOH); ^{1}H NMR (270 MHz, D_2O): δ 4.65 (d, 1 H, $J_{1,2}$ 7.3 Hz, H-1), 4.23 (t, 1 H, $J_{4,5} = J_{5,6exo} = 3.1$, $J_{5,6endo} \sim 0$ Hz, H-5), 4.08 (dd, 1 H, $J_{3,4}$ 5.9 Hz, H-4), 4.00 (t, 1 H, *J* 3.7 Hz, H-2'), 3.83 (dd, 1 H, $J_{3',4'}$ 8.4 Hz, H-3'), 3.75 (dd, 1 H, $J_{2,3}$ 1.8 Hz, H-2), 3.49 (s, 3 H, OMe), 3.28 (m, 1 H, H-3), 3.18 (d, 1 H, $J_{6(gem)}$ 11.7 Hz, H-6endo), 2.98 (dd, 1 H, H-6exo), 2.91 (q, 1 H, *J* 3.7 Hz, H-1'), 2.18–2.07 (m, 1 H, H-5'), 1.76–1.58 (m, 1 H, H-5'a).

*Methyl 6-azido-3,6-dideoxy-3-(3,4,6-tri-*O*-benzyl-5a-carba-α-*D-*mannopyranosylamino)-α-*D-*mannopyranoside* (**26**).—The crude amine **18** (62 mg, 0.28 mmol) was directly coupled with **6** (185 mg, 0.430 mmol) in 2-propanol (1 mL) in a sealed tube for 2 days at 120°C. The product was chromatographed (10 g, 1:4 acetone–toluene) to give **26** (113 mg, 61%) as a syrup, together with recovered **6** (78.8 mg, 43%); $[\alpha]_D^{22}$ +19° (*c* 0.91, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.35–7.24 (m, 15 H, 3 Ph), 4.73 and 4.50 (ABq, each 1 H, *J* 11.2 Hz, PhCH_2), 4.67 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 4.65 and 4.56 (ABq, each 1 H, *J* 11.4 Hz), and 4.45 (s, 2 H) (PhCH_2), 3.91 (t, 1 H, $J_{1',2'} = J_{2',3'} = 4.0$ Hz, H-2'), 3.57–3.42 (m, 4 H, H-6,6'), 3.40 (s, 3 H, OMe), 3.32 (t, 1 H, $J_{3,4} = J_{4,5} = 9.9$ Hz, H-4), 2.96 (q, 1 H, $J_{1',5'a(ax)} = J_{1',5'a(eq)} = 4.0$ Hz, H-1'), 2.74 (dd, 1 H, $J_{2,3}$ 2.6 Hz, H-3), 2.18–2.04 (m, 1 H, H-5'), 1.98 [ddd, 1 H, $J_{5'a(gem)}$ 13.9, $J_{5',5'a(ax)}$ 10.4 Hz, H-5'a(*ax*)], 1.63 [dt, 1 H, $J_{5',5'a(eq)}$ 4.0 Hz, H-5'a(*eq*)]. Anal. Calcd for $C_{35}H_{44}N_4O_8$: C, 64.80; H, 6.84; N, 8.64. Found: C, 64.81; H, 6.71; N, 8.42.

*Methyl 3,6-dideoxy-3,6-bis(3,4,6-tri-*O*-benzyl-5a-carba-α-*D-*mannopyranosyl-amino)-α-*D-*mannopyranoside* (**28**).—(*a*) A solution of **26** (75.3 mg, 0.116 mmol) in EtOH (1.5 mL) was hydrogenated in the presence of Raney Ni T-4 (0.5 mL) for 4 h at room temperature under atmospheric pressure of H_2. Catalyst was removed by filtration and the filtrate was evaporated to give a crude amine **27** (59 mg, ~82%) as a syrup. Without purification this compound (0.095 mmol) was directly coupled with **6** (45 mg, 0.104 mmol) in 2-propanol (0.5 mL) in a sealed tube for 5 days at 120°C, and the solvent then evaporated. The residue was chromatographed (5 g, 1:1 acetone–toluene) to give **28** (69.5 mg, 70%) as a syrup, together with recovered **6** (6.2 mg, 14%); $[\alpha]_D^{24}$ +33° (*c* 0.80, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.35–7.25 (m, 30 H, 6 Ph), 4.75–4.44 (m, 13 H, 6 PhCH_2, H-1), 3.99 (bt, 1 H, H-2''), 3.92 (bt, 1 H, H-2'), 3.34 (s, 3 H, OMe).

(*b*) Compound **18** (67.6 mg, 0.212 mmol) was hydrogenated as described above to give a crude amine (61 mg), which was treated with trifluoroacetic acid (1 mL) for 45 min at room temperature. The product was purified on a column of Dowex 50W-X2 (H^+) resin (5 mL, $H_2O \rightarrow$ 1:27 aq ammonia–MeOH) to give crude diamine **19** (33.3 mg, 82%) as crystals. Without further purification, this compound (0.173 mmol) was coupled with **6** (165 mg, 0.383 mmol) in 2-propanol (0.5 mL) for 9 days at 120°C. The

product was chromatographed (10 g, 1:2 acetone–toluene) to give **28** (132 mg, 72%) and recovered **6** (48.8 mg, 30%).

*Methyl 6-*N*-acetyl-2,4-di-*O*-acetyl-3,6-bis(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-5a-carba-α-*D*-mannopyranosylamino)-3,6-dideoxy-α-*D*-mannopyranoside* (**29**).—Compound **28** (17.5 mg, 0.0166 mmol) was acetylated conventionally and the product was purified by preparative TLC (1:4 acetone–toluene) to give **29** (17 mg, 81%) as a syrup; $[\alpha]_D^{24}$ +29° (*c* 0.75, $CHCl_3$); ν_{max}(KBr) 1735 (ester) and 1650 cm^{-1} (amide); ^1H NMR (270 MHz, $CDCl_3$): δ 7.33–7.20 (m, 30 H, 6 Ph), 5.09 (t, 1 H, *J* 3.4 Hz, H-2′), 4.89 (t, 1 H, *J* 4.8 Hz, H-2″), 3.24 (s, 3 H, OMe), 2.36 (m, 1 H, H-1″), 2.03, 2.01, 1.90, and 1.84 (4 s, 3, 6, 3, and 3 H, 5 Ac), 1.81–1.42 (m, 4 H, H-5′a,5″a). Anal. Calcd for $C_{73}H_{86}N_2O_{17}$: C, 69.39; H, 6.86; N, 2.22. Found: C, 68.99; H, 6.99;N, 2.21.

*Methyl 3,6-bis(5a-carba-α-*D*-mannopyranosylamino)-3,6-dideoxy-α-*D*-mannopyranoside* (**3**).—Compound **28** (25 mg, 0.0237 mmol) was hydrogenolyzed in EtOH (2 mL) in the presence of 10% Pd–C (20 mg) for 2 days at room temperature. The product was purified on a column of Dowex 50W-X2 (H^+) resin (5 mL, H_2O → 1:27 aq ammonia–MeOH) to give **3** (11.6 mg, 96%) as a hygroscopic syrup; $[\alpha]_D^{25}$ +29° (*c* 0.45, MeOH); ^1H NMR (270 MHz, D_2O): δ 4.62 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 3.87 (t, 1 H, $J_{1',2'} = J_{2',3'} = 2.9$ Hz, H-2′), 3.81 (dd, 1 H, $J_{2,3}$ 2.6 Hz, H-2), 3.20 (s, 3 H, OMe), 2.94–2.85 (m, 3 H, H-3,1′,1″), 2.72–2.64 (m, 2 H, H-6), 1.72–1.50 (m, 6 H, H-5′,5′a,5″,5″a).

*Methyl 6-*N*-acetyl-2,4-di-*O*-acetyl-3,6-dideoxy-3,6-bis[2,3,4-tri-*O*-acetyl-6-*O*-benzoyl-5a-carba-α-*D*-*lyxo*-hex-5(5a)-enopyranosylamino]-α-*D*-mannopyranoside* (**31**).—A mixture of **19** (9.2 mg, 0.0479 mmol) and **30** [15] (38.6 mg, 0.111 mmol) in 2-propanol (0.5 mL) was heated in a sealed tube for 1 week at 50°C, and then evaporated. The residue was acetylated conventionally and the product was purified by preparative TLC (1:11 acetone–toluene) to give **31** (17.6 mg, 34%) as a syrup; $[\alpha]_D^{26}$ +2° (*c* 1.2, $CHCl_3$); ν_{max} (neat) 1745 cm^{-1} (ester), 1650 (amide); ^1H NMR (270 MHz, Me_2SO-d_6): δ 7.96–7.49 (m, 10 H, 2 Ph), 6.06 (bs, 1 H, H-5″a), 5.82 (d, 1 H, $J_{1',5'a}$ 2.9 Hz, H-5′a), 5.53 (d, 1 H, $J_{3',4'}$ 5.9 Hz, H-4′), 3.08 (s, 3 H, OMe), 2.09, 2.05, 2.04, 2.01, 2.00, 1.99, 1.98, and 1.94 (8 s, 3, 3, 3, 3, 3, 6, 3, and 3 H, 9 Ac). Anal. Calcd for $C_{53}H_{62}N_2O_{23}$: C, 58.13; H, 5.71; N, 2.56. Found: C, 57.51; H, 5.95; N, 2.19.

*Methyl-3,6-bis[5a-carba-α-*D*-*lyxo*-hex-5(5a)-enopyranosylamino]-3,6-dideoxy-α-*D*-mannopyranoside* (**4**).—To a solution of **31** (17.6 mg, 0.0161 mmol) in MeOH (1 mL) was added 1 M methanolic NaOMe (30 μL), and the mixture was stirred overnight at room temperature and then heated for 2 days at reflux. After neutralization with AcOH, the mixture was evaporated and the residue was chromatographed [Dowex 50W-X2 (H^+) resin, H_2O → 1:27 aq ammonia–MeOH] to give **4** (6.0 mg, 73%) as a hygroscopic syrup; $[\alpha]_D^{24}$ +77° (*c* 0.30, MeOH); ^1H NMR (270 MHz, D_2O): δ 5.69 (d, 1 H, $J_{1',5'a}$ 1.8 Hz, H-5′a), 5.64 (d, 1 H, $J_{1'',5''a}$ 2.6 Hz, H-5″a), 4.62 (bs, 1 H, H-1), 4.05–3.99 (m, 4 H, H-6′,6″), 3.58 (m, 1 H, H-5), 3.49 (t, 1 H, $J_{3,4} = J_{4,5} = 9.9$ Hz, H-4), 2.89 (dd, 1 H, $J_{5,6a}$ 1.8, $J_{6(gem)}$ 11.7 Hz, H-6a), 2.83 (dd, 1 H, $J_{2,3}$ 2.9 Hz, H-3), 2.75 (dd, 1 H, $J_{5,6b}$ 8.4 Hz, H-6b).

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