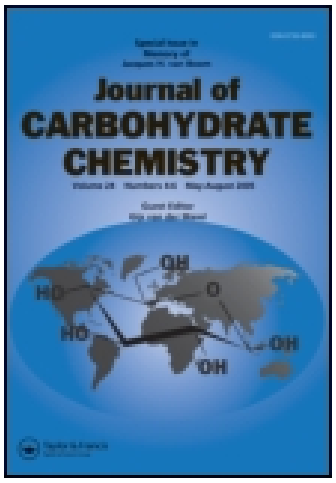

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CONVENIENT SYNTHESIS OF METHYL L-*GLYCERO*-D-*MANNO*-HEPTOPYRANOSIDE

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ABSTRACT

Methyl L-*glycero*-D-*manno*-heptoside was prepared from a butane diacetal (BDA) derivative of methyl mannoside. Benzylation of the 3,4-BDA mannoside gave the 2-benzyl ether as a major product, which eliminated blocking and deblocking of the primary hydroxy group for the preparation of a mannoside bearing a free 6-OH. Swern oxidation of the 2-*O*-Bn-3,4-BDA mannoside followed by a Grignard reaction and osmylation gave L-*glycero*-D-*manno*-3, 4-BDA heptoside in 79 % yield. We found that the 3,4-BDA mannoside, its 2-*O*-Bn mannoside, and the 3,4-BDA heptoside could be prepared in a semi-preparative scale (20∼50 g). The 3,4-BDA mannoside is a convenient precursor for preparation of L-*glycero*-D-*manno*-heptose.

INTRODUCTION

L-*Glycero*-D-*manno*-heptose is a common carbohydrate component of lipooligo- and lipopolysaccharides produced by Gram-negative bacteria.[1–3] The heptose is expressed as a di- or trisaccharide in the inner cores of those glycolipids. This carbohydrate has been generally synthesized by using methyl or benzyl mannoside as a starting material.[4–8] Swern oxidation of the 6-OH of suitably protected mannosides and subsequent Grignard reaction provides the *manno*-heptosides.

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This work describes synthesis of methyl L-*glycero*-D-*manno*-heptoside from methyl α-D-mannoside. Conversion of the mannoside to its 3,4-butane diacetal (BDA)[9] mannoside and subsequent benzylation provided a precursor bearing a free 6-OH. Sequential oxidation and elongation of this compound provided a 3,4-BDA mannoheptoside.

RESULTS AND DISCUSSION

Methyl 3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-mannopyranoside (**2**) was prepared in 98% yield by treating methyl α-D-mannoside (**1**) with 2,3-butanedione (1.1 M equiv) and trimethyl orthoformate (3 M equiv) in methanol. Instead of BF3/Et2O, [9] (±)-camphor-10-sulfonic acid (0.1 M equiv) was used as a catalyst for this acetalation. We also found that this reaction could be carried out on a semi-preparative scale. Treatment of compound **1** (50 g, 257 mmol) with the same equivalents of the reagents as described above gave compound **2** in 94% yield.

Treatment of compound **2** with *t*-butyldiphenylsilyl (TBDPS) chloride in DMF for 20 h at room temperature followed by flash chromatography gave the 6-*O*-TBDPS ether **3** in 69 % yield. Benzylation of compound **3** with benzyl bromide and NaH in DMF gave the benzyl ether **4** in 94 % yield, and this compound was treated with tetrabutylammonium fluoride in THF to give crystalline **5** in 93 % yield.

Alternatively, compound **5** was prepared directly from compound **2**. Similar to the use of a cyclohexane 1,2-diacetal (CDA) derivative of methyl mannoside,[10] benzylation of compound **2** (20 g) with BnBr (1M equiv) and NaH (2M equiv) in DMF for 2 h at 0°C gave the 2-*O*-benzyl ether **5** in 68 % yield after purification by flash chromatography. In addition to the 2,6-di-*O*-benzyl ether derivative (7 %), the unreacted compound **2** (17 %) was recovered. Preferential benzylation of the OH-2 was reproducible in a larger scale of the reaction. Treatment of 60 g of compound **2** with BnBr and NaH in DMF for 16 h at room temperature and subsequent purification by flash chromatography gave compound **5** in 62 % yield. Thus, isolation of the 2-*O*-benzyl ether **5** as a major product led to elimination of two steps, blocking and deblocking of the 6-OH of the mannoside, for the preparation of methy *mann*o-heptoside.

Although the pronounced reactivity of the 2-OH over the primary group has been reported in benzylation of methyl 3,4-*O*-isopropylidene-α-D-galactopyranoside[11] and the CDA derivative of methyl α-D-mannoside as described above[10], the reversed reactivity of the two hydroxyl groups has not yet been clarified. We were not be able to isolate a 6-*O*-benzyl ether of the BDA compound **2** from the reaction mixture, which indicated that the protecting group at O-3 and O-4 such as BDA and CDA of methyl α-D-mannoside favors the formation of the 2-oxyanion over the 6-oxyanion leading to preferential benzylation of the OH-2.

Swern oxidation of compound **5** (20 g) and subsequent treatment of the resulting aldehyde with vinylmagnesium bromide gave methyl L-*glycero*-D-*manno*-oct-7-eno-pyranoside **6** in 88 % yield after flash chromatography. We used similar reaction conditions to those described by Dasser et al[6] and found that the vinyla-

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tion of the oxidized product of the BDA compound is also highly stereoselective and yields the L-product dominantly. Although we did not characterize minor products of the reaction, the formation of the D-isomer was minimal based upon the isolated yield of **6** from the one-pot oxidation/elongation reaction. This reaction was repeated several times, and we found that this L-streoselectivity was reproducible. The vinyl function of compound **6** was confirmed by NMR spectroscopy (Table 1); H-7, H-8a and H-8b were detected at 5.97, 5.18 and 5.35 ppm, respectively.

Compound **6** was quantitatively converted into the 6-acetate **7** by acetylation with pyridine and acetic anhydride in the presence of catalytic amounts of dimethylaminopyridine. Oxidative cleavage of the acetate **7** with OsO4/NaIO4 and subsequent reduction of the resulting aldehyde with NaBH4 gave the 3,4-diacetal heptose derivative **8** (92 %) whose structure was confirmed by NMR analyses (Table 1).

The *O*-benzyl group of **8** was removed by hydrogenolysis to give **9** which was treated with TFA/H_2O (9/1, v/v) to yield methyl L-*glycero*-D-*manno*-heptopyranoside (**10**). The L-stereochemistry at C-6 of this compound was determined by HPAEC analysis.[12] TFA hydrolysis of compound **10** gave L-*glycero*-D-*manno*-heptose. Since L-*glycero*-D-*manno*-heptose is eluted much earlier than D-*glycero*-D-*manno*-heptose under the condition used, we are able to determine the C-6 stereochemistry of the D-*manno*-heptose. The identification of compound **10** confirmed that compounds **6–9** have the L-stereochemistry at C-6. Although methyl L-*glycero*-D-*manno*-heptoside has been cited in a couple of publications, [5;13] only partial ^{1}H NMR data[13] are available. Therefore, we included complete ^{1}H and ^{13}C NMR data as a reference in Table 1. Thus, methyl L-*glycero*-D-*manno*-heptoside **10** was prepared in 8 steps as a total yield of 53 % from methyl mannoside **1**.

As described earlier, methyl, benzyl, and allyl mannosides have been converted to their corresponding heptoside.[4–8] Recently, van Delft et al[8] reported that silicon-based hydroxymethylation of methyl 2,3,4-tri-*O*-benzyl-*manno*-hexodialdo-1,5-pyranoside gave 2,3,4-tri-*O*-benzyl heptoside in 66 % yield. Although the current procedure requires extra steps (Scheme 1), acetylation of the 6-OH of the elongated compound before oxidative cleavage with OsO4/NaIO4 and subsequent reduction, the yield (79 %) in converting a suitably protected mannopyranoside to its heptoside derivative is better than that reported in the hydroxymethylation procedure described above.

The use of the 3,4-diacetal mannoside **2** for the preparation of a heptoside has several advantages. First, the BDA derivative[9] can be prepared quantitatively in a semi-preparative scale. Second, protection of primary hydroxyl group and subsequent deprotection is unnecessary since benzylation of the 3,4-diacetal product gives the 2-*O*-benzyl ether as a major product. As described earlier, over 50 g of **6** can be prepared in a single experiment. Third, Swern oxidation and subsequent treatment with vinylmagnesium bromide of compound **5** gives an elongated product of L-stereochemistry dominantly. Fourth, in addition to **2** and **5**, compounds **6–8** are also crystalline, which is convenient for preparation of the heptoside.

We converted the 3,4-BDA mannoside **5** into its mannoheptoside **8** in 79 %. The BDA derivative of mannoside is a useful starting material to prepare L-*glycero*-D-*manno*-heptose.

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Table 1. ^{1}H(500 MHz) and ^{13}C(125 MHz) NMR Data for Compounds **6**, **9**, **10**

	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8
6[a]	4.68 $J_{1,2}$ = 2.0 Hz	3.69 $J_{2,3}$ = 3.0 Hz	4.06 $J_{3,4}$ = 10.5 Hz	4.36 $J_{4,5}$ = 10.0 Hz	3.67 $J_{5,6}$ = 1.5 Hz	4.41 $J_{6,7}$ = 5.5 Hz	5.97 $J_{7,8a}$ = 11.0 Hz $J_{7,8b}$ = 17.0 Hz	5.18 (6a) 5.35 (6b) $J_{8a,8b}$ = 1.5 Hz
9[a]	4.76 $J_{1,2}$ < 1.0 Hz	3.92 $J_{2,3}$ = 3.5 Hz	4.00 $J_{3,4}$ = 10.5 Hz	4.21 $J_{4,5}$ = 10.0 Hz	3.72 $J_{5,6}$ = 1.5 Hz	3.97 $J_{6,7a}$ = 4.0 Hz $J_{6,7b}$ = 6.0 Hz	3.67 (7a) 3.82 (7b) $J_{7a,7b}$ = 10.5 Hz	—
10[b]	4.58 $J_{1,2}$ = 1.0 Hz	3.74 $J_{2,3}$ = 2.0 Hz	3.57 $J_{3,4}$ = 9.5 Hz	3.67 $J_{4,5}$ = 10.0 Hz	3.38 n.d.	3.86 $J_{6,7a}$ = 5.5 Hz $J_{6,7b}$ = 6.5 Hz	3.53 (7a) 3.57 (7b) $J_{7a,7b}$ = 11.5 Hz	—

^{1}H-data of other protons for **6, 9** and **10** are as follows. **6**: 7.17 ~ 7.44 (Ar-H, 5H), 4.59, 4.65 (C*H*$_2$Ph), 3.26, 3.28, 3.33 (O*Me*), 1.31, 1.34 (diacetal-*Me*); **9**: 3.27, 3.30, 3.34 (O*Me*), 1.29, 1.32 (diacetal-C*Me*); **10**: 3.19 (1-O*Me*), n.d.: not determined. a: in $CDCl_3$ at 21 °C, b: in D_2O at 60 °C.

	C-1	C-2	C-3	C-4	C-5	C-6	H-7	H-8
6[a]	100.7	75.6	69.1	63.2	73.2	69.5	138.2	115.4
9[a]	101.2	69.4	68.0	62.3	70.9	68.7	64.8	—
10[b]	101.4	70.3	71.3	66.5	71.4	69.2	63.3	—

^{13}C-data of other carbons for **6, 9** and **10** are as follows. **6**: 17.8 (diacetal-*C*H$_3$), 48.0 (diacetal-O*Me*), 54.5 (1-O*Me*), 72.5 (*C*H$_2$Ph), 127.5, 128.0, 128.2, 138.6 (Ar-*C* × 6), 99.6, 99.9 (diacetal-*C*); **9**: 17.6, 17.7 (diacetal-*C*H3), 48.0, 48.0 (diacetal-O*Me*), 54.9 (1-O*Me*), 99.9, 99.9 (diacetal-*C*); **10**: 55.1 (1-O*Me*), n.d.: not determined. a: in $CDCl_3$ at 21 °C, b: in D_2O at 60 °C.

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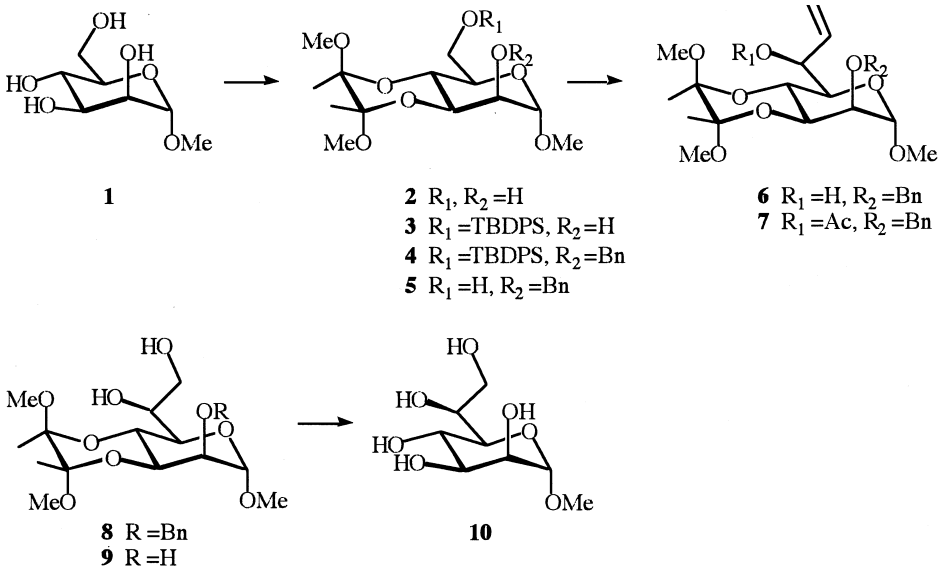

Scheme 1.

EXPERIMENTAL

General Methods. Optical rotations were measured with a HORIBA SEPA-200 polarimeter. Melting points were measured with a YANAGIMOTO micro melting point apparatus and are uncorrected. Elemental analyses were carried out by using a Perkin-Elmer 2400 Series II CHNS/O Analyzer. NMR spectra [270 MHz (JEOL GX) and 500 MHz (JEOL JNM-ECP 500)] were recorded in CDCl3 or D2O. TMS was used as an internal standard for CDCl3, and 1 % CH3CN (δ = 1.96 for ^{1}H; δ = 119.52, 1.30 for ^{13}C) was used for D2O. 2D NMR spectra (500 MHz, JEOL JNM-ECP 500) were obtained in a similar manner as described[14;15]; DQF-COSY (sweep width for *t*1 and *t*2 = 2084 Hz, the 2K × 512 data points were processed to give the final 1K × 256 points); HMQC (sweep width for *t*1 = 2084 Hz, sweep width for *t*2 = 16835 Hz, the 1K × 256 data points were processed to give the final 1K × 256 points). The data were processed by using an Alice2 program (JEOL) on an Impact 300 computer. IR spectra were recorded with a JASCO FT/IR-5300A spectrometer. FABMS spectra were obtained with a JEOL JMS-600H mass spectrometer using glycerol as a matrix (accelerating voltage of the primary ion, 3 kV; collision gas, xenon; collision energy, 6 keV; collision gas pressure, 0.5 Pa; the data were processed with a Hewlett Packard B132L computer). Merck Silica gel 60 (0.040–0.063 mm) and Merck Silica gel 60 (0.063–0.20 mm) was used for flash and open-column chromatography, respectively. Silica gel 60 F254 (Merck) was used for thin-layer chromatography, and compounds were detected under UV light or by spraying 10 % conc sulfuric acid in methanol and then by heating the plates at 120°C for 5 min. We analyzed L- and D-*glycero*-D-mannoheptoses by high-performance anion exchange chromatography as reported previously.[12]

Methyl α-D-mannoside was purchased from Sigma Chemical Co. (2′*S*,3′*S*)-Methyl 3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-mannopyranoside (**2**) was prepared in 98 % yield by treating methyl α-D-mannopyranoside (**1**) (1.2 g) with 1.1 M equiv of 2,3-butanedione according to the literature procedure[9] except for that (±)-camphor-10-sulfonic acid was used as a catalyst. $[\alpha]_D^{23}$ +213° (*c* 1.0, CHCl3), mp 140–141°C (ethyl acetate) {$[\alpha]_D^{23}$ +252° (*c* 1.05, CHCl3), mp 140°C}. This acetalation was also carried out in a semi-preparative scale as follows. A solution of compound **1** (50 g, 257 mmol), the dione (24.4 g, 283 mmol), trimethyl orthoformate (81.9 g, 772 mmol) and the sulfonic acid (6 g, 28 mmol) in methanol (500 mL) was refluxed for 24 h. After cooling, the solution was treated with triethyamine (43 mL) and then concentrated to a dark syrup. Purification of the syrup by chromatography (ethyl acetate/hexane 1/1 to 3/1 v/v) gave compound **2** (75g, 94%).

(2′*S*,3′*S*)-Methyl 6-*O*-*Tert*-butyldiphenylsilyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-mannopyranoside (3). Compound **2** (1.79 g, 5.8 mmol) was treated with *t*-butyldiphenylsilyl chloride (1.91 g, 7.0 mmol) in dry DMF (12 mL) in the presence of imidazole (987 mg, 15 mmol) for 20 h at room temperature. After terminating the reaction by adding water (10 mL), the product was extracted with ethyl acetate (50 mL × 3). The organic extracts were concentrated to give a residue which was purified by flash chromatography (hexane/ethyl acetate 3/1 v/v) to give **3** as a syrup (2.19 g, 69 %). ^{1}H NMR (270 MHz, CDCl3) δ: 7.73–7.71 (m, 4H, Ph), 7.41–7.35 (m, 6H, Ph), 4.74 (d, 1H, *J*1,2 = 1 Hz, H-1), 4.06–3.89 (5H, H-2, H-3, H-4, H-6a, H-6b), 3.82 (m, 1H, *J*4,5 = 10 Hz, H-5), 3.36, 3.27, 3.14 (s, 3H each, OMe), 2.31 (d, 1H, *J* = 3.0, 2-OH), 1.31 ,1.25 (s, 3H each, Me), 1.05 (s, 9H, *t*-Bu). $[\alpha]_D^{24}$ +107° (*c* 0.5, CHCl3).

Anal. Calcd for C29H42O8Si: C, 63.71; H, 7.74. Found: C, 63.42; H, 7.99.

(2′*S*,3′*S*)-Methyl 2-*O*-Benzyl-6-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-mannopyranoside (4). Compound **3** (1.68 g, 3.1 mmol) was benzylated with benzyl bromide (0.44 mL, 3.7 mmol) and NaH (60 % in paraffin liquid, 245 mg, 6.1 mmol) in dry DMF in the presence of molecular sieves 4Å at 0°C for 2 h. After filtering through Celite, the filtrate was washed with brine, dried over MgSO4, and concentrated to give a pale yellow syrup. Flash chromatography (hexane/ethyl acetate 20/1 to 3/1 v/v) of the syrup gave compound **4** (1.84 g, 94 %). ^{1}H NMR (270 MHz, CDCl3) δ: 7.72–7.70 (m, 4H, Ph), 7.44–7.25 (m, 11H, Ph), 4.95 (d, 1H, *J* = 12.2 Hz, PhCH), 4.69 (d, 1H, *J*1,2 = 1.1 Hz, H-1), 4.65 (d, 1H, *J* = 12.2 Hz, PhCH), 4.17 (t, 1H, *J*4,5 = 10 Hz, H-4), 4.06 (dd, 1H, *J*3,4 = 10 Hz, H-3), 3.91, 3.90 (s, 1H each, H-6a, H-6b), 3.78 (m, 1H, H-5,), 3.68 (dd, 1H, *J*2,3 = 3.0 Hz, H-2), 3.31, 3.27, 3.15 (s, 3H each, OMe), 1.32 ,1.26 (s, 3H each, Me), 1.02 (s, 9H, *t*-Bu). $[\alpha]_D^{22}$ +28° (*c* 0.5, CHCl3).

Anal. Calcd for C36H48O8Si: C, 67.89; H, 7.60. Found: C, 67.63; H, 7.85.

(2′*S*,3′*S*)-Methyl 2-*O*-Benzyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-mannopyranoside (5). Compound **4** (1.56 g, 2.5 mmol) was treated with tetrabutyl ammonium fluoride (1M in THF, 4.9 mL, 4.9 mmol) in dry THF (5 mL)

for 24 h. The reaction mixture was diluted with H2O (50 mL), and then extracted with ethyl acetate (30 mL × 2). The combined extracts were washed with brine, dried (MgSO4), and concentrated to a syrup. Purification of the syrup by flash chromatography (hexane/ethyl acetate 3/1 to 1/1 v/v) gave compound **5** as a solid (904 mg, 93 %). ^{1}H NMR (270 MHz, CDCl3) δ: 7.44–7.29 (m, 5H, Ph), 4.95 (d, 1H, J = 11.9 Hz, PhCH), 4.67 (d, 1H, J1,2 = 1.1 Hz, H-1), 4.65 (d, 1H, J = 11.9 Hz, PhCH), 4.19 (dd, 1H, J4,5 = 9.5 Hz, H-4), 4.06 (dd, 1H, J3,4 = 9.5 Hz, H-3), 3.83–3.73 (m, 3H, H-5, H-6a, H-6b), 3.69 (dd, 1H, J2,3 = 3.0 Hz, H-2), 3.31, 3.28, 3.27 (s, 3H each, OMe), 1.33 ,1.30 (s, 3H each, Me). mp 132–133°C (recrystallized from hexane-ethyl acetate), $[\alpha]_D^{22}$ +227° (*c* 0.5, CHCl3).

Anal. Calcd for C20H30O8: C, 60.29; H, 7.59. Found: C, 60.12; H, 7.54.

Compound **5** was also prepared by directly benzylating **2** (12.0 g, 39 mmol) with benzyl bromide (4.63 mL, 39 mmol) and NaH (3.12 g, 78 mmol) at 0°C for 2 h. The reaction was quenched with water (100 mL), and the mixture was extracted with ethyl acetate (100 mL × 2). The extracts were washed with brine (100 mL × 2), dried (MgSO4), and concentrated to a syrup. Flash chromatography (ethyl acetate/hexane 2/1 v/v) of the syrup gave compound **5** as a solid (11.2 g, 72 %). In addition to **5**, unreacted compound **2** (1.10 g, 17 %) and (2′*S*,3′*S*)-methyl 3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-2,6-di-*O*-benzyl-α-D-mannopyranoside [(1.31 g, 7 %), $[\alpha]_D^{23}$ +141° (*c* 1.0, CHCl3) {$[\alpha]_D^{22}$ +146° (*c* 1.0, CHCl3)}[9]] were obtained. This benzylation was also carried out on a larger scale. Compound **2** (60.0 g, 194 mmol) was treated with NaH (7.3 g, 185 mmol) and BnBr (21.5 mL, 181 mmol) in DMF (540 mL) for 16 h at room temperature. Similar work-up as described above and purification by flash chromatography (ethyl acetate/hexane 2/1 to 1/1 v/v) gave compound **5** (48.3 g, 63%).

(2′*S*,3′*S*)-Methyl 2-*O*-Benzyl-7,8-dideoxy-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-*manno*-oct-7-enopyranoside (6). To a chilled solution (to −70°C) of dry THF (150 mL), a mixture of oxalyl chloride (10.7 mL, 125 mmol) and DMSO (17.8 mL, 251 mmol) in dry THF (20 mL) was added, and the mixture was stirred for 15 min. Compound **5** (20.0 g, 50 mmol) in dry THF (100 mL) was added dropwise (∼15 min). The reaction mixture was stirred for 1 h at −60°C and then for 1 h at −40°C. After adding triethylamine (69.7 mL, 502 mmol) and stirring for 1 h at room temperature, the mixture was cooled down to −60°C. Vinyl magnesium bromide (1M in THF, 251 mmol) was added dropwise (30 min), and the mixture was stirred for 2 h at −60°C. The reaction was quenched with the addition of ethanol (20 mL), and after adding saturated aqueous NH4Cl (50 mL), the whole reaction mixture was warmed to room temperature. The mixture was extracted with ethyl acetate (50 mL × 3), and the combined extracts were sequentially washed with 5 % sodium hypochloride in water (100 mL × 4) and brine (100 mL × 2). After drying (MgSO4), the organic solution was concentrated to a syrup which was purified by flash chromatography (hexane/ethyl acetate 3/2 v/v) to give compound **6** as a solid (18.8 g, 88 %). mp 122–123°C (recrystallized from hexane-ethyl acetate), $[\alpha]_D^{24}$ +181° (*c* 0.5, CHCl3).

Anal. Calcd for C22H32O8: C, 62.25; H, 7.60. Found: C, 62.23; H, 7.63.

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(2′*S*,3′*S*)-Methyl 6-*O*-Acetyl-2-*O*-benzyl-7,8-dideoxy-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-*manno*-oct-7-enopyranoside (7). Compound **6** (8.55 g, 20 mmol) was acetylated with pyridine/acetic anhydride in the presence of catalytic amounts of dimethylaminopyridine. Usual work up and flash chromatography (hexane/ethyl acetate 2/1 v/v) gave compound **7** (9.07 g, 97 %). ^{1}H NMR (270 MHz, CDCl3) δ: 7.45–7.26 (m, 5H, Ph), 5.94 (ddd, 1H, *J*7,8a = 17.3 Hz, *J*7,8b = 10.8 Hz, H-7), 5.59 (m, 1H, *J*6,7 = 6.8 Hz, *J*6,8a = 1.6 Hz, *J*6,8b = 1.6 Hz, H-6), 5.35 (ddd, 1H, *J*8a,8b = 1.6 Hz, H-8a), 5.25 (ddd, 1H, H-8b), 4.91 (d, 1H, *J* = 12.2 Hz, PhCH), 4.76 (d, 1H, *J*1,2 = 1.1 Hz, H-1), 4.69 (d, 1H, *J* = 12.2 Hz, PhCH) , 4.22 (dd, 1H, *J*4,5 = 10.0 Hz, H-4), 4.05 (dd, 1H, *J*3,4 = 10.0 Hz, H-3), 3.77 (dd, 1H, *J*5,6 = 1.9 Hz, H-5), 3.68 (dd, 1H, *J*2,3 = 3.0 Hz, H-2), 3.27, 3.26, 3.18 (s, 3H each, OMe), 2.10 (s, 3H, CH3CO), 1.33 ,1.29 (s, 3H each, Me). mp 125°C (recrystallized from EtOH), $[\alpha]_D^{24}$ +157° (*c* 0.5, CHCl3).

Anal. Calcd for C24H34O9: C, 61.79; H, 7.35. Found: C, 61.83; H, 7.37.

(2′*S*,3′*S*)-Methyl 2-*O*-Benzyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-L-*glycero*-α-D-*manno*-heptopyranoside (8). Compound **7** (9.07 g, 19 mmol) in ethyl ether/water (240 mL, 1/1 v/v) was cooled in an ice bath and treated with sodium metaperiodate (20.8 g, 97 mmol) and 1 % aqueous OsO4 (24 mL). After stirring the mixture for 24 h at room temperature, it was extracted with ethyl ether (100 mL × 2) and the combined extracts were washed with water (100 mL × 2). The combined extracts were concentrated to a syrup which was then treated with NaBH4 (2.94 g, 78 mmol) in methanol/water (360 mL, 2/1 v/v) for 15 h at room temperature. The mixture was extracted with CH2Cl2 (100 mL × 2), and the combined extracts were washed with H2O (50 mL × 4). After drying (MgSO4), the combined extracts were concentrated to a residue which was purified by flash chromatography (ethyl acetate/hexane 2/1 v/v) to give compound **8** (7.66 g, 92 %). ^{1}H NMR (270 MHz, CDCl3) δ: 7.44–7.26 (m, 5H, Ph), 4.97 (d, 1H, *J* = 11.9 Hz, PhCH), 4.68 (d, 1H, *J*1,2 = 1.1 Hz, H-1), 4.64 (d, 1H, *J* = 11.9 Hz, PhCH) , 4.34 (dd, 1H, *J*4,5 = 10.3 Hz, H-4), 4.05 (dd, 1H, *J*2,3 = 2.7 Hz, *J*3,4 = 10.3 Hz, H-3), 3.96 (m, 1H, H-6), 3.81–3.69 (m, 4H, H-2, H-5, H-7), 3.33, 3.29, 3.27 (s, 3H each, OMe), 2.53 (br, 1H, OH), 2.28 (br, 1H, OH), 1.34 ,1.30 (s, 3H each, Me). mp 142–143°C (recrystallized from hexane-ethyl acetate), $[\alpha]_D^{23}$ +172° (*c* 0.5, CHCl3).

Anal. Calcd for C21H32O9: C, 58.87; H, 7.53. Found: C, 58.60; H, 7.46.

(2′*S*,3′*S*)-Methyl 3,4-*O*-(2′,3′-Dimethoxybutane-2′,3′-diyl)-L-*glycero*-α-D-*manno*-heptopyranoside (9). Compound **8** (7.66 g, 18 mmol) was hydrogenated with Pd-C (∼5 g) in EtOH (120 mL) for 20 h. After filtration, the reaction mixture was concentrated to a syrup which was purified by chromatography (CH2Cl2/methanol 10/1 v/v) to give compound **9** (5.95 g, 98 %). $[\alpha]_D^{24}$ +209° (*c* 1.0, CHCl3), FABMS: *m/z* [Found (MNa^+) 361.1474. C8H17O7 requires MNa, 361.1429].

Methyl L-*glycero*-α-D-*manno*-heptopyranoside (10). A solution of compound **9** (200 mg, 0.59 mmol) in TFA/H2O (5 mL, 9/1 v/v) was heated for 1 h.

After cooling, the mixture was concentrated to a residue. Purification by flash chromatography (ethyl acetate/methanol 9/1 to 1/9 v/v) to give a hygroscopic solid (130 mg, 98 %). $[\alpha]_D^{24}$ +70° (*c* 1.0, methanol), FABMS: *m/z* [Found (MH^+) 225.0975. C8H17O7 requires MH, 225.0723].

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