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Note

Synthesis and glycosidic coupling reaction of substituted 2,6-dioxabicyco[3.1.1] heptanes: 1,3-anhydro-2-azido-4,6-di-*O*-benzyl-2-deoxy-β-D-mannopyranose

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Abstract

The title 1,3-anhydro sugar was synthesized from methyl α-D-glucopyranoside. The key intermediate for the synthesis was 3-*O*-acetyl-2-azido-4,6-di-*O*-benzyl-2-deoxy-α-D-mannopyranosyl chloride (**11**) which was transformed into the target compound by ring closure with potassium *tert*-butoxide. © 1998 Elsevier Science Ltd. All rights reserved

Keywords: 2,6-Dioxabicyclo[3.1.1]heptanes; Synthesis; Coupling reaction

2-Amino-2-deoxy-D-mannose occurs in important natural materials. For example, the polysaccharide linked to the peptidoglycan of the cell wall of *Micrococcus lysodeikticus* contains residues of both D-glucose and 2-amino-2-deoxy-mannuronic acid [1], the *O*-antigenic polysaccharide from a strain of *Aeromonas caviae*, isolated from the stools of a patient with diarrhea, is composed of a pentasaccharide unit containing *N*-acetyl-mannosamine [2a], and the *O*-specific polysaccharide chain of lipopolysaccharide of *B. plantarii* is composed of *N*-acetyl-mannosamine and rhamnose [2b]. As a part of our program on the synthesis of the 2,6-dioxabicyclo[3.1.1]heptane ring system occurring in thromboxane A_2 (TXA_2) [3,4], a compound of substantial importance in biological chemistry, we have investigated 1,3-anhydro-β-L-rhamno- [5], -β-D-galacto- [6], -6-deoxy-β-D-gluco- [7], -6-azido-6-deoxy-β-D-manno- [8], -β-D-fuco- [9], -β-D-talo- [10], and -α-L-arabinopyranose [11] benzyl ethers. The synthesis of 1,3-anhydro-β-D-gluco- [12,13] and -β-D-mannopyranose derivatives [14,15] had been reported earlier by Schuerch's group. We now report the synthesis of 1,3-anhydro-2-azido-4,6-di-*O*-benzyl-2-deoxy-β-D-mannopyranose whose stereoregular polymerization and subsequent deprotection could afford α-(1→3) linked 2-amino-2-deoxy-D-mannopyranan and whose glycosidic coupling reaction followed by deblocking can afford oligosaccharides containing mannosamine units.

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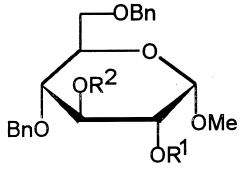
1. Results and discussion

Methyl 4,6-di-*O*-benzyl-α-D-glucopyranoside (**1**) [16], prepared from methyl 2,3-di-*O*-allyl-4,6-di-*O*-benzyl-α-D-glucopyranoside [17] via deallylation, was selectively 2-*O*-allylated by either the phase transfer method or via a dibutylstannylene complex to give methyl 2-*O*-allyl-4,6-di-*O*-benzyl-α-D-glucopyranoside **2**. The dibutylstannylene method gave better selectivity and yield (72%), while the phase transfer method is more suitable for large scale preparations. Benzoylation of **2** with benzoyl chloride in pyridine gave ester **3**, which was deallylated with palladium chloride (1/20 w/w) [18] in methanol at room temperature to give methyl 3-*O*-benzoyl-4,6-di-*O*-benzyl-*a*-D-glucopyranoside (**4**) crystals in good yield (75%). Isomerization of the allyl group of **3** with tris(triphenylphosphine)-rhodium(I) chloride followed by acid treatment was also used successfully for deallylation (80% yield). Triflation of compound **4** with triflic anhydride in dichloromethane and pyridine at −10 °C, then at room temperature for 4 h furnished methyl 3-*O*-benzoyl-4,6-di-*O*-benzyl-2-*O*-trifluoromethanesulfonyl-α-D-glucopyranoside (**5**). Treatment of **5** with sodium azide in DMF at 80 °C for 2–3 h gave methyl 2-azido-3-*O*-benzoyl-4,6-di-*O*-benzyl-2-deoxy-α-D-mannopyranoside (**6**).

In the conversion of **5** to **6**, some decomposition occurred when the reaction time was too long, and the addition of ammonium chloride reduced the decomposition [19]. Debenzoylation of **6** with a catalytic amount of sodium methoxide in methanol to give **7**, followed by acetylation with acetic anhydride in pyridine, gave methyl 3-*O*-acetyl-2-azido-4,6-di-*O*-benzyl-2-deoxy-α-D-mannopyranoside (**8**) quantitatively. Acetolysis of **8** with acetic anhydride–acetic acid using sulfuric acid as the catalyst ($Ac_2O/AcOH/H_2SO_4 = 50/20/0.1$) furnished 1,3-di-*O*-acetyl-2-azido-4,6-di-*O*-benzyl-2-deoxy-α-D-mannopyranose (**10**) and methyl 3,6-di-*O*-acetyl-2-azido-4-*O*-benzyl-2-deoxy-α-D-mannopyranoside (**15**) in a ratio of 1:1 as determined by ^{1}H NMR. TLC indicated that compounds **10** and **15** had the same R_f value, and could not be separated by HPLC, but further reaction products were easily separated. Since it was difficult to monitor the acetolysis by TLC and, to separate the products by column chromatography, and since the yields of acetolysis were variable, another method was used for the preparation of the 1,3-diacetate. Thus conversion of **8** to **9** by aqueous hydrolysis was carried out; hydrolysis in 70% acetic acid in the presence of *p*-toluenesulfonic acid or camphorsulfonic acid [20] at 100 °C for 16 h gave 3-*O*-acetyl-2-azido-4,6-di-*O*-benzyl-2-deoxy-D-mannopyranose (**9**) in an acceptable yield (65%), while hydrolysis in 70–80% acetic acid in the presence of hydrochloric acid produced a complex, unseparable mixture. Acetylation of **9** by standard methods afforded **10** as a mixture of α and β anomers in a ratio of 5/1. Chlorination of **10** with hydrogen chloride in diethyl ether furnished the key intermediate, 3-*O*-acetyl-2-azido-4,6-di-*O*-benzyl-2-deoxy-α-D-mannopyranosyl chloride (**11**) in satisfactory yield (84%). Ring closure of **11** proceeded smoothly with potassium *tert*-butoxide in oxolane, affording 1,3-anhydro-2-azido-4,6-di-*O*-benzyl-2-deoxy-β-D-mannopyranose (**12**) in good yield (82.5%). The 1,3-anhydro sugar was identified by elemental analysis and from its ^{1}H NMR spectrum, which showed a characteristic doublet at 5.39 for H-1 with $^4J_{1,3} = 3.6$ Hz, a triplet at δ 4.49 for H-3 with $J_{1,3} = J_{3,4} = 3.6$ Hz and a singlet [5]



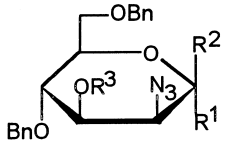
1 $R^1 = R^2 = H$

2 R^1 = All $R^2 = H$

3 R^1 = All R^2 = Bz

4 $R^1 = H$ R^2 = Bz

5 R^1 = Tf R^2 = Bz



6 R^1 = OMe $R^2 = H$ R^3 = OBz

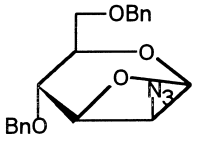
7 R^1 = OMe $R^2 = H$ $R^3 = H$

8 R^1 = OMe $R^2 = H$ R^3 = Ac

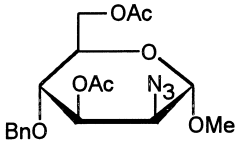
9 R^1, R^2 = H, OH R^3 = Ac

10 R^1, R^2 = H, OAc R^3 = Ac

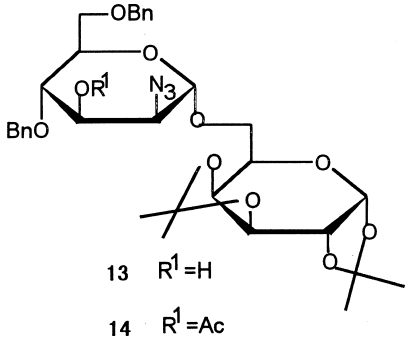
11 R^1 = Cl $R^2 = H$ R^3 = Ac



12



15



13 $R^1 = H$

14 R^1 = Ac

[15] at δ 4.21 for H-2. The anhydrosugar **12** was quite reactive; ring-opening with methanol in the presence of $ZnCl_2$ afforded the α-linked methyl mannopyranoside **7** as the sole product, while its coupling reaction with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose in dry oxolane with $ZnCl_2$ as the promoter gave α-linked disaccharide **13** in good yield (76%). Acetylation of **13** with acetic anhydride in pyridine gave **14** quantitatively, and its ^{1}H NMR spectrum showed a doublet of doublets at δ 5.35 ($J_{2',3'} = 3.9$ Hz, $J_{3',4'} = 9.6$ Hz) arising from H-3 of the mannose moiety and a singlet at δ 2.03 (CH_3CO), further confirming the structure of **12**.

2. Experimental

General methods.—Optical rotations were determined at 20 °C with a Perkin–Elmer Model 241-MC automatic polarimeter. Melting points were determined with a Mel-Temp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Varian XL-400 and XL-200 spectrometers in $CDCl_3$ solutions. Chemical shifts are given in ppm downfield from Me_4Si. Analytical LC was carried out in stainless-steel columns packed with Silica Gel (10×150 mm or 4.6×250 mm) or Lichrosorb-NH_2 (4.6×250 mm) , with peak detection by a differential refractometer (Perkin–Elmer LC-25 RI Detector). A mixture of ethyl acetate and petroleum ether (bp 60–90 °C) was used as the eluent, at a flow rate of 1–4 mL min^{-1}. TLC was performed on Silica Gel G and HF, with detection either by charring with 30% (v/v) H_2SO_4 in MeOH or by UV light. Preparative chromatography was performed on columns (16×240, 18×300, and 35×400 mm) of Silica Gel (100–200 mesh).

Methyl 2-O-allyl-4,6-di-O-benzyl-α-D-glucopyranoside (**2**).—*Method A*. To a solution of compound **1** (10.5 g, 28 mmol) [16], tetrabutylammonium hydrogen sulfate (1 g, 3 mmol), and allyl bromide (4 mL, 46 mmol) in dichloromethane (200 mL) was added aqueous sodium hydroxide (100 mL, 5%), and the mixture was stirred at room temperature for 48 h. TLC (2/1 petroleum ether–ethyl acetate) indicated that the reaction was complete. The mixture was extracted with dichloromethane and, washed with water, and the organic layer was concentrated to a syrup and purified by column chromatography using 2/1 petroleum ether-ethyl acetate as the eluent to give syrupy **2** (7 g, 60%).

Method B. Compound **1** (1 g, 2.7 mmol) and dibutyltin oxide (720 mg, 3.0 mmol) were suspended in methanol (10 mL), the mixture was refluxed for 2–3 h until the suspension became clear, and refluxing was continued for 1 h. The solution was cooled and evaporated to give a white, foamy residue. To the residue was added dry toluene (10 mL), tetrabutylammonium iodide (1 g, 2.7 mmol) and allyl bromide (0.3 mL, 3.5 mmol), and the mixture was boiled for 16 h, at the end of which time TLC (2/1 petroleum ether–ethyl acetate) showed the disappearance of the starting material. Sodium hydrogen carbonate (0.4 g) was added and, the reaction mixture was steam distilled to remove excess allyl bromide. The resulting syrup was subjected to chromatography (2/1 petroleum ether–ethyl acetate) over silica gel to give **2** as a syrup (0.8 g , 72%); $[\alpha]_D$ +107° (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.38–7.20 (m, 10 H, Ph-*H*), 5.94 (m, 1 H, J_{trans} 17.3 Hz, J_{cis} 10.0 Hz, *J* 6.0 Hz, $CH_2=CH$-CH_2), 5.30 (m, 1 H, J_{trans} 17.3 Hz, ^2J 1.4 Hz, ^4J 1.2 Hz, $CHH=CH$-CH_2), 5.22 (m, 1 H, J_{cis} 10.0 Hz, ^2J 1.4 Hz, ^4J 1.2 Hz, $CHH=CH$-CH_2), 4.86 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.85, 4.53 (q_{AB}, 2 H, ^2J 11.1 Hz, H, PhCH_2), 4.65, 4.50 (q_{AB}, 2 H, ^2J 12.1 Hz, PhCH_2), 4.16 (m, 2 H, *J* 6.0 Hz, ^4J 1.2 Hz, $CH_2=CH$-CH_2), 4.04 (t, 1 H, $J_{2,3}$ 9.3 Hz, $J_{3,4}$ 9.3 Hz, H-3), 3.78–3.64 (m, 3 H, H-5,6), 3.59 (t, 1 H, $J_{3,4}$ 9.3 Hz, $J_{4,5}$ 9.3 Hz, H-4), 3.39 (dd, 1 H, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.3 Hz, H-2), 3.40 (s, 3 H, OCH_3). Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.57; H, 7.25. Found: C, 69.55; H, 7.45.

Methyl 2-O-allyl-3-O-benzoyl-4,6-di-O-benzyl-α-D-glucopyranoside (**3**).—To a cold solution (0 °C) of **2** (2.96 g, 7.1 mmol) in dichloromethane (40 mL) and pyridine (4 mL) was added benzoyl chloride (1.6 mL), and the mixture was allowed to gradually warm to ambient temperature for 4 h, at the end of which time TLC (3/1 petroleum ether–ethyl acetate) indicated that the reaction was complete. The mixture was poured into ice water (100 mL) and, extracted with dichloromethane, and the organic phase was washed with 1 M HCl solution twice (50 mL) and, then with satd $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated. Column chromatography (3/1 petroleum ether–ethyl acetate) of the residue gave **3** as a syrup in quantitative yield (3.7 g, 100%); $[\alpha]_D$ +41° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.04 (d, 2 H, *J* 7 Hz. Bz-*H*), 7.60–6.98 (m, 13 H, Ph-*H* and Bz-*H*), 5.83–5.63 (m, 2 H, J_{trans} 17.9 Hz, J_{cis} 10.0 Hz, *J* 5.7 Hz, $J_{2,3}$ 9.3 Hz, $J_{3,4}$ 9.3 Hz, $CH_2=CH$-CH_2, H-3), 5.15 (m, 1 H, J_{trans}

17.9 Hz, ^2J 1.4 Hz, ^4J 1.2 Hz, C*H*H=CH-CH$_2$), 5.07 (m, 1H, J_{cis} 10.0 Hz, ^2J 1.4 Hz, ^4J 1.2 Hz, CH*H*=CH-CH$_2$), 4.89 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.68, 4.52 (q_{AB}, 2 H, ^2J 12.0 Hz, PhC*H*$_2$), 4.49, 4.38 (q_{AB}, 2 H, ^2J 10.7 Hz, PhC*H*$_2$), 4.03 (m, 2 H, J 5.7 Hz, ^4J 1.2 Hz, CH$_2$=CH-C*H*$_2$), 3.87–3.69 (m, 3 H, H-5,6), 3.70 (t, 1 H, $J_{3,4}$ 9.3 Hz, $J_{4,5}$ 9.3 Hz, H-4), 3.63 (dd, 1 H, $J_{1,2}$ 3.3 Hz, $J_{2,3}$ 9.3 Hz, H-2), 3.43 (s, 3 H, OC*H*$_3$). Anal. Calcd for $C_{31}H_{34}O_7$: C, 71.81; H, 6.56. Found: C, 71.62; H, 6.89.

*Methyl 3-*O*-benzoyl-4,6-di-*O*-benzyl-a-*D*-glucopyranoside* (**4**).—*Method A*. To a solution of compound **3** (0.7 g, 1.4 mmol) in ethanol (90%, 5 mL) was added tris(triphenylphosphine)rhodium chloride (35 mg), and the reaction mixture was heated under reflux for 12 h, at the end of which time TLC (2/1 petroleum ether–ethyl acetate) indicated the disappearance of the starting material. Hydrochloric acid (1 M, 0.5 mL) was added and the mixture was boiled for a further 2 h. The solution was concentrated, the residue was dissolved in dichloromethane, and the solution was washed with satd $NaHCO_3$, dried over Na_2SO_4, and concentrated. Column chromatography (2/1 petroleum ether–ethyl acetate) of the residue gave **4** as crystals (0.52 g, 80%).

Method B. To a solution of compound **3** (4.33 g, 8.4 mmol) in methanol (60 mL) was added palladium chloride (220 mg), and the mixture was stirred at room temperature for 12 h, at the end of which time TLC (2/1 petroleum ether–ethyl acetate) showed the disappearance of the starting material. The solution was concentrated, and the insoluble palladium chloride was removed by centrifugation. Purification by column chromatography using petroleum ether–ethyl acetate (2/1) as the eluent gave compound **4** as white crystals (3 g, 75%); mp 85–86 °C; $[\alpha]_D$ +88° (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.04 (d, 2 H, J 6.4 Hz. Bz-*H*), 7.60–6.95 (m, 13 H, Ph-*H* and Bz-*H*), 5.55 (t, 1 H, $J_{2,3}$ 9.1 Hz, $J_{3,4}$ 9.1 Hz, H-3), 4.86 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 4.68, 4.54 (q_{AB}, 2 H, ^2J 12.4 Hz, PhC*H*$_2$), 4.56, 4.43 (q_{AB}, 2 H, ^2J 10.5 Hz, PhC*H*$_2$), 3.92–3.65 (m, 5 H, H-2,4,5,6), 3.45 (s, 3 H, OC*H*$_3$). Anal. Calcd for $C_{28}H_{30}O_7$: C, 70.29; H, 6.28. Found: C, 70.40; H, 6.17.

*Methyl 3-*O*-benzoyl-4,6-di-*O*-benzyl-2-*O*-triflyl-*α*-*D*-glucopyranoside* (**5**).—To a solution of compound **4** (2.61 g, 5.5 mmol) in dichloromethane (60 mL) and pyridine (1.4 mL) at −10 °C was added trifluoromethanesulfonic anhydride (2.5 mL). The mixture was allowed to warm gradually to 0 °C over 2 h, and then at room temperature for 6 h, at the end of which time TLC (3/1 petroleum ether–ethyl acetate) showed that the reaction was complete. The mixture was poured into ice water (100 mL) and, extracted with dichloromethane, and the organic phase was washed with 1 M HCl twice, with satd. $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated. Column chromatography (3/1 petroleum ether–ethyl acetate) of the residue gave **5** as a syrup (3 g, 90%); $[\alpha]_D$ +56° (*c* 4.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.02 (d, 2 H, J 6.9 Hz. Bz-*H*), 7.65–6.95 (m, 13 H, Ph-*H* and Bz-*H*), 5.92 (t, 1 H, $J_{2,3}$ 10.4 Hz, $J_{3,4}$ 10.4 Hz, H-3), 5.05 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.87 (dd, 1 H, $J_{1,2}$ 3.4 Hz, $J_{2,3}$ 10.4 Hz, H-2), 4.66, 4.53 (q_{AB}, 2 H, ^2J 12.0 Hz, PhC*H*$_2$), 4.47, 4.41(q_{AB}, 2 H, ^2J 11.4 Hz, PhC*H*$_2$), 3.94 (t, 1 H, $J_{3,4}$ 10.4 Hz, $J_{4,5}$ 10.4 Hz, H-4), 3.94–3.88 (m, 1 H, H-5), 3.80 (dd, 1 H, $J_{5,6}$ 2.7 Hz, $J_{6,6'}$ 10.5 Hz, H-6), 3.69 (dd, 1 H, $J_{5,6'}$ 1.2 Hz, $J_{6,6'}$ 10.5 Hz, H-6′), 3.50 (s, 3 H, OC*H*$_3$). Anal. Calcd for $C_{29}H_{29}O_9F_3S$: C, 57.05; H, 4.75. Found: C, 57.00; H, 4.70.

*Methyl 2-azido-3-*O*-benzoyl-4,6-di-*O*-benzyl-2-deoxy-α-*D*-mannopyranoside* (**6**).—To a solution of compound **5** (2.90 g, 4.8 mmol) in dry DMF (30 mL) was added NaN_3 (1.9 g, 29 mmol) and NH_4Cl (70 mg), and the reaction mixture was heated out at 80 °C for 2 h, at the end of which time TLC (3/1 petroleum ether–ethyl acetate) indicated that the reaction was complete. The reaction solution was concentrated, the residue was dissolved in dichloromethane, washed with water, dried over Na_2SO_4, and concentrated. Column chromatography (4/1 petroleum ether–ethyl acetate) of the residue gave **6** as a syrup (1.90 g, 80%); $[\alpha]_D$ +72° (*c* 2.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.12 (d, 2 H, J 7.4 Hz. Bz-*H*), 7.63–7.01 (m, 13 H, Ph-*H* and Bz-*H*), 5.66 (d, 1 H, $J_{2,3}$ 4.2 Hz, $J_{3,4}$ 9.2 Hz, H-3), 4.79 (d, 1 H, $J_{1,2}$ 1.6 Hz, H-1), 4.72, 4.54 (q_{AB}, 2 H, ^2J 12.2 Hz, PhC*H*$_2$), 4.62, 4.48 (q_{AB}, 2 H, ^2J 10.6 Hz, PhC*H*$_2$), 4.14 (dd, 1 H, $J_{1,2}$ 1.6 Hz, $J_{2,3}$ 4.2 Hz, H-2), 4.04 (t, 1 H, $J_{3,4}$ 9.2 Hz, $J_{4,5}$ 9.2 Hz, H-4), 3.88–3.80 (m, 1 H, H-5), 3.79 (dd, 1 H, $J_{5,6}$ 3.9 Hz, $J_{6,6'}$ 10.7 Hz, H-6), 3.69 (dd, 1 H, $J_{5,6'}$ 1.7 Hz, $J_{6,6'}$ 10.7 Hz, H-6′), 3.42 (s, 3 H, OC*H*$_3$). Anal. Calcd for $C_{28}H_{29}N_3O_6$: C, 66.80; H, 5.77; N, 8.35. Found: C, 66.70; H, 5.80; N, 8.40.

*Methyl 2-azido-4,6-di-*O*-benzyl-2-deoxy-α-*D*-mannopyranoside* (**7**).—To a solution of compound **6** (1.80 g, 3.6 mmol) in methanol (20 mL) was added solid sodium methoxide (0.17 g, 3.2 mmol) at room temperature and the reaction was carried out

overnight. The solution was concentrated, and the resulting residue was purified by column chromatography (2/1 petroleum ether–ethyl acetate) to give compound **7** as a syrup (1.43 g, 100%); $[\alpha]_D$ +94.6° (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$): 7.37–7.20 (m, 10 H, Ph-*H*), 4.75 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1), 4.71, 4.54 (q_{AB}, 2 H, ^2J 12.5 Hz, PhCH_2), 4.67, 4.57 (q_{AB}, 2 H, ^2J 11.3 Hz, PhCH_2), 4.09 (d, 1 H, $J_{2,3}$ 4.0 Hz, $J_{3,4}$ 9.5 Hz, H-3), 3.89 (dd, 1 H, $J_{1,2}$ 1.8 Hz, $J_{2,3}$ 4.0 Hz, H-2), 3.77 (dd, 1 H, $J_{5,6}$ 3.8 Hz, $J_{6,6'}$ 11.3 Hz, H-6), 3.75 (t, 1 H, $J_{3,4}$ 9.5 Hz, $J_{4,5}$ 9.5 Hz, H-4), 3.72–3.65 (m, 2 H, H-5,6′), 3.37 (s, 3 H, OCH_3). Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.16; H, 6.27; N 10.53. Found: C, 63.20; H, 6.34; N, 10.50.

Methyl 3-O-*acetyl-2-azido-4,6-di*-O-*benzyl-2-deoxy*-α-D-*mannopyranoside* (**8**).—Acetylation of compound **7** (1.36 g, 3.4 mmol) with acetic anhydride (2 mL) in pyridine (4 mL) at room temperature for 4 h gave **8** (1.5 g) in quantitative yield as a syrup; $[\alpha]_D$ +72° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.39–7.14 (m, 10 H, Ph-*H*), 5.34 (dd, 1 H, $J_{2,3}$ 3.8 Hz, $J_{3,4}$ 9.5 Hz, H-3), 4.72 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 4.71, 4.52 (q_{AB}, 2 H, ^2J 12.3 Hz, PhCH_2), 4.62, 4.49 (q_{AB}, 2 H, ^2J 11.3 Hz, PhCH_2), 4.02 (dd, 1 H, $J_{1,2}$ 1.5 Hz, $J_{2,3}$ 3.8 Hz, H-2), 3.97 (t, 1 H, $J_{3,4}$ 9.5 Hz, $J_{4,5}$ 9.5 Hz, H-4), 3.78–3.73 (m, 2 H, H-5,6), 3.65 (dd, 1 H, $J_{5,6'}$ 1.5 Hz, $J_{6,6'}$ 9.2 Hz, H-6′), 3.38 (s, 3 H, OCH_3), 2.06 (s, 3 H, CH_3CO). Anal. Calcd for $C_{23}H_{27}N_3O_6$: C, 62.59; H, 6.12; N, 9.52. Found: C, 62.80; H, 6.62; N, 9.47.

1,3-di-O-*Acetyl-2-azido-4,6-di*-O-*benzyl-2-deoxy*-D-*mannopyranose* (**10**).—*Method A*. Acetolysis of compound **8** (100 mg, 0.23 mmol) with Ac_2O/AcOH/H_2SO_4 (50/20/0.1, 0.8 mL) at room temperature for 25 min furnished a mixture (95 mg) of **10** and methyl 3,6-di-*O*-acetyl-2-azido-4-*O*-benzyl-2-deoxy-α-D-mannopyranoside (**15**) in a ratio of 1:1 as determined by ^1H NMR. ^1H NMR ($CDCl_3$): δ 6.12 (d, 0.5 H, $J_{1,2}$ 1.5 Hz, H-1 for **10**), 5.39–5.30 (m, 1 H, H-3 for **10** and **15**), 3.39 (s, 1.5 H, OCH_3 for **15**), 2.13, 2.09 (for **10**), 2.08, 2.07 (for **15**) (4 s, 6 H, CH_3CO). TLC (3/1 or 2/1 petroleum ether–ethyl acetate) indicated that compounds **10** and **15** had the same R_f value and could not be separated. Further chlorination of the mixture with hydrogen chloride in diethyl ether transformed **10** to the corresponding chloride **11** but did not affect **15**.

Method B. To a solution of compound **8** (1.35 g, 3.1 mmol) in 70% AcOH (30 mL) was added camphorsulfonic acid (5 mg) and the mixture was heated at 100 °C for 16 h, at the end of which time TLC (2/1 petroleum ether–ethyl acetate) indicated that the starting material disappeared. The solution was extracted with dichloromethane, and the organic phase was washed with satd. $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated. Column chromatography (2/1 petroleum ether–ethyl acetate) of the residue gave crude **9** as a syrup (850 mg, 65%). Acetylation of **9** with acetic anhydride (3 mL) in pyridine (4 mL) at room temperature for 4 h gave **10** in quantitative yield as a syrupy mixture (920 mg, 99%) of α and β anomers in a ratio of 5/1; $[\alpha]_D$ +8.8° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.38–7.10 (m, 10 H, Ph-*H*), 6.12 (d, 5/6 H, $J_{1,2}$ 1.5 Hz, H_α-1), 5.80 (d, 1/6 H, $J_{1,2}$ 0.8 Hz, H_β-1), 5.35 (dd, 5/6 H, $J_{2,3}$ 4.1 Hz, $J_{3,4}$ 9.7 Hz, H_α-3), 5.02 (dd, 1/6 H, $J_{2,3}$ 4.9 Hz, $J_{3,4}$ 9.7 Hz, H_β-3), 4.74–4.45 (m, 4/6 H, Ph$CH_{2\beta}$), 4.70, 4.50 (q_{AB}, 10/6 H, ^2J 12.3 Hz, Ph$CH_{2\alpha}$), 4.63, 4.53 (q_{AB}, 10/6 H, ^2J 11.3 Hz, Ph$CH_{2\alpha}$), 4.16 (dd, 1/6 H, $J_{1,2}$ 0.8 Hz, $J_{2,3}$ 4.1 Hz, H_β-2), 4.10 (t, 5/6 H, $J_{3,4}$ 9.7 Hz, $J_{4,5}$ 9.7 Hz, H_α-4), 4.04 (dd, 5/6 H, $J_{1,2}$ 1.5 Hz, $J_{2,3}$ 4.1 Hz, H_α-2), 4.00 (t, 1/6 H, $J_{3,4}$ 9.7 Hz, $J_{4,5}$ 9.7 Hz, H_β-4), 3.87–3.85 (m, 5/6 H, H_α-5), 3.76 (dd, 5/6 H, $J_{5,6'}$ 4.6 Hz, $J_{6,6'}$ 12.3 Hz, H_α-6′), 3.72–3.68 (m, 1/6 H, H_β-5), 3.65 (dd, 5/6 H, $J_{5,6'}$ 1.0 Hz, $J_{6,6'}$ 12.3 Hz, H_α-6′), 3.56 (dd, 1/6 H, $J_{5,6'}$ 2.0 Hz, $J_{6,6'}$ 10.8 Hz, H_β-6′), 3.40 (d, 1/6 H, $J_{6,6'}$ 10.8 Hz, H_β-6′), 2.20, 2.10 (2 s, 6/6 H, CH_3CO for β form), 2.13, 2.09 (2 s, 30/6 H, CH_3CO for α form). Anal. Calcd for $C_{24}H_{27}N_3O_7$: C, 61.41; H, 5.76; N, 8.96. Found: C, 61.47; H, 5.85; N, 9.00.

3-O-*Acetyl-2-azido-4,6-di*-O-*benzyl-2-deoxy*-α-D-*mannopyranosyl chloride* (**11**).—Anhydrous HCl gas was bubbled into a solution of **10** (500 mg, 1.1 mmol) in dry diethyl ether (20 mL) under a nitrogen atmosphere at 0 °C until the solution was saturated. The solution was kept at room temperature in a sealed bottle for 2 h, at the end of which time TLC (3/1 petroleum ether–ethyl acetate) indicated that the reaction was complete. The solution was concentrated, then diluted with dichloromethane and concentrated again. This procedure was repeated several times to remove the hydrogen chloride. Purification of the product by column chromatography (3/1 petroleum ether–ethyl acetate) gave **11** as a syrup (400 mg, 84%); $[\alpha]_D$ +53.5° (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.35–7.12 (m, 10 H, Ph-*H*), 6.05 (d, 1 H, $J_{1,2}$ 1.3 Hz, H-1), 5.57 (dd, 1 H, $J_{2,3}$ 3.9 Hz, $J_{3,4}$ 9.1 Hz, H-3), 4.67, 4.45 (q_{AB}, 2 H, ^2J 11.9 Hz, PhCH_2), 4.63, 4.55 (q_{AB}, 2 H, ^2J 11.0 Hz, PhCH_2), 4.30 (t, 1 H, $J_{3,4}$ 9.1 Hz, $J_{4,5}$ 9.1 Hz, H-4), 4.25 (dd, 1 H, $J_{1,2}$

1.3 Hz, $J_{2,3}$ 3.9 Hz, H-2), 4.08–4.04 (m, 1 H, H-5), 3.79 (dd, 1 H, $J_{5,6}$ 2.8 Hz, $J_{6,6'}$ 11.9 Hz, H-6), 3.64 (dd, 1 H, $J_{5,6'}$ 1.3 Hz, $J_{6,6'}$ 11.9 Hz, H-6′), 2.06 (s, 3 H, CH_3CO). Anal. Calcd for $C_{22}H_{24}ClN_3O_5$: C, 59.26; H, 5.39; N, 9.43. Found: C, 59.50; H, 5.42; N, 9.45.

1,3-Anhydro-2-azido-4,6-di-O-*benzyl-2-deoxy*-β-D-*mannopyranose* (**12**).—To a solution of **11** (100 mg, 0.22 mmol) in dry oxolane (10 mL) was added potassium *tert*-butoxide (50 mg, 0.45 mmol) and the mixture was stirred at room temperature for 6 h, at the end of which time TLC (3/1 petroleum ether–ethyl acetate) indicated that the reaction was complete. The solution was concentrated to dryness, and the residue was repeatedly extracted with 3/1 petroleum ether–ethyl acetate. Concentration of the combined extracts followed by separation by analytical LC (3/1 petroleum ether–ethyl acetate) yielded **12** as a syrup (68 mg, 82.5%); $[\alpha]_D$ +25° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.36–7.17 (m, 10 H, Ph-*H*), 5.39 (d, 1 H, $J_{1,3}$ 3.6 Hz, H-1), 4.60, 4.56 (q_{AB}, 2 H, ^2J 12.7 Hz, PhCH_2), 4.53 (s, 2 H, PhCH_2), 4.49 (t, 1 H, $J_{1,3}$ 3.6 Hz, $J_{3,4}$ 3.6 Hz H-3), 4.29–4.25 (m, 1 H, H-5), 4.21 (s, 1 H, H-2), 4.07 (dd, 1 H, $J_{3,4}$ 3.6 Hz, $J_{4,5}$ 7.2 Hz, H-4), 3.62 (d, 2 H, $J_{5,6}$ 4.3 Hz, H-6). Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.40; H, 5.72; N, 11.44. Found: C, 65.32; H, 5.80; N, 11.40.

Ring-opening of the 1,3-anhydrosugar **12** *with methanol*.—To a solution of compound **12** (10 mg, 0.027 mmol) in dry methanol (0.5 mL) was added freshly prepared zinc chloride (5 mg, 0.04 mmol). The mixture was stirred at room temperature for 4 h, at the end of which time TLC (2/1 petroleum ether–ethyl acetate) indicated that the starting material had disappeared. The solution was concentrated and the residue was dissolved in dichloromethane, washed with water, dried over Na_2SO_4, and concentrated. Column chromatography (2/1 petroleum ether–ethyl acetate) of the residue gave a syrupy product (10 mg, 92%) that gave a ^{1}H NMR spectrum identical to that of **7**.

O-*(2-Azido-4,6-di*-O-*benzyl-2-deoxy*-α-D-*mannopyranosyl)-(1→6)-1,2:3,4-di*-O-*isopropylidene*-α-D-*galactopyranose* (**13**).—To a solution of **12** (20 mg, 0.054 mmol) in dry oxolane (1 mL) was added a mixture of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (17 mg, 0.065 mmol) [21] and freshly prepared zinc chloride (10 mg, 0.075 mmol) in dry oxolane (1.5 mL). The mixture was stirred at room temperature for 6 h, after which time TLC (2/1 petroleum ether–ethyl acetate) indicated that the 1,3-anhydro sugar ether had disappeared. The solution was concentrated to a syrup, which was subjected to separation by analytical LC using 2/1 petroleum ether–ethyl acetate as the eluent. Compound **13** was obtained as a syrup (26 mg, 76%); $[\alpha]_D$ +2° (c 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.38–7.20 (m, 10 H, Ph-*H*), 5.52 (d, 1 H, $J_{1,2}$ 6.2 Hz, H-1), 4.93 (d, 1 H, $J_{1',2'}$ 1.1 Hz, H-1′), 4.74, 4.53 (q_{AB}, 2 H, ^2J 12.7 Hz, PhCH_2), 4.68, 4.57 (q_{AB}, 2 H, ^2J 12.0 Hz, PhCH_2), 4.62 (dd, 1 H, $J_{2,3}$ 2.9 Hz, $J_{3,4}$ 8.4 Hz, H-3), 4.33 (dd, 1 H, $J_{1,2}$ 6.2 Hz, $J_{2,3}$ 2.9 Hz, H-2), 4.21 (dd, 1 H, $J_{3,4}$ 8.4 Hz, $J_{4,5}$ 1.8 Hz, H-4), 4.14 (dd, 1 H, $J_{2',3'}$ 4.4 Hz, $J_{3',4'}$ 9.8 Hz, H-3′), 3.77–3.72 (m, 2 H, H-2′,5), 3.84–3.66 (m, 6 H, H-4′,5′, 6, 6′), 1.55, 1.47, 1.35, 1.34 (4 s, 12 H, CH_3). Anal. Calcd for $C_{32}H_{41}N_3O_{10}$: C, 61.24; H, 6.54; N, 6.70. Found: C, 61.11; H, 6.31; N, 6.93.

O-*(3*-O-*Acetyl-2-azido-4,6-di*-O-*benzyl-2-deoxy*-α-D-*mannopyranosyl)-(1→6)-1,2:3,4-di*-O-*isopropylidene*-α-D-*galactopyranose* (**14**).—Compound **13** (20 mg, 0.033 mmol) was acetylated with acetic anhydride (0.6 mL) in pyridine (0.8 mL) by standard methods to afford **14** (21 mg, 98%) as a syrup; $[\alpha]_D$ +5° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.38–7.12 (m, 10 H, Ph-*H*), 5.49 (d, 1 H, $J_{1,2}$ 5.7 Hz, H-1), 5.35 (dd, 1 H, $J_{2',3'}$ 3.9 Hz, $J_{3',4'}$ 9.6 Hz, H-3′), 4.90 (d, 1 H, $J_{1',2'}$ 1.0 Hz, H-1′), 4.72, 4.48 (q_{AB}, 2 H, ^2J 12.4 Hz, PhCH_2), 4.60, 4.48 (q_{AB}, 2 H, ^2J 12.4 Hz, PhCH_2), 4.61 (dd, 1 H, $J_{2,3}$ 2.5 Hz, $J_{3,4}$ 7.8 Hz, H-3), 4.30 (dd, 1 H, $J_{1,2}$ 5.7 Hz, $J_{2,3}$ 2.5 Hz, H-2), 4.23 (dd, 1 H, $J_{3,4}$ 7.8 Hz, $J_{4,5}$ 1.4 Hz, H-4), 4.07 (dd, 1 H, $J_{1',2'}$ 1.0 Hz, $J_{2',3'}$ 3.9 Hz, H-2′), 4.01 (t, 1 H, $J_{3',4'}$ 9.6 Hz, $J_{4',5'}$ 9.6 Hz, H-4′), 3.97–3.91 (m, 1 H, H-5), 3.85–3.63 (m, 5 H, H-5′, 6, 6′), 2.03 (s, 3 H, CH_3CO), 1.55, 1.47, 1.35, 1.34 (4 s, 12 H, CH_3). Anal. Calcd for $C_{34}H_{43}N_3O_{11}$: C, 60.99; H, 6.43; N, 6.28. Found: C, 61.12; H, 6.53; N, 6.51.

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References

[1] Nasir-un-Din and R.W. Jeanloz, *Carbohydr. Res.*, 28 (1973) 243–251.

[2] (a) M. Linnerborg, G. Widmalm, M.M. Rahman, P.-E. Jansson, T. Holme, F. Qadri, and M.J. Albert, *Carbohydr. Res.*, 291 (1996) 165–174. (b) U. Zahringer, H. Rettenmaier, H. Mall,

S.N. Senchenkova, and Y.A. Knirel, *Carbohydr. Res.*, 300 (1997) 143–151.
[3] M. Hamberg, J. Svensson, and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, 72 (1975) 2994–2998.
[4] S.S. Bhagwat, P.R. Hamann, and W.C. Still, *J. Am. Chem. Soc.*, 107 (1985) 6372–6376.
[5] E. Wu, F. Kong, and B. Su, *Carbohydr. Res.*, 161 (1987) 235–246.
[6] F. Kong, D. Lu, and S. Zhou, *Carbohydr. Res.*, 198 (1990) 141–148.
[7] X. Wu, F. Kong, D. Lu, and P. Zhang, *Carbohydr. Res.*, 229 (1992) 75–87.
[8] X. Wu, F. Kong, and D. Lu, *J. Carbohydr. Chem.*, 10 (1991) 363–375.
[9] C. Yang, L. Cao, and F. Kong, *J. Carbohydr. Chem.*, 11 (1992) 379–395.
[10] Z. Gan and F. Kong, *Carbohydr. Lett.*, 1 (1994) 27–30.
[11] Y. Du and F. Kong, *Carbohydr. Res.*, 275 (1995) 259–273.
[12] H. Ito, R. Eby, S. Kramer, and C. Schuerch, *Carbohydr. Res.*, 86 (1980) 193–202.
[13] F. Good and C. Schuerch, *Carbohydr. Res.*, 125 (1984) 165–171.
[14] A.J. Varma and C. Schuerch, *J. Org. Chem.*, 46 (1981) 799–803.
[15] F. Kong and C. Schuerch, *Carbohydr. Res.*, 112 (1983) 141–147.
[16] P.J. Garegg and B. Samuelsson, *Synthesis*, (1979) 813–814.
[17] J.M. Kuester and I. Dyong, *Justus Liebigs Ann. Chem.*, (1975) 2179–2189.
[18] W. Liao and D. Lu, *Carbohydr. Res.*, 300 (1997) 347–349.
[19] J. Banoub, P. Boullanger, and D. Lafont. *Chem. Rev.*, 92 (1992) 1167–1195.
[20] S. Takahashi, H. Inoue, and H. Kuzuhara. *J. Carbohydr. Chem.*, 14 (1995) 273–285.
[21] R.L. Whistler, M.L. Wolfrom, and J.N. BeMiller. *Methods Carbohydr. Chem.*, 2 (1963) 318–325.