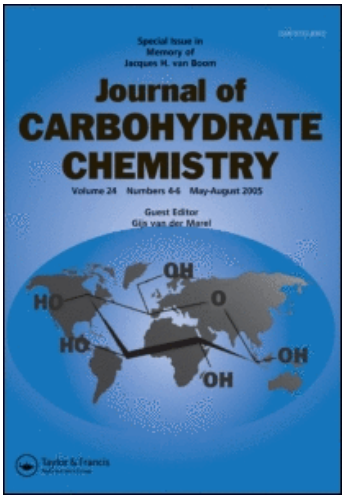


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis and Conformation of Substituted 2,6-Dioxabicyclo[3.1.1]Heptanes: 1,3-Anhydro-6-Azido-2,4-Di-O-Benzyl-6-Deoxy- And 1,3-Anhydro-6-Azido-2,4-Di-O-(P-Bromobenzyl)-6-Deoxy-β-D-Mannopyranose

Xinfu Wu; Fanzuo Kong; Depei Lu

To cite this Article Wu, Xinfu , Kong, Fanzuo and Lu, Depei(1991) 'Synthesis and Conformation of Substituted 2,6-Dioxabicyclo[3.1.1]Heptanes: 1,3-Anhydro-6-Azido-2,4-Di-O-Benzyl-6-Deoxy- And 1,3-Anhydro-6-Azido-2,4-Di-O-(P-Bromobenzyl)-6-Deoxy-β-D-Mannopyranose', Journal of Carbohydrate Chemistry, 10: 3, 363 — 375
To link to this Article: DOI: 10.1080/07328309108543914
URL: http://dx.doi.org/10.1080/07328309108543914

J. CARBOHYDRATE CHEMISTRY, 10(3), 363-375 (1991)

SYNTHESIS AND CONFORMATION OF SUBSTITUTED 2,6-DIOXABICYCLO[3.1.1]HEPTANES: 1,3-ANHYDRO-6-AZIDO-2,4-DI-O-BENZYL-6-DEOXY- AND 1,3-ANHYDRO-6-AZIDO-2,4-DI-O-(p-BROMOBENZYL)-6-DEOXY-β-D-MANNOPYRANOSE

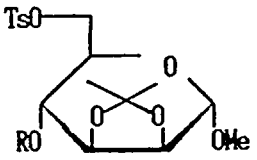
Xinfu Wu, Fanzuo Kong* and Depei Lu

Research Center for Eco-Environmental Sciences, Academia Sinica, P.O.Box 934, Beijing, P.R.China

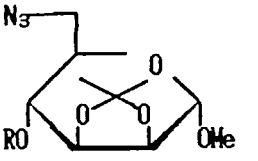
Received May 15, 1990 - Final form February 28, 1991

ABSTRACT

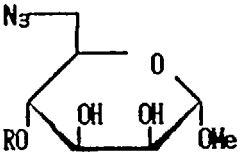
Methyl 6-azido-4-*O*-benzyl-6-deoxy- (**5**) and methyl 6-azido-4-*O*-(*p*-bromobenzyl)-6-deoxy- α-D-mannopyranoside (**6**) were obtained by reaction of methyl 4-*O*-benzyl- (**1**) and methyl 4-*O*-(*p*-bromobenzyl)- 2,3-*O*-isopropylidene-6-*O*-toluenesulfonyl-α-D-mannopyranoside (**2**) with sodium azide, followed by acid hydrolysis. Selective benzylation and *p*-bromobenzylation of **5** and **6** under phase transfer conditions afforded methyl 6-azido-2,4-di-*O*-benzyl-6-deoxy- (**7**) and methyl 6-azido-2,4-di-*O*-(*p*-bromobenzyl)-6-deoxy-α-D-mannopyranoside (**8**) respectively, which were acetylated and subsequently chlorinated to give 3-*O*-acetyl-6-azido-2,4-di-*O*-benzyl-6-deoxy- (**11**) and 3-*O*-acetyl-6-azido-2,4-di-*O*-(*p*-bromobenzyl)-6-deoxy-α-D-mannopyranosyl chloride (**12**). Ring closure of **11** and **12** was conducted in the presence of potassium *tert*-butoxide to give the title anhydro sugar ethers in almost quantitative yield. The full assignments of ^{1}H and ^{13}C NMR spectra of the anhydro sugar ethers were achieved by single frequency decoupling and $^{1}H-^{13}C$ two-dimensional heteronuclear correlated NMR spectroscopy. Vicinal and long-range proton-proton coupling constants suggested that the conformations of the 1,3-anhydro sugar ethers are essentially $B_{2,5}$ (**D**) for the pyranose rings and chairs for the 1.3-dioxane rings.



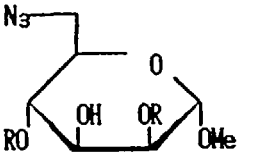
1 R=Bn
2 R=BBn



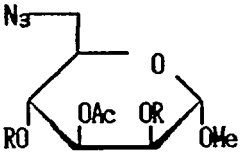
3 R=Bn
4 R=BBn



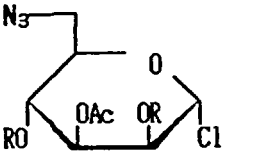
5 R=Bn
6 R=BBn



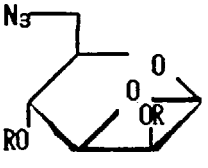
7 R=Bn
8 R=BBn



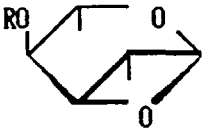
9 R=Bn
10 R=BBn



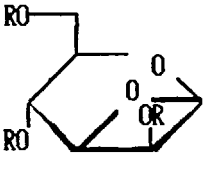
11 R=Bn
12 R=BBn



13 R=Bn
14 R=BBn



15 R=Bn
16 R=BBn



17 R=Bn
18 R=BBn

INTRODUCTION

Recent reports from this laboratory have described the synthesis and conformational analysis of 1,3-anhydrorhamno-[1,2] and -galactopyranose [3] derivatives. Earlier, 1,3-anhydroglucopyranose-[4,5] and -mannopyranose[6,7] derivatives had been prepared by Schuerch's group. Here, as a part of our program on the synthesis of the 2,6-dioxabicyclo[3.1.1]heptane ring system occurring[8,9] in thromboxane A_2 (TXA_2), a compound of substantial importance in biological chemistry, we now report the synthesis and conformations of 1,3-anhydro-6-azido-2,4-di-*O*-benzyl-6-deoxy- (**13**) and 1,3-anhydro-6-azido-2,4-di-*O*-(*p*-bromobenzyl) -6-deoxy-β-D-mannopyranose (**14**), the first azido containing 1,3-anhydro sugar ethers. These compounds can afford α- (1 $\rightarrow$ 3)-linked D-mannopyranans with 6-azido or amino groups by stereoregular polymerization and deprotection. The stereoregular polymerization[10] of 1,6-anhydro-3-azido-2,4-di-*O*-benzyl-3-deoxy-β-D-glucopyranose yielded benzylated 3-azido or 3-amino (1 $\rightarrow$ 6)-linked polysaccharides with blood anticoagulation activity.[11] It will be of interest to investigate the bioactivity of the corresponding (1 $\rightarrow$ 3)- linked mannans.

RESULTS AND DISCUSSION

Methyl 2,3-*O*-isopropylidene-6-*O*-(*p*-toluenesulfonyl)-α-D-mannopyranoside, prepared from methyl α-D-mannopyranoside as in the literature,[2] was converted to the corresponding 4-*O*-benzylated derivative (**1**) and 4-*O*-(*p*-bromobenzylated) derivative (**2**) by the conventional method. Treatment of **1** and **2** with sodium azide in DMF afforded almost quantitative yields of methyl 6-azido-4-*O*-benzyl-6-deoxy- (**3**) and methyl 6-azido-4-*O*-(*p*-bromobenzyl)-2,3-*O*-isopropylidene- 6-deoxy-α-D-mannopyranoside (**4**). To prevent the cleavage of anomeric methoxy groups, the acid hydrolysis of isopropylidene groups should be carried out under mild and carefully controlled conditions. Thus, acid hydrolysis of **3** and **4** in 60% glacial acetic acid by heating with a steam bath furnished crystalline methyl 6-azido-4-*O*-benzyl-6-deoxy- (**5**) and methyl 6-azido-4-*O*-(*p*-bromobenzyl)-6-deoxy-α-D-mannopyranoside (**6**). Selective benzylation and *p*-bromobenzylation under phase transfer conditions gave methyl 6-azido-2,4-di-*O*-benzyl-6-deoxy- (**7**) and methyl 6-azido-2,4-di-*O*-(*p*-bromobenzyl)-6-deoxy-α-D-mannopyranoside (**8**) respectively, which were crystallized after purification. Acetylation of **7** and **8** with

acetic anhydride in pyridine gave the 3-*O*-acetates **9** and **10** quantitatively. The conversion of **9** and **10** into 3-*O*-acetyl-6- azido-2,4-di-*O*-benzyl-6-deoxy- (**11**) and 3-*O*-acetyl-6-azido-2,4-di-*O*-(*p*-bromobenzyl)-6- deoxy-α-D-mannopyranosyl chloride (**12**) was carried out as described in the literature.[7] However, when compound **9** was treated with a saturated solution of hydrogen chloride in a mixed solvent of methylene chloride and acetic acid (1:1 Volume) at room temperature for 2 days, some decomposition occurred. To prevent serious decomposition, the conversion of **9** into **11** was carefully controlled to give a yield of 50-60 % along with about 40 % of the starting material that could be recovered and reused. When the reaction was conducted in ether or methylene chloride, little product was observed by TLC, and decomposition occurred when the reaction went further. The D-mannopyranosyl chlorides **11** and **12** were used as the key intermediates for the synthesis of the title compounds **13** and **14**. Ring closure of **11** and **12** with potassium *tert*-butoxide in oxolane at room temperature occurred readily. An attempt to monitor the reaction by TLC failed because the target compounds decomposed partially on the plate. However, purification of the crude products by analytical LC with a Lichrosorb-NH_2 packed column gave yields of 92% and 98% for **13** and **14** respectively.

1,3-Anhydro-6-azido-2,4-di-*O*-benzyl-6-deoxy- (**13**) and 1,3-anhydro-6-azido-2,4-di-*O*-(*p*-bromobenzyl)-6-deoxy-β-D-mannopyranose (**14**) were identified from their IR, mass, ^1H and ^{13}C NMR spectra, and by elemental analysis. The IR spectra showed strong absorptions at 2102 cm^{-1} due to the azido group and strong absorptions for the ether linkage and did not contain C=C absorption bands. The mass spectra showed parent peaks having low intensities at 367 and 523 daltons for **13** and **14** respectively. Moderate intensity peaks due to ($M^{\oplus} - CH_3N_3$) were observed both for **13** and **14**. Furthermore, relatively strong peaks characteristic of 1,3-anhydroglycopyranoses were observed at 253 and 409 daltons for **13** and **14** respectively. This was consistent with observations made for 1,3-anhydromannopyranose, 1,3-anhydrorhamnopyranose and 1,3-anhydrogalactopyranose derivatives. From high resolution e.i.mass spectra, the peak at 253 was considered to be ($BnOCH{=}CHCH{=}O^{\oplus}Bn$) and that at 409 to be ($BrBnOCH{=}CHCH{=}O^{\oplus}BnBr$).

The ^1H NMR spectrum of compound **13** was assigned by use of single frequency decoupling and from a two-dimensional, homonuclear correlated spectrum. The anomeric proton (H-1) appeared as a doublet at δ 5.358 with a coupling constant of 4.1 Hz, caused by coupling between H-1 and H-3. This coupling constant was

unusually large because coupling information is transmitted over two paths as in the case of cyclobutane derivatives.[12]

Single frequency irradiation of the signal for H-1 allowed assignment of the doublet of doublets at δ 4.504 as H-3. Decoupling the signal of H-3 simplified that of H-1 to a singlet and that of H-4, which appeared as a doublet of doublets at δ 4.008, to a doublet with $^3J_{4,5}$ of 6.6 Hz. Irradition of the two H-6 signals at δ 3.415 and δ 3.282 simplified the H-5 signal from a multiplet to a doublet. H-5, H-6 And H-6' comprised an ABX spin system with $^3J_{5,6}$ of 3.37, $^3J_{5,6'}$ of 5.86 and $^2J_{6,6'}$ of 13.04 Hz. A singlet at δ 4.406 was assigned to H-2.

In comparison with 1,3-anhydrorhamnopyranoses, the values of the coupling constants of $J_{1,2}$, $J_{1,3}$, $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ were basically the same. Therefore, the dihedral angles were also the same as for the rhamnose analogue[1,13] and the conformation of **13** was essentially $B_{2,5}$ **(D)** with some lowering of the boat head at C-5 for the pyranose ring, and with a chair for the 1,3-dioxane ring.[1]

Assignment of the fully decoupled and coupled ^{13}C NMR spectrum of compound **13** was complicated because the signals due to C-2, C-3, C-4, C-5, and the two benzyl methylene carbons were close together. Only C-1, C-6 and the aromatic carbons could be readily assigned. The C-1 resonance appeared at δ 106.80 with the largest coupling constant $^1J_{C,H}$ of 187.7 Hz. This also clearly excluded the possibility of double bond in the compound. A triplet at δ 53.34, a normal value for a methylene carbon attached to N_3, was assigned as C-6. C-3, a bridgehead atom, resonated at δ 81.47 with a coupling constant of 169.2 Hz, which was larger than the couplings observed for other mono-*O*-substituted carbons. Unambiguous assignment of the remaining signals was accomplished from the two-dimensional, heteronuclear-correlated spectrum.

Tables 1 and 2 show the ^1H and ^{13}C chemical shifts of **13**, **14** and 1,3-anhydro-rhamno-**(15)**, **(16)** and -mannopyranose **(17)**, **(18)** derivatives. It was found that the chemical shifts for **13** (or **14**) were basically the same, except for those of C-6 and H-6, as **17** (or **18**), while the differences for H-4 and C-4 between **13** (or **14**) and **15** (or **16**) were identical to the normally observed differences between methyl manno- pyranosides and methyl rhamnopyranosides.[14,15] This provides further evidence that all of the described 1,3-anhydro sugar ethers **13-18** were present in the same conformation.

The assignment of the ^1H NMR spectrum of compound **14** was accomplished by comparison with that of the compound **13** and by single frequency decoupling.

Methanolysis was used to investigate the reactivity of **13**. Methanolysis of compound **13** in methanol at ambient temperature for 3 days gave less than a

TABLE 1. ^1H Chemical Shifts (δ) for Compounds 13-16 and 18

Compound	H-1	H-2	H-3	H-4	H-5	H-6	H-6	Benzyl	methylene group		
13	5.358	4.406	4.504	4.008	4.201	3.407	3.291	4.619	4.584	4.515	4.489
	(d)	(s)	(dd)	(dd)	(m)	(dd)	(dd)	(d)	(d)	(d)	(d)
14	5.377	4.371	4.491	4.025	4.208	3.462	3.333	4.579	4.531	4.482	
	(d)	(s)	(dd)	(dd)	(m)	(dd)	(dd)	(d)	(d)	(s)	
15[a]	5.295	4.449	4.457	3.757	4.147	1.339		4.600	4.555	4.535	4.495
	(d)	(s)	(dd)	(dd)	(m)	(d)		(d)	(d)	(d)	(d)
16[a]	5.305	4.419	4.438	3.746	4.134	1.359		4.573	4.505	4.476	
	(d)	(s)	(dd)	(dd)	(m)	(d)		(d)	(d)	(s)	
18[b]	5.37	4.39	4.48	3.99	4.23	3.57					
	(d)	(s)	(dd)	(dd)	(m)	(d)					

a. Taken from ref. 1. b. Taken from ref. 16.

TABLE 2. ^{13}C Chemical Shifts (δ) and $^1J_{C,H}$ (Hz) for Compound 13 and 15-18

Compound	C-1	C-2	C-3	C-4	C-5	C-6	Benzyl	methylene
13	106.800	79.628	81.467	74.693	75.793	53.341	72.244,	72.056
	(d)	(d)	(d)	(d)	(d)	(t)	(t)	(t)
	187.7	157.2	169.2	150.6	156.2	143.1	146.7	142.1
15[a]	107.00	79.46	81.74	79.66	73.02	20.92	71.99	72.24
	(d)	(d)	(d)	(d)	(d)	(q)	(t)	(t)
	186.2	160.2	164.8	138.8	146.5	127.2	142.7,	145.0
16[a]	106.93	79.63	81.67	79.82	73.01	21.04	71.50,	71.26
	(d)	(d)	(d)	(d)	(d)	(q)	(t)	(t)
	185.0	161.3	165.6	139.6	148.8	127.4	142.2	143.1
17[b]	106.80	79.96	81.55	74.51	76.00	71.31	71.20,	71.31, 72.65
	(d)	(d)	(d)	(d)	(d)	(t)	(t)	(t) (t)
	184.9	154.0	165.8	146.7	146.7	137.2	137.4,	137.2, 136.5
18[b]	106.99	79.90	81.68	74.53	76.11	71.32	72.00,	72.14, 73.41
	(d)	(d)	(d)	(d)	(d)	(t)	(t)	(t) (t)
	185.6	157.5	166.0	147.7	162.4	142.2	142.2,	142.2, 142.2

a. Taken from ref. 1. b. Taken from ref. 17.

10 % yield of compound **7** as detected by TLC. TLC indicated that complete conversion to compound **7** occurred immediately when boron trifluoride etherate was added to the reaction mixture. The identification of the product as **7** was further confirmed by comparison of its ^{1}H NMR spectrum with that of compound **7**. No β-isomer was detected in the crude product by either TLC or ^{1}H NMR spectroscopy. The stereospecific inversion of the 1,3-anhydrosugar ether **13** with methanol to yield methyl α-D-glycopyranoside **7** suggests that 1,3-anhydrosugar ethers can be used as glycosyl donors with inversion of configuration at C-1 to form oligosaccharides. This kind of coupling reaction is under investigation by the authors.

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 were not corrected. Analytical LC was carried out by using stainless-steel columns packed with silica gel (10 × 150 mm, or 4.6 × 250 mm) or Lichrosorb-NH_2 (4.6 × 250 mm), a differential refractometer (Model 1107L, made by LDC, Division of Milton Roy Company, Florida, U.S.A.) and ethyl acetate-petroleum ether (b.p. 60-90 °C) as the eluant, at a flow rate of 1 to 4 mL/min. TLC was performed on Silica Gel G and HF, detection being effected either by charring with 30% (v/v) sulfuric acid in methanol or sometimes by u.v. detector. Column chromatography was performed by elution of columns (16 × 240, 18 × 300, and35 × 400mm) of silica gel (120-200 mesh). IR spectra were recorded with a Perkin-Elmer 125 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$ using Me_4Si as standard with Varian XL-400 and Varian XL-200 spectrometers. Chemical shifts were given in ppm (δ) downfield from the Me_4Si absorption. For conformational analyses, ^{1}H NMR spectra were measured in the pulsed, Fourier-transform mode for solutions in $CDCl_3$ at 20 °C.

Mass spectra were recorded with a JMS-D3005 mass spectrometer using a direct sample introduction technique.

The elemental analyses were performed by the Institute of Chemistry, Academia Sinica.

Methyl 6-Azido-4-O-benzyl-6-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside (3). —To a solution of methyl 2,3-*O*-isopropylidene-6-*O*-(*p*- tolue-

nesulfonyl)-α-D-mannopyranoside (5.5 g, 14.2 mmol) in dry oxolane (50 mL) was added sodium hydride (in oil, 80%; 840 mg, 38 mmol). Benzyl bromide (2.5 mL, 21 mmol) was added dropwise during 15 min. The mixture was refluxed and stirred vigorously for 3-4 h when TLC (1:3 ethyl acetate-petroleum ether) indicated that the starting material had disappeared. The remaining sodium hydride was filtered off and the filtrate was concentrated. Toluene (40 mL), then sodium hydrogencarbonate (1 g) were added to the residue, and the mixture was steam distilled to remove excess benzyl bromide. The mixture was repeatedly extracted with methylene chloride, and the extracts were combined, dried, and concentrated to give syrupy compound **1**.

To the solution of crude product **1** (one spot on TLC) in DMF (50 mL) was added sodium azide (4.6 g, 71 mmol) and ammonium chloride (3.9 g, 71 mmol). The mixture was heated at 80-90 °C overnight, and TLC (1:4 ethyl acetate-petroleum ether) showed that no starting material remained. The precipitate was filtered off and the filtrate was poured into ice water with stirring. Most of the product separated as a syrup. A second crop was obtained by repeated extraction of the aqueous phase with petroleum ether. The product **3** was crystallized from ethyl ether-petroleum ether, yield 4.41 g, 89 %; mp 54-55 °C; $[\alpha]_D^{20} + 67.1°$ (*c* 0.2, chloroform); ^{1}H NMR δ 7.36 - 7.30 (m, 5H, aromatic H), 4.93 (s, 1H, H-1), 4.89, 4.57 (ABq, 2H, ^2J = 11.0 Hz, CH_2Ph), 4.30 (bt, 1H, $J_{2,3} = J_{3,4} = 7.1$ Hz, H-3), 4.15 (d, 1H, $J_{2,3} = 6.1$ Hz, H-2), 3.74 (m, 1H, H-5), 3.56 - 3.31 (m, 3H, 2H-6 and H-4), 3.42 (s, 3H, OCH_3), 1.52, 1.38 (2s, 6H, $C(CH_3)_2$).

Anal. Calcd for $C_{17}H_{23}N_3O_5$: C, 58.45; H, 6.59; N, 12.03. Found: C, 58.33; H, 6.61; N, 11.95.

Methyl 6-Azido-4-O-benzyl-6-deoxy-α-D-mannopyranoside (5). —To compound **3** (4.0 g, 11.5 mmol) was added 6:4 (V/V) glacial acetic acid-water (50 mL). The mixture was heated on a gentle steam bath for 5 h, at which time TLC (1:1 ethyl acetate-petroleum ether) showed that no starting material remained. After evaporation of the solvent, the residue, compound **5** was crystallized from methylene chloride- petroleum ether, yield 3.02 g, 85% ; mp 73-75 °C; $[\alpha]_D^{20}$ + 94.7° (*c* 0.2, chloroform); ^{1}H NMR δ 7.37 - 7.31 (m, 5H, aromatic H), 4.80, 4.67 (ABq, 2H, ^2J = 11.28 Hz, CH_2Ph), 4.73 (s, 1H, H-1), 3.98 - 3.91 (m, 2H, H-2 and H-3), 3.75 (m, 1H, H-5), 3.64 - 3.47 (m, 3H, H-4 and 2H-6), 3.39 (s, 3H, OCH_3), 2.45 - 2.44 (bs, 2H, 2OH).

Anal. Calcd for $C_{14}H_{19}N_3O_5$: C, 54.37; H, 6.15; N, 13.59. Found: C, 54.33; H, 6.29; N, 13.17.

Methyl 6-Azido-2,4-di-O-benzyl-6-deoxy-α-D-mannopyranoside (7). —To a solution of compound **5** (2.0 g, 6.5 mmol) in methylene chloride (30 mL) was added aqueous sodium hydroxide (5 %, 7 mL), tetrabutylammonium hydrogensulfate (200 mg) and benzyl bromide (0.85 mL, 7.1 mmol) , and the mixture was vigorously stirred overnight at room temperature. The crude product **7**, obtained after conventional processing, was crystallized from ethyl ether-petroleum ether, and a second crop was obtained from separation of mother liquor by column chromatography, total yield 1.98 g, 76%; mp 65-66 °C; $[\alpha]_D^{20}$ + 58.0° (*c* 0.2, chloroform); ^{1}H NMR δ 7.37 - 7.27 (m, 10H, aromatic H), 4.94, 4.58, 4.75 and 4.57 (4d, ABq, ^2J = 10.9, 11.8 Hz, $2CH_2Ph$), 4.00 - 3.90 (bs, 1H, OH), 3.73 - 3.35 (m, 6H, H-2, 3, 4, 5, 6), 3.37 (s, 3H, OCH_3).

Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.16; H, 6.27; N, 10.53. Found: C, 63.14; H, 6.34; N, 10.43.

Methyl 3-O-Acetyl-6-azido-2,4-di-O-benzyl-6-deoxy-α-D-mannopyranoside (9). —Compound **7** (1.0 g, 2.5 mmol) was acetylated with acetic anhydride in pyridine by the standard procedure, to give **9** as a syrup in theoretical yield; $[\alpha]_D^{20}$ + 30.0° (c 0.3, chloroform); ^{1}H NMR δ 7.35 - 7.29 (m, 10H, aromatic H), 5.20 (dd, 1H, $J_{2,3}$ = 3.1 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 4.75 - 4.55 (m, 5H, H-1 and $2CH_2Ph$), 3.98 - 3.78 (m, 3H, H-2, 4, 5), 3.48 - 3.43 (m, 2H, 2H-6), 3.38 (s, 3H, OCH_3), 1.97 (s, 3H, CH_3CO).

Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 62.59; H, 6.12; N, 9.52. Found: C, 62.31; H, 6.27; N, 9.47.

3-O-Acetyl-6-azido-2,4-di-O-benzyl-6-deoxy-α-D-mannopyranosyl Chloride (11).—Compound **9** (440 mg, 1 mmol) was dissolved in a mixed solvent of ethyl ether (5 mL) and glacial acetic acid (5 mL), and hydrogen chloride was bubbled in to saturation under a nitrogen atmosphere and in an ice bath. After two days at room temperature, some decomposition occurred as indicated by TLC (1:3 ethyl acetate-petroleum ether). Thus, the solvents were evaporated and the product purified by analytical LC. The recovered starting material (180 mg) was chlorinated again and more syrupy **11** was obtained, yield 51 %; $[\alpha]_D^{20}$ + 135° (*c* 0.1 , chloroform); ^{1}H NMR δ 7,42 - 7.24 (m, 10H, aromatic H), 6.01 (d, 1H, $J_{1,2}$ = 1.8 Hz, H-1), 5.45 (m, 1H, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 9.4 Hz, H-3), 4.77 - 4.54 (m, 4H, $2CH_2Ph$), 4.09 - 4.04 (m, 3H, H-2,4,5), 3.59 (dd, 1H, $J_{5,6}$ = 1.5 Hz, $J_{6,6'}$ = 13.4 Hz, H-6), 3.44 (dd, 1H, $J_{5,6'}$ = 3.3 Hz, $J_{6,6'}$ = 13.4 Hz, H − 6'), 1.97 (s, 3H, CH_3CO).

1,3-Anhydro-6-azido-2,4-di-O-benzyl-6-deoxy-β-D-mannopyranose (13).—To a solution of **11** (110 mg, 0.25 mmol) in dry oxolane (5 mL) was added

potassium *tert*-butoxide (76 mg, 0.68 mmol), and the mixture was stirred for 4 h at ambient temperature. After evaporation of the solvent, methylene chloride was added, and the preciptate was removed by centrifugation. The crude product was identified by ^1H and ^{13}C NMR spectrometry as a pure compound. Further purification by analytical LC (1:4 ethyl acetate-petroleum ether) with a Lichrosorb-NH_2 packed column yielded syrupy **13** of high purity (85 mg, 92%); $[\alpha]_D^{20}$ +124° (*c* 0.1, chloroform); IR 2102 (N_3), 1142 and 1087 cm^{-1} (C-O); ^1H NMR δ 7.42 - 7.24 (m, 10H, aromatic H), 5.358 (d, 1H, $J_{1,3}$ = 4.14 Hz, H-1), 4.619, 4,584, 4.535, 4.489 (4d, ABq, 4H, ^2J = 11.87, 11.89 Hz, $2CH_2Ph$), 4.504 (dd, 1H, $J_{1,3}$ = 4.14 Hz, $J_{3,4}$ = 3.40 Hz, H-3), 4.406 (s, 1H, H-2), 4.201 (m, 1H, H-5), 4.008 (dd, 1H, $J_{3,4}$ = 3.40 Hz, $J_{4,5}$ = 6.60 Hz, H-4), 3.407 (dd, 1H, $J_{5,6}$ = 3.37 Hz, $J_{6,6'}$ = 13.04 Hz, H-6), 3.291 (dd, 1H, $J_{5,6'}$ = 5.86 Hz, $J_{6,6'}$ = 13.04 Hz, H – 6′); ^{13}C NMR δ 106.80 (C-1, $J_{C,H}$ 187.7 Hz), 81.47 (C-3, $J_{C,H}$ 169.2 Hz), 79.63 (C-2, $J_{C,H}$ 157.2 Hz), 75.79 (C-5, $J_{C,H}$ 156.2 Hz), 74.69 (C-4, $J_{C,H}$ 150.6 Hz), 72.24, 72.06 ($2CH_2Ph$, $J_{C,H}$ 146.7, 142.1 Hz), 53.34 (C-6, $J_{C,H}$ 143.1 Hz),

Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.40; H, 5.72; N, 11.44. Found: C, 65.45; H, 5.99; N, 11.52.

Methyl 6-Azido-4-O-(p-bromobenzyl)-6-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside (4). —A mixture of methyl 4-*O*-(*p*-bromobenzyl)- 2,3-*O*-isopropylidene-6-*O*-(*p*-toluenesulfonyl)-α-D-mannopyranoside[2] (**2**) (5.0 g, 8.98 mmol), sodium azide (2.9 g, 44.6 mmol) and ammonium chloride (2.9 g) in DMF (50 mL) was stirred for 48 h at 80-90 °C. The reaction mixture was processed and the product purified by the same procedure as used for conversion of **1** to **3**, yield 3.6 g (94%); mp 56-57 °C; $[\alpha]_D^{20}$ +80.9° (*c* 0.2, chloroform); ^1H NMR δ 7.47, 7.19 (2d, 4H, J 8.2 Hz, aromatic H), 4.93 (bs, 1H, H-1), 4.84, 4.53 (ABq, 2H, ^2J = 11.4 Hz, CH_2Ph), 4.27 (bt, 1H, $J_{2,3}$ = $J_{3,4}$ = 6.2 Hz, H-3), 4.14 (bd, 1H, $J_{2,3}$ = 5.4 Hz, H-2), 3.73 (m, $J_{4,5}$ = 9.4 Hz, $J_{5,6}$ = 2.9 Hz, $J_{5,6'}$ = 6.4 Hz, H-5), 3.54 - 3.34 (m, 3H, H-4 and 2H-6), 3.43 (s, 3H, OCH_3), 1.59, 1.51 (2s, 6H, $C(CH_3)_2$).

Methyl 6-Azido-4-O-(p-bromobenzyl)-6-deoxy-α-D-mannopyranoside (6).—Compound **4** (3.0 g, 7.0 mmol) was hydrolyzed by acid and the product **6** purified by the same procedure as for the conversion of **3** into **5**; yield 2.3 g (85%); mp 75-77 °C; $[\alpha]_D^{20}$ +105° (*c* 0.2, chloroform); ^1H NMR δ 7.49, 7.25 (2d, 4H, J = 8.2 Hz, aromatic H), 4.80, 4.60 (ABq, 2H, ^2J = 11.4 Hz, CH_2Ph), 4.73 (bs, 1H, H-1), 3.96 - 3.91 (m, 2H, H-2 and H-3), 3.77 - 3.70 (m, 1H, H-5), 3.62 - 3.42 (m, 3H, H-4 and 2H-6), 3.39 (s, 3H, OCH_3), 2.57 - 2.54 (bs, 2H, 2OH).

Anal. Calcd for $C_{14}H_{18}BrN_3O_5$: C, 43.30; H, 4.64; N, 10.82; Br, 20.62. Found: C, 43.47; H, 4.90; N, 10.79; Br, 20.46.

Methyl 6-Azido-2,4-di-O-(p-bromobenzyl)-6-deoxy-α-D-mannopyranoside (8).—To a solution of compound **6** (600 mg, 1.29 mmol), tetrabutylammonium hydrogensulfate (50 mg), and *p*-bromobenzyl bromide (480 mg, 1.92 mmol) in methylene chloride (20 mL) was added aqueous sodium hydroxide (5%, 1.6 mL) and the mixture was stirred overnight at room temperature. The reaction mixture was processed and the product was purified by the same procedure as used in the conversion of **5** to **7**. Crystalline **8** was obtained in 79% yield (680 mg); mp 88-89 °C; $[\alpha]_D^{20}$ +95.5° (*c* 0.1, chloroform); ^{1}H NMR δ 7.53 - 7.08 (m, 8H, aromatic H), 4.91 - 4.43 (m, 5H, H-1 and $2CH_2Ph$), 3.97 - 3.31 (m, 6H, H-2,3,4,5,6), 3.37(s, 3H, OCH_3).

Anal. Calcd for $C_{21}H_{23}Br_2N_3O_5$: C, 45.24; H, 4.13. Found: C, 45.42; H, 4.17.

Methyl 3-O-Acetyl-6-azido-2,4-di-O-(p-bromobenzyl)-6-deoxy-α-D-mannopyranoside (10).—Compound **8** (500 mg, 0.9 mmol) was acetylated with acetic anhydride and pyridine by the standard procedure, to give **10** as a syrup in theoretical yield; $[\alpha]_D^{20}$ +73.2° (*c* 0.1, chloroform); ^{1}H NMR δ 7.50 - 7.09 (m, 8H, aromatic H), 5.19 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.1 Hz, H-3), 4.73 - 4.48 (m, 5H, H-1 and $2CH_2Ph$), 3.92 (t, $J_{3,4} = J_{4,5}$ = 9.3 Hz, H-4), 3.85 - 3.75 (m, 2H, H-2 and H-5), 3.49 - 3.36 (m, 2H, 2H-6), 3.83 (s, 3H, OCH_3), 1.97 (s; 3H, $COCH_3$).

Anal. Calcd for $C_{23}H_{25}Br_2N_3O_6$: C, 46.08; H, 4.17. Found: C, 46.32; H, 4.20.

3-O-Acetyl-6-azido–2,4-di-O-(p-bromobenzyl)-6-deoxy-α-D-mannopyranosyl Chloride (12).—Compound **10** (500 mg, 0.83 mmol) was dissolved in a mixed solvent of methylene chloride (5 mL) and glacial acetic acid (5 mL), and hydrogen chloride was bubbled in to saturation under a nitrogen atmosphere and in an ice bath. After 4 days at room temperature, the reaction was worked up by the same procedure used for conversion of **9** to **11**. Pure syrupy **12** was obtained; yield 150 mg, 30%; $[\alpha]_D^{20}$ +123° (*c* 0.1, chloroform); ^{1}H NMR δ 7.51 - 7.13 (m, 8H, aromatic H), 6.01 (d, 1H, $J_{1,2}$ = 2.1 *Hz*, H-1), 5.44 (dd, 1H, $J_{2,3}$ = 3.4 *Hz*, $J_{3,4}$ = 9.2 *Hz*, H-3), 4.67, 4.63, 4.58, 4.52 (4d, ABq, 4H, ^2J = 11.0, 13.1 Hz, $2CH_2Ph$), 4.07 - 4.03 (m, 3H, H-2, 4, 5), 3.60 (dd, $J_{5,6}$ = 2.0 Hz, $J_{6,6'}$ = 13.7 Hz, H-6), 3.42 (dd, $J_{5,6'}$ = 4.3 Hz, $J_{6,6'}$ = 13.0 Hz, H – 6′), 1.98 (s, 3H, CH_3CO). ^{13}C NMR δ 169.91 (CO), 136.58, 136.12, 131.67, 129.91, 129.31, 129.21, 122.14 and 121.89 (Ph), 89.62 (C-1), 78.78, 74.28, 73.53, 72.50, 72.01 (C-3, 4, 5, $2CH_2Ph$), 50.53 (C-6), 20.90 (CH_3CO).

Anal. Calcd for $C_{22}H_{22}ClBr_2N_3O_5$: C, 43.78; H, 3.65. Found: C, 43.91; H, 3.78.

1,3-Anhydro-6-azido-2,4-di-O-(p-bromobenzyl)-6-deoxy-β-D-mannopyranose (14).—Compound **12** (70 mg, 0.12 mmol) was dissolved in dry oxolane

and potassium tert-butoxide (54 mg, 0.48 mmol) was added. After 6 h at room temperature, the reaction was complete. The target compound **14** was obtained as a syrup after purification of the crude product by the same procedure used in the conversion of **11** to **13**; yield 60 mg, 94% ; $[\alpha]_D^{20}$ + 78.7° (*c* 0.1, chloroform); IR 2102 (N_3), 1091 and 1072 cm^2 (C-O); ^1H NMR δ 7.50, 7.49, 7.25, and 7.16 (4d, 8H, J = 8.2 Hz, aromatic H), 5.377 (d, $J_{1,3}$ = 4.19 Hz, H-1), 4.579, 4.531 (ABq, 2H, ^2J = 11.77 Hz, CH_2Ph), 4.482 (s, 2H, CH_2Ph), 4.491 (dd, 1H, $J_{1,3}$ = 4.19 Hz, $J_{3,4}$ = 3.40 Hz, H-3), 4.371 (s, 1H, H-2), 4.208 (m, 1H, H-5), 4.025 (dd, $J_{3,4}$ = 3.40 Hz, $J_{4,5}$ = 6.47 Hz, H-4), 3.462 (dd, $J_{5,6}$ = 3.70 Hz, $J_{6,6'}$ = 12.73 Hz, H-6), 3.333 (dd, $J_{5,6'}$ = 5.68 Hz, $J_{6,6'}$ = 12.75 Hz, H – 6′)

Anal. Calcd for $C_{20}H_{18}Br_2N_3O_4$: C, 45.71; H, 3.62; N, 8.00; Br, 30.48. Found: C, 46.06; H, 3.67; N, 7.86; Br, 30.78.

Methanolysis of 1,3-Anhydro-6-azido-2,4-di-O-benzyl-6-deoxy-β-D-mannopyranose (13).—To a solution of **13** (5 mg, 0.014 mmol) in absolute methanol (0.5 mL) was added boron trifluoride etherate (μL) , and the solution was stirred at room temperature. TLC showed that complete conversion of the starting material to compound **7** occurred within 10 min. The solvent was removed in vacuo, water was added, and the mixture was extracted with methylene chloride. The organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The ^1H NMR spectrum of the product was identical to that of **7**.

ACKNOWLEGMNET

This project was supported by The National Natural Science Foundation of China.

REFERENCES

1. E. Wu, F. Kong, and B. Su, *Carbohydr. Res.*, **161**, 235 (1987).

2. Y. Fang, F. Kong, and Q. Wang, *J. Carbohydr. Chem.*, **6**, 169 (1987).

3. F. Kong, D. Lu, and S. Zhou, *Carbohydr. Res.*, **198**, 141 (1990).

4. H. Ito, R. Eby, S. Kramer, and C. Schuerch, *Carbohydr. Res.*, **86**, 193 (1980).

5. F. Good and C. Schuerch, *Carbohydr. Res.*, **125**, 165 (1984).

6. A. J. Varma and C. Schuerch, *J. Org. Chem.*, **96**, 799 (1981).

7. F. Kong and C. Schuerch, *Carbohydr. Res.*, **112**, 141 (1983).

8. M. Mamberg, J.Sevensson, and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 2994 (1975).

9. S. S. Bhagwat, P. R. Hamann, W. C. Still, S. Bunting, and F. A. Fitzpatric, *Nature (London)*, **315**, 511 (1985).

10. T. Uryu, K. Hatanaka, K. Matsuzaki, and H. Kuzuhara, *Macromolecules*, **16**, 853 (1983).

11. Institute of Physical and Chemical Research, Jpn. Kokai Tokkyo Koho JP 57,180,603 [82,180,603]–JP 57,180,606 [82,180,606].

12. K. B. Wiberg, D. E. Barth, and W. E. Pratt, *J. Am. Chem. Soc.*, **99**, 4288 (1977).

13. C. A. G. Haasnoot, F. A. A. M. De Leeuw, and C. Altona, *Bull. Soc. Chim. Belg.*, **89**, 125 (1980).

14. K. Bock and C. Pedersen, *Adv. Carbohydr. Chem. Biochem.*, **41**, 27 (1983).

15. K. Bock, and H. Thogersen, *Annual Reports on NMR Spectroscopy*, Academic Press, London, **13**, 1 (1983).

16. F. Kong, unpublished result.

17. B. Su, F. Kong, and T. Wei, *Chinese Sci. Bull.* **34**, 289 (1989).