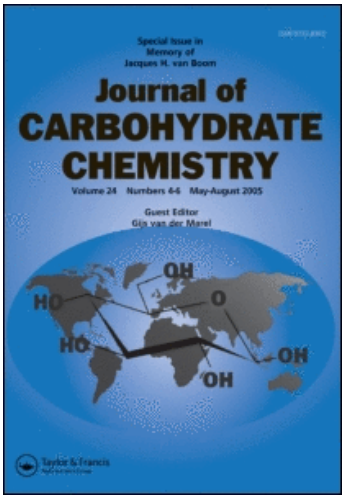


Journal of Carbohydrate Chemistry

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

Synthesis and Conformational Analysis of 1, 2-Anhydro-3, 4-di-O-benzyl-6-deoxy-α-D-glucopyranose

Guangbin Yang[a]; Fanzuo Kong[a]
[a] Research Center for Eco-Environmental Sciences, Academia Sinica, Beijing, P. R. China

To cite this Article Yang, Guangbin and Kong, Fanzuo(1992) 'Synthesis and Conformational Analysis of 1, 2-Anhydro-3, 4-di-O-benzyl-6-deoxy-α-D-glucopyranose', Journal of Carbohydrate Chemistry, 11: 5, 595 — 608
To link to this Article: DOI: 10.1080/07328309208016151
URL: http://dx.doi.org/10.1080/07328309208016151

J. CARBOHYDRATE CHEMISTRY, 11(5), 595-608 (1992)

SYNTHESIS AND CONFORMATIONAL ANALYSIS OF 1,2-ANHYDRO-3,4-DI-*O*-BENZYL-6-DEOXY-α-D-GLUCOPYRANOSE

Guangbin Yang and Fanzuo Kong*

Research Center for Eco-Environmental Sciences, Academia Sinica, P.O.Box 2871, Beijing, P.R.China

Received November 26, 1991 - Final Form March 11, 1992

ABSTRACT

The title 1,2-anhydro sugar **(10)** was synthesized from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside or from 1,2-*O*-ethylidene-α-D-glucopyranose. The key intermediate for the synthesis was 2-*O*-acetyl-3,4-di-*O*-benzyl-6-deoxy-ß-D-glucopyranosyl fluoride **(8)** which was transformed into the target compound by ring closure with potassium *tert*-butoxide. Calculations by the modified Karplus equation from vicinal coupling constants of **10** suggested that the conformation of **10** was almost an ideal $^4H_5$ for the pyranose ring. Conformational analysis for the 1,2-*O*-**(R)**-ethylidene intermediates **17** and **20** revealed that their pyranose ring basically adopted a $B_{2,5}$ conformation.

INTRODUCTION

1,2-Anhydro pyranose derivatives are novel monomers for the synthesis of the corresponding stereoregular (1⟶2) linked polysaccharides[1] that are important model compounds for immunological research.[1] The 1,2-anhydro sugar derivatives are also valuable glycosyl donors for the stereospecific synthesis of oligosaccharides[2] in the presence of Lewis acids with complete inversion of configuration at C-1. The synthesis of 1,2-anhydro-ß-D-manno-,[3] α-D-gluco-,[4] and α-D-galactopyranose[5] derivatives by an intramolecular S_N2 reaction of a free hydroxyl group on C-2 with C-1 bearing a leaving group has been reported. The synthesis of 1,2-anhydro-3,4-di-*O*-benzyl-6-deoxy-α-D-glucopyranose is of interest as its stereoregular polymerization and subsequent deprotection can afford ß-(1→2) linked 6-deoxy-D-glucopyranan, and its coupling reaction with a suitable glycosyl acceptor can afford

a ß-linked disaccharide containing the 6-deoxy-D-glucopyranose moiety. Here we report the synthesis of **10** and conformational analysis of **10** and a couple of related intermediates **17** and **20**.

RESULTS AND DISCUSSION

Iodination of methyl 2-*O*-allyl-3,4-di-*O*-benzyl-α-D-glucopyranoside **(1)**[10] with triphenylphosphine and iodine in the presence of imidazole furnished crystalline **2** (79% yield), which was then treated with sodium borohydride to give methyl 2-*O*-allyl-3,4-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside **(3)**. Treatment of **3** with 1 M hydrochloric acid-acetic acid under reflux afforded 2-*O*-allyl-3,4-di-*O*-benzyl-6-deoxy-D-glucopyranose **(4)** as crystals. Rearrangement of the allyl group to the propenyl group with tris(triphenylphosphine)chlororhodium and subsequent treatment with 1 M hydrochloric acid gave crystalline 3,4-di-*O*-benzyl-6-deoxy-D-glucopyranose **(5)**. Acetylation of **5** with acetic anhydride in pyridine afforded the 1,2-diacetate **6** (98% yield, as crystals), which was chlorinated with hydrogen chloride in diethyl ether to give 2-*O*-acetyl-3,4-di-*O*-benzyl-6-deoxy-α-D-glucopyranosyl chloride **(7)** (72% yield). Fluorination of **7** was carried out with silver fluoride in a dark room and crystalline 2-*O*-acetyl-3,4-di-*O*-benzyl-6-deoxy-ß-D-glucopyranosyl fluoride **(8)** was obtained as the major product (70% yield) together with a small amount of the α-anomer. Anhydro ring formation of **8** was readily carried out overnight at room temperature with potassium *tert*-butoxide in oxolane to give 1,2-anhydro-3,4-di-*O*-benzyl-6-deoxy-α-D-glucopyranose **(10)** in a high yield. It was also possible to get **10** in high yield by deacetylation of **8** with potassium *tert*-butoxide. Compound **9** was first formed in a short time and then through epoxide formation with sodium hydride yielded **10**.

The 1,2-diacetate **6** was also obtained *via* another process. Tosylation of methyl 3,4-di-*O*-benzyl-α-D-glucopyranoside **(11)**[11] afforded crystalline **12** which was reduced with lithium aluminium hydride to give crystalline methyl 3,4-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside **13**. Acetylation of **13** followed by acetolysis of the resulting acetate **14** furnished **6** in good yield.

The ethylidene group was reported to be a good protective group for the synthesis of 1,2-anhydro galactopyranose derivative.[5] Thus, preparation of 3,4-di-*O*-benzyl-6-deoxy-D-glucopyranose **(5)** starting from 1,2-*O*-**(R)**-ethylidene-α-D-glucopyranose **(15)**[12] was also carried out. Iodination of **15** with triphenylphosphine and iodine in the presence of imidazole yielded the iodide **16** that was acetylated to

give **17** followed by reduction with sodium borohydride to give **18**. Benzylation of **18** or its diacetate **19**, followed by acid hydrolysis, gave **5**.

The target 1,2-anhydro pyranose derivative **10**, a crystalline compound with a low melting point, was found to be acid-labile but relatively stable in basic media at -20 °C. It was not stable during storage at room temperature. Elemental analysis did not give a satisfactory result. Compound **10** was characterized by ^{1}H NMR spectrometry. The ^{1}H NMR spectrum of **10** showed an upfield signal of H-2 at δ 3.05 characteristic of the epoxide ring.[5,6]

Conformational analysis of the 1,2-anhydro sugar derivative was carried out by ^{1}H NMR spectromertry in conjunction with calculations using a modified Karplus equation.[7] Two conformations, $^4H_5$ and $^5H_4$, may be considered for **10**, as shown in Fig.1. In the $^4H_5$ conformation, the C-6, C-3, and C-4 substituents are all in equatorial positions, while in the $^5H_4$ conformation they are all axially oriented. Considering the thermodynamic stability, the $^5H_4$ conformation is not stable due to the unfavorable interaction between BnO-C-3 and CH_3-C-5, and between BnO-C-4 and epoxide oxygen. Therefore, the $^4H_5$ conformation will be favored. This postulate was supported by the experimental results as indicated later.

The ^{1}H NMR spectrum of **10** was fully assigned by use of single frequency decoupling. The anomeric proton signal appeared as a doublet of doublets at δ 4.87 with $J_{1,2}$ = 2.5 Hz, and $J_{1,3}$ = 0.8 Hz, The upfield doublet at δ 1.25 with $J_{5,6}$ = 7.1 Hz, was designated as H-6. The chemical shifts at δ 3.05, 3.93, 3.15, and 3.72 were assigned as H-2, H-3, H-4, and H-5, respectively. The large coupling constants, 9.9 Hz between H-4 and H-5 and 7.9 Hz between H-3 and H-4, clearly indicate that **10** has a conformation $^4H_5$ with *trans*-diaxial relation between H-4 and H-5, and between H-3 and H-4. The torsion angles between H-4 and H-5 ($\phi_{4,5}$) and between H-3 and H-4 ($\phi_{3,4}$) for **10** were 180° and 162°, respectively, according to the calculations by the modified Karplus equation[7] from the coupling constants $J_{4,5}$ and $J_{3,4}$. Because the modified Karplus equation is not valid for the planar portion of the pyranose ring, the H-H torsion angles $\phi_{1,2}$ and $\phi_{2,3}$ calculated by the equation did not represent the true angles of the molecule. Comparison of the torsion angles $\phi_{4,5}$ and $\phi_{3,4}$ for **10** to $\phi_{4,5}$ (180°) and $\phi_{3,4}$ (170°) for the Darling molecular model with the conformation $^4H_5$ indicated that **10** took almost an ideal $^4H_5$ conformation, similar to the

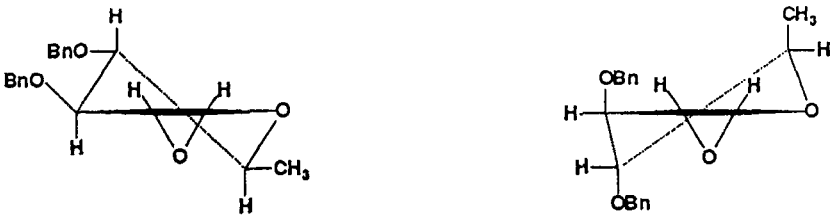
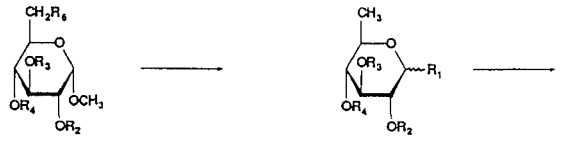
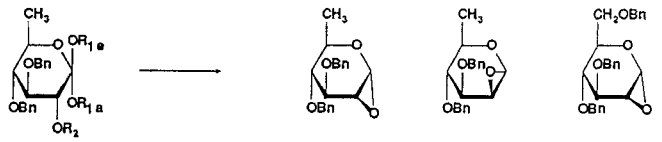


FIG. 1. Two possible conformations, $^{4}H_{5}$ and $^{5}H_{4}$, for **10**.



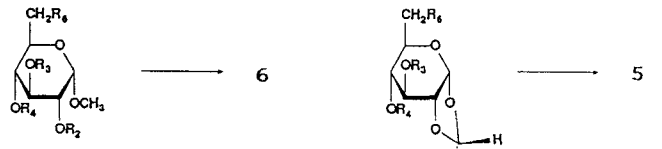
	R_2	R_3	R_4	R_6
1	All	Bn	Bn	OH
2	All	Bn	Bn	I
3	All	Bn	Bn	H

	R_1	R_2	R_3	R_4
4	OH	All	Bn	Bn
5	OH	H	Bn	Bn
6	OAc	Ac	Bn	Bn



	R_{1e}	R_{1a}	R_2
7	H	Cl	Ac
8	F	H	Ac
9	F	H	H

10 **21** **22**



	R_2	R_3	R_4	R_6
11	H	Bn	Bn	OH
12	H	Bn	Bn	OTs
13	H	Bn	Bn	H
14	Ac	Bn	Bn	H

	R_3	R_4	R_6
15	H	H	OH
16	H	H	I
17	Ac	Ac	I
18	H	H	H
19	Ac	Ac	H
20	Bn	Bn	H

conformation of 1,2-anhydro-3,4-di-*O*-benzyl-ß-**D**-rhamnopyranose[8] **(21)**, but slightly different from that of 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-**D**-glucopyranose[6] **(22)**. The chemical shifts, coupling constants, and torsion angles for **10, 21, and 22** are shown in Table 1.

Conformational analysis of the 1,2-*O*-**(R)**-ethylidene intermediates, diacetate of **16(17)** and **20**, were also carried out by the same method as described previously for **10**. The full assignments of the ^{1}H NMR spectra of **17** and **20** were accomplished by single frequency decoupling. H-3 and H-5 signals overlapped in **20** but were well resolved in **17**. H-2, H-3, H-4, and H-5 in both of the spectra appeared as complicated multiplets but the coupling constants $J_{2,3}$, $J_{3,4}$, $J_{2,4}$, and $J_{4,5}$ were obtained from the simplifield signals following selective decoupling. Both **17** and **20** gave an upfield signal at δ 5.09 as a quartet for the methine proton of the dioxolane ring, clearly indicating that it is in axial position (**R** configuration). The large $J_{4,5}$ = 9.2 Hz and 9.1 Hz for **17** and **20** implied their *trans*-diaxial relation. The small coupling constants $J_{2,3}$ = 2.9 Hz, and $J_{3,4}$ = 2.2 Hz for **17** and $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 3.1 Hz for **20** indicated that their pyranose ring had a considerable deformation in comparison with the normal $^4C_1$ conformation. Inspection of the molecular model in conjunction with the calculations by the modified Karplus equation[7] showed that the conformations of the pyranose ring in **17** and **20** were basically $B_{2,5}$ with slight deformation. This conformation was slightly different from that of 3,4,6-tri-*O*-acetyl-1,2-*O*-**(R)**-ethylidene-α-D-glucopyranose[10] having a skew-boat ($^oS_2$) conformation for the pyranose ring.

EXPERIMENTAL

General Methods.- Melting points were determined with a "Mel-Temp" apparatus. Optical rotations were determined with a Perkin-Elmer 241-MC automatic polarimeter for solutions in a 1-dm, jacketed cell. ^{1}H NMR spectra were recorded with Varian XL-400 spectrometer, for solutions in $CDCl_3$, with tetramethylsilane (Me_4Si) as internal standard. Chemical shifts were expressed in ppm down field from the internal Me_4Si absorption. Analytical LC was performed by use of a pump (Model YSB-2, made in China), stainless-steel columns packed with silica gel (10 x 150 mm, or 4.6 x 250 mm), a differential refractometer (Model 1107L, made by LDC, Division of Milton Roy Company, Florida, U. S. A.), and ethyl

TABLE 1.
Chemical Shifts(δ), H-H Coupling Constants(Hz), and H-H Torsion Angles($^{\circ}$) for Compounds **10**, **21** and **22**.

		H-1	H-2	H-3	H-4	H-5	H-6	H-6'
Experimental value of H chemical shifts	**10**	4.87	3.05	3.93	3.15	3.72	1.28	
	21	4.90	3.35	3.90	3.58	3.70	1.28	
	22	4.99	3.06	3.98	3.65	3.74	3.77	3.66

		$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
Experimental value of H-H coupling constants	**10**	2.5	0.8	0	7.9	9.9
	21	2.8	0	1.8	8.3	9.9
	22	2.4	1.0	0	7.8	7.8

		$\phi_{3,4}$	$\phi_{4,5}$
Calculated from the coupling conatants by the modified Karplus equation	**10**	162	180
	21	165	180
	22	161	151
Measured from model $^4H_5$		170	180

TABLE 2.
Chemical Shifts(δ), H-H Coupling Constants(Hz) and H-H Torsion Angles($^{\circ}$) for Compounds **17** and **20**

		H-1	H-2	H-3	H-4	H-5	H-6	H-6'
Experimental value of H chemical shifts	**17**	5.59	4.03	5.16	4.77	3.82	3.39	3.18
	20	5.42	4.02	3.80	3.29	3.80	1.30	

		$J_{1,2}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
Experimental value of H-H coupling constants	**17**	4.9	2.9	0.9	2.2	9.2	3.5	7.1	10.8
	20	4.9	3.4	0.5	3.1	9.1	6.6		

		$\phi_{1,2}$	$\phi_{2,3}$	$\phi_{3,4}$	$\phi_{4,5}$
Calculated from the coupling constants by the modified Karplus equation	**17**	339	293	124	173
	20	339	296	131	173
Measured from model $B_{2,5}$ with some puckering at C-4 and some some flattening at C-1		335	295	130	175

TABLE 3.

^{1}H NMR chemical shifts (δ) and coupling constants (Hz) for **2, 3, 4, 5, 6, 7, 8, 10, 12, 13, 17, 19, 20.**

	2	**3**	**4** α-anomer	**4** ß-anomer	**5** α-anomer	**5** ß-anomer	**6** α-anomer	**6** ß-anomer
H-1	4.83(d)	4.70(d)	5.22(d)	4.62(d)	5.16(d)	4.51(d)	6.21(d)	5.60(d)
$J_{1,2}$	3.9	3.9	3.8	9.2	3.7	8.9	3.7	8.5
H-2	3.38(m)	3.45(dd)	3.47(dd)	3.23(t)	3.65(dd)	3.43(t)	5.03(dd)	5.09(t)
$J_{2,3}$		9.0	9.2	9.2	9.3	8.9	9.4	8.5
H-3	4.00(t)	3.90(t)	3.87(t)	3.56(t)	3.76(t)	3.52(t)	3.96(t)	3.69(t)
$J_{3,4}$	9.2	9.0	9.2	9.2	9.3	8.9	9.4	8.5
H-4	3.38(m)	3.11(t)	3.12(t)	3.17(t)	3.14(t)	3.20(t)	3.31(t)	3.56(t)
$J_{4,5}$		9.0	9.2	9.2	9.3	8.9	9.4	8.5
H-5	3.38(m)	3.72(m)	4.10(m)	3.42(m)	4.00(m)	3.46(m)	3.86(m)	3.53(m)
H-6	3.39(m)	1.24(d)	1.24(d)	1.28(d)	1.27(d)	1.31(d)	1.28(d)	1.32(d)
$J_{5,6}$		6.1	6.1	7.1	6.0	6.1	6.0	6.1
Ar-H	7.30(m)	7.27(m)	7.28(m)	7.28(m)	7.31(m)	7.31(m)	7.31(m)	7.31(m)
PhC*H*$_2$	4.97	4.92	4.76(m)	4.76(m)	4.75(m)	4.75(m)	4.78(m)	4.78(m)
	4.79(q_{AB})	4.77(q_{AB})						
^2J	11.6	11.1						
PhC*H*'$_2$	4.96	4.87	4.76(m)	4.76(m)	4.75(m)	4.75(m)	4.78(m)	4.78(m)
	4.70(q_{AB})	4.60(q_{AB})						
^2J	11.0	11.1						
CH_2=C*H*	5.94(m)	5.90(m)	5.90(m)					
C*H*$_2$=CH	5.33	5.27	5.29					
	5.22(2bd)	5.17(2bd)	5.19(2bd)					
^2J	17.0	18.0	17.1					
^3J	9.8	9.6	10.4					
CH_2=CH-C*H*$_2$	4.20(m)	4.17(m)	4.20(m)					
C*H*$_3$O	3.48(s)	3.38(s)						
C*H*$_3$CO							2.12(s)	2.09(s)
							1.98(2s)	1.94(2s)

(continued)

TABLE 3. Continued

	7	8 α-anomer	8 ß-anomer	10	12	13	17	19	20
H-1	6.22(d)	5.54(dd)	5.17(dd)	4.87(d)	4.71(d)	4.67(d)	5.59(d)	5.54(d)	5.52(d)
$J_{1,2}$	3.7	3.2	9.5	2.5	3.8	4.4	4.9	4.7	4.9
$J_{1,F}$	54.0	52.3							
$J_{1,3}$			0.8						
H-2	4.92(dd)	5.20(m)	5.10(m)	3.05(d)	3.65(dd)	3.71(m)	4.03(m)	4.00(m)	4.02(m)
$J_{2,3}$	9.1			2.5	9.2		2.9		3.4
$J_{2,4}$							0.9		0.5
H-3	4.05(t)	3.70(m)	3.64(t)	3.93(dd)	3.76(t)	3.71(m)	5.16(dd)	5.17(dd)	3.80(m)
$J_{3,4}$	9.1		9.5	7.8	9.2		2.2	3.4	
H-4	3.27(t)	3.44(m)	3.42(m)	3.15(dd)	3.47(t)	3.13(t)	4.77(m)	4.71(dd)	3.29(m)
$J_{4,5}$	9.1		9.5	9.9	9.2	8.7	9.2	9.3	9.2
H-5	4.10(m)	3.60(m)	3.61(m)	3.73(m)	3.83(m)	3.71(m)	3.82(m)	4.00(m)	3.80(m)
H-6	1.31(d)	1.26(d)	1.36(d)	1.25(d)	4.25(d)	1.29(d)	3.39(d)	1.27(d)	1.30(d)
$J_{5,6}$	5.7	6.5	6.5	7.1	3.2	5.2	4.8	5.7	6.6
$J_{6,6'}$							10.6		
H-6'							3.18(d)		
$J_{5,6'}$							5.3		
Ar-H	7.30(m)	7.31(m)	7.29(m)	7.30(m)	7.29(m)	7.32(m)			7.32(m)
PhCH_2	4.88	5.36(m)	4.84	4.83	4.93	4.91			4.71
	4.66(q_{AB})		4.68(q_{AB})	4.64(q_{AB})	4.84(q_{AB})	4.85(q_{AB})			4.61(q_{AB})
^2J	10.8		10.6	10.9	11.4	10.4			11.8
PhCH'_2	4.84	5.36(m)	4.78	4.80	4.85	4.88			4.63
	4.78(q_{AB})		4.64(q_{AB})	4.69(q_{AB})	4.49(q_{AB})	4.64(q_{AB})			4.47(q_{AB})
^2J	11.5		11.3	11.1	10.8	10.5			12.0
CH_3CO	2.04(s)	2.00(s)	1.99(s)				2.44	2.13(2s)	
							2.13(2s)		
CH_3CH							5.09(q)	5.09(q)	5.09(q)
^3J							5.0	4.9	4.9
CH_3CH							1.52(d)	1.54(d)	1.49(d)
CH_3O					3.39(s)	3.41(s)			
CH_3 of Ts					2.44(s)				
ArH-2,6 of Ts					7.81(d)				
^3J					8.0				
ArH-3,5 of Ts					7.23(m)				

acetate-petroleum ether (bp 60-90 °C) as the eluant at a flow rate of 1-4 mL/min. Thin-layer chromatography (TLC) was performed on silica gel HF or GF, detection being affected by charring with 30% (v/v) sulfuric acid in methanol or sometimes by a UV detector. Column chromatography was conducted by elution of columns (16 x 240 mm, 18 x 300 mm, 35 x 400 mm) of silica gel (120-200 mesh, made in China). Solutions were concentrated at a temperature <50 °C under diminished pressure.

Methyl 2-*O*-Allyl-3,4-di-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside (2). To the solution of **1**[11] (2.8 g, 6.83 mmol) in toluene (100 mL) were added triphenylphosphine (3.55 g, 13.6 mmol), imidazole (2.43 g, 35.5 mmol), and iodine (3.17 g, 12.5 mmol). The mixture was heated under reflux with vigorous stirring until the colour disappeared (15 min). TLC (2:1 petroleum ether-ethyl acetate) indicated that the starting material disappeared. After cooling the mixture to room temperature, a solution of sodium hydrogencarbonate (3 g) in water (60 mL) was added with stirring, then iodine was added until the colour of the mixture remained purple. Agueous sodium thiosulfate (10%) was added dropwise with stirring until the purple colour was removed. The mixture was then diluted with ethyl acetate (100 mL), washed twice with water, and concentrated. The residue was dissolved in ether (70 mL) at 0 °C, and filtered to remove triphenylphosphine oxide. Concentration of the ether solution afforded crude product **2** which was purified by column chromatography to give white crystals (3.05 g, 79%); mp 55-57 °C; $[\alpha]_D^{20}$ +66.0° (*c* 3.5, chloroform).

Anal. Calcd for $C_{24}H_{29}O_5I$: C, 54.97; H, 5.57. Found: C, 54.61; H, 5.63.

Methyl 2-*O*-Allyl-3,4-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside (3). To a solution of **2** (3 g, 5.66 mmol) in acetonitrile (100 mL) was added sodium borohydride (450 mg, 12.2 mmol). The mixture was heated under reflux with vigorous stirring for 6 h. Then the mixture was concentrated and the residue was poured into ice-water (150 mL) with stirring. The mixture was extracted with dichloromethane (30 mL) three times, dried over sodium sulfate and concentrated. Purification of the syrup by column chromatography (3:1 petroleum ether-ethyl acetate) gave **3** (1.76 g, 80%); $[\alpha]_D^{20}$ +41.8° (*c* 5.2, chloroform).

Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.05; H, 7.51.

2-*O*-Allyl-3,4-di-*O*-benzyl-6-deoxy-D-glucopyranose (4). A mixture of **3** (1.7 g, 4.3 mmol), acetic acid (80%, 30 mL) and

hydrochloric acid (1 M, 10 mL) was boiled under reflux for 4 h. TLC (2 : 1 petroleum ether-ethyl acetate) indicated that the starting material disappeared. The mixture was extracted with dichloromethane, washed with saturated sodium hydrogencarbonate and then water, and concentrated to dryness. Purification of the crude crystals by column chromatography (2:1 petroleum ether-ethyl acetate) yielded white crystals **4** (1.3 g, 76%) which was a mixture of α and ß isomers in a ratio 3:2; mp 86.5-87.5 °C; $[\alpha]_D^{20}$ +24.5° (*c* 2.0, chloroform).

Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.78; H, 7.34. Found: C, 71.55; H, 7.40.

3,4-Di-*O*-benzyl-6-deoxy-D-glucopyranose (5). Compound **4** (1.2 g, 3.1 mmol) was dissolved in ethanol (90%, 30 mL) and tris(triphenylphosphine)chlororhodium (50 mg, 0.054 mmol) was added to the solution. The mixture was boiled under reflux with stirring for 9 h. TLC (2:1 petroleum ether-ethyl acetate) indicated that the starting material disappeared. The mixture was filtered and the filtrate concentracted to give crude crystals. Purification of the crystals by column chromatography (1:1 petroleum ether-ethyl acetate) yielded white crystals **5** (0.86 g, 80%) which was a mixture of α and ß isomers in a ratio of 7:3; mp 85-86 °C; $[\alpha]_D^{20}$ +62.1° (*c* 3.0, chloroform).

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.60; H, 6.96.

1,2-Di-*O*-acetyl-3,4-di-*O*-benzyl-6-deoxy-D-glucopyranose (6). Compound **5** (0.8 g, 2.3 mmol) was treated with pyridine (3 mL) and acetic anhydride (1.5 mL) by a standard method. Compound **6** was obtained in a quantitative yield as crystals consisting of α and ß anomer in a ratio of 4:5; mp 113-113.5 °C; $[\alpha]_D^{20}$ +21.1° (*c* 2.7, chloroform).

Anal. Calcd for $C_{24}H_{28}O_7$: C,67.27; H, 6.59. Found: C,67.35; H, 6.84.

2-*O*-Acetyl-3,4-di-*O*-benzyl-6-deoxy-α-D-glucopyranosyl chloride (7). A solution of compound **6** (830 mg, 2 mmol) in dry diethyl ether (30 mL) was saturated with hydrogen chloride gas under a nitrogen atmosphere at 0 °C. Then the solution was kept at room temperature in a sealed bottle for 2 h. TLC (3:1 petroleum ether-ethyl acetate) indicated the reaction to be complete. The solution was concentrated to a syrup which was dissoved in dichloromethane (2 mL), and the solution concentrated. This procedure was repeated several times, and the product was purified by column chromatography (3:1 petroleum ether-ethyl acetate) to give **7** as a syrup (560 mg, 72%); $[\alpha]_D^{20}$ +127.3 °C (*c* 5.6, chloroform).

Anal. Calcd for $C_{22}H_{25}O_5Cl$: C, 65.26; H, 6.22. Found: C, 65.36; H, 6.20.

2-*O*-Acetyl-3,4-di-*O*-benzyl-6-deoxy-ß-D-glucopyranosyl fluoride (8). To a solution of **7** (150 mg, 0.37 mmol) in 2:5 acetonitrile-benzene (3.5 mL) was added solid silver fluoride (60 mg, 0.41 mmol), and a white precipitate of silver chloride formed. The mixture was stirred vigorously in a dark room for 16 h at room temperature, then centrifuged, and the solid was washed repeatedly with benzene. The combined washings and supernatant liquor were concentrated to dryness and a crude crystalline mixture of **8** together with a small amount of α-isomer was obtained. Purification of the mixture by column chromatography (4:1 petroleum ether-ethyl acetate) yielded crystalline **8** (100 mg, 70%), and crystalline α-isomer (20 mg, 14%). Compound **8**: mp 125-126 °C; $[\alpha]_D^{20}$ +21° (*c* 5.8, chloroform).

Anal. Calcd for $C_{22}H_{25}O_5F$ (**8**): C, 68.04; H, 6.49. Found: C, 67.94, H, 6.53.

1,2-Anhydro-3,4-di-*O*-benzyl-6-deoxy-α-D-glucopyranose (10). To a solution of **8** (80 mg, 0.21 mmol) in dry oxolane (4 mL) was added potassium *tert*-butoxide (40 mg, 0.36 mmol), and the mixture was stirred at room temperature for 16 h. TLC (3:1 petroleum ether-ethyl acetate) indicated that the starting material **8** and the intermediate 3,4-di-*O*-benzyl-6-deoxy-ß-D-glucopyranosyl fluoride **(9)** had disappeared. The mixture was concentrated to dryness and the residue was repeatedly extracted with 3:1 petroleum ether-ethyl acetate, and the extracts was combined and concentrated to give **10** as white crystals (57 mg, 85%); mp 51-52 °C; $[\alpha]_D^{20}$ +5.8° (*c* 6.0, chloroform).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.61; 6.79. Found: C, 74.03; H, 6.80.

(b) To a solution of **8** (10 mg, 0.025 mmol) in dry oxolane (1 mL) was added potassium *tert*-butoxide (5 mg, 0.045 mmol) and the mixture was stirred at room temperature for 2 h. TLC (3:1 petroleum ether-ethyl acetate) indicated that the starting material disappeared. Then the mixture was filtered and the residue was washed with oxolane. To the filtrate was added sodium hydride (80%, 1.6 mg, 0.05 mmol) and the mixture was stirred at room temperature for 3 h. TLC (3:1 petroleum ether-ethyl acetate) indicated that the reaction was complete. Filtration, then concentration of the filtrate afforded crude **10** that was purified by recrystallization from ether-petroleum ether.

Methyl 3,4-Di-*O*-benzyl-6-*O*-*p*-toluenesulfonyl-α-D-glucopyranoside (12). Methyl 3,4-di-*O*-benzyl-α-D-glucopyranoside **(11)** was obtained

by mono-*O*-benzylation of methyl 4,6-*O*-benzylidene glucopyranoside as a by-product (33%) by phase transfer method,[11] and followed by reduction with anhydrous aluminium chloride and lithium aluminium hydride in dry diethyl ether and dichloromethane[10] (70%). To a solution of **11** (748 mg, 2 mmol) in dry pyridine (4 mL) was slowly added *p*-toluenesulfonyl chloride (380 mg, 2.05 mmol) at 0 °C and the reaction was carried out at room temperature for 16 h. TLC (2:1 petroleum ether-ethyl acetate) indicated that the starting material disappeared. The mixture was poured into ice-water (50 mL), extracted with dichloromethane (8 mL), washed with 1 N HCl and dried over sodium sulfate, and then concentrated. Purification of the syrup by column chromatography (3:1 petroleum ether-ethyl acetate) yielded white crystals **12** (950 mg, 90%); mp 69-70 °C; $[\alpha]_D^{20}$ +154° (*c* 3.1, chloroform).

Anal. Calcd for $C_{28}H_{32}O_8S$: C, 63.63; H, 6.06. Found: C, 63.56; H, 6.19.

Methyl 3,4-Di-*O*-benzyl-6-deoxy-α-D-glucopyranoside (13). To a solution of **12** (900 mg, 1.7 mmol) in dry oxolane was added lithium aluminium hydride (90 mg, 2.3 mmol). The mixture was boiled under reflux with stirring for 4 h. TLC (2:1 petroleum ether-ethyl acetate) indicated that the starting material disappered. Then the mixture was cooled, filtered and washed with dichloromethane. The organic phase was concentrated to a syrup. Purification of the syrup by column chromatography (3:1 petroleum ether-ethyl acetate) yielded white crystals of **13** (310 mg, 70%); mp 97-98 °C; $[\alpha]_D^{20}$ +33.2° (*c* 3.3, chloroform).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.39; H, 7.26. Found: C, 70.20, H, 7.35.

1,2-Di-*O*-acetyl-3,4-di-*O*-benzyl-6-deoxy-D-glucopyranose (6) from 13. Compound **13** (270 mg, 0.7 mmol) was treated with pyridine and acetic anhydride by a standard method to give compound **14** quantitatively (300 mg). A solution of **14** (300 mg, 0.84mmol) in acetic anhydride-acetic acid-sulfuric acid (50:20:0.5, 6mL) was stirred for 4 h at room temperature. TLC (3:1 petroleum ether-ethyl acetate) indicated that the reaction was complete. The mixture was poured into an ice-cooled solution of aqueous potassium carbonate. The product was extracted with dichloromethane, the extract was dried over sodium sulfate and concentrated to a syrup. Purification of the syrup by column chromatography (3:1 petroleum ether-ethyl acetate) yielded white crystals of **6** (210 mg, 60%).

6-Deoxy-1,2-*O*-(R)-ethylidene-6-iodo-α-D-glucopyranose (16) and its diacetate (17). To a solution of 1,2-*O*-(R)-ethylidene-α-D-

glucopyranose[12] **15** (1.2 g, 5.83 mmol) in dioxane (40 mL) were added triphenylphosphine (2.9 g, 11.7 mmol), imidazole (2 g, 29.6 mmol) and iodine (2.6 g, 10.2 mmol). The mixture was boiled under reflux for 20 min with vigorous stirring. TLC (ethyl acetate) indicated that the starting material disappeared. Then the mixture was cooled to room temperature and a solution of sodium hydrogencarbonate (2.5 g) in water (50 mL) was added with stirring. Iodine was added until the colour of the mixture remained purple. Aqueous sodium thiosulfate (10%) was added dropwise with stirring until the purple colour was removed. The mixture was then diluted with dichloromethane (20 mL), extracted with dichloromethane (10 mL) 7-8 times, dried over sodium sulfate and concentrated. Purification of the syrup by column chromatography (1:1 petroleum ether-ethyl acetate) gave **16** as a syrup (1 g, 54%). Acetylation of **16** gave the diacetate **17**; mp 116-117 0°C; $[\alpha]_D^{20}$ +15.5° (*c* 3.2, chloroform).

Anal. Calcd for $C_{12}H_{17}O_7I$: C, 36.00; H, 4.25. Found: C, 36.08; H, 4.06.

6-Deoxy-1,2-*O*-(R)-ethylidene-α-D-glucopyranose (18) and its Diacetate (19). To a solution of **16** (0.7 g, 2.2 mmol) in acetonitrile (30 mL) was added sodium borohydride (200 mg, 5.5 mmol). The mixture was boiled under reflux with vigorous stirring for 6 h. TLC (ethyl acetate) indicated that the starting material disappeared. The reaction mixture was concentrated and the residue was poured into ice-water (50 mL) with stirring, and the mixture extracted with dichloromethane repeatedly, dried over sodium sulfate and concentrated. Purification of the syrup by column chromatography (1:1 petroleum ether-ethyl acetate) gave **18** as a syrup (0.33 g, 78%). Acetylation of **18** give the diacetate **19**; $[\alpha]_D^{20}$ +54° (*c* 3.0, chloroform).

Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55; H, 6.57. Found: C, 52.53; H, 6.33.

3,4-Di-*O*-benzyl-6-deoxy-1,2-*O*-(R)-ethylidene-α-D-glucopyranose (20). To a solution of **19** (0.3 g, 1.1 mmol) in toluene (20 mL) was added finely powdered potassium hydroxide (440 mg, 11 mmol) with vigorous stirring. The mixture was boiled under reflux, and benzyl chloride (4.8 mL, 5.5 mmol) was added dropwise within 5 min. The reaction was continued with vigorous agitation under reflux for 2 h. TLC (3:1 petroleum ether-ethyl acetate) indicated that the reaction was complete. The reaction mixture was subjected to steam distillation directly for removal of excess benzyl chloride. Then the mixture was extracted with dichloromethane, dried over sodium

sulfate, and concentrated to a syrup. Purification of the syrup by column chromatography (3:1 petroleum ether-ethyl acetate) gave pure **20** (370 mg, 90%); $[\alpha]_D^{20}$ +21.1° (*c* 3.5, chloroform).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.31; H, 7.09; Found: C, 70.78; H, 7.43.

3,4-Di-*O*-benzyl-6-deoxy-D-glucopyranose (5) from 20. To a solution of **20** (300 mg, 0.81 mmol) in dioxane was added 1M sulfuric acid (3 mL), and the mixture was boiled under reflux with stirring for 4 h. TLC (2:1 petroleum ethyl-ethyl acetate) indicated that the reaction was complete. The mixture was neutralized with sodium bicarbonate with cooling, and then concentrated to a syrup that was partitioned between water and dichloromethane. The organic layer was dried over sodium sulfate and concentrated, and white crystals of **5** (210 mg, 85%) obtained.

REFERENCES

1. C. Schuerch, *Adv. Carbohydr. Chem. Biochem.*, **39**, 157 (1982).
2. R. L. Halcomb and J. Danishefsky, *J. Am. Chem. Soc.*, **111**, 6661 (1989).
3. S. J. Sondheimer, H. Yamaguchi, and C. Schuerch, *Carbohydr. Res.*, **74**, 307 (1979).
4. H. Yamaguchi and C. Schuerch, *Carbohydr. Res.*, **81**, 192 (1980).
5. F. Kong, J. Du, and H. Shang, *Carbohydr. Res.*, **162**, 217 (1987).
6. R. Eby and V. Srivastava, *Carbohydr. Res.*, **102**, 1 (1982).
7. C. A. G. Haasnoot, F. A. A. M. De Leeuw, and C. Altona, *Bull. Soc. Chim. Belg.*, **89**, 125 (1980).
8. Q. Chen, F. Kong, and L. Cao, unpublished results.
9. F. H. Cano, C. Foces-Foces, J. Jimenez-Barbero, M. Bernabe, and M. Martin-Lomas, *Carbohydr. Res.*, **145**, 319 (1986).
10. R. I. Hollingsworth, E. M. Hrabak, and F. B. Dazzo, *Carbohydr. Res.*, **154**, 103 (1986).
11. P. J. Garegg, T. Iverson, and S.Oscarson, *Carbohydr. Res.*, **50**, C12 (1976).
12. V. I. Betaneli, M. V. Ovchinnikov, L. V. Backinowsky, and N. K. Kochetkov, *Carbohydr. Res.*, **107**, 285 (1982).