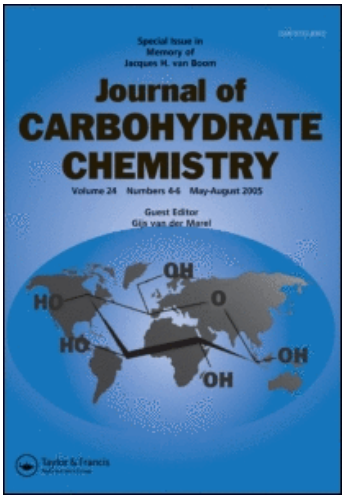

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Synthesis and Conformation of Substituted 2,6-Dioxabiocyclo[3.1.1]heptanes: 1, 3-Anhydro-2, 4-di-*O*-benzyl-β-D-fucopyranose

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SYNTHESIS AND CONFORMATION OF SUBSTITUTED 2,6-DIOXABIOCYCLO[3.1.1]HEPTANES: 1,3-ANHYDRO-2,4-DI-O-BENZYL-ß-D-FUCOPYRANOSE

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ABSTRACT

The title 1,3-anhydro sugar **(9)** was synthesized from methyl α-D-fucopyranoside in 7 steps, most of which were carried out readily in high yield. The key intermediate for the synthesis was 3-*O*-acetyl-2,4-di-*O*-benzyl-α-D-fucopyranosyl chloride **(7)**, which was transformable into the target compound by ring closure with potassium *tert*-butoxide. Calculations using the modified Karplus equation for vicinal coupling constants of compound **9** suggested that the conformation of the 1,3-anhydro sugar ether is essentially $B_{2,5}$ with some flattening of the boat head at C-5 for the pyranose ring. The 1,3-dioxane ring is in a chair conformation. The conformation of **9** was confirmed by empirical force-field calculations (MMP2). Conformational analysis with the MMP2 program for 1,3-anhydro-2,4-di-*O*-benzyl-6-deoxy-ß-D-glucopyranose **(13)** and 1,3-anhydro-2,4-di-*O*-benzyl-ß-D-rhamnopyranose **(14)** also showed good agreement with the results obtained by ^{1}H NMR spectrometry.

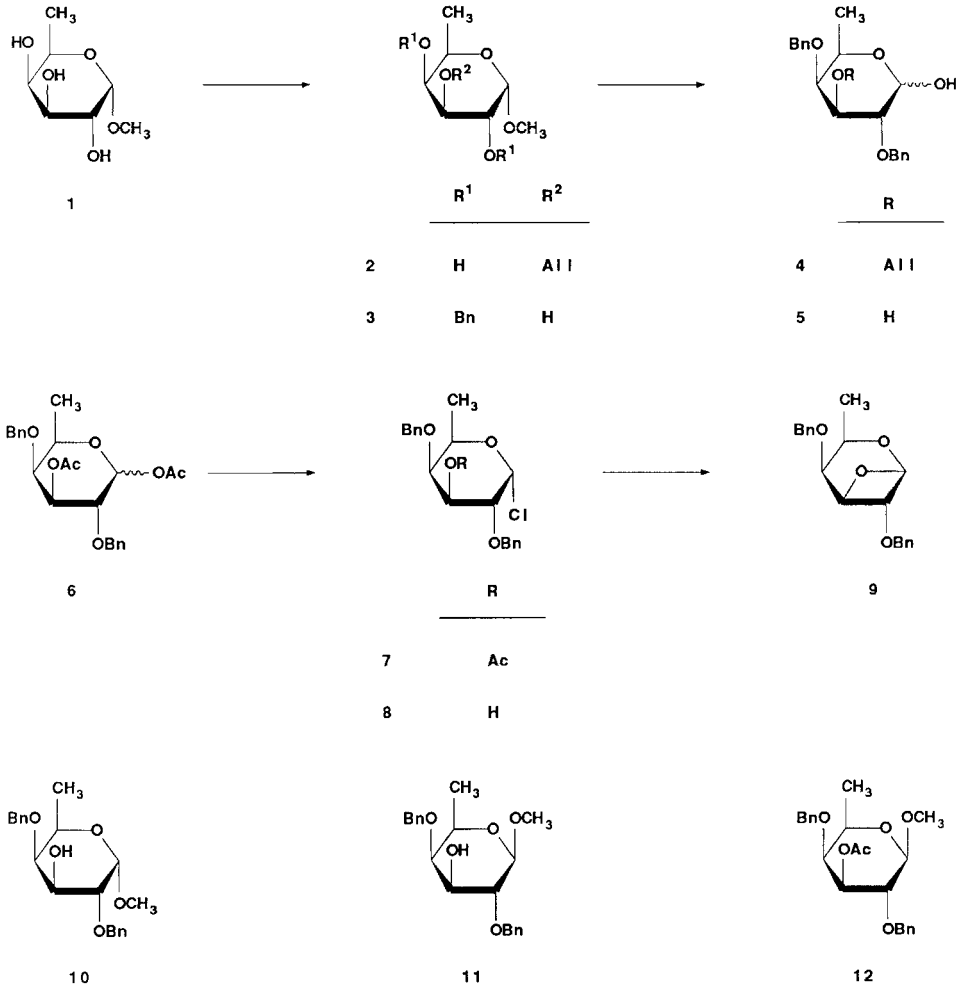
INTRODUCTION

A rationale for the investigation of simple derivatives of 1,3-anhydropyranoses was described in an article regarding the synthesis of 1,3-anhydro-L-rhamnopyranose benzyl ether.[1] The syntheses of 1,3-anhydro-D-rhamno-,[2] D-gluco-,[3,4] D-manno-[5,6]

and D-galactopyranose[7] derivatives have been reported. We now report the synthesis and conformation of 1,3-anhydro-2,4-di-*O*-benzyl-ß-D-fucopyranose, the polymerization of which can afford an α-(1 → 3)-linked D-fucopyranan, a useful model compound for polysaccharide research.

RESULTS AND DISCUSSION

D-Fucopyranose, obtained from 6-deoxy-6-iodo-1,2:3,4-di-*O* isopropylidene-α-D-galactopyranose by a photochemical method,[8] was converted to methyl α-D-fucopyranoside **(1)** with Dowex-50 resin (H^+ form) as catalyst.[9] Compound **1** was selectively allylated at C-3 as described[7] *via* stannylene complex to afford methyl 3-*O*-allyl-α-D-fucopyranoside **(2)**. Removal of most of the tetrabutylammonium iodide used in the monoallylation from the reaction mixture was helpful for the purification of **2** by column chromatography, and the recovered tetrabutylammonium iodide could be reused. Compound **2** was benzylated according to a conventional method to yield methyl 3-*O*-allyl-2,4-di-*O*-benzyl-α-D-fucopyranoside **(3)**. Acid hydrolysis of **3** followed by deallylation with tris(triphenylphosphine)chlororhodium as catalyst afforded 2,4-di-*O*-benzyl-D-fucopyranose **(5)**. Acetylation of **5** with acetic anhydride in pyridine gave the 1,3-diacetate **6**. Both of the compounds **5** and **6** were mixtures of α and ß anomers as shown by their ^1H NMR spectra. The conversion of **6** into 3-*O*-acetyl-2,4-di-*O*-benzyl-α-D-fucopyranosyl chloride **(7)** was carried out in ether solution of hydrogen chloride according to the method of Micheel and Kreutzer.[10] Compound **7** was found to be moisture-sensitive and to decompose when detected by TLC. After removal of excess hydrogen chloride, however, it was quite stable during storage at 0 °C in a basic atmosphere. Ring-closure reaction of **7** was conducted with potassium *tert*-butoxide in oxolane at room temperature and 1,3-anhydro-2,4-di-*O*-benzyl-ß-D-fucopyranose **(9)** was the only product. This 1,3-anhydropyranose **(9)** could also be prepared by an alternative method. Thus the fucopyranosyl chloride **7** was converted to the



de-*O*-acetylated derivative **8** by treatment of **7** with lithium methoxide (generated *in situ* from lithium hydride and absolute methanol) in refluxing oxolane or with sodium methoxide at room temperature. Then compound **9** was obtained in high yield by reaction of **8** with sodium hydride in refluxing oxolane.

It was reported that treatment of 3-*O*-acetyl-2,4,6-tri-*O*-benzyl-α-**D**-glucopyranosyl chloride with potassium *tert*-butoxide

in oxolane or 1,2-dimethoxyethane yielded a glucal derivative as the main product, formed by *trans*-diaxial elimination of hydrogen chloride from C-1 and C-2.[4] This was also true for the treatment of 3-*O*-acetyl-2,4-di-*O*-benzyl-6-deoxy-α-**D**-glucopyranosyl chloride with potassium *tert*-butoxide or sodium methoxide in oxolane.[11] Compared with 3-*O*-acetyl-2,4,6-tri-*O*-benzyl-α-**D**-glucopyranosyl chloride and 3-*O*-acetyl-2,4-di-*O*-benzyl-6-deoxy-α-**D**-glucopyranosyl chloride having an equatorial benzyloxy group at C-4, an axial group at C-4 in compound **8** may hinder *tert*-butoxy or methoxy group to attack C-2-H. Thus, the side reaction of *trans*-diaxial elimination of hydrogen chloride was avoided.

Methanolysis[12] of the 1,3-anhydropyranose **9** was conducted to investigate its reactivity. No reaction occurred when a methanol solution of **9** was stirred at room temperature for 2 days. However, when boron trifluoride etherate was added as a catalyst, all of the starting material disappeared and two products formed in a ratio of 3:1 as indicated by TLC. Separation by analytical LC furnished two compounds, one of which was the major product and identified by ^{1}H NMR as methyl 2,4-di-*O*-benzyl-α-**D**-fucopyranoside **(10)**. The minor product was methyl 2,4-di-*O*-benzyl-ß-**D**-fucopyranoside **(11)**. Since the H-2, 3, 4 and 5 signals in **11** overlapped, acetylation of **11** with acetic anhydride-pyridine was conducted to confirm the structure of **11** and the methyl 3-acetate **12** was obtained quantitatively. The fact that the methanolysis product was not the sole α-fucopyranoside shows that the ring opening was not a stereospecific reaction.

The 1,3-anhydro-ß-**D**-fucopyranose derivative **9** was found to be acid-labile but relatively stable in basic media. It decomposed during detection by TLC. Purification of **9** was carried out by LC using a column packed with Lichrosorb-NH_2.

The 1,3-anhydropyranose **9** was identified from its ^{1}H NMR, MS, elemental analysis and optical rotation data. In the mass spectrum of **9** there is a molecular ion of low intensity at m/z 326 and a relatively strong peak at 253 (BnO^+=CH-CH=CHOBn). Peaks of moderate intensity at m/z 181, 161, 133, and 107 were

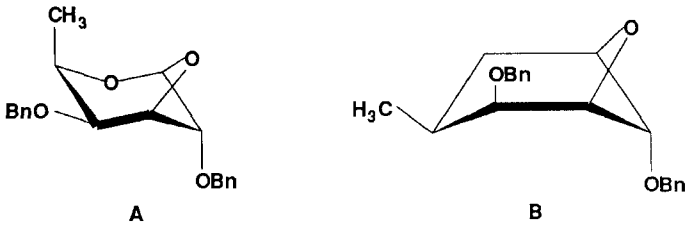


FIG. 1. Two possible conformations, A and B, for compound **9**.

also observed. The fragmentation pattern from **9** was basically the same as that of 1,3-anhydro sugar derivatives.[13]

A detailed conformational analysis of the 1,3-anhydro sugar ether **9** was performed experimentally by ^{1}H NMR spectrometry in conjunction with calculations by the modified Karplus equation,[14] and theoretically by MMP2 program[15] calculations.

Two possible conformations, A and B, may be considered for compound **9** as shown in Fig. 1. Conformation B with the large group C5-CH_3 in an equatorial position was predicted to be the favored one due to its thermodynamic stability. This postulate was confirmed as described later.

The ^{1}H NMR spectrum of compound **9** was assigned by use of single-frequency decoupling technique. The anomeric proton H-1 appeared as a characteristic triplet at δ 5.52, with a coupling constant of 3.48 Hz, due to vicinal H-1, H-2 coupling and H-1, H-3 long range coupling. The large value of $^4J_{1,3}$ is probably caused by coupling through two W paths, as found in cyclobutane derivatives.[16] Irradiation of H-6 identified H-5 at δ 4.94 with $J_{4,5}$ = 5.77 Hz. Irradiation of H-5 indicated H-4 at δ 3.64, and decoupling H-4 established H-3 at δ 4.74. The quartet at δ 4.52 was assigned as H-2 by irradiation of H-3. The assignments were also confirmed by irradiation in reverse order, H-1 to H-5. Thus, the ^{1}H NMR spectrum of **9** had similar features to that of the corresponding D-galactopyranose derivatives except for H-4 and H-6 being shifted upfield.

TABLE 1.
Some Important Bond Lengths and Non-bonded Distances (Å) of Compounds **9**, **13** and **14** by MMP2 Calculations Starting from Conformation B.

	9	**13**	**14**
C1 - C2	1.5526	1.5517	1.5539
C2 - C3	1.5518	1.5521	1.5532
C3 - C4	1.5401	1.5383	1.5390
C4 - C5	1.5546	1.5518	1.5553
C5 - O5	1.4287	1.4297	1.4358
O5 - C1	1.4235	1.4237	1.4314
C5 - C6	1.5382	1.5376	
C1 - O1	1.4316	1.4302	1.4252
O1 - C3	1.4327	1.4337	1.4349
C2 - O2	1.4118	1.4119	
C1, C3	1.9712	1.9709	1.9680
C2, O1	2.1075	2.1105	2.1415
C2, C5	2.8492	2.8564	2.7350
C5, O1	2.8148	2.8003	2.8229
C1, C4	2.6618	2.6602	
O1, O5	2.3299	2.3312	2.3097
C3, O5	2.6661	2.6675	

Conformations A and B are the same with regard to the four-membered ring C1-C2-C3-O1, but different with regard to the C4-C5-O5 part of the molecule. The conformations differ around the torsion angles between H-3 and H-4 ($\phi_{3,4}$) and between H-4 and H-5 ($\phi_{4,5}$).

The proton-proton torsion angles for compound **9** calculated from the modified Karplus equation[14] and measured from Darling Models are listed in Table IV. It was found that the calculated torsion angles $\phi_{3,4}$ and $\phi_{4,5}$ were in good agreement with those measured from model B with some flattening at C-5. Some deviation between calculated and measured values for the angles $\phi_{1,2}$ and $\phi_{2,3}$ may result from the modified Karplus equation not

TABLE 2.

Some Important Bond Angles (Degrees) of Compounds **9**, **13** and **14** Obtained by MMP2 Calculations Starting from Conformation B.

Atoms	**9**	**13**	**14**
O5-C1-C2	116.5	117.0	113.0
C1-C2-C3	78.8	78.8	78.5
C2-C3-C4	113.0	113.8	111.6
C3-C4-C5	109.4	109.5	107.8
C4-C5-O5	113.0	113.2	111.5
C5-O5-C1	114.0	114.1	113.1
O5-C1-O1	109.4	109.5	107.9
C1-O1-C3	87.0	87.0	87.0
O1-C3-C4	107.0	105.9	105.4
O1-C1-C2	89.8	90.0	91.7
O1-C3-C2	89.8	89.9	91.4
O2-C2-C1	116.1	116.9	
O2-C2-C3	116.5	115.5	
C4-C5-C6	114.6	112.0	
O5-C5-C6	108.6	108.8	

TABLE 3.

Some Important Torsion Angles (Degrees) of Compounds **9**, **13** and **14** Obtained by MMP2 Calculations Starting from Conformation B.

	9	**13**	**14**
O5-C1-C2-C3	-83.2	-84.7	-85.9
C1-C2-C3-C4	80.9	80.5	83.0
C2-C3-C4-C5	-40.8	-40.0	-35.2
C3-C4-C5-O5	-18.8	-18.5	-29.0
C4-C5-O5-C1	20.3	18.6	29.8
C5-O5-C1-C2	39.7	41.8	35.3
O5-C1-O1-C3	88.7	88.7	88.8
C1-O1-C3-C4	-84.7	-85.7	-86.8

TABLE 4.

H-H Coupling Constants (Hz) and H-H Torsion Angles (Degrees) for Compounds **9**, **13** and **14** .

		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
Experimental value of H-H coupling constants (Hz)	**9**	3.48	5.63	1.93	5.77
	13[11]	3.71	5.10	2.78	6.96
	14[2]	0	0	3.20	6.85
		$\phi_{1,2}$	$\phi_{2,3}$	$\phi_{3,4}$	$\phi_{4,5}$
Calculated from the coupling constants by modified Karplus equation according to model B	**9**	54	312	296	342
	13	51	308	68	215
	14	266	87	64	215
Calculated by MMP2 program starting from conformation B	**9**	28.1	328.4	300.7	339.7
	13	31	333	61	220
	14	256	112	68	204
Measured from model B	**9**	35	325	320	320
	13	35	325	80	200
	14	265	95	80	200
Measured from model B with some flattening boat head at C-5	**9**	35	325	305	340
	13	35	325	65	220
	14	265	95	65	220

being quite suitable for rigid four-membered rings. Therefore, the conformation of **9** is essentially $B_{2,5}$ with some flattening of the pyranose ring at c-5.

Empirical force-field calculations have proved effective for conformational analysis of 1,6-anhydro pyranoses.[17] Thus calculations using the MMP2 program were carried out for the conformational analysis of compound **9**. Starting from an input of the geometry of conformation A, the final coordinates with

the minimized total energy of 199.4 Kcal/mol was obtained. Starting from conformation B, the total energy was 83.0 Kcal/mol, indicating B is the favored conformation.

Torsion angles $\phi_{3,4}$ (301°) and $\phi_{4,5}$ (340°) calculated from conformation B by the MMP2 program and those of 296° and 342° respectively, obtained by the modified Karplus equation were in good agreement. All of the theoretically calculated proton-proton torsion angles were very close to the values measured from model B with some flattening at C-5. For comparison, similar conformational analyses of 1,3-anhydro-2,4-di-*O*-benzyl-6-deoxy-ß-**D**-glucopyranose[11] **(13)** and 1,3-anhydro-2,4-di-*O*-benzyl-ß-**D**-rhamnopyranose[2] **(14)** were performed by MMP2 program calculations. Results from calculations of the torsion angles $\phi_{3,4}$ and $\phi_{4,5}$ for compounds **13** and **14** were also consistent with the results obtained by ^{1}H NMR spectrometry in conjunction with the modified Karplus equation.[14] The calculations using MMP2 for all of the torsion angles were very close to those measured from the model.

Therefore, it is reasonable to conclude that the MMP2 program is effective for conformational analysis of 1,3-anhydropyranoses **9**, **13** and **14**, and that the coordinates obtained from theoretical calculations could represent the true conformation. The data calculated by MMP2 program indicated that compounds **9**, **13** and **14** basically adopted the same conformation. From the bond angles O5-C1-C2 (116.5°), C2-C3-C4 (113.0°), O5-C1-O1 (109.4°), and O1-C3-C4 (107.0°) for compound **9** and the corresponding bond angles 117.0°, 113.8°, 109.5°, and 105.9° for compound **13**, it was seen clearly that C-2 was flattened compared to the normal boat conformation. The corresponding bond angles for compound **14** (113.0°, 111.6°, 107.9°, 105.4° respectively) indicated that the flattening of C-2 in **14** was less than in compounds **9** and **13**. This may be caused by the interaction of the endo-axial BnO group at C-2 with C-5-H in **9** and **13**, leading to flattening at both C-2 and C-5, and puckering at O-1. The non-bond distances, ring torsion angles and the asymmetry parameters[18] also confirmed the little

difference in conformations for compounds **9**, **13**, and **14**. The asymmetry parameters $\Delta C_{2(3-4)}$ for the 1,3-dioxane chair ring of compounds **9**, **13**, and **14** were 67.2°, 68.7° and 58.5° and $\Delta C_{s(3-4)}$ for the fucopyranose boat ring of compounds **9**, **13** and **14** were 62.5°, 63.9° and 58.9°, respectively.

EXPERIMENTAL

General methods. Melting points were determined with a "Mel-Temp" apparatus. Optical rotations were determined with a Perkin-Elmer model 241-MC automatic polarimeter for solutions in a 1-dm, jacketed cell. ^{1}H and ^{13}C NMR spectra were recorded with Varian XL-400 and Varian XL-200 spectrometers, 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. Mass spectra were recorded with a JMS-D 3005 mass spectrometer by using a direct-insertion technique to introduce the samples. 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) or Lichrosorb-NH_2 (4.6 x 250 mm), a differential refractometer (Model 1107L, made by LDC, Division of Milton Roy Company, Florida, U.S.A.), and ethyl 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). Solutions were concentrated at a temperature <50 °C under diminished pressure

Methyl 3-O-Allyl-α-D-fucopyranose (2). A solution of D-fucopyranose (3.75 g, 23 mmol; prepared from galactose[8]) in absolute methanol (40 mL) was boiled under reflux with Dowex-50 resin (H^+ form, 3g) for 2 days. The Dowex resin was filtered off, the combined filtrate and washings concentrated *in vacuo*,

and the solid residue crystallized from ethanol to yield white crystals of compound **1** (1.61 g, 40%); mp 156-157 °C ;lit.[19] mp 157-158 °C.

A mixture of **1** (1.78 g, 10 mmol) and dibutyltin oxide (2.74 g, 11 mmol) in absolute methanol (80 mL) was boiled under reflux until the mixture became transparent. The solution was concentrated to give a white foamy residue. Tetrabutylammonium iodide (3.70 g, 10 mmol), allyl bromide (10.2 mL, 120 mmol) and toluene (100 mL) were added to the residue and the mixture was stirred for 1 day at 60 °C. TLC (ethyl acetate) showed the presence of major product **2** together with a small amount of the starting material **1** and a little of the di-*O*-allylated compound as a by-product. After evaporation of the solvent, most of tetrabutylammonium iodide was recovered from the residue by precipitation with ethyl acetate. The brownish residue was purified by chromatography on a column of silica gel (1:1 ethyl acetate-petroleum ether) to afford yellowish crystals of **2** (1.45 g, 67%). Decolorization of the crude product with silica gel gave **2** as white crystals: mp 43.5-45 °C; $[\alpha]^{20}$ +180.3° (*c* 8.9, chloroform); ^{1}H NMR δ 5.87-5.79 (m, 1H, CH_2=C*H*-), 5.22-5.06 (m, 2H, CH_2=CH-), 4.66 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.08-3.43 (m, 6H, CH_2=CH-CH_2-, H-2, 3, 4, 5), 3.31 (s, 3H, OCH_3), 1.20 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6).

Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.05; H, 8.26. Found: C, 54.69; H, 7.89.

Methyl 3-O-Allyl-2,4-di-O-benzyl-α-D-fucopyranoside(3). To a solution of **2** (1.09 g, 5 mmol) in dry oxolane cooled in an ice bath was added sodium hydride (80% in oil; 450 mg, 15 mmol) with stirring. Benzyl bromide (1.33 mL, 11 mmol) was added dropwise to the mixture and the mixture was boiled under reflux with vigorous agitation for 4 h. TLC (1:4 ethyl acetate-petroleum ether) indicated the reaction to be complete. The remaining sodium hydride was filtered off and the filtrate concentrated. The residue was partitioned between water and dichloromethane, and the organic layer was dried and concentrated. Crude product **3** was obtained as a yellowish syrup, yield 1.98 g, 99%. Column chromatography (1:5 ethyl

acetate-petroleum ether) gave **3**: $[\alpha]^{20}$ +39.9° (*c* 6.7, chloroform); ^{13}C NMR δ 142.35, 131.76, 131.65, 131.47, 131.07 (Ph-C), 138.90 (CH_2=*C*H-), 119.65 (*C*H_2=CH-), 102.45 (C-1), 82.62, 81.45, 79.76 (C-2, 3, 4), 78.30, 75.43 (2*C*H_2Ph, CH_2=CH-*C*H_2-), 69.64 (C-5), 58.70 (O*C*H_3), 20.15 (C-6).

Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.36; H 7.54. Found: C, 72.27; H, 7.34.

3-O-Allyl-2,4-di-O-benzyl-D-fucopyranose (4). A mixture of **3** (1.57 g, 3.94 mmol), acetic acid (80%, 36 mL) and hydrochloric acid (1 N, 12 mL) was boiled under reflux for 1 h, at which time TLC (1:2 ethyl acetate-petroleum ether) showed that all of the starting material was gone. The mixture was extracted with dichloromethane, washed with saturated sodium hydrogencarbonate and then water, and concentrated to a syrup. Purification of the syrup by column chromatography (1:2 ethyl acetate-petroleum ether) yielded white crystals **4** (1.28 g, 85%): mp 58.5-60 °C; $[\alpha]^{20}$ + 16.5° (*c* 8.0, chloroform); ^{1}H NMR δ 7.50-7.22 (m, 10H, 2 Ph-H), 6.00-5.91 (m, 1H, CH_2=C*H*-), 5.34, 5.18 (q, 1H, d, 1H, C*H*$_2$=CH-CH$_2$-), 5.23 (d, 0.63H, $J_{1,2}$ = 3.66 Hz, H-1 of α anomer), 4.97-4.63 (m, 4H, 2 C*H*$_2$Ph), 4.57 (d, 0.37H, $J_{1,2}$ = 7.12 Hz, H-1 of ß anomer), 4.30 (m, 2H, CH_2=CH-C*H*$_2$-), 4.08 (d, 0.63H, $J_{5,6}$ = 6.71 Hz, H-5 of α anomer), 3.97 (dd, 0.63H, $J_{2,3}$ = 9.7 Hz, $J_{3,4}$ = 3.67 Hz, H-3 of α anomer), 3.79 (dd, 0.63H, $J_{1,2}$ = 3.33 Hz, $J_{2,3}$ = 9.63 Hz, H-2 of α anomer), 3.62 (d, 0.63H, $J_{3,4}$ = 2.92 Hz, H-4 of α anomer), 3.69 -3.40 (m, 0.37H, H-2, 3, 4, 5 for ß anomer), 1.18 (d, 1.11H, $J_{5,6}$ = 6,98 Hz, H-6 for ß anomer), 1.13 (d, 1.89H, $J_{5,6}$ = 6.85 Hz, H-6 for α anomer).

Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.88; H, 7.29. Found: C, 71.50; H, 7.39.

2,4-Di-O-Benzyl-D-fucopyranose (5). Compound **4** (1.07 g, 2.8 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 and the reaction was monitored by TLC (1:1 ethyl acetate-petroleum ether) until all of the starting material was consumed. The

mixture was filtered and the filtrate concentrated to give yellowish crystals. Recrystallization of the crude product from ethyl acetate-petroleum ether afforded **5** as white crystals (787 mg, 82 %); mp 132-133.5 °C; $[\alpha]^{20}$ +67.7° (*c* 3.9, chloroform); ^{1}H NMR δ 7.41-7.27 (m, 10H, 2Ph-H), 5.30 (d, 0.64H, $J_{1,2}$ = 3.8 Hz, H-1 of α anomer), 5.01-4.71 (m, 4H, 2C*H*$_2$-Ph), 4.64 (d, 0.36H, $J_{1,2}$ = 7.2 Hz, H-1 of ß anomer), 4.17 (q, 0.64H, $J_{5,6}$ = 6.9 Hz, H-5 of α anomer), 4.03 (dd, 0.64H, $J_{2,3}$ = 10.3 Hz, $J_{3,4}$ = 3.2 Hz, H-3 of α anomer), 3.78 (dd, 0.64H, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 10.3 Hz, H-2 of α anomer), 3.67 (d, 0.64H, $J_{3,4}$ = 3.2 Hz, H-4 of α anomer), 3.66-3.50 (m, 0.36H, H-2, 3, 4, 5 for ß anomer), 1.62 (bs, 2H, 2O*H*), 1.27 (d, 1.08H, $J_{5,6}$ = 5.9 Hz, H-6 of ß anomer), 1.22 (d, 1.92H, $J_{5,6}$ = 6.9 Hz, H-6 of α anomer).

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.77; H, 6.98. Found: C, 69.61; H, 7.29.

1,3-Di-O-acetyl-2,4-di-O-benzyl-D-fucopyranose (6). Compound **5** (357 mg, 1.04 mmol) was treated with acetic anhydride (1.5 mL) and pyridine (3 mL) by a standard method. Compound **6** was obtained in a quantitative yield as a syrupy mixture of α and ß forms in a ratio of 2:1: $[\alpha]^{20}$ +109.7° (*c* 6.4, chloroform); ^{1}H NMR δ 7.33-7.29 (m, 10H, 2Ph-H), 6.38(d, 0.70H, $J_{1,2}$ = 3.82 Hz, H-1 of α anomer), 5.59 (d, 0.30H, $J_{1,2}$ = 7.8 Hz, H-1 of ß anomer), 5.20 (dd, 0.70H, $J_{2,3}$ = 11.46 Hz, $J_{3,4}$ = 3.12 Hz, H-3 of α anomer), 4.91 (dd, 0.30H, $J_{2,3}$ = 10.58 Hz, $J_{3,4}$ = 3.02 Hz, H-3 of ß anomer), 4.70-3.80 (m, 7H, 2C*H*$_2$-Ph, H-2, 4, 5), 2.12 (s, 2.1H, C*H*$_3$CO-1 for α anomer), 2.05 (s , 0.9H, C*H*$_3$CO-1 for ß anomer), 1.98 (s, 2.1H, C*H*$_3$CO-3 for α anomer), 1.92(s, 0.9H, C*H*$_3$CO-3 for ß anomer).

Anal. Calcd for $C_{24}H_{28}O_7$: C, 67.29; H, 6.54. Found: C, 67.29; H, 6.46.

3-O-Acetyl-2,4-di-O-benzyl-α-D-fucopyranosyl chloride (7). A solution of compound **6** (105 mg, 0.25 mmol) in dry diethyl ether (10 mL) was saturated with hydrogen chloride gas under a nitrogen atmosphere at 0 °C and the solution was kept at room temperature in a sealed bottle for 2 h. TLC (1:3 ethyl

acetate-petroleum ether) indicated the reaction to be complete. The solution was concentrated to a syrup which was dissolved in dichloromethane (1 mL), and the solvent evaporated. This procedure was repeated for 6-7 times. The product was then purified by analytical LC (1:3 ethyl acetate-petroleum ether) to give **7** (80 mg, 81%): $[\alpha]^{20}$ +155.5° (*c* 4.7, chloroform); ^{1}H NMR δ 7.35-7.28 (m, 10H, 2Ph-H), 6.13 (d, 1H, $J_{1,2}$ = 3.50 Hz H-1), 5.26 (dd, 1H, $J_{2,3}$ = 10.45 Hz, $J_{3,4}$ = 2.24 Hz, H-3), 4.71-4.55 (m, 4H, 2 C*H*$_2$Ph), 4.29 (q, 1H, $J_{5,6}$ = 5.97 Hz, H-5), 4.17 (dd, 1H, $J_{1,2}$ = 4,14 Hz, $J_{2,3}$ = 9.83 Hz, H-2), 3.83 (d, 1H, $J_{3,4}$ = 2.91 Hz, H-4), 2.00 (s, 3H, C*H*$_3$CO-1), 1.20 (d, 3H, $J_{5,6}$ = 5.77 Hz, H-6).

Anal. Calcd for $C_{22}H_{25}ClO_5$: C, 65.27; H, 6.22. Found: C, 64.96; H, 6.42.

1,3-Anhydro-2,4-di-O-benzyl-ß-D-fucopyranose (9). (a) To a solution of compound **7** (67 mg, o.17 mmol) in dry oxolane (3 mL) was added potassium *tert*-butoxide (92 mg, 0.82 mmol), and the mixture was stirred at room temperature. After 1 h the reaction was complete as indicated by TLC (1:3 ethyl acetate-petroleum ether). After evaporation of the solvent, petroleum ether was added, and the solid formed was separated by centrifugation and washed with petroleum ether. The combined supernatant and washings were concentrated to a syrup. Purification of the syrup by analytical LC (with Lichrosorb-NH_2 column, 1:3 ethyl acetate-petroleum ether) afforded **9** (47 mg, 87%): $[\alpha]^{20}$ + 6.2° (*c* 2.2, chloroform); ^{1}H NMR δ 7.36-7.26 (m, 10H, 2Ph-H), 5.52 (t, 1H, $J_{1,2}$ = $J_{1,3}$ = 3.48 Hz, H-1), 4.94 (m, 1H, $J_{4,5}$ = 5.77 Hz, $J_{5,6}$ = 7.23 Hz, H-5), 4.74 (m, 1H, $J_{1,3}$ = 3.48 Hz, $J_{2,3}$ = 5.63 Hz, $J_{3,4}$ = 1.93 Hz, H-3), 4.65-4.46 (m, 4H, 2C*H*$_2$Ph), 4.52 (m, 1H, $J_{1,2}$ = 3.48 Hz, $J_{2,3}$ = 5.63 Hz, H-2, 3.64 (q, 1H, $J_{3,4}$ = 1.93 Hz, $J_{4,5}$ = 5.77 Hz, H-4), 1.36 (d, 1H, $J_{5,6}$ = 7.23 Hz, H-6); MS m/z 326 (M^+), 253 (BnO$^+$=CH-CH=CHOBn), 181 (C_6H_5-C$^+$H-CH_2-C_6H_5), 161 (BnO$^+$=CH-CH=C=O), 133 ($C_9H_9O^+$), 107 ($C_7H_7O^+$), and 91 (benzyl group).

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.62; H, 6.75. Found: C, 73.66; H, 6.98.

(b)To a solution of compound **7** (55 mg, 0.136 mmol) in dry oxolane (6 mL) was added lithium hydride (3 mg, 0.38 mmol) and absolute methanol (4 μL, 0.1 mmol). The mixture was boiled under reflux for 2 h under nitrogen. TLC (1:3 ethyl acetate-petroleum ether) indicated that only one fourth of **7** was converted into **8**. Additional portions of lithium hydride and methanol were added, and the reaction was continued until all of the starting material disappeared. The solid was separated by centrifugation, and the residue was extracted with petroleum ether. After concentration of the combined supernatant liquor and washings, 2,4-di-*O*-benzyl-α-D-fucopyranosyl chloride **(8)** was obtained as a syrup: ^{1}H NMR δ 7.38-7.28 (m, 10H, 2Ph-H), 6.21 (d, 1H, $J_{1,2}$ = 3.21 Hz, H-1), 4.92-4.58 (m, 4H, 2CH_2Ph), 4.22 (q, 1H, $J_{5,6}$ = 6.59 Hz, H-5), 4.14 (q, 1H, $J_{2,3}$ = 9.75 Hz, $J_{3,4}$ = 2.91 Hz, H-3), 3.99 (q, 1H, $J_{1,2}$ = 3.2 Hz, $J_{2,3}$ = 9.77 Hz, H-2), 3.71 (m, 1H, H-4), 1.23 (d, 1H, $J_{5,6}$ = 6.18 Hz, H-6).

The crude product **8** was dissolved in dry oxolane (3 mL), sodium hydride (80% in oil; 20 mg, 0.67 mmol) was added to the solution and the mixture was boiled under reflux. After 3 h, the reaction was complete as indicated by TLC. The solid was separated by centrifugation, and the residue was washed with petroleum ether. Compound **9** was obtained as a syrup on concentration of the supernatant liquor and washings. Purification of the syrup by analytical LC afforded pure **9** (40 mg). The overall yield from **7** was 90%.

Compound **8** was also prepared with sodium methoxide from **7**. To a solution of compound **7** (10 mg, 0.025 mmol) in dry oxolane (2 mL) was added sodium methoxide (7mg, 0.13 mmol), and the mixture was stirred at room temperature for 24 h. TLC showed that no starting material remained. Working up the mixture as described for using lithium methoxide as reagent gave **8**.

Methyl 2,4-Di-O-benzyl-α-D-fucopyranoside (10) and Methyl 2,4-Di-O-benzyl-ß-D-fucopyranoside (11) (Methanolysis of 9). Compound **9** (30 mg, 1.09 mmol) was dissolved in absolute methanol (6 mL), and boron trifluoride etherate (20 μL) was added to the solution. The mixture was stirred at room

temperature for 20 min when TLC indicated all of the starting material was consumed. The solvent was evaporated and water was added to the residue. The mixture was extracted with dichloromethane and the extracts were combined, dried and concentrated. Analytical LC (1:3 ethyl acetate-petroleum ether) of the syrup gave **10** and **11** in a ratio of 3:1.

Compound **10** with a smaller Rf value was a syrup: ^{1}H NMR δ 7.40-7.25 (m, 10H, 2Ph-H), 4.90-4.60 (m, 4H, 2CH_2Ph), 4.68(d, 1H, $J_{1,2}$ = 4.3 Hz, H-1), 4.06 (dd, 1H, $J_{2,3}$ = 10.1 Hz, $J_{3,4}$ = 3.8 Hz, H-3), 3.90 (q, 1H, $J_{5,6}$ = 5.8 Hz, H-5), 3.75 (dd, 1H, $J_{1,2}$ = 4.3 Hz, $J_{2,3}$ = 10.1Hz, H-2), 3.63 (d, 1H, $J_{3,4}$ = 3.8 Hz, H-4), 3.30 (s, 3H, OCH_3), 2.30 (bs, 1H, O*H*), 1.18(d, 3H, $J_{5,6}$ = 5.8 Hz, H-6).

Compound **11** with a larger Rf value was a syrup: ^{1}H NMR δ 7.40-7.25 (m, 10H, 2Ph-H), 5.00-4.62 (m, 4H, 2CH_2-Ph), 4.20 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 3.68-3.50 (m, 7H, H-2, 3, 4, 5, OCH3), 2.30 (bs, 1H, O*H*), 1.24 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6).

Methyl 3-O-Acetyl-2,4-di-O-benzyl-ß-D-fucopyranoside (12). Acetylation of **11** gave the 3-acetate **12**: ^{1}H NMR δ 7.31-7.25 (m, 10H, 2Ph-H), 4.88-4.57 (m, 5H, H-3, 2CH_2Ph), 4.29 (d 1H, $J_{1,2}$ = 8.0 Hz, H-1), 3.75 (q, 1H, $J_{5,6}$ = 7.2 Hz, H-5), 3.67 (d, 1H, $J_{3,4}$ = 3.2 Hz, H-4), 3.61 (q, 1H, $J_{1,2}$ = 8.0 Hz, $J_{2,3}$ = 11 Hz, H-2), 3.55 (s, 3H, OCH_3), 1.91 (s, 3H, CH_3CO, 1.27 (d, 1H, $J_{5,6}$ = 7.2 Hz, H-6).

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