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Synthesis, conformation, and glycosidic coupling reactions of highly active substituted 2,7-dioxabicyclo[4.1.0]heptanes: 1,2-anhydro-3,4-di-*O*-benzyl-α-D-xylopyranose †

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Abstract

The title 1,2-anhydro sugar (**8**) was synthesized from D-xylose. The key intermediate for the synthesis was 2-*O*-acetyl-3,4-di-*O*-benzyl-β-D-xylopyranosyl fluoride, which was transformed into crystalline **8** by ring closure with potassium *tert*-butoxide. Comparison of the observed vicinal coupling constants for **8** with the results obtained from calculations by molecular mechanics suggested that the conformation of the pyranose ring is close to a $^4H_5$ half chair. The anhydro sugar was highly reactive, its condensation with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose proceeding in reasonable yield without any Lewis acid catalyst, and quantitatively in the presence of molecular sieves to give the β-linked disaccharide as the major product. The stereochemical outcome of the condensation was little affected by changes in solvent or reaction temperature. The presence of some Lewis acid catalysts caused a decrement in the $\beta:\alpha$ ratio, while predominantly α-linked disaccharide was obtained when trityl perchlorate was the catalyst.

1. Introduction

In a series of earlier researches we have synthesized 1,2-anhydro-α-D-galacto- [1], -β-D- and -β-L-rhamno- [2], -6-deoxy-α-D-gluco- [3], -β-D-talo- [4], -6-deoxy-β-D-talo- [5], and -α-D-fucopyranose [6] benzyl ethers. Prior to our work, 1,2-anhydro-α-D-gluco- [7], and -β-D-mannopyranose [8] benzyl ethers were reported by Schuerch's group. These 1,2-anhydro sugar derivatives are novel monomers for the

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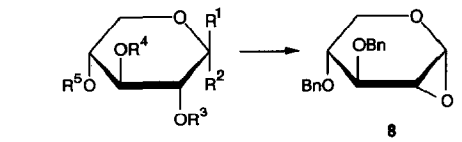

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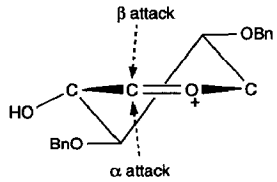
	R^1	R^2	R^3	R^4	R^5
1	H	Br	Ac	Ac	Ac
2	H	-CH(CH$_3$)O-		Ac	Ac
3	H	-CH(CH$_3$)O-		Bn	Bn
4	H	OH	H	Bn	Bn
5	H,OAc		Ac	Bn	Bn
6	H	Cl	Ac	Bn	Bn
7	F	H	Ac	Bn	Bn

	R^1	R^2	R^3
9	OMe	H	H
10	Gal	H	H
11	H	Gal	H
12	Gal	H	Ac

Gal = 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl



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Scheme 1.

preparation of the corresponding stereoregular, 1 → 2-linked polysaccharides [9], which are important model compounds for immunological research. Also they are valuable glycosyl donors for the stereospecific synthesis of oligosaccharides [10] and other useful carbohydrate derivatives [11]. Thus 1,2-anhydro-3,4-di-*O*-benzyl-α-D-xylopyranose is of interest because its stereoregular polymerization and subsequent deprotection should afford a β,1 → 2-linked D-xylopyranan, and its coupling to suitable glycosyl acceptors should give β-linked oligosaccharides containing a D-xylopyranose moiety, which are important reference substances for structure analysis [12,13]. Here we report on the synthesis, conformation, and glycosidic coupling reactions of this xylose derivative.

2. Results and discussion

3,4-Di-*O*-acetyl-1,2-*O*-[(*R*,*S*)-ethylidene]-α-D-xylopyranose (**2**, *R* isomer predominant) was prepared from D-xylose via the intermediate 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (**1**) by a reported method [14] (Scheme 1). Benzylation of **2** with potassium hydroxide and benzyl chloride in toluene yielded 3,4-di-*O*-benzyl-1,2-*O*-[(*R*)-ethylidene]-α-D-xylopyranose (**3**). Hydrolysis of **3** with sulfuric acid in dioxane afforded 3,4-di-*O*-benzyl α-D-xylopyranose (**4**) as crystals, and subsequent acetylation of **4** with acetic anhydride in pyridine furnished the diacetate **5**. Chlorination of **5** with hydrogen chloride in diethyl ether gave 2-*O*-acetyl-3,4-di-

O-benzyl-α-D-xylopyranosyl chloride (**6**) as crystals, and this was next treated with silver fluoride to afford 2-*O*-acetyl-3,4-di-*O*-benzyl-β-D-xylopyranosyl fluoride (**7**) as the major product, together with a little α isomer. The ring closure reaction of **7** was readily carried out at room temperature with potassium *tert*-butoxide in oxolane, and crystalline 1,2-anhydro-3,4-di-*O*-benzyl-α-D-xylopyranose (**8**) was obtained in high yield. The 1,2-anhydro sugar ether was characterized by ^{1}H NMR spectroscopy, mass spectrometry, and optical rotation. The ^{1}H NMR spectrum showed an upfield peak for H-2 at δ 3.20, which is characteristic for the epoxide ring. The mass spectrum gave a molecular ion (*m/z* 312) of low intensity together with some fragmentation peaks characteristic for per-*O*-benzylated 1,2-anhydropyranoses [15]. Crystalline **8** was found to be quite stable during lengthy storage in the refrigerator, but it decomposed when subjected to X-rays. This indicates that a 1,2-anhydro pentopyranose ether is more active than 1,2-anhydro hexopyranose benzyl ethers, as the crystal structure of 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-talopyranose has been successfully determined by X-ray analysis [16].

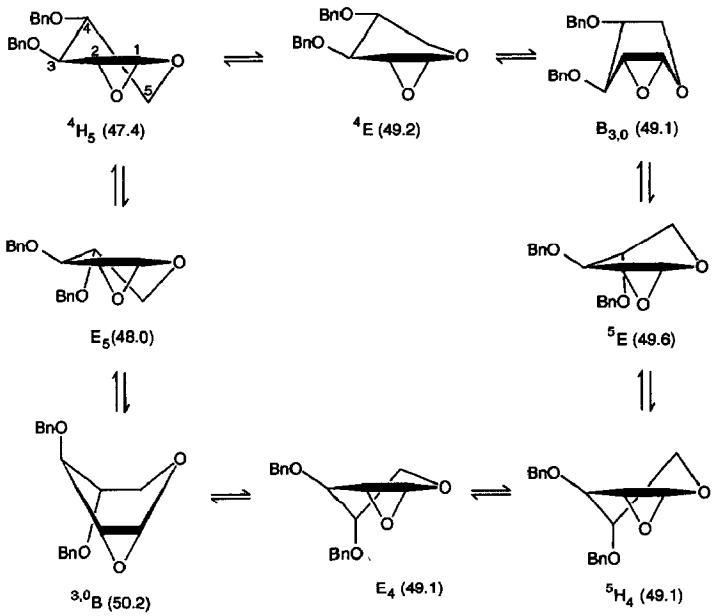
Conformational analysis of the 1,2-anhydro sugar derivative was carried out by ^{1}H NMR spectrometry in conjunction with calculations by molecular mechanics [17]. The ^{1}H NMR spectrum was fully assigned by the use of single frequency decoupling. The anomeric proton signal appeared as a doublet of doublets at δ 4.84 with $J_{1,2}$ 2.2 Hz and $J_{1,3}$ 0.7 Hz. An upfield doublet at δ 3.20 with $J_{1,2}$ 2.2 Hz was assigned to H-2. The signals at δ 3.92, 3.64, 3.53, and 3.40 were assigned to H-3, H-5, H-4, and H-5′, respectively. Large coupling constants of 9.8 Hz ($J_{4,5'}$) and 7.2 Hz ($J_{3,4}$) indicated trans-diaxial relationships between H-4 and H-5′, and H-3 and H-4.

Molecular mechanics calculations [17] were carried out for the conformations $^4H_5$, ^4E, $B_{3,o}$, ^5E, $^5H_4$, E_4, $^{3,o}B$, and E_5 involved in the probable pseudorotation [18]. As the modified Karplus equation [19] is not valid for the planar portion of the pyranose ring, tests of the calculations against experimental data were mainly based on $J_{3,4}$, $J_{4,5}$, and $J_{4,5'}$ (Table 1). It was found that the $^4H_5$ form has the lowest energy, the E_5 form an energy 0.6 kcal/mol higher, and the other forms considerably higher energies, namely 1.7 to 2.7 kcal/mol above that of the $^4H_5$ form (Scheme 2). The observed value of the vicinal coupling constant $J_{3,4}$ (7.2 Hz) was close to the value (6.8 Hz) calculated for the E_5 form, and the value of $J_{4,5'}$ (9.8 Hz) was similar to the calculated values (10.5 and 10.7 Hz) for both the $^4H_5$ and E_5 forms, while observed $J_{4,5}$ (3.2 Hz) was similar to calculated $J_{4,5}$ (3.9 Hz) of the $^4H_5$ form. Further calculation with the two torsion angles H-3–C-3–C-4–H-4 ($\phi_{3,4}$) and H-4–C-4–C-5–H-5 ($\phi_{4,5}$) fixed at values correlated to the observed coupling constants $J_{3,4}$ and $J_{4,5}$ gave a deduced conformation for **8** that is nearly $^4H_5$, with the dynamic equilibrium containing significant amounts of E_5 and lesser amounts of the other six forms shown in Scheme 2. Four of the six forms predicted by MMX to have higher energy have one of the *O*-benzyl groups axial, so those higher energies are consistent with chemical intuition. Although we feel that the agreement between prediction and experiment is good, we note that the parameterization of MMX did not include epoxide rings, which, for example, have shorter C–C bond lengths [16] than we observe in the MMX models.

Table 1
Selected torsional angles and vicinal coupling constants obtained from calculation by MMX

Angle	Magnitude (°)								
	$^4H_5$	Exp [a]	$^5H_4$	^4E	E_4	^5E	E_5	$B_{3,o}$	$^{3,o}B$
O-5-C-1-C-2-C-3	0 [b]	5	−1	0 [b]	1 [b]	1 [b]	0 [b]	0 [b]	0 [b]
C-1-C-2-C-3-C-4	−16	−15	16	−29	26	0 [b]	0 [b]	−52	46
C-2-C-3-C-4-C-5	49 [b]	46	−48 [b]	58	−54	−31	29	52	−46
C-3-C-4-C-5-O-5	−69	−69	68	−60	57	65	−59	0 [b]	0 [b]
C-4-C-5-O-5-C-1	54	58	53 [b]	30	−30	−64	60	−54	48
C-5-O-5-C-1-C-2	−20	−27	20	0 [b]	0 [b]	31	−31	56	−50
C-1-O-2-C-2-C-3	108	109	108	108	106	110	107	101	100
O-2-C-2-C-3-C-4	−81	−80	−49	−94	−39	−65	−66	−116	−19
Coupling constants (modified Karplus) for indicated torsion angles									
$J_{3,4}$ (Hz)	8.9	7.2	2.1	9.5	2.9	1.0	6.8	9.2	2.2
$\phi_{3,4}$ (°)	170	158 [b]	74	176	67	86	154	173	73
$J_{4,5'}$ (Hz)	10.5	9.8	3.4	10.7	2.6	3.4	10.7	4.6	8.8
$\phi_{4,5'}$ (°)	171	162 [b]	−55	−179	−62	−55	−178	−123	−1
$J_{4,5}$ (Hz)	3.9	3.2	0.6	5.0	1.3	0.6	5.3	9.0	4.0
$\phi_{4,5}$ (°)	−67	−72	65	−60	54	65	−57	−3.0	−119

[a] Reproduced conformation according to the experimentally determined ^{1}H NMR data. [b] Fixed torsional angle during energy minimization.



Scheme 2. Possible pseudorotation itinerary for 1,2-anhydro-3,4-di-*O*-benzyl-α-D-xylopyranose (**8**). Values in parentheses are energies in kcal/mol. Energy of reproduced conformation (see Table 1), 47.6 kcal/mol.

Table 2
The influences of solvent, temperature, and reaction time on the stereochemical outcome of the glycosidic coupling reaction [a]

Temp./Time	$\beta:\alpha$ ratios in the solvents shown					
	Oxolane	CH_2Cl_2	Et_2O	Petroleum ether	Benzene	Toluene
−76°C/4 h	2.0	2.2	2.0	2.5	–	2.2
RT/2 h	2.2	2.0	2.7	2.5	2.1	2.2
RT/10 min	2.2	2.0	2.5	2.5	2.0	2.2

[a] Reaction parameters: **8**, 10 mg (0.032 mmol); solvent 0.7 mL; 4A molecular sieves, 0.3 g; 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, 14 mg (0.054 mmol) in the same solvent, 0.3 mL. The ratios were determined by analytical LC.

Alcoholysis of **8** was conducted in absolute methanol at room temperature, quantitatively giving methyl 3,4-di-*O*-benzyl-β-D-xylopyranoside (**9**). It was interesting to find that the coupling reaction of **8** with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose in dry oxolane without any catalysts gave a fair yield of disaccharide, while an attempt at a similar reaction using 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose was unsuccessful. It was also interesting to note that the coupling reaction of **8** proceeded quantitatively in the presence of 4A molecular sieves. In either the absence or the presence of molecular sieves the produced disaccharide was a 2.5:1 mixture of β and α anomers. From this it may be supposed that the first formed intermediate in the coupling reaction is a delocalized cation (**13**). The influences of solvent, temperature, and reaction time on the coupling reaction were also investigated (see Table 2). It was found that the stereochemical outcome did not change substantially as the reaction temperature and time were varied over a wide range. It was also found that with $ZnCl_2$, TrCl, $BF_3 \cdot Et_2O$, or AgOTf as the catalyst, the $\beta:\alpha$ ratio decreased to 1.5–1.7:1 (Table 3). Trityl perchlorate was an exception, showing an inverse selectivity ($\alpha:\beta$ 2:1). Among the solvents used for the uncatalyzed reaction, diethyl ether afforded better selectivity than the others (oxolane, dichloromethane, petroleum ether, benzene, and toluene). Under all of the conditions just described, the coupling yield was quantitative (complete consumption of **8** in the presence of excess acceptor). The advantages of using 1,2-anhydroxylose benzyl ether as a glycosyl

Table 3
Influence of catalyst on the stereochemical outcome of the glycosidic coupling reaction [a]

Catalyst	$\beta:\alpha$ ratio
$BF_3 \cdot Et_2O$	1.7
AgOTf	1.5
TrCl	1.5
$ZnCl_2$	1.7
$TrClO_4$	0.5

[a] For reaction parameters see the text.

donor are thus obvious: it shows high reactivity and good selectivity, and makes the C-2 OH available for further reaction.

The major disaccharide prepared as described above was treated with acetic anhydride and the ^{1}H NMR spectrum of the acetylated product was used for further characterization. A triplet at δ 4.92 ($J_{1',2'} = J_{2',3'} = 7.3$ Hz) arose from H-2 of the xylose moiety, and the sole singlet at δ 2.02 (CH_3CO) indicated that the original disaccharide had only one free hydroxyl group. The doublet at δ 4.41 ($J_{1',2'}$ 7.3 Hz), assigned to H-1', confirmed the β-linked D-xylopyranoside structure.

3. Experimental

General methods.—Optical rotations were determined at 20°C with a Perkin–Elmer Model 241-MC automatic polarimeter. Melting points were determined with a 'Mel-Temp' apparatus and are uncorrected. ^{1}H And ^{13}C NMR spectra were recorded with Varian XL-400 and Varian XL-200 spectrometers for solutions in $CDCl_3$. Chemical shifts are given in ppm downfield from internal Me_4Si. For conformational analysis, ^{1}H NMR spectra were measured in the pulsed Fourier-transform mode at 20°C. Mass spectra were recorded with a JMS-3005 mass spectrometer, using a direct sample introduction technique. Analytical LC was carried out in stainless-steel columns packed with silica gel (10 × 150 mm or 4.6 × 250 mm) or Lichrosorb-NH_2 (4.6 × 250 mm), with peak detection by a differential refractometer (Perkin–Elmer LC-25 RI Detector). A mixture of ethyl acetate and petroleum ether (bp 60–90°C) was used as the eluent, at a flow rate of 1 to 4 mL min^{-1}. TLC was performed on Silica gels G and HF, with detection either by charring with 30% (v/v) H_2SO_4 in MeOH or by UV light. Preparative chromatography was performed on columns (16 × 240, 18 × 300, and 35 × 400 mm) of silica gel (120–200 mesh).

Calculations by molecular mechanics [17] were carried out using the MMX program [20] embedded in PCMODEL-386 on an AST-386 computer. The dielectric constant used throughout the calculations was 1.5. Each calculated total energy consisted of stretching, bending, stretching–bending, torsional, van der Waals, and dipole–dipole contributions. Calculations of each individual conformation involved in the pseudorotation from $^4H_5$ to $^5H_4$ were carried out with two fixed torsional angles that were different for the *E*, *B*, and *H* forms. As two torsion angles do not completely determine the conformation of a pyranose ring, one or two additional torsion angles were adjusted to the expected before minimization. During energy minimization the conformation of the pyranose ring sometimes changed from the desired form to another one, e.g., from E_4 to ^4E, or from $^{3,o}B$ to $B_{3,o}$. In that case, we adjusted additional angles and minimized the energy again. This procedure was repeated until the desired shape was reached. The minimum energy for each depicted conformation was obtained from the calculations with about 10 different side-chain conformations.

3,4-Di-O-acetyl-1,2-O-[(R,S)-ethylidene]-α-D-xylopyranose (**2**).—To a solution of 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (11.6 g, 34.3 mmol, prepared by a

standard method [21]) in anhyd MeCN (70 mL) was added tetrabutylammonium iodide (5 g, 13.6 mmol) and $NaBH_4$ (2.1 g, 56.8 mmol) at 0°C. Then the mixture was stirred for 18 h at room temperature, at the end of which time TLC (2:1 petroleum ether–EtOAc) indicated that the reaction was complete. Filtration then concentration of the filtrate gave a residue that was diluted with CH_2Cl_2 (50 mL). The solution was washed with water (3 × 30 mL) and concentrated to give a syrup. Column chromatography (2:1 petroleum ether–EtOAc) of the syrup afforded **2** as a mixture (7.8 g, 87%) consisting of predominantly the *R* isomer along with a small amount of *S* isomer; $[\alpha]_D$ +7.8° (*c* 4.5, $CHCl_3$); ^1H NMR,signals for the *R* isomer: δ 5.44 (d, 1 H, $J_{1,2}$ 4.4 Hz, H-1), 5.24 (t, 1 H, $J_{2,3} = J_{3,4} = 2.9$ Hz, H-3), 5.13 (q, 1 H, *J* 4.9 Hz, CH_3CH), 4.92–4.76 (m, 1 H, H-4), 4.14–3.68 (m, 3 H, H-2,5), 2.10, 2.09 (2 s, 6 H, CH_3CO), and 1.52 (d, 3 H, *J* 4.9 Hz, CH_3CH); for the S isomer: δ 5.59 (q, 1 H, *J* 4.9 Hz, CH_3CH), 5.42 (d, 1 H, $J_{1,2}$ 3.1 Hz, H-1), 5.31 (dd, 1 H, $J_{2,3}$ 5.1, $J_{3,4}$ 6.1 Hz, H-3), 4.93-4.76 (m, 1 H, H-4), 4.14–3.68 (m, 3 H, H-2,5,5′), 2.10, 2.08 (2 s, 6 H, CH_3CO), and 1.39 (d, 3 H, *J* 4.9 Hz, CH_3CH). Anal. Calcd for $C_{11}H_{16}O_7$: C, 50.77; H, 6.15. Found: C, 51.16; H,6.00.

3,4-Di-O-benzyl-1,2-O-[(R)-ethylidene]-α-D-xylopyranose (**3**).—To a solution of **2** (7.6 g, 29.2 mmol) in toluene (60 mL) was added, with vigorous stirring, finely powdered KOH (12 g). The mixture was boiled under reflux, and benzyl chloride (12 mL, 104 mmol) was added dropwise during 10 min. Boiling under reflux with vigorous agitation was continued for 2 h, at the end of which time TLC (3:1 petroleum ether–EtOAc) indicated that the benzylation was complete. Without neutralization or evaporation the mixture was subjected to steam distillation to remove excess benzyl chloride and byproduct dibenzyl ether, and then extracted with CH_2Cl_2. The organic layer was concentrated to a syrup that was purified by column chromatography with 4:1 petroleum ether–EtOAc as the eluent to give syrupy **3** (9.5 g, 91%); $[\alpha]_D$ +85° (*c* 0.3, $CHCl_3$); ^1H NMR: δ 7.33–7.25 (m, 10 H, Ph), 5.43 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 5.10 (q, 1 H, *J* 4.9 Hz, CH_3CH), 4.66, 4.58 (2 d, 2 H, *J* 10.8 Hz, CH_2Ph), 4.64, 4.55 (2 d, 2 H, *J* 10.8 Hz, CH_2Ph), 4.04 (dd, 1 H, $J_{1,2}$ 5.0, $J_{2,3}$ 4.2 Hz, H-2), 3.88 (dd, 1 H, $J_{3,4}$ 2.6, $J_{2,3}$ 4.2 Hz, H-3), 3.80 (dd, 1 H, $J_{5,5'}$ 9.5, $J_{4,5}$ 5.0 Hz, H-5), 3.71 (t, 1 H, $J_{4,5'} = J_{5,5'} = 9.5$ Hz, H-5′), 3.70–3.67 (m, 1 H, H-4), and 1.47 (d, 3 H, *J* 4.9 Hz, CH_3CH). Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.79; H, 6.74. Found: C, 70.77; H, 6.65.

3,4-Di-O-benzyl-α-D-xylopyranose (**4**).—To a solution of **3** (9 g, 25 mmol) in dioxane (50 mL) was added 1 M H_2SO_4 (5 mL), and the mixture was boiled under reflux with stirring for 4.5 h, at the end of which time TLC (2:1 petroleum ether–EtOAc) indicated that the reaction was complete. The mixture was carefully neutralized with solid $NaHCO_3$, and then concentrated to a syrup that was partitioned between water and CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated to give **4** as a white solid. Purification by column chromatography with 2:1 petroleum ether–EtOAc as the eluent furnished **4** as white crystals (7 g, 84%); mp 135–136°C; $[\alpha]_D$ −26° (*c* 2.0, $CHCl_3$); ^1H NMR: δ 7.33–7.25 (m, 10 H, Ph), 4.95 (s, 1 H, H-1), 4.69–4.52 (m, 4 H, 2 CH_2Ph), and 4.14–3.47 (m, 5 H, H-2,3,4,5). Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.09; H, 6.67. Found: C, 69.11; H, 6.88.

1,2-Di-O-acetyl-3,4-di-O-benzyl-α,β-D-xylopyranose (**5**).—Acetylation of **4** (1.0 g,

3.0 mmol) with pyridine (5 mL) and Ac_2O (4 mL) at room temperature for 4 h gave **5** in a quantitative yield as a syrup consisting predominantly of the α anomer together with a trace of the β anomer; $[\alpha]_D$ +127° (*c* 0.7, $CHCl_3$); ^1H NMR, signals for the α anomer: δ 7.37–7.24 (m, 10 H, Ph), 6.18 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.96 (dd, 1 H, $J_{1,2}$ 3.6, $J_{2,3}$ 9.8 Hz, H-2), 4.88, 4.74 (2 d, 2 H, *J* 11.3 Hz, CH_2Ph), 4.75, 4.64 (2 d, 2 H, *J* 11.5 Hz, CH_2Ph), 3.90 (dd, 1 H, $J_{2,3}$ 9.8, $J_{3,4}$ 9.2 Hz, H-3), 3.81 (dd, 1 H, $J_{4,5}$ 4.4, $J_{5,5'}$ 9.8 Hz, H-5), 3.74–3.68 (m, 1 H, H-4), 3.66 (t, 1 H, $J_{4,5'} = J_{5,5'} = 9.8$ Hz, H-5'), 2.13, and 1.98 (2 s, 6 H, CH_3CO); for the β anomer: δ 5.58 (d, 1 H, $J_{1,2}$ 9.8 Hz, H-1), 5.11 (t, 1 H, $J_{1,2} = J_{2,3} = 9.8$ Hz, H-2), and 3.23 (t, 1 H, $J_{3,4} = J_{4,5} = 9.8$ Hz, H-4). Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.67; H, 6.28. Found: C, 66.50; H, 6.34.

2-O-Acetyl-3,4-di-O-benzyl-α-D-xylopyranosyl chloride (**6**).—A solution of **5** (828 mg, 2 mmol) in dry diethyl ether (20 mL) was saturated with HCl gas under N_2 at 0°C. Then the solution was kept at room temperature in a sealed bottle for 2.5 h, at the end of which time TLC (3:1 petroleum ether–EtOAc) indicated that the reaction was complete. The solution was concentrated under reduced pressure to give white crystals (700 mg, 90%); mp 83–84°C; $[\alpha]_D$ +202° (*c* 0.8, $CHCl_3$); ^1H NMR: δ 7.36–7.26 (m, 10 H, Ph), 6.20 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.85 (dd, 1 H, $J_{1,2}$ 3.4, $J_{2,3}$ 9.4 Hz, H-2), 4.88, 4.76 (2 d, 2 H, *J* 11.5 Hz, CH_2Ph), 4.76, 4.64 (2 d, *J* 11.2 Hz, CH_2Ph), 3.99 (t, 1 H, $J_{2,3} = J_{3,4} = 9.4$ Hz, H-3), 3.85 (d, 2 H, $J_{4,5}$ 9.4 Hz, H-5), 3.69 (m, 1 H, $J_{3,4}$ 9.4, $J_{4,5}$ 9.4 Hz, H-4), and 2.06 (s, 3 H, CH_3CO). Anal. Calcd for $C_{21}H_{23}ClO_5$: C, 64.53; H, 5.89. Found: C, 64.75; H,6.03.

2-O-Acetyl-3,4-di-O-benzyl-β-D-xylopyranosyl fluoride (**7**).—To a solution of **6** (650 mg, 1.7 mmol) in 2:5 MeCN–benzene (15 mL) was added solid AgF (300 mg, 2.4 mmol), causing a white precipitate of AgCl to form immediately. The mixture was stirred vigorously in the dark for 16 h at room temperature, then centrifuged, and the pellet was washed repeatedly with CH_2Cl_2. The combined washings and supernatant liquor were concentrated to give a syrup. Purification by column chromatography (3.5:1 petroleum ether–EtOAc) yielded syrupy **7** (530 mg, 85%); $[\alpha]_D$ +18.6° (*c* 3.8, $CHCl_3$); ^1H NMR: δ 7.36–7.25 (m, 10 H, Ph), 5.41 (dd, 1 H, $J_{1,F}$ 52, $J_{1,2}$ 3.7 Hz, H-1), 5.04 (m, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 8.6, $J_{2,F}$ 4.9 Hz, H-2), 4.76, 4.64 (2 d, 2 H, *J* 12.2 Hz, CH_2Ph), 4.48 (s, 2 H, CH_2Ph), 4.19 (dd, 1 H, $J_{4,5}$ 4.0, $J_{5,5'}$ 12.2 Hz, H-5), 3.76–3.56 (m, 3 H, H-3,4,5'), and 2.05 (s, 3 H, CH_3CO). Anal. Calcd for $C_{21}H_{23}FO_5$: C, 67.38; H, 6.15. Found: C, 67.22; H, 6.28.

1,2-Anhydro-3,4-di-O-benzyl-α-D-xylopyranose (**8**).—To a solution of **7** (500 mg, 1.3 mmol) in dry oxolane was added potassium *tert*-butoxide (310 mg, 2.8 mmol), and the mixture was stirred at room temperature for 6 h, at the end of which time TLC (3:1 petroleum ether–EtOAc), indicated that the starting material had disappeared. Then the mixture was concentrated to dryness, and the residue was repeatedly extracted with 3:1 petroleum ether–EtOAc. Concentration of the combined extracts yielded **8** as white crystals (365 mg, 87%); mp 43–44°C; $[\alpha]_D$ −5.6° (*c* 0.5, $CHCl_3$); ^1H NMR: δ 7.37–7.25 (m, 10 H, Ph), 4.84 (dd, 1 H, $J_{1,2}$ 2.2, $J_{1,3}$ 0.7 Hz, H-1), 4.80, 4.73 (2 d, 2 H, *J* 11.0 Hz, CH_2Ph), 4.70, 4.62 (2 d, 2 H, *J* 12.3 Hz, CH_2Ph), 3.92 (dd, 1 H, $J_{1,3}$ 0.7, $J_{3,4}$ 7.2 Hz, H-3), 3.64 (dd, 1 H, $J_{4,5}$ 3.2, $J_{5,5'}$ 9.5 Hz, H-5), 3.53 (m, 1 H, $J_{3,4}$ 7.2, $J_{4,5}$ 3.2, $J_{4,5'}$ 9.8 Hz, H-4), 3.40 (dd, 1 H,

$J_{4,5'}$ 9.8, $J_{5,5'}$ 9.5 Hz, H-5'), and 3.20 (d, 1 H, $J_{1,2}$ 2.2 Hz, H-2); MS: m/z 312 (M^+), 221 ($M^+ - Bn$), 149, 107, and 91. Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.08; H, 6.41. Found: C, 73.07; H, 6.49.

Methyl 3,4-di-O-benzyl-β-D-xylopyranoside (**9**).—Compound **8** (20 mg, 0.064 mmol) was dissolved in anhyd MeOH (2 mL) and the solution was kept for 20 min at room temperature. TLC (2:1 petroleum ether–EtOAc) indicated that the reaction was complete. The solution was concentrated to afford **9** quantitatively as white crystals; mp 95–96°C; $[\alpha]_D$ −50° (*c* 0.3, $CHCl_3$); ^1H NMR: δ 7.37–7.28 (m, 10 H, Ph), 4.86, 4.82 (2 d, 2 H, *J* 11.3 Hz, CH_2Ph), 4.70, 4.63 (2 d, 2 H, *J* 11.3 Hz, CH_2Ph), 4.24 (d, 1 H, $J_{1,2}$ 7.4 Hz, H-1), 3.99 (bd, 1 H, $J_{5,5'}$ 11.3 Hz, H-5), 3.60–3.52 (m, 3 H, H-2,4,5'), 3.51 (s, 3 H, CH_3O), 3.34 (t, 1 H, $J_{2,3} = J_{3,4} = 9.9$ Hz, H-3), and 2.25 (bs, 1 H, O*H*). Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.77; H, 6.98. Found: C, 69.72; H, 7.08.

O-(3,4-Di-O-benzyl-β-D-xylopyranosyl)-(1 → 6)-1,2 : 3,4-di-O-isopropylidene-α-D-galactopyranose (**10**).–The 1,2-anhydro sugar ether (20 mg, 0.064 mmol) was dissolved in anhyd diethyl ether (1.5 mL), and 4A molecular sieves (0.3 g) was added. To this was added a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (28 mg, 0.11 mmol) in diethyl ether (1 mL), all at once. The mixture was stirred at room temperature for 2 h, at the end of which time TLC (2:1 petroleum ether–EtOAc) indicated that the anhydro sugar ether had disappeared. Then the solution was concentrated to a syrup that was subjected to separation by analytical LC with 2:1 petroleum ether–EtOAc as the eluent, and syrupy **10** was obtained as the major product (26.5 mg, 72%); $[\alpha]_D$ −57.7° (*c* 2.1, $CHCl_3$); ^1H NMR: δ 7.43–7.28 (m, 10 H, Ph), 5.54 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 4.93, 4.80 (2 d, 2 H, *J* 11.7 Hz, CH_2Ph), 4.72, 4.60 (2 d, 2 H, *J* 11.7 Hz, CH_2Ph), 4.58 (dd, 1 H, $J_{2,3}$ 2.3, $J_{3,4}$ 8.1 Hz, H-3), 4.38 (bd, 1 H, $J_{1',2'}$ 7.3 Hz, H-1'), 4.32 (dd, 1 H, $J_{1,2}$ 5.0, $J_{2,3}$ 2.3 Hz, H-2), 4.20 (dd, 1 H, $J_{3,4}$ 8.1, $J_{4,5}$ 1.2 Hz, H-4), 4.06–3.92 (m, 3 H, H-5,6a,6b), 3.80–3.74 (m, 4 H, H-2',4',5'a,5'b), 3.30 (dd, 1 H, $J_{2',3'}$ 7.3, $J_{3',4'}$ 8.4 Hz, H-3'), 2.68 (bs, 1 H, O*H*), 1.55, 1.46, 1.35, and 1.34 (4 s, 12 H,CCH_3). Anal. Calcd for $C_{31}H_{40}O_{10}$: C, 65.02; H, 6.99. Found: C, 65.00; H, 7.20.

Syrupy *O*-(3,4-di-*O*-benzyl-α-D-xylopyranosyl)-(1 → 6)-1,2 : 3,4-di-*O*-isopropylidene-α-D-galactopyranose (**11**) was obtained as the minor product (10.1 mg, 27%); ^1H NMR: δ 7.40–7.26 (m, 10 H, Ph), 5.53 (d, 1 H, $J_{1,2}$ 4.9 Hz, H-1), 4.91, 4.84 (2 d, 2 H, *J* 11.2 Hz, CH_2Ph), 4.83 (d, 1 H, $J_{1',2'}$ 3.2 Hz, H-1'), 4.73, 4.61 (2 d, 2 H, *J* 11.7 Hz, CH_2Ph), 4.63 (dd, 1 H, $J_{2,3}$ 2.4, $J_{3,4}$ 7.6 Hz, H-3), 4.33 (dd, 1 H, $J_{1,2}$ 4.9, $J_{2,3}$ 2.4 Hz, H-2), 4.27 (dd, 1 H, $J_{3,4}$ 7.6, $J_{4,5}$ 1.7 Hz, H-4), 4.00–3.84 (m, 3 H, H-5,6a,6b), 3.75–3.51 (m, 5 H, H-2',3',4',5'a,5'b), 1.88 (bs, 1 H, O*H*), 1.55, 1.46, 1.36, and 1.36 (4 s, 12 H, CCH_3).

The glycosidic coupling reaction in the absence of 4A molecular sieves was carried out in the same way as just described, and a 2.5:1 mixture of **10** and **11** was obtained in a total yield of 60%.

The glycosidic coupling reaction in the presence of Lewis-acid catalysts was carried out as follows: to a solution of **8** (10 mg, 0.032 mmol) in dry diethyl ether (0.7 mL) was added a mixture of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (14 mg, 0.054 mmol) and catalyst (0.04 mmol) in diethyl ether (0.3 mL), all at once.

The mixture was stirred at room temperature for 1 h. Then the solution was concentrated to a syrup that was partitioned between water and CH_2Cl_2. The organic layer was dried and concentrated to a syrup that was subjected to analysis by analytical LC with 2:1 petroleum ether-EtOAc as the eluent.

O-(2-O-Acetyl-3,4-di-O-benzyl-β-D-xylopyranosyl)-(1 → 6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**12**).—Compound **10** (20 mg, 0.035 mmol) was acetylated with Ac_2O (0.6 mL) in pyridine (1 mL) by the standard method to afford **12** (21 mg, 98%) as a syrup after workup of the mixture; $[\alpha]_D$ −42° (*c* 1.8, $CHCl_3$); ^1H NMR: δ 7.36–7.28 (m, 10 H, Ph), 5.50 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 4.92 (t, 1 H, $J_{1',2'} = J_{2',3'} = 7.3$ Hz, H-2'), 4.82, 4.67 (2 d, 2 H, *J* 11.5 Hz, CH_2Ph), 4.70, 4.60 (2 d, 2 H, *J* 11.4 Hz, CH_2Ph), 4.56 (dd, 1 H, $J_{2,3}$ 2.4, $J_{3,4}$ 7.7 Hz, H-3), 4.41 (d, 1 H, $J_{1',2'}$ 7.3 Hz, H-1'), 4.27 (dd, 1 H, $J_{1,2}$ 5.0, $J_{2,3}$ 2.4 Hz, H-2), 4.16 (dd, 1 H, $J_{3,4}$ 7.7, $J_{4,5}$ 1.2 Hz, H-4), 4.02–3.86 (m, 3 H, H-5,6a,6b), 3.72–3.52 (m, 3 H, H-4',5'a,5'b), 3.24 (dd, 1 H, $J_{2',3'}$ 7.3, $J_{3',4'}$ 8.4 Hz, H-3'), 2.02 (s, 3 H, CH_3CO), 1.49, 1.42, 1.30, and 1.29 (4 s, 12 H, CCH_3).

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