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# Synthesis, conformational analysis, and the glycosidic coupling reaction of substituted 2,7-dioxabicyclo[4.1.0]heptanes: 1,2-anhydro-3,4-di-*O*-benzyl-β-L- and β-D-rhamnopyranoses *

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## ABSTRACT

1,2-Anhydro-3,4-di-*O*-benzyl-α-L-rhamnopyranose was synthesized from L-rhamnose, while the D-enantiomer was synthesized from methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside. For both of the syntheses, the key intermediates were 2-*O*-acetyl-3,4-di-*O*-benzyl-α-D- and -α-L-rhamnopyranosyl chlorides that were quantitatively prepared from the corresponding diacetates by chlorination. Ring closure of the chlorides was carried out readily with potassium *tert*-butoxide in oxolane, and crystalline 1,2-anhydro-3,4-di-*O*-benzyl-β-D- and β-L-rhamnopyranose were obtained in high yields. Conformational calculations, which were carried out using vicinal proton–proton coupling constants by the modified Karplus equation, suggested that the conformations of the pyranose rings of the title compounds were basically a half chair ($^4H_5$) with some flattening at C-4. Force-field calculations (MMP2) confirmed the experimental conformation with good agreement. The coupling reaction of the 1,2-anhydro-L-rhamnose ether with 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose was effected in oxolane by catalysis by a Lewis acid, and only the α-linked disaccharide was obtained.

## INTRODUCTION

1,2-Anhydro pyranose ethers are novel monomers for the synthesis of the corresponding stereoregular (1 → 2)-linked polysaccharides[1] that are important model compounds for immunological research. Also, the 1,2-anhydro sugar ethers are valuable glycosyl donors for the stereospecific synthesis of oligosaccharides[2] in the presence of Lewis acids, which results in glycosides having inversion of

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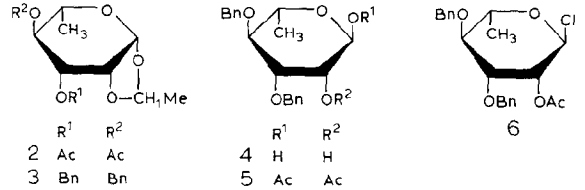
configuration at C-1. These compounds are also useful intermediates for a series of chemical modifications[3]. The synthesis of 1,2-anhydro-β-D-manno-[4] and -α-D-gluco-[5], and -α-D-galactopyranose[6] derivatives by an intramolecular $S_N2$ reaction of a free hydroxyl group on C-2 with C-1 bearing a leaving group have been reported. Recently a new method for the synthesis of 1,2-anhydro-α-D-hexopyranose derivatives by direct epoxidation of the corresponding glycals has been described[2,7]. It seemed, however, that the method is convenient only for the synthesis of 1,2-anhydro sugar derivatives with the epoxide and C-3 substituent on different sides of the pyranose ring. The synthesis of 1,2-anhydro-3,4-di-*O*-benzyl-β-D- and β-L-rhamnopyranose is of interest as their stereoregular polymerization and subsequent deprotection can afford α-(1 → 2)-linked D- and L-rhamnopyranan, and their coupling reaction with a suitable glycosyl acceptor can afford α-linked disaccharides containing either the D- or L-rhamnose moiety. It has been found that → 3)-α-D-Rha-(1 → 3)-α-D-Rha-(1 → 2)-α-D-Rha-(1 → 2)-α-D-Rha-(1 → was the backbone repeating unit of the *O*-antigenic polysaccharide of *Pseudomonas syringae*[8,9], and that the (1 → 2)-α-L-linkage of rhamnose occured in the lipopolysaccharide[10] of the reference strain for *Serratia marcescens* serogroup O18. Now we report the synthesis, conformational analysis, and glycoside coupling reaction of 1,2-anhydro-3,4-di-*O*-benzyl-β-D- and -β-L-rhamnopyranose.

## RESULTS AND DISCUSSION

3,4-Di-*O*-acetyl-1,2-*O*-[(*R*,*S*)-ethylidene]-β-L-rhamnopyranose (**2**), prepared from L-rhamnose (**1**) via the intermediate 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl bromide by the reported method[11], was converted to a crystalline mixture of 3,4-di-*O*-benzyl-1,2-*O*-[(*R*)-ethylidene]-β-L-rhmnopyranose (**3**) and a trace amount of the *S* isomer in a high yield with powdered potassium hydroxide and benzyl chloride in toluene. Compound **3** was also obtained by benzylation of 1,2-*O*-ethylidene-β-L-rhamnopyranose with benzyl bromide and sodium hydride in oxolane under reflux. The ethylidene group was found to be a good protecting group for the synthesis of the target anhydro sugar derivative as it is quite stable compared to the notoriously unstable 1-ethoxyethylidene group. Hydrolysis of **3** with sulfuric acid in dioxane afforded compound **4**, and subsequent acetylation of **4** with acetic anhydride in pyridine furnished the diacetate **5**. Quantitative conversion of compound **5** to 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl chloride (**6**) was readily effected by dry hydrogen chloride in diethyl ether. Without further purification, crude compound **6** was subjected to ring closure directly with potassium *tert*-butoxide in oxolane under reflux, and crystalline 1,2-anhydro-3,4-di-*O*-benzyl-β-L-rhamnopyranose (**7**), which was characterized by $^1$H NMR spectroscopy, mass spectrometry, and optical rotation, was obtained in a high yield. The $^1$H NMR spectrum of compound **7** showed an upfield peak for H-2 at δ 3.35, which is characteristic for the epoxide ring[12]. The mass spectrum gave a molecular ion (*m/z* 326) of low intensity, together with some fragmentation peaks characteristic



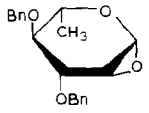
| | $R^1$ | $R^2$ |
|---|---|---|
| 2 | Ac | Ac |
| 3 | Bn | Bn |



| | $R^1$ | $R^2$ |
|---|---|---|
| 4 | H | H |
| 5 | Ac | Ac |



6



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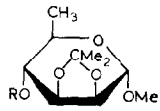
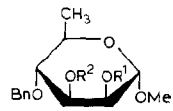
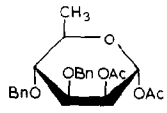


| | R |
|---|---|
| 8 | H |
| 9 | Bn |



| | $R^1$ | $R^2$ |
|---|---|---|
| 10 | H | H |
| 11 | H | Bn |
| 12 | Ac | Bn |



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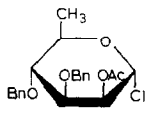

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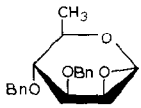

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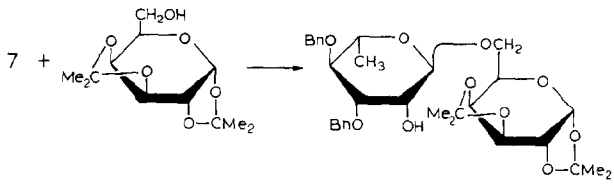

16

for per-*O*-benzyl-1,2-anhydropyranoses[13]. Crystalline **7** was found to be quite stable during lengthy storage in the refrigerator. Methanolysis of **7** was conducted in absolute methanol at room temperature, quantitatively giving methyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside in 1 h. The coupling reaction of **7** with 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose was carried out in dry oxolane using either zinc chloride or boron trifluoride etherate as catalyst. Only the (1 → 6)-α-L-linked disaccharide **16** was shown to form, together with some unreacted starting materials and a small amount of an oligomer of compound **7**. The synthesis of compound **16** was of interest as it demonstrated, aside from polymerization of an anhydro sugar by Schuerch[1], the first formation of a disaccharide containing the α-L-*manno* configuration from a 1,2-anhydrosugar. The disaccharide was identified by further acetylation, and the $^1$H NMR spectrum of the disaccharide acetate gave characteristic peaks. A doublet of doublets at δ 5.45 ($J_{1,2}$ 1.5 Hz and $J_{2,3}$ 6.0 Hz) represents H-2 of the rhamnose moiety, and the sole singlet at δ 2.16 indicates that the

original disaccharide had only one free hydroxyl group. The doublet at $\delta$ 4.79 ($J_{1,2}$ 1.5 Hz) is the peak characteristic of H-1 of the $\alpha$-linked L-rhamnopyranoside[14].

1,2-Anhydro-3,4-di-*O*-benzyl-$\beta$-D-rhamnopyranose (**15**) was synthesized from methyl 2,3-*O*-isopropylidene-$\alpha$-D-rhamnopyranoside (**8**), which was prepared by reduction of either methyl 2,3-*O*-isopropylidene-6-*O*-(*p*-tolylsulfonyl)-$\alpha$-D-mannopyranoside with lithium aluminum hydride[15] or methyl 6-deoxy-6-iodo-2,3-*O*-isopropylidene-$\alpha$-D-mannopyranoside[16] with sodium borohydride. Benzylation of compound **8** with benzyl chloride and powdered potassium hydroxide in toluene under reflux quantitatively gave methyl 4-*O*-benzyl-2,3-*O*-isopropylidene-$\alpha$-D-rhamnopyranoside (**9**). Removal of the isopropylidene group under acidic conditions, followed by selective 3-*O*-benzylation of the stannylene complex of compound **10**, and then acetylation, afforded methyl 2-*O*-acetyl-3,4-di-*O*-benzyl-$\alpha$-D-rhamnopyranoside (**12**). Acetolysis of compound **12** with acetic anhydride under catalysis by sulfuric acid furnished 1,2-di-*O*-acetyl-3,4-di-*O*-benzyl-$\alpha$-D-rhamnopyranose (**13**) in high yield. Reaction of compound **13** with dry hydrogen chloride and subsequent ring closure of the glycosyl chloride **14** were carried out under the same conditions as previously described for the L-enantiomers, giving crystalline 1,2-anhydro-3,4-di-*O*-benzyl-$\beta$-D-rhamnopyranose (**15**). An attempt to synthesize 1,2-*O*-ethylidene-$\beta$-D-rhamnopyranose by reduction of 1,2-*O*-ethylidene-6-*O*-(*p*-tolylsulfonyl)-$\beta$-D-mannopyranoside with lithium aluminum hydride was not successful. Iodination of 1,2-*O*-ethylidene-$\beta$-D-mannopyranoside with triphenyl phosphine, iodine, and imidazole[17] also failed. Almost no reaction occurred in both cases, perhaps because the 1,2-*O*-ethylidene group was orientated above the pyranose ring, severely inhibiting the reaction at C-6.

Conformational analysis of the 1,2-anhydro-$\beta$-D-rhamnose derivative **15** was carried out by $^1$H NMR spectroscopy in conjunction with the calculations by a modified Karplus equation[18], and also by a molecular mechanics method (MMP2)[19]. The latter method has been proved effective for 1,6-anhydro pyranoses[20] as the bond lengths, bond angles, and torsional angles calculated were found to be very close to those obtained from the X-ray diffraction data on these compounds. Application of the molecular mechanics method in our laboratory to calculate the conformation of 1,3-anyhydro-6-deoxy-$\beta$-D-manno-, galacto-, and glucopyranose benzyl ethers have also shown good agreement[21] with the results obtained by $^1$H NMR spectrometry in conjunction with the calculations by the modified Karplus equation. Thus it was expected that calculations of the conformation of compound **15** by the MMP2 program would give reasonable results. While the H–H torsional angles calculated by the modified Karplus equation only give a general idea about the geometry of the molecule, molecular mechanics calculations should provide all of the information necessary for determination of the relative stereochemistry of the molecule.

Two conformations, $^4H_5$ and $^5H_4$, may be considered for the ring closure product **15**. In conformation $^4H_5$, the C-6, C-3, and C-4 substituents are all in equatorial positions, while in conformation $^5H_4$ all of them are axial. Conformation

$^5H_4$ is not stable due to unfavorable interactions between $CH_3$–C-5 and the epoxide ring oxygen and between BnO–C-3 and $CH_3$–C-5, and between BnO–C-4 and lone-pair electrons on O–5. In contrast, all of the large groups in conformation $^4H_5$ are in equatorial positions; therefore, conformation $^4H_5$ is favored. This postulate was confirmed by the experimental (NMR) results and by molecular mechanics calculations as indicated later.

The $^1$H NMR spectrum of compound **15** was fully assigned by use of single-frequency decoupling. The anomeric proton appeared as a doublet at $\delta$ 4.90 ($J$ 2.9 Hz). The upfield doublet at $\delta$ 1.28 was designated as H-6. The chemical shifts at $\delta$ 3.35, 3.93, 3.58, 3.70 were assigned as H-2, H-3, H-4, H-5, respectively. The large coupling constant of 9.9 Hz between H-4 and H-5, and another large one at 8.4 Hz between H-3 and H-4, clearly indicate that compound **15** has a $^4H_5$ conformation with a *trans*-diaxial relationships between H-4 and H-5 and between H-3 and H-4, rather than conformation $^5H_4$. The torsional angle ($\phi_{3,4}$ 165°) between H-3 and H-4 and the angle ($\phi_{4,5}$ 180°) between H-4 and H-5 indicated some flattening at C-4.

The conformation of compound **15** was confirmed by MMP2 calculations. Initial coordinates for compound **15** were obtained from the geometry of conformation $^4H_5$. After energy minimizations, final coordinates were obtained with a total energy of 45.7 kcal/mol. The H–H torsional angles of $\phi_{3,4}$ and $\phi_{4,5}$ according to the final coordinates were 164 and 174°, respectively, which are very close to those obtained experimentally as described above. Because the modified Karplus equation[18] is not valid for the planar portion of the pyranose ring, the H–H torsional angles of $\phi_{1,2}$ and $\phi_{2,3}$ calculated by the equation[18] did not represent the true angles of the molecule. However, as the torsion angles of $\phi_{3,4}$ and $\phi_{4,5}$ obtained experimentally and obtained by the MMP2 calculations were very close, it is resonable to believe that the conformation $^4H_5$ according to the final coordinates with the minimized energy was the true conformation for compound **15**. Some important bond lengths, bond angles, and torsion angles obtained by the MMP2 calculations for the $^4H_5$ conformation are listed in Tables 1–IV. It was found from the data that the pyranose moiety of **15** basically adopted a half-chair conformation of $^4H_5$ with the torsion angle O-5–C-1–C-2–C-3 = −2.6°. Comparison of the torsion angle C-1–C-2–C-3–C-4 (−8.7°) with C-2–C-1–O-5–C-5 (−22°), and comparison of the torsion angle C-1–O-5–C-5–C-4 (57.2°) with C-2–C-3–C-4–C-5 (41.3°) indicated some flattening at C-4. This was further confirmed by calculation

TABLE I

Calculated values of some important interatomic distances (Å) of compound **15**

| | | | | | |
|---|---|---|---|---|---|
| C-1–C-2 | 1.506 | O-5–C-1 | 1.442 | C-5–O-1 | 3.231 |
| C-2–C-3 | 1.522 | C-2–O-1 | 1.439 | C-4–O-1 | 3.000 |
| C-3–C-4 | 1.547 | C-3–O-3 | 1.425 | C-2–C-4 | 2.576 |
| C-4–C-5 | 1.545 | C-4–O-4 | 1.428 | C-1–C-5 | 2.407 |
| C-5–C-6 | 1.539 | | | | |

TABLE II

Calculated values of some important bond angles (°) of compound **15**

| | | | |
|---|---|---|---|
| C-2–C-1–O-5 | 121.2 | C-1–C-2–O-1 | 58.5 |
| C-2–C-1–O-1 | 58.3 | C-1–C-2–H-2 | 120.4 |
| C-2–C-1–H-1 | 119.2 | C-3–C-2–H-2 | 117.5 |
| O-5–C-1–O-1 | 116.3 | C-2–C-3–C-4 | 114.5 |
| O-5–C-1–H-1 | 113.6 | C-3–C-4–C-5 | 108.9 |
| O-1–C-1–H-1 | 116.9 | C-4–C-5–O-5 | 109.3 |
| C-1–C-2–C-3 | 117.5 | C-1–O-5–C-5 | 114.4 |

TABLE III

Calculated values of some important torsional angles (°) of compound **15**

| | | | |
|---|---|---|---|
| C-1–C-2–C-3–C-4 | −8.7 | C-3–C-2–C-1–H-1 | −153.9 |
| C-1–O-5–C-5–C-4 | 57.2 | C-3–C-4–C-5–O-5 | −67.1 |
| C-1–O-1–C-2–H-2 | 111.2 | C-4–C-3–C-2–O-1 | 56.4 |
| C-2–C-1–O-5–C-5 | −22.0 | C-5–O-5–C-1–O-1 | −89.9 |
| C-2–C-3–C-4–C-5 | 41.3 | H-1–C-1–C-2–H-2 | 1.5 |
| C-2–O-1–C-1–O-5 | 112.0 | H-2–C-2–C-3–H-3 | −47.4 |
| C-3–C-2–C-1–O-5 | −2.6 | H-3–C-3–C-4–H-4 | 164.1 |
| C-3–C-2–C-1–O-1 | 100.9 | H-4–C-4–C-5–H-5 | 173.6 |

TABLE IV

H–H Torsion angles (°) of compound **15**

| | $\phi_{1,2}$ | $\phi_{2,3}$ | $\phi_{3,4}$ | $\phi_{4,5}$ |
|---|---|---|---|---|
| Measured from model of $^4H_5$ | 0 | −45 | 170 | 180 |
| Calculated from the coupling constants by the modified Karplus equation[18] | | | 164 | 180 |
| Calculated from the final coordinates with the minimum energy by MMP2 program[19] | 1.5 | −47.4 | 164.1 | 173.6 |

of the asymmetric parameter $\Delta C_2$ (1–2) = 14.7° according to a reported method[22]. The flattening at C-4 was probably caused by an unfavorable interaction between axial H-4 and the epoxide ring oxygen. The endocyclic bond angles C-2–C-1–O-5 (121°) and C-1–C-2–C-3 (118°) and the shortened bond length of C-1–C-2 (1.506 Å) indicated that the epoxide ring had properties similar to those of a double bond.

## EXPERIMENTAL

*General methods.* — Optical rotations were determined at 23°C with a Perkin–Elmer Model 241-MC automatic polarimeter. Melting points were determined with a "Mel-Temp" apparatus. Analytical LC was carried out by using stainless-steel columns packed with silica gel (10 × 150 mm) or Lichrosorb-$NH_2$ (4.6 × 250

mm), a differential refractometer LDC Model 1107L. (Division of Milton Roy Company, FL, USA), and EtOAc–petroleum ether (bp 60–90°C) as the eluent at a flow rate of 1 to 4 mL/min. Thin-layer chromatography (TLC) was performed on silica gel G, detection being effected by charring with 30% (v/v) $H_2SO_4$ in MeOH. Column chromatography was performed by elution of columns (16 × 240, 18 × 300, and 35 × 400 mm) of silica gel (100–200 mesh). $^1H$ NMR spectra were recorded for solutions in $CDCl_3$ (internal $Me_4Si$) with a Varian XL-200 spectrometer. For conformational analysis, $^1H$ NMR spectra were recorded with a JEOL GX-400 MHz spectrometer in the pulsed Fourier-transform mode for solutions in $CDCl_3$ at 27°C, with $Me_4Si$ as the internal standard. Chemical shifts are given in ppm ($\delta$) downfield from the internal $Me_4Si$ absorption. The working frequency was 399.78 MHz, and sweep widths were 4000 Hz at 2.048 s, pulse duration 1.0 s, and a pulse width of 2.8 $\mu$s. Mass spectra were recorded with a JMS-D 3005 mass spectrometer, using a direct sample introduction technique. For molecular mechanics calculations (MMP2), the MMIO program was used for the input, and a Tectronix emulator program was used for screen echo of the structure building. The dielectric constant used for calculation was 1.50.

*Preparation of 3,4-di-O-acetyl-6-deoxy-1,2-O-[(R,S)-ethylidene]-β-L-mannopyranose* (**2**). — 2,3,4-Tri-*O*-acetyl-6-deoxy-α-L-mannopyranosyl bromide (5.47 g, 15.5 mmol, prepared by a standard method[23]), $NaBH_4$ (3.1 g, 81.6 mmol), and anhyd acetonitrile (38 mL) were stirred for 24 h at room temperature, at the end of which time TLC (1:1 EtOAc–petroleum ether) indicated that the starting material had been consumed. The mixture was diluted with $CH_2Cl_2$ (50 mL), washed with water (3 × 50 mL), and then concentrated to give crystalline **2** (3.6 g, 85.7%); mp 72–75°C; $[\alpha]_D^{23}$ −21.2° (*c* 0.89, $CHCl_3$) [lit.[11] mp 77–79°C; $[\alpha]_D^{23}$ +33.0° (*c* 0.9, $CHCl_3$)].

*3,4-Di-O-benzyl-6-deoxy-1,2-O-[(R,S)-ethylidene]-β-L-mannopyranose* (**3**). — To a solution of compound **2** (3.6 g, 13.1 mmol) in toluene (30 mL) was added with vigorous stirring finely powdered KOH (25 g). The mixture was boiled under reflux, and benzyl chloride (20.1 mL, 174 mmol) was added dropwise within 20 min. The reaction was carried out under reflux and vigorous agitation for 2 h, at the end of which time TLC (1:2 EtOAc–petroleum ether) indicated that the reaction was complete. The mixture was directly subjected to steam distillation to remove excess benzyl chloride. The mixture was extracted with $CH_2Cl_2$, and the organic layer was concentrated to a syrup. Purification of the product was effected by column chromatography with 1:3 EtOAc–petroleum ether as the eluent to give **3** (4.85 g, 99.9%), consisting of predominantly the *R* isomer along with a trace amount of the *S* isomer; mp 68–71°C; $[\alpha]_D^{23}$ +7.8° (*c* 0.89, $CHCl_3$); $^1H$ NMR: for the *R* isomer: $\delta$ 7.41–7.25 (m, 10 H, Ph), 5.29 (q, 1 H, *J* 4.9 Hz, C*H*$CH_3$), 5.10 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1), 4.98–4.64 (4 d, 4 H, *J* 12 Hz, 2 C$H_2$Ph), 4.11 (dd, 1 H, $J_{1,2}$ 1.8, $J_{2,3}$ 3.8 Hz, H-2), 3.56 (t, 1 H, $J_{3,4}$ 9.4, $J_{4,5}$ 9.4 Hz, H-4), 3.37 (dd, 1 H, $J_{2,3}$ 3.8, $J_{3,4}$ 9.4 Hz, H-3), 3.34 (m, 1 H, H-5), 1.53 (d, 3 H, *J* 4.9 Hz, CHC$H_3$), and 1.3 (d, 3 H, $J_{5,6}$ 6.5 Hz, 3 H-6); *S* isomer: $\delta$ 5.68 (q, 1 H, C*H*$CH_3$) and 1.37 (d, 3 H, *J* 4.9

Hz, $CHCH_3$). The remainder of the proton signals overlapped those of the *R* isomer. Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.35; H, 7.03. Found: C, 71.29; H, 7.03.

*Preparation of 1,2-di-O-acetyl-3,4,-di-O-benzyl-6-deoxy-α-L-mannopyranose* (**5**). — To a solution of compound **3** (5.2 g, 14.1 mmol) in 1,4-dioxane (100 mL) was added M $H_2SO_4$ (20 mL), and the mixture was boiled under reflux with stirring for 2 h, after which TLC (1:1 EtOAc–petroleum ether) showed the hydrolysis to be complete. The mixture was neutralized with $NaHCO_3$ while cooling, and the solvent was evaporated to give a syrup that was partitioned between water and $CH_2Cl_2$. The organic layer was dried and concentrated to give crystalline **4** (4.0 g, 83.3%); mp 108°C; $[\alpha]_D^{23}$ −22.4° (*c* 0.53, $CHCl_3$) [lit.[24] mp 111–112°C; $[\alpha]_D^{23}$ −19.1° (*c* 0.60, $CHCl_3$)].

The 3,4-di-*O*-benzyl-6-deoxy-α-L-mannopyranose intermediate was acetylated with acetic anhydride in pyridine by the standard method to give **5**, which was purified by means of crystallizion of the crude product from petroleum ether; mp 100–103°C; $[\alpha]_D^{23}$ −24.5° (*c* 0.53, $CHCl_3$) [lit.[24] mp 106–108°C; $[\alpha]_D^{23}$ −22.3° (*c* 0.64, $CHCl_3$)].

*Preparation of 2-O-acetyl-3,4-di-O-benzyl-6-deoxy-α-L-mannopyranosyl chloride* (**6**). — Compound **6** (0.423 g, 0.988 mmol) was dissolved in anhyd ether (30 mL), and the solution was saturated with anhyd HCl gas at 0°C under $N_2$. After standing for 1 h at room temperature, the solvent was evaporated. The residue was dissolved in $CH_2Cl_2$ (1 mL), and the the solvent was again evaporated. This process was repeated several times in order to reduce the HCl concentration to a minimum. Compound **6** was quantitatively obtained as a syrup. The $^1H$ NMR spectrum of compound **6** was the same as described in a previous report[25].

*1,2-Anhydro-3,4-di-O-benzyl-6-deoxy-β-L-mannopyranose* (**7**). — Compound **6** (0.414 g, 1.023 mmol) was dissolved in anhyd oxolane (30 mL), and potassium *tert*-butoxide (0.25 g, 2.046 mmol) was added. The mixture was heated under stirring for 2 min in an oil bath (90°C), and TLC (1:3 EtOAc–petroleum ether) indicated the reaction was complete. The mixture was evaporated, the residue was extracted with 1:3 EtOAc–petroleum ether, and the colorless extracts were combined and evaporated. Compound **7** was obtained as white crystals from evaporation of the solvent (0.333 g, 99.8%); mp 100°C; $[\alpha]_D^{23}$ +5.1° (*c* 0.78, $CHCl_3$); $^1H$ NMR: δ 7.44–7.23 (m, 10 H, Ph), 4.94–462 (m, 4 H, 2 $CH_2Ph$) 4.90 (d, 1 H, $J_{1,2}$ 2.8 Hz, H-1), 3.91 (dd, 1 H, $J_{2,3}$ 1.9, $J_{3,4}$ 8.4 Hz, H-3), 3.68 (m, 1 H, $J_{5,6}$ 5.9 Hz, H-5), 3.56 (dd, 1-H, $J_{3,4}$ 8.4, $J_{4,5}$ 9.9 Hz, H-4), 3.35 (dd, 1 H, $J_{1,2}$ 2.8, $J_{2,3}$ 1.9 Hz, H-2), and 1.27 (d, 3 H, $J_{5,6}$ 5.9 Hz, 3 H-6); *m/z*: 326 ($M^+$), 235 ($M^+$ − Bn), 181, 163, 133, 107, and 91. Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.62; H, 6.75. Found: C, 73.83; H, 6.55.

*Preparation of methyl 6-deoxy-2,3-O-isopropylidene-α-D-mannopyranose* (**8**). — Methyl 2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranoside (9.5 g, 34.7 mmol) was treated with 1:3 acetic acid–water (80 mL) under vigorous agitation for 2 days at 0°C until the starting material disappeared. After neutralization with solid $NaHCO_3$, the mixture was extracted with $CH_2Cl_2$. The extracts were concen-

trated, and methyl 2,3-*O*-isopropylidene-α-D-mannopyranose was obtained as crystals (7.0 g, 86.4%); mp 101°C; [lit.[26] mp 102–104°C]. The crystalline product was treated with triphenylphosphine, imidazole, and iodine in toluene according to a reported method[16] to give methyl 6-deoxy-6-iodo-2,3-*O*-isopropylidene-α-D-mannopyranose. The iodo intermediate (2.53 g, 7.35 mmol) was then converted into compound **8** with $NaBH_4$ (0.532 g, 14.0 mmol) in anhyd acetonitrile (40 mL) under reflux with stirring for 2.5 h to give compound **8**, as a syrup (1.37 g, 85.6%). The $^1H$ NMR spectrum of **8** was the same as that described in the literature[15].

*Methyl 3,4-di-O-benzyl-6-deoxy-α-D-mannopyranose* (**11**). — Methyl 4-*O*-benzyl-6-deoxy-α-D-mannopyranoside (0.26 g, 0.97 mmol, prepared by benzylation of compound **8**, followed by hydrolysis), dibutyltin oxide (0.241 g, 0.97 mmol), and abs MeOH (10 mL) were mixed, and the mixture was stirred under reflux until it became clear. The solvent was removed under diminished pressure, and a white, foamy product was obtained. The residue was subjected to selective benzylation at C-3 with tetrabutylammonium iodide (0.358 g, 0.97 mmol) and benzyl bromide (0.14 mL, 1.14 mmol) in toluene (15 mL) for 5 h at 80°C. The reaction mixture was concentrated and separated by column chromatography on silica gel to give **11** as a syrup (0.194 g, 56%); $[\alpha]_D^{23}$ +51.5° (*c* 0.27, $CHCl_3$); $^1H$ NMR: δ 7.37–7.28 (m, 10 H, Ph), 4.96–4.57 (m, 6 H, H-1, 2 and 2 C$H_2$Ph), 3.98 (m, 1 H, H-3), 3.74 (m, 1 H, H-5), 3.42 (m, 1 H, H-4), 3.35 (s, 3 H, OC$H_3$), and 1.30 (d, 3 H, 3 H-6). Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.39; H, 7.26. Found: C, 70.25; H, 7.02.

*Methyl 2-O-acetyl-3,4-di-O-benzyl-6-deoxy-α-D-mannopyranose* (**12**). — Acetylation of **11** with acetic anhydride and pyridine quantitatively afforded **12**; $[\alpha]_D^{23}$ +26.3° (*c* 0.57, $CHCl_3$); $^1H$ NMR: δ 7.36–7.24 (m, 10 H, Ph), 5.23 (m, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 3.2 Hz, H-2), 4.98–4.42 (m, 5 H, H-1 and 2 C$H_2$Ph), 3.88 (dd, 1 H, $J_{2,3}$ 3.2, $J_{3,4}$ 8.9 Hz, H-3), 3.63 (m, 1 H, H-5), 3.39 (t, 1 H, $J_{3,4}$ 8.9, $J_{4,5}$ 8.9 Hz, H-4), 3.32 (s, 3 H, OC$H_3$), 2.07 (s, 3 H, C$H_3$CO), 1.33 (d, 3 H, $J_{5,6}$ 5.5 Hz, 3 H-6).

*1,2-Di-O-acetyl-3,4-di-O-benzyl-6-deoxy-α-D-mannopyranose* (**13**). — Compound **12** (0.51 g, 1.28 mmol) was dissolved in a mixture of 50:20:0.5 acetic anhydride–acetic acid–$H_2SO_4$ (8.56 mL) with stirring for 3 h at room temperature, and then the mixture was poured into ice–aq $Na_2CO_3$. The product was extracted with $CH_2Cl_2$, and the extracts were concentrated to give crystalline **13** (0.45 g, 81.8%); mp 107–109°C; $[\alpha]_D^{23}$ +17.3° (*c* 0.75, $CHCl_3$); $^1H$ NMR: δ 7.37–7.27 (m, 10 H, Ph), 6.03 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 5.38 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 3.4 Hz, H-2), 4.97 (m, 4 H, 2 C$H_2$Ph), 3.95 (dd, 1 H, $J_{2,3}$ 3.4, $J_{3,4}$ 9.0 Hz, H-3), 3.83 (m, 1 H, H-5), 3.50 (t, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.0 Hz, H-4), 2.20, 2.10 (2 s, 6 H, 2 C$H_3$CO), and 1.37 (d, 3 H, $J_{5,6}$ 5.8 Hz, 3 H-6). Anal. Calcd for $C_{24}H_{28}O_7$: C, 67.29; H, 6.54. Found: C, 67.05; H, 6.56.

*2-O-Acetyl-3,4-di-O-benzyl-6-deoxy-α-D-mannopyranosyl chloride* (**14**). — A solution of compound **13** (0.678 g, 1.58 mmol) in dry diethyl ether (45 mL) was saturated with HCl at 0°C under $N_2$. After reaction for 1 h at room temperature, the mixture was processed as described for the conversion of **5** to **6** to give syrupy **14** (0.638 g, 99%); $[\alpha]_D^{23}$ +41° (*c* 0.17, $CHCl_3$); $^1H$ NMR: δ 7.44–7.31 (m, 10 H,

Ph), 5.96 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 5.45 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 3.1 Hz, H-2), 5.00–4.48 (m, 4 H, 2 C$H_2$Ph), 4.28 (dd, 1 H, $J_{2,3}$ 3.1, $J_{3,4}$ 9.3 Hz, H-3), 3.90 (m, 1 H, H-5), 3.49 (t, 1 H, $J_{3,4}$ 9.3, $J_{4,5}$ 9.3 Hz, H-4), 2.22 (s, 3 H, C$H_3$CO), and 1.25 (d, 3 H, $J_{5,6}$ 5.9 Hz, 3 H-6). Anal. Calcd for $C_{22}H_{25}ClO_5$: C, 65.18; H, 6.17. Found: H, 64.88; H, 5.95.

*1,2-Anhydro-3,4-di-*O*-benzyl-6-deoxy-β-*D*-mannopyranose* (**15**). — To a solution of compound **14** (0.581 g, 1.436 mmol) in anhyd oxolane (35 mL) was added potassium *tert*-butoxide (0.376 g, 3.077 mmol), and the mixture was boiled under reflux for 2 min, at the end of which time TLC (1:3 EtOAc–petroleum ether) indicated that the reaction was complete. The solvent was evaporated, and the residue was extracted with 1:3 EtOAc–petroleum ether. The extracts were combined and evaporated, and compound **15** was obtained as crystals (0.466 g, 99.5%); mp 101°C; $[\alpha]_D^{23}$ −5.6° (*c* 0.72, $CHCl_3$); $^1$H NMR: δ 7.45–7.28 (m, 10 H, Ph), 4.91–4.62 (m, 4 H, 2 C$H_2$Ph), 4.90 (d, 1 H, $J_{1,2}$ 2.8 Hz, H-1), 3.93 (dd, 1 H, $J_{2,3}$ 1.8, $J_{3,4}$ 8.3 Hz, H-3), 3.70 (m, 1 H, $J_{5,6}$ 5.8 Hz, H-5), 3.58 (dd, (1 H, $J_{3,4}$ 8.4, $J_{4,5}$ 9.9 Hz, H-4), 3.35 (dd, 1 H, $J_{1,2}$ 2.8, $J_{2,3}$ 1.8 Hz, H-2), and 1.28 (d, 3 H, $J_{5,6}$ 5.8 Hz, 3 H-6). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.62; H, 6.75. Found: C, 73.15; H, 6.93.

*Methanolysis of compound* **15**. — Compound **15** (0.020 g, 0.061 mmol) was dissolved in anhyd MeOH (0.05 mL) for 1 h, at the end of which time TLC (1:2 EtOAc–petroleum ether) showed that the reaction was complete. The solution was evaporated to afford **11** in quantitative yield. Methanolysis of compound **7** was carried out as described for **15**, and the $^1$H NMR spectrum of the methanolysis product was identical to that of compound **11**.

*O-(3,4-Di-*O*-benzyl-6-deoxy-α-*L*-mannopyranosyl)-(1 → 6)-1,2;3,4-di-*O*-isopropylidene-α-*D*-galactopyranose* (**16**). — Compound **7** (0.0518 g, 0.16 mmol) was dissolved in oxolane (0.30 mL), and the resulting solution was cooled with liquid nitrogen to −195°C. A solution of 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.0625 g, 0.25 mmol) and $ZnCl_2$ (0.0408 g, 0.3 mmol) in oxolane (0.30 mL) was added, and the mixture was warmed to room temperature and stirred for 2 h. The solution was evaporated to a syrup that was partitioned between water and $CH_2Cl_2$. The organic layer was dried and concentrated to a syrup which was then purified by HPLC using 1:2 EtOAc–petroleum ether as the eluant. Pure compound **16** (0.0466 g, 50%) was obtained as a colorless syrup; $[\alpha]_D^{23}$ −9.1° (*c* 0.60, $CHCl_3$); $^1$H NMR δ 7.32–7.17 (m, 10 H, Ph), 5.47 (d, 1 H, $J_{1,2}$ 4.8 Hz, H-1), 4.80 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1′), 4.61–4.50 (m, 5 H, H-2 and 2 C$H_2$Ph), 4.23 (dd, 1 H, $J_{3,4}$ 2.0, $J_{4,5}$ 5.0 Hz, H-4), 4.13 (dd, 1 H, $J_{2,3}$ 7.6, $J_{3,4}$ 2.0 Hz, H-3), 4.03 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 6.0 Hz, H-2′), 3.86–3.74 (m, 4 H, H-5,5′, 6), 3.53 (dd, 1 H, $J_{2,3}$ 6.0, $J_{3,4}$ 9.8 Hz, H-3′), 3.38 (t, 1 H, $J_{3,4}$ 9.8, $J_{4,5}$ 9.8 Hz, H-4′), 1.46, 1.37, 1.27, 1.24 (4 s, 12 H, 4 CC$H_3$), and 1.21 (d, 3 H, $J_{5,6}$ 6.0 Hz, 3 H-6′). Anal. Calcd for $C_{32}H_{42}O_{10}$: C, 65.52; H, 7.16. Found: C, 65.21; H, 7.38.

*O-(2-*O*-Acetyl-3,4-di-*O*-benzyl-6-deoxy-α-*L*-mannopyranosyl)-(1 → 6)-1,2;3,4-di-*O*-isopropylidene-α-*D*-galactopyranose* (**17**). — Compound **16** (0.020 g, 0.034 mmol) was acetylated with acetic anhydride in pyridine by the standard method to give **17**

(0.021 g, 98%) as a syrup after workup of the mixture. $^1$H NMR: $\delta$ 7.33–7.25 (m, 10 H, Ph), 5.53 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1), 5.45 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 6.0 Hz, Hz, H-2′), 4.59 (dd, 1 H, $J_{1,2}$ 4.0, $J_{2,3}$ 8.0 Hz, H-2), 4.32 (dd, 1 H, $J_{3,4}$ 2.2, $J_{4,4}$ 2.0 Hz, H-3), 3.95–3.80 (m, 4 H, H-5,5′,6), 3.58 (dd, 1 H, $J_{2,3}$ 6.0, $J_{3,4}$ 9.6 Hz, H-3′), 3.42 (t, 1 H, $J_{3,4}$ 9.6, $J_{4,5}$ 9.6 Hz, H-4′), 2.16 (s, 3 H, C$H_3$CO), 1.53, 1.43, 1.34, 1.32 (4 s, 12 H, 4 CC$H_3$), and 1.31 (d, 3 H, $J_{5,6}$ 5.9 Hz, 3 H-6′).

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