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Note

Synthesis and glycosidic coupling reaction of substituted 2,6-dioxabicyclo[3.1.0]hexanes: 1,2-anhydro-3,5-di-*O*-benzyl-α-D-ribofuranose

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It has been well-known for many years that nucleoside analogues are used extensively as antibiotic substances and as biological probes [1]. Recently, however, much attention has been paid to this class of compounds because some nucleosides have been found to be efficient as antiparasitic and antiviral agents [2]. Zidovudine [3] (3′-azido-3′-deoxy-thymidine, AZT) and Stavudine [4] (2′,3′-didehydro-3′-deoxythymidine, d4T) have been approved by the FDA as antiviral drugs for the treatment of AIDS patients. The broadspectrum antiviral activity of virazole (ribavirin, 1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide) has recently been shown to extend to the treatment of plant as well as animal viruses [5]. At the same time, a considerable number of nucleoside derivatives containing carbohydrate moieties have been isolated from both plants and animals, and their structures have been determined [6,7]. For example, Shimofuridins A–G [6], isolated from the Okinawan marine tunicate *Aplidum multiplicatum Sluiter*, have a basic structure of 2′-*O*-(α-fucopyranosyl)-6-hydroxypurine and exhibit strong cytotoxic and antimicrobial activities. In addition, 2′-*O*-methylnucleosides have found important applications in the preparation of synthetic ribozymes [8]. The synthesis of Shimofuridins and the use of 2′-*O*-methylnucleosides for the synthesis of ribozymes from the corresponding nucleosides as the starting materials involved selective protection of the 3′ and 5′-hydroxyl groups in the nucleoside, and was nonselective and inefficient [9–11]. Therefore, it is of interest to develop new and effective methods for the synthesis of substituted nucleosides.

During our studies of the syntheses and coupling reactions of 1,2-anhydrosugars, we have found that these compounds have excellent reactivity. In most of the cases nucleophilic opening of the epoxides takes place via C-1 attack to give 1,2-*trans*-glycoside derivatives with a high degree of stereoselectivity [12], and the resulting 2′-free hydroxy compounds are useful intermediates for further chemical modifications. These results prompted us to synthesize 1,2-anhydroribofuranose derivatives as a precursor for the preparation of substituted nucleosides. In 1990, Danishefsky's group for the first time prepared a 1,2-anhydroribofuranose derivative by the oxidative conversion of the corresponding furanose glycal using 3,3-dimethyloxirane. However, they obtained an isomeric mixture of 1,2-anhydroglycofuranoses [13] that limited its application in the synthesis of nucleosides. Recently we developed an intramolecular ring closure strategy, namely 'inverse ring closure' by

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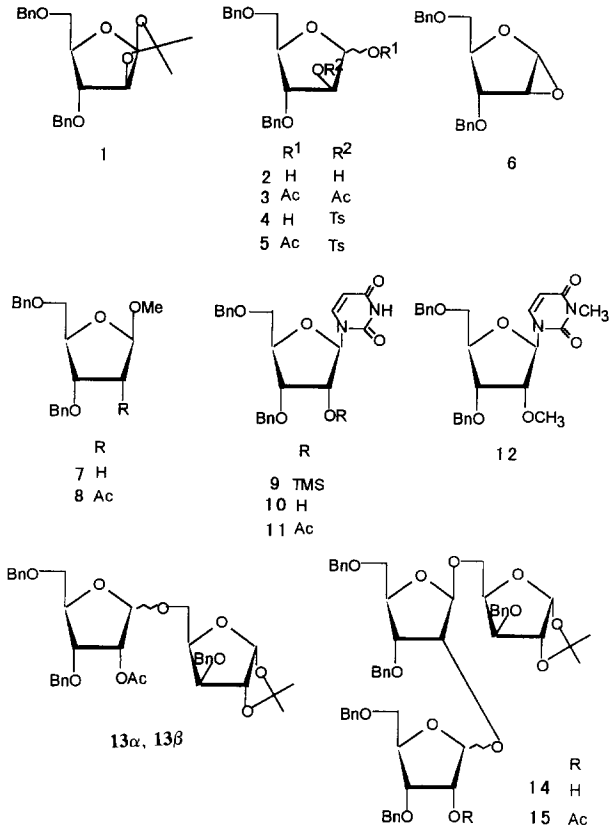

Fig. 1.

reaction of the C-1 alkoxide with C-2 bearing a leaving group [14]. Employing this method, we successfully synthesized 1,2-anhydromanno-, gluco-, lyxo-, xylo-, gulo- and arabinofuranose benzyl ethers [12]. We wish to report here synthesis of 1,2-anhydro-3,5-di-*O*-benzyl-α-D-ribofuranose starting from D-arabinose, and its coupling reaction with silylated uracil to give a β-linked nucleoside as the sole product in excellent yield in the absence of a Lewis acid catalyst at room temperature. Also, the coupling reaction of the 1,2-anhydride with 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-xylofuranose gave the 1,2-*trans*-linked disaccharide as the main product.

1. Results and discussion

1,2-*O*-Isopropylidene-3,5-di-*O*-benzyl-β-D-arabinofuranose (**1**) was prepared from D-arabinose according to reported methods [15]. See Fig. 1. Hydrolysis of **1** in 30% acetic acid under reflux gave 3,5-di-*O*-benzyl-D-arabinofuranose (**2**) in excellent yield (91%) as a mixture of α and β anomers. Acetylation of **2** with acetic anhydride in pyridine gave 1,2-di-*O*-acetyl-3,5-di-*O*-benzyl-D-arabinofuranose (**3**) as an anomeric mixture in quantitative yield, which was separated by HPLC and identified by ^{1}H NMR spectroscopy. The key intermediate, 3,5-di-*O*-benzyl-2-*O*-tosyl-D-arabinofuranose (**4**), was prepared in good yield (62%) from the reaction of **2** with tosyl chloride in anhydrous pyridine in the presence of potassium carbonate at 0 °C (mixture of α and β anomers). The pure α isomer can be obtained by HPLC, but a ^{1}H NMR spectrum of this anomer could not be obtained due to anomerization during the determination in $CDCl_3$. Acetylation of **4** with acetic anhydride in pyridine afforded 1-*O*-acetyl-3,5-di-*O*-benzyl-2-*O*-tosyl-D-arabinofuranose (**5**) quantitatively as an anomeric mixture. Ring closure of **4** with potassium *tert*-butoxide in dry tetrahydrofuran gave syrupy 1,2-anhydro-3,5-di-*O*-benzyl-α-D-ribofuranose (**6**) quantitatively within 10 min. Compound **6** was very sensitive to acidic and hydroxylic solvent, and attempts to obtain an accurate elemental analysis of **6** were unsuccessful. The ^{1}H NMR spectrum of **6** showed an upfield signal for H-2 at δ 3.58 ppm, which is a characteristic feature of the 1,2-epoxide ring of carbohydrate compounds [16]. Further verification of the structure was performed by alcoholysis of **6** in dry MeOH at room temperature, giving methyl-3,5-di-*O*-benzyl-β-D-ribofuranose (**7**) quantitatively. The structure of **7** was confirmed by its acetylation, and the acetylated compound **8** gave a easily identified ^{1}H NMR spectrum. Reaction of the epoxide with silylated uracil in the absence of Lewis acid provided a mixture of **9** (62%) and **10** (26%) in a total yield of 88%. Compound **9** was unstable and easily converted to **10** under weakly acidic conditions. We could find no evidence of the α-anomer by HPLC or ^{1}H NMR spectroscopy.

Compound **10** with a free C-2 hydroxy group can be used for further functionalization or glycosylation. 1′-*O*-(3′,5′-di-*O*-benzyl-2′-*O*-methyl-β-D-ribofuranosyl)-3-methyl-uracil **12** was obtained in a high yield (85%) from the reaction of **10** with methyl iodide in the presence of silver oxide. The 2′-*O*-Methyluridine also may be prepared conveniently from **10** using diazomethane and stannous chloride [17] followed by catalytic reductive hydrogenolysis [18]. Acetylation of **10** with acetic anhydride in pyridine gave compound **11**, further confirming the structure of **10**. The coupling reaction of the 1,2-anhydride with 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-xylofuranose did not occur under the same conditions as used for the preparation of the nucleoside. However, with $ZnCl_2$ as the catalyst, **6** disappeared in 4 h. The resulting

mixture, after acetylation with acetic anhydride in pyridine, was subjected to silica gel chromatography, and two compounds, *O*-(2-*O*-acetyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)-(1 → 5)-1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-xylofuranose (**13**β) and *O*-(2-*O*-acetyl-3,5-di-*O*-benzyl-α-D-ribofuranosyl)-(1 → 5)-1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-xylo- furanose (**13**α), were obtained (54%) in a ratio of 7:1. The ^{1}H NMR spectrum of **13**α showed H′-1 at lower field (δ 5.20 ppm) compared to that of **13**β (δ 5.08 ppm). Th use of 2 equivalents of **6** did not improve the yield of the disaccharides, but a new product **14** formed. To identify **14**, acetylation was carried out and the acetate **15** showed a longer retention time on HPLC compared **13**α and **13**β, and gave only one acetyl methyl signal in its ^{1}H NMR spectrum. Further analysis by ESIMS spectrometry gave an $(M + H^+)^+$ signal at 948.1 indicating that **15** was a trisaccharide (Calcd: 947.046). We believe that **14** was obtained by the reaction of excess **6** with 13β generated from the coupling reaction.

2. 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 NMR spectra were recorded with Varian XL-400 and Varian XL-200 spectrometers, for solutions in $CDCl_3$ with tetramethylsilane (Me_4Si) as the internal standard. Chemical shifts are expressed in ppm downfield from the internal Me_4Si absorption. Mass spectra were recorded with a VG PLATFORM mass spectrometer using the ESI technique to introduce the sample. Analytical LC was performed with a Gilson HPLC consisting of a pump (model 306), stainless-steel columns packed with silica gel (10 × 300 mm, or 4.6 × 250 mm), a differential refractometer (132 RI detector), a UV/VIS detector (model 118), and EtOAc–petroleum ether (bp 60–90 °C) as the eluent at a flow rate of 1–4 mL/min. Thin-layer chromatography (TLC) was performed on silica gel HF, detection being afforded by charring with 30% (v/v) sulfuric acid in MeOH or by UV detection. Column chromatography was conducted on columns (16 × 240 mm, 18 × 300 mm, 35 × 400 mm) of silica gel (100–200 mesh). Solutions were concentrated at < 60 °C under diminished pressure.

3, 5 - Di - O - benzyl - D - arabinofuranose (**2**).—A solution of **1** (3.31 g, 8.94 mmol) in 30% acetic acid (100 mL) was refluxed with stirring for 5 h, at the end of which time TLC (2:1 petroleum ether–EtOAc) indicated that the reaction was complete. The mixture was concentrated to a syrup, which was subjected to column chromatography with 2:1 petroleum ether–EtOAc as the eluent. Compound **2** was obtained as a syrupy anomeric mixture (2.7 g, 91%, α:β 1:1); $[\alpha]_D$ +67.4° (*c* 4.8, $CHCl_3$); ^{1}H NMR: δ 7.43–7.22 (m, 10 H, 2 Ph), 5.29 (d, 0.5 H, $J_{1,2}$ 3.4 Hz, H-1 of β anomer), 5.22 (s, 0.5 H, H-1 of α anomer), 4.75–3.40 (m, 11 H, H-2,3,4,5,5′, 2 PhCH_2, 2 O*H*). Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.09; H, 6.67. Found: C, 69.32; H, 6.58.

*1,2-Di-*O*-acetyl-3,5-di-*O*-benzyl-*D*-arabinofuranose* (**3**).—Acetylation of **2** (100 mg, 0.3 mmol) with acetic anhydride (4 mL) in pyridine (5 mL) at room temperature for 4 h gave compound **3** in a quantitative yield as a syrup consisting of α and β anomers in a ratio of 2:1. The mixture was separated by HPLC with 4:1 petroleum ether–EtOAc as the eluent; for α anomer, $[\alpha]_D$ +90.8° (*c* 1.5, $CHCl_3$); ^{1}H NMR: δ 7,42–7.22 (m, 10 H, Ph), 6.21 (s, 1 H, H-1), 5.22 (d, 1 H, $J_{2,3}$ 1.5 Hz, H-2), 4.80–4.50 (m, 4 H, 2 PhCH_2), 4.40 (m, 1 H, $J_{3,4}$ 4.8, $J_{4,5}$ 4.4 Hz, H-4), 4.00 (dd, 1 H, $J_{2,3}$ 1.5, $J_{3,4}$ 4.8 Hz, H-3), 3.62 (d, 2 H, $J_{4,5}$ 4.4 Hz, 2 H-5′), 2.14, 2.03 (2 s, 6 H, 2 COCH_3). Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.67; H, 6.28. Found: C, 66,93; H, 6.29. For β anomer, $[\alpha]_D$ −67.5° (*c* 0.7, $CHCl_3$), ^{1}H NMR: δ 7.40–7.22 (m, 10 H, Ph), 6.37 (d, 1 H, $J_{1,2}$ 4.6 Hz, H-1), 5.25 (dd, 1 H, $J_{1,2}$ 4.6, $J_{2,3}$ 6.7 Hz, H-2), 4.62 (s, 2 H, PhCH_2), 4.58 (s, 2 H, PhCH_2), 4.38 (m, 2 H, H-3,4), 3.60 (d, 2 H, $J_{4,5}$ 5.3 Hz, 2 H-5), 2.04, 1.97 (2 s, 6 H, 2 COCH_3).

3, 5 - Di - O - benzyl - 2 - O - toluenesulfonyl - D - arabinofuranose (**4**).—To a solution of **2** (614 mg, 1.86 mmol) in pyridine (5 mL) was added TsCl (1.1 g, 5.6 mmol) and powdered K_2CO_3 (257 mg, 1.86 mmol) at 0 °C. The mixture was stirred at 0 °C for about 20 h, then poured into ice-cold water and extracted with dichloromethane (30 mL). The organic layer was washed with cold water (50 mL), 1 N HCl (4 × 20 mL), and dried over Na_2SO_4. The solution was concentrated and the resultant residue was subjected to column chromatography with 3:1 petroleum ether–EtOAc as the eluent to give **4** (565 mg, 62.8%) as an α:β mixture in a ratio of 3:1; $[\alpha]_D$ +42.0° (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 7.85 (d, 0.5 H, Ph–H of Ts for β anomer), 7.78 (d, 1.5 H, Ph–*H* of Ts for α anomer), 7.47–7.14 (m, 12 H, Ph*H*), 5.26 (d, 0.75 H, $J_{H1,OH}$ 6.3 Hz, H-1 of α anomer), 5.15 (dd, 0.25 H, $J_{1,2}$ 9.7, $J_{H1,OH}$ 4.3 Hz, H-1 of β anomer), 4.79

(d, 0.75 H, $J_{2,3}$ 1.2 Hz, H-2 of α anomer), 4.82 (dd, 0.25 H, H-2 of β anomer), 4.70–4.50 (m, 4 H, 2 PhCH_2), 4.40–4.25 (m, 1 H, H-4), 4.07–3.89 (m, 1 H, H-3), 3.60–3.15 (m, 3 H, 2 H-5, O*H*), 2.46 (s, 3 H, PhCH_3). Anal. Calcd for $C_{26}H_{28}O_7S_1$: C, 64.64; H, 5.79. Found: C, 65.00; H, 5.79.

1-O-Acetyl-3,5-di-O-benzyl-2-O-toluenesulfonyl-D-arabinofuranose (**5**).—Compound **4** (50 mg, 0.1 mmol) was acetylated with acetic anhydride (1 mL) in pyridine (1.5 mL) to afford **5** (53 mg, 98%) as a syrup (α:β 4:1); $[\alpha]_D$ +22.4° (*c* 1.1, $CHCl_3$); ^{1}H NMR: δ 7.81 (d, 2 × 0.2 H, Ph–*H* of Ts for β isomer), 7.80 (d, 2 × 0.8 H, Ph–*H* of Ts for α anomer), 7.42–7.16 (m, 12 H, Ph), 6.08 (d, 0.2 H. $J_{1,2}$ 4.2 Hz, H-1 of β anomer), 6.05 (s, 0.8 H, H-1 of α anomer), 5.00 (d, 0.8 H, $J_{2,3}$ 2.0 Hz, H-2 of α anomer), 4.90 (dd, 0.2 H, $J_{1,2}$ 4.2, $J_{2,3}$ 7.0 Hz, H-2 of β anomer), 4.62–4.40 (m, 4 H, 2 PhCH_2), 4.37–4.20 (m, 1 H, H-4), 4.18–4.10 (m, 1 H, H-3), 3.58–3.44 (m, 2 H, 2 H-5), 2.47 (s, 3 H, PhCH_3), 2.02 (s, 3 × 0.8 H, COCH_3 of α anomer), 1.88 (s, 3 × 0.2 H, COCH_3 of β anomer). Anal. Calcd for $C_{28}H_{30}O_8S_1$: C, 63.88; H, 5.70. Found: C, 64.29; H, 5.62.

1,2-Anhydro-3,5-di-O-benzyl-α-D-ribofuranose (**6**).—To a solution of **4** (215 mg, 0.445 mmol) in dry oxolane (6 mL) was added potassium *tert*-butoxide (75 mg, 0.65 mmol), and the mixture was stirred at room temperature for 10 min, at the end of which time TLC (3:1 petroleum ether–EtOAc) indicated that the starting material had disappeared. The mixture was concentrated to dryness, and the residue was repeatedly extracted with 3:1 petroleum ether–EtOAc. Concentration of the combined extracts yielded **6** as a syrup (135 mg, 97%); $[\alpha]_D$ +58° (*c* 0.25, $CHCl_3$); ^{1}H NMR: δ 7.41–7.26 (m, 10 H, 2 Ph), 5.22 (d, 1 H, $J_{1,2}$ 2.0 Hz, H-1), 4.72, 4.63 (ABdd, 2 H, *J* 12.0 Hz, PhCH_2), 4.56, 4.48 (ABdd, 2 H, *J* 12.2 Hz, PhCH_2), 4.17 (dd, 1 H, $J_{2,3}$ 1.7, $J_{3,4}$ 6.6 Hz, H-3), 3.92 (m, 1 H, H-4), 3.63 (dd, 1 H $J_{4,5}$ 2.8, $J_{5,5'}$ 11.0 Hz, H-5), 3.58 (t, 1 H, $J_{1,2}$ 2.0, $J_{2,3}$ 1.7 Hz, H-2), 3.51 (dd, 1 H, $J_{4,5'}$ 4.0, $J_{5,5'}$ 11.0 Hz, H-5′).

Methyl 3, 5 - di - O - benzyl - β - D - ribofuranoside (**7**).—Compound **6** (40 mg, 0.128 mmol) was dissolved in anhydrous MeOH (4 mL) and kept for 1 h at room temperature. TLC (2:1 petroleum ether–EtOAc) indicated that the reaction was complete. The solution was concentrated to afford **7** quantitatively as a syrup; $[\alpha]_D$ +17.4° (*c* 0.4, $CHCl_3$); ^{1}H NMR: δ 7.40–7.20 (m, 10 H, 2 Ph), 4.88 (s, 1 H, H-1), 4.59 (s, 4 H, 2 PhCH_2), 4.22 (t, 1 H, $J_{3,4}$ 4.4, $J_{4,5}$ 4.4 Hz, H-4), 4.12–4.03 (m, 2 H, H-2,3), 3.55 (d, 2 H, $J_{4,5}$ 4.4 Hz, 2 H-5), 3.35 (s, 3 H, OCH_3). Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.77; H, 6.98. Found: C, 70.01; H, 6.96.

Methyl 2 - O - acetyl - 3, 5 - di - O - benzyl - β - D - ribofuranoside (**8**).—Compound **7** (60 mg, 0.16 mmol) was acetylated with acetic anhydride (1.5 mL) in pyridine (3 mL) to afford **8** (65 mg, 98%) as a syrup; $[\alpha]_D$ +14.1° (*c* 1.6, $CHCl_3$); ^{1}H NMR: δ 7.40–7.20 (m, 10 H, 2 Ph), 5.20 (d, 1 H, $J_{2,3}$ 6.0 Hz, H-2), 4.88 (s, 1 H, H-1), 4.60–4.40 (m, 4 H, 2 PHCH_2), 4.23 (m, 1 H, H-4), 4.12 (dd, 1 H, $J_{2,3}$ 6.0, $J_{3,4}$ 9.5 Hz, H-3), 3.60 (dd, 1 H, $J_{4,5}$ 2.4, $J_{5,5'}$ 10.0 Hz, H-5), 3.50 (dd, 1 H, $J_{4,5'}$ 6.4, $J_{5,5'}$ 10.0 Hz, H-5′), 3.35 (s, 3 H, OCH_3), 2.13 (s, 3 H, COCH_3). Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.39; H, 6.74. Found: C, 68.79; H, 6.75.

1′-(3′, 5′-Di-O-benzyl-β-D-ribofuranosyl)-uracil (**10**) *and 1′-(2′-O-acetyl-3′,5′-di-O-benzyl-β-D-ribofuranosyl)-uracil* (**11**).—To a stirred solution of *O,O*-bis-(trimethylsilyl)-uracil (195 mg, 0.69 mmol) in dry CH_2Cl_2 (4 mL) with molecular sieves (4 Å, 0.5 g) was added compound **6** (104 mg, 0.32 mmol) in dry CH_2Cl_2 (4 mL). The mixture was stirred for 8 h at room temperature, at the end of which time TLC (1:1 petroleum ether–EtOAc) indicated that the starting material **6** had disappeared. The mixture was diluted with CH_2Cl_2 (30 mL) and filtered, and the solution was concentrated to a syrup which was subjected to column chromatography with 1:2 petroleum ether–EtOAc as the eluent. Compounds **9** (98 mg, 62%) and **10** (35 mg, 26%) were obtained. Compound **9** was readily converted to **10** quantitatively in a solution of CH_3CN (10 mL) containing HCOOH (0.4 mL) within 5 min. Compound **10** was obtained as white needles after evaporation of the solvents; mp 70–72 °C; $[\alpha]_D$ +31.7° (*c* 2.1, $CHCl_3$); ^{1}H NMR: δ 8.80 (s, 1 H, N–*H*), 7.70 (d, 1 H, $J_{5,6}$ 8.1 Hz, H-6), 7.38 (s, 10 H, 2 Ph), 5.95 (d, 1 H, $J_{1',2'}$ 4.1 Hz, H-1′), 5.27 (d, 1 H, $J_{5,6}$ 8.05 Hz, H-5), 4.70, 4.60 (ABdd, 2 H, *J* 11.7 Hz, PhCH_2), 4.50 (s, 2 H, PhCH_2), 4.30–4.18 (m, 2 H, H-3,4′), 4.10 (t, 1 H, $J_{1',2'}$ 4.1, $J_{2',3'}$ 4.1 Hz, H-2′), 3.82 (dd, 1 H, $J_{4',5'}$ 2.4, $J_{5',5''}$ 10.5 Hz, H-5′), 3.58 (dd, 1 H, $J_{4',5''}$ 1.7, $J_{5',5''}$ 10.5 Hz, H-5″), 2.50 (s, 1 H, O*H*). Anal. Calcd for $C_{23}H_{24}O_6N_2$. 0.5 H_2O: C, 63.74; H, 5.54. Found: C, 63.74; H, 5.60. Compound **10** (20 mg, 0.046 mmol) was acetylated with acetic anhydride (0.5 mL) in pyridine (1 mL) to afford **11** (19 mg, 93%); $[\alpha]_D$ +20° (*c* 0.12, $CHCl_3$); ^{1}H NMR: δ 8.15 (s, 1 H, N–*H*), 7.75 (d, 1 H, $J_{5,6}$ 8.2 Hz, H-6), 7.40–7.10 (m, 10 H, 2 Ph), 6.03 (d, 1 H, $J_{1',2'}$ 2.5 Hz, H-1′), 5.28–5.20 (m, 2 H, H-2′,5), 4.60–4.30 (m, 4 H, 2 PhCH_2), 4.20–4.10 (m, 2 H, H-3′,4′), 3.80 (dd, 1 H,

$J_{4',5'}$ 1.3, $J_{5',5''}$ 10.2 Hz, H-5'), 3.50 (dd, 1 H, $J_{4'5''}$ 1.0, $J_{5',5''}$ 10.2 Hz, H-5''), 2.10 (s, 3 H, COCH_3).

*1'-(3',5'-Di-*O*-benzyl-2'-*O*-methyl-β-*D*-ribofuranosyl)-3-methyl-uracil* (**12**).—To a solution of **10** (20 mg, 0.046 mmol) in methyl iodide (5 mL) was added portionwise silver oxide (40 mg, 0.17 mmol). The reaction was complete within 4 h. After filtration and purification, **12** was obtained as a syrup (21 mg, 85%); $[\alpha]_D$ +24.6° (*c* 2.0, $CHCl_3$); ^{1}H NMR: δ 7.95 (d, 1 H, $J_{5,6}$ 9.1 Hz, H-6), 7.40–7.20 (m, 10 H, 2 Ph), 5.95 (d, 1 H, $J_{1',2'}$ 0.8 Hz, H-1'), 5.30 (d, 1 H, $J_{5,6}$ 9.1 Hz, H-5), 4.70–4.40 (m, 4 H, 2 PhCH_2), 4.30 (m, 1 H, H-4'), 4.08 (dd, 1 H, $J_{2',3'}$ 6.0, $J_{3',4'}$ 10 Hz, H-3'), 3.95 (dd, 1 H, $J_{4',5'}$ 2.0, $J_{5',5''}$ 11 Hz, H-5'), 3.72 (dd, 1 H, $J_{1',2'}$ 0.8, $J_{2',3'}$ 6 Hz, H-2'), 3.70 (dd, 1 H, $J_{4',5''}$ 1.0, $J_{5',5''}$ 11 Hz, H-5''), 3.61 (s, 3 H, OCH_3), 3.30 (s, 3 H, N–CH_3). Anal. Calcd for $C_{25}H_{28}N_2O_6$: C, 66.37; H. 6.19. Found: C, 66.43; H, 6.21.

O-(2-O-Acetyl-3,5-di-O-benzyl-β-D-ribofuranosyl)-(1 → 5)-3-O-benzyl-1,2-O-isopropylidene-α-D-xylofuranose (**13β**), *O-(2-O-acetyl-3,5-di-O-benzyl-α-D-ribofuranosyl)-(1 → 5)-3-O-benzyl-1,2-O-isopropylidene-α-D-xylofuranose* (**13α**), *and O-(2-O-acetyl-3,5-di-O-benzyl-D-ribofuranosyl)-(1 → 2)-O-(3,5-di-benzyl-β-D-ribofuranosyl)-(1 → 5)-3-O-benzyl-1,2-O-isopropylidene-α-D-xylofuranose* (**15**).—Experiment 1: To a solution of 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-xylofuranose (160 mg, 0.57 mmol) in anhydrous dichloromethane (4 mL) was added 4 Å molecular sieves (1 g) and $ZnCl_2$ (0.5 g). The mixture was stirred for 10 min at room temperature, and a solution of **6** (98 mg, 0.3 mmol) in methylene chloride (1 mL) was added. The mixture was stirred at room temperature for 12 h, at the end of which time TLC (2:1 petroleum ether–EtOAc) indicated that **6** had disappeared. The suspension was filtered to remove solid material, and the filtrate was washed with water (3 × 50 mL), dried over Na_2SO_4, and concentrated to a syrup. The syrup was dissolved in pyridine (4 mL) and to the solution was added acetic anhydride (3 mL) at room temperature. After 2 h, the mixture was poured into ice-cold water and extracted with dichloromethane (50 mL). The organic layer was washed with cold 1 N HCl (3 × 20 mL) and then dried over Na_2SO_4. The solution was concentrated to a syrup which was subjected to HPLC with 4:1 petroleum ether–EtOAc as the eluent to afford compound **13β** (90 mg, 47%) and **13α** (13 mg, 7%) as syrups; for **13β**, $[\alpha]_D$ −22.4° (*c* 2.8, $CHCl_3$); ^{1}H NMR: δ 7.40–7.20 (m, 15 H, 3 Ph), 5.95 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 5.33 (d, 1 H, $J_{1',2'}$ 3.4 Hz, H-2'), 5.08 (s, 1 H, H-1'), 4.68–4.38 (m, 7 H, H-2,3 PhCH_2), 4.30–4.15 (m, 3 H, H-4, H-3',4'), 3.90 (dd, 1 H, $J_{4,5a}$ 3.9, $J_{5a,5b}$ 11 Hz, H-5a), 3.82 (d, 1 H, $J_{3,4}$ 3.4 Hz, H-3), 3.70 (dd, 1 H, $J_{4,5b}$ 7.3, $J_{5a,5b}$ 11 Hz, H-5b), 3.60 (dd, 1 H, $J_{4',5'a}$ 2.9, $J_{5'a,5'b}$ 10 Hz, H-5'a), 3.46 (dd, 1 H, $J_{4',5'b}$ 4.6, $J_{5'a,5'b}$ 10 Hz, H-5'b), 2.12 (s, 3 H, COCH_3), 1.50, 1.32 (2 s, 6 H, 2 CCH_3). Anal. Calcd for $C_{36}H_{42}O_{10}$: C, 68.13; H, 6.62. Found: C, 68.06; H, 6.70. For **13α**, $[\alpha]_D$ +2.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 7.38–7.21 (m, 15 H, 3 Ph), 5.91 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.20 (d, 1 H, $J_{1',2'}$ 4.4 Hz, H-1'), 4.90 (dd, 1 H, $J_{1',2'}$ 4.4, $J_{2',3'}$ 7.0 Hz, H-2'), 4.65–4.40 (m, 8 H, H-2,4, 3 PhCH_2), 4.19 (m, 1 H, H-4'), 4.08–3.95 (m, 3 H, H-3, H-5a,5b), 3.80 (dd, 1 H, $J_{2',3'}$ 7.0, $J_{3',4'}$ 10.2 Hz, H-3'), 3.51 (dd, 1 H, $J_{4',5'a}$ 3.4, $J_{5'a,5'b}$ 10.7 Hz, H-5'a), 3.37 (dd, 1 H, $J_{4',5'b}$ 3.9, $J_{5'a,5'b}$ 10.7 Hz, H-5'b), 2.11 (s, 3 H, COCH_3), 1.52, 1.31 (2 s, 6 H, 2 CCH_3). Experiment 2: To a solution of 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-xylofuranose (82 mg, 0.3 mmol) in dry dichloromethane (5 mL) containing 4 Å molecular sieves (1 g) and $ZnCl_2$ (0.5 g) was added compound **6** (200 mg, 0.6 mmol) in CH_2Cl_2 (4 mL). Compounds **13β** (79 mg, 41%), **13α** (23 mg, 12%) and **15** (42 mg, 15%) were obtained after the workup and purification procedures described in Experiment 1. For compound **15**, $[\alpha]_D$ +48° (*c* 0.25, $CHCl_3$); ^{1}H NMR: δ 7.40–7.20 (m, 25 H, 5 Ph), 5.92 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 5.42 (d, 1 H, $J_{1'',2''}$ 4.2 Hz, H-1''), 5.03 (s, 1 H, H-1'), 4.97 (dd, 1 H, $J_{1'',2''}$ 4.2, $J_{2'',3''}$ 8 Hz, H-2''), 2.10 (s, 3 H, COCH_3), 1.49, 1.30 (2 s, 6 H, 2 CCH_3). ESIMS $[M + H^+]^+$, 948.1. Calcd for $C_{55}H_{62}O_{14}$: 947.046.

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