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Note

Synthesis of 1,2-*O*-isopropylidene-α-D-ribofuranose from D-ribose

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1,2-*O*-Isopropylidene-α-D-ribofuranose (**6**) was first isolated in a study of the preparation of 2,3-*O*-isopropylidene-D-ribofuranose[1]. Preparative synthesis of **6** has not hitherto been achieved from D-ribose, but from (*a*) D-xylose, through oxidation of OH-3 of 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose, followed by reduction and *O*-debenzoylation[2], and (*b*) D-glucose, through oxidation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, followed by sequential reduction, *O*-deisopropylidenation, periodate oxidation, and reduction[3]. We now report a synthesis of **6** from 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**1**).

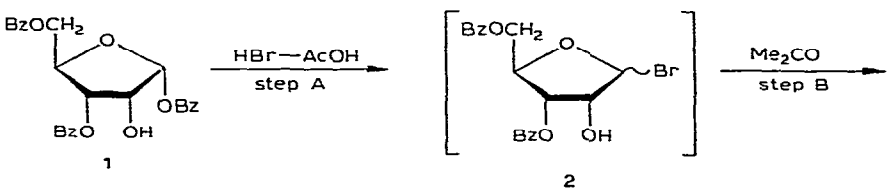
2,3,5-Tri-*O*-benzoyl-D-ribofuranose and 1,2,3,5-tetra-*O*-benzoyl-D-ribofuranose have been shown to give **1** (~45% yield), in addition to 2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, on treatment with 32% hydrogen bromide in glacial acetic acid at room temperature, followed by reaction of the resulting bromide (**2**) with aqueous acetone at room temperature[4,5]. Compound **1** used here was prepared from methyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside, and was found to be successfully converted into **3** by steps A and B, namely, A, conversion of **1** into 3,5-di-*O*-benzoyl-D-ribofuranosyl bromide (**2**) with 32% hydrogen bromide in glacial acetic acid, and B, conversion of **2** into 3,5-di-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-ribofuranose (**3**) by treatment with acetone, either pure or containing other agents. For step B, examination of the reaction conditions gave the results summarized in Table I. Treatment in pure acetone (entry 1) gave 3,5-di-*O*-benzoyl-D-ribofuranose monoacetates (**4a** and **4b**) (39 and 4% yields, respectively) in addition to **3** (52% yield). Although attempted purification to provide analytically pure samples was unsuccessful, **4a** and **4b** gave acetyl methyl proton signals at δ 2.03 and 2.07 in their n.m.r. spectra; t.l.c. in 9:1 (v/v) benzene–acetone gave spots having R_F values of 0.25 and 0.15, respectively, and both gave 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-D-ribofuranose (**5**) on acetylation with acetic anhydride in pyridine. A similar trend was observed on treatment with aqueous acetone (entries 2 and 3). In order to improve the yield of **3**, the solution containing **2** was, prior to step B, additionally washed twice with aqueous sodium hydrogencarbonate solution, and then subjected to treatment with 1:49 (v/v) water–

TABLE I

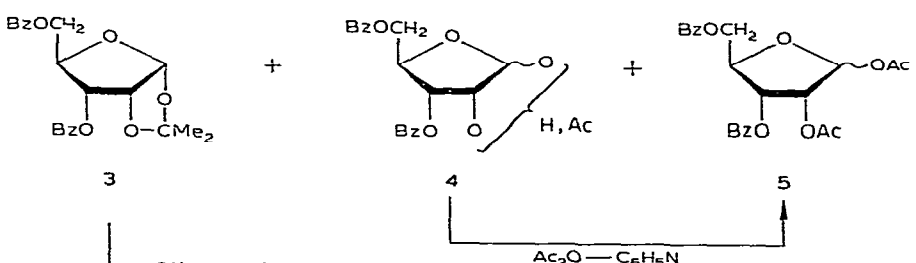
EXAMINATION OF THE TREATMENT (STEP B) FOR THE FORMATION OF 3,5-DI-*O*-BENZOYL-1,2-*O*-ISOPROPYLIDENE-α-D-RIBOFURANOSE[a]

Entry	*Agent*	*Yield of product (%)*			
		3	4a	4b	5
1	acetone	52	39	4	—
2	1:49 (v/v) water–acetone	56	30	10	—
3	1:49 (v/v) water–acetone	50 (40[b])	36	12	—
4[c]	1:49 (v/v) water–acetone	27	58	10	—
5[d]	1:49 (v/v) water–acetone	36 (28[b])	37	10	13
6	1:4 (v/v) 2,2-dimethoxypropane–acetone	32 (17[b])	59	3	—
7	1:24 (v/v) triethylamine–acetone	—	81	13	—

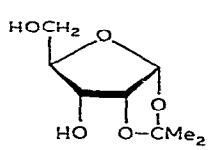
[a]A solution of **1** (5 mmol) in dichloromethane (25 mL) was treated with 32% hydrogen bromide in acetic acid (10 mL) for 1 h at room temperature, and, after dilution with dichloromethane (50 mL), the mixture was successively washed with chilled water (75 mL), a saturated, aqueous solution of sodium hydrogencarbonate (75 mL), and chilled water (75 mL), and separately processed with each of the agents (25 mL) shown here. The amounts of **1**, agent, and solvents used in Entries 1, 2, and 7 were one-fifth of those in other entries. [b]These are the yields obtained on crystallization from methanol. [c]Prior to step B, the solution was washed thrice with saturated aqueous, $NaHCO_3$ solution (75 mL). [d]Prior to step B, the solution was evaporated at 25°/2660 Pa.



1 2



3 4 5



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acetone; however, **3** was then obtained in only 27% yield, and the yields of **4a** and **4b** were increased (entry 4).

On performing the removal of the agent by merely evaporating in step A, compound **5** (13% yield) was unexpectedly isolated, in addition to **3** (36% yield) and **4a,b** (entry 5). We subsequently performed step B by use of 1:4 (v/v) 2,2-dimethoxypropane–acetone, but obtained **3** (32% yield), **4a,b** (62% yield), and a small proportion of an as-yet-unidentified, syrupy product (entry 6). Moreover, treatment with 1:24 (v/v) triethylamine–acetone gave no **3**, but **4a** (81% yield) and **4b** (13% yield). The formation of the acetates **4a**, **4b**, and **5** probably arose from the reaction potentially catalyzed by hydrogen bromide in glacial acetic acid. Therefore, **1** was treated with 4% hydrogen bromide in dichloromethane, followed by step B as described in entry 3, to give **3** in 59% yield as a syrup (44% yield on crystallization). In this case, the other products were detected as three spots in t.l.c., but we were unable to isolate them in the pure state. A detailed discussion of the mechanism of formation of the acetates must await further investigation.

Treatment of **3** with sodium methoxide–methanol gave **6** in quantitative yield. This investigation has furnished a rather simple method for the synthesis of **6**, a compound of wide, potential use in nucleoside and nucleotide chemistry.

EXPERIMENTAL

General. — Melting points are uncorrected. Specific rotations were determined with a Hitachi PO-B polarimeter. N.m.r. spectra were recorded with a Varian T-60 instrument for solutions in chloroform-*d* with tetramethylsilane as the internal standard. I.r. spectra were recorded with a Hitachi 285 spectrophotometer. T.l.c. was performed on precoated plates (thickness 0.2 mm) of Merck silica gel 60 F_{254}. Elemental analyses were made by a member of the Laboratory of Organic Analysis, Tokyo Institute of Technology.

Reaction of **1** *with hydrogen bromide, followed by treatment with acetone.* — Compound **1** (2.31 g, 5.0 mmol), prepared from methyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside[6] by treatment with 32% hydrogen bromide–glacial acetic acid[4,5], was dissolved in dichloromethane (25 mL). The solution was mixed with 32% hydrogen bomide–glacial acetic acid (10 mL), and stirred for 1 h at room temperature (step A). The resulting mixture was diluted with dichloromethane (50 mL), and the solution was washed successively with chilled water (75 mL), a saturated, aqueous solution of sodium hydrogencarbonate (75 mL), and chilled water (75 mL), dried (anhydrous sodium sulfate), and evaporated to a syrup. The syrup was dissolved in 49:1 (v/v) water–acetone (25 mL), and the solution was stirred for 15 h at room temperature (step B). The resulting solution was mixed with dichloromethane (75 mL), washed successively with chilled water, a saturated, aqueous solution of sodium hydrogencarbonate (50 mL), and water, dried (anhydrous sodium sulfate), and evaporated to a syrup, which was chromatographed on a column of silica gel (Wakogel C-300). Elution with chloroform gave **3** (0.988 g; 50% yield as syrup; 40% yield

after crystallization), m.p. 100.5–101.5° (from methanol), $[\alpha]_D^{22}$ +125° (*c* 1.0, chloroform); ν_{max}^{KBr} 1718 cm^{-1}; n.m.r. ($CDCl_3$–Me_4Si): δ 1.35 (s, 3 H, C-CH_3), 1.58 (s, 3 H, C-CH_3), 4.5–5.3 (m, 5 H, H-2,3,4,5,5′), 6.00 (s, 1 H, $J_{1,2}$ 3.5 Hz, H-1), and 7.2–8.2 (m, 10 H, 2 Bz).

Anal. Calc. for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.15; H, 5.58.

Subsequent elution with 1:99 methanol–chloroform gave 3,5-di-*O*-benzoyl-D-ribofuranose monoacetate (**4a**) (0.724 g, 36% yield) as the second fraction, and **4b** (0.246 g, 12% yield) as the third fraction. Compound **4a** was dissolved in chloroform (5 mL), and to the solution was added pyridine (2 mL), and then acetic anhydride (2 mL) dropwise under ice-cooling. The usual processing gave a quantitative yield of **5** [0.8 g (α:β = 1:4); 0.49 g (62% yield) after crystallization]. Compound **4b** also gave **5**.

The β anomer of **5** had m.p. 127.5–128° (from dichloromethane–diethyl ether–hexane) [lit.[5] m.p. 126–127° (from ethanol)], $[\alpha]_D^{22}$ −2° (*c* 1.0, chloroform) [lit.[5] $[\alpha]_D$ −3° (*c* 1.67, chloroform)]; ν_{max}^{KBr} 1742 and 1722 cm^{-1}; n.m.r. ($CDCl_3$–Me_4Si): δ 1.97 (s, 3 H, C-CH_3), 2.07 (s, 3 H, C-CH_3), 4.2–5.0 (m, 3 H, H-4,5,5′), 5.55 (d, 1 H, $J_{2,3}$ 5.0 Hz, H-2), 5.78 (t, 1 H, $J_{2,3} = J_{3,4}$ = 5.0 Hz, H-3), 6.29 (s, 1 H, H-1), and 7.1–8.1 (m, 10 H, 2 Bz).

The α anomer of **5** gave, in n.m.r. ($CDCl_3$–Me_4Si): δ 2.00 (s, 3 H, C-CH_3), 2.15 (s, 3 H, C-CH_3), and 6.75 (d, 1 H, $J_{1,2}$ 4.2 Hz, H-1).

O-Debenzoylation of **3**. — Compound **3** was treated with M sodium methoxide–methanol (1 mL) in methanol (30 mL) overnight at room temperature, and the solution evaporated to a syrup which was chromatographed on a column of silica gel (5 g). Elution with 49:1 (v/v) chloroform–methanol gave syrupy **6** (553 mg, 97% yield), which gave crystalline **6** (450 mg, 79% yield), m.p. 85.5–86° (from ethyl acetate–hexane) (lit.[2] m.p. 85°), $[\alpha]_D^{22}$ +65° (*c* 1.0, ethanol); n.m.r. ($CDCl_3$–D_2O–Me_4Si): δ 1.50 (s, 3 H, C-CH_3), 1.73 (s, 3 H, C-CH_3), 3.5–4.2 (m, 5 H, H-2,3,4,5,5′), and 5.90 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1).

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