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A CONVENIENT SYNTHESIS OF *C*-α-D-RIBOFURANOSYL COMPOUNDS FROM 1-*O*-ACETYL-2,3,5-TRI-*O*-BENZYL-β-D-RIBOSE BY THE PROMOTION OF TRIPHENYLMETHYL PERCHLORATE

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ABSTRACT

In the presence of a catalytic amount of triphenylmethyl perchlorate (trityl perchlorate), 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-β-D-ribose stereoselectively reacted with trimethylsilyl nucleophiles, such as trimethylsilyl enol ether, allylsilane, and trimethylsilyl cyanide, to give the corresponding *C*-α-D-ribofuranosyl derivatives in excellent yields. Similarly, a *C*-α-D-ribofuranosyl compound was obtained stereoselectively in high yield by use of a flow system with polymer-supported triphenylmethyl perchlorate, prepared from polystyrene-bound triphenylmethanol, packed in a glass-tube column.

INTRODUCTION

Stereoselective synthesis of functionalized *C*-glycosyl compounds is one of the most effective and used approaches to the preparation of *C*-nucleosides. Although several methods are already known for the synthesis of *C*-β-D-ribofuranosyl compounds[1], few general and versatile methods for the synthesis of *C*-α-D-ribofuranosyl compounds have been reported[2,3]. In a previous paper[4], we have shown that, in the presence of trityl perchlorate, 1-*O*-acyl sugars stereoselectively react with alcohols to afford the corresponding α-D-glycosides in good yields. We describe herein an equally efficient method for the preparation of *C*-α-D-ribofuranosyl compounds by the reaction of 1-*O*-acetyl-D-ribose with trimethylsilyl nucleophiles in the presence of a catalytic amount of trityl perchlorate[5]. We also report the convenient synthesis of *C*-α-D-ribofuranosyl compounds by simply passing the reagents through polymer-supported trityl perchlorate, packed in a glass-tube column.

RESULTS AND DISCUSSION

In the presence of a catalytic amount of trityl perchlorate (5 mol/100 mol), 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-β-D-ribofuranose (**1**) reacted with the trimethylsilyl

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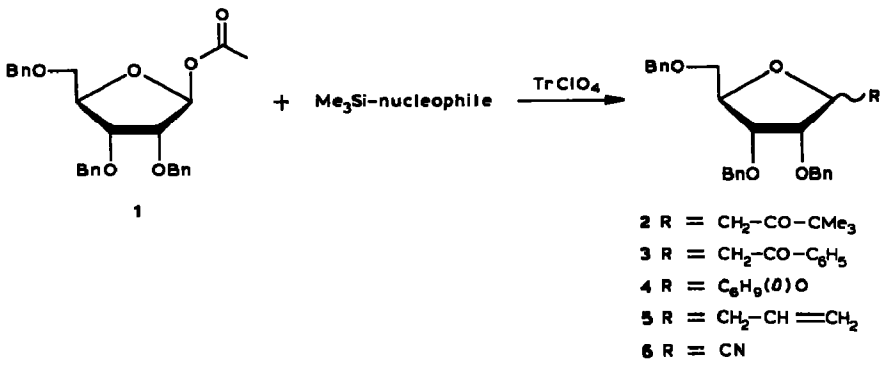


enol ether of *tert*-butyl methyl ketone to afford two anomers of 3,3-dimethyl-1-(2,3,5-tri-*O*-benzyl-D-ribofuranosyl)-2-butanone (**2**) (93%, 99:1 stereoselectivity). The ^{1}H-n.m.r. spectra showed two doublets of doublets for $-CH_2-$ protons at δ 3.00 and 2.95 for the major anomer (**2α**), and 2.70 and 2.55 for the minor anomer (**2β**). In the ^{13}C-n.m.r. spectra, C-2 resonated at δ 37.3 for the major anomer and 40.4 for the minor anomer (see Table I). Treament of the major anomer with sodium methoxide (under thermodynamic conditions) gave a mixture of **2α** and **2β** (**2α**:**2β** 21:29) which were separated by column chromatography on silica gel. The results suggested that **2α** and **2β** were the α-D and the β-D anomer, respectively, especially the definitive evidence[6] that the signal of the methylene group carbon atom in the α position to the carbonyl group of **2α** was at a field higher than that of the corresponding group of **2β***.

TABLE I

CHEMICAL SHIFTS (δ) OF THE METHYLENE OR METHINE GROUP CARBON ATOM IN POSITION α TO THE CARBONYL GROUP

Compound	*Chemical shifts of anomers*	
	α	β
2	37.3	40.4
3	39.2	42.7
4 (less polar)	51.0	53.4
(more polar)	52.0	53.3

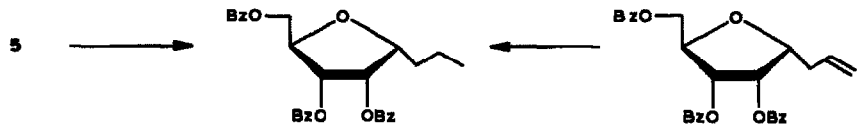
*In addition to the n.m.r. data, unambiguous chemical transformations of **2α** supported this assignment. Namely, the Bayer–Villiger oxidation of **2α**, followed by hydrolysis of the *tert*-butyl ester gave the corresponding carboxylic acid. Diazomethane treatment afforded the methyl ribofuranosylacetate whose spectral data were in complete agreement with those of the α-D anomer reported in the literature[6].

TABLE II

SYNTHESIS OF C-D-RIBOFURANOSYL COMPOUNDS 2–6

Nucleophile	*Solvent*	*Product*	*Yield (%)*	*Ratio α to β*
Me_3-C(OSiMe_3)=CH_2	$(MeO)_2C_2H_4$	2	93	99:1
Ph-C(OSiMe_3)=CH_2	$(MeO)_2C_2H_4$	3	97	100:0
C_6H_9-OSiMe_3	$(MeO)_2C_2H_4$	4	93	96:4
Me_3Si-CH_2-CH=CH_2	$(MeO)_2C_2H_4$	5	90	100:0
Me_3SiCN	$(MeO)_2C_2H_4$	6	97	63:37
Me_3SiCN	Et_2O	6	93	93:7

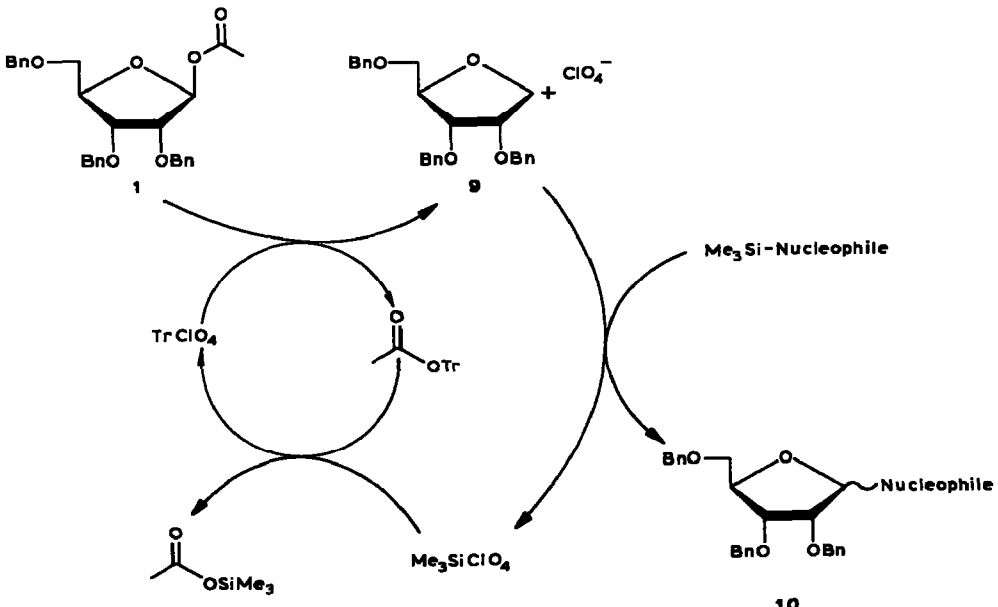
Similarly, the α-D anomers **3α** and **4α** were stereoselectively obtained in excellent yields in the case of the silyl enol ethers derived from acetophenone and cyclohexanone. Also, the α-D anomer **5** was exclusively prepared by employing 4,4-dimethyl-4-sila-1-pentene as a *C*-nucleophile under the same reaction conditions (Table II). The structure of this compound was confirmed by debenzylation by hydrogenolysis, followed by benzoylation to afford the *O*-benzoyl-*C*-α-D-ribosyl compound **7** which was identical with a sample prepared by hydrogenation of the *C*-allyl-*O*-benzoyl-α-D-ribosyl compound **8**.



The reaction of **1** with trimethylsilyl cyanide under the same reaction conditions afforded an anomeric mixture, but the α-D anomer **6α** could be obtained stereoselectively by performing the reaction in ether solvent (Table II).

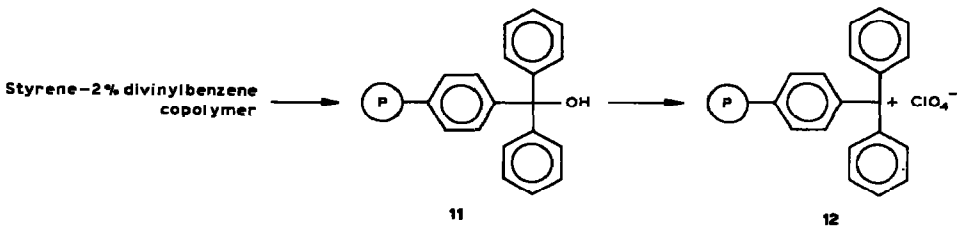
In the catalytic cycle (Scheme 1), trityl perchlorate activates **1** to generate the intermediate ion pair **9** and trityl acetate. This intermediate smoothly reacts with a trimethylsilylated nucleophile to give the *C*-ribofuranosyl compound **10** and trimethylsilyl perchlorate, which immediately reacts with trityl acetate to regenerate trityl perchlorate.

We have recently demonstrated the new possibilities of various trityl salts in synthetic reactions[3–5,7]. In these reactions, trityl salts effectively activate acyloxy groups of anomeric centers, alkoxy groups of acetals, aldehydes, or α,β-unsaturated ketones. The characteristic point of trityl salts, compared with other Lewis acids such as titanium tetrachloride, borontrifluoride, and tin tetrachloride, is that the reactions are effectively promoted by catalytic use. In order to develop a more efficient catalyst with wider applicability directed to synthetic control, the trityl



Scheme 1.

cation was immobilized on a polymer to prepare a polymer-bound trityl perchlorate[8], which was used for the synthesis of *C*-α-D-ribofuranosyl compounds. The polystyrene-bound triphenylmethanol **11** (ref. 9) was converted into the perchlorate salt **12** by treatment with perchloric acid in acetic anhydride; quantitative analysis[8] indicated that ~7% of the aromatic rings of polystyrene were converted into a perchlorate salt.



11 12

The *C*-glycosylation reaction was carried out in a flow system with the immobilized catalyst **12** packed in a glass-tube column. The dichloromethane solution of **1** and the trimethylsilyl enol ether of *tert*-butyl methyl ketone was charged onto the column and **2** was instantly obtained at the bottom (yield, 86%; ratio α to β, 24:1). Thus, *C*-α-D-ribofuranosyl compounds were successfully obtained in good yield by the flow-type reaction. This method has the practical advantage that the resulting compounds are separated quickly from the reaction system and that the catalyst is re-used.

EXPERIMENTAL

General. — Melting points were uncorrected. Optical rotations were measured with a Jasco DIP-181 digital polarimeter. ^{1}H-N.m.r. spectra for solutions in $CDCl_3$ were recorded with a Varian EM-390 spectrometer, and ^{13}C-n.m.r. spectra for solutions in $CDCl_3$ with a Jeol FX-90Q FT spectrometer. Column chromatography was performed on Silica gel 60 (Merck) or Wakogel C-200.

Trityl perchlorate was prepared by the method of Dauben *et al.*[10] and purified by that of Kochetkov *et al.*[11]. 1,2-Dimethoxyethane (DME) was distilled from $LiAlH_4$ before use. Polystyrene-bound trityl alcohol **11** was prepared according to a known method[9] from commercially available macroporous styrene–2% divinylbenzene copolymer (Mitsubishi Kasei Co.; DIAION HP-50).

1-O-Acetyl-2,3,5-tri-O-benzyl-β-D-ribofuranose (**1**). — To a solution of 2,3,5-tri-*O*-benzyl-D-ribofuranose (10 mmol) in pyridine (15 mL) was slowly added acetic anhydride (10 mL) at 0°. The mixture was stirred overnight at room temperature and was poured into a cold M HCl solution. The aqueous layer was extracted with ethyl acetate and the organic layer washed successively with aqueous $CuSO_4$, water, aqueous $NaHCO_3$, and water, dried, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **1** (quant.), $[\alpha]_D^{26}$ +59° (*c* 1.0, chloroform); ^{1}H-n.m.r.: δ 1.90 (s, 3 H), 3.50–3.70 (m, 2 H), 3.75–4.05 (m, 2 H), 4.10–4.70 (m, 7 H), 6.10 (s, 1 H), and 6.70–7.70 (m, 15 H); ^{13}C-n.m.r.: δ 21.0, 98.9 (C-1), and 169.5.

Anal. Calc. for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 73.00; H, 6.73.

General procedure for the preparation of C-α-D-ribofuranosyl compounds. — Trityl perchlorate (15 μmol, 5 mg) was dried *in vacuo* for 1 h. To this was added the mixture of **1** (0.3 mmol, 139 mg) and a trimethylsilylated nucleophile (0.5 mmol) in 1,2-dimethoxyethane or ether (4 mL) at 0° under Ar. The mixture was stirred for 0.5–1 h at 0°. Phosphate buffer (pH 7) was added and the aqueous layer extracted with ether. The organic layer was dried, the solvent removed under reduced pressure, and the residue chromatographed on silica gel.

3,3-Dimethyl-1-(2,3,5-tri-O-benzyl-α-D-ribofuranosyl)-2-butanone (**2α**). — $[\alpha]_D^{25}$ +35° (*c* 1.0, chloroform); ^{1}H-n.m.r.: δ 1.05 (s, 9 H), 2.95 (dd, 1 H, *J* 5 Hz), 3.00 (dd, 1 H, *J* 8 Hz), 3.50 (m, 2 H), 3.95–4.85 (m, 10 H), and 7.00–7.40 (m, 15 H); ^{13}C-n.m.r.: δ 26.4, 37.3, 44.1, 70.2, 72.7, 73.4, 73.6, 76.5, 77.8, 79.1, 80.3, and 214.5

Anal. Calc. for $C_{32}H_{38}O_5$: C, 76.46; H, 7.62. Found: C, 76.35; H, 7.66.

2-(2,3,5-Tri-O-benzyl-α-D-ribofuranosyl)acetophenone (**3α**). — $[\alpha]_D^{24}$ +38° (*c* 1.1, chloroform); ^{1}H-n.m.r.: δ 3.25 (dd, 1 H, *J* 6, 17 Hz), 3.55 (dd, 1 H, *J* 5, 17 Hz), 3.45–3.65 (m, 2 H), 3.95–4.85 (m, 10 H), 6.95–7.55 (m, 18 H), and 7.80–8.00 (m, 2 H); ^{13}C-n.m.r.: δ 39.2, 70.3, 72.8, 73.5, 73.6, 76.7, 78.0, 79.6, 80.2, and 198.6.

Anal. Calc. for $C_{34}H_{34}O_5$: C, 78.14; H, 6.56. Found: C, 78.19; H, 6.43.

2-(2,3,5-Tri-O-benzyl-α-D-ribofuranosyl)cyclohexanone (**4α**). — Less polar isomer. M.p. 60.5–61.0°, $[\alpha]_D^{24}$ +57° (*c* 1.0, chloroform); ^{1}H-n.m.r.: δ 1.15–2.60

(m, 8 H), 2.70–3.10 (m, 1 H), 3.35–3.75 (m, 2 H), 3.95–4.90 (m, 10 H), and 7.10–7.40 (m, 15 H); ^{13}C-n.m.r.: δ 25.0, 28.6, 31.8, 42.6, 51.0, and 212.4

Anal. Calc. for $C_{32}H_{36}O_5$: C, 76.77; H, 7.25. Found: C, 76.76; H, 7.26.

More polar isomer. $[\alpha]_D^{25}$ +17° (*c* 1.1, chloroform); ^{1}H-n.m.r.: δ 1.30–2.45 (m, 8 H), 2.70–3.05 (m, 1 H), 3.50–3.70 (m, 2 H), 3.95–5.05 (m, 10 H), and 7.10–7.45 (m, 15 H); ^{13}C-n.m.r.: δ 24.4, 28.1, 30.0, 42.2, 52.0, and 211.3.

Anal. Calc. for $C_{32}H_{36}O_5$: C, 76.77; H, 7.25. Found: C, 76.06; H, 7.16.

Epimerization of **2α** *to give 3,3-dimethyl-1-(2,3,5-tri-*O*-benzyl-α-*D*-ribofuranosyl)-2-butanone* (**2β**). — The procedure of Ohrui *et al.*[6] was employed. Treatment of **2α** (0.3 mmol, 150 mg) with 0.1M sodium methoxide gave a mixture of **2α** (63 mg) and **2β** (87 mg) (yield, 84%; ratio α to β, 21:29).

2β. M.p. 30–31°, $[\alpha]_D^{25}$ +27° (*c* 1.0, chloroform); ^{1}H-n.m.r.: δ 1.05 (s, 9 H), 2.55 (dd, 1 H, *J* 5, 17 Hz), 2.70 (dd, 1 H, *J* 7, 17 Hz), 3.45–4.65 (m, 12 H), and 7.15–7.45 (m, 15 H); ^{13}C-n.m.r.: δ 26.1, 40.4, 44.2, 70.1, 71.6, 71.7, 73.4, 76.8, 77.6, 80.0, 80.8, and 213.3.

Anal. Calc. for $C_{32}H_{38}O_5$: C, 76.46; H, 7.62. Found: C, 76.44; H, 7.80.

Similarly, the β-D anomers **3β** and **4β** were obtained and the chemical shifts of the methylene or methine group carbon atom in position α to the carbonyl group are reported in Table I.

*3-(2,3,5-Tri-*O*-benzyl-α-*D*-ribofuranosyl)-1-propene* (**5**). — M.p. 55.5–56.0°, $[\alpha]_D^{24}$ +49° (*c* 1.0, chloroform); ^{1}H-n.m.r.: δ 2.35–2.65 (m, 2 H), 3.45–3.65 (m, 2 H), 3.90–4.30 (m, 4 H), 4.30–4.80 (m, 6 H), 4.80–5.20 (m, 2 H), 5.50–6.60 (m, 1 H), and 7.10–7.45 (m, 15 H); ^{13}C-n.m.r.: δ 34.3, 70.3, 72.7, 73.3, 73.4, 77.9, 79.6, 80.1, 80.3, 116.6, and 138.1.

Anal. Calc. for $C_{29}H_{32}O_4$: C, 78.35; H, 7.25. Found: C, 78.47; H, 7.28.

*1-(2,3,5-Tri-*O*-benzoyl-α-*D*-ribofuranosyl)propane* (**7**). — Debenzylation of **5** by hydrogenolysis in the presence of Pd–C, followed by benzoylation in the usual manner (benzoyl chloride–pyridine) afforded **7**, $[\alpha]_D^{23}$ +110° (*c* 0.47, chloroform); ^{1}H-n.m.r.: δ 0.95 (t, 3 H, *J* 6.6 Hz), 1.15–2.00 (m, 4 H), 4.30–4.80 (m, 4 H), 5.60–5.95 (m, 2 H), 7.15–7.70 (m, 9 H), and 7.70–8.15 (m, 6 H). The optical rotation and ^{1}H-n.m.r. data were consistent with those of an authentic sample prepared by hydrogenation (H_2; Pd–C) of 3-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)-1-propene[3] (**8**).

Anal. Calc. for $C_{29}H_{28}O_7$: C, 71.30; H, 5.78. Found: C, 71.28; H, 5.67.

*2,3,5-Tri-*O*-benzyl-α-*D*-ribofuranosyl cyanide* (**7α**). — $[\alpha]_D^{24}$ +73° (*c* 1.0, chloroform); lit.[12] $[\alpha]_D^{25}$ +70° (*c* 1, chloroform); ^{1}H-n.m.r.: δ 3.25–3.45 (m, 2 H), 3.75–4.70 (m, 10 H), and 6.70–7.40 (m, 15 H); ^{13}C-n.m.r.: δ 68.6, 69.2, 72.6, 73.4, 73.5, 77.0, 77.9, 83.1, and 116.5.

Procedure for the preparation of C-D-*ribofuranosyl compounds by use of polymer-supported trityl perchlorate* (**12**) *packed in a glass-tube column.* — Polystyrene-bound triphenylmethanol (**11**; 60 mg) and chopped glass fiber (300 mg) was packed in a glass column (3 mm diam.). A solution of 70% $HClO_4$ (500 mg) in acetic anhydride (2 mL) was slowly passed through the column. The column was

washed successively with acetic anhydride (2 × 1 mL) and dichloromethane (2 × 1 mL), and dried *in vacuo*. The mixture of **1** (0.15 mmol) and a trimethylsilyl nucleophile (0.25 mmol) in dichloromethane (2 mL) was charged onto the column and the crude C-D-ribofuranosyl compound was obtained at the bottom. It was chromatographed on silica gel to afford the pure α-D compound.

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