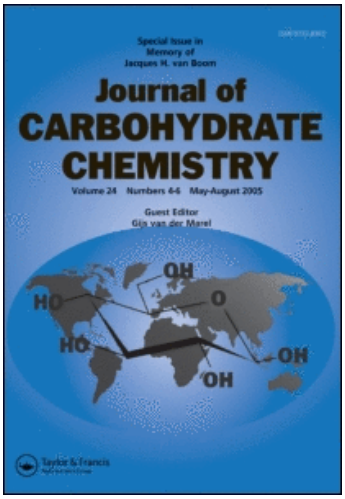


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# Simple Synthesis of 3,5-Di-*O*-Substituted 1,4-Anhydro-2-deoxy-D-*Erythro*-pent-1-enitol from D-Ribose

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*COMMUNICATION*

# SIMPLE SYNTHESIS OF 3,5-DI-*O*-SUBSTITUTED 1,4-ANHYDRO-2-DEOXY-D-*ERYTHRO*-PENT-1-ENITOL FROM D-RIBOSE

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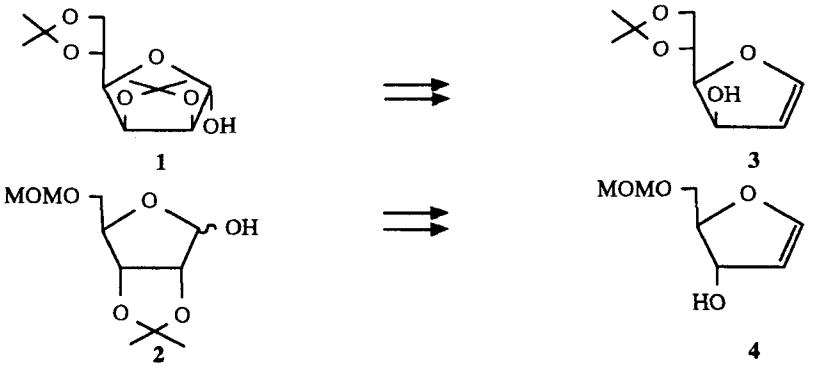
1,4-Anhydro-2-deoxypent and hex-1-enitols (furanoid glycals) are readily available by a number of reductive methods from corresponding furanoid glycosyl halides.[1-5] The crucial problem of their synthesis is related to the accessibility of the appropriate protected sugar having a free anomeric hydroxyl which allows introduction of the halide. Readily available 2,3:5,6-di-*O*-isopropylidene-D-mannose (**1**) and 2,3-*O*-isopropylidene-5-*O*-methoxymethyl-D-ribose (**2**), which is not so available, are the most common substrates used to provide alternative *cis* and *trans* disubstituted dihydrofurans **3** and **4**, respectively (SCHEME 1).[1-5]

Compound **2** has been obtained from D-ribono-1,4-lactone according to the known procedure which allows consecutive introduction of the isopropylidene[6] and 5-*O*-methoxymethyl substituent.[5] Subsequent reduction of the lactone to the hemiacetal stage **2** followed by introduction of the chlorine atom and then reduction of the glycosyl chloride in anhydrous neutral[2] or basic[1,3,5] conditions have yielded glycal **4**.

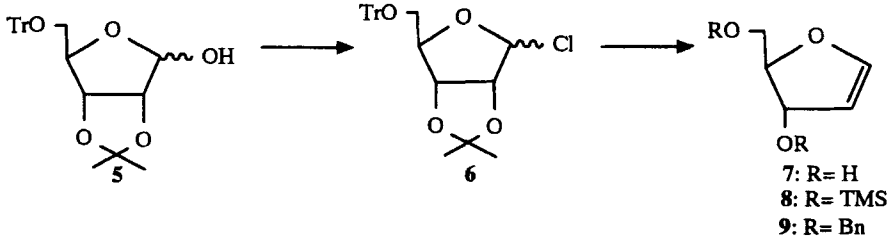
In this paper we describe a simple transformation of D-ribose, which is much cheaper than D-ribono-1,4-lactone, into the furanoid glycal of D-*erythro* configuration (**8**). D-Ribose was converted into 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribose (**5**) according to a known procedure.[7,8] Subsequently, **5** was transformed into ribosyl chloride **6** using either pyridine-thionyl chloride[1,9] or carbon tetrachloride-triphenylphosphine, the latter being a

better method.[2,4,5,7] Reduction of chloride **6** was carried out using a lithium in liquid ammonia procedure;[4,5] reduction of **6** with potassium-graphite[3] or sodium naphthalenide[1] gave negative results. Lithium in liquid ammonia removed also the trityl group providing unprotected glycal **7**. We found that the glycal **7** was stable only in the presence of a base. Addition of ammonium chloride to the reaction mixture and subsequent evaporation of ammonia caused decomposition of the glycal. Rapid benzylation of the crude post-reduction mixture with benzyl chloride - dimethyl sulfoxide - potassium hydroxide gave glycal **9** in 5% yield only, whereas silylation of the mixture with trimethylsilyl chloride - pyridine afforded glycal **8** in 10% yield. However, if the addition of pyridine preceded the evaporation of ammonia, silylation of the glycal could be achieved in 60% overall yield. 3,5-Di-*O*-trimethylsilyl glycal **8** was isolated and purified by distillation. Unstable silyl protections could be replaced by benzyl groups, when compound **8** was treated with benzyl bromide in dimethyl sulfoxide in the presence of sodium hydroxide and potassium carbonate.

SCHEME 1




The presented method is simpler and offers a substantial economic advantage over the preparation based on D-ribono-1,4-lactone.



## EXPERIMENTAL

Optical rotations were measured with a JASCO Dip-360 digital polarimeter. IR spectra were taken with a Beckman 4240 spectrophotometer. $^1H$ NMR spectra were recorded with Varian Gemini 200 and Bruker AM 500 spectrometers, and mass spectra were performed with a AMD 604 spectrometer.

Compound **5** was obtained by the reaction sequence described earlier.[7,8]

**2,3-*O*-Isopropylidene-5-*O*-trityl-α and β-D-ribofuranosyl chloride (6). Method A**, from **5** and carbon tetrachloride/triphenylphosphine (90%) according to the ref. 10. **Method B.** Compound **5** (2.7 g, 6.2 mmol) dissolved in toluene (25 mL) and pyridine (25 mL) was cooled to +5 °C and treated with a solution containing thionyl chloride (3 mL) in pyridine (10 mL). The temperature was maintained for 2 h. Subsequently toluene (30 mL) was added, the mixture was cooled to -30 °C and treated with ice-water (25 mL). The toluene layer was washed three times with water, dried and concentrated to afford **6** (1.4 g, 50%) identical to that reported in ref. 7.

**1,4-Anhydro-2-deoxy-3,5-di-*O*-trimethylsilyl-D-*erythro*-pent-1-enitol (8).** To a mechanically stirred solution of lithium (0.6 g, 8.7 mmol) in anhydrous liquid ammonia (100 mL) under argon atmosphere at -78 °C was added a solution of the furanosyl chloride **6** (3.7 g, 8.2 mmol) in dry tetrahydrofuran (15 mL). Cooling was then discontinued (ammonia reflux) and after 2 h anhydrous ammonium chloride (6 g) was cautiously added. The colorless mixture was diluted with pyridine (200 mL) and the ammonia was allowed to evaporate. The traces of ammonia and about 100 mL of pyridine were removed under reduced pressure. The concentrated mixture was cooled to -20 °C and treated with trimethylsilyl chloride (10 mL). After 1 h at room temperature the reaction mixture was cooled to -20 °C, poured into ice-water, and extracted with hexane (3 x 100 mL). The extract was washed dried and concentrated. The residue was distilled [kugelrohr, 40-60 °C (0.07 mm Hg)] to afford **8** (1.3 g, 60%; purity above 90%); $[\alpha]_D^{25}$ +166.9° (*c* 1, methylene chloride); IR (film) 1620 $cm^{-1}$ (C=C); $^1H$ NMR ($CDCl_3$) δ 0.13, 0.15 (2s, 18H, 2 x $SiMe_3$), 3.44 (dd, 1H, $J_{4,5}$ = 6.7 and $J_{5,5'}$ = 10.7 Hz, H-5), 3.66 (dd, 1H, $J_{4,5'}$ = 6.2 Hz, H-5'), 4.32 (ddd, 1H, $J_{3,4}$ = 2.7 Hz, H-4), 4.82 (dt, 1H, $J_{1,3}$ = 1.0 and $J_{2,3}$ = 2.7 Hz, H-3), 5.02 (t, 1H, $J_{1,2}$ = 2.7 Hz, H-2), 6.49 (dd, 1H, H-1); MS *m/z*: $M^+$ Calcd for $C_{11}H_{24}O_3Si_2$: 260.1264. Found: 260.1264.

Anal. Calcd for $C_{11}H_{24}O_3Si_2$: C, 50.72; H, 9.29. Found: C, 49.92; H, 9.97.

**1,4-Anhydro-3,5-di-*O*-benzyl-2-deoxy-D-*erythro*-pent-1-enitol (9)**. Compound **8** (0.05 g, 0.19 mmol) was added to a mixture of pulverized sodium hydroxide (0.3 g) and anhydrous potassium carbonate (0.05 g) in dimethyl sulfoxide (2 mL). To this stirred mixture, benzyl bromide (0.2 mL) was added at room temperature . After being stirred at room temperature for 2 h, the mixture was diluted with toluene (15 mL) and water (5 mL). The toluene layer was washed with water, dried, and concentrated. The crude product was purified on silica gel using hexane - ethyl acetate 10:1 v/v as an eluent to afford glycal **9** (0.052 g, 91%); $[\alpha]_D^{25}$ +161.8° (*c* 1, methylene chloride); IR (film) 1625 $cm^{-1}$ (C=C); $^1H$ NMR ($CDCl_3$) δ 3.42 (dd, 1H, $J_{4,5}$ = 5.5 and $J_{5,5'}$ = 10.3 Hz, H-5), 3.55 (dd, 1H, $J_{4,5'}$ = 6.2 Hz, H-5'), 4.50, 4.52, 4.55, 4.59 (4d, 4H, 2 x benzyl), 4.61-4.66 (m, 2H, H-3,4), 5.15 (t, 1H, $J_{1,2}$ = 2.8 and $J_{2,3}$ = 2.4 Hz, H-2), 6.08 (dd, 1H, $J_{1,3}$ = 1.0 Hz, H-1); MS (LSIMS) *m/z* 295 $(M+1)^+$.

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.04; H, 6.82.

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