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Preliminary communication

Facile access to ethyl 2-*C*-β-D-ribofuranosylacetates*

STEPHEN HANESSIAN, TOMOYA OGAWA**, and YVAN GUINDON***
Department of Chemistry, University of Montreal, Quebec H3C 3V1 (Canada)
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In connection with a continuing program aimed at the synthesis of functionalized *C*-glycosyl compounds[1–3], we now report the stereocontrolled introduction of a carbon-bound, two-carbon chain at the anomeric carbon atom of the D-ribofuranosyl group.

Treatment of the readily available 2,3-*O*-isopropylidene-D-ribofuranose[4] (**1**) with a slight excess of (ethoxycarbonylmethylene)triphenylphosphorane in boiling toluene under reflux for 2 h, followed by chromatography on silica gel, gave ethyl 2-*C*-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)acetate† (**2**) as a colorless syrup in 65% yield; $[\alpha]_D^{25}$ −9.3° (*c* 6.4, MeOH), ν_{max} 1730 cm^{-1} (C=O); M−CH_3 (*m/e* 245), M−OCH_2CH_3 (*m/e* 215), and M−CH_2OH (*m/e* 229). The crystalline *p*-nitrobenzoic ester (**3**), prepared in 84% yield, had m.p. 58.5–59°, $[\alpha]_D^{25}$ +1° (*c* 1.6, $CHCl_3$); ν_{max} 1530 cm^{-1} (NO_2); n.m.r. data (100 MHz, $CDCl_3$)‡: δ 1.24 (t, CH_2CH_3), 1.36, 1.56 (s, C-CH_3), 2.65, and 2.71 p.p.m. (s, CH_2CO_2Et). Benzoylation of **2** gave the syrupy benzoate **4**; $[\alpha]_D^{25}$ −5.1° (*c* 2.15, $CHCl_3$); M−CH_3 (calc. 349.1270; found 349.1280).

Treatment of 2,3,5-tri-*O*-benzoyl-D-ribofuranose (**5**) with a slight excess of the phosphorane in *N*,*N*-dimethylformamide for 6 h at 95°, followed by conventional processing, and purification by column chromatography on silica gel, gave a 38% yield of syrupy ethyl 2-*C*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)acetate (**7**); $[\alpha]_D^{24}$ +22.2° (*c* 3.5, $CHCl_3$); n.m.r. data (60 MHz): δ 1.15 (t, CH_2CH_3), 2.71, and 2.83 p.p.m. (s, CH_2CO_2Et); M^++1 (calc. 533.1811; found 533.1812); M^+−OCH_2CH_3 (calc. 487.1393; found 487.1396). Selective hydrolysis of the acetal group in **4** with 50% aq. CF_3CO_2H for 30 min at 25°, followed by benzoylation, also gave **7**, thus establishing the configuration at C-1 of the ribosyl group in both products (**4** and **7**).

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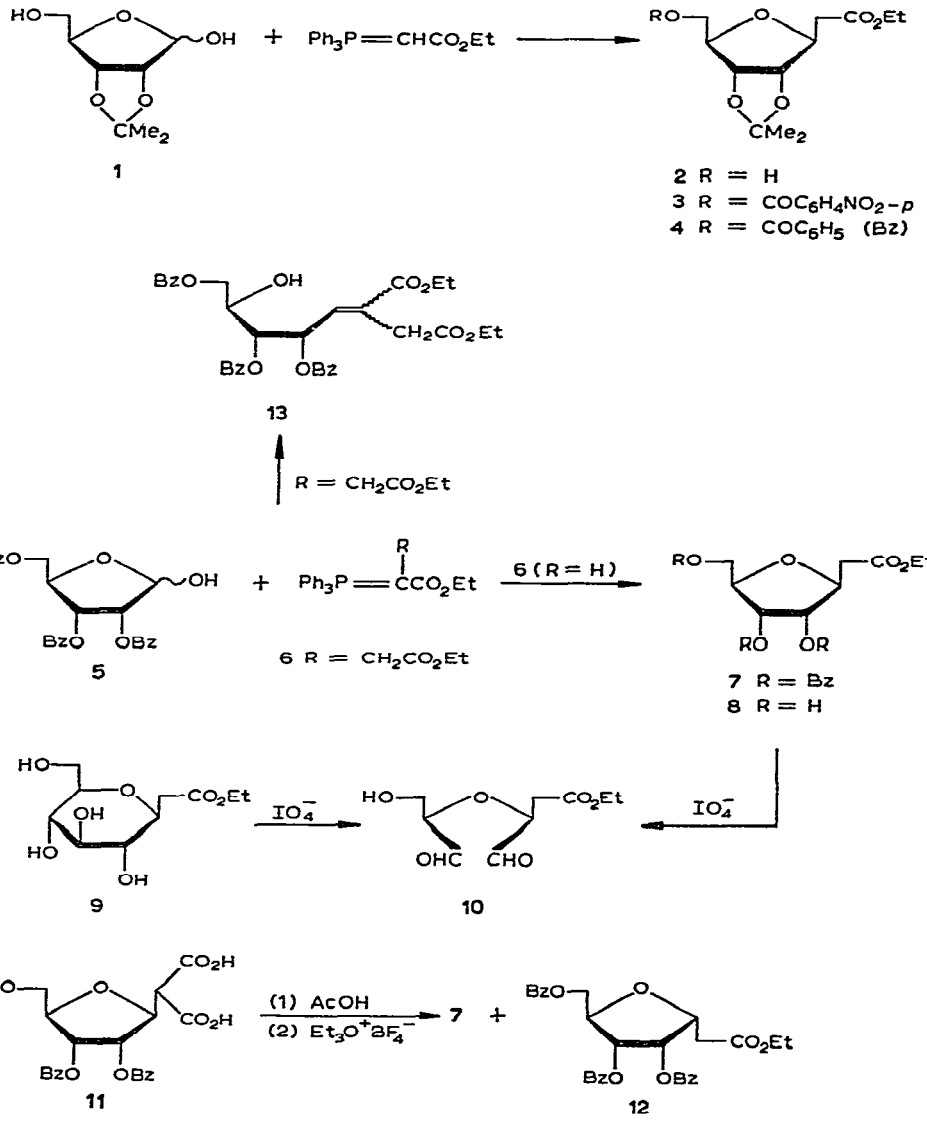
**Post-doctoral fellow, 1973–1974.
***Undergraduate research participant.
†Alternative name: ethyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*allo*-heptonate.
‡Crystalline products afforded satisfactory microanalyses. Melting points are uncorrected. Mass spectra were recorded with an AEI-MS9 high-resolution, mass spectrometer.



Definitive evidence for the β-D configuration of these *C*-glycosyl compounds was secured from correlation studies with an analog of known configuration[3]. Thus, debenzoylation (NaOEt–EtOH) of **7** gave the triol **8** as a syrup (5:1 $CHCl_3$–MeOH, R_F 0.3), that was treated with potassium periodate in 3:1 water–ethanol for 20 h at 25°. The dialdehyde **10**, isolated as a homogeneous syrup, showed $[\alpha]_D^{24}$ −23.6° (*c* 0.45, $CHCl_3$). Similar oxidation of compound[3] **9** gave the same dialdehyde, $[\alpha]_D^{24}$ −25° (*c* 1, $CHCl_3$).

The α-D anomer **12** of **7** was independently synthesized by the thermal decarboxylation of 2-*C*-β-D-ribofuranosylmalonic acid[1,2] (**11**), followed by esterification.

Interestingly, when compound **12**, $[\alpha]_D^{25}$ +50.3° (*c* 2.65, $CHCl_3$); $M^{\ddagger}+1$ (calc. 533.1811; found 533.1807) was debenzoylated with NaOEt–EtOH, and the resulting triol was oxidized with potassium periodate in aqueous ethanol, the dialdehyde **10** was again isolated; $[\alpha]_D^{25}$ −17.4° (*c* 0.82, $CHCl_3$)*,†. Thus, it appears that **12** undergoes a base-catalyzed epimerization at C-1 of the D-ribofuranosyl group during the debenzoylation reaction. Actually, a favorable stereoelectronic (*trans*-periplanar) disposition may exist in the carbanionic or enolate ion intermediate arising from **12**, with respect to the D-ribosyl C-1–O-4 bond, thus leading to ring opening (*β*-elimination)**. Evidently, in the ensuing ring-closure process of the C-1–C-2 ene intermediate, preponderant (if not exclusive) formation of the *β*-D anomer occurs‡,§.

Treatment of **5** with the phosphorane **6** [prepared from (ethoxycarbonylmethylene)triphenylphosphorane and ethyl bromoacetate in boiling EtOAc under reflux for 5 h] in *N*,*N*-dimethylformamide for 15 h at 95°, followed by chromatography, gave a product to which the open-chain structure **13** is assigned, based on spectroscopic and other data; $[\alpha]_D^{25}$ −21.2° (*c* 4.0, $CHCl_3$); $M^{\ddagger}$ (calc. 618.2101; found 618.2097).

The remarkable stereocontrol during the Wittig reaction of **1** provides easy access to *C*-D-ribofuranosyl compounds having the desired *β*-D orientation for possible elaboration to *C*-nucleosides[1–3,5].

ACKNOWLEDGMENT

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*In support of this observation, it was found that, when **12** was debenzoylated (NaOEt–EtOH), and rebenzoylated, essentially complete conversion into the *β*-anomer **7** occurred. The products **7** and **12** could be readily distinguished by t.l.c. (10:1 CCl_4–acetone). After similar treatment, **7** was recovered unchanged.

†The optical rotation of the corresponding dialdehyde[3] resulting from diethyl 2-*C*-*β*-D-glucopyranosylmalonate is $[\alpha]_D^{25}$ −24° (*c* 2.1, $CHCl_3$), and that of the dialdehyde resulting from the *α* anomer is $[\alpha]_D^{25}$ +26° (*c* 2.1, $CHCl_3$)[3].

**Other factors, based on steric considerations, could also be invoked.

‡Preliminary experiments indicate, however, that epimerization takes place during the debenzoylation (NaOEt–EtOH) of compound **4**.

§ Stereochemical aspects pertaining to potentially epimerizable groups at the anomeric center in such compounds as **2** are also under study elsewhere; personal communication, H. Ohrui, G. H. Jones, and J. G. Moffatt.