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Easy and Stereoselective Synthesis of the Phosphono Analogue of α-L-Rhamnose 1-phosphate

Laura Cipolla, Barbara La Ferla, Francesco Nicotra,* Luigi Panza

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, CNR Centro di Studio sulle Sostanze Organiche Naturali, Via Venezian 21, 20133 Milano

Abstract: The C-glycosidic analogue of α-L-rhamnose 1-phosphate has been stereoselectively synthesised reacting 2,3,4-tri-*O*-benzyl-L-rhamnopyranose with tetraethyl methylenediphosphonate and sodium hydride in diglyme, and then deprotecting with iodotrimethylsilane.

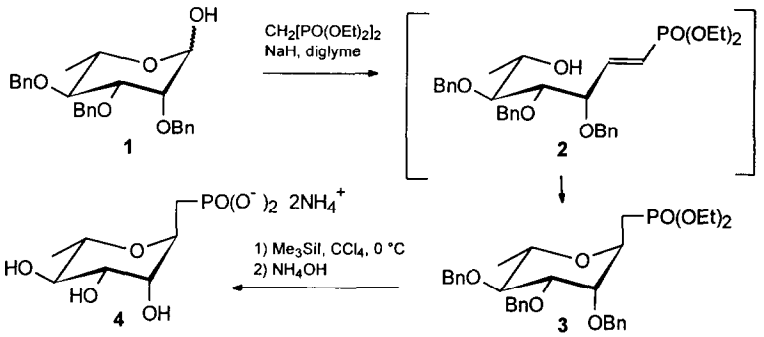
The recently observed pharmacological properties of inhibitors or regulators of carbohydrate processing enzymes, have stimulated the interest in the synthesis of new glycomimetics.[1] Particular attention has been devoted to glycosyl phosphates and their NDP-derivatives, the biological glycosyl donors, and many stable analogues of these molecules have been synthesised.[2] These analogues can interfere in the glycosylation process, as competitive inhibitors of glycosyltransferases.

Among the sugars which constitute the immunogenic repeating units of many bacterial polysaccharides,[3] L-rhamnose is widely present. Nevertheless, mimetics of this sugar are rare and in particular, to our knowledge, analogues of α-L-rhamnose 1-phosphate have never been synthesised.

We now describe a very short, easy and stereoselective synthesis of the phosphono analogue α-L-rhamnosyl 1-phosphate, in which the phosphorus is linked to the sugar through a stable methylenic bridge. This modification does not change in great extent the geometry of the molecule,[4] but suppresses its reactivity at the anomeric centre.

2,3,4-Tri-O-benzyl-L-rhamnopyranose[5] was reacted with tetraethyl methylenediphosphonate in different solvents and bases. This Horner-Emmons reaction afforded directly the cyclized product, as the α,β-unsaturated phosphonate intermediate undergoes immediately an intramolecular Michael reaction (Scheme). The best result was obtained using 5 equivalents of tetraethyl methylenediphosphonate and of NaH, in diglyme at room temperature. In these conditions the phosphonate **3**[6] was obtained in 72% yield and 60% d.e. and easily isolated from the β-isomer by chromatography. The anomeric configuration of **3** has been determined by n.O.e. experiments, which indicate the 1,3-diaxial correlation among CH_2P, H-2 and H-4. Moreover, the comparison of the chemical shift values of the "anomeric" hydrogen of **3** (δ 4.43) and its β-epimer (δ 3.75) clearly indicate the equatorial orientation of the first, which resonates at lower fields. The stereochemical

outcome of the reaction can be explained in the light of the stability of the products. Althought an axial orientation of a 6-membered ring in the chair conformation is in general disfavoured due to the 1,3-diaxial interactions, in the case of an L-rhamnopyranose (as for D-mannopyranose), an equatorial "anomeric" substituent suffers from a repulsive and presumably greater interaction with the alkoxy group at C-2.



The phosphonate **3** was deprotected with Me_3SiI (10 equivalents, in CCl_4 at 0 °C), the solvent was evaporated and the residue was dissolved in EtOH. Addition of 25% aqueous NH_3 affording the ammonium salt of phosphono analogue of α-L-rhamnosyl 1-phosphate (**4**)[5] (88% yield).

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References and Notes

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6. All new products gave satisfactory elemental analysis. **3**, oil, $[\alpha]_D$ +8.3 (c 1, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (6 H, dt, *J* 7.0, 1.7 Hz, $POCH_2CH_3$), 1.32 (3 H, d, *J* 6.0 Hz, CH_3), 2.05 (2 H, dd, *J* 19.5, 7.1 Hz, CH_2P), 3.58 (1 H, t, *J* 7.5 Hz, H-4), 3.63 (1 H, dq., *J* 6.0 Hz, H-5), 3.71 (1 H, dd, *J* 7.5, 3.0 Hz, H-3), 3.83 (1 H, t, *J* 3.0 Hz, H-2), 4.05 (4 H, dq, *J* 7.0 Hz, $POCH_2CH_3$), 4.43 (1 H, ddt, *J* 10.0, 7.0, 3.0 Hz, H-1), 4.50-4.85 (6 H, OCH_2Ph), 7.30 (15 H, PhH). ^{31}P NMR ($CDCl_3$) δ 29.56. **4**, hygroscopic solid, m.p. 202-204 °C; $[\alpha]_D$ 0.0 (c 2, H_2O, HCl); ^1H NMR (300 MHz, D_2O) δ 1.34 (3 H, d, *J* 5.9 Hz, CH_3), 1.84 (1 H, ddd, *J* 14.8, 10.4, 4.4 Hz, CHP), 2.05 (1 H, dt, *J* 14.8, 10.0 Hz, CHP), 3.50 (1 H, t, *J* 9.1 Hz, H-4), 3.66-3.80 (2 H, m, H-1 and H-4), 3.93 (1 H, dd, *J* 9.1, 3.1 Hz, H-3), 4.28 (1 H, m, H-2). ^{13}C NMR (D_2O) δ 19.91 (q, CH_3) 32.6 (dt, $J_{C,P}$ 125 Hz, CH_2P), 72.0, 72.8, 74.2, 75.3, 78.5. ^{31}P NMR (D_2O) δ 17.81.

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