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A concise synthesis of *C*-glycosyl phosphate and phosphonate analogues of *N*-acetyl-α-D-glucosamine 1-phosphate

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Abstract

An easy preparation of the *C*-glycosyl phosphate and phosphonate analogues of *N*-acetyl-α-D-glucosamine 1-phosphate is described. The readily available 3-(2′-acetamido-3′,4′,6′-tri-*O*-acetyl-2′-deoxy-α-D-glucopyranosyl)-1-propene **3** has been used as a common intermediate.

Keywords: glycosyl phosphates; *C*-glycosyl phosphate; *C*-glycosyl phosphonate; amino *C*-glycosides.

Glycosyl phosphates are the main metabolic precursors and the key glycosylating agents in the biosynthesis of glycoconjugates. Recently, the synthesis of hydrolytically stable *C*-glycosidic analogues of glycosyl phosphates has attracted increasing attention because of the biological importance of these phosphates.[1]

Among the anomeric sugar phosphates, the *N*-acetyl-α-D-glucosamine 1-phosphate (GlcNAc-1-P) is of particular interest. It is known to be the key intermediate in the biosynthesis of *N*-linked glycoproteins, and also the metabolic precursor of the bacterial cell-wall components teichoic acid and mureine. Despite its important biological implication, only two synthetic analogues of GlcNAc-1-P have been reported. Nicotra and co-workers synthesised the phosphonate isostere with a multi-step sequence by introducing the amino function at the end of synthesis because of the difficulty encountered during the preparation of the corresponding amino *C*-glycosyl halides and their subsequent conversion to phosphonate.[2] Junker and Fessner prepared the diethyl 2-(3′,4′,6′-tri-*O*-acetyl-2′-deoxy-2′-trifluoroacetamido-α-D-glucopyranosyl)ethane phosphonate by radical promoted C–C bond formation between diethyl vinylphosphonate and the corresponding glycosyl bromide, in 44% yield.[3] We are interested in the modification of GlcNAc-1-P and we describe here a new approach to the synthesis of related, homologous *C*-ethylene phosphate and phosphonate sugars **1** and **2**.

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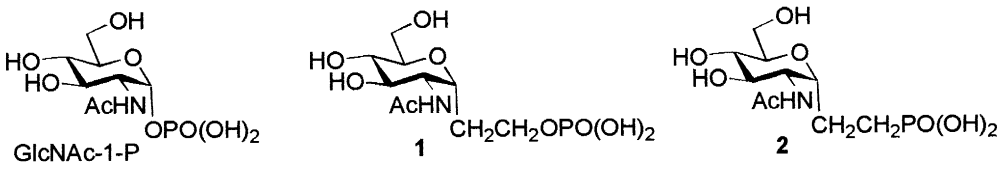
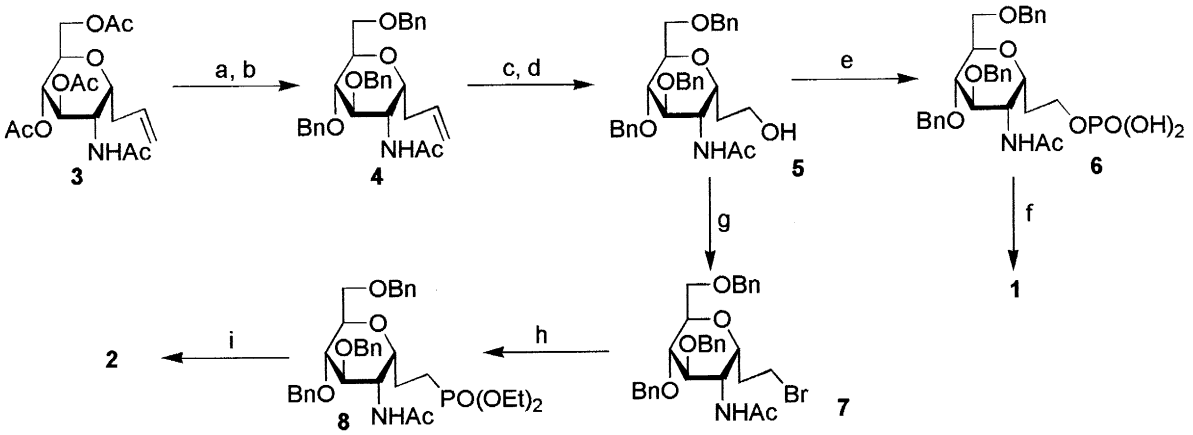


Our strategy was to proceed from the known 3-(2′-acetamido-3′,4′,6-tri-*O*-acetyl-2′-deoxy-α-D-glucopyranosyl)-1-propene **3**[4,5] as shown in Scheme 1. The acetyl protecting group in **3** was first transformed into benzyl ether thus affording compound **4**. Oxidation (OsO_4/$NaIO_4$) of the allyl function, followed by reduction of the so-obtained aldehyde then furnished alcohol **5** in good yield. Reaction of **5** with $POCl_3$[6] afforded the protected phosphate **6**. Removal of benzyl ether was realised by catalytic hydrogenolysis, leading to the desired *C*-glycopyranosyl phosphate **1**[7] in excellent yield.



Scheme 1. *Reagents and conditions:* (a) MeONa, MeOH, 0°C to rt; (b) NaH, BnBr, DMF, 94% for two steps; (c) OsO_4, $NaIO_4$, THF/H_2O, quant.; (d) $NaBH_4$, CH_2Cl_2/MeOH, 75%; (e) $POCl_3$, THF, Ar, 0°C to rt, then H_2O, 93%; (f) H_2, Pd/C, MeOH, AcOH cat. quant.; (g) CBr_4, PPh_3, CH_2Cl_2, quant.; (h) $P(OEt)_3$, 120°C, 91%; (i) TMSI, CCl_4, 0°C to rt, quant.

Synthesis of the phosphonate analogue was achieved by conversion of alcohol **5** into bromide **7** with CBr_4/PPh_3. The Arbuzov reaction with $P(OEt)_3$ afforded **8** in 91% yield. Finally, treatment of **8** with Me_3SiI (20 equiv. in CCl_4) led to the expected phosphonate **2**.[7]

In conclusion, the preparation of *C*-glycosyl phosphate and phosphonate analogues of GlcNAc-1-P could be efficiently accomplished from the readily available α-*C*-allyl glycoside of *N*-acetyl D-glucosamine **3**. Compounds **1** and **2** are versatile intermediates for the synthesis of inhibitors of *N*-acetyl glycosaminyl transferases and might themselves exhibit inhibition towards these enzymes. Biological evaluation of these new compounds towards various glycosyltransferases and further elaboration are under way.

Acknowledgements

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7. Selected physical data: Compound **1**, ^{1}H NMR (250 MHz, D_2O) δ=4.20 (ddd, 1H, *J*=11.5, 5.7 and 3.5 Hz, H-1′), 3.95 (m, 3H, H-1, H-2′), 3.82 (dd, 1H, *J*=12.0 and 2.1 Hz, H-6′), 3.71 (dd, 1H, *J*=12.0 and 5.0 Hz, H-6′′), 3.70 (t, 1H, *J*=9.1 Hz, H-3′), 3.55 (ddd, 1H, *J*=9.1, 5.0 and 2.1 Hz, H-5′), 3.40 (t, 1H, *J*=9.1 Hz, H-4′), 3.05 (m, 1H, H-2), 2.00 (s, 3H, Me), 1.85 (m, 1H, H-2); ^{31}P NMR (202.46 MHz, D_2O) δ=2.82. Compound **2**, ^{1}H NMR (250 MHz, D_2O) δ=4.05 (m, 1H, H-1′), 3.95 (m, 1H, H-2′), 3.84 (dd, 1H, *J*=12.0 and 1.8 Hz, H-6′), 3.71 (t, 1H, *J*=9.0 Hz, H-3′), 3.69 (dd, 1H, *J*=12.0 and 5.0 Hz, H-6′′), 3.47 (ddd, 1H, *J*=9.0, 5.0 and 1.8 Hz, H-5′), 3.36 (t, 1H, *J*=9.0 Hz, H-4′), 1.91 (s, 3H, Me), 1.80 (m, 2H, H-2), 1.65 (m, 2H, H-1); ^{31}P NMR (202.46 MHz, D_2O) δ=32.04.