First Synthesis of the Phosphono Analogue of *N*-Acetyl-α-D-mannosamine 1-Phosphate

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Reaction of 2,3,5-tri-*O*-benzyl-D-arabinose with divinylzinc, and subsequent mercuriocyclisation and iododemercuriation stereoselectivity affords the α-C-glucopyranosyl iodide **3** with a free hydroxy group at C-2; temporary protection of the free hydroxy group, treatment of the iodide with triethylphosphite to afford the corresponding phosphonate, deprotection of the hydroxy group, oxidation, oximation, catalytic hydrogenation and acetylation, afford the phosphono analogue of *N*-acetyl-α-D-mannosamine 1-phosphate.

N-Acetyl-α-D-mannosamine 1-phosphate is a key intermediate in the biosynthesis of *N*-acetylneuraminic acid. This acid, a sialic acid, is present in many oligosaccharides of great pharmacological importance, such as Sialyl Lewis X, a tumour associated antigenic determinant.[1] Molecules that interfere with the biosynthesis of *N*-acetylneuraminic acid, *e.g.* analogues of *N*-acetyl-α-D-mannosamine 1-phosphate, are important synthetic targets.

Furthermore, *N*-acetyl-D-mannosamine is largely present in bacterial polysaccharides[2] as a component of antigenic repeating units of Gram-positive and -negative bacteria.

The synthesis of antimetabolites of sugar phosphates in which the phosphoester linkage is substituted by a phosphono linkage has been described by us[3] and others.[4]

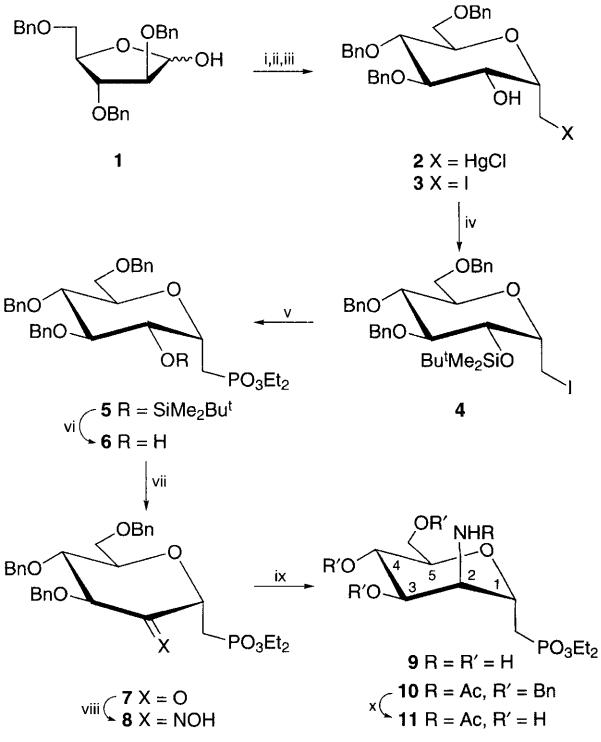
To our knowledge, neither the phosphono analogue of *N*-acetyl-α-D-mannosamine 1-phosphate, nor any other 2-amino-2-deoxy-sugar-phosphonates has been synthesised. One of the reasons for this probably lies in the difficulties encountered in the formation of C-glycosides of 2-amino-2-deoxysugars, as only a few examples, mainly derived from D-glucosamine, have been described.[5,6] Moreover, in our hands, any attempt to convert a C-glycosidic carbon of 2-amino-2-deoxy-C-glycosides into an electrophile, such as CH_2I (which allows the subsequent introduction of the phosphonic group), failed.[7] In the light of these difficulties, we decided to follow a synthetic strategy in which the phosphono-function is introduced at the C-glycosidic carbon before the amino group. To efficiently develop this strategy, we took advantage of our procedure for the synthesis of C-glycosides fully protected except at the C-2 hydroxy group.[8] This free hydroxy group can be selectively converted into an amino group at the end of the synthesis.

2,3,5-Tri-*O*-benzyl-D-arabinose **1** (5 g) was reacted with divinylzinc and after subsequent mercuriocyclisation the α-C-glucopyranoside **2** was obtained stereoselectively in 78% overall isolated yield.[8] In order to introduce the phosphono function, the mercurioderivative **2** was converted into the iodide **3** (78%) (oil, $[\alpha]_D$ +25.4)† by treatment with iodine in CH_2Cl_2. The free hydroxy group of **3** was then protected as *tert*-butyldimethylsilyl ether (Bu^tMe_2SiCl, imidazole, DMF), affording **4** (oil, $[\alpha]_D$ +61.4) in 83% yield. Reaction of **4** with $P(OEt)_3$ under reflux gave the phosphonate **5** (mp 76–77 °C, $[\alpha]_D$ +28.4) in 77% yield. Deprotection of the silylated hydroxy group of **5** required CF_3CO_2H–H_2O (9 : 1) at 0 °C (93%), since Bu_4NF afforded a complex mixture of products, while $MeCO_2H$ was ineffective. In order to introduce the amino function at C-2, the free hydroxy group of the phosphonate **6** (mp 80–81 °C, $[\alpha]_D$ +38.3) was oxidised with DMSO–Ac_2O, and the ketone **7** (oil, $[\alpha]_D$ +32.7), obtained in 83% yield, was treated with NH_2OH·HCl–AcONa–AcOH, (pH 4.5) affording the corresponding oxime **8** (amorphous solid) as a mixture of the *E*- and *Z*-isomers in 82% yield.

It is well established that with *O*-glycopyranosides the reduction of oximes such as **8**, affords the equatorial amine (gluco) when the anomeric configuration is α, and the axial amine (manno) in the case of the β-anomer.[9] Interestingly, in our case the catalytic hydrogenation of **8** with $Pd(OH)_2/C$ stereoselectively afforded the phosphono analogue of α-D-mannosamine 1-phosphate **9** (hygroscopic solid, $[\alpha]_D$ +18.3, c = 0.6 in H_2O), in quantitative yield. No traces of the gluco-isomer were detected. The selective acetylation of the amino function of **9**, attempted with Ac_2O in MeOH–H_2O, gave unsatisfactory results. When Raney–nickel was used as a catalyst in the reduction of **8**, followed by acetylation of the crude reduction product, the protected phosphono analogue of *N*-acetyl-α-D-mannosamine 1-phosphate **10**‡ was obtained in 50% yield together with a small amount of the gluco isomer (13% yield). Purification of **10** by HPLC (Supelcosil LC-Si, 25 cm × 21.2 mm ID, AcOEt–CH_2Cl_2–MeOH, 7 : 5 : 1)§ and deprotection by catalytic hydrogenation (H_2, Pd/C, MeOH, quantitative yield) afforded the phosphono analogue of *N*-acetyl-α-D-mannosamine 1-phosphate **11**¶ as diethylester. This esterified form should allow easier transport through the cell wall which is interdicted to a phosphonic acid.

The α-manno structure of **11** was deduced from the ^1H NMR coupling constants which indicated the axial orientation of H-1 and H-2 ($J_{1,2}$ = 8.0 Hz) and the equatorial orientation of H-3 and H-4 ($J_{2,3}$ = 3.5, $J_{3,4}$ = 4.5 Hz).¶

The procedure described can be easily extended to the synthesis of different 2-amino-2-deoxy-glycosyl phosphonates, starting from the pentose and converting the free hydroxy group into an amine with the desired stereochemistry.



Scheme 1 *Reagents and conditions*: i, $(CH_2{=}CH)_2Zn$, THF, 20 °C; ii, $Hg(OAc)_2$, THF, then KCl; iii, I_2, CH_2Cl_2; iv, Bu^tMe_2SiCl, Im, DMF; v, $P(OEt)_3$, reflux; vi, CF_3CO_2H–H_2O, 0 °C; vii, DMSO–Ac_2O; viii, NH_2OH.HCl, H_2O–AcOH, pH 4.5; ix, H_2, Pd/C, MeOH, to afford **9** (H_2, Raney-Ni, MeOH, then Ac_2O–Py, to afford **10**); x, H_2, Pd/C, MeOH

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Footnotes

† The yields are calculated on the isolated products, which were purified by flash chromatography on SiO_2. The $[\alpha]_D$ values were determined in $CHCl_3$, c = 1, unless otherwise stated.

‡ *Physical and spectroscopic data* for compound **10**, $[\alpha]_D^{20}$ +19.9 (c = 0.8 in $CHCl_3$). ^{31}P NMR (80.961 MHz, $CDCl_3$, 25 °C, H_3PO_4): δ 29.03. ^1H NMR (300 MHz, C_6D_6 + D_2O, 30 °C, Me_4Si, J in Hz) δ 1.06 (6 H, quint, J = 7.0, Me), 1.53 (3 H, s, MeCO), 2.12 (2 H, dd, $J_{H,P}$ = 18.0, 7.0, CH_2P) and 4.83 (1 H, m, H-1).

§ Further preparations were efficiently purified by flash chromatography on SiO_2 using AcOEt–CH_2Cl_2–MeOH (5 : 5 : 0.5) as solvent system.

¶ *Physical and spectroscopic data* for compound **11**, $[\alpha]_D^{20}$ +17.7 (c = 1 in MeOH). ^{31}P NMR (80.961 MHz, D_2O, 25 °C, H_3PO_4): δ 30.99. ^1H NMR (300 MHz, [D_5]Py, 30 °C, Me_4Si) δ 1.18 (6 H, q, J = 7.0, Me), 2.04 (3 H, s, MeCO), 2.44 (1 H, dt, J = 16.0, 16.0 and 5.0, CHP), 2.52 (1 H, dt, J = 16.0, 16.0 and 10.0, CHP), 4.09 (3 H, m, H-6a and CH_2OP), 4.21 (4 H, quint, J = 7.3, CH_2OP), 4.31 (1 H, t, J = 4.5, H-4), 4.50 (1 H, dd, J = 11.8, 9.0, H-6b), 4.79 (1 H, m, H-1) and 5.09 (1 H, dt, J = 8.0, 8.0 and 3.5, H-2).

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