Synthesis of phosphonic acid analogues of sialic acid Neu5Ac

Tak-Hang Chan* and Yan-Chao Xin

Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6

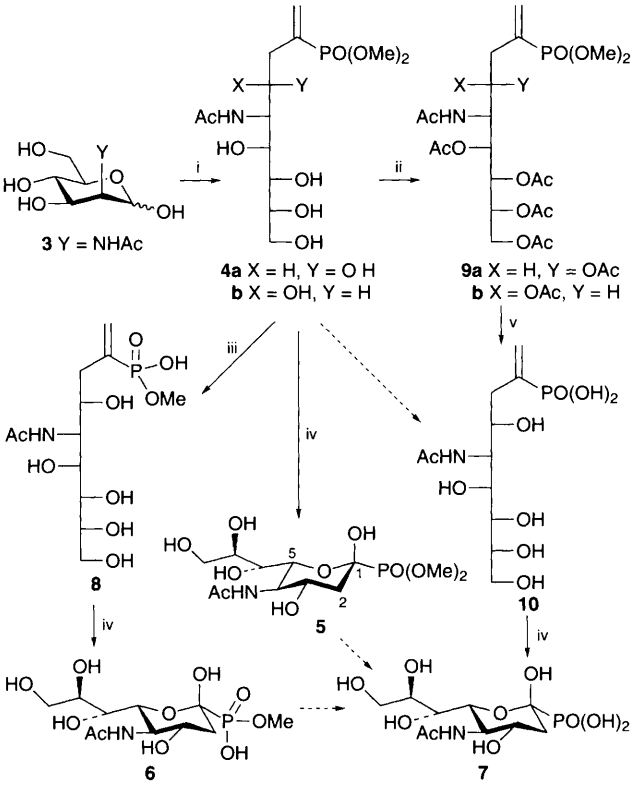
Two phosphonic acid analogues of Neu5Ac 1 are synthesised.

The sialic acid, *N*-acetylneuraminic acid (Neu5Ac, **1**), has emerged as a key biomolecule in the regulation of many biological phenomena.[1] Binding to terminal α-glycosides of sialic acid on cell surface glycoproteins and glycolipids is the initiating process of cell infection by viruses.[2] The interaction between selectins and sialylated oligosaccharides is believed to be involved in the early stage of adhesion of leukocytes to activated endothelial cells in the inflammatory response.[3] Gangliosides, with one or more residues of sialic acid, are receptor molecules located on the outer surface of vertebrate cell membrane interacting with external biological factors such as toxin proteins.[4] In all cases, it is believed that the carboxylic acid group of **1**, in its anionic form, is essential for binding.[5] Here we report the synthesis of novel phosphonic acid analogues of **1** in the expectation that the phosphonic acid group should play the same role as the carboxylic acid in providing the negative charge for binding.

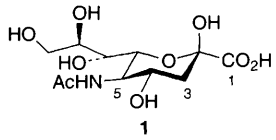
Dimethyl 3-bromopropenyl-2-phosphonate **2** (Fig. 2)[6] was coupled with *N*-acetylmannosamine **3** in water mediated by indium†[7] to give compound **4** (90% yield) as a mixture of diastereoisomers, 5 : 1 (*syn* : *anti*). The desired major isomer **4a** (32%) was crystallised from methanol–ethyl acetate (1 : 2) as a solid, mp 134–135 °C. Ozonolysis of **4a** gave the pyranose **5** in 86% yield. The stereochemistry at the anomeric centre was assigned to have the phosphonate group equatorial on the basis of similar phosphorus coupling of 5 Hz for the two non-equivalent hydrogens at C-2 of the pyranose ring.[8] Hydrolysis of the phosphonate ester **5** to give either **6** or **7** proved to be difficult. On the other hand, compound **4a** could be easily quantitatively hydrolysed by sodium hydroxide in aqueous methanol to the monoester **8**. Ozonolysis of **8** gave compound **6** in 87% yield as one anomer with the phosphonate group equatorial. Attempts to hydrolyse either **6** or **8** further to the free acid were not successful.

In order to obtain the free phosphonic acid, compound **4** was first fully acetylated to **9** with acetic anhydride–DMAP in pyridine in 86% overall yield. The desired major isomer **9a** could be crystallised in 51% yield from cyclohexane–ethyl acetate (2 : 1) as a needle like crystals, mp 151 °C. Treatment of **9a** with bromotrimethylsilane in CH_2Cl_2 followed by NaOH–MeOH hydrolysis gave the free acid **10** in 74% yield. Ozonolysis of **10** gave the desired compound **7**‡ in 84% yield. The stereochemistry of the anomeric centre has the phosphonic acid group in the equatorial position.

The present approach provides a general synthesis of phosphonic acid analogues of sialic acids. Compound **11**‡ the analogue of KDN,[9] was synthesized from mannose.

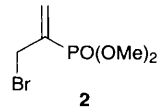


Scheme 1 *Reagents and conditions*: i, **2**, Indium, H_2O, room temp., 15 h; ii, Ac_2O, pyridine, DMAP, room temp., 10 h, iii, NaOH, MeOH–H_2O, 0 °C, 4 h; iv, O_3, MeOH–CH_2Cl_2, −78 °C, then Me_2S, room temp., 12 h; v, bromotrimethylsilane, CH_2Cl_2, 0 °C, 10 h, then NaOH, MeOH–H_2O, room temp., 5 h



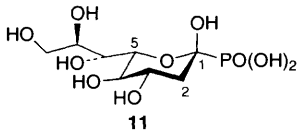
1

Fig. 1



2

Fig. 2



11

Fig. 3

Footnotes

† Indium (622 mg, 5.4 mmol) was added to a solution of *N*-acetylmannosamine (200 mg, 0.9 mmol) and **2** (1.24 g, 5.4 mmol) in water (50 ml). The reaction mixture was stirred at ambient temperature for 20 h. After filtration and evaporation *in vacuo*, compounds **4a** and **4b** (302 mg, 90%) were purified by flash chromatography (methanol–ethyl acetate, 1 : 3) as an epimeric mixture (*syn* : *anti*, 5 : 1). The major isomer **4a** was obtained by crystallization (methanol–ethyl acetate, 1 : 2) (107 mg, 32%).

‡ *Spectroscopic data* for **7** $[\alpha]_D$ −23 (*c* = 0.5, methanol); ^{1}H NMR (500 MHz, D_2O) δ 1.69 (ddd, 1 H, *J* 13.0, 11.0 Hz, $J_{H\text{-}P}$ 4.5 Hz, H-2_{ax}), 1.88 (s, 3 H, H-Me), 2.14 (dd, 1 H, *J* 13.0, 5.0 Hz, H-2_{eq}), 3.35 (d, 1 H, *J* 9.0 Hz, H-6), 3.45 (dd, 1 H, *J* 11.5, 6.5 Hz, H-8b), 3.65 (m, 1 H, H-7), 3.69 (dd, 1 H, *J* 11.5, 2.5 Hz, H-8a), 3.73 (d, 1 H, *J* 10.0 Hz, H-5) and 3.89 (m, 2 H, H-3, 4); ^{13}C NMR (50 MHz, D_2O), δ 22.11 (C-Me), 37.40 (d, $J_{C\text{-}P}$ 8.4 Hz, C-2), 52.27, 66.78 (d, $J_{C\text{-}P}$ 11.1 Hz), 68.48, 69.47 (d, $J_{C\text{-}P}$ 10.9 Hz), 70.14, 96.33 (d, $J_{C\text{-}P}$ 198.6 Hz, C-1) and 174.77 (C–C=O); ^{31}P NMR (109 MHz, D_2O) δ 13.52; MS (FAB) *m/z* 346 (M + 1); HRMS (FAB) calc. for $C_{10}H_{21}NO_{10}P$ (M + 1) 346.09031, found 346.09046. For **11**: $[\alpha]_D$ −25 (*c* = 0.5, methanol); ^{1}H NMR (500 MHz, D_2O) δ, 1.78 (ddd, 1 H, *J* 12.6, 12.6, 5.0 Hz, H-2_{ax}), 2.43 (dd, 1 H, *J* 13.0, 5.0 Hz, H-2_{eq}), 3.53 (dd, 1 H, *J* 9.3, 9.3 Hz), 3.63 (dd, 1 H, *J* 11.0, 5.4 Hz), 3.74–3.88 (m, 3 H) and 3.94–4.02 (m, 2 H); ^{13}C NMR (50 MHz, D_2O) δ 36.99 (d, $J_{C\text{-}P}$ 8.8 Hz, C-2), 63.27, 68.01, 68.52 (d, $J_{C\text{-}P}$ 11.8 Hz), 70.01, 70.36, 70.79 (d, $J_{C\text{-}P}$ 11.4 Hz) and 96.36 (d, $J_{C\text{-}P}$ 200.6 Hz, C-1); ^{31}P NMR (109 MHz, D_2O) δ, 15.10 s; MS (FAB) *m/z* 305 (M + 1); HRMS (FAB) calc. for $C_8H_{18}O_{10}P$ (M + 1) 305.06376, found 305.06383.

References

1 R. Schauer, *Adv. Carbohydr. Chem. and Biochem.*, 1982, **40**, 132.
2 J. C. Paulson, in *The Receptors*, ed. M. Conn, Academic Press, New York, 1985, vol. 2, pp. 131–219.
3 L. A. Lasky, *Annu. Rev. Biochem.*, 1995, **64**, 113.
4 P. H. Fishman, in *New Trends in Ganglioside Research*, Liviana Press, Padova, 1988.
5 T. Uchiyama, V. P. Vassilev, T. Kajimoto, W. Wong, H. Huang, C.-C. Lin and C.-H. Wong, *J. Am. Chem. Soc.*, 1995, **117**, 5395.
6 P. Knochel and J. F. Normant, *Tetrahedron Lett.*, 1984, **25**, 1475.
7 T. H. Chan and M.-C. Lee, *J. Org. Chem.*, 1995, **60**, 4228.
8 S. Sheffer-Dee-Noor, V. Belakhov and T. Baasov, *Tetrahedron Lett.*, 1994, **35**, 5077.
9 T. H. Chan and C. J. Li, *J. Chem. Soc., Chem. Commun.*, 1992, 747.

Received, 28th November 1995; Com. 5/07753B