Synthesis of 2-Amino-2,5-dideoxy-5-hydroxyphosphinyl-D-mannopyranose Derivatives: New Phospho-sugar Analogues of D-Mannosamine†

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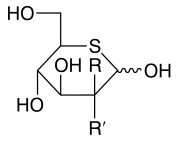
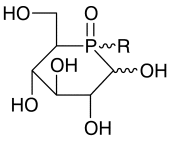
3,6-Di-*O*-benzyl-5-deoxy-5-dimethylphosphinyl-1,2-*O*-isopropylidene-α-D-glucofuranose **5** was converted, in four steps, into methyl 2-acetamido-3,6-di-*O*-benzyl-2,5-dideoxy-5-dimethoxyphosphinyl-α-D-mannofuranoside **7**, which led to 3,5-di-*O*-benzyl derivatives **9** of a P-in-the-ring D-mannosamine analogue.

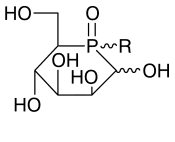
Various sugar analogues containing a heteroatom instead of oxygen in the ring have been prepared because of the wide interest in their chemical and biochemical properties.[1,2] Heteroatom-in-the-ring sugar analogues of 2-amino- and 2-acetamido-2-deoxyhexopyranoses, which widely occur as a component of many natural products, have also attracted considerable interest. Thiasugar analogues of 2-acetamido-2-deoxy-D-glucose **1**[3] and D-mannose **2**,[4] for example, are potentially useful owing to their inhibitory activity in the biosynthesis of important constituents of higher animal cell walls.[5] In view of such a chemical modification by heteroatoms, we have prepared various sugar analogues having a phosphorus atom in the ring (phospho-sugar),[6,7] such as D-glucopyranose **3**[8] and D-mannopyranose analogues **4**.[9] We describe herein the first synthetic route to a new phospho-sugar of a mannosamine analogue.



1 R = H, R′ = NHAc
2 R = NHAc, R′ = H



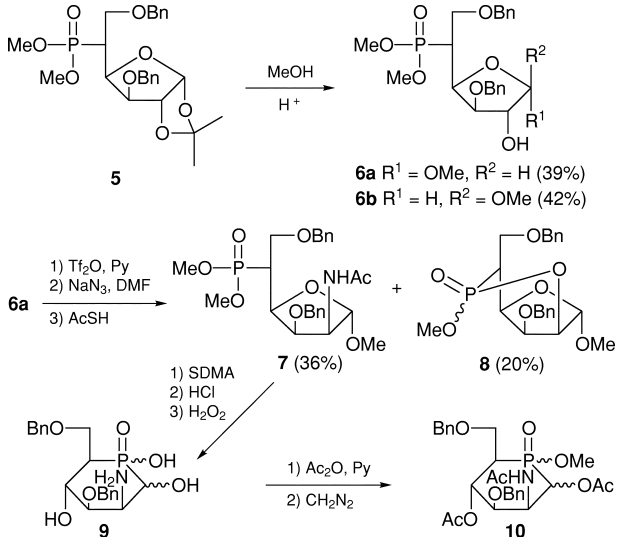
3 R = OH, Ph, Et



4 R = OH, Me

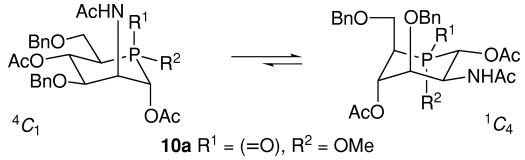
Treatment of the 5-phosphinyl-D-glucofuranose derivative **5**[10] with methanol in the presence of an acidic ion-exchange resin gave methyl α-D-glucofuranoside **6a** (39%) and its β-anomer **6b** (42%). The conversion of **6a** into the 2-*O*-triflate, followed by the treatment with sodium azide, afforded the corresponding 2-azido-2-deoxy-α-D-mannofuranoside; a byproduct, 5-(2-*O*-*cyclo*-methoxyphosphinyl)-α-D-mannofuranoside **8**, was present but it was separable only after the subsequent step (see below). The treatment of the above mixture with thioacetic acid provided, after chromatographic separation, the 2-acetamido-2-deoxy-α-D-mannofuranoside **7** (36% overall yield from **6a**) and **8** (20%). Attempts to convert the β-anomer **6b** into the corresponding 2-C-azide (the β-anomer of **7**) using similar procedures have remained unsuccessful.

Compound **7** was then reduced with sodium dihydrobis-(2-methoxyethoxy)aluminate (SDMA) to give its 5-phosphino derivative, which was immediately subjected to acid hydrolysis and then to oxidation with hydrogen peroxide, affording 5-hydroxyphosphinyl-D-mannopyranose **9**. This was characterized, after peracetylation and methylation, as 2-acetamido-5-[(*R*)-methoxyphosphinyl]-α-D-mannopyranose **10a** (13% overall yield from **7**) and its 5-[(*S*)-methoxyphosphinyl] isomer **10b** (12%). A small amount of an inseparable mixture (1.7%) was obtained as a colourless syrup, which was presumed by NMR spectra to be the β-anomers of **10a** and **10b**.



Scheme 1

The structural assignments of **10a**,**b** were made by the analysis of the ^{1}H NMR spectra. Both compounds have medium $J_{2,P}$ and $J_{4,P}$ values (14–21 Hz), indicating that they existed as a conformational mixture of $^4C_1$ and $^1C_4$ forms.[7,9] By employing the additivity rule[11] for vicinal coupling constants, the equilibrium populations of $^4C_1$ and $^1C_4$ conformers were estimated to be 33:67 for **10a** and 42:58 for **10b**.‡ Such equilibria were observed in the case of only the α-anomer of D-mannopyranose phospho-sugars **4**.[9] A slight downfield shift of H-2 signal of **10b** in comparison with that of **10a** indicates an axial P=O orientation for the $^1C_4$ form of **10b**. A similar downfield shift of the H-4 signal of **10a** compared with that of **10b** shows an axial P=O orientation for the $^4C_1$ form of **10a**.



10a R^1 = (=O), R^2 = OMe
10b R^1 = OMe, R^2 = (=O)

Experimental

The general methods followed those described earlier,[7] the TLC solvent system being (*A*) AcOEt, (*B*) 1:19 (v/v) EtOH–AcOEt and (*C*) 1:19 (v/v) AcOEt–$CHCl_3$. All the products were purified by

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‡The ratios of the conformers were estimated by use of the following values, $J_{1,2} = J_{2,3} = 3.8$, $J_{3,4}$ 9.8, $J_{4,5}$ 11.55 for the pure $^4C_1$ form, $J_{1,2}$ 12.1, $J_{2,3}$ 2.9, $J_{3,4}$ 3.6, $J_{4,5}$ 3.5 for the pure $^1C_4$ form.

column chromatography on silica gel. NMR spectra were measured in $CDCl_3$ with Varian VXR-500 (500 MHz for ^1H) and VXR-200 (81 MHz for ^{31}P) instruments (SC-NMR Lab., Okayama Univ.) at 23 °C. *J* values are given in Hz. The mass spectra were taken on a VG 70-SE instrument and are given as *m*/*z* (relative intensity).

Methyl 3,6-*Di-O-benzyl*-5-*deoxy*-5-*dimethoxyphosphinyl*-α-D-*glucofuranoside* **6a** *and its* β-*Anomer* **6b**.—A mixture of **5**[10] (4.79 g, 9.73 mmol) and Amberlite IR-120(H^+) in dry methanol (96 cm^3) was stirred at 60 °C for 8 h. The resin was filtered off and the filtrate was evaporated *in vacuo* to give **6a** and **6b**.

6a: Colourless prisms (1.78 g, 39%), mp 84–85 °C [Found: ($M^+ + H$), 467.1850. $C_{23}H_{32}O_8P$ requires (M + 1), 467.1836]; $R_F = 0.50$ (*C*); δ_H 2.81 (1 H, dddd, $J_{5,P}$ 20.1, $J_{4,5}$ 9.8, $J_{5,6'}$ 5.5, $J_{5,6}$ 3.1, H-5), 2.98 (1 H, d, $J_{2,OH}$ 4.9, HO-2), 3.46 (3 H, s, MeO-1), 3.67, 3.675 [3 H each, 2 d, J_{POMe} 10.8, $P(OMe)_2$], 3.90 (1 H, ddd, $J_{6',P}$ 27.5, $J_{6,6'}$ 9.5, H-6′), 3.95 (1 H, ddd, $J_{6,P}$ 17.1, H-6), 3.98 (1 H, dd, $J_{3,4}$ 4.2, $J_{2,3}$ 1.8, H-3), 4.24 (1 H, td, $J_{1,2}$ 4.8, H-2), 4.53, 4.59 (1 H each, 2 d, *J* 11.9, CH_2O-3 or -6), 4.55 (1 H, ddd, $J_{4,P}$ 6.2, H-4), 4.54, 4.68 (1 H each, 2 d, *J* 11.0, CH_2O-6 or -3), 5.01 (1 H, d, H-1) and 7.25–7.35 (10 H, m, Ph); δ_P 32.5; FAB *m*/*z* 467 ($M^+ + 1$, 23), 387 (6), 297 (12), 181 (9) and 91 (100).

6b: Colourless needles (1.93 g, 42%), mp 123–124 °C [Found: ($M^+ + H$), 467.1828. $C_{23}H_{32}O_8P$ requires (M + 1), 467.1836]; $R_F = 0.40$ (*C*); δ_H 2.83 (1 H, d, $J_{2,OH}$ 4.0, HO-2), 2.90 (1 H, dddd, $J_{5,P}$ 19.2, $J_{4,5}$ 9.5, $J_{5,6'}$ 5.5, $J_{5,6}$ 3.4, H-5), 3.36 (3 H, s, MeO-1), 3.62, 3.67 [3 H each, 2 d, J_{POMe} 10.8, $P(OMe)_2$], 3.93 (1 H, ddd, $J_{6',P}$ 25.6, $J_{6,6'}$ 9.5, H-6′), 3.955 (1 H, ddd, $J_{6,P}$ 19.5, H-6), 3.96 (1 H, dd, $J_{3,4}$ 4.3, $J_{2,3}$ 1.0, H-3), 4.17 (1 H, td, $J_{1,2}$ 0.8, H-2), 4.53, 4.58 (1 H each, 2 d, *J* 12.2, CH_2O-3 or -6), 4.55, 4.65 (1 H each, 2 d, *J* 11.6, $PhCH_2O$-6 or -3), 4.65 (1 H, ddd, $J_{4,P}$ 7.0, H-4), 4.80 (1 H, d, H-1) and 7.23–7.36 (10 H, m, Ph); δ_P 32.7; FAB *m*/*z* ($M^+ + 1$, 24), 435 (15), 297 (39), 207 (9) and 91 (100).

Methyl 2-*Acetamido*-3,6-*di-O-benzyl*-2,5-*dideoxy*-5-*dimethoxyphosphinyl*-α-D-*glucofuranoside* **7** *and Methyl* 3-*O-Benzyl*-5-*deoxy*-5-[(5*R*,*S*)-2-*O-cyclomethoxyphosphinyl*]-α-D-*mannofuranoside* **8**.—Trifluoromethanesulfonic anhydride (0.54 cm^3, 3.21 mmol) was added to a solution of **6a** (750 mg, 1.61 mmol) in pyridine (0.52 cm^3, 6.43 mmol) in dry CH_2Cl_2 (25 cm^3) at −40 °C. The mixture was stirred at −40 °C for 30 min under argon, poured into water and extracted with CH_2Cl_2. The organic layer was evaporated *in vacuo* to give the crude 2-*O*-triflate as a colourless syrup [$R_F = 0.63$ (*A*)]. A mixture of this syrup and sodium azide (520 mg, 8.00 mmol) in dry DMF (25 cm^3) was stirred at 40 °C for 3 d under argon, poured into water and extracted with $CHCl_3$. The organic layer was evaporated *in vacuo*, giving an inseparable mixture (573 mg) of the 2-azido compound and **8**. This was dissolved in thioacetic acid (5.0 cm^3, 7.0 mmol) and stirred at 23 °C for 1 d under argon. The excess thioacetic acid was evaporated *in vacuo*, giving **7** and **8**.

7: Colourless prisms (295 mg, 36% from **6a**), mp 42–44 °C [Found: ($M^+ + H$), 508.2118. $C_{25}H_{35}O_8NP$ requires (M + 1), 508.2102]; $R_F = 0.18$ (*A*); δ_H 1.72 (3 H, s, Ac), 2.92 (1 H, dtd, $J_{5,P}$ 21.7, $J_{5,6}$ 6.7, $J_{4,5}$ 6.1, $J_{5,6'}$ 4.3, H-5), 3.30 (3 H, s, MeO-1), 3.62, 3.70 [3 H each, 2 d, J_{POMe} 10.7, $P(OMe)_2$], 3.81 (1 H, ddd, $J_{6,P}$ 16.5, $J_{6,6'}$ 10.1, H-6′), 3.98 (1 H, td, $J_{6,P}$ 10.1, H-6), 4.41 (1 H, dd, $J_{3,4}$ 6.5, $J_{2,3}$ 6.0, H-3), 4.43, 4.52 (1 H each, 2 d, *J* 11.3, CH_2O-3 or -6), 4.44, 4.52 (1 H each, 2 d, *J* 11.6, CH_2O-6 or -3), 4.54 (1 H, ddd, $J_{2,NH}$ 8.9, $J_{1,2}$ 1.2, H-2), 4.60 (1 H, td, $J_{4,P}$ 18.0, H-4), 4.76 (1 H, d, H-1), 7.04 (1 H, br d, HN-2) and 7.25–7.35 (10 H, m, Ph); δ_P 32.1; FAB *m*/*z* 508 ($M^+ + 1$, 15), 476 (14), 368 (9), 338 (38), 248 (10) and 91 (100).

8: Yellow syrup (143 mg, 20%) [Found: ($M^+ + H$), 435.1560. $C_{22}H_{28}O_7P$ requires (M + 1), 435.1573]; $R_F = 0.55$ (*A*); (for the main isomer) δ_H 2.79 (1 H, dddd, $J_{5,P}$ 19.5, $J_{5,6}$ 9.2, $J_{5,6'}$ 6.1, $J_{4,5}$ 3.0, H-5), 3.50 (3 H, s, MeO-1), 3.78 [3 H, d, J_{POMe} 12.0, POMe], 3.88 (1 H, ddd, $J_{6,6'}$ 10.4, $J_{6',P}$ 7.9, H-6′), 3.92 (1 H, td, $J_{6,P}$ 11.0, H-6), 4.29 (1 H, ddd, $J_{3,4}$ 6.1, $J_{2,3}$ 3.1, $^5J_{3,P}$ 1.2, H-3), 4.41, 4.54 (1 H each, 2 d, *J* 12.2, CH_2O-3 or -6), 4.49, 4.77 (1 H each, 2 d, *J* 11.6, CH_2O-6 or -3), 4.51 (1 H, dd, $J_{2,P}$ 18.9, $J_{1,2} \approx 0$, H-2), 4.71 (1 H, ddd, $J_{4,P}$ 31.1, H-4), 5.11 (1 H, br s, H-1) and 7.23–7.38 (10 H, m, Ph); δ_P 22.6; FAB *m*/*z* 435 ($M^+ + 1$, 16), 345 (5), 237 (5), 181 (10) and 91 (100).

2-*Acetamido*-1,4-*di-O-acetyl*-3,6-*di-O-benzyl*-2,5-*dideoxy*-5-[(*R*)-*methoxyphosphinyl*]-α-D-*mannopyranose* **10a** *and its* 5-[(*S*)-*Methoxyphosphinyl*] *Isomer* **10b**.—To a solution of **7** (157 mg, 0.309 mmol) in dry toluene (1.5 cm^3) was added SDMA (0.34 M in toluene, 3.20 cm^3, 1.09 mmol) at 0 °C under argon. The mixture was stirred at 0 °C for 1 h and then water (0.12 cm^3) was added. The mixture was centrifuged and the precipitate was extracted with benzene. The organic layer was evaporated *in vacuo*, giving the 5-phosphino derivative as a colourless syrup; $R_F = 0.70$ (*A*). This syrup was immediately treated with 1:1 (v/v) propan-2-ol–0.5 M HCl (3.0 cm^3) at 90 °C for 2 h under argon. After cooling, 30% hydrogen peroxide (1.0 cm^3) was added. The solution was stirred at 23 °C for 18 h and concentrated *in vacuo*. The residue was dissolved in MeOH (1.5 cm^3), treated with propylene oxide (0.8 ml) at 23 °C for 6 h and evaporated *in vacuo* to give crude **9** as a colourless syrup. This was dissolved in dry pyridine (1.5 cm^3) and acetic anhydride (0.8 cm^3) at 23 °C for 20 h, and concentrated *in vacuo*. The residue was dissolved in ethanol and passed through a column of Amberlite IR-120(H^+). The eluent was evaporated *in vacuo* and the residue was methylated with ethereal diazomethane in dry CH_2Cl_2 (2.0 cm^3) at 0 °C. After evaporation of the solvent, the residue was separated by chromatography into three fractions A–C.

Fraction A [$R_F = 0.27$ (*B*)] gave **10a** as colourless needles, mp 168–169 °C (21.3 mg, 13% from **7**) [Found: ($M^+ + 1$), 548.2062. $C_{27}H_{34}O_9NP$ requires (M + 1), 548.2051]; δ_H 1.73, 2.03, 1.78 (3 H each, 3 s, Ac-1,2,4), 2.66 (1 H, ddt, $J_{5,P}$ 19.2, $J_{5,6'}$ 9.5, $J_{4,5}$ 6.1, $J_{5,6}$ 5.8, H-5), 3.73 (1 H, dd, $J_{3,4}$ 5.8, $J_{2,3}$ 3.1, H-3), 3.81 (3 H, d, J_{POMe} 11.0, POMe), 3.87 (1 H, q, $J_{6,6'}$ 9.8, $J_{6',P}$ 9.4, H-6′), 3.92 (1 H, dt, $J_{6,P}$ 6.4, H-6), 4.45, 4.54 (1 H each, 2 d, *J* 11.9, CH_2O-3 or -6), 4.51, 4.57 (1 H each, 2 d, *J* 11.9, CH_2O-6 or -3), 4.79 (1 H, dtd, $J_{2,P}$ 14.7, $J_{2,NH}$ 9.8, $J_{1,2}$ 9.4, H-2), 5.39 (1 H, dd, $J_{1,P}$ 5.3, H-1), 5.63 (1 H, dt, $J_{4,P}$ 21.4, H-4), 5.92 (1 H, br d, NH-2), 7.25–7.36 (10 H, m, Ph); δ_P 41.4; FAB *m*/*z* 548 ($M^+ + 1$, 22). 506 (8), 488 (10), 181 (14) and 91 (100).

Fraction B [$R_F = 0.22$ (*B*)] gave an inseparable mixture (1:1) of (5-[(*R*)- and (*S*)-methoxyphosphinyl]-β-isomers (3.2 mg, 1.8%) containing a small amount of **10a**,**b**.

Fraction C [$R_F = 0.18$ (*B*)] gave **10b** as a colourless syrup (20.2 mg, 12% from **7**); δ_H 1.81, 2.03, 2.13 (3 H each, 3 s, Ac-1,2,4), 2.70 (1 H, dtd, $J_{5,P}$ 18.9, $J_{4,5}$ 7.1, $J_{5,6}$ 6.9, $J_{5,6'}$ 5.2, H-5), 3.72 (1 H, ddd, $J_{6'P}$ 9.8, H-6′), 3.73 (1 H, dd, $J_{3,4}$ 6.0, $J_{2,3}$ 3.4 Hz, H-3), 3.74 (3 H, d, J_{POMe} 10.7, POMe), 3.84 (1 H, td, $J_{6,P}$ 9.6, H-6), 4.49 (2 H, s, CH_2O-6), 4.50, 4.61 (1 H each, 2 d, *J* 11.9, CH_2O-3), 4.84 (1 H, dtd, $J_{2,P}$ 14.3, $J_{2,NH}$ 9.2, $J_{1,2}$ 8.7, H-2), 5.32 (1 H, dd, $J_{1,P}$ 7.9, H-1), 5.54 (1 H, ddd, $J_{4,P}$ 16.9, H-4), 5.63 (1 H, br d, NH-2), 7.26–7.36 (10 H, m, Ph); δ_P 41.3.

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