Synthesis of 6-Amino-5,6-dideoxy-5-hyroxyphosphinyl-D-glucopyranose

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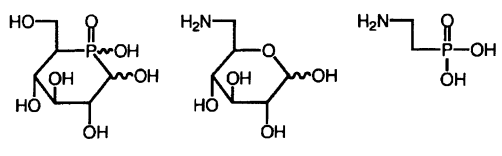
Synopsis. The title sugar analogue (**9**) was conveniently synthesized from known 3-*O*-acetyl-5,6-dideoxy-5-dimethoxyphosphinyl-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose in 4 steps via the 6-*t*-butoxycarbonylamino derivative. The structure of **9** was established by spectroscopy after conversion into the 6-acetamido-1,2,3,4-tetra-*O*-acetyl-5-methoxyphosphinyl derivatives.

A large number of sugar analogues containing nitrogen or sulfur as a ring heteroatom have been synthesized,[1,2] largely due to interest in their potential as biologically active compounds. In view of such a chemical modification by heteroatoms, we have prepared various phospha sugars,[3—5] such as a D-glucopyranose analogue **1** containing ring-phosphorus.[6] On the other side, there exist many naturally occurring sugars in which a hydroxyl group is replaced by an amino group. These amino sugars play important roles as components of various aminoglycoside antibiotics. We report herein a convenient syntheses of P-in-the-ring sugar analogue **9** of 6-amino-6-deoxy-D-glucose (**2**), which has been identified as a component of kanamycin A.[7] In addition, the presence of a partial structure of a natural aminophosphonic acid ciliatine (**3**)[8] in the D-glucose skeleton of **9** is considered to also be of interest regarding a sugar derivative of an aminophosphinic acid (Chart 1).

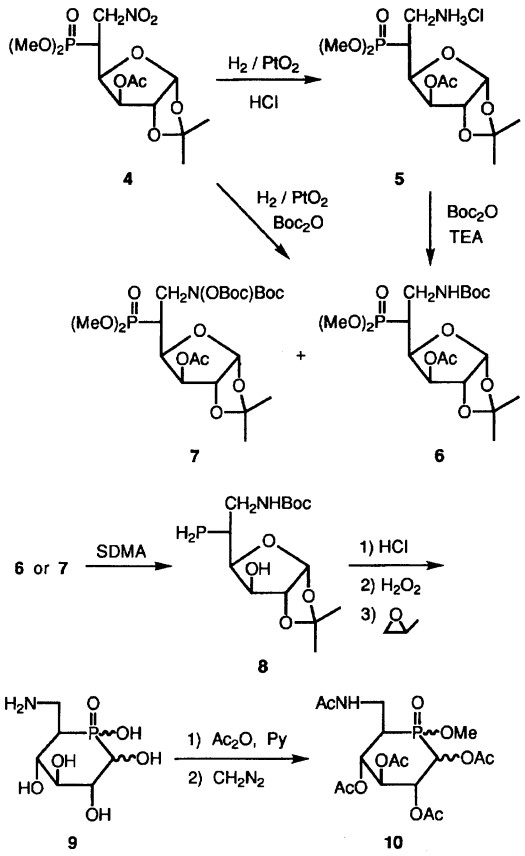
3-*O*-Acetyl-5,6-dideoxy-5-dimethoxyphosphinyl-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose (**4**)[9] served as the starting material (Scheme 1). This was converted into the 6-amino hydrochloride **5** in a quantitative yield by a slight modification of the previous method[6] (see Experimental section). We then attempted to obtain the target compound **9** from **5** in the usual way involving reduction, hydrolysis, and oxidation.[5,6] However, the reduction of **5** with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA)[10] resulted in only a decomposition of the reaction products; no 6-amino-5,6-dideoxy-5-phosphino derivative was isolated.

This led us to examine the immediate protection of the 6-amino group formed by the reduction; we found that *t*-butoxycarbonyl (Boc) protection is most suitable. Thus, the 6-Boc-amino derivative **6** was prepared best



1 2 3

Chart 1.



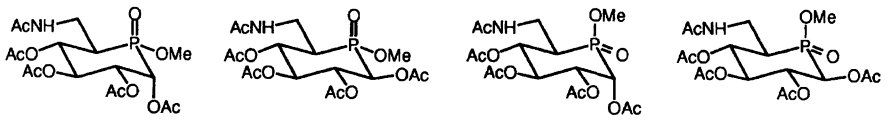
Scheme 1.

by the treatment of **5** with di-*t*-butyl dicarbonate in dichloromethane in the presence of triethylamine (TEA) (93% yield). A short-cut procedure was then devised for preparing the Boc-amino derivative **6**: the hydrogenolysis of **4** in the presence of platinum oxide and di-*t*-butyl dicarbonate in ethyl acetate under hydrogen atmosphere gave **6** (78%) together with the 6-[*N*,*O*-bis-(*t*-butoxycarbonyl)hydroxyamino] derivative **7** (19%). These products were chromatographically separable. A minor compound **7** was presumably formed as the result of *N*,*O*-bis-*t*-butoxycarbonylation of the 6-hydroxyamino intermediate during the hydrogenation of **4**.

Compound **6** was reduced with SDMA to give 5-phosphino derivative **8**, which, due to the action of hydrochloric acid, and then oxidation with hydrogen peroxide, afforded 6-amino-5,6-dideoxy-5-hydroxyphosphinyl-D-glucopyranose hydrochloride. The treatment of the hydrochloride with propene oxide furnished the target compound **9**.

The isolation and structural assignments of **9**[11] were made by a well-established method:[5,6] compound **9**

Table 1. ^{1}H NMR (500 MHz) Parameters for **10a**—**d** in $CDCl_3$



10a **10b** **10c** **10d**

Compd	Chemical shift (δ)														
	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	NH-6	AcN-6	AcO-1,2,3,4[a]				MeO	^{31}P
10a	5.65	5.45	5.46	5.475	2.47	4.11	3.31	6.32	2.20	2.05,	2.00,	1.995,	1.94	3.79	40.7
10b	5.32	5.50	5.19	5.48	2.26	4.12	3.35	6.42	2.15	2.045,	1.995,	1.99,	1.94	3.84	38.8
10c	5.77	5.07	5.42	5.14	2.60	3.87	3.37	6.23	2.23	2.09,	2.00,	1.98,	1.97	3.96	38.4
10d	5.52	5.31	5.20	5.17	2.32	3.88	3.34	6.27	2.14	2.08,	1.99,	1.985,	1.96	4.02	35.8

	Coupling constant (Hz)														
	$J_{1,2}$	$J_{1,P}$	$J_{2,3}$	$J_{2,P}$	$J_{3,4}$	$J_{4,5}$	$J_{4,P}$	$J_{5,6}$	$J_{5,6'}$	$J_{5,P}$	$J_{6,6'}$	$J_{6,P}$	$J_{6',P}$	$J_{6,NH}$	$J_{6',NH}$	J_{POMe}
10a	1.9	14.5	10.0	1.0	9.5	11.8	2.1	5.1	1.8	14.2	14.5	27.7	10.4	9.3	2.9	11.1
10b	10.6	5.2	9.5	4.3	9.8	11.6	4.0	5.2	2.0	13.5	14.5	26.7	10.5	9.0	2.5	10.9
10c	3.0	15.2	10.7	0	9.6	11.9	1.6	3.2	9.3	11.5	14.2	23.0	15.4	7.5	4.1	10.4
10d	10.8	2.6	9.7	1.7	9.7	11.5	1.8	3.4	9.2	9.5	14.2	23.0	14.5	7.5	4.0	10.2

a) The assignments of acetyl signals may have to be interchanged.

was acetylated with acetic anhydride–pyridine and then treated with ethereal diazomethane to give 6-acetamido-5-methoxyphosphinyl tetraacetates **10**. Purification of the crude mixture by column chromatography on silica gel afforded 6-acetamido-1,2,3,4-tetra-*O*-acetyl-5,6-dideoxy-5-[(*R*)-methoxyphosphinyl]-α-D-glucopyranose **10a** (9.2% overall yield from **6**), its β-anomer **10b** (1.3%), 5-[(*S*)-methoxyphosphinyl]-α-D-glucopyranose **10c** (8.5%), and its β-anomer **10d** (4.1%).[12]

Similarly, compound **7** was converted into **9** via **8** by the same procedures as those described above. After acetylation and a subsequent methylation of **8**, compounds **10a** (9.9% from **7**), **10b** (1.5%), **10c** (9.4%), and **10d** (4.4%) were obtained.[12]

The precise structures of **10a**—**d** were established by an analysis of their 500 MHz ^{1}H NMR spectra: all assignments of the signals are recorded in Table 1. The anomeric orientation at C-1 is readily perceived by the magnitudes of $J_{1,2}$ and $J_{1,P}$.[3,5,6] A slight downfield shift (0.2—0.4 ppm) of the H-2,4 signals of **10a**,**b**, compared with those of **10c**,**d**, indicates an axial P=O orientation of **10a**,**b** and an equatorial P=O orientation of **10c**,**d**.

The present work demonstrates a convenient way to prepare the P-in-the-ring analogues of 6-amino-6-deoxyhexoses. An extension of this work, including preparative studies on other amino sugar analogues, as well as a biological evaluation of the compounds, is in progress.

Experimental

The general methods followed those described earlier,[5,6,9] the TLC solvent system being (A) 2:1 AcOEt–hexane, (B) 19:1 AcOEt–ethanol, and (C) 5:3:1 2-propanol–AcOEt–water. Optical rotations were measured with a Nihon-Bunko DIP-370 polarimeter at 19 °C. The NMR spectra were measured in $CDCl_3$ with Varian VXR-500 (500 MHz for ^{1}H) and VXR-200 (81 MHz for ^{31}P) instruments (the SC-NMR Lab., Okayama Univ.) at 21 °C. The mass spectra were taken on a VG 70-SE instrument and are given in terms of *m/z* (rel intensity).

Hydrogenolysis and Subsequent *N*-*t*-Butoxycarbonylation of 4. Compound **4**[9] (150 mg, 0.391 mmol) dissolved in a mixture of ethanol (1.5 ml) and 2 M hydrochloric acid (1 M=1 mol dm^{-3}) (0.196 ml, 0.392 mmol) was hydrogenolyzed in the presence of platinum oxide (30 mg, 0.13 mmol) at room temp under an atmospheric pressure of H_2. After 12 h, the catalyst was filtered off and the filtrate was evaporated in vacuo to give 6-amino-5,6-dideoxy-5-dimethoxyphosphinyl-1,2-*O*-isopropylidene-α-D-glucofuranose hydrochloride (**5**)[6] as a colorless solid (152 mg, 100% yield; cf. lit,[6] in MeOH and 0.1 M HCl, 91% yield): ^{1}H NMR[13] δ=1.28, 1.51 (3H each, 2s, CMe_2), 2.17 (3H, s, AcO-3), 3.18 (1H, dddd, $J_{5,P}$=20.5, $J_{4,5}$=10.2, $J_{5,6}$=8.0, $J_{5,6'}$=5.5 Hz, H-5), 3.48—3.52 (2H, m, H,H′-6), 3.77, 3.82 [3H each, 2d, J_{POMe}=11.0 Hz, $P(OMe)_2$], 4.44 (1H, ddd, $J_{4,P}$=5.3, $J_{3,4}$=2.8 Hz, H-4), 4.48 (1H, d, $J_{1,2}$=3.6, $J_{2,3}$=0 Hz, H-2), 5.24 (1H, d, H-3), 5.92 (1H, br d, $^5J_{1,P}$=0.5 Hz, H-1), 8.47 (3H, br s, H_3N^+-6); ^{31}P NMR δ=24.8. The product was spectroscopically pure and used directly for the next step.

To a solution of **5** and di-*t*-butyl dicarbonate (100 mg, 0.458 mmol) in dry CH_2Cl_2 (2 ml) was dropwise added TEA (0.060 ml, 0.430 mmol) at 0 °C. The mixture was stirred at room temp for 0.5 h, diluted with CH_2Cl_2 (10 ml), and washed with water. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by column chromatography to give 3-*O*-acetyl-6-*t*-butoxycarbonylamino-5,6-dideoxy-5-dimethoxyphosphinyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**6**) as a colorless syrup: 165 mg (93% overall yield from **4**); R_f=0.16 (A); $[\alpha]_D$ −22° (*c* 1.5, $CHCl_3$); ^{1}H NMR δ=1.29, 1.51 (3H each, 2s, CMe_2), 1.43 (9H, s, *t*-Bu), 2.08 (3H, s, AcO-3), 2.48 (1H, ddt, $J_{5,P}$=19.9, $J_{4,5}$=10.6, $J_{5,6}$=$J_{5,6'}$=5.8 Hz, H-5), 3.55—3.75 (2H, m, H, H′-6), 3.73, 3.75 [3H each, 2d, J_{POMe}=10.8 Hz, $P(OMe)_2$],

4.39 (1H, ddd, $J_{4,P}=4.8$, $J_{3,4}=2.9$ Hz, H-4), 4.45 (1H, d, $J_{1,2}=3.8$ Hz, H-2), 5.21 (1H, d, $J_{3,4}=2.9$ Hz, H-3), 5.43 (1H, m, HN-6), 5.86 (1H, dd, $^5J_{1,P}=0.8$ Hz, H-1); ^{31}P NMR $\delta=27.7$; FAB MS m/z 454 [$(M+H)^+$; 21], 398 (15), 354 (100), 236 (11), 207 (12), 153 (11). Found: m/z 454.1839. Calcd for $C_{18}H_{33}NO_{10}P$: M+1, 454.1841.

One-Pot *N*-*t*-Butoxycarbonylation of 4. A mixture of **4** (300 mg, 0.783 mmol), di-*t*-butyl dicarbonate (250 mg, 1.15 mmol), and platinum oxide (75 mg, 0.33 mmol) in ethyl acetate (3 ml) was stirred at room temp under an atmospheric pressure of H_2. After 20 h, the catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was separated by column chromatography to give **6** (278 mg, 78%) and 6-[*N*,*O*-bis(*t*-butoxycarbonyl)hydroxyamino]-5,6-dideoxy-5-dimethoxyphosphinyl-1,2-*O*-isopropylidene-α-D-glucofuranose **7** (84 mg, 19%).

7: Colorless syrup; $R_f=0.23$ (A); $[\alpha]_D$ −22° (*c* 1.3, $CHCl_3$); ^{1}H NMR $\delta=1.28$, 1.51 (3H each, 2s, CMe_2), 1.48, 1.52 (9H each, 2s, Boc-*N*, Boc-*O*), 2.08 (3H, s, AcO-3), 2.68 (1H, dddd, $J_{5,P}=20.3$, $J_{4,5}=10.3$, $J_{5,6}=5.9$, $J_{5,6'}=4.1$ Hz, H-5), 3.65—3.78 (2H, m, H,H′-6), 3.71, 3.74 [3H each, 2d, $J_{POMe}=10.9$ Hz, $P(OMe)_2$], 4.44 (1H, d, $J_{1,2}=3.8$ Hz, H-2), 4.50 (1H, m, H-4), 5.23 (1H, d, $J_{3,4}=2.8$ Hz, H-3), 5.81 (1H, dd, $^5J_{1,P}=0.8$ Hz, H-1); ^{31}P NMR $\delta=27.4$; FAB MS m/z 570 [$(M+H)^+$; 11], 470 (8), 370 (100), 354 (16), 207 (11), 153 (11). Found: m/z 570.2338. Calcd for $C_{23}H_{41}NO_{13}P$: M+1, 570.2316.

6-Acetamido-1,2,3,4-tetra-*O*-acetyl-5,6-dideoxy-5-[(*R* and *S*)-methoxyphosphinyl]-α,β-D-glucopyranoses (10a—d). To a solution of **6** (160 mg, 0.353 mmol) in dry toluene (2 ml) was added a solution of SDMA (3.4 M in toluene, 0.43 ml, 4.1 equiv) in dry toluene (1 ml), in small portions at −5 °C under argon. The mixture was stirred at this temp for 1 h; then, water (0.4 ml) was added. The mixture was centrifuged, and the precipitate was extracted with several portions of benzene. The combined organic layers were evaporated in vacuo, giving unstable (to air) 6-*t*-butoxycarbonylamino-5,6-dideoxy-1,2-*O*-isopropylidene-5-phosphino-α-D-glucofuranose (**8**) as a colorless syrup: $R_f=0.55$ (A).

The syrup was immediately treated with 1 : 1 2-propanol–0.5 M hydrochloric acid (3 ml) at 100 °C for 1 h under argon. After cooling, 30% aqueous hydrogen peroxide (0.3 ml) was added. The solution was stirred at room temp for 12 h and concentrated in vacuo. The residue was dissolved in water (1.5 ml), treated with propylene oxide (0.3 ml) at room temp for 5 h, and evaporated in vacuo to give a colorless syrup (65 mg) which predominantly contained (TLC) 6-amino-5,6-dideoxy-5-hydroxyphosphinyl-D-glucopyranose (**9**):[11] $R_f=0.08$ (C).

The product was acetylated with acetic anhydride (0.8 ml) in dry pyridine (2 ml) at room temp for 48 h. After concentration in vacuo, the residue was dissolved in ethanol and passed through a column of Amberlite IR-120B (15 ml). The eluant was evaporated in vacuo and the residue [$R_f=0.40$ (C)] was methylated with ethereal diazomethane in dry CH_2Cl_2 (2 ml) at 0 °C. After evaporation of the solvent, the residue was separated by column chromatography with a gradient eluent of AcOEt→9 : 1 AcOEt–ethanol into two fractions.

The faster-eluting fraction [$R_f=0.17$ (B)] gave a colorless syrup (16.8 mg) which consisted of 5-[(*R*)-methoxyphosphinyl]-α-D-glucopyranose **10a** (9.2% from **6**) and 5-[(*R*)-*P*]-β-isomer **10b** (1.3%), the relative amount being determined by the integral ratio of ^{31}P NMR signals; ^{1}H and ^{31}P NMR, see Table 1; FAB MS m/z 452 [$(M+H)^+$; 100], 410 (29), 368 (11), 350 (8), 248 (10), 188 (14). Found: m/z 452.1310. Calcd for $C_{17}H_{26}NO_{11}P$: M+1, 452.1321.

The slower-eluting fraction [$R_f=0.12$ (B)] gave a colorless syrup (20.1 mg) which consisted of 5-[(*S*)-*P*]-α-D-glucopyranose **10c** (8.5% from **5**) and 5-[(*S*)-*P*]-β-D-isomer (4.1%); ^{1}H and ^{31}P NMR, see Table 1; FAB MS m/z 452 [$(M+H)^+$; 100], 410 (28), 368 (10), 350 (10), 248 (9), 188 (12). Found: m/z 452.1333. Calcd for $C_{17}H_{26}NO_{11}P$: M+1, 452.1321.

When compound **7** was subjected to the same procedures as those described for **6**, compounds **10a—d** were similarly obtained: **10a**, 9.7% from **7**; **10b**, 1.5%; **10c**, 9.4%; **10d**, 4.3%.

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11) The overall yield of **9** from **6** or **7** is estimated to be ca. 50—70% (from TLC), although isolation of pure **9** has not been achieved.

12) The relatively low figures (23—25%) of the combined yields of **10a**—**d** from **6** or **7** are mostly owing to the loss during the multistep reactions and the chromatographic separation of the final products.

13) Although insufficiently resolved ^{1}H NMR data at 60 MHz in a different solvent (DMSO-d_6) were reported[6] for **5**, the complete parameters obtained at 500 MHz in the present study are shown here.