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Note

# Synthesis and structural analyses of 3-acetamido-1,4-di-*O*-acetyl-2,3,5-trideoxy-5-*C*-(isopropylphosphinyl)-D-*erythro*-pentopyranoses

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**Abstract**

$^1$H NMR spectroscopy of phosphorus containing hetero sugars (phospha sugars), revealed the α and β configurations and chair conformations for 3-acetamido-1,4-di-*O*-acetyl-2,3,5-trideoxy-5-*C*-(isopropylphosphinyl)-α- and β-D-*erythro*-pentopyranoses. The conformation of the title compounds was determined by $^1$H NMR as $^1C_4$ in $CDCl_3$ and the conformation was in accord with that in solid state determined by X-ray crystallographic analysis. © 2002 Elsevier Science Ltd. All rights reserved.

*Keywords:* Phospha sugar; $^1C_4$ conformation; NMR; X-ray

In order to prepare potentially bioactive hetero sugars, the present phospha sugar synthesis was performed and the conformations of 3-acetamido-1,4-di-*O*-acetyl-2,3,5-trideoxy-phospha sugar derivatives elucidated. Yamamoto et al. reported the syntheses of phospha sugars[1] and their NMR analysis which established the configuration at the phosphorus in the pyranoid rings and the conformation of the six membered heterocycles. The X-ray analyses of phospha sugar analogs had been reported by Luger et al. and ourselves.[2,3] In the present paper the phospha sugar **16** was synthesized from D-xylose as a starting material via the process shown in Scheme 1. Methyl 3,5-*O*-isopropylidene-D-xylofuranoside (**1**) was prepared according to the reported procedure,[4] 2-*O*-methylthiocarbonylation of methyl-compound (**1**) with an excess amount of carbon disulfide and methyl iodide in DMSO under alkaline solution was carried out to afford **2α** and **2β**, easily separated by column chromatography on silica gel. Treatment of **2β** with acidic methanol gave compound **3**. 5-*O*-Triphenylmethylation of **3** with 1 equiv. of triphenylmethyl chloride in pyridine afforded **4**. 3-*O*-Mesylation of 4 with methanesulfonyl chloride in pyridine afforded **5** in good yield. 2-*O*-Deoxygenation of compound **5** in accordance with the reported procedure[5,6] gave compound **6** in quantitative yield. Conversion of **6** into **8** was readily achieved by heating with sodium azide and successive treatment with acidic methanol. Compounds **8α** and **8β** were separated by column chromatography on silica gel. 5-*O*-Tosylation of the separated **8β** with 1 equiv. of tosyl chloride in pyridine afforded **9** in quantitative yield. 3-Acetoamido-2-deoxy derivative **11** was prepared by reduction of **9** with $n$-$Bu_3SnH$, followed by acetylation with acetic anhydride. On heating compound **11** with sodium iodide in acetone in a sealed tube methyl 3-acetoamido-2,3,5-trideoxy-5-iodo-β-D-*erythro*-pentofuranoside **12** was obtained in quantitative yield. Conversion of **12** into the phosphinate **13** was readily performed by heating with an excess amount of diethyl isopropylphosphonite at 150 °C. Treatment of compound **13** with sodium dihydrobis(2-methoxyethoxy)aluminate (SDMA) gave compound **14** which was subsequently followed by ring-enlargement

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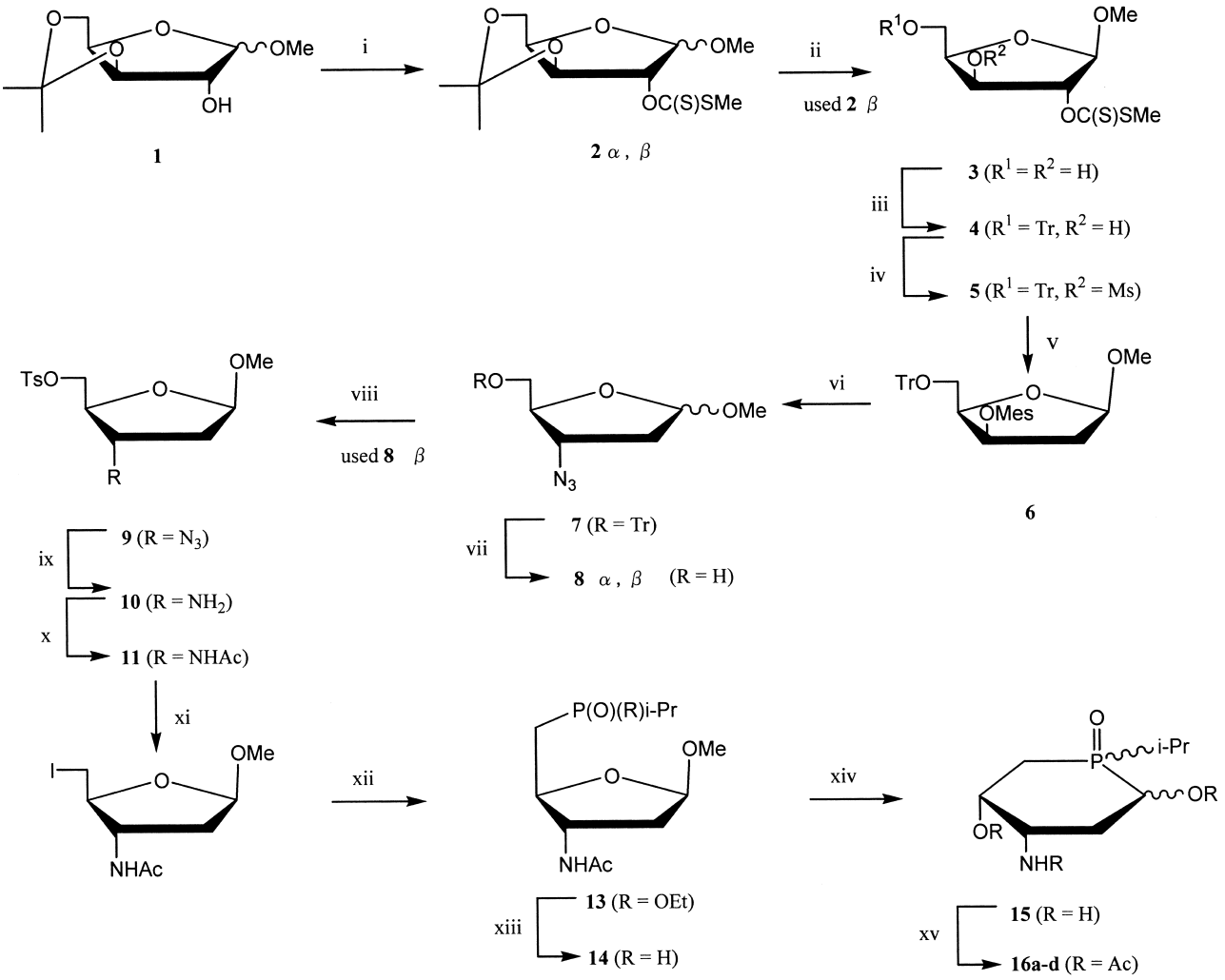
caused by the opening of the furanoid ring (**15**) and the successive closing to prepare a pyranoid ring under acidic conditions. The known two step procedure[3,7] gave trideoxy-ribopyranose type phospha sugars **16a**–**d**. Diastereomers **16a**, **16b**, **16c**, and **16d** were separated, respectively, by using flash chromatography on silica gel (eluent; ethyl acetate/methanol = 4/1, v/v) from the mixture of products. The overall chemical yields of diastereomers **16a**, **16b**, **16c**, and **16d** were 7, 5, 5 and 11%, respectively, from compound **13**.

The precise structures of these compounds **16a**, **16b**, **16c**, and **16d** were determined on the basis of the 500 MHz $^1$H NMR spectra and by X-ray crystallography (Fig. 1). The assignments of all signals were readily made by employing first-order analysis with the aid of a decoupling technique. The analyzed results are summarized in Table 1. The conformations of these phospha sugar derivatives (in $CDCl_3$ solution) was derived by the careful analysis of the magnitudes of $J_{2R,P}$ (20.5 Hz for 16a vs. 2.0–9.8 Hz for **16b**–**d**), $J_{2S,P}$ (7.3 Hz for **16a** vs. 20.5–21.7 Hz for **16b**–**d**), and $J_{4,P}$ (9.2 Hz for 16a vs. 21.4–22.0 Hz for **16b**–**d**) with respect to the corresponding vicinal dihedral angles. As a result, compounds **16a** and **16b**–**d** were shown to exist predominantly in the $^4C_1$ and $^1C_4$ conformations, respectively. The orientation of the P=O group could be established by the $\delta$ values of H-4 for **16a**, and HR-2 and HS-2 for **16b**–**d**. An appreciable downfield shift (0.05–0.31 ppm) is observed for **16a** compared with **16b**–**d**, the observation shows the axial orientation of the ring P=O group for compound **16a**. The equatorial P=O orientation was assigned to the result of upfield shift for products **16a**–**d**. The small magnitudes of $J_{5R,P}$ support the anti orientation of HR-5–C5–P=O for **16c** and **16d**. The equatorial P=O group orientation was assigned to the rest of the compounds, products **16c** and **16d**. The appreciable downfield shift observed for HR-2 of **16c** and **16d** could be explained by its axial orientation. The anomeric orientation at C-1 was derived from the magnitudes of $J_{1,2}$ and $J_{1,P}$. The moderate magnitudes of




Scheme 1. Reagents: (i) $CS_2$/MeI; (ii) $MeOH/H_2SO_4$; (iii) TrCl/py; (iv) MsCl/py; (v) $n$-$Bu_3SnH$; (vi) $NaN_3$; (viii) TsCl/py; (ix) $n$-$Bu_3SnH$; (x) $Ac_2O$/py; (xi) NaI; (xii) $P(OEt)_2i$-Pr; (xiii) SDMA; (xiv) HCl; (xv) $Ac_2O$/py.

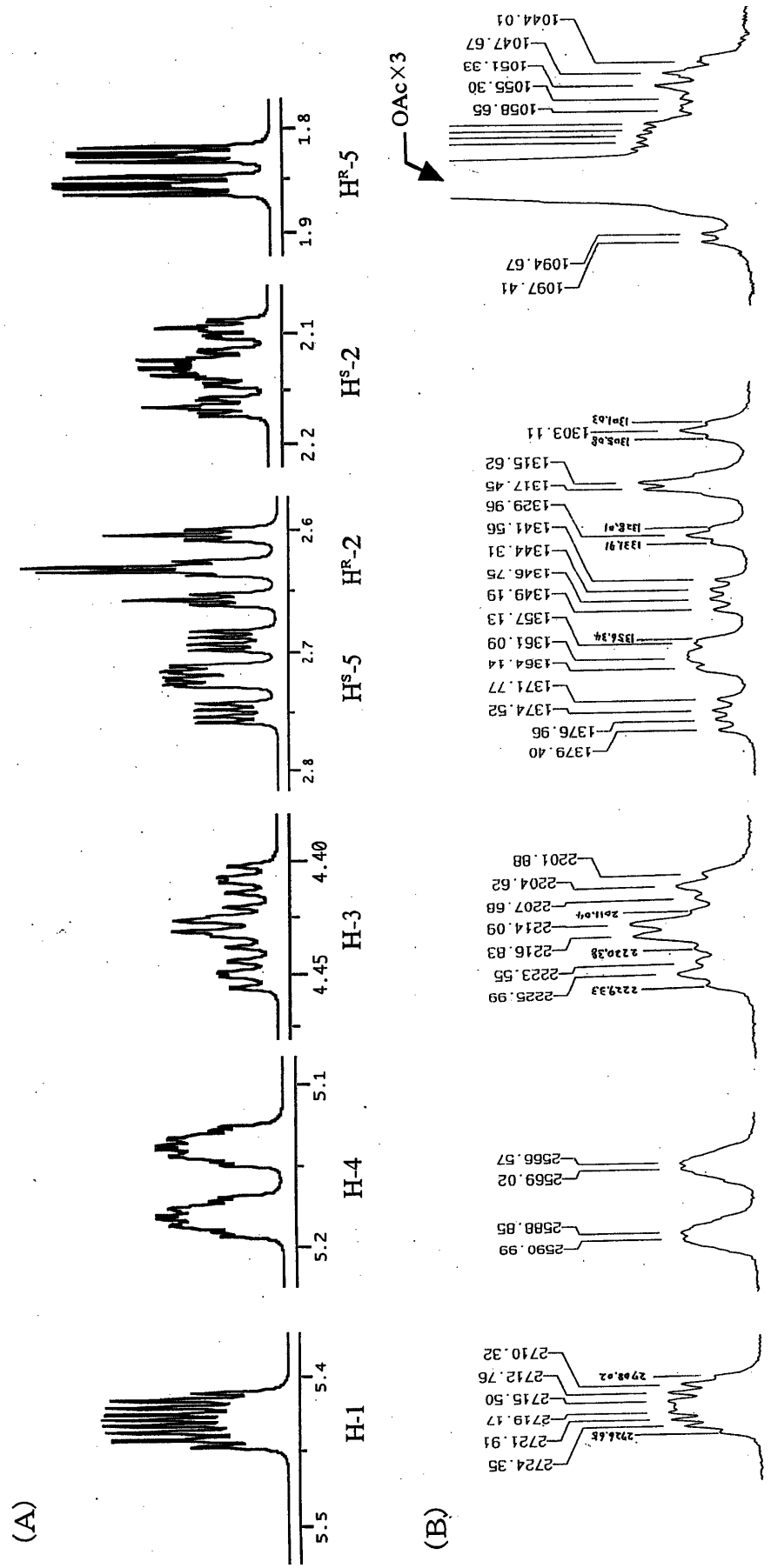



Fig. 1. $^1$H NMR spectrum for **16d** in $CDCl_3$. (A) Top is simulated spectrum, where calculation was performed by using parameters of Table 1. (B) Bottom is actual spectrum (500 MHz).

Table 1
$^{1}$H NMR (500 MHz) parameters and $^{31}$P chemical shifts for **16a**, **16b**, **16c**, and **16d** (Scheme 2)

Chemical shift ($\delta$), ppm

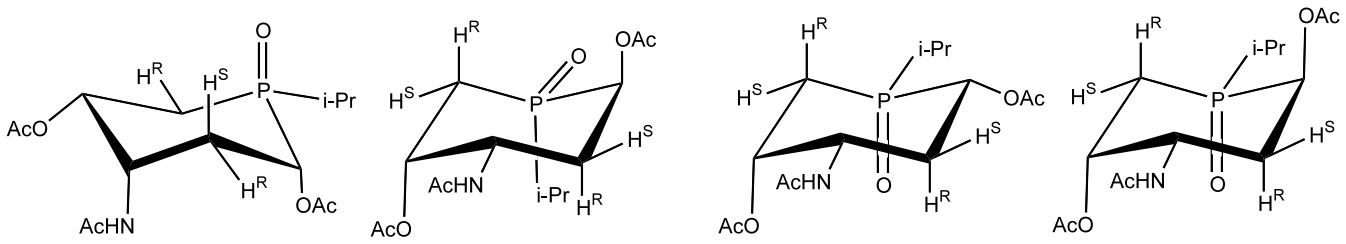
| Compd | H-1 | HR-2 | HS-2 | H-3 [a] | H-4 | HR-5 | HS-5 | Ac0-1,3,4 [a] | NH-3 | HC–P | $CH_3$–C–P | $^{31}$P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **16a** | 2.45 | 2.17 | 2.44 | 4.64 | 5.38 | 2.20 | 2.15 | 2.16, 2.01, 1.97 | 6.03 | 1.94 | 1.23, 1.23 | 46.9 |
| **16b** | 5.50 | 2.09 | 2.25 | 4.51 | 5.33 | 2.30 | 2.44 | 2.19, 2.10, 1.96 | 5.86 | 2.01 | 1.28, 1.21 | 39.2 |
| **16c** | 5.28 | 2.57 | 2.07 | 4.30 | 5.07 | 1.77 | 2.60 | 2.15, 2.15, 1.98 | 5.99 | 1.95 | 1.20, 1.18 | 40.2 |
| **16d** | 5.43 | 2.63 | 2.13 | 4.43 | 5.16 | 1.84 | 2.72 | 2.16, 2.16, 1.99 | 5.70 | 1.80 | 1.19, 1.13 | 41.0 |

Coupling constant (Hz)

| | $J_{1,2R}$ | $J_{1,2S}$ | $J_{1,P}$ | $J_{1,5R}$ | $J_{1,5S}$ | $J_{2R,2S}$ | $J_{2R,3}$ | $J_{2R,P}$ | $J_{2S,3}$ | $J_{2S,P}$ | $J_{2S,4}$ | $J_{3,4}$ | $J_{3,NH}$ | $J_{3,5R}$ | $J_{4,5R}$ | $J_{4,5S}$ | $J_{4,P}$ | $J_{5R,5S}$ | $J_{5R,P}$ | $J_{5S,P}$ | $^{2}J_{H,P}$ [b] | $^{3}J_{H,H}$ [b] | $^{3}J_{H,P}$ [b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **16a** | 6.1 | 3.4 | 9.2 | 1.2 | 0 | 15.3 | 5.0 | 20.5 | 3.7 | 7.3 | 0 | 3.4 | 8.9 | 1.0 | 3.7 | 11.0 | 9.2 | 14.7 | 17.4 | 8.2 | 5.2 | 7.3 | 16.8 |
| **16b** | 2.8 | 6.1 | 5.0 | 0 | 1.8 | 14.7 | 11.0 | 6.7 | 3.1 | 21.7 | 1.2 | 3.1 | 9.1 | 0 | 3.4 | 6.1 | 21.7 | 16.2 | 18.9 | 9.5 | 3.1 | 7.3 | 16.2 |
| **16c** | 11.6 | 5.2 | 5.2 | 0 | 0 | 12.8 | 11.6 | 9.8 | 3.4 | 20.5 | 1.1 | 2.4 | 9.0 | 0 | 3.2 | 5.2 | 21.4 | 15.9 | 4.9 | 15.8 | 10.7 | 7.3 | 16.2 |
| **16d** | 2.2 | 4.8 | 9.2 | 0 | 2.4 | 14.4 | 12.5 | 2.0 | 3.4 | 21.3 | 1.2 | 2.4 | 8.9 | 0 | 3.1 | 5.2 | 22.0 | 15.6 | 4.9 | 14.6 | 7.0 | 7.3 | 16.2 |

[a] The assignment of acetyl groups may have to be interchanged.

[b] Coupling constants of isopropyl group on phosphorus atom are $^{2}J_{H,P} = 5.2$ Hz, $^{3}J_{H,H} = 7.3$ Hz and $^{3}J_{H,P} = 16.8$ Hz for **16a**, $^{2}J_{H,P} = 3.1$ Hz, $^{3}J_{H,H} = 7.3$ Hz and $^{3}J_{H,P} = 16.2$ Hz for **16b**, $^{2}J_{H,P} = 10.7$ Hz, $^{3}J_{H,H} = 7.3$ Hz and $^{3}J_{H,P} = 16.0$ Hz for **16c** and $^{2}J_{H,P} = 7.0$ Hz, $^{3}J_{H,H} = 7.3$ Hz and $^{3}J_{H,P} = 16.2$ Hz for **16d**, respectively.




**16a** **16b** **16c** **16d**

Scheme 2.

Table 2
$^{13}C$ NMR (67.80 MHz) chemical shifts for **16a**, **16b**, **16c**, and **16d**

| Chemical shift $\delta$ ppm, ($J_{P-C}$, Hz) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Compd. | C-1 | C-2 | C-3 | C-4 | C-5 | P–$CH(CH_3)_2$ | P–$CH(CH_3)_2$ | $C$=O | $CH_3$–C=O |
| **16a** | 65.81 (73.1) | 46.32 (2.4) | 29.62 | 68.61 (0.0) | 24.87 (68.3) | 25.10 (54.8) | 14.57 (4.2) | 167.92, 169.27, 169.60 | 20.86 20.96 23.45 |
| **16b** | 64.33 (70.8) | 45.44 (6.1) | 30.32 | 69.99 (4.8) | 26.45 (71.1) | 25.63 (56.3) | 14.77 (7.3) | 169.99, 169.78, 169.52 | 23.11 20.95 20.85 |
| **16c** | 65.07 (70.7) | 47.78 (0.0) | 29.27 | 69.32 (6.1) | 27.18 (67.1) | 24.77 (57.3) | 15.15 (0.0) | 169.24, 169.61, 170.71 | 20.79 21.15 23.17 |
| **16d** | 65.09 (75.7) | 44.86 (6.1) | 28.56 | 69.78 (7.3) | 24.57 (70.8) | 25.36 (58.6) | 14.32 (0.0) | 170.78, 169.25, 168.98 | 23.29 21.28 20.99 |

$J_{1,P}$ of **16a** and **16d** suggest the *syn* connection of H–C-1–P=O for these compounds. The large magnitude of $J_{1,2R}$ (11.6 Hz) indicated axial H-1 orientation for **16c**, whereas the smaller $J_{1,2R}$ values (2.2–2.8 Hz) suggested the equatorial H-1 orientation for **16b** and **16d**. Small coupling constants $J_{1,5S}$ and $J_{2S,4} = 1.1–2.4$ Hz were shown in the compounds **16b**–**d**. Obviously compounds **16b**–**d** retain the conformation of $^1C_4$ from the above conformation analyses, and the long range couplings ($J_{1,5S} = 1.8$ Hz for **16b**, $J_{1,5S} = 2.4$ Hz for **16d**, and $J_{2S,4} = 1.1–1.2$ Hz for **16b**–**d**) of compounds **16a**–**d** support. As for the more precise conformation of **16b**–**d**, it is noted that the magnitudes of $J_{2R,P}$ and $J_{2S,P}$ tend to become appreciably closer to intermediate values, which suggest an equilibrium mixture of $^4C_1$ and $^1C_4$ conformers at room temperature (ca. 20% of the $^4C_1$ conformation was contained in the compounds **16b**–**d** from the observed coupling constant values). A part of the $^1H$ NMR spectra of compounds **16a**–**d** were assigned with difficulty, because the methylene protons on C-2 and C-5 overlapped with the acetyl group, and it was reexamined more precisely by using a simulation program,[8] giving a good fit with the measured spectrum. The chemical shift values of $^{13}C$ NMR are shown in Table 2.

Rod-shaped crystals of **16c** and **16d** were grown from ethyl acetate–hexane. Precise lattice constants and three dimensional intensity data were obtained by a RIGAKU AFC7R four-circle diffractometer with Ni-filtered CuK$\alpha$ radiation. Phase determination was made by a direct method (SIR92).[9] the molecular structures for compounds **16c** and **16d** are shown in Fig. 2. A water molecule is present in crystal **16c** (**16c**/$H_2O = 1/1$) but is not shown in Fig. 2. A summary of crystal data for compounds **16c** and **16d** is shown in Table 3. In **16c**, the substituent groups at C-1, C-3, and P are orientated equatorially, while those are at C-4 and P=O are axial. However, in molecular structure of **16d**, the substituents at C-3 and P are equatorial, while those at C-1, C-4, and P=O are axial. The acetoxy groups on C-1, C-3, and C-4 have usual *syn* arrangement between the C=O bond and the adjacent C–H bond. The Cremer–Pople puckering parameters[10] are $Q = 0.600$ Å, $\theta = 168.5°$, $\psi = 252.5°$ for **16c** and $Q = 0.5602$ Å, $\theta = 167.4°$, $\psi =$

262.2° for **16d**, respectively, and the six membered rings of the compounds **16c** and **16d** were distorted slightly from the $^1C_4$ conformation. The X-ray analysis of crystals **16c** and **16d**, the structures were first solved at 223 K, but they could not be resolved at 295 K because carbon and phosphorus atoms of six membered ring are disordered at 295 K. In the crystals **16c** and **16d** may exist in the same way of equilibrium as the obtained results by $^1$H NMR, where the compounds exist in an equilibrium mixture of $^1C_4$ and $^4C_1$ in $CDCl_3$ solution. This is the first observed $^1C_4$ conformation of phospha sugar by X-ray crystal structure analysis.

## 1. Experimental

### 1.1. General procedures

Synthetic procedures for compound **5** from **1** as starting material were in with a previous paper.[1] $^1$H NMR spectra were measured in $CDCl_3$ (TMS as the internal standard) on a Brucker 500 (500 MHz) and $^{13}$C NMR were measured in $CDCl_3$ ($CDCl_3$ as the internal standard) on a JASCO EX270 (67.80 MHz). Melting points were measured with a micro melting point apparatus (Yanagimoto Co., Ltd., Japan) and are uncorrected. Column chromatography was performed by Merck Lobar silica gel. The reaction were monitored by TLC on Kieselgel 60 F254 (Merck) with detection by $H_2SO_4$. Optical rotations were determined with a digital polarimeter DIP-4 (JASCO Ltd.). Mass spectra were recorded on Shimadzu GCMS-AP5050 gas-chromatograph-mass spectrometer using electron impact 70 eV. X-Ray single crystallographic measurements were conducted on a RIGAKU AFC7R using cut crystals of size ($0.2 \times 0.2 \times 0.6$ mm). Phase determination was made by a direct method (SIR 92) and expanded using Fourier techniques. After convergence of all parameters, final $R$ values were 5.6% for **16c** and 6.4% for **16d**, respectively.

### 1.2. Methyl 2-deoxy-3-*O*-methanesulfonyl-5-*O*-triphenylmethyl-β-D-*threo*-pentofuranoside (6)

To a dried toluene (80 mL) solution of compound **5** (4.17 g) were added $n$-$Bu_3SnH$ (2.83 g) and a catalytic amount of AIBN. The reaction mixture was heated for 2 h under a nitrogen atmosphere. Toluene was removed under reduced pressure. The residue was dissolved in acetonitrile, and washed several times with n-hexane to remove organic tin compound. The hexane layer was further extracted with acetonitrile. The acetonitrile extract was collected and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to afford syrupy product **6** in quantitative yield. $^1$H NMR ($CDCl_3$): $\delta$, 2.3–2.4 (m, 2H, H-2 and 2′), 2.78 (s, 3H, $OSO_2CH_3$), 3.2–3.6 (m, 2H, H-5 and 5′), 3.40 (s, 3H, $OCH_3$), 4.2–4.3 (m, 1H, H-4), 5.08 (dd, $J = 4.3$ and 2.5 Hz, 1H, H-1), 5.2–5.3 (m, 1H, H-3), 7.2–7.5 (m, 15H, aroma).

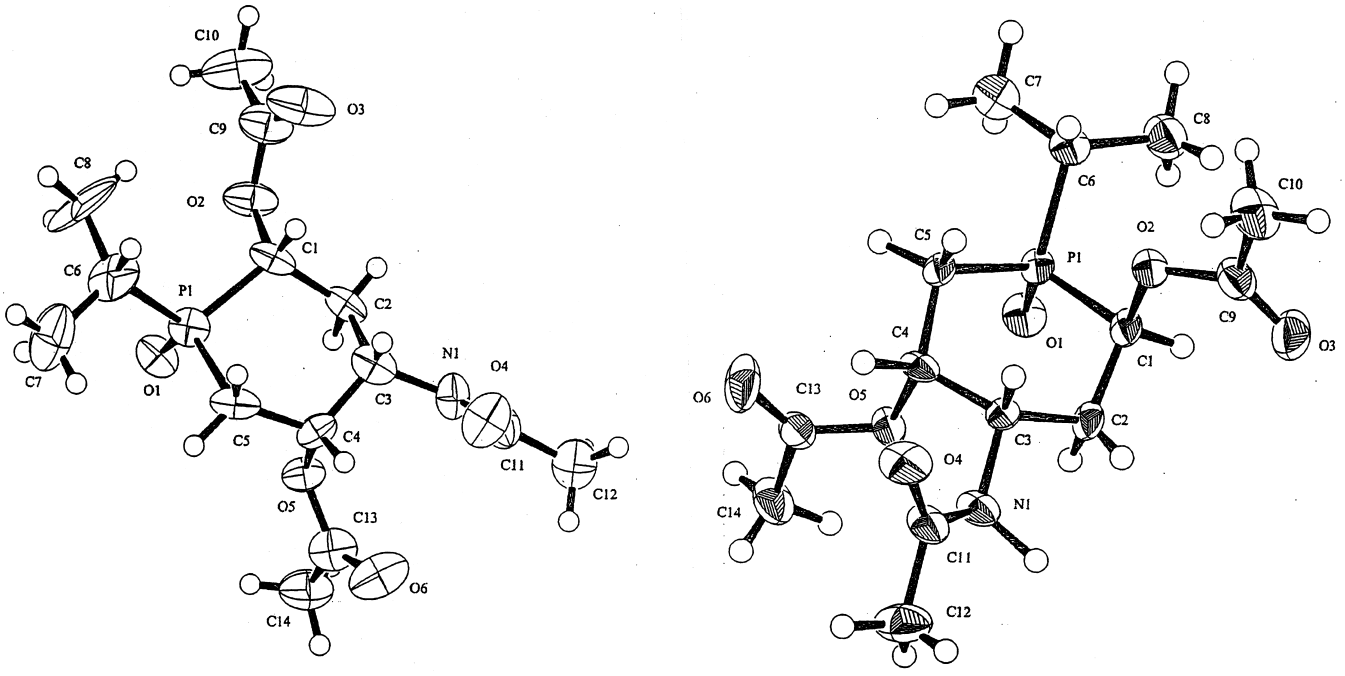



Fig. 2. Molecular structure for compounds **16c** (left) and **16d** (right).

Table 3
Crystal and structure refinements for **16c** and **16d**

| | **16c** | **16d** |
|---|---|---|
| Molecular formula | $C_{14}H_{24}NPO_6 \cdot H_2O$ | $C_{14}H_{24}NPO_6$ |
| Molecular weight | 351.34 | 333.32 |
| Temperature (K) | 223 | 223 |
| Crystal system | orthorhombic | monoclinic |
| Space group | $P2_12_12_1$ ( # 19) | $P2_1$ ( # 4) |
| Unit cell dimensions (Å) | | |
| *a* | 14.877(3) | 9.7660(8) |
| *b* | 23.416(3) | 8.588(1) |
| *c* | 5.253(2) | 10.1716(5) |
| $\beta$ (°) | 90.296(5) | |
| Volume (Å$^3$) | 1830.1(6) | 853.1(1) |
| *Z* (molecules/cell) | 4 | 2 |
| $D_{calcd}$ (g cm$^{-3}$) | 1.275 | 1.235 |
| Absorption coefficient (mm$^{-1}$) | | |
| *F*(000) | 712.00 | 340.00 |
| Crystal size (mm) | $0.20 \times 0.20 \times 0.30$ | $0.2 \times 0.2 \times 0.6$ |
| Reflections collected | 1359 | 1457 |
| Independent reflections | 1346 ($R_{int} = 0.302$) | 1633 ($R_{int} = 0.059$) |
| Refinement method | Full-matrix least-squares on $F^2$ | Full-matrix least-squares on $F^2$ |
| Goodness-of-fit indicator | 3.44 | 2.77 |
| Final *R* indices [$I > 2\sigma(I)$] | | |
| $R_1$ | 0.056 | 0.064 |
| *wR* | 0.059 | 0.180 |

### 1.3. Methyl 3-azido-2,3-dideoxy-5-*O*-(triphenylmethyl)-α- and -D-*erythro*-pentofuranoside (7)

To a solution of compound **6** (3.39 g) in DMF (40 mL) was added sodium azide (7.5 g), and the mixture heated for 2 h at 110 °C. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The syrupy residue was dissolved in chloroform and washed with water several times. The water layer was further extracted with chloroform several times. The organic layer were collected, dried with anhydrous sodium sulfate, and evaporated. The residue was purified by column chromatography on silica gel (eluent; ethyl acetate/hexane = 1/2, v/v) to obtain syrupy product **7** (2.74 g) in 93% yield. $^1$H NMR ($CDCl_3$): $\delta$, 1.9–2.2 (m, 2H, H-2 and 2′), 2.86 and 2.91 (2s, 2H, H-5 and 5′), 3.28 (s, 3H, $OCH_3$), 3.9–4.3 (m, 2H, H-3 and 4), 5.03 (dd, $J = 4.8$ and 2.0 Hz, 1H, H-1), 7.2–7.6 (m, 15H, aroma).

### 1.4. Methyl 3-azido-2,3-dideoxy-α- and β-D-*erythro*-pentofuranoside (8)

To a solution of **7** (2.0 g) in dried methanol (10 mL) was added HCl in methanol solution (0.5 wt%, 0.4 mL), and the mixture was stirred for 1 h at 40–50 °C. The reaction mixture was neutralized with lead carbonate and left overnight in a refrigerator. The precipitate was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent; ethyl acetate/hexan = 1/2, v/v) to obtain syrupy product **8α** (0.44 g) in 51% yield and **8β** (0.26 g) in 30% yield. $^1$H NMR ($CDCl_3$) for **8α**: $\delta$, 1.90–2.60 (m, 3H, H-2, 2′ and OH), 3.38 (s, 3H, $OCH_3$), 3.5–4.0 (m, 4H, H-3, 4, 5 and 5′), 5.07 (d, $J = 5.3$ Hz, 1H, H-1). $^1$H NMR ($CDCl_3$) for **8β**: $\delta$, 2.0–2.5 (m, 2H, H-2 and 2′), 2.9–3.1 (br s, 1H, OH), 3.38 (s, 3H, $OCH_3$), 3.6–3.8 (br m, 2H, H-5 and 5′), 4.0–4.3 (m, 2H, H-3 and 4), 5.09 (dd, $J = 2.1$ and 5.0 Hz, 1H, H-1). Anal. Calcd for $C_6H_{11}N_3O_3$: C, 41.61; H, 6.40; N, 24.27. Found: C, 41.65; H, 6.32; N, 24.25.

### 1.5. Methyl 3-azido-2,3-dideoxy-5-*O*-*p*-toluenesulfonyl-β-D-*erythro*-pentofuranoside (9)

To a solution of **8β** (1.10 g) in pyridine (15 mL) was added *p*-toluenesulfonyl chloride (1.2 g), and the reaction and wash-up were the same as that for compound **8**. Compound **9** was purified by column chromatography on silica gel (ethyl acetate/hexane = 1/2, v/v) (1.85 g, 98%). $^1$H NMR ($CDCl_3$): $\delta$, 1.9–2.4 (m, 2H, H-2,2′), 2.45 (s, 3H, CH3 of tosyl), 3.27 (s, 3H, $OCH_3$), 3.9–4.2 (m, 4H, H-3,4,5, and 5′), 5.01 (dd, $J = 1.9$ and 4.7 Hz, 1H, H-1), 7.31 and 7.84 (2H each, 2 br d, $J = 8.3$ Hz, $C_6H_4$–S).

### 1.6. Methyl 3-acetamido-2,3-dideoxy-5-*O*-*p*-toluenesulfonyl-β-D-*erythro*-pentofuranoside (11)

To a solution of **9** (1.85 g) in dried toluene (100 mL) was added *n*-$Bu_3SnH$ (2.17 g) under a nitrogen atmosphere at 120 °C for 15 min. Concentration of the reaction mixture afforded compound **10**, which was dissolved in pyridine (10 mL). Acetic anhydride (0.75 mL) was added, the reaction mixture stirred for overnight at room temperature, and then the solvents were removed under reduced pressure. The crude products was dissolved in acetonitrile, and excess organo tin was removed by hexane extraction (several times). The syrupy crude product was dissolved in $CHCl_3$, and the organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated. The product was purified by column chromatography on silica gel (ethyl acetate/methanol = 10/1, v/v) and gave pure **11** in 89% yield. $^1$H NMR ($CDCl_3$): $\delta$, 1.9–2.3 (m, 2H, H-2,2′), 1.92 (s, 3H, N–Ac), 2.44 (s, 3H, $CH_3$ of tosyl), 3.16 (s, 3H, $OCH_3$), 3.9–4.6 (m, 4H, H-3, 4. 5, and 5′), 4.98 (d, $J = 3.7$ Hz, 1H, H-1), 3.89 (br d, $J = 7.5$ Hz, 1H, NH), 7.31 and 7.84 (2H each, 2br d, $J = 8.3$ Hz, $C_6H_4$–S). Anal. Calcd for $C_{15}H_{21}NO_6S$: C, 52.46; H, 6.16; N, 4.08. Found: C, 52.44; H, 6.19; N, 4.10.

### 1.7. Methyl 3-acetamido-2,3,5-trideoxy-5-iodo-β-D-ribofuranoside (12)

A mixture of compound **11** (1.97 g) and sodium iodide (1.8 g) in acetone (30 mL) in a sealed tube was heated for 4 h in a boiling water bath, and precipitate was filtered, the filtrate was concentrated. The residue was dissolved in chloroform and washed with water. The water layer was further extracted with chloroform. The organic layer was collected, dried over anhydrous sodium sulfate, and evaporated to afford crystalline 12 (1.43 g) in 96% yield. $^1$H NMR ($CDCl_3$): $\delta$, 1.9–2.6 (m, 2H, H-2 and 2′), 1.98 (s, 3H, N–Ac), 3.2–3.5 (m, 2H, H-5,5′), 3.39 (s, 3H, OMe), 3.9–4.7 (m, 2H, H-3,4), 5.08 (dd, $J = 1.3$ and 5.3 Hz, 1H, H-1), 6.10 (br s, 1H, NH).

### 1.8. Methyl 3-acetamido-2,3,5-trideoxy-5-*C*-(ethoxyisopropylphosphinyl)-β-D-*erythro*-pentofuranoside (13)

The mixture of **12** (1.09 g) and diethyl isopropylphosphonite (10 mL) was heated at 150 °C for 8 h. Excess amount of phosphonite was remove under reduced pressure, and crude product **13** was purified by column chromatography on silica gel (ethyl acetate/methanol = 10/1, v/v) to afford in quant. yield. $^1$H NMR ($CDCl_3$): $\delta$, 1.0–1.4 (m, 10H, P–$CH(CH_3)_2$ and P–$OCCH_3$), 1.6–2.4 (m, 4H, H-2,2′,5, and 5′). 1.97 (s, 3H, N–Ac), 3.33 (s, 3H, $OCH_3$), 3.8–4.6 (m, 4H, H-3,4,P–$OCH_2$), 4.97 (br d, J = 4.6 Hz, 1H, H-1), 7.9 (br d, $J = 7.1$ Hz, 1H, NH). Anal. Calcd for $C_{13}H_{26}NO_5P$: C, 50.81; H, 8.53; N, 4.56. Found: C, 50.83; H, 8.50; N, 4.55.

### 1.9. Preparation of phospha sugar derivatives (16)

To a solution **13** (776 mg) in dry THF (25 mL) SDMA (70% in toluene, 1.2 g) was added at 0 °C, and the mixture was stirred for 1 h. A small amount of water containing concd HCl was added. The precipitate was filtered off, the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel (ethylacetate/methanol = 3/1, v/v) to give syrupy compound **14** (305 mg). This syrup was immediately dissolved in water containing a small amount of THF and hydrochloric acid (0.2 mL) was added. The mixture was heated under nitrogen for 3.5 h at 110 °C (bath temp.). The mixture was cooled, diluted with water, and the acid neutralized with Amberlite IR-45A ion-exchenge resin, and filtered. The resin was washed with water and ethanol and filtered. The filtrates were combined, and evaporated in vacuo to give syrupy **15** (223 mg). This syrup was treated with acetic anhydride (1.0 mL) in dry pyridine (15 mL). Pyridine was evaporated in vacuo to give syrupy **16**. This syrup was immediately purified by column chromatography on silica gel (ethylacetate/methanol = 2/1, v/v), and separated by column chromatography on silica gel (ethylacetate/methanol = 4/1–2/1, v/v) to give **16a**–**d**. Chemical yields of **16a**, **16b**, **16c** and **16d** were 59 mg (7% from **13**), 46 mg (5%), 44 mg (5%), and 90 mg (11%), respectively. and optical rotations were $[\alpha]_D$ −21.7° (*c* 1.15) for **16a**, −34.5° (*c* 1.45) for **16b**, −28.1° (*c* 1.78) for **16c**, and −66.4° (*c* 1.28) for **16d** in $CHCl_3$, respectively. Anal. Calcd for $C_{14}H_{24}NO_6P$ (**16a**): C, 50.45; H, 7.26; N, 4.20. Found: C, 50.40; H, 7.29; N, 4.22. Anal. Calcd for $C_{14}H_{24}NO_6P$ (**16b**): C, 50.45; H, 7.26; N, 4.20. Found: C, 50.44; H, 7.24; N, 4.25. Anal. Calcd for $C_{14}H_{24}NO_6P$ (**16c**): C, 50.45; H, 7.26; N, 4.20. Found: C, 50.44; H, 7.26; N, 4.22. Anal. Calcd for $C_{14}H_{24}NO_6P$ (**16d**): C, 50.45; H, 7.26; N, 4.20. Found: C, 50.48; H, 7.20; N, 4.21.

## 2. Supplementary material

Full crystallographic details excluding structure features have been deposited with the Cambridge Crystallographic Data Centre (CCDC). These data may be obtained, on request, from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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