SYNTHESIS AND STRUCTURE ANALYSES OF 1,2,4-TRI-*O*-ACETYL-3,5-DI-DEOXY-5-*C*-(ISOPROPYL- AND PHENYL-PHOSPHINYL)-D-*erythro*-PENTOPYRANOSES

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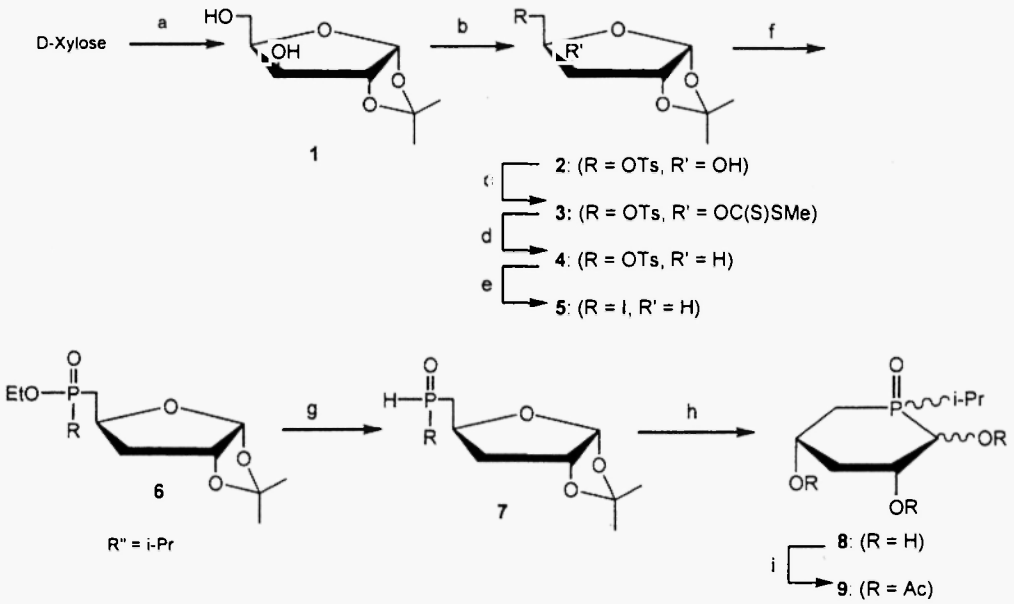
Abstract: ^{1}H NMR spectroscopy for phosphorus containing hetero sugars (phospha sugars **9a-d** and **17a-d**) revealed the stereoisomeric configurations and the chair conformations for α - and β -1,2,4-tri-*O*-acetyl-3,5-di-deoxy-5-*C*-(isopropyl- and phenyl-phosphinyl)-D-*erythro*-pentopyranoses. The conformations of the title compounds were characterized as $^4C_1$ chair form in $CDCl_3$ by ^{1}H NMR (500 MHz), and the conformations were in accord with those in the solid state determined by X-ray crystallographic analyses.

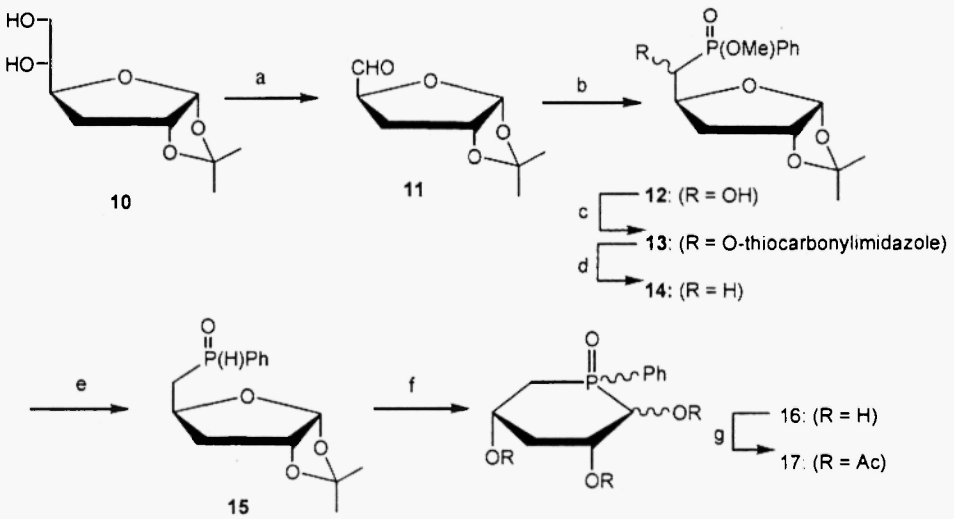
Studies on hetero sugars have been often enhanced by expectation that these modified sugars ought to be active compounds in biochemical sense. Appropriate examples for biologically active hetero sugars, aza-sugar [1] and thia-sugar [2] have been shown to be bioactive for antibiotics and adjusting glucose concentration in blood. We have been synthesizing phospha sugar derivatives in which the oxygen atom in

the franose or pyranose ring was replaced by a phosphorus atom [3, 4]. In the present work, we examined the synthesis and structure analysis of 3,5-dideoxygenated pyranose type phospha sugars. The title compounds were synthesized from D-xylose as the starting material. Synthetic routes for target compounds **9** and **17** are shown in Schemes 1 and 2. Deoxygenating reaction of compounds **3** and **13** accorded with the reported procedure [5]. Carbon-phosphorus bond forming reaction of compounds **6** and **12** were executed by either Arbusov reaction of diethyl isopropylphosphonite with iodo compound **5** or addition reaction of methyl phenylphosphonate to carbonyl group of compound **11**, respectively. Treatment of **6** and **14** with sodium dihydrobis(2-methoxyethoxy)alminate (SDMA) gave **7** and **15** (P-H signals were shown 6.79 ppm (J_{PH} = 457 Hz) for **7** and 7.50 ppm (J_{PH} = 454 Hz) for **15** on ^{1}H-NMR), respectively, which was subsequently followed by ring-enlargement via the ring opening of **7** and **15**, and the successive ring closing to prepare pyranose rings under aq. HCl conditions. Compounds **8** and **16** were pertriacetylated by treatment with acetic anhydride in pyridine to afford compounds **9** and **17**, respectively. Sets of diastereomers **9a-d**, and **17a-d** were separated by flash column chromatography on silica gel from diastereo mixtures of **9** and **17**, respectively [6]. The precise structures of these compounds **9a-d** and **17a-d** were determined on the basis of the 500 MHz ^{1}H NMR spectroscopy. The assignments of all signals were readily made by employing first-order analysis with the aid of a decoupling technique and 2D COSY spectral analyses. The analyzed spectrum data for compound **9** are summarized in Table 1, and those for compound **17** in Table 2. Conformations of these phospha sugar derivatives (in $CDCl_3$ solution) are derived by the careful analysis of the coupling constants magnitudes. As large $J_{4,5a}$ values (11.5-12.1 Hz) of **9a-d** and **17a-d** are characteristic coupling constants for an axial-axial relation of H-4 and H-5a in pyranose conformation, all derivatives of **9a-d** and **17a-d** have $^4C_1$ conformation in the D-glucopyranose forms. With regard to the anomeric orientation of C-1, small $J_{1,2}$ values (2.4 Hz) for **9a** and **9c**, and $J_{1,2}$ values (2.4-2.8 Hz) for **17a** and **17c** clearly indicate α-anomers. In the same way, large $J_{1,2}$ values (10.7 and 11.0 Hz) for **9b** and **9d**, and $J_{1,2}$ values (11.0 Hz) for **17b** and **17d** show β-anomers. Obviously compounds **9a-d** and **17a-d** retain the $^4C_1$ conformation from the above conformation analyses as well as the long range couplings ($J_{1,5e}$ = 1.3 Hz for **9a**, $J_{1,5e}$ = 1.8 Hz for **9c**, $J_{1,5e}$ = 1.8 Hz for **17a**, and $J_{1,5e}$ = 2.0 Hz for **17c**) for all compounds **9a-d** and **17a-d** by their zig-zag structure. As H-2 and H-4 signals of **9a**, **9b**, **17a** and **17b** appear at the appreciably lower magnetic field compared with those signals of **9c**, **9d**, **17c**, and **17d**, therefore axial P=O for **9a**, **9b**, **17a**, and **17b**, and equatorial P=O for **9c**, **9d**, **17c**, and **17d** are assigned, respectively. A part of ^{1}H NMR spectra of phospha sugars **9a-d** and **17a-d** were assigned ambiguously. The reason is that the methylene protons on C-3 and C-5 overlapped with protons of three acetyl groups, and the splitting pattern was overlapped each other because the chemical shift differences were so small. We reexamined more precise ^{1}H NMR analyses for compounds **9a-d** and **17a-d** by using ^{1}H NMR simulation program [7]. The calculation results for compound **17d** is shown in Fig. 1 as an example.



Preparation conditions: a) several steps; b) TsCl / py; c) CS_2 / DMSO / NaOH;
d) n-Bu_3SnH / AIBN; e) NaI; f) i-Pr-$P(OEt)_2$; g) SDMA; h) HCl; i) Ac_2O / py

Scheme 1



Preparation conditions: a) $NaIO_4$; b) H(O)P(OMe)Ph / Et_3N, c) thiocarbonyldiimidazole (TCDI);
d) n-Bu_3SnH ; e) SDMA, f) HCl, g) Ac_2O / py

Scheme 2

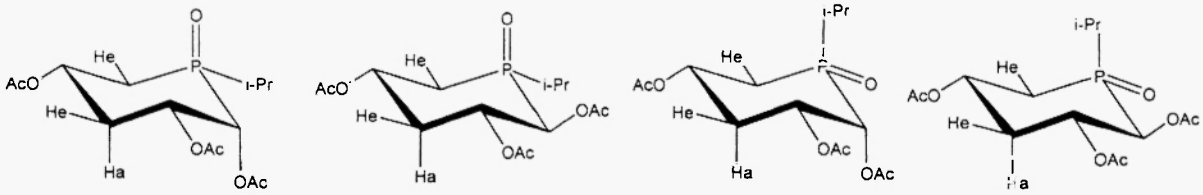


Table 1. ^{1}H NMR (500 MHz) parameters and ^{31}P NMR chemical shifts for **9a-d**.

	NMR Chemical shift (δ, ppm) of ^{1}H and ^{31}P NMR										
	H-1	H-2	He-3	Ha-3	H-4	He-5	Ha-5	AcO-1,2,4[a]	HC-P	$(CH_3)_2C$	^{31}P
9a	5.71	5.47	2.21	1.96	5.34	2.50	1.74	2.16, 2.95, 1.99	1.84	1.23, 1.17	47.2
9b	5.33	5.48	2.51	1.71	5.37	2.46	1.71	2.15, 2.03, 2.01	2.08	1.24, 1.20	42.9
9c	5.78	4.87	2.04[b]	2.08[b]	4.76	2.54	2.14	2.12, 2.07, 2.01	1.82	1.35, 1.32	41.2
9d	5.63	5.03	2.34	1.88	4.80	2.69	2.04[b]	2.16, 2.16, 1.99	2.02[b]	1.40, 1.34	39.6

	J values (Hz) for H-H and H-P coupling										
	$J_{1,2}$	$J_{1,1'}$	$J_{1,3e}$	$J_{1,5e}$	$J_{2,3e}$	$J_{2,3a}$	$J_{2,P}$	$J_{3a,3e}$	$J_{3e,4}$	$J_{3a,4}$	$J_{3e,5e}$
9a	2.4	8.9	1.5	1.3	4.0	12.5	0	12.7	4.0	11.7	1.8
9b	10.7	3.4	0	0	4.0	11.4	3.4	12.7	4.5	11.6	2.2
9c	2.4	8.6	1.2	1.8	4.3	12.2	0	c)	4.5	11.5	2.1
9d	11.0	11.6	0	0	4.2	11.6	2.8	12.8	4.0	11.9	2.4
	$J_{4,5e}$	$J_{4,5a}$	$J_{4,P}$	$J_{3a,5e}$	$J_{5e,P}$	$J_{5a,P}$	$^{2}J_{H,P}$	$^{2}J_{H,H}$	$^{3}J_{H,P}$	$^{3}J_{H',1}$	
9a	4.3	12.0	2.4	13.6	16.2	5.2	6.5	7.3	16.8	16.8	
9b	4.2	12.0	3.7	14.2	14.5	4.0	13.5	7.3	16.8	17.7	
9c	4.2	12.0	1.6	14.0	14.9	19.2	8.8	7.0	12.8	12.5	
9d	3.9	11.9	2.8	14.5	15.3	c)	14.6	7.0	15.3	17.4	

a) The assignment of acetyl groups may be interchangeable. b) Confirmed by 2D COSY measurement.

c) Uncertainly in analysis because of overlapping with other signals.

Fig. 1 show that the splitting pattern being outputted by simulation program fits well in with the actually measured spectra for compound **17d**, therefore, the analyzed ^{1}H NMR data for compound **17d** as well as compounds **17a-c** shown in Tables 1 and 2 might be correct. These stereochemical conclusions based on ^{1}H NMR analysis prompted us to carry out X-ray crystallographic analysis for compounds **9b** and **17b** for the completely precise stereochemical analyses of these phospha sugars. Rod-shaped crystals of **9b** and **17b** were grown from ethyl acetate-hexane. Precise lattice constants and three dimensional intensity data were obtained by a RIGAKU AFC7R four-circle diffract meter. Phase determination was made by a direct method

(SIR92) [8]. Molecular structure for compounds **9b** and **17b** are shown in Fig. 2, and crystal structure data for **9b** and **17d** are shown in Table 3.

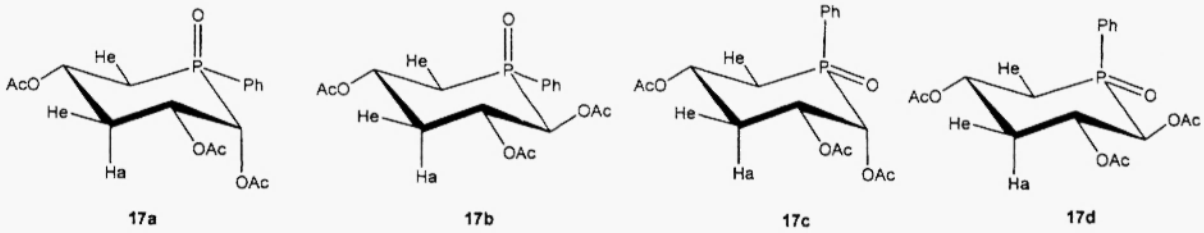


Table 2. ^{1}H NMR (500 MHz) parameters and ^{31}P NMR chemical shifts for **17a-d**.

	NMR Chemical shift (δ, ppm) of ^{1}H and ^{31}P NMR											
	H-1	H-2	He-3	Ha-3	H-4	He-5	Ha-5	AcO-1,2,4[a]	Ph(*o*)	Ph(*m*)	Ph(*p*)	^{31}P
17a	5.69	5.61	2.31	2.07	5.51	2.60	2.37	2.08, 1.99, 1.96	7.75	7.51	7.60	31.3
17b	5.56	5.61	2.64	1.89	5.51	2.69	2.08	2.04, 2.01, 1.94	7.77	7.53	7.60	27.9
17c	6.13	4.62	1.97	2.16	4.79	3.06	2.39	2.27, 2.09, 1.97	7.88	7.59	7.63	27.4
17d	5.81	4.93	2.37	2.00	4.99	3.07	2.34	2.12, 2.09, 2.02	7.94	7.58	7.64	27.0

	J values (Hz) for H-H and H-P coupling																
	$J_{1,2}$	$J_{1,P}$	$J_{1,3e}$	$J_{1,5e}$	$J_{2,3e}$	$J_{2,3a}$	$J_{2,P}$	$J_{3a,3e}$	$J_{3e,4}$	$J_{3a,4}$	$J_{3e,5e}$	$J_{4,5e}$	$J_{4,5a}$	$J_{4,P}$	$J_{5a,5e}$	$J_{5e,P}$	$J_{5a,P}$
17a	2.8	10.1	1.5	1.8	4.0	12.5	0	12.8	3.8	11.9	1.8	4.2	11.9	2.1	13.5	17.6	6.7
17b	11.0	2.4	0	0	4.0	11.0	3.4	13.2	4.4	11.5	1.0	4.0	12.1	2.7	14.3	18.6	4.9
17c	2.4	9.5	1.8	2.0	4.0	12.5	0	12.8	4.0	11.9	2.0	4.0	11.9	2.1	14.7	15.6	19.2
17d	11.0	11.3	0	0	4.0	13.4	4.0	13.4	4.0	11.6	2.4	4.0	11.6	3.6	14.7	15.8	18.3

a) The assignment of acetyl groups may be interchangeable.

As Fig. 2 shows, compounds **9b** and **17b** are 1,2,4-tri-acetyl-3,5-dideoxy-5-*C*-[(S_P)-isopropyl- and (S_P)-phenyl-phosphinyl]-*erythro*-pentopyranoses, respectively, whose pyranose rings are $^{4}C_1$ chair conformation. In molecular structures of **9b** and **17b**, the substitutents at C-1, C-2, C-4 and P atoms link equatorially fashion, while those at P=O is axial. The acetoxy groups on C-1, C-2, and C-4 atoms have usual *syn* arrangement between the C=O bond and the C-H bond on the same carbon skeletal atoms. The Cremer-Pople puckering parameters are Q = 0.600 Å, θ= 168.5°, ψ= 252.5° for **9b** and Q = 0.5602 Å, θ= 167.4°, ψ= 262.2° for **17b**, respectively, and the six membered ring of the compounds **9b** and **17b** were slightly distorted from the $^{4}C_1$ conformation based on results of calculation of the Cremer-Pople parameters [9]. The examination is being carried out on the bioactivities of all synthesized phospha sugar derivatives in this report.

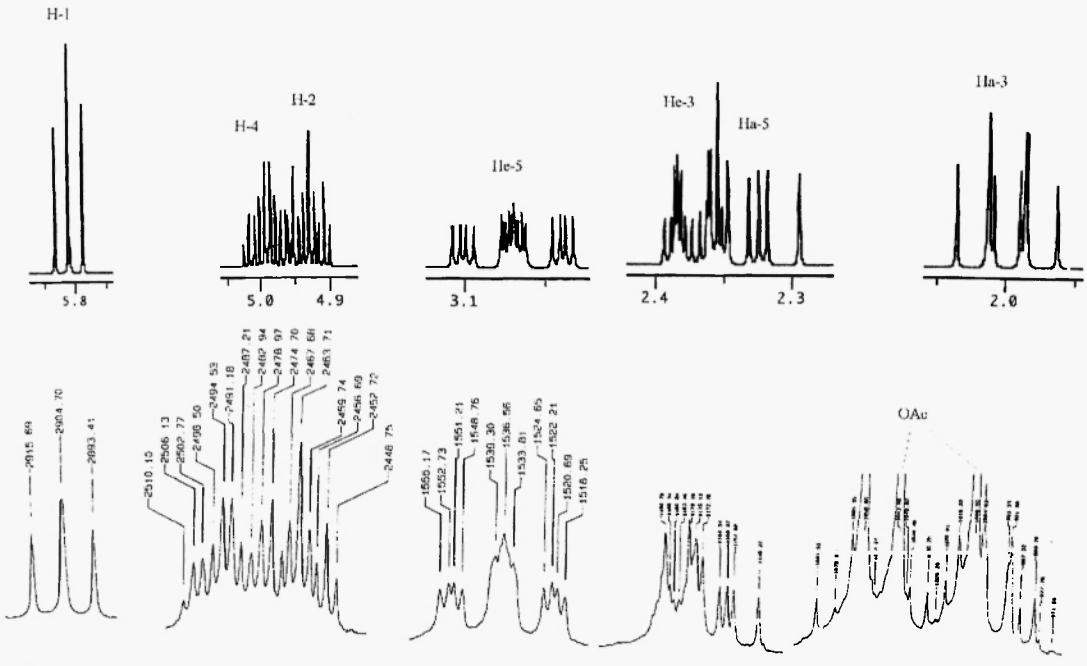


Fig 1. ^{1}H NMR spectra for compound **17d**. (Top: simulated spectra prepared by using parameters in Table 2; Bottom: actual spectra obtained by 500 MHz NMR).

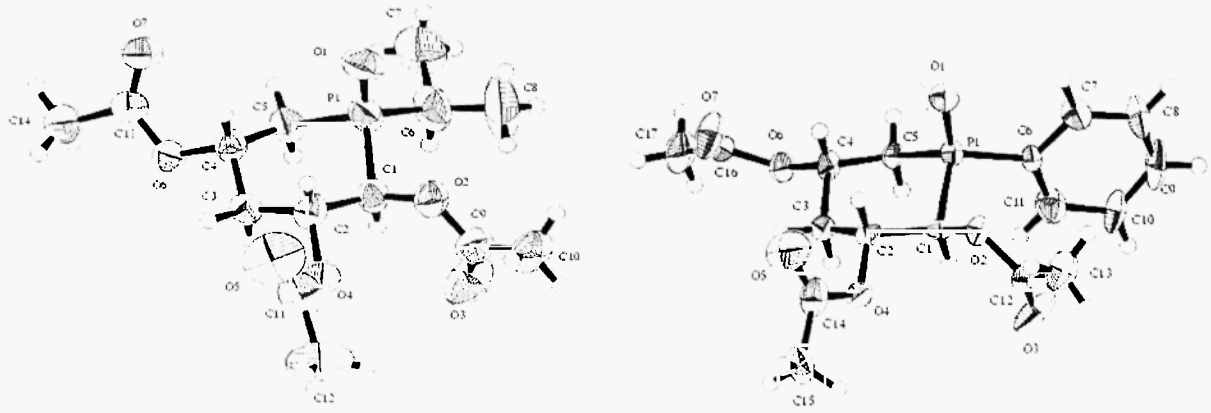


Fig. 2. Molecular structure for **9b** (left) and **17b** (right).

Table 3. Crystal and structure refinements for **9b** and **17b**.

	Compound **9b**	Compound **17b**
Molecular formula	$C_{14}H_{23}O_7P$	$C_{17}H_{21}O_7P$
Molecular weight	334.31	368.32
Temperature (K)	298	298
Crystal system	hexagonal	orthorhombic
Space group	P65 (#170)	$P2_12_12_1$ (#19)
Unit cell dimensions (Å) a	9.234(4)	8.52(7)
b		38.30(8)
c	35.541(10)	5.68(9)
β(°)	90.0	
Volume (Å^3)	2624(2)	1854(31)
Z (molecules / cell)	6	4
Density (calculated , g cm^{-3})	1.27	1.319
F(000)	1068.00	776.00
Crystal size (mm)	0.30 × 0.40 × 0.60	0.20 × 0.20 × 0.5
Reflections collected	1620	1693
Independent reflections	1356	1122
Refinement method	Full matrix least-squares on F^2	Full matrix least-squares on F^2
R_1	0.049	0.049
R_w	0.037	0.027

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[6] $[\alpha]^{23}_D$ + 33.5° (c = 1.64) for **9a**; $[\alpha]^{23}_D$ – 20.7° (c = 1.09, $CHCl_3$) for **9b**; $[\alpha]^{23}_D$ + 31.9° (c = 1.88, $CHCl_3$) for **9c**; $[\alpha]^{23}_D$ 0.0° (c = 1.09, $CHCl_3$) for **9d**. $[\alpha]^{23}_D$ + 57.0° (c = 1.93, $CHCl_3$) for **17a**; $[\alpha]^{23}_D$ + 13.8° (c = 1.16, $CHCl_3$) for **17b**; $[\alpha]^{23}_D$ – 49.6° (c = 1.415, $CHCl_3$) for **17c**; $[\alpha]^{23}_D$ – 49.6° (c

= 1.41, $CHCl_3$) for **17d.**

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