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Preliminary communication

Synthesis of carbohydrates having phosphorus in the anomeric position

ANDRZEJ E. WROBLEWSKI

Institite of Organic Chemistry, Technical University (Politechnika), 90-924 Łódź, Zwirki 36 (Poland)

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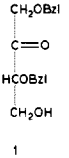
Analogues of carbohydrates with phosphorus as the ring heteroatom have been described[1,2] and we now report on analogues in which phosphorus replaces the anomeric carbon. Our interest in this area was stimulated by the transformation[3] of a model γ-keto-phosphite into diastereomeric 1,2-oxaphospholan-3-ols and the corresponding α,γ-dihydroxyphosphonate. We anticipated that this approach could be applied to the synthesis of C-2 branched-chain sugars.

1,3-Di-*O*-benzyl-D-*glycero*-tetrulose[4] (**1**) was transformed quantitatively under standard conditions [$(MeO)_2PCl/NEt_3$] into the mixed phosphite **2**, which was immediately hydrolysed[3]. ^{31}P-N.m.r. spectroscopy of the crude reaction mixture revealed (2*R*,3*R*,4*R*)- (**3a**) and (2*S*,3*R*,4*R*)-4-*O*-benzyl-3-*C*-(benzyloxymethyl)-2-methoxy-2-oxo-1,2-oxaphospholane-3,4-diol (**3b**), and 1,3-di-*O*-benzyl-2-*C*-(dimethoxyphosphinyl)-D-erythritol (**4**) together with a trace of 1,3-di-*O*-benzyl-2-*C*-(dimethoxyphosphinyl)-D-threitol. The C-3 epimers of **3a** and **3b** were not detected and the cyclisation of **2** appears to be stereospecific. Column chromatography of the crude product gave 23% of a 2:1 mixture of **3a** and **3b**, and 22% of **4** {oil, $[\alpha]_D^{20}$ −13° (*c* 2.4, chloroform)}.



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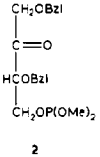

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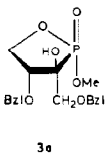

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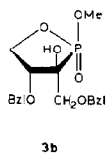

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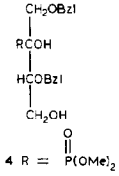

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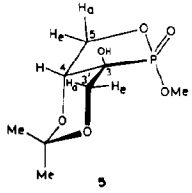

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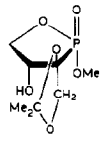

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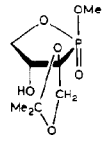
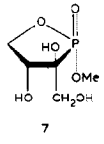


6b



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0008-6215/84/$03.00

Treatment of **4** with 10% triethylamine in benzene at 20° afforded 73% of a 2:1 mixture of **3a** and **3b**, and attempts to separate these products failed. Hydrogenolysis of the 2:1 mixture of **3a** and **3b** gave the corresponding triols, which were immediately treated with 2,2-dimethoxypropane–toluene-*p*-sulfonic acid monohydrate[5]. From the resulting mixture, (2*R*,3*R*,4*R*)-3-*C*-(hydroxymethyl)-4,3^1-*O*-isopropylidene-2-methoxy-2-oxo-1,2-oxaphospholane-3,4-diol (**5**, 8.1%) and (2*R*,3*R*,4*R*)-(**6a**, 22.6%) and (2*S*,3*R*,4*R*)-3-*C*-(hydroxymethyl)-3,3^1-*O*-isopropylidene-2-methoxy-2-oxo-1,2-oxaphospholane-3,4-diol (**6b**, 10.2%) were isolated.

The ^{13}C resonances at 99.15 (*C*Me$_2$) and 19.97 and 28.17 p.p.m. (C*Me*$_2$) for **5** strongly support the formation of the 1,3-dioxane ring[6]. On the other hand, the ^{13}C resonances at 112.43 and 111.91 p.p.m. for *C*Me$_2$ in **6a** and **6b**, respectively, together with those for *Me*$_2$C at 25.48 and 26.29 p.p.m. for **6a**, and 25.38 and 26.29 p.p.m. for **6b**, are characteristic for non-fused 1,3-dioxolane rings[6]. Furthermore, both spiro derivatives had $^3J_{P,CMe_2}$ values of 4.4 Hz. Detailed configurational and conformational relationships for **5** were assigned on the basis of ^{1}H-n.m.r. data (Table I). Each ring hydrogen in **5** is three bonds away from phosphorus, and the $J_{H,P}$ values reflect the stereochemistry[7]. The large $^3J_{4,P}$ value of 24.5 Hz is observed only for *cis*-fused 1,2-oxaphospholane and 1,3-dioxane rings. From the values of $^3J_{4,5a}$ and $^3J_{4,5e}$, and $^3J_{5a,P}$ and $^3J_{5e,P}$ it is evident that the 1,2-oxaphospholane ring in **5** exists in the E_4 conformation. Furthermore, the $^3J_{P,3^1a}$ and $^3J_{P,3^1e}$ values clearly show that the 1,3-dioxane ring is in the chair conformation. In the alternative 4,3^1-*O*-isopropylidene derivative, having the opposite configuration at position 3, no coupling between H-4 and phosphorus is expected. The above conclusion reflects the $^1T_3$ conformation that the 1,2-oxaphospholane ring is forced to adopt in the *trans*-fused system with the 1,3-dioxane ring. Isopropylidenation studies proved the 2:1 mixture of **3a** and **3b** obtained by hydrolysis of **2** to be identical with that prepared by intramolecular cyclisation of **4**.

The relative configurations of HO-3 and P=O in **3a** and **3b** were deduced from the chemical shifts of the ^{31}P resonances, namely, 41.7 p.p.m. for the isomer (**3a**) with *cis* groups and 39.5 p.p.m. for the isomer (**3b**) with *trans* groups.

Treatment of **6a** in chloroform with toluene-*p*-sulfonic acid monohydrate at 40° for 1 h and then with methanol gave (2*R*,3*R*,4*R*)-3-*C*-(hydroxymethyl)-2-methoxy-2-oxo-1,2-oxaphospholane-3,4-diol (**7**, 72%), m.p. 145–146°, $[\alpha]_D^{22}$ −14° (*c* 1, methanol). ^{13}C-N.m.r. data (CD_3OD): δ 54.78 (d, *J* 6.6 Hz, Me), 63.20 (d, *J* 8.1 Hz, C-3^1), 73.99 (d, *J* 8.1 Hz, C-5), 76.17 (d, *J* 136.8 Hz, C-3), and 76.41 (d, *J* 14.7 Hz, C-4).

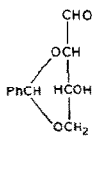
TABLE I

^{1}H-N.M.R. (90 MHz) PARAMETERS [a] ($CDCl_3$, INTERNAL Me_4Si) FOR COMPOUND **5**

Me$_2$*C*	*MeOP*	*H-3*^{1}a	*H-3*^{1}e	*H-4*	*H-5*a	*H-5*e
1.41 s	3.91 d	4.00 dd	4.14 dd	4.25 dd	4.55 ddd	4.08 dd
1.50 s	$J_{H,P}$ 11.1	$J_{3^1a,3^1e}$ 13.5	$J_{3^1e,P}$ 12.9	$J_{4,5a}$ 3.2	$J_{5a,5e}$ 10.3	$J_{5e,P}$ 18.2
		$J_{3^1a,P}$ 23.7		$J_{4,P}$ 24.5	$J_{5a,P}$ 3.2	

[a] Chemical shifts on the δ scale, *J* in Hz.

Triethylamine-catalysed addition of dimethyl phosphite to 2,4-*O*-benzylidene-D-threose[8] (8) afforded (1*R*)-2,4-*O*-benzylidene-1-*C*-(dimethoxyphosphinyl)-D-threitol (9) (^{31}P 27.1 p.p.m.) and (1*S*)-2,4-*O*-benzylidene-1-*C*-(dimethoxyphosphinyl)-D-threitol (10) (^{31}P 27.5 p.p.m.) in the ratio 9:1. Column chromatography of the mixture on silica gel gave **9** (14%), m.p. 121–122°, $[\alpha]_D^{18}$ +13° (*c* 2.1, chloroform). Hydrogenolysis of **9** followed by acetylation afforded the tetra-acetate **11**, m.p. 54–55°, $[\alpha]_D^{18}$ +22° (*c* 1.1, chloroform). N.m.r. data: $J_{2,3}$ 2.6 and $J_{1,2}$ 9.1 Hz. The former *J* value accords with the *threo* configuration around the C-2–C-3 bond, and the latter shows[9] that the configuration at C-1 is *R*.



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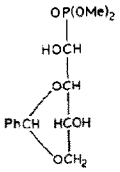

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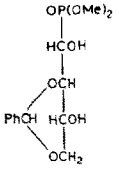

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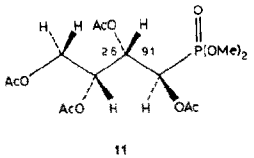

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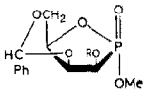
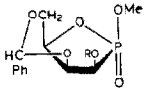


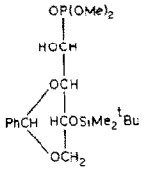
12a

R = $SiMe_2{}^tBu$



12b

R = $SiMe_2{}^tBu$



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Treatment of **9** with 2.2 equiv. of *tert*-butyldimethylsilyl chloride in *N*,*N*-dimethylformamide in the presence of 4.4 equiv. of imidazole[10] afforded (2*R*,3*R*,4*S*,5*R*)-(**12a**) and (2*S*,3*R*,4*S*,5*R*)-4,5[1]-*O*-benzylidene-3-*O*-(*tert*-butyldimethylsilyl)-5-*C*-(hydroxymethyl)-2-methoxy-2-oxo-1,2-oxaphospholane-3,4-diol (**12b**), and (1*R*)-2,4-*O*-benzylidene-3-*O*-(*tert*-butyldimethylsilyl)-1-*C*-(dimethoxyphosphinyl)-D-threitol (**13**). On the basis of ^{31}P-n.m.r. data, the ratios of **12a** (^{31}P 35.27 p.p.m.), **12b** (^{31}P 34.00 p.p.m.), and **13** (^{31}P 27.36 p.p.m.) were 1:1:1. Column chromatography of the mixture on silica gel gave **13** as a colorless syrup, $[\alpha]_D^{20}$ −5° (*c* 1.3, chloroform). For the *p*-nitrobenzoate of **13** {m.p. 106–107°, $[\alpha]_D^{20}$ −25° (*c* 1.5, chloroform)}, H-1 resonated at δ 5.72 and a $^2J_{1,P}$ value of 4.8 Hz was observed. These data proved that **13** was formed by preferential silylation of the ring hydroxyl group in **9**. After the removal of **13**, fractional crystallisation gave **12a** {m.p. 159–160°, $[\alpha]_D^{20}$ +49.5° (*c* 1.6, chloroform)} and **12b** {m.p. 189–190°, $[\alpha]_D^{20}$ +30° (*c* 1.5, chloroform)}. The assignment of configuration at phosphorus was based on the deshielding effect of the phosphoryl group[7], which causes the resonance of H-3 in **12b** to fall 0.16 p.p.m. below that in **12a**. The $^2J_{3,P}$ values for **12a** and **12b** were similar (−8.6 and −9.9 Hz, respectively) and could not be used for configurational assignments[7].

The method for cyclisation of **9** should be useful for the preparation of other

analogues of pentofuranosides having phosphorus in the anomeric position. The intramolecular cyclisation of **4** corresponds to the hemiacetal formation–glycosidation sequence of simple monosaccharides.

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