PHOSPHONYLATION OF SUGAR DERIVATIVES USING PHOSPHANYLIUM CATION

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Abstracts : Chloro (diisopropylamino) phosphanylium cation **1** reacts with 4,6 -*O*-benzylidene - D-allal **2** to give regioselectively phosphonylated sugar **3** . The cation **1** also reacted with 2-enopyranoside **6** to give phosphonylated sugar **7**.

Introduction

Phosphonates are interesting complements to phosphates in terms of biological activity and have been well documented in recent literature. Unlike phosphates, the phosphonate linkage is not susceptible to hydrolysis by esterases and is chemically stable. Acyclic nucleoside phosphonates are a novel class of antiviral agents that exhibit broad-spectrum inhibition of DNA viruses (e.g., adenovirus, Epstein-Barr virus, hepatitis B virus, acyclovir-resistant herpes simplex virus, and ganciclovirresistant cytomegalovirus)(1-3) and retroviruses (e.g., HIV-1, HIV-2, SIV, and MSV).(2) Oligonucleoside methylphosphonates act effectively as specific antisense inhibitors of gene expression in mammalian cells.(4) Phosphonates also show promise as useful broad-spectrum antibiotics.(5-7) Bisphosphonates have become important in the treatment of hypercalcemia and tumor-induced osteolysis.(5,7,8) In the area of agricultural chemistry, phosphonates have been developed as insecticides,(6,7) herbicides,(6-8) fungicides,(7,10) and plant growth regulators.(9) Furthermore, Gross, Mehdi and McCarthy designed (E)- and (Z)-fluorovinyl phosphonate analogs as potential mechanism-based inhibitors of inositol synthase (5.5.1.4).(11) This enzyme converts glucose-6-phosphate into *myo*-inositol-1-phosphate through an NAD oxidation, aldol cyclization, and NADH reduction sequence.(12) Inhibition of the synthase would control the phosphoinositide pool in cells where uptake of inositol is absent or inefficient because of blood-tissue barriers.(13)

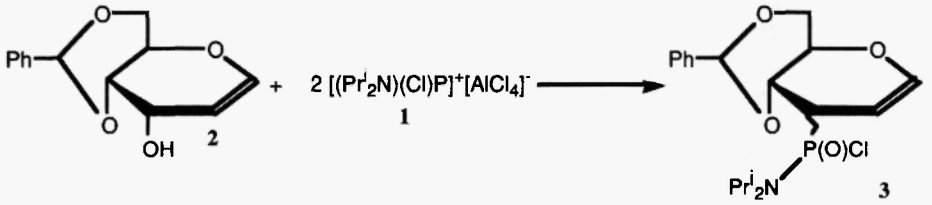
No paper, however, has been published on the compounds of phosphonylated 6 membered sugars having unsaturated bond.

Recently, we reported the reactions of chloro(diisopropylamino) phosphanylium cation**1** with unsaturated

alcohols to form phosphonylated compounds having unsaturated bond.(14) In the present paper, the reactions of chloro(diisopropylamino)phosphanylium cation(15,16) **1** with enopyranosides are described.

Results and Discussion

4,6-*O*-benzylidene-D-allal(17) **2** reacted with 2 equiv. of chloro (diisopropylamino) phosphanylium cation **1** at 0°C for 1hr. to give *N, N*-diisopropyl-*P*-(3-(4,6-benzylidene)-α-D-altro-1-enopyranosidyl)phosphonamidic chloride **3** in 51% yield as a diastereoisomeric mixture which was separated by column chromatography on



Entry	reaction time	temp	product (Yield; %)
1	1hr	r.t.	**3** trace
2	1hr	-78°C	**3** (40%)
3	1hr	0°C	**3** (51%)
4	1hr	-78°C--->0°C	**3** (44%)[a]

[a] The ratio of pseudo-axial:pseudo-equatorial was about 4:1 which was estimated from the signal of ^{31}P in the NMR at δ -43.5 (pseudo-axial) and -39.5 (pseudo-equatorial).

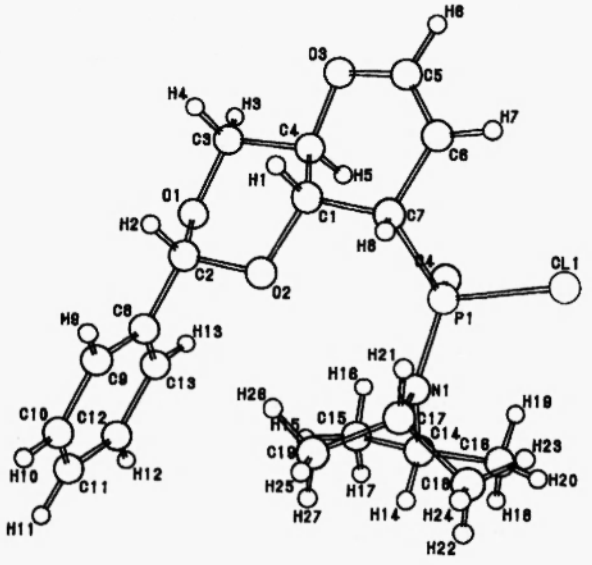
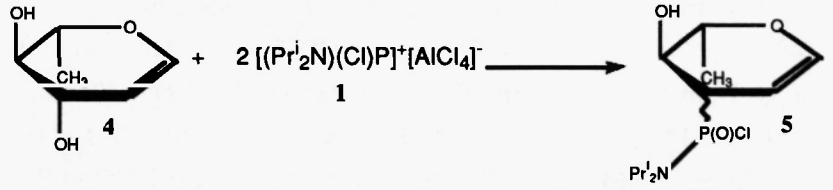


Fig. 1 Crystal structure of **3** (pseudo-axial)

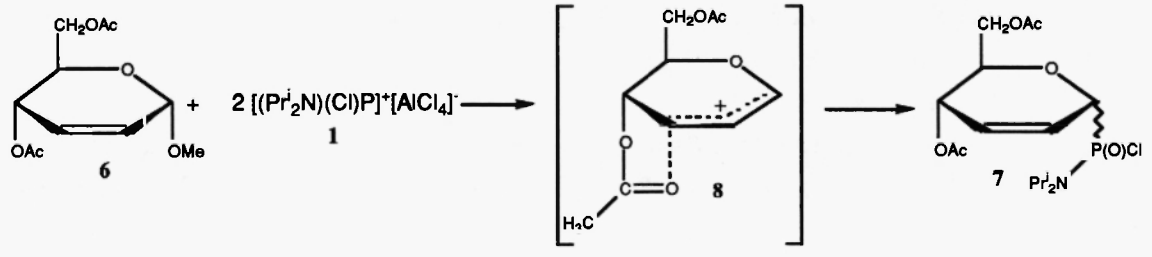
silica gel.

The structure of *N*, *N*-diisopropyl-*P*-(3-(4,6-benzylidene)-α-D-altro-1-enopyranosidyl)phosphonamidic chloride **3** (pseudo-axial) , being established on the basis of ^{13}C NMR spectral evidence and the results of elemental analysis, was confirmed by X-ray crystallography (fig.1)(18).

The reaction of phosphanylium cation **1** with L-rhamnal(19) **4** yielded the corresponding phosphonamidic chloride **5** in 5 % yield. This low yield for the reaction of L-rhamnal **4** may be to result from low solubility of **4** in CH_2Cl_2.



Furthermore, reaction of cation **1** with methyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2- eno-pyranoside(20) **6** gave phosphonamidic chloride **7** in 64% yield as anomers mixture. The mixture could not be separated completely, but the major anomer could be separated partially by column chromatography which showed a long range coupling between protons on 1- and 4- position in H-H cosy spectrum and a nuclear Overhauser effect was also observed between the above protons. These results suggest the phosphorous group should be attached to 1-position of sugar moiety and the conformation should be a pseudo-axial. In this case the reaction might proceed *via* a bicyclic cationic intermediate **8** attributed to an anchimeric assistance of acetyl group, which could not be attacked on 3-position by phosphorus group.



Based on the above results, these reactions would proceed *via* a stable carbocation intermediate[14]. Extension of this reaction to synthesis of nucleotide analogues is currently under active investigation.

Experimental

General procedure: *Synthesis of* N, N-*diisopropyl*-P-*(3-(4,6-benzylidene)-α-D-altro-1-eno pyranosidyl)phosphonamidic Chloride 3*(pseudo-axial) —A solution of dichlorodiisopropylaminophosphine **1** (1.38g,6.82mmol) in anhydrous dichloromethane (15cm^3)) was added to a stirred solution of aluminium chloride (anhydrous) (910mg, 6.81mmol) in anhydrous dichloromethane (15cm^3) under nitrogen at -78°C. The mixture

was allowed to warm to room temperature for 1 hr. Then cooled to -78°C, a solution of 4,6-*O*-benzylidene-D-allal **2**(800mg, 3.41mmol) in anhydrous dichloromethane (15cm^3) was added, and stirred for an additional hour at -78°C. Then the mixture was allowed to warm to room temperature, quenched with water (20cm^3). The mixture was extracted with dichloromethane (30 cm^3 x 3), washed with brine (30cm^3) and dried over Na_2SO_4. Removal of solvent under reduced pressure and purification by chromatography on silica gel eluting with EtOAc-n-hexane (1:1-1:3) to give a solid **3**(pseudo-axial) and a pale yellow syrup **3**(pseudo-equatorial)(trace) in 51%(700mg, 1.75mmol) yield. The solid product **3** (pseudo-axial) was recrystallized from AcOEt-n-hexane to gave **3**(pseudo-axial) as a colorless crystalline solid.

3(pseudo-axial) has m.p. 160-161°C; IR(KBr)υ(cm^{-1}) 3075, 3050, 2980, 2950, 2875, 1640, 1450, 1400, 1380, 1240, 1125, 1080, 990, 740, 695, 670 and 660;^{1}H NMR (90MHz, $CDCl_3$)δ 0.93(6H, d, J6.8, $NCCH_3$), 1.25 (6H, d, J6.7, $NCCH_3$), 3.14-5.03 (8H, m), 5.52 (1H, s, Ph-CH), 6.54 (1H, m, H_1), 7.27-7.53 (5H, m, Ph); ^{13}C NMR (22.63MHz, $CDCl_3$)δ 21.5(d, $^3J_{PC}$14.7, $NCCH_3$), 21.7(d, $^3J_{PC}$15.6, $NCCH_3$), 40.1(d, $^1J_{PC}$116.2, PC3), 47.9(d, $^2J_{PC}$2.4, NCH), 65.7(C5), 69.2(C6), 77.6(d, $^2J_{PC}$9.3, C4), 93.8(d, $^2J_{PC}$10.3, C2), 102.8(O-C-O), 126.8(C2', C6'), 127.9(C3', C5'), 129.1(C4'), 136.7(C1') ; m/z 399(M^+); Anal. Calcd for $C_{19}H_{27}NO_4PCl$ (399.86):C 57.07, H 6.81, N 3.50; Found: C, 57.25, H, 6.86, N, 3.43.

Acknowledgments

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(18) *X-Ray structure analysis of compound* **3** (pseudo-axial)

Suitable single crystals of **3** (pseudo-axial) were obtained by recrystallization from EtOAc-hexane. Initial lattice parameters were obtained from least-squares fits to 25 reflections, $20.19° < 2\theta < 25.64°$, accurately centered on a Rigaku AFC5S diffractometer and refined subsequently using higher angle data.

Crystal data for **3** (Pseudo-axial): $C_{19}H_{27}NO_4PCl$, Mr=399.85, monoclinic space group $P4_32_12$(#96), a=10.12 (2), c=40.51 (2) Å, U=4151(20) Å^3, Dc=1.280g/cm^3, Z=8, λ(MoKa)=0.71069 Å, μ(MoKa)=2.8cm^{-1}.

Totals of 2498 unique reflections were collected at 24±1°C, using the ω-2θ scan technique to a maximum 2θ value of 55.0°. Data sets were corrected for Lorentz and polarization effects. Absorption correction was not necessary for the compound. Structure was solved by direct methods using 738 reflections with $I>3\sigma(I)$. The final residuals were R=0.064 and Rw=0.073.

Table 1 Selected bond lengths for **3** (pseudo-axial)

Atom 1	Atom 2	Bond length (Å)	Atom 1	Atom 2	Bond length (Å)[a]
CL1	P1	2.089 (9)	P1	O4	1.46 (1)
P1	N1	1.62 (1)	P1	C7	1.88 (2)
O1	C2	1.39 (2)	O1	C3	1.43 (2)
O2	C1	1.49 (2)	O2	C2	1.43 (2)
O3	C4	1.38 (2)	O3	C5	1.38 (3)
C1	C4	1.53 (2)	C1	C7	1.45 (3)
C2	C8	1.43 (3)	C3	C4	1.54 (3)
C5	C6	1.32 (3)	C6	C7	1.48 (2)

[a] Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parenteses.

Table 2 Selected bond Angles for **3** (pseudo-axial)

Bonded atoms	Bond angle (°)[a]	Bonded atoms	Bond angle (°)[a]
CL1-P1-O4	108.7 (6)	CL1-P1-N1	105.8 (6)
CL1-P1-C7	99.1 (7)	O4-P1-N1	115.9 (8)
O4-P1-C7	111.9 (9)	N1-P1-C7	113.6 (8)
C2-O1-C3	111 (2)	C1-O2-C2	114 (1)
C4-O3-C5	109 (2)	O2-C1-C4	107 (2)
O2-C1-C7	113 (2)	O2-C1-H1	107.99
C4-C1-C7	113 (2)	C4-C1-H1	107.69

C7-C1-H1	108.13	O1-C2-O2	112 (1)
O1-C2-C8	109 (2)	O1-C2-H2	108.64
O2-C2-C8	110 (2)	O2-C2-H2	108.79
C8-C2-H2	108.86	O1-C3-C4	111 (2)
O1-C3-H3	108.47	O1-C3-H4	109.16
C4-C3-H3	109.09	C4-C3-H4	109.71
H3-C3-H4	109.55	O3-C4-C1	111 (2)
O3-C4-C3	108 (2)	O3-C4-H5	108.75
C1-C4-C3	111 (2)	C1-C4-H5	108.36
C3-C4-H5	109.24	O3-C5-C6	130 (2)
O3-C5-H6	115.28	C6-C5-H6	114.30
C5-C6-C7	119 (2)	C5-C6-H7	120.17
C7-C6-H7	120.45	P1-C7-C1	114 (1)
P1-C7-C6	111 (1)	P1-C7-H8	107.98
C1-C7-C6	108 (2)	C1-C7-H8	108.51
C6-C7-H8	108.09		

[a] Angles are in degrees. Estimated standard deviations in the least significant figre are given in parentheses.

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