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An efficient synthesis of novel deoxy phospha sugar pyrimidine nucleosides

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Abstract—An efficient method is described in the synthesis of several novel deoxy phospha sugar pyrimidine nucleosides in racemic form, analogs of normal sugar nucleosides, in high yields by treatment of (±)-2-aminophospholane 1-oxide with several, α-cyano-, -acetyl-, -ethoxycarbonyl-β-ethoxy-*N*-ethoxycarbonylacrylamides.

It is well established that alterations of either the furanose or the base moiety of naturally occurring purine and pyrimidine nucleosides may produce their derivatives which exhibit powerful and interesting biological effects.[1] The first example of this class of compounds, racemic dioxalane T, was independently reported in 1989 by Norbeck et al.[2] and Belleau et al.[3] and was found to exhibit potent anti-HIV activity[4] in vitro in both the purine and pyrimidine series. Replacement of the hemiacetal ring oxygen by methylene, nitrogen, or sulfur is one approach for making functional changes in the nucleoside subunits.[5,6] Several novel classes of hetero sugar nucleosides such as carba-,[7] aza-,[8] and thia sugar[9] in racemic or enantiomerically pure form have been extensively studied and widely developed.

The term phospha sugar belongs to the class of hetero sugars and denotes the replacement of hemiacetal oxygen of normal sugar by phosphorus moiety. In recent years, phospha sugar molecules have attracted considerable synthetic interest in view of their physicochemical properties as well as potential biological activity.[10]

Though several routes are available for the synthesis of carba-, aza-, and thia sugar nucleosides, no method has been described hitherto in the synthesis of phospha sugar pyrimidine or purine nucleosides. Riley and coworkers reported some ribavirin analogs of nucleosides containing phosphorus in the nucleoside base subunit, but not in the sugar subunit.[11]

Moreover, synthesis of phospha sugars was rather difficult due to long reaction sequences and low yields,[12] and preparations generally were normal sugars as starting materials. Therefore, it would be interesting to establish facile synthetic approaches and newer concepts in the synthesis and development of phospha sugar molecules. Hence, we wished to develop efficient protocols and reported the synthesis of several tetrofuranose analogs in high yields via simple reaction methods.[13] Our aim to develop potential inhibitors of HIV led us to synthesis of phospha sugar nucleosides and nucleotides. We now report our initial studies on the synthesis and conformational analysis of deoxy phospha sugar pyrimidine nucleosides in racemic form. In developing the synthesis of phospha sugar nucleosides we desired a synthetic route that would satisfy two requirements. First, the approach should be flexible enough to allow further synthesis of phospha sugar nucleoside and nucleotide analogs. Secondly, the synthesis should be practical in that the number of synthetic steps be limited, easy to scale-up and that intermediates should be easy to prepare.

Keywords: phospha sugars; hetero sugars; phospha sugar nucleosides; aminophospholanes.

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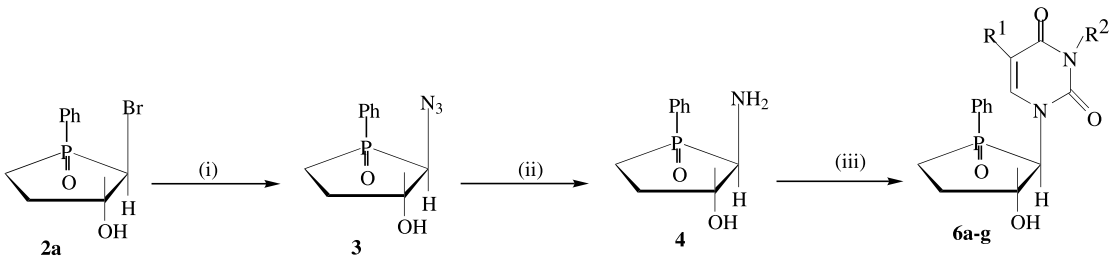
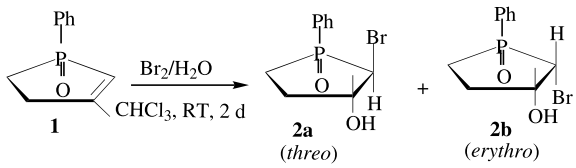


Scheme 1. Synthesis of (±)-2-(5′-substituted)uracil deoxy phospha sugar pyrimidine nucleosides. *Reagents and conditions*: (i) NaN_3, DMF, 70°C, 24 h; (ii) 10% Pd/C, H_2, MeOH, 2 days; (iii) (a) dry EtOH, precursors **5a**–**c**, reflux, 4 h; (b) dry EtOH, NaOEt, precursors **5d**–**g**, reflux, 4 h.

Therefore, we developed such a strategy as outlined in Scheme 1, the desired compounds **6a**–**g** were prepared by the reaction of (±)-2-aminophopholane 1-oxide **4** with various acyclic precursors of the substituted uracil ring systems **5a**–**g**. We previously reported[14] the synthesis of (±)-2-aminophospholane 1-oxide derivative **4** which was prepared via bromohydrination of (±)-3-methyl-1-phenyl-2-phospholene 1-oxide **1** (Scheme 2). Further conversion of *threo* isomer of bromohydrin to azide **3** and subsequent hydrogenolysis of azide derivative gave (±)-2-aminophospholane 1-oxide **4**. On the other hand, the retention of configuration at C-2 (during formation of azide derivative) was achieved via a double inversion presumably through epoxide intermediate formation.[14] The acyclic precursors **5a**–**g** ($EtOCH=CR^1CONR^2CO_2Et$) were prepared by literature methods.[15] These upon treatment with (±)-2-aminophospholane 1-oxide **4** in ethanol at reflux temperature afforded the corresponding (±)-2-(5′-substituted)uracil deoxy phospha sugar nucleosides **6a**–**g** in high yields (Table 1).[16] It should be noted that the acyclic precursors **5a**–**c** produced the desired compounds without any additional base required. In contrast, **5d**–**g** produced uncyclized compounds **7d**–**g** (Fig. 1) in the similar reaction conditions. These compounds were structurally confirmed from NMR spectral data, and the β-configuration is assumed from the ready cyclization of **7d**–**g** when treated with 1 equiv. of NaOEt base in ethanol at reflux temperature afforded **6d**–**g**, respectively. The difference in the reactivity arose due to the stronger electron-withdrawing nature of the cyano group in comparison to those of other substituted groups. Therefore, it has been confirmed that the base promotion is essential in the case of R^1 of less electron-withdrawing groups. All reactions proceeded smoothly, isolation and purification of final products were easy in all cases.[17]

Interestingly, ^1H NMR spectral analysis of compounds **6a**–**g** showed that the H-2 proton of phospholane ring resonated as doublet of doublets with coupling constants 1.6–2.0 and 10.0–14.5 Hz. The smaller coupling constants 1.6–2.0 Hz indicating the presence of long range coupling of the four σ bonds between H-2 and H-4e ($^4J_{HH}$), which was also confirmed by homospin decoupling studies, and is attributed to '*W conformation*' of the four σ bonds in the phospholane ring. The larger coupling constants10.0–14.5 Hz are attributed to $^2J_{PH}$ coupling and suggests the *cis* (or *gauche*) relationship of H-2–C-2–P=O.[19] Therefore, these results supported a *twist conformer* ($^3T_2$ or $^2T_3$) for the phospholane ring (Fig. 2) in a solution.

A single crystal of compound **6b** was developed from $CHCl_3$ by slow evaporation method, and determination of configuration at P-1, C-1 and C-2 from the X-ray analysis of **6b**[20] paved the way to establish the absolute configuration of **6b** as ($1S_P$,2*S*,3*S*) (Fig. 3) and ($1R_P$,2*R*,3*R*) for its enantiomer. It has been revealed that the *+ve* torsion angle of P-1–C-4–C-3–C-2 and the *−ve* torsion angle of C-1–P-1–C-4–C-3 in the phospholane showed that the ring puckers of C-3-*exo* (above the



Scheme 2. Preparation of bromohydrin derivatives from (±)-3-methyl-1-phenyl-2-phospholene 1-oxide.[14]

Table 1. Deoxy phospha sugar pyrimidine nucleosides **6a**–**g** prepared via Scheme 1

Compound	R^1	R^2	Yield (%)
6a	CN	Me	88
6b	CN	*p*-ClBn	68[a]
6c	CN	H	82
6d	COMe	H	75
6e	CO_2Et	H	73
6f	Me	H	72
6g	H	H	76

[a] % of yield of compound **6b** was decreased due to steric hindrance of *p*-ClBn substituent on the uracil ring.

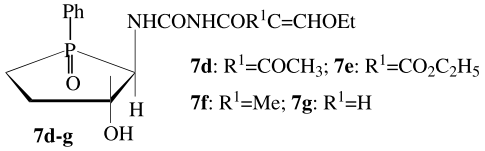


Figure 1. 2-Uncyclized substituted uracil phospholane derivatives **7d**–**g**.

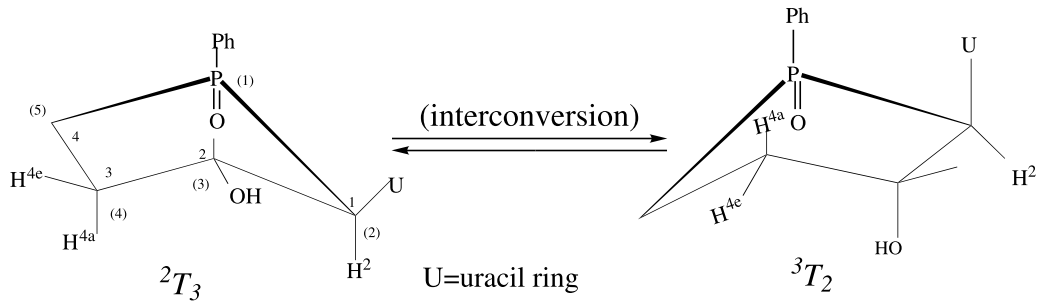


Figure 2. Favored conformers for the phospholane ring of **6a–g**, based on ^{1}H NMR analysis in a solution.[18]

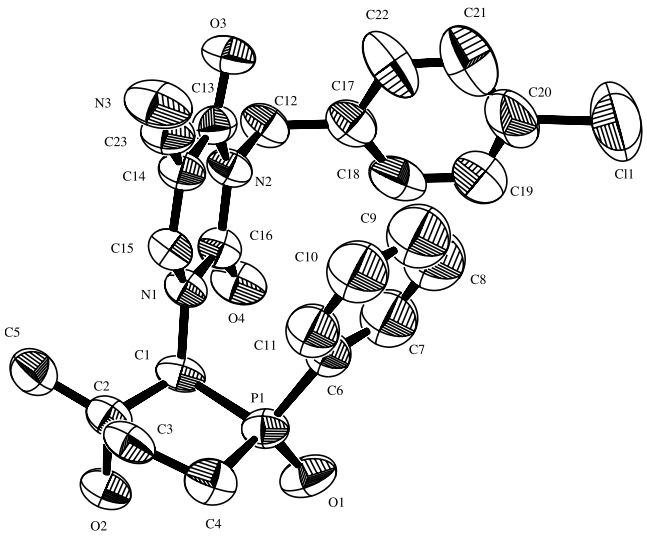


Figure 3. The crystal structure of compound **6b**. Selected bond length (Å), bond angle (°), and torsion angles (°): P-1–C-1, 1.861(8), P-1–C-4, 1.800(10); C-1–P-1–C-4, 97.0(4); P-1–C-4–C-3–C-2, 34.7(8), C-1–P-1–C-4–C-3, −12.3(6).

plane) and C-2-*endo* (below the plane). The C-3 atom of the phospholane is displaced by +0.547 Å (19.85°) from the best possible four-atom mean-square plane of C-4–P-1–C-1–C-2, and C-2 is displaced by −0.547 Å (19.86°) from the next best possible four-atom mean-square plane of C-1–P-1–C-4–C-3, supporting the existence of $^3T_2$ (C-3-*exo* and C-2-*endo*) *twist envelope conformer* for phospholane ring in the solid state. On the other hand, the substitution of O by P in the hemiacetal ring caused several changes in the geometry and conformation of the five-membered ring. The C-1–P-1–C-4 bond angle of the phospha sugar was observed as 97°, as compared to the 110° of C-1–O–C-4 in ribofuranose and 93.5° of C-1–S–C-4 in thia sugar.[21] As can be seen from the crystal structure that the phenyl ring on P-1 atom and uracil ring at C-1 lie in parallel planes.

In conclusion, we have developed an efficient protocol in the synthesis of phospha sugar pyrimidine nucleosides in high yields under mild reaction conditions and with operational simplicity. We believe that this method offers considerable advantages in the synthesis of hetero sugar nucleosides and nucleotides. Further synthesis of phospha sugar nucleosides and bioactive studies are currently under progress in our laboratory.

Acknowledgements

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16. (a) The general experimental procedure for the preparation of compounds **6a–c** is as follows: The acryloylcarbamates **5a–c** (1 mmol) were added to the readily prepared solution of 2-aminophospholane 1-oxide **4** (0.25 g, 1 mmol) in dry ethanol (10 mL) and the resultant reaction mixture was refluxed for 4 h, then cooled to room temperature and concentrated under vacuum to get crude compounds **6a–c**. The crude compounds were purified by column chromatography on silica gel using $CHCl_3$:MeOH (10:1) eluent to get pure compounds; (b) The general experimental procedure for the preparation of compounds **6d–g** is as follows: To a solution of 2-aminophospholane 1-oxide **4** (0.25 g, 1 mmol) in dry ethanol (10 mL) was added a solution of sodium ethoxide (1 mmol) in dry ethanol (5 mL) followed by the addition of acryloylcarbamates **5d–g** (1 mmol). The resultant reaction mixture was refluxed for 4 h, and then cooled to room temperature. The reaction mixture was washed with water (10 mL) and extracted with chloroform (20 mL×3). The combined extracts were dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using $CHCl_3$:MeOH (10:1) eluent to get pure compounds **6d–g**.
17. All compounds were structurally characterized by spectral ^{1}H NMR (JEOL JNM-300 at 300.40 MHz), ^{13}C NMR (JEOL JNM-300 at 75.0 MHz), ^{31}P NMR (JEOL JNM EX-90 at 36.18 MHz), mass (Kompact MALDI-TOF MS using α-cyano-4-hydroxycinnamic acid as a matrix, reflectron flight path and 100 profiles per sample) and IR (FT/IR-8000) analyses.
(±)-2-(5′-Cyano-3′-methyl)uracil-3-hydroxy-3-methyl-1-phenylphospholane 1-oxide (**6a**): ^{1}H NMR (DMSO-d_6): δ 1.19 (s, 3H, CH_3), 2.00–2.95 (m, 4H, H-4,5), 3.00 (s, 3H, C$\underline{H}_3$N), 5.02 (dd, 1H, $^4J_{HH}=2.0$ Hz, $^2J_{PH}=14.49$ Hz, H-2), 5.80 (br s, 1H, OH), 7.30–7.70 (m, 5H, Ph), 7.83 (s, 1H, H-6′); ^{13}C NMR (DMSO-d_6): δ 23.05 (d, $J_{CP}=64.96$ Hz, C-5), 23.84 (d, $^3J_{CP}=6.03$ Hz, CH_3), 28.48 (C-4), 47.43 (C$\underline{H}_3$N)), 68.48 (d, $J_{CP}=67.89$ Hz, C-2), 77.41 (d, $^2J_{CP}=18.70$ Hz, C-3), 113.48 (CN), 128.92 (d, $^3J_{CP}=11.36$ Hz, C-3,5 of Ph), 130.03 (d, $J_{CP}=87.54$, C-1 of Ph), 130.81 (d, $^2J_{CP}=9.36$ Hz, C-2,6 of Ph), 132.82 (C-5′), 132.82 (d, $^4J_{CP}=3.33$ Hz, C-4 of Ph), 149.94 (C-2′), 158.47 (C-4′); ^{31}P NMR (DMSO-d_6, H_3PO_4): δ 67.28. MS (m/z): 359 (M^+). IR (KBr): ν (cm^{-1}) 3200 (OH), 2229 (CN), 1760 (4′-CO), 1620 (2′-CO), 1440 (P-Ph), 1194 (P=O). Mp: 240–242°C.
(±)-2-[5′-Cyano-3′-(*p*-chlorobenzyl)]uracil-3-hydroxy-3-methyl-1-phenylphospholane 1-oxide (**6b**): ^{1}H NMR (DMSO-d_6): δ 1.20 (s, 3H, CH_3), 2.00–2.95 (m, 4H, H-4,5), 4.82 (*AB* q, 2H, $J_{HH}=14.99$ Hz, C$\underline{H}_2$C$_6$H$_4$), 5.02 (dd, 1H, $^4J_{HH}=1.9$ Hz, $^2J_{PH}=14.13$ Hz, H-2), 7.19 (s, 4H, C$_6\underline{H}_4$CH$_2$), 7.30–7.70 (m, 5H, Ph), 7.87 (s, 1H, H-6′), OH peak was not detected clearly; ^{13}C NMR (DMSO-d_6): δ 23.34 (d, $J_{CP}=64.83$ Hz, C-5), 23.75 (d, $^3J_{CP}=6.0$ Hz, CH_3), 44.35 (C-4), 67.92 (d, $J_{CP}=64.15$ Hz, C-2), 77.34 (d, $^2J_{CP}=19.38$ Hz, C-3), 87.76 (CH_2), 113.15 (CN), 128.52 (C$\underline{H}$ of *m*-CH_2 and *o*-Cl of Bn), 128.58 (d, $^3J_{CP}=11.36$ Hz, C-3,5 of Ph), 129.86 (C$\underline{H}$ of *m*-Cl and *o*-CH_2 of Bn), 129.91 (d, $J_{CP}=87.54$, C-1 of Ph), 130.55 (d, $^2J_{CP}=9.36$ Hz, C-2,6 of Ph), 132.46 (C-5′), 132.80 (d, $^4J_{CP}=2.02$ Hz, C-4 of Ph), 134.72 (C-6′), 150.01 (d, $^3J_{CP}=3.34$ Hz, C-2′), 158.26 (C-4′); ^{31}P NMR (DMSO-d_6, H_3PO_4): δ 71.24. MS (m/z): 469 (M^+). IR (KBr): ν (cm^{-1}) 3150 (OH), 2226 (CN), 1765 (4′-CO), 1635 (2′-CO), 1450 (P-Ph), 1210 (P=O). Mp: 114–116°C.
18. This suggests an averaging between the interconverting $^3T_2$ and $^2T_3$ conformations; see Ref. 18. Numbers outside the parenthesis correspond to carbohydrate nomenclature numbering while those within the parenthesis correspond to heterocyclic nomenclature numbering, respectively.
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20. X-Ray crystallographic analysis for **6b**: During crystallographic analysis we found that the single crystal consists of water molecule, and the ratio of uracil and water molecule was found to be 1:1, respectively. However, the ORTEP diagram (Fig. 3) was plotted for uracil molecule only. The structure was solved by direct methods and expanded using Fourier techniques. All calculations were performed using the teXsan crystallographic package of Molecular Structure Corporation.
Crystal data: $C_{23}H_{21}N_3O_4PCl\cdot H_2O$, $M=487.88$, colorless, prismatic, 0.30×0.20×0.20 mm, triclinic, *P*-1 (no. 2), $a=13.722(1)$, $b=23.804(1)$, $c=7.8615(8)$ Å, $\beta=90.206(8)$ Å, $V=2495.1(4)$ Å^3, $Z=4$, $D_{calcd}=1.299$ g cm^{-3}, $F(000)=1016.00$; $\mu=22.85$ cm^{-1}, $T=293$ K, observations [$I>2.00\sigma(I)$]=4536, variables=598, reflection/parameter ratio=7.59, R, $Rw=0.117$, 0.339. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center. Copies may be requested free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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