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PHOSPHONO NUCLEOSIDE. 1. SYNTHESIS OF 2,3'-ANHYDRO-1'-DEOXY-1'-PHOSPHONO-1-β-D-FRUCTOFURANOSYL URACIL

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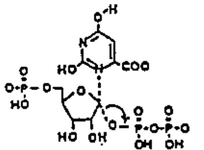
Abstract —— New phosphono nucleosides, phosphono methyl derivatives of anhydro nucleoside substituted at C-1', were synthesized starting from 2,3'-anhydro-1-β-D-fructofuranosyl uracil.

A great many efforts[1] have been made to synthesize phosphonates and investigate their biological activities as analogues of natural phosphates in both "non isosteric" and "isosteric" systems. These phosphonates (methylene substituted for oxygen of the phosphates) may function in metabolic regulation or perturbation, since they are incapable of being hydrolyzed by the ordinary enzymes involved in phosphate cleavage.

Various phosphonate analogues of metabolically important phosphate compounds have been synthesized. Only a few examples[2] of phosphono methyl replacement of an anomeric carbon of a carbohydrate are known and there are none reported for a nucleoside.

We postulated the following structure as the transition state for the condensation reaction of orotic acid and phosphoribosylpyrophosphate(PRPP) in the biosynthetic pathway of pyrimidine nucleotide. Then we synthesized nucleosides having a phosphono methyl group at the C-1' position, which may inhibit or regulate the enzymatic reaction. We designed a compound (A) as a key intermediate for the synthesis of transition state analogues of the condensation reaction. This intermediate could also be transformed into other types of phosphono nucleosides (i.e. arabino, deoxy-ribo and ribo type).

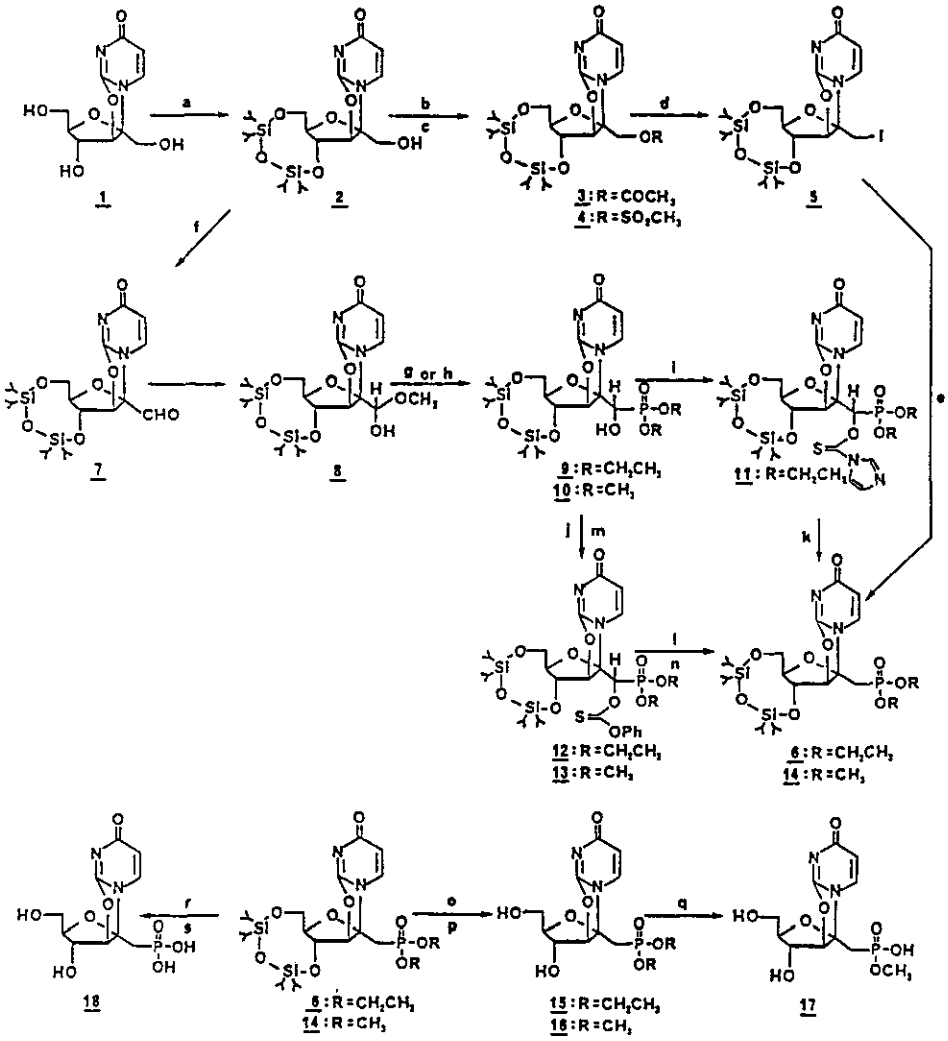


Hypothetic Transition State
for Condensation of
Orotic Acid and PRPP

A

Now we report the first examples of the synthesis of phosphono nucleosides and phosphono methyl derivatives of anhydro nucleoside substituted at the anomeric carbon.

We chose 2,3'-anhydro-1-β-D-fructofuranosyl uracil (1) as a starting material which was easily synthesized from D-fructose by two steps.[3] Selective protection of the 4'- and 6'-hydroxy group of (1) was performed by the Markiewicz method.[4] Silyl protected (2)[5] was obtained by treatment with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (53% yield). The position of silyl protection was confirmed by further transformation of (2) to its acetate (3) by acetic anhydride and pyridine. The NMR spectrum shows its methylene protons of C-1' as an AB quartet (J=12.29Hz) at 4.32 and 4.60ppm.



a) DIPSCl/imidazole/DMF/−20°C to 25°C/3h/53%; b) Ac_2O/Py/25°C/16h/∿100%; c) MsCl/Et_3N/CH_2Cl_2/25°C/1h/∿100%; d) KI/DMF/150°C/1h/76%; e) $P(OCH_2CH_3)_3$/165°C/16h; f) DMSO/DCC/CF_3COOH/Py/benzene/25°C/16h/97%; g) $HP(O)(OCH_2CH_3)_3$/Et_3N/THF/25°C/16h/94%; h) $HP(O)(OCH_3)_3$/Et_3N/THF/25°C/16h/91%; i) TCDI/$ClCH_2CH_2Cl$/25°C/3h/97%; j) PhOCSCl/4-DMAP/$ClCH_2CH_2Cl$/25°C/1h/98%; k) n-Bu_3SnH/AIBN/toluene/90°C/1h/84%; l) n-Bu_3SnH/AIBN/toluene/90°C/1h/70%; m) PhOCSCl/4-DMAP/$ClCH_2CH_2Cl$/25°C/1h/93%; n) n-Bu_3SnH/AIBN/toluene/90°C/1h/75%; o) n-Bu_4NF/THF/0°C/0.5h/64%; p) n-Bu_4NF/THF/0°C/0.5h/94%; q) t-$BuNH_2$/reflux/4h/∿100%; r) TMSI/CH_2Cl_2/0°C/0.5h/83%; s) TMSI/CH_2Cl_2/0°C/0.5h/65%.

Mesylation of (2) by methanesulfonyl chloride in the presence of triethylamine in methylene chloride gave mesylate (4) in good yield. Compound (4) was transformed to (5) by treatment with KI in DMF (76% yield). An Arbuzov reaction of (5) in triethyl phosphite gave only a trace amount of phosphonate (6)[6], probably because of steric hindrance at the C-1' position. The silyl protected primary alcohol (2) was oxidized to the aldehyde (7) using DMSO-DCC with a catalytic amount of CF_3COOH and pyridine in benzene (97% yield). Purification of the product by silica gel column chromatography eluted with CH_2Cl_2:CH_3OH (97:3 to 90:10) afforded an isomeric mixture of the hemiacetal (8). An aldehyde equivalent (8) was condenced with diethylphosphite and/or dimethylphosphite in THF in the presence of triethylamine[7] to give (9) and (10) as their isomeric mixture (94% yield and/or 91% yield, respectively). The C-P bond formation was supported by the coupling constants between proton the at C-1' and P, and the hydroxy proton and P, for example, $J_{H-1',P}$=12.5Hz and $J_{O-H,P}$=14.4Hz in case of an isomer of (9). The hydroxy group at C-1' was removed in two steps either through an imidazole thioester (11) or a phenoxy thiocarbonate (12) followed by a hydride reduction which resulted in the formation of (6).

Dimethylphosphonate (14)[8] could be obtained from (10) through the thiocarbonate (13) followed by hydride reduction. Cleavage of the silyl protecting group of (6) and (14) afforded their corresponding triester type dialkylphosphonates (15)[9] and (16)[10] in 64% and 94% yield, respectively.

The diester type of compound (17)[11] was obtained by selective demethylation of (16) by refluxing with t-butyl amine. Treatment of (6) and/or (14) with trimethylsilyl iodide gave only the free acid analogue of the phosphono nuceloside (18)[12] in 83% overall yield from (6) and in 65% yield from (14).

These anhydro phosphono nucleosides are also very useful as key compounds for synthesis of other types of phosphono nucleosides.

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3. A.Holy, Nucleic Acid Res., 1, 289 (1974).
4. W.T.Markiewicz, J. Chem. Res. (S), 24 (1979).
5. NMR(δin $CDCl_3$) 0.9-1.15(m, 28H, isopropyl), 3.82-4.01(m, 4H, H-1'α, H-5',H-6'α and H-6'β), 4.16(dd, 1H, Jgem=13.54Hz, $J_{OH,1'\beta}$=6.04Hz, H-1'β), 4.47(dd, 1H, $J_{3',4'}$=5.18Hz, $J_{5',4'}$=8.35Hz, H-4'), 5.41(d, 1H, $J_{4',3'}$= 5.18Hz, H-3'), 5.92(d, 1H, $J_{6,5}$=8.06Hz, H-5), 5.98(dd, 1H, $J_{1'\alpha,OH}$=9.22 Hz, $J_{1'\beta,OH}$=6.04Hz, 1'-OH), 7.33(d, 1H, $J_{5,6}$=8.06Hz, H-6).

6. $[\alpha]_D^{25}$=-66.7(c=0.3, $CHCl_3$); IR(KBr, cm^{-1}) 1630, 1540, 1460; UV(λmax, nm in EtOH) 225(ε=9040), 247(ε=7640); HiMS(Calcd.=618.2555; Found=618.2542); NMR(δ in $CDCl_3$):0.93-1.13(m, 28H, isopropyl), 1.25(t, 3H, J=7.2Hz, CH_3), 1.27(t. 3H, J=7.2Hz, CH_3), 2.56(dd, 1H, Jgem=18.72Hz, $J_{P,1'\alpha}$=16.70Hz, H-1'α),2.63(dd, 1H, Jgem=18.72Hz, $J_{P,1'\beta}$=16.70Hz, H-1'β), 3.85-4.03(m, 3H, H-5',H-6'α and H-6'β), 4.04-4.23(m, 4H, CH_2x2), 4.49(dd, 1H, $J_{3',4'}$= 5.18Hz, $J_{5',4'}$ =8.35Hz, H-4'), 5.48(d, 1H, $J_{4',3'}$ =5.18Hz, H-3'), 6.09(d, 1H, $J_{6,5}$=7.78Hz, H-5), 7.34(d, 1H, $J_{5,6}$=7.78Hz, H-6).
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8. $[\alpha]_D^{25}$=-57.3(c=0.3, $CHCl_3$); IR(KBr, cm^{-1}) 1650, 1550, 1470; UV(λmax, nm in EtOH) 226(ε=9000), 248(ε=7830); NMR(δ in $CDCl_3$) 0.85-1.13(m, 28H, isopropyl), 2.62(ABdq, 2H, J=16.70Hz and 18.43Hz, H-1'α and H-1'β), 3.73(d, 3H, J_{P,CH_3}=11.23Hz, O-CH_3), 3.76(d, 3H, J_{P,CH_3}=11.23Hz, O-CH_3), 3.89(dd, 1H, Jgem=12.96Hz,$J_{5',6'\alpha}$=4.90Hz, H-6'α), 3.96(dd, 1H, Jgem=12.96Hz, $J_{5',6'\beta}$=2.88Hz, H-6'β), 4.03(m, 1H, H-5'), 4.50(dd, 1H, $J_{5',4'}$=8.93Hz, $J_{3',4'}$= 5.47Hz, H-4'), 5.43(d, 1H, $J_{4',3'}$=5.47Hz, H-3'), 6.09(d, 1H, $J_{6,5}$=8.06Hz, H-5), 7.39(d, 1H, $J_{5,6}$=8.06Hz, H-6).
9. $[\alpha]_D^{25}$=-6.82(c=0.4, $CHCl_3$); IR(KBr, cm^{-1}) 3300, 1660, 1530, 1480; UV(λmax, nm in EtOH) 255(ε=5590); HiMS(Calcd.=376.1035; Found=376.1055); NMR(δ in $CDCl_3$) 1.30(t, 3H, J=6.62Hz, CH_3), 1.34(t, 3H, J=6.90Hz, CH_3), 2.83(d, 2H, $J_{P,1'}$=17.9Hz, H-1'), 3.52-3.67(m, 2H, H-6'), 4.05-4.18(m, 5H, H-5' and CH_2x2), 4.38(m, 1H, H-4'), 5.45(s, 1H, H-3'), 6.01(d, 1H, $J_{6,5}$=7.8Hz, H-5), 7.48(d, 1H, $J_{5,6}$=7.8Hz, H-6).
10. $[\alpha]_D^{25}$ =-13.5(c=0.2, CH_3OH); IR(KBr, cm^{-1}) 3300 1660, 1630, 1530, 1480; UV (λmax, nm in EtOH) 224(ε=9670), 249(ε=7480); NMR(δ in $CDCl_3$) 2.96(dd, 1H, $J_{P,1'}$=19.0Hz, $J_{\alpha,\beta}$=16.1Hz, H-1'β), 3.10-3.40(m, 1H, H-1'α), 3.42-3.50(m, 2H, H-6'), 3.72(d, 3H, J_{P,CH_3} =11.5Hz, OCH_3), 3.78(d, 3H, J_{P,CH_3}=11.0Hz, OCH_3), 4.25-4.33(m, 1H, H-5'), 4.52-4.56(d, 1H, H-4'), 5.41(s, 1H, H-3'), 6.07(d, 1H, $J_{6,5}$=7.4Hz, H-5), 7.98(d, 1H, $J_{5,6}$=7.4Hz, H-6).
11. $[\alpha]_D^{25}$ =-23.9(c=0.4, CH_3OH); IR(KBr, cm^{-1}) 3500, 1660, 1540, 1480; UV(λmax, nm in EtOH) 222(ε=7440), 253(ε=6660); NMR(δ in CD_3OD) 2.73(dd, 1H, $J_{P,1'}$ =18.2Hz, $J_{\alpha,\beta}$=16.3Hz, H-1'β), 2.88(dd, 1H, $J_{P,1'}$=17.3Hz, $J_{\alpha,\beta}$=16.3Hz, H-1'α), 3.46(t, 2H, $J_{5',6'}$=3.8Hz, H-6'), 3.63(d, 3H, J_{P,CH_3}=11.0Hz, OCH_3), 4.25-4.32(m, 1H, H-5'), 4.50-4.53(m, 1H, H-4'), 5.50(s, 1H, H-3'), 6.09(d, 1H, $J_{6,5}$=7.2Hz, H-5), 7.97(d, 1H, $J_{5,6}$=7.2Hz, H-6).
12. $[\alpha]_D^{25}$ =-6.51(c=0.3, CH_3OH); IR(KBr, cm^{-1}) 3500, 1660, 1480; UV(λmax, in EtOH) 223(ε=6730), 253(ε=6720); NMR(δ in CD_3OD) 2.76(dd, 1H, $J_{P,1'}$=18.3 Hz, $J_{\alpha,\beta}$=15.6Hz, H-1'β), 3.10(dd, 1H, $J_{P,1'}$=18.3Hz, $J_{\alpha,\beta}$=15.6Hz, H-1'α), 3.47(dd, 1H, $J_{\alpha,\beta}$=12.4Hz, $J_{5',6'\beta}$=3.0Hz, H-6'β), 3.56(dd, 1H, $J_{\alpha,\beta}$=12.4Hz, $J_{5',6'\alpha}$=3.0Hz, H-6'α), 4.37-4.41(m, 1H, H-5'), 4.61(d, 1H, $J_{5',4'}$=1.1Hz, H-4'), 5.64(s, 1H, H-3'), 6.43(d, 1H, $J_{6,5}$=7.3Hz, H-5), 8.33(d, 1H, $J_{5,6}$=7.3Hz, H-6).

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