PHOSPHONO NUCLEOSIDE. 2. SYNTHESIS OF 1'-DEOXY-1'-PHOSPHONO-1-β-D-FRUCTOFURANOSYLURACIL AND 1',3'-DIDEOXY-1'-PHOSPHONO-1-β-D-FRUCTOFURANOSYLURACIL

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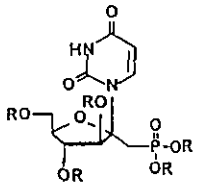
Abstract — New phosphono nucleosides, phosphono methyl derivatives of arabinofuranosyl- and of deoxyribofuranosyluracil, substituted at C-1' position were synthesized.

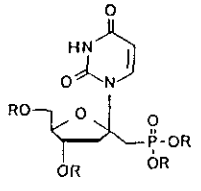
Considerable interest has developed in the preparation and investigation of phosphonic analogues of naturally occurring phosphates in recent years.[1] These phosphonates (methylene substituted for oxygen of the phosphates) may possess possibilities for metabolic regulation or perturbation owing to their geometrical similarity with the phosphates and to the incapability of being hydrolyzed by the ordinary enzymes at the carbon-phosphorous bond.

We have recently reported the first example for the synthesis of phosphono nucleosides, phosphono methyl derivatives of anhydro nucleoside substituted at the anomeric carbon, as the transition state analogues in the condensation reaction of orotic acid and phosphoribosylpyrophosphate (PRPP) catalyzed by orotate phosphoribosyl transferase in the biosynthetic pathway of pyrimidine nucleotide.[2]

As a part of the preparation of phosphono nucleosides as the transition state analogues for the enzymatic reaction, we made an approach to the synthesis of arabino type and deoxyribo type phosphono nucleosides, phosphono methyl derivatives of arabinofuranosyl- and of deoxyribofuranosyluracil substituted by phosphono methyl at the anomeric carbon, with their biological and synthetical interest.



arabino type

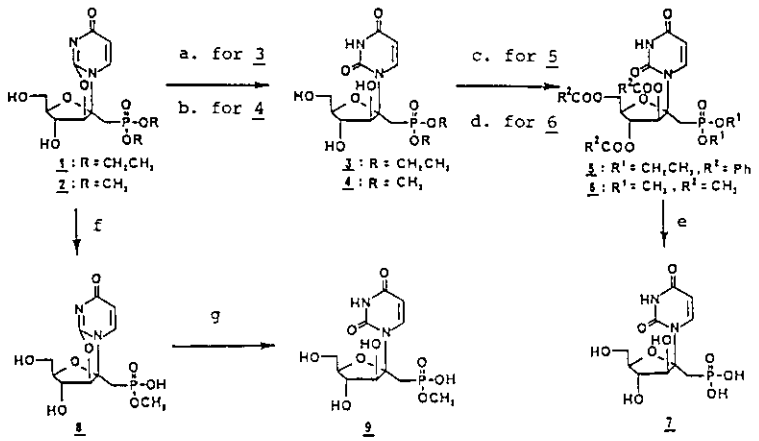


deoxyribo type

The arabino type nuclosides, 1'-deoxy-1'-phosphono-1-β-D-fructofuranosyluracils, were easily synthesized from 2,3'-anhydro-1'-deoxy-1'-phosphono-1-β-D-fructofuranosyluracils (1) and/or (2).[2] Their synthetic processes were summarized in Scheme 1.

Treatment of (1) and/or (2) with 3N hydrochloric acid in ethanol gave the triester type of phosphono nucleosides (3)[3] and/or (4)[4] in 82% and/or 76% yield, respectively. Structures of those compounds were ascertained by further transformation to their esters (5) and (6).

Scheme 1



a) 3N HCl/25°C/4days/82%;b) 3N HCl/25°C/4days/76%;c) PhCOCN/Et_3N/CH_3CN/25°C/2h/95%

d) Ac_2O/Py/25°C/3h/87%;e) TMSI/CH_2Cl_2/-30°C/2h/65%;

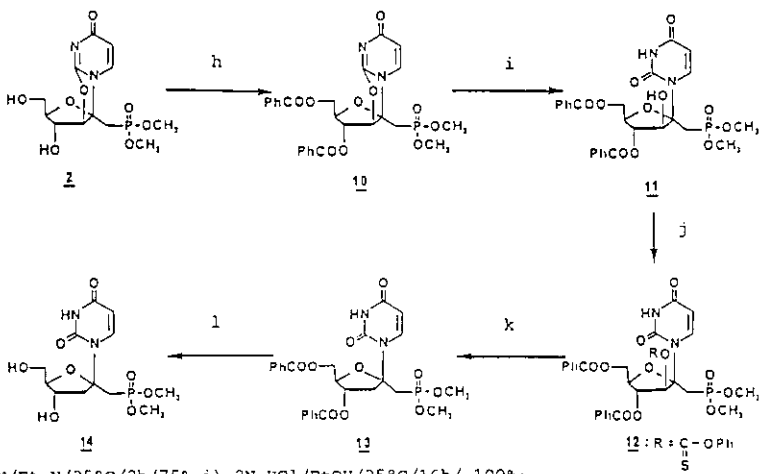
f) t-$BuNH_2$/reflux/4h/~100%;g) 3N HCl/25°C/2days/95%

Monoester type of phosphono nucleoside, completely free phosphonic acid, (7),[5] was obtained by treatment of (5) and/or (6) with trimethylsilyl iodide.

Diester type of phosphono nucleoside (9)[6] was synthesized from (1) by two steps, partial hydrolysis of phosphonate by t-butylamine[7] to (8) and subsequent cleavage of the 2,3'-anhydro bond of (8) with 3N hydrochloric acid, in 95% yield.

On the other hand, the synthesis of deoxyribo type of phosphono nucleosides was tried by two different routes. The first approach was summarized in Scheme 2.

Scheme 2



h) PhCOCN/Et_3N/25°C/2h/75%;i) 2N HCl/EtOH/25°C/16h/~100%;

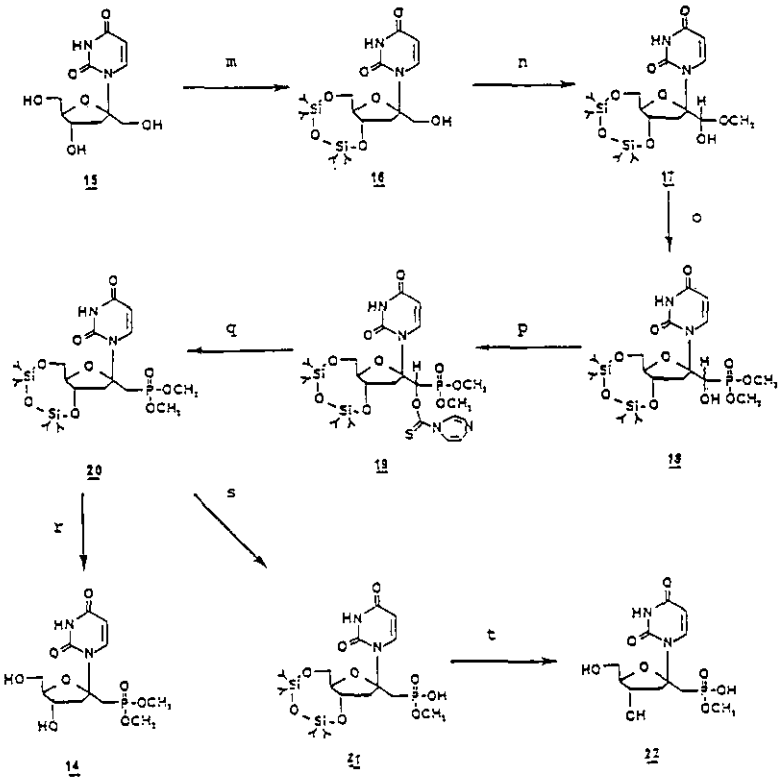
j) PhOCSCl/DMAP/$ClCH_2CH_2Cl$/reflux/2h/57%;k) n-Bu_3SnH/AIBN/toluene/90°C/1h/80%;

l) K_2CO_3/CH_3OH/0°C/8h/30%

Benzoylation of (2) with benzoyl cyanide and triethylamine in acetonitrile gave (10) in 75% yield. Cleavage of the 2,3'-anhydro bond by 2N hydrochloric acid gave an arabino type of phosphono nucleoside (11), nearly quantitatively. Removal of the 3'-hydroxy group was achieved by two steps with the transformation to thiocarbonate (12) by pheny chlorothiocarbonate and subsequent hydride reduction with tri-n-butyltin hydride resulting in a formation of (13) in 46% yield. Hydrolysis of (13) with basic medium afforded triester type of phosphono nucleoside (14) in contamination with the product derived from the elimination of uracil moiety.

Another approach for the synthesis of deoxyribo type of phosphono nucleosides was performed by the application of Fields reaction for the selectively protected hemiacetal and subsequent hydride reduction of thioester. (Sheme 3)

Scheme 3



m) TIPSCl/imidazole/DMF/-40~25°C/3h/50%; n) DMSO/DCC/Py/CF_3COOH/Benzene/25°C/16h/50%;
o) HP(O)$(OCH_3)_2$/Et_3N/THF/25°C/11h/76%; p) TCDI/$ClCH_2CH_2Cl$/reflux/4h/~100%;
q) n-Bu_3SnH/AIBN/Benzene/reflux/0.5h/77%; r) n-Bu_4NF/THF/-35°C/0.5h/68%;
s) t-$BuNH_2$/100°C/6h/50%; t) n-Bu_4NF/THF/-50°C/10min/83%

3'-Deoxy-1-β-D-fructofuranosyluracil (15)[8] was treated with 1,3-dichloro-1,1,3,3-tetra-isopropyldisiloxan in the presence of imidazole to give a selectively protected alcohol (16) in 50% yield. Oxidation of (16) with DMSO-DCC followed by silica-gel column chromatography eluted with CH_2Cl_2:CH_3OH (97:3) afforded the aldehyde hemiacetal (17) as its isomeric mixture in 94% yield. C-P bond formation was accomplished by Fields reaction by condensing

(17) and dimethyl phosphite in the presence of triethylamine to give (18) in 76% yield. The hydroxy group at C-1' was removed by two steps through imidazole thioester (19) and subsequent hydride reduction with tri-n-butyltin hydride resulting in a formation of (20) in 77% yield. Deprotection of the silyl group in (20) with tetra-n-butylammonium fluoride afforded triester type of phosphono nucleoside (14)[9] in 68% yield.
The diester type of phosphono nucleoside (22)[10] was obtained by treatment of (20) with t-butylamine and subsequent deprotection of (21) with tetra-n-butylammonium fluoride in 42% yield.

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REFERENCES AND NOTES

1. R.Engel, Chem. Rev., 77, 349 (1977), and references therein.
2. T.Tatsuoka, K.Imao, and K.Suzuki, Heterocycles, 24, 617 (1986).
3. $[\alpha]_D^{25}$=+16.2(c=0.2, CH_3OH); IR(KBr, cm^{-1}) 3400, 1700,1460; UV(λmax, nm in EtOH) 263 (ε=11500); NMR(δ in CD_3OD) 1.27(t, 6H, J=7.0Hz, CH_3x2), 2.94(dd, 1H, $J_{p,1'\beta}$=19.4Hz, $J_{\alpha,\beta}$ =18.9Hz, H-1'β), 3.20-3.35(m, 1H, H-1'α), 3.72(d, 2H, $J_{5',6'}$=4.6Hz, H-6'), 3.96-4.12(m, 4H, OCH_2x2), 4.07(bs, 1H, H-4'), 4.26(dt, 1H, $J_{4',5'}$=2.8Hz, $J_{6',5'}$=4.6Hz, H-5'), 4.34(bs, 1H, H-3'), 5.61(d, 1H, $J_{6,5}$=8.4Hz, H-5), 8.03(d, 1H, $J_{5,6}$=8.4Hz, H-6).
4. $[\alpha]_D^{25}$=+18.1(c=0.3, CH_3OH); IR(KBr, cm^{-1}) 3400, 1690, 1460; UV(λmax, nm in EtOH) 263 (ε=10400); NMR(δ in CD_3OD) 2.97(dd, 1H, $J_{p,1'\beta}$=19.4Hz, $J_{\alpha,\beta}$=15.7Hz, H-1'β), 3.20-3.40 (m, 1H, H-1'α), 3.66(d, 3H, J_{p,CH_3}=11.1Hz, OCH), 3.70(d, 3H, J_{p,CH_3}=11.3Hz, OCH_3), 3.72(d, 2H, $J_{5',6'}$=4.3Hz, H-6'), 4.08(d, 1H, $J_{5',4'}$=0.8Hz, H-4'), 4.27(dt, 1H,$J_{4',5'}$ =0.8Hz, $J_{6',5'}$=4.3Hz, H-5'), 4.35(s, 1H, H-3'), 5.60(d, 1H, $J_{6,5}$=8.4Hz, H-5), 8.03 (d, 1H, $J_{5,6}$=8.4Hz, H-6).
5. NMR(δ in CD_3OD) 2.92(dd, 1H, $J_{\alpha,\beta}$=15.6Hz, $J_{p,1'\beta}$=18.5Hz, H-1'β), 3.10-3.20(m, 1H, H-1'α), 3.78(t, 1H, $J_{5',6'}$=4.4Hz, H-6'), 4.11-4.15(m, 1H, H-4'), 4.30-4.35(m, 1H, H-5'), 4.41(s, 1H, H-3'), 5.62(d, 1H, $J_{6,5}$=8.4Hz, H-5), 8.09(d, 1H, $J_{5,6}$=8.4Hz, H-6).
6. IR(KBr, cm^{-1}) 3400, 1570, 1420; UV(λmax, nm in EtOH) 263(ε=10830); NMR(δ in CD_3OD) 2.51(dd, 1H, $J_{p,1'\beta}$=17.0Hz, $J_{\alpha,\beta}$=16.2Hz, H-1'β), 2.95(dd, 1H, $J_{p,1'\alpha}$=17.0Hz, $J_{\beta,\alpha}$ =16.2Hz, H-1'α), 3.52(d, 3H, J_{p,OCH_3}=10.5Hz, OCH_3), 3.55-3.85(m, 2H, H-6'), 4.08(d, 1H, $J_{5',4'}$=2.2Hz, H-4'), 4.27-4.33(m, 1H, H-5'), 4.41(s, 1H, H-3'), 5.60(d, 1H, $J_{6,5}$ =8.4Hz, H-5), 8.12(d, 1H, $J_{5,6}$=8.4Hz, H-6).
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8. A.Holy, Nucleic Acid Res., 1, 289 (1974).
9. NMR(δ in CD_3OD) 2.56-2.80(m, 2H, H-3'), 2.82(dd, 1H, $J_{p,1'\beta}$=17.6Hz, $J_{\alpha,\beta}$=15.9Hz, H-1'β) 3.15-3.30(m, 1H, H-1'α), 3.50-3.80(m, 2H, H-4',5'), 3.67(d, 3H, J_{p,CH_3}=10.1Hz, OCH_3), 3.71(d, 3H, J_{p,CH_3}=10.6Hz, OCH_3), 4.23(m, 2H, H-6'), 5.59(d, 1H, $J_{6,5}$=7.9Hz, H-5), 8.14(d, 1H, $J_{5,6}$=7.9Hz, H-6).
10. NMR(δ in CD_3OD) 2.67(dd, 1H, $J_{p,1'\beta}$=18.1z, $J_{\alpha,\beta}$=15.9Hz, H-1'β), 2.98(m, 2H, H-3'), 3.00-3.20(m, 1H, H-1'α), 3.57(d, 3H, J_{p,CH_3}=10.6Hz, OCH_3), 3.50-3.70(m, 1H, H-5'), 4.16(m, 1H, H-4'), 4.20-4.28(m, 2H, H-6'), 5.52(d, 1H, $J_{6,5}$=8.0Hz, H-5), 8.07(d, 1H, $J_{5,6}$=8.0Hz, H-6).

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