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SYNTHESIS OF 5'-*O*-PHOSPHONOMETHYL-2',3'-DIDEHYDRO-2',3'-DIDEOXYURIDINE BY USE OF P-METHOXYBENZYL AS A N^3-PROTECTING GROUP.

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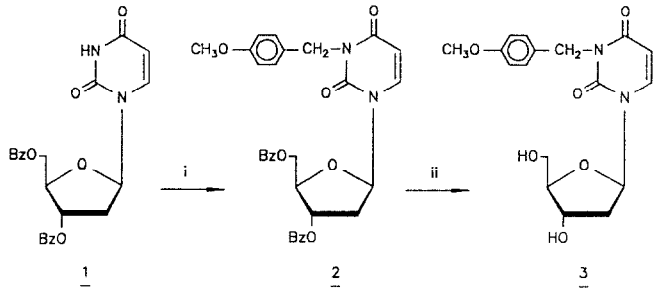
Summary
Uridine derivatives are protected at N^3-position with a p-methoxybenzyl group under Mitsunobu conditons. Selective removal is possible with ceric ammonium nitrate. The otherwise difficult to obtain 5'-*O*-phosphonomethyl d4U was prepared using this strategy.

Phosphate esters are ubiquitous components of biological systems. Isosteric and isopolar phosphonates have therefore always attracted considerable interest among chemists as they can be considered as biologically stable analogues of these phosphorylated materials. In the field of antiviral and antitumoral nucleosides, phosphorylation of 5'-hydroxyl group is often a prerequisite for activity. Therefore, a lot of efforts have been made for the preparation of as well cyclic[1] as acyclic[2] phosphorylated nucleoside analogues. These efforts met with variable success. Suffice to mention the broad spectrum anti-DNA virus activity of HPMPA [(*S*)-9-[3-hydroxy-2-(phosphonomethoxy)propyl]adenine][3] and the anti-retrovirus activity of PMEA [9-[2-(phosphonomethoxy)ethyl]adenine][4].

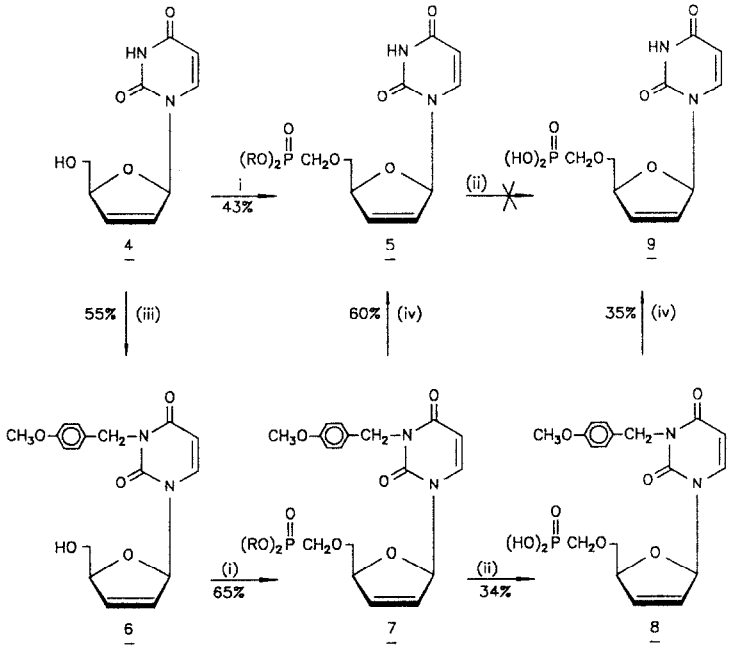
We recently reported on the synthesis and anti-HIV activity of 5'-*O*-phosphonomethyl-2',3'-dideoxynucleosides[5]. The synthesis of phosphonomethylated 2',3'-didehydro-2',3'-dideoxyuridine (d4U) and of its 5-methyluracil congener (d4T) however, were not successful due to cleavage of the glycosidic bond during deprotection of the phosphonate ester functionalities with trimethylsilyl iodide. Addition of bis(trimethylsilyl)acetamide or of collidine as acid scavengers could not save the phosphonylated products from total destruction.

5'-O-Alkylation of thymidine and uridine analogues with diethyl [(p-tolylsulfonyl)oxy]methanephosphonate also suffers from side reaction due to base alkylation. In an effort to avoid this side reaction we explored the use of different base protecting groups. However, the use of O^4-methylated 2',3'-dideoxyuridine gave anomerisation upon deprotection[5], while a N^3-benzoyl group migrates to the 5'-*O*-position under the alkylation conditions[5]. We therefore looked for another group which could be used to protect the N^3-position. This group had to be stable under the basic conditions of alkylation



i : $CH_3OC_6H_4CH_2OH$, Ph_3P, DEAD;

ii : conc. NH_4OH, CH_3OH, $C_4H_8O_2$ (1:1:1)



i : $(EtO)_2P(O)CH_2OTos$, NaH, DMF; ii : $(CH_3)_3SiBr$, DMF;

iii : $(CH_3CO)_2O$, C_5H_5N; $CH_3OC_6H_4CH_2OH$, Ph_3P, DEAD; NH_4OH, CH_3OH;

iv : $(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O (4:1)

and should be removable under non-acidic conditions (glycosidic bond cleavage). p-Methoxybenzyl (PMB) is a stable protecting group for alcohol functions, which can be cleaved selectively by DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) oxidation[6] or by treatment with ceric ammonium nitrate (CAN) in aqueous acetonitrile[7]. PMB was easily introduced on the lactam function of 3',5'-di-*O*-benzoyl-2'-deoxyuridine (1) under Mitsunobu conditions. These conditions are known to yield N^3-alkylated pyrimidines. Reaction of 4 mmol of 1 with 6 mmol of PMB alcohol in the presence of 6 mmol triphenylphosphine and 6 mmol of diethyl azodicarboxylate (DEAD) in dioxane for 10 min at room temperature afforded the alkylated product 2 which was deprotected on the sugar moiety with ammonia to yield 2.3 mmol (57%, not optimized) of 3[8] after purification on silica gel. Treatment of the benzoylated uridine derivative 2 with 3 equiv. of CAN at room temperature overnight afforded the base-deprotected nucleoside 1 in 80% yield. This reaction proceeds much slower than the oxidative removal of a PMB ether function (30 min at RT)[7].

The feasibility of this base protecting group for the synthesis of labile 2',3'-unsaturated nucleoside analogues was confirmed by the synthesis of the title compound. 5'-*O*-Propionyl-2',3'-didehydro-2',3'-dideoxyuridine (4) was alkylated and deesterified to afford 6 in 55% yield. ^{13}C and ^{1}H NMR clearly indicated the PMB group to reside at the N^3-position[9]. Phosphonylation with diethyl [(p-tolylsulfonyl)oxy]methanephosponate afforded 7 in 65% yield, while phosphonylation of unprotected 1 gave 5 in 43% yield only after cumbersome purification on silica gel. Overnight treatment of 7 with 3 equiv. of CAN at RT, likewise afforded 5 in 60% yield.

As mentioned before, attempted deesterification of 5 under different reaction conditions only caused cleavage of the glycosidic bond or anomerisation. However, treatment of 7 with trimethylsilyl bromide in DMF afforded 34% of 8 after purification on DEAE cellulose. Trimethylsilyl bromide mediated hydrolysis of the phosphonate esters therefore seems feasible only when the uracil base is locked into its lactam tautomer by a N^3-protecting group. An O^4-alkyl or O^4-silyl (unprotected base with trimethylsilyl bromide) group apparently renders the heterocyclic base a better leaving group. This anomerisation problem was recently also noticed by Holy et al. for thymidine and 2'-deoxyuridine. After protection of the N^3-position with a benzyloxymethyl group, no anomerisation was detected[10].

Treatment of 8 with 4 equiv. of CAN afforded 9. The purification of this compound, however, was complicated by the fact that the phosphonate precipitated under the deprotection conditions presumably as its cerium salt. After reaction for 48 h at RT followed by DEAE cellulose chromatography, 35% of the title compound was obtained.

During the course of this work PMB was also used as a N^3-imide protecting group by other authors[11]. However, alkylation was done by use of the PMB bromide in the presence of ethyldiisopropylamine and removal was accomplished by treatment with $AlCl_3$ in anisole, conditions not applicable to deprotection of the phosphonate 8.

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8. mp (acetone) 134°C; MS m/z 348 (M^+); UV (MeOH) λ_{max} 264 nm (ε=10000); ^1H NMR (DMSO-d_6, selected data) δ 3.70 (s,CH_3O), 4.90 (s,Ph$\underline{CH}_2$), 5.80 (d,H-5), 6.18 (t,J=6.6Hz,H-1'), 7.92 (d,H-6)ppm; ^{13}C NMR (DMSO-d_6, selected data) δ 42.8 (Ph$\underline{CH}_2$), 87.6 (C-1'), 100.9 (C-5), 139.1 (C-6)ppm. Anal. : calcd. for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found : C, 58.46, H, 5.86, N, 8.06.

9. UV (H_2O) λ_{max} 261 nm (ε = 11400); ^1H NMR (D_2O, selected data) δ 3.41 (d,$J_{P,H}$=8.1Hz,OCH_2P), 3.75 (m,H-5',H-5"), 6.97 (m,H-1')ppm; ^{13}C NMR (D_2O, selected data) δ 67.2 ($J_{P,C}$=150.2Hz,OCH_2P), 71.4 ($J_{P,C}$=9.8Hz,C-5'), 88.2 (C-1')ppm.

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