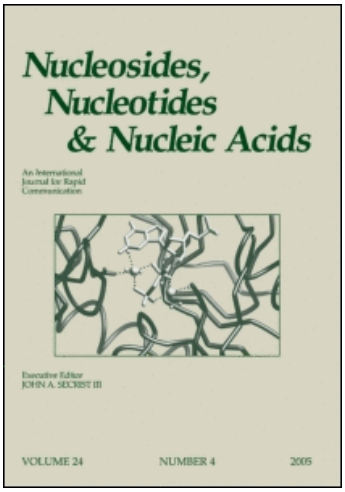

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EFFICIENT SYNTHESIS OF N-4 ALKYL DERIVATIVES OF 2',3'-DIDEOXYCYTIDINE (ddC).

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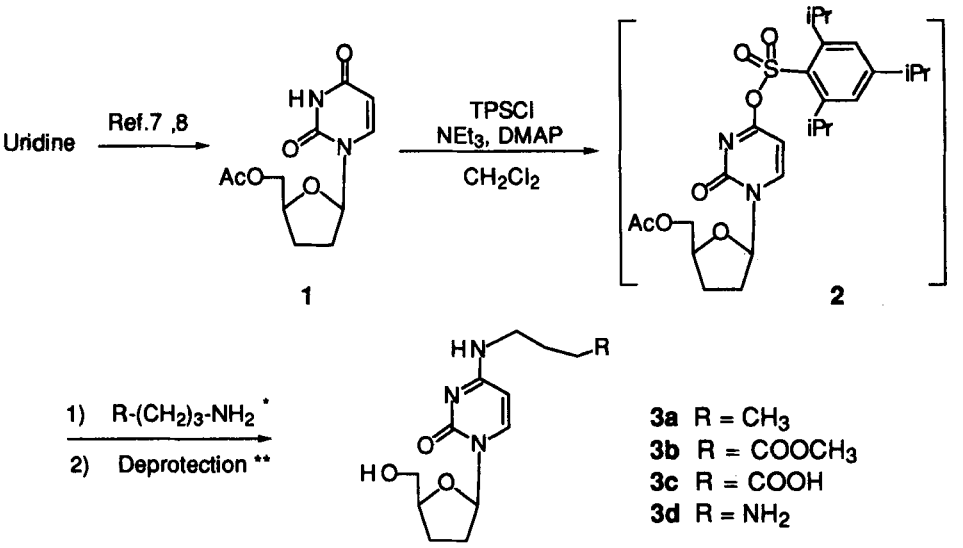
Abstract : The C-4 triisopropylphenylsulfonyl (TPS) group of the 2',3'-dideoxyuridine derivative **2** is readily displaced *in situ* by nitrogen nucleophiles forming N-4 substituted ddC in acceptable yields.

Modified nucleosides are still the main therapeutic agents in the treatment of patients with acquired immune deficiency syndrome (AIDS).[1] Among these compounds, AZT, ddI, ddC, D4T and 3TC are currently under clinical use. Up to date, much effort has be devoted to search for new nucleoside analogs more active and specific against HIV, and less likely to induce drug resistance.[2] In this quest, we became interested in N-4 alkylated 2',3'-dideoxycytidine.

Our aim was to develop an efficient, direct method for the synthesis of N-4 modified cytosine analogs from uracil nucleosides. Originally, such transformations were achieved following a chlorination[3] or thiation step.[4] Then, it was found that nucleophilic substitution of a 1,2,4-triazolyl group[5] by amines was an efficient procedure for the preparation of 4-substituted pyrimidinone nucleosides. For our part we chose the triisopropylphenylsulfonyl (TPS) group[6] for subsequent displacement by nitrogen nucleophiles. Three aliphatic amines were used, butylamine and its corresponding diamine or γ amino ester.

5'-*O*-Acetyl-2',3'-dideoxyuridine **1** was obtained from uridine by treatment with acetyl bromide[7] followed by reductive elimination[8] of the resulting 3'-acetoxy-2'-bromo derivative and subsequent hydrogenation of the unsaturated intermediate (56% yield from uridine). Nucleoside **1** was converted, by reaction with TPSCl in the presence of triethyl amine, to its corresponding 4-*O*-sulfonate derivative **2**, but this proved not to be stable

during chromatography on silica gel. Thus, the sulfonate **2**, without isolation, was treated with amines *in situ* . Displacement by butylamine (2 eq., 2h) was smoothly achieved, and deacetylation of the resulting adduct with methanolic ammonia produced N-4-butyl ddC **3a** (65% yield from **1**). Ester **3b** was prepared (60% yield) by the same procedure. When deprotection of the 5'-OH was carried out using 2% NaOH instead of ammonia, carboxylic compound **3c** was formed in 55% yield. By treating crude sulfonate with 1,3-diaminopropane in excess (10 eq.), the amino derivative **3d** was obtained as the only recovered product (60% yield). Under these reaction conditions, concomitant deacetylation occurred, nevertheless formation of dimeric compound[9] was not observed.



* Addition of NEt_3 in stoechiometric amount before $HCl,H_2N(CH_2)_3COOCH_3$

** NH_3/MeOH for R = CH_3 and $COOCH_3$, NaOH 2%/MeOH for R = COOH

Thus, 5'-*O*-acetyl-2',3'-dideoxyuridine was rapidly and smoothly converted into 2',3'-dideoxycytidine derivatives bearing a functionalizated tether at the N-4 position. Unfortunately, derivatives **3a-d** appeared to be devoid of activity when evaluated for their inhibitory effect on the cytopathogenicity of HIV-1 on MT4 and CEM-SS cells .

Experimental

Melting points were determinated using an Electrothermal apparatus and are uncorrected. ^1H NMR spectra were obtained on a Bruker AC-300 spectrometer. High-resolution mass spectra were determined on a Jeol 700. Elemental analysis was performed by the Service de Microanalyse du CNRS (Vernaison-Lyon, France).

*Procedure for the synthesis of amino derivative **3d** :*

4-N-(3-Aminopropyl)-2',3'-dideoxycytidine (3d) : **1**[10] (310 mg, 1.22 mmol), after being dried by coevaporating twice with anhydrous pyridine, was dissolved in anhydrous dichloromethane (50 mL). Triethylamine (0.42 mL, 3.0 mmol) was added, followed by (2,4,6-triisopropylphenyl)sulfonyl chloride (740 mg, 2.44 mmol) and 4-(dimethylamino)pyridine (30 mg, 0.24 mmol). The reaction was stirred for 2 h under argon at room temperature, at which time analytical TLC (CH_2Cl_2/MeOH 5%) indicated that the reaction was complete.[11] Then, 1,3-diaminopropane (1 mL, 12 mmol) was added and the mixture was stirred for 1 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH/Et_3N : 10/10/1) to give 195 mg (60%) of **3d** as a clear oil: $[\alpha]_D$ +70.5° (*c* 1.0, MeOH); ^1H NMR (DMSO-d_6) δ 1.63 (2H, m, $CH_2CH_2CH_2$), 1.75-1.90 (5H, m, CH-2'a, CH_2-3' and NH_2), 2.25 (1H, m, CH-2'b), 2.62 (2H, m, CH_2NH_2), 3.29 (2H, m, CH_2NH) 3.54 (1H, dd, J = 12, 4 Hz, CH-5'a), 3.67 (1H, dd, J = 12, 3.5 Hz, CH-5'b), 4.02 (1H, m, CH-4'), 5.72 (1H, d, J = 7.5 Hz, CH-5), 5.94 (1H, dd, J = 6.5, 3 Hz, CH-1'), 7.80 (1H, sl, NH), 7.85 (1H, d, J = 7.5 Hz, CH-6); HRMS (CH_4-CI) *m/z* 269.1616 [$(M + H)^+$ calcd for $C_{12}H_{21}N_4O_3$: 269.1614].

*Selected data for compounds **3a, 3b** and **3c** :*

4-N-Butyl-2',3'-dideoxycytidine (3a): Pure **3a** was obtained as a clear oil after flash chromatography (silica gel, EtOAc/MeOH/Et_3N : 90/10/0.2) : $[\alpha]_D$ + 80.5° (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$) δ 0.92 (3H, t, J = 7 Hz, CH_3), 1.38 (2H, m, CH_2CH_3), 1.56 (2H, m, $CH_2CH_2CH_2$), 1.92 (2H, m, CH_2-3'), 2.15 (1H, m, CH-2'a), 2.40 (1H, m, CH-2'b), 3.48 (2H, m, CH_2NH), 3.72 (1H, dd, J = 11, 4 Hz, CH-5'a), 3.97 (1H, d, J = 11 Hz, CH-5'b), 4.18 (1H, m, CH-4'), 5.20 (1H, sl, OH) 5.59 (1H, d, J = 7.5 Hz, CH-5), 6.06 (1H, dd, J = 6.5, 3.5 Hz, CH-1'), 7.68 (1H, d, J = 7.5 Hz, CH-6), 8.10 (1H, sl, NH); HRMS (CH_4-CI) m/z 268.1693 [$(M + H)^+$ calcd for $C_{13}H_{22}N_3O_3$: 268.1661].

4-N-(3-Carbomethoxypropyl)-2',3'-dideoxycytidine (3b): Pure **3b** was obtained as a foam after flash chromatography (silica gel, CH_2Cl_2/MeOH : 95/5) : $[\alpha]_D$ + 70° (*c* 1.0, MeOH); ^1H NMR (DMSO-d_6) δ 1.70-1.90 (5H, m, CH-2'a, CH_2-3' and $CH_2CH_2CH_2$), 2.23 (1H, m, CH-2'b), 2.36 (2H, t, J = 7.5 Hz, CH_2CO), 3.24 (2H, m, CH_2NH), 3.55 (1H, m, CH-5'a), 3.60 (3H, s, OCH_3), 3.64 (1H, m, CH-5'b), 4.00 (1H, m, CH-4'), 4.98 (1H, t, J = 5 Hz, OH), 5.69 (1H, d, J = 7.5 Hz, CH-5), 5.92 (1H, dd, J = 6.5, 3 Hz, CH-1'), 7.65 (1H, t, J = 5.5 Hz, NH), 7.84 (1H, d, J = 7.5 Hz, CH-6); HRMS (CH_4-CI) m/z 312.1561 [$(M + H)^+$ calcd for $C_{14}H_{22}N_3O_5$: 312.1559].

4-N-(3-Carboxypropyl)-2',3'-dideoxycytidine (3c): Pure **3c** was obtained as a white cristalline solid after flash chromatography (silica gel, CH_2Cl_2/MeOH/Et_3N: 70/30/

1): mp 172-174 °C (EtOAc), $[\alpha]_D$ +62.5° (*c* 0.76, MeOH /H_2O : 1/1); ^1H NMR (DMSO-d_6) δ 1.65 (2H, m, $CH_2CH_2CH_2$), 1.75-1.85 (3H, m, CH-2'a and CH_2-3'), 2.05 (2H, t, J = 7 Hz, CH_2CO), 2.21 (1H, m, CH-2'b), 3.18 (2H, m, CH_2NH), 3.35-3.60 (3H, m, CH_2-5' and OH), 3.99 (1H, m, CH-4'), 5.69 (1H, d, J = 7.5 Hz, CH-5), 5.92 (1H, dd, J = 6.5, 3 Hz, CH-1'), 7.82 (1H, d, J = 7.5 Hz, CH-6), 8.15 (1H, sl, NH); Anal. Calcd for $C_{13}H_{19}N_3O_5$: C 52.52; H 6.44; N 14.13; Found C 52.25; H 6.46; N 13.97.

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11. Following aqueous work-up and flash chromatography (silica gel, CH_2Cl_2/MeOH/Et_3N : 98/2/0.5) pure sulfonate **2** could be isolated for characterization: ^1H NMR ($CDCl_3$) δ 1.20-1.35 (18H, m, CH_3 x 6), 1.95-2.25 (6H, m, CH-2'a, CH_2-3' and $COCH_3$), 2.52 (1H, m, CH-2'b), 2.91 (1H, m, *H*-iPr), 4.20-4.40 (5H, m, CH-4', CH_2-5' and *H*-iPr x 2), 5.92 (1H, dd, J = 6.5, 2 Hz, CH-1'), 6.10 (1H, d, J = 7 Hz, CH-5), 7.21 (2H, s, Ar), 8.21 (1H, d, J = 7 Hz, CH-6).

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