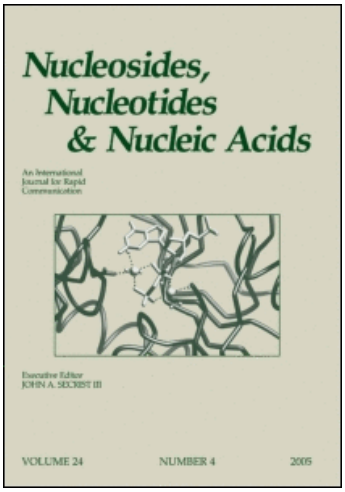

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NEW SHORT ROUTE TO UNSATURATED FLUOROKETONUCLEOSIDES: CASE OF 5-FLUORO-1-(6-O-ACETYL-3,4-DI-DEOXY-3-FLUORO-β-D-*GLYCERO*-HEX-3-ENO-PYRANOS-2-ULOSYL) URACIL

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▫ *The proposed short synthesis involves two key steps: Oxidation of the isopropylidene derivative of the 3-fluoronucleoside possessing a free hydroxyl group in 2-position and acetylation of deprotected 3-fluoro-2-ketonucleoside which, after a β-elimination reaction, gives the desired unsaturated ketonucleoside 5.*

INTRODUCTION

The antineoplastic activity and the immunosuppressive effects of unsaturated ketonucleosides are well established.[1,2] The introduction of a fluorine atom in the sugar moiety of such nucleosides increases the activity.[3] It appears that the high strength of the C-F bond may hinder metabolism pathways and may increase the effective lifetime of the active molecule. Also, the introduction of a fluorine atom

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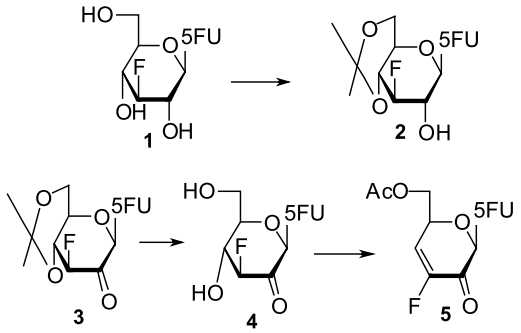
raises the lipophilicity of the molecule and makes the permeability of the drug through the cell membrane easier.[4–7] The comparative study of such molecules with analogs possessing an additional fluorine atom in the nitrogeneous base (case of 5-fluorouracil), could give interesting indications in the variation of biological activity.

All the previous reported methods on the synthesis of fluoroketonucleosides are tedious, involving a great number of steps.[8,9,12] Because of the instability of the molecule possessing the keto-fluoro system, the keto group should be introduced at the end of the synthetic routes. We report now a new and short method to the biologically active unsaturated 2′-ketofluoronucleoside 5, requiring only three steps starting from the protected 5-fluoro-1-(3-deoxy-3-fluoro-β-D-glucopyranosyl)uracil 2. This method permits to carry out the crucial reactions directly on the 3′-fluoronucleoside bearing the keto group in 2-position.

Specific acetalation of 1 using dimethoxypropane in DMF[10] led to the 4,6-*O*-isopropyliden derivative 2 isolated as crystalline material. Oxidation of free hydroxyl with the PDC/molecular sieves method,[11] under conditions described recently,[12] gave the desired 2′-ketonucleoside (5-fluoro-1(3-deoxy-3-fluoro-4,6-*O*-isopropylidene-β-D-glucopyranosyl-2-ulose)uracil 3. The deacetalation of 3 was performed with IR 120 resin in methanol under reflux for 1 h. Two compounds have been detected by TLC and their proportions were estimated by NMR spectroscopy, the desired free ketonucleoside 4 and its gem-diol being present in equal proportions. Conversion of the gem-diol to its dehydrated form was obtained by heating the mixture at 45°C under vacuum. The free hydroxyls in positions 4′ and 6′ of compound 4 subsequently were acetylated with acetic anhydride in pyridine to give, after β-elimination reaction, the target compound, 5-fluoro-1(6-acetyl-3,4-dideoxy-3-fluoro-β-D-glycero-hex-3-enopyranosyl-2-ulose) uracil 5. The later reaction involves also strict anhydrous conditions in order to avoid the formation of gem-diol in such way that the β-elimination reaction is favored, thus leading to the desired unsaturated ketonucleoside 5. Column chromatography was, however, necessary to eliminate small quantities of side derivatives.



EXPERIMENTAL

General methods: Melting points (uncorrected) were recorded using a Mel-Temp apparatus. TLC were performed on Silica Gel 60 (240–400 mesh, Merck). NMR spectra were recorded at room temperature with a Brucker 300 MSL spectrometer with internal Me_4Si for ^1H and C_6F_6 for ^{19}F; the positions in carbohydrate moieties are designated by primes. Solvents were distilled over CaH_2 under reduced pressure and stored over 3A° molecular sieves. Oxalyl chloride was freshly distilled under N_2 and kept in a sealed bottle.

5-Fluoro-1(3-deoxy-3-fluoro-4,6-*O*-isopropylidene-β-D-glucopyranosyl)uracil (2). 7.686 g (21 mmol) of 5-fluoro-1(3,4-dideoxy-3-fluoro-β-D-glucopyranosyl)uracil (1) according Ollapally's method,[8] was dissolved in a mixture of 19 mL of dimethoxypropyl and 50 mL of DMF. Twenty drops of conc. H_2SO_4 were then added. The reaction was neutralized with $NaHCO_3$ after 5 h. The mixture was filtered and the liquid phase concentrated under high vacuum to eliminate the DMF. The desired compound (2) was obtained as pure crystalline material from a mixture of heptane and ethyl acetate. Yield 60%. Melt. point. 152–154°C. Anal. $C_{13}H_{16}O_8N_2F_2$; Calcd. (1/2 heptane (C_7H_{16})); C, 47.59; H, 5.77; N, 6.73; Found: C, 47.92; H, 5.61; N, 7.16. ^{1}HNMR ($CDCl_3$): δ 5.73 (d, 1H, $J_{1',2'}$ = 8.72 Hz, H1′), 4.69 (tr, 1H, $J_{3',2'}$ = 8.7 Hz, $J_{F,3'}$ = 53.19 Hz, H3′), 4.10–3.95 (m, 1H, $J_{F,4'}$ = 20.74 Hz, $J_{4',5'}$ = 10.8, Hz, $J_{5',4'}$ = 9.69 Hz, H4′), 3.98–3.79 (m, 2H, $J_{3',6'}$ = 9.7 Hz, $J_{6'a,6'b}$ = 10.52 Hz, $H_{6'}$), 3.82–3.93 (m, 1H, $J_{5',2'}$ = 5.65 Hz, H2′), 3.53 (m, 1H, $J_{5',4'}$ = 4.5, Hz, H5′), 1.4–1.5 (2s, CH3 × 2).

5-Fluoro-1(3-deoxy-3-fluoro-4,6-*O*-isopropylidene-β-D-glucopyranosyl-2-ulose)uracil (3). One mmol (366 mg) of (2) and 752 mg of PDC are dehydrated in benzene. Freshly activated molecular sieves 3 Å (1 g) in anhydrous dichloromethane (10 mL) and 5 drops of acetic acid are added in the mixture and stirred at room temperature for 5 h. The mixture was filtered on silicagel G, washed with dichloromethane (1l), and concentrated under vacuum. A study by thin-layer chromatography showed that the optimum time for the reaction is 2 h. The compound (3) has been isolated as semi-crystalline material from pentane/ethyl acetate in 50% of yield. Anal. $C_{13}H_{14}O_8N_2F_2$; Calcd. C, 46.98; H, 4.22; N, 8.43; Found: C, 47.52; H, 4.80; N, 8.29. ^{1}HNMR (CD_3CN) : δ 6.28 (1s, 1H, $H_{1'}$), 5.27 (d, d 1H, $J_{F3'}$ = 49.74 Hz, $J_{3',4'}$ = 10.3 Hz, H3′), 4.31 (m, 1H, $J_{F,4'}$ = 21.19 Hz, $J_{3',4'}$ = 12. 43 Hz, $J_{4',5'}$ = 7.90 Hz, H4′), 4.07 (m, 1H, $J_{5',6'a}$ = 3.7 Hz, $J_{5',6'b}$ = 5.5 Hz, H5′), 3.98–3.85 (dq, 2H, $J_{6'a,6'b}$ = 10.34 Hz, H6′), 1.53–1.42 (6H, 2 × H3).

5-Fluoro-1(3-deoxy-3-fluoro-β-D-glucopyranosyl-2-ulose) uracil (4). One mmol (364 mg) of (3) was dissolved in methanol (10 mL). IR 120 resin was added and the mixture was heated in reflux for 1 h. The neutralization of the mixture is obtained using IR45 resin and after concentration under vacuum, we obtained a mixture of the keto derivative (4) and its gem-diol. After heating under vacuum during 12 h at 45°C, (4) was isolated from methanol as a powder in 90%

yield. The syncrystallization of (4) with methanol has been shown by the NMR spectrum. Anal. $C_{10}H_{10}O_6N2\ F_2$-CH3OH; Calcd. C, 40.74; H, 4.32; N, 8.64; Found: C, 40.46; H, 4.67; N, 8.31. *gem-diol:* ^{1}HNMR (CD_3COCD_3): δ 5.95 (1s, 1H, H1′), 5.65(d,1H, $J_{3',4'}$ = 8.74 Hz, H4′), 4.55 (1H, $J_{F,4'}$ = 23.5 Hz, $J_{F,\ 3'}$ = 50.62 Hz, H3′), 4.35–4.15 (m, 1H, H4′), 4.10–3.5 (m, 3H, H5′,H6′), 3.2 (1s, 0CH3). *2-keto:* ^{1}HNMR (CD_3COCD_3): δ 6.20 (1s, 1H, H1′), 5.25 (dd, $J_{F,3'}$ = 49 Hz, $J_{3',4'}$ = 9.2 Hz, H3′), 4.4–4.5 (H4′), 4–3.5 (H5′, H6′a,H6′b).

5-Fluoro-1(6-*O*-Acetyl-3,4-dideoxy-3-fluoro-β-D-glycero-hex-3-enopyranosyl-2-ulose) uracil (5). One mmol (292 mg) of (4) were dissolved in a mixture of dried pyridine (2 mL) and acetic anhydride (1 mL). The reaction was carried out at 0°C for 5 h. In order to avoid the formation of gem-diol, the reaction must be performed in strict anhydrous conditions. The solvents were removed under vacuum (high vacuum pump). Column chromatography on silicagel-60 using diethyl ether as eluent, led to the desired compound (5) isolated as a powder in 60% yield. Anal. $C_{12}H_{10}O_6N2\ F_2$-1/2H_2O; Calcd. C, 44.30; H, 3.38; N, 8.61; Found: C, 44.67; H, 3.63; N, 8.12. ^{1}HNMR (CDCl3): δ 6.66 (dd, 1H, $J_{F,4'}$ = 11.02 Hz, $J_{4',5'}$ = 1.75 Hz, H4′), 6.37 (1s, 1H, H1′), 5.09 (m, 1H, $J_{5',6'a}$ = 4.33 Hz, $J_{5',6'b}$ = 5.66 Hz, H5′), 4.34 (dq, 2H, $J_{6a',6b'}$ = 11.93 Hz, H6a, H6b), 2.2 (1s, 3H, CH_3CO).

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