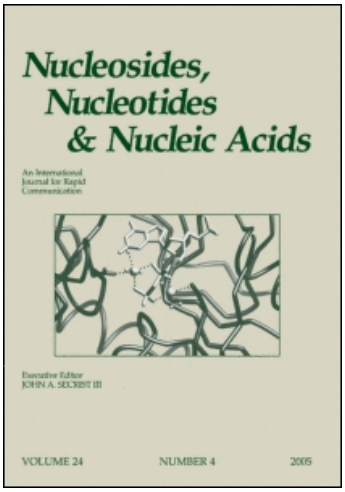

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SYNTHESIS OF 5-CHLORO-1-(2,3-DIDEOXY-3-FLUORO-β-D-GLYCERO-HEX-2-ENOPYRANOSE-4-ULOSYL)URACIL AS POTENTIAL ANTICANCER/ANTIVIRAL AGENT

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ABSTRACT

Peracetylated α-D-glucose was coupled with silylated 5-chlorouracil. The product (**2**) was deacetylated and 4′,6′-hydroxyls were then protected with 4′,6′-O-isopropylidene group. Fluorine was introduced at the 3′-position, followed by acetylation, deprotection, tritylation, oxidation and deritylation of subsequent compounds gave the target compound (**10**).

INTRODUCTION

As an extension of our studies on the unique class of fluoroenone hexopyranose nucleosides with 5-fluorouracil, which showed both anticancer as well as antiviral activities (1–3), we decided to synthesize another ketounsaturated nucleoside with the nucleobase 5-chlorouracil, to study any variation in biological activity. In addition, we are reporting here an alternative method for synthesizing the title compound.

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CHEMISTRY

The strategy initially attempted to successfully synthesize the title compound was based on the synthesis of 1,2,4,6-tetra-O-acetyl-3-deoxy-3-fluoro-D-glucose using 3-deoxy-3-fluoro-1,2:5,6-di-O-ispropylidene-α-D-glucofuranose as an intermediate (4–6). But due to high cost, instability and arduous method, we synthesized the title compound through an alternative method based on the previous reported preparation of 7-(3-deoxy-3-fluoro-4,6-O-isopropylidene-β-D-allopyranosyl) theophylline (7).

To this end, we first coupled the α-D-glucose pentaacetate with silylated 5-chlorouracil in the presence of TMS-triflate to get the nucleoside **2**. Deacetylation of **2** in methanolic ammonia gave **3** in quantitative yield. **3** was then reacted with 2,2-dimethoxypropane in presence of pTSA in anhydrous DMF (7) in order to protect 4′,6′-hydroxyls to give **4**. Direct and selective fluorination (7) of 3′-OH in **4** was done with DAST in presence of DMAP in anhydrous CH_2Cl_2 to get **5**. It was then acetylated with acetic anhydride in pyridine to give **6**. 4′,6′-O-isopropylidene protective group was then cleaved with 40% aq. trifluoroacetic acid in a small amount of ethanol to afford **7**, which was dried well overnight and treated with well dried triphenylmethyl chloride in presence of DMAP in pyridine giving the 6′-O-trityl nucleoside **8**. Oxidation (8) of **8** with pyridinium dichromate in presence of molecular sieves (3 Å) in anhydrous CH_2Cl_2 afforded **9**. Finally, detritylation with 1.0 eq of boron trichloride (9) in anhydrous CH_2Cl_2 at -30 to 40°C gave the ketounsaturated nucleoside **10**, the target compound. The structure of the compound was determined by its ^{1}H NMR, ^{19}F NMR and IR spectra.

EXPERIMENTAL

Acetonitrile, DMF, and methylene chloride are of anhydrous grade (sure/seal^{TM}) and all chemicals unless otherwise stated were purchased from Aldrich Chemical Co. Thin layer chromatography (TLC) was performed on precoated silica gel plastic sheets $60F_{254}$ (0.2 mm) EM. Compounds were detected under short wavelength UV light and also by heating after spraying with 3% sulfuric acid in methanol (v/v). Silica gel 60 (70–230 mesh ASTM) EM science was used for column chromatography. Duration of the reactions was monitered by TLC. All reaction were carried out under N_2 atmosphere.

Melting points (uncorrected) were recorded using a MEL-Temp apparatus. ^{1}H NMR and ^{19}F NMR spectra were recorded on a Bruker/IBM-SY200 spectrometer at 270 MHz using tetramethylsilane as an internal standard and trifluoroacetic acid as an external standard respectively. The chemical shifts of NMR spectra were expressed in parts per million (ppm). Molecular sieves (3 Å), used for oxidation, was finely powdered, and then heated for 30 min. on a flame *in vacuo* in the vicinity of P_2O_5 in a specially designed vessel just before the oxidation and cooled to room temprature *in vacuo*.

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5-Chloro-1-(2,3,4,6-tetra-O-acetyl-β-D-gluco-hexopyranosyl)uracil(2): A mixture of 5-chlorouracil (10 g, 68.24 mmol), HMDS (14.45 ml, 89.75 mmol) and saccharine (50 mg) was refluxed in anhydrous acetonitrile (20 ml) for 3 hr to get a clear solution. Excess solvent was removed by evaporation under vacuum. A solution of **1** (9.12 g, 23.61 mmol) in anhydrous acetonitrile (30 ml) was then added to the silylated base. The reaction mixture was then cooled to 0°C in an ice bath. The stirred, cooled reaction mixture was finally treated dropwise with TMS-triflate (5.39 ml, 24.28 mmol) in anhydrous acetonitrile (3.0 ml). After complete addition, the reaction mixture was stirred at room temperature for 30 min and at 85°C for 3 hr. After being stirred overnight at room temperature the reaction was neutralized with $MeOH/NH_3$ at below 5°C. Solvent was evaporated and the residue obtained was mixed with ethyl acetate. The precipitate that separated was filtered and washed with excess ethyl acetate. The combined filtrate was concentrated and purified by column chromatography (silica gel) using hexane:ethyl acetate (3:2) as eluant. Yield 90%; M.P. 218–220°C; ^{1}H NMR ($CDCl_3$): δ 8.59 (bs, 1H, NH proton); 7.15 (s, 1H, H-6); 5.89 & 5.86 (dd, 1H, J = 10 Hz & 7 Hz, H-1′); 5.56 (m, 1H, H-4′); 5.16 (m, 1H, H-3′); 4.28 & 4.26 (dd, J = 12 Hz & 4 Hz, 1H, H-6′$_a$); 4.10 & 4.06 (dd, J = 12 Hz & 4.5 Hz, 1H, H-6′$_b$); 3.80 (m, 1H, H-5′); 2.12, 2.11, 2.03 & 2.01 (4s, 12H, 4 × $COCH_3$).

5-Chloro-1-(3-deoxy-3-fluoro-4,6-O-isopropylidene-β-D-allopyranosyl)-uracil (5). A stirred solution of **4** (1.55 g, 4.45 mmol) and 4-dimethylaminopyridine (1 g, 8.00 mmol) in dry CH_2Cl_2 (10 ml) at −60°C was treated with DAST (1.0 ml, 8.5 mmol) during 15 min under nitrogen. The mixture was then allowed to attain room temperature. After 24–28 hr, the mixture was cooled to 0°C, methanol was added, solvents were removed under vacuum and the resulting oil was purified by column chromatography (ethyl acetate-hexane, 3:1) give **5**. Yield 42%; ^{1}H NMR ($CDCl_3$): δ 8.68 (bs, 1H, NH proton); 7.64 (s, 1H, H-5); 5.91 (d, 1H, J = 12 Hz, H-1′); 5.36 (t, 1/2H, J = 3.5 Hz, H-3′); 5.18 (t, 1/2H, J = 3.5 Hz, H-3′); 4.98 (m, 1H, H-2′); 4.24 (m, 1H, H- 4′); 3.98 (m, 2H, H-6′); 3.74 (m, 1H, H-5′); 1.58 & 1.56 (2s, 6H, 2 × CH_3). ^{19}F NMR ($CDCl_3$): −78.38.

5-Chloro-1-(2,3-dideoxy-3-fluoro-6-O-trityl-β-D-glycero-hex-2-enopyranosyl-4-ulose)uracil(9). 1.10 g (2.05 mmol) of **8** and (2.50 g, 5.50 mmol) of PDC were reacted in anhydrous CH_2Cl_2 (35 ml) in the presence of freshly activated room temperature molecular sieves (3 Å) under N_2 atmosphere. After 6–8 hr of stirring at room temperature the mixture was diluted with an equal amount of ethyl acetate and stirred further for 30 min. It was then filtered over a bed of silica gel and celite and washed copiously with methylene chloride. The combined filtrate was concentrated and purified by column chromatography using hexane:ethyl acetate (3:2) as eluant to obtain pure compound **9**. Yield 44%; sirup; ^{1}H NMR ($CDCl_3$): δ 7.58 (s, 1H, H-6); 7.22–7.50 (m, 15H, 3 × C_6H_5); 5.58 (d, 1H, J = 10 Hz, H-1′); 5.28 (m, 1H, H-2′); 4.12 (m, 1H, H-5′); 3.58 (dd, 1H, J = 8.0 Hz & 5.4 Hz, H-6′$_a$);

3.36 (dd, 1H, J = 8.2 Hz & 5.5 Hz, H-6′$_b$). ^{19}F NMR (CD_3OD): $\delta -78.42$; IR (Neat): 1720 cm^{-1}.

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REFERENCES

1: Komiotis, D.; Delatre, S.; Holt, L.; Ollapally, A.P.; Balzarini, J.; De Clercq, E.; Iigo, M. *Nucleosides and Nucleotides*, **1991**, *10*, 431–455.
2: Akhtar, M.S.; Carthy, M.; De Clercq, E.; Balzarini, J.; Ollapally, A.P. *Communicated to J. Med. Chem.*
3: Ollapally, A.P.; Bennouna-Dorange, I.; Whitaker, T.L. *Nucleosides and Nucleotides*, **1999**, *18* (*4&5*), 703–705.
4: Tewson, T.J.; Welch, M.J. *J. Org. Chem.*, **1978**, *43*, 1090–1092.
5: Lemieux, R.U.; Driguez, H. *J. Am. Chem. Soc*., **1975**, *97*, 4069–4075.
6: Stevens, J.D. *Methods in Carbohydrate Chemistry*, **1972**, *VI*, 123–125.
7: Leclercq, F.; Antonakis, K. *Carbohydrate Research*., **1989**, *193*, 307–313.
8: Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun*., **1980**, 561–563.
9: Jones, G.B.; Hynd, G.; Wright, J.M.; Sharma, A., *J. Org. Chem*., **2000**, *65*, 263–265.

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