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Synthesis of 3'-Deoxy-5'-S-ethyl-5'-thio-β-D-*erythro*-pentofuranosylthymine as Potential Antitumor Agent

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Absract: The title compound **6** was prepared from the key sugarintermediate 3-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranosylthymine (**1**) *via* five steps. Alternatively, **6** was synthesized from the nucleoside 3'-deoxy-β-D-*erythro*-pentofuranosylthymine (**7**) in two steps.

Key words: Antitumor activity, Glycosylation, Hilbert-Johnson reaction, Nucleosides, Thiosugars

The cytoplasmic-thymidine kinase (C-TK) is described as the essential precursor in human tumor cell lines.[1] It has been suggested[2] that the use of a drug which blocks *de novo* TMP biosynthesis and then selectively inhibit the C-TK might offer the possibility for effective neoplastic chemotherapy. Among several 5'-alkylthionucleosides, the 5'-ethylthio-5'-deoxythymidine has been found to be a noncompetitive inhibitor of the C-TK.[2] Some other 5'-alkylthionucleosides were found to exhibit activity as antitumor or antiviral agents.[3-5] Agrofoglio and co-workers[1] reported recently the synthesis of some 2',3'-didehydro-3'-deoxy-5'-thioether-thymidines with their preliminary antitumor evaluation which did not show any significant acitvity except 5'-ethylthio analogue with a modrate activity on the L1210 Leukemia cells. These interesting nucleosides prompted us to synthesize the 3'-deoxy-5'-S-ethyl-5'-thio-β-D-*erythro*-pentofuranosylthymine (**6**) as promising potential antitumor agent.

Reaction of **1**[6], which prepared from D-xylose *via* six steps, with p-toluenesulphonyl chloride at room temperature afforded the crystalline tosylate **2**.[6] Treatment of **3** at ~ 5 °C with an excess of sodium ethylthiolate in DMF gave the 5-ethylthio analogue in 95% yield, as syrup. Subsequent treatment with acetic anhydride in HOAc and catalytic H_2SO_4 provided **4** as an α/β anomeric mixture. The silylated thymine was condensed with **4** under Hilbert-Johnson reaction as developed by Vorbrüggen condition[7] using trimethylsilyl triflate in dry 1,2-dicholoethane to give, after chromatographic purification, **5** in 80% yield. Deblocking of **5** with 16% methanolic ammonia afforded the title nucleoside **6**[8] in 91% yield (Scheme 1).[10]

Alternatively, **6** was prepared from the previously reported free nucleoside **7**.[9] Thus, **7** was obtained, according to our procedure, from deblocking of the 3'-deoxy-5'-*O*-toluoyl-β-D-*erythro*-pentofuranosylthymine. Selective tosylation of **7** at the 5'-position, at low temperature, afforded the corresponding crystalline 5'-*O*-tosylate derivative **8** in 45% yield which was converted into ist 5'-ethylthionucleoside analogue **6** in 50% yield by treatment with an excess of sodium ethylthiolate at ~ 5 °C in DMF. The anticancer acitvity of **6** is under evaluation.

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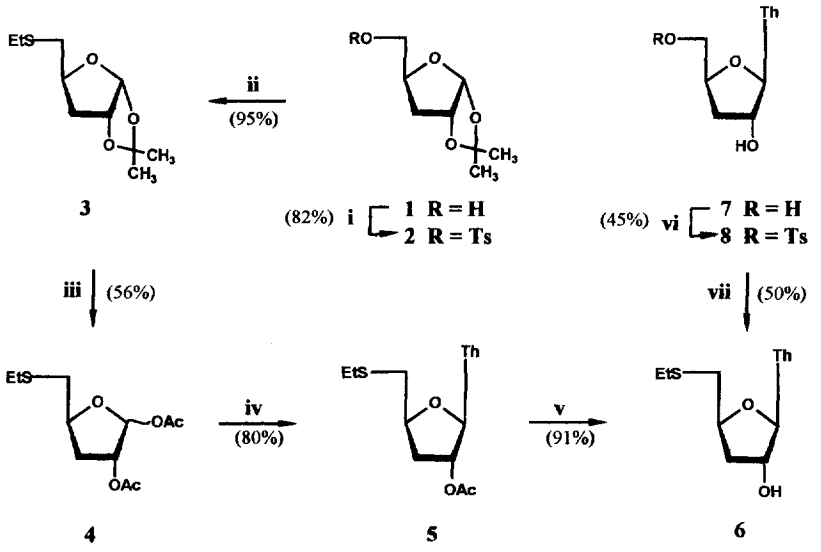

Scheme 1. Reagents: (i) TsCl/pyridine; (ii) NaSEt/DMF/0 °C; (iii) $HOAc/Ac_2O/H_2SO_4$; (iv) silylated Th./$Me_3SiOSO_2CF_3$; (v) NH_3/MeOH; (vi) TsCl/pyridine; (vii) NaSEt/DMF/0 °C.

References and Notes

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8. Selected spectroscopic data of **6**: ^{1}H NMR (DMSO-d_6): δ 9.10 (s, 1H, NH); 7.50 (s, 1H, H-6); 5.67 (d, 1H, $J_{1',2'}$ 2.0 Hz, H-1'); 4.57 (ddd, 1H, $J_{2',3'}$ < 1.0 Hz, $J_{2',3''}$ 4.6 Hz, H-2'); 4.32 (m, 1H, $J_{4',5''}$ 4.8 Hz, H-4'); 2.70 (dd, 1H, $J_{4',5'}$ 6.4 Hz, H-5'); 2.63 (dd, 1H, $J_{5',5''}$ 12.0 Hz, H-5''); 2.60 (q, 2H, J 7.4 Hz, $\underline{CH_2}CH_3$); 2.03 (dd, 1H, $J_{3',4'}$ 4.4 Hz, H-3''); 1.64 (ddd, 1H, $J_{3',4'}$ 10.4 Hz, $J_{3',3''}$ 13.5 Hz, H-3'); 1.61 (t, 3H, $CH_2\underline{CH_3}$). ^{13}C NMR (DMSO-d_6): δ 163.7 (C-4); 150.3 (C-2); 136.3 (C-6); 108.3 (C-5); 90.8 (C-1'); 78.9 (C-4'); 74.6 (C-2'); 33.9 (C-3'); 26.8 ($\underline{CH_2}CH_3$); 14.6 ($CH_2\underline{CH_3}$); 12.2 (C_5-$\underline{CH_3}$).
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