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Straightforward Synthesis of 1-(2,3-Dideoxy- β -D-Glycero-Pent-2-Enofuranosyl)-Thymine

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NOTE

STRAIGHTFORWARD SYNTHESIS OF 1-(2,3-DIDEOXY- β -D-GLYCERO-PENT-2-ENOFURANOSYL)-THYMINE

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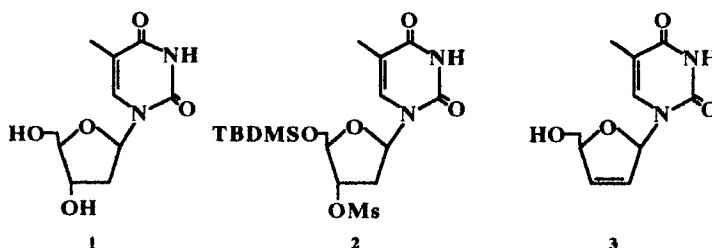
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Abstract: A two steps synthesis of the antiviral drug (d4T) **3** from thymidine **1** is proposed, which implies a concomitant deprotection-elimination process by action of *t*-BuOK in DMF on 5'-O-*t*-butyldimethylsilyl-3'-O-methanesulfonyl-thymidine **2**.

1-(2, 3-Dideoxy- β -D-glycero-pent-eno-furanosyl) thymine (d4T), is currently in clinical trial of acquired immunodeficiency syndrome AIDS⁽¹⁾. The original synthesis of d4T was that of Horwitz⁽²⁾ and recently others groups have examined alternatives to this procedure⁽³⁾.

We propose here a new access to this compound, in two steps from thymidine **1**. It is based on a fast and highly efficient desilylation of the 5' position of nucleoside **2**.



Silyl ethers are usually conveniently cleaved by fluoride salts in various conditions (4,5,6). The removal from the 5' position of nucleosides is however known to be difficult(7). We have observed that a simple treatment of compound **2** by the mixture *t*BuOK-DMF allows a very fast formation in high yield of the title compound **3**, resulting from desilylation and mesylate elimination.

EXPERIMENTALS

5'-O-*t*-Butyl-dimethylsilyl-3'-O-methanesulfonyl-thymidine 2. To a stirred solution of thymidine **1** (484 mg, 2.00 mmol) in pyridine (5 mL) was added *t*-butyl-dimethylsilyl chloride (282 mg, 2.40 mmol). The reaction mixture was stirred for 48 hrs under nitrogen. At that time *tlc* showed all thymidine had been consumed, methanesulphonyl chloride (0.12 mL, 1.5 mmol) was added at 0°, and the reaction was allowed to proceed further for 24 hr. Ice water (1ml) was added, the mixture kept at 0° for 1hr then poured into ice-water (20 mL) with vigorous stirring, and kept a 0° for several hours. The crystalline product **2** was collected and dried, (600 mg, 1.38 mmol, 69 %) as solid mp 63-65°C. MS: (C.I., *m/z*): 435 (MH)⁺, 339 (MH-CH₃SO₃H)⁺, 127 (base+H)⁺. ¹H NMR (200 MHz, CDCl₃), δ ppm 8.81 (s, 1H, NH); 7.45 (s, 1H, H₆); 6.33-6.43 (dd, J H₁ H_{2a} = 9.6 Hz; J H₁ H_{2b} = 9.6 Hz, 1H, H₁); 5.25-5.32 (m, 1H, H₃); 4.32-4.38 (m, 1H, H₄); 3.86-3.92 (d, J H₄ H₅ = 2.2 Hz, 2H, H₅); 3.10 (s, 3H, CH₃SO₂); 2.54-2.67 (m, 1H, H₂); 2.10-2.30 (m, 1H, H₂); 1.92 (s, 3H, CH₃); 0.95 s, 9H, C(CH₃)₃; 0.15 s, 6H, Si(CH₃)₂ ¹³CNMR (CDCl₃), δ 163.59 (C-6); 150.32 (C-9); 134.65 (C-7); 111.41 (C-8); 85.00 (C-4'); 84.49 (C-1'); 79.88 (C-3'); 62.90 (C-5'); 38.76 (CH₃SO₂); 38.55 (C-2'); 25.87 ([CH₃]₃); 18.25 (CMe₃); 12.48 (CH₃); -5.44 (Si[CH₃]₂).

2', 3'-Didehydro-3'-dideoxythymidine 3. Treatment of crude product **2** (434 mg, 1.00 mmol) with potassium-*t*-butoxide (370 mg, 3.30 mmol) in DMF (10 mL) at room temperature for 0.50 hr, yielded, after chromatography on silica gel (MeOH-CH₂Cl₂) (1:9) compound **3** (179 mg, 0.88 mmoles, 80 %), identical with an authentic sample of d4T.(8)

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