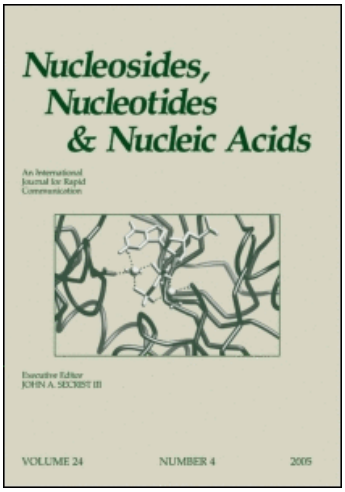

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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

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To cite this Article Negrón, G. , Islas, G. , Díaz, Y. , Cruz, R. and Quiclet-Sire, B.(1994) 'Straightforward Synthesis of 1-(2,3-Dideoxy-β-D-Glycero-Pent-2-Enofuranosyl)-Thymine', Nucleosides, Nucleotides and Nucleic Acids, 13: 4, 1011 — 1013
To link to this Article: DOI: 10.1080/15257779408011874
URL: http://dx.doi.org/10.1080/15257779408011874

NUCLEOSIDES & NUCLEOTIDES, 13(4), 1011-1013 (1994)

NOTE

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

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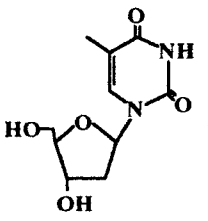
Abstract: A two steps synthesis of the antiviral drug (d4T) **3** from thymidine **1** is proposed, which implies a concomitant deprotection-elimination process by action of *t*-BuOK in DMF on 5'-O-*t*-butyldimethylsylil-3'-O-methanesulfonyl-thymidine **2**.

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**.



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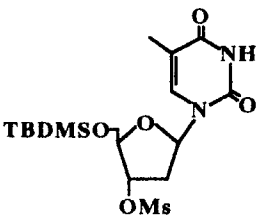

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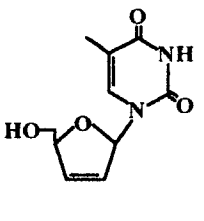

3

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-dimethylsylil-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 $(MH\text{-}CH_3SO_3H)^+$, 127 $(base+H)^+$. ^1H NMR (200 MHz, $CDCl_3$), δ ppm 8.81 (s, 1H, NH); 7.45 (s, 1H, H_6); 6.33-6.43 (dd, J H_1H_{2a} = 9.6 Hz; J H_1H_{2b} = 9.6 Hz, 1H, H_1); 5.25-5.32 (m, 1H, H_3); 4.32-4.38 (m, 1H, H_4); 3.86-3.92 (d, J H_4H_5 = 2.2 Hz, 2H, H_5); 3.10 (s, 3H, CH_3SO_2); 2.54-2.67 (m, 1H, H_2); 2.10-2.30 (m, 1H, H_2); 1.92 (s, 3H, CH_3); 0.95 s, 9H, $C(CH_3)_3$; 0.15 s, 6H, $Si(CH_3)_2$ ^{13}CNMR ($CDCl_3$), 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 (CH_3SO_2); 38.55 (C-2'); 25.87 ($[CH_3]_3$); 18.25 (CMe_3); 12.48 (CH_3); -5.44 ($Si[CH_3]_2$).

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-CH_2Cl_2) (1:9) compound **3** (179 mg, 0.88 mmoles, 80 %), identical with an authentic sample of d4T.[8]

ACKNOWLEDGMENTS: We are very grateful to the National Science and Technology Council (CONACyT) for a fellowship (No. 1348-E9206), Drs. G. Roussi and R. Gaviño for their discussion and Messrs. F. Pérez and L. Velasco for their technical assistance.

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Received 8/5/93
Accepted 10/18/93