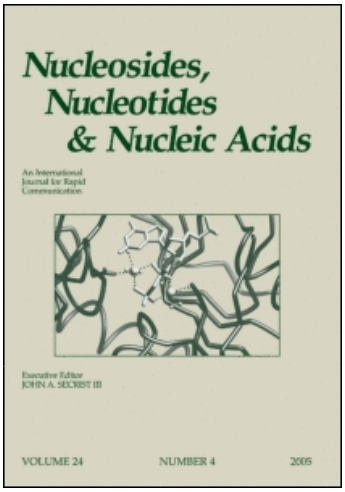

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Negrón, G. , Quiclet-Sire, B. , Diaz, Y. , Gaviño, R. and Cruz, R.(1995) 'A New Synthesis of 2',3'-Didehydro-3'-deoxy-3-Alkylthymidine', Nucleosides, Nucleotides and Nucleic Acids, 14: 7, 1539 — 1543
To link to this Article: DOI: 10.1080/15257779508009490
URL: http://dx.doi.org/10.1080/15257779508009490

NUCLEOSIDES & NUCLEOTIDES, 14(7), 1539-1543 (1995)

A NEW SYNTHESIS OF 2', 3'-DIDEHYDRO-3'-DEOXY-3-ALKYLTHYMIDINE

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Abstract: The preparation of 3-alkyl D4T derivatives has been carried out starting from the corresponding 5'-O-*t*-butyldimethylsilyl-3'-O-methanesulfonylthymidine **2** by way of deprotection-elimination and succesive alkylation reactions.

Intensive efforts are under way worldwide in the search for new therapeutic agents to be used in the treatment of acquired immunodeficiency syndrome (AIDS). In the early studies of Mitsuya and Broder[1], a class of compounds known as 2', 3'-dideoxynucleosides were found to be potent in vitro inhibitors of HIV replication. 3'-Azido-3'-deoxythymidine (AZT, zidovudine, Retrovir, Wellcome, 1987), 2', 3'-dideoxyinosine (DDI, didanosine, Videx, Bristol Myers Squibb, 1992) are the drugs clinically approved by the U.S. Food and Drug Administration for the treatment of AIDS; furthermore 2', 3'-Dideoxycytosine (DDC, zalcitabine, HIVID, Hoffmann La Roche, 1992) was recently introduced for limited use, and 2', 3'-didehydro-3'-deoxythymidine (D4T, Stavudine) is being evaluated in clinical trials[2].

On the other hand, a number of reports from several laboratories have recently appeared that show which chemical modification at the N^3-position of pyrimidine nucleosides is applicable to the preparation of new nucleoside analogs possessing anti-HIV activity[3,4]. Our own interest in the design of drug candidates against AIDS is mainly concentrated in the development of analogs of D4T substituted at the N^3-position. TheN^3-alkylation of protected uridine nucleosides using sodium hydride is well-documented[5].

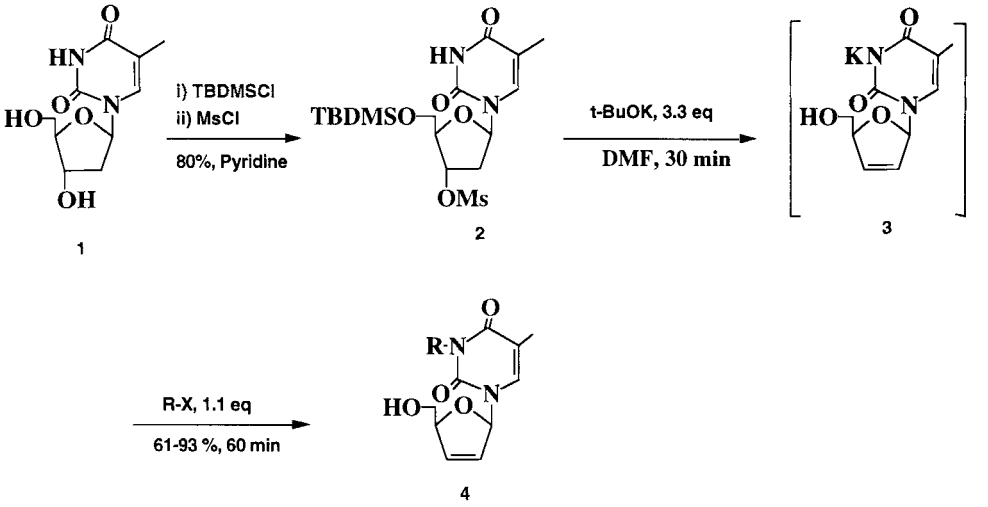
In the present work we describe a very useful and efficient one-pot method for the synthesis of 2',3'-didehydro-3'-deoxy-3-alkylthymidine **4** using the 5'-O-*t*-butyldimethylsilyl-3'-O-methanesulfonylthymidine **2** as starting material. We have recently

reported a simple method for the preparation of 2', 3'-didehydro-3'-deoxythymidine (D4T) **3** from the commercially available thymidine. Indeed, thymidine can be protected in one-pot procedure by treatment with *tert*-butyldimethylsilyl chloride in the presence of pyridine, followed by the addition of methanesulfonyl chloride to afford **2** in 80 % yield. In order to prepare the N^3-alkylated derivatives **4a-4g**, the diprotected nucleoside **2** was reacted under nitrogen a atmosphere with 3.3 molar eq. of potassium tert-butoxide in DMF at room temperature to afford **3.** Succesive alkylation with 1.1 mol eq. of alkylating agents such as methyl iodide, ethyl bromide, propyl bromide, allyl bromide, isobutyl bromide, benzyl bromide and prenyl bromide added at room temperature gave the corresponding N^{-3} alkylated nucleosides **4a-4g** in 63-91% yield (scheme 1).

Experimental

The ^1H NMR spectra were recorded on a Varian VXR-300 S or a Gemini-200 spectrometer and the chemical shift data are reported in parts per million (δ)withtetramethylsilane as internal standard, where s, dd, t, q and m designate singlet, doublet, doublet of doublets, triplet, quartet and multiplet, respectively. Infrared (IR) spectra were recorded on a Nicolet 5-SX FT IR spectrophotometer. Thin layer chromatography (TLC) was performed using Merck 60 F_{254} plates and the spots were detected under UV light (254 nm). Column chromatography was performed using Kieselgel 60, 230-400 mesh ASTM type 9385. Mass spectra (MS) were recorded on a Hewlett Packard 5985 B GCMS spectrometer for chemical ionization (CI). Elemental analyses were performed by the microanalysis laboratory at the ICSN, Gif-sur Yvette, France.

General procedure.- A typical procedure for N-alkylation of 2', 3'-didehydro-3'-deoxythymidine is given by the preparation of **4f**. To a solution of 5'-*t*-butyldimethylsilyl-3'-O-methanesulfonylthymidine (434 mg, 1.00 mmol) **2** in DMF (20 mL) was added *t*-BuOK (370 mg, 3.30 mmol) at 0 °C under a nitrogen atmosphere. After 5 min, the solution was allowed to warm to room temperature and stirring was continued another 25 min to yield a cloudy solution of **3**. Benzyl bromide (0.13 mL, 1.10 mmol) was added through a septum and the mixture was stirred for 1 hr. Evaporation of the solvent to dryness in vacuo followed by purification of the residue by silica gel column chromatography (10 % MeOH in CH_2Cl_2) gave the monoalkyl 2', 3'-didehydro-3'-deoxy-



a: R = Methyl, b: R = ethyl, c: R = propyl, d: R = allyl, e: R = isobutyl, f: R = benzyl, g: R = prenyl

Scheme 1

3-benzylthymidine 4g (286 mg, 0.91 mmol, 91 %). Spectroscopic data for 2', 3'-didehydro-3'-deoxy-3-alkylthymidine **4a-g** follow.

2', 3'-Didehydro-3'-deoxy-3-methylthymidine **4a**. Colorless solid, yield 63 %. m.p.144 °C. IR ($CHCl_3$) 3624, 1703, 1670, 1641, 1471, 1294, 1086 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89 (d, 3H, J=1.20, 5-CH_3), 2.29 (m, 1H, $J_{1/2}$=4.0, OH), 3.35 (s, 3H, N-CH_3), 3.79 (dt, 1H, J=4.5, 12.0, 5'-H), 3.92 (dt, 1H, J=4.5, 12.0, 5''-H), 4.93 (m, 1H, $J_{1/2}$=10.0, 4'-H), 5.87 (ddd, 1H, J=6, 2.28, 1.5, 3'-H), 6.34 (dt, 1H, J=6.15, 2'-H), 7.04 (ddd, 1H, J=3.6, 2.28, 1.5, 1'-H), 7.44 (q, 1H, J=1.20, 6-H). MS: (CI) m/z 239 $(MH)^+$, 141 (base-R+H)$^+$. Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.46; H, 5.79; N, 11.46.

2', 3'-Didehydro-3'-deoxy-3-ethylthymidine **4b.** Colorless solid, yield 87 %, m.p.143-144 °C. IR ($CHCl_3$) 3624, 1700, 1690,1640, 1468, 1351, 1087 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3H, J=7.1, $CH_2\underline{CH_3}$), 1.89 (d, 3H, J=1.24, 5-CH_3), 2.40 (m, 1H, $J_{1/2}$=4.0, OH), 3.80 (dt, 1H, J=12.0, 3.20, 5'-H), 3.94 (dt, 1H, J=12.5, 3.20, 5''-H), 4.02 (q, 2H, J=7.10, N-$\underline{CH_2}CH_3$), 4.93 (m, 1H. $J_{1/2}$=10, 4'-H), 5.86 (ddd, 1H, J=6.0, 1.50, 0.60, 3'-H), 6.34 (dt, 1H, J=6.0, 1.50, 2'-H), 7.05 (ddd, 1H, J=3.70, 1.50, 0.60, 1'-H), 7.43(q, 1H, J=1.24, 6-H). MS: (CI) m/z 253 $(MH)^+$, 155 (base-R+H)$^+$. Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 56.80; H, 6.27; N, 10.90.

2', 3'-Didehydro-3'-deoxy-3-propylthymidine **4c.** Colorless solid, yield 64 %, m.p.130-131 °C. IR ($CHCl_3$) 3623, 1701, 1670,1640, 1467, 1362, 1087 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, 3H, J=7.50, $\underline{CH_3}CH_2$), 1.65(qt, 2H, J=7.50, 7.80 $CH_3\underline{CH_2}CH_2$), 1.88 (d, 1H, J=1.24, 5-CH_3), 2.20 (m, 1H, $J_{1/2}$=4.00, OH), 3.87 (t, 2H, J=7.87, N-$\underline{CH_2}CH_2$), 3.92(ddd, 2H, J=3.10, 12.0, 5'-H, 5"-H), 4.89 (m, 1H, J1/2=10, 4'-H), 5.83 (ddd, 1H, J=6.15, 0.60, 3'-H), 6.29 (dt, 1H, J=6.00, 1.70, 2'-H), 7.01 (ddd, 1H, J=3.70, 1.50, 0.60, 1'-H), 7.38 (q, 1H, J=1.24, 6H). MS: (CI) m/z 267 $(MH)^+$, 169 (base-R+H)$^+$, 127 (base+H)$^+$, 126 (base). Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.64; H, 6.81; N, 10.52. Found: C, 58.63; H, 6.58; N, 10.46.

2', 3'-Didehydro-3'-deoxy-3-allylthymidine **4d.** Colorless solid, yield 68 % m.p.131-132 °C. IR ($CHCl_3$) 3623, 1702, 1669,1642, 1466, 1336, 1086 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (d, 3H, J=1.24, 5-CH_3), 3.87(ddq, 2H, J=15.0, 5.26, 3.16, 5'-H, 5"-H), 4.57(dt, 2H, J=6.0, 1.30, Hd)#, 4.93 (m, 1H, J1/2=10.0, 4'-H), 5.19 (dq, 1H, J=10.0, 1.36, Ha)#, 5.28 (dq, 1H, J=1.44, 17.0, Hb)#, 5.86 (m, 1H, $J_{1/2}$=5.0, 3'-H), 5.89 (dqt,1H, J=6.0, 10.0,17.0, Hc)#, 6.33(dt, 1H, J=6.0, 1.6, 2'-H), 7.04 (ddd, 1H, J=3.70, 1.50, 0.60, 1'-H), 7.44 (q, 1H, J=1.24, 6-H). MS: (CI) m / z 265 $(MH)^+$, 167 (base-R+H)$^+$. Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.80. Found: C, 58.81; H, 5.93; N, 11.15.

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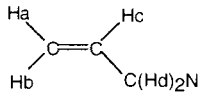

2', 3'-Didehydro-3'-deoxy-3-isobutylthymidine **4e.** Colorless oil, yield 64 %. IR ($CHCl_3$) 3622, 3599, 1797, 1766, 1705, 1672, 1643, 1465, 1086 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 6H, J=6.60, $(\underline{CH_3})_2CH$), 1.89 (d, 1H, J=1.24, 5-CH_3), 2.17 (septet, 1H, J=6.60, $\underline{CH}(CH_3)_2$), 2.18 (m, 1H, $J_{1/2}$=3.00, OH), 3.79 (d, 2H, N-$\underline{CH_2}CH$), 3.80 (dd, 1H, J=3.10, 12.0, 5'-H), 3.93 (dd, 1H, J=3.10, 12.0, 5"-H), 4.93 (m, 1H, $J_{1/2}$=10.0, 4'-H), 5.87 (ddd, 1H, J=6.00, 1.50, 0.60, 3'-H), 6.33 (dt, 1H, J=6.00, 1.50, 2'-H), 7.04 (ddd, 1H, J=3.70, 1.50, 0.60, 1'-H), 7.47 (q, 1H, 1.24, 6-H). MS: (CI) m/z 281 $(MH)^+$, 183 (base-R+H)$^+$, 127 (base+H)$^+$.

2', 3'-Didehydro-3'-deoxy-3-benzylthymidine **4f.** Colorless oil, yield 91 %. IR ($CHCl_3$) 3623, 1702, 1669, 1642, 1465, 1351, 1087 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (d, 1H, J=1.20, 5-CH_3), 2.40 (m, 1H, OH), 3.76 (dt, 1H, J=12.2, 3.40, 5'-H), 3.89 (dt, 1H, J=12.2, 3.40, 5"-H), 4.90 (m, 1H, $J_{1/2}$=10.0, 4'-H), 5.13 (d, 2H, J=3.2, $\underline{CH_2}Ph$), 5.83 (ddd, 1H, J=1.7, 6.0, 2.28, 3'-H), 6.30 (dt, 1H, J=6.0, 1.7, 2'-H), 7.04 (ddd, 1H, J=3.40, 1.70, 0.60, 1'-H), 7.35 (m, 6H, $\underline{Ph}CH_2$, 6-H). MS: (CI) m/z 315 $(MH)^+$, 217 (base-R+ H)$^+$, 216 (base-R).

2', 3'-Didehydro-3'-deoxy-3-prenylthymidine **4g.** Colorless solid, yield 62 %, m.p.100-101 °C. IR ($CHCl_3$) 3623, 1797, 1703, 1671, 1641, 1465, 1086 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (d, 3H, J=0.60, $(\underline{CH_3})_2C=CH$), 1.82 (d, 3H, J=0.60, $(\underline{CH_3})_2C=CH$), 1.90 (d, 3H, J=1.24, 5-CH_3), 2.48 (m, 1H, $J_{1/2}$=6.0, OH), 3.79 (dd, 1H, J=3.0, 12.0, 5'-H), 3.92 (dd, 1H, J=3.0, 12.0, 5"-H), 4.54 (d, 2H, J=7.0, $C=CH\underline{CH_2}$-N), 4.92 (m, 1H, $J_{1/2}$=10.0, 4'-H), 5.23 (tq, 1H, J=7.0, 0.60, $(CH_3)_2C=\underline{CH}CH_2$), 5.85 (ddd, 1H, J=6.0, 1.80, 0.60, 3'-H), 6.33 (dt, 1H, J=6.0, 1.80, 2'-H), 7.05 (ddd, 1H, J=3.70, 1.80, 0.60, 1'-H), 7.25 (q, 1H, J=1.24, 6-H). MS: (CI) m/z 293 $(MH)^+$, 195 (base-R+ H)$^+$, 127 (base+ H)$^+$.

ACKNOWLEDGMENTS. The authors are indebted to Consejo Nacional de Ciencia y Tecnologia (CONACyT) for financial support (Proyect No 1348-E9206) and Messrs. F. Pérez and L. Velasco for their technical assistance.

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Received March 13, 1995
Accepted April 21, 1995