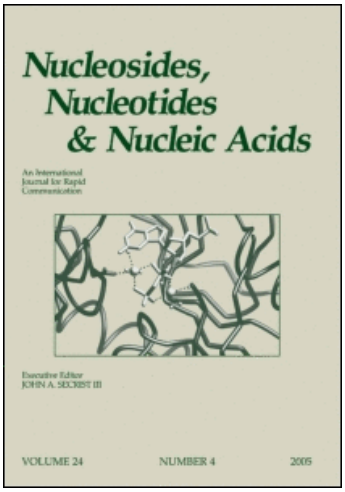

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Chen, Yaoquan , Bauman, John G. and Chu, Chung K.(1992) 'Practical Synthesis of AZT and AZDU from Xylose: Efficient Deoxygenation via Nucleoside 2'-Xanthates', Nucleosides, Nucleotides and Nucleic Acids, 11: 2, 693 — 705
To link to this Article: DOI: 10.1080/07328319208021734
URL: http://dx.doi.org/10.1080/07328319208021734

NUCLEOSIDES & NUCLEOTIDES, 11(2-4), 693-705 (1992)

PRACTICAL SYNTHESIS OF AZT AND AZDU FROM XYLOSE: EFFICIENT DEOXYGENATION VIA NUCLEOSIDE 2'-XANTHATES†

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Abstract - An efficient deoxygenation procedure for nucleoside 2'-xanthates has been developed and applied to the total synthesis of AZT and AZDU from xylose.

AZT (3'-azido-3'-deoxythymidine) is a potent anti-HIV agent with clinical efficacy,[1] which was originally synthesized by Horwitz et al.[2] from thymidine in 1964. Since then several other laboratories have reported the synthesis of AZT from thymidine.[3-6] Several synthetic approaches have also been reported in which the 3-azido sugar was utilized as the key intermediate.[7-9] AZDU (3'-azido-2',3'-dideoxyuridine)[10,11] has been undergoing clinical trials for patients with AIDS and AIDS-related complex. Its main advantage seems to be low bone marrow toxicity. AZDU was originally synthesized by Lin and Mancini[12] as an intermediate in the synthesis of 3'-amino-2',3'-dideoxyuridine. We have developed a total synthetic method for AZDU from D-mannitol,[9] however, stereoselectivity during the condensation of the 3-azido carbohydrate intermediate and silylated uracil was poor, resulting in only a 2:1 β/α-anomer ratio. Thus, we turned our attention toward developing a synthetic procedure which would utilize the inexpensive carbohydrate xylose as a starting material. One major advantage of utilizing xylose is that it affords a high degree of stereoselectivity for the β-anomer during condensation with a heterocycle, due

†This paper is dedicated to the memory of Prof. Tohru Ueda.

to the neighboring group effect of the O-2 acyl protecting group.
A major difficulty encountered previously in this approach[13-15] has been the lack of efficient methods for deoxygenation of the 2'-position of pyrimidine nucleosides.[16]

Nakayama and Saneyoshi[17] have already reported the synthesis of the xylonucleosides 3 (a = H, b = CH_3) via the condensation of 1-acetoxy-2,3,5-tri-O-benzoylxylose with silylated uracil or thymine to obtain the 2',3',5'-tri-O-benzoyl protected nucleosides which were debenzoylated with sodium methoxide to obtain the free xylonucleosides 3 in five steps. Thus, we followed the sequence of Nakayama and Saneyoshi for the preparation of benzoylated xylonucleosides 2. The benzoylated nucleosides 2 were treated with either methanolic ammonia or sodium methoxide to remove the benzoyl groups, and without isolation, the free nucleosides 3 were isopropylidenated with acetone and 1M HCl in ethyl ether to obtain the 3',5'-isopropylidene derivatives 4 in excellent yields. The 3',5'-protected nucleosides 4 were then treated with CS_2 and NaOH in DMSO followed by the addition of 3-bromopropionitrile to obtain the cyanoethylxanthates 5 in excellent yields. It should be mentioned that N3-methylation can be a major drawback in the formation of methylxanthates with methyl iodide for deoxygenation of pyrimidine nucleosides.[18] However, N3-alkylation has not been observed during the preparation of the xanthates 5 with 3-bromopropionitrile.[18]

A number of deoxygenation methods have been explored to optimize the yield of the 2'-deoxynucleosides 6. The standard methods which were previously utilized in our laboratory such as tri-*n*-butyltinhydride/AIBN or tri-*n*-butyltinhydride/Et_3B[18] were tried first. Although these conditions provided reasonable yields for the synthesis of 6a (X = H), in the case of 6b (X = CH_3) these conditions gave unreproducable results from reaction to reaction, resulting in several side products including 4 and several unidentified products. After extensive investigation we found that tris(trimethylsilyl)silane/Et_3B in toluene or benzene at room temperature afforded excellent yields of both 6a and 6b (96.6% and 93.3%, respectively). Based on our experience this particular method appears superior to other deoxygenation procedures. One significant advantage of using Et_3B rather than AIBN is that the reaction can be

run at room temperature. The procedure with AIBN as free radical initiator requires higher temperatures and results in partial reversion of the xanthate 5 to the alcohol 4.

The isopropylidene groups of 6 were removed by treatment with 5% trifluoroacetic acid in methanol to give the free nucleosides 7 in good yields. Tritylations were sluggish in pyridine at 90-100°C; however, addition of triethylamine to the reaction mixtures drove the reactions to completion. Without isolation, the trityl nucleosides 8 were treated with methanesulfonyl chloride to give the known intermediates 9. These were previously reported by Horwitz et al.[2] and Lin et al.[4,12] as intermediates in the synthesis of AZT and AZDU.

In summary, an efficient and mild xanthate deoxygenation procedure has been developed, and its utility in the synthesis of pyrimidine nucleosides such as AZT and AZDU has been demonstrated. The overall yields for AZDU and AZT from 2a and 2b were 44.8% and 40.0%, respectively.

Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or a Mel-Temp II with digital thermometer. The ^{1}H NMR spectra were recorded on a JEOL FX 90Q fourier transform spectrometer (90 MHz). Tetramethylsilane was the internal standard for organic solvents; chemical shifts are reported in parts per million (δ), and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), and m (multiplet). Ultraviolet spectra were recorded on a Beckman DU-7 spectrophotometer. Infrared spectra were recorded on a Nicolet 510P FT-IR spectrometer. Optical rotation was measured on a JASCO DIP-370 digital polarimeter. Elemental analyses were performed by Atlantic Microblab Inc., Norcross, GA.

1-(3,5-O-Isopropylidene-β-D-xylofuranosyl)uracil (4a)

A suspension of 2a[17] (127.8 g) in saturated methanolic ammonia (I L) was stirred at room temperature for 48 h. Solvent was removed *in vacuo* to give 3a as a pale yellow syrup. An analytical sample of 3a was prepared by preparative TLC (chloroform-methanol, 8:2), mp 158-159°C [lit.[17] 156-157°C]. UV (methanol): λ_{max} 262 nm; $[\alpha]_D^{24}$ + 20.28° (c 0.51, water) [lit.[19] $[\alpha]_D^{24}$ + 29°)(c 0.4, water]; ^{1}H NMR (DMSO-d_6): δ 3.65-3.80 (m, 2 H, H-5'), 3.90-4.20 (m, 3 H, H-

2', 3' and 4'), 4.71 (t, 1 H, 5'-OH, D_2O exchangeable, $J_{5'\text{-OH},5'}$ = 5.3 Hz), 5.39 (d, 1 H, 3'-OH, D_2O exchangeable, $J_{3'\text{-OH},3'}$ = 3.2 Hz), 5.57-5.75 (m, 3 H, H-1',5 and 2'-OH, partially D_2O exchangeable), 7.80 (d, 1 H, H-6, $J_{6,5}$ = 8.2 Hz), 11.26 (br s, 1 H, 3-NH, D_2O exchangeable). The syrup was stirred with a mixture of acetone (500 mL) and 1 M HCl in ethyl ether (50 mL) at room temperature overnight and then stored in a refrigerator overnight. The resulting solid product was collected by filtration, washed with acetone until the washings were neutral, and dried to give 4a as a white powder 56 g (88.9%), mp 266-268°C [lit.[19] 264-266°C]; UV (methanol): λ_{max} 262 nm; ^1H NMR (DMSO-d_6): δ 1.30 (s, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 3.90-4.30 (m, 5 H, H-2', 3', 4' and 5'), 5.57 (m, 2 H, H-1' and 5), 5.97 (d, 1 H, 2'-OH, partially D_2O exchangeable, $J_{2'\text{-OH},2'}$ = 4.4 Hz), 7.95 (d, 1 H, H-6, $J_{6,5}$ = 8.2 Hz), 11.28 (br s, 1 H, 3-NH, D_2O exchangeable).

1-(3,5-O-Isopropylidene-β-D-xylofuranosyl)thymine (4b)

A suspension of 2b (48 g, 85 mmol) in 0.5 M sodium methoxide in methanol (600 mL) was stirred at room temperature overnight. Water (200 mL) was added and the mixture was neutralized with acidic resin (Dowex 50, H+ form) and filtered. The resin was washed with 80% methanol. The combined filtrate and washings were evaporated *in vacuo*. The residual aqueous solution was extracted with ethyl acetate (3 x 200 mL). The aqueous phase was evaporated and then co-evaporated with ethanol to give 3b as a pale yellow foam (21.28 g, 95.4 %) which was pure enough for the next reaction. An analytical sample was obtained by crystallization from ethanol to give 3b as white needles, mp 159 - 160°C [lit.[17] 164-165°]; UV (methanol): λ_{max} 267 nm; $[\alpha]_D^{23}$ -20.0° (c 0.55, methanol); ^1H NMR (DMSO-d_6): δ 1.76 (s, 3 H, CH_3), 3.69 (m, 2 H, H-5'), 3.94 (m, 3 H, H-2', 3', and 4'), 4.72 (t, 1 H, 5'-OH, $J_{5'\text{-OH},5'}$ = 3.5 Hz, D_2O exchangeable), 5.68 (m, 2 H, H-1', and 2'-OH, partially D_2O exchangeable), 7.65 (s, 1 H, H-6), 11.26 (s, 1 H, 3-NH, D_2O exchangeable). The pale yellow foam was stirred with a mixture of acetone (200 mL) and 1M HCl in ether (20 mL) at room temperature overnight. Molecular sieves (4Å,15 g) were added and stirring was continued for another 2 h to complete the reaction. Molecular sieves were removed by filtration and washed with acetone. The combined

filtrate and washings were neutralized with basic resin (Amberlite IR-45) and then evaporated *in vacuo* to give 4b as pale yellow syrup, which was crystallized from methanol to give white needles (23.45 g, 95.3%), mp 183-184°C; UV (methanol): λ_{max} 267 nm; ^{1}H NMR (DMSO-d_6): δ 1.26 and 1.43 (s, s, 2 x 3 H, isopropylidene), 1.76 (d, 3 H, C5-CH_3, $J_{CH3,6}$ = 0.88 Hz), 3.96-4.27 (m, 5 H, H-2',3',4', and 5'), 5.66 (s, 1 H, H-1'), 5.95 (br s, 1 H, 2'-OH, D_2O exchangeable), 7.84 (d, 1 H, H-6, $J_{6,CH3}$ = 1.2 Hz), 11.27 (br s, 1 H, 3-NH, D_2O exchangeable).

1-[3,5-O-Isopropylidene-2-O-(cyanoethylthio)thiocarbonyl-β-D-xylofuranosyl]uracil (5a)

To a mixture of 4a (55 g, 193 mmol) and carbon disulfide (90 mL) in DMSO (200 mL), 10 N NaOH (50 mL) was added dropwise with stirring. After 30 min, 3-bromopropionitrile (80 g, 50 mL) was added. The mixture was stirred at room temperature for 4 h, and added dropwise into saturated sodium chloride solution with vigorous stirring. The resulting solid was collected by filtration, dissolved in ethyl acetate, washed with water, and dried over anhydrous sodium sulfate. Evaporation *in vacuo* gave 5a as a pale yellow syrup (70.7 g, 88.6%). Crystallization from 95% ethanol gave white needles, mp 179 -181°C; $[\alpha]^{24}_D$ + 32° (c 0.53, methanol); UV (methanol): λ_{max} 261 nm; IR (KBr) 2250 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 2.86 (t, 2 H, CH_2CH_2, J = 6.7 Hz), 3.44 (t, 2 H, CH_2CH_2), 4.13-4.21 (m, 3 H, H-4' and 5'), 4.49 (m, 1 H, H-3'), 5.72-5.81 (m, 2 H, H-2' and 5, $J_{5,6}$ = 7.9 Hz), 6.07 (s, 1 H, H-1'), 8.04 (d, 1 H, H-6, $J_{6,5}$ = 8.2 Hz), 8.89 (br s, 1 H, 3-NH). Anal. Calcd for $C_{16}H_{19}N_3O_6S_2$: C, 46.48; H, 4.63; N, 10.15; S, 15.51. Found: C, 46.58; H, 4.64; N, 10.08; S, 15.41.

1-[3,5-O-Isopropylidene-2-O-(cyanoethylthio)thiocarbonyl-β-D-xylofuranosyl]thymine (5b)

Compound 4b (17.7 g, 59.3 mmol) was treated according to the same procedure for 5a to give 5b (21.3 g, 84%) as pale yellow needles, which were crystallized from petroleum ether. An analytical sample was obtained by recrystallization from acetone-ethyl ether, mp 166 - 167°C; UV (methanol); λ_{max}

273 nm; $[\alpha]_D^{24}$ +10.6° (c 0.6, methanol); ^{1}H NMR ($CDCl_3$): δ 1.43 and 1.49 (s, s, 2 x 3 H, isopropylidene), 1.96 (d, 3 H, C5-CH_3, $J_{CH3,6}$ = 1.1 Hz), 2.85 (t, 2 H, CH_2CH_2, J = 6.8 Hz), 3.43 (t, 2 H, CH_2CH_2; J = 6.8 Hz) 4.06-4.08 (m, 1 H, H-4'), 4.19 (s, 2 H, H-5'), 4.51 (m, 1 H, H-3'), 5.75 (s, 1 H, H-2'), 6.12 (d, 1 H, H-1', $J_{1',2'}$ = 1.1 Hz), 7.87 (d, 1 H, H-6, $J_{6,CH3}$ = 1.1 Hz), 8.76 (br s, 1 H, 3-NH). Anal. Calcd for $C_{17}H_{21}N_3O_6S_2$: C, 47.76; H, 4.95; N, 9.83; S, 15.00. Found: C, 47.69; H, 5.01; N, 9.76; S, 15.06.

1-(3,5-O-Isopropylidene-β-D-2-deoxyxylofuranosyl)uracil (6a)

Method A (Bu_3SnH/AIBN procedure):

A mixture of 5a (75 g, 181 mmol) and azobisisobutyronitrile (AIBN) (4 g) in dry toluene (500 mL) was heated at 100°C with stirring under nitrogen atmosphere. Tributyltin hydride (86.4 g, 0.3 mol) was added dropwise and heating was continued for 1.5h, before the mixture was cooled to room temperature and filtered. The resulting brown cake was washed with acetonitrile. The combined filtrate and washings were evaporated *in vacuo* to give a pale yellow solid. This crude product was dissolved in acetonitrile (1.52 L) and washed with hexanes (5 x 800 mL). The acetonitrile phase was evaporated and the resulting syrup was dried *in vacuo* to give pale yellow crystals, which were recrystallized from acetone-hexanes to give 6a as white prisms (40 g, 82.6%), mp 154 -155°C; $[\alpha]_D^{23}$ + 44° (c 0.57, methanol); UV (water) λ_{max} 262 nm; ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 2.13-2.74 (m, 2 H, H-2'), 3.82-3.88 (m, 1 H, H-4'), 4.19 (s, 2 H, H-5"), 4.41-4.49 (m, 1 H, H-3'), 5.70 (d, 1 H, H-5, $J_{5,6}$ = 8.1 Hz), 6.09 (dd, 1 H, H-1', J = 1.1 Hz and 7.2 Hz), 8.12 (d, 1 H, H-6, $J_{6,5}$ = 8.1 Hz), 8.95 (br s, 1 H, 3-NH). Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.01; N, 10.45. Found: C, 53.47; H, 6.05; N, 10.35.

Method B [$(Me_3Si)_3SiH/Et_3B$ procedure]:

To a mixture of 5a (556 mg, 1.35 mmol) and triethylborane (1 M in hexanes, 2.0 mL) in dry benzene (10 mL), tris(trimethylsilyl)silane (0.7 mL) was added dropwise with stirring at room temperature and the reaction mixture was stirred under nitrogen atmosphere for 48 h. TLC (chloroform-methanol, 95:5) showed

the starting material had completely disappeared and compound 6a was the sole product. The resulting white solid was collected by filtration to give 325 mg of 6a. From the filtrate another crop of the product (25 mg) was obtained. Total yield was 355 mg (96.6%).

1-(3,5-O-Isopropylidene-β-D-2-deoxyxylofuranosyl)thymine (6b)

Method A (Bu_3SnH/AIBN procedure):

Compound 5b (6.3 g, 15 mmol) was treated according to the same procedure for 6a to give 6b (3.59 g, 86.3%) as white needles, which were crystallized from acetone-hexanes, mp 165 - 167°C; $[\alpha]_D^{24}$ -5.50° (c 0.65, methanol). [lit.[2] mp 165-167°C, $[\alpha]^{25}_D$ -11.4°]; UV (methanol): λ_{max} 266 nm; ^1H NMR ($CDCl_3$): δ 1.38 and 1.48 (s, s, 2 x 3H, isopropylidene), 1.95 (s, 3H, C5-CH_3), 2.07-2.75 (m, 2H, H-2'), 3.81 (m, 1H, H-4') 4.18 (s, 2H, H-5'), 4.44 (m, 1H, H-3'), 6.16 (d, 1H, H-1', $J_{1',2'}$ = 7.7 Hz), 7.99 (s, 1H, H-6), 8.72 (br s, 1H, 3-NH). Anal. Calcd. for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.93. Found: C, 55.29; H, 6.43; N, 9.88.

Method B [$(Me_3Si)_3SiH/Et_3B$ procedure]:

Compound 5b (3.46 g, 8.1 mmol) was treated according to the same procedure for 6a to give 6b (2.37 g, 93.3%) as white crystals, which were crystallized from hot toluene.

1-β-D-(2-Deoxyxylofuranosyl)uracil (7a)

A solution of 6a (40 g) in 5% trifluoroacetic acid in methanol (600 mL) was heated under reflux for 6 h. Evaporation of the solvent and co-evaporation with ethanol gave white crystals which were collected by filtration, washed with acetone, and dried *in vacuo* to give 7a (26.6 g). The combined mother liquor and washings were evaporated to dryness, the residue was dissolved in water and extracted with ethyl acetate. The neutral aqueous phase was evaporated and the residue was crystallized from ethanol to give additional amounts (3.5 g). Total yield of 7a was 30.1 g (88.5%), mp 167 -168°C [lit.[21,22] 160-162°C, 165-166°C]; $[\alpha]^{24}_D$ + 44° (c 0.52, water) [lit.[22] $[\alpha]^{22}_D$ + 40° (c 1.4, water)]; UV (methanol): λ_{max} 261 nm; ^1H NMR (DMSO-d_6): δ 1.75-1.95, 2.40-2.75 (m, 2 H, H-2'), 3.56-3.86 (m, 3 H, H-4' and 5'), 4.25 (m, 1 H, H-3'), 4.67 (t, 1 H, 5'-OH, D_2O

exchangeable, $J_{5'\text{-}OH,5'}$ = 5.6 Hz), 5.23 (d, 1 H, 3'-OH, D_2O exchangeable, $J_{3'\text{-}OH,3'}$ = 3.2 Hz), 5.65 (d, 1 H, H-5, $J_{5,6}$ = 7.9 Hz), 6.05 (dd, 1 H, H-1', J = 1.8 Hz and 5.2 Hz), 7.90 (d, 1 H, H-6, $J_{6,5}$ = 7.9 Hz), 11.20 (br s, 1 H, 3-NH, D_2O exchangeable).

1-β-D-(2-Deoxyxylofuranosyl)thymine (7b)

Compound 6b (22.36 g, 79 mmol) was treated according to the same procedure for 7a to give 7b (15.9 g, 83.2%) as white crystals, which were crystallized from methanol, mp 169 - 170°C; [lit.[22] 170-171°C]. $[\alpha]_D^{24}$ +8.6° (c 0.5, methanol); $[\alpha]_D^{23}$ +7.9° (c 0.68, water), [lit.[22] $[\alpha]_D^{25}$ +12° (c 0.36, water)]; ^1H NMR (DMSO-d_6): δ 1.77 (d, 3 H, CH_3, $J_{CH3,6}$ = 0.88 Hz), 1.91-2.00 and 2.40-2.71 (m, m, 2 H, H-2'), 3.61-3.88 (m, 3 H, H-4' and 5'), 4.25 (m, 1 H, H-3'), 4.70 (br s, 1 H, 5'-OH, D_2O exchangeable), 5.23 (br s, 1 H, 3'-OH, D_2O exchangeable), 6.05 (dd, 1 H, H-1', J = 2.6 Hz and 8.2 Hz), 7.80 (d, 1 H, H-6, $J_{6,CH3}$ = 0.87 Hz), 11.16 (br s, 1 H, 3-NH, D_2O exchangeable). Anal. Calcd. for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.50; H, 5.85; N, 11.51.

1-(5-O-Trityl-3-O-mesyl-β-D-2-deoxyxylofuranosyl)uracil (9a)

To a solution of 7a (10 g, 48.9 mmol) and triethylamine (6.5 mL) in dry pyridine (200 mL), trityl chloride (13.66 g, 53.8 mmol) was added portionwise. The mixture was heated under reflux for 8 h. TLC (chloroform-methanol, 95:5) showed the starting material had almost completely disappeared and 8a was the major component. The solution was cooled in an ice-water bath and mesyl chloride (12.3 mL, 0.16 mol) was added dropwise with stirring. The reaction mixture was stirred at room temperature overnight, and then added into a mixture of ice water (4 L). The precipitate was collected by filtration, washed with water, and then dried to give 9a as a pale yellow powder 25.87 g (quant.).

Analytical samples of 8a and 9a were prepared by silica gel chromatography. For compound 8a, the column was eluted with chloroform-methanol (95:5). The desired fraction was crystallized from acetone to give pale yellow needles, mp 225-228°C. [lit.[12] 230-231°C]; UV (methanol): λ_{max} 262 nm and 210 nm.

For compound 9a, the column was eluted first with chloroform and then with chloroform-methanol (95:5). The desired fraction was crystallized from acetone-hexanes to give pale yellow needles, mp 154°C (dec) [lit.[12] 152-155°C (dec)]; UV (methanol): λ_{max} 261 nm and 214 nm; ^{1}H NMR ($CDCl_3$): δ 2.35-2.75 (m, 2 H, H-2'), 2.77 (s, 3 H, CH_3SO_2), 3.28-3.73 (m, 2 H, H-5'), 4.13-4.35 (m, 1 H, H-4'), 5.21-5.35 (m, 1 H, H-3'), 5.64 (d, 1 H, H-5, $J_{5,6}$ = 7.0), 6.20 (dd, 1 H, H-1', J =3.1 Hz, 7.4 Hz), 7.22-7.51 (m, 16 H, H-6 and trityl), 8.80 (br s, 1 H, 3-NH).

1-(5-O-Trityl-3-O-mesyl-β-D-2-deoxyxylofuranosyl)thymine (9b)

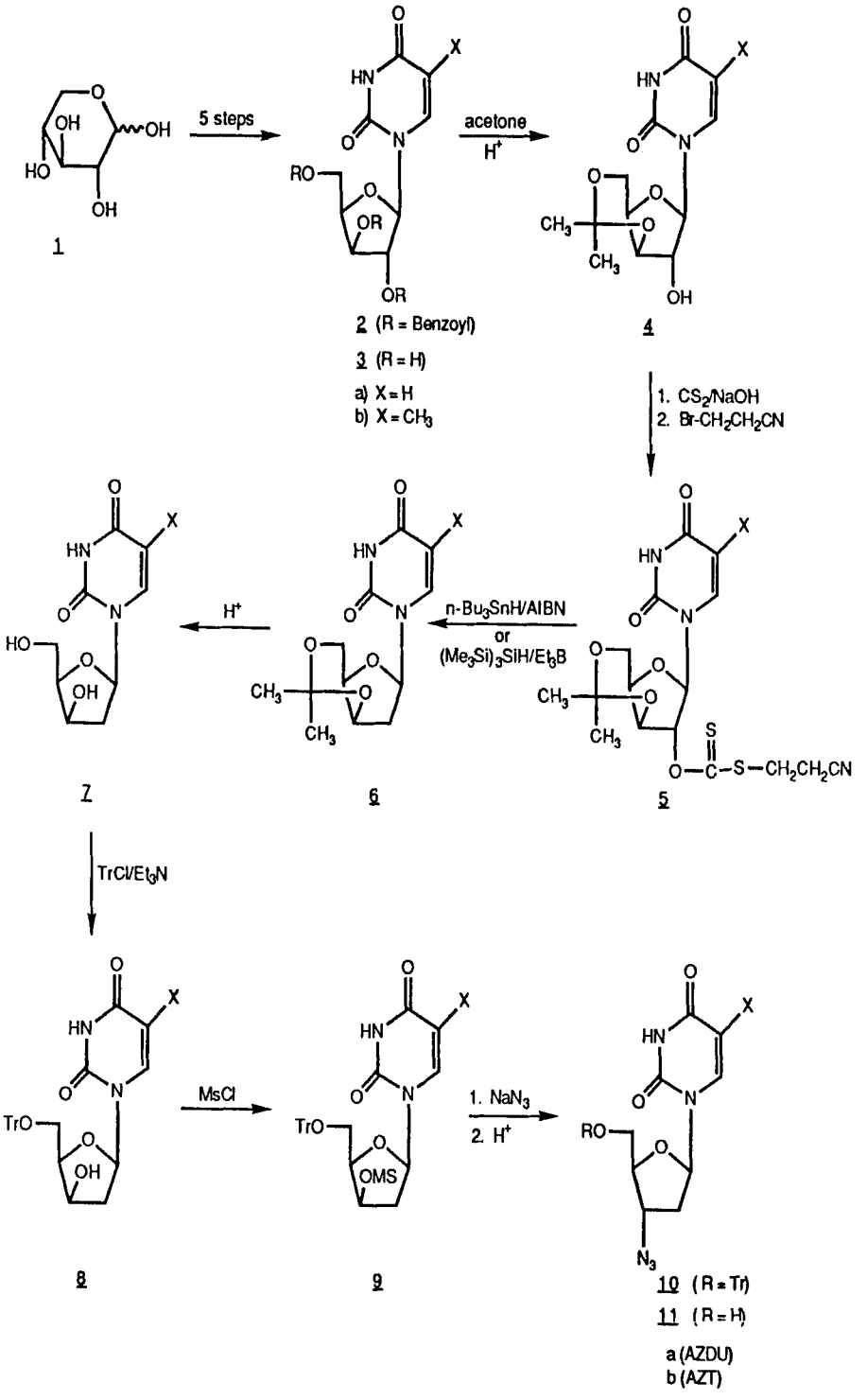
Compound 8b (12.9 g, 53.3 mmol) was treated according to the same procedure for 9a to give 9b (32.9 g) as a tan solid. An analytical sample was prepared by preparative TLC (chloroform-methanol, 96:4). UV (methanol): λ_{max} 265 and 225 nm; ^{1}H NMR ($CDCl_3$): δ 1.80 (d, 3 H, C5-CH_3, $J_{CH3,6}$ = 0.66 Hz), 2.30-2.91 (m, 2 H, H-2'), 2.75 (s, 3 H, CH_3SO_2), 3.23-3.74 (m, 2 H, H-5'), 4.10-4.27 (m, 1 H, H-4'), 5.21-5.31 (m, 1 H, H-3'), 6.25 (dd, 1 H, H-1', J = 3.5 and 7.7 Hz), 7.25-7.50 (m, 16 H, H-6 and trityl), 8.63 (br s, 1 H, 3-NH).

1-(5-O-Trityl-3-azido-β-D-2,3-dideoxyribofuranosyl)uracil (10a)

A solution of 9a (25.87 g, 47.2 mmol) in dry dimethylformamide (200 mL) was treated with sodium azide (13.32 g, 0.205 mol) at 80 ~ 90°C with stirring for 3 h. The mixture was cooled to room temperature and poured into water (3 L) with vigorous stirring. The precipitate was collected by filtration, washed with water, and dried to give 10a as a pale yellow powder (22.44 g, 96.1%), which was crystallized from ethanol to give pale yellow needles, mp 174 - 175°C (lit.[12] 175-176°C). UV (methanol): λ_{max} 261nm and 224 nm; IR (KBr): 2102 cm^{-1} (azido); ^{1}H NMR ($CDCl_3$): δ 2.35-2.53 (m, 2 H, H-2'), 3.45-3.52 (m, 2 H, H-5'), 3.85-4.05 (m, 1 H, H-4'), 4.33 (m, 1 H, H-3'), 5.40 (d, 1 H, 5-H, $J_{5,6}$ = 7.8 Hz), 6.20 (t, 1 H, H-1', $J_{1',2'}$ = 5.7 Hz), 7.20-7.60 (m, 15 H, trityl), 7.31 (d, 1 H, H-6, $J_{6,5}$ = 8.1 Hz), 8.88 (br s, 1 H, 3-NH).

1-(5-O-Trityl-3-azido-β-D-2,3-dideoxyribofuranosyl)thymine (10b)

Compound 9b (32 g) was treated according to the same procedure for 10a to give 10b (27.5 g, 94.6%) as a pale yellow powder. UV (methanol): λ_{max} 265



and 213 nm; IR (KBr): 2104 cm^{-1} (azido); ^1H NMR ($CDCl_3$): δ 1.52 (d, 3H, C5-CH_3, $J_{CH3,6}$ = 1.1 Hz), 2.36-2.53 (m, 2H, H-2'), 3.45 (dd, 2H, H-5', J = 3.1 and 10.8 Hz), 3.92-4.03 (m, 1H, H-4'), 4.27-4.43 (m, 1H, H-3'), 6.25 (t, 1H, H-1', $J_{1',2'}$ = 6.3 Hz), 7.25-7.55 (m, 16H, H-6 and trityl), 8.59 (br s, 1H, 3-NH).

1-(3-Azido-β-D-2,3-dideoxyribofuranosyl)uracil (AZDU) (11a)

A suspension of 10a (11.7 g, 23.6 mmol) in 80% acetic acid (100 mL) was heated under reflux for 20 min., and water (20 mL) was added. The resulting trityl alcohol was removed by filtration. The filter cake was washed with water. The combined filtrate and washings were treated with activated charcoal, filtered and then evaporated *in vacuo* to give 11a as a yellow solid (4.68 g, 77.8%). Recrystallization from methanol gave white crystals which were identical to an authentic sample of AZDU (CS-87), mp 174 - 175 °C [lit.[12] 161-163°C]; UV (methanol): λ_{max} 261 nm; IR (KBr) 2089 cm^{-1} (azido); ^1H NMR (DMSO-d_6): δ 2.27-2.48 (m, 2 H, H-2'), 3.62 (m, 2 H, H-5'), 3.78-3.91 (m, 1 H, H-4'), 4.30-4.47 (m, 1 H, H-3'), 5.18 (br s, 1 H, 5'-OH, D_2O exchangeable), 5.63 (d, 1 H, H-5, $J_{5,6}$ = 7.9 Hz), 6.07 (t, 1 H, H-1', $J_{1',2'}$ = 6.4 Hz), 7.82 (d, 1 H, H-6, $J_{6,5}$ = 7.9 Hz), 11.31 (br s, 1 H, 3-NH, D_2O exchangeable).

3'-Azido-3'-deoxythymidine (AZT) (11b)

Compound 10b (27 g) was treated according to the same procedure for 11a to give 11b (9.78 g, 68%) which was cryatallized from hot water. An analytical sample, obtained by further recrystallizing this material twice from water was identical to an authentic sample, mp. 121 - 122°C [lit.[2,3] 119-121°C, 120-122°C]; UV (water): λ_{max} 266 nm; IR (KBr): 2087 cm^{-1} (azido); ^1H NMR (DMSO-d_6): δ 1.78 (d, 3 H, C5-CH_3, $J_{CH3,6}$ = 0.88 Hz), 2.24-2.41 (m, 2 H, H-2'), 3.57-3.67 (m, 2 H, H-5'), 3.79-3.85 (m, 1 H, H-4'), 4.27-4.50 (m, 1 H, H-3'), 5.18 (t, 1 H, 5'-OH, $J_{5'-OH,5'}$ = 5.3 Hz, D_2O exchangeable), 7.67 (d, 1 H, H-6, $J_{6,CH3}$ = 1.2 Hz), 11.27 (br s, 1 H, 3-NH, D_2O exchangeable).

ACKNOWLEDGEMENTS

This research was supported by Berlex Laboratories
(formerly Triton Biosciences)

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Received 9/9/91
Accepted 11/20/91