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Synthesis of 2,2'-Anhydro-1-(3'-deoxy-3'-bromo-β-D-arabinofuranosyl)thymine and Its Derivatives from 5'-*O*-Trityl-2',3'-thymidinene

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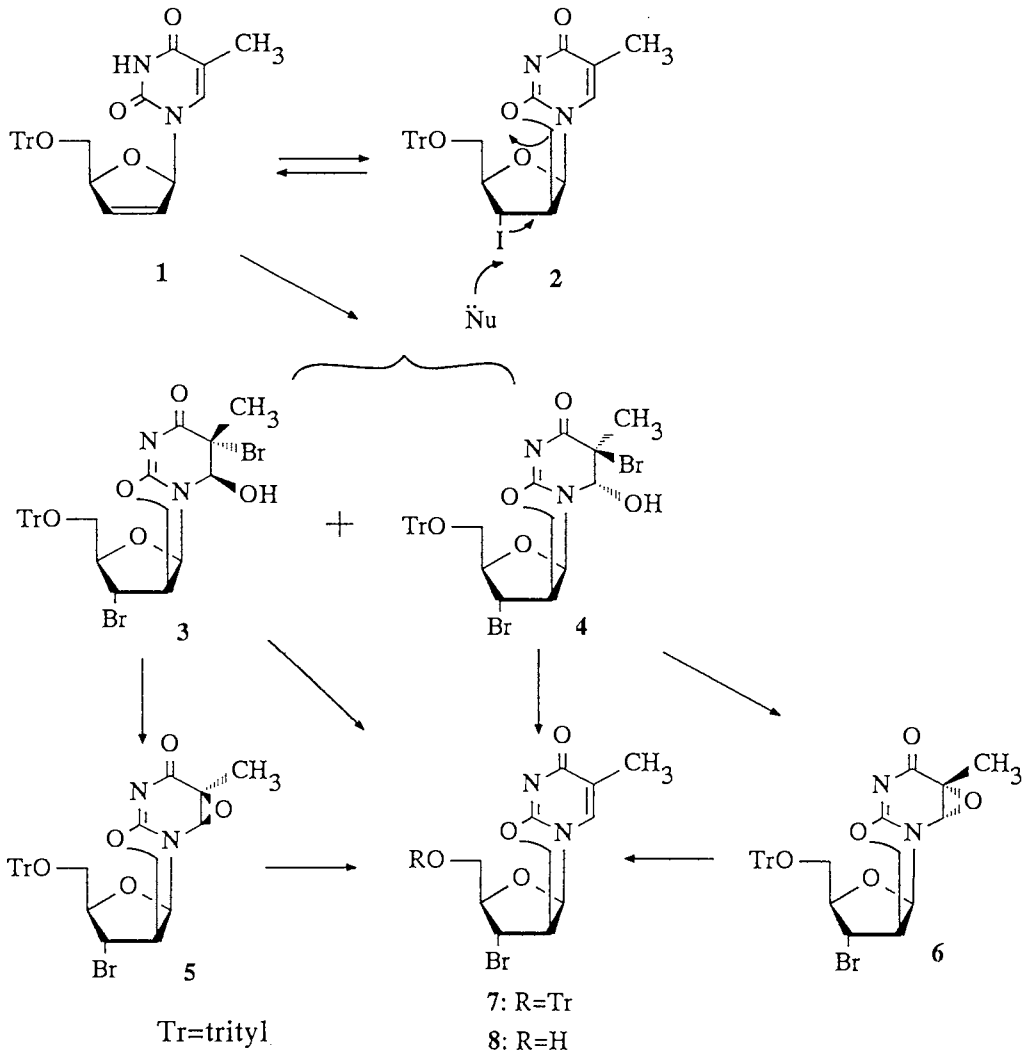
Reaction of 5'-*O*-trityl-2',3'-thymidinene with hypobromous acid gave 2,2'-anhydro-1-(3'-deoxy-3'-bromo-5'-*O*-trityl-β-D-arabinofuranosyl)-(5R,6R)-*trans*-5-bromo-6-hydroxy-5,6-dihydrothymine (**3**) and its (5S,6S) *trans* analogue (**4**). These were transformed into the corresponding 5,6-epoxy analogues. Compounds **3** and **4** were debromohydrinated to the title 2,2'-anhydro nucleoside in high yields.

Spurred by the current continued efforts to synthesize modified thymine nucleosides as possible anti-AIDS drugs,[1] we have recently synthesized 2,2'-anhydro-1-(3'-deoxy-3'-iodo-5'-*O*-trityl-β-D-arabinofuranosyl)thymine (**2**)[2] as a versatile synthetic intermediate starting from 2',3'-didehydro-5'-*O*-trityl-3'-deoxythymidine (**1**)[3] easily obtainable from thymidine. In this work, our major concern was exploitation of a simple method for functionalization at the 2'- and 3'-positions of thymidine lacking a 2'-hydroxyl group.[4] In fact, most of the 2'-functionalized thymine furanosides described until today have originated from self-made ribosyl[5] or arabinosyl thymine.[6]

Although compound **2** was readily converted into another series of important intermediates, 2',3'-anhydro-lyxofuranosyl derivatives of thymine and other modified thymines, the 3'-iodo group in **2**, especially in its detritylated form, was found to be considerably susceptible to various nucleophiles and protonic acids to regenerate **1**. Light-induced, gradual decomposition of **2** was also observed especially in solution. Hence, an analogue of **2** having a 3'-halogen atom other than iodine was desirable as a more appropriate intermediate. This communication deals with the results of reaction of hypobromous acid generated *in situ* from N-bromoacetamide (NBA) with **1** from several trials using various electrophiles involving Chloramine-T, t-BuOCl, NCS, pyridinium bromide perbromide, etc.

The reaction of **1** with 2.4-2.5 equivalent amounts of NBA in acetone/H_2O (4:1) at 0 °C for 40 h gave 2,2'-anhydro-1-(3'-deoxy-3'-bromo-5'-*O*-trityl-β-D-arabinofuranosyl)-(5R,6R)-*trans*-5-bromo-6-hydroxy-5,6-dihydrothymine (**3**)[7] (53%) and its (5S,6S)-*trans* analogue (**4**) (32%).[8] The structure of **3** was confirmed by X-ray analysis (Fig. 1).[9] When less than 2 equivalent amounts of NBA were used, a 5,6-bromohydrinated derivative of **1** was isolated as a far minor product. Since this compound disappeared from the reaction mixture when further NBA was added and no TLC-spot corresponding to **7** was observed, the



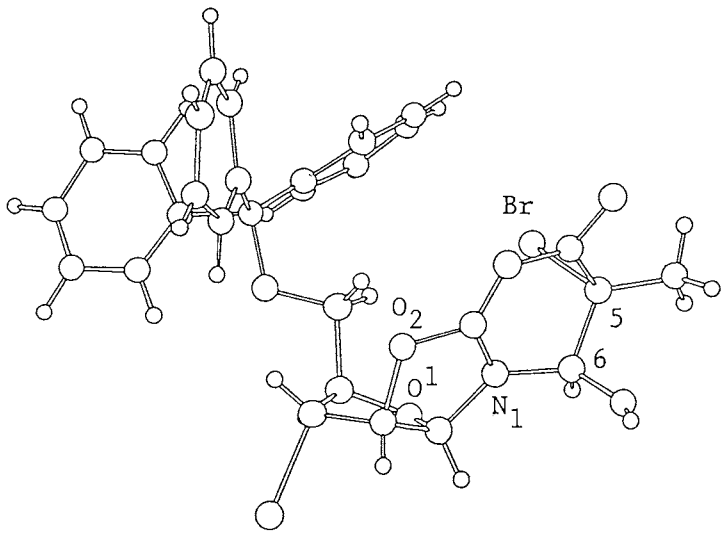


Fig. 1. Molecular Structure of 3.

5,6-bromohydrination appears to have preceded the 2,2'-cyclization. Similar synthesis and chemical reactions of 5,6-bromohydrins of thymidine were extensively studied recently by Yoneda and co-workers in connection with the oxidative damage and repair of pyrimidine bases in DNA.[11] Treatment of **3** with excess Et_3N/acetone (reflux, 5 h) gave 2,2'-anhydro-1-(3'-deoxy-3'-bromo-5'-*O*-trityl-β-D-arabinofuranosyl)-(5S,6R)-5,6-epoxythymine (**5**) (82%),[12] while similar treatment of **4** (room temp, 1 h) afforded its (5R,6S) analogue (**6**)[13] in 99% yield. Deoxygenation of **5** with excess triphenylphosphine in refluxing ethyl acetate (15 h) gave desired 2,2'-anhydro-1-(3'-deoxy-3'-bromo-5'-*O*-trityl-β-D-arabinofuranosyl) thymine (**7**) (30%),[14] which is also obtainable by similar treatment of **6** in ca. 50% yield. It must be noted that the debromohydrination of the 2,2'-cyclized form, **3** or **4**, could not be attained by treatment with heat, sunlight or a radical initiator, 2,2'-azobisisobutyronitrile, in contrast with the reported radical-initiated repair of 5,6-bromohydrins of 1,3-dimethylthymine as well as thymidine.[11]

In view of the rather unacceptable yields of **7** from **5** and **6**, the usual debromohydrination of **3** using zinc powder in DMF-AcOH or DMF-MeOH (room temp) was tried. However, this reagent proved to be inappropriate, since **1** was reproduced probably due to its attack on the 3'-bromo group to cause eliminative ring opening (process **2**→**1**). It was finally found that **3** or **4** can be smoothly converted into **7** with the use of triphenylphosphine. Thus, a mixture of compound **3** (1 mM), triphenylphosphine (1.2 mM) and sodium hydrogen carbonate (2.7 mM) in DMF (10 ml) was stirred under argon atmosphere for 3.5 h to give **7** in 80% yield after chromatography. Similarly, **4** was converted into **7** in 86% yield within 70 min in a far smaller scale experiment (TLC-monitoring indicated quantitative conversion).[15] This method can be applicable, in a more time-saving manner, to a mixture of **3** and **4**, or to a crude reaction mixture containing a high, combined yield of **3** and **4**, giving a reasonable yield of **7** for further transformation. To our knowledge, this debromohydrination using triphenylphosphine is unprecedented and needs a mechanistic investigation. As expected, compound **7** is sufficiently stable to allow detritylation to 2,2'-anhydro-1-(3'-deoxy-3'-bromo-β-D-arabinofuranosyl)thymine (**8**)[16] even with the use of 80% acetic acid.

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4) The range of sugar modification of thymidine lacking a 2'-hydroxy group is notably limited as compared to that of a pyrimidine ribo- or arabinoside.

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7) All new compounds gave satisfactory elemental analysis values. λ max (MeOH) nm (ε) 233.7 (5990, infl) and 250.4 (3500, infl); ^{1}H NMR (Me_2SO-d_6) δ 1.74 (3H, s, 5-Me), 3.22 (dd, J_{gem}= 11.0, $J_{5'a,4'}$=

5.0, $H_{5'a}$), 3.27 (dd, J_{gem}= 11.0, $J_{5'b,4'}$= 7.2, $H_{5'b}$), 4.34 (dt, $J_{4',3'}$= 4.5, $J_{4',5'a}$= 5.0, $J_{4',5'b}$= 7.2, $H_{4'}$), 4.63 (dd, $J_{3',2'}$= 2.5, $J_{3',4'}$= 4.0, $H_{3'}$), 5.70 (dd, $J_{2',1'}$= 6.5, $J_{2',3'}$= 2.5, $H_{2'}$), 6.10 (d, $J_{1',2'}$= 6.5, $H_{1'}$), 5.61 (d, J= 6.4, H_6), 7.51 (d, J= 6.4, 6-OH, D_2O-exchangeable).

8) λmax (MeOH) nm (ε) 233.2 (15210, infl) and 250.3 (10430, infl); ^{1}H NMR (Me_2SO-d_6) δ 1.68 (3H, s, 5-Me), 2.96 (dd, J_{gem}= 11.12, $J_{5'a,4'}$= 7.15, $H_{5'a}$), 3.20 (dd, J_{gem}= 11.12, $J_{5'b,4'}$= 4.77, $H_{5'b}$), 4.43 (dt, $J_{4',3'}$= 3.97, $J_{4',5'a}$= 7.15, $J_{4',5'b}$= 4.77, $H_{4'}$), 4.67 (d, J= 6.36, H_6), 4.74 (dd, $J_{3',2'}$= 1.59, $J_{3',4'}$= 3.97, $H_{3'}$), 5.70 (dd, $J_{2',1'}$= 5.57, $J_{2',3'}$= 1.59, $H_{2'}$), 6.11 (d, $J_{1',2'}$= 5.57, $H_{1'}$).

9) Crystal Data for **3**: $C_{29}H_{26}Br_2N_2O_5$+C_3H_6O (acetone), M = 700.42, orthorhombic, space group $P2_12_12_1$, a = 14.918(8)Å, b = 18.560(6)Å, c = 10.962(6)Å, V = 3035(2)Å^3, Z = 4, and Dc = 1.533 g cm^{-3}. The reflection data were collected on a Rigaku AFC5S diffractometer using monochromated MoKα and ω-2θ scan technique. The structure was solved by direct method (MITHRIL)[10] and refined by full-matrix least squares. The final R value was 0.091 for 1084 independent reflections [I>3.00σ(I)].

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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12) λmax (MeOH) nm (ε) 204.2 (54400) and 231.5 (18490); ^{1}H NMR ($CDCl_3$) δ 1.51 (3H, s, 5-Me), 3.10 (dd, J_{gem}= 10.0, $J_{5'a,4'}$= 6.5, $H_{5'a}$), 3.26 (dd, J_{gem}= 10.0, $J_{5'b,4'}$= 6.0, $H_{5'b}$), 4.53 (ddd, $J_{4',3'}$= 3.2, $J_{4',5'a}$= 6.5, $J_{4',5'b}$= 6.0, $H_{4'}$), 4.49 (t, $J_{3',2'}$= 2.5, $J_{3',4'}$= 3.2, $H_{3'}$), 5.36 (dd, $J_{2',1'}$= 5.5, $J_{2',3'}$= 2.5, $H_{2'}$), 6.12 (d, $J_{1',2'}$= 5.5, $H_{1'}$), 4.70 (s, H_6).

13) λmax (MeOH) nm (ε) 203.4 (26650) and 231.6 (8360); ^{1}H NMR ($CDCl_3$) δ 1.54 (3H, s, 5-Me), 2.46 (dd, J_{gem}= 10.4, $J_{5'a,4'}$= 9.6, $H_{5'a}$), 3.37 (dd, J_{gem}= 10.4, $J_{5'b,4'}$= 5.6, $H_{5'b}$), 4.56 (dd, $J_{4',5'a}$= 9.6, $J_{4',5'b}$= 5.6, $H_{4'}$), 4.60 (br s, overlapped the H_6-signal), 5.37 (d, $J_{2',1'}$= 4.8, $H_{2'}$), 6.08 (d, $J_{1',2'}$= 4.8, $H_{1'}$).

14) λmax (MeOH) nm (ε) 204.3 (40180), 225.0 (16200, infl) and 252.6 (7600); ^{1}H NMR ($CDCl_3$) δ 1.78 (3H, s, 5-Me), 2.81 (dd, J_{gem}= 11.0, $J_{5'a,4'}$= 8.0, $H_{5'a}$), 3.10 (dd, J_{gem}= 11.0, $J_{5'b,4'}$= 4.0, $H_{5'b}$), 4.61 (dt, $J_{4',3'}$= 3.5, $J_{4',5'a}$= 8.0, $J_{4',5'b}$= 4.0, $H_{4'}$), 4.82 (dd, $J_{3',2'}$= 1.5, $J_{3',4'}$= 3.5, $H_{3'}$), 5.64 (dd, $J_{2',1'}$= 5.5, $J_{2',3'}$= 1.5, $H_{2'}$), 6.43 (d, $J_{1',2'}$= 5.5, $H_{1'}$), 7.86 (s, H_6).

15) In the absence of sodium hydrogen carbonate, hydrogen bromide released in the reaction of **3** or **4** with Ph_3P partially cleaves the trityloxy and 2,2'-anhydro bond.

16) λmax (MeOH) nm (ε) 202.4 (4030), 229.0 (2900) and 252.4 (5800); ^{1}H NMR (Me_2SO-d_6) δ 1.81 (3H, d, J= 1.6, 5-Me), 3.22 (dd, J_{gem}= 12.0, $J_{5'a,4'}$= 5.5, $H_{5'a}$), 3.25 (dd, J_{gem}= 12.0, $J_{5'b,4'}$= 5.5, $H_{5'b}$), 4.46 (dt, $J_{4',3'}$= 2.5, $J_{4',5'a}$= $J_{4',5'b}$= 5.5, $H_{4'}$), 4.84 (br s, $H_{3'}$), 5.68 (d, $J_{2',1'}$= 5.6, $H_{2'}$), 6.44 (d, $J_{1',2'}$= 5.6, $H_{1'}$), 7.79 (br s, H_6), 5.14 (br s, 5'-OH, D_2O-exchangeable).

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