Highly Efficient Synthesis of 2,2'-Anhydro-1-(3'-bromo-3'-deoxy-5'-*O*-trityl-β-D-arabinofuranosyl)thymine and its Derivatives from an Unsaturated Thymine Nucleoside

Katsumaro Minamoto,*[a] Masataka Oishi,[a] Akikazu Kakehi,[b] Naoki Ohta,[a] Isamu Matsuda,[a] Kenji Watanabe,[a] Kazufumi Yanagihara,[a] Toyohide Takeuchi[c] and Keizo Tanigawa[d]

[a] *Department of Applied Chemistry, School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464, Japan*

[b] *Department of Material Chemistry, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380, Japan*

[c] *Faculty of Engineering, Gifu University, 1-1 621-1 Yanagido, Gifu 501-11, Japan*

[d] *Synthesis Research Dept., Central Research Institute, Nissan Chemical Industries, Ltd., 722-1, Tsuboi-cho, Funabashi-shi, Chiba 274, Japan*

Reaction of 5'-*O*-trityl-2',3'-thymidinene **1** with hypobromous acid gave (5*R*,6*R*)-2,2'-anhydro-5-bromo-1-(3'-bromo-3'-deoxy-5'-*O*-trityl-β-D-arabinofuranosyl)-6-hydroxy-5,6-dihydrothymine **3a** and its (5*S*,6*S*)-*trans* isomer **4a**. Similarly, 6-methoxy analogues (**3b** and **4b**) and 6-acetoxy analogues (**3c** and **4c**) of **3a** and **4a** were synthesized. Compounds **3a** and **4a** were converted into the corresponding 5,6-epoxy derivatives, **5** and **6**. Deoxygenation of oxiranes **5** and **6** with Ph_3P gave 2,2'-anhydro-1-(3'-bromo-3'-deoxy-5'-*O*-trityl-β-D-arabinofuranosyl)thymine **7**, which was also obtainable in excellent yields from compounds **3a**, **b** or/and **4a**, **b** by treatment with Ph_3P–$NaHCO_3$, or directly from unsaturated furanose **1** by one-pot synthesis *via* methyl ethers **3b** and **4b** or acetates **3c** and **4c**. Compound **7** was deprotected to give the mother compound **8** and was also converted into the 2,3-*lyxo* epoxy thymine furanosides, **11** and **12**, in high yields.

Since the finding that dideoxynucleosides such as 2',3'-dideoxycytidine (ddC),[1] 2',3'-dideoxyinosine (ddI)[1] and 3'-azido-3'-deoxythymidine (AZT)[2] are potentially effective anti-AIDS† agents, much effort has been directed toward the effective deoxygenation of natural nucleosides to 2',3'-dideoxynucleosides.[3] 3'-Deoxythymidine, 2',3'-didehydro-3'-deoxythymidine (d4T) and others are also under clinical investigation.[4] On the other hand, considerable effort has been devoted to the synthesis of nucleosides carrying a sugar moiety modified in a variety of ways. However, from the viewpoint of synthesis, the range of sugar modifications of the 2'-deoxynucleosides is notably limited by the absence of a 2'-hydroxy group as compared with that of *ribo* or *arabino* nucleosides. Hence, the chemistry of thymine furanosides involving the 2'-functionalization has developed starting from the ribosyl[5] or arabinosyl thymine.[5c,6]

Largely owing to the current interest in modified thymidine analogues as potential anti-AIDS agents and the far easier commercial availability of thymidine as compared with the other thymine furanosides (thymine ribo- or arabino-sides)‡ or general 2'-deoxynucleosides, we recently exploited a method for synthesizing 2,2'-anhydro-1-(3'-deoxy-3'-iodo-5'-*O*-trityl-β-D-arabinofuranosyl)thymine **2**[7] from 5'-*O*-trityl-2',3'-thymidinene **1**,[8] which is easily available from thymidine. Although compound **2** was readily converted into another series of important intermediates, 2,3-anhydrolyxofuranosyl derivatives of thymine and other modified thymines,[7] the 3'-iodo group of compound **2**, especially in its detritylated form, was found to be quite susceptible to various nucleophiles and protonic acids to regenerate unsaturated furanose **1**. Light-induced, gradual decomposition of iodide **2** was also observed, especially in solution. Therefore, an analogue of compound **2** having a 3'-halogen atom other than iodine was desirable as a more appropriate intermediate. This paper describes the results of the reaction of compound **1** with hypobromous acid generated *in situ* from *N*-bromoacetamide (NBA).

The reaction of compound **1** with 2.4 mole equivalents of NBA in a mixture of acetone and water gave (5*R*,6*R*)-2,2'-anhydro-5-bromo-1-(3'-bromo-3'-deoxy-5'-*O*-trityl-β-D-arabinofuranosyl)-6-hydroxy-5,6-dihydrothymine **3a** (53%) and its (5*S*,6*S*)-*trans* analogue **4a** (32%) (Scheme 1). The 2,2'-anhydro structures of these compounds are in accord with the ^1H NMR data lacking an N^3-H signal and showing an abnormally deshielded 2'-H signal (δ 5.70 in each case) as well as the large $J_{1',2'}$-values (6.50 and 5.75 Hz, respectively) (Table 1). Both compounds displayed only inflections in the UV spectra (see Experimental section). The (5*R*,6*R*)-*trans* structure of compound **3a** was confirmed by X-ray analysis (*vide infra*, Fig. 1). Hence the counterpart **4a** should be a (5*S*,6*S*)-*trans* diastereoisomer.

When fewer than 2 mole equivalents of NBA were used, a 5,6-bromohydrinated derivative of compound **1** was isolated as a very minor product.§ Since this compound disappeared from the reaction mixture on addition of further NBA, and no TLC spot corresponding to bromide **7** was observed, the 5,6-bromohydrination appears to have preceded the 2,2'-cyclization. Treatment of the alcohol **3a** with an excess of triethylamine in acetone under reflux gave a high yield of (5*S*,6*R*)-2,2'-anhydro-1-(3'-bromo-3'-deoxy-5'-*O*-trityl-β-D-arabinofuranosyl)-5,6-epoxy-5,6-dihydrothymine **5**, while similar epoxidation of

† AIDS: Acquired Immune Deficiency Syndrome.

‡ 1-β-D-Arabinosyl- or ribosyl-thymine is several tens of times more expensive than thymidine.

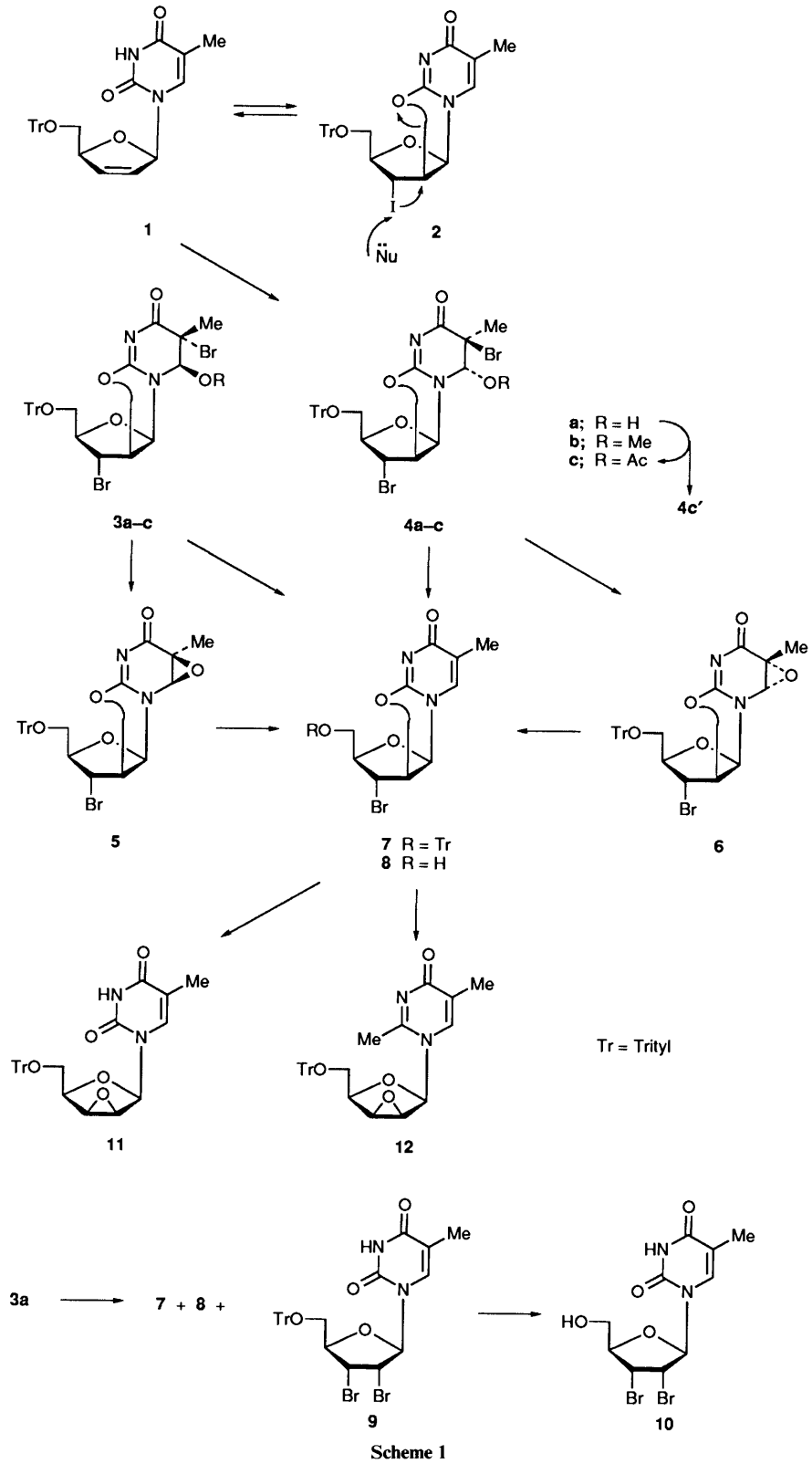
§ This product melted between 146 and 151 °C (Found: C, 61.6; H, 5.0; N, 4.95. $C_{29}H_{27}BrN_2O_5$ requires C, 61.82; H, 4.83; N, 4.97%); $\delta_H(CDCl_3)$ 1.56 (3 H, s, 5-Me), 3.32 (1 H, dd, J_{gem} 10.2, $J_{5'a,4'}$ 3.8, 5'-H[a]), 3.46 (1 H, dd, J_{gem} 10.2, $J_{5'b,4'}$ 4.4, 5'-H[b]), 4.93 (1 H, ddd, $J_{4',1'}$ 4.0, $J_{4',2'}$ 1.6, $J_{4',3'}$ 2.4, 4'-H), 5.16 (1 H, s, 6-H), 6.07 (1 H, ddd, $J_{3',1'}$ 1.4, $J_{3',2'}$ 6.0, $J_{3',4'}$ 2.4, 3'-H), 6.31 (1 H, dt, $J_{2',1'}$ 2.0, $J_{2',3'}$ 6.0, $J_{2',4'}$ 1.6, 2'-H), 6.87 (1 H, ddd, $J_{1',2'}$ 2.0, $J_{1',3'}$ 1.4, $J_{1',4'}$ 4.0, 1'-H), 7.28–7.46 (16 H, m, ArH and 6-OH) and 8.32 (1 H, s, N^3-H).

Table 1 ^{1}H NMR resonances of compounds **3–10**[a–c]

Compd.	5′-H	4′-H	3′-H	2′-H	1′-H	5-Me	6-H	Others
3a	3.22 (1 H, dd, J_{gem} 11.0, $J_{5'a,4'}$ 5.0, 5′-H[a]) 3.27 (1 H, dd, J_{gem} 11.0, $J_{5'b,4'}$ 7.20, 5′-H[b])	4.34 (1 H, ddd, $J_{4',3'}$ 4.50, $J_{4',5'a}$ 5.0, $J_{4',5'b}$ 7.20)	4.63 (1 H, dd, $J_{3',2'}$ 2.50, $J_{3',4'}$ 4.5)	5.70 (1 H, dd, $J_{2',1'}$ 6.50, $J_{2',3'}$ 2.50)	6.10 (1 H, d, $J_{1',2'}$ 6.50)	1.74 (3 H, s)	5.16 (1 H, d, J 6.40)	7.51 (1 H, d, J 6.40, 6-OH), 7.25–7.36 (ArH)
4a	2.96 (1 H, dd, J_{gem} 11.12, $J_{5'a,4'}$ 7.15, 5′-H[a]) 3.20 (1 H, dd, J_{gem} 11.12, $J_{5'b,4'}$ 4.77, 5′-H[b])	4.43 (1 H, ddd, $J_{4',3'}$ 3.97, $J_{4',5'a}$ 7.15, $J_{4',5'b}$ 4.77)	4.74 (1 H, dd, $J_{3',2'}$ 1.59, $J_{3',4'}$ 3.97)	5.70 (1 H, dd, $J_{2',1'}$ 5.75, $J_{2',3'}$ 1.59)	6.11 (1 H, d, $J_{1',2'}$ 5.75)	1.68 (3 H, s)	4.67 (1 H, d, J 6.36)	7.91 (1 H, d, J 6.36, 6-OH), 7.24–7.44 (ArH)
3b	3.18 (1 H, dd, J_{gem} 10.8, $J_{5'a,4'}$ 5.6, 5′-H[a]) 3.27 (1 H, dd, J_{gem} 10.8, $J_{5'b,4'}$ 6.8, 5′-H[b])	4.32 (1 H, m)	4.72 (1 H, dd, $J_{3',2'}$ 2.0, $J_{3',4'}$ 3.8)	5.77 (1 H, dd, $J_{2',1'}$ 5.4, $J_{2',3'}$ 2.0)	6.28 (1 H, d, $J_{1',2'}$ 5.4)	1.77 (3 H, s)	5.26 (1 H, s)	3.50 (3 H, s, 6-OMe), 7.28–7.36 (15 H, ArH)
4b	3.07 (1 H, dd, J_{gem} 10.6, $J_{5'a,4'}$ 6.9, 5′-H[a]) 3.19 (1 H, dd, J_{gem} 10.6, $J_{5'b,4'}$ 4.6, 5′-H[b])	4.45 (1 H, m)	4.81 (1 H, dd, $J_{3',2'}$ 2.1, $J_{3',4'}$ 4.3)	5.78 (1 H, dd, $J_{2',1'}$ 5.6, $J_{2',3'}$ 2.1)	6.23 (1 H, d, $J_{1',2'}$ 5.6)	1.79 (3 H, s)	5.36 (1 H, s)	3.41 (3 H, s, 6-OMe), 7.25–7.38 (15 H, ArH)
3c	3.19 (1 H, dd, J_{gem} 10.2, $J_{5'a,4'}$ 9.2, 5′-H[a]) 3.45 (1 H, dd, J_{gem} 10.2, $J_{5'b,4'}$ 4.8, 5′-H[b])	4.48 (1 H, ddd, $J_{4',3'}$ 2.8, $J_{4',5'a}$ 9.2, $J_{4',5'b}$ 4.8)	4.59 (1 H, dd, $J_{3',2'}$ 1.4, $J_{3',4'}$ 2.8)	5.36 (1 H, dd, $J_{2',1'}$ 5.6, $J_{2',3'}$ 1.4)	6.05 (1 H, d, $J_{1',2'}$ 5.6)	1.84 (3 H, s)	6.16 (1 H, s)	2.11 (3 H, s, 6-OAc), 7.27–7.37 (15 H, ArH)
4c	3.07 (1 H, dd, J_{gem} 10.2, $J_{5'a,4'}$ 8.0, 5′-H[a]) 3.21 (1 H, dd, J_{gem} 10.2 $J_{5'b,4'}$ 5.6, 5′-H[b])	4.47 (1 H, ddd, $J_{4',3'}$ 2.4, $J_{4',5a}$ 8.0, $J_{4',5'b}$ 5.6)	4.55 (1 H, dd, $J_{3',2'}$ 0.8, $J_{3',4'}$ 2.4)	5.41 (1 H, dd, $J_{2',1'}$ 5.0, $J_{2',3'}$ 0.8)	6.02 (1 H, d, $J_{1',2'}$ 5.0)	1.75 (3 H, s)	6.48 (1 H, s)	1.81 (3 H, s, 6-OAc), 7.27–7.39 (15 H, ArH)

5	3.10 (1 H, dd, J_{gem} 10.0, $J_{5'a,4'}$ 6.5, 5'-H[a]) 3.26 (1 H, dd, J_{gem} 10.0, $J_{5'b,4'}$ 6.0, 5'-H[b])	4.53 (1 H, ddd, $J_{4',3'}$ 3.2, $J_{4',5'a}$ 6.5, $J_{4',5'b}$ 6.0)	4.49 (1 H, t, $J_{3',2'}$ 2.5, $J_{3',4'}$ 3.2)	5.36 (1 H, dd, $J_{2',1'}$ 5.5, $J_{2',3'}$ 2.5)	6.12 (1 H, d, $J_{1',2'}$ 5.5)	1.51 (3 H, s)	4.70 (1 H, s)	7.24–7.38 (15 H, ArH)
6	2.46 (1 H, dd, J_{gem} 10.4, $J_{5'a,4'}$ 9.6, 5'-H[a]) 3.37 (1 H, dd, J_{gem} 10.4, $J_{5'b,4'}$ 5.6, 5'-H[b])	4.56 (1 H, dd, $J_{4',5'a}$ 9.6, $J_{4',5'b}$ 5.6)	4.60 (1 H, br s, overlapped with 6-H)	5.37 (1 H, d, $J_{2',1'}$ 4.8)	6.08 (1 H, d, $J_{1',2'}$ 4.8)	1.54 (3 H, s)	4.60 (1 H, overlapped with 3'-H)	7.24–7.38 (15 H, ArH)
7	2.81 (1 H, dd, J_{gem} 11.0, $J_{5'a,4'}$ 8.0, 5'-H[a]) 3.10 (1 H, dd, J_{gem} 11.0, $J_{5'b,4'}$ 4.0, 5'-H[b])	4.61 (1 H, dt, $J_{4',3'}$ 3.5, $J_{4',5'a}$ 8.0, $J_{4',5'b}$ 4.0)	4.82 (1 H, dd, $J_{3',2'}$ 1.5, $J_{3',4'}$ 3.5)	5.64 (1 H, dd, $J_{2',1'}$ 5.5, $J_{2',3'}$ 1.5)	6.43 (1 H, d, $J_{1',2'}$ 5.5)	1.78 (3 H, s)	7.86 (1 H, s)	7.22–7.31 (15 H, ArH)
8	3.22 (1 H, dd, J_{gem} 12.0, $J_{5'a,4'}$ 5.5, 5'-H[a]) 3.25 (1 H, dd, J_{gem} 12.0, $J_{5'b,4'}$ 5.5, 5'-H[b])	4.46 (1 H, dt, $J_{4',3'}$ 2.5, $J_{4',5'a}$ = $J_{4',5'b}$ 5.5)	4.84 (1 H, br s)	5.68 (1 H, d, $J_{2',1'}$ 5.6)	6.44 (1 H, d, $J_{1',2'}$ 5.6)	1.81 (3 H, s)	7.79 (1 H, s)	5.14 (1 H, br s, 5'-OH)
9	3.53 (1 H, dd, J_{gem} 11.4, $J_{5'a,4'}$ 2.2, 5'-H[a]) 3.65 (1 H, dd, J_{gem} 11.4, $J_{5'b,4'}$ 2.0, 5'-H[b])	4.53 (1 H, dt, $J_{4',3'}$ 7.6, $J_{4',5'a}$ 2.2, $J_{4',5'b}$ 2.0)	4.64 (1 H, d, $J_{3',2'}$ 5.2, $J_{3',4'}$ 7.6)	4.76 (1 H, dd, $J_{2',1'}$ 2.8, $J_{2',3'}$ 5.2)	6.27 (1 H, d, $J_{1',2'}$ 2.8)	1.36 (3 H, s)	7.69 (1H, d, J 1.2)	7.27–7.45 (15 H, m, ArH), 8.57 (1 H, s, N^3-H)
10	3.67 (1 H, dd, J_{gem} 12.6, $J_{5'a,4'}$ 2.6, 5'-H[a]) 3.83 (1 H, dd, J_{gem} 12.6, $J_{5'b,4'}$ 2.8, 5'-H[b])	4.35 (1 H, dt, $J_{4',3'}$ 6.7, $J_{4',5'a}$ 2.6, $J_{4',5'b}$ 2.8)	4.68 (1 H, dd, $J_{3',2'}$ 5.0, $J_{3',4'}$ 6.7)	4.98 (1 H, dd, $J_{2',1'}$ 4.0, $J_{2',3'}$ 5.0)	6.19 (1 H, d, $J_{1',2'}$ 4.0)	1.75 (3 H, s)	7.90 (1 H, d, J 1.1)	5.56 (1 H, t, 5'-OH), 11.44 (1 H, s, N^3-H)

[a] Chemical shifts (δ) are given in ppm and J-values in Hz. [b] The spectra of the alcohols **3a** and **4a** were measured at 500 MHz, and those of all the other compounds at 200 MHz. [c] The spectra of compounds **3a**, **4a**, **3b**, **4b**, **8** and **10** were recorded in $(CD_3)_2SO$, and those of the other compounds in $CDCl_3$.



Scheme 1

compound **4a** proceeded more smoothly at room temperature to give the (5*R*,6*S*) analogue **6** quantitatively. Similar synthesis and 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.[9] This research demonstrated the easy repair of 5,6-bromohydrins of 1,3-dimethylthymine as well as those of thymidine by treatment with heat, sunlight or a radical initiator, 2,2′-azoisobutyronitrile.[9] In contrast with these results, our initial trials of debromohydrination of compounds **3a** and **4a** to 2,2′-anhydro-1-(3′-bromo-3′-deoxy-5-*O*-trityl-β-D-arabino-furanosyl)thymine **7** by these means were all unsuccessful, no change having been observed. Clearly, the present 2,2′-cyclized form, **3a** or **4a**, is unable to generate a bromo radical.[9] Deoxygenation of epoxides **5** and **6** with the use of triphenylphosphine was therefore tried and gave compound **7** in

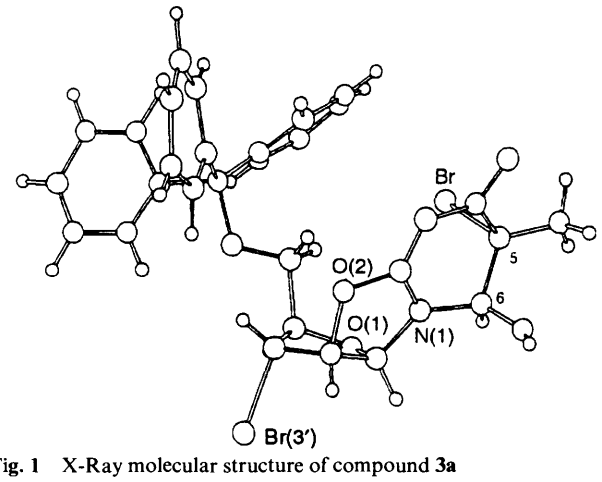


Fig. 1 X-Ray molecular structure of compound **3a**

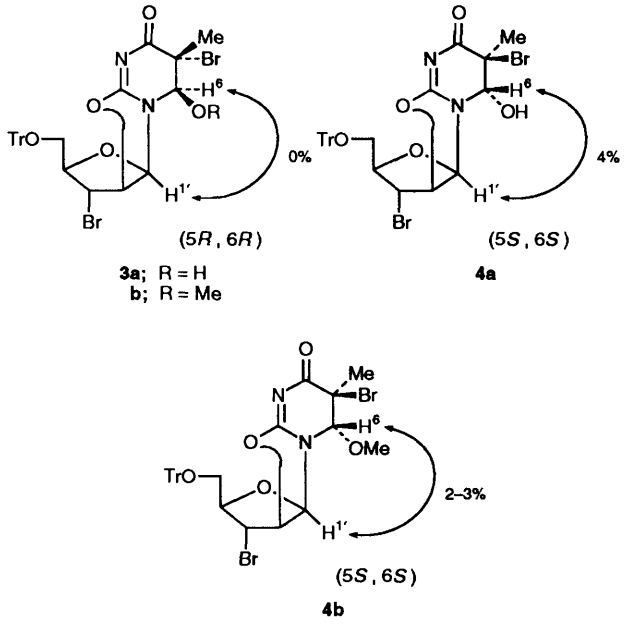


Fig. 2 ^{1}H NMR NOE measurements on compounds **3a**, **b** and **4a**, **b**

moderate yields. Selected experiments are given in the Experimental section [experiment (A-1) and (A-2)]. In view of the rather unacceptable yields of compound **7** from substrates **5** and **6**, the common debromohydrination of compounds **3** by using zinc powder in dimethylformamide (DMF)–AcOH or DMF–MeOH (room temperature) was tried. However, this reagent proved to be inappropriate, since the unsaturated furanose **1** was reproduced, probably due to attack of zinc on the 3'-bromo group to cause eliminative ring opening (process **2** ⟶ **1**). It was finally found that compounds **3a** and **4a** can be smoothly converted into compound **7** with the use of a combination of Ph_3P and sodium hydrogen carbonate. Thus, treatment of compound **3a** with 1.9 mol equiv. of Ph_3P in the presence of an excess of $NaHCO_3$ gave compound **7** in 80% yield [experiment (B-1)], while similar treatment of compound **4a** gave compound **7** in 86% yield after a shorter reaction time [experiment (B-2)]. Application of the same reaction to an equimolar mixture of isomers **3a** and **4a** afforded compound **7** in 65% yield when a 3-fold excess of Ph_3P was used [experiment (B-3)]. The reason for the retardation of the reaction and the rather low yield in this case is unclear at present. However, this point suggested a possible intermolecular association between isomers **3a** and **4a** through hydrogen bonding by the 6-hydroxy group of compound **3a** or **4a**, sterically disturbing the access of the bulky triphenylphosphine. Accordingly, we decided to prepare some analogues of the alcohols **3a** and **4a** carrying a 6-methoxy or 6-acetoxy group instead of the 6-hydroxy group and to examine their chemical behaviour toward triphenylphosphine. Additionally, the difference in electronegativity of alkoxy and ester oxygens might shed some light on the mechanism. Thus, compound **1** was treated with 2 mol equiv. of NBA in methanol containing acetone to afford (5*R*,6*R*)-2,2'-anhydro-5-bromo-1-(3'-bromo-3'-deoxy-5'-*O*-trityl-β-D-arabinofuranosyl)-6-methoxy-5,6-dihydrothymine **3b** and (5*S*,6*S*)-2,2'-anhydro-5-bromo-1-(3'-bromo-3'-deoxy-5'-*O*-trityl-β-D-arabinofuranosyl)-6-methoxy-5,6-dihydrothymine **4b** in 48 and 36% yield, respectively. The UV and ^{1}H NMR data of structural importance are quite similar to those for the parent alcohols **3a** and **4a**. The stereochemistry at C-5 and C-6 of the base was deduced from a comparison of the results of ^{1}H NMR nuclear Overhauser effect (NOE) measurements of compounds **3a**, **b** and **4a**, **b** (Fig. 2): 5*R*,6*R*-compounds **3a**, **b** showed no NOE between 1'-H and 6-H, while 5*S*,6*S*-compounds **4a** and **4b** showed the corresponding NOE of 4 and 2–3%, respectively. A molecular-model study also indicated the closer proximity of 1'-H and 6-H in the (5*S*,6*S*) series. Similarly, treatment of compound **1** with NBA in the presence of 2 mol equiv. of acetic acid gave (5*R*,6*R*)-6-acetoxy-5-bromo-2,2'-anhydro-1-(3'-bromo-3'-deoxy-5'-*O*-trityl-β-D-arabinofuranosyl)-5,6-dihydrothymine **3c** and its (5*S*,6*S*)-*trans* analogue **4c** in similar yields. The latter compound was spectroscopically identical with a product obtained by acetylation of the alcohol **4a** and hence compound **3c** should have the (5*R*,6*R*)-*trans* structure. The notably deshielded 6-H signals in the ^{1}H NMR spectra of these compounds confirmed the presence of the acetoxy group at C-6. Interestingly, the (5*S*,6*S*)-*trans* isomers **4a–c** are all less polar than the corresponding 5*R*,6*R* counterparts **3a–c** in TLC (see Experimental section). In the acetylation of the alcohol **4a**, another product, **4c'**, having a polarity between those of acetates **3c** and **4c** was obtained. On the basis of elemental analysis, UV and ^{1}H NMR data (Experimental section) compound **4c'** seems to be a structural isomer of acetates **3c** and **4c**.* Attempted X-ray analysis failed owing to decomposition of compound **4c'** on X-ray irradiation and hence its structural elucidation was abandoned.

Debromomethoxylation of the ethers **3b** and **4b** with the use of Ph_3P–$NaHCO_3$ proceeded extremely rapidly (10–20 min) to give an excellent yield of compound **7** in each case. Finally, one-pot synthesis of compound **7** from compound **1** *via* the ethers **3b** and **4b** was tried [experiment (C-3)] to give compound **7** in 85% overall yield. Also, one-pot synthesis of compound **7** *via* acetates **3c** and **4c** was successful [experiment (D-1)], giving compound **7** in 81% yield. Compound **7** could be easily deprotected to 2,2'-anhydro-1-(3'-bromo-3'-deoxy-β-D-arabinofuranosyl)thymine **8** with the use of boron trifluoride–diethyl ether or 80% acetic acid in contrast to compound **2**, which tended to decompose or/and regenerate unsaturated substrate **1** when treated with 80% acetic acid.[7] In these repair reactions, it is imperative to intercept the released hydrogen bromide molecules instantaneously by $NaHCO_3$ or other appropriate bases. Otherwise, hydrogen bromide attacks the 2,2'-anhydro bridge to cause ring opening and/or 5'-deprotection. Thus, the reaction of compound **3a** with Ph_3P in the absence of sodium hydrogen carbonate gave 1-(2,3-dibromo-2,3-dideoxy-5-*O*-trityl-β-D-ribofuranosyl)thymine **9** as a major product, together with

* On the basis of the upfield shift of the 6-H signal (δ 5.98) of compound **4c'** as compared with that of compounds **3c** and **4c** (δ 6.05 and 6.02, respectively), we propose compound **4c'** to be a *trans*-5-acetoxy-6-bromo analogue formed from acetate **4c** through an ortho-ester intermediate.

compound **8**. Compound **9** was deprotected to crystalline 1-(2,3-dibromo-2,3-dideoxy-β-D-ribofuranosyl)thymine **10** for analysis. Compound **7** was converted into the known 1-(2,3-anhydro-5-*O*-trityl-β-D-lyxofuranosyl)thymine **11**[7,10] and its 2-*O*-methylthymine analogue **12**[7] in 93 and 85% yield, respectively: these results are far better than those obtained starting from compound **2**.[7]

Experimental

M.p.s were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. UV spectra were measured on a JASCO Model V-560 spectrophotometer. The 200 MHz ^{1}H NMR spectra of compounds **3b, c**, **4b, c**, **5–10** were recorded on a GEMINI-200 FT NMR spectrometer, and the 500 MHz ^{1}H NMR spectra of compounds **3a**, **4a** and **4c′** on a JEOL-JNM-GS500 FT NMR spectrometer in the laboratory of the Daiichi Seiyaku Co., Ltd. *J*-Values are in Hz. Elemental analyses were conducted using a Perkin-Elmer 240B elemental analyser. For preparative-scale thick-layer chromatography (PLC), glass plates coated with a 2 mm thick layer of Wakogel B-5F silica gel were used after activation at 100 °C for 10–12 h. All evaporations were carried out under reduced pressure at or below 40 °C.

Crystallography of Compound **3a**.—A single crystal (0.12 × 0.20 × 0.68 mm), which was grown from acetone solution, was used for the unit-cell determinations and the data collections of a Rigaku AFC5S four-circle diffractometer, with graphite-monochromated Mo-Kα radiation (λ = 0.710 69 Å). This crystal was orthorhombic, space group $P2_12_12_1$, Z = 4 with a = 14.918(8), b = 18.560(6), c = 10.962(6) Å, V = 3035(2) Å^3, and D_{calc} = 1.533 g cm^{-3}. The computer program used was TEXSAN,[11] the structure was solved by direct methods (MITHRIL),[12] and the non-hydrogen atoms were refined isotropically. The hydrogen atoms were included in the structure-factor calculations in idealized positions. The final *R*-factor after the full-matrix least-squares refinement was 0.091 for 1084 observed reflections. The PLUTO[13] drawing of compound **3a** is shown in Fig. 1.

(5R,6R)-2,2′-*Anhydro*-5-*bromo*-1-(3′-*bromo*-3′-*deoxy*-5′-O-*trityl*-β-D-*arabinofuranosyl*)-6-*hydroxy*-5,6-*dihydrothymine* **3a** *and* (5S,6S)-2,2′-*Anhydro*-5-*bromo*-1-(3′-*bromo*-3′-*deoxy*-5′-O-*trityl*-β-D-*arabinofuranosyl*)-6-*hydroxy*-5,6-*dihydrothymine* **4a**.—To a stirred, ice-cold solution (or suspension) of compound **1** (2.0 g, 4.28 mmol) in a mixture of acetone (8.0 cm^3) and water (2.0 cm^3) was added NBA (717 mg, 5.2 mmol). After the mixture had been stirred for 5 h at 0 °C, more NBA (700 mg, 5.1 mmol) was added and the mixture was stirred at 0 °C for a further 35 h to give a TLC-pure solid precipitate, which was more polar than substrate **1** in TLC [silica; $CHCl_3$–EtOAc (1:1)]. The solid was collected by suction and was recrystallized from MeOH to give *compound* **3a** (1.45 g, 53%), which gradually decomposed at between 145 and 167 °C; λ_{max}(MeOH)/nm (ε) 233.7 (6000, infl.) and 250.4 (3500, infl.) (Found: C, 54.0; H, 4.2; N, 4.4. $C_{29}H_{26}Br_2N_2O_5$ requires C, 54.22; H, 4.08; N, 4.36%).

TLC monitoring of the filtrate separated from the solid showed another, less polar, product together with a negligible amount of *R,R*-compound **3a** and no starting material. The filtrate was evaporated and the residue was partitioned between EtOAc (30 cm^3) and water (10 cm^3). The separated organic layer was dried over sodium sulfate, and evaporated, and the residue was left with MeOH (4 cm^3) to give TLC-homogeneous crystals, which were collected, and recrystallized from MeOH to afford *compound* **4a** (914 mg, 32%), which gradually melted between 120 and 129 °C; λ_{max}(MeOH)/nm (ε) 232.2 (15 200, infl.) and 250.3 (10 400, infl.) (Found: C, 53.6; H, 4.4; N, 4.1. $C_{29}H_{26}Br_2N_2O_5$·MeOH requires C, 53.43; H, 4.48; N, 4.15%).

(5R,6R)-2,2′-*Anhydro*-5-*bromo*-1-(3′-*bromo*-3′-*deoxy*-5′-O-*trityl*-β-D-*arabinofuranosyl*)-6-*methoxy*-5,6-*dihydrothymine* **3b** *and* (5S,6S)-2,2′-*Anhydro*-5-*bromo*-1-(3′-*bromo*-3′-*deoxy*-5′-O-*trityl*-β-D-*arabinofuranosyl*)-6-*methoxy*-5,6-*dihydrothymine* **4b**.—To a stirred, ice-cold solution of compound **1** (1.0 g, 2.1 mmol) in a mixture of acetone (4 cm^3) and MeOH (1 cm^3) was added NBA (580 mg, 4.2 mmol). After 4 h, the mixture was stirred at room temperature for 2 h. TLC monitoring at this stage showed that the starting material was consumed and two less polar products had been formed. The mixture was evaporated and the residue was partitioned between EtOAc (30 cm^3) and water (10 cm^3). The separated organic layer was dried over sodium sulfate and evaporated, and the residue was fractionated on 2 sheets of silica plates [20 × 20 cm; $CHCl_3$–EtOAc (5:1), developed twice] to give, from the polar band *compound* **3b** (660 mg, 48%) as crystals, m.p. 214–215 °C (from EtOAc): λ_{max}(MeOH)/nm (ε) 230.4 (14 000, infl.) and 245.6 (9600, infl.) (Found: C, 55.1; H, 4.3; N, 4.05. $C_{30}H_{28}Br_2N_2O_5$ requires C, 54.89; H, 4.30; N, 4.27%).

Elution of the less polar fraction with acetone gave *compound* **4b** as a homogeneous foam (495 mg, 36%); λ_{max}(MeOH)/nm (ε) 230.6 (11 000, infl.) and 246.4 (6400, infl) (Found: C, 54.93; H, 4.53; N, 4.05%).

(5R,6R)-6-*Acetoxy*-2,2′-*anhydro*-5-*bromo*-1-(3′-*bromo*-3′-*deoxy*-5′-O-*trityl*-β-D-*arabinofuranosyl*)-5,6-*dihydrothymine* **3c** *and* (5S,6S)-6-*Acetoxy*-2,2′-*anhydro*-5-*bromo*-1-(3′-*bromo*-3′-*deoxy*-5′-O-*trityl*-β-D-*arabinofuranosyl*)-5,6-*dihydrothymine* **4c**.—NBA (1.11 g, 8.06 mmol) was added to a stirred, ice-cooled solution of compound **1** (2.0 g, 4.30 mmol) in a mixture of acetone (15 cm^3) and acetic acid (0.50 cm^3, 8.77 mmol). After 5 h, more NBA (160 mg, 1.16 mmol) was added. After 23 h, further NBA (106 mg, 0.77 mmol) was added (total 1.38 g, 9.99 mmol) and the mixture was stirred for an additional 25 h under ice-cooling. The solvent was evaporated off and the residue was partitioned between $CHCl_3$ (40 cm^3) and water (10 cm^3). The separated organic layer was dried over sodium sulfate and evaporated, and the residue was chromatographed on a silica gel column (3.5 × 40 cm) with $CHCl_3$–EtOAc (5:1) to give, from the faster running fractions, *compound* **4c** (1.032 g, 35.1%) as crystals, m.p. 180–182 °C (after recrystallization from EtOAc); λ_{max}(MeOH)/nm (ε) 230.4 (13 500, infl.) and 244.8 (9300, infl.); ν_{max}(KBr)/cm^{-1} 1770 (6-acetoxy) (Found: C, 54.4; H, 4.3; N, 3.9. $C_{31}H_{28}Br_2N_2O_6$·$\frac{1}{3}$EtOAc requires C, 54.41; H, 4.33; N, 3.93%).

The slower running fractions gave *compound* **3c** (1.037 g, 35.3%) as crystals, m.p. 212–213 °C (after recrystallization from MeOH at room temperature); λ_{max}(MeOH)/nm (ε) 231.2 (17 500, infl.) and 243.6 (12 600, infl.); ν_{max}(KBr)/cm^{-1} 1780 (Found: C, 54.3; H, 4.1; N, 4.1. $C_{31}H_{28}Br_2N_2O_6$ requires C, 54.40; H, 4.12; N, 4.09%).

Acetylation of Alcohol **4a**.—To a solution of compound **4a** (methanolate) (200 mg, 0.3 mmol) in pyridine (1 cm^3) was added acetic anhydride (0.13 cm^3, 1.4 mmol) and the mixture was stirred at room temperature overnight. TLC monitoring [silica; $CHCl_3$–EtOAc (3:1 or 5:1)] showed the formation of two less polar, major products, the faster running of which coincided with acetate **4c** in terms of TLC mobility. The mixture was treated with MeOH (1 cm^3) at room temperature for 1 h, evaporated, and repeatedly co-evaporated with MeOH. The residue was partitioned between EtOAc (15 cm^3) and water (5 cm^3). The separated organic layer was dried over sodium sulfate and evaporated, and the residue was fractionated on a silica plate [20 × 20 cm; $CHCl_3$–EtOAc (3:1), developed 3

times] to give, from the least polar fraction, compound **4c** (63 mg, 29.8%), identical with an authentic sample in terms of IR and UV spectroscopic data.

The more polar fraction gave *compound* **4c'** (80 mg, 39.5%) as crystals, m.p. 214–216 °C (after recrystallization from MeOH at room temperature); λ_{max}(MeOH)/nm (ε) 229 (13 400); δ_H($CDCl_3$) 1.68 (3 H, s, 5-Me), 2.18 (3 H, s, AcO), 3.07 (1 H, dd, J_{gem} 10.33, $J_{5'a,4'}$ 7.15, 5'-H^a), 3.28 (1 H, dd, J_{gem} 10.33, $J_{5'b,4'}$ 4.77, 5'-H^b), 4.50 (1 H, complex m, 4'-H), 4.60 (1 H, m, 3'-H), 5.40 (1 H, dd, $J_{2',3'}$ 1.59, $J_{2',1'}$ 4.77, 2'-H), 5.98 (1 H, s, 6-H), 5.99 (1 H, d, $J_{1',2'}$ 4.77, 1'-H) and 7.24–7.37 (15 H, m, ArH) (Found: C, 54.4; H, 4.1; N, 4.1%).

(5S,6R)-2,2'-*Anhydro*-1-(3'-*bromo*-3'-*deoxy*-5'-O-*trityl*-β-D-*arabinofuranosyl*)-5,6-*epoxy*-5,6-*dihydrothymine* **5**.—A mixture of the alcohol **3a** (500 mg, 0.78 mmol) and triethylamine (0.50 cm^3, 3.6 mmol) in acetone (8 cm^3) was heated to reflux for 5 h. After cooling, the solid precipitate of triethylamine hydrobromide was filtered off and the filter-cake was washed with a small volume of EtOAc. The filtrate was evaporated to give a gum, which was subjected to PLC [silica; 20 × 20 cm; $CHCl_3$–EtOAc (3:1), developed twice] to afford *epoxide* **5** (358 mg, 82%) as a homogeneous foam; λ_{max}(MeOH)/nm (ε) 232 (18 500, sh) (Found: C, 62.25; H, 4.5; N, 4.7. $C_{29}H_{25}BrN_2O_5$ requires C, 62.04; H, 4.49; N, 4.99%).

(5R,6S)-2,2'-*Anhydro*-1-(3'-*bromo*-3'-*deoxy*-5'-O-*trityl*-β-D-*arabinofuranosyl*)-5,6-*epoxy*-5,6-*dihydrothymine* **6**.—A mixture of the alcohol **4a** (623 mg, 0.92 mmol) and triethylamine (0.58 cm^3, 4.2 mmol) in acetone (12 cm^3) was stirred at room temp. for 1 h. The precipitate of triethylamine salt was filtered off and the filtrate was evaporated. The residue was partitioned between EtOAc (13 cm^3) and water (3 cm^3). The separated organic layer was treated with Norit and evaporated to give a crystalline solid, which was again dissolved in acetone and then the solvent was removed under reduced pressure to afford a foam. Trituration of the foam with MeOH (4 cm^3) gave pure crystals (453 mg). A further crop (58 mg) of *compound* **6** was obtained from the filtrate (total 511 mg, 99%); λ_{max}(MeOH)/nm (ε) 231.6 (8400, sh) (Found: C, 62.0; H, 4.5; N, 5.0%).

2,2'-*Anhydro*-1-(3'-*bromo*-3'-*deoxy*-5'-O-*trityl*-β-D-*arabinofuranosyl*)*thymine* **7**.—(*A-1*) *Deoxygenation of compound* **5**. To a solution of compound **5** (358 mg, 0.64 mmol) in EtOAc (8 cm^3) was added Ph_3P (184 mg, 0.70 mmol) and the mixture was heated at 80 °C for 20 h. After cooling, the mixture was evaporated and the residue was fractionated on a silica plate [20 × 20 cm; $CHCl_3$–EtOAc (3:1)] to give, from the major band, *compound* **7** (166 mg, 48%) as crystals, m.p. 210–212 °C; λ_{max}(MeOH)/nm (ε) 225 (16 200, infl.) and 253 (7600, infl.) (Found: C, 63.9; H, 4.5; N, 5.2. $C_{29}H_{25}BrN_2O_4$ requires C, 63.86; H, 4.62; N, 5.14%).

(*A-2*) *Deoxygenation of compound* **6**. A mixture of compound **6** (200 mg, 0.36 mmol) and Ph_3P (121 mg, 0.46 mmol) in EtOAc (5 cm^3) was heated to reflux for 14.5 h, during which time substrate **6** disappeared. The mixture was concentrated, and fractionated on a silica plate [20 × 20 cm; $CHCl_3$–EtOAc (1:1), developed twice] to give, from the major band, compound **7** (58 mg, 30%), identical with the above obtained product **7** in terms of IR, UV and ^{1}H NMR data.

(*B-1*) *Debromohydrination of compound* **3a**. To a vigorously stirred mixture of compound **3a** (642.4 mg, 1 mmol) and finely pulverized $NaHCO_3$ (227 mg, 2.7 mmol) in DMF (10 cm^3) was added Ph_3P (510 mg, 1.94 mmol). After 3.5 h, TLC showed 3 spots corresponding to Ph_3P=O, compound **7** and Ph_3P. The inorganic salts were filtered off and the filtrate was evaporated. The residue in $CHCl_3$ (10 cm^3) was filtered with Norit, the filtrate was concentrated, and the residue was fractionated on silica plates [20 × 20 cm, 2 sheets; $CHCl_3$–EtOAc (1:1), developed 3 times] to give, from the most polar fraction, compound **7** (436 mg, 80%), identical with an authentic specimen in every respect.

(*B-2*) *Debromohydration of compound* **4a**. To a vigorously stirred mixture of compound **4a** (methanolate) (100 mg, 0.148 mmol) and finely ground $NaHCO_3$ (34 mg, 0.4 mmol) in DMF (1.5 cm^3) was added Ph_3P (58 mg, 0.22 mmol). After 70 min, the mixture was worked up as in experiment (B-1) to give compound **7** (69 mg, 86%) after PLC [silica, 20 × 20 cm; $CHCl_3$–EtOAc (3:1)].

(*B-3*) *Debromohydration of a mixture of alcohols* **3a** *and* **4a**. Triphenylphosphine (115 mg, 0.44 mmol) was added to a stirred mixture of compounds **4a** (methanolate) (100 mg, 0.148 mmol), **3a** (95.1 mg, 0.148 mmol) and fine $NaHCO_3$ powder (67.2 mg, 0.8 mmol) in DMF (3.0 cm^3). After 4 h, the inorganic salts were filtered off and the filtrate was evaporated. The residue was partitioned between EtOAc (20 cm^3) and water (7 cm^3). The separated organic layer was dried over sodium sulfate and concentrated, and the residue was fractionated on a silica plate [20 × 20 cm; $CHCl_3$–EtOAc (1:1)] to give compound **7** (105 mg, 65%), identical with the above obtained authentic sample.

(*C-1*) *Debromomethoxylation of the ether* **3b**. A vigorously stirred mixture of compound **3b** (200 mg, 0.305 mmol) and powdered $NaHCO_3$ (69 mg, 0.82 mmol) in DMF (3.1 cm^3) was treated with Ph_3P (152 mg, 0.58 mmol). After 10 min, the mixture was worked up as above to give compound **7** (142 mg, 85.3%) after PLC [silica, 20 × 20 cm; $CHCl_3$–EtOAc (3:1)].

(*C-2*) *Debromomethoxylation of the ether* **4b**. A stirred mixture of compound **4b** (300 mg, 0.46 mmol) and finely pulverized $NaHCO_3$ (77 mg, 0.92 mmol) in DMF (4.0 cm^3) was treated with Ph_3P (180 mg, 0.69 mmol) under argon for 20 min and was then worked up as above to give compound **7** (202 mg, 81%).

(*C-3*) *One-pot synthesis from compound* **1** via *ethers* **3b** *and* **4b**. A mixture of compound **1** (200 mg, 0.42 mmol) and NBA (116 mg, 0.84 mmol) in a mixture of EtOAc (0.8 cm^3) and MeOH (0.1 cm^3) was stirred overnight. TLC monitoring indicated that substrate **1** was completely consumed and that compounds **3b** and **4b** had formed. After addition of EtOAc (2 cm^3) and powdered $NaHCO_3$ (106 mg, 1.26 mmol), Ph_3P (132 mg, 0.50 mmol) was added in 3 portions to the vigorously stirred mixture. After 1 h, the inorganic material was filtered off. The filtrate was directly partitioned between EtOAc (20 cm^3) and water (5 cm^3), and the separated organic layer was worked up as above to give compound **7** (195 mg, 85.2%) after PLC [silica, 20 × 20 cm; $CHCl_3$–EtOAc (1:1)].

(*D-1*) *One-pot synthesis from compound* **1** via *acetates* **3c** *and* **4c**. To a stirred, ice-cold solution of compound **1** (500 mg, 1.07 mmol) and acetic acid (0.3 cm^3, 2.58 mmol) in acetone (10 cm^3) was added NBA (350 mg, 2.54 mmol). The reaction mixture was allowed to warm up gradually to room temperature during 4 h before being evaporated, and then co-evaporated with acetone a couple of times, and the residue was taken up into EtOAc (15 cm^3). Finely powdered $NaHCO_3$ (500 mg, 5.95 mmol) was added and the mixture was vigorously stirred to remove the residual acetic acid. After 30 min, Ph_3P (400 mg, 1.53 mmol) was added and the mixture was stirred for another 1.5 h. The inorganic material was filtered off and the filtrate was evaporated. The residue was fractionated on a silica plate [20 × 20 cm; $CHCl_3$–EtOAc (3:1)] and the most polar fraction was eluted with acetone to give compound **7** (472 mg, 81%) after crystallization from MeOH.

2,2'-*Anhydro*-1-(3'-*bromo*-3'-*deoxy*-β-D-*arabinofuranosyl*)-*thymine* **8**.—(*A*). To a stirred solution of compound **7** (500 mg, 0.917 mmol) in chloroform (20 cm^3) was added boron

trifluoride–diethyl ether (0.06 cm^3, 0.48 mmol). After 2 h, more boron trifluoride–diethyl ether (0.02 cm^3, 0.16 mmol) was added and the mixture was stirred for additional 1 h. The mixture was thoroughly evaporated and the residue, dissolved in acetone, was applied to a silica plate (20 × 20 cm). After development with $CHCl_3$–MeOH (85:15), the desired fraction was eluted with acetone and recrystallized from the same solvent to give *compound* **8** (187 mg, 67.3%), m.p. 224–226 °C; λ_{max}(MeOH)/ nm (ε) 229.0 (2900) and 252.4 (5800) (Found: C, 39.75; H, 3.5; N, 9.3. $C_{10}H_{11}BrN_2O_4$ requires C, 39.62; H, 3.60; N, 9.24%).

(*B*). A solution of compound **7** (200 mg, 0.37 mmol) in 80% acetic acid (40 cm^3) was left at room temperature for 40 h and was then evaporated below 35 °C. The residue was repeatedly co-evaporated with MeOH to remove the residual acetic acid. The obtained solid residue was digested with diethyl ether (20 cm^3) and the sparingly soluble solid was collected by suction. The filter-cake was washed with diethyl ether (5 × 2 cm^3), dried over silica gel under high vacuum, and recrystallized from acetone to give compound **8** (76 mg, 68%), identical with the above obtained product in terms of mixed m.p. and IR spectroscopy.

Debromohydrination of Compound **3a** *in the Absence of* $NaHCO_3$.—To a suspension of the alcohol **3a** (200 mg, 0.31 mmol) in EtOAc (8 cm^3) was added Ph_3P (87 mg, 0.33 mmol). The mixture gradually became clear. After 3 h, the mixture was concentrated and subjected to PLC [silica, 20 × 20 cm; $CHCl_3$–MeOH (9:1), developed twice] to give, from the most polar fraction, a tiny amount of compound **8**, which was identical with an authentic sample by IR and UV spectroscopy after crystallization from acetone.

The intermediate fraction was eluted with acetone to give compound **7** (23 mg, 14%), identical with an authentic sample after recrystallization from EtOAc.

The highly mobile fraction was again fractionated on a silica plate [10 × 20 cm; $CHCl_3$–EtOAc (3:1)] to give dibromide **9** (85 mg, 44%) as a homogeneous foam; λ_{max}(MeOH)/nm 266 (ε 2600). Compound **9** was analysed after deprotection to compound **10**.

2′,3′-*Dibromo*-3′-*deoxythymidine* **10**.—A stirred solution of compound **9** (111 mg, 0.18 mmol) in $CHCl_3$ (5 cm^3) was cooled to −10 °C and boron trifluoride–diethyl ether (0.01 cm^3, 0.08 mmol) was added. After the mixture had been left at 0 °C for 20 h, the precipitate was collected by suction, washed with $CHCl_3$, and recrystallized from MeOH to give *compound* **10** (40 mg, 59%), m.p. 206–208 °C; λ_{max}(MeOH)/nm 265 (ε 12 100) (Found: C, 31.3; H, 3.7; N, 6.95. $C_{10}H_{12}Br_2N_2O_4 \cdot \frac{1}{2}$MeOH requires C, 31.52; H, 3.53; N, 7.00%).

Conversion of Bromide **7** *into* 1-(2,3-*Anhydro*-5-O-*trityl*-β-D-*lyxofuranosyl*)*thymine* **11**.—To a stirred solution of compound **7** (150 mg, 0.275 mmol) in acetone (1.4 cm^3) was added 1 mol dm^{-3} NaOH (0.63 cm^3, 0.63 mmol). After 20 min, the mixture was neutralized with 1 mol dm^{-3} AcOH–EtOH and evaporated, and the residue was partitioned between EtOAc (20 cm^3) and water (7 cm^3). The separated organic layer was dried over sodium sulfate and concentrated to give compound **11** (146 mg, 93%) as the mono ethyl acetate solvate, identical with an authentic sample[7] in terms of IR and UV spectroscopic data.

Conversion of Bromide **7** *into* 1-(2,3-*Anhydro*-5-O-*trityl*-β-D-*lyxofuranosyl*)-2-O-*methylthymine* **12**.—To a stirred solution of compound **7** (200 mg, 0.366 mmol) in a mixture of acetone (1 cm^3) and MeOH (1 cm^3) was added NaOMe (60 mg, 1.1 mmol). After 2 h, further NaOMe (50 mg, 0.93 mmol) was added (total 2.03 mmol). After 2 h, TLC monitoring [silica; $CHCl_3$–MeOH (9:1)] showed that the starting material had disappeared and that a less polar product had formed with a negligible amount of a faster running by-product. The total product was neutralized with 1 mol dm^{-3} AcOH–EtOH, the mixture was evaporated, and the residue was partitioned between EtOAc (30 cm^3) and water (10 cm^3). The separated organic layer was dried over sodium sulfate and evaporated, and the residue was fractionated on a silica plate [20 × 20 cm; $CHCl_3$–MeOH (9:1), developed twice]. Elution of the major band with acetone gave compound **12** (155 mg, 85%) as a foam, identical with an authentic sample[7] in every respect.

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