Stereo-structures of Reaction Products of Thymidine Epoxides with Amines and L-Amino Acid Ethyl Esters

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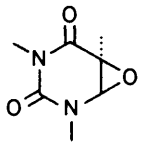
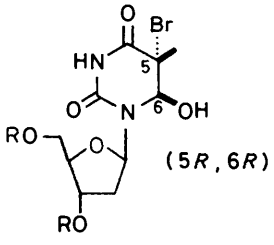
Reaction of thymidine epoxide (**6**) derived from (5*R*,6*R*)-*trans*-(+)-5-bromo-6-hydroxy-5,6-dihydrothymidine (**2**) with amines and L-amino acid ethyl esters afforded *cis* adduct (**10**) and that of the epoxide (**8**) derived from (5*S*,6*S*)-*trans*-(−)-5-bromo-6-hydroxy-5,6-dihydrothymidine (**4**) *cis* and *trans* adducts (**12**) and (**14**). The stereo-structures of the products were elucidated on the basis of isomerisation of the *trans* adducts to the *cis* adducts by using boron trifluoride–diethyl ether, *X*-ray analyses of (**10a**) and (**10d**), and the specific rotations of the compounds.

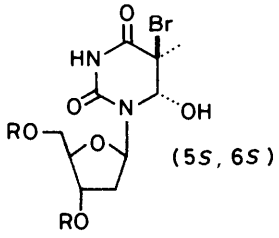
Much attention has been focussed on the oxidative damage effected by active oxygen species such as hydroxy radical, superoxide anion. hydrogen peroxide, and singlet oxygen or other oxidising biocomponents such as lipid hydroperoxides on nucleic acids and related compounds.[1–14] We are especially interested in the oxidation of pyrimidine bases such as thymine or thymidine. which is a component of deoxyribonucleic acid (DNA), in relation to mutagenesis, carcinogenesis, and aging. It has been reported that the *cis* isomers of thymine and thymidine glycols are released in human and rat urine as the result of the repair of oxidatively damaged DNA.[15] It should also be considered that the intermediates of these oxidation reactions may also react with nucleophiles such as amino acids or purine and pyrimidine nucleic acid components. We have studied the reaction of (±)-1,3-dimethylthymine epoxide (**1**) with several amines and L-amino acid derivatives as a model reaction for nucleic acid–protein cross-links and have



(±)-(**1**)

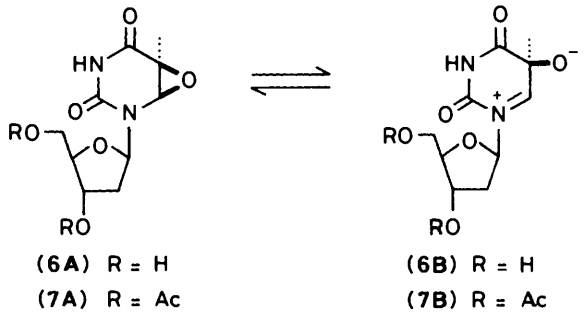


(**2**) R = H
(**3**) R = Ac



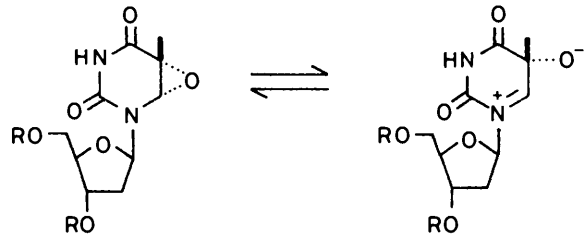
(**4**) R = H
(**5**) R = Ac

already reported both the stereo-structures of the cross-linked products of (**1**) with these nucleophiles[16–18] and the solvent effect in the reaction of (**1**) with amines.[19] Subsequently, we investigated the reaction of the thymidine epoxides (**6A**) and (**8A**), and/or their equivalents (**6B**) and (**8B**), which may be the precursors of the *cis*-thymidine



(**6A**) R = H
(**7A**) R = Ac

(**6B**) R = H
(**7B**) R = Ac



(**8A**) R = H
(**9A**) R = Ac

(**8B**) R = H
(**9B**) R = Ac

glycol mentioned above, together with amines, and L-amino acid ethyl esters. We briefly described the stereo-structures of the reaction products of thymidine epoxides with these nucleophiles.[20] The details of these results are the subject of this paper.

Reaction of thymidine with *N*-bromosuccinimide (NBS) in water with ice-cooling afforded (5*R*,6*R*)-*trans*-(+)-5-bromo-6-hydroxy-5,6-dihydrothymidine (**2**) and (5*S*,6*S*)-*trans*-(−)-5-bromo-6-hydroxy-5,6-dihydrothymidine (**4**) in 66 and 31% yield, respectively. These stereo-structures, including absolute configuration, were determined by direct comparison with authentic samples prepared by the bromine method[21] and confirmed by an *X*-ray analysis of (**2**) (see Figure 1). Next, we examined the cross-coupling reaction of the two bromohydrins (**2**) and (**4**) with nucleophiles. Reaction of (**6**) prepared *in situ* from (**2**) and triethylamine with achiral amines or L-amino acid derivatives in tetrahydrofuran (THF) at room temperature gave the cross-coupling products (**10**) in high yield.

Table 1. The results of reaction of (**6**) and (**7**) with nucleophiles[a]

Nucleophile	Product	Yield (%)	Reaction time	$[\alpha]_D$/° (*c* 1.0 in EtOH)
Ethylamine	(**10a**)	98.4	20.0 min	+20.1
Tryptamine	(**10b**)	95.0	20.0 h	+19.5
Morpholine(A)	(**10c**)	Quant.	20.0 h	+29.1
Aniline	(**10d**)	61.6	18.0 h	+37.3
Pro-OEt	(**10e**)	97.3	18.0 h	−25.1
Met-OEt	(**10f**)	96.6	24.0 h	+4.3
Phe-OEt	(**10g**)	81.0	24.0 h	+13.1
Trp-OEt	(**10h**)	98.7	24.0 h	+16.7
m-NO_2-aniline	(**10i**)	45.2	1.5 h	−2.1
p-NO_2-aniline	(**10j**)	63.4	18.5 h	+15.2
Morpholine(B)	(**11c**)	56.1	20.0 h	+15.7

[a] Carried out by using 1.5 equiv. of triethylamine and 20 equiv. of nucleophile except ethylamine, tryptamine, and morpholine(A) (each 2 equiv.).

Table 2. The results of reaction of (**8**) and (**9**) with nucleophiles[a]

Nucleophile	Product	Yield(%)	(Total yield)	Reaction time	$[\alpha]_D$/° (*c* 1.0 in EtOH)
Ethylamine	(**12a**)	53.3		20.0 min	−20.7
	(**14a**)	*b*			
Tryptamine	(**12b**)	53.4		16.0 h	−23.1
	(**14b**)	*b*			
Morpholine	(**12c**)	34.3	(81.0)	18.0 h	−1.1
	(**14c**)	46.7			+72.9
Aniline	(**12d**)	22.0	(62.8)	42.0 h	+26.3
	(**14d**)	40.8			+91.3
Pro-OEt	(**12e**)	31.7	(63.3)	40.0 h	−69.2
	(**14e**)	31.6			+12.3
Met-OEt	(**12f**)	32.1	(44.2)	45.0 h	−65.0
	(**14f**)	12.1			+10.5
Phe-OEt	(**12g**)	36.8	(60.9)	45.0 h	−43.9
	(**14g**)	24.1			+22.1
Trp-OEt	(**12h**)	31.5			−34.6
	(**14h**)	*b*		45.0 h	
Morpholine	(**13c**)	8.3	(33.7)	20.0 h	−4.5
	(**15c**)	25.4			+49.4

[a] Carried out using 1.5 equiv. of triethylamine and 20 equiv. of nucleophile except for ethylamine (2 equiv.). [b] Not isolable in a pure state because of its instability.

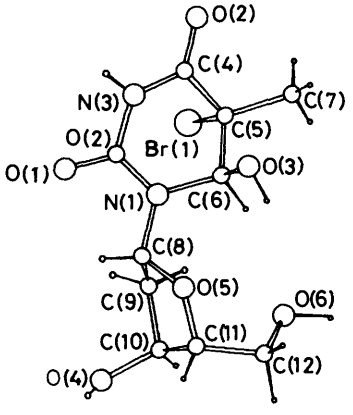


Figure 1. Molecular structure of compound (**2**)

In contrast, reaction of (**8**) prepared from (**4**) under similar experimental conditions gave two cross-coupling products (**12**) and (**14**); these results are summarized in Tables 1 and 2. respectively. Since some reactions with 2 equiv. of nucleophile were sluggish and gave products in low yield, 20 equiv. of nucleophile were used in several cross-coupling reactions (see footnote in Tables 1 and 2). In order to elucidate their stereo-structures, compounds (**10**), (**12**), and (**14**) were treated with boron trifluoride–diethyl ether (BF_3·Et_2O), conditions under which the *trans* to *cis* adduct isomerization occurs;[16–18] a mechanism for the latter has appeared in the literature.[18] Treatment of compounds (**10a—h**) with BF_3·Et_2O in THF at room temperature gave only recovery of starting material (see Table 3), a result which suggests they have *cis* orientation, with 5*S* and 6*S*; this was confirmed by *X*-ray analyses of (**10a**) and (**10d**) (see Figures 2 and 3). This finding supports an S_N2 mechanism for substitution of the bromine atom in (**2**) in

Table 3. The results of reaction of (**10**) with BF_3·Et_2O over 20 h

Starting material	BF_3·Et_2O (equiv.)	Product	Yield (%)
(**10a**)	1.2	(**10a**)	43.4
(**10b**)	1.2	(**10b**)	41.7
(**10c**)	1.2	(**10c**)	77.5
(**10d**)	1.2	(**10d**)	71.8
(**10e**)	1.2	(**10e**)	84.2
(**10f**)	1.2	(**10f**)	61.8
(**10g**)	1.2	(**10g**)	95.0
(**10h**)	1.2	(**10h**)	53.1

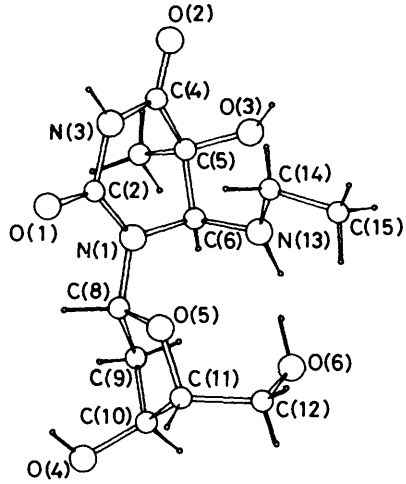


Figure 2. Molecular structure of compound (**10a**)

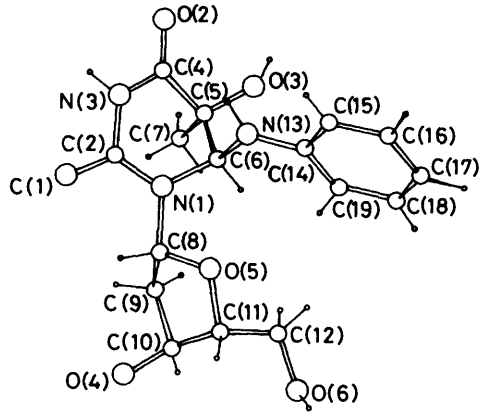
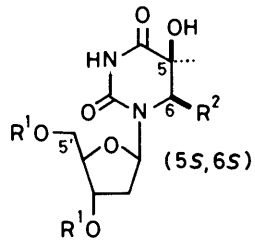
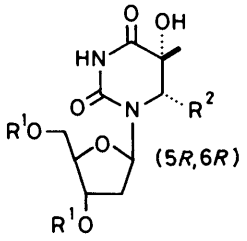


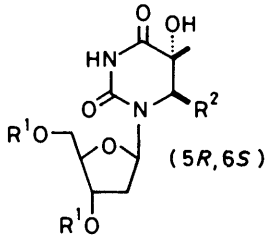
Figure 3. Molecular structure of compound (**10d**)



(10) R^1 = H
(11) R^1 = Ac

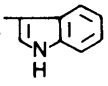


(12) R^1 = H
(13) R^1 = Ac



(14) R^1 = H
(15) R^1 = Ac

a; R^2 = NHEt

b; R^2 = NH(CH$_2$)$_2$ 

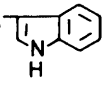
c; R^2 =

d; R^2 = NHPh

e; R^2 =

f; R^2 = NH–CH(CO$_2$Et)–(CH$_2$)$_3$SMe

g; R^2 = NH–CH(CO$_2$Et)–CH$_2$Ph

h; R^2 = NH–CH(CO$_2$Et)–CH$_2$ 

i; R^2 = NHC$_6$H$_4$NO$_2$–*m*

j; R^2 = NHC$_6$H$_4$NO$_2$–*p*

which there is a participation of the vicinal 6-hydroxy group.[22] Actual treatment of compounds (**12a—h**) with BF_3·Et_2O also resulted in recovery of starting material (see Table 4), compounds (**14c—g**) isomerised to give the products (**12c—f**) in poor yield (see Table 4) along with the unidentified products (**16c—e**) and (**16g**); compound (**12g**) was not obtained since (**14g**) decomposed under these conditions. These results suggest that (**12a—h**) are *cis* products and (**14c—g**) are the corresponding *trans* isomers. In a recent report we suggested that the 5*R*,6*R* diastereoisomers obtained from the reaction of (±)-1,3-dimethylthymine epoxide with L-amino acid ethyl esters[17] are more laevorotatory than the 5*R*,6*S* isomers. Therefore it seems reasonable to assume that compound (**12**), which is more laevorotatory, has a 5*R*,6*R* configuration whereas (**14**) has a 5*R*,6*S* configuration. Consequently, among the products derived from compound (**4**), the stereo-structures of the 5*R*,6*R*-*cis* products can be represented by formulae (**12a—h**) and those of the 5*R*,6*S*-*trans* products by formulae (**4c—g**), respectively. In addition, reaction of compound (**2**) with *m*-nitroaniline and *p*-nitroaniline under similar conditions gave compounds (**10i**) and (**10j**), respectively, the stereo-structures of which were assumed to have a 5*S*,6*S* configuration on the basis of results mentioned above (Table 1).

In order to investigate whether the 5′-hydroxy group participates in forming a single product in a cross-coupling reaction of compound (**2**) or not, the diacetyl bromohydrins (**3**) and (**5**) were prepared according to a literature method.[21] Reaction of (**3**) with morpholine, *via* (**7**) produced a single product (**11c**), which was identical with the acetylation product of (**10c**). On the other hand, reaction of (**5**) with morpholine, *via* (**9**), produced two cross-coupling products (**13c**) and (**15c**), which were identical with the acetylation products of (**12c**) and (**14c**), respectively. Therefore, it is clear that the 5′-hydroxy group, at least, does not participate in forming a single product, although the reason why (**6**) gives a sole product still remains unclear.

The present results may be useful in gaining a better understanding of the chemistry of the cross-linking products of nucleic acid with protein *in vivo*.

Table 4. The results of reaction of (**12**) and (**14**) with BF_3·Et_2O

Starting material	BF_3·Et_2O (equiv.)	Reaction time (h)	Product	Yield (%)
(**12a**)	1.2	20	(**12a**)	37.8
(**12b**)	1.2	20	(**12b**)	73.2
(**12c**)	1.2	20	(**12c**)	64.0
(**12d**)	1.2	20	(**12d**)	95.0
(**12e**)	1.2	20	(**12e**)	89.8
(**12f**)	1.2	20	(**12f**)	76.6
(**12g**)	1.2	20	(**12g**)	88.9
(**12h**)	1.2	20	(**12h**)	72.9
(**14c**)	1.2	20	(**12c**)	9.1
			(**16c**)	6.1
(**14d**)	1.2	20	(**12d**)	3.9
			(**16d**)	12.9
(**14e**)	1.2	20	(**12e**)	20.0
			(**16e**)	17.1
(**14f**)	2.2	40	(**12f**)	37.0
(**14g**)	1.2	20	(**16g**)	12.3

Table 5. Atomic parameters for non-hydrogen atoms in the thymidine bromohydrin (**2**). Estimated standard deviations are given in parentheses

Atom	*x*	*y*	*z*
Br(1)	0.267 5(1)	−0.054 1(1)	0.578 4(0)
N(1)	0.025 6(4)	0.094 3(3)	0.500 1(3)
C(2)	0.093 7(4)	0.197 2(4)	0.483 1(4)
N(3)	0.174 4(4)	0.233 2(3)	0.567 1(3)
C(4)	0.207 8(4)	0.170 9(4)	0.660 2(4)
C(5)	0.151 3(5)	0.046 3(4)	0.667 9(4)
C(6)	0.017 9(4)	0.046 8(4)	0.613 6(3)
C(7)	0.146 0(6)	−0.001 2(6)	0.786 5(4)
C(8)	−0.060 2(4)	0.051 0(4)	0.415 3(3)
C(9)	−0.034 5(4)	−0.075 9(4)	0.377 5(4)
C(10)	−0.166 2(5)	0.113 9(4)	0.336 3(3)
C(11)	−0.261 5(4)	−0.052 4(4)	0.415 9(4)
C(12)	−0.310 6(6)	0.128 8(5)	0.509 3(5)
O(1)	0.081 7(4)	0.257 2(3)	0.398 6(3)
O(2)	0.279 4(3)	0.211 5(3)	0.731 2(3)
O(3)	−0.058 0(3)	0.120 4(4)	0.681 9(3)
O(4)	−0.192 6(3)	−0.070 0(3)	0.225 3(2)
O(5)	−0.189 9(3)	0.048 4(2)	0.460 5(2)
O(6)	−0.203 1(4)	−0.184 2(4)	0.562 2(3)

Experimental

M.p.s were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. I.r. spectra were obtained on a Shimadzu IR-400 spectrometer and ^{1}H n.m.r. spectra in $(CD_3)_2SO$–D_2O at 200 MHz on a JEOL FX 200 spectrometer unless otherwise stated. The n.m.r. data are reported relative to

Table 6. Atomic parameters for non-hydrogen atoms in the thymidine–ethylamine adduct (**10a**). Estimated standard deviations are given in parentheses

Atom	*x*	*y*	*z*
N(1)	0.170 6(4)	0.152 0(0)	0.141 9(3)
C(2)	−0.0279	0.140 4(2)	0.008 1(4)
N(3)	−0.143 4(5)	0.215 1(2)	−0.076 9(3)
C(4)	−0.069 8(5)	0.301 4(2)	−0.046 4(4)
C(5)	0.170 8(6)	0.313 6(2)	0.071 6(4)
C(6)	0.247 3(6)	0.242 0(2)	0.215 4(4)
C(7)	0.327 8(7)	0.310 4(3)	−0.039 2(5)
C(8)	0.272 1(6)	0.072 4(2)	0.236 0(4)
C(9)	0.527 3(6)	0.073 5(3)	0.331 8(5)
C(10)	0.552 8(6)	0.002 8(3)	0.470 7(4)
C(11)	0.335 2(6)	0.015 4(2)	0.516 5(4)
C(12)	0.356 4(7)	0.072 9(3)	0.674 1(5)
N(13)	0.189 5(4)	0.259 3(2)	0.371 5(3)
C(14)	−0.056 2(6)	0.263 5(3)	0.345 2(4)
C(15)	−0.092 7(7)	0.274 9(3)	0.518 6(5)
O(1)	−0.108 5(5)	0.066 8(2)	−0.040 8(4)
O(2)	−0.190 2(4)	0.363 8(2)	−0.119 5(3)
O(3)	0.198 6(5)	0.395 7(2)	0.160 7(3)
O(4)	0.575 2(5)	−0.085 2(2)	0.414 0(4)
O(5)	0.170 3(4)	0.054 3(2)	0.366 6(3)
O(6)	0.446 2(4)	0.158 9(2)	0.661 3(3)

Table 7. Atomic parameters for non-hydrogen atoms in the thymidine–aniline adduct (**10d**). Estimated standard deviations are given in parentheses

Atom	*x*	*y*	*z*
N(1)	0.181 0(4)	0.569 9(1)	0.276 6(1)
C(2)	0.368 3(5)	0.608 7(2)	0.258 8(1)
N(3)	0.373 6(4)	0.654 9(1)	0.186 8(1)
C(4)	0.200 9(5)	0.681 6(1)	0.144 2(1)
C(5)	−0.014 6(4)	0.663 4(2)	0.184 5(1)
C(6)	−0.001 7(4)	0.572 1(2)	0.221 1(1)
C(7)	−0.056 9(5)	0.733 1(2)	0.246 5(2)
C(8)	0.168 8(5)	0.522 2(2)	0.352 7(2)
C(9)	0.056 5(6)	0.567 8(2)	0.421 1(2)
C(10)	0.012 0(5)	0.491 2(2)	0.475 9(2)
C(11)	−0.050 6(5)	0.421 4(2)	0.415 8(2)
C(12)	−0.289 6(5)	0.417 4(2)	0.401 0(2)
N(13)	0.016 7(4)	0.507 0(1)	0.160 0(1)
C(14)	−0.129 1(5)	0.441 0(2)	0.145 6(1)
C(15)	−0.325 2(5)	0.434 0(2)	0.184 8(2)
C(16)	−0.462 3(6)	0.366 2(2)	0.166 9(2)
C(17)	−0.411 6(7)	0.305 9(2)	0.110 3(2)
C(18)	−0.222 0(7)	0.313 4(2)	0.070 0(2)
C(19)	−0.080 1(6)	0.379 9(2)	0.087 0(2)
O(1)	0.529 3(3)	0.605 4(1)	0.300 8(1)
O(2)	0.217 4(3)	0.719 3(1)	0.080 0(1)
O(3)	−0.185 6(3)	0.666 9(1)	0.129 0(1)
O(4)	0.197 8(4)	0.469 0(1)	0.521 4(1)
O(5)	0.048 6(4)	0.446 0(1)	0.340 5(1)
O(6)	−0.404 0(4)	0.378 5(1)	0.466 3(1)

internal tetramethylsilane. Mass spectra were taken on a JEOL JMS 01SG-2 instrument by direct insertion at 70 eV, fast atom bombardment (f.a.b.) mass spectra were run on JEOL JMS-DX300, and second ion mass spectra (s.i.m.s.) were run on Hitachi M-80A using glycerol. Column chromatography was carried out on Wakogel C-200 (WAKO Pure Chemical Industries, Ltd., Tokyo). Preparative (prep.) t.l.c. was run on 20 × 20 cm plates coated with a 0.25 mm layer of Merck silica gel PF_{254} and GF_{254}. Column chromatography and prep. t.l.c. were performed using lower phase of chloroform–methanol–water (8:2:1) to which was added 2% of methanol (solvent A), ethyl acetate–propan-2-ol–water (75:16:5)(solvent B), ethyl acetate–propan-2-ol–water (600:6:1) (solvent C), or lower phase of chloroform–ethanol–water (8:2:1) to which was added 3% of ethanol (solvent D). I.r. data are listed in Table 8 (see end of Experimental section). Compounds for which no melting point is given are oils.

Table 8. I.r. spectral data for products (**10**), (**12**), and (**14**) in THF and (**11c**), (**13c**), and (**15c**) in $CHCl_3$)

	$\nu_{max.}$ cm^{-1}
(**10a**)	3 400, 3 200, 1 700
(**10b**)	3 400, 3 350, 1 700
(**10c**)	3 500, 1 735, 1 700
(**10d**)	3 400, 1 755, 1 732, 1 700
(**10e**)	3 400, 1 730, 1 695
(**10f**)	3 470, 3 430, 1 730, 1 725, 1 705
(**10g**)	3 400, 3 200. 1 730. 1 720, 1 700
(**10h**)	3 400, 3 350, 3 300, 1 730
(**10i**)	3 380, 3 300, 1 715, 1 705
(**10j**)	3 400, 3 300, 1 730, 1 705
(**12a**)	3 400, 3 230, 1 725, 1 700
(**12b**)	3 500, 1 730, 1 700
(**12c**)	3 450, 1 730. 1 705
(**14c**)	3 450. 1 725, 1 700
(**12d**)	3 400, 1 730, 1 710
(**14d**)	3 400, 1 720, 1 700
(**12e**)	3 500, 1 740, 1 705
(**14e**)	3 500, 1 730, 1 705
(**12f**)	3 420, 1 735, 1 710
(**14f**)	3 430, 1 730, 1 725, 1 710
(**12g**)	3 500, 1 730, 1 700
(**14g**)	3 500, 1 720, 1 700
(**12h**)	3 400, 3 350, 1 730, 1 705
(**11c**)	3 500. 3 380, 1 740, 1 700
(**13c**)	3 370, 1 730, 1 695
(**15c**)	3 400, 1 735, 1 700

(5R,6R)-trans-(+)-5-*Bromo*-6-*hydroxy*-5,6-*dihydrothymidine* (**2**) *and* (5S,6S)-trans-(−)-5-*Bromo*-6-*hydroxy*-5,6-*dihydrothymidine* (**4**)—A solution of NBS (3.53 g, 19.8 mmol) in water (100 ml) was added to a solution of thymidine (4.00 g, 16.5 mmol) in water (50 ml) and stirred for 10 min with ice-cooling. The mixture was evaporated to dryness under reduced pressure at room temperature and the residue in solvent A was subjected to column chromatography on silica gel. Elution with solvent A gave (**2**) as colourless prisms (3.68 g, 66%), m.p. 132 °C (decomp., from $CHCl_3$–MeOH) and successive elution with the same solvent gave (**4**) as colourless prisms (1.75 g, 31%), m.p. 122 °C (decomp., from $CHCl_3$–MeOH). The compounds were identified by comparison with authentic samples prepared by the bromine method.[22]

General Procedure for Reaction of Bromohydrins (**2**) *and* (**4**) *with Amines and* L-*Amino Acid Ethyl Esters.*—A solution of bromohydrin (339 mg, 1 mmol), triethylamine (152 mg, 1.5 mmol), and nucleophile in dry THF (20 ml) was stirred under argon at room temperature for the time indicated in Tables 1 and 2. After removal of the solvent under reduced pressure, the residue was subjected to column chromatography on silica gel in order to remove triethylamine hydrobromide using solvent B. Fractions containing product(s) were collected and evaporated.

(5S,6S)-cis-(+)-6-*Ethylamino*-5-*hydroxy*-5,6-*dihydrothymidine* (**10a**). The residue was purified by prep. t.l.c. using solvent A to give (**10a**) as colourless prisms (298 mg, 98.4%), m.p. 161–162 °C (from $CHCl_3$–MeOH) (Found: C, 47.3; H, 7.0; N, 13.6. $C_{12}H_{21}N_3O_6$ requires C, 47.5; H, 7.0; N, 13.9%); δ_H 0.93 (3 H, t, *J* 7.1 Hz, CH_2CH_3), 1.26 (3 H, s, 5-Me), 1.78—1.91

(1 H, m, 2′-H), 2.09—2.23 (1 H, m, 2′-H), 2.57 (2 H, q, *J* 7.1 Hz, CH_2CH_3), 3.44 (2 H, d, *J* 5.1 Hz, 5′-H_2), 3.65—3.68 (1 H, m, 4′-H), 4.15 (1 H, s, 6-H), 4.13—4.20 (1 H, m, 3′-H), and 5.91 (1 H, dd, *J* 5.7 and 8.6 Hz, 1′-H).

(5S,6S)-cis-(+)-5-*Hydroxy*-6-[2-(1H-*indol*-3-*yl*)*ethylamino*]-5,6-*dihydrothymidine* (**10b**). The residue was purified by prep. t.l.c. using solvent A to give (**10b**) (397 mg, 95.0%); δ_H 1.26 (3 H, s, 5-Me), 1.86—1.90 (1 H, m, 2′-H), 2.14—2.19 (1 H, m, 2′-H), 2.73—2.78 (2 H, m, CH_2), 2.78—2.93 (2 H, m, CH_2), 3.43 (2 H, d, *J* 5.1 Hz, 5′-H_2), 3.65—3.68 (1 H, m, 4′-H), 4.12—4.18 (1 H, m. 3′-H), 4.23 (1 H, s, 6-H), 5.92 (1 H, dd, *J* 6.1 and 8.5 Hz, 1′-H), 6.94 (1 H, dd, *J* 7.7 and 7.7 Hz, ArH), 7.05 (1 H, dd, *J* 7.7 and 7.7 Hz, ArH), 7.08 (1 H, s, ArH), 7.31 (1 H, d, *J* 7.7 Hz, ArH), and 7.50 (1 H, d, *J* 7.7 Hz, ArH); *m/z* (f.a.b.) 441 (MNa$^+$) and 419 (MH$^+$).

(5S,6S)-cis-(+)-5-*Hydroxy*-6-*morpholino*-5,6-*dihydrothymidine* (**10c**). The residue was purified by prep. t.l.c. using solvent A to give (**10c**) as colourless prisms (345 mg, quant.), m.p. 182 °C (from $CHCl_3$–MeOH) (Found: C, 46.4; H, 6.9; N, 11.5. $C_{14}H_{25}N_3O_8$ requires C. 46.3; H, 6.9; N, 11.6%); δ_H 1.29 (3 H, s, 5-Me), 1.96—2.00 (1 H, m, 2′-H), 2.20—2.25 (1 H, m, 2′-H), 2.55—2.60 (4 H, m, 2 × NCH_2), 3.60—3.68 (6 H, m, 2 × OCH_2 and 5′-H_2), 3.69—3.76 (1 H, m, 4′-H), 4.13—4.19 (1 H, m, 3′-H), 4.19 (1 H, s, 6-H), and 5.70 (1 H, dd, *J* 6.1 and 7.6 Hz, 1′-H).

(5S,6S)-cis-(+)-6-*Anilino*-5-*hydroxy*-5,6-*dihydrothymidine* (**10d**). The residue was purified by prep. t.l.c. by using solvent A to give (**10d**) as colourless prisms (216 mg, 61.6%), m.p. 205—206 °C (from $CHCl_3$–MeOH) (Found: C, 54.6; H, 6.0; N, 11.9. $C_{16}H_{21}N_3O_6$ requires C, 54.7; H, 6.0; N, 12.0%); δ_H 1.36 (3 H, s, 5-Me), 1.86—1.90 (1 H, m, 2′-H), 2.06—2.11 (1 H, m, 2′-H), 2.89—3.00 (2 H, m, 5′-H_2), 3.47—3.52 (1 H, m, 4′-H), 4.02—4.11 (1 H, m, 3′-H), 4.79 (1 H, s, 6-H), 5.86 (1 H, dd, *J* 5.7 and 7.9 Hz, 1′-H), 6.55 (1 H, t, *J* 7.2 Hz, ArH), 6.76 (2 H, d, *J* 7.6 Hz, 2 × ArH), and 7.02 (2 H, dd, *J* 7.2 and 7.6 Hz, 2 × ArH).

Ethyl N-[(5S,6S)-cis-(−)-5-*hydroxy*-5,6-*dihydro*-6-*thymidyl*]-L-*prolinate* (**10e**). The residue was purified by prep. t.l.c. by using solvent A to give (**10e**) (390 mg, 97.3%); δ_H 1.19 (3 H, t, *J* 7.1 Hz, CH_2CH_3), 1.28 (3 H, s, 5-Me), 1.68—1.77 (3 H, m, 3 × CH), 1.81—2.06 (2 H, m, CH and 2′-H), 2.19—2.33 (1 H, m, 2′-H), 2.82—3.00 (2 H, m, CH_2), 3.39—3.56 (2 H, m, 5′-H_2), 3.62—3.73 (2 H, m, 4′-H and CH), 4.02 (2 H, q, *J* 7.1 Hz, CH_2CH_3), 4.13—4.14 (1 H, m, 3′-H), 4.42 (1 H, s, 6-H), and 5.71 (1 H, dd, *J* 6.2 and 7.7 Hz, 1′-H); *m/z* (f.a.b.) 424 (MNa$^+$) and 402 (MH$^+$).

Ethyl N-[(5S,6S)-cis-(+)-5-*hydroxy*-5,6-*dihydro*-6-*thymidyl*]-L-*methioninate* (**10e**). The residue was purified by prep. t.l.c. using solvent A to give (**10f**) (420 mg, 96.6%); δ_H 1.18 (3 H, t, *J* 7.1 Hz, CH_2CH_3), 1.25 (3 H, s, 5-Me), 1.72—1.87 (3 H, m, 2′-H and CH_2), 1.95—2.02 (1 H, m, 2′-H), 2.02 (3 H, s, SMe), 2.03—2.45 (2 H, m, CH_2), 3.49 (2 H, d, *J* 4.0 Hz, 5′-H), 3.64—3.67 (1 H, m, 4′-H), 3.73—3.78 (1 H, m, CH), 4.05 (2 H, q, *J* 7.1 Hz, CH_2CH_3), 4.10—4.15 (1 H, m, 3′-H), 4.28 (1 H, s, 6-H), and 5.87 (1 H, dd, *J* 5.7 and 9.0 Hz, 1′-H); *m/z* (f.a.b.) 458 (MNa$^+$) and 436 (MH$^+$).

Ethyl N-[(5S,6S)-cis-(+)-5-*hydroxy*-5,6-*dihydro*-6-*thymidyl*]-L-*phenylalaninate* (**10g**). The residue was purified by prep. t.l.c. using solvent A to give (**10g**) (365 mg, 81.0%); δ_H 1.01 (3 H, t, *J* 7.0 Hz, CH_2CH_3), 1.26 (3 H, s, 5-Me), 1.87—1.92 (1 H, m, 2′-H), 1.97—2.07 (1 H, m, 2′-H), 2.76 (1 H, dd, *J* 7.1 and 13.5 Hz, CH), 3.00 (1 H, dd, *J* 5.9 and 13.5 Hz, CH), 3.50 (2 H, dd, *J* 4.4 and 5.1 Hz, 5′-H_2), 3.72 (1 H, m, 4′-H), 3.90 (2 H, q, *J* 7.0 Hz, CH_2CH_3), 4.14 (1 H, m, 3′-H), 4.42 (1 H, s, 6-H), 5.91 (1 H, dd, *J* 5.3 and 8.6 Hz, 1′-H), and 7.11—7.30 (5 H, m, 5 × ArH); *m/z* (s.i.m.s.) 474 (MNa$^+$) and 452 (MH$^+$).

Ethyl N-[(5S,6S)-cis-(+)-5-*hydroxy*-5,6-*dihydro*-6-*thymidyl*]-L-*tryptophanate* (**10h**). The residue was purified by prep. t.l.c. using solvent A to give (**10h**) (484 mg, 98.7%); δ_H 0.97 (3 H, t, *J* 7.1 Hz, CH_2CH_3), 1.26 (3 H, s, 5-Me), 1.82—1.91 (1 H, m, 2′-H), 1.98—2.06 (1 H, m, 2′-H), 2.96—3.06 (2 H, m, CH_2), 3.48—3.52 (2 H, m, 5′-H_2), 3.69—3.71 (1 H, m, 4′-H), 3.80—3.87 (2 H, q, *J* 7.1 Hz, CH_2CH_3), 3.88—3.97 (1 H, m, CH), 4.10—4.18 (1 H, m, 3′-H), 4.41 (1 H, s, 6-H), 5.89 (1 H, dd, *J* 5.5 and 8.8 Hz, 1′-H), 6.94 (1 H, dd, *J* 7.3 and 7.3 Hz, ArH), 7.04 (1 H, dd, *J* 7.3 and 7.3 Hz, ArH), 7.11 (1 H, s, ArH), 7.30 (1 H, d, *J* 7.3 Hz, ArH), and 7.46 (1 H, d, *J* 7.3 Hz, ArH); *m/z* (s.i.m.s.) 491 (MH$^+$).

(5S,6S)-cis-(−)-5-*Hydroxy*-6-(m-*nitrophenylamino*)-5,6-*dihydrothymidine* (**10i**). The residue was purified by prep. t.l.c. using solvent A to give (**10i**) (179 mg, 45.2%); δ_H 1.40 (3 H, s, 5-Me), 1.83—1.98 (1 H, m, 2′-H), 2.03—2.20 (1 H, m, 2′-H), 2.85—3.07 (2 H, m, 5′-H_2), 3.46—3.56 (1 H, m, 4′-H), 4.02—4.10 (1 H, m, 3′-H), 4.98 (1 H, s, 6-H), 5.93 (1 H, dd, *J* 5.7 and 7.9 Hz, 1′-H), 7.18 (1 H, d, *J* 7.9 Hz, ArH), 7.28 (1 H, dd, *J* 7.8 and 7.9 Hz, ArH), 7.39 (1 H, d, *J* 7.8 Hz, ArH), and 7.61 (1 H, s, ArH) (Found: *m/z* 396.128 79. $C_{16}H_{20}N_4O_8$ requires *M*, 396.128 10).

(5S,6S)-cis-(+)-5-*Hydroxy*-6-(p-*nitrophenylamino*)-5,6-*dihydrothymidine* (**10j**). The residue was purified by prep. t.l.c. using solvent A to give (**10j**) (251 mg, 63.4%); δ_H 1.41 (3 H, s, 5-Me), 1.87—2.00 (1 H, m, 2′-H), 2.06—2.23 (1 H, m, 2′-H), 3.00—3.18 (2 H, m, 5′-H_2), 3.50—3.60 (1 H, m, 4′-H), 4.05—4.13 (1 H, m, 3′-H), 5.21 (1 H, s, 6-H), 5.95 (1 H, dd, *J* 5.7 and 7.7 Hz, 1′-H), 6.85 (2 H, d, *J* 9.3 Hz, 2 × ArH), and 7.49 (2 H, d, *J* 9.3 Hz, 2 × ArH) (Found: *m/z* 396.130 36. $C_{16}H_{20}N_4O_8$ requires *M*, 396.128 10).

(5R,6R)-cis-(−)-6-*Ethylamino*-5-*hydroxy*-5,6-*dihydrothymidine* (**12a**). The residue was purified by prep. t.l.c. using solvent A to give (**12a**) (161 mg, 53.3%); δ_H 0.93 (3 H, s, *J* 7.0 Hz, CH_2CH_3), 1.25 (3 H, s, 5-Me), 1.75—1.90 (1 H, m, 2′-H), 2.13—2.35 (1 H, m, 2′-H), 2.35—2.65 (2 H, q, *J* 7.0 Hz, CH_2CH_3), 3.39—3.48 (2 H, m, 5′-H_2), 3.62—3.65 (1 H, m, 4′-H), 4.11—4.16 (1 H, m, 3′-H), 4.16 (1 H, s, 6-H), and 5.99 (1 H, dd, *J* 5.5 and 9.5 Hz, 1′-H); *m/z* (f.a.b.) 326 (MNa$^+$) and 304 (MH$^+$).

(5R,6R)-cis-(−)-5-*Hydroxy*-6-[2-(1H-*indol*-3-*yl*)*ethylamino*]-5,6-*dihydrothymidine* (**12b**). The residue was purified by prep. t.l.c. using solvent A to give (**12b**) as colourless prisms (223 mg, 53.4%), m.p. 190—192 °C (from $CHCl_3$–MeOH) (Found: C, 57.1; H, 6.3; N, 13.1. $C_{20}H_{26}N_4O_6$ requires C, 57.4; H, 6.3; N, 13.4%); δ_H 1.25 (3 H, s, 5-Me), 1.68—1.79 (1 H, m, 2′-H), 2.11—2.26 (1 H, m, 2′-H), 3.40—3.43 (2 H, m, 5′-H), 3.61—3.67 (1 H, m, 4′-H), 4.11—4.14 (1 H, m, 3′-H), 4.22 (1 H, s, 6-H), 5.99 (1 H, dd, *J* 5.3 and 9.4 Hz, 1′-H), 6.95 (1 H, dd, *J* 7.3 and 8.1 Hz, ArH), 7.05 (1 H, dd, *J* 7.7 and 8.1 Hz, ArH), 7.10 (1 H, s, ArH), 7.32 (1 H, d, *J* 7.7 Hz, ArH), and 7.49 (1 H, d, *J* 7.3 Hz, ArH).

(5R,6R)-cis-(−)-5-*Hydroxy*-6-*morpholino*-5,6-*dihydrothymidine* (**12c**) *and* (5R,6S)-trans-(+)-5-*hydroxy*-6-*morpholino*-5,6-*dihydrothymidine* (**14c**). The residue was separated by prep. t.l.c. (Merck Aluminium oxide 150 PF_{254}) using solvent A. The upper zone gave (**12c**) (118 mg, 34.3%) and the lower zone gave (**14c**) (161 mg, 46.7%). Compound (**7c**): δ_H 1.29 (3 H, s, 5-Me), 1.79—1.91 (1 H, m, 2′-H), 2.63—2.71 (2 H, m, NCH_2), 2.79—2.87 (2 H, m, NCH_2), 3.42—3.51 (6 H, m, 2 × OCH_2 and 5′-H_2), 3.62—3.66 (1 H, m, 4′-H), 4.16—4.20 (1 H, m, 3′-H), 4.38 (1 H, s, 6-H), and 6.11 (1 H, dd, *J* 6.1 and 8.3 Hz, 1′-H) (Found: *m/z* 345.154 29. $C_{14}H_{23}N_3O_7$ requires *M*, 345.153 58). Compound (**14c**): δ_H 1.34 (3 H, s, 5-Me), 1.77—1.89 (1 H, m, 2′-H), 2.04—2.18 (1 H, m, 2′-H), 3.39—3.51 (6 H, m, 2 × OCH_2 and 5′-H_2), 3.68—3.71 (1 H, m, 4′-H), 4.00 (1 H, s, 6-H), 4.09—4.13 (1 H, m, 3′-H), and 5.91 (1 H, dd, *J* 5.9 and 8.1 Hz, 1′-H) (Found: *m/z* 345.152 81. $C_{14}H_{23}N_3O_7$ requires *M*, 345.153 58).

(5R,6R)-cis-(+)-6-*Anilino*-5-*hydroxy*-5,6-*dihydrothymidine* (**12d**) *and* (5R,6S)-trans-(+)-6-*anilino*-5-*hydroxy*-5,6-*dihydrothymidine* (**14d**). The residue was separated by prep. t.l.c. using solvent C. The upper zone gave (**12d**) (77 mg, 22.0%) and the lower zone gave (**14d**) (143 mg, 40.8%). Compound (**12d**); δ_H 1.35 (3 H, s, 5-Me), 1.63—1.67 (2 H, m, 2′-H_2), 3.34—3.40 (2 H, m, 5′-H_2), 3.91—3.92 (1 H, m, 3′-H), 4.78 (1 H, s, 6-H), 6.09

(1 H, dd, *J* 7.4 and 7.4 Hz, 1′-H), 6.56 (1 H, dd, *J* 7.3 and 7.3 Hz, ArH), 6.72 (2 H, d, *J* 7.7 Hz, 2 × ArH), and 7.04 (2 H, dd, *J* 7.3 and 7.7 Hz, 2 × ArH) (Found: *m/z* 351.142 82. $C_{16}H_{21}N_3O_6$ requires *M*, 351.143 02). Compound (**14d**): δ_H 1.28 (3 H, s, 5-Me), 1.73—1.85 (1 H, m, 2′-H), 2.03—2.18 (1 H, m, 2′-H), 2.84—3.07 (2 H, m, 5′-H_2), 3.43—3.50 (1 H, m, 4′-H). 3.97—4.01 (1 H, m, 3′-H), 4.81 (1 H, s, 6-H), 5.93 (1 H, dd, *J* 5.9 and 8.1 Hz, 1′-H), 6.56 (1 H, dd, *J* 7.3 and 7.3 Hz, ArH), 6.72 (2 H, d, *J* 8.1 Hz, 2 × ArH), and 7.05 (2 H, dd, *J* 7.3 and 8.1 Hz, 2 × ArH) (Found: *m/z* 351.143 85. $C_{16}H_{21}N_3O_6$ requires *M*, 351.143 02).

Ethyl N-[(5R,6R)-cis-(−)-5-*Hydroxy*-5,6-*dihydro*-6-*thymidyl*]-L-*prolinate* (**12e**) *and Ethyl* N-[(5R,6S)-trans-(+)-5-*Hydroxy*-5,6-*dihydro*-6-*thymidyl*]-L-*prolinate* (**14e**).—The residue was separated by prep. t.l.c. using solvent D. The upper zone gave (**12e**) (127.1 mg, 31.7%) and the lower zone gave (**14e**) (126.7 mg, 31.6%). Compound (**12e**); δ_H 1.18 (3 H, t, 7.0 Hz, CH_2CH_3), 1.25 (3 H, s, 5-Me), 1.57—2.20 (5 H, m, 2 × CH_2 and 2′-H), 2.84—2.91 (2 H, m, CH_2), 3.46—3.51 (2 H, m, 5′-H_2), 3.63—3.71 (2 H, m, CH and 4′-H), 4.02 (2 H, q, *J* 7.0 Hz, CH_2CH_3), 4.17—4.21 (1 H, m, 3′-H), 4.63 (1 H, s, 6-H), and 6.01 (1 H, dd, *J* 6.1 and 9.0 Hz, 1′-H); *m/z* (f.a.b.) 424 (MNa^+) and 402 (MH^+). Compound (**14e**); δ_H 1.14 (3 H, t, *J* 7.2 Hz, $CHCH_3$), 1.39 (3 H, s, 5-Me), 1.56—2.17 (5 H, m, 2 × CH_2 and 2′-H), 2.83—3.07 (2 H, m, CH_2), 3.46 (2 H, d, *J* 4.4 Hz, 5′-H_2), 3.55—3.63 (2 H, m, CH and 4′-H), 3.87—4.03 (2 H, m, CH_2CH_3), 4.04—4.07 (1 H, m, 3′-H), 4.12 (1 H, s, 6-H), and 6.03 (1 H, dd, *J* 5.7 and 8.3 Hz, 1′-H); *m/z* (f.a.b.) 424 (MNa^+) and 402 (MH^+).

Ethyl N-[(5R,6R)-cis-(−)-5-*Hydroxy*-5,6-*dihydro*-6-*thymidyl*]-L-*methioninate* (**12f**) *and Ethyl* N-[(5R,6S)-trans-(+)-5-*Hydroxy*-5,6-*dihydro*-6-*thymidyl*]-L-*methioninate* (**14f**).—The residue was separated by prep. t.l.c. using solvent A. The upper zone gave (**12f**) (140 mg, 32.1%) and the lower zone gave (**14f**) (53 mg, 12.1%). Compound (**12f**); δ_H 1.21 (3 H, t, *J* 7.3 Hz, CH_2CH_3), 1.25 (3 H, s, 5-Me), 1.52—1.66 (1 H, m, 2′-H), 1.73—1.84 (2 H, m, 2′-H and CH), 1.99 (3 H, s, SMe), 1.96—2.02 (1 H, m, CH), 3.61—3.66 (2 H, m, 4′-H and CH), 4.03—4.19 (3 H, m, 3′-H and CH_2CH_3), 4.19 (1 H, s, 6-H), and 6.00 (1 H, dd, *J* 5.9 and 10.7 Hz, 1′-H); *m/z* (f.a.b.) 458 (MNa^+) and 436 (MH^+). Compound (**14f**); δ_H 1.17 (3 H, t, *J* 7.3 Hz, CH_2CH_3), 1.35 (3 H, s, 5-Me), 1.61—2.06 (4 H, m, 2′-H_2 and CH_2), 2.01 (3 H, s, SMe), 3.42—3.51 (2 H, m, 5′-H_2), 3.60—3.63 (1 H, m, 4′-H), 3.70—3.77 (1 H, m, 3′-H), 4.01—4.11 (3 H, m, CH_2 and CH), 4.05 (1 H, s, 6-H), and 5.90 (1 H, dd, *J* 5.0 and 7.9 Hz, 1′-H); *m/z* (f.a.b.) 458 (MNa^+) and 436 (MH^+).

Ethyl N-[(5R,6R)-cis-(−)-5-*Hydroxy*-5,6-*dihydro*-6-*thymidyl*]-L-*phenylalaninate* (**12g**) *and Ethyl* N-[(5R,6S)-trans-(+)-5-*Hydroxy*-5,6-*dihydro*-6-*thymidyl*]-L-*phenylalaninate* (**14g**).—The residue was separated by prep. t.l.c. using solvent A. The upper zone gave (**12g**) as colourless prisms (166 mg, 36.8%) and the lower zone gave (**14g**) (109 mg, 24.1%). Compound (**12g**); m.p. 157—158 °C (from $CHCl_3$–MeOH) (Found; C, 54.0; H, 6.3; N, 9.2. $C_{21}H_{29}N_3O_8$ H_2O requires C, 53.7; H, 6.7; N, 8.95%); δ_H 1.09 (3 H, t, *J* 7.2 Hz, CH_2CH_3), 1.24 (3 H, s, 5-Me). 1.60—1.77 (1 H, m, 2′-H), 1.95—2.22 (1 H, m, 2′-H), 2.76 (1 H, dd, *J* 4.4 and 11.6 Hz, CH), 2.81 (1 H, dd, *J* 4.8 and 11.6 Hz, CH), 3.20—3.45 (2 H, m, 5′-H_2), 3.57—3.67 (2 H, m, 4′-H and CH), 3.91—4.02 (2 H, m, CH_2CH_3), 4.10—4.16 (2 H, 6-H and 3′-H), 5.87 (1 H, dd, *J* 5.1 and 9.2 Hz, 1′-H), and 7.08—7.29 (5 H, m, 5 × ArH); *m/z* (f.a.b.) 474 (MNa^+) and 452 (MH^+). Compound (**14g**); δ_H 1.09 (3 H, s, 5-Me), 1.12 (3 H, t, *J* 7.0 Hz, CH_2CH_3), 1.66—1.75 (1 H, m, 2′-H), 1.90—2.06 (1 H, m, 2′-H), 2.75 (1 H, dd, *J* 5.5 and 13.0 Hz, CH), 2.84 (1 H, dd, *J* 4.8 and 13.0 Hz, CH), 3.54—3.56 (2 H, m, 5′-H_2), 3.63—3.65 (2 H, m, 4′-H and CH), 3.93—4.14 (3 H, m, 3′-H and CH_2CH_3), 4.06 (1 H, s, 6-H), 5.91 (1 H, dd, *J* 5.5 and 8.4 Hz, 1′-H), and 7.10—7.25 (5 H, m, 5 × ArH); *m/z* (f.a.b.) 474 (MNa^+) and 452 (MH^+).

Ethyl N-[(5R,6R)-cis-(−)-5-*Hydroxy*-5,6-*dihydro*-6-*thymidyl*]-L-*tryptophanate* (**12h**).—The residue was purified by prep. t.l.c. using solvent A to give (**12h**) (154 mg, 31.5%); δ_H 1.04 (3 H, t, *J* 7.2 Hz, CH_2CH_3), 1.24 (3 H, s, 5-Me), 1.66—1.76 (1 H, m, 2′-H), 1.98—2.17 (1 H, m, 2′-H), 2.80—2.95 (2 H, m, CH_2), 3.60—3.72 (2 H, m, 4′-H and CH), 3.90—4.10 (2 H, m, CH_2CH_3), 4.10—4.13 (1 H, m, 3′-H), 4.13 (1 H, s, 6-H), 5.90 (1 H, dd, *J* 5.7 and 9.7 Hz, 1′-H), 6.94 (1 H, dd, *J* 7.0 and 8.1 Hz, ArH), 7.01 (1 H, s, ArH), 7.05 (1 H, dd *J* 7.0 and 7.3 Hz, ArH), 7.31 (1 H, d. *J* 8.1 Hz, ArH) and 7.42 (1 H, d, *J* 7.3 Hz, ArH); *m/z* (f.a.b.) 513 (MNa^+) and 491 (MH^+).

General Procedure for Isomerisation with BF_3·Et_2O.—A solution of compound (**10**), (**12**), or (**14**) (1 mmol) and BF_3·Et_2O (see Tables 3 and 4) in dry THF (20 ml) was stirred under argon at room temperature for the time specified in Tables 3 and 4. The reaction mixture was then neutralized with aqueous saturated sodium hydrogen carbonate, stirred at room temperature for 30 min, and evaporated under reduced pressure. The residue was separated by prep. t.l.c. and the known product was identified by ^1H n.m.r. spectral comparison with an authentic sample. Treatment of compounds (**12a—h**) resulted in recovery of starting material in moderate yield, while compounds (**14c—g**) afforded the unidentified products (**16c—e,g**) in 6.1, 12.9, 17.1, and 12.3% yield besides the isomerisation products (**12c—f**).

Compound (**16c**). The residue was separated by prep. t.l.c. (Merck Aluminium oxide 150 PF_{254}) using solvent A. The upper zone gave (**12c**) (31 mg, 9.1%) and the lower zone gave (**16c**) (21 mg, 6.1%). (**16c**); δ_H 1.34 (3 H, s, 5-Me), 1.50—1.70 (1 H, m, 2′-H), 1.81—2.02 (1 H, m, 2′-H), 3.35—3.62 (6 H, m, 2 × OCH_2 and 5′-H_2), 3.55—3.62 (1 H, m, 4′-H), 3.90—4.00 (2 H, m, 3′-H and 6-H), and 5.58—5.65 (1 H, d, *J* 8.0 Hz, 1′-H) (Found: *m/z* 345.155 35. $C_{14}H_{23}N_3O_7$ requires *M*, 345.153 58).

Compound (**16d**). The residue was separated by prep. t.l.c. using solvent C. The upper zone gave (**16d**) (45 mg, 12.9%) and the lower zone gave (**12d**) (14 mg, 3.9%). (**12d**); δ_H 1.34 (3 H, s, 5-Me), 1.60—1.75 (1 H, m, 2′-H), 3.46—3.60 (2 H, m, 5′-H_2), 3.65—3.78 (2 H, m, 3′-H and 4′-H), 4.56 (1 H, s, 6-H), 5.70 (1 H, d, *J* 10.3 Hz, 1′-H), 6.58 (1 H, dd, *J* 7.3 and 7.3 Hz, ArH), 6.71 (2 H d. *J* 7.7 Hz, 2 × ArH), and 7.06 (2 H, dd, *J* 7.3 and 7.7 Hz, 2 × ArH) (Found: *m/z* 351.143 33. $C_{16}H_{21}N_3O_6$ requires *M*, 351.143 02).

Compound (**16e**). The residue was separated by prep. t.l.c. using solvent A. The upper zone gave (**12e**) (80 mg, 20.0%) and the lower zone gave (**16e**) (69 mg, 17.1%). (**16e**); δ_H 1.19 (3 H, t, *J* 7.1 Hz, CH_2CH_3), 1.25 (3 H, s, 5-Me), 1.44—2.10 (6 H, m, 2′-H_2 and 2 × CH_2), 3.80—4.27 (2 H, m, 3′-H and 4′-H), 4.06 (2 H, q, *J* 7.1 Hz, CH_2CH_3), 4.65 (1 H, s, 6-H), and 6.13 (1 H, dd, *J* 4.0 and 7.7 Hz, 1′-H); *m/z* (f.a.b.) 424 (MNa^+) and 402 (MH^+).

Compound (**16g**). The residue was purified by prep. t.l.c. using solvent A to give (**16**) (55 mg, 12.3%). (**16g**); δ_H 1.11 (3 H, t, *J* 7.2 Hz CH_2CH_3), 1.26 (3 H, s, 5-Me), 1.66—1.84 (1 H, m, 2′-H), 3.72—3.83 (1 H, m, 4′-H), 4.00 (2 H, q, *J* 7.2 Hz, CH_2CH_3), 4.08—4.16 (1 H, m, 3′-H), 4.40 (1 H, s, 6-H), and 5.92 (1 H, dd, *J* 5.2 and 7.4 Hz, 1′-H); *m/z* (f.a.b.) 474 (MNa^+) and 452 (MH^+).

Syntheses of the Bromohydrins (**3**) *and* (**5**).—The bromohydrins were prepared by a literature method,[21] O,O-(5*R*,6*R*)-*trans*-(+)-5-bromo-6-hydroxy-5,6-dihydrothymidine-3′,5′-diyldiacetate (**3**), m.p. 120 °C (colourless prisms for benzene–hexane); $[\alpha]_D$ +23.1° (*c* 1.00 in EtOH); δ_H($CDCl_3$) 2.02 (3 H, s, 5-Me), 2.12 (3 H, s, $COCH_3$), 2.13 (3 H, s, $COCH_3$), 2.25—2.38 (2 H, m, 2′-H_2), 4.11—4.18 (1 H, m, 4′-H), 4.27 (1 H, dd, *J* 2.8 and 12.1 Hz. 5′-H), 4.45 (1 H, dd, *J* 5.0 and 12.1 Hz, 5′-H), 5.13—

5.19 (1 H, m, 3′-H), 5.14 (1 H, s, 6-H), and 6.49 (1 H, dd, *J* 6.6 and 8.3 Hz, 1′-H).

(5*S*,6*S*)-*trans*-(−)-5-Bromo-6-hydroxy-5,6-dihydrothymidine (**5**); m.p. 169 °C (colourless prisms from hexane–AcOEt); $[\alpha]_D$ −58.2° (*c* 1.00 in EtOH); $\delta_H(CDCl_3)$ 1.97 (3 H, s, 5-Me), 2.11 (3 H, s, $COCH_3$), 2.13 (3 H, s, $COCH_3$), 2.25—2.45 (1 H, m, 2′-H), 2.52—2.70 (1 H, m, 2′-H), 4.19—4.23 (1 H, m, 4′-H), 4.28—4.44 (2 H, m, 5′-H_2), 5.18—5.28 (1 H, m, 3′-H), 5.21 (1 H, s, 6-H), and 6.01 (1 H, dd, *J* 6.1 and 7.8 Hz, 1′-H).

Reaction of Compounds (**3**) *and* (**5**) *with Morpholine.*—A solution of (**3**) or (**5**) (423 mg, 1 mmol), triethylamine (152 mg, 1.5 mmol), and morpholine (1.740 g, 20 mmol) in dry THF (20 ml) was stirred under argon at room temperature for the time indicated in Tables 1 and 2. The solution was poured into water and extracted with chloroform. The extract was dried (K_2CO_3), filtered, and evaporated to dryness under reduced pressure. The residue obtained from (**3**) was purified by prep. t.l.c. using ethyl acetate to give O,O-[(5S,6S)-cis-(+)-5-*hydroxy*-6-*morpholino*-5,6-*dihydrothymidine*-3′,5′-*diyl*]diacetate (**11c**) (241 mg, 56.1%); $\delta_H(CDCl_3)$ 1.50 (3 H, s, 5-Me), 2.09 (3 H, s, $COCH_3$), 2.11 (3 H, s, $COCH_3$), 2.40 (2 H, dd, *J* 4.6 and 6.8 Hz, 2′-H_2), 2.55—2.77 (4 H, m, 2 × NCH_2), 3.63—3.69 (4 H, m, 2 × OCH_2), 4.06 (1 H, s, 6-H), 4.17—4.24 (1 H, m, 4′-H), 4.31 (2 H, d, *J* 3.9 Hz, 5′-H_2), 5.23 (1 H, dd, *J* 4.6 and 7.6 Hz, 3′-H), and 5.85 (1 H, t, *J* 7.0 Hz, 1′-H) (Found: *m/z* 429.175 42. $C_{18}H_{27}N_3O_9$ requires *M*, 429.174 71). The residue obtained from (**5**) was separated by prep. t.l.c. using 3% methanol in $CHCl_3$. The upper zone gave O,O-[(5R,6R)-cis-(−)-5-*hydroxy*-6-*morpholino*-5,6-*dihydrothymidine*-3′,5′-*diyl*]*diacetate* (**13c**) (36 mg, 8.3%) and the lower zone gave O,O-[(5R,6S)-trans-(+)-5-*hydroxy*-6-*morpholino*-5,6-*dihydrothymidine*-3′,5′-*diyl*]*diacetate* (**15c**) (109 mg, 25.4%). Compound (**13c**); $\delta_H(CDCl_3)$ 1.46 (3 H, s, 5-Me), 2.11 (3 H, s, $COCH_3$), 2.12 (3 H, s, $COCH_3$), 2.17—2.29 (1 H, m, 2′-H), 2.59—2.80 (3 H, m, 2′-H and NCH_2), 2.88—3.00 (2 H, m, NCH_2), 3.59—3.65 (4 H, m, 2 × OCH_2), 4.09—4.16 (1 H, m, 4′-H), 4.29 (2 H, d, *J* 3.9 Hz, 5′-H_2), 4.30 (1 H, s, 6-H), 5.15—5.23 (1 H, m, 3′-H), and 6.13 (1 H, dd, *J* 6.2 and 8.2 Hz, 1′-H) (Found: *m/z* 429.176 54. $C_{18}H_{27}N_3O_9$ requires *M*, 429.174 71). Compound (**15c**); $\delta_H(CDCl_3)$ 1.56 (3 H, s, 5-Me), 2.10 (6 H, s, 2 × $COCH_3$), 2.39—2.48 (2 H, m, 2′-H_2), 2.49—2.69 (4 H, m, 2 × NCH_2), 3.59—3.66 (4 H, m, 2 × OCH_2), 4.14 (1 H, s, 6-H), 4.15—4.25 (1 H, m, 4′-H), 4.33 (2 H, d, *J* 5.1 Hz, 5′-H_2), 5.17—5.24 (1 H, m, 3′-H), and 5.91 (1 H, t, *J* 6.9 Hz, 1′-H) (Found: *m/z* 429.174 47. $C_{18}H_{27}N_3O_9$ requires *M*, 429.174 71).

Acetylation of Compounds (**10c**), (**12c**), *and* (**14c**).—A solution of (**10c**), (**12c**), or (**14c**) (345 mg, 1 mmol) in acetic anhydride (10 ml) and dry pyridine (20 ml) was stirred under argon at room temperature for 40 h. The solution was evaporated to dryness under reduced pressure and the residue in each case was purified by short column chromatography using ethyl acetate to give (**11c**) (429 mg, quant.) and (**13c**) (429 mg, quant.), respectively. The residue obtained from (**14c**) was purified by prep. t.l.c. using hexane–ethyl acetate (1:2) to give (**15c**) (300 mg, 70.0%). The identity of each acetylation product was confirmed on the basis of i.r. and ^1H n.m.r. spectral comparisons.

Crystal Structure Determinations.—(*a*) (5R,6R)-trans-(+)-5-*Bromo*-6-*hydroxy*-5,6-*dihydrothymidine* (**2**). $C_{10}H_{15}BrN_2O_6$, *M* = 339.0, orthorhombic, space group $P2_12_12_1$, *a* = 10.310(4), *b* = 11.224(3), *c* = 12.013(3)Å, *U* = 1 390.1Å^3, *Z* = 4, D_c = 1.620 g cm^{-3}, $R(R_w)$ = 0.039 (0.050) for 1 181 unique reflections $|F_0 > 3\sigma(F_0)|$. Crystal size (0.20 × 0.20 × 0.10 mm).

(*b*) (5S,6S)-cis-(+)-6-*Ethylamino*-5-*hydroxy*-5,6-*dihydrothymidine* (**10a**). $C_{12}H_{21}N_3O_6$, *M* = 303.1, monoclinic, space group $P2_1$, *a* = 6.209(0), *b* = 14.977(1), *c* = 8.180(1)Å, β = 109.42(1)°, *U* = 717.4Å^3, *Z* = 2, D_c = 1.404 g cm^{-3}, $R(R_w)$ = 0.036 (0.049) for 1 078 unique reflections $|F_0 > 3\sigma(F_0)|$. Crystal size 0.10 × 0.20 × 0.30 mm.

(*c*) (5S,6S)-cis-(+)-6-*Anilino*-5-*hydroxy*-5,6-*dihydrothymidine* (**10d**). $C_{16}H_{21}N_3O_6$, *M* = 351.1, orthorhombic, space group $P2_12_12_1$, *a* = 6.243(2), b = 15.500(4), *c* = 16.689(4)Å. *U* = 1 614.9Å^3, *Z* = 4, D_c = 1.445 g cm^{-3}, $R(R_w)$ = 0.036 (0.050) for 1 358 unique reflections $|F_0 > 3\sigma(F_0)|$. Crystal size 0.20 × 0.20 × 0.20 mm. The intensity data were collected on a Rigaku AFC-5RU diffractometer for 0 < θ < 60° using monochromated Cu-K_α radiation (λ = 1.541 78 Å), and the ω—2θ scan method at an ω scan speed of 16° min^{-1}. Three standard reflections were measured every 56 reflections to monitor intensity fluctuations. Absorption corrections were not applied. The structure was solved by the direct method using MULTAN program[23] and was refined by full-matrix least-squares method, minimizing the function $\Sigma_\omega(|F_0| - |F_c|)^2$ with $\omega = 1/\sigma^2$. The hydrogen atoms were located from the D-map and refined with the isotropic thermal parameters. All computations were performed on a FACOM M 382 computer in the Data Processing Centre of Kyoto University, using the KPPXRAY programs.[24] Tables of the hydrogen atomic co-ordinates and thermal parameters are available on request from the Cambridge Crystallographic Data Centre.*

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