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Each reaction of *dl*-1,3-dimethylthymine epoxide (**1**) with L-amino acid ethyl esters (Pro-OEt, Met-OEt, Phe-OEt, and Trp-OEt) afforded the respective four optically active diastereomers **4-7**, stereo structures of which were definitely elucidated as shown in Chart 1 by an X-ray analysis of **4A** and chemical means.

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In connection with studies of oxidative modification and damage of nucleic acids and related compounds [1-7], we reported oxidation of pyrimidine bases with *m*-chloroperbenzoic acid as a representative of acylperoxide [8]. Recently, we reported the stereo structures of reaction products of *dl*-1,3-dimethylthymine epoxide (**1**) with achiral amines [9], wherein we proposed the isomerization mechanism of *trans* product **2** to *cis* product **3** with boron trifluoride etherate as shown in Chart 1. Subsequently, we have investigated reaction of **1** with chiral amino acid derivatives as a model reaction for nucleic acid-protein interactions. The present communication describes the stereo structures including absolute configurations of the reaction products of **1** with L-amino acid ethyl esters and the usefulness and generality of our isomerization procedure [9] for elucidating structures of the products.

Attempts were made to react the epoxide **1** prepared *in situ* from *dl*-*trans*-5-bromo-6-hydroxy-1,3-dimethyl-5,6-dihydrothymine and triethylamine [1,9] with L-amino acid

ethyl esters (Pro-OEt, Met-OEt, Phe-OEt, and Trp-OEt) in tetrahydrofuran (THF) under reflux. Each reaction afforded four optically active diastereomers **4-7**, respectively, yields and specific rotations of which are summarized in Table I [10-12]. Subsequently, the isomerization procedure was applied to the products **4-8** in order to investigate those stereo structures [9]. Thus, treatment of **6** and **7** with boron trifluoride etherate in THF at rt gave isomerized products **4** and **5** including specific rotations, respectively, as listed in Table II. These facts indicate that both **4** and **5** are *cis* products and both **6** and **7** are *trans* products. In order to determine each stereo structure containing absolute configuration, a *levorotatory cis* product **4A**, mp 97-98°, was subjected to an X-ray analysis [13]. The molecular structure of **4A** was depicted in Figure 1, showing that absolute configurations of two chiral centers on pyrimidine ring are *5R* and *6R*. Therefore, in *cis* products **4** and **5**, the *levorotatory cis* products can be represented by formula **4** with *5R* and *6R* and the *dextrorotatory cis* products by formula **5** with *5S* and *6S*. Moreover, according to our isomerization mechanism [9] the stereo structures of *dextrorotatory trans* products which isomerized to **4** can be represented by formula **6** with *5R* and *6S* and those of *levorotatory trans* products which isomerized to **5** can be represented by formula **7** with *5S* and *6R*. The present results would be very useful for chemistry of the cross-linkage of nucleic acid with protein or other chiral amino acids.

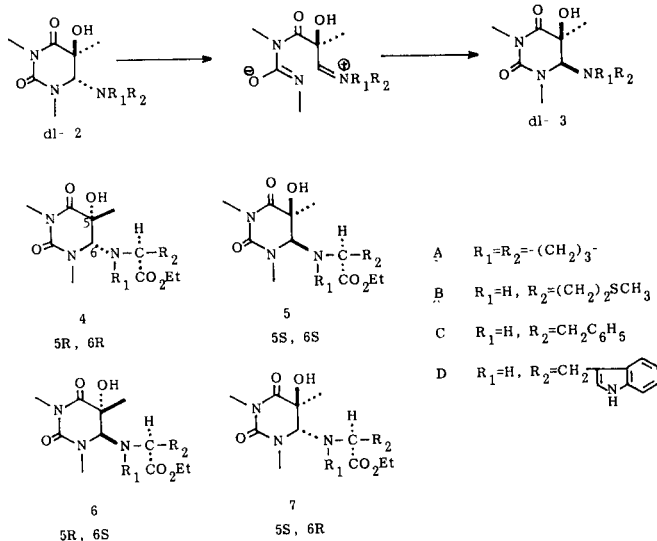


Chart 1

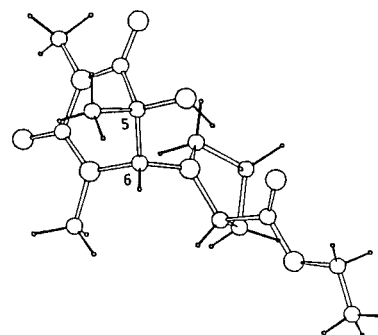


Figure 1. Molecular Structure of **4a**.

Table I
Results of Reactions of **1** with L-Amino Acid Ethyl Esters [a]

	Pro-OEt A		Met-OEt B		Phe-OEt C		Trp-OEt D	
	Yield (%)	$[\alpha]_D$	Yield (%)	$[\alpha]_D$	Yield (%)	$[\alpha]_D$	Yield (%)	$[\alpha]_D$
4	10.3	-100.6°	17.9	-119.0°	21.6	-80.7°	20.0	-59.4°
5	16.7	+ 2.8°	22.9	+ 26.4°	28.0	+52.6° [b]	19.2	+33.5°
6	34.3	+ 42.2°	31.1	+ 41.2°	28.2	+78.9°	29.5	+60.2°
7	29.3	-156.7°	21.4	-120.2°	19.8	-81.6°	30.2	-62.7°
Total yield (%)	90.6		93.3		97.6		98.9	

[a] Specific rotations were measured in ethanol solution ($c = 1.0$), unless otherwise noted. [b] $c = 0.86$.

Table II
Results of Isomerizations of **6** and **7**

Starting material	Product	Yield (%)	$[\alpha]_D$ ($c = 1.0$ in ethanol)
6A	4A	96.0	- 99.5°
6B	4B	94.5	-121.8°
6C	4C	79.5	- 85.7°
6D	4D	quantitative	- 63.5°
7A	5A	91.7	+ 2.5°
7B	5B	81.5	+ 26.2°
7C	5C	83.3	+ 59.0° [a]
7D	5D	quantitative	+ 39.0°

[a] $c = 0.85$.

General Procedure.

1) Reaction of *dl-trans*-5-Bromo-6-hydroxy-1,3-dimethyl-5,6-dihydrothymine with L-amino Acid Ethyl Esters in the Presence of Triethylamine.

A solution of 1 mmole of *dl*-bromohydrin, 2 mmoles of L-amino acid ethyl ester, and 1.5 mmoles of triethylamine in 20 ml of dry THF was refluxed for 24-48 hours under argon atmosphere. The reaction mixture was made alkaline with ammonia and extracted with chloroform. The extract was dried over potassium carbonate, filtered, and evaporated to dryness *in vacuo*. The products were separated by combination of column chromatography (silica gel) and preparative tlc.

2) Isomerizations of **6** and **7** with Boron Trifluoride Etherate.

A solution of 1 mmole of **6** and **7** and 1.2 mmoles of boron trifluoride etherate in 20 ml of dry THF was stirred at room temperature for 20 hours under an argon atmosphere. The reaction mixture was made alkaline with saturated sodium bicarbonate solution and stirred for 30 minutes and then extracted with chloroform. The extract was dried over potassium carbonate, filtered, and evaporated to dryness *in vacuo*. The isomerization product was purified by preparative tlc.

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- [9] T. Harayama, R. Yanada, T. Taga, and F. Yoneda, *Tetrahedron Letters*, **26**, 3587 (1985).
- [10] All new compounds gave satisfactory data of ir (chloroform); ¹H-nmr (200 MHz in deuteriochloroform-deuterium oxide), and mass spectrum.
- [11] Reaction of **1** with Phe-OCH₂C₆H₅, **E** also gave four optically active diastereomers, **4E** [$\alpha]_D^{25}$ -65.3°, **5E** [$\alpha]_D^{25}$ +50.3°, **6E** [$\alpha]_D^{25}$ +72.7°, and **7E** [$\alpha]_D^{25}$ -89.7°, in 20.0, 24.1, 28.4, and 23.3% yields, respectively. The ¹H-nmr data of these compounds are given in reference [12].
- [12] ¹H-nmr data for products **4A-E-7A-E**:

Product	CH ₂ CH ₃	5-CH ₃	N-CH ₃	N-CH ₃	6-H	CH ₂ CH ₃
4A	1.28 (t) J = 7.2 Hz	1.48 (s)	3.11 (s)	3.21 (s)	4.16 (s)	4.19 (m)
5A	1.27 (t) J = 7.1 Hz	1.46 (s)	3.15 (s)	3.18 (s)	4.25 (s)	4.15 (q) J = 7.1 Hz
6A	1.25 (t) J = 7.1 Hz	1.53 (s)	3.08 (s)	3.13 (s)	4.20 (s)	4.10 (q) J = 7.1 Hz
7A	1.29 (t) J = 7.1 Hz	1.49 (s)	3.13 (s)	3.15 (s)	4.36 (s)	4.18 (m)
4B	1.30 (t) J = 7.1 Hz	1.39 (s)	3.16 (s)	3.21 (s)	4.08 (s)	4.23 (q) J = 7.1 Hz
5B	1.29 (t) J = 7.1 Hz	1.39 (s)	3.17 (s)	3.21 (s)	3.87 (s)	4.19 (q) J = 7.1 Hz
6B	1.28 (t) J = 7.2 Hz	1.50 (s)	3.08 (s)	3.18 (s)	3.90 (s)	4.19 (m)
7B	1.29 (t) J = 7.1 Hz	1.41 (s)	3.10 (s)	3.18 (s)	4.07 (s)	4.21 (q) J = 7.1 Hz
4C	1.23 (t) J = 7.1 Hz	1.34 (s)	3.03 (s)	3.04 (s)	3.97 (s)	4.17 (q) J = 7.1 Hz
5C	1.22 (t) J = 7.2 Hz	1.32 (s)	3.02 (s)	3.19 (s)	3.77 (s)	4.14 (m)
6C	1.20 (t) J = 7.2 Hz	1.25 (s)	3.03 (s)	3.15 (s)	3.81 (s)	4.13 (m)

7C	1.23 (t) J = 7.2 Hz	1.31 (s)	2.87 (s)	3.06 (s)	3.96 (s)	4.16 (q) J = 7.2 Hz
4D	1.19 (t) J = 7.2 Hz	1.34 (s)	2.99 (s)	3.04 (s)	3.97 (s)	4.14 (q) J = 7.2 Hz
5D	1.23 (t) J = 7.1 Hz	1.29 (s)	2.99 (s)	3.19 (s)	3.75 (s)	4.15 (m)
6D	1.17 (t) J = 7.2 Hz	1.23 (s)	3.00 (s)	3.13 (s)	3.84 (s)	4.09 (m)
7D	1.19 (t) J = 7.1 Hz	1.32 (s)	2.87 (s)	2.95 (s)	3.98 (s)	4.13 (q) J = 7.1 Hz
4E		1.30 (s)	2.95 (s)	3.01 (s)	3.91 (s)	
5E		1.31 (s)	2.97 (s)	3.13 (s)	3.78 (s)	

6E	1.25 (s)	2.97 (s)	3.08 (s)	3.80 (s)
7E	1.28 (s)	2.83 (s)	3.00 (s)	3.93 (s)

[13] Crystal data for **4A**: $C_{14}H_{23}N_3O_5$, $M = 313.35$, orthorhombic; space group $P2_12_12_1$, $a = 12.185(1)$, $b = 11.765(1)$, $c = 11.446(2)$ Å, $U = 1640$ Å³, $Z = 4$, and $D_c = 1.268$ gcm⁻³. The reflection data were collected on Rigaku AFC-5 diffractometer for $0 < \theta < 60^\circ$ using monochromated $CuK\alpha$ radiation and ω - 2θ scan technique. The structure was solved by direct method and refined by full-matrix least-squares method. The final R value was 0.075 for 1274 independent reflections [$F > 3\sigma(F)$].