A STEREOSELECTIVE SYNTHESIS OF 3-ALKYL-6-METHOXY-2,5-PIPERAZINEDIONE DERIVATIVES

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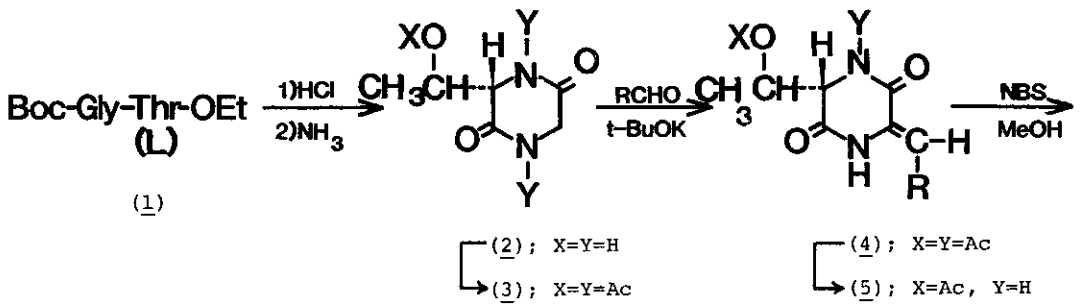
Abstract —— A stereoselective formation of 3-alkyl-6-methoxy-2,5-piperazinedione derivatives by the addition of methanol in the presence of NBS to 3-alkyl-6-alkylidene-2,5-piperazinediones is described.

In a previous paper,[1] we reported the stereoselective synthesis of α,α-diamino acid derivatives by the addition of a chiral α-amino acid to the C=N bond of an α-imino acid. Although there are a few reports on the asymmetric hydrogenation of 3-alkylidene-2,5-piperazinedione (PDO)[2-4] having a chiral center, no report has been known on the stereoselective addition to the 3-alkylidene-PDO derivative. In this paper, we wish to report a facile synthesis of the optically active 3-alkyl- and 3-alkylidene-6-methoxy-PDO by the addition of methanol in the presence of NBS to (L)-Thr-DHA (α-dehydroamino acid residue), followed by the successive hydrogenolysis of bromine and β-elimination reaction.

Cyclization of Boc-Gly-(L)-Thr-OMe (1; 100 ml), which was derived from Boc-Gly-OH and (L)-Thr-OMe by the usual method, with dry HCl gas in dry methanol (200 ml) at room temperature for 1 h gave the expected PDO, (L)-Thr-Gly {2: yield 58%, colorless needles from methanol, mp 250-254°C (decomp.); $[\alpha]_D^{20}$ 84.5° (c 0.1, acetic acid)}. After acetylation of 2 (60 mmol) with acetic anhydride (120 ml) under reflux for 12 h, 1,4-diacetyl-Thr(OAc)-Gly {3: yield 75%, colorless syrup, $[\alpha]_D^{20}$ 114.5° (c 0.16, methanol)} obtained was condensed with 5 moles of an appropriate aldehyde (50 ml) in the presence of an equimolar potassium t-butoxide (10 mmol) in DMF (20 ml) for 12 h to give 4-acetyl-Thr(OAc)-DHA {ΔAla[6] deriv-

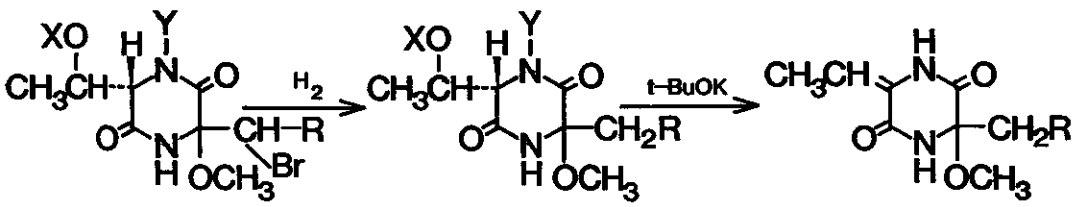
ative (4a): yield 75%, colorless syrup, $[\alpha]_D^{20}$ 96.8° (c 0.2, methanol). ΔPhe derivative (4b): yield 75%, colorless fibers from ethanol-H_2O, mp 52-54°C, $[\alpha]_D^{20}$ -321.0° (c 0.5, methanol)}. Subsequent N-deacetylation of 4 (5 mmol) with 6M-HCl (3 ml) in ethanol (20 ml) at room temperature for 2.5 h was performed to give the expected Thr(OAc)-DHA {5a: yield 95%, colorless fibers from ethanol, mp 260-263°C (decomp.), $[\alpha]_D^{20}$ -157.5° (c 0.2, methanol). 5b: yield 95%, colorless needles from ethanol, mp 288-290°C (decomp.), $[\alpha]_D^{20}$ -336.9° (c 0.2, acetic acid)}. In order to introduce a methoxy group stereoselectively into the 6-position of 4, according to the method reported previously,[7] compound 4 (10 mmol) was treated with an equimolar NBS in methanol (30 ml) for 30 min to give the expected 3-acetoxyethyl-4-acetyl-6-(2-bromoalkyl)-6-methoxy-PDO (7a; R=CH_3, 7b; R=C_6H_5) in a good yield. Similar treatment of 5 with NBS was worked up to give 3-acetoxyethyl-



(1)

(2); X=Y=H
(3); X=Y=Ac

(4); X=Y=Ac
(5); X=Ac, Y=H



(6); X=Ac, Y=H
(7); X=Y=Ac

(8); X=Ac, Y=H
(9); X=Y=Ac

(10)

a; R=CH_3, b; R=C_6H_5

6-(2-bromoalkyl)-6-methoxy-PDO (6a,b) almost quantitatively.

Each of two isomers of 6b and 7b (R=C_6H_5), which was deduced to be a mixture of stereoisomers with respect to the steric configuration of vicinal carbons having a methoxy group and a bromine atom respectively, could be separated by fractional recrystallization (see Table 1). In order to ascertain the above presumption, the bromine atom in the isomer of each 6b and 7b (2 mmol) was subjected to the catalytic hydrogenolysis with 10% Pd-C (150 mg) in the presence of triethylamine (2 mmol) in methanol (50 ml) for 1 h to give the corresponding 6-benzyl-6-methoxy-PDO derivatives (8b and 9b). Consequently, it was found that the products, derived from the each of two isomers, were completely the same (see Table 1). Moreover, the similar hydrogenolysis of 6a and 7a was worked up to give 6-ethyl-6-methoxy-PDO derivatives (8a and 9a) in good yields respectively.

Table 1. 6-Methoxy-2,5-piperazinedione derivatives (6-9, and 10)

Compound No.	Yield (%)	Mp °C (decomp.)	NMR spectrum, δ ($CDCl_3$) $-OCH_3$ (s)	(-CH-) -CH=	d. e.[d] (%)	$[\alpha]_D^{20}$ (c 0.2)
6a	95	126-127	3.48, 3.51	(5.75m)		-30.1 (MeOH)
6b[a]	54	105-107	3.25	(5.40s)		-114.5 (MeOH)
	40	170-171	3.18	(5.50s)		-78.5 (MeOH)
7a	80	syrup	3.46	(4.75m)		-22.1 ($CHCl_3$)
7b[a]	60	200	3.34	(5.56s)		+259.5 ($CHCl_3$)
	22	196	3.62	(5.66s)		+71.9 ($CHCl_3$)
8a	85	203-206	3.10, 3.16		19.5	+10.4 (MeOH)
8b	81[b]	234-235	3.16, 3.25		50.3	-29.5 (MeOH)
9a	82	syrup	3.26, 3.35		70.3	+119.9 (MeOH)
9b	81[c]	syrup	3.35, 3.47		87.0	+111.3 (MeOH)
10a	80	320	3.12	5.95q[e]		+11.5 (MeOH)
10b	75	285	2.85	5.65q[e]		+41.6 (MeOH)

a) A mixture of stereoisomers. b) Yield from each isomer of 6b. c) Yield from each isomer of 7b. d) Diastereomeric excess. e) Coupling constant, J=7.5Hz.

From the NMR spectral data of 8 and 9, the presence of the two stereoisomers regarding the two carbons in the 3- and 6-positions was recognized and the diastereomeric excess yield (d. e., %) could be easily calculated. Comparison of the d. e. of 9 with that of 8 indicates that the asymmetric yield of 4-acetyl-PDO derivative (9) is considerably higher than that of deacetylated PDO (8). On the other hand, about the effect of 6-substituent, it was found that the d. e. of 6-benzyl-PDO derivatives (8b and 9b) was higher than that of 6-ethyl-PDO derivative (8a and 9a). In particular, the d. e. of 9b was found to reach to nearly 90%. Consequently, among the acetylated PDO derivatives (4a, 4b, 5a, and 5b), the asymmetric yield of 9b obtained by the addition of methanol to 4-acetyl-6-benzylidene-PDO (4b) was found to be the highest.

From the above results, it is supposed that, in the case of 4b, a bromonium ion added initially to exo-olefin carbon, followed by the predominant attack of methoxy anion from opposite side of the adduct which are structurally folded[8] by phenyl and acetyl groups.

Furthermore, the above stereoselective addition could be confirmed unambiguously, because 3-ethylidene-6-methoxy-6-alkyl-PDO (10) showed still large rotation, even after the chirality of the 3-position of threonine residue was extinguished.

REFERENCES

1. C. Shin, H. Ohmatsu, Y. Sato, and J. Yoshimura, Chem. Lett., 1981, 701.

2. S. Akabori, T. Ikenaga, and K. Matsumoto, Nippon Kagaku Zasshi, 73, 112 (1952).

3. H. Poisel and U. Schmidt, Chem. Ber., 106, 3408 (1974).

4. N. Izumiya, S. Lee, T. Kanmera, and H. Aoyagi, J. Am. Chem. Soc., 99, 8346 (1977).

5. C. Gallina and A. Liberatori, Tetrahedron, 1974, 664.

6. In this paper, the symbol Δ indicates an exocyclic carbon-carbon double bond of 6-position in 2,5-piperazinedione derivatives.

7. C. Shin, Y. Sato, H. Ohmatsu, and J. Yoshimura, Bull. Chem. Soc. Jpn., 54, 1137 (1981).

8. U. Schollkopf, U. Groth, and W. Hartwig, Ann. Chem., 1981, 2407.

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