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A NEW DETERMINATION OF THE ABSOLUTE CONFIGURATION OF THE CHIRAL AMINE

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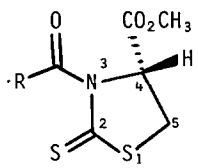
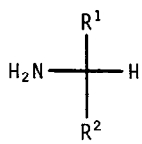
Summary: A new method for assignment of the absolute configuration of the asymmetric carbon atom attached to an amino or imino group using *rac*.-3-hexadecanoyl-4-methoxycarbonyl-1,3-thiazolidine-2-thione (*rac*.-HDMTT) (4) is described.

In the preceding paper,[1] we reported a new synthetic method for the optically active amide 3 utilizing chiral recognition of racemic amine 2 with 3-acyl-4(R)-methoxycarbonyl-1,3-thiazolidine-2-thione [4(R)-AMTT] 1. In this reaction, 4(R)-AMTT 1 showed a preferential reactivity to the (S)-amine. This chiral recognition should be available for determination of the absolute configuration of the chiral amine.



1



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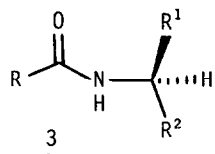
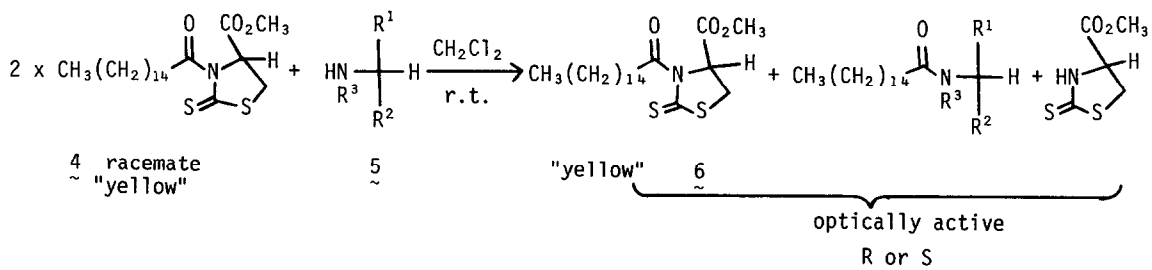


3 $R^1 < R^2$ in sequence rule

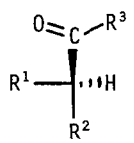
Our method is explicable as follows. After aminolysis of 2 mol. equiv. of *rac*.-3-hexadecanoyl-4-methoxycarbonyl-1,3-thiazolidine-2-thione [*rac*.-HDMTT] (4)[2] with 1 mol. equiv. of optically active amine (or imine) 5, the specific rotation of the recovered HDMTT (6) is determined. By the sign of its specific rotation the absolute configuration of the amine (or imine) used can be assigned.



4 racemate "yellow" 5 "yellow" 6

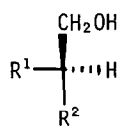
Scheme 1

Thus we tried aminolyses of *rac.*-HDMTT (4) with several types of amines, *i.e.* α-amino acid derivatives 7a~l, β-amino alcohols 8a~d, and 3-amino-β-lactams 9a,b and 10a~e, in order to judge the availability of this method.



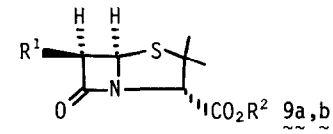
7a~l

a : R^1 = NH_2·HCl, R^2 = Ph, R^3 = OMe
b : R^1 = CH_2Ph, R^2 = NH_2·HCl, R^3 = OMe
c : R^1 = NH_2·HCl, R^2 = CH_3, R^3 = OMe
d : R^1 = CH_3, R^2 = NH_2·HCl, R^3 = OMe
e : R^1 = $CH_2CH(CH_3)_2$, R^2 = NH_2·HCl, R^3 = OMe
f : R^1 = CH_2OH, R^2 = NH_2·HCl, R^3 = OMe
g : R^1 = CH_2SH, R^2 = NH_2·HCl, R^3 = OMe
h : R^1 = CH_3, R^2 = NH_2·HCl, R^3 = $NHCH_2CO_2H$
i : R^1 = $CH_2CH(CH_3)_2$, R^2 = NH_2, R^3 = $NHCH(CH_3)CO_2H$
j : R^1 = $CH_2SSCH_2CH(NH_2$·HCl$)CO_2Me$,
R^2 = NH_2·HCl, R^3 = OMe
k : R^1 = CH_2Ph, R^2 = NH_2, R^3 = OH
l : R^1 = $-(CH_2)_3-R^2$, R^2 = -NH-, R^3 = OH



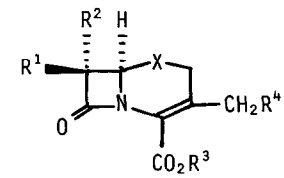
8a~d

a : R^1 = CH_2Ph, R^2 = NH_2
b : R^1 = $CH(CH_3)_2$, R^2 = NH_2
c : R^1 = NH_2, R^2 = Ph
d : R^1 = $-(CH_2)_3-R^2$, R^2 = -NH-

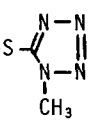
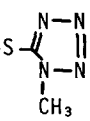


9a,b

a : R^1 = NH_2, R^2 = H
b : R^1 = NH_2·TsOH, R^2 = $CHPh_2$



10a~e

a : X = S, R^1 = NH_2, R^2 = R^3 = R^4 = H
b : X = O, R^1 = NH_2·HCl,
R^2 = R^4 = H, R^3 = $CHPh_2$
c : X = O, R^1 = R^4 = H,
R^2 = NH_2, R^3 = $CHPh_2$
d : X = O, R^1 = NH_2, R^2 = H
R^3=$CHPh_2$, R^4= 
e : X = O, R^1 = H, R^2 = NH_2·HCl
R^3=$CHPh_2$, R^4= 

The results are summarized in Tables 1, 2, and 3.

In the case of α-amino acid derivatives, the (S)-enantiomer reacted with 4(R)-HDMTT preferentially and *vice versa* [(R)-7+4(S)-HDMTT], which is in good coincidence with the chiral recognition of racemic amine with 4(R)-AMTT l. Apparent opposite chiral recognitions with 7g and 7j are attributed only to the R,S sequence rule by Cahn, Ingold, and Prelog.[3)]

In the β-amino alcohol derivatives, the (S)-enantiomer showed a preferential reactivity to 4(S)-HDMTT resulting in the recovery of 4(R)-HDMTT.

Table 1. Chiral Recognition of *rac.*-HDMTT (4) with α-Amino Acid Derivative 7

compound 7	R or S	reaction solvent	reaction time (hr)	cy[b] (%)	recovered HDMTT 6 R or S excess	ee[c] (%)
7a	R	CH_2Cl_2	13	99.4	R(-)	60.5
7b	S	CH_2Cl_2	8	92.1	S(+)	63.3
7c	R	CH_2Cl_2	1.5	95.2	R(-)	42.3
7d	S	CH_2Cl_2	1.5	91.6	S(+)	44.2
7e	S	CH_2Cl_2	3.3	88.8	S(+)	45.6
7f	S	CH_2Cl_2	4	90.8	S(+)	23.7
7g	R	CH_2Cl_2	1.5	44.3	S(+)	33.8
7h	S	CH_2Cl_2-THF (1:1)	144	150.1	S(+)	8.4
7i	S	CH_2Cl_2-THF (1:1)	6	99.1	S(+)	25.4
7j[d]	R	CH_2Cl_2	2	110.8	S(+)	33.7
7k	S	THF	44	91.6	S(+)	11.4
7l	S	CH_2Cl_2-THF (1:1)	17	89.8	S(+)	21.8

a) All reactions were carried out in the presence of Et_3N (1.42 mol. equiv. to compound 7). b) The maximum chemical yield (cy) of recovery of HDMTT is calculated as 200%. c) Enantiomeric excess percent (ee%) of the recovered HDMTT and the configuration of C-4 were determined based on 4(R)-HDMTT [1: R = $(CH_2)_{14}CH_3$].[2] d) 4 Mol. equiv. of *rac.*-HDMTT 4 were employed.

Table 2. Chiral Recognition of *rac.*-HDMTT (4) with β-Amino Alcohol 8[a]

compound 8	R or S	reaction time (hr)	cy[b] (%)	recovered HDMTT 6 R or S excess	ee[b] (%)
8a	S	1.5	91.4	R(-)	11.1
8b	S	7	87.6	R(-)	19.2
8c	R	5.8	93 4	S(+)	40.4
8d	S	4.5	93.5	R(-)	7.3

a) All reactions were carried out in CH_2Cl_2. b) See footnotes on Table 1.

Table 3. Chiral Recognition of *rac.*-HDMTT (4) with 3-Amino-β-lactams 9 and 10

compound 9,10	configuration	reaction solvent	reaction time (day)	cy[c] (%)	recovered HDMTT 6 R or S excess	ee[c] (%)
9a	R[a]β[b]	CH_2Cl_2-THF (1:1)	1.1	107.4	R(-)	32.9
9b[d]	Rβ	CH_2Cl_2	3	117.2	R(-)	15.3
10a[d]	Rβ	CH_2Cl_2	6	141.5	R(-)	3.2
10b[d]	Sβ	CH_2Cl_2	4	136.6	R(-)	9.3
10c	Rα	CH_2Cl_2	2.7	111.0	S(+)	7.9
10d	Sβ	CH_2Cl_2	4	185.0	R(-)	0.4
10e[d]	Rα	CH_2Cl_2	4	164.1	S(+)	10.5

a) Configuration of the carbon atom attached to the amino group. b) Relative configuration of the amino group. c) See footnotes on Table 1. d) 1.0~1.4 Mol. equiv. of Et_3N was used.

In the 3-amino-β-lactams,[4] (R)-penam-, (R)-cephem-, and (S)-oxacephem-derivatives showed a preferential reactivity to 4(S)-HDMTT; (R)-oxacephem-derivatives reacted predominantly with 4(R)-HDMTT.

On the basis of these results, the absolute configuration of chiral amines (or imines) can be determined, as summarized below.

	preferred configuration (R or S) of the recovered HDMTT (6)	the absolute configuration of the optically active sample
(1) α-amino acid derivatives:	R(-)	→ R
	S(+)	→ S
	sulfur compounds like 7f and 7i: R(-)	→ S
	sulfur compounds like 7f and 7i: S(+)	→ R
(2) β-amino alcohol derivatives:	R(-)	→ S
	S(+)	→ R
(3) 3-amino-β-lactam derivatives:	oxacephem and oxapenam: R(-)	→ S
	oxacephem and oxapenam: S(+)	→ R
	cephem and penam: R(-)	→ R
	cephem and penam: S(+)	→ S

Because HDMTT is yellow crystal, one can easily monitor it on its separation by the column chromatography.

This convenient method for determination of the absolute configuration of the chiral amines will promise a wide utility.

References and Notes

1) Y. Nagao, M. Yagi, T. Ikeda, and E. Fujita, the preceding paper.

2) Because 4(R)-HDMTT [1: R = $(CH_2)_{14}CH_3$] showed the highest specific rotation $[[\alpha]_D^{22}$-78.17° (c = 1.02, $CHCl_3$)] among several 4(R)-AMTT 1[1], *rac.*-HDMTT (4) (mp 74.5~75°, yellow needles from ether-n-hexane) was employed for this purpose.

3) R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem. Int. Ed. Engl.* 5, 385 (1966).

4) We appreciate Dr. W. Nagata, Shionogi Research Laboratory, Shionogi & Co. Ltd., for his kind gifts of β-lactams, 9a and 10a~e.

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