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A NEW SYNTHESIS OF OPTICALLY ACTIVE β-MERCAPTOCARBOXYLIC ACID ESTERS [1]

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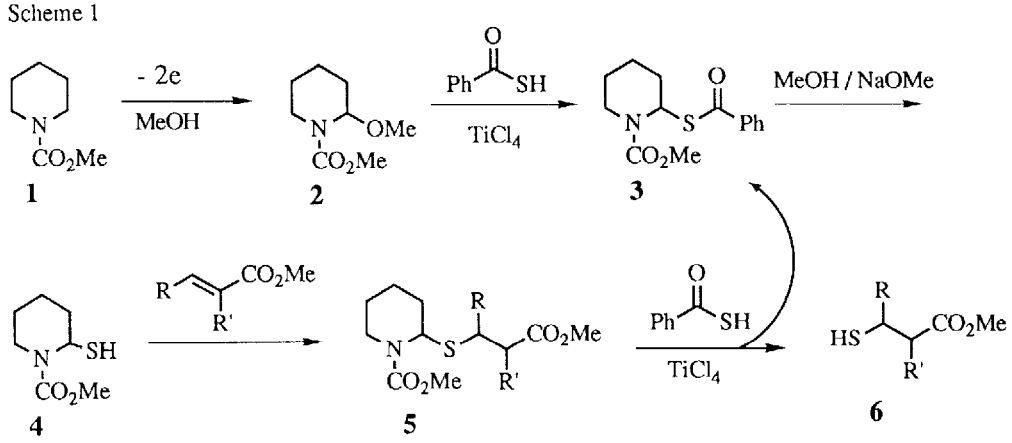
Synthesis of optically active β-mercaptocarboxylic acid esters has been achieved by a new method utilizing optically active N-methoxycarbonylpiperidine derivative as a template which can be prepared from L-lysine by anodic oxidation.

Although there have been reported a variety of methods for the synthesis of thiols,[2] only few methods may be applicable to the synthesis of optically active ones.[3,4] We wish to report a new convenient synthetic method of thiols which is effective to the synthesis of optically active β-mercaptocarboxylic acid esters.

Scheme 1 shows the new method which consists of five steps, that is, the transformation of N-methoxycarbonylpiperidine **1** to α-thiobenzoylpiperidine derivative **3** through anodic α-methoxylation of **1** followed by reaction of the product, N,O-acetal **2** with thiobenzoic acid,[6] the hydrolysis of **3** to a thiol **4**, formation of N,S-acetals **5** by the Michael addition of **4** to α,β-unsaturated carboxylic acid esters, and preparation of β-mercaptocarboxylic acid esters **6** by acid catalyzed cleavage of C-S bond of the N,S-acetal moiety.

Scheme 1



This method shown in Scheme 1 has two advantages. First, **3** is recycled by using thiobenzoic acid for the formation of **6** from **5** at the last step. Second, this method is effective to the preparation of optically active **6** as described in Scheme 3.

The general procedures for the synthesis of **6** are as follows : Anodic α-methoxylation of **1** was carried out according to our already reported method (86%).[6] α-Methoxy group of **2** was easily replaced with a thiobenzoyl group by treatment of **2** (0.1 mol) with thiobenzoic acid (0.12 mol) in methylene chloride (150 mL) containing

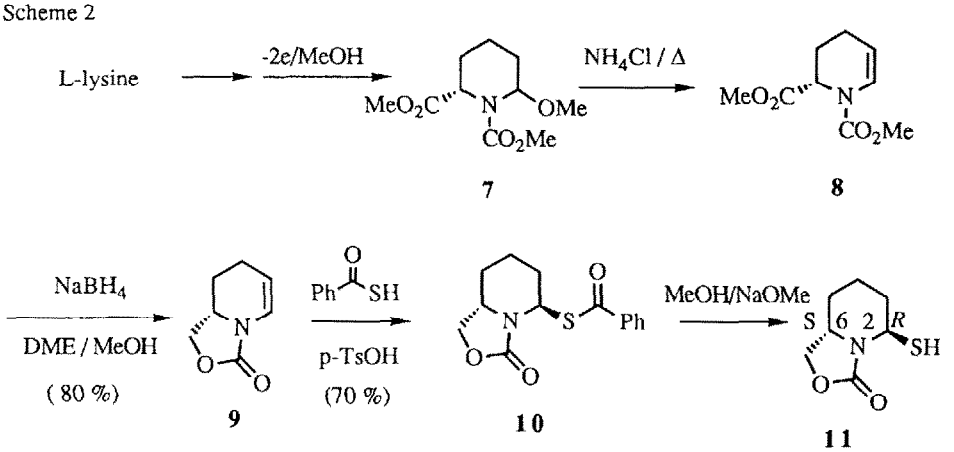
titanium tetrachloride (0.11 mol, 12 mL), yield of **3** (mp 97 °C) being 67 %. A solution of **3** (10 mmol) in methanol (30 mL) was treated with sodium methoxide (30 mmol) at room temperature for 2 hrs to give a thiol **4** (94%). An α,β-unsaturated carboxylic acid ester (3 mmol) was added into a solution of **4** (2 mmol) in methanol (10 mL) containing sodium methoxide (2 mmol) and the solution was stirred for 3 hrs at room temperature to yield the Michael adduct **5**. The addition of titanium tetrachloride (1.1 mmol) to a solution of **5** (1 mmol) and thiobenzoic acid (2 mmol) in methylene chloride (10 ml) at -78 °C and subsequent stirring of the solution for 20 min gave **6**. Table 1 shows the yields of **5a-d** and **6a-d.**

Table 1. Yield of **5** and **6**

run	R	R'	product **5**	yield(%)	product **6**	yield(%)
1	H	H	**5a**	93	**6a**	85
2	Me	H	**5b**	81	**6b**	81
3	Ph	H	**5c**	62	**6c**	94
4	H	Me	**5d**	93	**6d**	74

In order to synthesize optically active β-mercaptocarboxylic acid esters, optically active thiol **11** was prepared from L-lysine passing through the intermediates **7**-**10** as shown in Scheme 2.[7] The stereochemistry of **11** is estimated to be (2-R,6-S) by the facts which are described later.

Scheme 2



The Michael addition of **11** to α,β-unsaturated carboxylic acid esters was carried out under a variety of conditions to give optically active **6** (Scheme 3 and Table 2). The results in Table 2 show that types of solvent and base highly influenced the Michael addition reaction. Namely, the combination of methanol and sodium methoxide gave a moderate enantiomeric excess of **6b** (run 1) whereas it was improved to 88% under conditions of use of the

Grignard reagent as a base in ether (run 3). The reaction carried out in toluene gave a similar enantiomeric excess (run 4).

Scheme 3

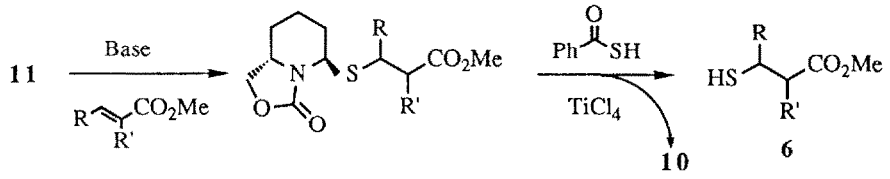


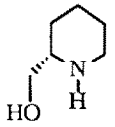
Table 2. Chemical yield and enantiomeric excess of **6** in the reaction of **11** with α,β-unsaturated carboxylic acid esters

run	R	R'	solvent	base	reaction time[a] (hr)	product **6**	yield (%)	ee (%)[c]
1	Me	H	MeOH	NaOMe	48[b]	**6b**	67	39
2	Me	H	THF	PrMgBr	5	**6b**	66	75
3	Me	H	Et_2O	PrMgBr	72	**6b**	54	88
4	Me	H	Toluene	PrMgBr	72	**6b**	52	82
5	Ph	H	THF	PrMgBr	120	**6c**	57	51
6	H	Me	Et_2O	PrMgBr	72	**6d**	51	48[d]

a) Reaction temperature was 0 °C. b) Reaction temperature was -20 °C.
c) Enantiomeric excess (ee) was measured by ^{1}H-NMR in the presence of Eu(hfc).
d) The enantioselectivity in the Michael addition of **11** to methyl methacrylate is determined at the stage of the protonation of the resultant enolate anion intermediate, though the enantiomeric excess shown in runs 1-5 are determined at the stage of the addition of the thiolate anion of **11** to α,β-unsaturated β-alkylcarboxylic acid esters.

The absolute stereochemistry of **11** was estimated as follows. The 6-position of **11** was proved to be a S-configuration since hydrogenation of **9** followed by hydrolysis gave α-hydroxymethylpiperidine **12**, of which optical rotation ($[\alpha]^{20}_D$=-16.1 (c=1:34, EtOH)) was identical with that of authentic sample.[10] On the other hand, the stereochemistry of 2-position of **11** was not always completely confirmed but it was estimated as R-configuration since the thiobenzoyl group would approach **9** from the opposite direction of the oxazolidone ring. The R-configuration of 2-position of **11** was also indirectly supported by the following facts. Namely, the compound **13** synthesized by the reaction of **7** with thiobenzoic acid (Scheme 4) would have a S-configuration at the 2-position since it has been known that the replacement of 2-methoxy group of **7** with a nucleophile predominantly took place from α-side.[8] Hydrolysis of **13** with sodium methoxide in methanol followed by

addition of the resultant thiol **14** to methyl crotonate gave L-**6b** ($[\alpha]^{20}_D$=-21.0° (c=1.0, $CHCl_3$)) (38% ee), while the reaction of **11** with methyl crotonate in methanol (run 1 in Table 2) gave R-**6b** ($[\alpha]^{20}_D$=+21.1° (c=1.0, $CHCl_3$)) (39% ee). Hence, the configuration of the 2-position of **11** seemed just opposite of that of **14**.



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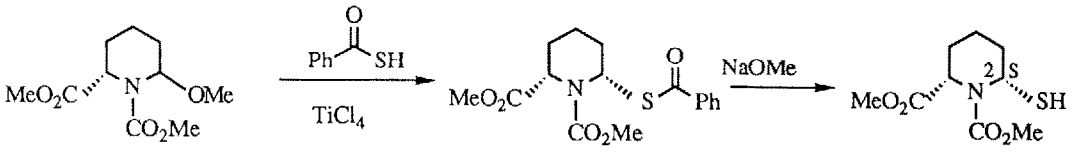
Scheme 4



7 **13** **14**

References and Notes

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