Asymmetric Reduction of Aromatic Ketones. II.[1] An Enantioselective Synthesis of Methyl (2*R*,3*S*)-3-(4-Methoxyphenyl)glycidate

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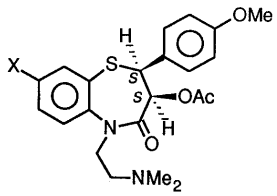
Received July 28, 1992

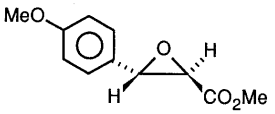
Asymmetric reduction of some 3-keto esters (6, 8, and 11) to 3-hydroxy esters (7, 9, and 12) with various chiral reducing agents was investigated. The products (9 and 12) were converted to methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (2*R*,3*S*-3), a key intermediate in the practical enantioselective synthesis of diltiazem (1).

Keywords diltiazem; asymmetric reduction; methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate; methyl 3-(4-methoxyphenyl)-3-oxopropionate; sodium (*S*)-prolinate–borane complex; methyl 2-chloro-3-(4-methoxyphenyl)-3-oxopropionate

Diltiazem (**1**) is a typical calcium channel blocker and has been used throughout the world as an effective antianginal and antihypertensive agent.[3] The enantiomerically pure compound (**1**) has been produced *via* the effective optical resolution of the intermediate nitro carboxylic acid (**4b**).[3b,4] Several alternative routes have been developed on account of the clinical importance of **1**. These include Sharpless epoxidation,[5] OsO_4-catalyzed asymmetric dihydroxylation,[6] asymmetric hydrocyanation,[7] Darzens reaction,[8] and Michael addition of thiophenol[9] with the use of various chiral auxiliaries, giving enantiomerically pure intermediates for the synthesis of **1**. Enzymatic kinetic resolution of the precursor of the intermediate (**4b**) has also been reported.[10]

However, the most plausible and practical candidate for the intermediate is apparently enantiomerically pure methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (2*R*,3*S*-**3**), since the reaction of **3** with 2-nitro- or 2-aminothiophenol diastereoselectively gave the *threo*-thiopropionic acid (**4**), leading to diltiazem *via* straightforward series of reactions (Chart 2).[3,11,12] The glycidate (2*R*,3*S*-**3**) can also be a useful intermediate for the synthesis of clentiazem (**2**), the 8-chloro isomer of diltiazem.[13]





3

diltiazem (**1**) : X=H

clentiazem (**2**) : X=Cl

Chart 1

To date, several synthetic approaches to (2*R*,3*S*)-**3** have been reported. These include conventional optical resolution of 3-(4-methoxyphenyl)glycidic acid,[14] enzymatic kinetic resolution of (±)-**3**,[15] and Darzens reaction in the presence of the lithium salt of a chiral organic base.[16] In this paper, we wish to report an efficient synthesis of (2*R*,3*S*)-**3** *via* asymmetric reduction of 3-keto esters (**6**, **8**, and **11**).

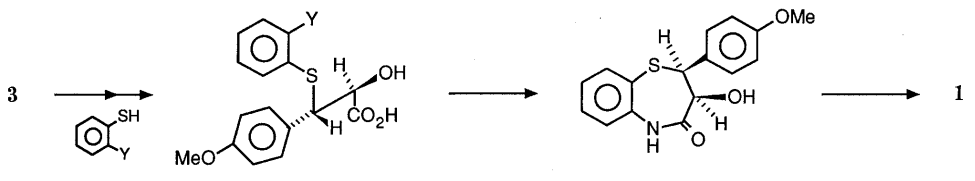
Asymmetric Reduction of Methyl 3-(4-Methoxyphenyl)-3-oxopropionate (6) Reduction of **6** with the reductant prepared from (*R*, *R'*)-*N*,*N'*-dibenzoylcystine, $LiBH_4$, and *tert*-BuOH according to Soai's procedure[17] (reductant A) gave the desired (*R*)-3-hydroxy ester ((*R*)-**7**) with high optical purity (86% ee) in 64% yield. On the other hand, reduction of **6** with sodium (*S*)-prolinate–borane complex (reducant B)[18] in tetrahydrofuran (THF) gave (*S*)-**7** with 75% ee in 81% yield (Table I). Conversion of **7** to the desired *trans*-glycidic ester (**3**) was examined by the method reported by Kraus and Taschner.[19] As a model experiment, however, treatment of (±)-**7** with lithium diisopropyl amide (LDA) followed by reaction with iodine (I_2) gave (±)-**3** in rather unsatisfactory yield (43.4%).

Asymmetric Reduction of Methyl 2-Chloro-3-(4-methoxyphenyl)-3-oxopropionate (8) The (3*S*)-alcohol (**9b**, **c**) was

TABLE I. Asymmetric Reduction of **6**

Reductant[a]	Conditions	Yield of 7[b] (%)	Enantiomeric excess[c] of 7 (% ee)	Configuration of C_3-OH
A	−78 °C, 1 h, THF	63	86	*R*
B	r.t., 3 d, THF	81	75	*S*

a) See text. *b*) Recovered starting material **6** was deduced. *c*) Determined by HPLC analysis (Optipac XC, *n*-hexane–EtOH (80 : 1)).



a : Y = NH_2 **b** : Y = NO_2

Chart 2

TABLE II. Asymmetric Reduction of **8** with Various Chiral Reducing Agents in THF

Entry	Reductant[a]	Condition	Yield of **9** (%)	Enantiomeric[b] excess (% ee)	Configuration[b] of C_3-OH	Ratio of isomers[c]			
						9a (2*R*,3*R*)	**9b** (2*S*,3*S*)	**9c** (2*R*,3*S*)	**9d** (2*S*,3*R*)
1	B	0 °C, 20 h	48[d]	69.3	*R*	40.8	8.6	6.8	43.9
2	C	0 °C, 17 h	58[d]	0.8	*S*	16.2	16.2	34.2	33.5
3	D	−5 °C, 22 h	44[d]	17.2	*R*	18.1	15.5	25.9	40.5
4	E	−78 °C, 3 h	28[e]	66.2	*R*	<1	<1	16.9	83.1
5	A	−78 °C, 1 h	76	75.4	*S*	5.0	45.5	42.2	7.3
6	F[f]	0 °C, 20 h	44	17.6	*S*	6.6	11.1	47.7	17.6
7	G	−78 °C, 2 h	44[d]	76.4	*S*	5.1	60.1	28.0	6.7
8	H	−78 °C, 0.5 h	68	66.8	*S*	7.1	54.2	29.2	9.5
9	I	−78 °C, 1.5 h	55[g]	60.0	*S*	3.6	35.5	45.5	16.3
10	J	−78 °C, 1.5 h	40[h]	54.0	*S*	2.9	34.1	42.9	20.0
11	K	−78 °C, 0.5 h	65[d]	36.4	*S*	2.1	6.3	60.9	29.6
12	L	r.t., 11 d	36[i]	59.1	*S*	7.3	25.1	54.5	13.1
13	M	0 °C, 1 h	11[j]	43.0	*R*	2.9	0.9	27.6	68.7
14	N	−78 °C, 4 h	11[k]	6.6	*S*	6.5	6.6	46.7	40.1
15	O	0 °C, 2 h	44[l]	5.4	*S*	0.5	0.4	52.2	46.9

a) Reductants A, B: see text. Reductant C: (*R*)-phenylglycine–$NaBH_4$. Reductant D: (*S*)-*tert*-leucine–$NaBH_4$. Reductant E: (*S*)-BINAL-H ($LiAlH_4$–(*S*)-(−)-1,1′-bi-2-naphthol–ethanol).[21] Reductant F: (*R*,*R*′)-*N*,*N*′-dibenzoylcystine–$NaBH_4$–*tert*-BuOH. Reductant G: (*R*,*R*′)-*N*,*N*′-bis(4-chlorobenzoyl)cystine–$LiBH_4$–*tert*-BuOH. Reductant H: (*R*,*R*′)-*N*,*N*′-bis(4-methoxybenzoyl)cystine–$LiBH_4$–*tert*-BuOH. Reductant I: (*R*,*R*′)-*N*,*N*′-di(1-naphthoyl)cystine–$LiBH_4$–*tert*-BuOH. Reductant J: (*R*,*R*′)-*N*,*N*′-dipivaloylcystine–$LiBH_4$–*tert*-BuOH. Reductant K: (*R*,*R*′)-*N*,*N*′-diisobutyrylcystine–$LiBH_4$–*tert*-BuOH. Reductant L: (+)-*B*-chlorodiisopinocamphenylborane.[23] Reductant M: (*R*)-3,3-diphenyl-1-methyltetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazapyrrole–B_2H_6.[26] Reductant N: (+)-Alpine-H.[27] Reductant O: 1,2;5,6-diisopropylidene-D-glucofuranoside–$NaBH_4$–isobutyric acid.[28] *b*) Enantiomeric excess and configuration at C_3 of the major isomer. *c*) The ratio was determined by HPLC analysis (Chiralcel OJ, *n*-hexane–iso-PrOH (7:3)). *d*) Starting material (**8**) and the diol (**10**) were detected in the crude reaction mixture but not isolated. *e*) Starting material (**8**) was recovered in 64% yield. *f*) When KBH_4 was used instead of $NaBH_4$, the reduction of **8** did not proceed. *g*) The main by-product was the diol (**10**) but it was not isolated. *h*) The dechlorinated product (**6**) was obtained in 31% yield. *i*) Formation of **6** and **10** was not observed. *j*) Starting material (**8**) was recovered in 57.2% yield. *k*) Recovered **8** (25%) was the main product. *l*) Starting material (**8**) was recovered in 26% yield.

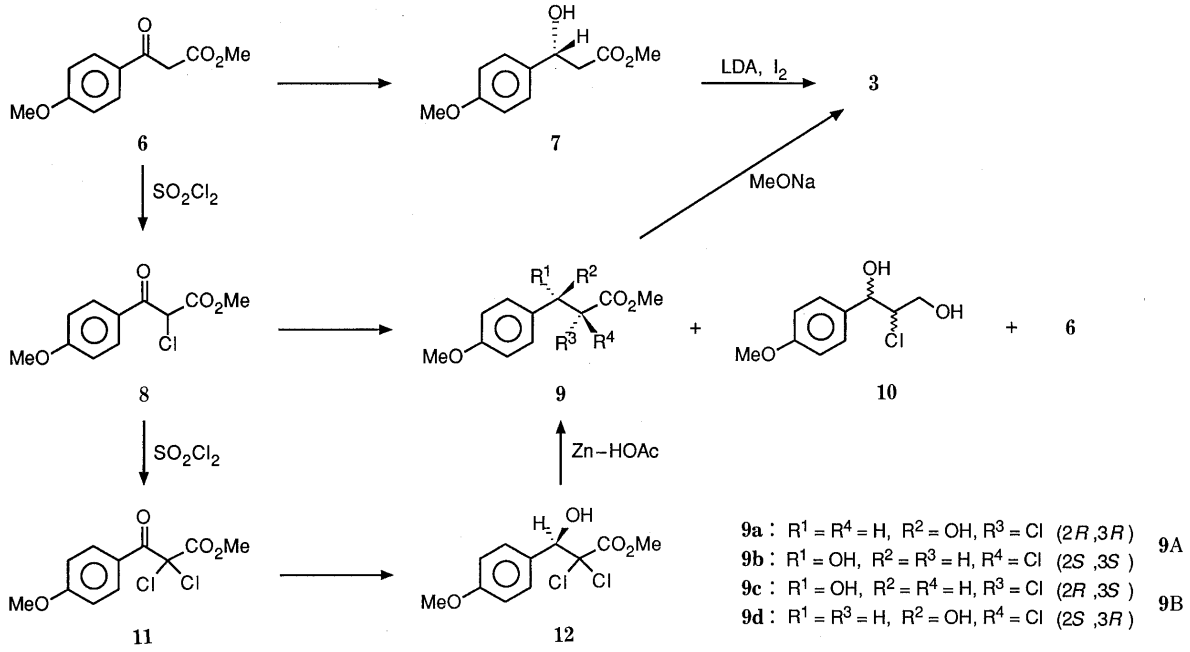


Chart 3

reported to afford easily the desired (2*R*,3*S*)-glycidic ester ((2*R*,3*S*)-**3**) on treatment with sodium methoxide in methanol, regardless of the configuration of the chloro substituent at the C_2-position.[16] Similar observations were also reported for analogous compounds.[20] Therefore, enantioselective formation of the (3*S*)-alcohol is required to obtain (2*R*,3*S*)-**3**. We next examined the reduction of **8** using various chiral reducing agents. The 2-chloro-3-oxo-ester **8** was easily prepared from **6**. The results are summarized in Table II. Reduction of **8** with the reductant B in THF at 0 °C gave the alcohol (**9**) with 3*R*-configuration predominantly (69%) (entry 1). By means of high-performance liquid chromatographic (HPLC) analysis using a Chiralcel OJ column, the ratio of the four optically active isomers, **9a** (2*R*,3*R*), **9b** (2*S*,3*S*), **9c** (2*R*,3*S*), and **9d** (2*S*,3*R*) was determined to be 40.8 : 8.6 : 6.8 : 43.9 (see below). Use of other amino acids such as (*R*)-(−)-phenylglycine and (*S*)-(−)-*tert*-leucine (entries 2 and 3) greatly lowered the enantioselectivity.

In the series of reductions with amino acid–borane complexes described above, however, use of the unnatural series of amino acids appears to be necessary to obtain the

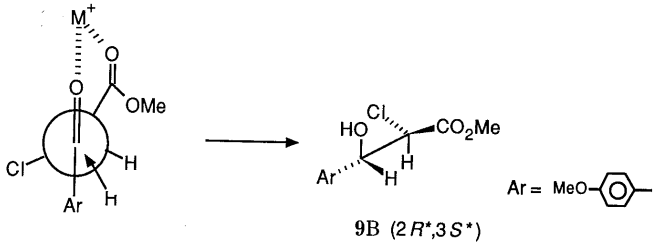


Chart 4

desired enantioselectivity at the C_3-position.

Reduction of **8** with litium aluminium hydride-ethanol-(*S*)-1,1′-bi-2-naphthol complex ((*S*)-BINAL-H[21]) at −78 °C gave **9c** and **9d** in a ratio of 17:83 in 28% yield together with recovery of the starting material (64%) (Table II, entry 4). The undesired (3*R*)-hydroxy ester (**9d**) was also obtained as a main product in this case. Moreover, the reduction was influenced by the configuration of the chloro substituent at the C_2-position, giving (2*R**,3*S**) isomers selectively. Attack of hydride may take place only from the less hindered side in the chelated intermediate depicted in Chart 4. So-called kinetic resolution of **8** at the C_2-position was conjectured.

Then, the desired enantioselectivity at the C_3-position was successfully obtained by use of reductant A. The reduction of **8** with reductant A at −78 °C in THF gave **9** in 76% yield. HPLC analysis of the product revealed that the ratio of the four isomers (**9a**, **b**, **c**, and **d**) was 5.0:45.5:42.2:7.3 (entry 5). Accordingly, the desired (3*S*)-hydroxy ester (3*S*-**9**) was obtained in 75% ee regardless of the configuration of the chloro substituent. On treatment with sodium methoxide in methanol, this mixture was successfully converted to the desired glycidate ((2*R*,3*S*)-**3**; 82% ee) in 81% yield.

To improve the enantioselectivity at the C_3-position of the above reduction, we examined the effects of several modifications of reductant A (Table II). Replacement of $LiBH_4$ with $NaBH_4$ resulted in a marked decrease of both reactivity and enantioselectivity (entry 6). No reaction was observed when KBH_4 was used. As regards the effect of modifying the *N*-acyl group of cystine, the 4-substituted benzoyl (entries 7 and 8) and 1-naphthoyl (entry 9) derivatives gave results similar to those obtained with the *N*-benzoyl derivative (reductant A). The use of bulky aliphatic acyl groups such as pivaloyl (entry 10) and isobutyryl (entry 11) lowered the enantioselectivity.

In the reduction of **8** described above, concomitant formation of the diol (**10**) was observed in most cases (Table II). Use of (*S*)-2-(2,6-dimethylphenyl)aminomethyl-pyrrolidine–$LiBH_4$ complex[22] at −78 °C afforded **10** as a main product with no detectable formation of **9**. The stereochemistry of **10** was not ascertained. In the reduction with reductant A, the formation of **10** was not observed. Formation of the dechlorinated product (**6**) was observed in entry 10.

Reductant A was thus found to be an useful chiral reducing agent in the reduction of **8** to the desired alcohol (**9**) with 3*S*-configuration, with good chemo- and enantioselectivity.

Asymmetric Reduction of Methyl 2,2-Dichloro-3-(4-methoxyphenyl)-3-oxopropionate (11) Finally, we examined the reduction of **11** with several chiral reducing agents (Table III). Good enantioselectivity was observed only with reductant L[23] (entry 4). However, the configuration of the main product was 3*R*, the chemical yield being quite low (28%). On treatment with Zn and HOAc, the 2,2-dichloro-3-hydroxy ester (**12**) obtained in entry 2 was converted to a mixture of **9a**, **b**, **c**, and **d** (25.6:15.5:18.2:40.7) in 88% yield.

Table III. Asymmetric Reduction of **11** in THF

Entry	Reductant[a]	Conditions	Yield of **12** (%)	Enantiomeric[b] excess of **12** (% ee)	Configuration at the C_3 of major product
1	A	−78 °C, 1 h	80.1	7.7	*R*
2	Q	−78 °C, 0.5 h	70.6	29.4	*R*
3	B	0 °C, 5 h	17.2[c]	3.2	*R*
4	L	r.t., 14 d	27.9	92.2	*R*
5	C	−78 °C, 1 h	28.2[d]	22.6	*R*

a) Reductants A, B, L, C: see Tables I and II, and footnote 1. Reductant Q: (*S*)-2-amino-3-methyl-1,1-diphenylpentan-1-ol–B_2H_6.[29] *b*) Determined by HPLC analysis (Chiralcel OJ, *n*-hexane–iso-PrOH (7:3)). *c*) Starting material (**11**) was recovered in 25.2% yield. *d*) Starting material (**11**) was recovered in 61.8% yield.

Table IV. ^{1}H-NMR Spectral Data for **9**

	9A (*R**,*R**) (**9a**, **b**)	**9**B (*R**,*S**) (**9c**, **d**)
C_2-H	δ 4.35 (J_{2-3} = 7.8 Hz)	δ 4.42 (J_{2-3} = 6.8 Hz)
C_3-H	δ 5.00 (J_{2-3} = 7.8 Hz)	δ 5.08 (J_{2-3} = 6.8 Hz)

9A (**9a,b**) (2*R**,3*R**) 9B (**9c,d**) (2*R**,3*S**)

Chart 5

Absolute Configurations of the Intermediates (9a—d) The absolute configurations of **9a**, **b**, **c**, and **d** were determined as follows. As described above, the configuration of the hydroxyl group at the C_3-position of the two major components (**9b** and **9c**) obtained by the reduction of **8** with reductant A (Table II, entry 5) is *S*, since (2*R*,3*S*)-**3** (82% ee) was obtained in good yield on treatment of the whole mixture with sodium methoxide.

The mixture of **9a—d** could be separated into the two diastereoisomers (**9**A and **9**B) by flash column chromatography (silica gel). Oishi and Nakata reported that reduction of 3-keto ester with metal hydride gave the product derived from the attack of hydride from the less hindered side when a counter metal has a coordinating ability to the carbonyl oxygen.[24]

Reduction of **8** with $LiBH_4$ gave a single diastereoisomer whose ^{1}H-NMR spectrum was identical to that of diastereoisomer (**9**B) (2*R**, 3*S**). The stereochemistry of **9**A and **9**B was also deduced from their ^{1}H-NMR spectra (Table IV). When the substituents on vicinal carbon atoms can form a hydrogen bond in a six-membered chair conformation, the *J* value between the vicinal hydrogens is known to be larger for the *R**,*R**-isomer than for the *R**,*S**-isomer.[25] On the basis of the J_{2-3}-values (Table IV) and the plausible conformations depicted in Chart 5, the

relative configurations of the diastereoisomers (**9A** and **9B**) were assigned as 2*R**,3*R** and 2*R**,3*S**, respectively.

Each diastereoisomer (**9A** and **9B**) could be separated by HPLC (Chiralcel OJ column) into the optical isomers (**9a** and **9b**) and (**9c** and **9d**), respectively. The absolute configurations of the four optical isomers (**9a**, **b**, **c**, and **d**) were, therefore, determined to be (2*R*,3*R*), (2*S*,3*S*), (2*R*,3*S*), and (2*S*,3*R*), respectively.

Experimental

All melting points are uncorrected. IR spectra were recorded on an Analect RFX-65 spectrophotometer. Mass spectra (MS) were recorded on an INCOS 50 (Finnigan MAT Inc.) or JEOL JMS HX-100, and ^{1}H-NMR on a JEOL FX-200 or Hitachi RH-90H spectrometer with tetramethylsilane as the internal standard. Optical rotations were measured at 20 °C with an Union Giken PM-201 polarimeter. The characterization of the products was performed by comparison of IR, ^{1}H-NMR, and mass spectra and thin-layer chromatographic (TLC) behavior with those of authentic samples.

Methyl 3-(4-Methoxyphenyl)-3-oxopropionate (6) A solution of 4-methoxyacetophenone (100 g, 0.67 mol) in toluene (250 ml) was added to a mixture of Na (sand, 30.7 g, 1.33 mol) and dimethylcarbonate (300 g, 3.33 mol) in toluene (600 ml) at 84—86 °C during a period of 2.5 h. The reaction mixture was stirred at 82—83 °C for 1.5 h, concentrated *in vacuo* and diluted with iso-Pr_2O (1 l). After cooling, the precipitated crystals were collected on a filter and washed with iso-Pr_2O (500 ml) to give the Na salt of **6**, which was added to a stirred solution of AcOH (100 g, 1.66 mol) in a large amount of water. The mixture was extracted with EtOAc. The extracts were combined, washed with water, dried, concentrated, and distilled to give **6** (131.6 g, 95%), bp 148—150 °C (0.9 mmHg).[30]

Asymmetric Reduction of Methyl 3-(4-Methoxyphenyl)-3-oxo-propionate 6 with Reductant B $NaBH_4$ (266 mg, 7 mmol) was slowly added to a stirred suspension of (*S*)-proline (920 mg, 8 mmol) in THF (20 ml). After heating of the mixture under reflux for 1.5 h, a solution of **6** (416 mg, 2 mmol) in THF (5 ml) was added at room temperature and the reaction mixture was stirred at room temperature for 3 d. Then 10% aqueous HCl was added to the reaction mixture and the whole was extracted with AcOEt. The extracts were combined, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over Na_2SO_4, and then concentrated *in vacuo*. The residual oil was purified by column chromatography (silica gel), eluted with AcOEt–*n*-hexane (1 : 3) to give (*S*)-**7** (210 mg, 50% (81% yield allowing for the recovered starting material)), 75% ee as determined by HPLC [column, Optipack XC; eluent, *n*-hexane–EtOH (80 : 1); retention times, 35.8 min for (*R*)-**7** and 38.0 min for (*S*)-**7**; flow rate, 1.0 ml/min]. The starting material **6** was recovered in 38% yield (160 mg).

Conversion of (±)-7 to (±)-3 i) A solution of $NaBH_4$ (1.60 g, 42.1 mmol) in EtOH (30 ml) was added to a solution of **6** (8.57 g, 41.2 mmol) in EtOH (30 ml) at −30 °C. The mixture was stirred at −30 °C for 1 h, warmed to 0 °C, decomposed by addition of 10% aqueous HCl, concentrated to remove EtOH, and extracted with AcOEt. The extracts were combined, washed with saturated aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and then concentrated. The residual oil was purified by column chromatography (silica gel, eluted with *n*-hexane–AcOEt (1 : 1) to give (±)-**7** (7.92 g, 91%), as a colorless solid, mp 49—50 °C.[31] IR (neat) *v*: 3480, 1735, 1610 cm^{-1}. MS *m/z*: 210 (M^+), 137 (base peak). ^{1}H-NMR ($CDCl_3$) *δ*: 2.50—3.00 (2H, m, CH_2), 3.10 (1H, d, *J*=3.3 Hz, OH), 3.71 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 5.08 (1H, m, CHOH), 6.85 (2H, d, *J*=8.0 Hz), and 7.28 (2H, d, *J*=8.0 Hz).

ii) A solution of (±)-**7** (525 mg, 2.5 mmol) in THF (5 ml) was added to a solution of LDA (6 mmol) in THF (10 ml) at −78 °C. Stirring was continued at −78 °C for 1.5 h, then I_2 (635 mg, 2.5 mmol) was added and the reaction mixture was warmed to room temperature, concentrated *in vacuo*, diluted with water, and extracted with AcOEt. The extracts were combined, washed with water, dried, concentrated, and purified by column chromatography (silica gel, eluted with *n*-hexane–AcOEt (4 : 1)) to give (±)-*trans*-glycidic ester **3** (226 mg, 43%) as a colorless solid, which was identical with an authentic sample.[32]

Methyl 2-Chloro-3-(4-methoxyphenyl)-3-oxopropionate (8) SO_2Cl_2 (85 g, 0.63 mol) was added to a solution of **6** (131 g, 0.63 mol) in CCl_4 (1.3 l) at 45—50 °C during a period of 1 h. The reaction mixture was stirred at 45—50 °C for 1 h, then diluted with ice-water. The organic layer was separated, washed with water, dried, and distilled to give **8** (140 g, 92%) as a pale yellow oil, bp 143.5—145 °C (0.3 mmHg). IR (liquid) *v*: 1750, 1660 cm^{-1}. MS *m/z*: 244 (M^++2), 242 (M^+). ^{1}H-NMR ($CDCl_3$) *δ*: 3.82 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 5.91 (1H, s, –CHCl–), 6.92 (2H, d, *J*=9.0 Hz), 7.97 (2H, d, *J*=9.0 Hz). *Anal.* Calcd for $C_{11}H_{11}ClO_4$: C, 54.45; H, 4.57; Cl, 14.61. Found: C, 54.39; H, 4.51; Cl, 14.95.

Asymmetric Reduction of 8 with Reductant A (Table II, Entry 5) A solution of 2 M $LiBH_4$ in THF (5.4 ml, 10.8 mmol) was added to a mixture of (*R*,*R*')-*N*,*N*'-dibenzoylcystine (1.62 g, 3.6 mmol) and *tert*-BuOH (357 mg, 4.8 mmol) in THF (20 ml) at room temperature. The reaction mixture was heated under reflux for 1 h, then a solution of **8** (728 mg, 3 mmol) in THF (5 ml) was added to it (reductant A) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, then decomposed by addition of 10% HCl at −78 °C to adjust the pH to 3—4, and finally adjusted to pH 7—8 with aqueous $NaHCO_3$. The reaction mixture was warmed to room temperature, concentrated *in vacuo*, diluted with water, and extracted with AcOEt. The extracts were combined, washed with saturated aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated. The residual oil was separated by column chromatography (silica gel, eluted with *n*-hexane–AcOEt (4 : 1)) to give a mixture of (*R**,*R**)- and (*R**,*S**)-2-chloro-3-hydroxy ester (**9**) (555 mg, 76%) as a colorless oil. A value of 75.4% ee at the C_3-position of the major isomer was determined by HPLC analysis [column, Chiralcel OJ (Daicel Chemical Industry); eluent, *n*-hexane–iso-PrOH (7 : 3); flow rate, 0.5 ml/min; detector, 254 nm; retention times, 27.06, 29.84, 37.63, and 49.43 min for **9a**, **9b**, **9c**, and **9d**, respectively].

Isomers **9A** (*R**,*R**-isomer) and **9B** (*R**,*S**-isomer) were separated by flash column chromatography (silica gel, eluted with *n*-hexane–AcOEt (4 : 1)): **9B** was obtained from the first eluate and then pure **9A** was obtained from the third eluate after the elution of a mixture of **9A** and **9B**. **9B** (**9c**, **9d** (*R**,*S**-**9**)): IR (liquid) *v*: 3490, 1745, 1610 cm^{-1}. MS *m/z*: 244 (M^+), 246 (M^++2), 137 (base peak). ^{1}H-NMR ($CDCl_3$) *δ*: 2.90 (1H, d, *J*=3.9 Hz, OH), 3.67 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.42 (1H, d, *J*=6.8 Hz, CHCl), 5.08 (1H, dd, *J*=3.9, 6.8 Hz, CHOH), 6.89 (2H, d, *J*=8.8 Hz, arom. H), 7.30 (2H, d, *J*=8.8 Hz, arom. H). **9A** (**9a**, **9b** (*R**,*R**-**9**)): IR (liquid) *v*: 3480, 1740, 1610 cm^{-1}. MS *m/z*: 244 (M^+), 246 (M^++2), 137 (base peak). ^{1}H-NMR ($CDCl_3$) *δ*: 2.88 (1H, d, *J*=4.4 Hz, OH), 3.81 (6H, s, OCH_3), 4.35 (1H, d, *J*=7.8 Hz, CHCl), 5.00 (1H, dd, *J*=4.4, 7.8 Hz, CHOH–), 6.91 (2H, d, *J*=8.8 Hz, arom. H), 7.32 (2H, d, *J*=8.9 Hz, arom. H). Compounds **6** and **10** were detected by TLC but they were not isolated.

Asymmetric Reduction of 8 with Reductant B (Table II, Entry 1) A mixture of $NaBH_4$ (266 mg, 7 mmol) and (*S*)-proline (920 mg, 8 mmol) in THF (10 ml) was heated under reflux and under an argon atmosphere for 2 h. A solution of **8** (364 mg, 1.5 mmol) in THF (5 ml) was added to the mixture at 0 °C. The reaction mixture was stirred at 0 °C for 20 h, then decomposed by addition of 10% aqueous HCl and worked up in the same manner as described above. The obtained oil was separated by column chromatography (silica gel, eluted with EtOAc–*n*-hexane (1 : 3)). The hydroxy ester (3*R*)-**9** (230 mg, 47.5%) was obtained as a colorless oil. 69.3% ee. Recovery of the starting material **8** and formation of the diol **10** were observed on TLC.

The diol **10** was obtained quantitatively as a mixture of diastereoisomers when the reaction mixture was stirred at room temperature overnight. IR (liquid) *v*: 3400 cm^{-1}. MS *m/z*: 216 (M^+), 218 (M^++2), 137 (base peak). ^{1}H-NMR ($CDCl_3$) *δ*: 2.04 (0.5H, t, *J*=6.0 Hz, OH), 2.30 (0.5H, t, *J*=6.0 Hz, OH), 2.63 (0.5H, d, *J*=3.4 Hz, OH), 2.67 (0.5H, d, *J*=3.4 Hz, OH), 3.6—4.0 (2H, m, CH_2O), 4.0—4.4 (1H, m, CHCl), 4.8—5.0 (1H, m, CHOH), 3.81 (3H, s, OCH_3), 6.91 (2H, d, *J*=8.8 Hz, arom. H), 7.31 (2H, d, *J*=8.8 Hz, arom. H).

Conversion of 9 to (−)-3 A solution of 28% NaOMe in MeOH (0.312 ml, 1.62 mmol) in MeOH (3 ml) was slowly added to a solution of **9** (377 mg, 1.54 mmol) (Table II, entry 5) in MeOH (9 ml) at 0 °C under an argon atmosphere. The reaction mixture was stirred at 0 °C for 1.5 h and then at room temperature for 10 min, diluted with ice-water, and extracted with Et_2O. The extracts were combined, washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by flash column chromatography (silica gel, eluted with EtOAc–*n*-hexane (1 : 3)) and then triturated with iso-PrOH–*n*-hexane (1 : 1) to give (−)-**3** (259 mg, 81%) as colorless crystals of 82% ee as determined by HPLC analysis [column, Chiralcel OJ; eluent, *n*-hexane–iso-PrOH (7 : 3); flow rate, 1 ml/min; detector, 254 nm; retention times, 13.9 and 16.4 min for (+)-**3** and (−)-**3**, respectively]. mp 84—86 °C $[\alpha]_D^{20}$ −143.3° (*c*=0.3, MeOH).[15]

Synthesis of (*R*,*R*')-*N*,*N*'-Diacylcystine Under ice-cooling and vigorous

stirring, 1-naphthoyl chloride (21.0 g, 110 mmol) and 2 N NaOH (50 ml) were added simultanously to a mixture of a solution of (*R*)-cystine (12.02 g, 50 mmol) in 2 N NaOH (50 ml) and Et_2O (30 ml) during a period of 30 min. The reaction mixture was stirred at room temperature for 1 h, then acidified with 10% HCl and the precipitated crystals were collected on a filter, washed with Et_2O and water, and then dried to give (*R,R'*)-*N,N'*-di(1-naphthoyl)cystine (9.2 g, 34%). mp 156—159 °C (iso-PrOH). IR (Nujol) *v*: 3280, 1725, 1705, 1645, 1620 cm^{-1}. MS *m/z*: 549 (MH^+). ^{1}H-NMR (DMSO-d_6) δ: 3.31 (4H, m, $CH_2 \times 2$), 4.85 (2H, m, –CH– × 2), 7.6 (8H, m), 8.0 (4H, m), 8.3 (2H, m), 8.94 (2H, d, J=7.8 Hz, NH × 2), 12.7 (2H, br s). *Anal.* Calcd for $C_{28}H_{24}N_2O_6S_2$: C, 61.30; H, 4.41; N, 5.11; S, 11.69. Found: C, 61.11; H, 4.35; N, 5.23; S, 11.77.

N,N'-Dipivaloyl-, *N,N'*-bis(4-methoxybenzoyl)-, *N,N'*-bis (4-chlorobenzoyl)-, and *N,N'*-diisobutyrylcystine were synthesized in the same manner as described above.

(*R,R'*)-*N,N'*-Dipivaloylcystine: 84.3% yield, mp 163—165 °C (dec.) (AcOEt–Et_2O). IR (Nujol) *v*: 3435, 3420, 1735, 1615 cm^{-1}. MS (FAB) *m/z*: 409 (MH^+), 204 (base peak). ^{1}H-NMR (DMSO-d_6) δ: 1.11 (18 H, s), 3.1 (4H, m), 4.45 (2H, m), 7.65 (2H, d, J=8.1 Hz), 12.7 (2H, br s, $CO_2H \times 2$). *Anal.* Calcd for $C_{16}H_{28}N_2O_6S_2$: C, 47.04; H, 6.91; N, 6.86; S, 15.70. Found: C, 47.24; H, 7.01; N, 6.68; S, 15.69.

(*R,R'*)-*N,N'*-Bis(4-methoxybenzoyl)cystine: 47% yield. mp 130—132 °C (dec.) (EtOH). IR (Nujol) *v*: 3330, 3460, 1725, 1635 cm^{-1}. MS (FAB) *m/z*: 530 (M + Na^+). ^{1}H-NMR (DMSO-d_6) δ: 3.25 (4H, m, $-CH_2- \times 2$), 3.80 (6H, s, $OCH_3 \times 2$), 4.6 (2H, m, –CH– × 2), 6.98 (4H, d, J=8.8 Hz), 7.83 (4H, d, J=8.8 Hz), 8.14 (2H, d, J=7.0 Hz, NH × 2). *Anal.* Calcd for $C_{22}H_{24}N_2O_8S_2$: C, 51.96; H, 4.76; N, 5.51; S, 12.61. Found: C, 51.12; H, 4.64; N, 5.58; S, 12.74.

(*R,R'*)-*N,N'*-Bis(4-chlorobenzoyl)cystine: 35% yield. mp 225—226.5 °C (dec.) (H_2O). IR (Nujol) *v*: 3380, 1725, 1705, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.25 (4H, m, $-CH_2- \times 2$), 4.70 (2H, m, –CH– × 2), 7.50 (4H, d, J=8.6 Hz), 7.87 (4H, d, J=8.6 Hz), 8.84 (2H, d, J=8.0 Hz, NH × 2). *Anal.* Calcd for $C_{20}H_{18}Cl_2N_2O_6S_2$: C, 46.43; H, 3.51; Cl, 13.70; N, 5.41; S, 12.39. Found: C, 46.61; H, 3.70; Cl, 13.55; N, 5.59; S, 12.45.

(*R, R'*)-*N,N'*-Diisobutyrylcystine: 49% yield. mp 151—153 °C (dec.) (EtOH–Et_2O). IR (Nujol) *v*: 3310, 1735, 1635 cm^{-1}. MS (FAB) *m/z*: 403 (M^+ + Na). ^{1}H-NMR (DMSO-d_6) δ: 1.00 (12H, d, J=6.8 Hz, $CH_3 \times 4$), 2.45 (2H, m, CH), 3.05 (4H, m, $-CH_2- \times 2$), 4.45 (2H, m, –CH– × 2), 8.08 (2H, d, J=8.1 Hz, NH × 2), 12.6 (2H, br s, COOH × 2). *Anal.* Calcd for $C_{14}H_{24}N_2O_6S_2$: C, 44.20; H, 6.36; N, 7.36; S, 16.85. Found: C, 44.22; H, 6.54; N, 7.47; S, 16.76.

Methyl 2,2-Dichloro-3-(4-methoxyphenyl)-3-oxopropionate (11) Sulfuryl chloride (34 g, 252 mmol) was added to a solution of **6** (20 g, 96.1 mmol) in CCl_4 (200 ml) at room temperature. The mixture was heated under reflux for 20 h, concentrated, diluted with water, and extracted with AcOEt. The extracts were combined, washed with water, dried, and concentrated. The residual oil was purified by column chromatography (silica gel, eluted with *n*-hexane–AcOEt (20 : 3)) to give **11** (22.5 g, 84.5%) as a colorless oil. IR (liquid) *v*: 1765, 1740, 1700, 1680 cm^{-1}. MS *m/z*: 276 (M^+), 278 (M^+ + 2), 135 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.94 (2H, d, J=9.2 Hz, arom. H), 8.05 (2H, d, J=9.2 Hz, arom. H).

Asymmetric Reduction of 11 with Reductant Q and Conversion to 9 Diborane in THF (1.0 M solution, 30 ml) was added to a solution of (*S*)-2-amino-3-methyl-1,1-diphenylpentan-1-ol (404 mg, 1.5 mmol) in THF (4 ml) under an argon atmosphere at −78 °C, and the mixture was slowly warmed to 0 °C (reductant Q). Under cooling with dry ice–acetone a solution of **11** (262 mg, 1.07 mmol) in THF (5 ml) was added to the solution of reductant Q and the reaction mixture was stirred for 0.5 h. After quenching of the reaction with 10% aqueous HCl, the reaction mixture was worked up in the same manner as described above and purified by column chromatography (silica gel, eluted with *n*-hexane–AcOEt (4 : 1)) to give (*R*)-**12** (211 mg, 70.6%). The enantiomeric excess was determined to be 29.4% ee by HPLC analysis [column, Chiralcel OJ; eluant, *n*-hexane–iso-PrOH (70 : 30); flow rate, 0.6 ml/min; pressure, 17 kg/cm^2; detector, 230 nm; retention times, 30.9 min for (*R*)-**12** and 37.04 min for (*S*)-**12**].

The (*R*)-rich-**12** obtained above (151 mg, 0.54 mmol) was dissolved in AcOH (0.5 mol) and Zn powder (37 mg, 0.57 mmol) was added to the solution at room temperature. The reaction mixture was stirred at room temperature for 1.5 h, diluted with water and extracted with AcOEt. The extracts were combined, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried, and concentrated. The residual oil was purified by column chromatography (silica gel, eluted with *n*-hexane–iso-PrOH (7 : 3)) to give **9** (116 mg, 87.8% (32.6% ee) as a colorless oil, which was analyzed by HPLC. The ratio of **9a** : **9b** : **9c** : **9d** was 25.6 : 15.5 : 18.2 : 40.7.

Acknowledgments We thank Dr. H. Abe of this laboratory for HPLC analysis and the staff of the Analytical Department for elemental analysis and spectral measurements. Thanks are also extended to Dr. S. Saito, R&D Executive of this company for his interest and encouragement.

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