HETEROCYCLES, Vol. 65, No. 5, 2005, pp. 1139 - 1157
Received, 31st January, 2005, Accepted, 11th March, 2005, Published online, 11th March, 2005

PRACTICAL SYNTHESIS OF CHIRAL *CIS*-CYCLOHEX-4-ENE-1,2-DICARBOXYLIC ACID DERIVATIVES BY UTILIZING (4*S*)-ISOPROPYL-1,3-THIAZOLIDINE-2-THIONE †

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Abstract – Both enantiomers of chiral *cis*-cyclohex-4-ene-1,2-dicarboxylic acid derivatives were synthesized by optical resolution of the corresponding enantiomeric mixtures by utilizing (4*S*)-isopropyl-1,3-thiazolidine-2-thione followed by mild aminolysis, methanolysis, and hydrolysis.

INTRODUCTION

Chiral differentiation between two identical carbonyl groups of prochiral □□symmetric dicarboxylic acids utilizing an enzymatic or a nonenzymatic procedure should be a rational strategy for asymmetric syntheses of biologically active compounds, because the resultant chiral products can be subjected to further "enantioconvergent and enantiodivergent" transformation on the basis of latent □-symmetry.[1] Previously, we reported a novel nonenzymatic chiral induction into prochiral □-symmetric dicarboxylic acids by utilizing a functional heterocycle, (4*R* or 4*S*)-methoxycarbonyl-1,3-thiazolidine-2-thione.[1-4] In the course of our series of studies on the chiral induction utilizing C4-chiral 1,3-thiazolidine-2-thiones,[2-6] we achieved a highly enantioselective aminolysis of *cis*-cyclohex-4-ene-1,2-dicarboxylic anhydride (**1**) by employing the sodium salt of (4*S*)-isopropyl-1,3-thiazolidine-2-thione [(4*S*)-IPTT][6] in THF-DMSO.[7] This particular *meso* compound (**1**) is a useful prochiral precursor for asymmetric synthesis of biologically active compounds such as carbapenems, (+)-carbacyclin, and enzyme inhibitors (*vide infra*).[8,9] (4*S*)-IPTT seemed to be available not only for asymmetric aminolysis of prochiral dicarboxylic anhydrides but

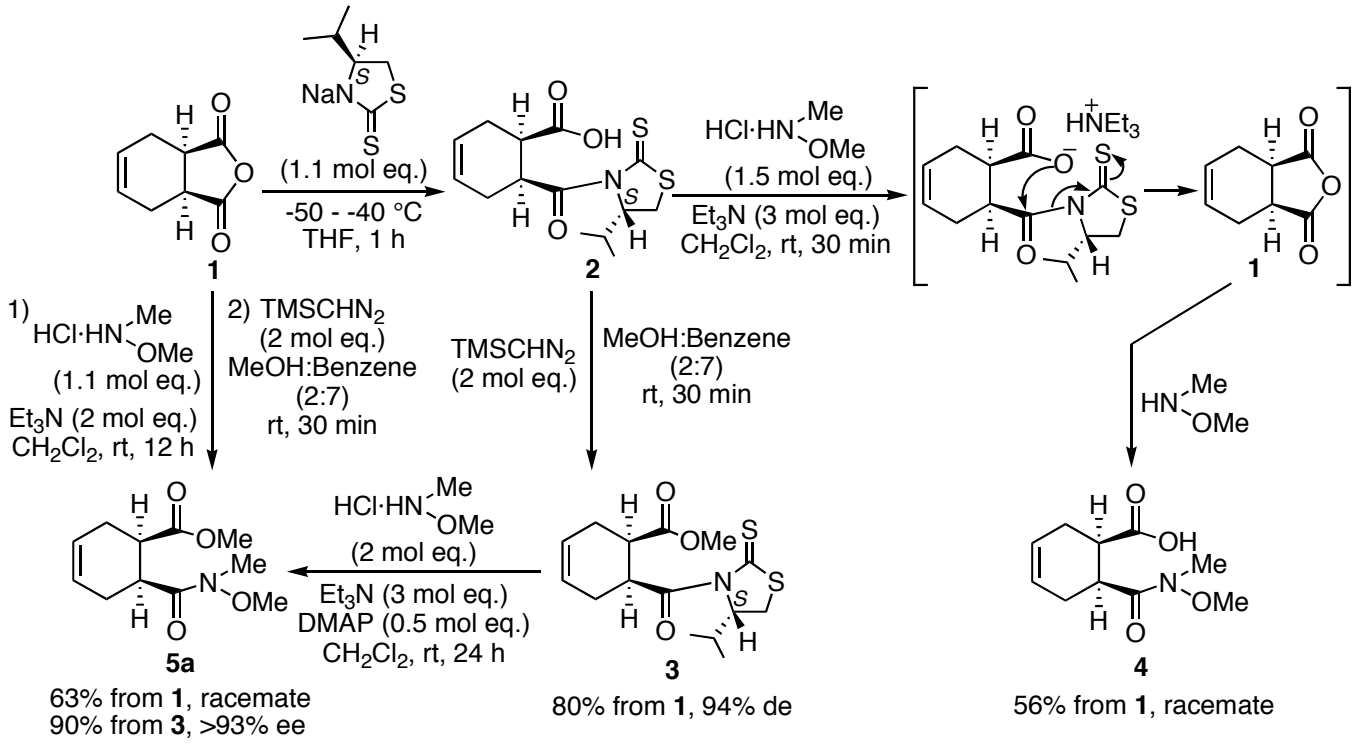
† Dedicated to Dr. Pierre Potier, Emeritus Director of C.N.R.S., in celebration of his 70th birthday.

also practically useful for optical resolution of the enantiomeric mixtures of various chiral carboxylic acids, due to the easy crystallization of its carboxylic amides and easy separation of both the yellow diastereomers by monitoring their yellow bands on a silica gel column. Acylamides of *N*-methoxy-*N*-methylamine (Weinreb amine) have been widely used as versatile synthetic intermediates in organic synthesis since they react with Grignard and other organometallic reagents to give the corresponding ketones.[10] Here, we report the practical syntheses of chiral *cis*-cyclohex-4-ene-1,2-dicarboxylic acid derivatives by utilizing asymmetric aminolysis or optical resolution with (4*S*)-IPTT followed by aminolysis of the (4*S*)-IPTT amides with the Weinreb amine and other amines. Both enantiomers of chiral *cis*-cyclohex-4-ene-1,2-dicarboxylic acid derivatives should be useful for development of new enzyme inhibitors (*vide infra*).

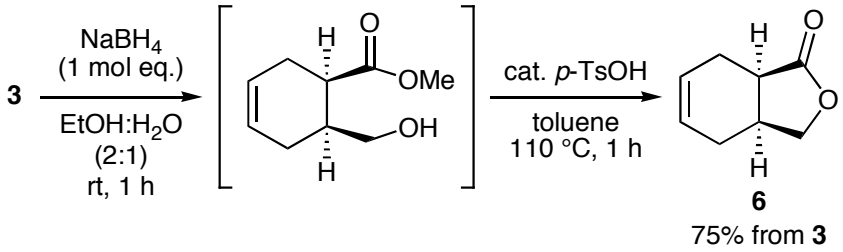
RESULTS AND DISCUSSION

Asymmetric aminolysis of dicarboxylic anhydride (**1**) with sodium salt of (4*S*)-IPTT in THF-DMSO at –50 - –40 °C gave a crude monocarboxylic acid (**2**), which was treated with $TMSCHN_2$ in MeOH-benzene (2:7) to afford methyl ester (**3**) in 80% yield and 94% ee as shown in Scheme 1. The stereochemistry of **3** was determined by its chemical conversion to the antipodal compound (**6**) of the known lactone *via* reduction of **3** with $NaBH_4$ in EtOH-H_2O (2:1) followed by lactonization of the resulting hydroxymethyl derivative with a catalytic amount of TsOH in toluene at 110 °C for 1 h as shown in Scheme 2.[9] The crude (4*S*)-IPTT amide (**2**) was allowed to react with *N*-methoxy-*N*-methylamine hydrochloride in the presence of Et_3N to afford the optically active amide (**4**). However, the chiral Weinreb monoamide (**4**) could not be furnished; instead, racemic amide (**4**) was obtained in 56% yield from **1**. This outcome can be explained as follows. In the presence of a small excess of Et_3N and *N*-methoxy-*N*-methylamine, the resulting carboxylate would attack to the carbonyl group of the (4*S*)-IPTT amide moiety bearing an "active amide structure" to generate anhydride (**1**), which has been shown to react with the Weinreb amine to afford racemic amide (**4**). When dicarboxylic anhydride (**1**) was subjected to aminolysis with the Weinreb amine followed by methylation with $TMSCHN_2$, a racemic methyl ester (**5a** and **5b**) was obtained in 63% yield from **1**. Thus, the chiral Weinreb monoamide (**5a**) (> 93% ee) could be obtained in 90% yield by reaction of **3** (94% de, 80% yield from **1**) with *N*-methoxy-*N*-methylamine. In this reaction (**3** → **5a**), no cyclization and no epimerization occurred as shown in Scheme 1.

Optical resolution of racemic amide (**4**) obtained from **1** in 71% yield was carried out by utilizing (4*S*)-IPTT. Dehydrative condensation of **4** with (4*S*)-IPTT in the presence of 1-ethyl-3-(3-



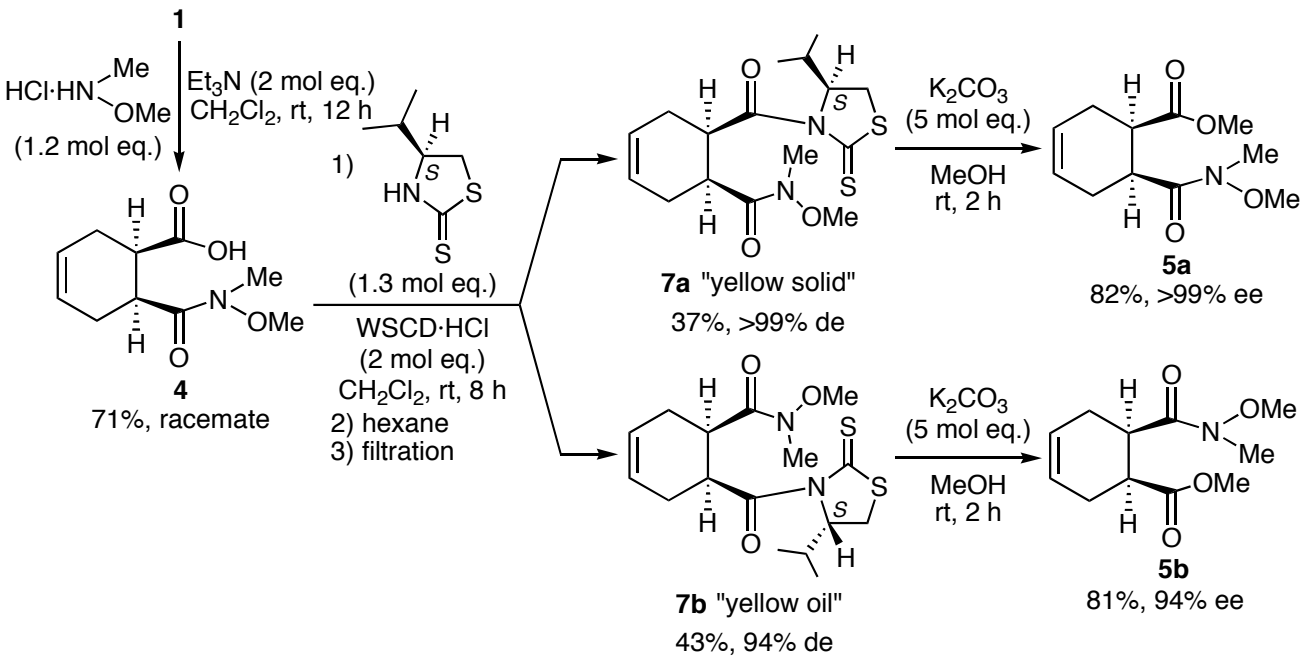
Scheme 1



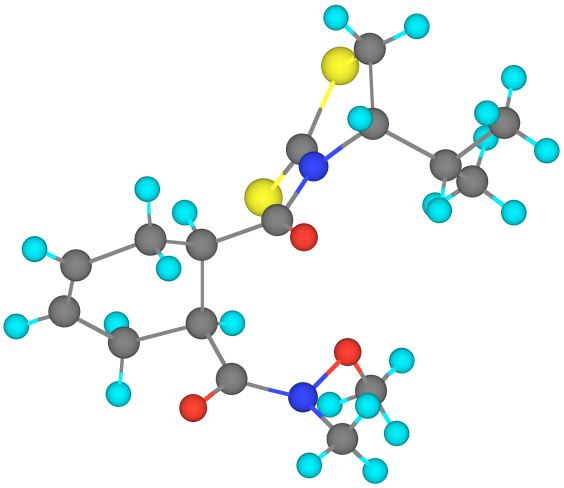
Scheme 2

dimethylaminopropyl)carbodimide hydrochloride (WSCD·HCl) in CH_2Cl_2 gave a mixture of two diasteromers (**7a** and **7b**); these compounds could not be separated on a silica gel column. When the mixture of diasteromers (**7a** and **7b**) was treated with hexane, one of them completely dissolved in hexane at room temperature. After removing the solvent by filtration, chiral monoamide (**7a**) remained as a yellow solid (37% yield, > 99% de) and then another chiral monoamide (**7b**) was obtained as a yellow oil (43% yield, 94% de) from the filtrate. Diasteromers (**7a** and **7b**) were converted to the corresponding enantiomers [**5a** (82% yield, > 99% ee) and **5b** (81% yield, 94% ee)] by methanolysis with K_2CO_3/MeOH, respectively.

The stereochemistries of compounds (**7a,b** and **5a,b**) were precisely established by X-Ray crystallographic analysis of **7a** (Figure 1) and chemical conversion of **7a** to the known chiral monoamide (**5a**), as shown in Scheme 3. Based on the above results, (4*S*)-IPTT is not only available for asymmetric



Scheme 3

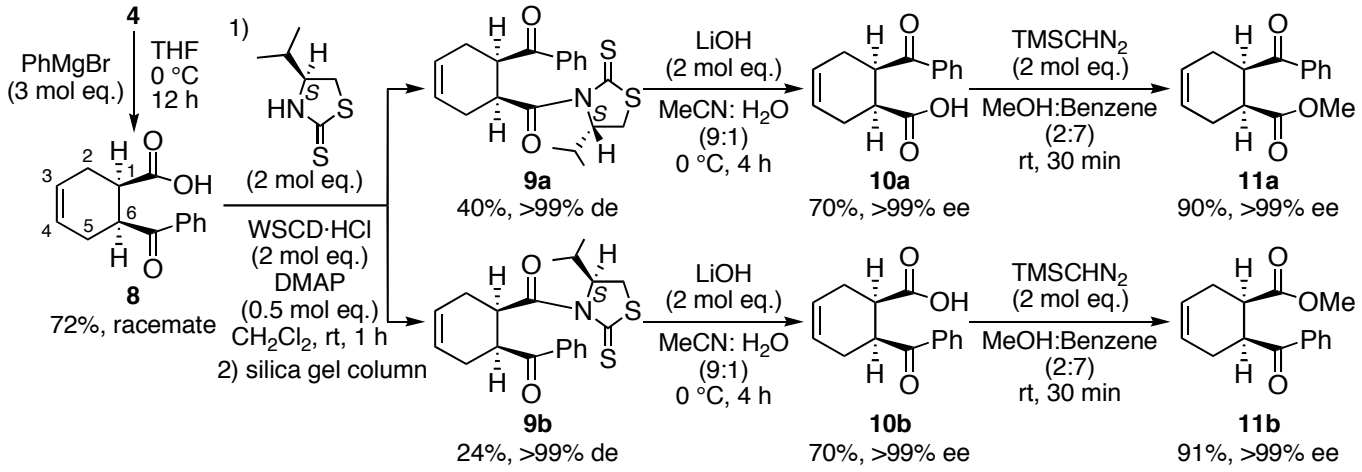


7a

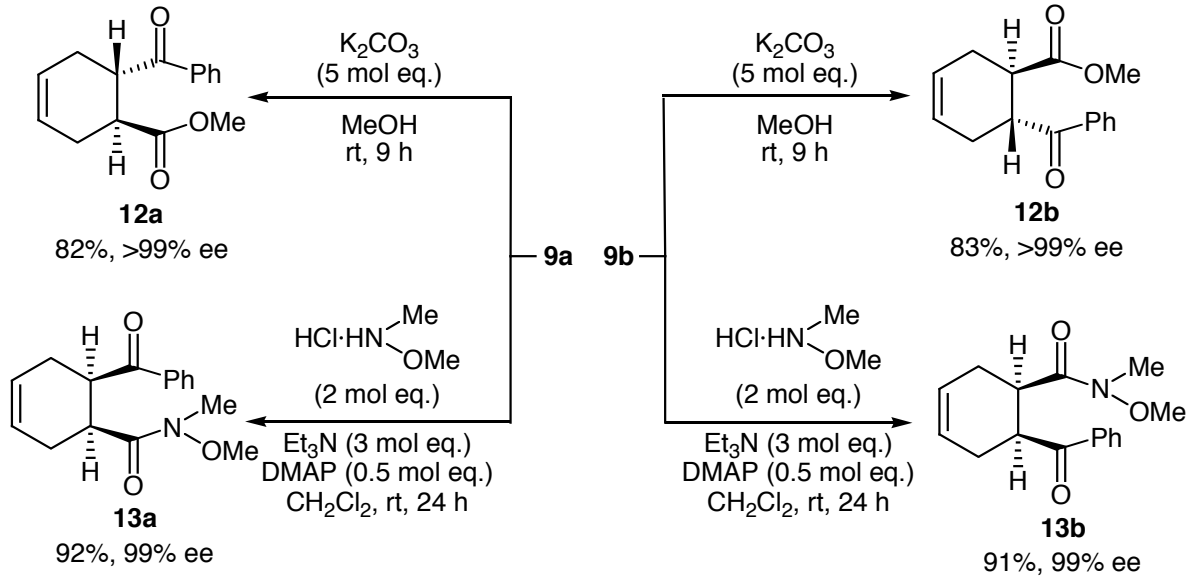
Figure 1. Computer-generated drawing from the X-Ray coordinates of compound (**7a**)

aminolysis of prochiral dicarboxylic acid anhydride (**1**) with an excellent diastereoselectivity but also practically useful for optical resolution.

Subsequently, we attempted an optical resolution of racemic *cis*-6-benzoylcyclohex-3-enecarboxylic acid **(8)** (72% yield) that was obtained by treatment of **4** with PhMgBr in THF at 0 °C. Namely, dehydrative condensation of **8** with (4*S*)-IPTT in the presence of WSCD·HCl and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 gave a diasteromeric mixture of **9a** and **9b**. These mixtures were completely separated on a silica gel column [hexane-AcOEt (5:1)] to give pure (4*S*)-IPTT amide **(9a)** or **(9b)** as a yellow solid in 40% or 24% yield with each excellent diasteromer excess (> 99% de).

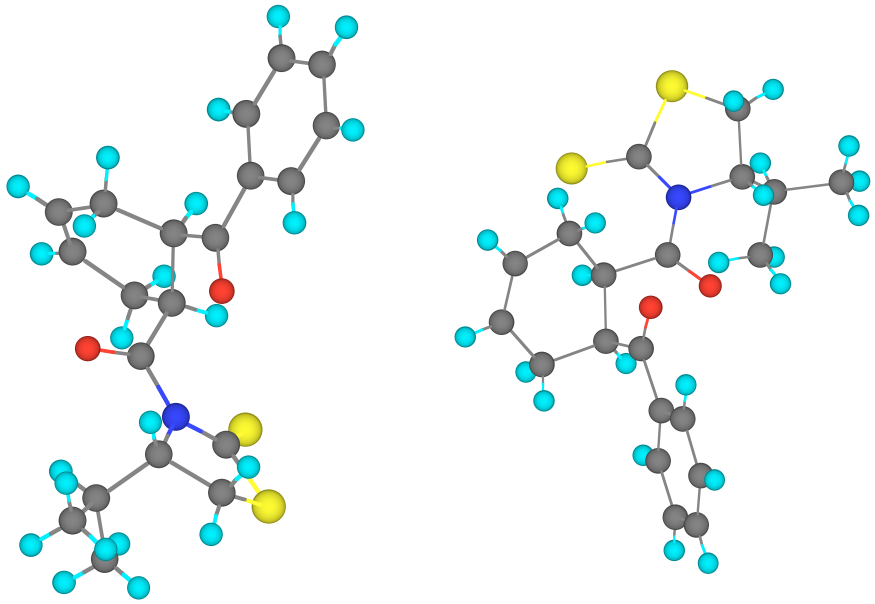


Scheme 4



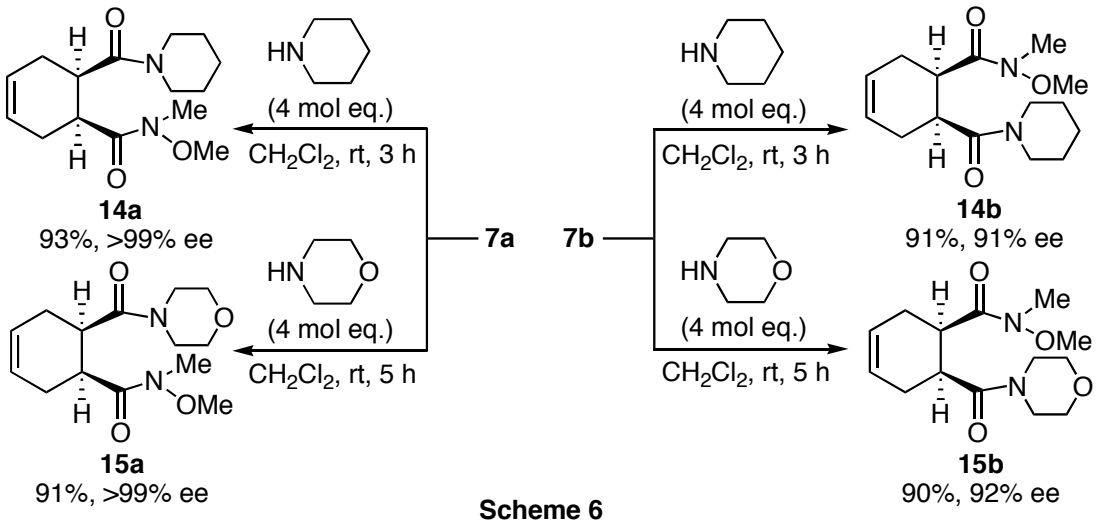
Scheme 5

The stereochemistries of **9a** and **9b** were established by their X-Ray crystallographic analyses (Figure 2) and by hydrolysis of **9a** with LiOH in MeCN-H_2O (9:1) at 0 °C to afford a known carboxylic acid, (1*S*, 6*R*)-6-benzoylcyclohex-3-enecarboxylic acid (**10a**)[11] [mp 122–123.5 °C (hexane—$CHCl_3$), $[\alpha]_D^{24}$ -41.4° (c 0.5, $CHCl_3$); lit.,[11] 91% ee, mp 106–108 °C (MeOH—CH_2Cl_2), $[\alpha]_D^{23}$ -31.9° (c 0.48, $CHCl_3$)] in 70% yield and >99% ee as shown in Scheme 4. The similar hydrolysis of **9b** with LiOH furnished another chiral carboxylic acid (**10b**) in 70% yield and >99% ee. Methylation of enantiomers (**10a** and **10b**) with $TMSCHN_2$ gave the corresponding *cis*-methyl esters (**11a**) (>99% ee) and (**11b**) (>99% ee) in 90% and 91% yields, respectively. Interestingly, methanolysis of (4*S*)-IPTT amides **(9a)** and **(9b)** with K_2CO_3 in MeOH at room temperature furnished the corresponding *trans*-methyl esters [**12a** (82% yield, >99% ee) and **12b** (83% yield, >99% ee)], respectively, as shown in Scheme 5. The *trans* geometry of **12a,b** was confirmed by comparing their spectroscopic data with those of the *cis*-methyl esters (**11a,b**) having the

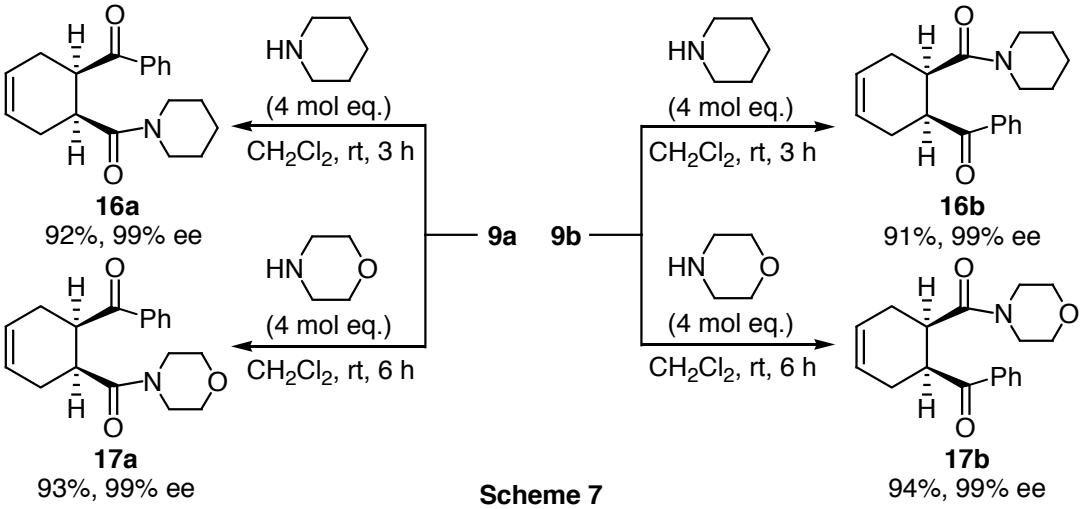


9a **9b**

Figure 2. Computer-generated drawing from the X-Ray coordinates of compounds (**9a** and **9b**)



Scheme 6

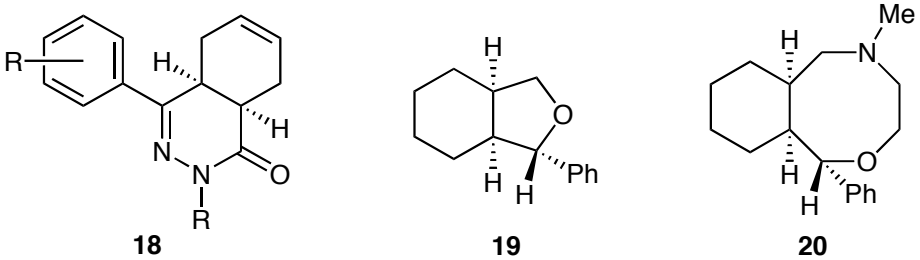


Scheme 7

same elemental analysis data. In this reaction (**9a,b** → **12a,b**), epimerization occurred at the enolizable chiral carbon atom bearing the benzoyl group.[12]

The (4*S*)-IPTT group of the amides bearing an "active amide structure" can be readily removed by the reactions with a variety of nucleophiles, which allows the products to be transformed into a wide range of derivatives.[6,13] Thus, the (4*S*)-IPTT amides (**7a,b** and **9a,b**) were subjected to mild aminolyses with the Weinreb amine and some amines to obtain the corresponding enantiomerically pure Weinreb amides (**13a,b**), piperidine amides (**14a,b** and **16a,b**), and morpholine amides (**15a,b** and **17a,b**) in excellent yields, respectively, as shown in Schemes 5, 6 and 7. In all cases, the end point of the aminolysis could be monitored by disappearance of the original yellow color of the (4*S*)-IPTT amides. The (4*S*)-IPTT was recovered by flash column chromatography of each reaction mixture in a good yield.

In conclusion, we have developed practically useful procedures for the syntheses of several enantiomerically pure amides of *cis*-cyclohex-4-ene-1,2-dicarboxylic acid utilizing diastereoselective aminolysis of a prochiral dicarboxylic anhydride and optical resolution of some enantiomeric mixtures of monocarboxylic acids by the efficient use of (4*S*)-IPTT. The resulting chiral amides can be useful for the development of new enzyme inhibitors.[14] The chiral compounds (**9a,b** and **10a,b**) should specifically be useful for syntheses of specific enzyme inhibitors and biologically active compounds such as chiral *cis*-tetra- and *cis*-hexahydrophthalazinone **(18)**,[14] chiral 3-phenylhexahydro-1(*3H*)-isobenzofuranone **(19)**,[15] chiral 5-methyl-1-phenyl-1*H*-2,5-benzoxacine **(20)**,[16] and other biologically active natural products and drugs.



18 **19** **20**

Scheme 8

EXPERIMENTAL

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-420 IR Fourier transform spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL JNM-AL400 spectrometer. Chemical shifts are given in δ value (ppm) using tetramethylsilane (TMS) as an internal standard. EI-MS spectrum was recorded on a JEOL JMS SX-102A spectrometer. Elementary combustion analyses were performed using a YANACO CHN CORDER MT-5. All reactions were monitored by TLC employing 0.25 mm

silica gel plates (Merck 5715; 60 F_{254}). Preparative TLC (PTLC) was performed on 0.5 mm silica gel plates (Merck 5744; 60 F_{254}). Column chromatography was carried out on silica gel [Kanto chemical 60N (spherical, neutral); 63-210 □m]. Analytical high performance liquid chromatography (HPLC) was performed on a JASCO model 807-IT HPLC equipped with a JASCO UV-970 intelligent UV/VIS detector. Optical rotations were measured on a DIP-370 digital polarimeter in a 1 dm cell. Anhydrous THF and anhydrous CH_2Cl_2 were used as purchased from Kanto chemical. All other reagents were used as purchased. All reactions were carried out under argon.

Methyl (1*R*, 6*S*)-6-[(4*S*)-4-Isopropyl-1,3-thiazolidine-2-thion-3-yl]carbonylcyclohex-3-enecarboxylate (3)

A suspension of 60% NaH (coated type with mineral oil, 220 mg, 5.5 mmol) in THF (6 mL) was added to a solution of (4*S*)-IPTT (805 mg, 5 mmol) in THF (5 mL) at 0 °C with stirring. The mixture was stirred at 0 °C for 10 min and then anhydrous DMSO (0.43 mL, 6 mmol) was added at rt. After being stirred at rt for 1 h, the reaction mixture was added to a solution of **1** (836.8 mg, 5.5 mmol) in THF (6 mL) at -50 ºC. The mixture was stirred at –50 - –40 °C for 1 h. The reaction was quenched with an aqueous solution (20 mL) saturated with $NaHSO_4$ and extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated *in vacuo* to give a crude carboxylic acid **(2)**, which was treated with $TMSCHN_2$ in ether affording methyl ester **(3)** (1.30 g, 80%) as a yellow oil after purification by column chromatography on silica gel with hexane-AcOEt (4:1). $[□]_D^{18}$ +544.8° (c 0.90, $CHCl_3$). IR (neat) 3029, 1731, 1691 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) □0.95-0.97 (d, 3H, *J* = 7.08 Hz), 1.05-1.07 (d, 3H, *J* = 6.84 Hz), 2.05-2.18 (m, 1H), 2.31-2.35 (m, 1H), 2.48-2.52 (m, 1H), 2.82-2.88 (m, 1H), 3.02-3.05 (d, 1H, *J* = 11.47 Hz), 3.06-3.12 (m, 1H), 3.64-3.70 (m, 1H), 3.68 (s, 3H), 4.39-4.46 (ddd, 1H, *J* = 16.12, 10.99, 5.13 Hz), 5.02-5.05 (t, 1H, *J* = 7.57 Hz), 5.68-5.72 (m, 2H); HREI-MS calcd for $C_{15}H_{21}NO_3S_2$ MW 327.0963, found *m/z* 327.0955 (M^+); Anal. Calcd for $C_{15}H_{21}NO_3S_2$: C, 55.02; H, 6.46; N, 4.28. Found: C, 55.27; H, 6.57; N, 4.49. HPLC analysis [TSK-gel Silica 60, hexane—AcOEt (9:1), 1.0 mL/min, 305 nm; t_R (minor) = 13.22 min, t_R (major) = 15.47 min] gave the isomeric composition of the product: 94% de.

Racemic *cis*-6-(*N*-Methoxy-*N*-methylaminocarbonyl)cyclohex-3-enecarboxylic Acid (4)

Method 1: A crude carboxylic acid **(2)**, obtained by the synthetic method described for **3**, was treated with *N*-methoxy-*N*-methylamine hydrochloride (731 mg, 7.5 mmol) and Et_3N (2.08 mL, 15 mmol) in CH_2Cl_2 (30 mL) at rt for 30 min. The reaction mixture was acidified with 10% HCl, and extracted with $CHCl_3$ (3□100 mL). The usual work-up of the $CHCl_3$ extract followed by purification on a silica gel column with hexane—EtOAc (1:3) afforded racemic amide **(4)** (0.59 g, 56%) as a white solid.

Method 2: To a solution of **1** (3.35 g, 20 mmol) in CH_2Cl_2 (60 mL) were added *N*-methoxy-*N*-methylamine hydrochloride (2.34 g, 24 mmol) and Et_3N (5.5 mL, 40 mmol) at rt. The mixture was stirred at rt for 12 h. The reaction mixture was acidified with 10% HCl and then extracted with $CHCl_3$ (3×100 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with hexane—EtOAc (1:3) to give racemic amide **(4)** (3.02 g, 71%) as a white solid. mp 96-97 °C ($CHCl_3$—hexane); IR (KBr) 1702, 1651 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.28-2.29 (m, 1H), 2.36-2.38 (m, 2H), 2.82-2.89 (m, 1H), 2.99-3.01 (m, 1H), 3.28 (s, 3H), 3.39-3.40 (m, 1H), 3.78 (s, 3H), 5.69-5.71 (m, 1H), 5.77-5.79 (m, 1H); HREI-MS calcd for $C_{10}H_{15}NO_4$ MW 213.1001, found *m/z* 213.1000 (M^+); Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.21; H, 7.04; N, 6.47.

Methyl (1*R*, 6*S*)-6-(*N*-Methoxy-*N*-methylaminocarbonyl)cyclohex-3-enecarboxylate (5a)

Method 1: To a solution of **3** (327 mg, 1 mmol) and *N*-methoxy-*N*-methylamine hydrochloride (195 mg, 2 mmol) in CH_2Cl_2 (6 mL) were added 4-dimethylaminopyridine (61 mg, 0.5 mmol) and Et_3N (0.45 mL, 3 mmol) at rt. After being stirred at rt for 24 h, the reaction mixture was acidified with 10% HCl and then extracted with $CHCl_3$ (3×20 mL). The extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated *in vacuo* to give an oily residue, which was purified by column chromatography on silica gel with hexane—EtOAc (1:1) to afford chiral amide **(5a)** (204 mg, 90%; >93% ee) as a colorless oil. $[\alpha]_D^{24}$ -14° (c 0.63, $CHCl_3$). IR (neat) 1738, 1666 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.36-2.48 (m, 3H), 2.68-2.78 (m, 1H), 2.89-2.93 (m, 1H), 3.18 (s, 3H), 3.34-3.41 (m, 1H), 3.70 (s, 3H), 3.74 (s, 3H), 5.70-5.75 (m, 2H); HREI-MS calcd for $C_{11}H_{17}NO_4$ MW 227.1158, found *m/z* 227.1161 (M^+); Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found C, 57.97; H, 7.54; N, 6.14.

Method 2: A mixture of **7a** (*vide infra)* (356 mg, 1 mmol) and K_2CO_3 (691 mg, 5 mmol) in methanol (9 mL) was stirred at rt for 2 h. The reaction was quenched with 10% HCl and then the mixture was extracted with $CHCl_3$ (3×20 mL). The extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated *in vacuo* to give an oily residue, which was purified by column chromatography on silica gel with hexane—EtOAc (2:1) to afford chiral amide **(5a)** (186 mg, 82%; > 99% ee) as a colorless oil. $[\alpha]_D^{23}$ -16° (c 0.78, $CHCl_3$). HPLC analysis [Chiralcel OD-H, hexane—*i*-PrOH (5:1), 0.3 mL/min, 225 nm; t_R (minor) = 20.9 min, t_R (major) = 29.5 min] gave the isomeric composition of the product: >93% ee (Method 1) and >99% ee (Method 2).

Racemic Methyl *cis*-6-(*N*-Methoxy-*N*-methylaminocarbonyl)cyclohex-3-enecarboxylate (5)

To a solution of racemic compound (**4**) (213 mg, 10 mmol) in MeOH—benzene (2:7) (4.5 mL) was added $TMSCHN_2$ (2.0 M in diethyl ether: 1 mL, 2 mmol) at rt. After being stirred at rt for 30 min, the reaction mixture was treated with 10% HCl and then extracted with $CHCl_3$ (3 □20 mL). The extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated *in vacuo* to give an oily residue, which was purified by column chromatography on silica gel with hexane—EtOAc (2:1) to afford racemic methyl ester (**5a**) (202 mg, 89%) as a colorless oil.

Methyl (1*S*, 6*R*)-6-(*N*-Methoxy-*N*-methylaminocarbonyl)cyclohex-3-enecarboxylate (5b)

The similar metahnolysis of **7b** (356 mg, 1 mmol) to the case (Method 2) of **5a** afforded chiral methyl ester **(5b)** as a colorless oil (184 mg, 81% yield) in 94% ee. $[□]_D^{23}$ +15.6° (c 0.71, $CHCl_3$). IR (neat) 1732, 1659 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) □ 2.36-2.48 (m, 3H), 2.68-2.78 (m, 1H), 2.89-2.93 (m, 1H), 3.18 (s, 3H), 3.34-3.41 (m, 1H), 3.70 (s, 3H), 3.74 (s, 3H), 5.70-5.75 (m, 2H); HREI-MS calcd for $C_{11}H_{17}NO_4$ MW 227.1158, found *m/z* 227.1163 (M^+). HPLC analysis [Chiralcel OD-H, hexane—*i*-PrOH (5:1), 0.3 mL/min, 225 nm; t_R (major) = 20.85 min, t_R (minor) = 29.48 min] gave the isomeric composition of the product: 94% ee.

(1*R*, 5*S*)-2-Oxo-3-oxabicyclo[4.3.0]non-7-ene (6)

To a solution of **3** (600 mg, 1.83 mmol) in EtOH—H_2O (2:1) (14.6 mL) was added $NaBH_4$ (77.1 mg, 1.83 mmol) under ice cooling. After being stirred at rt for 1 h, the reaction mixture was treated with an aqueous solution saturated with $NaHSO_4$ and then EtOH was evaporated *in vacuo*. The aqueous residue was extracted with Et_2O and the extract was concentrated *in vacuo* to give an oily residue, which was treated with toluene (6.1 mL) and a catalytic amount of *p*-TsOH under heating at 110 °C for 1 h. After toluene was evaporated *in vacuo*, the residue was purified by column chromatography on silica gel with hexane—$CHCl_3$—acetone (20:19:1) to afford chiral lactone **(6)** (90 mg, 75%) as a colorless oil. $[□]_D^{20}$ +79.8° (c 1.1, acetone) [lit.,[9] $[□]_D^{20}$ -85.4° (c 2.63, acetone)]. IR ($CHCl_3$) 1770 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) □ 1.68-2.88 (m, 6H), 4.02 (dd, 1H, *J* = 8.79, 1.76 Hz), 4.33 (dd, 1H, *J* = 8.79, 4.62 Hz), 5.56-5.88 (m, 2H); HREI-MS calcd for $C_8H_{10}O_2$ MW 138.0680, found *m/z* 138.0646 (M^+); Anal. Calcd for $C_8H_{10}O_2 \cdot 1/9H_2O$ C, 68.55; H, 7.35. Found: C, 68.51; H, 7.39.

Optical Resolution of Racemic *cis*-6-(*N*-Methoxy-*N*-methylaminocarbonyl)cyclohex-3-enecarboxylic Acid (4)

To a solution of racemic carboxylic acid **(4)** (213 mg, 1 mmol) and (4*S*)-IPTT (218 mg, 1.3 mmol) in CH_2Cl_2 (6 mL) were added DMAP (61 mg, 0.5 mmol) and WSCD·HCl (400 mg, 2 mmol) at rt. The

mixture was stirred at rt for 8 h. The reaction mixture was acidified with 10% HCl and then extracted with $CHCl_3$ (3×20 mL). The extract was subjected to the usual work-up to give an oily residue, which was chromatographed on a silica gel column with hexane—EtOAc (2:1) to afford a diasteromer mixture of **7a,b** as a yellow oil (285 mg, 80%). The diastereomeric mixture of **7a,b** was treated with hexane and then a yellow precipitation was filtered off. Crystallization of the precipitation in $CHCl_3$—hexane gave (4*S*)-IPTT amide (**7a**) (132 mg, 37%) as yellow prisms. The resulting filtrate was evaporated *in vacuo* to give another (4*S*)-IPTT amide (**7b**) (153 mg, 43%) as a yellow oil.

(1*S*, 6*R*)-6-[(4*S*)-4-Isopropyl-1,3-thiazolidine-2-thion-3-yl]carbonyl-*N*-methoxy-*N*-methylcyclohex-3-enecarboxamide (7a)

Yellow prisms, mp 135-136.5 °C ($CHCl_3$—hexane); $[\alpha]_D^{24}$ +314.7° (c 1.05, $CHCl_3$). IR (neat) 3381, 1701, 1657 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.98-1.00 (d, 3H, *J* = 7.18 Hz), 1.06-1.07 (d, 3H, *J* = 7.08 Hz), 2.25-2.32 (m, 1H), 2.35-2.41 (m, 1H), 2.48-2.55 (m, 1H), 2.62-2.68 (m, 1H), 2.99-3.03 (d, 1H, *J* = 12.21 Hz), 3.15 (s, 3H), 3.44-3.50 (dd, 1H, *J* = 11.47, 8.54 Hz), 3.64-3.67 (m, 1H), 3.68 (s, 3H), 4.70-4.75 (m, 1H), 5.06-5.09 (dd, 1H, *J* = 8.30, 4.64 Hz), 5.70-5.73 (m, 2H); HREI-MS calcd for $C_{16}H_{24}N_2O_3S_2$ MW 356.1228, found *m/z* 356.1238 (M^+); Anal. Calcd for $C_{16}H_{24}N_2O_3S_2$: C, 53.90; H, 6.79; N, 7.86. Found: C, 53.76; H, 6.76; N, 7.82. HPLC analysis [TSK-gel Silica 60, hexane—AcOEt (4:1), 1.5 mL/min, 305 nm; t_R (minor) = 27.07 min, t_R (major) = 32.77 min] gave the isomeric composition of the product: >99% de.

(1*R*, 6*S*)-6-[(4*S*)-4-Isopropyl-1,3-thiazolidine-2-thion-3-yl]carbonyl-*N*-methoxy-*N*-methylcyclohex-3-enecarboxamide (7b)

Yellow oil; $[\alpha]_D^{24}$ +269.2° (c 1.05, $CHCl_3$). IR (neat) 3181, 1776, 1650 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.96-0.98 (d, 3H, *J* = 7.08 Hz), 1.04-1.06 (d, 3H, *J* = 6.84 Hz), 2.25-2.55 (m, 4H), 2.98-3.00 (d, 1H, *J* = 12.20 Hz), 3.18 (s, 3H), 3.19-3.26 (m, 1H), 3.64-3.69 (dd, 1H, *J* = 10.99, 7.81 Hz), 4.86-4.89 (m, 1H), 5.0-5.01 (dd, 1H, *J* = 7.81, 6.59 Hz), 5.70-5.75 (m, 1H), 5.78-5.84 (m, 1H); HREI-MS calcd for $C_{16}H_{24}N_2O_3S_2$ MW 356.1228, found *m/z* 356.1204 (M^+); Anal. Calcd for $C_{16}H_{24}N_2O_3S_2$: C, 53.90; H, 6.79; N, 7.86. Found: C, 53.72; H, 6.70; N, 7.85. HPLC analysis [TSK-gel Silica 60, hexane—AcOEt (4:1), 1.5 mL/min, 305 nm; t_R (major) = 27.06 min, t_R (minor) = 33.06 min] gave the isomeric composition of the product: 94% de.

Racemic *cis*-6-Benzoylcyclohex-3-enecarboxylic Acid (8)

To a solution of racemic carboxylic acid **(4)** (213 mg, 1 mmol) in anhydrous THF (6 mL) was added PhMgBr (1.0 M in THF : 3 mL, 3 mmol) at 0 °C. After being stirred at 0 °C for 12 h, the reaction mixture

was treated with 10% HCl, and extracted with $CHCl_3$ (3×20 mL). The extract was washed with brine, dried over $MgSO_4$, and filtered. Evaporation of the filtrate *in vacuo* gave a solid residue, which was purified by column chromatography on silica gel with hexane—EtOAc (1:1) to afford benzoyl derivative **(8)** (165 mg, 72%) as a white solid. mp 131-132 °C ($CHCl_3$—hexane), (lit.,[17] mp 130-131 °C); IR (KBr) 1690, 1669 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.49-2.50 (m, 3H), 2.78-2.83 (m, 1 H), 3.02-3.03 (m, 1H), 3.96-3.97 (m, 1H), 5.60-5.65 (m, 1H), 5.75-5.92 (m, 1H), 7.43-7.48 (m, 2H), 7.53-7.56 (m, 1H), 7.85-7.88 (m, 2H); HREI-MS calcd for $C_{14}H_{14}O_3$ MW 230.0943, found *m/z* 230.0946 (M^+); Anal. Calcd for $C_{10}H_{15}NO_4$: C, 73.03; H, 6.13. Found: C, 72.96; H, 6.20.

Optical Resolution of Racemic *cis*-6-Benzoylcyclohex-3-enecarboxylic Acid (8)

To a solution of **8** (230 mg, 1 mmol) and (4*S*)-IPTT (335 mg, 2 mmol) in CH_2Cl_2 (6 mL) were added DMAP (61 mg, 0.5 mmol) and WSCD·HCl (400 mg, 2 mmol) at rt. After being stirred at rt for 1 h, the reaction mixture was allowed to treat with the usual work-up to give a yellow solid residue, which was subjected to column chromatography on silica gel with hexane—EtOAc (5:1) to furnish (4*S*)-IPTT amide (**9a**) (149 mg, 40%) as a yellow solid and then another (4*S*)-IPTT amide (**9b**) (90 mg, 24%) as a yellow solid.

(1*S*, 6*R*)-6-Benzoyl-1-[(4*S*)-4-isopropyl-1,3-thiazolidine-2-thion-3-yl]carbonylcyclohex-3-ene (9a)

Yellow prisms, mp 84-86 °C (hexane); $[\alpha]_D^{24}$+354.8° (c 0.5, $CHCl_3$). IR (neat) 3323, 1698, 1671 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.96-0.98 (d, 3H, *J* = 7.08 Hz), 1.06-1.07 (d, 3H, *J* = 6.84 Hz), 2.40-2.65 (m, 5H), 3.03-3.06 (d, 1H, *J* = 12.45 Hz), 3.68-3.73 (dd, 1H, *J* = 11.48, 8.06 Hz), 3.84-3.89 (m, 1H), 4.80-4.82 (m, 1H), 5.00-5.05 (m, 1H), 5.75-5.88 (m, 2 H), 7.40-7.50 (m, 2H), 7.55-7.58 (m, 1H), 7.85-7.90 (m, 2H); HREI-MS calcd for $C_{20}H_{23}NO_2S_2$ MW 373.1170, found *m/z* 373.1150 (M^+); Anal. Calcd for $C_{20}H_{23}NO_2S_2$: C, 64.31; H, 6.21; N, 3.75. Found: C, 63.96; H, 6.23; N, 3.73. HPLC analysis [TSK-gel Silica 60, hexane—AcOEt (15:1), 0.5 mL/min, 305 nm; t_R (major) = 34.6 min, t_R (minor) = 49.2 min] gave the isomeric composition of the product: >99% de.

(1*R*, 6*S*)-6-Benzoyl-1-[(4*S*)-4-isopropyl-1,3-thiazolidine-2-thion-3-yl]carbonylcyclohex-3-ene (9b)

Pale yellow prisms, mp 98-100 °C (hexane); $[\alpha]_D^{24}$+291° (c 0.5, $CHCl_3$). IR (neat) 3031, 1701, 1679 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.89-0.91 (d, 3H, *J* = 6.84 Hz), 0.98-1.00 (d, 3H, *J* = 6.83 Hz), 2.25-2.30 (m, 1H), 2.45-2.55 (m, 3H), 2.70-2.78 (m, 1H), 2.96-2.99 (d, 1H, *J* = 12.69 Hz), 3.43-3.48 (dd, 1H, *J* = 11.47, 8.30 Hz), 4.10-4.15 (m, 1H), 5.02-5.07 (m, 1H), 5.09-5.13 (m, 1H), 5.72-5.76 (m, 2H), 7.40-7.50 (m, 2H), 7.55-7.58 (m, 1H), 7.85-7.90 (m, 2H); HREI-MS calcd for $C_{20}H_{23}NO_2S_2$ MW 373.1170, found

m/z 373.1172 (M^+); Anal. Calcd for $C_{20}H_{23}NO_2S_2$: C, 64.31; H, 6.21; N, 3.75. Found: C, 64.13; H, 6.25; N, 3.71. HPLC analysis [TSK-gel Silica 60, hexane—AcOEt (15:1), 0.5 mL/min, 305 nm; t_R (minor) = 34.6 min, t_R (major) = 49.2 min] gave the isomeric composition of the product: >99% de.

(1*S*, 6*R*)-6-Benzoylcyclohex-3-enecarboxylic Acid (10a)

To a solution of LiOH (47 mg, 2 mmol) in MeCN—H_2O (9:1) (9 mL) was added **9a** (373 mg, 1 mmol) at 0 °C. After being stirred at 0 °C for 4 h, the reaction was quenched 10% HCl and then the mixture was extracted with $CHCl_3$ (3□20 mL). The extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated *in vacuo* and then the resulting residue was purified by column chromatography on silica gel with hexane—EtOAc (2:1) to afford chiral carboxylic acid (**10a**) (162 mg, 70%) as a white solid. mp 122-123.5 °C ($CHCl_3$—hexane); $[□]_D^{24}$ -41.4° (c 0.5, $CHCl_3$); [lit.,[11] mp 106-108 °C (MeOH—CH_2Cl_2); $[\alpha]_D^{23}$ -31.9° (c 0.48, $CHCl_3$)]; IR (KBr) 1694, 1680 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) □ 2.48-2.51 (m, 3H), 2.78-2.83 (m, 1H), 3.02-3.04 (m, 1H), 3.96-3.97 (m, 1H), 5.64-5.65 (m, 1H), 5.75-5.76 (m, 1H), 7.43-7.48 (m, 2H), 7.53-7.55 (m, 1H), 7.85-7.88 (m, 2H); HREI-MS calcd for $C_{15}H_{16}O_3$, MW 230.0943, found *m/z* 230.0930 (M^+); Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.90; H, 6.13. The corresponding methyl ester **(11a)** was exploited for the ee determination of **10a**: >99% ee.

(1R, 6S)-6-Benzoylcyclohex-3-enecarboxylic Acid (10b)

The similar alkaline hydrolysis of **9b** (373 mg, 1 mmol) with LiOH (47 mg, 2 mmol) utilizing the procedure described for **10a** gave chiral carboxylic acid **(10b)** (162 mg, 70%) as a white solid. mp 122-123.5 °C ($CHCl_3$—hexane); $[□]_D^{24}$ +41.2° (c 0.5, $CHCl_3$). IR (KBr) see **10a**; ^{1}H-NMR (400 MHz, $CDCl_3$) see **10a**; HREI-MS calcd for $C_{14}H_{14}O_3$ MW 230.0943, found *m/z* 230.0930 (M^+). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.91; H, 6.18. The corresponding methyl ester **(11b)** was exploited for the ee determination of **10b**: >99% ee.

Methyl (1*S*, 6*R*)-6-Benzoylcyclohex-3-enecarboxylate (11a)

To a solution of **10a** (230 mg, 1 mmol) in MeOH—benzene (2:7) (4.5 mL) was added $TMSCHN_2$ (2.0 M in ether: 1 mL, 2 mmol) at rt. The mixture was stirred at rt for 30 min and then subjected to the usual work-up to obtain a crude product, which was purified by column chromatography on silica gel with hexane—EtOAc (2:1). The pure chiral methyl ester **(11a)** (219 mg, 90%) was obtained as a white solid. mp 66-68 °C ($CHCl_3$—hexane); $[□]_D^{24}$ -23.8° (c 0.8, $CHCl_3$); IR (KBr) 1710, 1689 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) □ 2.49-2.50 (m, 3H), 2.68-2.81 (m, 1H), 3.02-3.05 (m, 1H), 3.63 (s, 3H), 3.96-4.01 (m, 1H), 5.61-5.69 (m, 1H), 5.72-5.80 (m, 1H), 7.44-7.48 (m, 2H), 7.53-7.55 (m, 1H), 7.85-7.88 (m, 2H); HREI-MS calcd for $C_{15}H_{16}O_3$, MW 244.1099, found *m/z* 244.1097 (M^+); Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H,

6.60. Found: C, 73.54; H, 6.68. HPLC analysis [Chiralcel OD-H, hexane—*i*-PrOH (97:3), 0.5 mL/min, 254 nm; t_R (minor) = 31.39 min, t_R (major) = 36.12 min] gave the isomeric composition of the product: >99% ee.

Methyl (1*R*, 6*S*)-6-Benzoylcyclohex-3-enecarboxylate (11b)

The similar methylation of **10b** (230 mg, 1 mmol) with $TMSCHN_2$ (2.0 M in ether: 1 mL, 2 mmol) utilizing the procedure described for **11a** gave chiral methyl ester **(11b)** (221 mg, 91%) as white solid. mp 66-68 °C ($CHCl_3$—hexane); $[\alpha]_D^{24}$ +25.1° (c 0.8, $CHCl_3$). IR (KBr) see **11a**; ^{1}H-NMR (400 MHz, $CDCl_3$) see **11a**; HREI-MS calcd for $C_{13}H_{16}O_3$ MW 244.1099, found *m/z* 244.1089 (M^+). HPLC analysis [Chiralcel OD-H, hexane—*i*-PrOH (97:3), 0.5 mL/min, 254 nm; t_R (major) = 31.39 min, t_R (minor) = 36.12 min] gave the isomeric composition of the product: >99% ee.

Methyl (1*S*, 6*S*)-6-Benzoylcyclohex-3-enecarboxylate (12a)

A mixture of **9a** (373 mg, 1 mmol) and K_2CO_3 (691 mg, 5 mmol) in methanol (9 mL) was stirred at rt for 9 h. The reaction was quenched with 10% HCl, and the mixture was extracted with $CHCl_3$ (3×20 mL). The extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated *in vacuo* and then the residue was purified by column chromatography on silica gel with hexane—EtOAc (1:1) to afford chiral methyl ester **(12a)** (200 mg, 82%) as a colorless oil. $[\alpha]_D^{24}$ +91.4° (c 0.7, $CHCl_3$). IR (neat) 1733, 1680 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.03-2.12 (m, 1H), 2.20-2.30 (m, 1H), 2.41-2.48 (m, 1H), 2.50-2.57 (m, 1H), 3.12-3.14 (m, 1H), 3.60 (s, 3H), 3.85-3.87 (m, 1H), 5.74-5.75 (m, 2H), 7.45-7.49 (m, 2H), 7.55-7.57 (m, 1H), 7.99-8.01 (m, 2H); HREI-MS calcd for $C_{15}H_{16}O_3$ MW 244.1099, found *m/z* 244.1098 (M^+); Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.37; H, 6.61. HPLC analysis [Chiralcel OD-H, hexane—EtOH (100:1), 0.5 mL/min, 254 nm; t_R (major) = 18.80 min, t_R (minor) = 19.69 min] gave the isomeric composition of the product: >99% ee.

Methyl (1R, 6R)-6-Benzoylcyclohex-3-enecarboxylate (12b)

The similar methanolysis of **9b** (373 mg, 1 mmol) utilizing the procedure described for **12a** gave chiral methyl ester **(12b)** (202 mg, 83%) as a colorless oil. $[\alpha]_D^{20}$ -94.1° (c 2.35, $CHCl_3$). IR (neat) see **12a**; ^{1}H-NMR (400 MHz, $CDCl_3$) see **12a**; HREI-MS calcd for $C_{15}H_{16}O_3$ MW 244.1099, found *m/z* 244.1076 (M^+). HPLC analysis [Chiralcel OD-H, hexane—EtOH (100:1), 0.5 mL/min, 254 nm; t_R (minor) = 18.90 min, t_R (major) = 19.62 min] gave the isomeric composition of the product: >99% ee.

(1*S*, 6*R*)-6-Benzoyl-*N*-methoxy-*N*-methylcyclohex-3-enecarboxamide (13a)

To a solution of **9a** (373 mg, 1 mmol) and *N*-methoxy-*N*-methylamine hydrochloride (195 mg, 2 mmol) in CH_2Cl_2 (6 mL) were added DMAP (61 mg, 0.5 mmol) and Et_3N (0.4 mL, 3 mmol) at rt. After being stirred at rt for 24 h, the reaction mixture was acidified with 10% HCl and then extracted with $CHCl_3$ (3×20 mL). The extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated *in vacuo* to give an oily residue, which was purified by column chromatography on silica gel with hexane—EtOAc (2:1) to afford chiral amide (**13a**) (251 mg, 92%) as a colorless oil. $[\alpha]_D^{24}$ -67.9°(c 0.8, $CHCl_3$). IR (neat) 1681, 1660 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.38-2.50 (m, 3H), 2.65-2.72 (m, 1H), 3.51 (s, 3H), 3.38-3.42 (m, 1H), 3.65 (s, 3H), 3.85-3.89 (m, 1H), 5.81-6.02 (m, 2H), 7.42-7.44 (m, 2H), 7.52-7.53 (m, 1H), 7.87-7.89 (m, 2H); HREI-MS calcd for $C_{16}H_{19}NO_3$ MW 273.1365, found *m/z* 273.1342 (M^+); Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.73; H, 7.13, N, 5.08. HPLC analysis [Chiralcel OD, hexane—EtOH (5:1), 1.0 mL/min, 254 nm; t_R (major) = 7.28 min, t_R (minor) = 8.45 min] gave the isomeric composition of the product: 99% ee.

(1*R*, 6*S*)-6-Benzoyl-*N*-methoxy-*N*-methylcyclohex-3-enecarboxamide (13b)

The similar aminolysis of **9b** (373 mg, 1 mmol) with *N*-methoxy-*N*-methylamine hydrochloride (195 mg, 2 mmol) based on the procedure described for **13a** gave amide **(13b)** (248 mg, 91%) as a colorless oil. $[\alpha]_D^{24}$ +67.3° (c 1.3, $CHCl_3$). IR (neat) see **13a**; ^{1}H-NMR (400 MHz, $CDCl_3$) see **13a**; HREI-MS calcd for $C_{16}H_{19}NO_3$ MW 273.1365, found *m/z* 273.1390 (M^+); Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 69.85; H, 7.04, N, 4.99. HPLC analysis [Chiralcel OD, hexane—EtOH (5:1), 1.0 mL/min, 254 nm; t_R (minor) = 7.6 min, t_R (major) = 9.0 min] gave the isomeric composition of the product: 99% ee.

(1*S*, 6*R*)-6-Piperidinocarbonyl-*N*-methoxy-*N*-methylcyclohex-3-enecarboxamide (14a)

To a solution of **7a** (356 mg, 1 mmol) in CH_2Cl_2(6 mL) was added piperidine (0.4 mL, 4 mmol) at rt. After being stirred at rt for 3 h, the reaction mixture was treated with 10% HCl and extracted with $CHCl_3$ (3×20 mL). The extract was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in *vacuo* and the oily residue was purified by column chromatography on silica gel with hexane—EtOAc (3:97) to afford chiral piperidine amide (**14a**) (261 mg, 93%) as a colorless oil. $[\alpha]_D^{24}$ +16° (c 1.1, $CHCl_3$). IR (neat) 3498, 1643 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.45-1.60 (m, 6H), 2.15-2.25 (m, 1H), 2.35-2.42 (m, 2H), 2.81-2.86 (m, 1H), 3.05-3.08 (m, 1H), 3.20 (s, 3H), 3.30-3.40 (m, 3H), 3.45-3.55 (m, 1H), 3.73 (s, 3H), 5.74-5.76 (m, 1H), 5.79-5.83 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.6, 171.9, 125.7, 124.0, 60.9, 46.6, 42.6, 37.4, 33.9, 32.1, 27.2, 26.5, 26.2, 25.4, 24.5; HREI-MS calcd for $C_{15}H_{24}N_2O_4$ MW 280.1787, found *m/z* 280.1786 (M^+). HPLC analysis [Chiralcel OD-H,

hexane—*i*–PrOH (5:1), 0.5 mL/min, 225 nm; t_R (minor) = 15.30 min, t_R (major) = 22.54 min] gave the isomeric composition of the product: >99% ee.

(1*R*, 6*S*)-6-Piperidinocarbonyl-*N*-methoxy-*N*-methylcyclohex-3-enecarboxamide (14b)

The similar aminolysis of **7b** (356 mg, 1 mmol) based on the procedure described for **14a** gave chiral piperidine amide **(14b)** (255 mg, 91%) as a colorless oil. $[\alpha]_D^{24}$ -13.6° (c 1.1, $CHCl_3$). IR (neat) see **14a**; ^{1}H-NMR (400 MHz, $CDCl_3$) see **14a**; ^{13}C-NMR (100 MHz, $CDCl_3$) see **14a**; HREI-MS calcd for $C_{15}H_{24}N_2O_4$ MW 280.1787, found *m/z* 280.1804 (M^+). HPLC analysis [Chiralcel OD-H, hexane—*i*-PrOH (5:1), 0.5 mL/min, 225 nm; t_R (major) = 14.73 min, t_R (minor) = 23.41 min] gave the isomeric composition of the product: 91% ee.

(1*S*, 6*R*)-6-Morpholinocarbonyl-*N*-methoxy-*N*-methylcyclohex-3-enecarboxamide (15a)

To a solution of **7a** (356 mg, 1 mmol) in CH_2Cl_2(6 mL) was added morpholine (0.35 mL, 4 mmol) at rt. After being stirred at rt for 5 h, the reaction mixture was subjected to the usual work-up to give a crude product, which was purified by column chromatography on silica gel with hexane—EtOAc (3:97) to afford chiral morpholine amide (**15a**) (257 mg, 91%) as a white solid. mp 86-87.5 °C ($CHCl_3$—hexane); $[\alpha]_D^{24}$ +8.2° (c 1.08, $CHCl_3$). IR (KBr) 3498, 1659, 1643 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.18-2.25 (m, 1H), 2.33-2.50 (m, 2H), 2.71-2.78 (m, 1H), 3.02-3.08 (m, 1H), 3.18 (s, 3H), 3.28-3.33 (m, 1H), 3.42-3.69 (m, 8H), 3.71 (s, 3H), 5.74-5.76 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.2, 172.3, 125.0, 124.4, 66.7, 66.6, 66.5, 61.0, 46.1, 41.9, 36.4, 32.1, 26.8, 26.3; HREI-MS calcd for $C_{14}H_{22}N_2O_4$ MW 282.1580, found *m/z* 282.1566 (M^+); Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.31; H, 7.82; N, 9.81. HPLC analysis [Chiralcel OD-H, hexane—*i*-PrOH (5:1), 0.5 mL/min, 225 nm; t_R (minor) = 28.49 min, t_R (major) = 35.24 min] gave the isomeric composition of the product: >99% ee.

(1*R*, 6*S*)-6-Morpholinocarbonyl-*N*-methoxy-*N*-methylcyclohex-3-enecarboxamide (15b)

The similar aminolysis of **7b** (356 mg, 1 mmol) with morpholine (0.35 mL, 4 mmol) based on the procedure described for **15a** gave chiral morpholine amide **(15b)**(254 mg, 90%) as a colorless oil. $[\alpha]_D^{24}$ -8.3° (c 1.1, $CHCl_3$). IR (neat) see **15a**; ^{1}H-NMR (400 MHz, $CDCl_3$) see **15a**; ^{13}C-NMR (100 MHz, $CDCl_3$) see **15a**; HREI-MS calcd for $C_{14}H_{22}N_2O_4$ MW 282.1580, found *m/z* 282.1589 (M^+). HPLC analysis [Chiralcel OD-H, hexane—*i*-PrOH (5:1), 0.5 mL/min, 225 nm; t_R (major) = 28.49 min, t_R (minor) = 35.81 min] gave the isomeric composition of the product: 92% ee.

(1*S*, 6*R*)-6-Benzoyl-1-piperidinocarbonylcyclohex-3-ene (16a)

To a solution of **9a** (373 mg, 1 mmol) in CH_2Cl_2(6 mL) was added piperidine (0.4 mL, 4 mmol) at rt. After being stirred at rt for 3 h, the reaction mixture was subjected to the usual work-up to give a crude product, which was purified by column chromatography on silica gel with hexane—EtOAc (2:1) to afford chiral piperidine amide (**16a**) (273 mg, 92%) as a colorless oil. $[\alpha]_D^{24}$ -67.9° (c 1.17, $CHCl_3$). IR (neat) 3477, 1681, 1633 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.52-1.63 (m, 6H), 2.35-2.48 (m, 3H), 2.72-2.82 (m, 1H), 3.22-3.26 (m, 1H), 3.41-3.53 (m, 4H), 3.82-3.86 (m, 1H), 5.74-5.76 (m, 1H), 5.82-5.86 (m, 1H), 7.41-7.45 (m, 2H), 7.46-7.52 (m, 1H), 7.89-7.92 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.8, 172.1, 137.6, 131.9, 128.2, 128.0, 125.6, 124.3, 46.9, 42.9, 39.8, 38.2, 27.0, 26.7, 26.6, 25.5, 24.6; HREI-MS calcd for $C_{19}H_{23}NO_2$ MW 297.1729, found *m/z* 297.1721 (M^+). HPLC analysis [Chiralcel OD, hexane—EtOH (5:1), 1.0 mL/min, 254 nm; t_R (major) = 6.56 min, t_R (minor) = 8.91 min] gave the isomeric composition of the product: 99% ee.

(1*R*, 6*S*)-6-Benzoyl-1-piperidinocarbonylcyclohex-3-ene (16b)

The similar aminolysis of **9b** (373 mg, 1 mmol) with piperidine (0.4 mL, 4 mmol) based on the procedure described for **16a** gave chira piperidine amide **(16b)** (270 mg, 91%) as a colorless oil. $[\alpha]_D^{24}$ +69.2° (c 1.22, $CHCl_3$). IR (neat) see **16a**; ^{1}H-NMR (400 MHz, $CDCl_3$) see **16a**; ^{13}C-NMR (100 MHz, $CDCl_3$) see **16a**; HREI-MS calcd for $C_{19}H_{23}NO_2$ MW 297.1729, found *m/z* 297.1720 (M^+). HPLC analysis [Chiralcel OD, hexane—EtOH (5:1), 1.0 mL/min, 254 nm; t_R (minor) = 6.56 min, t_R (major) = 8.91 min] gave the isomeric composition of the product: 99% ee.

(1*S*, 6*R*)-6-Benzoyl-1-morpholinocarbonylcyclohex-3-ene (17a)

To a solution of **9a** (373 mg, 1 mmol) in CH_2Cl_2 (6 mL) was added morpholine (0.35 mL, 4 mmol) at rt. The mixture was stirred at rt for 6 h and then subjected to the usual work-up to give a crude product, which was purified by column chromatography on silica gel with hexane—EtOAc (2:1) to afford chiral morpholine amide (**17a**) (321 mg, 93%) as a colorless oil. $[\alpha]_D^{24}$ -60.4° (c 2.2, $CHCl_3$). IR (neat) 3498, 1680, 1632 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.42-2.71 (m, 4H), 3.22-3.24 (m, 1H), 3.51-3.67 (m, 8H), 3.81-3.83 (m, 1H), 5.76-5.80 (m, 2H), 5.76-5.80 (m, 2H), 7.42-7.46 (m, 2H), 7.88-7.90 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.6, 172.5, 137.1, 132.2, 128.3, 128.0, 127.9, 124.8, 124.7, 66.8, 66.7, 66.6, 66.5, 46.4, 42.0, 40.4, 36.8, 26.8; HREI-MS calcd for $C_{18}H_{21}NO_3$ MW 299.1521, found *m/z* 299.1521 (M^+). HPLC analysis [Chiralcel OD, hexane—EtOH (5:1), 1.0 mL/min, 254 nm; t_R (major) = 12.60 min, t_R (minor) = 15.26 min] gave the isomeric composition of the product: 99% ee.

(1*R*, 6*S*)-6-Benzoyl-1-morpholinocarbonylcyclohex-3-ene (17b)

The similar aminolysis of **9b** (373 mg, 1 mmol) with morpholine (0.35 mL, 4 mmol) based on the procedure described for **17a** gave chira morpholine amide **(17b)** (281 mg, 94%) as a colorless oil. $[\alpha]_D^{24}$ +59.7° (c 1.9, $CHCl_3$). IR (neat) see **17a**; ^{1}H-NMR (400 MHz, $CDCl_3$) see **17a**; ^{13}C-NMR (100 MHz, $CDCl_3$) see **17a**; HREI-MS calcd for $C_{18}H_{21}NO_3$ MW 299.1521, found *m/z* 299.1509 (M^+). HPLC analysis [Chiralcel OD, hexane—EtOH (5:1), 1.0 mL/min, 254 nm; t_R (minor) = 12.60 min, t_R (major) = 15.26 min] gave the isomeric composition of the product: 99% ee.

Crystal Data for X-Ray Crystallographic Analysis of Compounds (7a, 9a, and 9b)

7a: $C_{16}H_{24}N_2O_3S_2$, MW = 356.50, yellow block, monoclinic, space group $P2_1$(#4), a = 8.738(3)Å, b = 11.399(5)Å, c = 10.074(4)Å, V = 899.2(6)Å^3, β = 116.35(1)°, Z = 2, R = 0.026, Rw = 0.068; **9a:** $C_{20}H_{23}NO_2S_2$, MW = 373.53, yellow block, orthorhombic, $P2_12_12_1$(#19), a = 9.842(3)Å, b = 10.807(3)Å, c = 17.396(3)Å, V = 1850.4(8)Å^3, Z = 4, R = 0.031, Rw = 0.067; **9b:** $C_{20}H_{23}NO_2S_2$, MW = 373.53, pale yellow block, monoclinic, $P2_1$(#4), a = 9.009(3)Å, b = 10.882(4)Å, c = 9.532(4)Å, V = 932.3(6)Å^3, β = 94.00(2)°, Z = 2, R = 0.025, Rw = 0.071. Structure factors are available from author (e-mail : ynagao@ph.tokushima-u.ac.jp) upon request.

ACKNOWLEDGEMENTS

This work was supported by a Grant-in-Aid from the Tokyo Biochemical Research Foundation (TBRF).

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