PRACTICAL SYNTHESIS OF NEW CHIRAL CIS-PHTHALAZINONES WITH POTENTIAL FOR HIGH PHOSPHODIESTERASE(PDE4) INHIBITORY ACTIVITY

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Abstract – New chiral cis-tetrahydrophthalazinones were synthesized directly from the corresponding chiral (4R)- and (4S)-isopropyl-1,3-thiazolidine-2-thione amides in one-pot reaction involving mild aminolysis with hydrazine monohydrate followed by intramolecular condensation.

INTRODUCTION

In most of the inflammatory cells, elevated cAMP levels are known to inhibit cellular response.1 One effective means to elevate cyclic nucleotide levels is to attenuate cyclic nucleotide breakdown mediated by the action of phosphodiesterase (PDE) enzymes. Therefore, in recent years, some extensive research focused on the discovery and development of potent and selective phosphodiesterase inhibitors for the treatment of acute and chronic inflammatory diseases such as rheumatoid arthritis and asthma.2 Van der Mey et al. reported the synthesis and in vitro and in vivo pharmacological investigations of 4-catechol-substituted rac-cis-4a,5,6,7,8,8a-hexahydro-2H-phthalazin-1-ones and rac-cis-4a,5,8,8a-tetrahydro-2H-phthalazin-1-ones with high PDE4 inhibitory activity, while the corresponding trans racemic mixtures exhibit only weak to moderate activity.3 To determine the relationship between the absolute configuration and PDE4 inhibitory activity of the individual cis-enantiomer, several optically active phthalazinones have been synthesized.4 Both enantiomers of the various γ-ketocarboxylic acids such as rac-cis-6-benzoylecyclohex-3-enecarboxylic acid (rac-1) were resolved in a classical way by the formation of diastereomeric salts of chiral amines, and each enantiomer was converted to the
corresponding chiral phthalazinone in an enatioselective manner. The absolute configuration of the (+)-enantiomer of cis-4a,5,6,7,8a-hexahydro-2H-phthalazin-1-ones was determined by X-Ray crystallographic analysis. The carbon atoms at the 4a and 8a positions were found to have the S- and R-configuration, respectively. In the present series of hexa- and tetrahydrophthalazinones, stereoselectivity for PDE4 inhibition was observed; the (+)-cis-enantiomers of the phthalazinones displayed high inhibitor activity, whereas their (-)-counterparts exhibited only weak to moderate activity. However the absolute configuration of the (+)- or (-)-enantiomer of cis-tetrahydrophthalazinone has never been determined. Recently, we have developed practically useful procedures for the synthesis 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 (4S)-isopropyl-1,3-thiazolidine-2-thione [(4S)-IPTT]. The resulting chiral amides can be useful for the development of new enzyme inhibitors. Here, we report the practical syntheses of new chiral 4-phenyl- and 4-(substituted-phenyl)-cis-tetrahydrophthalazinones, which are synthesized directly from the corresponding chiral (4R)- or (4S)-IPTT amides in one-pot reaction involving mild aminolysis with hydrazine monohydrate followed by intramolecular condensation.

**RESULTS AND DISCUSSION**

Previously, we reported that optical resolution of rac-1 by using (4S)-IPTT gave (1R,6S)-(4S)-IPTT amide (2a) as minor product and (1S,6R)-(4S)-IPTT amide (2b) as major product. In order to obtain (1R,6S)-benzoyl derivative as major product, we repeated the optical resolution of rac-1 by utilizing alternative (4R)-IPTT. Namely, dehydrative condensation of rac-1 with (4R)-IPTT in the presence of WSCD·HCl and 4-dimethylaminopyridine (DMAP) in CH2Cl2 gave a diasteromeric mixture of 3a and 3b. These mixtures were completely separated on a silica gel column [n-hexane-AcOEt (5:1)] to give each pure (4R)-IPTT amide (3a) or (3b) as a yellow solid in 41% or 26% yield with each excellent diasteromer excess (> 99% de), as shown in Scheme 1.

The target racemic compound (rac-4) was synthesized according to the procedure depicted in Scheme 2. The γ-keto-acid (rac-1) readily underwent cyclization upon treatment with hydrazine monohydrate in EtOH to give the corresponding racemate (rac-4) of cis-phthalazinone in 73% yield. In the same procedure (Scheme 2), the target chiral compounds (4a,b) seemed to be obtained from the corresponding chiral γ-keto acids, which could be prepared from (4S)- and (4R)-IPTT amides (2a,b), (4R)-IPTT amides (3a,b), and cis-cyclohex-4-ene-1,2-dicarboxylic anhydride. The (4S)-IPTT group of
the amides (2a,b and 3a,b) 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.\textsuperscript{5,7}

Thus, the (4S)- and (4R)-IPTT amides (2b and 3a) were subjected to mild aminolysis with hydrazine monohydrate. Interestingly, both enantiomers (4a,b) of 4-phenyl-cis-tetrahydrophthalazinones were obtained directly from the corresponding chiral (4S)- and (4R)-IPTT amides (2b and 3a) in one-pot reaction involving mild aminolysis with hydrazine monohydrate in EtOH followed by intramolecular condensation under refluxing. The desired chiral phenyl-cis-tetrahydrophthalazinones (4a,b) were prepared in 71-72% yield and >99% ee, as shown in Scheme 3. The stereochemistry of compounds (3a,b and 4a,b) were precisely determined on the basis of X-Ray crystallographic analysis of chiral 4b (Figure 1).\textsuperscript{5}
The synthesis and biological activities of a series of N-substituted rac-cis-4a,5,6,7,8,8a-hexahydro- and rac-cis-4a,5,8,8a-tetrahydro-2H-phthalazin-1-ones were reported by Van der Mey et al.\textsuperscript{3} It was recognized that the compounds bearing a cycloalkyl group at the N2-position exhibited the highest PDE4 inhibitory activities.\textsuperscript{3}

The N-cycloheptyl- and N-adamantanyltetrahydrophthalazinones showed high \textit{in vivo} anti-inflammatory activities after oral application.\textsuperscript{3} Therefore, rac-cis-N-cycloheptylphthalazinone (\textit{rac}-5) and chiral \textit{cis}-N-cycloheptylphthalazinone (5a,b) were synthesized from \textit{rac}-4 and chiral compounds (4a,b), as shown in Scheme 4. After treatment of \textit{rac}-4 and 4a,b with NaH in DMF, the resulting sodium phthalazinones were allowed to react with cycloheptyl bromide to give the desired compounds, \textit{rac}-5 in

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{4b.png}
\caption{Computer-generated drawing from the X-Ray coordinates of compound (4b)}
\end{figure}
40% yield and chiral compounds (5a,b) in 35 and 36% yields with 81 and 82% ee, respectively. In the reaction (4a,b→5a,b), epimerization occurred in part at the both chiral carbon atoms (4a and 8).
The racemic cis-6-(3,4-diethoxybenzoyl)cyclohex-3-enecarboxylic acid (rac-6) was prepared by a Friedel-Crafts reaction between 1,2-diethoxybenzene and cis-cyclohex-4-ene-1,2-dicarboxylic anhydride in the presence of aluminum chloride. Then, dehydrative condensation of rac-6 with (4R)-IPTT in the presence of WSCD·HCl and DMAP in CH₂Cl₂ gave a diasteromeric mixture of rac-7a and rac-7b. These diastereomers were separated on a silica gel column [n-hexane-AcOEt (3:1)] to give each pure (4R)-IPTT amide (7a) or (7b) as a yellow oil in 36% or 20% yield with 98% de or 87% de, as shown in Scheme 5. Because the active amide moiety of 7a and 7b was fairly unstable, the suitable (4R)-IPTT amide (7a) was instantly subjected to the following reaction, as shown in Scheme 6.

The (+)-cis-enantiomers of the phthalazinones display high inhibitory activity, whereas their (-)-counterparts exhibit only weak to moderate activity. Thus, (+)-cis-4-(3,4-diethoxyphenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one (8) was synthesized directly from the corresponding chiral (4R)-IPTT amide (7a) in one-pot reaction involving mild aminolysis with hydrazine monohydrate in EtOH followed by intramolecular condensation under refluxing. Chiral compound (8) was obtained in 60% yield with 98% ee, as shown in Scheme 7. The ¹H-NMR and IR spectra data of 8 were identical with those of the known compound (rac-8). 

In conclusion, we have developed a practically useful procedure for the syntheses of several new chiral 4-phenyl- and 4-(substituted-phenyl)-cis-tetrahydrophthalazinones, which were synthesized directly from the corresponding chiral (4R)- or (4S)-IPTT amides in one-pot reaction involving mild aminolysis with hydrazine monohydrate followed by intramolecular condensation. The resulting chiral cis-tetrahydrophthalazinones may exhibit a high PDE4 inhibitory activity. The chiral compounds (4a and 8) should be useful for development of novel PDE4 and PDE3 inhibitors and biologically active compounds such as chiral (+)-cis-4-(3,4-diethoxyphenyl)-2-{4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenoxy}butyl]-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one and other biologically active natural products and drugs.
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 $\delta$ value (ppm) using tetramethylsilane (TMS) as an internal standard. EI-MS spectrum was recorded on a JEOL JMS SX-102A spectrometer. ESI-MS were recorded on a Waters LCT Premier 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 $\mu$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$_2$Cl$_2$ were used as purchased from Kanto Chemical. All other reagents were used as purchased. All reactions were carried out under argon.

Optical Resolution of Racemic cis-6-Benzoylcyclohex-3-enecarboxylic Acid (1)

To a solution of racemic carboxylic acid (rac-1) (230 mg, 1 mmol) and (4R)-IPTT (335 mg, 2 mmol) in CH$_2$Cl$_2$ (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 subjected to the usual work-up$^5$ to give a yellow solid residue, which was chromatographed on a silica gel column with hexane—EtOAc (5:1) to furnish (4S)-IPTT amide (3a) (154 mg, 41%) as a yellow solid and then another (4S)-IPTT amide (3b) (98 mg, 26%) as a yellow solid.

Yellow prisms, mp 90-92 °C (hexane); [\(\alpha\)]$_D$$^{21}$ -362° (c 0.4, CHCl$_3$). IR (KBr) 2965, 1758, 1698, 1671 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 0.96-0.98 (d, 3H, $J = 6.83$ Hz), 1.05-1.07 (d, 3H, $J = 6.83$ 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, 1H), 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$_2$S$_2$ MW 373.1170, found m/z 373.1206 (M$^+$); Anal. Calcd for C$_{20}$H$_{23}$NO$_2$S$_2$: C, 64.31; H, 6.21; N, 3.75. Found: C, 64.21; H, 6.20; N, 3.75. HPLC analysis [TSK-gel Silica 60, hexane—AcOEt (4:1), 0.5 mL/min, 310 nm; $t_R$ (minor) = 12.41 min, $t_R$ (major) = 15.01 min] gave the isomeric composition of the product: >99% de.
(1S, 6R)-6-Benzoyl-1-[(4R)-4-isopropyl-1,3-thiazolidine-2-thion-3-yl]carbonylcyclohex-3-ene (3b)

Yellow prisms, mp 101-103 °C (hexane); [α]D21-301° (c 0.5, CHCl3). IR (KBr) 2965, 1760, 1699, 1679 cm⁻¹; ¹H-NMR (400 MHz, CDCl3) δ 0.89-0.91 (d, 3H, J = 6.84 Hz), 0.98-1.00 (d, 3H, J = 6.84 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 C20H23NO2S2 MW 373.1170, found m/z 373.1176 (M⁺); Anal. Calcd for C20H23NO2S2: C, 64.31; H, 6.21; N, 3.75. Found: C, 64.11; H, 6.15; N, 3.76. HPLC analysis [TSK-gel Silica 60, hexane—AcOEt (4:1), 0.5 mL/min, 310 nm; tR (major) = 15.01 min, tR (minor) = 12.37 min] gave the isomeric composition of the product: >99% de.

Racemic cis-4-Phenyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one (4)

A mixture of rac-1 (230 mg, 1 mmol) and hydrazine monohydrate (0.15 mL, 3 mmol) in EtOH (10 mL) was refluxed for 6 h, excess EtOH was evaporated in vacuo, and the oily residue was dissolved in ethyl acetate. The solution was washed with water, dilute NaHCO₃, and 1 N HCl and then dried over MgSO₄. After filtration of the mixture, the filtrate was evaporated in vacuo to give a crude product, which was purified by column chromatography on silica gel with hexane—EtOAc (2:1) to afford racemic tetrahydrophthalazinone (rac-4) (165 mg, 73%) as a white solid. mp 180-182 °C (CHCl₃—hexane); IR (KBr) 3197, 3091, 2948, 2360, 1673 cm⁻¹; ¹H-NMR (400 MHz, CDCl3) δ 2.22-2.26 (m, 3H), 2.83-2.88 (m, 1H), 2.95-3.02 (m, 1H), 3.41-3.43 (m, 1H), 5.72-5.78 (m, 2H), 7.42-7.44 (m, 3H), 7.77-7.79 (m, 2H), 8.60 (s, 1H); HREI-MS calcd for C14H14N2O, MW 226.1106, found m/z 226.1088 (M⁺); Anal. Calcd for C14H14N2O: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.19; H, 6.35; N, 12.41.

(+)-cis-4-Phenyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one (4a)

A mixture of 3a (374 mg, 1 mmol) and hydrazine monohydrate (0.20 mL, 4 mmol) in EtOH (10 mL) was refluxed for 12 h, excess EtOH was evaporated in vacuo, and the oily residue was dissolved in ethyl acetate. The solution was washed with water, dilute NaHCO₃, and 1 N HCl and then dried over MgSO₄. Evaporation of the filtrate in vacuo gave an oily residue, which was purified by column chromatography on silica gel with hexane—EtOAc (2:1) to afford chiral tetrahydrophthalazinone (4a) (161 mg, 71%) as a colorless block. mp 149-151 °C (CHCl₃—hexane); [α]D23 +887° (c 0.36, CHCl₃). IR (KBr) 3295, 3043, 2950, 2358, 1679 cm⁻¹; ¹H-NMR (400 MHz, CDCl3) δ 2.22-2.26 (m, 3H), 2.83-2.86 (m, 1H), 2.95-3.04 (m, 1H), 3.41-3.43 (m, 1H), 5.69-5.82 (m, 2H), 7.41-7.44 (m, 3H), 7.77-7.79 (m, 2H), 8.58 (s, 1H); HREI-MS calcd for C14H14N2O, MW 226.1106, found m/z 226.1088 (M⁺); Anal. Calcd for C14H14N2O: C,
74.31; H, 6.24; N, 12.38. Found: C, 74.01; H, 6.27; N, 12.33. HPLC analysis [Chiralcel OD-H, hexane—i-PrOH (5:1), 0.5 mL/min, 254 nm; \( t_R \) (minor) = 18.54 min, \( t_R \) (major) = 21.22 min] gave the isomeric composition of the product: >99% ee.

**(-)-cis-4-Phenyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one (4b)**

The similar ring closure reaction of 2b (374 mg, 1 mmol) with hydrazine monohydrate (0.20 mL, 4 mmol) in EtOH (10 mL) utilizing the procedure described for 4a gave chiral tetrahydrophthalazinone (4b) (163 mg, 72%) as a colorless block. mp 149-151 °C (CHCl₃—hexane); \([\alpha]_D^{23} \) -883° (c 0.37, CHCl₃). IR (KBr) 3297, 3043, 2950, 2360, 1679 cm⁻¹; \(^1\)H-NMR (400 MHz, CDCl₃) see 4a; HREI-MS calcd for \( C_{14}H_{14}N_2O \), MW 226.1106, found m/z 226.1108 (M⁺). Anal. Calcd for \( C_{14}H_{14}N_2O \): C, 74.31; H, 6.24; N, 12.38. Found: C, 74.01; H, 6.30; N, 12.37. HPLC analysis [Chiralcel OD-H, hexane—i-PrOH (5:1), 0.5 mL/min, 254 nm; \( t_R \) (major) = 18.36 min, \( t_R \) (minor) = 21.20 min] gave the isomeric composition of the product: >99% ee.

**Racemic cis-2-Cycloheptyl-4-phenyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one (5)**

Sodium hydride (60% dispersion in mineral oil, 44 mg, 1.1 mmol) was added to a suspension of the tetrahydrophthalazinone (4) (226 mg, 1 mmol) in DMF (9 mL). After the mixture was stirred at rt for 1 h, cycloheptyl bromide (0.163 mL, 1 mmol) was added and then the mixture was stirred at rt for 4 h. The reaction mixture was poured into water, and the aqueous solution was extracted with ethyl acetate. The extract was washed with water, brine, and then dried over MgSO₄. Evaporation of the filtrate gave an oily residue, which was purified by column chromatography on silica gel with hexane—EtOAc (3:1) to afford racemic 2-cycloheptyltetrahydrophthalazinone (5) (129 mg, 40%) as a white solid. mp 173-175 °C (Et₂O—hexane); IR (KBr) 3041, 2923, 2856, 1662 cm⁻¹; \(^1\)H-NMR (400 MHz, CDCl₃) \( \delta \) 1.50-2.25 (m, 15H), 2.72-2.75 (m, 1H), 2.90-3.11 (m, 1H), 3.30-3.35 (m, 1H), 4.78-4.88 (m, 1H), 5.65-5.85 (m, 2H), 7.40-7.48 (m, 3H), 7.82-7.86 (m, 2H); HREI-MS calcd for \( C_{21}H_{26}N_2O \), MW 322.2045, found m/z 322.2070 (M⁺); Anal. Calcd for \( C_{21}H_{26}N_2O \): C, 78.22; H, 8.13; N, 8.69. Found: C, 78.09; H, 8.18; N, 8.70.

**(+)-cis-2-Cycloheptyl-4-phenyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one (5a)**

The similar alkylation of 4a (226 mg, 1 mmol) with cycloheptyl bromide (0.163 mL, 1 mmol) utilizing the procedure described for rac-5 gave chiral (+)-2-cycloheptyltetrahydrophthalazinone (5a) (113 mg, 35%) as a white solid. mp 140-142 °C (Et₂O); \([\alpha]_D^{19} \) +713° (c 0.15, CHCl₃). IR (KBr) 3035, 2923, 2856, 1660 cm⁻¹; \(^1\)H-NMR (400 MHz, CDCl₃) \( \delta \) 1.50-2.25 (m, 15H), 2.72-2.75 (m, 1H), 2.90-3.11 (m, 1H), 3.30-3.35 (m, 1H), 4.78-4.88 (m, 1H), 5.65-5.85 (m, 2H), 7.40-7.48 (m, 3H), 7.82-7.86 (m, 2H); HREI-MS calcd for \( C_{21}H_{26}N_2O \), MW 322.2045, found m/z 322.2070 (M⁺); Anal. Calcd for \( C_{21}H_{26}N_2O \): C, 78.22; H, 8.13; N, 8.69. Found: C, 78.09; H, 8.18; N, 8.70.
3.30-3.35 (m, 1H), 4.78-4.88 (m, 1H), 5.65-5.85 (m, 2H), 7.40-7.48 (m, 3H), 7.82-7.86 (m, 2H); HREI-MS calcd for C_{21}H_{26}N_{2}O, MW 322.2045, found m/z 322.2032 (M+); Anal. Calcd for C_{21}H_{26}N_{2}O: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.26; H, 8.25; N, 8.54. HPLC analysis [Chiralcel OD-H, hexane—i-PrOH (5:1), 0.2 mL/min, 254 nm; t_r (minor) = 22.67 min, t_R (major) = 24.94 min] gave the isomeric composition of the product: 81% ee.

(−)-cis-2-Cycloheptyl-4-phenyl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one (5b)
The similar alkylation of 4b (226 mg, 1 mmol) with cycloheptyl bromide (0.163 mL, 1 mmol) utilizing the procedure described for rac-5 gave chiral (−)-2-cycloheptyltetrahydrophthalazinone (5b) (116 mg, 36%) as a white solid. mp 140-142 °C (Et_2O); [α]_D^{19} = -690° (c 0.14, CHCl_3). IR (KBr) 3035, 2925, 2850, 1660 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) see 5a; HREI-MS calcd for C_{21}H_{26}N_{2}O, MW 322.2045, found m/z 322.2070 (M⁺); HPLC analysis [Chiralcel OD-H, hexane—i-PrOH (5:1), 0.2 mL/min, 254 nm; t_R (major) = 22.69 min, t_R (minor) = 24.97 min] gave the isomeric composition of the product: 82% ee.

Optical Resolution of Racemic cis-6-(3,4-Diethoxybenzoyl)cyclohex-3-ene carboxylic Acid (6)
To a solution of rac-6 (318 mg, 1 mmol) and (4R)-IPTT (335 mg, 2 mmol) in CH₂Cl₂ (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 subjected to the usual work-up to give a yellow solid residue, which was chromatographed on a silica gel column with hexane—EtOAc (5:1) to furnish (4S)-IPTT amide (7a) (166 mg, 36%) as a yellow oil and then another (4S)-IPTT amide (7b) (92 mg, 20%) as a yellow oil.

(1R, 6S)-6-(3,4-Diethoxybenzoyl)-1-[(4R)-4-isopropyl-1,3-thiazolidine-2-thion-3-yl]carbonylcyclohex-3-ene (7a)
Yellow oil, IR (neat) 2975, 2360, 1789, 1704, 1668 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.96-0.98 (d, 3H, J = 6.83 Hz), 1.06-1.07 (d, 3H, J = 6.83 Hz), 1.44-1.52 (m, 6H), 2.40-2.50 (m, 3H), 2.55-2.65 (m, 2H), 3.03-3.06 (d, 1H, J = 12.47 Hz), 3.68-3.73 (dd, 1H, J = 11.48, 8.06 Hz), 4.12-4.19 (m, 4H), 4.80-4.82 (m, 1H), 5.01-5.05 (m, 1H), 5.75-5.86 (m, 2H), 6.86-6.89 (d, 1H, J = 8.54 Hz), 7.49-7.53 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ 203.0, 200.1, 175.3, 153.0, 148.5, 128.6, 125.8, 124.0, 122.8, 112.5, 111.3, 76.7, 73.2, 64.6, 64.5, 43.5, 36.3, 31.2, 30.9, 27.7, 27.4, 19.2, 17.9, 14.8, 14.7; HRESI-MS calcd for C_{24}H_{31}NO_{4}S_{2}Na MW 484.1592, found m/z 484.1589 (M+Na⁺); HPLC analysis [TSK-gel Silica 60, hexane—AcOEt (4:1), 0.3 mL/min, 310 nm; t_R (major) = 27.42 min, t_R (minor) = 29.30 min] gave the isomeric composition of the product: 98% de. The correct optical rotation value of 7a could not be determined because of its instability.
(1S, 6R)-6-(3,4-Diethoxybenzoyl)-1-[(4R)-4-isopropyl-1,3-thiazolidine-2-thion-3-yl]carbonylcyclohex-3-ene (7b)

Yellow oil, IR (neat) 2975, 2360, 1789, 1704, 1668 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) δ 0.89-0.91 (d, 3H, $J = 7.08$ Hz), 0.98-1.01 (d, 3H, $J = 6.84$ Hz), 1.44-1.52 (m, 6H), 1.95-2.00 (m, 1H), 2.35-2.40 (m, 1H), 2.40-2.55 (m, 2H), 2.72-2.80 (m, 1H), 2.96-2.99 (d, 1H, $J = 12.69$ Hz), 3.68-3.73 (m, 1H), 4.12-4.18 (m, 4H), 5.02-5.07 (m, 1H), 5.09-5.13 (m, 1H), 5.72-5.76 (m, 1H), 6.86-6.89 (d, 1H, $J = 8.7$ Hz), 7.49-7.53 (m, 2H); HRESI-MS calcd for C$_{24}$H$_{31}$NO$_4$S$_2$Na MW 484.1592, found m/z 484.1603 (M+Na)$^+$. HPLC analysis [TSK-gel Silica 60, hexane—AcOEt (4:1), 0.3 mL/min, 310 nm; $t_R$ (minor) = 27.36 min, $t_R$ (major) = 29.26 min] gave the isomeric composition of the product: 87% de. The correct optical rotation value of 7b could not be determined because of its instability.

(+)-cis-4-(3,4-Diethoxyphenyl)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one (8)

A mixture of 7a (461 mg, 1 mmol) and hydrazine monohydrate (0.20 mL, 4 mmol) in EtOH (10 mL) was refluxed for 12 h, excess EtOH was evaporated in vacuo, and the oily residue was dissolved in ethyl acetate. The solution was washed with water, dilute NaHCO$_3$, and 1 N HCl and then dried over MgSO$_4$. Evaporation of the filtrate in vacuo gave an oily residue, which was purified by column chromatography on silica gel with hexane—EtOAc (1:1) to afford chiral tetrahydrophthalazinone (8) (188 mg, 60%) as a white solid. mp 113-115 °C (Et$_2$O); [α]$_D$ 19$^0$ +691° (c 0.3, CHCl$_3$). IR (KBr) 3259, 2933, 2362, 1685 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) δ 1.37-1.44 (m, 6H), 2.11-2.16 (m, 3H), 2.74-2.77 (m, 1H), 2.88-2.95 (m, 1H), 3.29-3.33 (m, 1H), 4.03-4.12 (m, 4H), 5.60-5.73 (m, 2H), 6.77-6.80 (d, 1H, $J = 8.30$ Hz), 7.13-7.20 (dd, 1H, $J = 2.0$, 8.30 Hz), 7.38-7.39 (d, 1H, $J = 2.0$ Hz), 9.03 (s, 1H); HREI-MS calcd for C$_{18}$H$_{22}$N$_2$O$_3$, MW 314.1630, found m/z 314.1600 (M$^+$); Anal. Calcd for C$_{18}$H$_{22}$N$_2$O$_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.41; H, 7.16; N, 8.72. HPLC analysis [Chiralcel OD-H, hexane—i-PrOH (5:1), 0.5 mL/min, 254 nm; $t_R$ (major) = 25.19 min, $t_R$ (minor) = 30.41 min] gave the isomeric composition of the product: 98% ee.

Crystal Data for X-Ray Crystallographic Analysis of Compound (4b)

C$_{14}$H$_{14}$N$_2$O$_3$, MW = 226.28, colorless block, orthorhombic, P2$_1$2$_1$2$_1$(#19), a = 7.726(2)Å, b = 11.472(3)Å, c = 12.481(3)Å, V = 1106.2(6)Å$^3$, Z = 4, R = 0.040, Rw = 0.087. Structure factors are available from author (e-mail: y nagao@ph.tokushima-u.ac.jp) upon request.
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REFERENCES AND NOTES