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ASYMMETRIC SYNTHESIS OF *cis*-4a,5,8,8a-TETRAHYDROPHTHALAZIN-1(2*H*)-ONE DERIVATIVES BASED ON ORGANOCATALYTIC ALCOHOLYSIS OF CYCLIC DICARBOXYLIC ANHYDRIDE

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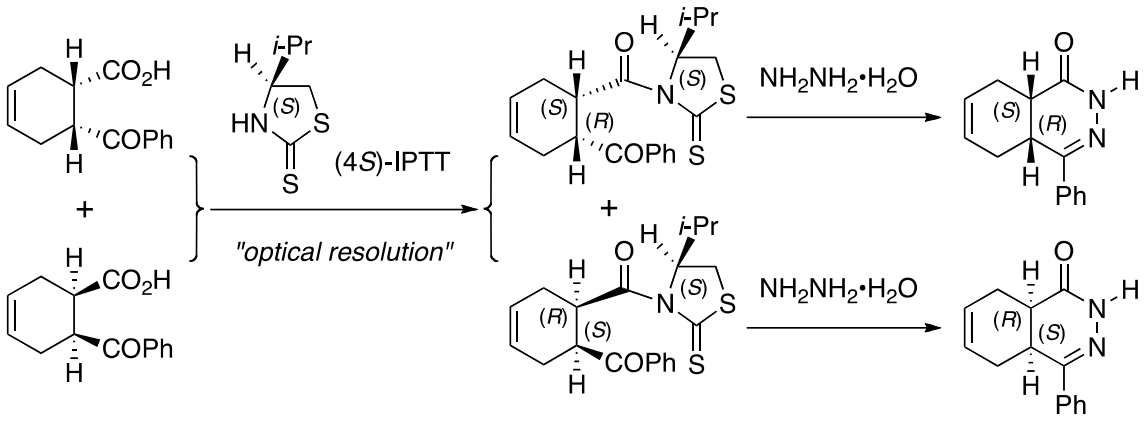
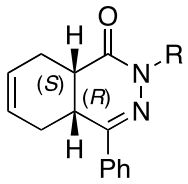
Abstract – Asymmetric synthesis of optically active *cis*-4-phenyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one and its *N*-alkylated derivatives based on an organocatalytic enantioselective alcoholysis of cyclic dicarboxylic anhydride was described.

4a,5,8,8a-Tetrahydrophthalazin-1(2*H*)-ones, some of which are known as phosphodiesterase type 4 (PDE4) inhibitors,[1] are an important class of heterocyclic compounds. We have already reported the synthesis of both enantiomers of *cis*-4-phenyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one based on the practical optical resolution of a racemic mixture of *cis*-6-benzoylcyclohex-3-enecarboxylic acid using (4*S*)-isopropyl-1,3-thiazolidine-2-thione [(4*S*)-IPTT][2] as a resolving reagent (Scheme 1).[3,4] However, there are only a limited number of reports concerning the asymmetric synthesis of *cis*-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-ones.[5]



Scheme 1. Optical resolution of *cis*-6-benzoylcyclohex-3-enecarboxylic acid using (4*S*)-IPTT

Previously, we reported the enantioselective thiolysis and alcoholysis of σ-symmetric cyclic dicarboxylic anhydrides catalyzed by a chiral bifunctional sulfonamide.[6] Thus, our interest in 4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-ones led us to investigate the application of the organocatalytic enantioselective alcoholysis of *cis*-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione to the preparation of (1*S*,6*R*)-6-benzoylcyclohex-3-ene-1-carboxylic acid [(1*S*,6*R*)-**7**],[3] a key intermediate for the synthesis of optically active *cis*-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-ones. Herein we present a novel synthesis of (4a*R*,8a*S*)-4-phenyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one [(4a*R*,8a*S*)-**1a**] and its *N*-alkylated derivatives (4a*R*,8a*S*)-**1b**-**f**.



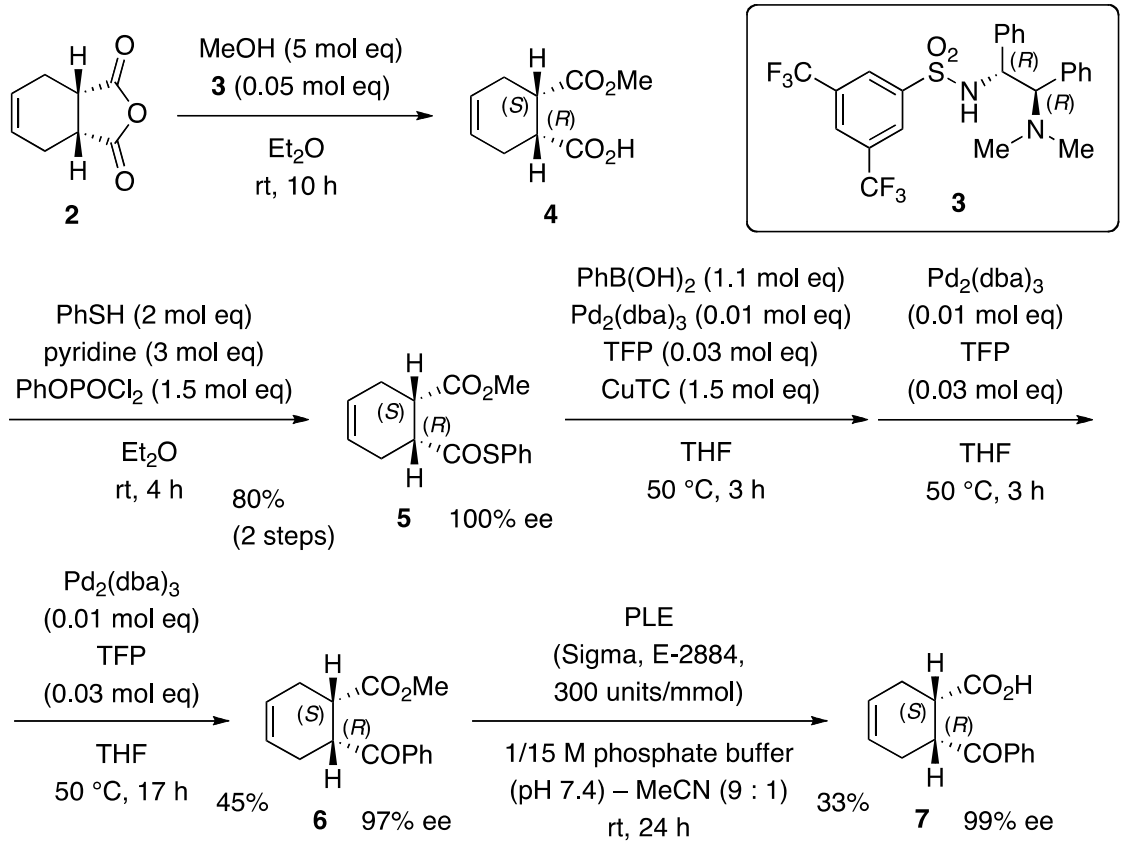
1a-f

a: R = H, **b**: R = Me, **c**: R = Et,
d: R = *n*-Pr, **e**: R = *n*-Bu, **f**: R = *c*-Hept

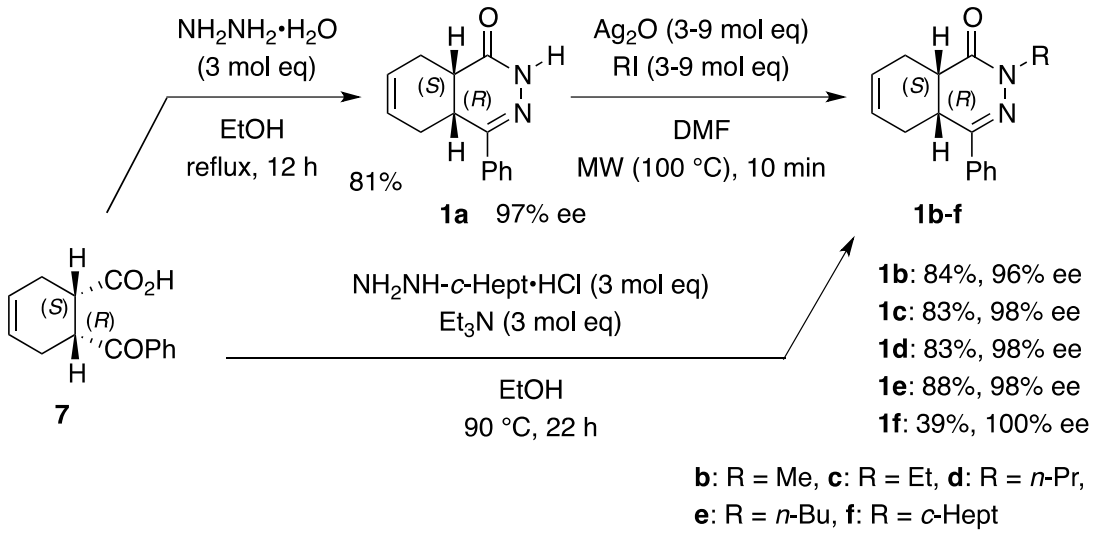
Figure 1. Chiral *cis*-4-phenyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-ones (4a*R*,8a*S*)-**1a**-**f**

Construction of the chiral key intermediate (1*S*,6*R*)-**7** was performed as shown in Scheme 2. Enantioselective alcoholysis of *cis*-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (**2**) in the presence of a catalytic amount of chiral sulfonamide (1*R*,2*R*)-**3** followed by direct transformation of the carboxyl group with phenyl dichlorophosphate and thiophenol afforded the corresponding thioester (1*S*,6*R*)-**5** in 80% yield (2 steps) with 100% ee. Copper(I) thiophene-2-carboxylate (CuTC) mediated cross-coupling of the resulting *S*-phenyl thioester (1*S*,6*R*)-**5** and phenylboronic acid in the presence of catalytic amounts of tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] and tris(2-furyl)phosphine (TFP) gave phenyl ketone (1*S*,6*R*)-**6** in 45% yield with 97% ee.[7] Enzymatic hydrolysis of (1*S*,6*R*)-**6** with porcine liver esterase (PLE) in a pH 7.4 buffered solution furnished (1*S*,6*R*)-**7** in 33% yield with 99% ee.[8,9] The enantiomeric excess of (1*S*,6*R*)-**7** was determined by means of HPLC analysis using a chiral stationary phase (CSP) after quantitative methylation with an excess amount of (trimethylsilyl)diazomethane ($TMSCHN_2$).[10] Condensation of γ-keto acid (1*S*,6*R*)-**7** with hydrazine monohydrate in ethanol under reflux conditions furnished 4-phenyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one (**1a**) in 81% yield with 97% ee as shown in Scheme 3. The absolute configuration of the resultant **1a** was determined to be 4a*R*,8a*S* by comparison of the specific rotation {$[\alpha]_D^{17}$ -802 (*c* 1.00, $CHCl_3$), lit.[4] (4a*R*,8a*S*)-**1a** $[\alpha]_D^{23}$ -883 (*c* 0.37, $CHCl_3$)} with that reported for (4a*R*,8a*S*)-**1a**. *N*-Alkylation of (4a*R*,8a*S*)-**1a** using various alkyl iodides and silver(I) oxide[11] under microwave irradiation with a single-mode microwave reactor (Initiator^{TM} 60; Biotage AB) at 100 °C in DMF for 10 min afforded the corresponding *N*-alkylated

derivatives (4a*R*,8a*S*)-**1b**-**e**. In addition, a preliminary investigation of condensation of (1*S*,6*R*)-**7** with cycloheptylhydrazine hydrochloride under conventional heating conditions furnished the corresponding *N*-cycloheptyl derivative (4a*R*,8a*S*)-**1f** without loss of the enantiomeric excess.



Scheme 2. Synthesis of chiral key intermediate (1*S*,6*R*)-**7**



Scheme 3. Synthesis of chiral *cis*-4-phenyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-ones (4a*R*,8a*S*)-**1a**-**f**

In conclusion, we have presented an asymmetric synthesis of optically active *cis*-4-phenyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one [(4a*R*,8a*S*)-**1a**] and its *N*-alkylated derivatives (4a*R*,8a*S*)-**1b**-**f** based on an enantioselective alcoholysis of σ-symmetric cyclic dicarboxylic anhydride **2** using a chiral sulfonamide (1*R*,2*R*)-**3** as an organocatalyst. We believe this synthetic method will be of great benefit in the medicinal chemistry of PDE4 inhibitors having a 4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one structure.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-6200 IR Fourier transform spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker AV500 spectrometer. Chemical shifts are given in δ values (parts per million) using tetramethylsilane (TMS) as an internal standard. Electron spray ionization mass spectra (ESIMS) were recorded on a Waters LCT Premier spectrometer. Elemental combustion analyses were performed using a Yanagimoto CHN CORDER MT-5 and a J-SCIENCE LAB JM10. The microwave-assisted reaction was performed utilizing an automated single-mode microwave synthesizer (Initiator^{TM} 60; Biotage AB). All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F_{254}). Column chromatography was carried out on silica gel [Kanto Chemical 60N (spherical, neutral); 63-210 □m]. Anhydrous Et_2O, THF, and DMF were used as purchased from Kanto Chemical. All other reagents were used as purchased.

(1*S*,6*R*)-Methyl 6-(phenylthiocarbonyl)cyclohex-3-enecarboxylate [(1*S*,6*R*)-5]

Chiral sulfonamide (1*R*,2*R*)-**3** (50 mg, 0.097 mmol) and MeOH (0.4 mL, 9.7 mmol) were added to a solution of *cis*-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (**2**) (295 mg, 1.94 mmol) in anhydrous Et_2O (20 mL) under argon. After being stirred for 10 h at rt, the reaction mixture was treated with 1N HCl (3 mL) and then extracted with AcOEt (10 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford carboxylic acid (1*R*,6*S*)-**4** as a colorless oil, which was used in the next reaction without further purification.

To a solution of carboxylic acid (1*R*,6*S*)-**4** in anhydrous Et_2O (9 mL) were added pyridine (0.5 mL, 5.82 mmol), thiophenol (0.4 mL, 3.9 mmol), and phenyl dichlorophosphate (0.4 mL, 2.9 mmol) at 0 °C under argon. The reaction mixture was allowed to warm to rt and stirred for 4 h, then treated with 1N NaOH (3 mL) and extracted with $CHCl_3$ (10 mL x 3). The extract was washed with brine (5 mL) and dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by column chromatography [*n*-hexane–AcOEt (6:1)], then again by column chromatography [*n*-hexane–AcOEt (9:1)] to afford (1*S*,6*R*)-**5** (428 mg, 80%, 100% ee). The enantiomeric excess of (1*S*,6*R*)-**5** was determined

by HPLC analysis [CHIRALPAK AS-H, *n*-hexane–2-propanol (15:1); flow rate: 1.0 mL/min; detection: 254 nm; t_R (major) = 7.88 min].

Colorless oil; $[\alpha]_D^{27}$ -4.2 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.36–2.42 (m, 1H), 2.50–2.61 (m, 2H), 2.68–2.74 (m, 1H), 3.08 (td, *J* = 3.6, 6.6 Hz, 1H), 3.33 (td, *J* = 3.6, 6.2 Hz, 1H), 3.70 (s, 3H), 5.68–5.76 (m, 2H), 7.37–7.42 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.9, 26.5, 40.3, 48.0, 51.9, 124.2, 125.7, 127.5, 129.1, 129.2, 134.8, 173.2, 198.3; IR (neat) 3029, 2950, 2919, 2846, 1736, 1704, 1439, 1202, 1026, 748, 690 cm^{-1}; ESI-MS *m*/*z*: calcd for $C_{15}H_{16}NaO_3S$ $[M+Na]^+$, 299.0718; found, 299.0706. Anal. Calcd for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.84. Found: C, 65.32; H, 6.14%.

(4a*R*,8a*S*)-4-Phenyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one [(4a*R*,8a*S*)-1a][4]

Hydrazine monohydrate (80% in H_2O) (332 μL, 5.46 mmol) was added to a solution of carboxylic acid (1*S*,6*R*)-**7** (419 mg, 1.82 mmol) in EtOH (18.2 mL). After being refluxed for 12 h, the reaction mixture was concentrated *in vacuo* and AcOEt (20 mL) was added. The solution was washed with H_2O, sat. $NaHCO_3$, and 1N HCl, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography [*n*-hexane–AcOEt (1:1)] to afford (4a*R*,8a*S*)-**1a** (333 mg, 81%, 97% ee). The enantiomeric excess of (4a*R*,8a*S*)-**1a** was determined by HPLC analysis [CHIRALCEL OD-H, *n*-hexane–2-propanol (5:1); flow rate: 0.5 mL/min; detection: 254 nm; t_R (major) = 21.18 min; t_R (minor) = 23.87 min].

Colorless prisms ($CHCl_3$–*n*-hexane); mp 195.5–197 °C; $[\alpha]_D^{17}$ -802 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.21–2.25 (m, 3H), 2.86 (t, *J* = 6.1 Hz, 1H), 2.97–3.01 (m, 1H), 3.40–3.44 (m, 1H), 5.70–5.73 (m, 1H), 5.77–5.80 (m, 1H), 7.41–7.43 (m, 3H), 7.77–7.79 (m, 2H), 8.56 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 23.1, 31.6, 34.2, 124.1, 125.6, 125.8, 128.8, 129.9, 134.7, 154.8, 169.5; IR (KBr) 3233, 3117, 2950, 2900, 1682, 1277, 774 cm^{-1}; ESI-MS *m*/*z*: calcd for $C_{14}H_{14}N_2NaO$ $[M+Na]^+$, 249.1004; found, 249.0991. Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.01; H, 6.29; N, 12.21%.

(4a*R*,8a*S*)-2-Methyl-4-phenyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one [(4a*R*,8a*S*)-1b]

A suspension of (4a*R*,8a*S*)-**1a** (30.3 mg, 0.13 mmol), silver(I) oxide (90.2 mg, 0.39 mmol), and iodomethane (24 μL, 0.39 mmol) in DMF (1.3 mL) was irradiated at 100 °C for 10 min using a Biotage Initiator™ microwave synthesizer. AcOEt (5 mL) was added to the reaction mixture and silver(I) oxide was removed by filtration. The filtrate was treated with H_2O (10 mL) and then extracted with AcOEt (30 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography [*n*-hexane–AcOEt (3:1)] to afford (4a*R*,8a*S*)-**1b** (26.2 mg, 84%, 96% ee). The enantiomeric excess of (4a*R*,8a*S*)-**1b** was determined by HPLC analysis [CHIRALPAK

AD-H, *n*-hexane–2-propanol (97:3); flow rate: 0.5 mL/min; detection: 254 nm; t_R (major) = 18.02 min; t_R (minor) = 19.70 min].

Colorless solid; mp 54.0–55.1 °C; $[\alpha]_D^{20}$ -941 (*c* 0.93, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.08–2.26 (m, 3H), 2.80 (t, *J* = 6.0 Hz, 1H), 2.98–3.04 (m, 1H), 3.37 (dt, *J* = 5.7, 11.5 Hz, 1H), 3.47 (s, 3H), 5.68–5.71 (m, 1H), 5.77–5.80 (m, 1H), 7.40–7.43 (m, 3H), 7.79–7.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 23.4, 31.9, 34.4, 37.0, 124.0, 125.7, 125.9, 128.7, 129.8, 134.8, 154.3, 167.7; IR (KBr) 3040, 2946, 2890, 2869, 2845, 1677 cm^{-1}; ESI-MS *m*/*z*: calcd for $C_{15}H_{16}N_2NaO$ $[M+Na]^+$, 263.1160; found, 263.1155.

(4a*R*,8a*S*)-2-Ethyl-4-phenyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one [(4a*R*,8a*S*)-1c]

Colorless oil; $[\alpha]_D^{17}$ -893 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H), 2.05–2.24 (m, 3H), 2.77 (t, *J* = 6.1 Hz, 1H), 2.97–3.05 (m, 1H), 3.34 (dt, *J* = 5.7, 11.4 Hz, 1H), 3.87 (dq, *J* = 7.1, 13.3 Hz, 1H), 3.97 (dq, *J* = 7.1, 13.3 Hz, 1H), 5.66–5.72 (m, 1H), 5.76–5.79 (m, 1H), 7.37–7.43 (m, 3H), 7.80–7.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 22.2, 23.2, 31.7, 34.5, 43.7, 123.9, 125.7, 125.9, 128.7, 129.7, 134.9, 154.2, 166.9; IR (neat) 3028, 2973, 2934, 2891, 1675, 1445, 1401, 1340, 1269 cm^{-1}; ESI-MS *m*/*z*: calcd for $C_{16}H_{18}N_2NaO$ $[M+Na]^+$, 277.1317; found, 277.1308. Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.77; H, 7.27; N, 10.76%.

(4a*R*,8a*S*)-4-Phenyl-2-propyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one [(4a*R*,8a*S*)-1d]

Colorless oil; $[\alpha]_D^{17}$ -820 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.4 Hz, 3H), 1.73 (sext, *J* = 7.3 Hz, 2H), 2.07–2.26 (m, 3H), 2.81 (t, *J* = 6.1 Hz, 1H), 2.98–3.05 (m, 1H), 3.36 (dt, *J* = 5.7, 11.4 Hz, 1H), 3.73 (dt, *J* = 7.1, 13.2 Hz, 1H), 3.95 (dq, *J* = 7.3, 13.2 Hz, 1H), 5.67–5.71 (m, 1H), 5.78–5.81 (m, 1H), 7.39–7.45 (m, 3H), 7.80–7.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 21.6, 22.2, 23.3, 31.7, 34.5, 50.4, 123.9, 125.8, 126.0, 128.7, 129.7, 135.0, 153.9, 167.3; IR (neat) 3028, 2962, 2933, 2873, 1675, 1354, 1256 cm^{-1}; ESI-MS *m*/*z*: calcd for $C_{17}H_{20}N_2NaO$ $[M+Na]^+$, 291.1473; found, 291.1472. Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 75.99; H, 7.63; N, 10.14%.

(4a*R*,8a*S*)-2-Butyl-4-phenyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one [(4a*R*,8a*S*)-1e]

Colorless solid; mp 54.0–55.5 °C; $[\alpha]_D^{20}$ -732 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.36 (sext, *J* = 7.4 Hz, 2H), 1.68 (quint, *J* = 7.4 Hz, 2H), 2.05–2.26 (m, 3H), 2.79 (t, *J* = 6.1 Hz, 1H), 2.99–3.04 (m, 1H), 3.35 (dt, *J* = 5.7, 11.4 Hz, 1H), 3.77 (dt, *J* = 7.2, 13.2 Hz, 1H), 3.98 (dt, *J* = 7.3, 13.2 Hz, 1H), 5.68–5.71 (m, 1H), 5.76–5.81 (m, 1H), 7.39–7.44 (m, 3H), 7.79–7.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 20.1, 22.2, 23.3, 30.4, 31.7, 34.5, 48.6, 123.9, 125.8, 126.0, 128.7, 129.7, 135.0, 153.9, 167.2; IR (KBr) 3290, 3061, 3027, 2959, 2873, 1660 cm^{-1}; ESI-MS *m*/*z*: calcd for $C_{18}H_{23}N_2O$ $[M+H]^+$, 283.1810; found, 283.1785.

(4a*R*,8a*S*)-2-Cycloheptyl-4-phenyl-4a,5,8,8a-tetrahydrophthalazin-1(2*H*)-one [(4a*R*,8a*S*)-1f][4]

Cycloheptylhydrazine hydrochloride (43.8 mg, 0.27 mmol) and triethylamine (37.6 μL, 0.27 mmol) were added to a solution of carboxylic acid (1*S*,6*R*)-**7** (20.4 mg, 0.089 mmol) in EtOH (0.89 mL). The reaction mixture was heated at 90 °C for 22 h in a sealed tube. The reaction mixture was evaporated to remove EtOH, and AcOEt (20 mL) was added to the residue. The solution was washed with 1N NaOH, 1N HCl, and H_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography [*n*-hexane–AcOEt (6:1)] to afford (4a*R*,8a*S*)-**1f** (11.2 mg, 39%, 100% ee). The enantiomeric excess of (4a*R*,8a*S*)-**1f** was determined by HPLC analysis [CHIRALCEL OD-H, *n*-hexane–2-propanol (5:1); flow rate: 0.2 mL/min; detection: 254 nm; t_R (major) = 24.95 min].

Colorless needles (Et_2O–*n*-hexane); mp 114.0–116.0 °C; $[\alpha]_D^{20}$ -593 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.46–2.23 (m, 15H), 2.73 (t, *J* = 6.0 Hz, 1H), 2.99–3.04 (m, 1H), 3.33 (dt, *J* = 5.7, 11.5 Hz, 1H), 4.82 (tt, *J* = 4.7, 9.4 Hz, 1H), 5.64–5.70 (m, 1H), 5.76–5.81 (m, 1H), 7.39–7.44 (m, 3H), 7.80–7.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 23.1, 25.0, 25.1, 28.37, 28.41, 31.1, 33.0, 33.3, 34.7, 56.3, 123.9, 125.7, 126.0, 128.7, 129.5, 135.2, 153.7, 166.1; IR (KBr) 3061, 2925, 2857, 1660 cm^{-1}; ESI-MS *m*/*z*: calcd for $C_{21}H_{26}N_2NaO$ $[M+Na]^+$, 345.1943; found, 345.1944.

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