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Synthesis of the Conformationally Constrained Tyrosine Analogues, (*R*)- and (*S*)-5-Hydroxy-2-aminoindan-2-carboxylic Acids

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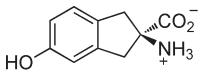
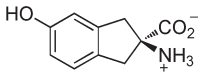


(*R*)-**1**



(*S*)-**1**

The conformationally constrained tyrosine analogues, (*R*)- and (*S*)-5-hydroxy-2-aminoindan-2-carboxylic acids, were prepared by chromatographic separation of diastereomeric dipeptide derivatives formed from *N*-Boc-L-phenylalanine. Absolute configurations were assigned by X-ray crystallographic analysis.

L-Tyrosine is a nonessential amino acid involved in protein phosphorylation, a process important in regulation of cellular processes including cell growth and differentiation.[1−3] Enzymes involved in the transfer of the phosphoryl group from adenosine-5′-triphosphate to the tyrosine residues of proteins are known as protein tyrosine kinases (PTKs). Researchers are interested in understanding how PTKs recognize substrates.[3,4] Some reported studies involve PTK substrate modification where the tyrosine residue is replaced with conformationally constrained tyrosine analogues (CCTAs), such as α-methyltyrosine[1] (α-MeTyr), *β*-methyltyrosine[5] (*β*-MeTyr), 6-hydroxy-2-aminotetralin-2-carboxylic acid[1] (Hat), 5-hydroxy-2-aminoindan-2-carboxylic acid[6] (Hai), and 6-hydroxytetrahydroisoquinoline-3-carboxylic acid[7] (6-OH-Tic).

CCTAs may stabilize the α-helical and *β*-turn motifs in peptides due to achievement of low-energy conformations.[1] Restriction of side chain flexibility can affect signal transduction, resulting in antagonistic behavior of constrained peptides. CCTAs have been used to develop structure−activity relationships (SARs).[8,9] Incorporation of CCTAs produced useful information about the conformational requirements for peptide hormone/opioid receptor interactions.[8−10]

While the use of enantiomerically pure amino acids is important in establishing a SAR, some CCTAs, including Hai, are not available in enantiomerically pure form.[3,8,9] This Note describes a method for the preparation of (*R*)-**1** and (*S*)-**1**, the enantiomers of Hai.

Amino acids (*R*)-**1** and (*S*)-**1** were prepared as outlined in Schemes 1 and 2. 4-Methoxy-1,2-dimethylbenzene (**2**) was brominated at −70 °C to afford bromide **3**[11] in 91% yield (Scheme 1). Bromide **3** was subjected to free radical bromination to give tribromide **4** in 60% yield.[12] Reaction of tribromide **4** with ethyl isocyanoacetate following the method of Kotha[13] produced **5** in 57% yield. Acid hydrolysis of **5** gave racemic amino ester **6** in 87% yield. Coupling of **6** with *N*-Boc-L-phenylalanine using (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate[14] (BOP reagent) afforded a mixture of diastereomers **7** in 93% yield. Although diastereomers **7** were separable by gravity-driven silica gel column chromatography (see the Supporting Information), diastereomer separation was effected at a later point in the synthesis.

Treatment of the mixture of diastereomers **7** with trifluoroacetic acid removed the Boc group, and reaction of the free amine with phenylisothiocyanate gave a 1:1 mixture of the diastereomeric thioureas (*S*,*S*)-**8** and (*R*,*S*)-**8** in 90% yield over two steps (Scheme 1). These diastereomers were separated by repeated cycles of gravity-driven column chromatography on 70−230 mesh silica gel 60 eluted with 10% ethyl acetate/dichloromethane. Results of this separation are summarized in Table 1. The absolute stereochemistries of the separated diastereomers were assigned by means of an X-ray crystallographic analysis of the less polar thiourea, (*R*,*S*)-**8** (Figure 1).[15]

Thiourea (*R*,*S*)-**8** was heated in TFA to afford the amino ester (*R*)-**9** in 80% yield (Scheme 2). Hydrogenolysis of (*R*)-**9** with 10% Pd/C in ethanol gave amino ester (*S*)-**10** in

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(15) Crystal data for (*R*,*S*)-**8**: $C_{29}H_{30}BrN_3O_4S$; M = 596.53 g mol^{-1}, T = 100(2) K, Cu Kα, thin colorless plates, orthorhombic, $P2_12_12_1$, a = 10.2029(2), b = 10.3818(2), c = 25.7025(4) Å, α = 90°, β = 90°, γ = 90°, V = 2722.52(9) Å^3, Z = 4, 5021 reflections, R_{int} 0.0567, GOF on F^2 = 1.196, R_1 = 0.0433 and wR_2 = 0.1011 ([$F^2 > 2\sigma$]), R_1 = 0.0463 and wR_2 = 0.1024 (all data).

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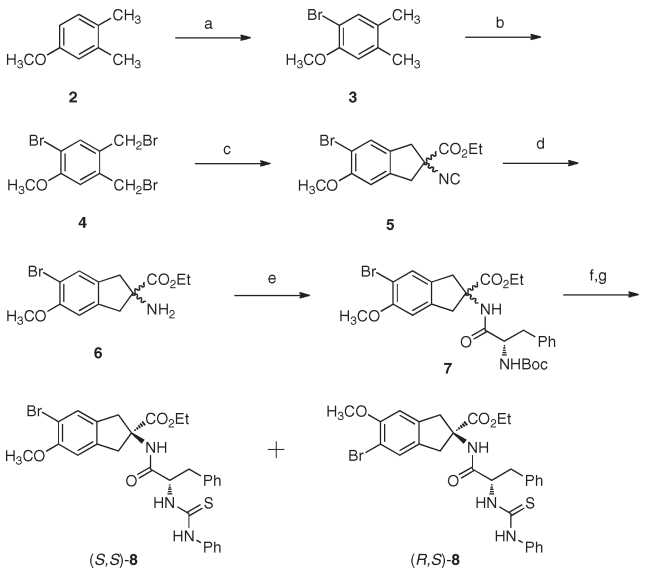
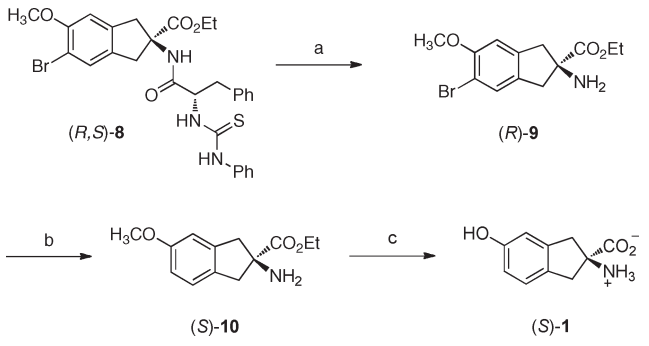
SCHEME 1. Synthesis of Diastereomers (*S*,*S*)-8 and (*R*,*S*)-8[a]



[a]Reagents and yields: (a) Br_2, CH_2Cl_2, −70 °C, 91%. (b) NBS, CCl_4, *hν*, 60%. (c) $CNCH_2CO_2Et$, K_2CO_3, TBAI, CH_3CN, C_6H_5Cl, 57%. (d) HCl, EtOH, EtOAc, 87%. (e) Boc-L-Phe, BOP, Et_3N, DMF, 93%. (f) TFA, CH_2Cl_2. (g) C_6H_5NCS, Et_3N, EtOH, 90% (two steps).

SCHEME 2. Synthesis of (*S*)-1[a]



[a]Reagents and yields: (a) TFA, 72 °C, 80%. (b) H_2, Pd/C, EtOH, 83%. (c) 48% HBr, CH_3CO_2H, heat, 75%.

83% yield.[16] Treatment of (*S*)-**10** with 48% aqueous HBr cleaved the ester and ether bonds, producing amino acid (*S*)-**1** in 75% yield. In a similar manner, thiourea (*S*,*S*)-**8** was transformed to amino acid (*R*)-**1** (not depicted). Compound (*S*)-**1** was characterized by X-ray crystallographic analysis (see the Supporting Information). The CD spectra of (*S*)-**1** and (*R*)-**1** confirm they are enantiomeric (see the Supporting Information).

Experimental Section

1-Bromo-2-methoxy-4,5-dimethylbenzene (3). A solution of bromine (1.84 mL, 5.72 g, 35.8 mmol) in CH_2Cl_2 (200 mL) was added dropwise to a solution of 3,4-dimethylanisole (**2**, 5.00 mL, 4.87 g, 35.8 mmol) in CH_2Cl_2 (300 mL) at −70 °C under argon until a pale orange color was observed. The pale orange solution was washed with sat. $NaHCO_3$ (150 mL), sat. Na_2SO_3 (100 mL), and brine (100 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo to afford a crude product. Purification by flash chromatography (230−400 mesh silica) with 10% CH_2Cl_2/hexanes gave 7.00 g (32.5 mmol, 91%) of **3** as crystalline solid, mp 29−30 °C (lit.[11] mp 30−32 °C), R_f 0.49 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.21 (s, 3H), 3.84 (s, 3H), 6.68 (s, 1H), 7.26 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.5, 19.8, 56.3, 108.0, 113.8, 130.0, 133.8, 136.8, 153.7.

TABLE 1. Separation of Diastereomeric Thioureas (*S*,*S*)-8 and (*R*,*S*)-8 by Gravity-Driven Silica Gel Column Chromatography

fraction	composition	amount
1	100% (*R*,*S*)	1.18 g (36%)
2	95+% (*R*,*S*)	270 mg (8%)
3	mixture	100 mg (3%)
4	95+% (*S*,*S*)	20 mg (0.6%)
5	100% (*S*,*S*)	1.32 g (40%)

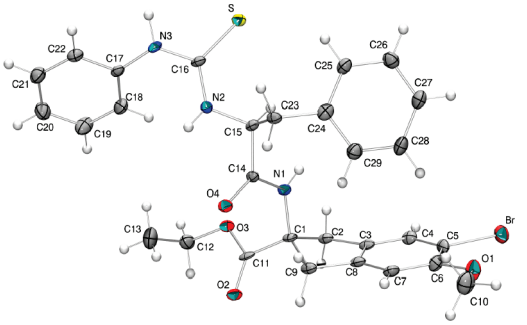


FIGURE 1. ORTEP of the less polar thiourea, (*R*,*S*)-**8**.

1-Bromo-4,5-bis(bromomethyl)-2-methoxybenzene (4). *N*-Bromosuccinimide (1.66 g, 9.30 mmol) was added to a solution of **3** (2.00 g, 9.30 mmol) in CCl_4 (24 mL) under argon. A 250 W heat lamp was positioned near the reaction flask to ensure a gentle reflux. After 2 h, additional NBS (1.66 g, 9.30 mmol) was added to the reaction mixture and refluxing continued for 2 h. The solution was allowed to cool to rt and filtered, then the solid was washed with CCl_4 (30 mL). The combined filtrates were washed with sat. $NaHCO_3$ (30 mL), sat. Na_2SO_3 (30 mL), and brine (30 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to yield a pale yellow oil. Ethyl acetate (10 drops) was added and the oil kept at −22 °C overnight to form crystals. The white crystalline solid was collected by filtration to afford 2.07 g (5.55 mmol, 60%) of **4**, mp 85−86 °C; R_f 0.43 (10% EtOAc/hexanes); IR (KBr, cm^{-1}) 2972, 1596, 1496, 1274, 1044; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 3H), 4.56 (s, 2H), 4.58 (s, 2H), 6.85 (s, 1H), 7.53 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.2, 29.4, 56.4, 112.1, 113.9, 129.7, 135.6, 137.1, 156.3; HRGCMS (EI$^+$) calcd for $C_9H_9Br_3O$ (M^+) 369.8203, found 369.8223.

Ethyl 5-Bromo-2-isocyano-6-methoxyindan-2-carboxylate (5). Dry acetonitrile (45 mL) was added to a flask containing ethyl isocyanoacetate (0.44 mL, 0.45 g, 3.97 mmol) under argon. Finely ground potassium carbonate (6.67 g, 48.03 mmol), tetrabutylammonium iodide (0.30 g, 0.80 mmol), and a solution of **4** (1.48 g, 3.97 mmol) in chlorobenzene (45 mL) were added to the flask. The reaction mixture was heated in an oil bath at 85−90 °C for 10 h, cooled to rt and filtered, then the residue was thoroughly washed with acetonitrile. Volatiles were removed under reduced pressure to give a brown oily residue that was dissolved in a 1:1 mixture of EtOAc and diethyl ether (250 mL). The solution was washed with water (90 mL × 2) and brine (90 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a brown oil. Flash chromatography (230−400 mesh silica) with 15% EtOAc/hexanes afforded 0.73 g (2.25 mmol, 57%) of **5** as a white solid, mp 100−101 °C; R_f 0.48 (30% EtOAc/hexanes); IR (KBr, cm^{-1})

(16) Hydrogenolysis of bromide **9** affords a convenient method for introduction of an isotopic label into the resolved amino acid.

2977, 2145, 1743, 1485, 1226, 1064; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32 (t, 3H, J = 7.3 Hz), 3.37 (d, 2H, J = 15.6 Hz), 3.60 (d, 1H, J = 17.4 Hz), 3.63 (d, 1H, J = 17.4 Hz), 3.85 (s, 3H), 4.29 (q, 2H, J = 7.3 Hz), 6.77 (s, 1H), 7.38 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.9, 45.3, 46.1, 56.3, 63.2, 68.3, 108.2, 110.9, 129.0, 130.9, 138.6, 155.7, 158.9, 168.1; HRMS (ESI) calcd for $C_{14}H_{14}BrNO_3Na$ $(M + Na)^+$ 346.00493, found 346.00492.

Ethyl 2-Amino-5-bromo-6-methoxyindan-2-carboxylate (6). A solution of **5** (1.61 g, 4.97 mmol) in a mixture of EtOAc (16 mL), absolute EtOH (32 mL), and concd HCl (5.75 mL) was stirred for 20 h at rt. Volatiles were then removed in vacuo to leave a pale yellow solution (about 2 mL). Water (50 mL) was added and the resulting aqueous solution was basified with concd NH_4OH to pH 9.0. The aqueous solution was extracted with EtOAc (3 × 50 mL), then the organic extracts were washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo to give a brown oil. Flash chromatography (230−400 mesh silica) with EtOAc as elutant afforded 1.36 g (4.33 mmol, 87%) of **6** as a white solid, mp 38−39 °C; R_f 0.39 (100% EtOAc); IR (KBr, cm^{-1}) 3370, 2968, 1724, 1486, 1215, 1049; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.0 Hz), 1.75 (s, 2H), 2.78 (d, 1H, J = 15.5 Hz), 2.79 (d, 1H, J = 16.0 Hz), 3.45 (d, 1H, J = 15.5 Hz), 3.48 (d, 1H, J = 16.0 Hz), 3.84 (s, 3H), 4.20 (q, 2H, J = 7.0 Hz), 6.76 (s, 1H), 7.34 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 45.3, 46.1, 56.4, 61.4, 65.5, 108.8, 109.9, 129.2, 133.8, 141.2, 155.0, 176.0; HRMS (ESI) calcd for $C_{13}H_{17}BrNO_3$ $(M + H)^+$ 314.03863, found 314.03871.

Ethyl (*R*,*S*)-5-Bromo-2-(3-phenyl-2-(3-phenylthioureido)propanamido)-6-methoxyindan-2-carboxylate [(*R*,*S*)-8] and Ethyl (*S*,*S*)-5-Bromo-2-(3-phenyl-2-(3-phenylthioureido)propanamido)-6-methoxyindan-2-carboxylate [(*S*,*S*)-8]. BOP reagent (3.93 g, 8.88 mmol) was added to a solution of **6** (1.86 g, 5.92 mmol), *N*-(Boc)-L-phenylalanine (2.36 g, 8.88 mmol), and triethylamine (2 mL) in DMF (27 mL). The reaction mixture was stirred at rt for 18 h, then diluted with EtOAc (200 mL) and water (100 mL). The phases were separated and the aqueous phase extracted with EtOAc (2 × 75 mL). The organic extracts were combined, washed with 1 M HCl (2 × 80 mL), water (100 mL), sat. $NaHCO_3$ (2 × 80 mL), water (2 × 100 mL), and brine (100 mL), then dried over anhydrous $MgSO_4$ and filtered. Volatiles were removed in vacuo to give a solid. Flash chromatography (230−400 mesh silica) with 50% EtOAc/hexanes afforded a mixture of diastereoisomers **7** as a white solid (3.10 g, 5.52 mmol, 93%). These diastereomers could be separated chromatographically and characterized (see the Supporting Information). Alternatively, TFA (35 mL) was added to a solution of the above mixture of diastereomers in CH_2Cl_2 (35 mL). After the reaction was stirred for 2 h at rt, the solution volume was reduced to ∼6 mL with use of a rotavap and basified to pH 9 by addition of 2 M NaOH. The resulting aqueous solution was extracted with CH_2Cl_2 (3 × 100 mL), then the extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give a pale yellow solid (2.76 g). This solid was dissolved in ethanol (35 mL) and triethylamine (1.6 mL) and phenylisothiocyanate (3.39 g, 3.00 mL, 25.1 mmol) were added with stirring. A white solid precipitated after 30 min, and stirring was continued for 90 min. Volatiles were removed in vacuo to leave a pale orange solid. Flash chromatography (230−400 mesh silica) with 30% EtOAc/hexanes as elutant afforded a mixture of diastereomers **8** (2.98 g, 4.99 mmol, 90%) as a white solid. Repeated gravity chromatography on silica gel (70−230 mesh) eluted with 10% EtOAc/CH_2Cl_2 achieved separation of diastereomers (see Table 1). The stereochemistry of the less polar diastereomer was established as (*R*,*S*) by single crystal X-ray diffraction analysis. Data for (*R*,*S*)-**8**: $[\alpha]^{25}_D$ −18.4 (*c* 2.00, $CHCl_3$); mp 184−185 °C; R_f 0.58 (25% EtOAc/benzene); IR (KBr, cm^{-1}) 3303, 3221, 3038, 1722, 1657, 1522, 1495, 1234, 1040; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (t, 3H, J = 7.0 Hz), 2.98 (dd, 1H, J = 8.0, 13.5 Hz), 3.00 (d, 1H, J = 16.0 Hz), 3.08 (d, 1H, J = 17.0 Hz), 3.26 (dd, 1H, J = 6.0, 14.0 Hz), 3.39 (d, 1H, J = 16.0 Hz), 3.53 (d, 1H, J = 16.5 Hz), 3.84 (s, 3H), 4.13 (m, 2H), 5.20 (q, 1H, J = 7.0 Hz), 6.65(s, 1H), 6.68 (s, 1H), 6.84 (d, 1H, J = 7.0 Hz), 7.02 (d, 2H, J = 7.5 Hz), 7.20 (m, 7H), 7.26 (s, 2H), 7.32 (t, 2H, J = 7.5 Hz), 8.19 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 37.8, 42.8, 43.2, 56.3, 59.0, 61.8, 66.0, 108.2, 110.0, 124.7, 126.9, 127.0, 128.6, 128.8, 129.2, 129.9, 132.5, 135.8, 136.2, 140.5, 155.1, 170.3, 172.1, 179.6; HRMS (ESI) calcd for $C_{29}H_{30}BrN_3O_4SNa$ $(M + Na)^+$ 618.10326, found 618.10213. Data for (*S*,*S*)-**8**: $[\alpha]^{25}_D$ +7.36 (*c* 2.00, $CHCl_3$); mp 196−197 °C; R_f 0.50 (25% EtOAc/benzene); IR (KBr, cm^{-1}) 3303, 3221, 3038, 1722, 1657, 1522, 1495, 1234, 1040; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (t, 3H, J = 7.0 Hz), 2.97 (dd, 1H, J = 8.0, 13.5 Hz), 2.98 (d, 1H, J = 16.5 Hz), 3.07 (d, 1H, J = 16.5 Hz), 3.27 (dd, 1H, J = 6.0, 13.5 Hz), 3.44 (d, 1H, J = 16.5 Hz), 3.46 (d, 1H, J = 16.5 Hz), 3.83 (s, 3H), 4.14 (m, 2H), 5.17 (q, 1H, J = 7.5 Hz), 6.52 (s, 1H), 6.66 (s, 1H), 6.86 (d, 1H, J = 7.0 Hz), 7.03 (d, 2H, J = 7.5 Hz), 7.22 (m, 6H), 7.26 (s, 1H), 7.33 (t, 2H, J = 7.5 Hz), 8.11 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 38.0, 42.5, 43.5, 56.3, 59.2, 61.8, 66.1, 108.4, 110.1, 124.7, 127.0, 127.1, 128.6, 128.8, 129.3, 129.9, 132.7, 135.8, 136.2, 140.3, 155.1, 170.3, 172.0, 179.7; HRMS (ESI) calcd for $C_{29}H_{30}BrN_3O_4SNa$ $(M + Na)^+$ 618.10326, found 618.10213.

Ethyl (*R*)-2-Amino-5-bromo-6-methoxyindan-2-carboxylate [(*R*)-9]. A solution of (*R*,*S*)-**8** (500 mg, 0.84 mmol) in TFA (10 mL) was heated at reflux for 2 h. The reaction mixture was allowed to cool to rt and added to water (20 mL). The aqueous solution was extracted with hexanes (3 × 30 mL) and these extracts were discarded. The aqueous phase was basified to pH 9.0 by addition of aqueous NH_4OH and extracted with EtOAc (3 × 50 mL). The EtOAc extracts were combined, washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give an orange oil. Flash chromatography (230−400 mesh silica) with EtOAc as elutant afforded (*R*)-**9** as a colorless oil (210 mg, 0.67 mmol, 80%), which later solidified to a white solid, mp 55−56 °C; R_f 0.38 (EtOAc); $[\alpha]^{24}_D$ −0.98 (*c* 2.00, $CHCl_3$); IR (KBr, cm^{-1}) 3369, 2967, 1724, 1486, 1049; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.0 Hz), 1.74 (s, 2H), 2.77 (d, 1H, J = 16.0 Hz), 2.79 (d, 1H, J = 16.0 Hz), 3.45 (d, 1H, J = 15.5 Hz), 3.47 (d, 1H, J = 15.5 Hz), 3.83 (s, 3H), 4.18 (q, 2H, J = 7.0 Hz), 6.75 (s, 1H), 7.33 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 45.2, 46.0, 56.3, 61.3, 65.4, 108.7, 109.8, 129.1, 133.7, 141.1, 154.9, 176.0; HRMS (ESI) calcd for $C_{13}H_{17}BrNO_3$ $(M + H)^+$ 314.03863, found 314.03871.

Ethyl (*S*)-2-Amino-5-methoxyindan-2-carboxylate [(*S*)-10]. To a solution of (*R*)-**9** (320 mg, 1.02 mmol) in ethanol (10 mL) in a hydrogenation vessel was added 10% Pd/C (90 mg). The mixture was shaken under hydrogen at 60 psi for 2 d and filtered, then the solid residue was washed with ethanol and CH_2Cl_2. The filtrates were concentrated in vacuo to leave an orange oil. The oil was dissolved in EtOAc (60 mL), washed with sat. $NaHCO_3$ (2 × 20 mL), water (20 mL), and brine (20 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to a pale orange oil. Flash chromatography (230−400 mesh silica) with 80% EtOAc/hexanes as elutant gave (*S*)-**10** as a colorless oil (200 mg, 0.85 mmol, 83%), R_f 0.45 (5% MeOH/CH_2Cl_2); $[\alpha]^{24}_D$ −11.9 (*c* 3.00, $CHCl_3$); IR (NaCl plate, cm^{-1}) 3369, 2935, 1727, 1493, 1049; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.0 Hz), 1.77 (s, 2H), 2.78 (d, 1H, J = 15.0 Hz), 2.81 (d, 1H, J = 16.0 Hz), 3.46 (d, 1H, J = 15.5 Hz), 3.52 (d, 1H, J = 16.0 Hz), 3.75 (s, 3H), 4.19 (q, 2H, J = 7.0 Hz), 6.71 (dd, 1H, J = 2.0, 8.0 Hz), 6.74 (s, 1H), 7.07 (d, 1H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 45.5, 46.3, 55.4, 61.2, 65.4, 110.3, 112.7, 125.2, 132.3, 141.8, 159.0, 176.3; HRMS (ESI) calcd for $C_{13}H_{18}NO_3$ $(M + H)^+$ 236.1281, found 236.1279.

(*S*)-5-Hydroxy-2-aminoindan-2-carboxylic Acid [(*S*)-1]. A solution of 48% aqueous HBr (2.5 mL) in acetic acid (4.0 mL) was prepared in a flask under argon. The solution was stirred for 30 min and transferred via syringe to a second flask containing (*S*)-**10** (300 mg, 1.27 mmol) under argon. The resulting solution was stirred for 30 min, then placed in an oil bath heated to 100 °C. After 24 h, the reaction mixture was allowed to cool to rt and transferred with stirring into a 250 mL beaker containing ice (4 g), 1 M HCl (3 mL), and diethyl ether (10 mL). The phases were separated, the aqueous layer was extracted with diethyl ether (2 × 15 mL), and the extracts were discarded. The aqueous phase was placed in an ice−water bath and the pH adjusted to 6.33 by addition of 6 M NaOH solution. The product began to precipitate, and the mixture was kept at 4 °C overnight. The solid was then collected by filtration, affording 184 mg (0.95 mmol, 75%) of (*S*)-**1** as a solid, mp > 280 °C dec; $[\alpha]^{24}_{D}$ −3.83 (*c* 1.00, 1 M HCl); IR (KBr, cm^{-1}) 3191, 1643, 1552, 1405; ^{1}H NMR (500 MHz, D_2O/NaOD) δ 2.46 (d, 1H, J = 15.5 Hz), 2.48 (d, 1H, J = 16.5 Hz), 3.06 (d, 1H, J = 15.5 Hz), 3.12 (d, 1H, J = 16.5 Hz), 6.23 (dd, 1H, J = 2.0, 8.0 Hz), 6.28 (s, 1H), 6.74 (d, 1H, J = 8.0 Hz); ^{13}C NMR [125 MHz, D_2O/NaOD (CD_3OD used as reference)] δ 46.2, 47.1, 67.4, 115.5, 117.7, 126.1, 127.7, 144.1, 166.1, 185.5; HRMS (ESI) calcd for $C_{10}H_{12}NO_3$ $(M + H)^+$ 194.0812, found 194.0810.

Ethyl (*S*)-2-Amino-5-bromo-6-methoxyindan-2-carboxylate [(*S*)-9]. Using a procedure analogous to that described for the synthesis of (*R*)-**9**, (*S*,*S*)-**8** (500 mg, 0.84 mmol) afforded (*S*)-**9** as a colorless oil (225 mg, 0.72 mmol, 86%) that later solidified to a white solid, mp 53−54 °C, R_f 0.34 (EtOAc); $[\alpha]^{23}_{D}$ 1.74 (*c* 1.00, $CHCl_3$); IR (KBr, cm^{-1}) 3369, 2967, 1724, 1486, 1049; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.0 Hz), 1.78 (s, 2H), 2.78 (d, 1H, J = 15.5 Hz), 2.80 (d, 1H, J = 16.0 Hz), 3.46 (d, 1H, J = 15.5 Hz), 3.48 (d, 1H, J = 16.0 Hz), 3.84 (s, 3H), 4.20 (q, 2H, J = 7.0 Hz), 6.76 (s, 1H), 7.34 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 45.3, 46.1, 56.4, 61.4, 65.5, 108.8, 109.9, 129.2, 133.7, 141.2, 155.0, 176.0; HRMS (ESI) calcd for $C_{13}H_{17}BrNO_3$ $(M + H)^+$ 314.03863, found 314.03871.

Ethyl (*R*)-2-Amino-5-methoxyindan-2-carboxylate [(*R*)-10]. Using a procedure analogous to that described for the synthesis of (*S*)-**10**, (*S*)-**9** (320 mg, 1.02 mmol) afforded (*R*)-**10** as a colorless oil (222 mg, 0.94 mmol, 92%), R_f 0.43 (5% MeOH/CH_2Cl_2); $[\alpha]^{24}_{D}$ 11.0 (*c* 2.20, $CHCl_3$); IR (NaCl plate, cm^{-1}) 3369, 2935, 1727, 1493, 1049; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.0 Hz), 1.80 (s, 2H), 2.79 (d, 1H, J = 15.5 Hz), 2.82 (d, 1H, J = 15.5 Hz), 3.47 (d, 1H, J = 15.5 Hz), 3.53 (d, 1H, J = 16.0 Hz), 3.76 (s, 3H), 4.20 (q, 2H, J = 7.0 Hz), 6.71 (dd, 1H, J = 2.0, 8.0 Hz), 6.75 (s, 1H), 7.08 (d, 1H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 45.5, 46.3, 55.4, 61.2, 65.4, 110.3, 112.8, 125.3, 132.3, 141.9, 159.1, 176.3; HRMS (ESI) calcd for $C_{13}H_{18}NO_3$ $(M + H)^+$ 236.1281, found 236.1279.

(*R*)-5-Hydroxy-2-aminoindan-2-carboxylic Acid [(*R*)-1]. Using a procedure analogous to that described for the synthesis of (*S*)-**1**, (*R*)-**10** (491 mg, 2.09 mmol) afforded (*R*)-**1** (314 mg, 1.62 mmol, 78%) as a solid, mp > 270 °C dec; $[\alpha]^{24}_{D}$ 2.12 (*c* 1.00, 1 M HCl); IR (KBr, cm^{-1}) 3191, 1643, 1552, 1405; ^{1}H NMR (500 MHz, D_2O/NaOD) δ 2.52 (d, 1H, J = 15.5 Hz), 2.55 (d, 1H, J = 16.0 Hz), 3.12 (d, 1H, J = 15.5 Hz), 3.18 (d, 1H, J = 16.5 Hz), 6.29 (dd, 1H, J = 2.0, 8.0 Hz), 6.34 (s, 1H), 6.80 (d, 1H, J = 8.0 Hz); ^{13}C NMR [125 MHz, D_2O/NaOD (CD_3OD used as reference)] δ 46.2, 47.0, 67.4, 115.5, 117.7, 126.1, 127.8, 144.0, 166.0, 185.4; HRMS (ESI) calcd for $C_{10}H_{12}NO_3$ $(M + H)^+$ 194.0812, found 194.0810.

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Supporting Information Available: General experimental methods, compound characterization data for the separated diastereomer (*R*,*S*)-**7**, copies of ^{1}H and ^{13}C NMR spectra for compounds **1** and **3**−**10**, CD spectra for compounds (*S*)-**1**, (*R*)-**1**, (*S*)-**9**, and (*R*)-**9**, and structure reports and crystallographic information files (CIFs) for compounds (*S*)-**1** and (*R*,*S*)-**8**. This material is available free of charge via the Internet at http://pubs.acs.org.