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Amino Acids as a Chiral Pool: Synthesis of (S)-and (R)-2-N-Carbomethoxy-5-aminoindane from (S)- and (R)-Phenylalanines

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Amino Acids as a Chiral Pool: Synthesis of (*S*)- and (*R*)-2-*N*-Carbomethoxy-5-aminoindane from (*S*)- and (*R*)-Phenylalanines

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Abstract: Enantioselective syntheses of (*R*)- and (*S*)-2-*N*-carbomethoxy-5-aminoindanes from (*R*)- and (*S*)-phenylalanines, respectively, are described. A Friedel–Crafts reaction employing *N*-carbomethoxy phenylalanine leads to chiral 2-*N*-carbomethoxy-1-indanone, which is diastereoselectively reduced to 1-hydroxy-2-*N*-carbomethoxyindane. After protection of the hydroxyl group, a regioselective nitration gives a 6-nitroindane intermediate, which upon hydrogenation affords (*R*)- or (*S*)-2-*N*-carbomethoxy-5-aminoindane.

Keywords: Amino acids, aminoindane, chiral pool, phenylalanine

INTRODUCTION

Substituted indanes, especially with a vicinal amino-alcohol, constitute an important subunit of biologically significant molecules. The most important feature of these medicinal agents is the chirality at the stereogenic centers.[1] Synthetic procedures that deliver indane derivatives with known absolute configurations are needed. Our interest in this area was to prepare

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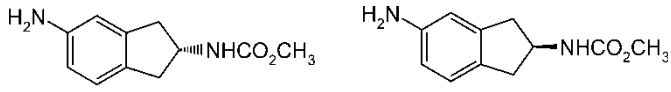


[(*R*)-8] [(*S*)-8]

Figure 1. 2-*N*-carbomethoxy-5-aminoindane.

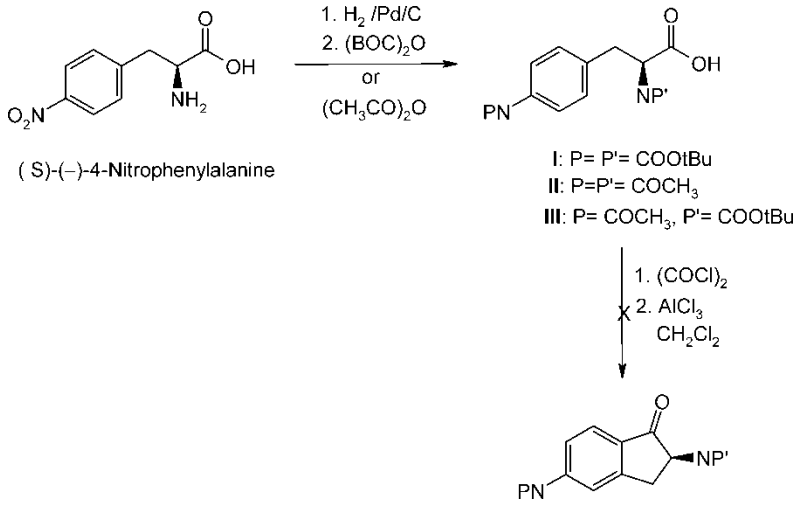
(*R*)-2-*N*-carbomethoxy-5-aminoindane [(***R***)-**8**] and (*S*)-2-*N*-carbomethoxy-5-aminoindane [(***S***)-**8**] (Fig. 1). These are pivotal intermediates in the syntheses of several of the compounds in our MTP (microsomal triglyceride-transfer protein) inhibitor program.[2]

Racemic 2,5-diaminoindane or 2-amino-5-nitroindane[3] can be easily prepared. However, one must rely on classical resolution to afford enantiopure compounds and prove the absolute configuration at C-2 by some unambiguous method. Although chiral *cis*-1-amino-2-indanol has been studied extensively,[1,4] the isomeric 2-amino-1-indanol and its aromatic-substituted derivatives have been studied to a limited extent.[5,6] We envisioned that an appropriately protected chiral 2-amino-1-indanol derivative, prepared from a chiral amino acid, might lend itself to regioselective nitration, which upon further manipulation would provide the target compound. Unfortunately, literature points to a severe racemization problem of the amino ketone intermediate in this synthesis.[5,6] Despite this, we decided to pursue this approach because the absolute configuration at the C-2 center of the target compound is known, cheaper and easily accessible starting materials are available, and racemization might be controlled through optimized reaction conditions. In this article, we describe a synthesis of enantiomerically pure [(***R***)-**8**] and [(***S***)-**8**] from optically pure phenylalanines.

RESULTS AND DISCUSSION

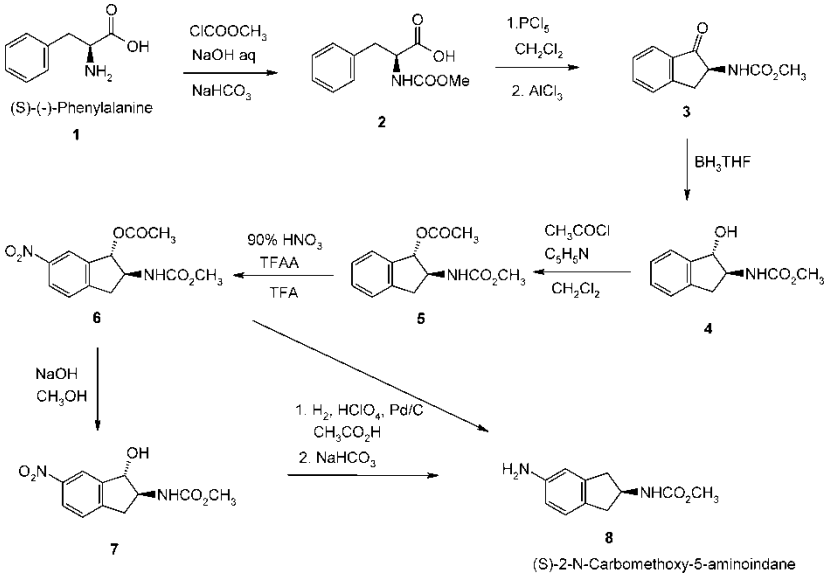
An efficient preparation of intermediates [(***R***)-**8**] and [(***S***)-**8**] would be via intramolecular Friedel–Crafts cyclization of appropriately protected (*R*)-4-aminophenylalanine or (*S*)-4-aminophenylalanine, prepared from commercially available (*R*)-(+)-4-nitrophenylalanine or (*S*)-(−)-4-nitrophenylalanine, to the appropriately substituted indanone followed by deoxygenation (Scheme 1). Buckley and Rapoport have reported such aminoacylation.[7] Thus, we attempted a regioselective cyclization of appropriately substituted enantiopure amino acids (**I**–**III**) to a desired 5-substituted 2-aminoindanone derivative (Scheme 1). However, these attempts were futile in spite of the use of various *N*-protecting groups (e.g., Boc, acetyl) and combinations in different solvents under different experimental conditions.

After these disappointing results, we set out to pursue cyclization of an appropriately *N*-protected (*S*)-phenylalanine to a 2-*N*-protected



Scheme 1.

amino-1-indanone and then introduce the amino functionality at the 6-position via nitration (Scheme 2). Unsubstituted phenylalanine undergoes intramolecular Friedel–Craft aminoacylation to afford 2-amino-1-indanone.[5,6] Thus, carbomethoxylation of (*S*)-phenylalanine under Schotten–Baumann



Scheme 2.

conditions followed by intramolecular Friedel–Crafts acylation of the resulting (*S*)-2-*N*-carbomethoxyphenylalanine with an excess of phosphorus pentachloride and aluminum trichloride (3.0 equiv) in dichloromethane afforded **3**. We found that the acid chloride formation was most efficient using phosphorus pentachloride. Methyl carbamate was the choice of protecting group because it was also part of the desired active compound[3] and was stable under these conditions. One of the major hurdles was to avoid the racemization of the 2-carbomethoxyamino-1-indanone (**3**).[5,6] Reverse quenching of the reaction mixture at low temperature (−5 to 1°C) into 3 N HCl over 45 min controlled racemization. The pH of the mixture had to be adjusted to 6.9 by adding aqueous sodium bicarbonate. This afforded 2-carbomethoxyamino-1-indanone (**3**) without racemization in 75% yield.

Because indanone **(3)** is extremely sensitive to racemization, we decided to reduce the ketone to alcohol **4**. The stereoselective reduction of 2-carbomethoxyamino-1-indanone **(3)** has been reported[6] with BH_3 and sodium bis(2-methoxyethoxy)aluminum hydride with no racemization when the substrate was added to the reagent. We found that such a reduction of **3** with sodium bis(2-methoxyethoxy)aluminum hydride gave **4** in a 95:5 ratio of *trans:cis*, and the *trans*-isomer could be easily purified by recrystallization from *t*-butyl methyl ether in 70% yield.

Direct nitration of **4** was unsuccessful, and the alcohol required protection. Thus, **4** was acylated with acetyl chloride and pyridine in dichloromethane to afford **5**. We realized that anhydrous conditions were essential for a successful regioselective nitration of **5**. We decided to make use of a combination of nitric acid in trifluoroacetic acid and trifluoroacetic anhydride as the nitrating agent. To our delight, the nitration of **5** went smoothly to afford a 80:20 mixture of 6-nitro and 5-nitro derivatives. The desired 6-nitro compound **6** was isolated in 52% yield after recrystallization from ethyl acetate. Because the nitration step utilized trifluoroacetic anhydride, it is quite possible that protection of alcohol in **4** and nitration could be accomplished in one pot, had the acetyl protecting group been changed to trifluoroacetyl.

The next step was the reduction of the nitro group and the reductive cleavage of the benzylic hydroxyl group. Ideally both of these transformations could be accomplished in one hydrogenation step. Under catalytic hydrogenation conditions, the nitro group was easily reduced to the amino group. However, the benzylic acetoxy moiety or the hydroxyl group was not reduced, and harsher reaction conditions were required. Attempts using triethylsilane/TFA, sodium borohydride/aluminum trichloride, and TMSCl/NaI were unsuccessful. A saponification to a free hydroxyl group followed by reduction gave the same results as when the benzylic acetoxy group was present. However, reduction of **6** or **7** using Pd/C in acetic acid and $HClO_4$ at room temperature afforded [(***S***)-**8**] in 71% and 88% yield, respectively.

The stereochemical outcome was established based on spectroscopic data and chiral HPLC.[3] The synthesis of the antipode [(***R***)-**8**] was carried out following the same protocol starting with enantiopure (*R*)-phenylalanine.

In summary, we have developed an efficient enantioselective syntheses for [(***R***)-**8**] and [(***S***)-**8**] from commercially available enantiopure phenylalanines as the chiral pool. A regioselective nitration of 2-carbomethoxy-1-acetoxy-indane was also developed.

EXPERIMENTAL

General Methods

All solvents were used as received from the suppliers. All reagents were used as received from Aldrich Chemical Co. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained on a Bruker 300 instrument, and ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were obtained on a Bruker ARX 500-MHz spectrometer. Desorption chemical ionization (DCI) mass-spectral data were recorded on a Hewlett-Packard 598B mass spectrometer. Electrospray ionization (ESI) mass spectra were recorded on a Micromass Platform II mass spectrometer. Optical rotations were determined on a Rudolph Research Autopol III polarimeter. Melting points were measured on a Büchi 535 melting-point apparatus and are uncorrected. The enantiopurity of compounds was determined by chiral high performance liquid chromatography (HPLC) on a Waters Alliance system with photodiode array UV detector.

(*S*)-*N*-(Methoxycarbonyl) phenylalanine [(*S*)-2]

To a solution of (*S*)-(−)-phenylalanine **1** (16.5 g, 0.1 mol) in 1 N NaOH (100 mL, 0.1 mol) at 23°C, sodium carbonate (5.3 g, 0.05 mol) was added, and the mixture was cooled to 0°C. Methyl chloroformate (9.4 g, 0.1 mol) was added to the mixture over 3 min and stirred for 30 min at 0°C. It was allowed to warm to 23°C and stirred for 30 min until a clear solution resulted. The reaction mixture was acidified to pH 3 with 3 N HCl. The solution was extracted with dichloromethane (2 × 100 mL). The dichloromethane extract was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under vacuum at 20°C to afford the carbamate **2** (21 g, 94.1%). The spectroscopic data matched with those described in literature.[8]

(*S*)-2-[(Methoxycarbonyl)amino]-1-indanone [(*S*)-3]

The carbamate **2** (34 g, 0.152 mol) was dissolved in dichloromethane (300 mL) under nitrogen and cooled to −10°C. Phosphorus pentachloride (31.3 g, 0.15 mol) was added in portions over 10 min, maintaining the temperature at −10 to −5°C. The mixture was warmed to 0°C and held for 30 min prior to warming to 20°C. Aluminum chloride (60 g, 0.45 mol) was added in

portions over 10 min at 22°C to 28°C to afford a dark red solution and stirred at 23°C for 30 min (TLC indicated complete reaction). The mixture was added to 3 N HCl (800 mL) over 45 min with rapid stirring at −5 to 1°C. The resulting mixture was stirred at 0°C for 30 min. The dichloromethane layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 300 mL). Ice-cold water (700 mL) was added to the organic extract, and pH was adjusted to 6.9 by adding aqueous saturated sodium bicarbonate at 1°C. The dichloromethane layer was separated, dried over $MgSO_4$ and silica gel (3 teaspoons each), and filtered. It was concentrated under vacuum at 15°C to afford **3** (23.3 g, 75%, >99% ee), mp 153–157°C. HPLC (Chiralpak AD column, hexanes/2-propanol (80:20) isocratic, 1 mL/min, at $\lambda = 200$–300 nm): t_R (*R*-3) 7.8 min, t_R (*S*-3) 7.2 min.

The spectroscopy data of the product matched those described in the literature.[6]

trans-(1*S*,2*S*)-2-[(Methoxycarbonyl)amino]-1-indanol [*trans*-(*S*,*S*)-4]

Procedure A

Ketone **3** (5.15 g, 0.025 mol) was dissolved in THF (150 mL) under nitrogen and cooled to 0°C. Borane solution in THF (1 N, 50 mL, 0.05 mol) was added over 10 min at 0°C and allowed to warm to 23°C. The mixture was stirred for 1 h, and acetic acid (25 mL) was added dropwise, keeping the mixture at 20°C. Methanol (25 mL) was added dropwise, and the mixture was stirred for 10 min. The yellow solution was evaporated under vacuum at 30°C, followed by high vacuum at 20°C. This was repeated twice to afford a yellow residue, which upon trituration with (50 mL) afforded **4** (2.4 g, 47%); mp 176–178°C. The spectroscopy data matched those described in the literature.[6]

Procedure B

The Red-Al solution in toluene (528 mL, 1.79 mol, 65+ wt% solution of sodium bis(2-methoxyethoxy)aluminum hydride) was cooled to 0°C under nitrogen. The anhydrous THF (2.4 L) was added with stirring. Ketone **3** (246 g, 1.2 mol) was added in portions over 1 h at −10 to 0°C. The mixture was stirred rapidly for 30 min. After checking an aliquot for completion of the reduction, the reaction mixture was quenched by pouring it into an aqueous saturated solution of sodium potassium tartarate (2.0 L) over 1 h, keeping the temperature at −2 to 1°C. The layers were separated, and the aqueous layer was extracted with THF (2 × 1.5 L). The combined THF extracts were washed with brine (1.5 L), dried over anhydrous $MgSO_4$ (600 g), and filtered and concentrated under vacuum at 20°C. The gray solid residue was stirred in *tert*-butyl methyl ether (1.5 L) at 23°C for 15 min,

filtered and washed with *tert*-butyl methyl ether (0.2 L). The solid was dried at 29°C for 20 h under vacuum to obtain **4** (175 g, 70.6%, >99% ee); mp 176–178°C. Chiral HPLC (4.6 × 250 mm Chiralpak AS column, hexanes/ethanol/TFA (95:5:0.1) isocratic, 1 mL/min, at $\lambda = 200–300$ nm): t_R (1*S*,2*R*-4) 19.9 min, t_R (1*S*,2*S*-4) 21.6 min. The spectroscopy data matched those described in the literature.[6]

trans-(1*S*,2*S*)-2-[(Methoxycarbonyl)amino]-1-acetoxyindane [*trans*-(*S*,*S*)-5]

The alcohol **4** (219 g, 1.05 mol) was suspended in dichlromethane (2.8 L) and cooled to 0°C. Pyridine (124.5 g, 1.575 mol) was added to the suspension under nitrogen. Acetyl chloride (122.9 g, 1.575 mol) was added to the mixture, keeping the temperature at −5 to 0°C. The mixture was stirred for 1 h at 0°C. After checking an aliquot for completion of the reaction by TLC (silica, EtOAc/heptane, 1:1), the mixture was washed at 0°C with aqueous saturated $NaHCO_3$ (2 × 2 L), 1 N HCl (2 × 2 L), and brine (2 L). The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum to afford **5** as a yellow solid (265 g, 100% with >99% ee); mp 84–88°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2–7.4 (m, 4H), 6.15 (d, 1H, $J = 7$ Hz), 5.4 (H, bs), 4.3 (m, 1H), 3.6 (s, 3 H), 3.5 (dd, 1H, $J = 10$, 18 Hz), 2.8 (dd, 1H, $J = 10$, 18 Hz), 2.1 (s, 3H). Chiral HPLC (4.6 × 250 mm Chiralpak AS column, hexanes/ethanol/TFA (95:5:0.1) isocratic, 1 mL/min, at $\lambda = 200–300$ nm): t_R (1*R*, 2R-5) 20 min, t_R (1*S*,2*S*-5) 16 min.

trans-(1*S*,2*S*)-6-Nitro-2-[(methoxycarbonyl)amino]-1-acetoxyindane [*trans*-(*S*,*S*)-6]

A 90% HNO_3 solution (324.5 g, 4.72 mol) was placed in a four-necked reaction flask under nitrogen and cooled to −30°C. Trifluoroacetic acid (600 mL) was added, and the mixture was cooled to −35°C. Trifluoroacetic anhydride (590 g, 2.8 mol) was added over 5 min to the reaction mixture. Carbamate **5** (118 g, 0.47 mol) dissolved in dichloromethane (200 mL) was added over 45 min with stirring while maintaining the reaction temperature at −35°C to −30°C. The reaction was checked by TLC (silica, EtOAc/heptane, 1:1). The reaction was worked up by addition of water (750 mL) at −30°C and warmed to 0°C. The upper dichloromethane layer was separated, and the lower aqueous layer was extracted with dichloromethane (1 L). The combined organic extract was washed with water (2 × 1 L), and the pH was adjusted to 8.5 using aqueous saturated $NaHCO_3$ solution (100 mL). It was again washed with cold water (1 L). The organic extract was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under vacuum to afford crude solid (144 g), which was dissolved in EtOAc (560 mL) at 70°C to obtain a yellow-orange solution. The solution was

slowly cooled to 47°C, resulting in a thick slurry. Heptane (1 L) was added to the slurry over 1 h at 47°C to 23°C and cooled to 0°C prior to filtration. The filter cake was washed with heptane (500 mL). The solid was dried at 23°C for 20 h under vacuum to obtain **6** (73 g, 52.6%); mp 165–167°C. $[\alpha]_D^{25}$ +16.88 (c = 1.0, MeOH). MH^+ 294.9. IR (Nujol) cm^{-1} 3370, 1735, 1695, 1544, 1525, 1344, 1278, 1240, 1066, 1037, 900, 740. ^1H NMR (300 MHz, $CDCl_3$) δ 8.1 (dd, 1H, $J = 9$, 3 Hz), 8.0 (s, 1H), 7.2 (d, 1H, $J = 9$ Hz), 6.1 (d, 1H, $J = 7$ Hz), 5.5 (bs, 1H), 4.4 (m, 1H), 3.6 (s, 3H), 3.5 (dd, 1H, $J = 10$, 18 Hz), 2.9 (dd, 1H, $J = 10$, 18 Hz), 2.2 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 156.6, 147.7, 147.5, 140.3, 125.6, 124.5, 120.3, 79.7, 59.1, 52.3, 37.0, 20.9. Anal. calcd. for $C_{13}H_{14}O_6N_2$: C, 53.06; H 4.80; N, 9.52. Found: C, 53.1; H, 4.85; N, 9.42.

trans-(1*S*,2*S*)-6-Nitro-2-[(methoxycarbonyl)amino]-1-indanol [*trans*-(*S*,*S*)-7]

Acetate **6** (16.5 g, 0.056 mol) was suspended in methanol (275 mL) in a three-necked reaction flask at 23°C under nitrogen. To the suspension, 1 N NaOH (112 mL) was added dropwise, maintaining the temperature at 23°C. The mixture was stirred for another 15 min and checked by TLC (dissolve sample in excess MeOH, silica, EtOAc/heptane, 1:1). After completion of the reaction, the mixture was diluted with water (275 mL). The solid was filtered, washed with water (275 mL), and dried at 23°C under vacuum to afford **7** (13.1 g, 92.9%, >99% ee); mp 201–203°C. MH^+ 252.98 IR (KBr) cm^{-1} 3500, 3350, 1691, 1533, 1355, 1288, 1272, 1234, 1041, 740. ^1H NMR (500 MHz, DMSO-d_6) δ 8.1 (dd, 1H, $J = 9$, 3 Hz), 8.0 (s, 1H), 7.6 (d, 1 H, $J = 7$ Hz), 7.45 (d, 1H, $J = 9$ Hz), 9 Hz, 5.9 (d, 1H, $J = 7$ Hz), 5.0 (d, 1H, $J = 7$ Hz), 4.0 (m, 1H), 3.5 (s, 3H), 3.2 (dd, 1H, $J = 18$, 6 Hz), 2.7 (dd, 1H, $J = 18$, 10 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.5, 147.2, 146.9, 146.0, 125.8, 125.1, 118.8, 77.1, 60.9, 51.3, 35.5. Chiral HPLC (4.6 × 250 mm Chiralpak AS column, hexanes/ethanol (80:20) isocratic, 1 mL/min, at $\lambda = 200$–300 nm): t_R (1*S*,2*R*-7) 7.8 min, t_R (1*S*,2*S*-7) 9.0 min.

(S)-(+)-5-Amino-2-[(methoxycarbonyl)amino]-1-indane [(*S*)-8] from 7

A 2-L Parr hydrogenation reactor was charged with alcohol **7** (25 g, 0.099 mol) in acetic acid (300 mL) at 23°C under nitrogen. Perchloric acid (70%, 25 g) was added. To the mixture, 10% Pd/C (25 g, 50% water wet) was added, and the mixture was hydrogenated at 50 psi of hydrogen for 1.5 h and 42 psi of hydrogen overnight (14 h). The mixture was filtered through a Celite® pad, prewashed with acetic acid. The filtrate was evaporated under high vacuum at 35–40°C to an oil. The oily residue was triturated with *tert*-butyl methyl

ether (2 × 400 mL), and *tert*-butyl methyl ether was decanted off. The gummy residue was dissolved in water (deionized, 1 L) at 23°C and dichloromethane (1 L). The pH of the mixture was adjusted to pH 8.0 by dropwise addition of aqueous saturated $NaHCO_3$ (300 mL). The dichloromethane layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 500 mL). The combined organic extracts were washed with cold water (500 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated under vacuum at 25°C to obtain [(*S*)-8] (14.7 g, 71.4%, >99% ee); mp 145–146°C. MH^+ 207. $[\alpha]_D^{25} = +26.40$ (c = 1.0, DMSO). ^1H NMR (300 MHz, $CDCl_3$) δ 7.0 (d, $J = 9$ Hz, 1H), 6.8 (s, 1H), 6.5 (d, $J = 9$ Hz, 1H), 4.9 (bs, 1H), 4.5 (bs, 1H), 3.7 (s, 3H), 3.5 (bs, 2H), 3.2 (m, 2H), 2.7 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.3, 147.3, 141.6, 127.8, 124.4, 112.5, 110.0, 52.0, 51.1, 38.1. Chiral HPLC (4.6 × 250 mm Chiralpak AD column, hexanes/2-propanol (80:20) isocratic, 1 mL/min, at $\lambda = 200–300$ nm): t_R (2*R*-8) 13.0 min, t_R (2*S*-8) 11.5 min.

(S)-(+)-5-Amino-2-[(methoxycarbonyl)amino]-1-indane [(*S*)-8] from 6

A 2-L Parr hydrogenation flask was charged with **6** (60 g, 0.2 mol), acetic acid (800 mL), and perchloric acid (70%, 60 g) under nitrogen. A 10% Pd/C (40 g, 50% water wet) was added to the mixture at 25°C. The mixture was hydrogenated at 50 psi at 25°C over 6 h. The catalyst was filtered off using a Celite® pad, prewashed with acetic acid. The filter cake was washed with acetic acid (200 mL), and the filtrate was concentrated under vacuum at 30–34°C. The residue was dissolved in water (1.5 L) and dichloromethane (1.5 L) and cooled to −2°C. The pH of the mixture was adjusted to pH 6.8–8 by adding aqueous saturated $NaHCO_3$ (1L). The dichloromethane layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 500 mL). The combined organic extracts were washed with ice water (1 L), dried over $MgSO_4$ (200 g), and filtered. The filtrate was concentrated under vacuum at 20°C to afford [(***S***)-**8**] (36.5 g, 88.5%) as an off-white solid.

Purification

The crude product [(***S***)-**8**] (131 g) was dissolved in EtOAc (1.3 L) at 70°C to obtain an orange-colored solution. The solution was allowed to cool to 23°C. A thick suspension resulted. Heptane (1.3 L) was added to the slurry over 1.5 h. The solid was filtered and washed with heptane (2 × 0.5 L). The solid was dried under vacuum at 28°C over 20 h to afford pure **8** (104 g, 79% recovery, >99% chiral purity),[3] mp 143–146°C.

(*R*)-(−)-5-Amino-2-[(methoxycarbonyl)amino]-1-indane [(*R*)-8]

(*R*)-(−)-5-Amino-2-[(methoxycarbonyl)amino]-1-indane [(*R*)-**8**] with more than 99% ee was prepared from (*R*)-(+)-phenylalanine following the same procedures as described previously. All spectroscopy data were the same as for the (*S*)-enatiomer except the optical rotation. $[\alpha]_D^{25}$ −25.47 (c = 1.04, DMSO). Anal. calcd. for $C_{11}H_{14}O_2N_2$: C, 64.04; H 6.84; N, 13.58. Found: C, 63.92; H, 6.71; N, 13.56.

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