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An Efficient Synthesis of Enantiomerically Pure (*R*)-Pipecolic Acid, (*S*)-Proline, and Their *N*-Alkylated Derivatives

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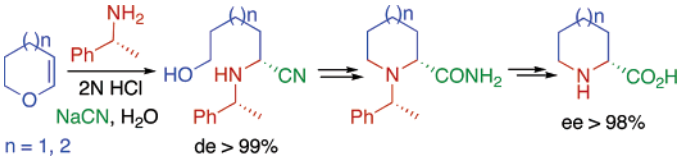

Enantiomerically pure (*R*)-(+)-pipecolic acid was synthesized in four steps and 42% overall yield starting from dihydropyran and (*R*)-α-methylbenzylamine. A general short strategy is also described for preparing (*S*)-proline (47.5% overall yield) and derivatives.

Introduction

Cyclic α-amino acids are expected to play key roles, once incorporated into proteins, in improving their biological activity and functions.[1] In peptides, these cyclic amino acids confer rigidity on the protein, which influences cell recognition events.[2,3] In this context, the asymmetric synthesis of proline and pipecolic acid (homoproline) is of importance because they are key constituents of bioactive molecules and are useful building blocks for asymmetric synthesis[4,5] and used in many synthetic drugs.[6] The importance of (*S*)-pipecolic acid, which occurred in nature as a nonproteinogenic amino acid, has fostered the development of many synthetic approaches involving enzymatic reactions,[7] alkylation of chiral glycine enolates,[8] derivatization of natural amino acids,[9] enantioselective reactions,[10] resolution,[11] and asymmetric Strecker reaction.[12] Nevertheless, many synthetic precursors had been very limited by

(1) (a) For a review, see: Hanessian, S.; Mc Naughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789−12854. (b) Barrett, G. C., Ed. *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London, 1985.

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(3) For example, see: Smith, A. B., III; Benowitz, A. B.; Sprengeler, P. A.; Barbosa, J.; Guzman, M. C.; Hirschmann, R.; Schweiger, E. J.; Bolin, D. R.; Nagy, Z.; Campbell, R. M.; Cox, D. C.; Olson, G. L. *J. Am. Chem. Soc.* **1999**, *121*, 9286−9298.

(4) For reviews on the applications of amino acids to asymmetric synthesis, see: (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149−164. (b) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825−1872. (c) Remuzon, P. *Tetrahedron* **1996**, *52*, 13803−13835. (d) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun*. **1998**, 633−640.

(5) Davis, F. A.; Fang, T.; Chao, B.; Burns, D. M. *Synthesis* **2000**, 2106−2112.

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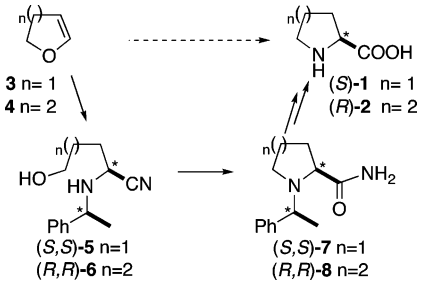
SCHEME 1



a lack of simple synthetic methods for their preparation in high enantiomeric purity and on a multigram scale.

We decided in connection with our ongoing program on the asymmetric Strecker reaction[13] to study a new diastereoselective synthesis of proline **1** and pipecolic acid **2** from inexpensive and commercially available dihydrofuran **3** and dihydropyran **4**, respectively.

This methodology is based on the combination of the known Strecker reaction already developed to prepare racemic amino acid[14,15] and subsequent cyclization. We anticipated that this method should occur: (i) with an efficient stereocontrol of asymmetric Strecker reaction in the presence of chiral amine and (ii) with good cyclization without racemization of the newly formed chiral center (Scheme 1).

Results and Discussion

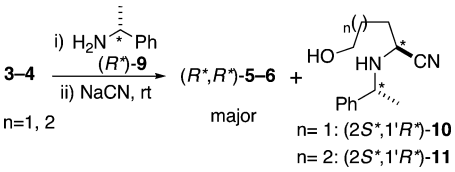
The amino nitriles (*R*,*R*)-**5** and -**6** and (*S*,*S*)-**5** were readily prepared by a one-pot ring-opening reaction at room temperature of the corresponding 2,3-dihydrofuran **3** and 3,4-dihydro-2*H*-pyran **4**, using a modified literature procedure,[14d] in the presence of optically active methylbenzylamine (*R*)- or (*S*)-**9**, respectively, and sodium cyanide in HCl aqueous solution (Scheme 2 and Table 1). Thus, these amino nitriles were generated, within 2−4 days,[16] with high yields and excellent diastereoselectivity in 98 and 96% de for **5** and **6**, respectively, and can be improved to >99% de after a simple crystallization. These diastereoisomeric excesses were determined by ^{1}H and ^{13}C NMR of the mother liquid residue that remained after crystallizations of the crude amino nitriles **5** and **6** (see the Supporting Information).

TABLE 1. Synthesis of Amino Nitriles 5 and 6 from Cyclic Enol Ethers 3 and 4

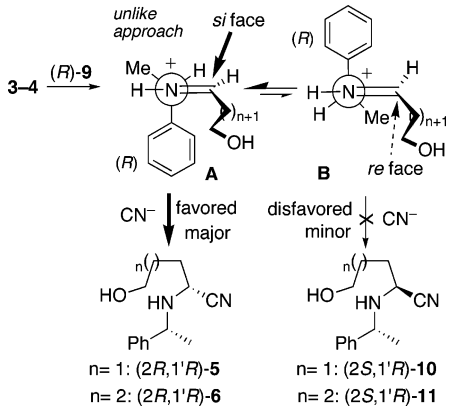
			5−**6** (yield%)[a]		
entry	enol	amine **9**	(*S*,*S*)	(*R*,*R*)	de[b] (%)
1	**3**	*R*		**5** (86)	>98
2	**4**	*R*		**6** (86)	>96
3	**3**	*S*	**5** (86)		>98

[a] Isolated yields of major products. [b] Diastereoisomeric excesses were determined by ^{1}H NMR spectra from (2*R*,1′*R*)/(2*S*,1′*R*) crude mixture.

SCHEME 2



SCHEME 3



In all cases, the diastereoselectivity achieved by this method can be explained on the basis of the aza analogue of the Anh−Eisenstein hypothesis.[17] According to this hypothesis, nucleophilic attack should take place antiperiplanar to the α-phenyl group with an unlike approach, on the more stable iminium intermediate **A**, giving exclusively the major amino nitriles (2*R*,1′*R*)-**5**−**6** when using amine (*R*)-**9** and (2*S*,1′*S*)-**5** when starting from amine (*S*)-**9**. Likewise, the reaction is under thermodynamic control (2−4 days reaction);[16] consequently, the resulting major amino nitriles should be the thermodynamic compounds **5**−**6** (Scheme 3). The major isomers **5** and **6** were assumed to have the (2*R*,1′*R*)- or (2*S*,1′*S*) configuration in accordance with the stereochemistry of the resulting (*R*)- or (*S*)-proline **1** and (*R*)- or (*S*)-pipecolic acid **2** described below.

Under basic conditions, the cyclizations of (*S*,*S*)-**5** and (*R*,*R*)-**6** were achieved by using MsCl/NEt$_3$ in the presence of catalytic DMAP in CH_2Cl_2 to furnish cyclic nitriles in good yields as inseparable diastereomeric mixtures of (*S*,*S*)-**12**/(2*R*,1′*S*)-**13** and (*R*,*R*)-**14**/(2*S*,1′*R*)-**15**, respectively. Neither changing reaction solvent (Et_2O, toluene, or hexane) nor using other conditions (PPh_3/DEAD) improved the diastereomeric ratio. Only a 70:30

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(15) For a ring-opening reaction of semicyclic *N*,*O*-acetals, see: Sugiura, M.; Kobayashi, S. *Org. Lett.* **2001**, *3*, 477−480.

(16) Strecker reaction was known to perform slowly and gave in our case the thermodynamic amino nitriles in only 50% yield after 1 day.

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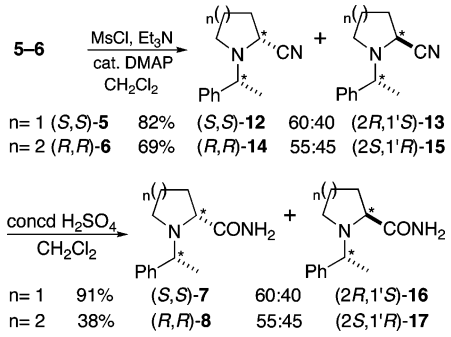
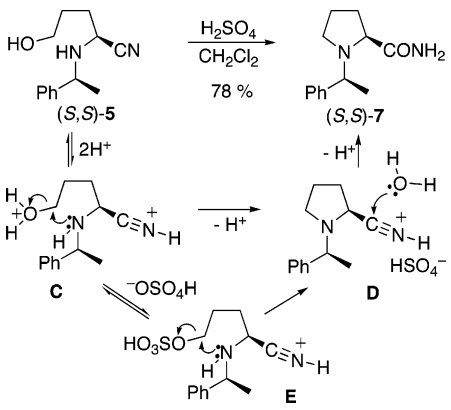
SCHEME 4



SCHEME 5



ratio, by using ether, was obtained in moderate yield (53%) (Scheme 4).

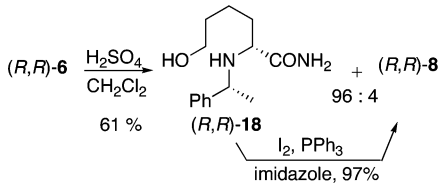
Subsequent acidic hydrolysis of cyclic nitriles **12**/**13** and **14**/**15** (epimeric mixture) was carried out with concd H_2SO_4 (18 M) at 20 °C in CH_2Cl_2. Amides **7**/**16** and **8**/**17** were obtained with good ($n = 1$) to moderate ($n = 2$) yields with the same epimeric mixture, respectively, and were easily separated by chromatography.

To avoid epimerization at the C-2 centers during the cyclization reaction, we decided to transform amino nitrile under acidic conditions into amide prior to cyclization. To our surprise, treatment of the amino nitrile (*S*,*S*)-**5** ($n = 1$) with concd H_2SO_4 (18 M) at room temperature gave exclusively, via a one-pot reaction, the cyclic amide (*S*,*S*)-**7** in good overall yield without any epimerization at the C-2 center. This product was probably formed via an easy 5-membered-ring cyclization of **C** followed independently by a hydrolysis of nitrile function of **D** into amide, before or after such cyclization. On the other hand, it may again by either an S_N1 or S_N2 route be attacked by the nucleophile HSO_4^-, converting to **E**,[18] which in turn cyclized into **D** as depicted in Scheme 5.

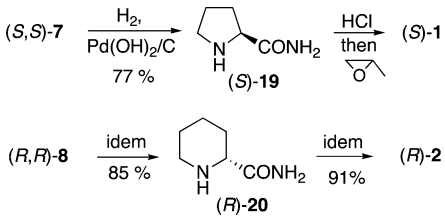
However, the same treatment applied to (*R*,*R*)-**6** gave only 4% of 6-membered ring amide **8** and acyclic amide **18** in a 4:96 ratio, respectively (Scheme 6). Subsequent cyclization of **18** with I_2/PPh_3/imidazole furnished the desired amide **8** in 97% yield without any epimerization, while, when MsCl/NEt_3 was used for cyclization, 50% yield of amide **8** was only obtained.

At this point, it was crucial to measure the enantiomeric excesses of the final products in order to check the possible

SCHEME 6



SCHEME 7



racemization of the C-2 centers. Thus, amide (2*S*,1′*S*)-**7** was hydrogenolyzed under mild conditions (20% $Pd(OH)_2$/C, and 1 atom H_2, in EtOH), affording the (*S*)-prolinamide **19** ($[\alpha]_D$ −105 (*c* 2.00, EtOH)) in good yield, in agreement with the literature ($[\alpha]_D$ −106 (*c* 2.00, EtOH)).[19] Consequently, its enantiomeric excess was >98%. Subsequent treatment of the (*S*)-prolinamide **19** with 6 M HCl at reflux, followed by the addition of propylene oxide in ethanol in order to remove HCl, furnished free (*S*)-proline **1** in 92% yield {$[\alpha]_D$ −83.2 (*c* 4.00, H_2O); authentic sample $[\alpha]_D$ −84 (*c* 4.00, H_2O)} (Scheme 7).

The same reaction sequence, applied to amide (*R*,*R*)-**8**, afforded the pipecolinamide (*R*)-**20** ($[\alpha]_D$ +33.1 (*c* 2.00, EtOH)) and the pipecolic acid (*R*)-(+)-**2** ($[\alpha]_D$ + 26.7 (*c* 1.00, H_2O)) in good yields, respectively. The specific rotation of (*R*)-**2** was in agreement with the literature ($[\alpha]_D$ +26.3 (*c* 1.00, H_2O));[7h] its enantiomeric excess was >98%.

Conclusion

We have developed an easy and efficient four-step synthesis of enantiopure pipecolic acid (*R*)-**2** and proline (*S*)-**1**, starting from commercially available dihydropyran **4** and dihydrofuran **3**. These acids were obtained from amino nitriles **5**−**6**, which were prepared by asymmetric Strecker reaction with excellent selectivity (dr up to 99.5:0.5). The final products can be obtained in any configuration in very high enantiomeric purity (>99% ee). This approach can be used in the synthesis of other heterocyclic rings, a possibility that is currently being explored in our group.

Experimental

For the general experimental methods, see the Supporting Information.

General Procedure A: Preparation of Hydroxyaminonitrile 5−6 by a Modified Gaudry's Procedure.[14] To an aqueous solution of HCl (0.2 M, 80 mL) was added dihydrofuran **3** or dihydropyran **4** (0.300 mol), and the mixture was stirred at rt until complete dissolution of adduct (10 min). Then the resulting solution was slowly added to another solution of NaCN (0.360 mol, 1.2 equiv)

(18) For formation of inorganic ester with sulfuric acid from alcohol, see: Feuer, H.; Hooz, J. In *The Chemistry of Ether Linkage*; Patai, S., Ed.; Interscience: New York, 1967; pp 457−460 and 468−470.

(19) (a) Johnson, R. L.; Rajukumar, G.; Mishra, R. K. *J. Med. Chem.* **1986**, *29*, 2100−2104. (b) *Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra*; Aldrich: Milwaukee, 1992; Vol. 1, pp 889 A−C, 1085B.

and chiral amine **9** (0.30 mol) in 1 M HCl solution (320 mL), and the mixture was stirred at rt for 2−4 days. The basic mixture was then extracted with EtOAc (3 × 200 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and then concentrated under vacuum to give the crude hydroxy aminonitriles **5**−**6**. Purification was performed by flash chromatography (FC) on silica gel or by crystallization from ether/pentane mixture.

(2*S*,1′*S*)-5-Hydroxy-2-(1′-phenylethylamino)pentane nitrile [(*S*,*S*)-(+)-5]. Following procedure A: From 2,3-dihydrofuran **3** (21 g, 300 mmol), (*S*)-α-phenylethylamine (*S*)-**9** (36.30 g, 300 mmol), and NaCN (17.65 g, 360 mmol) in 1 M HCl (300 mL), stirring at rt for 2−4 days, was obtained 65.20 g of crude desired amino nitrile (*S*,*S*)-**5**. Crystallization from ether/pentane afforded 56.20 g (86%, in three crops) of pure amino nitrile: mp 97.0 °C; $[\alpha]_D$ −212.4 (*c* 1.00, $CHCl_3$); t_R = 12.68 min (Cydex B, 130 °C, 1 bar); R_f = 0.16 (EtOAc/petroleum ether 3/7); IR (neat) 3238, 2225, 1453, 1265 cm^{-1}; ^1H NMR δ 1.41 (d, *J* = 6.6 Hz, 3H), 1.60−1.94 (m, 4H), 2.02 (br s, 2H, NH and OH), 3.19 (t, *J* = 6.8 Hz, 1H), 3.50−3.80 (m, 2H), 4.11 (q, *J* = 6.6 Hz, 1H), 7.20−7.72 (m, 5H); ^{13}C NMR δ 24.6, 28.9, 30.8, 47.9, 56.5, 61.6, 120.3, 126.6, 126.8, 127.6, 142.8; MS (EI) *m*/*z* no peak parent, 190 (1.3), 176 (41), 160 (11), 106 (51), *105* (100), 104 (55), 79 (19). Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.57; H, 8.16; N, 13.03.

(2*R*,1′*R*)-6-Hydroxy-2-(1′-phenylethylamino)hexanonitrile [(*R*,*R*)-(+)-6]. Following procedure A: From 3,4-dihydropyran **4** (8.40 g, 100 mmol), (*R*)-α-phenylethylamine (*R*)-**9** (12.1 g, 100 mmol), and NaCN (5.88 g, 120 mmol) in 1 M HCl (100 mL), stirring at rt for 2 days, was obtained 23.5 g of crude desired amino nitrile (*R*,*R*)-**6**. Crystallization from ether/pentane furnished 20.20 g (86.2%, in three crops) of pure amino nitrile: mp 59.1 °C; $[\alpha]_D$ +185 (*c* 1.00, $CHCl_3$); t_R = 13.18 min (Cydex B, 130 °C, 1 bar); R_f = 0.24 (EtOAc/petroleum ether: 3/7); IR (neat) 3323, 2226, 1453 cm^{-1}; ^1H NMR δ 1.39 (d, *J* = 6.7 Hz, 3H), 1.45 (br s, 2H, NH and OH), 1.40−1.67 (m, 4H), 1.67−1.90 (m, 2H), 3.17 (t, *J* = 6.8 Hz, 1H), 3.55−3.77 (m, 2H), 4.09 (q, *J* = 6.7 Hz, 1H), 7.20−7.46 (m, 5H); ^{13}C NMR δ 21.7, 24.6, 31.6, 33.1, 48.0, 56.3, 61.7, 120.2, 126.6, 127.4, 128.5, 143.0; MS (EI) *m*/*z* no peak parent, 204 (3), 190 (49), 172 (30), 147 (62), 106 (50), *105* (100), 79 (18). Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.32; H, 8.71; N, 12.11.

General Procedure C: Formation of Amides 7 and 8 from Nitriles 5 and 6. A solution of nitrile **5** or **6** (10 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C, and concd sulfuric acid (18 M, 15 mL) was added very slowly with efficient stirring. The reaction mixture was allowed to warm to rt and stirred for 8−48 h. The aqueous layer was separated, washed with CH_2Cl_2 (4 mL), poured onto crushed ice (30 g), and then slowly basified with concd ammonia. The mixture was extracted with EtOAc (4 × 100 mL), dried over $MgSO_4$, and then concentrated to give, after FC (silica gel, 75 g, eluent: MeOH/EtOAc: 4/96), the title amide **7** or **8**.

(2*S*,1′*S*)-1-(1′-Phenylethyl)pyrrolidine-2-carboxamide [(2*S*,1′*S*)-(−)-7]. One-pot formation from hydroxyamino nitrile, according to procedure C: From hydroxyamino nitrile (2*S*,1′*S*)-**5** (21.8 g, 10 mmol), concd H_2SO_4 (18 M, 15 mL), and CH_2Cl_2 (30 mL) with stirring at rt for 2 days was obtained after FC (eluent, MeOH/EtOAc 4/96) 1.700 g (78%) of pure amide (2*S*,1′*S*)-**7**: mp 80.3 °C; $[\alpha]_D$ −73 (*c* 1.00, $CHCl_3$); t_R = 55.97 min (Cydex B, 130 °C, 1 bar); R_f = 0.23 (EtOAc/CH_2Cl_2: 5/5); IR (neat) 3423, 1682, 1454 cm^{-1}; ^1H NMR δ 1.40 (d, *J* = 6.7 Hz, 3H), 1.57−1.83 (m, 2H), 1.87−2.07 (m, 1H), 2.07−2.40 (m, 2H), 2.85 (ddd, *J* = 8.4 Hz, *J* = 4.2 Hz, *J* = 3.7 Hz, 1H), 3.33 (dd, *J* = 10.5 Hz, *J* = 3.7 Hz, 1H), 3.60 (q, *J* = 6.7 Hz, 1H), 6.35 (br s, 1H), 7.14−7.39 (m, 5H), 7.44 (br s, 1H); ^{13}C NMR δ 22.7, 24.3, 31.4, 53.4, 64.4, 64.7, 127.1, 127.2, 128.3, 144.0, 179.9; MS (EI) *m*/*z* 218 (M^+) (1.5), 175 (15), 174 (94), *105* (100), 70 (92); ES^+MS *m*/*z* 241.1 $[M + Na]^+$; HRMS (EI) calcd for $C_{13}H_{18}N_2O$ 218.1419, found 218.1421.

(2*R*,1′*R*)-6-Hydroxy-2-(1-phenylethylamino)hexanamide [(+)-18]. Following procedure C: From amino nitrile (2*R*,1′*R*)-**6** (464 mg, 2 mmol), concd H_2SO_4 (18 M, 3 mL), and CH_2Cl_2 (7 mL) with stirring at rt for 3 days was obtained after FC (eluent, MeOH/EtOAc 10/90) 290 mg (58%) of pure hydroxy amide (2*R*,1′*R*)-**18**, and 14 mg (3%) of cyclic amide (2*R*,1′*R*)-**8**.

Data for the major acyclic amide (2*R*,1′*R*)-**18**: mp 74.5 °C; $[\alpha]_D$ +37.8 (*c* 1.00, $CHCl_3$); R_f = 0.20 (MeOH/AcOEt 5/95); IR (neat) 3355, 3249, 3178, 1674, 1455 cm^{-1}; ^1H NMR δ 1.35 (d, *J* = 6.6 Hz, 3H), 1.20−1.74 (m, 6H), 2.40 (br s, 2H, NH and OH), 2.86 (dd, *J* = 7.1 Hz, *J* = 5.8 Hz, 1H), 3.56 t, *J* = 5.8 Hz, 1H), 3.68 (q, *J* = 6.6 Hz, 1H), 5.81 (br s, *J* = 3.6 Hz, 1H),), 6.89 (br s, *J* = 3.6 Hz, 1H), 7.18−7.40 (m, 5H); ^{13}C NMR δ 21.8, 24.3, 32.1, 33.6, 57.0, 60.0, 61.8, 126.4, 127.1, 128.5, 144.7, 178.4; HRMS (EI) *m*/*z* calcd for $C_{14}H_{22}N_2O_2$ 250.1681, found 250.1664.

Data for the minor cyclic amide (2*R*,1′*R*)-**8** are identical with those noted below.

(2*R*,1′*R*)-1-(1′-Phenylethyl)piperidine-2-carboxamide [(+)-(8)]. Cyclization of Hydroxy Amide 18 with I_2/PPh_3/Imidazole. To a solution of hydroxy amide **18** (2 mmol) in toluene (30 mL) were successively added at rt PPh_3 (630 mg, 2.4 mmol) and imidazole (163 mg, 2.4 mmol) and then dropwise a solution of I_2 (610 mg, 2.4 mmol) in toluene (4 mL). The mixture was then heated at reflux for 3 h. After being cooled to rt, the solvent was removed and the residue was washed with ether (2 × 10 mL). The solid residue was basified to pH 9 with a 1 M solution of $NaHCO_3$ and then extracted with EtOAc (3 × 60 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated under vacuum to yield after flash chromatography on silica gel (eluent: MeOH/CH_2Cl_2 3/97 → 10/90), as an amorphous solid, 450 mg (97%) of pure amide (2*R*,1′*R*)-**8**, ee > 99% determined by GC using a chiral column: t_R = 122.96 min for (*R*,*R*)/t_R = 125.55 min for (*S*,*S*) (Cydex B, 25 m, 140 °C, 1 bar).

Data for amide (2*R*,1′*R*)-(+)-**8**: mp 92.0 °C; $[\alpha]_D$ +80.5 (*c* 1.00, $CHCl_3$); ee >99%; t_R = 122.96 min (Cydex B, 140 °C, 1 bar); R_f = 0.38 (MeOH/CH_2Cl_2 1/9); IR (neat) 3445, 3000, 1675, 1452 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05−1.25 (m, 1H), 1.25−1.45 (m, 1H), 1.46 (d, *J* = 7.0 Hz, 3H), 1.53−1.78 (m, 3H), 1.78−2.00 (m, 2H), 2.92 (ddd, *J* = 11.5 Hz, *J* = 4.6 Hz, *J* = 4.6 Hz, 1H), 3.06 (dd, *J* = 4.1 Hz, *J* = 8.8 Hz, 1H), 4.01 (q, *J* = 7.0 Hz, 1H), 5.75 (br s, 1H), 6.81 (br s, 1H), 7.16−7.45 (m, 5H); ^{13}C NMR δ 19.4, 22.9, 23.95, 28.8, 44.5, 59.7, 63.5, 127.2, 127.9, 128.7, 139.2, 177.9; MS (EI) 232 (M^+, 0.1), 188 (44), 105 (65), 103 (8), *84* (100), 77 (15); HRMS (EI) calcd for $C_{14}H_{20}N_2O$ 232.1576, found 232.1583.

Procedure D: Hydrogenolysis of Benzylic Amine. To a solution of amino amide adduct **7** or **8** (2.00 mmol) in a mixture of EtOH/AcOH (1:1) (4 mL) was added 20% $Pd(OH)_2$/C (Pearlman's catalyst, 150 mg). The mixture was stirred at rt under H_2 (1 atm) for 10 h and then degassed under a stream of argon and filtered through Celite, and the collected solid was washed with EtOH (3 × 10 mL). The combined filtrate and washings were concentrated, and the residue was neutralized with concd NH_4OH (2 mL) then subjected to FC (eluent, MeOH/CH_2Cl_2/concd NH_4OH 50/50/1) to afford pure free amino amides **19** or **20**.

2-Piperidinecarboxamide [(*R*)-Pipecolinamide] [(*R*)-(+)-20]. Following procedure D: From amino amide (2*R*,1′*R*)-**8** (232 mg, 1 mmol), AcOH (4 mL), and 20% $Pd(OH)_2$/C (100 mg) with stirring at rt for 10 h was obtained, after FC, 95 mg (85%) of pure (*R*)-pipecolinamide **20**: $[\alpha]_D$ + 33.1 (*c* 2.00, EtOH) [lit.[20a] $[\alpha]_D$ + 33

(20) (a) Hardtman, G. E.; Houlihan, W. J.; Giger, R. K. A. US Patent, 4.760.065, July 26, 1988. (b) Perumattam, J.; Shearer, B. G.; Confer, W. L.; Mathew, R. M. *Tetrahedron Lett.* **1991**, *32*, 7183−7186.

(*c* 2.00, EtOH)]; mp 161.0−162.5 °C (from EtOH/hexane) (lit.[20b] mp 162−163 °C); R_f = 0.45 (MeOH/CH_2Cl_2/concd NH_4OH 50/50/1); IR (neat) 3382, 3303, 3191, 1620, 1408, 1318 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30−1.75 (m, 4H), 1.73−1.90 (m, 1H), 1.90−2.08 (m, 1H), 2.19 (br s, 1H), 2.57−2.80 (m, 1H), 3.05 (dt, J = 12.2 Hz, J = 2.5 Hz, 1H), 3.22 (dd, J = 9.8 Hz, J = 3.3 Hz, 1H), 5.95 (br s, 1H), 6.75 (br s, 1H); ^{13}C NMR δ 24.1, 25.9, 23.0, 45.8, 60.2, 177.2; HRMS (EI) calcd for $C_6H_{12}N_2O$ 128.0950, found 128.0949.

Supporting Information Available: Experimental procedures, ^1H and ^{13}C NMR spectra, and characterization data for (2*S*,1′*S*)-**5**, (2*R*,1′*R*)-**5**, (2*R*,1′*R*)-**6**, (2*R*,1′*R*)-**6**/(2*S*,1′*R*)-**11**, (2*S**,1′*S*)-**12** and **13**, (2*R**,1′*R*)-**14** and **15**, (2*S*,1′*S*)-**7**, (2*R*,1′*S*)-**16**, (2*R*,1′*R*)-**8**, (2*S*,1′*R*)-**17**, (2*R*,1′*R*)-**18**, (*S*)-**19**, (*R*)-**20**, (*S*)-**1**, and (*R*)-**2**·HCl. This material is available free of charge via the Internet at http://pubs.acs.org.

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