An Efficient Synthesis of (*S*)-(+)-Ethyl *β*-Amino-3-pyridinepropanoate Using Enantiopure Sulfinimines

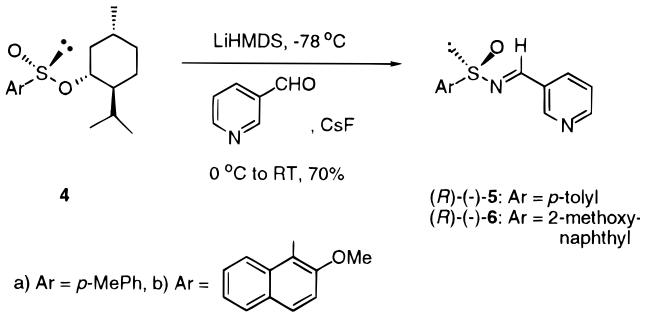
Franklin A. Davis,*,† Joanna M. Szewczyk,† and Rajarathnam E. Reddy‡

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122-2585 and Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

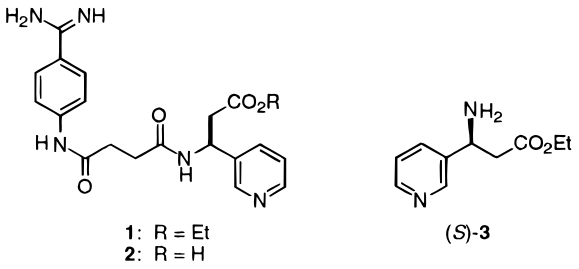
Received October 27, 1995

The development of new and improved methodology for the asymmetric synthesis of *β*-amino acids[1] is of current interest because these compounds are found as key components of antibiotics,[2] peptides,[3] and other bioactive materials. Furthermore, cyclization of *β*-amino acids is an important route to the *β*-lactam class of antibiotics,[4,5] and substitution for α-amino acids is useful in the preparation of peptide analogs with increased activity and enzymatic stability.[6] Recently, we described an efficient asymmetric synthesis of (*R*)-(+)-*β*-phenylalanine,[7] an important constituent of the antitumor astins A-C[7] and the taxane alkaloids,[8] via the highly diastereoselective (>98% de) addition of the sodium enolate of methyl acetate to enantiopure sulfinimines.[9] In related studies the asymmetric syntheses of amines,[10] α-amino acids,[11] *N*-sulfinyl *cis*-aziridine 2-carboxylic acids,[12ab] *N*-sulfinylaziridines,[12c] *β*-amino acids,[7,13] the taxol C-13 side chain[13a] and its fluorinated analog[14] have been described by us and others using sulfinimines (thiooxime *S*-oxides) as chiral ammonia imine building blocks.

Scheme 1



As an extension of our *β*-amino acid protocol we report the asymmetric synthesis of (*S*)-ethyl *β*-amino-3-pyridinepropanoate (**3**), a key component of (*S*)-ethyl *β*-[[4-[[4-(aminoiminomethyl)phenyl]amino]-1,4-dioxobutyl]-amino]-3-pyridinepropanoate (**1**).[15] Compound **1** is a peptidomimetic for the Arg-Gly-Asp-Phe sequence of fibrinogen and is an orally active antiplatelet agent and prodrug form of **2** that may be useful in treatment of myocardial infarction and unstable angina.[15] *β*-Amino acid **3** was previously prepared via a sequence involving the diastereoselective addition of lithium *N*-(trimethylsilyl)-(*R*)-1-phenylethylamide to (*E*)-ethyl 3-pyridineacrylate.[15] Because of the basic pyridine unit in (*S*)-**3**, its synthesis was anticipated to be a particularly challenging test of our *β*-amino acid methodology.



1: R = Et
2: R = H

(*S*)-**3**

The enantiopure sulfinimines, (*R*)-(−)-**5** and (*R*)-(−)-**6**, were prepared by treatment of (*1S*,*2R*,*5S*)-(+)-menthyl (*R*)-*p*-toluenesulfinate (**4a**)[16] and (*R*)-(+)-menthyl-2-methoxy-1-naphthalenesulfinate (**4b**)[17] with 1.5 equiv of lithium bis(trimethylsilyl)amide at −78 °C followed by reaction with 2 equiv of 3-pyridinecarboxaldehyde in the presence of cesium fluoride (Scheme 1).[18] The products were isolated in 70% yield by flash chromatography. The imino proton, appearing at ca *δ* 9.0 ppm, in the ^{1}H NMR of **5**/**6** is particularly diagnostic for these compounds.

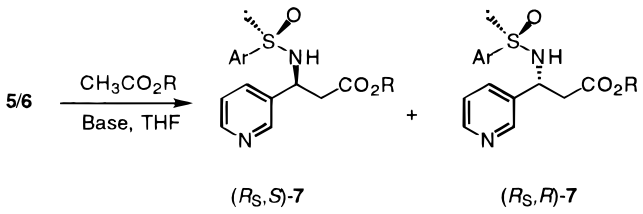
While addition of sulfinimine (*R*)-(−)-**5** to 1.5 equiv of sodium enolate of ethyl acetate (NaHMDS and ethyl acetate) in THF at −78 °C afforded **7b** in 70% isolated yield, the de was only 64% (Scheme 2). In our earlier synthesis of *β*-phenylalanine the sodium enolate of methyl acetate in diethyl ether gave better de's than in THF; >98 vs 92%, respectively.[9] Unfortunately, the insolubil-

† Temple University.
‡ Drexel University.

(1) For recent reviews on the asymmetric synthesis of *β*-amino acids see Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3. Cole, D. C *Tetrahedron* **1994**, *50*, 9517.
(2) For leading references see: Kiers, D.; Moffat, D.; Tomanek, R. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1041.
(3) (a) Barrett, G. C., Ed. *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London, 1985. (b) Hecht, S. M. *Acc. Chem. Res.* **1986**, *19*, 383. (c) Morita, H.; Nagashima, S.; Takeya, K.; Itokava, H. *Chem. Pharm. Bull.* **1993**, *41*, 992.
(4) See, for example: Mayachim N.; Shibasaki, M. *J. Org. Chem.* **1990**, *55*, 1975. Kim, S.; Lee, P. H.; Lee, T. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1242. Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 613. Kunieda, T.; Nagamatsu, T.; Kiguchi, T.; Hirobe, M. *Tetrahedron Lett.* **1988**, *29*, 2203.
(5) (a) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447. (b) Ojima, I.; Habus, I. *Tetrahedron Lett.* **1990**, *30*, 4289.
(6) Spatola, A. F. In *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*; Weinstein, B., Ed.; Marcel Dekker: New York, 1983; Vol. 7, pp 331−333 and references cited therein.
(7) Jiang, J.; Schumacher, K. K.; Joullie, M. M.; Davis, F. A.; Reddy, R. E. *Tetrahedron Lett.* **1994**, *35*, 2121.
(8) Graf, F.; Boeddeker, H. *Liebigs Ann. Chem.* **1958**, *613*, 111. Graf, E.; Weinandy, S.; Koch, B.; Breitmaier, E. *Liebigs Ann. Chem.* **1986**, *7*, 1147.
(9) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. *J. Org. Chem.* **1995**, *60*, 7037.
(10) (a) Yang, T.-K.; Chen, R.-Y.; Lee, D.-S.; Peng, W.-S.; Jiang, Y.-Z.; Mi, A.-Q.; Jong, T.-T. *J. Org. Chem.* **1994**, *59*, 914. (b) Hose, D. R. J.; Raynham, T.; Wills, M. *Tetrahedron: Asymmetry* **1993**, *4*, 2159.
(11) (a) Davis, F. A.; Reddy, R. T.; Portonovo, P. *Tetrahedron Lett.* **1994**, *35*, 9351. (b) Hua, D. H.; Lagneau, N.; Chen, J. *Tetrahedron: Asymmetry* **1995**, *5*, 349.
(12) (a) Davis, F. A.; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243. (b) Davis, F. A.; Zhou, P. *Tetrahedron Lett.* **1994**, *35*, 7525. (c) Davis, F. A.; Zhou, P.; Liang, C.-H.; Reddy, R. E. *Tetrahedron: Asymmetry* **1995**, *6*, 1511.
(13) (a) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387. (b) Hua, D. H.; Miao, S. W.; Chen, U.; J. S. Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4.
(14) Davis, F. A.; Reddy, R. E. *Tetrahedron: Asymmetry* **1994**, *5*, 955.
(15) Rico, J. G.; Lindmark, J. R.; Rogers, T. E.; Bovy, P. R. *J. Org. Chem.* **1993**, *58*, 7948.
(16) (a) Mioskowski, C.;Solladie, G. *Tetrahedron* **1980**, *36*, 227. (b) Hulce, M.; Mallamo, J. P.; Frye, L. L.; Kogan, T. P.; Posner, G. H. *Org. Synth.* **1984**, *64*, 196.
(17) Pyne, S. G.; Hajipour, A. R.; Prabakaran, K. *Tetrahedron Lett.* **1994**, *35*, 645.
(18) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Portonovo, P. S. *Tetrahedron Lett.* **1993**, *34*, 6229.
(19) Davis, F. A.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1993**, *58*, 4890.

0022-3263/96/1961-2222$12.00/0

Scheme 2



a) Ar = *p*-tolyl, R = Me
b) Ar = *p*-tolyl, R = Et
c) Ar = *p*-tolyl, R = *t*-Bu
d) Ar = *p*-tolyl, R = CH_2Ph
e) Ar = 2-methoxynaphthyl, R = Me
f) Ar = 2-methoxynaphthyl, R = Et
g) Ar = 2-methoxynaphthyl, R = CH_2Ph

Table 1. Stereoselective Addition of Ester Enolates to Sulfinimines 5/6

entry	sulfinimine **5/6**	R	base (1.5 equiv)	sulfinamide **7**, %yield[a]	sulfinamide (R_S,3*S*)/(R_S,3*R*)	sulfinamide **7**, % de[b]
1	(*R*)-(−)-**5**	Me	NaHMDS	**7a**, 80	87:13	74
2		Et	NaHMDS	**7b**, 72	82:18	64
3		Et	LDA	56	78:22	56
4		Et	LiHMDS	59	76:24	52
5		*t*-Bu	NaHMDS	**7c**, 76	55:45	10
6		CH_2Ph	NaHMDS	**7d**, 65	86:14	72
7	(*R*)-(−)-**6**	Me	LiHMDS	**7e**, 86	86:14	72
8		Et	NaHMDS	**7f**, 63	74:26	48
9		Et	LDA	82	85:15	70
10		Et	LiHMDS	85	89:11	78
11		CH_2Ph	LiHMDS	**7g**, 87	86:14	72

[a] Isolated yields. [b] The diastereomeric ratios were determined by ^1H NMR.

ity of **5** in diethyl ether precluded attempts to reproduce these conditions. Efforts to improve the diastereoselectivity by variation of the counterion and the R group in the enolate are summarized in Table 1.

Sodium enolates gave slightly higher de's than the lithium enolates; 64 vs 52-56% (Table 1, compare entries 2 with 3 and 4). The highest de's, 72−74%, were observed for the sodium enolates of methyl and benzyl acetates (entries 1 and 6) and the lowest, 10%, for the sodium enolate of *tert*-butyl acetate (entry 5). The latter result may be due to destabilization of the chairlike transition state, proposed for enolate additions to sulfinimines, by the bulky *tert*-butyl group.[13a] This model correctly predicts that the (*S*)-configuration is generated at the amino carbon in **7** on addition of enolates to (*R*)-**5**. The generally lower selectivities for **5** vs **5** (pyridyl = phenyl)[9] is probably the result of coordination of the metal enolate with the pyridyl nitrogen which disrupts the transition state for enolate addition. Although these are auxiliary-based asymmetric syntheses, all attempts to separate diastereoisomers (R_S,*S*)-**7a**−**d**/(R_S,*R*)-**7a**−**d** by chromatography or by crystallization failed (Scheme 1).

Fortunately, addition of the lithium enolate of ethyl acetate to (*R*)-(−)-*N*-(3-pyridylmethylidene)-*β*-methoxynaphthalenesulfinimide (**6**) gave sulfinamide **7f** in 85% yield and 78% de (entry 10). The major isomer (R_s,3*S*)-**7b** was readily separated by flash chromatography to give diastereomerically pure (R_s,3*S*)-(−)-ethyl *β*-[*N*-(2-methoxynaphthalenesulfinyl)amino]-3-pyridinepropanoate (**7b**) in 75% yield as a thick gum.

The sulfinamide (R_s,3*S*)-(−)-**7b** was hydrolyzed by treatment with 4 equiv of trifluoroacetic acid in ethanol at 0 °C to rt affording (+)-**3** in 90% yield as its bistrifluoroacetic acid salt following flash chromatography (Scheme 1). The chiral auxiliary in (*R*)-(−)-**6** can be effectively recycled by replacement of ethanol by (+)-menthol giving (1*S*,2*R*,5*S*)-(±)-menthyl 2-methoxy-1-naphthalenesulfinate (**4b**) in 75% isolated yield and *β*-amino ester (+)-**3** in 85% yield.[9] Diastereomeric **4b** is upgraded by crystallization from acetone/HCl as previously described.[16b] Difficulty was experienced in obtaining a consistent optical rotational value for (+)-**3**, reported to be $[\alpha]^{20}_D$ +3.3°.[15] The enantiomeric purity of (+)-**3** was determined using a Daicel CrownPak CR (+) column and was found to be >97% ee [1.4/98.6 *R*/*S*].

Experimental Section

General Procedure. Column chromatography was performed on silica gel, Merck grade 60 (230−400 mesh). Analytical thin layer chromatography was performed on precoated silica gel plates (250) purchased from Analtech Inc. TLC plates were visualized with UV light and/or in an iodine chamber unless noted otherwise. THF was freshly distilled under nitrogen from a purple solution of sodium and benzophenone. LDA was freshly prepared according to the procedure described in reference 19. Elemental analyses were performed by the Department of Chemistry, University of Pennsylvania, Philadelphia. HRMS were performed on a Fissons ZAB HF double-focusing mass spectrometer at Drexel University.

(*R*)-(−)-*N*-(3-Pyridinemethylidene)-*p*-toluenesulfinamide (5). In a 100 mL single-necked, round-bottomed flask equipped with a magnetic stir bar, rubber septum, and an argon inlet was placed 2.94 g (10.0 mmol) of (1*S*,2*R*,5*S*)-(+)-menthyl (*R*)-*p*-toluenesulfinate (**4a**)[16b] dissolved in 60 mL of freshly distilled THF cooled to −78 °C. A solution of 15.0 mL of LiHMDS (1 M solution in THF) was added dropwise via syringe, warmed to rt after 15 min, and stirred for 5.5 h. The reaction mixture was cooled to 0 °C, and 1.9 mL (20.0 mmol) of 3-pyridinecarboxaldehyde (Aldrich) was added dropwise via syringe, followed by the addition of 3.04 g (20.0 mmol) of powdered CsF (99.9%). After stirring overnight at rt the reaction mixture was quenched with saturated NH_4Cl solution (3 mL) and diluted with ethyl acetate (200 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was washed with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), and concentrated to give a slightly yellow solid which was purified by flash chromatography on silica gel eluting with 70% EtOAc/*n*-hexane. Crystallization of the solid from *n*-hexane/EtOAc afforded 1.69 g (two crops) of (*R*)-(−)-**5** in 70% yield: mp 77−78 °C; $[\alpha]^{20}_D$ −149.8° (*c* 1.17, $CHCl_3$); IR (KBr) 1609, 1587, 1567, 1493, 1325, 1100, 1024, 810, 797, 698, 609 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 2.39 (s, 3H), 7.31 (d, 2H, *J* = 8.2 Hz), 7.35−7.41 (m, 1H), 7.62 (d, 2H, *J* = 8.2 Hz), 8.14−8.17 (m, 1H), 8.71 (d, 1H, *J* = 3.8 Hz), 8.79 (s, 1H), 9.00 (s, 1H); ^{13}C NMR *δ* 158.1, 153.0, 151,2, 142.0, 141.1, 135.8, 129.9, 129.5, 124.6, 123.8, 21.4; MS *m*/*z* 244 (M^+), 139, 123, 111, 105, 99, 77. Anal. Calcd for $C_{13}H_{12}N_2SO$: C, 63.90; H, 4.95; N, 11.47. Found: C, 63.87; H, 5.08; N, 11.04.

(*R*)-(−)-*N*-(3-Pyridinemethylidene)-2-methoxynaphthalenesulfinamide (6). Prepared from 3.49 g (9.7 mmol) of (*R*)-(+)-menthyl 2-methoxy-1-naphthalenesulfinate (**4b**)[17] as described in the preceding section and isolated by flash chromatography to give 2.13 g (71%) of (*R*)-(−)-**6** as a thick oil: $[\alpha]^{20}_D$ −106.0° (*c* 1.9, $CHCl_3$); IR (KBr) 1605, 1590, 1506, 1468, 1413, 1273, 1252, 1063, 811 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 3.98 (s, 3H), 7.26−7.43 (m, 3H), 7.49−7.56 (m, 1H), 7.82 (d, 1H, *J* = 7.9 Hz), 8.00 (d, 1H, *J* = 9.1 Hz), 8.18 (dt, *J* = 7.9 Hz, *J* = 1.9 Hz), 8.57 (d, 1H, *J* = 8.5 Hz), 8.71 (dd, 1H, *J* = 4.9 Hz, *J* = 1.7 Hz), 9.04 (d, 1H, *J* = 2.1Hz), 9.09 (s, 1H); ^{13}C NMR *δ* 159.2, 157.3, 152.8, 151.1, 135.6, 134.8, 131.3, 129.6, 129.2, 128.8, 128.1, 124.4, 123.8, 121.9, 121.3, 113.3, 56.9; MS *m*/*z* 310 (M^+), 262, 205, 188, 147, 131, 115. Anal. Calcd for $C_{17}H_{14}N_2SO_2$: C, 65.78; H, 4.54; N, 9.02. Found: C, 65.65; H, 4.61; N, 9.01.

Typical Procedure for the Addition of Ester Enolates to Sulfinimines: (R_s,*S*)-(−)-Ethyl β-[*N*-(2-Methoxynaphthalenesulfinyl)amino]-3-pyridinepropanoate (7f). In a 100 mL dry single-necked round bottom flask equipped with a magnetic stir bar, argon inlet, and rubber septum was placed freshly distilled THF (27.0 mL). The solution was cooled to −78 °C, 7.50 mL of LiHMDS (1.0 M solution in THF, 7.5 mmol, 1.6 equiv) was added followed by 0.69 mL of anhydrous ethyl acetate (7.03 mmol, 1.5 equiv). The reaction mixture was stirred for 50 min at which time a solution of 1.45 g (4.69 mmol) of (*R*)-(−)-**6** in THF (12.0 mL) was added dropwise via syringe at −78 °C. After stirring for 5.5 h the reaction was quenched at −78 °C by addition of saturated NH_4Cl solution (3 mL), warm to room temperature, and diluted with ethyl acetate (75 mL). The organic layer was washed with water (20 mL), the aqueous portion was extracted with ethyl acetate (50 mL), and the combined organic extracts were washed with water (25 mL) and brine (20 mL) and dried ($MgSO_4$). Concentration of the solvent gave an oil [78% de by ^{1}H NMR] which was purified by silica gel column chromatography (90% EtOAc/petroleum ether to 5% methanol/ethyl acetate) to afford 1.39 g (76%) of (R_S,*S*)-(−)-**7f** (>99% de) and of 0.16 g (9%) of (R_S,*R*)-**7f** (minor diastereomer). Major diastereomer: thick oil; $[\alpha]^{20}_D$ −80.0° (*c* 1.25, $CHCl_3$); IR (KBr) 3248, 2974, 1716, 1591, 1506, 1271, 1192, 1080, 1023 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, *J* = 7.2 Hz), 2.90−3.05 (m, 3H), 4.13 (s, 3H), 4.15 (q, 2H, *J* = 6.4), 5.02 (q, 1H, *J* = 6.3), 7.13 (d, 1H, *J* = 4.3), 7.20−7.55 (m, 4H), 7.71 (dd, 1H, *J* = 7.8, 1.5 Hz), 7.78 (d, 1H, *J* = 8.1), 7.94 (d, 1H, *J* = 9.0), 8.40 (d, 1H, *J* = 8.5 Hz), 8.55 (d, 1H, *J* = 4.7), 8.66 (s, 1H); ^{13}C NMR δ 170.6, 155.5, 149.3, 149.0, 135.7, 135.0, 133.5, 130.6, 128.8, 128.5, 128.1, 125.4, 124.4, 123.3, 121.9, 113.4, 60.9, 56.8, 53.7, 42.0, 14.0; HRMS calcd for $C_{21}H_{22}N_2O_4S$ 399.1379 (M + 1), found 399.1386.

Minor isomer (R_S,*R*)-**7f**, ^{1}H NMR ($CDCl_3$) δ 1.12 (t, 3H, *J* = 7.1 Hz), 2.98 (ddd, 2H, J = 63.0, 16.0, 7.5 Hz), 4.02 (q, 2H, *J* = 4 Hz), 4.05 (s, 3H), 4.98 (q, 1H, *J* = 6.5 Hz), 6.49 (d, 1H, J = 5.6 Hz), 7.23−7.57 (m, 4H), 7.77−7.81 (m, 2H), 7.91 (d, 1H, *J* = 9.0 Hz), 8.51−8.59 (m, 3H); MS *m*/*z* 399 (M + 1), 378, 346, 205, 195, 189, 115, 107, 80.

(*R*,*3S*)-Methyl β-[*N*-(*p*-Tolylsulfinyl)amino]-3-pyridinepropanoate (7a). yield 80% (thick gum); 74% de; IR (neat) 3176, 2950, 1735, 1593, 1435, 1089, 1055, 812, 713 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 13/100 3H), 2.42 (s, 87/100 3H), 2.89 (d, 87/100 2H, *J* = 6.3 Hz), 3.03 (d, 13/100 2H, *J* = 6.0 Hz), 3.62 (s, 87/100 3H), 3.64 (s, 13/100 3H), 4.77 (q, 13/100 1H, *J* = 7.4 Hz), 4.89 (q, 87/100 1H, *J* = 6.2 Hz), 5.33 (d, 87/100 1H *J* = 6.2 Hz), 5.63 (d, 13/100 1H, *J* = 7.8 Hz), 7.16−7.82 (m, 6H), 8.38 (br s, 13/100 1H), 8.44 (d, 13/100 1H, *J* = 4.1 Hz), 8.56 (d, 87/100 1H, *J* = 4.0 Hz), 8.67 (br s, 87/100 1H); MS *m*/*z* 318 (M$^+$), 301, 270, 238, 180, 165, 139, 105, 91, 77; HRMS calcd for $C_{16}H_{18}N_2SO_3$, 319.1116 (M + 1), found 319.1118. Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.69; N, 8.79. Found: C, 60.11; H, 5.82; N, 8.44.

(*R*,*3S*)-Ethyl β-[*N*-(*p*-Tolylsulfinyl)amino]-3-pyridinepropanoate (using LiHMDS) (7b). The crude compound was purified by silica gel chromatography (10% ethanol/ethyl acetate): yield 59%; 52% de; IR (neat) 3021, 2924, 1731, 1619, 1592, 1429, 1271, 1250, 1063 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 76/100 3H, *J* = 7.1 Hz), 1.17 (t, 24/100 3H, *J* = 7.1 Hz), 2.35 (s, 24/100 3H), 2.42 (s, 76/100 3H), 2.87 (d, 76/100 2H, *J* = 6.2 Hz), 3.01 (m, 24/100 2H), 4.06 (q, 2H, *J* = 7.2 Hz), 4.77 (q, 24/100 1H, *J* = 7.0 Hz), 4.88 (q, 76/100 1H, *J* = 6.2 Hz), 5.41 (d, 76/100 1H, *J* = 6.0 Hz), 5.74 (d, 24/100 1H, *J* = 6.2 Hz), 7.16−7.80 (m, 6H), 8.35 (br s, 24/100 1H), 8.44 (d, 24/100 1H, *J* = 3.9 Hz), 8.57 (d, 76/100 1H, *J* = 4.0 Hz), 8.67 (br s, 76/100 1H); MS *m*/*z* 333 (M$^+$ + 1), 315, 284, 193, 178, 147, 139, 107, 91, 78; HRMS calcd for $C_{17}H_{21}N_2SO_3$, 333.1273 (M + 1), found 333.1281.

(R_s,*S*)-*tert*-Butyl β-[*N*-(*p*-Tolylsulfinyl)amino]-3-pyridinepropanoate (7c). The crude compound was purified by preparative thin layer chromatography (10% ethanol/ethyl acetate): thick gum, yield 76%; 10% de; IR (neat) 1725, 1367, 1286, 1152, 1089, 1054, 812, 713 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 55/100 9H), 1.34 (s, 45/100 9H), 2.34 (s, 45/100 3H), 2.42 (s, 55/100 3H), 2.79 (dd, 55/100 2H, *J* = 7.2, 1.2 Hz), 2.92 (d, 45/100 2H, *J* = 6.0 Hz), 4.74 (q, 45/100 1H, *J* = 6.9 Hz), 4.86 (q, 55/100 1H, *J* = 6.0 Hz), 5.29 (d, 55/100 1H, *J* = 4.0 Hz), 5.63 (d, 45/100 1H, *J* = 7.3 Hz), 7.14−7.81 (m, 6H), 8.37 (br s, 45/100 1H), 8.42 (d, 45/100 1H, *J* = 4.2 Hz), 8.55 (d, 55/100 1H, *J* = 4.0 Hz), 8.66 (br s, 55/100 1H); MS *m*/*z* 360 (M$^+$), 343, 287, 278, 246, 221, 155, 139, 107, 91, 57; HRMS calcd for $C_{19}H_{24}N_2SO_3$, 360.1507, found 360.1517. Anal. Calcd for $C_{19}H_{24}N_2O_3S$: C, 63.31; H, 6.71; N, 7.77. Found: C, 63.02; H, 6.99; N, 7.42.

(R_s,*S*)-Benzyl β-[*N*-(*p*-Tolylsulfinyl)amino]-3-pyridinepropanoate (7d). The crude compound was purified by preparative thin layer chromatography (10% ethanol/ethyl acetate): thick gum; yield 65%; 72% de; IR (neat) 1734, 1577, 1491, 1427, 1277, 1159, 1089, 1062, 811, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 14/100 3H), 2.43 (s, 86/100 3H), 2.93 (d, 86/100 2H, *J* = 6.3 Hz), 3.04−3.06 (m, 14/100 2H), 4.75 (q, 14/100 1H, *J* = 6.5 Hz), 4.91 (q, 86/100 1H, *J* = 6.1 Hz), 5.03 (s, 86/100 2H), 5.06 (s, 14/100 2H), 5.15 (d, 86/100 1H, *J* = 6.0 Hz), 5.45 (d, 14/100 1H, *J* = 7Hz), 7.18−7.76 (m, 11H), 8.47 (d, 14/100 1H, *J* = 2.0 Hz), 8.43−8.45 (m, 14/100 1H), 8.54−8.57 (m, 86/100 1H) 8.65 (d, 86/100 1H, *J* = 2.0 Hz); MS *m*/*z* 394 (M$^+$), 377, 346, 238, 180, 165, 139, 105, 91, 77; HRMS calcd for $C_{22}H_{22}N_2SO_3$, 395.1429, found 395.1428. Anal. Calcd for $C_{22}H_{22}N_2O_3S$: C, 66.98; H, 5.62; N, 7.10. Found: C, 67.19; H, 5.88; N, 6.77.

(±)-Methyl β-[*N*-(2-Methoxynaphthalenesulfinyl)amino]-3-pyridinepropanoate (7e). The crude compound was purified by preparative thin layer chromatography (10% ethanol/ethyl acetate): yield 86%; 72% de. Major isomer: yield 74%; IR (neat) 1732, 1592, 1506, 1431, 1272, 1250, 1064, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.85−3.05 (m, 2H), 3.69 (s, 3H), 4.12 (s, 3H), 5.02 (q, 1H, *J* = 5.5 Hz), 7.13 (d, 1H, *J* = 4.1 Hz), 7.23−7.54 (m, 4H), 7.71 (d, 1H, *J* = 6.9 Hz), 7.80 (d, 1H, *J* = 8.1 Hz), 7.95 (d, 1H, *J* = 9.1 Hz), 8.39 (d, 1H, *J* = 8.5 Hz), 8.55 (d, 1H, *J* = 4.7 Hz), 8.65 (bs, 1H); HRMS calcd for $C_{20}H_{20}N_2SO_4$, 385.1222 (M + 1), found 385.1224.

Minor diastereomer: yield 12%; IR (neat) 1734, 1619, 1592, 1507, 1431 1272, 1251, 1063, 1024, 813, 712 cm^{-1}; ^{1}H NMR δ 3.00 (ddd, 2H, *J* = 61.2, 16.1, 6.0 Hz), 3.58 (s, 3H), 4.07 (s, 3H), 4.98 (q, 1H, *J* = 7.0 Hz), 6.48 (d, 1H, *J* = 5.5 Hz), 7.25−7.55 (m, 4H), 7.80 (d, 2H, *J* = 8.0 Hz), 7.94 (d, 1H, *J* = 9.1 Hz), 8.52−8.59 (m, 3H); MS *m*/*z* 385 (M + 1), 336, 205, 179.

(±)-Benzyl β-[*N*-(2-Methoxynaphthalenesulfinyl)amino]-3-pyridinepropanoate (7g). The crude compound was purified by preparative thin layer chromatography (10% ethanol/ethyl acetate): oil; yield 87%; 72% de. Major diastereomer yield 75%; IR (neat) 1727, 1592, 1508, 1272, 1251, 1152, 1064, 1024, 812, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.92−3.10 (m, 2H), 4.08 (s, 3H), 5.05 (q, 1H, *J* = 5.2 Hz), 5.11 (s, 2H), 7.12 (d, 1H, *J* = 4.7 Hz), 7.24−7.53 (m, 9H), 7.65−7.71 (m, 1H), 7.80 (d, 1H, *J* = 7.9 Hz), 7.95 (d, 1H, *J* = 9.1 Hz), 8.38 (d, 1H, *J* = 8.6 Hz), 8.55 (d, 1H, *J* = 3.7 Hz), 8.65 (bs, 1H); HRMS calcd for $C_{26}H_{24}N_2SO_4$, 461.1535 (M + 1), found: 461.1528.

Minor diastereomer: yield 12%; IR (neat) 1734, 1654, 1636, 1618, 1271, 1250, 1063, 1024 cm^1; ^{1}H NMR ($CDCl_3$) δ 3.05 (ddd, 2H, *J* = 64.7, 16.0, 7.5 Hz), 4.04 (s, 3H), 4.89−5.15 (m, 2H), 6.46 (d, 1H, *J* = 5.6Hz), 7.17−7.54 (m, 9H), 7.79 (t, 2H, *J* = 8.1 Hz), 7.93 (d, 1H, *J* = 9.1 Hz), 8.52−8.58 (m, 3H); MS *m*/*z* 461 (M + 1), 412, 255, 205, 107.

(*S*)-(+)-Ethyl 3-Amino-3-pyridinepropanoate (3). In a 50 mL dry single-necked round bottom flask fitted with magnetic stir bar, argon inlet and rubber septum was placed 1.08 g (2.71 mmol) of (R_s,*S*)-(−)-ethyl β-[*N*-(2-methoxynaphthalenesulfinyl)-amino]-3-pyridinepropanoate (**7f**) in 20 mL of dry ethanol and cooled to 0 °C. Trifluoroacetic acid (1.04 mL, 5.0 equiv) was added, and the reaction mixture was stirred at rt for 2 h at which time the solvent was removed to dryness below 40 °C on the rotary evaporator. To remove traces of TFA, 5 mL of toluene was added and the solvent removed. The residue was purified by silica gel chromatography (20% ethanol in CH_2Cl_2), and the resulting oil was dried under vacuum for 48 h to give 1.03 g (90%) of (+)-(*S*)-**3** as its bis-ditrifluoroacetic acid salt as thick pale yellow gum; $[\alpha]^{20}_D$ +3.67° (*c* 7.1, DMF) [lit.[15] $[\alpha]^{20}_D$ +3.3° (c, 10 DMF)]; ^{1}H NMR (DMSO) δ 1.08 (t, 3H, *J* = 7.1 Hz), 3.06 (m, 2H), 4.01 (qd, 2H, *J* = 7.1, *J* = 1 Hz), 4.70 (t, 1H, *J* = 7.2 Hz), 7.49 (m, 1H), 7.91 (dt, 1H, *J* = 7.9 Hz, *J* = 1.9 Hz), 8.48 (bs, 1H), 8.58 (m, 1H), 8.67 (d, 1H, *J* = 2.3 Hz).

The enantiomeric purity of the (*S*)-(+)-**3** was determined to be >97% ee [1.4/98.6 *R*/*S*] using a Daicel CrownPak CR (+) column under the following conditions: $HClO_4$ at pH = 1, rt, flow rate: 0.45 mL/min, UV detector at 200 nm.

(*S*)-(+)-Ethyl 3-Amino-3-pyridinepropanoate (3). Recovery of (*1S*,*2R*,*5S*)-(±)-Menthyl 2-Methoxy-1-naphthalenesulfinate. In a 25 mL dry single-necked round bottom flask equipped with magnetic stir bar, argon inlet and rubber septum

were placed 0.253 g (0.635 mmol) of (−)-(R_s,*S*)-ethyl β-[*N*-(2-methoxynaphthalenesulfinyl)amino]-3-pyridinepropanoate (**7f**) and 0.130 g (1.3 equiv) of (*1S*,*2R*,*5S*)-(+)-menthol in 8 mL of methylene chloride and cooled to 0 °C. Trifluoroacetic acid (0.19 mL, 4.0 equiv) was added, and the reaction mixture was stirred at rt for 4 h. The mixture was diluted with 50 mL of water, another 0.19 mL (4 equiv) of TFA was added, and the solution was extracted with methylene chloride (3 × 20 mL). Drying ($MgSO_4$) and concentration of the solvent gave an oily solid which was purified by flash chromatography on silica gel (EtOAc/hexanes 2:8) to give 0.17 g (75%) of (*1S*,*2R*,*5S*)-(±)-menthyl 2-methoxy-1-naphthalenesulfinate (**4b**).[17]

The water layer was concentrated to dryness and the β-amino ester (+)-(*S*)-**3** was dried overnight under vacuum and purified on a short silica gel column (ethanol/CH_2Cl_2 2:8) to give 0.20 g (85%); $[\alpha]^{20}_D$ +4.23° (*c* 7.3, DMF) [lit.[15] $[\alpha]^{20}_D$ +3.3° (*c* 10, DMF)].

The enantiomeric purity of the (*S*)-(+)-**3** was determined to be >97% ee using a Daicel CrownPak CR (+) column as described above.

Acknowledgment. This work was supported by grants from the National Science Foundation and the National Institutes of Health. We thank Dr. Joseph G. Rico of Monsanto Corporate Research for a sample of racemic **3** dihydrochloride.

Supporting Information Available: ^{1}H NMR ($CDCl_3$) spectra of compounds **7b** (250 MHz), **7e**, **7f**, **7g** (300 MHz) (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951917X